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MINI REVIEW

Preventing and managing herpes zoster: key actions to foster healthy aging

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Abstract Population aging is the demographic phenomenon characterizing all countries in the world, and it is challenging the national infrastructures, in particular health systems. However, aging itself is not associated with increased medical spending, but disability and comorbidity that affect older individuals are the actual drivers for health expenditures. Therefore, if people age in better health, medical spending may be significantly reduced. Preventative interventions proved to be effective in reducing/preventing disease and disability and often found to be cost effective, include diet and exercise interventions, medications, routine disease screenings, and immunizations. Vaccination can protect older citizens against life-threatening diseases, such as influenza, pneumococcal infections, tetanus, and against diseases which adversely impact their quality of life, such as herpes zoster (HZ). Including HZ vaccination in its citizens' lifetime immunization calendar can reinforce Europe's commitment toward active, healthy aging. This paper outlines the consensus statement of a group of Italian experts on HZ.

Keywords Vaccine · Herpes zoster · Immunosenescence

Introduction

Population aging is the most relevant worldwide demographic phenomenon of our century. In Europe, there are 183.5 million individuals aged over 50, more than a third of the total population. Demographic projections predict that citizens aged over 50 will represent 40 % of the European population by 2060; the number will increase to 212 million in 2020 and to 248 million in 2060. Half of this population falls into the "elderly people" bracket which includes persons aged 65 or above [1]. In Italy, where life expectancy is almost 80 for men and 85 for women, one of the highest expectancies in the world, about 22 % of the population is >65 years of age [2].

This demographic trend is challenging national infrastructures and, in particular, healthcare systems. While

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aging itself is not associated with increased medical spending, the disability and comorbidity that affect older individuals are what is actually impacting healthcare expenditure. Multimorbidity is quite common in elderly people as it affects more than 60 % of those aged 65 and above. This proportion rises with age, together with the number of simultaneous underlying conditions [3].

But it is also true that when individuals in good health age, medical spending can result to be significantly lower with respect to predicted estimates. Evidence-based preventive services have proved to be effective in reducing/preventing disease and disability and are often found to be cost effective and/or at times even cost saving. These measures can include diet and exercise interventions, medications, routine disease screenings, and immunizations. The last are, in particular, among the most cost-effective public health interventions because they reduce or eliminate the burden of many infectious diseases and their health consequences. Common vaccine-preventable diseases of older individuals include influenza, pneumococcal infections, pertussis, tetanus, and herpes zoster (HZ) [4]. Including HZ vaccination in its citizens' lifetime immunization calendar can reinforce Europe's commitment toward active, healthy aging. This paper outlines the consensus statement of a group of Italian experts on HZ: particular emphasis is placed on the disease's burden on the country's senior citizens [5].

Clinical aspects and epidemiology

Caused by a reactivation of the varicella-zoster virus (VZV) that has remained dormant often for decades after the patient's initial exposure, HZ is a common, painful, and debilitating disease. After the initial episode of varicella, the virus remains latent and clinically silent within the ganglia. While VZV reactivation is primarily correlated to an age-related decline in VZV-specific immunity [6], it is also linked to lower immune function, chronic diseases, stress and illness, recent trauma or surgery.

Several chronic diseases have been found to be associated with a higher risk of developing HZ, which in any case increases with aging. Ninety percent of HZ cases, nevertheless, occur in immunocompetent individuals [7, 8]. Lymphoma, cancer, autoimmune disease, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and major depression are recognized risk factors for HZ [9]. There is also growing evidence that chronic obstructive pulmonary disease (COPD) increases the risk of developing HZ in the general population, probably due to systemic and local chronic inflammation affecting the immune system [10]. Diabetes is one of the conditions that can modify cell-mediated immunity and can therefore increase the risk of HZ, and some studies suggest that there is an increased risk in patients with type II diabetes [11]. The clinical relevance of HZ has also been confirmed by recent data on the association between an acute episode of HZ followed by an incident stroke. Survival curves of these patients show that an HZ attack is followed, a few weeks later, by an increase in the mortality rate due to stroke [12].

As varicella is mainly a childhood disease, 95 % of the population is infected by young adulthood, and virtually the entire adult population is at risk of developing HZ at some stage. The lifetime risk is between 25–30 % and it is 50 % for those reaching their 8th decade [13].

HZ's most well-known feature is a characteristic cutaneous rash occurring in a dermatomal distribution that is associated with unilateral pain and discomfort. The initial rash is erythematous with multiple maculopapular lesions that subsequently become vesicular. New vesicular lesions may continue to appear for up to 7 days, before the lesions form a crust that falls off after 2–3 weeks [14]. Involvement of the ophthalmic division of the trigeminal nerve is noted in10–20 % of all HZ episodes [15, 16]. Pain, which is one of the main symptoms of HZ, often precedes the rash by several days. When compared to the pain associated with other acute or chronic conditions, the one associated with HZ and PHN is rated as quite intense. With reference to the total pain rating index scores using the Short-Form McGill Pain Questionnaire (SF-MPQ) for acute and chronic conditions, pain in the acute phase of the disease has been rated as more intense than labor or post-surgical pain, and chronic pain has been rated more intense than musculoskeletal pain [17].

Post-herpetic neuralgia (PHN) is the most common debilitating complication of HZ, one of the most challenging to treat, and the cause of the greatest HZ-related burden of illness. PHN is neuropathic syndrome that is characterized by pain along the cutaneous nerves, described as spontaneous aching or burning, paroxysmal shooting pain, allodynia and/or hyperalgesia [18]. PHN has been defined as "a chronic long-lasting HZ-related pain occurring or persisting for at least 3 months after the HZ rash or pain onset."

The condition appears to respond poorly to treatment, has a significant impact on quality of life, and poses an economic burden on the individual and the healthcare system. The risk of developing PHN varies from 5 % to more than 30 % [19]. According to the Shingles Prevention Study, the proportion of HZ patients who develop PHN is 12.5 % at 3 months and 5.1 % at 6 months. These data refer to subjects aged above 60 who had for the most part received antiviral medication [20]. Schmader found PHN at 6 months from HZ onset in about 20 to 30 % of treated patients in antiviral drug trials. These data indicate that even optimally treated patients can develop PHN [21].

In Italy, the estimated number of new HZ cases occurring each year in the population aged over 50 is about 160,000, and the annual incidence rate is 6.3/1,000 person-years [22].

An Italian longitudinal study reported that about 21 % of HZ patients aged >50 years had PHN at 3 months and more than 9 % still had it at 6 months, notwithstanding early antiviral treatment (within 72 h of skin rash onset) [23]. Another study analyzing all hospitalization discharges between 1999 and 2005 reported an annual average of 4,503 regular admissions (mean length of stay was 8 days) and 543 day-hospital admissions, meaning an average of 14 admissions/day. 62 % of these patients were above 65 [24]. These studies confirm the high clinical, epidemiological, and economic burden of HZ/PHN in the Italian population as a whole and in the older population in particular.

Pain and discomfort associated with HZ and PHN can significantly affect the functional status of patients as well as their overall health-related quality of life (HRQoL), a fact well known by family practitioners, especially those caring for a large number of elderly patients [25]. Zoster-related pain, which can last for months and even years, has a significant effect on patients' quality of daily life and well-being from the onset of the acute phase of the disease and throughout its evolution. Two-thirds of patients with persistent pain define it, in fact, as moderate to very severe. The disease affects all aspects of life: social, mental, physical, and functional [8, 26, 27]. During the acute phase, 73 % of patients experience problems with their daily activities including housework and leisure activities [29], and approximately 60 % report mobility problems (walking ability) and sleep disorders [30]. In the chronic phase, 90 % of PHN patients report having difficulty with their usual daily tasks and sleep disturbances [31, 32]. PHN is significantly associated with pain intensity at HZ presentation, age, smoking, symptoms of anxiety and depression, trauma, and missed antiviral prescription [33, 34].

The presence and severity of acute and chronic neuropathic pain conditions are associated with substantial impairments across all four HRQoL domains (physical, functional, social, and psychological) [35, 36]. Recently, the quality of life was found to be significantly reduced in a group of Italian patients with PHN lasting at least 6 months from the onset of HZ [37]. Overall health, assessed by PHN patients using global health rating scales, is also poor. Defined by many as devastating, the impact of HZ equals that associated to common debilitating chronic conditions such as congestive heart failure, diabetes mellitus, myocardial infarction, and clinical depression [39].

The objectives of HZ treatments include then reducing the extent, the severity and the duration of the infection, and preventing or reducing its complications [40]. Therapeutic approaches include symptomatic treatments, antibiotics to treat bacterial superinfections, antiviral therapy, and nerve blocks [41]. Disease guidelines highlight the importance of beginning antiviral therapy early, if possible within 72 h from symptom onset, in order to avoid loss of efficacy [42]. Clinical trials have, nevertheless, shown that about 20 to 30 % of patients treated within 72 h still develop post-herpetic neuralgia, and a Cochrane review demonstrated that antiviral drugs do not prevent PHN [43].

Although several treatments are available, PHN is very difficult to treat [44–47]. Briefly, after a baseline pain assessment has been made, the clinician should attempt to treat the patient with lidocaine patches. If benefit is not achieved, pregabalin or gabapentin should be added. While the overall efficacy of these agents is similar to that of tricyclic antidepressant drugs, they have a lower risk of adverse events. If the treatment response is inadequate, a tricyclic antidepressant should also be considered. Regular follow-ups are necessary to assess pain, to evaluate the need to increase drugs doses, to control for side effects, and to evaluate the impact on patients' quality of life and physical and emotional functioning. In a recent Italian longitudinal study, undesirable effects of analgesic therapies were observed in 15.3–28.8 % of the PHN patients [37]. In view of these considerations, prevention through HZ vaccination which significantly reduces the risk of PHN [48] should be given appropriate assessment.

Vaccine prevention of Herpes Zoster and PHN

The data presented here underline the clinical and economic impact of HZ and its complications, as well as the sub-optimal treatments that are available. Most importantly, they explain the rationale for searching adequate preventive measures. The incidence of HZ increases with age, mainly because of immunosenescence, which leads to a decline in the response to infection by both the innate and adaptive immune systems. The aging process includes numerous alterations in the immune system including age-related changes in the T- and B-lymphocyte patterns in conjunction with a reduction in the numbers and efficiency of antigen-presenting cells [49–54].

The vaccine to prevent HZ and PHN is a single-dose live attenuated form that was approved in the United States in 2006. It was also approved by the European Medicines Agency (EMA) in 2006 and it is currently on the market. The vaccine has antigen content higher than at least 19,400 PFU (Plaque-Forming Units), i.e., at least 14 times higher than the antigen content in the pediatric varicella vaccine [55]. It was licensed to prevent the disease in patients already infected with the pathogen (VZV) [56] in order to

diminish, as was said, the disease burden by reducing the incidence, duration, and/or severity of HZ and PHN in persons aged 50 and above. By boosting VZV-specific cellular immunity, the vaccine is able, in fact, to control both the reactivation and replication of the latent virus to reduce the incidence and/or severity of HZ and PHN [57]. The level of cellular immunity determines the risk and severity of HZ and PHN. A weak immune response allows the reactivated virus to replicate unchecked, resulting in higher morbidity [58].

The vaccine's clinical efficacy has been confirmed by two large phase III clinical trials involving more than 38,000 [20] and 22,000 [59] subjects, respectively, aged ≥60 and 50–59 years.

The "Shingles Prevention Study" (SPS), a randomized, double-blind, placebo-controlled trial, assessed 38,546 subjects (19,270 vaccinated and 19,276 treated with placebo) with a mean age of 69 years who were enrolled in the study. Study data showed there was a 51.3 % reduction in the number of HZ cases, a 66.5 % reduction in the number of PHN cases, and a 61.1 % reduction in the overall burden of the disease (BOI) [60].

The zoster efficacy and safety trial (ZEST) evaluated the efficacy of the vaccine against HZ in subjects between 50 and 59; its efficacy was 70 % [59].

Long-term follow-up studies (up to 10-year post-vaccination in persons ≥60) have reported persisting efficacy, although protection decreases gradually over time and as the patient ages [61].

Evidence suggests that the benefit of the zoster vaccine varies with age: it prevents shingles in the youngest, while it prevents PHN and reduces disease severity in the oldest [62]. In fact,

- its efficacy in preventing HZ is maximal in the youngest age group: 70 % in the 50–59;
- its efficacy in preventing HZ severity(i.e., incidence of PHN) is maximal in the oldest age group(67 % in the ≥70 age group) in which at least 2/3 of PHN cases occur;
- its efficacy in reducing the burden of illness (BOI), which reflects the incidence, severity, and duration of HZ-related pain and discomfort, is maximal in patients aged 60 years and above (61 %);
- its efficacy in reducing the impact on quality of daily life is maximal in patients aged 60 years and above (66 %).

The vaccination's clinical profile has been confirmed by real-life effectiveness showing similar levels of protection against HZ and PHN:

- In two population-based studies, the vaccine was associated with a 55 and 51 % reduction in incidence of HZ among the immunocompetent population, respectively, aged ≥60 and ≥65 [63, 64].
- The first results showed that the vaccine's effectiveness against PHN reached 59 % in the general population aged ≥65 (including both immunocompetent and immunosuppressed individuals) [64].
- Another retrospective study on subjects enrolled in Medicare, aged >60 years (average age 74 + 8 years) with immune-mediated diseases (i.e., rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis or ulcerative colitis), showed an effectiveness against HZ that was equal to 39 % [65].

The safety, efficacy data on ZOSTAVAX which were produced by both a comprehensive clinical development plan and long-term follow-up studies clearly support a favorable risk–benefit ratio [66–69].

Herpes zoster vaccine: indications for use in clinical practice and recommendations

According to the summary of product characteristics (SPC) [55], the Zoster vaccine is indicated for the prevention of HZ and HZ-related post-herpetic neuralgia (PHN). Considered effective and safe in HZ history-positive subjects, it is indicated for the immunization of individuals aged 50 years or above [70]. The vaccine is not indicated for the prevention of primary varicella infection (chickenpox) and should not be used in children or adolescents.

Contraindications to the vaccine include history of hypersensitivity to any of the excipients or trace residuals (e.g., Neomycin), primary and acquired immunodeficiency due to acute and chronic leukemias, lymphoma, other conditions affecting the bone marrow or lymphatic system, immunosuppression due to HIV/AIDS, cellular immune deficiencies, immunosuppressive therapy, including high-dose corticosteroids (however, it is not contraindicated for use in individuals who are receiving topical/inhaled corticosteroids or low-dose systemic corticosteroids), and active untreated tuberculosis.

Individuals should receive a single dose (0.65 ml) administered subcutaneously, preferably in the deltoid region; the need for a second dose is currently unknown.

With regard to interactions with other products, the vaccine can be administered concomitantly with inactivated influenza vaccine as separate injections at different body sites.

Zoster vaccine and 23-valent pneumococcal polysaccharide vaccine should not be administered concomitantly because co-administration during clinical trials has led to reduced immunogenicity. No data are currently available regarding concomitant use with other vaccines;

co-administration of Zoster vaccine and antiviral drugs known to be effective against VZV has not been evaluated.

Zoster vaccination is not recommended for persons who have received the varicella vaccine, but virtually all persons currently or soon to enter the recommended age bracket have not received it. The number of persons eligible for zoster vaccination who have received the varicella vaccine is extremely small and will remain so for at least a few decades [71].

It is interesting that persons with a reported history of zoster can be eligible for vaccination although the efficacy of the vaccine in this population has not been assessed. Disease recurrence is not in any case frequent as the active replication of acute VZV boosts VZV-specific immunity reducing the future risk of a subsequent attack.

Those persons intending to initiate immunosuppressive treatments should plan to receive a zoster vaccination at least 14 days before beginning treatment. Persons receiving corticosteroids (<=20 mg/day of prednisone or equivalent) are not considered immunosuppressed and this is not a contraindication for zoster vaccination.

Therapy with methotrexate (<0.4 mg/kg/week), azathioprine (<3 mg/Kg/day), or 6-mercaptopurine (<1.5 mg/Kg/day) is not considered sufficiently immunosuppressive to be treated as a contraindication for zoster vaccine.

Global immunization programs with or without public funding have already been mobilized. In the USA and Canada, immunization has been recommended for patients aged 60 years or above since, respectively, 2006 and 2010. The HZ vaccine has recently been recognized in Europe as an important addition to the medical care of aging individuals, and several countries have decided to recommend and/or fund the vaccination, including Austria [72], Greece [73], Saxony (Germany) [74], Sweden [75], the UK [76], and France [77], with different target populations based on age (e.g., 50+, 70–79, 60+, 65–74, 65–79).

The European Network of Agencies or national institutions dealing with Health Technology Assessment, HTA (EUnetHTA) have recently acknowledged the added benefit provided by the zoster vaccine, confirmed its clinical efficacy/effectiveness in the population of persons over 50 years, and highlighted that its protection duration lasts up to 10 years [78].

The zoster vaccination should, nevertheless, be subjected to country-specific assessments taking into consideration a combination of factors before optimal vaccination strategies and priority target populations are defined.

A recent cost-effective analysis evaluating the impact of the vaccination in subjects aged ≥65 years and in seniors in the 70–79-year-age group concluded that the vaccination is indeed cost effective [79]. Similar results have been reported by Italian investigators with regard to individuals between 60 and 79 years of age [80].

Conclusions

As the immune response in elderly declines and the outcome of infections is often poor, prevention of infections is critically important as a strategic intervention for healthy aging. Immunization, it is known, can protect the elderly against life-threatening diseases such as influenza, tetanus, pneumococcal pneumonia, as well as against diseases which adversely impact their quality of life (pertussis and HZ). In view of the poor vaccine coverage in elderly adults, the EUGMS and IAGG-ER have advocated vaccination of the older population in the effort to promote healthy aging by limiting the burden of vaccine- preventable infectious diseases [81].

Scientific data support public health strategies to vaccinate the population between 60 and 70. As aging is the main risk factor for HZ, an age-based strategy would allow health care providers to reach subjects over 50 years with chronic diseases in whom the onset of HZ could cause serious complications.

Public policy should offer vaccination to the target population ensuring an equitable offer compatible with available resources. A life-course approach to immunization recognizes that vaccination in children, adults, and older individuals is a cost-effective strategy that promotes public health. An effective vaccination program for adults aged 50 and above is a particularly wise public health strategy that promotes healthy aging.

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Conflict of interest None.

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