RESEARCH PAPER

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Reducing the burden of Herpes Zoster in Italy

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Abbreviations: HZ, Herpes Zoster; PHN, Post-Herpetic Neuralgia; VZV, Varicella Zoster Virus; CMI, Cell-mediated immunity; QoL, quality of life; TIA, Transient Ischaemic Attack; SCP, summary of product characteristics; SPS, Shingles Prevention Study; USA, United States of America; BOI, burden of illness; ZEST, Zoster efficacy and safety trial; STPS, short term prevention study; LTPS, long term prevention study; KPSC, Kaiser Permanente Southern California; KPNC, Kaiser Permanente Northern California; EMA, European Medicines Agency; EunetHTA, European Network of Agencies or national institutions dealing with Health Technology Assessment; UK, United Kingdom

Herpes Zoster (HZ) is a viral disease with painful neuro-dermatologic manifestations. Incidence increases with age. In Italy, the estimated incidence is 6.3 cases/1000 person/year; hospital admissions are less than 2%, 69% in patients aged over 65 years. The most frequent complication of HZ is Post-Herpetic Neuralgia (PHN) characterized by metameric pain, allodynia, and hyperalgesia. In Italy 20.6% and 9.2% of HZ patients experience PHN after 3 and 6 months, respectively. Available antiviral and analgesic treatments are relatively unsatisfactory in reducing pain and length of the disease. Prevention has recently become possible with the live attenuated vaccine Oka/Merck. Clinical studies show a reduction of 51% in the incidence of the disease, 61% of its burden and 67% of PHN in vaccinees. Protection seems to be long lasting and vaccine safety matches registration requirements. Available evidence suggests that the costs for QALY (less than € 20 000) and avoided cases is favorable. Due to the heavy burden of disease, it is time to offer this vaccination to elderly population.

Introduction

Varicella (chickenpox) is a highly contagious illness sustained by an α Herpes virus called varicella-zoster virus (VZV). Epidemiologically, this is an infection with an endemic-epidemic pattern that only affects humans and is air-transmitted as well as by direct contact with blisters. The causative agent is ubiquitous and mostly affects children; the maximum incidence is seen in the 0 to 14-y-age group.[1]

A particular characteristic of the causative agent is its ability to infect, during primary infection, skin nervous endings and become latent in nerve sensory ganglia.[2] In detail, a replication phase in the penetration site is followed by a viremic phase when VZV spreads to skin and mucosae; the consequent replication leads to the typical rash and infection of nerve sensory ganglia in the epithelium. From here, the virus gains access to sensory ganglia where it remains latent. Reactivation of latent VZV virus, several years or even decades after experiencing primary infection, leads to a typical clinical manifestation called Herpes Zoster (HZ).[3]

Etiopathogenesis and Immunology

During primary infection, VZV migrates through sensory nerve fibers to corresponding dorsal root nerve ganglia. VZV becomes latent in the ganglia and remains there for the patient lifetime (latency). During the reactivation, nerve ganglia are the site of viral replication with ensuing neuropathic damage to nerve fibers; VZV follows the corresponding sensory ending until it reaches skin branches resulting into clinically evident HZ.[4-7] Therefore, HZ can be defined as an acute vesicular dermatitis, with typical unilateral distribution due to the reactivation of VZV acquired during the primary infection usually in pediatric age (chickenpox).[8]

With regard to immunology, natural VZV infection induces a long-term antibody-mediated and cell-mediated immunity (CMI) against the clinical form of the disease.[9] However, natural acquired immunity does not prevent virus latentization nor the possible subsequent reactivation (HZ). The lack of specific anti-VZV antibodies does not necessarily imply susceptibility, since the corresponding CMI can persist.[10,11] Approximately 20% of subjects aged >50 y do not show a measurable specific CMI,

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notwithstanding persistence of specific antibodies and a positive history of varicella.[12,13]

HZ is strictly related to a reduction in VZV-specific T lymphocytes; a Zoster episode reactivates specific T-cell response.[14] Since varicella is an infectious disease that can virtually affect all subjects, especially in the pediatric age, most of the adult population has specific anti-VZV antibodies that are the expression of a previous contact with the infectious agent and has a latent form of VZV.[15,16] As a consequence, most of the adult population is potentially susceptible to develop an episode of HZ in its lifetime.

Epidemiology

HZ is sporadic and occurs all over the year, completely un-related to varicella outbreaks. HZ cannot be transmitted. The only event that may occur is the transmission of the reactivated virus to subjects who had not been previously exposed to the virus; in this case, infected subjects contract varicella. All HZ-infected subjects constantly show a positive history of varicella.[17]

HZ is painful and unilateral, with a dermatomal distribution in the skin area corresponding to the nervous fiber that originates from a dorsal root ganglion. The most frequent localization is the thoracic segment (50–60%); other possible localizations are the trigeminal (cranial; 10–20% of HZ cases have an ocular localization: ophthalmic HZ), cervical, lumbar and sacral segments.[18-21] After the acute phase, 20% of patients can experience complications, while recurrences are relatively rare (1–5%).[22] The most fearful complication, being the expression of VZV neurotropism, is Post-Herpetic Neuralgia (PHN). PHN is a painful chronic condition, resistant to a number of treatments, affecting 10 to 20% of patients (some estimates report up to a third of patients) who have experienced an acute HZ episode.[23-25]

All authors agree that some factors are typically associated with HZ epidemiology, including age, cell-mediated immunity depression, intrauterine exposure to VZV and varicella occurring in early age (<18 months).[26,27] Age and CMI depression are strictly related since increasing age leads to CMI decrease. Other authors maintain that also gender, seasonality, race, psychological distress, exposure to immunotoxic agents, mechanical traumas and genetic predisposition can play a crucial role in the development of HZ.

HZ incidence is similar all over the world and its trend is related to population age, with 2 to 3 cases/1000 person/years in the 20–50 y age group up to 5/1000 in the >60 age group, to 6–7/1000 in the 70–80 age group.[28,29] It was estimated that over lifetime, at least 25% of the subjects will experience a HZ episode; two thirds of the cases in the world affect subjects aged >50 y. Considering the increase in the elderly and frail population, an increase in the number of cases is foreseen in the future. However, today over 1.7 million HZ cases are estimated to occur globally every year.[29]

Therefore, immunosenescence plays a crucial role; however, 90% of HZ patients are not specifically immunocompromised. Besides age, HZ risk can be related to other co-morbidities (including diabetes, major depression, stressful events, immunosuppressive therapies) that induce reduced VZV-specific CMI response.[30-32]

In Europe, 95% of the adult population is estimated to be seropositive for anti-VZV antibodies and thus potentially susceptible to develop HZ in its lifetime.[15]

In Italy, over 22 million people aged >50 y live; 157 000 new cases of HZ are estimated to occur every year. The annual incidence is 6.3/1000 person-years; 73% of cases affect adult subjects.[33]

A perspective study performed all over Italy in cooperation with General Practitioners showed that 20.6% and 9.2% of HZ patients aged >50 y had PHN at 3 and 6 months, respectively, notwithstanding an early antiviral treatment (started within 72 h from skin rash onset). Also based on this study, the HZ/PHN burden is confirmed to increase with increasing age and HZ/PHN considerably impact on the patient quality of life.[34]

Another study on hospital discharge records shows that over the period 1999–2005, 35 328 admissions due to HZ were recorded overall, of which 31 526 regular admissions and 3802 in day-hospital setting. The annual average was 4503 regular admissions and 543 day-hospital admissions, i.e., about 14 admissions/day. In the 1999–2005 period, 61.9% of admissions involved subjects aged ≥65 y and the average stay was 8 days.[35] These data, although taking into consideration only hospitalized cases recorded at national level, also confirm the epidemiological impact of HZ and associated complications.

Clinical Overview and Impact on Quality of Life

HZ is clinically characterized by vesicular rash and neuropathic pain with radicular distribution to which loss of sensitivity is often associated. The triad of HZ symptoms includes subjective symptoms, typical unilateral dermatomal rash, and regional painful lymphadenopathy.[36]

The clinical pattern is usually preceded by a prodromic phase with acute photophobia, pain, headache and general malaise. The acute phase, that appears suddenly, is characterized by rash with a dermatomal distribution, pain, unbearable pruritus and allodynia. The acute phase is usually followed by recovery; however, a number of possible complications, especially neurologic ones, may occur.[6]

Although HZ skin rash is temporarily disfiguring and quite annoying in a number of patients, the most important issue for patients is undoubtedly pain. HZ is basically a disease of the nervous system, being the most common infectious neurological manifestation.

HZ typical manifestations are limited to a specific body area but patient wellbeing is generally compromised.[37]

Around 20% of patients experience complications. In immunocompromised hosts, the main complication following HZ is pain persistence defined as Post-Herpetic Neuralgia (PHN). PHN is a fearful painful chronic condition, resistant to a number of treatments that affects 10–20% of patients (some estimates report up to a third of patients) who have experienced an

acute HZ episode. HZ is an extremely debilitating experience, for the affected subjects, with an impairment of physical, productive, and interpersonal abilities and with psychological effects in case of chronicization of the disease.[38] HZ and PHN negatively affect the patient quality of life (QoL); besides suffering due to the typical symptoms of skin lesions and the associated pain, subjects can also have an impaired ability to perform daily activities or maintain social and family relationships. The whole spectrum of symptoms and related functional and social symptoms can cause a chronic alteration in the psychological status of the affected subject.[39]

The results from two trials, both performed in the United Kingdom, have been published very recently. The first study shows that HZ is an independent risk factor for vascular disease, in particular stroke, TIA and myocardial infarction in HZ subjects aged less than 40 y.[40] The second study shows a relationship between HZ and stroke in the 6 months following Zoster appearance. The risk is particularly increased in patients with ophthalmic HZ.[41]

The objectives of the therapeutic treatments to be used in case of HZ include reducing the extent, the severity and duration of the infection, trying to prevent post-herpetic neuralgia and reduce any possible complications.[42]

The therapeutic approach includes symptomatic treatments, antibiotics to treat bacterial superinfections, antiviral therapy and nerve blocks.[43] The guidelines highlight the importance to start antiviral therapy early, within 72 hours from symptom onset, in order to avoid loss of efficacy.[28]

Clinical trials show that 20–30% of patients treated within 72 hours have developed post-herpetic neuralgia even so, and a Cochrane review demonstrated that use of antivirals does not prevent PHN.[44]

PHN is very difficult to treat, though several treatments are available. Briefly, corticosteroids reduce pain intensity, but do not prevent PHN and have several undesirable effects in elderly patients; analgesics can only reduce pain in the acute phase but a limited number of studies on PHN have been performed; antidepressants reduce PHN but are associated with a number of undesirable effects that impact patient QoL; opioids reduce PHN, but are associated with undesirable effects that make them difficult to manage especially in elderly patients; antiepileptics/neuromodulators, i.e., gabapentin and pregabalin, reduce PHN, but do not improve patient Qol; topical analgesics lidocaine and capsaicin have limited efficacy.[5,45-49]

Prevention: Vaccines Currently Available

The evaluation of the epidemiological impact, the frequent and debilitating complications (especially PHN), the sub-optimal treatments of complications and the costs related to the diagnosis and clinical/therapeutic management of HZ patients (also including costs related to complications and hospitalizations, as well as societal costs) are the rationale and the reason for the search of an adequate preventive measure against this relevant disease. The target of this specific intervention is to reduce the frequency and severity of HZ and related complications by stimulating cell-mediated immunity.

Over the years, varicella vaccines, especially those with a high antigen level, have resulted able to elicit a significant increase in cell-mediated immune response in immunocompetent elderly patients.[50-54]

Zoster vaccine developed by Merck, and currently available on the market, has an antigen content higher than at least 19,400 PFU (Plaque-Forming Units), i.e., at least 10 times higher than the antigen content in paediatric varicella vaccine.[55]

High-antigen Zoster vaccine was evaluated in a wide clinical trial called "Shingles Prevention Study" (SPS). SPS was a randomized, double-blind, placebo-controlled trial performed in the United States of America (USA) to establish if vaccination with a single dose of experimental live attenuated Oka/Merck strain vaccine can reduce the incidence and/or severity of HZ and PHN in men and women ≥60 y of age with a negative history of HZ but a positive history of varicella. Overall, 38 546 subjects (19 270 vaccinated and 19 276 treated with placebo) with a mean age of 69 y were enrolled in the study. Overall data on study population showed a reduction of 51.3% in the number of HZ cases, a reduction of 66.5% in PHN cases and a reduction of the overall burden of illness (BOI) of 61.1%.[56]

After the SPS, other trials on the efficacy and the effectiveness were performed.

The study called ZEST (Zoster Efficacy and Safety Trial) evaluated the efficacy of the vaccine against HZ in subjects aged from 50–59 y; efficacy was 70%.[57]

Within the SPS trial, other efficacy evaluations were performed in the short-term (STPS) as well as in the long-term (LTPS) prevention study. The short-term efficacy was 40%, 60%, and 50% against HZ, PHN and HZ-induced pain, respectively.[58]

LTPS is currently ongoing; the estimated vaccine efficacy during the sub-study follow-up period was 21% for HZ incidence, 35% for PHN incidence, and 37.3% for the impact of HZ-induced pain.[55]

Also with regard to effectiveness, short-term and long-term trials are currently ongoing. With regard to short-term effectiveness, an efficacy study has been recently published based on data from the Kaiser Permanente Southern California (KPSC), aimed at assessing the risk of HZ in the general practice setting after vaccine administration. The results have shown an effectiveness of 55% against HZ; the reduced incidence in vaccinees was reported in all age groups, also in subjects with chronic diseases. The study showed an effectiveness of 63% against ophthalmic HZ and 65% against hospitalizations coded as HZ.[59]

Another retrospective study on subjects enrolled in Medicare aged >60 y (average age 74 y ± 8 y) with immune-mediated diseases (i.e., rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or ulcerative colitis) showed an effectiveness against HZ equal to 39%.[60]

With regard to the long-term effectiveness study, a pilot phase started in May 2012 at Kaiser Permanente Northern California (KPNC) and will continue until the end of 2014; two *ad interim* analyses will be available at the end of 2016 and end 2020 while the final report will be available by the end of 2024.

With regard to safety and tolerability, Zoster vaccine was evaluated in large clinical trials that enrolled and vaccinated over 32 000 adults. Key trials were the Shingles Prevention Study (SPS) in subjects aged ≥60 y (SPS safety sub-study) and the Zoster Efficacy and Safety Trial (ZEST) in subjects aged 50–59 y.[56,57] Other clinical trials and post-marketing studies followed. In the SPS, the frequency of serious adverse events, systemic adverse events and hospitalizations was low; the vaccine used did not cause or induce HZ, not even in the weeks immediately following vaccination. In the ZEST study, the most frequent adverse reactions were injection-site adverse reactions (63.9% in the vaccinated group vs. 14.4% in the placebo group), most of which were of moderate intensity.

Taken together, clinical trials show that Zoster vaccine is generally well tolerated, the most commonly reported side effects (occurring in at least 1 in 10 individuals) being reactions at the injection site (redness, swelling, pain and itching) and headache (occurring in at least 1 of 100 and less than 1 of 10 individuals); the rate of zosteriform or varicella-like rashes not localized in the injection site within 42 days postvaccination was similar in the group of vaccinated subjects and in the placebo group and no cases of secondary tranmission of the vaccine virus were reported.[61]

The analysis of available data in the post-marketing period shows that the overall risk-benefit ratio for Zoster vaccine is favourable and supports claims on the vaccine safety; moreover, no age-related safety issues were reported.[62-64]

Indications of Use for Zoster Vaccine

In May 2006, Zoster vaccine received FDA marketing approval in the United States and then the early recommendations for its use were issued. In 2006, the vaccine was approved also by the European Medicines Agency (EMA) and it is currently on the market.[55]

According to the Summary of Product Characteristics (SPC),[55] Zoster vaccine is indicated for the prevention of HZ and HZ-related Post-Herpetic Neuralgia (PHN). The vaccine is indicated for immunization of individuals 50 y of age or older and is effective and safe in subjects with a positive history of HZ.[65] The vaccine is not indicated for the prevention of primary varicella infection (chickenpox) and should not be used in children and adolescents.

Contraindications include:

- history of hypersensitivity to any of the excipients or trace residuals (e.g., Neomycin)
- primary and acquired immunodeficiency due to acute and chronic leukaemias; 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 or in patients who are receiving corticosteroids as replacement therapy
- active untreated tuberculosis
- pregnancy

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. Contact with disinfectants should be avoided; it is recommended that the vaccine be administered immediately after reconstitution to minimize loss of potency. Reconstituted vaccine should be discarded if it is not used within 30 min.

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

Zoster vaccine and 23-valent pneumococcal polysaccharide vaccine should not be given concomitantly because co-administration in clinical trials resulted in reduced immunogenicity of Zoster vaccine. No data are currently available regarding concomitant use with other vaccines; co-administration of Zoster vaccine and anti-viral medications known to be effective against VZV has not been evaluated.

EUnetHTA (European Network of Agencies or national institutions dealing with Health Technology Assessment, HTA) has recently acknowledged the clinical efficacy/effectiveness of Zoster vaccine in the population aged >50 y also highlighting a protection duration up to 10 years.[66]

Globally, immunization with this vaccine is recommended, with or without public funding, in a number of countries:

1) in USA and Canada, it has been recommended in patients aged 60 y or older, since 2006 and 2010, respectively;
2) in Europe, vaccination is recommended and/or reimbursed:
   - in Austria since 2007 (cohorts aged over 50 y of age)
   - in United Kingdom (UK) (cohorts aged 70 y and catch up in cohorts aged 71 to 79 y) since 2010
   - Germany/Saxony (cohorts aged over 50 y of age) since 2010
   - Sweden (cohorts aged over 50 y of age) since 2010
   - Greece (cohorts aged over 60 y at high risk) since 2011
   - France (cohorts aged 65 to 74 y, catch up in cohorts aged 75 to 79 y) since 2013

A recent cost-efficacy study measured the impact of vaccination in subjects aged ≥65 y and in the 70–79 y age group, concluding that the vaccination is cost-effective.[67]

In Italy, an economic evaluation study has been performed; it showed that the vaccination program against HZ and PHN is cost-effective from both the societal and third-payer perspectives in subjects aged 60–79 y.[68]

Expert Recommendations

Herpes Zoster is a relevant public health issue. Over 95% of the adult population is seropositive to specific anti-VZV antibodies and therefore is potentially at risk of developing HZ in its lifetime.

The risk to develop HZ and PHN increases with age and 25% of adults will develop HZ in their lifetime. The risk to develop HZ seems to be related to a decline in cell-mediated immunity (CMI) against VZV virus. HZ clinical pattern and associated acute and chronic pain are debilitating and have a considerable impact on patient quality of life. Treatment options of HZ and PHN are often sub-optimal. Finally, costs for the diagnosis

and clinical and therapeutical management of acute HZ, for hospitalizations, complications and societal costs are high. The epidemiological data available in Italy are scientifically robust and consistent with similar data reported in Europe and in the United States. HZ-related suffering is also aggravated by a considerable economic burden: pharmacoeconomic studies estimate an annual cost ranging from 41 to 99 billion Euro in Europe and a cost of 41 million Euro in Italy.

All above mentioned reasons represent the rationale for the prevention of this important infectious disease; the possibility to prevent this disease by means of vaccination is a very interesting perspective.

Zoster vaccine was conceived in order to increase VZV-specific immunity just like a natural case of HZ can increase immunity. Zoster vaccine has a booster effect in immunized subjects by eliciting a significant increase in CMI; this CMI increase can only be obtained by a high-potency vaccine.

The vaccine that is currently available has good immunogenicity, clinical efficacy, effectiveness and safety profiles: briefly, at least half of the cases would be avoided by vaccination with a considerable impact also in terms of reduction of disease severity and complications, mainly post-herpetic neuralgia. Moreover, pharmacoeconomic studies provide evidence of the cost-effectiveness profile of the vaccination that is already recommended, with or without public funding, in a number of countries all over the world.

Based on scientific data, the Public Health best strategy would be to offer the vaccine to the population aged 60–70 y. Aging is the main risk factor for HZ and an age-based strategy would allow to reach also subjects aged over 50 y with chronic diseases, in which the onset of HZ could cause serious complications.

The way the vaccine can be offered to the target population should include a common strategy to progressively ensure an equitable offer compatible with the available resources, being convinced that vaccination is convenient both in terms of quality of life and health economy.

This immunization shows that vaccinations in adults and in elderly people should not be considered separately from those for children and adolescents, but as a fundamental part of a preventive strategy against infectious diseases that should involve all age groups. There is a need for vaccination continuity in all age groups, considering that the increase of coverage rates in adults and elderly subjects necessarily requires an increase in the demand by the community, an optimization of organizational issues as well as a greater awareness by Healthcare Professionals.

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Giovanni Gabutti received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, and Pfizer for taking part in advisory boards, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.

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References

1. Marin M, Güris D, Chaves SS, Schmid S, Seward JF; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC). Prevention of varicella. Recommendations of the Advisory Committee on immunization practices (ACIP). MMWR Recomm Rep 2007; 56(RR-4):1-40; PMID:17585291
2. Grose C. Varicella vaccination of children in the United States: assessment after the first decade 1995-2005. J Clin Virol 2005; 33:89-95, discussion 96-8; PMID:15911422; http://dx.doi.org/10.1016/j.jcv.2005.02.003
3. Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57(RR-5):1-30, quiz CE2-4; PMID:18528318
4. Kimberlin DW, Whitley RJ. Varicella-zoster vaccine for the prevention of herpes zoster. N Engl J Med 2007; 356:1338-43; PMID:17392303; http://dx.doi.org/10.1056/NEJMct066061
5. Johnson RW, Wasner G, Saddier P, Baron R. Herpes zoster and postherpetic neuralgia: optimizing management in the elderly patient. Drugs Aging 2008; 25:991-1006; PMID:19021299; http://dx.doi.org/10.2165/0002512-200825120-00002
6. Weaver BA. Herpes zoster overview: natural history and incidence. J Am Osteopath Assoc 2009; 109(Suppl 2):S2-6; PMID:19553632
7. Oxman MN. Herpes zoster pathogenesis and cell-mediated immunity and immunosenescence. J Am Osteopath Assoc 2009; 109(Suppl 2):S13-7; PMID:19553630
8. Gabutti G, Serenelli C, Sarno O, Marconi S, Corazza M, Virgili A. Epidemiologic features of patients affected by herpes zoster: database analysis of the Ferrara University Dermatology Unit, Italy. Med Mal Infect 2010; 40:268-72; PMID:19836913; http://dx.doi.org/10.1016/j.medmal.2009.09.005
9. Heininger U, Seward JF. Varicella. Lancet 2006; 368:1365-76; PMID:17046469; http://dx.doi.org/10.1016/S0140-6736(06)69561-5
10. Arvin A. Aging, immunity, and the varicella-zoster virus. N Engl J Med 2005; 352:2266-7; PMID:15930416; http://dx.doi.org/10.1056/NEJMp058091
11. Gershon AA, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol 2010; 48(Suppl 1):S2-7; PMID:20510263; http://dx.doi.org/10.1016/S1386-6532(10)70002-0
12. Sadaoka K, Okamoto S, Gomi Y, Tanimoto T, Ishikawa T, Yoshikawa T, Asano Y, Yamanishi K, Mori Y. Measurement of varicella-zoster virus (VZV)-specific cell-mediated immunity: comparison between VZV skin test and interferon-gamma enzyme-linked immunospot assay. J Infect Dis 2008; 198:1327-33; PMID:18774884; http://dx.doi.org/10.1086/592219
13. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology 2013; 81:928-30; PMID:23999562; http://dx.doi.org/10.1212/WNL.0b013e3182a3516e
14. Gershon AA, Gershon MD. Pathogenesis and current approaches to control of varicella-zoster virus infections. Clin Microbiol Rev 2013; 26:728-43; PMID:24092852; http://dx.doi.org/10.1128/CMR.00052-13
15. Nardone A, de Ory F, Carton M, Cohen D, van Damme P, Davidkin I, Rota MC, de Melker H, Mossong J, Slacikova M, et al. The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region. Vaccine 2007; 25:7866-72; PMID:17919788; http://dx.doi.org/10.1016/j.vaccine.2007.07.036
16. Guido M, Tinelli A, De Donno A, Quattrocchi M, Malvasi A, Campilongo F, Zizza A; Seroepidemiology Group. Susceptibility to varicella-zoster among pregnant women in the province of Lecce, Italy. J Clin Virol 2012; 53:72-6; PMID:22074933; http://dx.doi.org/10.1016/j.jcv.2011.10.007
17. Viner K, Perella D, Lopez A, Bialek S, Newbern C, Pierre R, Spells N, Watson B. Transmission of varicella zoster virus from individuals with herpes zoster or varicella in school and day care settings. J Infect Dis 2012; 205:1336-41; PMID:22454467; http://dx.doi.org/10.1093/infdis/jis207
18. Ragozzino MW, Melton LJ 3rd, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) 1982; 61:310-6; PMID:6981045; http://dx.doi.org/10.1097/00005792-198209000-00003
19. Meister W, Neiss A, Gross G, Doerr H, Höbel W, Malin J, von Essen J, Reimann B, Witke C, Wutzler P. Demography, symptomatology, and course of disease in ambulatory zoster patients. A physician-based survey in Germany. Intervirology 1998; 41:272-7; PMID:10325537; http://dx.doi.org/10.1159/000024949
20. Cunningham AL, Breuer J, Dwyer DE, Gronow DW, Helme RD, Litt JC, Levin MJ, Macintyre CR. The prevention and management of herpes zoster. Med J Aust 2008; 188:171-6; PMID:18241179
21. Choi WS. Herpes zoster vaccine in Korea. Clin Exp Vaccine Res 2013; 2:92-6; PMID:23858399; http://dx.doi.org/10.7774/cevr.2013.2.2.92
22. Volpi A, Gatti A, Pica F. Frequency of herpes zoster recurrence. Mayo Clin Proc 2011; 86:586, author reply 586-7; PMID:21628622; http://dx.doi.org/10.4065/mcp.2011.0096
23. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. Mayo Clin Proc 2009; 84:274-80; PMID:19252116; http://dx.doi.org/10.4065/84.3.274
24. Johnson RW. Herpes zoster and postherpetic neuralgia. Expert Rev Vaccines 2010; 9(Suppl):21-6; PMID:20192714; http://dx.doi.org/10.1586/erv.10.30
25. Watson P. Postherpetic neuralgia. Am Fam Physician 2011; 84:690-2; PMID:21916395
26. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis 2004; 4:26-33; PMID:14720565; http://dx.doi.org/10.1016/S1473-3099(03)00857-0
27. Chen SY, Suaya JA, Li Q, Galindo CM, Misurski D, Burstin S, Levin MJ. Incidence of herpes zoster in patients with altered immune function. Infection 2014; 42:325-34; PMID:24214127; http://dx.doi.org/10.1007/s15010-013-0550-8
28. Whitley RJ, Volpi A, McKendrick M, Wijck Av, Oaklander AL. Management of herpes zoster and post-herpetic neuralgia now and in the future. J Clin Virol 2010; 48(Suppl 1):S20-8; PMID:20510264; http://dx.doi.org/10.1016/S1386-6532(10)70005-6
29. Pinchinat S, Cebrián-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. BMC Infect Dis 2013; 13:170; PMID:23574765; http://dx.doi.org/10.1186/1471-2334-13-170
30. Chidiac C, Bruxelle J, Daures JP, Hoang-Xuan T, Morel P, Leplège A, El Hasnaoui A, de Labareyre C. Characteristics of patients with herpes zoster on presentation to practitioners in France. Clin Infect Dis 2001; 33:62-9; PMID:11389496; http://dx.doi.org/10.1086/320884
31. Heymann AD, Chodick G, Karpati T, Kamer L, Kremer E, Green MS, Kokia E, Shalev V. Diabetes as a risk factor for herpes zoster infection: results of a population-based study in Israel. Infection 2008; 36:226-30; PMID:18454342; http://dx.doi.org/10.1007/s15010-007-6347-x
32. Okamoto S, Hata A, Sadaoka K, Yamanishi K, Mori Y. Comparison of varicella-zoster virus-specific immunity of patients with diabetes mellitus and healthy individuals. J Infect Dis 2009; 200:1606-10; PMID:19821719; http://dx.doi.org/10.1086/644646
33. Gialloreti LE, Merito M, Pezzotti P, Naldi L, Gatti A, Beillat M, Serradell L, di Marzo R, Volpi A. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis 2010; 10:230; PMID:20682044; http://dx.doi.org/10.1186/1471-2334-10-230
34. Franco E, Perinetti E, Marchettini P, et al. Proportion of Post-Herpetic Neuralgia among patients with Herpes Zoster in Italy - a multicenter prospective observational study (Heroes study). EUGMS Venice 2-4 Oct 2013, Poster session
35. Gabutti G, Serenelli C, Cavallaro A, Ragni P. Herpes zoster associated hospital admissions in Italy: review of the hospital discharge forms. Int J Environ Res Public Health 2009; 6:2344-53; PMID:19826547; http://dx.doi.org/10.3390/ijerph6092344
36. Kempf W, Meylan P, Gerber S, Aebi C, Agosti R, Büchner S, Coradi B, Garweg J, Hirsch H, Kind C, et al. Swiss recommendations for the management of varicella zoster virus infections. Swiss Med Wkly 2007; 137:239-51; PMID:17557214
37. Song H, Lee J, Lee M, Choi WS, Choi JH, Lee MS, Hashemi M, Rampakakis E, Kawai K, White R, et al. Burden of illness, quality of life, and healthcare utilization among patients with herpes zoster in South Korea: a prospective clinical-epidemiological study. Int J Infect Dis 2014; 20:23-30; PMID:24412314; http://dx.doi.org/10.1016/j.ijid.2013.11.018
38. Studahl M, Petzold M, Cassel T. Disease burden of herpes zoster in Sweden--predominance in the elderly and in women - a register based study. BMC Infect Dis 2013; 13:586; PMID:24330510; http://dx.doi.org/10.1186/1471-2334-13-586
39. Lukas K, Edte A, Bertrand I. The impact of herpes zoster and post-herpetic neuralgia on quality of life: patient-reported outcomes in six European countries. Z Gesundh Wiss 2012; 20:441-51; PMID:22822293; http://dx.doi.org/10.1007/s10389-011-0481-8
40. Breuer J, Pacou M, Gauthier A, Brown MM. Herpes zoster as a risk factor for stroke and TIA: a retrospective cohort study in the UK. Neurology 2014; 82:206-12; PMID:24384645; http://dx.doi.org/10.1212/WNL.0000000000000038
41. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. Clin Infect Dis 2014; 58:1497-503; PMID:24700656; http://dx.doi.org/10.1093/cid/ciu098
42. Kim SR, Khan F, Ramirez-Fort MK, Downing C, Tyring SK. Varicella zoster: an update on current treatment options and future perspectives. Expert Opin Pharmacother 2014; 15:61-71; PMID:24289750; http://dx.doi.org/10.1517/14656566.2014.860443

43. Christo PJ, Hobelmann G, Maine DN. Postherpetic neuralgia in older adults: evidence-based approaches to clinical management. Drugs Aging 2007; 24:1-19; PMID:17233544; http://dx.doi.org/10.2165/00002512-200724010-00001
44. Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2014; 2:CD006866; PMID:24500927; http://dx.doi.org/10.1002/14651858.CD006866.pub3
45. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998; 280:1837-42; PMID:9846778; http://dx.doi.org/10.1001/jama.280.21.1837
46. Schmader K. Herpes zoster in older adults. Clin Infect Dis 2001; 32:1481-6; PMID:11317250; http://dx.doi.org/10.1086/320169
47. Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med 2005; 2:e164; PMID:16013891; http://dx.doi.org/10.1371/journal.pmed.0020164
48. Johnson RW. Zoster-associated pain: what is known, who is at risk and how can it be managed? Herpes 2007; 14(Suppl 2):30-4; PMID:17939893
49. Johnson RW, McElhaney J. Postherpetic neuralgia in the elderly. Int J Clin Pract 2009; 63:1386-91; PMID:19691624; http://dx.doi.org/10.1111/j.1742-1241.2009.02089.x
50. Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. Neurology 1995; 45(Suppl 8):S41-6; PMID:8545018; http://dx.doi.org/10.1212/WNL.45.12_Suppl_8.S41
51. Levin MJ, Barber D, Goldblatt E, Jones M, LaFleur B, Chan C, Stinson D, Zerbe GO, Hayward AR. Use of a live attenuated varicella vaccine to boost varicella-specific immune responses in seropositive people 55 years of age and older: duration of booster effect. J Infect Dis 1998; 178(Suppl 1):S109-12; PMID:9852987; http://dx.doi.org/10.1086/514264
52. Trannoy E, Berger R, Holländer G, Bailleux F, Heimendinger P, Vuillier D, Creusvaux H. Vaccination of immunocompetent elderly subjects with a live attenuated Oka strain of varicella zoster virus: a randomized, controlled, dose-response trial. Vaccine 2000; 18:1700-6; PMID:10689152; http://dx.doi.org/10.1016/S0264-410X(99)00510-1
53. Breuer J. Vaccination to prevent varicella and shingles. J Clin Pathol 2001; 54:743-7; PMID:11577118; http://dx.doi.org/10.1136/jcp.54.10.743
54. Levin MJ, Smith JG, Kaufhold RM, Barber D, Hayward AR, Chan CY, Chan IS, Li DJ, Wang W, Keller PM, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis 2003; 188:1336-44; PMID:14593591; http://dx.doi.org/10.1086/379048
55. Herpes Zoster vaccine (live). Zostavax Summary of product characteristics 2013. revision 18 December 2013
56. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, Arbeit RD, Simberkoff MS, Gershon AA, Davis LE, et al.; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352:2271-84; PMID:15930418; http://dx.doi.org/10.1056/NEJMoa051016
57. Schmader KE, Levin MJ, Gnann JW Jr., McNeil SA, Vesikari T, Betts RF, Keay S, Stek JE, Bundick ND, Su SC, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect Dis 2012; 54:922-8; PMID:22291101; http://dx.doi.org/10.1093/cid/cir970
58. Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, Morrison VA, Gelb L, Guatelli JC, Harbecke R, et al.; Shingles Prevention Study Group. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clin Infect Dis 2012; 55:1320-8; PMID:22828595; http://dx.doi.org/10.1093/cid/cis638
59. Tseng HF, Smith N, Harpaz R, Bialek SR, Sy LS, Jacobsen SJ. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. JAMA 2011; 305:160-6; PMID:21224457; http://dx.doi.org/10.1001/jama.2010.1983
60. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, Saag KG, Baddley JW, Curtis JR. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA 2012; 308:43-9; PMID:22760290; http://dx.doi.org/10.1001/jama.2012.7304
61. Gagliardi AMZ, Gomez Liva BN, Torloni MR, Soares BGO. Vaccines for preventing Herpes Zoster in older adults (review). The Cochrane Library 2012
62. Murray AV, Reisinger KS, Kerzner B, Stek JE, Sausser TA, Xu J, Wang WW, Chan IS, Annunziato PW, Parrino J. Safety and tolerability of zoster vaccine in adults ³60 years old. Hum Vaccin 2011; 7:1130-6; PMID:22048110; http://dx.doi.org/10.4161/hv.7.11.17982
63. Tseng HF, Liu A, Sy L, Marcy SM, Fireman B, Weintraub E, Baggs J, Weinmann S, Baxter R, Nordin J, et al.; Vaccine Safety Datalink (VSD) Team. Safety of zoster vaccine in adults from a large managed-care cohort: a Vaccine Safety Datalink study. J Intern Med 2012; 271:510-20; PMID:22026504; http://dx.doi.org/10.1111/j.1365-2796.2011.02474.x
64. Baxter R, Tran TN, Hansen J, Emery M, Fireman B, Bartlett J, Lewis N, Saddier P. Safety of Zostavax™--a cohort study in a managed care organization. Vaccine 2012; 30:6636-41; PMID:22963800; http://dx.doi.org/10.1016/j.vaccine.2012.08.070
65. Mills R, Tyring SK, Levin MJ, Parrino J, Li X, Coll KE, Stek JE, Schlienger K, Chan IS, Silber JL. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. Vaccine 2010; 28:4204-9; PMID:20416263; http://dx.doi.org/10.1016/j.vaccine.2010.04.003
66. EUnetHTA. Zostavax for the prevention of Herpes Zoster and Post-Herpetic Neuralgia. Pilot assessment using the draft HTA Core Model for rapid relative effectiveness assessment. September 2013; http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Zostavax_main%20report%20including%20appendices_20130922.pdf (last access April 2014)
67. Bresse X, Annemans L, Préaud E, Bloch K, Duru G, Gauthier A. Vaccination against herpes zoster and postherpetic neuralgia in France: a cost-effectiveness analysis. Expert Rev Pharmacoecon Outcomes Res 2013; 13:393-406; PMID:23537397; http://dx.doi.org/10.1586/erp.13.19
68. Ruggeri M. Analisi di costo-efficacia del vaccino contro l'Herpes Zoster e la nevralgia posterpetica in Italia. 6° Congresso Nazionale SIHTA. Bari 7-9 Novembre 2013