RESEARCH PAPER

Prevention of Herpes Zoster and its complications: From clinical evidence to real life experience

Giovanni Gabutti^a, Paolo Bonanni^b, Michele Conversano^c, Guido Fanelli^d, Elisabetta Franco^e, Donato Greco^f, Giancarlo Icardi^g, Marzia Lazzari^e, Alessandro Rossi^h, Silvestro Scottiⁱ, and Antonio Volpi^e

^aUniversity of Ferrara, Ferrara, Italy; ^bUniversity of Florence, Florence, Italy; ^cLHU Taranto, Taranto, Italy; ^dUniversity of Parma, Parma, Italy; ^eUniversity Tor Vergata, Rome, Italy; ^fEpidemiologist, Rome, Italy; ^gUniversity of Genoa, Genoa, Italy; ^hBoard of the Italian Society of General Medicine, Italy; ⁱBoard of the Italian Federation of General Practitioners, Italy

ABSTRACT

Herpes zoster (HZ) is an acute viral illness characterized by a vesicular rash with unilateral distribution, which can also result in severe complications such as post-herpetic neuralgia (PHN), ophthalmic zoster, stroke or other neurological complications. The estimate incidence in Europe ranges between 2.0 and 4.6 cases per 1,000 person-years, with a sharp increase in >50 year-old subjects. Currently, treatment options for HZ are only partially effective in limiting the acute phase, while the management of complications is complex and often unsatisfactory. The total burden of the disease and the high costs related to its diagnostic and therapeutic management led researchers to develop a new preventive approach through a live attenuated virus vaccine. The currently available vaccine, with a high antigen content, is safe, well tolerated and reduces the incidence of HZ, PHN and the burden of illness. Several countries have introduced this vaccination, albeit with different recommendations and methods of financing. Taking into account the barriers to this immunization registered in some areas (difficulty of vaccine distribution, lack of physician recommendations, the cost of vaccine for patients, etc.), this group of Italian experts advocate that a common strategy able to guarantee a good compliance with this vaccination should be implemented. The same group addresses some practical questions concerning the use of zoster vaccine.

KEYWORDS

Herpes zoster; prevention; immunization; clinical evidence; real world experiences

Introduction

This document represents the position of a Group of Experts involved in the Advisory Board on Herpes Zoster and its prevention by vaccination; these experts have already discussed and published some articles on this topic.^{1,2} The objective of this paper is to update newly available data on real world experiences with this immunization and to give health workers some practical advices on the use of zoster vaccine in the current practice.

The clinical relevance of HZ deserves a preventive approach by immunization not only for the impact of the acute form but also for the possibility of visceral complications; besides, approximately 20–30% of subjects affected by HZ develops post-herpetic neuralgia (PHN), a highly debilitating chronic neuropathic pain.³

The clinical relevance of HZ has also been reinforced by the described correlation between the acute episode of HZ and ischemic stroke.^{4,5} The estimated survival curves show that mortality from ischemic stroke increases after an episode of HZ, with an increased risk of stroke in the first weeks after acute HZ and a stronger correlation in cases of ophthalmic zoster (HZO).⁶

In 1999–2005, in Italy 35,328 hospitalizations for HZ have been registered (annual average of 4,503 and 543 hospitalizations and day-hospital admissions, respectively). Most part

(61.9%) of hospitalizations involved subjects >65 y of age with an average hospital stay of about 8 d.⁷

New effectiveness data on zoster vaccine have been recently achieved, being effective in preventing 54% and 67.1% of HZ cases in subjects >60 y and aged 60–69 years, respectively. The effectiveness in preventing PHN ranged between 60.5% and 69.1%. A reduced frequency and severity of prodromal pain as well as a 70% decrease of the cases that needed medical examination prior to the onset of the rash was registered in immunized subjects.⁸

Herpes zoster: A challenge for active and healthy aging

The progressively aging population, as nowadays is registered in industrialized countries, is and will be a challenging issue for health care system today and in the future. Demand for health and health care needs in the coming years will sharply increase driven by demographic dynamics and by the impact of chronic diseases in aging population. Currently the >50 y of age European people constitute the 36.5% of the total population; it is estimated that in 2020 this rate will be equal to 41% and it is reasonable to assume that the increasing trend of the expectation of life at birth will continue in the coming decades.^{9,10}

In 2050 more than a third of the Italian population will be >65 y of age; noteworthy, this age class already uses up to 50% of health spending resources. The World Health Organization (WHO) has found that at least 90% of > 65 year-old subjects suffers any of the following chronic conditions: cancer, neuro-psychiatric or cardiovascular diseases (myocardial infarction, hypertension), diabetes.¹¹

Among the available preventive strategies, adult and elderly vaccination is a key element and plays an important role in promoting an active and healthy aging. In Europe it is recognized the need to develop measures able to maintain elderly people active and able to work.¹²

The promotion of active aging is not only useful to provide a longer permanence in the workplace, but it allows people to continue to maintain a good social, economic, and cultural level.¹¹

HZ has a negative impact on quality of life: the health-related quality of life (HRQoL) parameters are inversely proportional to the level of pain, especially in patients with PHN, with a negative impact on social relations. Up to 50% of patients with HZ and up to 81% of patients with PHN report a negative impact on their social and familiar relationships.^{13,14}

Several studies have shown that pain and other physical and psychological symptoms associated to HZ and PHN can significantly affect the productivity and working capacity of the affected population.¹⁵ About 75% and 66% of subjects with HZ infection report a decrease of their concentration and work ability, and stopped working, respectively.^{16,17}

Besides, the symptoms associated with shingles often prevent to complete activities of daily living, such as cooking, going to the bathroom, put on the clothes, climbing stairs; these activities can suddenly become difficult and painful.^{18,19}

In elderly patients, HZ can imply a permanent loss of independence, inability to maintain their lifestyle, their interests or their level of activity.¹⁵ The loss of functional independence affects both the patients and their relatives and increases the use of long-term care facilities.²⁰

Zoster vaccine: Experiences in Europe and in Italy

Zoster vaccine can positively improve the quality of life through mitigation and/or prevention of HZ and HZ-related chronic neuropathic pain; it is also a good example of how immunization policies “for life” could contribute to healthy aging, with a consequent positive impact on the community and health systems.

Live attenuated Zoster vaccine (Oka/Merck strain) has been licensed in Europe in May 2006 and in Italy in 2010; since March 2014 it is commercially available in Italy.²¹ In Europe, Zoster vaccine is available and in use, with partial or total reimbursement systems, at national or regional level, in countries such as United Kingdom (UK), France, Holland, Germany, Spain, Austria and Greece.

In particular, in the UK the vaccination program began in September 2013, including 2 cohorts of 70 and 79 year-old subjects. The average vaccination coverage rate after one year was equal to 61.8% and 59% in the 2 cohorts, respectively.²² Given the positive response from the population, the health authorities have decided to extend the program (active call and

funding) to the cohort of 78 year-old subjects. The compliance of the target population has been very good, and only 8.5%–10.3% of eligible subjects have declined immunization proposal.²³

In Italy, some regions (Liguria, Sicily, Calabria, Autonomous Province of Trento) have independently included zoster immunization in the latest update of the regional vaccination schedule.

In 2015, Liguria has introduced zoster vaccine in an active and universal free offer in the cohort of 65 year-old subjects.²⁴ In Sicily, the inclusion of new vaccines is presented as an opportunity to re-launch of vaccine prevention policies, through a partnership involving prevention departments, pediatricians (PLS), general practitioners (GPs), institutions and citizens.²⁵ In Calabria the recent Regional Vaccination Plan provides for the free offer of zoster vaccine to cohorts of 65 and 70 year-old subjects and to at risk subjects.²⁶ The autonomous province of Trento has provided vaccination for 65 year-old subjects and at-risk groups. It is desirable that the vaccination is implemented throughout the national territory.²⁷

Taking into account this last point, in Italy the 2014 Lifetime Immunization Schedule, a document approved by the Italian Scientific Societies (Italian Society of Hygiene, Preventive Medicine and Public Health: SItI; Italian Society of Pediatrics: SIP; Italian Federation of Pediatricians: FIMP; Italian Federation of General Practitioners: FIMG) recommends the administration of 1 dose of zoster vaccine at least to 1 cohort of ≥ 60 years-old and to at risk subjects.²⁸

The National Immunization Prevention Plan (PNPV) 2012–2014 currently in force has no reference to the zoster vaccine, approved by the European Commission on 19th May, 2006.²⁹

To date, the draft of the new PNPV 2016–2018 is still in the approval process, and is expected to contain most of the recommendations included in the Lifetime Immunization Schedule; among other innovations, it should recommend also zoster vaccination to a cohort of 65 year-old subjects and to those ≥ 50 y of age at risk.

Future perspectives

Wishing for the approval of the new PNPV 2016–2018 and the active and free offer of zoster vaccine at national level, the Group of Experts involved in the Advisory Board on Herpes Zoster and its prevention by vaccination points out that, thanks to the availability of an effective, safe and well-tolerated vaccine, there is a great opportunity to achieve a positive impact on the health of vulnerable elderly people helping to provide a healthy aging, free from HZ and its complications.

A common strategy able to guarantee a good compliance with this vaccination should be implemented, and any effort should be made in order to remove barriers and increase the knowledge of and the compliance with this immunization.

Besides, in view of the implementation of zoster vaccination throughout the national territory, the Group of Experts decided to evaluate and to answer the topics of practical interest that Public Health’s professionals and the medical and scientific community could have about this vaccination.

Which are the main at risk groups?

Increasing age is universally recognized by the international scientific community as the main risk for reactivation of Varicella-Zoster virus (VZV), mainly due immunosenescence, with an age-related increase in the incidence of HZ and PHN. An increased risk of HZ, which in any case is age-related, is also associated to some underlying medical conditions as diabetes, Chronic Obstructive Pulmonary Disease (COPD), in addition to stressful events/traumatic events, immunosuppression and immunosuppressive treatments.^{1,30,31}

Some chronic diseases are possibly associated with an altered functionality of the cell-mediated immune response (CMI) which can lead to an increase of HZ cases.³² Some researches suggest that patients with HZ are more likely to have a history of myocardial infarction, hypertension, heart failure, diabetes mellitus, asthma, and COPD.³²

A recent prospective cohort study identified an increased risk of shingles in individuals with diabetes, cardiovascular and respiratory diseases.³³

A retrospective cohort study found that patients with diabetes mellitus, kidney failure, cancer and other conditions have a risk of developing shingles 1.8–8.4 times higher than patients with other diseases.³¹ A case-control study conducted in the US population found that the risk of developing HZ was significantly greater in patients who had risk factors (diabetes, cardiovascular disease, COPD). The same study found that 7.6% of the considered population was suffering from immunosuppression.³⁴

Patients affected by chronic diseases are also fragile subjects that, besides having a higher relative risk of suffering from herpes zoster compared with healthy people of the same age, have a higher risk of imbalance of the underlying chronic disease because of HZ, with a greater frequency and severity of HZ-related complications.³⁵ Stressful life events may be risk factors for the development of HZ.^{36,37} With regard to major depression, the presence of HZ may interfere or severely unbalance the underlying disease in patients already receiving multiple treatment, increasing the risk of suicide, especially in case of PHN.³⁵ Mechanical trauma is also associated with an increased incidence of HZ, in the following months, assuming that the traumatic nerve stimulation can trigger viral reactivation in dorsal root ganglion.³⁸ Even the female gender, though not all data are consistent, appears to be associated in some studies with an increased incidence of HZ.³⁹

Is HZ recurrence a significant clinical problem? Are any epidemiological data available on HZ recurrence?

Taking into account that a case of HZ implies the reactivation of VZV-specific CMI, HZ is usually considered a unique event, being recurrences limited to immunocompromised patients.⁴⁰

However, it is possible to have more than one episode of HZ but the recurrence rate is low and accordingly to the literature ranges between 1.5 and 12.5%; the most likely rate is in the range of 4–5%.⁴¹ The most important factor for recurrence is the duration of the pain during the acute episode. Individuals who experience pain for more than 30 d after the onset of the disease have an increased risk of recurrence, especially in the first 3–4 y after the HZ occurrence.⁴²

Can zoster vaccine be used in subjects with a previous history of HZ/PHN? If yes, when the vaccine should be ideally administered? Are there any available data about vaccine efficacy against relapses in such subjects?

There is no fixed time between an episode of HZ and a possible following vaccination. In any case the decision should be based on the clinical judgment of the attending physician. A HZ episode acts as a booster on CMI. For the first 3 y after immunization VZV-specific CMI is similar to the one elicited by an acute HZ episode; for this reason, an HZ episode should reduce the risk of recurrence for at least 3 y.⁴³

Noteworthy, the administration of the vaccine, prescribed by the attending physician, should be delayed until the completion of systemic antiviral therapy. No data on vaccine efficacy in subjects who already suffered from HZ are available. A previous episode of HZ greatly reduces the possibility of having a second one.⁴⁴

The vaccine, however, is also immunogenic and safe in patients with a positive history of HZ, whether or not these subjects had HZ more than or less than 5 y before vaccine administration.^{45,46}

Can zoster vaccine be administered to a subject with acute HZ/PHN?

Live attenuated zoster vaccine (Oka/Merck strain) is not indicated for the treatment of HZ and PHN. Zoster vaccine is indicated only for the prevention of HZ and PHN.⁴⁷

While varicella vaccine can also be given post-exposure, zoster vaccine has no effect after the disease has been established. VZV primary infection (varicella) elicits a long lasting antibody-mediated and cell-mediated immune response; VZV-specific antibodies (Abs) play a relevant role on the healing of varicella but are not able to avoid viral latency.⁴⁸ Live attenuated zoster vaccine (Oka/Merck strain) with its high antigen content is able to boost VZV-specific CMI preventing reactivation of latent VZV, VZV replication and subsequent neurological damages. It cannot have an impact on an already ongoing HZ and/or PHN.

Can zoster vaccine be administered to a VZV naïve subject?

The probability to administer zoster vaccine to a VZV naïve adult is quite low in Europe; in fact, >95% of adults have VZV-specific Abs.⁴⁹

The vaccine can be administered regardless of the VZV history of the subject; there is no recommendation to preliminarily evaluate the VZV-specific immunological situation before the administration of zoster vaccine.^{44,50}

The vaccine has been shown to be immunogenic and generally well tolerated regardless of the immunological situation (seronegativity, low-seropositivity, seropositivity).^{47,51}

Can zoster vaccine be administered to a subject already immunized against varicella?

Zoster vaccine is not recommended for subjects who already received varicella vaccine. Anyway, it is not necessary to investigate

the immunological status and the medical history of the subject before routine immunization.⁵²

Noteworthy, in the USA, as well as in Italy, >50 year-old subjects already immunized for varicella are very few. This problem must be tackled at least many years after the introduction of universal vaccination for chickenpox, after a careful evaluation of both clinical and epidemiological data.

Can zoster vaccine be used to prevent varicella?

Zoster vaccine is not indicated for the prevention of varicella. If zoster vaccine was administered by mistake to a child or to an adult instead of varicella vaccine, it can be assumed that it elicits the same level of protection. However, it is appropriate to administer a second dose of varicella vaccine accordingly to the routine schedule.⁵²

If a dose of varicella vaccine was accidentally administered to an adult instead of zoster vaccine, the dose of zoster vaccine should be done (at the same visit or, if the mistake has been detected later, after at least 4 weeks the previous varicella vaccine dose). No specific safety concern do exist in this case.

Can zoster vaccine be co-administered to other vaccines?

Zoster vaccine may be co-administered (separate injections on separate areas of the body) with the inactivated influenza vaccine (TIV or QIV).

Zoster vaccine and 23-valent pneumococcal polysaccharide vaccine should not be co-administered as reduced immunogenicity of zoster component has been highlighted in clinical trials.⁴⁷

Which immunization strategy could have the best impact on the burden of disease (BoD) in Italy?

Age is the main risk factor for HZ and the age-based preventive strategy is based on sound scientific evidence. It would also allow to reach groups of >50 year-old subjects with chronic medical conditions, that could suffer serious complications following the acquisition of HZ.

Patients with chronic diseases are a broad and diverse group of people to whom vaccination can be recommended, provided that possible concomitant immunosuppression and/or other contraindications are not in progress. Vaccination coverage rate for HZ in the US in 2012 was equal to 20.1% and 22% in >60 y and >65 y of age adults, respectively. In 2013, 24.2% of ≥60 y of age adults had received zoster vaccination.⁵³ The Centers for Disease Control and Prevention (CDC) has estimated to achieve a coverage rate equal to 30% of eligible subjects by 2020. In the UK, as previously reported, thanks to the active and free of charge offer of zoster vaccine an immunization coverage rate equal to 60% has quite rapidly achieved in the target population.^{22,23}

Does universal mass vaccination (UMV) for varicella have any impact on HZ epidemiology?

One of the major misconceptions concerning UMV for varicella is that zoster could become epidemic as a consequence of widespread varicella immunization. It has been demonstrated

that varicella vaccination can reduce the risk of HZ in vaccinees. The incidence of HZ after vaccination has been consistently lower in healthy immunocompetent vaccinees as well as in immunocompromised patients than in patients who experienced natural VZV infection.^{54,55}

Some authors, supporting the exogenous booster hypothesis, have speculated that the introduction of UMV for varicella could be related to an increase of HZ incidence in subjects that had in the past the natural infection. Accordingly to the exogenous boosting theory, the decrease of the spreading of wild-type VZV following universal immunization, should decrease the opportunities to have VZV-specific CMI boosted and should cause, at least for some decades, an increase of HZ cases in unvaccinated subjects.⁵⁶ Other authors support the endogenous booster hypothesis, accordingly to which latent VZV could silently reactivate and boost VZV-specific CMI. Endogenous boosting is very difficult to evaluate and demonstrate; anyway, VZV latency in enteric neurons and the following possible silent reactivation could lead, at least for some time, to long-term protection and maintenance of VZV-specific CMI.⁵⁷

Exogenous boosting hypothesis has been evaluated with both epidemiological risk studies and mathematical modeling studies; the results have not been conclusive at all.⁵⁸

A model-based evaluation on the impact of varicella immunization on HZ in Italy has shown that an increase of HZ incidence related to varicella extensive immunization should be not certain.⁵⁹

In conclusion, evidence of an increase of HZ in countries with a universal varicella vaccination program is not consistent;⁶⁰ many studies have shown evidence of increasing incidence trends in HZ in countries with or without a universal varicella vaccination program.^{61,62,63}

Besides, in some countries, HZ incidence started to increase years before the vaccine was introduced. For these reasons, continuous monitoring is needed to understand the secular trends in HZ before and after introduction of varicella vaccination programmes.

Are there any indications available about the use of zoster vaccine in special sub-groups such as subjects under therapy for immuno-mediated disease and Human Immunodeficiency Virus (HIV)-positive subjects?

Accordingly to the Summary of product characteristics (SCP) zoster vaccine is contraindicated in case of history of hypersensitivity to the active substance, to any of the excipients or trace residuals (e.g., neomycin); primary and acquired immunodeficiency states due to conditions such as: acute and chronic leukemia; lymphoma; other conditions affecting the bone marrow or lymphatic system; immunosuppression due to HIV/AIDS (Acquired Immune Deficiency Syndrome); cellular immune deficiencies; immunosuppressive therapy (including high-dose corticosteroids); active untreated tuberculosis; pregnancy. However, zoster vaccine 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 (for example, for adrenal insufficiency).⁴⁷

The IDSA (Infectious Diseases Society of America) guidelines, based on available evidence, provide specific recommendations for

HZ prevention in immunocompromised hosts by vaccination of ≥ 60 y of age patients if the vaccine can be administered ≥ 4 weeks before the start of high immunocompromising situation (strength of recommendation and level of evidence: strong, low).

Zoster vaccine may be considered for 50–59 year-old patients with a history of chickenpox or VZV Abs-positive and who did not received the varicella vaccine, if zoster vaccine can be administered ≥ 4 weeks before the start of immunosuppressive therapy (strength of recommendation and level of evidence: weak, low). Zoster vaccination should be offered to ≥ 60 year-old patients who are receiving treatment that induces a low level of immunosuppression (strength of recommendation and level of evidence: strong, low); it should not be administered to highly immunocompromised patients (strength of recommendation and level of evidence: strong, very low).⁶⁴

SCP reports that, in a randomized, double-blind, placebo-controlled study, the vaccine was administered to 206 >60 year-old subjects who were receiving systemic chronic corticosteroid maintenance therapy, equivalent to a daily dose of 5–20 mg of prednisone, for at least 2 weeks prior to enrollment, and 6 weeks or more after vaccination to assess the immunogenicity and safety profile. Compared with placebo, the vaccine induced a higher geometric mean titer (GMT) of VZV-specific Abs by gpELISA (VZV glycoprotein-based enzyme-linked immunosorbent assay) 6 weeks after vaccination (531.1 vs. 224.3 gpELISA units/ml, respectively). The geometric mean of the increase of the immune response following vaccination as measured by gpELISA was 2.3-fold (95% confidence interval CI: 2.0–2.7) compare with 1.1 times (95% CI: 1.0–1.2) in the placebo group.⁴⁷

Even on the basis of the above results, ACIP considers as not immunosuppressive doses of cortisone or cortisone equivalent to 20 mg/day of prednisone or cortisone therapy lasting less than 14 days, and the intra-articular administration. The vaccine should be administered at least 14 d before the start of immunosuppressive therapy or 1 month after cessation of the same.^{52,65}

According to international guidelines, treatment with low doses of methotrexate (<0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day), or 6-mercaptopurine (<1.5 mg/kg/day) for the treatment of psoriasis, rheumatoid arthritis, polymyositis, sarcoidosis, inflammatory bowel disease and other conditions is not sufficiently immunosuppressive and there are no contraindications for administration of zoster vaccine. Zoster vaccine is not provided when these drugs are used in combination.^{44,52,65}

As for the use of the vaccine in relation to people with conditions for which a treatment with anti-Tumor necrosis factor (TNF) agents or other biotechnological drugs, ACIP provides that specific biological drugs (adalimumab, infliximab and etanercept) as well as prednisone/prednisone equivalent dose >20 mg/day contraindicate the use of zoster vaccine. The ACIP also recommends that GPs should assess the immune status of their patient case by case to establish the relative benefit of zoster vaccine. General recommendations on immunization with live attenuated vaccines also apply to zoster vaccination but there are no specific data related to this vaccine.⁵²

The Canadian National Advisory Committee on immunization (NACI) provides for the use of zoster vaccine in immunocompromised individuals: the vaccine may be administered in case of low-dose immunosuppressant use while the use of anti-TNF biologic drugs must be based on clinical evaluation case by case.⁶⁶

A recent review on the topic HZ and anti-TNF (etanercept, adalimumab, infliximab, an inhibitor of interleukin-12/23, ustekinumab) has found a clear association between the use of infliximab and increased risk of HZ, while it seems there still is a controversial association between adalimumab, etanercept, and ustekinumab and increased risk of HZ.⁶⁷

The authors conclude that the zoster vaccine should be considered, with a clinical assessment of the individual case, prior to the start of any therapy with biologic drugs. There is no experience in stem cell transplantation cases but, after the evaluation of each single case, the vaccine should be administered at least 24 months after a transplant.

Zoster vaccine has not been specifically tested in randomized clinical trials (RCTs) enrolling patients with altered immune response. A reduced incidence of HZ in patients vaccinated with zoster vaccine compare with non-vaccinated subjects has been pointed out in a mean observation period of 2 y in a cohort of 463,541 >60 y of age patients with autoimmune diseases (assisted by the Medicare system in the USA), including subjects receiving anti-TNF.⁶⁸

An observational study has been done in a cohort of >60 year-old subjects receiving chemotherapy for cancer; patients received vaccination before starting chemotherapy treatment (follow-up of 30 months, and variable exposure time to the chemotherapy). A total of 91 and 583 HZ cases with an incidence ratio of 12.87 (95% CI, 10.48–15.80) and 22.05 (95% CI, 20.33–23.92) per 1,000 people-year were registered in vaccinated and non-vaccinated subjects, respectively.⁶⁹ An hazard ratio equal to 0.58, adjusted for sex, age, race, health care in the 6 months prior to vaccination and use of antiviral drugs in the 6 months following vaccination, suggests that the vaccine administered when you are immunocompetent continues to be protective even after chemotherapy.

Abbreviations

Abs	antibodies
AIDS	Acquired Immune Deficiency Syndrome
BoD	burden of disease
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMI	cell-mediated immune response
COPD	Chronic Obstructive Pulmonary Disease
FIMG	Italian Federation of General Practitioners
FIMP	Italian Federation of Pediatricians
gpELISA	VZV glycoprotein-based enzyme-linked immunosorbent assay
GPs	general practitioners
HIV	Human Immunodeficiency Virus
HRQoL	health-related quality of life
HZ	Herpes Zoster
HZO	ophthalmic zoster
IDSA	Infectious Diseases Society of America
NACI	Canadian National Advisory Committee on immunization
PHN	post-herpetic neuralgia
PLS	pediatricians
PNPV	National Immunization Prevention Plan
RCTs	randomized clinical trials

SCP	Summary of product characteristics
SIP	Italian Society of Pediatrics
StI	Italian Society of Hygiene Preventive Medicine and Public Health
TNF	Tumor necrosis factor
UK	United Kingdom
UMV	universal mass vaccination
VZV	Varicella-Zoster Virus
WHO	World Health Organization

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ORCID

Elisabetta Franco <http://orcid.org/0000-0002-1179-4411>

Giancarlo Icardi <http://orcid.org/0000-0002-8463-8487>

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