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Abstract

Objective

In view of the availability of a HZ vaccine, the aim of the study was to evaluate the awareness about the VZV and the acceptability of the HZ vaccine in the general population aged 50 years old and over.

Design

The research was observational.

Setting

The study was carried out by administering a questionnaire at the outpatient clinics of General Practitioners (GPs) and of the Public Health Department of the Local Health Unit of Ferrara.

Participants

The research involved 1,001 residents in the Province of Ferrara (57% were female).

Results

The 98% and 95% of respondents knew varicella and zoster, respectively, and the 58% were in favor of vaccination for HZ. The variables that positively affect the acceptability of the vaccine were: the age (p=0.005); to know someone who suffered of HZ (p=0.05); being in support of the vaccinations (p<0.0001), and the GP's advice (<0.0001); willingness to get vaccinated even upon payment (p<0.0001). The 73% of the interviewed people were disposed to pay to get vaccinated, indicating an ideal cost of 50 €. This choice was positively influenced by higher education (p=0.04), being in favor of vaccinations (p<0.0001) and the GP's advise (p<0.0001). Moreover the recommendation of GP modified the decision not to vaccinate in the 61% of the subjects initially unfavorable (p<0.0001).

Conclusions

The study contributed to assess the level of awareness and the attitudes of the over 50 years old population, pointing out the factors to be targeted to promote the vaccination against HZ, given that the available scientific evidence suggests that the best Public Health strategy would be represented by the offer of the HZ immunization to over 50 years old subjects at risk and to the elderly population (60-70 years).

Strengths and limitations of this study

- The major strength of the present study is that findings can be used to determine the factors that influence people's intention regarding HZ vaccination and investigate the barriers for vaccination in view of the upcoming availability of the vaccine throughout Italy.
- Limitations include that people are not always willing to tell a stranger what they really think at interview.
- There is no way to tell how truthful respondents are being because they may be forgetful or not thinking within the full context of the situation.

Background

Worldwide, the infection with Varicella Zoster Virus (VZV) affects millions of individuals, representing a great source of suffering. The virus causes varicella, the primary infection that occurs mainly in children and confers immunity in the long term, both cell mediated and humoral against new episodes of varicella. The virus can establish a latency state in the neurons of the spinal and cranial ganglia and along the whole neuraxis.[1]

In the 10-30% of people who had varicella, the virus can reactivate causing Herpes Zoster (HZ), an acute viral infection that affects the skin and the nervous system with an overall rate of incidence of 35 cases/1,000 persons per year.[2] Although the onset of the HZ is the result of a multifactorial process, an important role in the virus reactivation is attributed to the decline of T cell-mediated VZV-specific response, due to immunosenescence related to age or to immunosuppressive conditions, as a result of certain diseases (HIV, Hodgkin and non Hodgkin's disease, lymphomas, leukemias, bone marrow or other organs transplants, systemic erythematosus lupus), medications, psychological stress or malnutrition.[3-4]

The incidence rapidly increases with age. It is estimated that about 50% of people aged ≥80 years will develop at least one episode of acute HZ, mostly localized in the region of the concerned sensory ganglion, often preceded by acute pain or itching.[5] The rash is initially erythematous with multiple maculopapular injuries and later becomes vesicular; new lesions may continue to appear for a maximum of seven days, after which they form a scab, which drops after 2-3 weeks.[6] The rash is often accompanied by a painful dermatomeric syndrome caused by the neuritis following the viral replication, described with burning, tingling, itching, a mild to severe pain, loss of sensation and weakness, if the roots of the motor nerves are implicated. In the 10-20% of HZ episodes the ophthalmic branch of the trigeminal nerve can be involved.[7]

Among all complications, that occur in 20% of cases, the most frequent is post herpetic neuralgia (PHN), defined as "a chronic long lasting HZ-correlated pain that persists for at least three months after the eruption of HZ or the onset of the pain". The PHN is a neuropathic syndrome characterized

by pain along the cutaneous nerve endings, described with constant or intermittent pain, burning, allodynia and/or hyperalgesia, but also chronic fatigue, sleep disorders, depression, anorexia, weight loss and social isolation, in which case the functional status of the patient may be compromised due to the difficulty in performing everyday activities.[8] Other complications that can occur, in particularly in immune-compromised individuals, are disseminated Zoster, ophthalmic Zoster, encephalitis, inflammation of spinal cord, cranial and peripheral nerves paralysis including Bell's palsy and Ramsay Hunt syndrome.

According to the Shingles Prevention Study (SPS), the percentage of patients who develop PHN is 12.5% after three months and 5.1% after six months;[9] in addition to the significant impact on the quality of life, this condition implies an important economic weight for the Public Health responsible for the clinical and therapeutical management.

The annual HZ incidence is analogous all around Europe and increases with age from about 1-4/1,000 adults under 50 years old to about 7-8/1,000 in people over 50 years old and up to 10/1,000 in over 80 years old.[10]

In Italy, HZ is included in 5th class of the notification system for infectious diseases, but the obligation of notification is widely disregarded. It is, however, estimated that every year at least 157,000 new HZ cases occur, with an incidence of 6.3/1,000 /year with 9.4% and 7.2% of patients who suffer of PHN at 1 month and 3 months, respectively.[11]

In the period 1999-2005, in Italy, 35,328 hospitalizations were recorded with an annual average of 4,503 of which 453 were day hospital admissions; the 62% of hospitalizations concerned subjects aged over 65 years old, with a mean length of stay of eight days and a total of more than 22,000 days in hospital per year.[12]

In 2006, in order to prevent the epidemiological impact of the disease and to limit the costs of clinical and therapeutical management, the US Food and Drug Administration (FDA) approved a HZ vaccine, recommended by the Advisory Committee on Immunization Practices (ACIP) for the prevention of HZ in patients of 60 years old and over.[13-14] In the same year, the European

Medicines Agency (EMA) authorized the marketing of the vaccine in the European Union, suggesting starting the immunization from the age of 50 years. In Europe the marketing authorization was granted in May 2006, at first, starting from 60 years old, and, in July 2007, it was extended from 50 years old.

The new vaccine is constituted by the same live attenuated strain used for varicella immunization, but with an antigenic content at least 14 times higher,[15] able to stimulate the cell mediated immune response (CMI) against HZ, countering the virus reactivation and replication and thereby reducing the incidence and severity of the disease.

The efficacy, the safety and the tolerability of the vaccine against HZ and its sequelae were demonstrated in 28 pre- and post-marketing clinical trials with about 96,700 enrolled subjects, 57,700 of which vaccinated against HZ.[16-18]

The report EUnetHTA recognized both the impact of the disease and associated complications that the efficacy and the good safety profile of the vaccine, expressing a positive opinion regarding the value of the intervention vaccination against HZ.[19]

A cost-efficacy Italian study showed the vaccine is highly cost effective with a cost per Quality Adjusted Life Year (QALY) equal to € 11,943 for the subjects of 60-79 years (€ 9,779 for people aged 65-79 years and € 8,729 for those between 70 and 79 years).[20]

In Italy the vaccine is recommended in people at risk aged over 50 years, with exclusion of those seriously immunocompromised. The vaccine administration began during the 2015 in active and free offer: Sicily for at-risk individuals above 50 years of age and in the cohort from 65 to 75 years old,[21] in Liguria to people over 65 years old [22] and in Calabria to people aged 65 or 70 years old.[23] In Veneto and in Friuli Venezia Giulia the HZ vaccine is offered only to over 50 years old subjects at-risk and on medical prescription, or in co-payment for people not belonging to at risk groups.[24-25] Outside of these categories, the vaccine is administered upon payment of a fee as specified in regional price list.

The awareness of population about the burden of HZ on health and quality of life and regarding the relevance of immunization as a tool of prevention are issues rarely investigated until now.[26] The aim of the study is to evaluate, in the population aged 50 years old and over of Ferrara, the awareness towards the VZV and the degree of acceptability of a vaccine against HZ in view of the upcoming availability of the vaccine throughout Italy.

Materials and methods

The study was observational and recruited people aged 50 years old and over, living in the Province of Ferrara. The involvement of interviewed subjects took place at the clinics of the Department of Public Health of Local Health Unit of Ferrara and of General Practitioners of Ferrara participating to the study. Exclusion criteria were: age under 50 years old, not understanding the study procedures and the information contained in the leaflet and finally failure to desire to participate to the study.

The questionnaire

The questionnaire consisted of 27 questions, for some of them more than an answer could be provided. In the first section, socio-demographic data were collected: age, educational level, employment status, nationality and municipality of residence. The second part investigated the level of awareness against varicella and HZ, as well as the attitude toward vaccination for HZ. The questionnaire was validated by a panel of trained expert on the issue.

Ethical aspects

The study was approved by the Ethical Committee of the Province of Ferrara. All information were confidentially processed and kept according to law (Legislative Decree number 196/2003 “Code concerning the protection of personal data”).

Data collection and statistical analysis

The interviews were conducted during the period October 2014 –April 2015; the questionnaire was

administered by trained personnel. The collected data were recorded in a database in Excel format. The statistical analysis was conducted by the chi square and the multivariate logistic analysis using the software StatView® 5.0.1 (Abacus Concepts, Berkeley, CA, USA). Univariate and multivariate logistic regression were performed with STATA SE ® (13.1 version). In particular, obstacles and limitations of acceptability of vaccination were evaluated with multivariate logistic regression linking, separately, the dependent variables "willing to be vaccinated against HZ" and "willing to be vaccinated against HZ even upon payment" with all the independent variables proved to be significant at the univariate logistic analysis, considering statistical significance for values of odds ratio greater than 1 and p lower or equal to 0.05. Statistical significance was set at 0.05.

Results

A total of 1,001 subjects were interviewed; 57% were female and the mean age was 67 years old. The main socio-demographic characteristics are reported in Table 1. The 69% were retired, the 29% were workers and 2% were unemployed. The educational level was average-high: the 36% was high school licensed, the 23% attended the primary school, the 23% completed the secondary school and the 18% was graduated; only the 0.5% did not possess any educational qualification.

As expected, since it is a well-known rash illness, the 98% of respondents knew varicella and the 72% experienced it in the past. As predictable, according to the widespread popular beliefs on HZ, the disease was known by the 95% of interviewed subjects. For people (5%) that declared to not know HZ, the questionnaire war interrupted.[Table 2] Among those who knew HZ, the 22% had the disease, while the 80% indicated that they knew at least one person who had the disease in the past.

Assessing the knowledge on HZ symptoms, the "rash" resulted the main symptom associated to the disease (794 respondents), probably because this is the most evident. Other symptoms were "pain" and "itching" stated by 789 and 680 respondents, respectively. About half of interviewed people (427 subjects) associated "malaise", 99 subjects indicated "ocular problems" and 86 people

designated “headache”. Finally, 32 subjects preferred not to answer, since they could not associate any symptoms to HZ.

The perception of the level of the chronic pain and the impact on daily life was assessed. Pain was considered “serious” by 46.6% of respondents and “moderate” by the 39.3%. Only the 7.2% of the interviewed subjects described pain as “mild”, while the 6.9% were unable to answer. The impact of the disease, however, was defined of “little importance” by the 20% of the respondents, “relevant” by the 46%, instead of “very important” by the 25%; the 10% of subjects were not aware to define it.[Table 3]

Considering the knowledge of the HZ vaccine, the 91% of interviewed people were not aware of it. People who knew the vaccine indicated as source of information principally the “press” or “radio, Internet, TV”; other sources were friend/contacts, family or GP.

The 58% of the respondents claimed to be in favor of the HZ vaccination; those against (42%) motivated their answer mostly for fear of possible side effects (15%), the 10% considered not to be at risk of developing the disease, the 6% were opposed to vaccinations.

Other reasons were not believing in the efficacy of the vaccine (3%), not consider the disease enough long, dangerous and painful (3%), or the trouble to go to the doctor for vaccination (1%). On the contrary, the 62% of subjects favorable to vaccination justified as follows: the 31% believed in “the efficacy of the vaccine”, the 26% knew someone who had the disease, the 19% thought that “vaccine can improve health”, the 11% feared to be at risk of developing the disease, while the 1% gave other reasons.

The questionnaire also investigated the role of the GP. The 83% of respondents would be ready to be vaccinated if recommended by GP. The 61% (248 subjects) of 405 individuals opposed to vaccination against HZ said that would change his mind if advised by the GP. It also emerged that the 73% of respondents would be willing to get vaccinated even if the vaccine would be administered upon payment. When a fee was required, the majority of respondents (49%) would be

willing to spend up to 50€, while the 11% would prefer a lower amount. Despite a 10% of interviewed people favorable to pay a higher sum, the 14% believed that vaccination should be free. According to the multivariate logistic regression analysis [Table 4], the decision to get vaccinated against HZ was influenced by age, with younger people more prone to the vaccination, while the educational degree and the employment were not significant. The knowledge of a family member, friend or contact who had HZ seemed to be able to influence the decision of vaccinate ($p=0.05$). The advice of GP, "be favorable to vaccination in general" and the willing to vaccinate even upon payment turned out to highly influence the decision to vaccinate against HZ. The decision to get vaccinated against HZ upon payment was affected by a high educational degree ($p=0.04$), being favorable to vaccination and the GP's advice ($p<0.0001$).

Discussion

In Western countries, about the 20-30% of individuals experiences the VZV reactivation during the lifetime, with an incidence that increases dramatically with age. The impact on health and quality of life is relevant, as the HZ can lead to debilitating consequences, the drug treatments are often suboptimal and the public health costs are relevant. Therefore the development of a HZ vaccine was crucial, because it strengthens the immune system and avoids the onset of the disease and therefore all its possible sequelae. The vaccine was effective, safe and well tolerated. It is showed that it can decrease the HZ risk by the 64% in the population between 60 and 69 years old and reduce the risk of complications by the 70% in over 70 years old, as demonstrated by the Shingles Prevention Study [9]. The effectiveness studies, conducted in various parts of the world, were consistent with marketing studies, confirming a good profile of safety and tolerability, as well as of efficacy for prevention of HZ and PHN in subjects over 60 years old.[27-28]

The vaccine can be administered to VZV-naïve or with HZ medical history subjects, to patients with immune-mediated diseases [29] or with mild immunosuppression. When beginning an

immunosuppressive therapy, vaccine should be administered at least 14 days before or 1 month after the cessation of it,[30] referring to the contraindications reported in the datasheet and evaluating possible immunodeficiency prior the administration.[31]

In the United States, the immunization is recommended by 2006. Despite the benefits of vaccination, however, the acceptability during the first years was very low: only the 1.9% in 2007, the 6.7% in 2008 and the 10% in 2011 were vaccinated. The reasons could be that target people are not aware of immunization advantages, as well as the cost effectiveness, in the absence or reduced health care, or the lack of recommendation by GP.[32]

Several European countries decided to recommend and/or fund the HZ vaccination. The English vaccine program is an interesting experience as, began in September 2013 on two cohorts (70 and 79 years old) after one year recorded a mean national coverage of the 61.8% and the 59.6% respectively, showing a positive response to vaccination by the population.[33]

The aim of the present study was to evaluate the awareness of VZV and the acceptability of a HZ vaccine in the over 50 years old population of Ferrara. The collected questionnaires showed that the variables that influence the acceptability of vaccination are the age (younger people are more prone to immunization) and to be in general favorable to vaccinations. An explanation could be the self-confidence of people already favorable to vaccinations, who are not worried about side effects and do not have financial problems when the goal is health protection. The key role of the GP in promoting vaccination emerged: the trust in GP was a positive factor towards the willingness to be vaccinated. The knowledge of a family member, friend or contact who had HZ, although of statistically borderline significance, seemed to influence the willing of vaccinate, probably due to a deeper awareness of the disease and its consequences.

Considering the willingness to be vaccinated upon payment, it was positively influenced by the educational degree, being in favor of vaccinations and GP advice. Probably trained people, with sound cultural background, tended to be more informed about the relevance of vaccination and, consequently, more prone to pay for it.

In conclusion, the study contributes to better understand the awareness and the attitudes of general population towards a new vaccination. It would provide additional support to available scientific data that, currently, recommend the new HZ vaccine in at risk (with the exception of severely immunocompromised individuals) over 50 years old subjects and in at least one cohort of the elderly population (60 or 65years old).

Author's Contribution

AS and GG contributed to the overall design of the study, analysed the data and drafted the manuscript. NV, SL, NS, MC, LP contributed to the study design, supervised the acquisition of data, contribute to data analysis and reviewed the manuscript. The working group participated in the fieldwork. All authors critically read and revised the drafts of the manuscripts. All authors read and approved the final manuscript.

Competing interests

There are no potential competing interests of the authors. Gabutti G received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Pfizer and Sequirus for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.

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Data sharing statement

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Table 1. Socio-demographic characteristics of interviewed subjects.

Involved subjects N=1.001		**N (%)**
Gender	*Male*	569 (56.8)
	Female	432 (43.2)
Age	*50-54 years old*	114 (11.4)
	55-59 years old	134 (13.4)
	60-64 years old	148 (14.8)
	65-69 years old	190 (19.0)
	70-74 years old	157 (15.7)
	75-79 years old	145 (14.5)
	≥80 years old	113 (11.3)
Employment status	*Retired*	693 (69.2)
	Worker	292 (29.2)
	Unemployed	16 (1.6)
Educational level	*Primary school*	231 (23.1)
	Secondary school	228 (22.8)
	High scool	361 (36.1)
	University	176 (17.6)
	No qualification	5 (0.5)

Table 2. Knowledge concerning varicella and Herpes Zoster.

	Varicella N=1.001			Zoster N=953		
	Yes (%)	No (%)	Not remember (%)	Yes (%)	No (%)	Not remember (%)
Do you know the disease?	98	2	---	95	5	----
Did you have the disease?	72	11	17	22	78	---
Are you vaccinated for Varicella?	5	81	14	---	---	---
Do you know someone who had Zoster?	---	---	---	80	20	---

Table 3. Awareness of HZ's impact on daily life activities (N=953).

HZ's impact	N (%)
Little importance	193 (20.2)
Relevant	434 (45.5)
Very important	234 (24.6)
Do not know	92 (9.7)

Table 4. Determinants of being in favor of vaccination against HZ and being favorable to get vaccinated even upon payment.

Are you in favor of vaccinate against HZ?	**OR**	**95% CI**	**p**
Age	0.97	0.94-0.99	*0.005*
Educational level	0.97	0.70-1.34	0.844
Employment status	1.01	061-1.67	0.971
Knowing someone who had Zoster	1.46	1.00-2.14	*0.050*
Having had Zoster	0.76	0.53-1.10	0.158
Being in favor of vaccinations	6.05	2.89-12.66	*<0.0001*
Following GP's advice	44.66	15.41-129.41	*<0.0001*
I would vaccinate even upon payment	2.19	1.42-3.39	*<0.0001*
Are you in favor of vaccinate against HZ even upon payment?	**OR**	**95% CI**	**p**
Age	1.51	1.01-2.26	*0.04*
Being in favor of vaccinations	2.97	0.53-2.49	0.72
I would vaccinate against HZ	2.15	1.41-3.29	*<0.0001*
Following GP's advice	69.71	0.02-0.11	*<0.0001*

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants	Page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	n.a.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	n.a.
Bias	9	Describe any efforts to address potential sources of bias	n.a.
Study size	10	Explain how the study size was arrived at	n.a.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n.a.
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8
		(b) Indicate number of participants with missing data for each variable of interest	Page 8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n.a.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 8-9
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	n.a.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population: an Italian observational study.

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Title of the article: Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population: an Italian observational study.

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Key words: Acceptability, Herpes Zoster, Vaccine.

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Abstract

Objective

In view of the availability of a Herpes Zoster (HZ) vaccine, the aim of the study was to evaluate the awareness about the Varicella-Zoster-Virus (VZV) and the acceptability of the HZ vaccine in the general population aged 50 years old and over.

Design

The research was observational.

Setting

The study was carried out by administering a questionnaire at the outpatient clinics of General Practitioners (GPs) and of the Public Health Department of the Local Health Unit (LHU) of Ferrara.

Participants

The research involved 1,001 residents in the Province of Ferrara (57% were female).

Results

The 98% and 95% of respondents knew varicella and HZ, respectively. The 91% of interviewed people were not aware of HZ vaccine and the 58% were in favor of this vaccination . The variables that positively affect the acceptability of the vaccine were: the age ($p=0.005$); to know someone who suffered of HZ ($p=0.05$); being in support of the vaccinations ($p<0.0001$), and the GP's advice ($p<0.0001$); the willingness to get vaccinated even upon payment ($p<0.0001$). The 73% of the interviewed people were disposed to pay to get vaccinated, indicating an ideal cost of 50€. This choice was positively influenced by higher education ($p=0.04$), being in favor of vaccinations ($p<0.0001$) and the GP's advice ($p<0.0001$). Moreover the GP's advice modified the decision not to vaccinate in the 61% of the subjects initially unfavorable ($p<0.0001$).

Conclusions

The study contributed to assess the level of awareness and the attitudes of the over 50 years old population, pointing out the factors to be targeted to promote the vaccination against HZ, given that the available scientific evidence suggests that the best Public Health strategy would be represented by the offer of the HZ immunization to over 50 years old subjects at risk and to the elderly population (60-70 years).

Strengths and limitations of this study

- The major strength of the present study is that its findings can be used to determine the factors that influence people's intention regarding HZ vaccination and investigate the barriers for the vaccination in view of the upcoming availability of the vaccine throughout Italy.
- Limitations include that people are not always willing to tell a stranger what they really think in an interview. The answers can be influenced by recall biases because the respondents could have forgotten what happened during childhood or they got embarrassed.

Background

Worldwide, the infection with Varicella Zoster Virus (VZV) affects millions of individuals, representing a great source of suffering. The virus spreads worldwide and most people become infected by mid-adulthood. [1] The virus causes varicella, the primary infection that occurs mainly in children and confers immunity in the long term, both cell mediated and humoral, against new episodes of varicella. The virus can establish a latency state in the neurons of the spinal and cranial ganglia and along the whole neuraxis.[2]

In the 10-30% of people who had varicella, the virus can reactivate causing Herpes Zoster (HZ), an acute viral infection that affects the skin and the nervous system with an overall rate of incidence of 3-5 cases/1,000 persons per year.[3] Although the onset of the HZ is the result of a multifactorial process, an important role in the virus reactivation is attributed to the decline of T cell-mediated VZV-specific response, due to immunosenescence related to age or to immunosuppressive conditions, as a result of certain diseases (HIV, Hodgkin and non Hodgkin's disease, lymphomas, leukemias, bone marrow or other organs transplants, systemic erythematosus lupus), medications, psychological stress or malnutrition.[4-5]

The incidence rapidly increases with age. About 50% of people aged ≥80 years will develop at least one episode of acute HZ, mostly localized in the region of the concerned sensory ganglion, often preceded by acute pain or itching.[6] The rash is initially erythematous with multiple maculopapular injuries and later becomes vesicular; new lesions may continue to appear for a maximum of seven days, after forming a scab, which drops after 2-3 weeks.[7] The rash is often accompanied by a painful dermatomeric syndrome caused by the neuritis following the viral replication, described with burning, tingling, itching, a mild to severe pain, loss of sensation and weakness, if the roots of the motor nerves are implicated. In the 10-20% of HZ episodes the ophthalmic branch of the trigeminal nerve can be involved.[8]

Complications occur in 20% of cases; post-herpetic neuralgia (PHN), defined as "a chronic long lasting HZ-correlated pain that persists for at least three months after the eruption of HZ or the

onset of the pain", is the most frequent one. The PHN is a neuropathic syndrome characterized by pain along the cutaneous nerve endings, described with constant or intermittent pain, burning, allodynia and/or hyperalgesia, but also chronic fatigue, sleep disorders, depression, anorexia, weight loss and social isolation, compromising the functional status of the patient due to the difficulty in performing everyday activities.[9] Other complications, particularly in immune-compromised individuals, are disseminated Zoster, ophthalmic Zoster (HZO), encephalitis, inflammation of spinal cord, cranial and peripheral nerves paralysis including Bell's palsy and Ramsay Hunt syndrome.

According to the Shingles Prevention Study (SPS), the percentage of patients who develop PHN is 12.5% after three months and 5.1% after six months;[10] in addition to the significant impact on the quality of life, this condition implies an important economic burden related to the clinical and therapeutic management.

The annual HZ incidence is similar all around Europe and increases with age from about 1-4/1,000 adults under 50 years old to about 7-8/1,000 in people over 50 years old and up to 10/1,000 in over 80 years old.[11]

In Italy, HZ is included in 5th class of the notification system for infectious diseases, but compulsory notification is widely disregarded. It is, however, estimated that every year at least 157,000 new HZ cases occur, with an incidence of 6.3/1,000 /year with 9.4% and 7.2% of patients suffering for PHN at 1 month and 3 months, respectively.[12]

In the period 1999-2005, in Italy, 35,328 hospitalizations were recorded with an annual average of 4,503 of which 453 were day hospital admissions; the 62% of hospitalizations concerned subjects aged over 65 years old, with a mean length of stay of eight days and a total of more than 22,000 hospitalization days per year.[13]

In 2006, in order to prevent the epidemiological impact of the disease and to limit the costs of clinical and therapeutic management, the US Food and Drug Administration (FDA) approved a HZ vaccine, recommended by the Advisory Committee on Immunization Practices (ACIP) for the prevention of HZ in patients of 60 years old and over.[14-15] In the same year, the European

Medicines Agency (EMA) authorized the marketing of the vaccine in the European Union. In Europe the marketing authorization was granted in May 2006, at first, starting from 60 years old, and, in July 2007, it was extended from 50 years old.

The new vaccine contains the same live attenuated strain used for pediatric varicella immunization, but with an antigenic content at least 14 times higher,[16] able to stimulate the cell mediated immune (CMI) response against HZ, countering the virus reactivation and replication and thereby reducing the incidence and severity of the disease.

The efficacy, the safety and the tolerability of the vaccine against HZ and its sequelae were demonstrated in 28 pre- and post-marketing clinical trials with about 96,700 enrolled subjects, 57,700 vaccinated against HZ.[17-19]

The report EUnetHTA recognized both the impact of the disease and associated complications as well as the efficacy and the good safety profile of the vaccine, expressing a positive opinion regarding the value of immunization against HZ.[20]

A cost-efficacy Italian study showed that the vaccine is highly cost effective with a cost per Quality Adjusted Life Year (QALY) equal to € 11,943 for 60-79 year-old subjects (€ 9,779 for people aged 65-79 years and € 8,729 for those between 70 and 79 years).[21]

In Italy the vaccine is recommended in some regions in elderly (>65years of age) and in subjects at risk aged over 50 years, with exclusion of those seriously immunocompromised. People at risk include patients affected by co-morbidities (e.g. COPD, CVD, diabetes, etc.).The vaccine administration started being actively and free of charge offered during the 2015 in Sicily to at-risk individuals above 50 years of age and to the cohort from 65 to 75 years old,[22] in Liguria to people over 65 years old [23] and in Calabria to people aged 65 or 70 years old.[24] In Veneto and in Friuli Venezia Giulia the HZ vaccine is offered only to over 50 years old subjects at-risk and on medical prescription, or in co-payment for people not belonging to at risk groups.[25-26]. Since July 2016, in the Autonomous Province of Trento HZ vaccine will be provided free of charge to subjects >65 years of age and to at risk individuals.

Outside of these categories, the vaccine is administered upon payment of a fee as specified in the regional price list

The awareness of population about the burden of HZ on health and quality of life and regarding the relevance of immunization as a tool of prevention are issues rarely investigated up to now. A survey conducted on two Italian regions showed an elevated level of awareness of HZ and a favourable disposition towards the vaccination in young adults [27] The aim of the study is to evaluate, in the population of Ferrara aged 50 years old and over, the awareness towards the VZV and the degree of acceptability of a vaccine against HZ in view of the upcoming availability of the vaccine throughout Italy.

Materials and methods

The study was observational and recruited people aged 50 years old and over, living in the Province of Ferrara. The interviews were performed at the outpatient clinics of General Practitioners (GPs) and of the Public Health Department of the LHU of Ferrara.. Exclusion criteria were: age <50 years, not understanding the study procedures and the information contained in the leaflet, and failure to desire to participate to the study.

The questionnaire

The questionnaire (Supplementary file), specifically developed for this study, consisted of 27 questions; for some of them more than one answer could be provided. In the first section, socio-demographic data were collected: age, sex, educational level, employment status, nationality and municipality of residence. The second part investigated the level of awareness against varicella and HZ (symptoms, level and impact of pain), as well as the attitude toward vaccination for HZ (role of GPs and cost). The interview was terminated (after question number 12), if a partecipant did not know about HZ.

The questionnaire was validated by a panel of trained experts on the topic, that confirmed its validity and reliability.

Ethical aspects

The study was approved by the Ethical Committee of the Province of Ferrara. All information were confidentially processed and kept according to law (Legislative Decree number 196/2003 "Code concerning the protection of personal data").

Data collection and statistical analysis

The interviews were conducted during the period October 2014 –April 2015; the questionnaire was administered by trained personnel. The collected data were recorded in a database in Excel format. The statistical analysis was conducted by the chi square and the multivariate logistic analysis using the software StatView® 5.0.1 (Abacus Concepts, Berkeley, CA, USA). Univariate and multivariate logistic regression were performed with STATA SE ® (13.1 version). In particular, obstacles and limitations of acceptability of vaccination were evaluated with multivariate logistic regression linking, separately, the dependent variables "willing to be vaccinated against HZ" and "willing to be vaccinated against HZ even upon payment" with all the independent variables proved to be significant at the univariate logistic analysis, considering statistical significance for values of odds ratio greater than 1 and p lower or equal to 0.05. Statistical significance was set at 0.05.

Results

A total of 1,001 subjects were interviewed; 57% were female and the mean age was 67 years old. The main socio-demographic characteristics are reported in Table 1. A great part of enrolled subjects (69%) were retired; 29% and 2% of them were active workers and unemployed, respectively. The educational level was average-high: the 36% was high school licensed, the 23% attended the primary school, the 23% completed the secondary school and the 18% was graduated; only the 0.5% did not possess any educational qualification.

Table 1. Socio-demographic characteristics of interviewed subjects.

Involved subjects N=1.001		**N (%)**
Gender	*Female*	569 (56.8)
	Male	432 (43.2)
Age	*50-54 years old*	114 (11.4)
	55-59 years old	134 (13.4)
	60-64 years old	148 (14.8)
	65-69 years old	190 (19.0)
	70-74 years old	157 (15.7)
	75-79 years old	145 (14.5)
	≥80 years old	113 (11.3)
Employment status	*Retired*	693 (69.2)
	Worker	292 (29.2)
	Unemployed	16 (1.6)
Educational level	*Primary school*	231 (23.1)
	Secondary school	228 (22.8)
	High scool	361 (36.1)
	University	176 (17.6)
	No qualification	5 (0.5)

As expected, since it is a well-known rash illness, the 98% of respondents knew varicella and the 72% experienced it in the past. As predictable, according to the widespread popular beliefs on HZ, the disease was known by the 95% of interviewed subjects. For people (5%) that declared to not know HZ, the questionnaire was interrupted.[Table 2]

Table 2. Knowledge concerning varicella and Herpes Zoster.

	Varicella N=1.001			Zoster N=953		
	Yes (%)	**No (%)**	**Not remember (%)**	**Yes (%)**	**No (%)**	**Not remember (%)**
Do you know the disease?	982 (98)	19 (2)	---	953 (95)	48 (5)	----
Did you have the disease?	724 (72)	111 (11)	166 (17)	212 (22)	741 (78)	---
Are you vaccinated for Varicella?	49 (5)	813 (81)	139 (14)	---	---	---
Do you know someone who had Zoster?	---	---	---	761 (80)	192 (20)	---

Among those who knew HZ, the 22% had the disease, while the 80% knew at least one person who had the disease in the past.

Assessing the knowledge on HZ symptoms, the "rash" resulted the main symptom associated to the disease (794 respondents), probably because this is the most evident clinical outcome. Other symptoms were "pain" and "itching" stated by 789 and 680 respondents, respectively. About half of interviewed people (427 subjects) associated "malaise", 99 subjects indicated "ocular problems" and 86 people designated "headache". Finally, 32 subjects preferred not to answer, since they could not associate any symptoms with HZ.

The perception of the level of the chronic pain and the impact on daily life was assessed. The pain was considered "serious" by 46.6% of respondents and "moderate" by the 39.3%. Only the 7.2% of the interviewed subjects described pain as "mild", while the 6.9% were unable to answer. The impact of the disease was defined of "little importance" by the 20% of the respondents, "relevant"

by the 46%, instead of "very important" by the 25%; the 10% of subjects were not aware to define it.[Table 3]

Table 3. Awareness of HZ's impact on daily life activities (N=953).

HZ's impact	N (%)
Little importance	193 (20.2)
Relevant	434 (45.5)
Very important	234 (24.6)
Do not know	92 (9.7)

Taking into account the knowledge of the HZ vaccine, the 91% of interviewed people were not aware of it. People who knew the vaccine indicated as source of information principally the "press" or "radio, Internet, TV"; other sources were friend/contacts, family or GP.

The 58% of the respondents claimed to be in favor of the HZ vaccination; those against (42%) motivated their answer mostly for fear of possible side effects (15%), the 10% considered not to be at risk of developing the disease, the 6% were opposed to vaccinations.

Other reasons were: not believe in the efficacy of the vaccine (3%), not consider the disease enough long, dangerous and painful (3%), or the trouble to go to the doctor for vaccination (1%). On the contrary, the 62% of subjects favorable to vaccination justified as follows: the 31% believed in "the efficacy of the vaccine", the 26% knew someone who had the disease, the 19% thought that "vaccine can improve health", the 11% feared to be at risk of developing the disease, while the 1% gave other reasons.

The questionnaire also investigated the role of GPs. The 83% of respondents would be ready to be vaccinated if recommended by GPs. The 61% (248 subjects) of 405 individuals opposed to vaccination against HZ said that would change his mind if advised by the GP. It also emerged that the 73% of respondents would be willing to get vaccinated even if the vaccine would be

administered upon payment. When a fee was required, the majority of respondents (49%) would be willing to spend up to 50€, while the 11% would prefer a lower amount. Despite a 10% of interviewed people favorable to pay a higher sum, the 14% believed that vaccination should be free. According to the multivariate logistic regression analysis [Table 4], the decision to get vaccinated against HZ was influenced by age, with younger people more prone to the vaccination, while the educational degree and the employment were not significant.

Table 4. Determinants of being in favor of vaccination against HZ and being favorable to get vaccinated even upon payment.

Are you in favor of vaccinate against HZ?	**OR**	**95% CI**	**p**
Age	0.97	0.94-0.99	*0.005*
Educational level	0.97	0.70-1.34	0.844
Employment status	1.01	061-1.67	0.971
Knowing someone who had Zoster	1.46	1.00-2.14	*0.050*
Having had Zoster	0.76	0.53-1.10	0.158
Being in favor of vaccinations	6.05	2.89-12.66	*<0.0001*
Following GP's advice	44.66	15.41-129.41	*<0.0001*
I would vaccinate even upon payment	2.19	1.42-3.39	*<0.0001*
Are you in favor of vaccinate against HZ even upon payment?	**OR**	**95% CI**	**p**
Age	1.51	1.01-2.26	*0.04*
Being in favor of vaccinations	2.97	0.53-2.49	0.72
I would vaccinate against HZ	2.15	1.41-3.29	*<0.0001*
Following GP's advice	69.71	0.02-0.11	*<0.0001*

The knowledge of a family member, friend or contact who had HZ seemed to be able to influence the decision of vaccinate (p=0.05). The advice of GP, "be favorable to vaccination in general" and the willing to vaccinate even upon payment turned out to highly influence the decision to vaccinate against HZ. The decision to get vaccinated against HZ upon payment was affected by a high educational degree (p=0.04), being favorable to vaccination and the GP's advice (p<0.0001).

Discussion

In Western countries, about the 20-30% of individuals experiences the VZV reactivation during the lifetime, with an incidence that increases dramatically with age. The impact on health and quality of life is relevant, as the HZ can lead to debilitating consequences, the drug treatments are often suboptimal and the public health costs are relevant. Therefore the development of a HZ vaccine was crucial, because it strengthens the immune system and avoids the onset of the disease and therefore all its possible sequelae. The vaccine was effective, safe and well tolerated. The Shinges Prevention Study showed an efficacy of the vaccine in the age group 60-69 years equal to 65.5% and 65.7% against incidence of HZ and PHN, respectively.[10]. The effectiveness studies, conducted in several countries, were consistent with results obtained in randomized and controlled clinical trials, confirming a good profile of safety and tolerability, as well as of efficacy for prevention of HZ and PHN in subjects >60 years of age.[28-29]

The vaccine can be administered to VZV-naïve or with a previous HZ medical history subjects, to patients with immune-mediated diseases [30] or with mild immunosuppression. In case of a concomitant immunosuppressive therapy, vaccine should be administered at least 14 days before or 1 month after the cessation of it,[31] referring to the contraindications reported in the datasheet and evaluating possible immunodeficiency prior the administration.[32]

In the United States, the immunization is recommended by 2006. Despite the benefits of vaccination, however, the acceptability during the first years was very low: only the 1.9% in 2007, the 6.7% in 2008 and the 10% in 2011 were vaccinated. Target people could be not aware of immunization advantages, as well as the cost effectiveness, in the absence or reduced health care, or the lack of recommendation by GP.[33]

Several European countries decided to recommend and/or fund the HZ vaccination. The English vaccine program, started in September 2013 on two cohorts (70 and 79 years old), is proving to be very interesting: after only one year, it recorded a mean national coverage equal to 61.8% and 59.6% in the 70 and 79 years old cohorts, respectively, showing a positive compliance to vaccination by the population.[34]

The aim of the present study was to evaluate the awareness of VZV and the acceptability of a HZ vaccine in the over 50 years old population of Ferrara. As expected the majority of interviewed people knew varicella and HZ but the 91% of them was not aware of the vaccine against HZ. The collected questionnaires figured out two variables that influence the acceptability of vaccination: the age (younger people were more prone to immunization) and to be in general favorable to vaccinations. An explanation could be the self-confidence of people already favorable to vaccinations, who were not worried about possible side effects and did not have financial problems when the goal was health protection. Furthermore, the key role of the GP in promoting vaccination emerged: the trust in GP was a positive factor towards the willingness to be vaccinated. The knowledge of a family member, friend or contact who had HZ, although the borderline statistical significance seemed to influence the willing of vaccinate, probably due to a deeper awareness of the disease and its consequences.

Considering the willingness to be vaccinated upon payment, the educational degree was a positive factor, as well as being in favor of vaccinations and GP advice. Probably trained people, with sound cultural background, tended to be more informed about the relevance of vaccination and, consequently, more prone to pay for it.

The received answers may have been partly influenced by recall bias, considering the age of the respondents; however, the administration of the questionnaire by trained medical personnel could have reduced this kind of inaccuracy.

It was also created a comfortable atmosphere with the respondents in order to minimize the possibility of answers influenced by embarrassment. In conclusion, the study contributed to better understand the awareness and the attitudes of general population towards a new vaccination, also highlighting the major barriers against this upcoming preventive tool. It would provide an additional support to available scientific data that, currently, recommend the new HZ vaccine in at risk (with the exception of severely immunocompromised individuals) over 50 years old subjects and in at least one cohort of the elderly population (60 or 65years old).

Author's Contribution

AS and GG contributed to the overall design of the study, analysed the data and drafted the manuscript. NV, SL, NS, MC, LP contributed to the study design, supervised the acquisition of data, contributed to data analysis and reviewed the manuscript. The working group participated in the fieldwork. All authors critically read and revised the drafts of the manuscripts. All authors read and approved the final manuscript.

Competing interests

There are no potential competing interests of the authors. GG received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Pfizer and Sequirus for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.

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Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population.

Date __-__-____

Thanks for agreeing to participate in the study. The information contained in this form will be kept confidential under the legislation (Legislative Decree no. 196/2003 "Code regarding the protection of personal data").

1. **Gender** □ M □ F **2. Age** _____
3. **Nationality** _____
4. **City of residence** _____
5. **Educational level**

☐ No qualification ☐ Primary school
☐ Secondary school ☐ High school
☐ University

6. Employment status

☐ Retired ☐ Worker

7. Do you know the disease called Varicella?

☐ No ☐ Yes

8. Have you had Varicella in the past?

☐ No ☐ Yes ☐ I do not remember

9. If yes, how old were you? _____

10. Have you been vaccinated against Varicella?

☐ No ☐ Yes ☐ I do not remember

11. If yes, how old were you ? ☐☐ ☐ I do not remember

---

12. Do you know the disease called shingles (Herpes Zoster)?

☐ No ☐ Yes

(if you answer "no" to question number 12 the interview ends here)

13. Do you know someone who had shingles (Herpes Zoster)?

☐ No ☐Yes

14. Do you had shingles in the past (Herpes Zoster)?

☐ No ☐ Yes

15. If yes, how old were you? ☐☐ ☐ I do not remember

16. In your opinion what are the consequences of shingles (Herpes Zoster)?
(multiple choice question: you can give more than one answer)

☐ Pain ☐Rash
☐ Headache ☐Itching
☐ Eye problems ☐Malaise
☐ I do not know

17. In your opinion, the pain associated to shingles (Herpes Zoster) is:

☐ Mild, with duration of few days
☐ Moderate, with duration of few weeks
☐ Serious, with a term of months or years
☐ I do not know

18. In your opinion, the chronic pain associated to shingles can have an impact on the normal activities of daily life activities:

☐ Little relevance
☐ Relevant
☐ Very relevant
☐ I do not know

19. Are you aware about the vaccine against shingles?

☐ No ☐ Yes

20. If you have answered yes to the previous question, how it came to knowledge?
(multiple choice question: you can give more than one answer)

☐ General Practitioner ☐ Internet
☐ Family ☐ TV
☐ Friends/ contacts ☐ Books/brochures/magazines
☐ Radio ☐ Other (specify) _____

21. Do you think that vaccines are an effective tool for prevention?

☐ No ☐ Yes

22. Would you vaccinate against shingles?

☐ No ☐ Yes

23. If you would not vaccinate against shingles, why? *(multiple choice question: you can give more than one answer)*

☐ I do not think of being at high risk of having the disease
☐ I have trouble to go to the doctor for vaccination
☐ In general, I am opposed to vaccinations
☐ I think that vaccination is not completely effective
☐ I fear the possible side effects of vaccination (eg, immune system disorders)
☐ I do not think that the disease is particularly harmful, long or painful
☐ Other (specify)_____

24. If your GP would recommend the vaccine against shingles, would you vaccinate?

☐ No ☐ Yes

25. If yes, why? *(multiple choice question: you can give more than one answer)*

☐ I think the vaccine is effective
☐ I think I can have the diseases
☐ I knew someone who had the shingles and I do not want that it happen to me
☐ I think the vaccine can improve my health
☐ Other (specify)……

26. Are you in favor of being immunized against HZ even upon payment?

☐ No ☐ Yes

27. How much would you pay for the vaccine against shingles?

☐ Up to 50 euro
☐ Up to 100 euro
☐ Up to 150 euro
☐ Other (specify)……

Thanks for your collaboration

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants	Page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7
Bias	9	Describe any efforts to address potential sources of bias	Page 13
Study size	10	Explain how the study size was arrived at	Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n.a.
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8
		(b) Indicate number of participants with missing data for each variable of interest	Page 8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n.a.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 9-10
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population: an Italian observational study.

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Title of the article: Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population: an Italian observational study.

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Key words: Acceptability, Herpes Zoster, Vaccine.

Word count: 3.007

Abstract

Objective

The aim of the study was to evaluate the awareness about the Varicella-Zoster-Virus (VZV) and the acceptability of the newly available Herpes Zoster (HZ) vaccine in the general population aged 50 years old and over.

Design

The research was observational.

Setting

The study was carried out in Ferrara by administering a questionnaire at the outpatient clinics of the General Practitioners (GPs) and of the Public Health Department of the Local Health Unit (LHU).

Participants

The research involved 1,001 residents in the Province of Ferrara.

Results

The 98% and 95% of respondents (57% female) knew varicella and HZ, respectively. The 91% of interviewed people were not aware of HZ vaccine; anyway 58% of them declared to be in favor of this vaccination. The acceptability of the vaccine was positively affected by: age ($p=0.005$); knowing someone who suffered of HZ ($p=0.05$); being in support of the vaccinations ($p<0.0001$), and receiving the GP's advice ($p<0.0001$); the willingness to get vaccinated even upon payment ($p<0.0001$). Most (73%) of the interviewed people were willing to pay to get vaccinated, indicating an ideal cost of 50€. Higher education ($p=0.04$), being in favor of vaccinations ($p<0.0001$) and GP's advice ($p<0.0001$) positively affected this choice. The 61% of the subjects initially unfavorable ($p<0.0001$) to this immunization modified their decision not to vaccinate thanks to their GP's advice.

Conclusions

This study assessed the level of awareness and the attitudes of the over 50 years old population, pointing out the aspects to be focused to promote the HZ vaccine.

Strengths and limitations of this study

- The major strength of the present study is that its findings can be useful to define the main issues that can influence people's willingness to HZ vaccination and the potential obstacles in view of the upcoming availability of the vaccine throughout Italy.
- Limitations include that the study was conducted by administering a questionnaire and, in some cases, people are not prone to declare what they really think. The answers can be influenced by recall biases because the respondents could have forgotten what happened during childhood or they got embarrassed.

Background

Varicella Zoster Virus (VZV) infection affects millions of individuals worldwide, representing a great source of suffering. The virus easily spreads and most people become infected by mid-adulthood. [1] Varicella represents the primary infection, occurs mainly in children and confers cell mediated and humoral immunity in the long term. The VZV can establish a latency state in the neurons of the spinal and cranial ganglia and along the whole neuraxis. [2]

The reactivation of the virus, which occurs in about the 10-30% of people who had varicella, causes Herpes Zoster (HZ), an acute viral infection that affects the skin and the nervous system with an overall incidence of 3-5 cases/1,000 persons per year.[3] The onset of HZ is a complex process; anyway, an important role in the virus reactivation is attributed to the decline of VZV-specific T cell-mediated response. This latter is strictly related to immunosenescence or to immunosuppressive conditions, outcome of certain diseases (HIV, Hodgkin and non Hodgkin's disease, lymphomas, leukemia, bone marrow or other organs transplants, systemic erythematosus lupus), therapies, psychological stress or malnutrition. [4-5]

HZ incidence rapidly increases with age. About 50% of people aged ≥80 years will develop at least one episode of acute HZ, often preceded by acute pain or itching.[6] The rash, initially erythematous with multiple maculopapular lesions, later becomes vesicular. New lesions may continue to appear for a maximum of seven days, then form a scab, which drops 2-3 weeks after. [7] The rash is often accompanied by a painful dermatomeric syndrome, sustained by the neuritis following the viral replication. Pain is described as burning, tingling, itching, from mild to severe and can be combined with skin sense and weakness, when the roots of the motor nerves are implicated. The ophthalmic branch of the trigeminal nerve can be involved in 10-20% of HZ episodes. [8]

Complications occur in 20% of patients. Post-herpetic neuralgia (PHN), defined as "a chronic long lasting HZ-related pain persisting for at least three months after the eruption of HZ or the onset of the pain", is the most common one. PHN is a neuropathic syndrome characterized by pain along the

cutaneous nerve endings. It is described as constant or intermittent pain, burning, allodynia and/or hyperalgesia, but also chronic fatigue, sleep disorders, depression, anorexia, weight loss and social isolation and it has a negative impact on quality of life and activities of daily living. [9] Other complications, particularly in immune-compromised individuals, are disseminated Zoster, HZ ophthalmicus (HZO), encephalitis, inflammation of spinal cord, cranial and peripheral nerves paralysis, including Bell's palsy and Ramsay Hunt syndrome.

According to the Shingles Prevention Study (SPS), the percentage of patients who develop PHN is 12.5% after three months and 5.1% after six months.[10] In addition to the significant impact on the quality of life, this condition implies a relevant economic burden related to its clinical and therapeutic management.

The annual HZ incidence is similar all around Europe and increases with age from about 1-4/1,000 adults under 50 years old to about 7-8/1,000 in people over 50 years old and up to 10/1,000 in over 80 years old. [11]

In Italy, HZ compulsory notification is widely disregarded. However, it is estimated that every year at least 157,000 new HZ cases occur, with an incidence of 6.3/1,000 /year, and that 9.4% and 7.2% of patients suffer for PHN at 1 month and 3 months, respectively. [12]

In the period 1999-2005, 35,328 hospital admissions were recorded in Italy, with an annual average of 4,503 hospitalizations and 543 day-hospital admissions; more than 22,000 hospitalization days per year were registered. Many hospitalizations (62%) involved subjects >65 years of age. The average length of stay was equal to eight days. [13]

In 2006, in order to prevent the epidemiological impact of the disease and to limit the costs of its clinical and therapeutic management, the US Food and Drug Administration (FDA) approved a HZ vaccine, recommended by the Advisory Committee on Immunization Practices (ACIP) for the prevention of HZ in patients of 60 years old and over. [14-15] In the same year, the European Medicines Agency (EMA) authorized the marketing of the vaccine in the European Union. In Europe the authorization was granted in May 2006, at first, starting from 60 years of age, and

subsequently, in July 2007, the vaccine was indicated for immunization of individuals 50 years of age or older.

The new vaccine contains the same live attenuated strain used for pediatric varicella immunization; with an antigenic content at least 14 times higher. [16] It boosts VZV-specific cell mediated immune (CMI) response, controlling the virus reactivation and replication and, thereby, reducing the incidence and severity of the disease.

The efficacy, safety and tolerability of the vaccine against HZ and its sequelae were evaluated and demonstrated in 28 pre- and post-marketing clinical studies with about 57,700 subjects immunized with zoster vaccine. [17-19]

The EUnetHTA report recognized both the impact of the disease and of its associated complications as well as the efficacy and the good safety profile of the vaccine, giving a positive opinion regarding the value of immunization against HZ. [20]

A Italian study showed that the vaccine is highly cost effective, with a cost per Quality Adjusted Life Year (QALY) equal to € 11,943 for 60-79 year-old subjects (€ 9,779 and € 8,729 for people aged 65-79 years and 70 and 79 years, respectively). [21]

In Italy the vaccine is recommended in some regions in elderly (>65years of age) and in subjects at risk aged over 50 years, with exclusion of those seriously immunocompromised. People at risk include patients affected by co-morbidities (e.g. COPD, CVD, diabetes, etc.). In 2015, the actively and free of charge offer of zoster vaccine started in Sicily to at-risk individuals >50 years of age and to the cohort of 65 to 75 years old subjects, [22] in Liguria to people >65 years of age [23] and in Calabria to 65 or 70 years old subjects. [24] In Veneto and in Friuli Venezia Giulia, the HZ vaccine is offered only to >50 years old subjects at-risk and on medical prescription, or in co-payment for people not belonging to at risk groups. [25-26]. Since July 2016, in the Autonomous Province of Trento the HZ vaccine will be provided free of charge to subjects >65 years of age and to at risk individuals. Outside of these categories, the vaccine is administered upon payment of a fee as specified in the regional price list.

The awareness of population about the burden of HZ on health and quality of life and the relevance of immunization as a tool of prevention are issues rarely investigated up to now. A survey conducted on two Italian regions showed an elevated level of awareness of HZ and a favorable disposition towards vaccination in young adults. [27] The aim of the study is to evaluate in the 50 years of age or older population of Ferrara, the awareness about VZV and HZ and the degree of acceptability of a zoster vaccine in view of the upcoming availability of this immunization throughout Italy.

Materials and methods

This observational study enrolled 50 years of age or older subjects living in the Province of Ferrara. The interviews were performed at the outpatient clinics of General Practitioners (GPs) and of the Public Health Department (LHU of Ferrara). Exclusion criteria were: age <50 years, not understanding the study procedures and the information contained in the leaflet, and failure to desire to participate to the study.

The questionnaire

The questionnaire (Supplementary file), specifically developed for this study, consisted of 27 questions; for some of them, more than one answer could be provided. In the first section, socio-demographic data were collected: age, sex, educational level, employment status, nationality and municipality of residence. The second part investigated the level of awareness against varicella and HZ (symptoms, level and impact of pain), as well as the attitude toward zoster vaccination (role of GPs and cost). The interview was terminated (after question number 12), if a participant did not know HZ. The questionnaire was validated by a panel of trained experts on the topic, that confirmed its validity and reliability.

Ethical aspects

The study was approved by the Ethical Committee of the Province of Ferrara. All information were confidentially processed and kept according to law (Legislative Decree number 196/2003 "Code concerning the protection of personal data").

Data collection and statistical analysis

The interviews were conducted during the period October 2014 –April 2015; the questionnaire was administered by trained personnel. Collected data were recorded in a database in Excel format. The statistical analysis was conducted by the chi square and the multivariate logistic analysis using the software StatView® 5.0.1 (Abacus Concepts, Berkeley, CA, USA). Univariate and multivariate logistic regression were performed with STATA SE ® (13.1 version). In particular, obstacles and limitations of acceptability of vaccination were evaluated with multivariate logistic regression linking, separately, the dependent variables "willing to be vaccinated against HZ" and "willing to be vaccinated against HZ even upon payment" with all the independent variables proved to be significant at the univariate logistic analysis, considering statistical significance for values of odds ratio greater than 1 and p lower or equal to 0.05. Statistical significance was set at 0.05.

Results

A total of 1,001 subjects (57% female) were interviewed; the mean age was 67 years. The main socio-demographic characteristics are reported in Table 1. A great part of enrolled subjects (69%) were retired; 29% and 2% of them were active workers and unemployed, respectively. The educational level was average-high (36%, 23%, 23% of subjects attended high school, primary and secondary school, respectively; 18% of subjects was graduated); only 0.5% of interviewed subjects did not possess any educational qualification.

Table 1. Socio-demographic characteristics of interviewed subjects.

Enrolled subjects N=1.001		**N (%)**
Gender	*Female*	569 (56.8)
	Male	432 (43.2)
Age	*50-54 years old*	114 (11.4)
	55-59 years old	134 (13.4)
	60-64 years old	148 (14.8)
	65-69 years old	190 (19.0)
	70-74 years old	157 (15.7)
	75-79 years old	145 (14.5)
	≥80 years old	113 (11.3)
Employment status	*Retired*	693 (69.2)
	Worker	292 (29.2)
	Unemployed	16 (1.6)
Educational level	*Primary school*	231 (23.1)
	Secondary school	228 (22.8)
	High school	361 (36.1)
	University	176 (17.6)
	No qualification	5 (0.5)

As expected, since it is a well-known rash illness, the 98% of respondents knew varicella and the 72% experienced it in the past. As predictable, according to the widespread popular beliefs on HZ, the disease was known by the 95% of interviewed subjects. The questionnaire was interrupted when a subject declared (5% of interviewed people) to not know HZ. [Table 2]

Table 2. Knowledge concerning varicella and Herpes Zoster.

	Varicella N=1.001			Herpes Zoster N=953		
	Yes (%)	**No (%)**	**Not remember (%)**	**Yes (%)**	**No (%)**	**Not remember (%)**
Do you know the disease?	982 (98)	19 (2)	---	953 (95)	48 (5)	----
Did you have the disease?	724 (72)	111 (11)	166 (17)	212 (22)	741 (78)	---
Are you vaccinated for Varicella?	49 (5)	813 (81)	139 (14)	---	---	---
Do you know someone who had Zoster?	---	---	---	761 (80)	192 (20)	---

Among those who knew HZ, 22% had the disease, while 80% knew at least one person who had the disease in the past.

Assessing the knowledge on HZ symptoms, the “rash” resulted the main known symptom associated with the disease (794 respondents), probably because this is the most evident clinical outcome. Other well-known symptoms were “pain” and “itching” (indicated by 789 and 680 respondents, respectively). "Malaise", “ocular problems” and “headache” were related to HZ as well (427, 99 and 86 subjects, respectively). Finally, 32 subjects could not associate any symptom with HZ.

The opinion on the level of the chronic pain and on the impact on daily life was assessed. The pain was considered “serious” and "moderate" by 46.6% and 39.3% of respondents, respectively. Only 7.2% of interviewed subjects described pain as “mild”, while 6.9% of them were unable to answer. The impact of the disease was defined of “little value”, "relevant" and “very important" by 20%, 46% and 25% of the respondents, respectively; 10% of subjects were not able to define it.

The 91% of interviewed people were not aware of the availability of the zoster vaccine. People who knew the vaccine indicated as source of information principally the media (press or radio, Internet, TV) and other sources such as friends, relatives or GPs.

The 58% of the respondents claimed to be in favor of HZ vaccination. Many of these subjects believed in "the efficacy of the vaccine" (35%), knew someone who had the disease (29%), thought that "vaccine can improve health" (22%), feared to be at risk of developing the disease (12%) or other reasons (2%). The 38% of interviewed people were against this immunization. The reasons provided were the fear of possible side effects (15%), the belief not to be at risk of developing the disease (10%) and the opposition to any immunization (6%); other subjects distrust the efficacy of the vaccine (3%), did not consider the disease enough long, dangerous and painful (3%), or just wanted to avoid the trouble to go to the doctor (1%).

The questionnaire also investigated the role of GPs. The 83% of respondents would be ready to be vaccinated provided that immunization was recommended by GPs. The 61% (248 subjects) of 405 individuals unfavorable to zoster vaccination said that they would change opinion if advised by their own GP. Noteworthy, 73% of respondents would be willing to get vaccinated even if the vaccine would be administered upon payment. In this case, the majority of respondents (49%) would be willing to spend up to 50€. Besides, 11%, 10% and 14% of respondents would prefer a lower amount, were favorable to pay a higher sum or believed that vaccination should be free, respectively.

Data were analyzed by the method of multivariate logistic regression to find an equation that best predicts the probability and understanding functional relationships of the decision to get vaccinated against HZ as a function of one or more variables (age, educational level, etc.). [Table 3]

The decision to get vaccinated against HZ was influenced by age (p=0.005), with younger people more prone to vaccination, while educational degree and employment had not a significant impact on being immunized. The knowledge of a family member, friend or contact who previously had HZ seemed to influence the decision of being vaccinated (p=0.05). The advice of GP, to "be favorable

to vaccination in general" and the willing to be immunized even upon payment turned out to highly influence the decision in favor of HZ immunization.

Table 3. Determinants of being in favor of vaccination against HZ and to get vaccinated even upon payment.

Are you in favor of vaccinate against HZ?	**OR**	**95% CI**	**p**
Age	0.97	0.94-0.99	*0.005*
Educational level	0.97	0.70-1.34	0.844
Employment status	1.01	061-1.67	0.971
Knowing someone who had Zoster	1.46	1.00-2.14	*0.050*
Having had Zoster	0.76	0.53-1.10	0.158
Being in favor of vaccinations	6.05	2.89-12.66	*<0.0001*
Following GP's advice	44.66	15.41-129.41	*<0.0001*
I would vaccinate even upon payment	2.19	1.42-3.39	*<0.0001*
Are you in favor of vaccinate against HZ even upon payment?	**OR**	**95% CI**	**p**
Educational level	1.51	1.01-2.26	*0.04*
Being in favor of vaccinations	2.97	0.53-2.49	0.72
I would vaccinate against HZ	2.15	1.41-3.29	*<0.0001*
Following GP's advice	69.71	0.02-0.11	*<0.0001*

A second multivariate logistic regression was developed by changing the dependent variable "are you in favor of vaccinate against HZ even upon payment?" and keeping the same independent variables. The decision to get vaccinated against HZ upon payment was affected by a high educational degree (p=0.04), being favorable to HZ vaccination and the GP's advice (p<0.0001).

Discussion

In Western countries, about 20-30% of individuals experiences VZV reactivation during the lifetime, with an incidence that dramatically increases with age. The impact on health and quality of life is relevant, as HZ can lead to debilitating consequences, therapeutic options are often suboptimal and public health costs are relevant. Therefore the development of a HZ vaccine was crucial, because it strengthens the immune system and avoids the onset of the disease and therefore of all its possible sequelae. The vaccine is effective, safe and well tolerated. The Shingles Prevention Study showed an efficacy of the vaccine in the age group 60-69 years equal to 65.5% and 65.7% against incidence of HZ and PHN, respectively. [10] The effectiveness studies, conducted in several countries, were consistent with results obtained in randomized and controlled clinical trials, confirming a good safety and tolerability profile, as well as a good efficacy/effectiveness against HZ and PHN in subjects >60 years of age. [28-29]

The vaccine can be administered to VZV-naïve or with a previous HZ medical history subjects, to patients with immune-mediated diseases [30] or with mild immunosuppression. In case of a concomitant immunosuppressive therapy, vaccine should be administered at least 14 days before or 1 month after the cessation of it, [31] referring to the contraindications reported in the datasheet and evaluating possible immunodeficiency prior the administration. [32]

In the United States, the immunization is recommended by 2006. However, despite the benefits of vaccination, the acceptability during the first years was very low: only 1.9%, 6.7% and 10% of the target population was vaccinated in 2006, 2007 and 2008, respectively. The main barriers to vaccination were lack of or low patient awareness and lack of or insufficient GP's advice. [33]

Several European countries decided to recommend and/or fund HZ vaccination. The English vaccine program, started in September 2013 on two cohorts (70 and 79 years old). After only one year, the mean national coverage was equal to 61.8% and 59.6% in the 70 and 79 years old cohorts, respectively, showing a positive compliance to vaccination by the population. [34]

The aim of the present study was to evaluate the awareness of VZV and the acceptability of HZ vaccine in the >50 years old population of Ferrara. As expected, the majority of interviewed people knew varicella and HZ but most of them (91%) was not aware of zoster vaccine. The collected questionnaires figured out two variables that influence vaccination acceptability: age (younger people were more prone to immunization) and to be in general favorable to vaccinations. An explanation could be the self-confidence of people already favorable to vaccinations, who are not worried about possible side effects and do not have financial problems when the goal is health protection. Furthermore, the role of the GP in promoting vaccination is crucial: the trust in GP was a positive factor towards the willingness to be vaccinated. The knowledge of a family member, friend or relative who had HZ, even if with a borderline statistical significance, seemed to influence the willing of being immunized. This could be related to a deeper awareness of the disease and its consequences.

Considering the willingness to be vaccinated upon payment, the educational degree was a positive factor, as well as being in favor of vaccination against HZ and receiving/trusting the GP's advice. Probably trained people, with sound cultural background, tended to be more informed about the relevance of vaccination and, consequently, more prone to pay for it.

The received answers may have been partly influenced by recall bias, considering the age of the respondents; however, the administration of the questionnaire by trained medical personnel could have reduced this kind of inaccuracy. A comfortable atmosphere with the respondents was also created in order to minimize the possibility of answers influenced by embarrassment.

In conclusion, the study contributed to better understand the awareness and the attitudes of general population towards a new vaccination, also highlighting the major barriers against this upcoming preventive tool. It would provide an additional support to available scientific data that, currently, recommend the new HZ vaccine in at risk (with the exception of severely immunocompromised individuals) >50 years old subjects and in at least one cohort of elderly population (60 or 65 years old).

Author's Contribution

AS and GG contributed to the overall design of the study, analysed the data and drafted the manuscript. NV, SL, NS, MC, LP contributed to the study design, supervised the acquisition of data, contributed to data analysis and reviewed the manuscript. The working group participated in the fieldwork. All authors critically read and revised the drafts of the manuscripts. All authors read and approved the final manuscript.

Competing interests

There are no potential competing interests of the authors. GG received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Pfizer and Sequirus for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.

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Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population.

Date __-__-____

Thanks for agreeing to participate in the study. The information contained in this form will be kept confidential under the legislation (Legislative Decree no. 196/2003 "Code regarding the protection of personal data").

1. **Gender** □ M □ F **2. Age** _____
3. **Nationality** _____
4. **City of residence** _____
5. **Educational level**

☐ No qualification ☐ Primary school
☐ Secondary school ☐ High school
☐ University

6. Employment status

☐ Retired ☐ Worker

7. Do you know the disease called Varicella?

☐ No ☐ Yes

8. Have you had Varicella in the past?

☐ No ☐ Yes ☐ I do not remember

9. If yes, how old were you? _____

10. Have you been vaccinated against Varicella?

☐ No ☐ Yes ☐ I do not remember

11. If yes, how old were you ? ☐☐ ☐ I do not remember

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12. Do you know the disease called shingles (Herpes Zoster)?

☐ No ☐ Yes

(if you answer "no" to question number 12 the interview ends here)

13. Do you know someone who had shingles (Herpes Zoster)?

☐ No ☐Yes

14. Do you had shingles in the past (Herpes Zoster)?

☐ No ☐ Yes

15. If yes, how old were you? ☐☐ ☐ I do not remember

16. In your opinion what are the consequences of shingles (Herpes Zoster)?
(multiple choice question: you can give more than one answer)

☐ Pain ☐Rash
☐ Headache ☐Itching
☐ Eye problems ☐Malaise
☐ I do not know

17. In your opinion, the pain associated to shingles (Herpes Zoster) is:

☐ Mild, with duration of few days
☐ Moderate, with duration of few weeks
☐ Serious, with a term of months or years
☐ I do not know

18. In your opinion, the chronic pain associated to shingles can have an impact on the normal activities of daily life activities:

☐ Little relevance
☐ Relevant
☐ Very relevant
☐ I do not know

19. Are you aware about the vaccine against shingles?

☐ No ☐ Yes

20. If you have answered yes to the previous question, how it came to knowledge?
(multiple choice question: you can give more than one answer)

☐ General Practitioner ☐ Internet
☐ Family ☐ TV
☐ Friends/ contacts ☐ Books/brochures/magazines
☐ Radio ☐ Other (specify) _____

21. Do you think that vaccines are an effective tool for prevention?

☐ No ☐ Yes

22. Would you vaccinate against shingles?

☐ No ☐ Yes

23. If you would not vaccinate against shingles, why? *(multiple choice question: you can give more than one answer)*

☐ I do not think of being at high risk of having the disease
☐ I have trouble to go to the doctor for vaccination
☐ In general, I am opposed to vaccinations
☐ I think that vaccination is not completely effective
☐ I fear the possible side effects of vaccination (eg, immune system disorders)
☐ I do not think that the disease is particularly harmful, long or painful
☐ Other (specify)_____

24. If your GP would recommend the vaccine against shingles, would you vaccinate?

☐ No ☐ Yes

25. If yes, why? *(multiple choice question: you can give more than one answer)*

☐ I think the vaccine is effective
☐ I think I can have the diseases
☐ I knew someone who had the shingles and I do not want that it happen to me
☐ I think the vaccine can improve my health
☐ Other (specify)……

26. Are you in favor of being immunized against HZ even upon payment?

☐ No ☐ Yes

27. How much would you pay for the vaccine against shingles?

☐ Up to 50 euro
☐ Up to 100 euro
☐ Up to 150 euro
☐ Other (specify)……

Thanks for your collaboration

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	Page 14
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n.a.
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8-9
		(b) Indicate number of participants with missing data for each variable of interest	Page 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n.a.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 10-12
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population: an Italian observational study.

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Title of the article: Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population: an Italian observational study.

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Abstract

Objective

The aim of the study was to evaluate the awareness about the Varicella-Zoster-Virus (VZV) and the acceptability of the newly available Herpes Zoster (HZ) vaccine in the general population aged 50 years old and over.

Design

The research was observational.

Setting

The study was carried out in Ferrara by administering a questionnaire at the outpatient clinics of the General Practitioners (GPs) and of the Public Health Department of the Local Health Unit (LHU).

Participants

The research involved 1,001 residents in the Province of Ferrara.

Results

The 98% and 95% of respondents (57% female) knew varicella and HZ, respectively. The 91% of interviewed people were not aware of HZ vaccine; anyway 58% of them declared to be in favor of this vaccination. The acceptability of the vaccine was positively affected by: age ($p=0.005$); knowing someone who suffered of HZ ($p=0.05$); being in support of the vaccinations ($p<0.0001$), and receiving the GP's advice ($p<0.0001$); the willingness to get vaccinated even upon payment ($p<0.0001$). Most (73%) of the interviewed people were willing to pay to get vaccinated, indicating an ideal cost of 50€. Higher education ($p=0.04$), being in favor of vaccinations ($p<0.0001$) and GP's advice ($p<0.0001$) positively affected this choice. The 61% of the subjects initially unfavorable ($p<0.0001$) to this immunization modified their decision not to vaccinate thanks to their GP's advice.

Conclusions

This study assessed the level of awareness and the attitudes of the over 50 years old population, pointing out the aspects to be focused to promote the HZ vaccine.

Strengths and limitations of this study

- The major strength of the present study is that its findings can be useful to define the main issues that can influence people's willingness to HZ vaccination and the potential obstacles in view of the upcoming availability of the vaccine throughout Italy.
- Limitations include that the study was conducted by administering a questionnaire and, in some cases, people are not prone to declare what they really think. The answers can be influenced by recall biases because the respondents could have forgotten what happened during childhood or they got embarrassed.

Background

Varicella Zoster Virus (VZV) infection affects millions of individuals worldwide, representing a great source of suffering. The virus easily spreads and most people become infected by mid-adulthood. [1] Varicella represents the primary infection. It occurs mainly in children and confers cell mediated and humoral immunity in the long term. The VZV can establish a latency state in the neurons of the spinal and cranial ganglia and along the whole neuraxis. [2]

The reactivation of the virus, which occurs in about the 10-30% of people who had varicella, causes Herpes Zoster (HZ), an acute viral infection that affects the skin and the nervous system with an overall incidence of 3-5 cases/1,000 persons per year.[3] The onset of HZ is a complex process;however , an important role in the virus reactivation is ascribed to the decline of VZV-specific T cell-mediated response. This weakening is strictly related to immunosenescence or to immunosuppressive conditions, as result of some diseases (HIV, Hodgkin and non Hodgkin's disease, lymphomas, leukemia, bone marrow or other organs transplants, systemic erythematosus lupus), therapies, psychological stress or malnutrition. [4-5]

HZ incidence rapidly increases with age. About 50% of people aged ≥80 years will develop at least one episode of acute HZ, often preceded by acute pain or itching.[6] The rash, initially erythematous with multiple maculopapular lesions, later becomes vesicular. New lesions may continue to appear for a maximum of seven days; a scab forms subsequently and drops within 2-3 weeks. [7] The rash is often accompanied by a painful dermatomeric syndrome, sustained by the neuritis following the viral replication. Pain is described as burning, tingling, itching, from mild to severe and it can be combined with sensitivity loss and weakness, when the roots of the motor nerves are implicated. The ophthalmic branch of the trigeminal nerve can be involved in 10-20% of HZ episodes. [8]

Complications occur in 20% of patients. Post-herpetic neuralgia (PHN), defined as "a chronic long lasting HZ-related pain persisting for at least three months after the eruption of HZ or the onset of the pain", is the most common one. PHN is a neuropathic syndrome characterized by pain along the

cutaneous nerve endings. It is described as constant or intermittent pain, burning, allodynia and/or hyperalgesia, but also chronic fatigue, sleep disorders, depression, anorexia, weight loss and social isolation and it has a negative impact on the quality of life and the activities of daily living. [9] Other complications, particularly in immune-compromised individuals, are disseminated Zoster, HZ ophthalmicus (HZO), encephalitis, inflammation of spinal cord, cranial and peripheral nerves paralysis, including Bell's palsy and Ramsay Hunt syndrome.

According to the Shingles Prevention Study (SPS), the percentage of patients who develop PHN is 12.5% after three months and 5.1% after six months.[10] In addition to the significant impact on the quality of life, this condition implies a relevant economic burden related to its clinical and therapeutic management.

The annual HZ incidence is similar all around Europe and increases with age from about 1-4/1,000 adults under 50 years old to about 7-8/1,000 in people over 50 years old and up to 10/1,000 in over 80 years old. [11]

In Italy, HZ compulsory notification is widely disregarded. However, it is estimated that every year at least 157,000 new HZ cases occur, with an incidence of 6.3/1,000 /year, and that 9.4% and 7.2% of patients suffer for PHN at 1 month and 3 months, respectively. [12]

In the period 1999-2005, 35,328 hospital admissions were recorded in Italy, with an annual average of 4,503 hospitalizations and 543 day-hospital admissions; more than 22,000 hospitalization days per year were registered. Many hospitalizations (62%) involved subjects >65 years of age. The average length of stay was equal to eight days. [13]

In 2006, in order to prevent the epidemiological impact of the disease and to limit the costs of its clinical and therapeutic management, the US Food and Drug Administration (FDA) approved a HZ vaccine, recommended by the Advisory Committee on Immunization Practices (ACIP) for the prevention of HZ in patients of 60 years old and over. [14-15] In the same year, the European Medicines Agency (EMA) authorized the marketing of the vaccine in the European Union. In Europe the authorization was granted in May 2006, at first, starting from 60 years of age, and

subsequently, in July 2007, the vaccine was indicated for immunization of individuals 50 years of age or older.

The new vaccine contains the same live attenuated strain used for pediatric varicella immunization; with an antigenic content at least 14 times higher. [16] It boosts VZV-specific cell mediated immune (CMI) response, controlling the virus reactivation and replication and, thereby, reducing the incidence and severity of the disease.

The efficacy, safety and tolerability of the vaccine against HZ and its sequelae were evaluated and demonstrated in 28 pre- and post-marketing clinical studies with about 57,700 subjects immunized with zoster vaccine. [17-19]

The EUnetHTA report recognized both the impact of the disease and of its associated complications as well as the efficacy and the good safety profile of the vaccine, giving a positive advice regarding the value of immunization against HZ. [20]

An Italian study showed that the vaccine is highly cost effective, with a cost per Quality Adjusted Life Year (QALY) equal to € 11,943 for 60-79 year-old subjects (€ 9,779 and € 8,729 for people aged 65-79 years and 70 and 79 years, respectively). [21]

In Italy the vaccine is recommended in some regions in elderly (>65years of age) and in subjects at risk aged over 50 years, with exclusion of those seriously immunocompromised. People at risk include patients affected by co-morbidities (e.g. COPD, CVD, diabetes, etc.). In 2015, the actively and free of charge offer of zoster vaccine started in Sicily to at-risk individuals >50 years of age and to the cohort of 65 to 75 years old subjects, [22] in Liguria to people >65 years of age [23] and in Calabria to 65 or 70 years old subjects. [24] In Veneto and in Friuli Venezia Giulia, the HZ vaccine is offered only to >50 years old subjects at-risk and on medical prescription, or in co-payment for people not belonging to at risk groups. [25-26]. Since July 2016, in the Autonomous Province of Trento, the HZ vaccine is provided free of charge to subjects >65 years of age and to at risk individuals. Outside of these categories, the vaccine is administered upon payment of a fee as specified in the regional price list.

The awareness of population about the burden of HZ on health and quality of life and the relevance of immunization as a tool of prevention have been rarely investigated up to now. A survey conducted on two Italian regions showed an elevated level of awareness of HZ and a favorable disposition towards vaccination in young adults. [27] The aim of the study is to evaluate in the 50 years of age or older population of Ferrara, the awareness about VZV and HZ and the degree of acceptability of a zoster vaccine in view of the upcoming availability of this immunization throughout Italy.

Materials and methods

This observational study enrolled 50 years of age or older subjects living in the Province of Ferrara. The interviews were performed at the outpatient clinics of General Practitioners (GPs) and of the Public Health Department (LHU of Ferrara). Exclusion criteria were: age <50 years, not understanding the study procedures and the information contained in the leaflet, and failure to desire to participate to the study.

The questionnaire

The questionnaire (Supplementary file), specifically developed for this study, consisted of 27 questions; for some of them, more than one answer could be provided. In the first section, socio-demographic data were collected: age, sex, educational level, employment status, nationality and municipality of residence. The second part investigated the level of awareness against varicella and HZ (symptoms, level and impact of pain), as well as the attitude toward zoster vaccination (role of GPs and cost). The interview was terminated (after question number 12), if a participant did not know HZ. The questionnaire was validated by a panel of trained experts on the topic, that confirmed its validity and reliability.

Ethical aspects

The study was approved by the Ethical Committee of the Province of Ferrara. All information were confidentially processed and kept according to law (Legislative Decree number 196/2003 "Code concerning the protection of personal data").

Data collection and statistical analysis

The interviews were conducted during the period October 2014 –April 2015; the questionnaire was administered by trained personnel. Collected data were recorded in a database in Excel format. The statistical analysis was conducted by the chi square and the multivariate logistic analysis using the software StatView® 5.0.1 (Abacus Concepts, Berkeley, CA, USA). Univariate and multivariate logistic regression were performed with STATA SE ® (13.1 version). In particular, obstacles and limitations of acceptability of vaccination were evaluated with multivariate logistic regression linking all the independent variables proved to be significant at the univariate logistic analysis, considering statistical significance for values of odds ratio greater than 1 and p lower or equal to 0.05. Data were analyzed by the method of multivariate logistic regression to find an equation that best predicts the probability and understanding functional relationships of the decision to get vaccinated against HZ as a function of one or more variables (age, educational level, etc.). A second multivariate logistic regression was developed by changing the dependent variable "are you in favor of vaccinate against HZ even upon payment?" and keeping the same independent variables., Statistical significance was set at 0.05.

Results

A total of 1,001 subjects (57% female) were interviewed; the mean age was 67 years. The main socio-demographic characteristics are reported in Table 1. The majority of enrolled subjects (69%) were retired; 29% and 2% of them were active workers and unemployed, respectively. The educational level was medium-high (36%, 23%, 23% of subjects attended high school, primary and

secondary school, respectively; 18% of subjects was graduated); only 0.5% of interviewed subjects did not possess any educational qualification.

Table 1. Socio-demographic characteristics of interviewed subjects.

Enrolled subjects N=1.001		**N (%)**
Gender	*Female*	569 (56.8)
	Male	432 (43.2)
Age	*50-54 years old*	114 (11.4)
	55-59 years old	134 (13.4)
	60-64 years old	148 (14.8)
	65-69 years old	190 (19.0)
	70-74 years old	157 (15.7)
	75-79 years old	145 (14.5)
	≥80 years old	113 (11.3)
Employment status	*Retired*	693 (69.2)
	Worker	292 (29.2)
	Unemployed	16 (1.6)
Educational level	*Primary school*	231 (23.1)
	Secondary school	228 (22.8)
	High school	361 (36.1)
	University	176 (17.6)
	No qualification	5 (0.5)

As expected, since it is a well-known rash illness, the 98% of respondents knew varicella and the 72% experienced it in the past. As predictable, according to the widespread popular beliefs on HZ,

the disease was known by the 95% of interviewed subjects. The questionnaire was interrupted when a subject declared (5% of interviewed people) to not know HZ. [Table 2]

Table 2. Knowledge concerning varicella and Herpes Zoster.

	Varicella N=1.001			Herpes Zoster N=953		
	Yes (%)	**No (%)**	**Not remember (%)**	**Yes (%)**	**No (%)**	**Not remember (%)**
Do you know the disease?	982 (98)	19 (2)	---	953 (95)	48 (5)	----
Did you have the disease?	724 (72)	111 (11)	166 (17)	212 (22)	741 (78)	---
Are you vaccinated for Varicella?	49 (5)	813 (81)	139 (14)	---	---	---
Do you know someone who had Zoster?	---	---	---	761 (80)	192 (20)	---

Among those who knew HZ, 22% had the disease, while 80% knew at least one person who had the disease in the past.

Assessing the knowledge on HZ symptoms, considering it was a multiple choice question, the percentages were calculated on total of respondents. The “rash” resulted the main known symptom associated with the disease (83% of respondents), probably because this is the most evident clinical outcome. Other well-known symptoms were “pain” and “itching” (indicated by 83% and 71% of respondents, respectively). "Malaise", “ocular problems” and “headache” were related to HZ as well (45% , 10% and 9% of subjects, respectively). Finally, 3% of subjects could not relate any symptom to HZ.

The opinion on the level of the chronic pain and on the impact on daily life was assessed. The pain was considered “serious” and "moderate" by 46.6% and 39.3% of respondents, respectively. Only 7.2% of interviewed subjects described pain as “mild”, while 6.9% of them were unable to answer. The impact of the disease was defined of “little value”, "relevant" and “very important" by 20%, 46% and 25% of the respondents, respectively; 10% of subjects were not able to define it.

The 91% of interviewed people were not aware of the availability of the zoster vaccine. People who knew the vaccine indicated as source of information mainly the media (press or radio, Internet, TV) and other sources such as friends, relatives or GPs.

The 58% of the respondents claimed to be in favor of HZ vaccination. Many of these subjects believed in “the efficacy of the vaccine” (35%), knew someone who had the disease (29%), thought that “vaccine can improve health” (22%), feared to be at risk of developing the disease (12%) or other reasons (2%). The 38% of interviewed people were against this immunization. The reasons provided were the fear of possible side effects (15%), the belief not to be at risk of developing the disease (10%) and the opposition to any immunization (6%); other subjects distrust the efficacy of the vaccine (3%), did not consider the disease enough long, dangerous and painful (3%), or just wanted to avoid the trouble to go to the doctor (1%).

The questionnaire also investigated the role of GPs. The 83% of respondents would be ready to be vaccinated provided that immunization was recommended by GPs. The 61% (248 subjects) of 405 individuals unfavorable to zoster vaccination said that they would change opinion if advised by their own GP. Noteworthy, 73% of respondents would be willing to get vaccinated even if the vaccine would be administered upon payment. In this case, the majority of respondents (49%) would be willing to spend up to 50€. Besides, 11%, 10% and 14% of respondents would prefer a lower amount, were favorable to pay a higher sum or believed that vaccination should be free, respectively.

Considering the factors that could foster to get vaccinated against HZ [Table 3], we found age as a main driver (p=0.005), being younger people more prone to vaccination. On the other hand,

educational degree and employment did not have a significant impact on being immunized. The knowledge of a family member, friend or contact who previously had HZ seemed to influence the decision of being vaccinated (p=0.05). The advice of GP, to "be favorable to vaccination in general" and the willing to be immunized even upon payment turned out to highly influence the decision in favor of HZ immunization.

Table 3. Determinants of being in favor of vaccination against HZ and to get vaccinated even upon payment.

Are you in favor of vaccinate against HZ?	**OR**	**95% CI**	**p**
Age	0.97	0.94-0.99	*0.005*
Educational level	0.97	0.70-1.34	0.844
Employment status	1.01	061-1.67	0.971
Knowing someone who had Zoster	1.46	1.00-2.14	*0.050*
Having had Zoster	0.76	0.53-1.10	0.158
Being in favor of vaccinations	6.05	2.89-12.66	*<0.0001*
Following GP's advice	44.66	15.41-129.41	*<0.0001*
I would vaccinate even upon payment	2.19	1.42-3.39	*<0.0001*
Are you in favor of vaccinate against HZ even upon payment?	**OR**	**95% CI**	**p**
Educational level	1.51	1.01-2.26	*0.04*
Being in favor of vaccinations	2.97	0.53-2.49	0.72
I would vaccinate against HZ	2.15	1.41-3.29	*<0.0001*
Following GP's advice	69.71	0.02-0.11	*<0.0001*

The decision to get vaccinated against HZ upon payment was affected by a high educational degree ($p=0.04$), being favorable to HZ vaccination and the GP's advice ($p<0.0001$).

Discussion

In Western countries, about 20-30% of individuals experiences VZV reactivation during the lifetime, with an incidence that dramatically increases with age. The impact on health and quality of life is relevant, as HZ can lead to debilitating consequences, therapeutic options are often suboptimal and public health costs are important. The development of a HZ vaccine was crucial, because it strengthens the immune system and avoids the onset of the disease and, therefore, of all the possible sequelae. The vaccine is effective, safe and well tolerated. The Shingles Prevention Study showed an efficacy in the age group 60-69 years equal to 65.5% and 65.7% against incidence of HZ and PHN, respectively. [10] The effectiveness studies, conducted in several countries, were consistent with results obtained in randomized and controlled clinical trials, confirming a good safety and tolerability profile, as well as a good efficacy/effectiveness against HZ and PHN in subjects >60 years of age. [28-29]

The vaccine can be administered to VZV-naïve or with a previous HZ medical history subjects, to patients with immune-mediated diseases [30] or with mild immunosuppression. In case of a concomitant immunosuppressive therapy, vaccine should be administered at least 14 days before or 1 month after the cessation of it, [31] according to the contraindications reported in the datasheet and evaluating possible immunodeficiency prior the administration. [32]

In the United States, the immunization is recommended by 2006. However, despite the benefits of vaccination, the acceptability during the first years was very low: only 1.9%, 6.7% and 10% of the target population was vaccinated in 2006, 2007 and 2008, respectively. The main barriers to vaccination were lack of or low patient awareness and lack of or insufficient GP's advice. [33]

Several European countries decided to recommend and/or fund HZ vaccination. The English vaccine program, started in September 2013 on two cohorts (70 and 79 years old). After only one

year, the mean national coverage was equal to 61.8% and 59.6% in the 70 and 79 years old cohorts, respectively, showing a positive compliance to vaccination by the population. [34]

The aim of the present study was to evaluate the awareness of VZV and the acceptability of HZ vaccine in the >50 years old population of Ferrara. As expected, the majority of interviewed people knew varicella and HZ but most of them (91%) was not aware of zoster vaccine. The collected questionnaires figured out two variables that influence vaccination acceptability: age (younger people were more prone to immunization) and to be in general favorable to vaccinations. An explanation could be the self-confidence of people already favorable to vaccinations, who are not worried about possible side effects and do not have financial problems when the goal is health protection. Furthermore, the role of the GP in promoting vaccination is crucial: the trust in GP was a positive factor towards the willingness to be vaccinated. The knowledge of a family member, friend or relative who had HZ, even if with a borderline statistical significance, seemed to influence the willing of being immunized. This could be related to a deeper awareness of the disease and its consequences.

Considering the willingness to be vaccinated upon payment, the educational degree was a positive factor, as well as being in favor of vaccination against HZ and receiving/trusting the GP's advice. Probably highly educated people, with sound cultural background, tended to be more informed about the relevance of vaccination and, consequently, more prone to pay for it.

The received answers may have been partly influenced by recall bias, considering the age of the respondents; however, the administration of the questionnaire by trained medical personnel could have reduced this sort of inaccuracy. A comfortable atmosphere with the respondents was also created in order to minimize the possibility of answers influenced by embarrassment.

In conclusion, the study contributed to better understand the awareness and the attitudes of general population towards a new vaccination, also highlighting the major barriers against this upcoming preventive tool. It would provide an additional support to available scientific data that, currently, recommend the new HZ vaccine in at risk (with the exception of severely immunocompromised

individuals) >50 years old subjects and in at least one cohort of elderly population (60 or 65 years old). As the major barrier seems to be a financial issue, the approach chosen by the Italian regions that have already introduced active and free of charge offer of HZ vaccination in their immunization schedule seems the most appropriate strategy in order to achieve satisfactory vaccination coverage rates.

Author's Contribution

AS and GG contributed to the overall design of the study, analysed the data and drafted the manuscript. NV, SL, NS, MC, LP contributed to the study design, supervised the acquisition of data, contributed to data analysis and reviewed the manuscript. The working group participated in the fieldwork. All authors critically read and revised the drafts of the manuscripts. All authors read and approved the final manuscript.

Competing interests

There are no potential competing interests of the authors. GG received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Pfizer and Sequirus for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.

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Data sharing statement

No data sharing statement.

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Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population.

Date __-__-____

Thanks for agreeing to participate in the study. The information contained in this form will be kept confidential under the legislation (Legislative Decree no. 196/2003 "Code regarding the protection of personal data").

1. **Gender** □ M □ F **2. Age** _____
3. **Nationality** _____
4. **City of residence** _____
5. **Educational level**

☐ No qualification ☐ Primary school
☐ Secondary school ☐ High school
☐ University

6. Employment status

☐ Retired ☐ Worker

7. Do you know the disease called Varicella?

☐ No ☐ Yes

8. Have you had Varicella in the past?

☐ No ☐ Yes ☐ I do not remember

9. If yes, how old were you? _____

10. Have you been vaccinated against Varicella?

☐ No ☐ Yes ☐ I do not remember

11. If yes, how old were you ? ☐☐ ☐ I do not remember

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12. Do you know the disease called shingles (Herpes Zoster)?

☐ No ☐ Yes

(if you answer "no" to question number 12 the interview ends here)

13. Do you know someone who had shingles (Herpes Zoster)?

☐ No ☐Yes

14. Do you had shingles in the past (Herpes Zoster)?

☐ No ☐ Yes

15. If yes, how old were you? ☐☐ ☐ I do not remember

16. In your opinion what are the consequences of shingles (Herpes Zoster)?
(multiple choice question: you can give more than one answer)

☐ Pain ☐Rash
☐ Headache ☐Itching
☐ Eye problems ☐Malaise
☐ I do not know

17. In your opinion, the pain associated to shingles (Herpes Zoster) is:

☐ Mild, with duration of few days
☐ Moderate, with duration of few weeks
☐ Serious, with a term of months or years
☐ I do not know

18. In your opinion, the chronic pain associated to shingles can have an impact on the normal activities of daily life activities:

☐ Little relevance
☐ Relevant
☐ Very relevant
☐ I do not know

19. Are you aware about the vaccine against shingles?

☐ No ☐ Yes

20. If you have answered yes to the previous question, how it came to knowledge?
(multiple choice question: you can give more than one answer)

☐ General Practitioner ☐ Internet
☐ Family ☐ TV
☐ Friends/ contacts ☐ Books/brochures/magazines
☐ Radio ☐ Other (specify) _____

21. Do you think that vaccines are an effective tool for prevention?

☐ No ☐ Yes

22. Would you vaccinate against shingles?

☐ No ☐ Yes

23. If you would not vaccinate against shingles, why? *(multiple choice question: you can give more than one answer)*

☐ I do not think of being at high risk of having the disease
☐ I have trouble to go to the doctor for vaccination
☐ In general, I am opposed to vaccinations
☐ I think that vaccination is not completely effective
☐ I fear the possible side effects of vaccination (eg, immune system disorders)
☐ I do not think that the disease is particularly harmful, long or painful
☐ Other (specify)_____

24. If your GP would recommend the vaccine against shingles, would you vaccinate?

☐ No ☐ Yes

25. If yes, why? *(multiple choice question: you can give more than one answer)*

☐ I think the vaccine is effective
☐ I think I can have the diseases
☐ I knew someone who had the shingles and I do not want that it happen to me
☐ I think the vaccine can improve my health
☐ Other (specify)……

26. Are you in favor of being immunized against HZ even upon payment?

☐ No ☐ Yes

27. How much would you pay for the vaccine against shingles?

☐ Up to 50 euro
☐ Up to 100 euro
☐ Up to 150 euro
☐ Other (specify)……

Thanks for your collaboration

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	Page 14
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n.a.
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8-9
		(b) Indicate number of participants with missing data for each variable of interest	Page 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n.a.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 10-12
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluation of the acceptability of a vaccine against Herpes Zoster in the over-50-year-olds: an Italian observational study.

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Abstract

Objective

The aim of the study was to evaluate awareness of the Varicella-Zoster-Virus (VZV) and the acceptability of the newly available Herpes Zoster (HZ) vaccine in over-50-year-olds in the general population.

Design

The research was observational.

Setting

The study was carried out in Ferrara by administering a questionnaire to patients of the Local Health Authority (LHA) general practitioner (GPs) and Public Health Department outpatient clinics.

Participants

The questionnaire was completed by 1,001 residents of Ferrara Province.

Results

Of the respondents, 98% and 95% (57% female) were aware of varicella and HZ, respectively, but 91% were unaware of the HZ vaccine. Nevertheless, 58% declared they were in favour of vaccination in this regard, and the acceptability of the vaccine was positively affected by: age ($p=0.005$); knowing someone who had suffered HZ ($p=0.05$); being in favour of vaccination in general ($p<0.0001$); receiving advice to do so from their GP ($p<0.0001$); and willingness to get vaccinated even on a fee-paying basis ($p<0.0001$). Indeed, most (73%) respondents were willing to pay to get vaccinated, indicating an ideal cost of €50. Higher education ($p=0.04$), being in favour of vaccinations in general ($p<0.0001$), and GP advice ($p<0.0001$) positively affected this choice. Furthermore, 61% of the subjects initially unfavourable ($p<0.0001$) to this immunization would change their decision not to vaccinate thanks to their GP's advice.

Conclusions

This study assessed the level of awareness and the attitudes of the over-50-year-old population, highlighting aspects to be focused on in the promotion of the HZ vaccine.

Strengths and limitations of this study

- The major strength of the present study is that its findings indicate several factors that can influence people's willingness to undergo HZ vaccination, highlighting potential obstacles to acceptance as the vaccine becomes available throughout Italy.
- As the study was conducted by administering a questionnaire, it may be limited by people's failure to declare what they really think (e.g. due to embarrassment). Responses are also subject to recall bias, as respondents may have forgotten their childhood experiences.

Background

Varicella Zoster Virus (VZV) infection affects millions of individuals worldwide, and represents a great source of suffering. The virus spreads easily, and most people become infected by mid-adulthood. [1] The primary infection is varicella, which mainly occurs in children, conferring cell-mediated and humoral immunity in the long term. However, latent VZV in the neurons of the spinal and cranial ganglia, and along the entire neuraxis [2] can reactivate in about 10–30% of former varicella sufferers. This causes Herpes Zoster (HZ), or shingles, an acute viral infection that affects the skin and the nervous system, and has an overall incidence of 3–5 cases/1,000 persons per year. [3] The onset of HZ is a complex process, but an important role in virus reactivation has been ascribed to a decline in VZV-specific T cell-mediated response. This weakening is closely related to immunosenescence, or to immunosuppressive conditions brought on by some disease states (HIV, Hodgkin's and non-Hodgkin's disease, lymphomas, leukaemia, systemic lupus erythematosus) and treatments (bone marrow or other organ transplants), as well as psychological stress or malnutrition. [4-5]

The incidence of HZ increases rapidly with age, and about 50% of people aged ≥80 years will develop at least one episode of acute HZ, often preceded by acute pain or itching. [6] The rash, initially erythematous with multiple maculopapular lesions, later becomes vesicular. New lesions may continue to appear for a maximum of seven days; scabs form and drop within 2–3 weeks. [7] The rash is often accompanied by a painful dermatomeric syndrome, sustained by neuritis following viral replication. Pain is from mild to severe, and described as burning, tingling or itching. It may be accompanied by loss of sensitivity and weakness when the roots of the motor nerves are affected. Ten to twenty percent of HZ episodes involve the ophthalmic branch of the trigeminal nerve [8], and complications occur in 20% of patients, the most common being post-herpetic neuralgia (PHN). Defined as "a chronic long lasting HZ-related pain persisting for at least three months after the eruption of HZ or the onset of the pain", PHN is a neuropathic syndrome characterized by pain along the cutaneous nerve endings. It is experienced as constant or intermittent pain, burning,

allodynia and/or hyperalgesia, but also through chronic fatigue, sleep disorders, depression, anorexia, weight loss and social isolation, and therefore has a negative impact on daily living activities and quality of life. [9]

According to the Shingles Prevention Study (SPS), the percentage of patients who develop PHN is 12.5% after three months, and 5.1% after six months. [10] In addition to the significant impact on quality of life, there is a large financial burden related to the clinical and therapeutic management of PHN and other complications. Immunocompromised individuals are particularly susceptible to other complications of HZ, namely disseminated zoster, HZ ophthalmicus (HZO), encephalitis, inflammation of the spinal cord, and cranial and peripheral nerve paralysis, including Bell's palsy and Ramsay Hunt syndrome.

The annual incidence of HZ is similar across Europe, and increases with age from about 1–4 cases per 1,000 adults under 50 years old to about 7–8/1,000 in the over-50s, and up to 10/1,000 in the over-80s. [11] Although in Italy compulsory HZ notification is widely disregarded, it is estimated that every year at least 157,000 new HZ cases occur, with an incidence of 6.3/1,000/year, and that 9.4% and 7.2% of patients suffer PHN at 1 month and 3 months, respectively. [12] In the period 1999–2005, 35,328 hospital admissions were recorded for HZ in Italy, with an annual average of 4,503 hospitalizations and 543 day-hospital admissions; more than 22,000 hospitalization days per year were registered, with the average length of stay being eight days. The majority of hospitalizations (62%) involved subjects >65 years of age. [13]

In 2006, in order to limit the epidemiological impact of the disease and the costs of its clinical and therapeutic management, the US Food and Drug Administration (FDA) approved a HZ vaccine, which was recommended by the Advisory Committee on Immunization Practices (ACIP) for the prevention of HZ in patients aged 60 years and over. [14-15] In the same year, the European Medicines Agency (EMA) authorized the use of the vaccine in the European Union for over-60-year-olds. In July 2007, however, the vaccine was indicated for immunization of individuals aged 50 or older.

The new vaccine contains the same live attenuated strain used for paediatric varicella immunization, albeit with an antigen content at least 14 times greater. [16] It boosts the VZV-specific cell-mediated immune (CMI) response, curbing viral reactivation and replication and, thereby, reducing the incidence and severity of the disease.

The efficacy, safety and tolerability of the vaccine against HZ and its sequelae have been demonstrated in 28 pre- and post-marketing clinical studies on a total of roughly 57,700 immunized subjects. [17-19] The efficacy and the good safety profile of the vaccine have been recognised in EUnetHTA report, which recommends immunization against HZ in order to mitigate the impact of both the disease and its associated complications [20]. Moreover, an Italian study showed that the vaccine is highly cost effective, with a cost per quality-adjusted life year (QALY) of € 11,943 in 60–79-year-old subjects (€ 9,779 for people aged 65–79 years and € 8,729 for 70–79–year-olds). [21] However, in Italy the vaccine is only recommended in some regions, specifically for the elderly (>65 years of age) and in subjects at risk aged over 50 years, with the exclusion of severely immunocompromised patients. People considered at risk include those affected by co-morbidities (e.g. COPD, CVD, diabetes, etc.). The vaccine was first offered free of charge in 2015, where it was made available to 65-to-75-year-olds and at-risk individuals >50 years of age in Sicily [22], people >65 years of age in Liguria [23], and the over 65- or 70-year-olds in Calabria. [24] In Veneto and Friuli Venezia Giulia, the HZ vaccine is only prescribed for at-risk patients of >50 years of age, but people not considered at risk may opt to part-pay for the vaccination. [25-26]. Similarly, the HZ vaccine has been provided free of charge to subjects >65 years of age and at-risk individuals in the Autonomous Province of Trento since July 2016, whereas a specific charge is levied on those who fall outside these categories.

Although HZ vaccination programmes are being rolled out across Italy, little investigation into the population's awareness of the burden of HZ on health and quality of life and the relevance of immunization as a preventative tool has been conducted to date. One survey conducted on two Italian regions showed a high level of HZ awareness, and a favourable disposition towards

vaccination in young adults, [27] but in order to supplement available data we set out to evaluate awareness of VZV and HZ and the acceptability of an HZ vaccine in the over 50s residing in Ferrara Province.

Materials and methods

This observational study was conducted on patients of 50 years of age or older from Ferrara Province. The interviews were performed at General Practitioner (GP) and Public Health Department outpatient clinics across Ferrara LHA. Exclusion criteria were: age <50 years, inability to understand the study procedures and/or the information contained in the dedicated leaflet, and unwillingness to participate in the study.

The questionnaire

The questionnaire (Supplementary file), specifically developed for this study, consisted of 27 items, some of which allowed more than one answer. The first section was designed to collect socio-demographic data, specifically: age, gender, education level, employment status, nationality and municipality of residence. The second part of the questionnaire investigated the level of awareness of varicella and HZ (symptoms, level and impact of pain), as well as the attitude toward HZ vaccination (role of GPs and cost). The interview was terminated (after question number 12), if a participant had not heard of HZ. The questionnaire was validated by a panel of trained experts on the topic to confirm its validity and reliability.

Ethical aspects

The study was approved by the Ferrara Province Ethics Committee, and all information was treated confidentially and stored according to law (Legislative Decree number 196/2003 “Code concerning the protection of personal data”).

Data collection and statistical analysis

The questionnaire was administered by trained medical personnel during the period October 2014–April 2015. Collected data were recorded in Excel format in a dedicated database. Statistical

analysis, via chi-square and multivariate logistic analyses, was conducted using the software StatView® 5.0.1 (Abacus Concepts, Berkeley, CA, USA), and univariate and multivariate logistic regressions were performed using STATA SE ® (13.1 version). In particular, obstacles and limitations to the acceptability of vaccination were evaluated with multivariate logistic regression, linking all the independent variables that proved to be significant in the univariate logistic analysis, considering odds ratio values greater than 1 and p values lower than or equal to 0.05 as statistically significant. Data were analysed by multivariate logistic regression to find an equation that best predicted the probability and understanding of the functional relationships of the decision to get vaccinated against HZ as a function of one or more variables (age, educational level, etc.). A second multivariate logistic regression was developed by changing the dependent variable "are you in favour of vaccination against HZ, even if you have to pay?" but keeping the same independent variables. Statistical significance was set at 0.05.

Results

A total of 1,001 subjects (57% female) were interviewed; the mean age was 67 years. The main socio-demographic characteristics are reported in Table 1. The majority of enrolled subjects (69%) were retired; 29% were in work and 2% were unemployed. The education level was medium–high (36%, 23% and 23% of subjects had attended high, primary and secondary schools, respectively; 18% of subjects had a university degree); only 0.5% of interviewed subjects possessed no educational qualifications.

Table 1. Socio-demographic characteristics of interviewed subjects

Enrolled subjects N=1.001		**N (%)**
Gender	*Female*	569 (56.8)
	Male	432 (43.2)
Age	*50–54 years old*	114 (11.4)
	55–59 years old	134 (13.4)
	60–64 years old	148 (14.8)
	65–69 years old	190 (19.0)
	70–74 years old	157 (15.7)
	75–79 years old	145 (14.5)
	≥80 years old	113 (11.3)
Employment status	*Retired*	693 (69.2)
	In work	292 (29.2)
	Unemployed	16 (1.6)
Education level	*Primary school*	231 (23.1)
	Secondary school	228 (22.8)
	High school	361 (36.1)
	University	176 (17.6)
	No qualification	5 (0.5)

As expected, since it is a well-known illness, 98% of respondents knew about varicella and 72% had experienced it in the past. Also as expected, 95% of interviewed subjects had heard of HZ, the subject of widespread popular beliefs. The questionnaire was interrupted (in 5% of respondents) when a subject declared they had no knowledge of HZ. [Table 2] Among those who knew of HZ, 22% had had the disease, while 80% knew at least one person who had had the disease in the past.

Table 2. Knowledge of varicella and Herpes Zoster

	Varicella N=1.001			Herpes Zoster N=953		
	Yes (%)	**No (%)**	**Don't remember (%)**	**Yes (%)**	**No (%)**	**Don't remember (%)**
Have you heard of the disease?	982 (98)	19 (2)	---	953 (95)	48 (5)	----
Have you ever had the disease?	724 (72)	111 (11)	166 (17)	212 (22)	741 (78)	---
Have you been vaccinated for Varicella?	49 (5)	813 (81)	139 (14)	---	---	---
Do you know someone who has had HZ?	---	---	---	761 (80)	192 (20)	---

Assessing the knowledge on HZ symptoms, considering the multiple responses possible for the question, the respective percentages were calculated for the total respondents. The "rash" was found to be the main symptom known to be associated with the disease (83% of respondents), probably because this is the most evident clinical outcome. Other well-known symptoms were "pain" and "itching" (indicated by 83% and 71% of respondents, respectively). "Malaise", "eye problems" and "headache" were also known to be associated with HZ (by 45%, 10% and 9% of subjects, respectively), while only 3% of subjects could not relate any symptom to HZ.

Assessment of opinion on the level of the chronic pain and the impact on daily life showed that pain was considered "serious" or "moderate" by 46.6% and 39.3% of respondents, respectively. Only 7.2% of interviewed subjects described pain as "mild", while 6.9% of them were unable to answer. The impact of the disease was defined as of "little value", "significant" and "very significant" by 20%, 46% and 25% of respondents, respectively; 10% of subjects were unable to define the impact.

As regards HZ vaccine awareness, 91% of interviewed people were unaware of its existence. People who had heard of the vaccine mainly indicated the media (press or radio, internet, and/or TV) as the primary source of information, while others had heard of it through friends, relatives or GPs.

Fifty-eight percent of respondents claimed to be in favour of HZ vaccination. Many of these subjects believed in "the efficacy of the vaccine" (35%), knew someone who had had the disease (29%), thought that "vaccination can improve health" (22%), feared they were at risk of developing the disease (12%), or other (2%). However, 38% of people interviewed were against this immunization, due to the fear of possible side effects (15%), the belief they were not at risk of developing the disease (10%), and opposition to any immunization (6%); other subjects distrusted the efficacy of the vaccine (3%), did not consider the disease long, dangerous and painful enough to warrant vaccination (3%), or just wanted to avoid taking the trouble to go to the doctor's (1%).

The questionnaire also investigated the role of GPs. Eighty-three percent of respondents said they would be vaccinated if immunization was recommended by GPs, and 61% (248 subjects) of the 405 individuals unfavourable to HZ vaccination said that they would change their minds if advised to do so by their own GP. Interestingly, 73% of respondents said they would be willing to get vaccinated even if the vaccine was not available free of charge. In this case, the majority of respondents (49%) said they would be willing to spend up to €50, while 11% would prefer a lower amount, 10% would pay more, and 14% felt the vaccination should be free.

Considering the factors that could promote vaccination against HZ [Table 3], age was the main driving force ($p=0.005$), younger people being more likely to get vaccinated, whereas education level and employment status had no significant impact. Having a family member, friend or contact who had previously had HZ seemed to positively influence the decision to get vaccinated ($p=0.05$), and GP advice, "being in favour of vaccination in general" and a willingness to be immunized even if charged were highly influential to the decision to opt for HZ immunization. The decision to get vaccinated against HZ even if not free of charge was affected by a high level of education ($p=0.04$), being in favour of HZ vaccination, and GP advice ($p<0.0001$).

Table 3. Determinants of being in favour of vaccination against HZ and the decision to get vaccinated even if charged

Are you in favour of vaccination against HZ?	**OR**	**95% CI**	**p**
Age	0.97	0.94–0.99	*0.005*
Education level	0.97	0.70–1.34	0.844
Employment status	1.01	0.61–1.67	0.971
Knowing someone who has had HZ	1.46	1.00-2.14	*0.050*
Having had HZ	0.76	0.53-1.10	0.158
Being in favour of vaccinations	6.05	2.89-12.66	*<0.0001*
Following GP's advice	44.66	15.41-129.41	*<0.0001*
Would vaccinate even if required to pay	2.19	1.42-3.39	*<0.0001*
Are you in favour of vaccination against HZ even if you have to pay?	**OR**	**95% CI**	**p**
Education level	1.51	1.01-2.26	*0.04*
Being in favour of vaccinations	1.15	0.53-2.49	0.72
Would vaccinate against HZ	2.15	1.41-3.29	*<0.0001*
Following GP's advice	69.72	33.12-146.78	*<0.0001*

Discussion

In Western countries, about 20–30% of individuals experience VZV reactivation during their lifetime, an incidence that dramatically increases with age. As HZ can have debilitating consequences, this creates a significant impact on health and quality of life, not to mention public

health costs. Since therapeutic options are often suboptimal, the development of an HZ vaccine was crucial, because it strengthens the immune system and prevents the onset of the disease and, therefore, of all the possible sequelae. The vaccine is effective, safe and well tolerated. Indeed, the Shingles Prevention Study showed 65.5% and 65.7% efficacy rates against the incidence of HZ and PHN, respectively, in the 60–69-year age group. [10] Effectiveness studies conducted in several countries yielded results consistent with those obtained in randomized and controlled clinical trials, and confirmed the good safety and tolerability profiles of the vaccine, as well as its good efficacy/effectiveness against HZ and PHN in subjects >60 years of age. [28-29]

The vaccine can be administered to VZV-naïve individuals and those with a previous medical history of HZ. It is also suitable for patients with immune-mediated diseases [30] or mild immunosuppression. According to the contraindications reported in the accompanying datasheet, in patients with concomitant immunosuppressive therapy, the vaccine should only be administered at least 14 days before or 1 month after its cessation, [31], and patients should in any case be assessed for possible immunodeficiency prior to its administration. [32]

In the United States, the vaccine has been recommended since 2006. However, despite the benefits of vaccination, its acceptability in the initial years was very low: only 1.9%, 6.7% and 10% of the target population was vaccinated in 2006, 2007 and 2008, respectively. The main barriers to vaccination were lack of or low patient awareness, and lack of or insufficient advice from GPs. [33]

Several European countries have also decided to recommend and/or fund HZ vaccination. For example, a British vaccination programme was begun on two cohorts (70 and 79 year olds) in September 2013. Compliance to the vaccination programme by the population was positive, and after only one year, the mean national coverage was 61.8% and 59.6% in the 70- and 79-year-old cohorts, respectively. [34]

We, on the other hand, set out to evaluate the awareness of VZV and the acceptability of the HZ vaccine in the >50-year-old population of Ferrara, Italy. As expected, the majority of interviewed people had heard of varicella and HZ, but the vast majority (91%) were unaware of the vaccine. We

show that two variables have a strong influence on vaccination acceptability: age (younger people were more open to immunization) and being in favour of vaccinations in general. An explanation could be the self-confidence of people already favourable to vaccinations, who are not worried about possible side effects and do not have financial problems when the goal is health protection. Our results also show that GPs have a vital role to play in promoting vaccination, as GP advice had a positive influence on the willingness to be vaccinated. Likewise, awareness of a family member, friend or relative who had had HZ, seemed to increase willingness to have the vaccine, presumably due to a greater awareness of the disease and its consequences, although this only reached borderline statistical significance.

As regards willingness to be vaccinated even if charged, the level of education had a positive influence, as did being in favour of vaccination against HZ and receiving/trusting the GP's advice. It is likely that better educated people, with a sound cultural background, tend to be better informed about the importance of vaccination and are consequently more willing to pay for it.

That being said, it is possible that collected responses were partially influenced by recall bias, especially considering the age of the respondents. However, the questionnaire was administered by trained medical personnel in order to minimize this source of error. Moreover, we deliberately created a comfortable environment/rapport with the respondents in order to minimize the possibility of embarrassment influencing responses.

In conclusion, our findings contribute to improving understanding of awareness and attitudes in the Italian general population as regards a newly available vaccine, highlighting the major barriers to its forthcoming roll-out. They provide additional support to available scientific data that currently recommend the new HZ vaccine in at-risk individuals (with the exception of the severely immunocompromised) of >50 years of age, and in at least one cohort of the elderly population (60 or 65 years old). As the major barrier seems to be financial, the strategy chosen by the Italian regions that have already introduced and actively promote free of charge HZ vaccination seems to the most appropriate in order to achieve satisfactory vaccination coverage rates. It is also important

to bear in mind the key role that general practitioners play as trusted information providers able to persuade those at risk to accept the vaccination.

Author Contributions

AS and GG contributed to the overall design of the study, analysed the data, and drafted the manuscript. NV, SL, NS, MC, LP contributed to the study design, supervised data collection, contributed to data analysis, and reviewed the manuscript. The working group participated in the fieldwork. All authors critically read and revised the drafts of the manuscripts. All authors read and approved the final manuscript.

Competing interests

There are no potential competing interests of the authors. GG received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Pfizer and Sequirus for being consultant or 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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Evaluation of the acceptability of a vaccine against Herpes Zoster in the over 50 years old population.

Date __-__-____

Thanks for agreeing to participate in the study. The information contained in this form will be kept confidential under the legislation (Legislative Decree no. 196/2003 "Code regarding the protection of personal data").

1. **Gender** □ M □ F **2. Age** _____
3. **Nationality** _____
4. **City of residence** _____
5. **Educational level**

☐ No qualification ☐ Primary school
☐ Secondary school ☐ High school
☐ University

6. Employment status

☐ Retired ☐ Worker

7. Do you know the disease called Varicella?

☐ No ☐ Yes

8. Have you had Varicella in the past?

☐ No ☐ Yes ☐ I do not remember

9. If yes, how old were you? _____

10. Have you been vaccinated against Varicella?

☐ No ☐ Yes ☐ I do not remember

11. If yes, how old were you ? ☐☐ ☐ I do not remember

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12. Do you know the disease called shingles (Herpes Zoster)?

☐ No ☐ Yes

(if you answer "no" to question number 12 the interview ends here)

13. Do you know someone who had shingles (Herpes Zoster)?

☐ No ☐Yes

14. Do you had shingles in the past (Herpes Zoster)?

☐ No ☐ Yes

15. If yes, how old were you? ☐☐ ☐ I do not remember

16. In your opinion what are the consequences of shingles (Herpes Zoster)?
(multiple choice question: you can give more than one answer)

☐ Pain ☐Rash
☐ Headache ☐Itching
☐ Eye problems ☐Malaise
☐ I do not know

17. In your opinion, the pain associated to shingles (Herpes Zoster) is:

☐ Mild, with duration of few days
☐ Moderate, with duration of few weeks
☐ Serious, with a term of months or years
☐ I do not know

18. In your opinion, the chronic pain associated to shingles can have an impact on the normal activities of daily life activities:

☐ Little relevance
☐ Relevant
☐ Very relevant
☐ I do not know

19. Are you aware about the vaccine against shingles?

☐ No ☐ Yes

20. If you have answered yes to the previous question, how it came to knowledge?
(multiple choice question: you can give more than one answer)

☐ General Practitioner ☐ Internet
☐ Family ☐ TV
☐ Friends/ contacts ☐ Books/brochures/magazines
☐ Radio ☐ Other (specify) _____

21. Do you think that vaccines are an effective tool for prevention?

☐ No ☐ Yes

22. Would you vaccinate against shingles?

☐ No ☐ Yes

23. If you would not vaccinate against shingles, why? *(multiple choice question: you can give more than one answer)*

☐ I do not think of being at high risk of having the disease
☐ I have trouble to go to the doctor for vaccination
☐ In general, I am opposed to vaccinations
☐ I think that vaccination is not completely effective
☐ I fear the possible side effects of vaccination (eg, immune system disorders)
☐ I do not think that the disease is particularly harmful, long or painful
☐ Other (specify)_____

24. If your GP would recommend the vaccine against shingles, would you vaccinate?

☐ No ☐ Yes

25. If yes, why? *(multiple choice question: you can give more than one answer)*

☐ I think the vaccine is effective
☐ I think I can have the diseases
☐ I knew someone who had the shingles and I do not want that it happen to me
☐ I think the vaccine can improve my health
☐ Other (specify)……

26. Are you in favor of being immunized against HZ even upon payment?

☐ No ☐ Yes

27. How much would you pay for the vaccine against shingles?

☐ Up to 50 euro
☐ Up to 100 euro
☐ Up to 150 euro
☐ Other (specify)……

Thanks for your collaboration

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-7
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6-7
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7
Participants	6	Give the eligibility criteria, and the sources and methods of selection of participants	Page 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7-8
Bias	9	Describe any efforts to address potential sources of bias	Page 14
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n.a.
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8-9
		(b) Indicate number of participants with missing data for each variable of interest	Page 9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n.a.
Outcome data	15*	Report numbers of outcome events or summary measures	Page 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 10-12
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.