

# BMJ Open Evaluation of the acceptability of a vaccine against herpes zoster in the over 50 years old: an Italian observational study

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## ABSTRACT

**Objective:** The aim of the study was to evaluate awareness of the varicella zoster virus and the acceptability of the newly available herpes zoster (HZ) vaccine in the over 50 years old 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 practitioners (GPs) and Public Health Department outpatient clinics.

**Participants:** The questionnaire was completed by 1001 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 that 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 from 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 participants initially unfavourable ( $p<0.0001$ ) to this immunisation 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 population aged over 50 years, highlighting aspects to be focused on in the promotion of the HZ vaccine.

## 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.<sup>1</sup> The primary infection is varicella, which mainly occurs in

## Strengths and limitations of this study

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

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<sup>2</sup> 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/1000 persons per year.<sup>3</sup> 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.<sup>4 5</sup>

The incidence of HZ increases rapidly with age, and about 50% of people aged  $\geq 80$  years will develop at least one episode of

acute HZ, often preceded by acute pain or itching.<sup>6</sup> The rash, initially erythematous with multiple maculopapular lesions, later becomes vesicular. New lesions may continue to appear for a maximum of 7 days; scabs form and drop within 2–3 weeks.<sup>7</sup> 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 20% of HZ episodes involve the ophthalmic branch of the trigeminal nerve,<sup>8</sup> 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 3 months after the eruption of HZ or the onset of the pain’, PHN is a neuropathic syndrome characterised by pain along the cutaneous nerve endings. It is experienced as constant or intermittent pain, burning, allodynia and/or hyperalgesia, as well as 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.<sup>9</sup>

According to the Shingles Prevention Study (SPS), the percentage of patients who develop PHN is 12.5% after 3 months, and 5.1% after 6 months.<sup>10</sup> 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, 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 1000 adults under 50 years old to about 7–8/1000 in the over 50s, and up to 10/1000 in the over 80s.<sup>11</sup> Although compulsory HZ notification is widely disregarded in Italy, it is estimated that every year at least 157 000 new HZ cases occur, with an incidence of 6.3/1000/year, and that 9.4% and 7.2% of patients suffer PHN at 1 and 3 months, respectively.<sup>12</sup> In the period 1999–2005, 35 328 hospital admissions were recorded for HZ in Italy, with an annual average of 4503 hospitalisations and 543-day hospital admissions; more than 22 000 hospitalisation days per year were registered, with the average length of stay being 8 days. The majority of hospitalisations (62%) involved participants >65 years of age.<sup>13</sup>

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 an 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.<sup>14 15</sup> In the same year, the European Medicines Agency (EMA) authorised

the use of the vaccine in the European Union for over 60 years old. In July 2007, however, the vaccine was indicated for immunisation of individuals aged 50 or older.

The new vaccine contains the same live attenuated strain used for paediatric varicella immunisation, albeit with an antigen content at least 14 times greater.<sup>16</sup> 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 premarketing and postmarketing clinical studies on a total of roughly 57 700 immunised participants.<sup>17–19</sup> The efficacy and the good safety profile of the vaccine have been recognised in the EUnetHTA report, which recommends immunisation against HZ in order to mitigate the impact of the disease and its associated complications.<sup>20</sup> Moreover, an Italian study showed that the vaccine is highly cost-effective, with a cost per quality-adjusted life year of €11 943 in participants aged 60–79 years (€9779 for people aged 65–79 years and €8729 for those aged 70–79 years).<sup>21</sup> However, in Italy, the vaccine is only recommended in some regions, specifically for the elderly (>65 years of age) and in participants at risk aged over 50 years, with the exclusion of severely immunocompromised patients. People considered at risk include those affected by comorbidities (eg, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, etc). The vaccine was first offered free of charge in 2015, where it was made available to those aged 65–75 years and at-risk individuals >50 years of age in Sicily,<sup>22</sup> people >65 years of age in Liguria<sup>23</sup> and those aged over 65 or 70 years in Calabria.<sup>24</sup> In Veneto and Friuli Venezia Giulia, the HZ vaccine is only prescribed for at-risk patients >50 years of age, but people not considered at risk may opt to part-pay for the vaccination.<sup>25 26</sup> Similarly, the HZ vaccine has been provided free of charge to participants >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 immunisation as a preventative tool has been conducted until now. One survey conducted on two Italian regions showed a high level of HZ awareness and a favourable disposition towards vaccination in young adults,<sup>27</sup> 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 aged 50 years or older from Ferrara Province. The interviews

were performed at general practitioner (GP) and Public Health Department outpatient clinics across Ferrara Local Health Authority (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 (see online 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 sociodemographic 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 towards 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

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 to April 2015. Collected data were recorded in Excel format in a dedicated database. Statistical analysis, via  $\chi^2$  and multivariate logistic analyses, was conducted using the software StatView V.5.0.1 (Abacus Concepts, Berkeley, California, USA), and univariate and multivariate logistic regressions were performed using STATA SE (V.13.1). 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 OR values >1 and p values  $\leq 0.05$  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 1001 participants (57% female) were interviewed; the mean age was 67 years. The main

sociodemographic characteristics are reported in table 1. The majority of enrolled participants (69%) were retired; 29% were in work and 2% were unemployed. The education level was medium-high (36%, 23% and 23% of participants had attended high, primary and secondary schools, respectively; 18% of participants had a university degree); only 0.5% of interviewed participants possessed no educational qualifications.

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 participants had heard of HZ, the subject of widespread popular beliefs. The questionnaire was interrupted (in 5% of respondents) when a participant declared that 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.

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 participants, respectively), while only 3% of participants could not relate any symptom to HZ.

**Table 1** Sociodemographic characteristics of interviewed participants

Enrolled participants N=1001	N (%)
Gender	
Female	569 (56.8)
Male	432 (43.2)
Age (years)	
50–54	114 (11.4)
55–59	134 (13.4)
60–64	148 (14.8)
65–69	190 (19.0)
70–74	157 (15.7)
75–79	145 (14.5)
≥80	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)

**Table 2** Knowledge of varicella and HZ

	Varicella N=1001			HZ 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)	–

HZ, herpes zoster.

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 participants 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 participants 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 per cent of respondents claimed to be in favour of HZ vaccination. Many of these participants 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 immunisation, due to the fear of possible side effects (15%), the belief that they were not at risk of developing the disease (10%) and opposition to any immunisation (6%); other participants 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 (1%).

The questionnaire also investigated the role of GPs. Eighty-three per cent of respondents said they would be vaccinated if immunisation was recommended by GPs, and 61% (248 participants) 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 that 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 immunised even if charged were highly influential to the decision to

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

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

Bold typeface denotes significance at  $p<0.05$ .

GP, general practitioner; HZ, herpes zoster.

opt for HZ immunisation. 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 ( $p<0.0001$ ).

## DISCUSSION

In Western countries, about 20–30% of individuals experience VZV reactivation during their lifetime, an incidence that dramatically increases with age. Since 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 SPS showed 65.5% and 65.7% efficacy rates against the incidence of HZ and PHN, respectively, in the 60–69-year age group.<sup>10</sup> Effectiveness studies conducted in several countries yielded results consistent with those obtained in randomised 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 participants >60 years of age.<sup>18 19</sup>

The vaccine can be administered to VZV-naïve individuals and those with a medical history of HZ. It is also suitable for patients with immune-mediated diseases<sup>28</sup> 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,<sup>29</sup> and patients should in any case be assessed for possible immunodeficiency prior to its administration.<sup>30</sup>

In the USA, 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.<sup>31</sup>

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 years old) in September 2013. Compliance to the vaccination programme by the population was positive, and after only 1 year, the mean national coverage was 61.8% and 59.6% in the 70 and 79 years old cohorts, respectively.<sup>32</sup>

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 immunisation) 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.

Having said that, 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 minimise this source of error. Moreover, we deliberately created a comfortable environment/rapport with the respondents in order to minimise the possibility of embarrassment influencing responses.

In conclusion, our findings contribute to improving the 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) >50 years of age, and in at least one cohort of the elderly population (60 or 65 years old). Since 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 be the most appropriate in order to achieve satisfactory vaccination coverage rates. It is also important to bear in mind the key role that GPs play as trusted information providers able to persuade those at risk to accept the vaccination.

**Collaborators** GPs' Study Group: Dario Burini, Andrea Fiorini, Carlo Alberto Guidoboni, Francesco Levato, Andrea Lunghi, Franco Miola.

**Contributors** AS and GG contributed to the overall design of the study, analysed the data and drafted the manuscript. NV, SL, NS, MC and LP contributed to the study design, supervised the 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 manuscript. All authors read and approved the final manuscript.

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being consultant or taking part in advisory boards, expert meetings, being a speaker or an organiser of congresses/conferences, and acting as investigator in clinical trials.

**Patient consent** Obtained.

**Ethics approval** The study was approved by the Ferrara Province Ethics Committee.

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**Data sharing statement** No additional data are available.

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