RESEARCH PAPER

Clinical and economic impact of herpes zoster vaccination in elderly in Italy

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ABSTRACT

Herpes zoster (HZ) is a very relevant pathology among elderly people (≥ 60 years of age), with a considerable disease burden and loss of quality of life. In the last years a new vaccine against HZ became available in Italy. Therefore, the Italian decision makers are now confronted with the decision whether that vaccination should be implemented. Pharmacoeconomic analyses represent useful tools to value the feasibility of new immunization programs and their sustainability. To this aim, an *ad hoc* population model was developed in order to value the clinical and economic impact of HZ vaccination program for the elderly in Italy. Particularly, different immunization scenarios were modeled: vaccination of 60 years-old subjects (single cohort strategy), simultaneous vaccination of people aged 60 and 65 years (double cohort strategy) and, lastly, immunization of people aged 60, 65 and 70 years (triple cohort strategy), thus leading to the vaccination of 5, 10 and 15 cohorts during the first 5 years of the program. The mathematical model valued the clinical impact of vaccination on the number of HZ, post-herpetic neuralgia (PHN) and ophthalmic HZ. The results of the analysis show that, in Italy, a cohort-based HZ vaccination program in elderly could have a relevant impact on the reduction of clinical cases and a favorable economic profile for the National Health Service (NHS), as already foreseen in other countries. In addition, further benefits could be obtained when extending the study period beyond the 5-year horizon of our analysis.

KEYWORDS

herpes zoster; vaccination; economic evaluation; budget impact

Introduction

Herpes zoster (HZ) is a very relevant pathology among elderly people (≥ 60 years of age), with a considerable disease burden and loss of quality of life. In the last years a new vaccine against HZ and its complications became available in Italy for subjects >49 years of age.

The most relevant criteria for making decisions about the implementation of new vaccines and immunization strategies in the national and regional vaccination schedule have been identified in those envisaged in the Health Technology Assessment (HTA) approach.¹ In particular, today the economic evaluations are the most significant issues that should be evaluated inside the HTA methodology, because of the current limited resources for the National Health Service (NHS).

As a matter of fact, in the current decision-making on the implementation of the new vaccine against HZ in the elderly, it is of great importance also the assessment of the possible clinical and economic impact of HZ immunization in both a short-term and long-term perspective, and, lastly, the assessment of the financial sustainability of this intervention for the NHS.

Therefore, an analysis of all possible clinical benefits and economic impact due to the introduction of HZ vaccination in the national immunization schedule for the older population in Italy has been carried out developing an *ad hoc* mathematical

simulation model. In particular, a budget impact analysis has been performed in order to assess the economic suitability of different cohort-based HZ vaccination strategies in elderly in the NHS and Societal perspectives.

The study was funded by the Italian Ministry of Health, Center for Disease Prevention and Control (CCM) in 2013.

Results

Baseline scenario

The population model allows to evaluate the clinical and economic impact due to the HZ immunization of one, 2 or 3 cohorts of elderly each year on the whole Italian population aged over 59 years, compared to the same unvaccinated elderly population, in a limited period of time (5 years).

The simulation results show that 33–81,000 cases of disease related to HZ (including HZ, PHN, and ophthalmic HZ), 400–1,400 hospitalizations and 1–4 deaths could be avoided in the aging population vaccinating against HZ every year one, 2 or 3 cohorts of elderly in 5 years. Therefore, the saving for the NHS due to the avoided clinical cases could amount to EUR 4–11 million, depending on the examined vaccination strategy (Table 1). Since vaccination of one, 2 or 3 cohorts each year in the 5-years period (4–11 million persons) has a cost that varies from EUR 175 to 486 million, the net cost of immunization

Table 1. Clinical and economic impact of HZ vaccination in elderly in Italy in 5 years.

Multi-cohort HZ vaccination	1 cohort/ year	2 cohorts/ year	3 cohorts/ year
Age of vaccinated cohorts	60 years	60 and 65 years	60, 65 and 70 years
N° of subjects in the vaccinated cohorts	3,928,318	7,535,272	10,946,807
N° of vaccinated cohorts in 5 years	5	10	15
Avoided cases			
HZ	30,727	49,359	68,265
PHN	2,552	5,589	10,181
Ophthalmic HZ	0	871	2,269
Hospitalisations due to HZ	331	775	1,097
Hospitalisations due to PHN	23	62	120
Hospitalisations due to HZ with ophthalmic complications	54	128	181
Deaths	1	2	4
NHS perspective			
Clinical savings	3,792,647	6,790,924	11,259,971
Vaccination costs	174,793,305	335,807,418	486,312,224
Total net costs	171,000,658	329,016,494	475,052,254
Total net costs per vaccinated cohort	34,200,132	32,901,649	31,670,150
Societal perspective			
Clinical savings	16,847,543	26,056,234	32,763,683
Vaccination costs	174,793,305	335,807,418	486,312,224
Total net costs	157,945,762	309,751,184	453,548,542
Total net costs per vaccinated cohort	31,589,152	30,975,118	30,236,569

could be equal at EUR 171–475 million, according to the adopted immunization strategy. The total net cost per vaccinated cohort stand from EUR 32 to 34 million. The net cost per vaccinated subject is about EUR 87.

It should be noted that these figures refer to the impact due to the HZ vaccination of one, 2 and 3 cohorts of elderly each year in 5 consecutive years (i.e. vaccination of 5, 10 and 15 cohorts of older people, respectively) on the entire population over the age of 59 years. Additional benefits due to vaccination could be expected after the fifth year of implementation, considering the additional cases of HZ disease avoided in immunized cohorts in the first 5 years.

In the Societal perspective, the economic impact of HZ vaccination results more favorable. In particular, the net total cost of HZ vaccination varies from EUR 158 to 454 million. The total net cost per vaccinated cohort amount to EUR 30–

32 million. The net cost per vaccinated subject is EUR 80, 82 and 83, respectively.

Mono-cohort vaccination strategy

Table 2 shows the clinical and economic impact due to mono-cohort immunization strategies vaccinating 3 different specific cohorts of elderly each year: the cohort of subjects aged 60 or 65 or 70 years.

The vaccination of the younger cohort (subjects aged 60 years) could avoid the greatest number of cases related to HZ (> 33,000 cases), followed by vaccination of the 70-years cohort. The cohort of subjects 65 years aged, however, could avoid the greatest number of hospitalizations due to HZ.

In particular, in the NHS perspective, the net total cost of mono-cohort immunization strategies varies from EUR 146 to 171 million (from the 70-years cohort to the cohort of subjects

Table 2. Clinical and economic evaluation of mono-cohort HZ vaccination in elderly in Italy in 5 years.

Mono-cohort HZ vaccination	1 cohort/ year	1 cohort/ year	1 cohort/ year
Age of vaccinated cohorts	60 years	65 years	70 years
N° of subjects in the vaccinated cohorts	3,928,318	3,606,954	3,411,535
N° of vaccinated cohorts in 5 years	5	5	5
Avoided cases			
HZ	30,727	18,632	18,906
PHN	2,552	3,037	4,592
Ophthalmic HZ	0	871	1,398
Hospitalisations due to HZ	331	444	322
Hospitalisations due to PHN	23	39	58
Hospitalisations due to HZ with ophthalmic complications	54	74	53
Deaths	1	1	2
NHS perspective			
Clinical savings	3,792,647	2,998,278	4,469,046
Vaccination costs	174,793,305	161,014,114	150,504,806
Total net costs	171,000,658	158,015,836	146,035,760
Total net costs per vaccinated cohort	34,200,132	31,603,167	29,207,152
Societal perspective			
Clinical savings	16,847,543	9,208,692	6,707,448
Vaccination costs	174,793,305	161,014,114	150,504,806
Total net costs	157,945,762	151,805,422	143,797,358
Total net costs per vaccinated cohort	31,589,152	15,180,542	9,586,491

Table 3. Clinical and economic evaluation of HZ vaccination in the elderly in Italy with increasing vaccination coverage.

Multi-cohort HZ vaccination Age of vaccinated cohorts	1 cohort/ year 60 years	2 cohorts/ year 60 and 65 years	3 cohorts/ year 60, 65 and 70 years
Avoided cases			
HZ	22,284	35,629	49,781
PHN	1,850	4,025	7,465
Ophthalmic HZ	0	624	1,670
Hospitalisations due to HZ	240	558	799
Hospitalisations due to PHN	17	45	88
Hospitalisations due to HZ with ophthalmic complications	39	92	132
Deaths	1	1	3
NHS perspective			
Clinical savings	2,733,784	4,868,401	8,194,698
Vaccination costs	140,874,029	269,232,076	393,895,336
Total net costs	138,140,246	264,363,675	385,700,638
Total net costs per vaccinated cohort	27,628,049	26,436,367	25,713,376
Societal perspective			
Clinical savings	12,143,707	18,700,384	23,692,394
Vaccination costs	140,874,029	269,232,076	393,895,336
Total net costs	128,730,322	250,531,692	370,202,942
Total net costs per vaccinated cohort	25,746,064	25,053,169	24,680,196

60 years aged). The total net cost per vaccinated cohort in 5 years stand from EUR 29 million to 34 million. The net cost per vaccinated subject is EUR 87.

In the Societal perspective, the total net cost per vaccinated cohort amounts to EUR 32–10 million. The net cost per vaccinated subject is EUR 80, 84 and 84 vaccinating subjects 60, 65 and 70 years aged each year, respectively.

Alternative scenarios

Increasing vaccination coverage

If the vaccination coverage rate of HZ immunization is 20% of the target population in the first year of implementation, 35% in the second year and, finally, 50% in the following years, the mathematical model has calculated the results shown in Table 3.

With an increasing vaccination coverage rate, the HZ immunization could avoid 24–59,000 cases of disease related to HZ, and 300–1,000 hospitalizations in the population, compared to total net cost per vaccinated cohort amounting to EUR 26–28 million and cost per vaccinated subject to EUR 85 in the NHS perspective.

In the Societal perspective, the total net cost per vaccinated cohort is slightly lower (EUR 25–26 million). The net cost per vaccinated subject is EUR 79, 81 and 82, respectively.

Effectiveness of HZ vaccine

Table 4 shows the clinical and economic impact of HZ vaccination applying the effectiveness data reported by Langan et al.,² instead of the efficacy data obtained by clinical trials.³

With the effectiveness data, the HZ vaccination could avoid 25–73,000 cases of disease related to HZ and 300–1,300 hospitalizations in the population. The total net cost per vaccinated cohort results EUR 32–34 million and the cost per vaccinated subject EUR 87 in the NHS perspective.

In the Societal perspective, the total net cost per vaccinated cohort amounts to EUR 32–31 million. The net cost per vaccinated subject is EUR 82, 84 and 84, respectively.

Wane of protection over time

Applying a wane rate of protection in the time equal to that reported by Tseng et al.⁴ to the vaccine efficacy data for both

Table 4. Clinical and economic evaluation of vaccination in the elderly in Italy with the effectiveness data of HZ vaccine.

Multi-cohort HZ vaccination Age of vaccinated cohorts	1 cohort/ year 60 years	2 cohorts/ year 60 and 65 years	3 cohorts/ year 60, 65 and 70 years
Avoided cases			
HZ	23,081	37,077	61,213
PHN	2,291	5,019	9,075
Ophthalmic HZ	0	654	2,439
Hospitalisations due to HZ	249	582	993
Hospitalisations due to PHN	21	56	107
Hospitalisations due to HZ with ophthalmic complications	40	96	163
Deaths	1	1	4
NHS perspective			
Clinical savings	2,976,563	5,283,134	10,190,231
Vaccination costs	174,793,305	335,807,418	486,312,224
Total net costs	171,816,742	330,524,284	476,121,993
Total net costs per vaccinated cohort	34,363,348	33,052,428	31,741,466
Societal perspective			
Clinical savings	12,801,348	19,848,629	27,255,213
Vaccination costs	174,793,305	335,807,418	486,312,224
Total net costs	161,991,957	315,958,789	459,057,012
Total net costs per vaccinated cohort	32,398,391	31,595,879	30,603,801

Table 5. Clinical and economic evaluation of HZ vaccination in the elderly in Italy with loss of protection over the time.

Multi-cohort HZ vaccination Age of vaccinated cohorts	1 cohort/ year 60 years	2 cohorts/ year 60 and 65 years	3 cohorts/ year 60, 65 and 70 years
Avoided cases			
HZ	23,566	37,804	51,662
PHN	1,957	4,278	7,645
Ophthalmic HZ	0	665	1,690
Hospitalisations due to HZ	254	593	829
Hospitalisations due to PHN	18	48	90
Hospitalisations due to HZ with ophthalmic complications	41	98	137
Deaths	1	1	3
NHS perspective			
Clinical savings	2,920,329	5,220,971	8,511,154
Vaccination costs	174,793,305	335,807,418	486,312,224
Total net costs	171,872,976	330,586,447	477,801,070
Total net costs per vaccinated cohort	34,374,595	33,058,645	31,853,405
Societal perspective			
Clinical savings	12,972,965	20,039,696	24,977,944
Vaccination costs	174,793,305	335,807,418	486,312,224
Total net costs	161,820,339	315,767,723	461,334,280
Total net costs per vaccinated cohort	32,364,068	31,576,772	30,755,619

HZ and PHN, the simulation model has calculated the results shown in Table 5.

The HZ vaccination could avoid 26–61,000 cases of disease related to HZ and 300–1,000 hospitalizations. On the other side, the total net cost per vaccinated cohort results EUR 32–34 million and the cost per subject vaccinated EUR 87 according to the NHS perspective.

In the Societal perspective, instead, the total net cost per vaccinated cohort could be EUR 31–32 million while the net cost per vaccinated subject EUR 82, 84 and 84.

Increasing vaccination coverage, effectiveness data and loss of protection over the time

The simulation results, assuming at the same time an increasing vaccination coverage, effectiveness data of HZ vaccine and loss of protection over the time, are shown in Table 6.

In this more realistic setting, the HZ vaccination could avoid a lower number of HZ cases (15–41,000) and hospitalizations (200–700). On the other side, the total net cost per vaccinated

cohort results EUR 26–28 million and the cost per subject vaccinated EUR 86 (NHS perspective).

In the Societal perspective, the total net cost per vaccinated cohort amounts to EUR 25–27 million. The net cost per vaccinated subject is EUR 82, 83 and 83, respectively.

Discussion and conclusions

In Italy, according to the simulation model, the multi-cohort HZ vaccination of elderly could avoid 33–81 thousand cases of illness related to HZ and 400–1,400 hospitalization in the older population in a short period (5 years), with average net cost per vaccinated cohort equal to EUR 32–34 million (or EUR 87 per vaccinated subject) in the baseline scenario. Therefore, cohort-based HZ vaccination in subjects > 59 years of age could have high clinical impact, in terms of avoided cases and reduction in hospitalizations related to HZ, with a low cost per vaccinated subject.

However, that benefits are related to the first years of HZ immunization. Additional benefits could be expected after the

Table 6. Clinical and economic evaluation of HZ vaccination in the elderly in Italy with increasing vaccination coverage, effectiveness data and loss of protection over the time.

Multi-cohort HZ vaccination Age of vaccinated cohorts	1 cohort/ year 60 years	2 cohorts/ year 60 and 65 years	3 cohorts/ year 60, 65 and 70 years
Avoided cases			
HZ	13,252	21,161	34,888
PHN	1,315	2,856	5,165
Ophthalmic HZ	0	370	1,385
Hospitalisations due to HZ	143	331	565
Hospitalisations due to PHN	12	32	61
Hospitalisations due to HZ with ophthalmic complications	23	55	93
Deaths	0	1	2
NHS perspective			
Clinical savings	1,703,715	3,003,427	5,788,117
Vaccination costs	140,874,029	269,232,076	393,895,336
Total net costs	139,170,315	266,228,649	388,107,219
Total net costs per vaccinated cohort	27,834,063	26,622,865	25,873,815
Societal perspective			
Clinical savings	7,327,277	11,298,967	15,501,790
Vaccination costs	140,874,029	269,232,076	393,895,336
Total net costs	133,546,752	257,933,109	378,393,546
Total net costs per vaccinated cohort	26,709,350	25,793,311	25,226,236

fifth year, considering future cases of disease related to HZ avoided in the immunized cohorts. Consequently, the favorable impact of HZ immunization could be further increased in longer analysis period, even if some considerations should be then performed on the duration of HZ vaccine protection. However, the implementation of mono-cohort vaccination program (with a lower economic impact) could be recommended after the first 5 years to maintain and increase the relevant achieved benefits.

The favorable economic profile of the multi-cohort HZ vaccination is not particularly changed varying the main assumptions included in the simulation mathematical model. As a matter of fact, applying contemporary the same assumptions used for the alternative scenarios, in a more realistic setting, the HZ vaccination could prevent fewer cases of disease related to HZ compared to the baseline scenario, with a parallel reduction of the cost net per vaccinated cohort in the NHS perspective (about EUR 27 million, or EUR 86 per vaccinated subject). However, the difference is not relevant.

In view of the Societal perspective, HZ vaccination in the elderly is slightly economically more favorable due to the low rate of old subjects officially workers, according to our survey. However, today the elderly people assume much more importance also in the supporting of the modern society (issue not included in the analysis).

In case of implementation of mono-cohort strategies, the cohort of subjects > 59 years of age who appears to have the greatest benefit from the HZ vaccination, in terms of avoided cases despite being the most expensive, is that of people 60 years aged. Even if the HZ vaccine is more efficient in older subjects, especially for the complications of HZ, the cohort of 60-years subjects is currently the largest in Italy, and, consequently is the most influenced by the immunization.

In conclusion, our results show that the economic resources used for the mono-cohort vaccination strategies or multi-cohort ones in Italy in subjects > 59 years of age are used correctly in the short period.

The results of our study agreed with other published economic studies.⁵⁻²² Although the mathematical models and the assumptions are different, these studies demonstrate clearly that the HZ vaccination in the elderly population has a favorable economic profile. Vaccination could have a significant

impact on HZ disease and, above all, results a very good investment for NHS and Society. Its value will increase further in the future because aging of the population and the fact that today the elderly people has an important role in business area but also in the Society. Therefore, it is desirable as soon as the inclusion of HZ vaccination in the recommendation for vaccination in the elderly, seen that, also from an economic point of view, it results to have a good acceptability and suitability profile.

Material & methods

A population mathematical model has been developed in order to assess the clinical and economic impact of cohort-based HZ vaccination programs in the elderly in Italy in short-term period (5 years). In particular, a static Markov model has been developed in Excel.

Essentially, the population model allows to assess the impact of HZ vaccination, carried out each year to specific cohorts of elderly, on the entire Italian elderly population in 5 years compared to the current setting of non-vaccination. Therefore, this model evaluates the financial sustainability of the vaccination program for specific cohorts in comparison to the benefits obtained in the older population.

Fig. 1 shows the decision tree behind the development of the mathematical model and, in particular, it represents the health conditions related to HZ included in the assessment: HZ, PHN (3 months) and ophthalmic HZ.

Baseline scenario

In the baseline scenario the impact of multi-cohort HZ vaccination strategies in the elderly has been evaluated. In particular, 3 possible vaccination strategies have been compared with respect to the scenario of non-vaccination:

- mono-cohort strategy, i.e., vaccination of one cohort (subjects 60 years aged);
- double-cohort strategy, i.e., simultaneous vaccination of 2 cohorts (subjects 60 and 65 years aged);
- triple-cohort strategy, i.e., simultaneous vaccination of 3 cohorts (subjects 60, 65 and 70 years aged).

Figure 1. Decision tree and health states related to HZ included in the mathematical model.

The assessment of the clinical and economic impact of HZ vaccination has been carried out both in the perspective of the NHS that of the Society (including the indirect costs of HZ conditions and loss of productivity due to illness).

The evaluation has been performed on the population over the age of 59 years resident in Italy on 1 January 2015.²³ The entire population has been assumed immuno-competent. Given the different impact of HZ on gender, the population has been allocated into males and females. Moreover, life expectancy counts up 80 years for males and 85 years for females.²⁴

The incidence rates of HZ, PHN and ophthalmic HZ have been broken down by gender and age groups (60–64, 65–69, 70–74, 75–79, 80–84, ≥85 years). They have been obtained from the analysis of questionnaires administered to general practitioners (GPs) in Liguria, Puglia, Tuscany and Veneto inside the CCM project. It has been assumed that there were no recurrences after the first case of HZ.

Hospitalization rates due to HZ, PHN and ophthalmic HZ and related costs, shared by gender and age groups, have been calculated as average value of data reported in the period 2001–2012 by national hospital discharge records (HDR national database of the Italian Ministry of Health).

In absence of national data, the case fatality rate due to HZ has been obtained from the study of Ulstch et al.²⁵ The lethality for PHN has been assumed equal to zero.

Direct and indirect costs due to HZ, PHN and ophthalmic HZ cases, broken down by age groups, have been collected from the analysis of questionnaires administered to GPs in Liguria, Puglia, Tuscany and Veneto.

In the baseline scenario the efficacy of HZ vaccine has been assumed equal to that obtained from the clinical trial Short-term Persistence Study.³ In particular, the direct effects of vaccine against HZ and PHN have been included in the mathematical model. However, it has not been included the effect of vaccination on Burden of Illness (BOI) or on hospitalizations related to HZ disease. It has been hypothesized that the efficacy of HZ vaccine is steady in 5-years analysis period.

HZ vaccination coverage has been assumed 50% of the target cohorts for the immunization program. In addition, it has been assumed that GPs participate to the vaccination program, immunizing 50% of elderly with a salary equivalent to that provided for the seasonal flu campaign (EUR 6.16 per dose).²⁶ The vaccine price per dose was EUR 87.45 (+ 10% VAT).²⁷ All costs have been updated to 2016.²⁸ In addition, a discount rate of 3% has been applied both the costs and the benefits.

In the perspective of the Society, the percentage of workers, broken down by age and gender, has been used for the calculation of lost productivity due to HZ illness. It has been derived from questionnaires administered to GPs in Liguria, Puglia, Tuscany and Veneto. The average salary has been collected by Gialloreti et al.²⁹

Finally, in the hypothesis that the multi-cohort vaccination strategies are still too onerous for the organizational and financial sustainability of the NHS, a clinical and economic evaluation has been performed to locate, in view of an alternative mono-cohort strategy, which cohort of elderly is preferable to vaccinate (i.e., the cohort of subjects 60, 65 or 70 years aged).

Alternative scenarios

The clinical and economic impact of HZ vaccination in the elderly, carried out with the basic assumptions described above, has been then varied assuming alternative scenarios. The following 3 alternative scenarios have been evaluated independently.

1. Increasing vaccination coverage rate. It has been hypothesized that the vaccination coverage for the target cohorts is not constantly equal to 50% but increases in the first years after the implementation of vaccination. In particular, it has been assumed that vaccination coverage is 20% in the first year, 35% in the second year, 50% in the third year and then remained steady.
2. Effectiveness of the HZ vaccine. The first studies on the effectiveness of HZ vaccine in the elderly start to be published. Therefore, it has been speculated to use the effectiveness data in the mathematical model, instead of those of efficacy obtained by clinical trials. In particular, in this alternative scenario we included the effectiveness data against HZ and PHN, reported by Langan et al.²
3. Loss of protection over the time. The study by Tseng et al.⁴ showed the decline and then the loss of vaccine efficacy against HZ in 8 years. At present, however, no data are available on loss of efficacy against PHN. In this scenario, then, the percentage of reduction reported by Tseng et al.⁴ has been applied to the vaccine efficacy against HZ reported in the clinical trials. It has been hypothesized a parallel loss of protection also for the vaccine efficacy against PHN.

Finally, the assumptions of these 3 alternative scenarios have been included simultaneously in the mathematical model to evaluate the overall impact of HZ immunization in this more realistic setting.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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