Herpes Zoster:
un vaccino per impedire che si accenda il “fuoco”

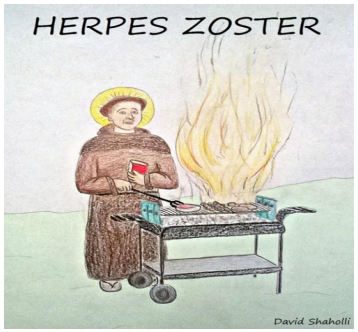
G. Gabutti

Università degli Studi di Ferrara

Il "fuoco di Sant'Antonio”

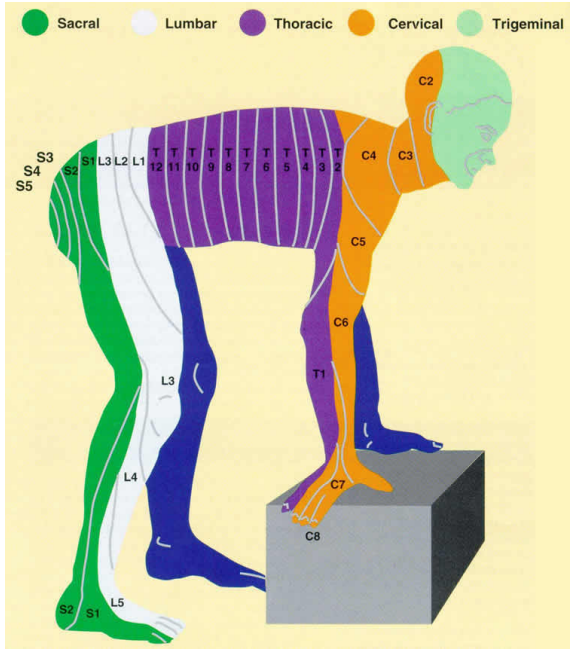
Tutti coloro che hanno a che fare con il fuoco vengono posti sotto la protezione di Sant'Antonio.

La tradizione riporta che tra i molti malati che chiedevano grazie e salute, molti erano afflitti dal *male degli ardenti*, conosciuto anche come “fuoco di Sant’Antonio” corrispondente all’Herpes Zoster, causato dal virus varicella-zoster (VZV)



HZ: caratteristiche epidemiologiche generali

HZ è una dermatite vescicolosa acuta, a tipica distribuzione unilaterale ganglionare, dovuta alla slatentizzazione del *VZV*



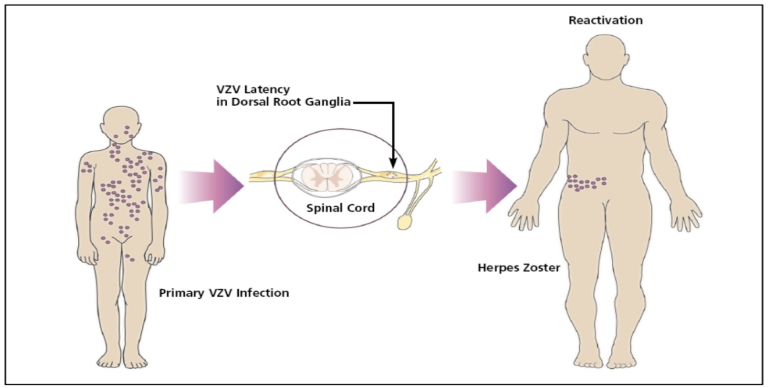
HZ si presenta in modo sporadico durante tutto l'anno, non aumenta durante le epidemie di Varicella e non può essere trasmesso *(fatta eccezione per gli individui mai esposti prima alla varicella, che contraggono però la Varicella e non HZ).*

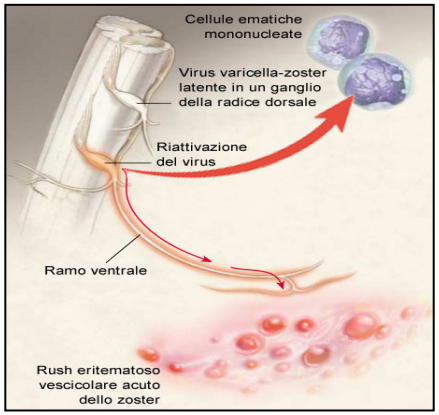
In tutti i pazienti colpiti da HZ è costante il dato anamnestico di <u>pregressa Varicella</u>.

Weinberg JM. J Am Acad Dermatol 2007; 57: S130-5

Varicella Zoster Virus (VZV)

Dopo l'infezione primaria il virus VZV si localizza, entrando in una fase di latenza, a livello dei nervi cranici e nei gangli delle radici posteriori





- **L'infezione naturale da VZV induce una risposta immune (umorale e cellulo-mediata-CMI) di lunga durata nei confronti della forma clinica**
- **L'immunità acquisita naturale non previene né la latentizzazione del VZV né la possibile successiva riattivazione (HZ)**

Heininger U et al., Lancet 2006; 368: 1365-76; Gershon AA et al., 2010; Gershon AA et al., 2012

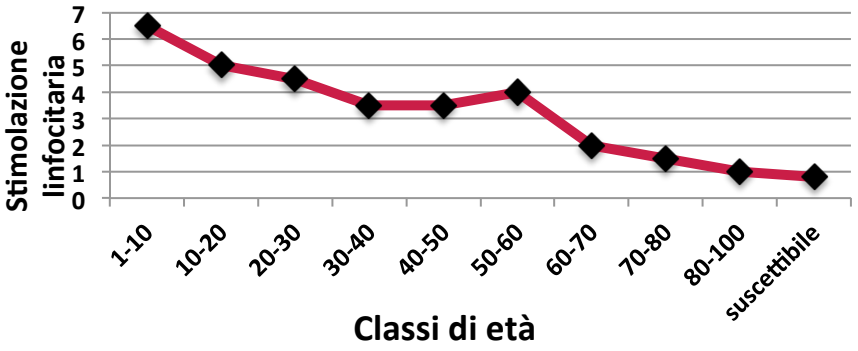
Risposta immunitaria

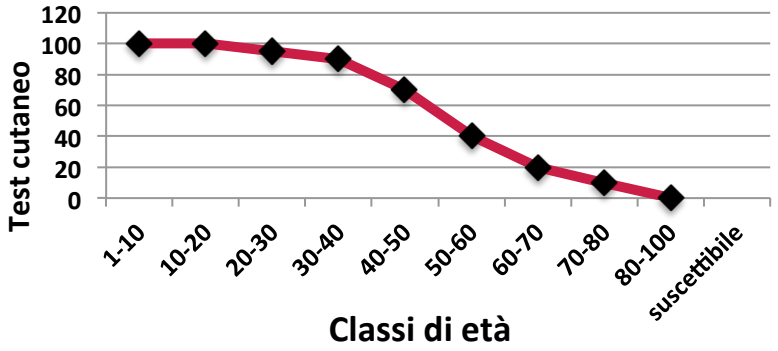
- Lo Zoster è strettamente correlato ad una diminuzione dei T-linfociti VZV specifici

- Un episodio di Zoster riattiva la risposta T-cellulare specifica

- Circa il 20% delle persone di 55-65 anni di età non ha una CMI specifica misurabile, nonostante la persistenza di Ab specifici ed un'anamnesi positiva

Immunità cellulo-mediata VZV-specifica in rapporto all'età





Arvin A. NEJM 2005; 352: 2266-7 ; Heininger U et al., Lancet 2006; 368: 1365-76; modificata da Gershon AA et al., J Clin Virol 2010; 48:S2-S7

ECDC **GUIDANCE**

Varicella vaccination in the European Union

European Centre for Disease Prevention and Control. Varicella vaccine in the European Union Stockholm: ECDC; 2014

In the absence of vaccination, the annual number of varicella cases in a given country is close to the country's birth cohort, with 52–78% of the incident cases occurring in children under six years and 89–95.9% of the cases before 12 years of age.

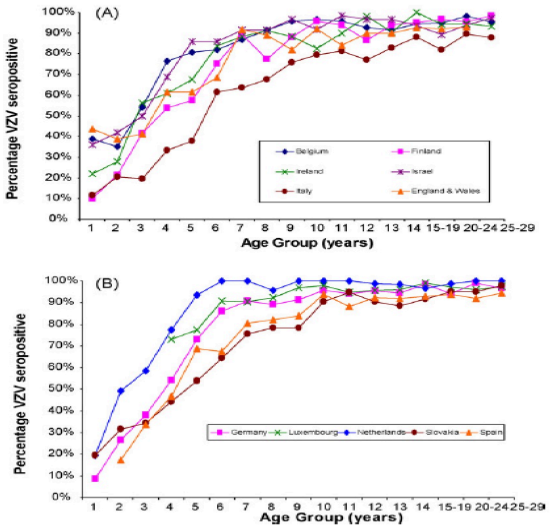
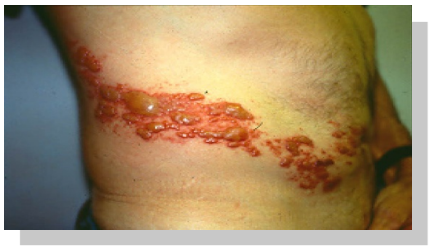


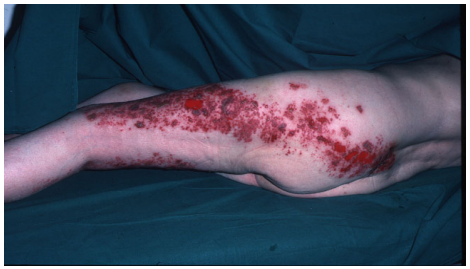
Fig. 1. Age-specific (<30 years of age) standardised sero-prevalence of VZV in 11 countries where samples were collected from either from residual sera (A) or from population sampling (B), 1995–2003.

Il 95% della popolazione adulta europea ha anticorpi anti-VZV

La maggior parte della popolazione europea può potenzialmente sviluppare Herpes Zoster nel corso della propria vita

da Nardone A et al., Vaccine 2007; 25: 7866-72





Le manifestazioni caratteristiche dell'HZ sono limitate ad un'area corporea circoscritta

il grado di compromissione dello stato di benessere del paziente è generale

L'HZ è di base una malattia del sistema nervoso (è la più comune manifestazione neurologica a carattere infettivo**)**

Il dolore dell'HZ riflette il neurotropismo del VZV.

Gilden D et al, F1000Res 2015; 4:1356; Johnson RW et al, Ther Adv Vaccines 2015; 3:109-20

Herpes Zoster
Complicanze neurologiche

- Nell'ospite immunocompetente la complicanza principale è la persistenza del dolore definita come **Nevralgia Post-Erpetica (PHN)**

- La PHN è una condizione dolorosa cronica che colpisce circa il 10-20% dei pazienti che hanno avuto un episodio di HZ acuto

Kawai K et al., BMJ Open 2014; 4: e004833; Forbes HJ et al., Pain 2016; 157: 30-54

Herpes Zoster
Complicanze oculari

- Il 10-20% dei casi di HZ coinvolge l'occhio: **herpes zoster oftalmico (HZO)**
- Il 50-72% di questi pazienti sviluppa patologie oculari croniche e/o perdita della vista
- Complicanze oculari correlate con HZO:
  - Congiuntiviti, ulcera corneale, cheratite, iridociclite, glaucoma, retinite, neurite ottica

Weinberg JM. J Am Acad Dermatol 2007; 57: S130-5; Johnson RW et al. Ther Adv Vaccines 2015; 3: 109-20

Caratteristiche epidemiologiche generali

- **Non esistono parametri immunologici specifici per prevedere chi svilupperà le manifestazioni cliniche dell'HZ**
- **L'incidenza dell'HZ è simile in tutto il mondo**
- **L'andamento correla con l'età della popolazione: da 2-3 casi/1000 persone/anno fra 20 e 50 anni a 5/1000 nella sesta decade, 6-7/1000 nella settima-ottava decade di vita**
- **Circa 1 persona su 4 sviluppa HZ nel corso della vita e due terzi dei casi si verificano in individui di età >50 anni**
- **In rapporto all'incremento della popolazione anziana e fragile, si attende un aumento dei casi di HZ nel prossimo futuro**

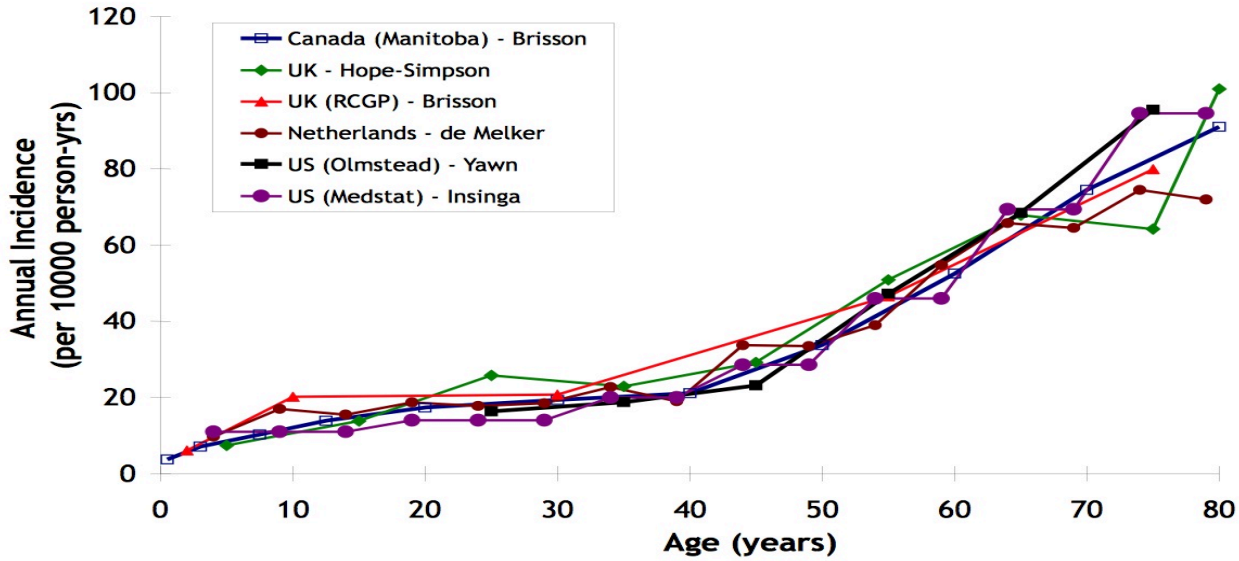
Johnson RW et al. Ther Adv Vaccines 2015; 3: 109-20

Herpes Zoster Disease

- Reactivation of VZV: Herpes zoster (shingles)
- Symptoms included rash with dermatomal distribution along with severe pain.
- Complications include:
  - Post-Herpetic Neuralgia (PHN) in 22% (8-26%) of herpes zoster patients: Pain persisting more than 90 days after rash onset
  - Herpes zoster Ophthalmicus: Ophthalmic division of trigeminal nerve ~15% of cases (If untreated, 50-70% develop acute ocular complications chronic complications, reduced vision, even blindness)
  - Neurologic: Invasion by VZV of vascular or neurologic structures can lead to Encephalitis, myelitis, optic neuritis, palsies, stroke syndromes, hearing impairment, vertigo, loss of taste sensation
  - Deaths mostly occur among the immunocompromised (0.25-0.51 per 1 million population; 7-25 per 100,000 cases)

Herpes Zoster incidence by age

Highly consistent findings between high income countries, no data from low and low-middle income countries



Lifetime risk=20-35%, steep increase in incidence with age

World Health Organization

Open Access Research

BMJ Open **Systematic review of incidence and complications of herpes zoster: towards a global perspective**

Kosuke Kawai,[1] Berhanu G Gebremeskel,[2] Camilo J Acosta[1]

Review sistematica di 130 studi in 26 Paesi

- *Incidenza di HZ → 3-5/1000 persone-anno*
- *Rischio di PHN → 5-30%*
- *Recidive → 1-6%*
- *Tasso di ospedalizzazione → 2-25/100.000 persone-anno*

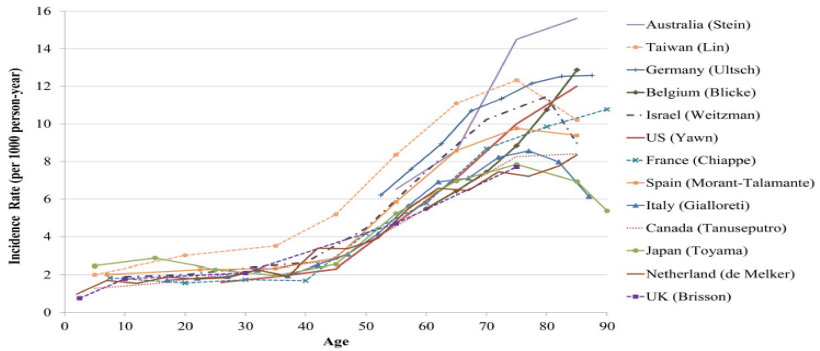


Figure 2 Age-specific incidence rate of herpes zoster in North America, Europe and Asia-Pacific.

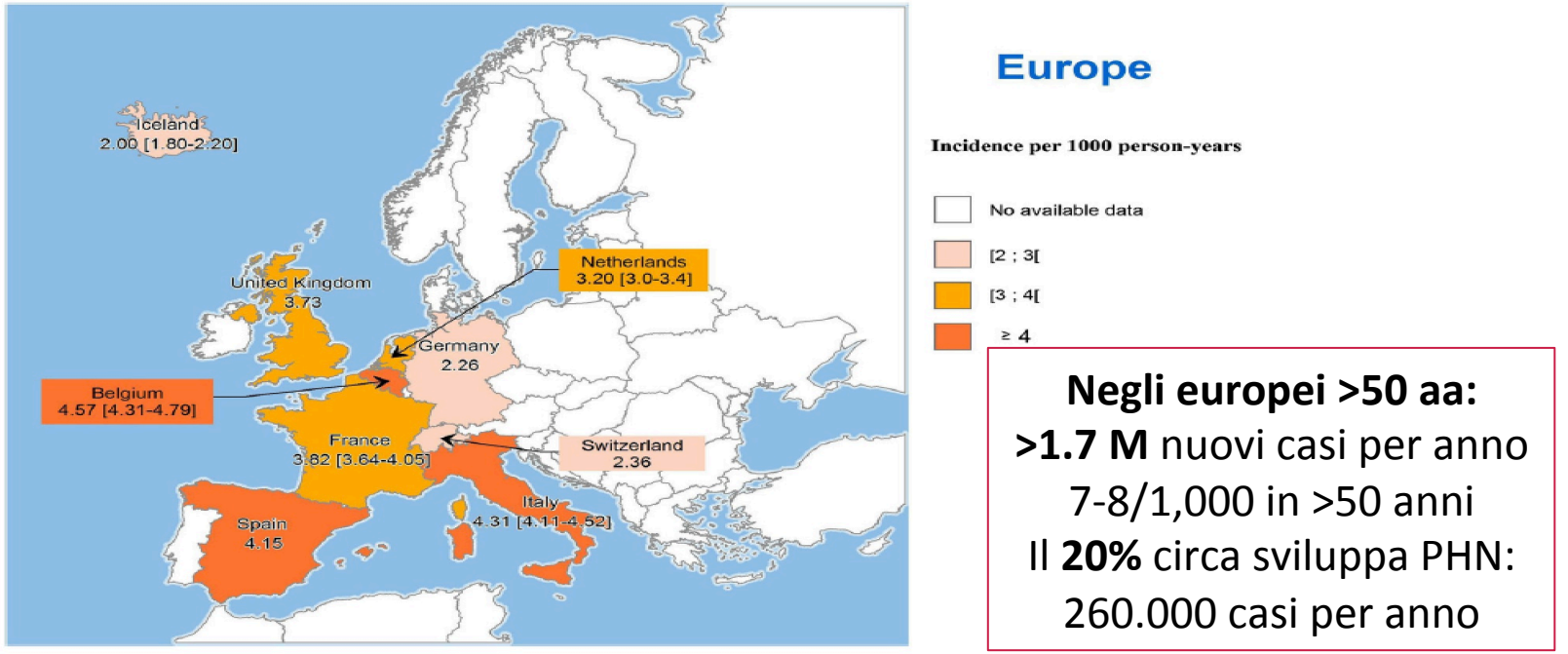
Pinchinat *et al. BMC Infectious Diseases* 2013, **13**:170
http://www.biomedcentral.com/1471-2334/13/170

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Similar herpes zoster incidence across Europe: results from a systematic literature review

Sybil Pinchinat[1], Ana M Cebrián-Cuenca[2], Hélène Bricout[3*] and Robert W Johnson[4]



Negli europei >50 aa:
>1.7 M nuovi casi per anno
7-8/1,000 in >50 anni
Il **20%** circa sviluppa PHN:
260.000 casi per anno

Figure 2 Overall annual herpes zoster (HZ) incidence rates in Europe (/1 000 person-years). Notes: The confidence interval is presented when available in the original publication. In case of several publications per country, the publication with the most recent data and that reported the overall HZ incidence rate is depicted.

Herpes Zoster
Fattori di rischio

Principali:

- **Età**
- **Depressione della immunità cellulo-mediata (CMI)**
- **Esposizione intrauterina**
- **Varicella acquisita in giovane età (<18 mesi)**

Altri:

Genere; Razza; Stress psicologico; Sostanze chimiche immunotossiche; Trauma meccanico; Predisposizione genetica

Thomas SL et al, Lancet Infect Dis 2004; 4: 26-33

Epidemiologia in Italia - Incidenza

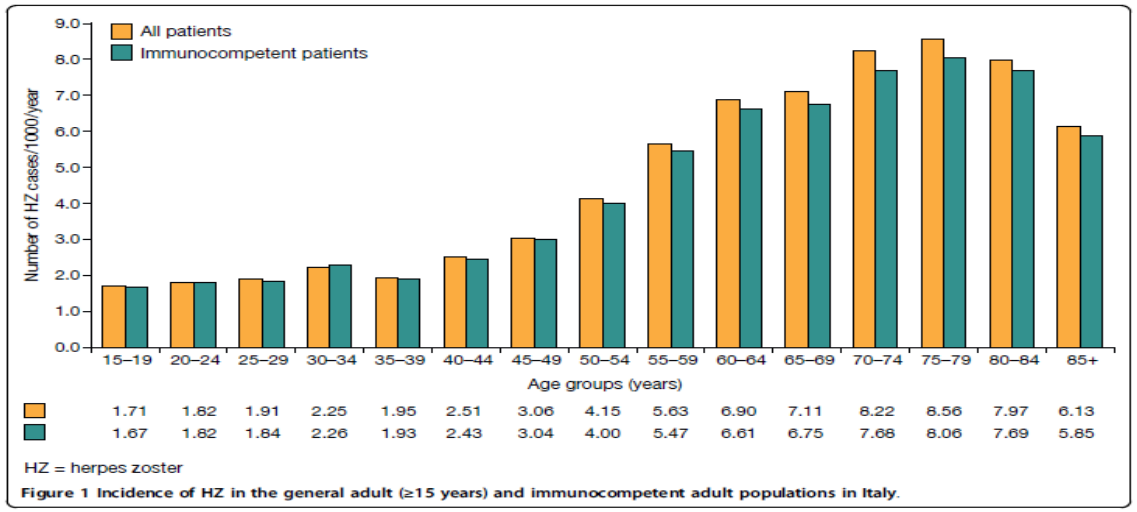
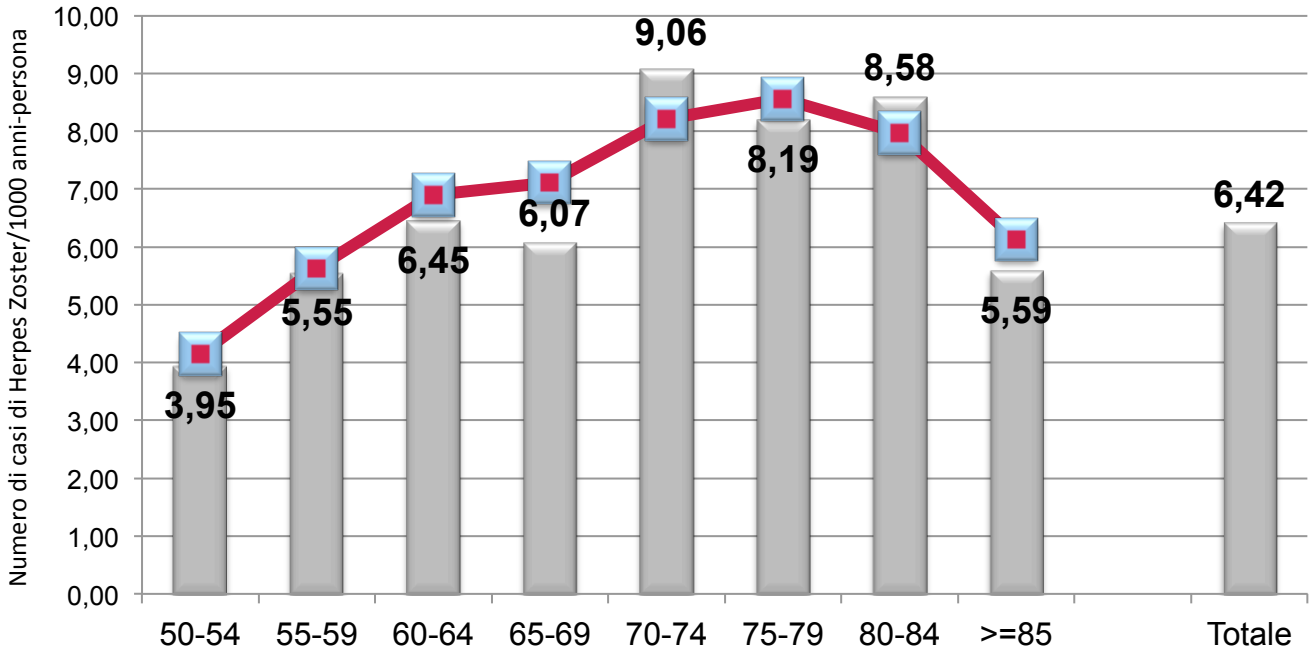


Figure 1 Incidence of HZ in the general adult (≥15 years) and immunocompetent adult populations in Italy.

- **Circa 22 milioni di persone di età ≥50,**
- **Stima di 157.100 nuovi casi di HZ ogni anno**
- **Incidenza annuale di 6,3/1.000 persone-anno**
- **88% dei casi sono immunocompetenti**

Gialloreti et al. BMC Infectious Diseases 2010

Incidenza di Herpes Zoster



56 MMG (2013-2015 Liguria, Puglia, Toscana e Veneto)

- **50 anni di età: 598 casi di HZ (93.145 anni persona)**
- **Incidenza complessiva: 6,42/1000 anni persona**

Alicino C et al. Hum Vaccin Immunother 2017: 2:399-404

Epidemiologia in Italia - PHN

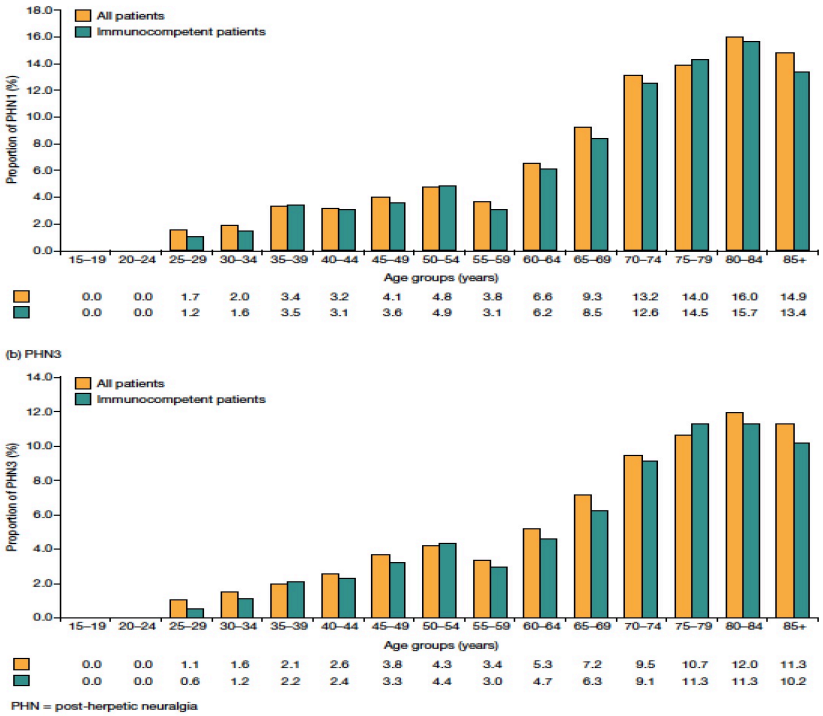


Figure 2 Proportion of PHN in the general adult (≥15 years) and immunocompetent adult populations in Italy.

Il 9,4% e il 7,2% dei soggetti >50aa. immunocompetenti ha sviluppato PHN a 1 e a 3 mesi rispettivamente

Gialloreti et al. BMC Infectious Diseases 2010

Bricout et al. BMC Infectious Diseases 2014, 14:637
http://www.biomedcentral.com/1471-2334/14/637

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Burden of herpes zoster-associated chronic pain in Italian patients aged 50 years and over (2009–2010): a GP-based prospective cohort study

Hélène Bricout[1*], Emilia Perinetti[2], Paolo Marchettini[3,9], Pietro Ragni[4], Carla Maria Zotti[5], Giovanni Gabutti[6], Antonio Volpi[7] and Elisabetta Franco[8]

Studio Heroes

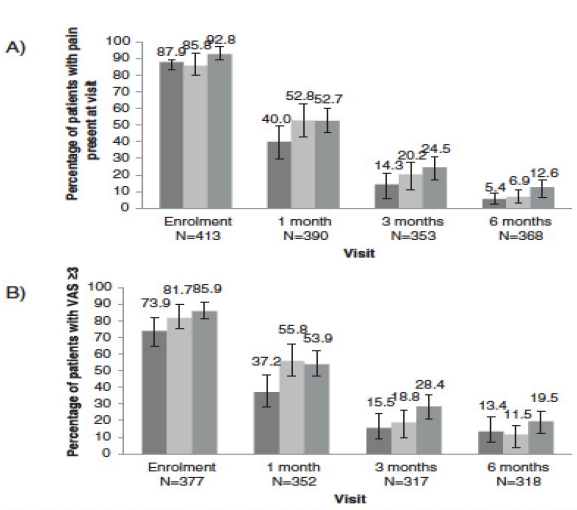


Figure 2 Percentage of patients with HZ-associated pain by age group (50–59; 60–69 and ≥70) and by visit A) presence of pain at visit and B) pain in the previous two weeks with a VAS score ≥3.

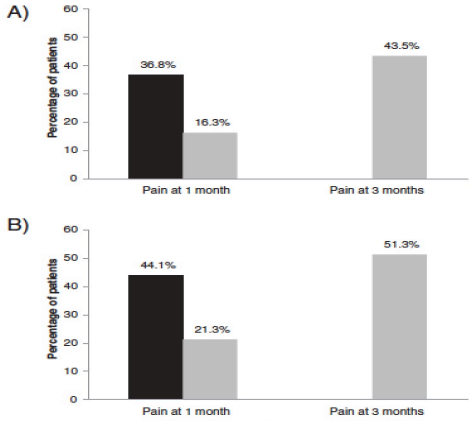


Figure 3 Percentage of patients with PHN (reported pain at the visit) at 3 (black bar) and 6 months (grey bar) among patients with pain at 1 month and 3 months. A: all patients aged ≥50; **B**: patients aged ≥ 70. 36.8% of patients aged ≥ 50 years and 44.1% of those aged ≥70 years with pain at 1 month had persistent pain at 3 months. 43.5% of patients aged ≥50 years and 51.3% of those aged ≥70 years with persistent pain at 3 months still had pain present at 6 months.

✓**Il 20,6% ed il 9,2% dei pazienti >50aa con HZ presentava PHN a 3 e 6 mesi, rispettivamente, nonostante il trattamento antivirale precoce (entro 72 ore dalla comparsa del rash).**

✓**HZ/PHN impatta sulla qualità della vita dei pazienti**

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 00, No. 00, 1–7
doi:10.1093/gerona/glw189
Advance Access publication October 28, 2016

OXFORD

Research Article

Impact of Underlying Conditions on Zoster-Related Pain and on Quality of Life Following Zoster

Laurence Torcel-Pagnon,[1] Hélène Bricout,[1] Isabelle Bertrand,[1] Emilia Perinetti,[2] Elisabetta Franco,[3] Giovanni Gabutti,[4] and Antonio Volpi[5]

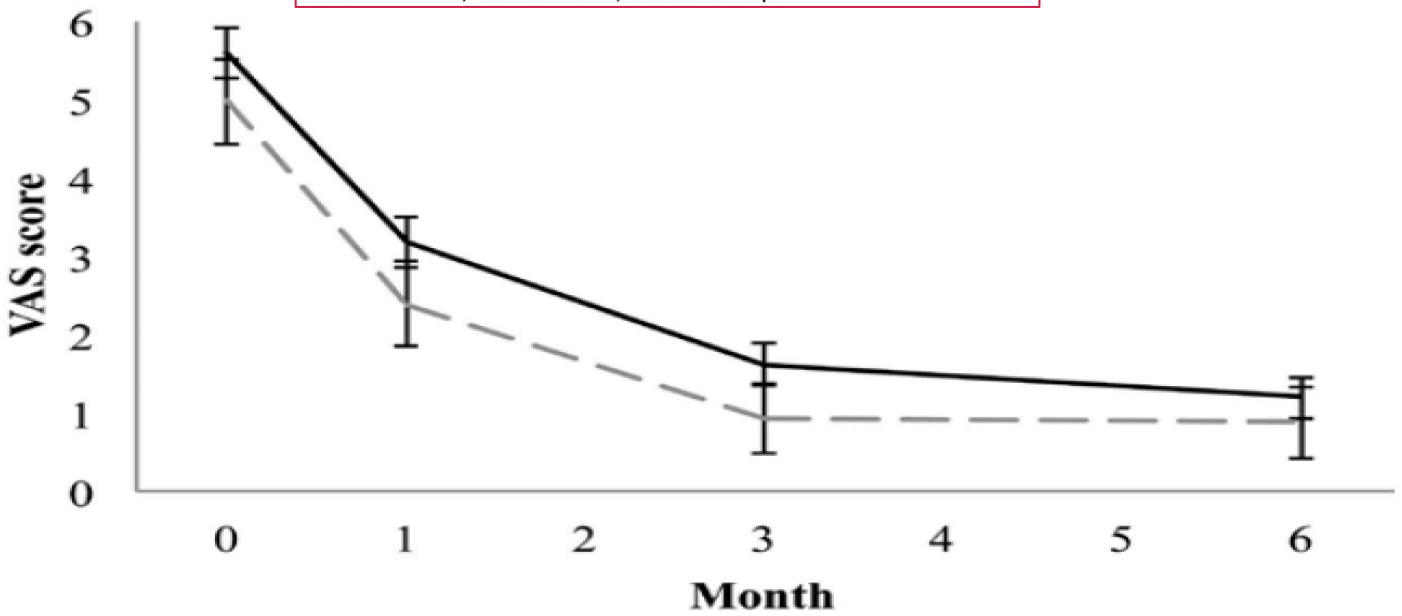


Figure 2. Changes in age-adjusted pain intensity during follow-up: estimated Visual Analog Scale score means by group over time. Solid black line represents patients with underlying conditions. Dashed gray line represents patients without underlying conditions.

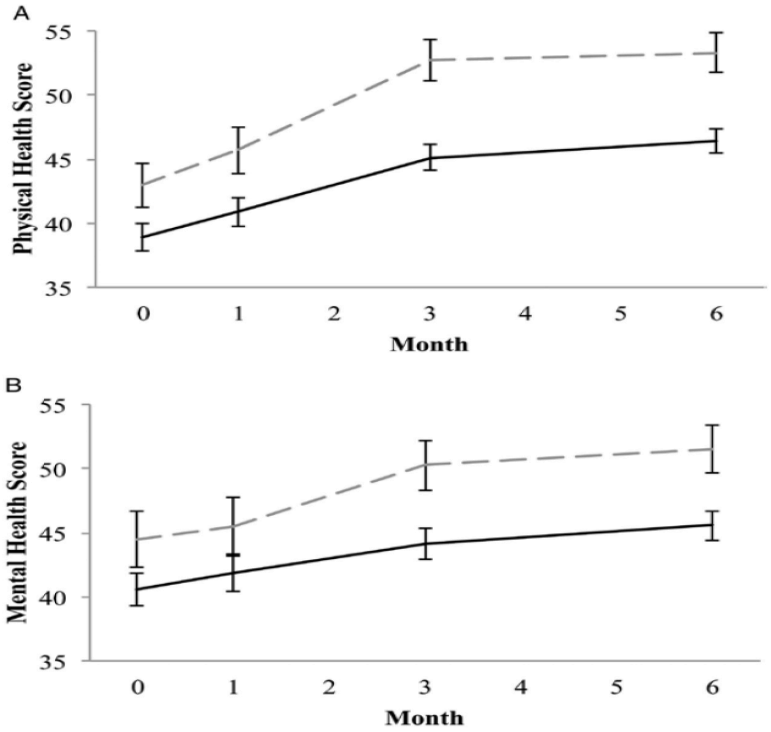


Figure 3. Changes in age-adjusted outcome measures during follow-up. (**A**) Estimated physical health score means by group over time. Solid black line represents patients with underlying conditions. Dashed gray line represents patients without underlying conditions. (**B**) Estimated mental health score means by group over time. Solid black line represents patients with underlying conditions. Dashed gray line represents patients without underlying conditions.

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 00, No. 00, 1–7
doi:10.1093/gerona/glw189
Advance Access publication October 28, 2016

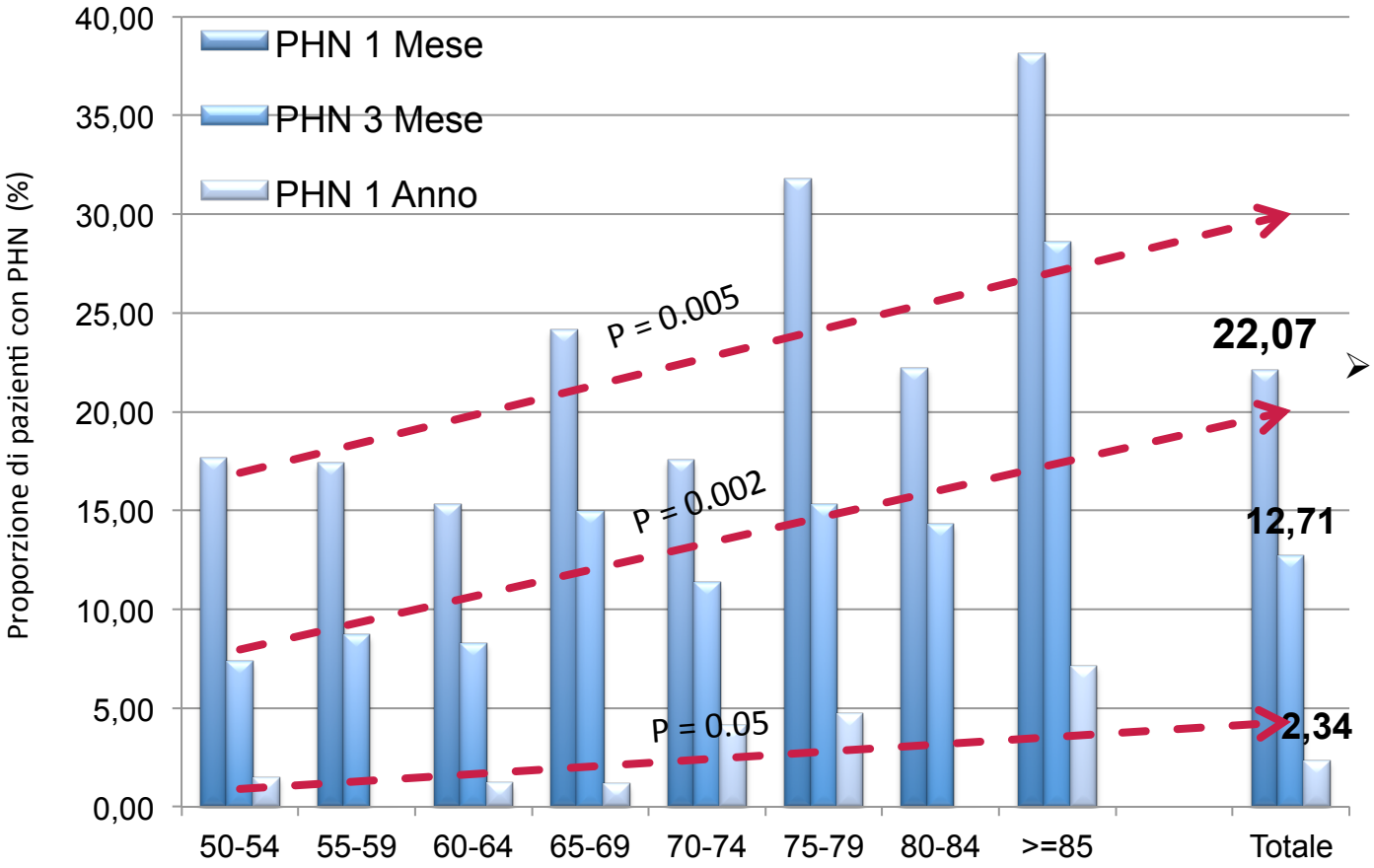
OXFORD

Research Article

Impact of Underlying Conditions on Zoster-Related Pain and on Quality of Life Following Zoster

Laurence Torcel-Pagnon,[1] Hélène Bricout,[1] Isabelle Bertrand,[1] Emilia Perinetti,[2] Elisabetta Franco,[3] Giovanni Gabutti,[4] and Antonio Volpi[5]

Proporzione di pazienti con PHN



56 MMG (2013-2015)
50 anni di età: 598 casi di HZ

Alicino C et al. Hum Vaccin Immunother 2017: 2:399-404

Herpes Zoster
Tassi di ospedalizzazione

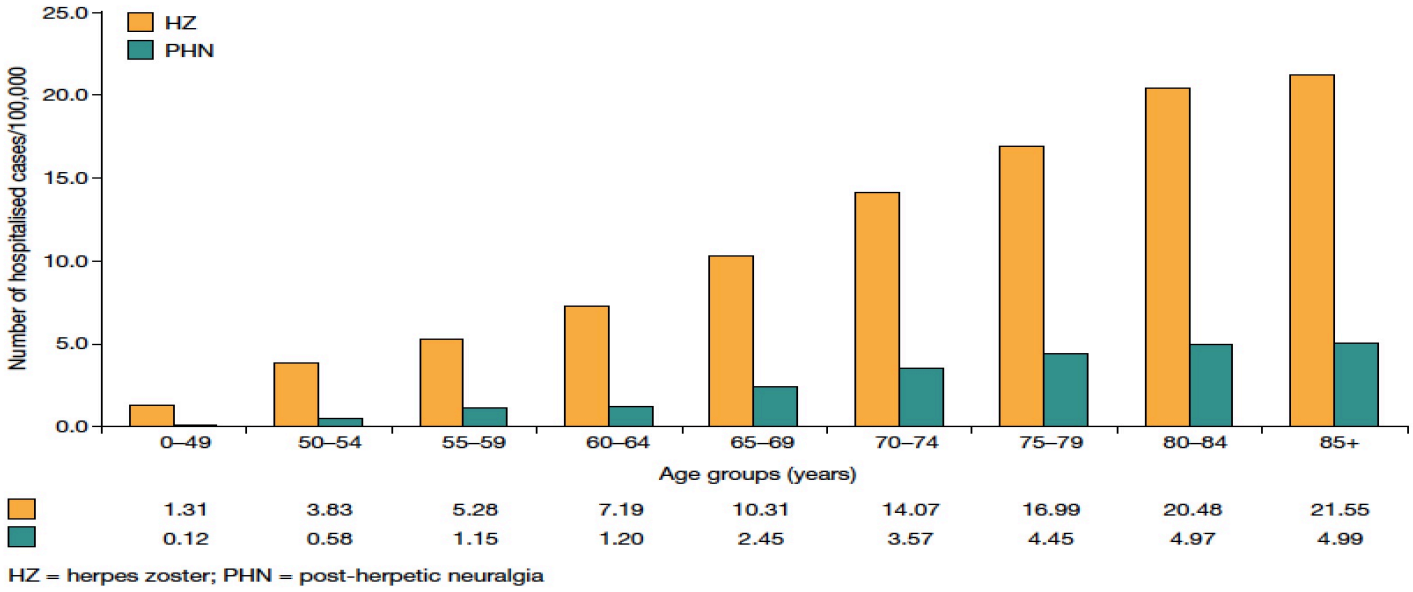
- **I tassi di ospedalizzazione HZ-correlati variano ampiamente fra i 2 ed i 25 ricoveri ogni 100.000 anni-persona di osservazione**

- **Le ospedalizzazioni con diagnosi primaria di HZ rappresentano fra il 29% ed il 42% di tutti i ricoveri associati ad HZ**

- **I tassi aumentano in maniera rilevante nei soggetti >50anni di età attestandosi a 10-13/100.000 nei soggetti 60-69 anni di età ed a 50-100 ospedalizzazioni/100.000 nei soggetti >80 anni.**

Kawai K et al, BMJ Open 2014; 4:e004833

Epidemiologia in Italia - Ricoveri



HZ = herpes zoster; PHN = post-herpetic neuralgia

Figure 3 Age-related incidence of hospitalisation for HZ and PHN in immunocompetent adults in Italy.

Il tasso di incidenza di ricoveri nei soggetti >50aa immunocompetenti è risultato pari a 10,34 e 1,89/100.000 persone/anno rispettivamente per HZ e PHN

Gialloreti et al. BMC Infectious Diseases 2010

	Primary diagnosis, *n* (%)	Secondary diagnosis, *n* (%)	Total
	47,198 (50.3)	46,610 (49.7)	93,808
Gender, *n* (%)			
Male	21,545 (45.6)	[illegible] (44.4)	42,263 (45.1)
Female	25,653 (54.4)	25,892 (55.6)	51,545 (54.9)
Age class, *n* (%)	65 (20.0)	69 (17.8)	67 (19.0)
<18	2091 (4.4)	912 (2.0)	3003 (3.2)
18–49	6431 (13.6)	5655 (12.1)	12,086 (12.9)
50–59	5160 (10.9)	4000 (8.6)	9160 (9.8)
60–69	9018 (19.1)	7790 (16.7)	16,808 (17.9)
70–79	13,495 (28.6)	13,596 (29.2)	27,091 (28.9)
80+	11,003 (23.3)	14,657 (31.4)	25,660 (27.4)
Average length of stay, average (SD)	15.6 (13.3)	27.0 (31.8)	21.3 (25.0)
Discharge, *n* (%)			
Alive	47,060 (99.7)	45,477 (97.6)	92,537 (98.6)
Dead	138 (0.3)	1133 (2.4)	1271 (1.4)
Type of hospitalization, *n* (%)			
Ordinary hospitalization	41,669 (88.3)	41,419 (88.9)	83,088 (88.6)
Day-hospital admission	5529 (11.7)	5191 (11.1)	10,720 (11.4)
HZ, *n* (%)			
Uncomplicated	22,377 (47.4)	27,541 (59.1)	49,918 (53.2)
With complications	24,821 (52.6)	19,069 (40.9)	43,890 (46.8)
Neurological	12,052 (25.5)	9814 (21.1)	21,866 (23.3)
Ophtalmic	7431 (15.7)	5111 (11.0)	12,542 (13.4)
Other specified complications	3606 (7.6)	2397 (5.1)	6003 (6.4)
Other unspecified complications	1732 (3.7)	1747 (3.7)	3479 (3.7)
Co-morbidity, *n* (%)			
Malignancy	3092 (6.6)	7608 (16.3)	10,700 (11.4)
COPD	2387 (5.1)	4983 (10.7)	7370 (7.9)
Kidney failure	1514 (3.2)	3421 (7.3)	4935 (5.3)
Diabetes	4736 (10.0)	5432 (11.7)	10,168 (10.8)
Autoimmune diseases	655 (1.4)	781 (1.7)	1436 (1.5)

Table 2 Main characteristics of subjects discharged with an HZ diagnosis (Italy, 2001–2013)

Aging Clin Exp Res
DOI 10.1007/s40520-017-0782-z

CrossMark

ORIGINAL ARTICLE

Temporal trends in herpes zoster-related hospitalizations in Italy, 2001–2013: differences between regions that have or have not implemented varicella vaccination

Nicoletta Valente[1] · Silvia Cocchio[2] · Armando Stefanati[1] · Tatjana Baldovin[2] · Domenico Martinelli[3] · Rosa Prato[3] · Vincenzo Baldo[2] · Giovanni Gabutti[1]

Aging Clin Exp Res
DOI 10.1007/s40520-017-0782-z

ORIGINAL ARTICLE

Temporal trends in herpes zoster-related hospitalizations in Italy, 2001–2013: differences between regions that have or have not implemented varicella vaccination

Nicoletta Valente[1] · Silvia Cocchio[2] · Armando Stefanati[1] · Tatjana Baldovin[2] · Domenico Martinelli[3] · Rosa Prato[3] · Vincenzo Baldo[2] · Giovanni Gabutti[1]

Table 3 Main characteristics of subjects discharged with a diagnosis of post-herpetic neuralgia (Italy, 2001–2013)

	Primary diagnosis, *n* (%)	Secondary diagnosis, *n* (%)	Total
	3408 (51.8)	3172 (48.2)	6580
Average length of stay, average (SD)	16.6 (19.1)	24.9 (26.0)	20.6 (23.1)
Discharge, *n* (%)			
Alive	3401 (99.8)	3145 (99.1)	6546 (99.5)
Dead	7 (0.2)	27 (0.9)	34 (0.5)
Type of hospitalization, *n* (%)			
Ordinary hospitalization	2435 (71.4)	2718 (85.7)	5153 (78.3)
Day-hospital admission	973 (28.6)	454 (14.3)	1427 (21.7)
Co-morbidity, *n* (%)			
Malignancy	111 (3.3)	355 (11.2)	466 (7.1)
COPD	170 (5.0)	375 (11.8)	545 (8.3)
Kidney failure	92 (2.7)	192 (6.1)	284 (4.3)
Diabetes	306 (9.0)	394 (12.4)	700 (10.6)
Autoimmune diseases	35 (1.0)	54 (1.7)	89 (1.4)

Herpes Zoster
Qualità della vita

- **HZ è un'esperienza estremamente debilitante per il soggetto con compromissione delle capacità fisiche, produttive, relazionali e, in caso di cronicizzazione, psicologiche**

- **HZ e le complicanze correlate influenzano negativamente la qualità della vita delle persone affette**

Gater et al. BMC Public Health (2015) 15:193

L'HZ impatta negativamente sulla Qualità della Vita

- **Numerosi dati mostrano che i parametri HRQoL*:**
  - **sono inversamente proporzionali ai livelli del dolore**
  - **hanno peggiori punteggi nei pazienti con PHN**

- **Impatto sulle relazioni sociali e sulla famiglia:**
  - **fino al 50% dei pz con HZ e fino al 81% di quelli con PHN riporta conseguenze negative sui rapporti familiari/sociali**

Livello di interferenza del dolore in diversi domini della salute (indagata con questionario ZBPI o simile)

Health state domains	HZ (mean scores)	PHN (mean scores)
General activity	3.8-4.4	3.1-5.7
Mood	3.4-4.5	3.4-5.9
Walking ability	1.7-4.0	1.7-5.8
Normal work	3.3-4.4	2.9-6.1
Social relations	2.1-3.5	2.1-5.4
Sleep	4.5-4.9	6.3-6.5
Enjoyment of life	3.6-4.0	3.8-5.2

Data from Bouhassira 2012 [15], Gater 2014 [50], Lukas 2012 [58], Serpell 2014 [14], Weinke 2010 [77].

HRQoL: health-related quality of life
*** Indagati con questionari come SF-12, WQ-5D; SIQ**

Gater et al. BMC Public Health (2015) 15:193

PLOS | ONE

RESEARCH ARTICLE

The Short- and Long-Term Risk of Stroke after Herpes Zoster: A Meta-Analysis

Xuechun Liu[1], Yeming Guan[1], Liang Hou[1], Haili Huang[1], Hongjuan Liu[1], Chuanwen Li[1], Yingying Zhu[1], Xingyong Tao[2], Qingsong Wang[1]*

Background

Accumulating evidence indicates that stroke risk may be increased following herpes zoster. The aim of this study is to perform a meta-analysis of current literature to systematically analyze and quantitatively estimate the short and long-term effects of herpes zoster on the risk of stroke.

Methods

Embase, PubMed and Cochrane library databases were searched for relevant studies up to March 2016. Studies were selected for analysis based on certain inclusion and exclusion criteria. Relative risks with 95% confidence interval (CI) were extracted to assess the association between herpes zoster and stroke.

Results

A total of 8 articles were included in our analysis. The present meta-analysis showed that the risks of stroke after herpes zoster were 2.36 (95% CI: 2.17–2.56) for first 2 weeks, 1.56 (95% CI: 1.46–1.66) for first month, 1.17 (95% CI: 1.13–1.22) for first year, and 1.09 (95% CI: 1.02–1.16) for more than 1 year, respectively.

Conclusion

The results of our study demonstrated that herpes zoster was associated with a higher risk of stroke, but the risks decreased along with the time after herpes zoster.

2016

Table 2. Summary of measures of association between herpes zoster (type unspecified) * and cardiovascular events in reviewed studies.

Outcome	Reference	Follow Up Period After HZ	*n* Events / *n* with HZ	Adjustment Variables	Measure of Association**	Adjusted Association Size (95% CI)
Cerebrovascular Events						
Stroke (Non-Specified)	Langan *et al.*	3 months	149**	AGE	IR	1.42 (1.21 to 1.68)
	Schink *et al.*	3 months	352**	AGE	IRR	1.29 (1.16 to 1.44)
	Yawn *et al.*	3 months	33 / 4,478	AGE, ARTHM, VASC	OR	1.53 (1.01 to 2.33)
	Yawn *et al.*	6 months	46 / NR	AGE, HTN, VASC	OR	1.28 (0.91 to 1.80)
	Kang *et al.*	1 year	133 / 7,760	AGE, SEX, HTN, DM, CHD, HYPLIP, RENAL, AF, HF, VALV, CRTD, INC, URBN, GEO	HR	1.31 (1.06 to 1.60)
	Sundström *et al.*	1 year	111 / 13,269	AGE, SEX	IRR	1.34 (1.12 to 1.62)
	Yawn *et al.*	1 year	71 / NR	AGE, SEX, HTN, DYSLIP, CHD, VASC	OR	1.04 (0.79 to 1.36)
	Yawn *et al.*	3 years	176 / 4,151	AGE, SEX, HTN, DYSLIP, CHD, VASC, DEP	OR	1.02 (0.86 to 1.22)
	Breuer *et al*	24 years	2,727 / 106,601	AGE, SEX, BMI, SMK, HYPLIP, HTN, DM, CHD, AF, PVD, CRTD, VALV	HR	1.02 (0.98 to 1.07)
Ischemic Stroke	Minassian *et al.*	1 week	499**	AGE	IR	2.37 (2.17 to 2.59)
	Schink *et al.*	3 months	310**	AGE	IRR	1.27 (1.13 to 1.42)
Hemorrhagic Stroke	Schink *et al.*	3 months	42**	AGE	IRR	1.53 (1.11 to 2.11)
TIA	Breuer *et al.*	24 years	2,275 / 106,601	AGE, SEX, BMI, SMK, HYPLIP, HTN, DM, CHD, AF, PVD, CRTD, VALV	HR	1.15 (1.09 to 1.21)
Stroke and TIA	Sreenivasan *et al.*	2 weeks	83 / 117,926	AGE, SEX, SN	IRR	2.27 (1.83 to 2.82)
	Sreenivasan *et al.*	1 year	4,876 / 117,926	AGE, SEX, SN	IRR	1.21 (1.14 to 1.29)
	Sreenivasan *et al.*	1 year				1.05 (1.02 to 1.09)
	Kwon *et al.*	11 years	5,069 / 77,781	AGE, SEX, HTN, HYPLIP, CHD, DM, HF, PVD, AF, RENAL, VALV	IRR	1.90 (1.85 to 1.95)

*Cases of herpes zoster ophthalmicus were included in all cases of the exposures,
** Comparison of patients with herpes zoster to those without (referent group)
Abbreviations (Alphabetically): AF: atrial fibrillation, ARTHM: arrhythmia, BMI: body mass index, CLIN: frequency of clinical visits, CNCR: cancer, CRTD: carotid disease, CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, CVD: cerebral vascular disease, DEP: depression, DM: diabetes mellitus, GEO: geographical region, HF: heart failure: HR: hazard ratio, HYPLIP: hyperlipidemia, HTN: hypertension, HZ: Herpes Zoster, INC: income, IR: incidence ratio, IRR: incidence rate ratio, MEDS: medication use, NR: not reported, OCC: occupation, PVD: peripheral vascular disease, RENAL: renal disease, SCCS: self-controlled case series, SN: season, SMK: smoking statin, URBN: urbanization level of patient's area of residence, VALV: valvular disease

Table 3. Summary of measures of association between herpes zoster (type unspecified) * and cardiac events in reviewed studies.

Outcome	Reference	Follow Up Period After HZ	*n* Events / *n* with HZ	Adjustment Variables	Measure of Association**	Adjusted Association Size (95% CI)
Cardiac Events						
Myocardial Infarction	Minassian *et al*	1 week	213**	AGE	IR	1.68 (1.47 to 1.92)
	Yawn *et al.*	3 months	24 / 4,405	AGE, CHD	OR	1.68 (1.03 to 2.75)
	Yawn *et al.*	6 months	35 / NR	AGE, CHD, DM	OR	1.44 (0.97 to 2.15)
	Yawn *et al.*	1 year	61 / NR	AGE, SEX, CHD, DM, DEP	OR	1.33 (0.99 to 1.80)
	Yawn *et al.*	3 year	154 / 4,102	AGE, SEX, HTN, CHD, DM	OR	1.17 (0.97 to 1.41)
	Breuer *et al.*	24 years	2,762 / 106,601	AGE, SEX, BMI, SMK, DYSLIP, HTN, DM, CHD, AF, PVD, CRTD, VALV	HR	1.10 (1.05 to 1.16)
Acute Coronary Syndromes	Wang *et al.*	3 months	58 / 57,958	AGE, SEX, URBN, INC, OCPTN, CLIN, HTN, DM, HYPLIP, CVD, COPD, RENAL, CNCR, MEDS	HR	1.20 (0.89 to 1.62)
	Wang *et al.*	1 year	193 / 57,958	AGE, SEX, URBN, INC, OCPTN, CLIN, HTN, DM, HYPLIP, CVD, COPD, RENAL, CNCR, MEDS	HR	1.14 (0.94 to 1.39)
	Wang *et al.*	12 years	860 / 57,958	AGE, SEX, URBN, INC, OCPTN, CLIN, HTN, DM, HYPLIP, CVD, COPD, RENAL, CNCR, MEDS	HR	1.15 (1.07 to 1.24)
Coronary Artery Disease	Wu *et al.*	2 years	388 / 19,483	AGE, SEX, DM, HTN, HYPLIP	HR	1.14 (1.02 to 1.28)
	Wu *et al.*	10 years	1,057 / 19,483	AGE, SEX, DM, HTN, HYPLIP	HR	1.11 (1.04 to 1.19)

*Cases of herpes zoster ophthalmicus were included in all cases of the exposures,
** Comparison of patients with herpes zoster to those without (referent group)
Abbreviations (Alphabetically): AF: atrial fibrillation, ARTHM: arrhythmia, BMI: body mass index, CLIN: frequency of clinical visits, CNCR: cancer, CRTD: carotid disease, CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, CVD: cerebral vascular disease, DEP: depression, DM: diabetes mellitus, GEO: geographical region, HF: heart failure: HR: hazard ratio, HYPLIP: hyperlipidemia, HTN: hypertension, HZ: Herpes Zoster, INC: income, IR: incidence ratio, IRR: incidence rate ratio, MEDS: medication use, NR: not reported, OCC: occupation, PVD: peripheral vascular disease, RENAL: renal disease, SCCS: self-controlled case series, SN: season, SMK: smoking statin, URBN: urbanization level of patient's area of residence, VALV: valvular disease

PLOS ONE

RESEARCH ARTICLE

A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events

Nathaniel Erskine[1], Hoang Tran[1], Leonard Levin[2], Christine Ulbricht[1], Joyce Fingeroth[3], Catarina Kiefe[1], Robert J. Goldberg[1]*, Sonal Singh[4,5]

Table 4. Summary of measures of association between herpes zoster ophthalmicus and cardiovascular events in reviewed studies.

Outcome	Reference	Follow Up Period After HZO	*n* Events / *n* with HZ	Adjustment Variables	Measure of Association*	Adjusted Association Size (95% CI)
Cerebrovascular Events						
Stroke (Non-Specified)	Schink *et al.*	3 months	31*	AGE	IRR	1.59 (1.10 to 2.32)
	Langan *et al.*	4 months	22*	AGE	IR	3.38 (2.18 to 5.24)
	Kang *et al.*	1 year	7 / 120	AGE, SEX, HTN, DM, CHD, HYPLYP, RENAL, AF, HF, VALV, CRTD, INC, URBN, GEO	HR	4.28 (2.01 to 9.03)
	Lin *et al.*	1 year	53 / 658	AGE, SEX, HTN, HYPLIP, DM, CHD, RHD, MEDS	HR	4.52 (2.45 to 8.33)
	Breuer *et al.*	24 years	68 / 1,710	AGE, SEX, BMI, SMK, DYSLIP, HTN, DM, CHD, AF, PVD, CRTD, VALV	HR	1.03 (0.77 to 1.39)
Ischemic Stroke	Minassian *et al.*	1 week	93*	AGE	IR	2.73 (2.22 to 3.35)
	Minassian *et al.*	3 months	326*	AGE	IR	1.29 (1.15 to 1.44)
	Schink *et al.*	3 months	27*	AGE	IRR	1.57 (1.05 to 2.35)
Hemorrhagic Stroke	Schink *et al.*	3 months	4*	AGE	IRR	1.82 (0.62 to 5.37)
Coronary Events						
Myocardial Infarction	Minassian *et al.*	1 week	43 (SCCS)	AGE	IR	2.06 (1.52 to 2.79)

* Comparison of patients with herpes zoster to those without (referent group)
Abbreviations (Alphabetically): AF: atrial fibrillation, BMI: body mass index, CLIN: frequency of clinical visits, CNCR: cancer, CRTD: carotid disease, CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, CVD: cerebral vascular disease, DEP: depression, DM: diabetes mellitus, GEO: geographical region, HF: heart failure: HR: hazard ratio, HYPLIP: hyperlipidemia, HTN: hypertension, HZ: Herpes Zoster, INC: income, IR: incidence ratio, IRR: incidence rate ratio, MEDS: medication use, NR: not reported, OCC: occupation, PVD: peripheral vascular disease, RENAL: renal disease, SSN: season, SMK: smoking statin, URBN: urbanization level of patient's area of residence, VALV: valvular disease

Herpes Zoster
Mortalità

- **Pur essendo i dati molto eterogenei, la mortalità totale a livello europeo varia da 0 a >0,07/100.000.**

- **Il tasso di letalità è compreso tra 2 e 61/100.000 nelle classi di età 45-65 e ≥65 anni, rispettivamente**

- **La mortalità HZ-associata aumenta con l'età.**

- **Gli anziani che sviluppano HZ hanno spesso patologie di base e sono ad aumentato rischio di declino funzionale e perdita di indipendenza.**

Bricout H et al. BPM PH 2015; 15: 466

Il Burden of Disease dell'HZ in Italia ha un impatto economico di 49 M€/anno (costi diretti e indiretti)

	HZ+PHN	HZ/caso trattato	PHN/caso trattato
Costi diretti	34 €M	€ 196	€ 662
Costi indiretti	15 €M	€ 657	€ 930
TOTALE	49 €M	€ 853	€ 1.592

Herpes Zoster
Razionale e motivazioni per la prevenzione

- **Impatto epidemiologico rilevante**
- **Complicanze frequenti e debilitanti (es. PHN)**
- **Impatto negativo sulla qualità della vita delle persone affette**
- **Possibilità sub-ottimale di trattamento delle complicanze**
- **Costi per la gestione diagnostica e clinico-terapeutica del paziente con Herpes Zoster acuto, delle ospedalizzazioni, complicanze e costi sociali HZ-correlati**

Gabutti G et al JMM 2016;65:1363-9; Khudari P et al, Ig San Pubbl 2016; 72:265-92; Gabutti G et al. Human Vaccin Immunother 2017; 2:1-8

Fin dagli anni '90 è stato dimostrato che i vaccini varicella, in particolare quelli ad elevato titolo antigenico, possono elicitare un incremento significativo della risposta cellulo-mediata VZV-specifica in anziani immunocompetenti

Vaccino Varicella Ceppo Oka/Merck → **≥ 1350 PFU**

PFU, unità formanti placca

Vaccino Zoster Ceppo Oka/Merck → **> 19400 PFU**

Eccipienti

Polvere:
- Saccarosio
- Gelatina idrolizzata
- Sodio cloruro
- Potassio diidrogeno fosfato
- Potassio cloruro
- Monosodio L-glutammato
- Disodio fosfato anidro
- Sodio idrossido
- Urea

Solvente:
- Acqua per preparazioni iniettabili

Vaccino Zoster SPC EMA 2016; Gagliardi AMZ et al, Cochrane Database of Systematic revieews 2016:3

Importanza della risposta immune cellulo-mediata (CMI) VZV-specifica nel controllo del virus latente

- **La CMI VZV-specifica ha un ruolo cruciale nel controllo dell'infezione latente.**

- **Una adeguata risposta CMI VZV-specifica previene o blocca la slatentizzazione**

- **I vaccini varicella, in particolare quelli ad elevato titolo antigenico, elicitano un incremento significativo della CMI in anziani immunocompetenti**

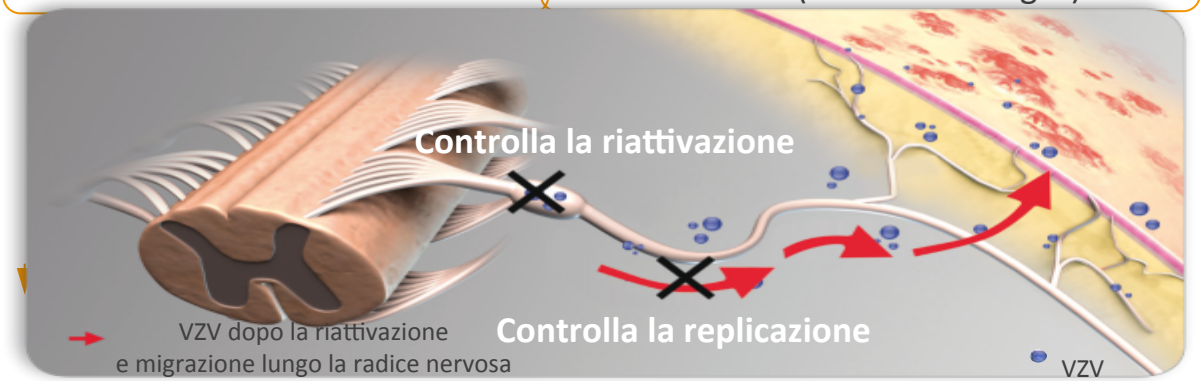
Oxman MN, Clin Infect Dis 2010; 51:197-213; Gabutti G et al., Human Vaccin Immunother 2015; 11:101-7

Aspetto innovativo: il vaccino Zoster vivo attenuato (ceppo OKA/Merck) previene la manifestazione clinica in un soggetto già infetto.

Il vaccino controlla

Riattivazione del virus latente della Varicella-Zoster

Replicazione e diffusione del VZV fino alla cute (danni neurologici)



AIUTA A PREVENIRE L'HERPES ZOSTER
Riducendo l'incidenza di HZ

ATTENUA LA SEVERITÀ DELLA PATOLOGIA
Riducendo la severità e la durata del dolore
Riducendo l'incidenza di PHN

Indicato per la prevenzione, ma non per il trattamento, dell' Herpes Zoster e della Nevralgia post-erpetica

Sintesi dei dati di efficacia ed effectiveness

		Efficacia HZ	Efficacia PHN
Studi clinici (RCT- efficacia)			
	SPS – (>60 anni) (Oxman MN, 2005)	51,3%	66,5%
	ZEST – (50-59 anni) (Schmader Ke, 2012	69,8%	-
Studi osservazionali (effectiveness)			
	Tzeng 2011 (>60 anni)	55%	-
	Langan 2013 (>65 anni)	48%	59%
	Zhang 2012 (>65 anni)	49%	-
	Tzeng 2014 (>60 anni, successiva chemioterapia)	42%	-
	Marin 2015 (>60 anni)	54%	61%

Oxman MN, et al.. N Engl J Med. 2005; 352:2271-84. Schmader KE et al.. Clin Infect Dis 2012; 54:922-8; Tseng HF et al. JAMA: 2011; 305:160-6 ; Langan SM et al. PLOS Med. 2013; 10: e1001420; Zhang J et al.. JAMA 2012; 308: 43-9; Tzeng CID 2014; 59: 913-9; . Marin Human Vacc Immunother 2015; 11: 1157-64

Esperienze applicative: effectiveness e sicurezza

- I risultati degli studi di efficacia (RTC) ed effectiveness sono coerenti
- I dati di effectiveness sono consistenti e coerenti tra di loro pur derivando da studi condotti con disegni ed in popolazioni con caratteristiche differenti.
- Buon profilo di tollerabilità e sicurezza confermato in tutti gli studi.

- Schedula con una sola dose (0,65ml) per via sottocutanea o intramuscolare, indipendentemente dalla storia clinica di Herpes Zoster o Varicella

Vaccino zoster SPC EMA 2016; Gabutti G et al. Hum Vaccin Immunother 2017; 13:391-8

Vaccino Zoster (ceppo Oka/Merck) - Indicazioni terapeutiche

L'uso del vaccino zoster è raccomandato negli USA dal 2006 ed in Canada dal 2010 per i soggetti ≥ 60 anni di età. In Europa, l'European Medicines Agency (EMA) ha approvato il vaccino per i soggetti >60 anni (2006) e successivamente per quelli >50 anni d'età (2007).

- **Indicato per la prevenzione dell'herpes zoster (HZ) e della nevralgia post-erpetica (PHN)**
- **Indicato per l'immunizzazione di soggetti di età pari a 50 anni e oltre.**
- **Non indicato per la prevenzione dell'infezione primaria da varicella**
- **Non deve essere usato nei bambini e negli adolescenti**
- **Il vaccino zoster può essere co-somministrato con il vaccino influenza inattivato**
- **Il vaccino zoster ed il vaccino pneumococcico polisaccaridico 23-valente non dovrebbero essere co-somministrati (a causa di una ridotta immunogenicità della componente zoster evidenziata nel corso di trial clinici)**
- **Non ci sono dati disponibili sulla co-somministrazione con altri vaccini**
- **La co-somministrazione del vaccino zoster con farmaci anti-virali efficaci contro il VZV non è stata valutata**

Vaccino Zoster (Ceppo OKA/Merck)

VE nei confronti di **HZ** durante il periodo dello studio e sulla media nel corso di 3 e 5 anni, per età al momento della vaccinazione. Dal 2007 al 2014

	Età alla vaccinazione*				
	50-59 anni	60-69 anni	70-79 anni	80+ anni	Tutti i gruppi d'età
	EV % (95% CI)	EV % (95% CI)	EV % (95% CI)	EV % (95% CI)	EV % (95% CI)
EV nel periodo di studio					
2007-2014	60% (53, 65)	51% (48, 53)	46% (43, 49)	47% (43, 52)	49% (48, 51)
EV media					
3-anni dopo la vaccinazione	60% (52, 66)	55% (52, 57)	50% (47, 53)	48% (43, 53)	¶
5-anni dopo la vaccinazione	¶	49% (47, 52)	46% (43, 48)	44% (38, 49)	¶

CHMP positive opinion June 2017 - procedura EMEA/H/C/000674/II/0112

Vaccino Zoster (Ceppo OKA/Merck)

VE contro la nevralgia posterpetica (**PHN**) durante il periodo dello studio e sulla media nel corso di 3 e 5 anni, per età al momento della vaccinazione. Dal 2007 al 2014

	Età alla vaccinazione*				
	50-59 anni	60-69 anni	70-79 anni	80+ anni	Tutti i gruppi d'età
	EV % (95% CI)	EV % (95% CI)	EV % (95% CI)	EV % (95% CI)	EV % (95% CI)
EV nel periodo di studio					
2007-2014	63% (11, 85)	71% (65, 76)	70% (63, 75)	62% (50, 71)	69% (65, 72)
EV media					
3-anni dopo la vaccinazione	98% (-∞, 100)	74% (66, 80)	73% (65, 79)	63% (49, 73)	¶
5-anni dopo la vaccinazione	¶	72% (65, 77)	69% (62, 75)	61% (47, 71)	¶

CHMP positive opinion June 2017 - procedura EMEA/H/C/000674/II/0112

Vaccino Zoster (ceppo Oka/Merck) - Modalità d'uso

- **Il vaccino può essere somministrato a soggetti che ignorano o possono essere venuti a contatto con virus varicella-zoster (VZV) e a pazienti con anamnesi positiva per HZ.**

- **I pazienti che devono iniziare una terapia immunosoppressiva dovrebbero ricevere il vaccino almeno due settimane (14-30 giorni) prima dell'inizio del trattamento**

- **Il vaccino zoster è risultato immunogeno e sicuro in soggetti con anamnesi positiva per HZ**

- **Non ci sono indicazioni per la vaccinazione zoster per coloro che hanno ricevuto il vaccino varicella**

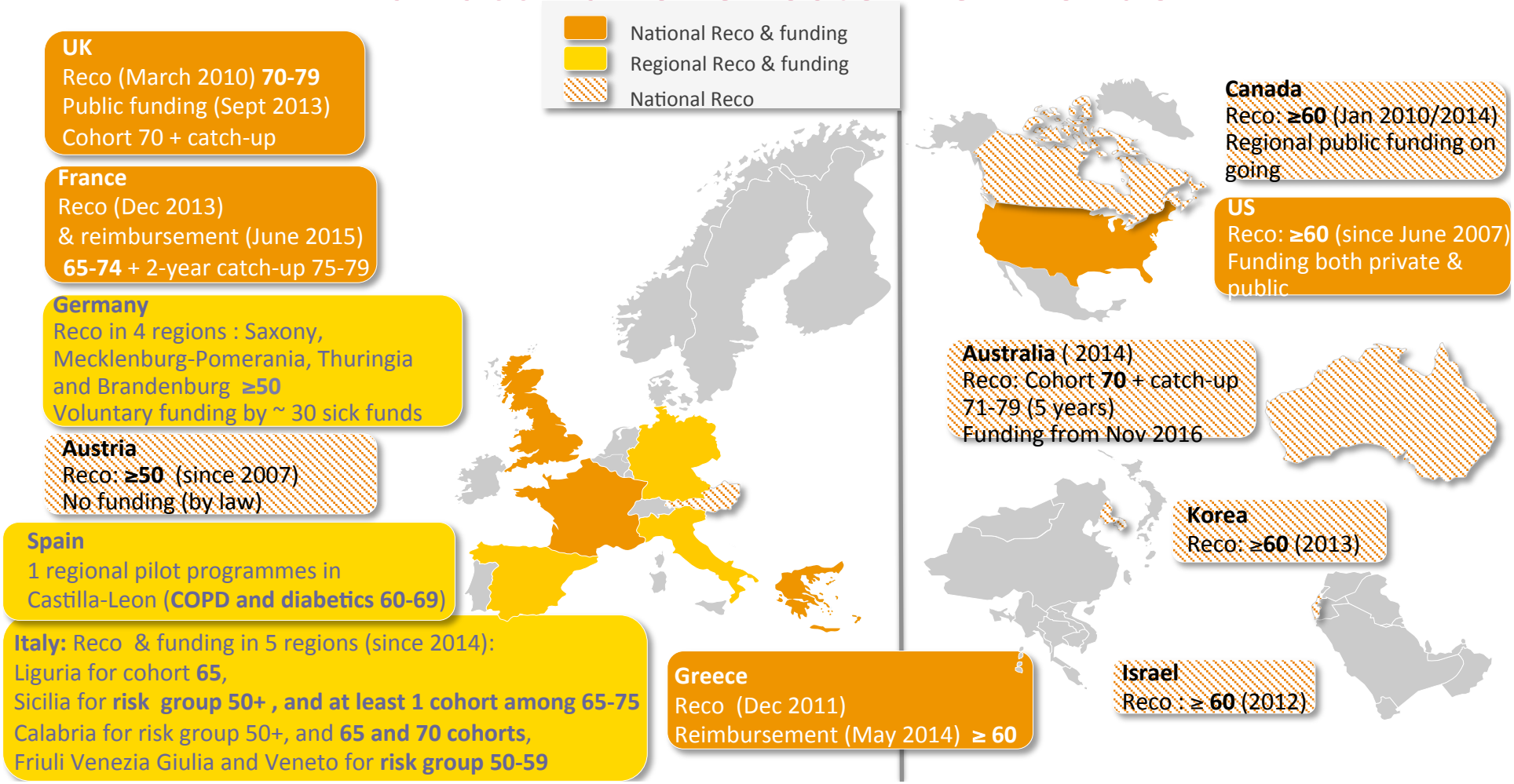
- **Comunque, ad oggi, il numero dei soggetti vaccinati per varicella ed eleggibili per il vaccino zoster è esiguo, e resterà tale ancora per qualche decade.**

Vaccino Zoster (ceppo Oka/Merck) - Controindicazioni

- **Terapia immunosoppressiva (corticosteroidi ad alte dosi inclusi) è una controindicazione**
- **“La vaccinazione, comunque, non è controindicata in soggetti che stanno ricevendo corticosteroidi per via topica o inalatoria o corticosteroidi a basso dosaggio o in pazienti che stanno ricevendo corticosteroidi come terapia sostitutiva “**

Fare sempre riferimento a SPC per le controindicazioni e tutti i pazienti devono essere valutati per eventuale immunodeficit prima della somministrazione del vaccino.

La vaccinazione zoster nel mondo



Il calendario vaccinale

Vaccino	0gg-30gg	3° mese	4° mese	5° mese	6° mese	7° mese	11° mese	13° mese	15° mese	⇨	6° anno	12°-18° anno	19-49 anni	50-64 anni	> 64 anni	Soggetti ad aumentato rischio
DTPa**		DTPa		DTPa			DTPa				DTPa***	dTpaIPV	1 dose dTpa**** ogni 10 anni			(1)
IPV		IPV		IPV			IPV				IPV					
Epatite B	EpB-EpB*	Ep B		Ep B			Ep B									(2)
Hib		Hib		Hib			Hib									(3)
Pneumococco		PCV		PCV			PCV								PCV+PPSV	(4)
MPRV								MPRV			MPRV					(6)
MPR								*oppure* MPR + V			*oppure* MPR + V					(5) (6)
Varicella																
Meningococco C								Men C§				Men ACWY coniugato				(7)
Meningococco B*^		Men B	Men B		Men B			Men B								
HPV												HPV°: 2-3 dosi (in funzione di età e vaccino)				(8)
Influenza															1 dose all'anno	(9)
Herpes Zoster															1 dose#	(10)
Rotavirus		Rotavirus## (due o tre dosi a seconda del tipo di vaccino)														
Epatite A																(11)

(10) Herpes zoster: a partire dai 50 anni di età

La terza vaccinazione rilevante per il soggetto anziano è quella contro l'Herpes zoster. Tale immunizzazione è in grado di ridurre di circa il 65% i casi di nevralgia post-erpetica, che è una delle complicanze più frequenti e debilitanti della malattia, e circa il 50% di tutti i casi clinici di zoster. La coorte cui la vaccinazione deve essere offerta attivamente è rappresentata dai soggetti di 65 anni di età.

PNPV 2017-2019

Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study

Gayatri Amirthalingam, Nick Andrews, Philip Keel, David Mullett, Ana Correa, Simon de Lusignan, Mary Ramsay

Lancet Public Health 2018; 3: e82–90

Background

In 2013, a herpes zoster vaccination programme was introduced in England for adults aged 70 years with a phased catch-up programme for those aged 71–79 years.

Interpretation

The herpes zoster vaccination programme in England has had a population impact equivalent to about 17000 fewer episodes of herpes zoster and 3300 fewer episodes of postherpetic neuralgia among 5·5 million eligible individuals in the first 3 years of the programme. Communication of the public health impact of this programme will be important to reverse the recent trend of declining vaccine coverage

Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study

Gayatri Amirthalingam, Nick Andrews, Philip Keel, David Mullett, Ana Correa, Simon de Lusignan, Mary Ramsay

Lancet Public Health 2018;
3: e82–90

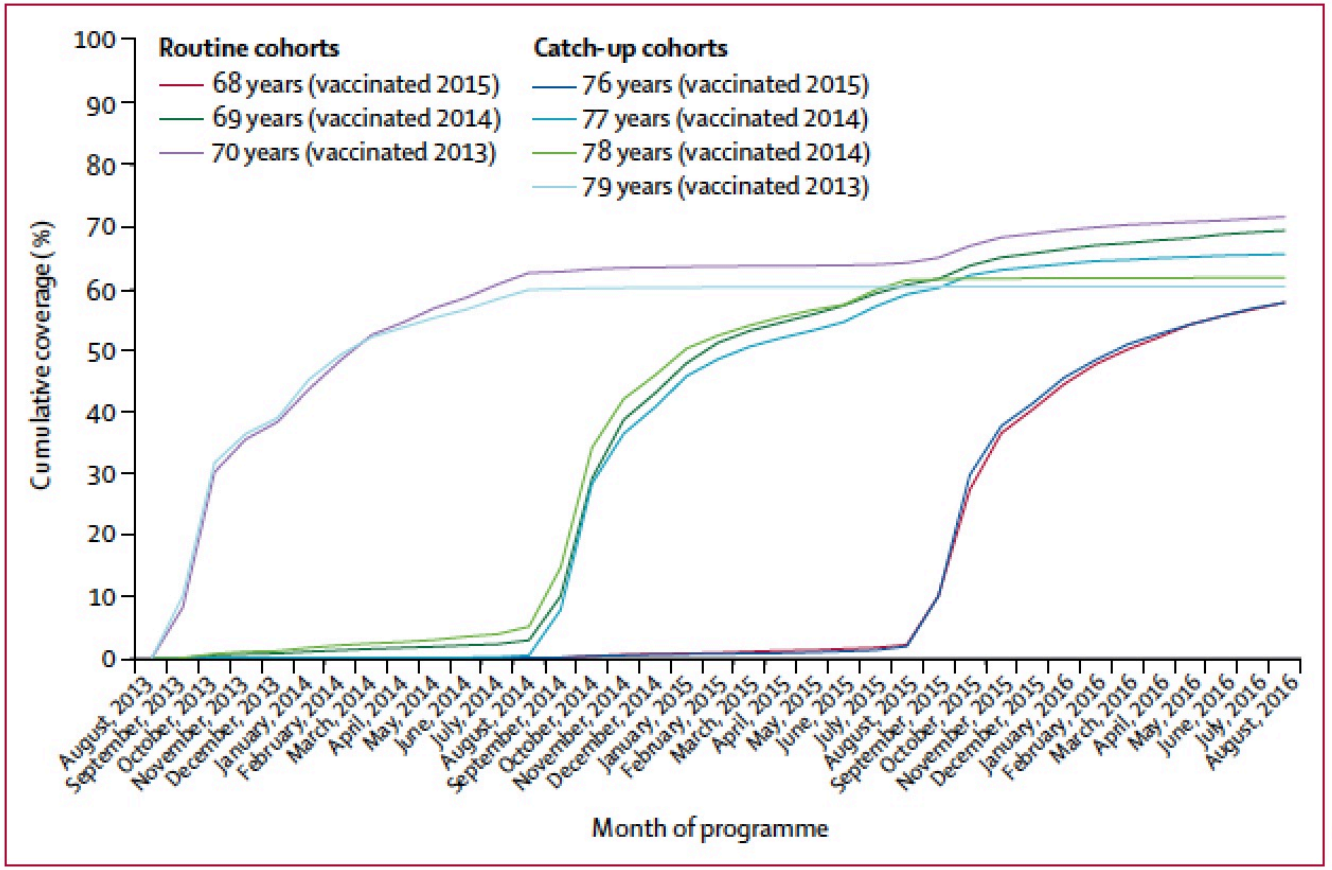


Figure 1: **Cumulative coverage for each age cohort throughout 3-year vaccination programme**
Cohorts are grouped by age on Sept 1, 2013.

Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study

Gayatri Amirthalingam, Nick Andrews, Philip Keel, David Mullett, Ana Correa, Simon de Lusignan, Mary Ramsay

Lancet Public Health 2018; 3: e82–90

	Age on Sept 1, 2013, (age when first eligible for vaccination)	Average cumulative uptake*	Expected events†	Observed events	Incidence rate ratio (95% CI)‡	Expected incidence per 1000 person-years	Incidence reduction per 1000 person-years (95% CI	Vaccine effectiveness (95% CI)§
Routine cohorts								
First year after vaccine eligibility	68–70 years (70–71 years)	46%	354	255	0·72 (0·64–0·82)	8·7	2·4 (1·6–5·6)	62% (39–78)
Second year after vaccine eligibility	69–70 years (70–71 years)	65%	241	143	0·59 (0·50–0·70)	8·9	3·6 (2·7–4·5)	62% (54–77)
Third year after vaccine eligibility	70 years (70–71 years)	70%	117	65	0·56 (0·44–0·71)	9·2	4·1 (2·7–5·2)	64% (41–80)
All years of the programme	68–70 years (70–71 years)	56%	712	463	0·65 (0·60–0·72)	8·8	3·1 (2·5–3·5)	62% (50–71)
Catch-up cohorts								
First year after vaccine eligibility	76–79 years (78–80 years)	46%	348	243	0·70 (0·62–0·79)	10·0	3·0 (2·1–3·8)	65% (46–83)
Second year after vaccine eligibility	77–79 years (78–80 years)	62%	251	151	0·60 (0·51–0·71)	10·2	4·0 (3·0–5·0)	64% (47–79)
Third year after vaccine eligibility	79 years (79–80 years)	60%	78	59	0·76 (0·59–0·98)	10·3	2·5 (0·2–4·2)	40% (3–68)
All years of the programme	76–79 years (78–80 years)	54%	677	453	0·67 (0·61–0·74)	10·1	3·1 (2·6–3·9)	62% (48–72)

Impact is shown by the incidence rate ratio (observed/expected events) and incidence reduction. GP=general practitioner. *Calculated by taking the mean of the cumulative uptake values in each month from October to September of the relevant years and cohorts. †Expected if the vaccine had not been introduced; based on model results for unvaccinated cohorts. ‡Estimated from the Poisson regression model with a log-linear time trend, quadratic age effect, and the factor for vaccine eligibility. §Effectiveness required to generate the observed reductions in the first 3 years after vaccination.

Table 3: **Impact of routine and catch-up herpes zoster vaccination on GP-diagnosed herpes zoster by time since cohorts were first eligible for vaccination**

Evaluation of the effect of the herpes zoster vaccination programme 3 years after its introduction in England: a population-based study

Gayatri Amirthalingam, Nick Andrews, Philip Keel, David Mullett, Ana Correa, Simon de Lusignan, Mary Ramsay

Lancet Public Health 2018; 3: e82–90

	Age on Sept 1, 2013, (age when first eligible for vaccination)	Average cumulative uptake*	Expected events†	Observed events	Incidence rate ratio (95% CI)‡	Expected incidence per 1000 person-years	Incidence reduction per 1000 person-years (95% CI)	Vaccine effectiveness (95% CI)§
Routine cohorts								
First year after vaccine eligibility	68–70 years (70–71 years)	46%	47·8	24	0·50 (0·34–0·75)	1·17	0·58 (0·82–0·77)	100% (54–100)
Second year after vaccine eligibility	69–70 years (70–71 years)	65%	43·1	21	0·62 (0·40–0·95)	1·26	0·48 (0·06–0·76)	59% (8–92)
Third year after vaccine eligibility	70 years (70–71 years)	70%	17·3	5	0·29 (0·12–0·70)	1·35	0·96 (0·41–1·19)	100% (43–100)
All years of the programme	68–70 years (70–71 years)	56%	99·1	50	0·50 (0·38–0·67)	1·23	0·61 (0·41–0·76)	88% (59–100)
Catch-up cohorts								
First year after vaccine eligibility	76–79 years (78–80 years)	46%	63·0	38	0·60 (0·44–0·83)	1·82	0·83 (0·31–1·02)	86% (37–100)
Second year after vaccine eligibility	77–79 years (78–80)	62%	47·1	31	0·66 (0·46–0·94)	1·91	0·64 (0·11–1·03)	55% (10–87)
Third year after vaccine eligibility	79 years (79–80 years)	60%	15·0	9	0·60 (0·31–1·16)	1·99	0·80 (–0·32–1·37)	66% (27–100)
All years of the programme	76–79 years (78–80 years)	54%	125·1	78	0·62 (0·50–0·79)	1·88	0·68 (0·39–0·94)	70% (39–93)

Impact is shown by the incidence rate ratio (observed/expected events) and incidence reduction. GP=general practitioner. *Calculated by taking the mean of the cumulative uptake values in each month from October to September of the relevant years and cohorts. †Expected if the vaccine had not been introduced; based on model results for unvaccinated cohorts. ‡Estimated from the Poisson regression model with a log-linear time trend, quadratic age effect, and the factor for vaccine eligibility. §Effectiveness required to generate the observed reductions in the first 3 years after vaccination.

***Table 4*: Impact of routine and catch-up herpes zoster vaccination on GP-diagnosed postherpetic neuralgia by time since cohorts were first eligible for vaccination**

Il futuro?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2016 VOL. 375 NO. 11

Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

A.L. Cunningham, H. Lal, M. Kovac, R. Chlibek, S.-J. Hwang, J. Díez-Domingo, O. Godeaux, M.J. Levin, J.E. McElhaney, J. Puig-Barberà, C. Vanden Abeele, T. Vesikari, D. Watanabe, T. Zahaf, A. Ahonen, E. Athan, J.F. Barba-Gomez, L. Campora, F. de Looze, H.J. Downey, W. Ghesquiere, I. Gorfinkel, T. Korhonen, E. Leung, S.A. McNeil, L. Oostvogels, L. Rombo, J. Smetana, L. Weckx, W. Yeo, and T.C. Heineman, for the ZOE-70 Study Group*

BACKGROUND

A trial involving adults 50 years of age or older (ZOE-50) showed that the herpes zoster subunit vaccine (HZ/su) containing recombinant varicella–zoster virus glycoprotein E and the $AS01_B$ adjuvant system was associated with a risk of herpes zoster that was 97.2% lower than that associated with placebo. A second trial was performed concurrently at the same sites and examined the safety and efficacy of HZ/su in adults 70 years of age or older (ZOE-70).

METHODS

This randomized, placebo-controlled, phase 3 trial was conducted in 18 countries and involved adults 70 years of age or older. Participants received two doses of HZ/su or placebo (assigned in a 1:1 ratio) administered intramuscularly 2 months apart. Vaccine efficacy against herpes zoster and postherpetic neuralgia was assessed in participants from ZOE-70 and in participants pooled from ZOE-70 and ZOE-50.

RESULTS

In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; P<0.001) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%). In pooled analyses of data from participants 70 years of age or older in ZOE-50 and ZOE-70 (16,596 participants), vaccine efficacy against herpes zoster was 91.3% (95% CI, 86.8 to 94.5; P<0.001), and vaccine efficacy against postherpetic neuralgia was 88.8% (95% CI, 68.7 to 97.1; P<0.001). Solicited reports of injection-site and systemic reactions within 7 days after injection were more frequent among HZ/su recipients than among placebo recipients (79.0% vs. 29.5%). Serious adverse events, potential immune-mediated diseases, and deaths occurred with similar frequencies in the two study groups.

CONCLUSIONS

In our trial, HZ/su was found to reduce the risks of herpes zoster and postherpetic neuralgia among adults 70 years of age or older. (Funded by GlaxoSmithKline Biologicals; ZOE-50 and ZOE-70 ClinicalTrials.gov numbers, NCT01165177 and NCT01165229.)

The Journal of Infectious Diseases
SUPPLEMENT ARTICLE

Herpes Zoster Vaccines

Anthony L. Cunningham,[1,2,a] and Myron J. Levin[3,a]

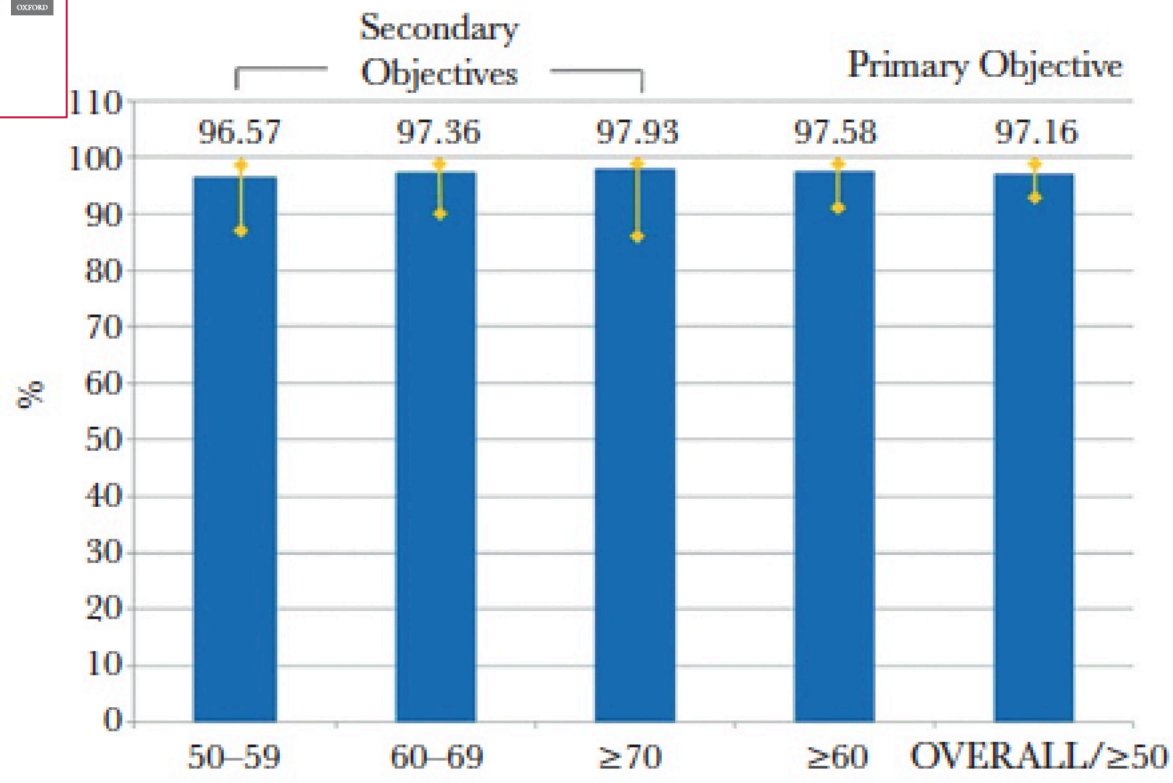


Figure 2. Recombinant subunit herpes zoster vaccine vaccine efficacy against first/only episode of herpes zoster stratified by age group. Graph adapted from Table 3 in [38]. Reproduced with permission.

The Journal of Infectious Diseases
SUPPLEMENT ARTICLE

Herpes Zoster Vaccines

Anthony L. Cunningham,[1,2,a] and Myron J. Levin[3,a]

CONCLUSIONS

The live attenuated vaccine (**ZVL**) was important for the prevention of HZ and for understanding the interaction of immunosenescence with immunization. Future investigation of the mechanisms of attenuation of disease and PHN by **ZVL** , beyond its effect on incidence of HZ, will provide important information. The recombinant HZ/su is highly efficacious in preventing HZ and PHN in all age groups, even those ≥80 years of age. Almost all subjects responded to HZ/su vaccination with robust antibody and $CD4^+$ T-cell responses, including vaccinees ≥70 years of age. Immune responses remained substantially above baseline up to 9 years after vaccination, which may translate into prolonged efficacy. The adjuvant combination is critical for the efficacy and durability of this response.

Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

A novel nonlive, adjuvanted herpes zoster subunit vaccine: a report on the emerging clinical data and safety profile

Federica Brosio[1]
Giulia Masetti[1]
Giulio Matteo[1]
Armando Stefanati[2]
Giovanni Gabutti[2]

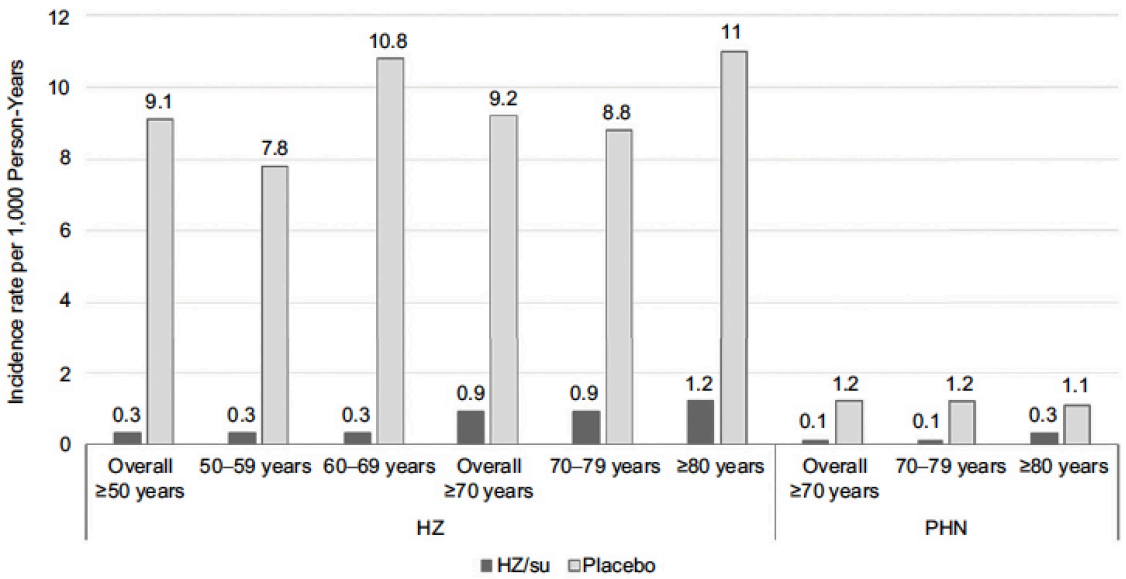


Figure 2 Incidence rate of HZ and PHN per 1,000 Person-Years in HZ/su group and in placebo group.
Note: Data from Food and Drugs Administration (FDA). *Shingrix Highlights of Prescribing Information*. Available from: https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm581605.pdf. Accessed May 14, 2018.[58]
Abbreviations: HZ, herpes zoster; HZ/su, HZ subunit vaccine; PHN, postherpetic neuralgia.