Health Burden of VPI in older adults – the Herpes zoster example (...for Italy)

Session 3: The epidemiology and health burden of selected adult VPIs • part 1

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HZ disease burden in Italy
WHAT ABOUT HZ INCIDENTE DATA AND QUALITY OF LIFE?
In 2010 Gialloreti et al.:  
- Estimated 157,100 new cases of HZ each year  
- Annual incidence of 6.3/1,000 person-years  
- 88% of cases were immunocompetent  

In 2010 in Italy there were approximately 22 million people aged ≥50 years old
Herpes Zoster: assessment of the health and socio-economic impact and possible vaccination strategies in the adult population in Italy funded by the Italian Ministry of Health (CCM 2013) – **Main Objectives**

- Estimate the **incidence of Herpes Zoster in subjects aged ≥ 50 years**
- Estimate the **frequency of complications**, especially Post-Herpetic Neuralgia PHN
- Describe the **characteristics of patients** with Herpes Zoster and the Herpes Zoster episode
- Describe **the diagnostic, therapeutic and care pathway**
- Estimate **the social and economic burden** for the NHS associated with the management of the patient with Herpes Zoster and PHN
- Describe the **perception of pain and the impact on quality of life**

4 Italian Regions involved in the CCM Project:
- Liguria (lead partner)
- Puglia
- Tuscany
- Veneto

Alicino C et al. Hum Vaccin Immunother 2017:2:399-404
Involvement of a **Network of General Practitioners** in the 4 Regions involved in the study (**about 100 GPs**)

- **Retrospective** and **prospective** identification of Herpes Zoster cases in subjects aged ≥ 50 years

- **Study Period**: January 2013 – December 2014 (later extended to December 2015)

- Data collected through a **questionnaire**

**TARGETS:**

**COLLECTION OF ABOUT 560 QUESTIONNAIRES**

**400 RETROSPECTIVE AND 160 PROSPECTIVE**
598 questionnaires collected from as many cases of Herpes Zoster

- 437 collected retrospectively (73.1%)
- 161 collected prospectively (26.9%)

36.10% Females
63.90% Males

Alicino C et al. Hum Vaccin Immunother 2017: 2:399-404
Incidence of Herpes Zoster and associated comorbidities

56 General practitioners (2013-2015 Liguria, Puglia, Toscana e Veneto)
➢ Over 50 years of age: **598 cases of HZ identified over 93,146 person-years of observation**
➢ **Overall incidence: 6.42/1,000 person-years**

449 patients had comorbidities (75.1%)
- Cardiovascular diseases
- Diabetes
- Cancer
- Respiratory diseases
- Neurological diseases
- Other diseases

Alicino C et al. Hum Vaccin Immunother 2017; 2:399-404
Incidence of Herpes Zoster and associated PHN

PHN persists at 1 month, 3 months and 1 year, mainly in older subjects.

The results in terms of incidence of the pathology and frequency of complications were in line with the national and international literature.

The CCM Project provided an overview on the epidemiology of Herpes Zoster and its complications in Italy in outpatients.
Despite early antiviral treatment (within 72 hours of rash onset) 20.6% and 9.2% of patients >50 years with HZ had PHN at 3 and 6 months, respectively.

HZ/PHN impacts on the quality of life.
IMPACT OF HERPES-ZOSTER RELATED PAIN AND COMPLICATIONS IN PATIENTS SUFFERING OF UNDERLYING CONDITIONS IN ITALY
L. Torcel-Pagano, H. Bricout, J. Bertrand, E. Perinetti, G. Gabutti, A. Vello, E. Franco

CONCLUSIONS

- HZ in patients with underlying conditions (cardiovascular, respiratory chronic diseases, diabetes and other relevant diseases) results in more painful and impactful episodes with an higher interference on patients’ quality of life and slower recovery.

- With 80% of people aged over 65 years suffering from at least one chronic disease in Europe, prevention of HZ/PHN in elderly may contribute to maintain their quality of life and thus healthy ageing.
WHAT ABOUT HOSPITALIZATIONS IN ITALY?

• HZ-related hospitalization is an indicator which expresses the most serious cases.
HZ-hospitalizations in Italy

HZ hospitalization rate
Italy, 2001-2012

No. of hospitalizations for HZ and proportion of hospitalizations for HZ in immunocompromised subjects*
Italy, 2001-2012

Hospitalization rate by HZ, by age Italy, 2001-2012

N. of hospitalizations for HZ and N. of hospitalizations for HZ with discharge as "deceased" Italy, 2001-2012

Herpes Zoster hospitalizations in Italy

- Stable length of stay over time

No. of hospitalizations per HZ and average hospital stays
Italia, 2001-2012

Average cost of Hospitalization for HZ among the causes of hospitalization
Italy, 2001-2012

The reduction of hospitalization for HZ as a contributing cause of hospitalization (secondary diagnosis):

- Less marked decrease than hospitalization for HZ as the primary cause of hospitalization
- High average hospital stay (almost double compared to HZ as primary cause)
- Increase in the average cost of hospitalizations
  - In 2012 total expenditure >12.211.000 €

Overall costs 2012 € 5.884.000
Overall cost 2012 € 12.211.000
Herpes Zoster hospitalizations in Italy: cost associated

- **Reduction of hospitalization for HZ**
  - Hospitalization rates in the elderly 15 times higher than in the younger ones
  - **Stable length of stay** over time
  - Increase in hospitalizations in the immunocompromised subjects
  - Average cost reduction
    - In 2012 average cost >5,800,000 €

- **Hospitalization reduction for PHN**
  - In 2012
    - 21% of hospitalizations for HZ
    - Total expenditure >1,000,000 €

- **Reduction of hospitalization for ophthalmic complications**

*The Burden of Disease of HZ in Italy has an economic impact of 49 M€/year (direct and indirect costs)*
Temporal trends in herpes zoster-related hospitalizations in Italy, 2001–2013: differences between regions that have or have not implemented varicella vaccination

In the period 2001–2013, 93,808 HZ hospitalizations were registered.

Age represents a risk factor for HZ, due to the decline in VZV-specific cell-mediated immunity.

Complicated HZ was diagnosed in 53.2% of cases.

32.5% of hospitalizations involved subjects with at least one comorbidity.

- Co-morbidities were higher in hospitalizations with HZ in secondary diagnosis than those in primary diagnosis (41.5% versus 23.6% respectively, p < 0.01).

- HZ was associated with malignancies (11.4%), diabetes (10.8%), COPD (7.9%), kidney failure (5.3%) and autoimmune diseases (1.5%) of cases.

In the three Italian "pilot" regions a greater decrease of HZ-related hospitalization rates occurred in comparison to other regions (Sicily UVV in 2003, Veneto in 2005 and Apulia in 2006).

Extensive vaccination for varicella, reducing the spreading of VZV in the community and, therefore, eliminating the exogenous boosters, could increase the incidence of HZ in the unimmunized population (adults, elderly). Not investigated the vaccination status of cases!

This decrease, consistent with the national trend, could be induced by the reduction of inappropriateness of admissions and by the possible changes of care settings in place in our country.
Objective: to estimate the burden of the HZ hospitalizations in Italy from 2003 to 2018 evaluating temporal trends. Overall, 99,036 patients were hospitalized with HZ in the 16-year period of the study, and 83,720 (84.5%) were over 50 years.

- **Hospitalization rate** showed a decreasing trend from 13.9 in 2003–2006 to 7.8 in 2015–2018 (p < 0.001).
- **Hospitalization rates** showed a 20-fold higher risk among subjects aged over 80 years and 11-fold higher risk among 70–79-year-old subjects with respect to those aged less than 50 years.
- Over time, a statistically significant increase was observed for the case fatality rate (from 1.2 to 1.7%; p < 0.001) and the median length of stay (from 7 to 8 days; p < 0.001).

The observed reduced trend over time could be due to a restriction in hospitalization criteria instead of a reduced burden of disease.
Increased incidence of stroke after HZ

- Stroke rate after HZ increased: \times 1.5 within 1 month
  - weeks 1–4 (IR* 1.63)
  - weeks 5–12 (IR 1.42)
  - weeks 13–26 (IR 1.23)

- The correlation is strongest in cases of ophthalmic zoster: \times 4 within 1 year
A retrospective cohort study to assess the risk of developing HZ following a COVID-19 diagnosis.

- **Individuals diagnosed with COVID-19:**
  - a **15% higher HZ risk than those without COVID-19** (aIRR, 1.15; 95% CI, 1.07-1.24; \( P < .001 \)).
  - The increased HZ risk was more pronounced (21%) following COVID-19 hospitalization (aIRR, 1.21; 95% CI, 1.03-1.41; \( P = .02 \)).

**SARS-CoV-2 infection may trigger reactivation of latent VZV?**

HZV preventive strategies in Europe and Italy
Herpes Zoster is a painful disease. If complicated by Post Herpetic Neuralgia it can become extremely debilitating for a long time.

95% of the world's population is at risk of HZ

1 out of 4 subjects will be able to develop HZ

The risk of HZ and PHN increases with increasing age

The treatment of HZ and PHN is complex and not very effective

The classic paradigm of vaccinations is changing: Vaccination is not only directed against acute childhood diseases with the aim of preventing deaths and serious cases, but also to improve the quality of life at all ages.

Varicella virus infection was very common in the pre-vaccine era.

95% of the European adult population has anti-VZV antibodies (99% of Italian men and women aged over 65 years are VZV seropositive)

In the absence of vaccination, virtually everyone contracts varicella by the age of 40 years

Anyone who has come into contact with the Varicella Zoster Virus (VZV) has the potential to develop Herpes Zoster.
Italian Population in the last 2 decades and in 2023

Italian population: 58,850,717
(National Institute of statistics - 1/01/2023)

Elderly ≥65 years of age: 24.1% (>14 millions)
People over 50 years of age: 47.4% (28 millions >50 years)
a 2-fold increase compared to the study of Gialloreti et al.

- The decay of the CMI is strictly age-dependent, increasing with age.
Two available vaccines

**Live herpes zoster vaccine (ZVL) product profile**

Vaccino vivo attenuato

- Contiene ceppo Oka/Merck di VZV
- Indicato per la prevenzione dell’HZ (e della PHN associata all’HZ [solo Europa e Australia]) in individui di 50 anni di età o più anziani
- Somministrato come iniezione singola; SC o IM (in base alla licenza specifica)
- Conservazione: congelato o in frigoriferi (variabile a seconda della formulazione commercializzata)

**Controindicato in popolazioni IC**

- HZ, herpes zoster; IC, immunocompromesso; IM, intramuscolare; PHN, neuralgia post-herpetica; SC, sottocutaneo; VZV, virus della varicella zoster

The ZVL vaccine has made an important contribution to the prevention of zoster and post-herpetic neuralgia, is contraindicated for immunocompromised subjects (vaccine coverage has so far been sub-optimal)

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**RZV product profile**

- Non-live subunit vaccine containing glycoprotein E
- Use the helper system AS01
- Indicated for prevention of HZ (and PHN [Europe, Australia, New Zealand only]) in adults 50 years of age or older, based on Phase III studies 3-9 years (and for adults 18 years of age and older at greatest risk of HZ [Europe only])
- Given in two IM doses, 2-6 months apart
- Storage: In the refrigerator

- Not contraindicated in immunocompromised individuals

The RZV vaccine represents a significant advance in terms of efficacy and duration of protection, and it is also the only weapon for the prevention of HZ in highly immunocompromised subjects

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**Vaccination acts by maintaining the level of Cell-mediated immunity over time**
HZ RECOMMENDATIONS IN COUNTRIES WHERE RZV IS REGISTERED (UP TO NOVEMBER 2021)

CDC (USA):
- Adults ≥50y
- Adults who received ZVL previously
- Preferred over ZVL

Only RZV is recommended
Both RZV and ZVL are recommended, no vaccine preference
Both RZV and ZVL are recommended, RZV is preferred
RZV is registered, but no national recommendation for RZV

[PLACEHOLDER FOR LOCAL RECOMMENDATIONS]
Herpes Zoster recommended vaccination in European Countries

- Only 8 countries recommend Herpes Zoster Vaccination.
- In 2 countries it is not funded by the NHS.
  - Diabetes
  - Cardiovascular pathologies
  - COPD
  - Subjects scheduled for immunosuppressive therapy

### Italy:
- general recommendation for subjects over 65 years old since NIP 2017-19
- recommendation for specific risk groups for subjects aged 50 - 64 years

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**Legend**
- **ZOS**
- General recommendation
- **Recommendation for specific groups only**
- **Catch-up (e.g. if previous doses missed)**
- Vaccination not funded by the National Health system
- Mandatory vaccination
Offerta vaccinale regionale del vaccino ricombinante adiuvato per la prevenzione dell’ Herpes Zoster

- Indicazione omogenea per il paziente 18+ immuno-compromesso
- Etereogenicità per il paziente cronico in termini di: indicazioni, sotto-categorie e età
- Per la coorte del 65enne sano indicazione di utilizzo prevalente per ZVL

**ABRUZZO**
- Soggetti 18+

**BASILICATA**
- Adulti di età pari a 65 anni
- Individui ad aumentato rischio a partire dai 18 anni di età

**CALABRIA**
- Per adulti di età uguale o superiore a 50 o per adulti di età uguale o superiore 18 anni ad aumentato rischio di Herpes Zoster. Coorte 65° anno a 70° anno di età

**CAMPANIA**
- Soggetti 18+ cronici e immunocompromessi
- Soggetti 50+ ad aumentato rischio

**EMILIA-ROMAGNA**
- Soggetti 18 cronici e immunocompromessi
- Soggetti 50+ ad aumentato rischio

**FRIULI VENZIA GIULIA**
- Soggetti 18+ cronici
- Soggetti 18+ immunocompromessi
- Soggetti 18+ con recidive o forme particolarmente gravi di HZ

**LAZIO**
- Soggetti 18+ immunocompromessi
- Soggetti 18+ con recidive o forme particolarmente gravi di HZ

**LIGURIA**
- Soggetti 18 di 65 anni di età
- Soggetti 50+ cronici da PMPV
- Soggetti 18+ immunocompromessi

**LOMBARDIA**
- Soggetti 18+ complicati
- Soggetti 18+ immunocompromessi
- Soggetti 18+ con recdive o forme particolarmente gravi di HZ

**MARCHE**
- Soggetti 18+ ad aumentato rischio

**MOLISE**
- Soggetti 18+ cronici e immunocompromessi
- Soggetti 50+ ad aumentato rischio

**PAOLIANO**
- Soggetti 18+ immunocompromessi
- Soggetti con insufficienza renale cronica in dialisi
- Soggetti 18+ con recidive o forme particolarmente gravi di Herpes Zoster

**PIEMONTE**
- Soggetti 18+ cronici e immunocompromessi
- Soggetti 18+ con recidive o forme particolarmente gravi di Herpes Zoster

**PUGLIA**
- Soggetti 50+ immunocompromessi
- Soggetti 18+ ad aumentato rischio

**SARDEGNA**
- Soggetti 18+

**SICILIA**
- Soggetti 50+
- Soggetti 18+ immunocompromessi

**TOSCANA**
- No specifica su dettaglio popolazione

**UMBRIA**
- Soggetti 18+ immunocompromessi
- Soggetti 18-49 cronici da PMPV

**VENETO**
- Soggetti 18-64 cronici e immunocompromessi
- Soggetti 18+ con recidive o forme particolarmente gravi di Herpes Zoster
- Soggetti di età pari a 65 anni (chiamata per coorte)
- Soggetti di età > di 65 anni
The Italian Ministry of Health, in the Circular of 9 March 2017, indicates as vaccination coverage objectives:

- 20% for 2018
- 35% for 2019
- 50% for 2020

VC against HZ are not available at the national level
Herpes Zoster awareness campaign in Italy

- On TV from 17 July 2022, on the radio, digital, social networks
- construction of an ad hoc site dedicated to the pathology.

The message is that: "With the fire of Sant'Antonio you don't joke".

The objective of the communication campaign is to increase understanding of the impact of the disease on people's lives, debunking commonplaces and promoting prevention through vaccination.

Those who experienced the disease know well that there is nothing to laugh about. They invite people to inform themselves and to protect themselves through vaccination.
The **FIND MY VACCINE** webpage: an **useful digital tool** for the **Italian CITIZEN** but also for the **HEALTHCARE OPERATOR** to identify the recommended vaccinations based on the personal characteristics of the subject/patient

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The value of the Herpes Zoster vaccine consists in preventing the disease and its complications in order to keep all the elderly healthy (...and happy)

• In the future, probably the disease burden of Herpes Zoster will increase due to:
  • the aging of the population
  • the longer life expectancy
  • the increase in subjects with chronic diseases and fragile groups (immunocompromised)
Understanding the epidemiology of HZ disease is fundamental to establish the most appropriate health strategies against HZ.

The observed downward trend in hospitalizations in Italy must not in any way limit public health efforts in promoting HZ vaccination especially in the elderly and in subjects with chronic diseases who continue to be at a higher risk for severe sequelae due to the virus reactivation.

Vaccination Coverage for HZ in Italy is lacking and it is a challenge for the future!

With the National Immunization Plan 2017-19, Italy has introduced the active and free offer of the HZ vaccination for all 65-year-olds and for some categories at risk. What’s about the next NIP 2023-2025?

Need to promote vaccination and increase awareness in HCWs and general population.
Thank you for your attention!