



Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Herpes zoster vaccination The Netherlands

Hester de Melker

Department NIP/Epidemiology and Surveillance unit (EPI)

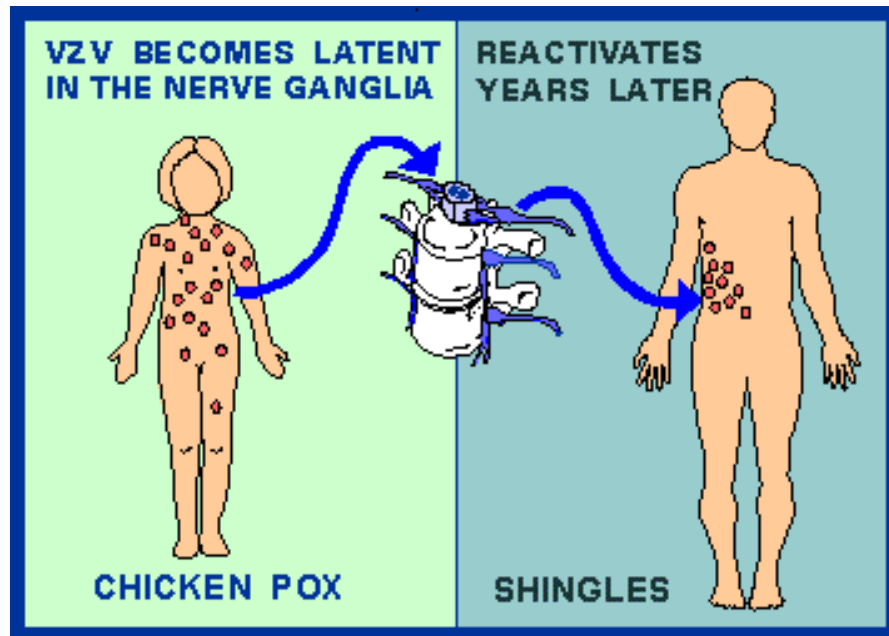
Center of Infectious Disease Control, RIVM, The Netherlands



Varicella zoster virus (VZV)

Primary infection

Reactivation



(*varicella*)

(*herpes zoster*)

- Herpes virus (HHV3 or VZV)
- Primary infection: **varicella**
- Latency in trigeminal and spinal ganglia
- After reactivation: **herpes zoster**



Herpes zoster – clinical manifestations

- > Life-time risk 23-30% in Europe
 - 50% of ≥ 85 -year-old people

- > Symptoms:
 - Pre-eruptive stage: pain (+/- headache, general malaise, photophobia)
 - Eruptive stage: painful rash (2-4 weeks)
 - Chronic HZ infection: herpetic neuralgia (>4 weeks – years)





Herpes zoster



Postherpetic neuralgia

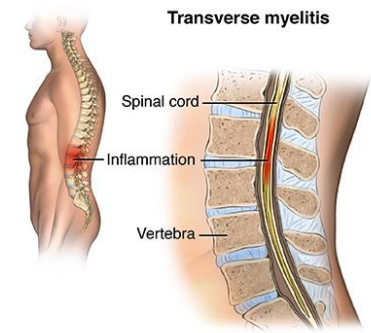


Bell's palsy



Ramsay-Hunt syndrome

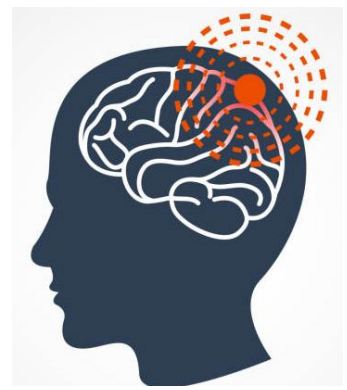
Possible complications



Transverse myelitis



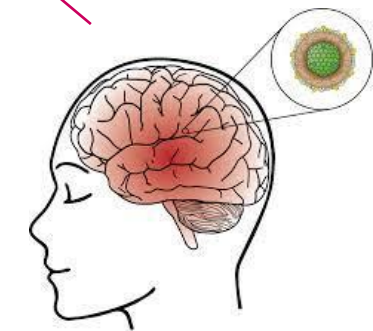
Eye involvement



Meningitis



Deafness



Encephalitis

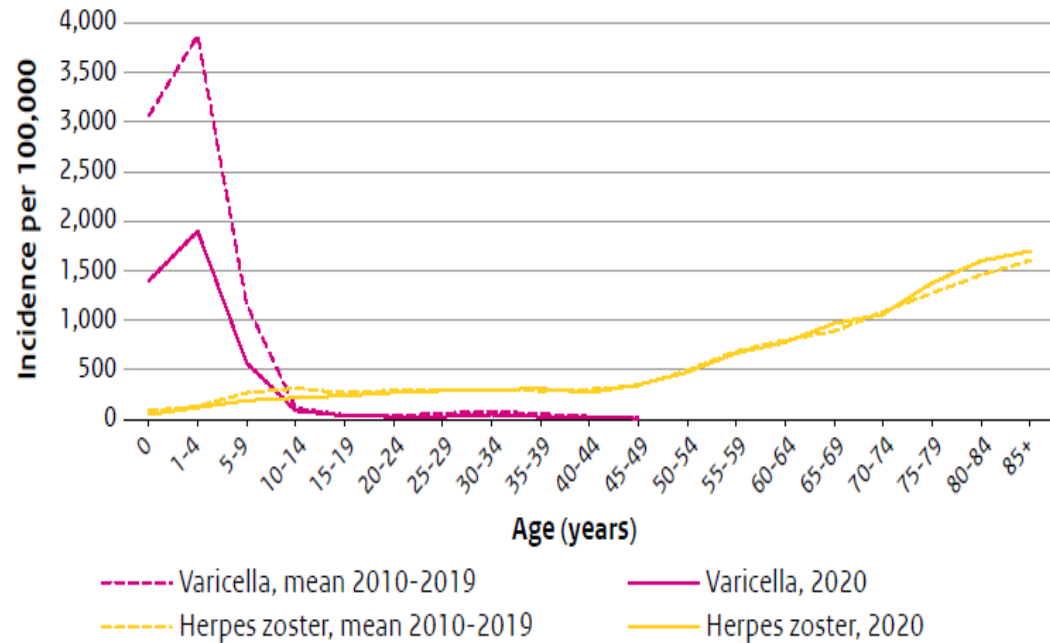


Health Council

- Disease burden
- Effectiveness
- Safety
- Acceptability
- Cost-effectiveness



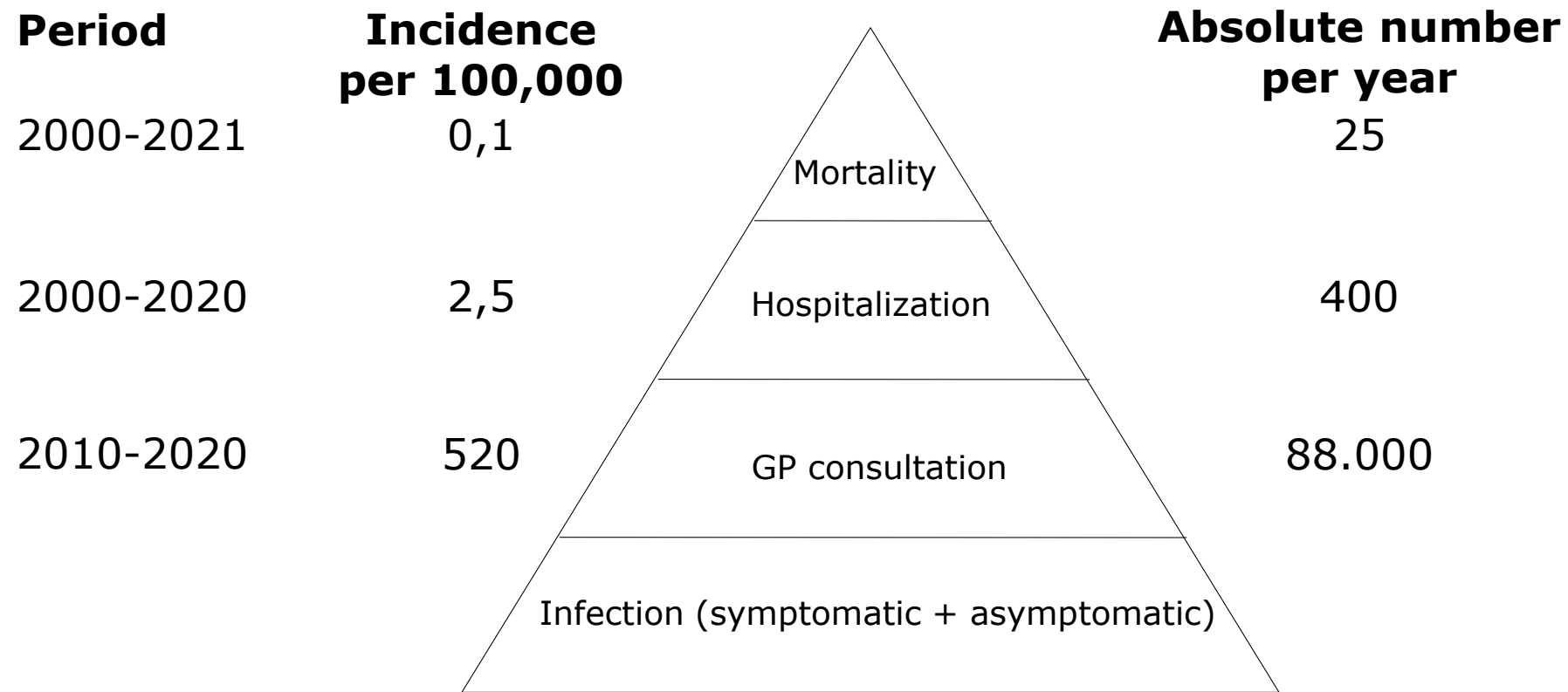
Epidemiology (GP consultations – The Netherlands)



Estimated incidence per 100,000 population of episodes of varicella and herpes zoster in 2020 versus mean 2010–2019 by age group GP consultations



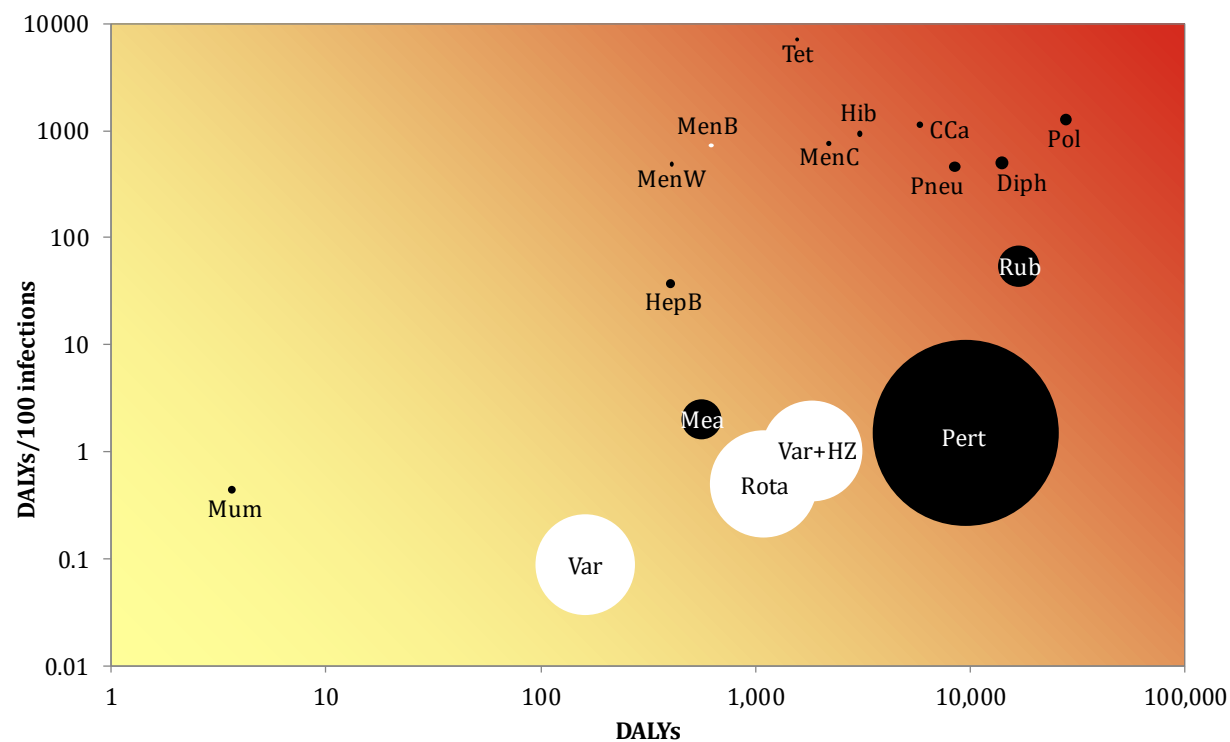
Epidemiology (Netherlands)



Sources: Nivel Primary Care data, Dutch Hospital Data, Statistics Netherlands
(Primary cause of death)



Disease burden VZV and herpes zoster in DALYs (Netherlands)



CCa: cervical cancer (human papillomavirus (HPV)-16/18), Diph: diphtheria, HepB: hepatitis B, Hib: invasive *Haemophilus influenzae* type B disease, HZ: herpes zoster, Mea: measles, MenC/W/B: invasive meningococcal C/W/B disease, Mum: mumps, Pert: pertussis, Pneu: invasive pneumococcal disease (PCV10 types), Pol: poliomyelitis, Rota: rotavirus gastroenteritis, Rub: rubella, Tet: tetanus, Var: varicella.

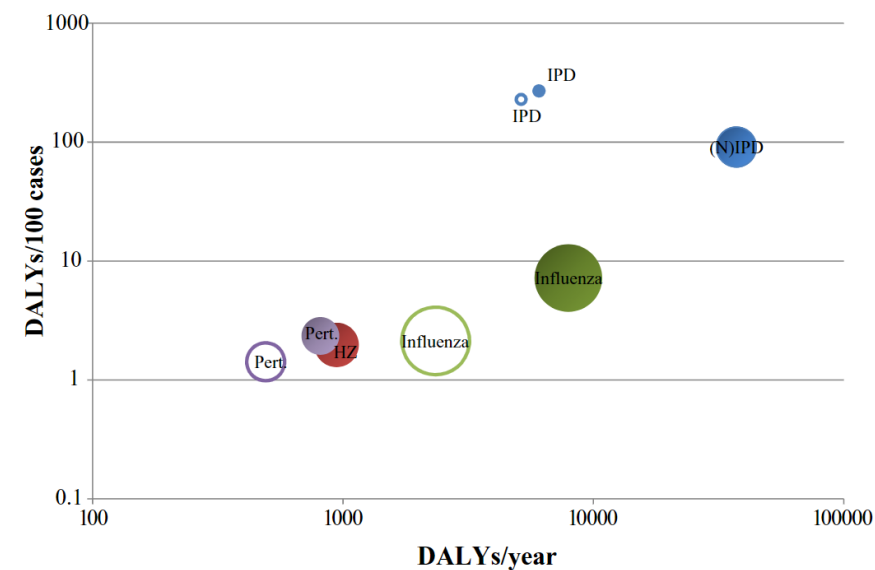


Fig. 2. Ranking of the four diseases by estimated burden at population level (DALYs/year) and individual level (DALYs per 100 cases) in the period 2010–2013, comparing the two disease burden calculation methods (GPM/OAM).



Vaccines

- > Recombinant zoster vaccine: RZV
 - Recombinant vaccine, adjuvanted
 - 2 doses
 - FDA approval: 2017
- > Zoster vaccine live: ZVL
 - Live-attenuated vaccine
 - 1 dose
 - FDA approval: 2006

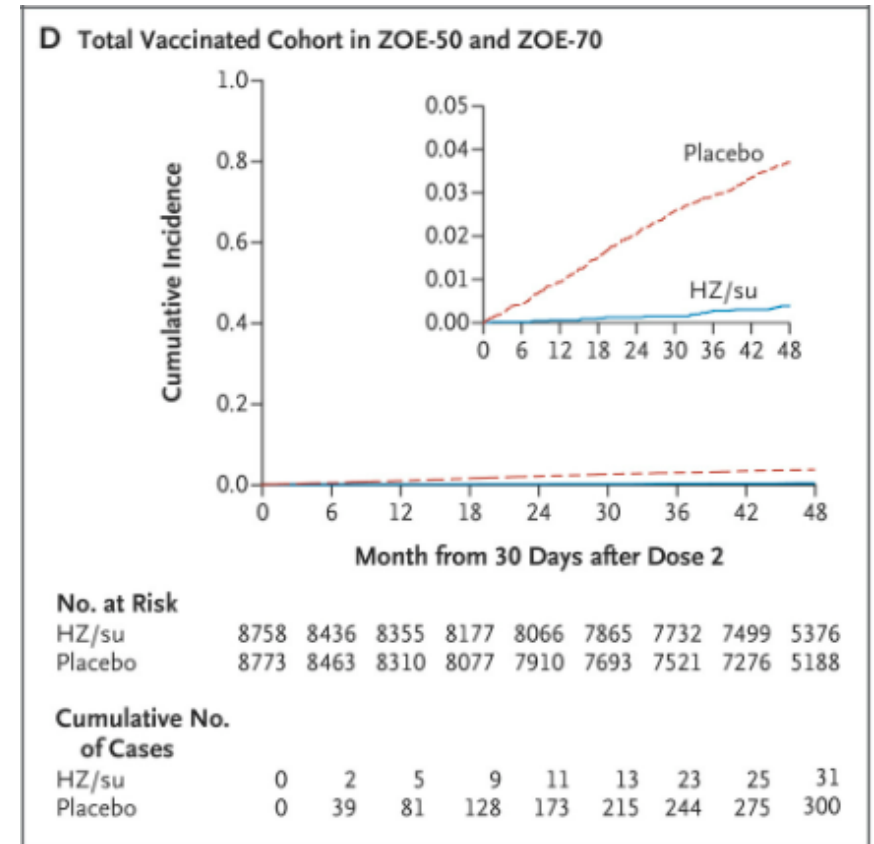
Health Council 2016:

"Currently only one vaccine available which provides insufficient protection"



RZV- Efficacy

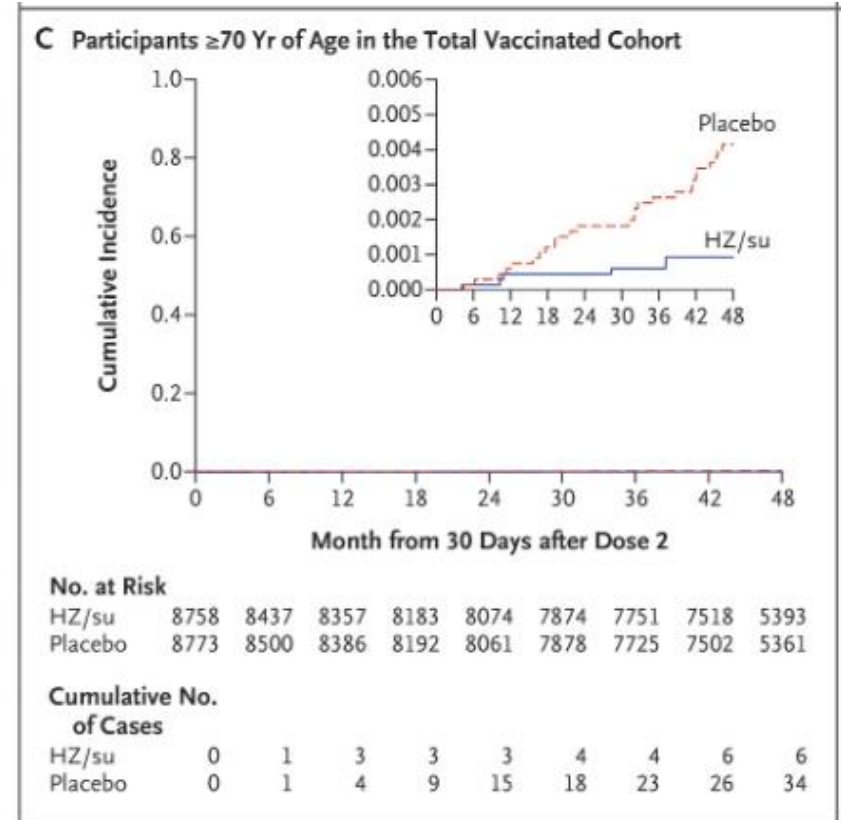
- > Two large trials: ZOE-50 and ZOE-70
 - In total, almost 28,000 participants
 - Pooled analysis of adults ≥ 70 years (n=16,596)
 - Efficacy against herpes zoster in adults ≥ 70 years: 91.3% (95%CI 86.0-94.9)





RZV - Efficacy

- > Two large trials: ZOE-50 and ZOE-70
 - In total, almost 28,000 participants
 - Pooled analysis of adults ≥ 70 years (n=16,596)
 - Efficacy against herpes zoster in adults ≥ 70 years: 91.3% (95%CI 86.0-94.9)
 - Efficacy against postherpetic neuralgia: 88.8% (95%CI 68.7-97.1)





RZV – Efficacy

Information after Health Council advice

- › Long-term follow-up
 - 7413 participants aged ≥ 50 years
 - Efficacy against herpes zoster: $>84\%$ between 5-7 years after 2-dose vaccination



RZV – Effectiveness

Information after Health Council advice

- > Cohort study among vaccinated and unvaccinated Medicare beneficiaries ≥ 65 years (n=15,589,546) (1)
 - VE for incidence of HZ was 56.9% and 70.1% for 1 and 2 doses of RZV
 - VE for PHN was 76.0% and 66.8% for ophthalmic HZ after 2 doses of RZV
 - The 2-dose VE in patients with immunocompromising chronic conditions was 64.1% versus 70.9% in immunocompetent patients
- > Cohort study in 4,769,819 patients > 50 years (2)
 - VE for incidence of HZ was 85.5% in RZV recipients 50–79 years and 80.2% in RZV recipients ≥ 80 years

1. Izurieta HS, Wu X, Forshee R, et al. Recombinant zoster vaccine (Shingrix) real-world effectiveness in the first two years post-licensure. Clin Infect Dis, 2021:ciab125.

2. Sun Y, Kim E, Kong CL, Arnold BF, Porco TC, Acharya NR. Effectiveness of the recombinant zoster vaccine in adults aged 50 and older in the United States: a claims-based cohort study. Clin Infect Dis 2021.



RZV - Safety

> ZOE-50

– Reactogenicity subgroup (n=8926)

- Solicited or unsolicited symptoms within 7 days after vaccination: **84.4% of vaccine group vs 37.8% of placebo group**
- Grade 3 symptoms (preventing normal everyday activities) in **17.0% of vaccine group vs 3.2% of placebo group**
 - Most common symptoms: pain at injection site, myalgia
- Median duration of symptoms: 1-3 days
- Serious adverse events within 3.5 years after vaccination: 9% of vaccine group vs 8.9% of placebo group (most unrelated to vaccine)



RZV - Safety

> ZOE-70

– Reactogenicity subgroup (n=1025)

- Solicited or unsolicited symptoms within 7 days after vaccination: 79.0% of vaccine group vs 29.5% of placebo group
- Grade 3 symptoms (preventing normal everyday activities) in 8.5% of vaccine group vs 0.2% of placebo group
 - Most common symptoms: pain at injection site, fatigue
 - Median duration of symptoms: 1-3 days
- Serious adverse events within 4 years after vaccination: 16.6% of vaccine group vs 17.5% of placebo group



RZV - Safety

- > ZOE-70 + ZOE-50 (1)
 - Long-term follow-up (5-7 years)
 - N=7413
 - No deaths or other SAEs causally related to vaccination
- > Several trials in immunocompromised people
 - RZV is safe and effective (2)
- > Postlicensure safety monitoring in VAERS during the first 8 months of use (3.2 million RZV doses distributed), showed a safety profile consistent with prelicensure efficacy trials (3)

1. Boutry C, Hastie A, Diez-Domingo J, et al. The Adjuvanted Recombinant Zoster Vaccine Confers Long-Term Protection Against Herpes Zoster: Interim Results of an Extension Study of the Pivotal Phase 3 Clinical Trials ZOE-50 and ZOE-70. *Clin Infect Dis*. 2022 Apr 28;74(8):1459-1467. doi: 10.1093/cid/ciab629.

2. Harbecke R, Cohen JI, Oxman MN. Herpes Zoster Vaccines. *J Infect Dis*. 2021 Sep 30;224(12 Suppl 2):S429-S442. doi: 10.1093/infdis/jiab387.

3. Hesse EM, Shimabukuro TT, Su JR, et al. Postlicensure safety surveillance of recombinant zoster vaccine (Shingrix) - United States, October 2017-June 2018. *MMWR Morb Mortal Wkly Rep* 2019; 68:91-4.



RZV - Safety

- > ZOE-70 + ZOE-50 (1)
 - Long-term follow-up (5-7 years)
 - N=7413
 - No deaths or other SAEs causally related to vaccination
- > Several trials in immunocompromised people
 - RZV is safe and effective (2)
- > Postlicensure safety monitoring in VAERS during the first 8 months of use (3.2 million RZV doses distributed), showed a safety profile consistent with prelicensure efficacy trials (3)

1. Boutry C, Hastie A, Diez-Domingo J, et al. The Adjuvanted Recombinant Zoster Vaccine Confers Long-Term Protection Against Herpes Zoster: Interim Results of an Extension Study of the Pivotal Phase 3 Clinical Trials ZOE-50 and ZOE-70. *Clin Infect Dis*. 2022 Apr 28;74(8):1459-1467. doi: 10.1093/cid/ciab629.

2. Harbecke R, Cohen JI, Oxman MN. Herpes Zoster Vaccines. *J Infect Dis*. 2021 Sep 30;224(12 Suppl 2):S429-S442. doi: 10.1093/infdis/jiab387.

3. Hesse EM, Shimabukuro TT, Su JR, et al. Postlicensure safety surveillance of recombinant zoster vaccine (Shingrix) - United States, October 2017-June 2018. *MMWR Morb Mortal Wkly Rep* 2019; 68:91-4.



RZV - Acceptability

- › Dutch Health Council judges benefits greater than risks
 - Also in immunocompromised people



Cost-effectiveness analysis (The Netherlands)

Interventions

- > Intervention strategies:
 - No vaccination
 - Shingrix[®] (2 doses within 2 months)
 - Zostavax[®] (single dose)
 - Zostavax[®] (single dose with booster after 10 years)
- > Population:
 - Cohorts of 50, 60, 70, 80 year-olds
 - Vaccination coverage of 50% (restricted to immunocompetent individuals)



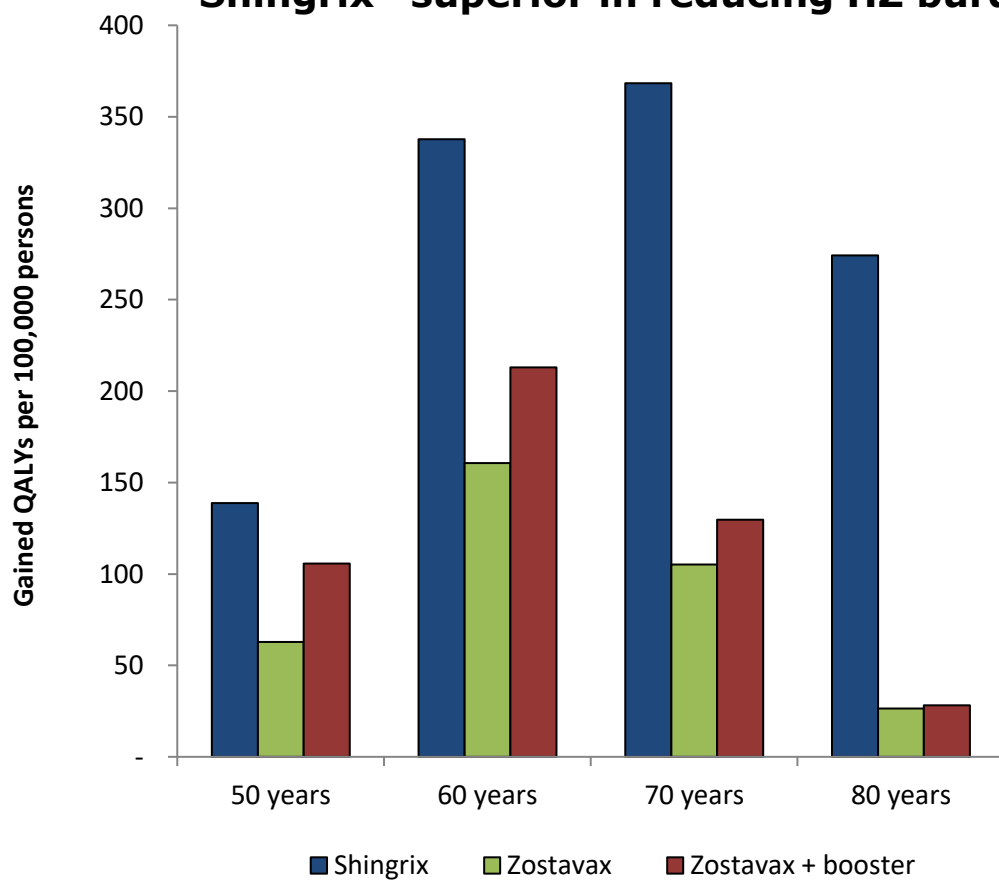
Model overview

- > Model structure: Markov model with decision tree, using annual cycles
- > Time horizon: 15 years
- > Discount rates: 4% for costs, 1.5% for QALYs
- > Perspective: societal
- > Model inputs herpes zoster:
 - Clinical outcomes: national registries (GP sentinel surveillance NIVEL, DHD, Statistics Netherlands)
 - Vaccine efficacy: randomized clinical trials
 - QALY loss and costs: Dutch prospective cohort study
 - Vaccine administration costs: Dutch flu tariff of €11,79 per dose

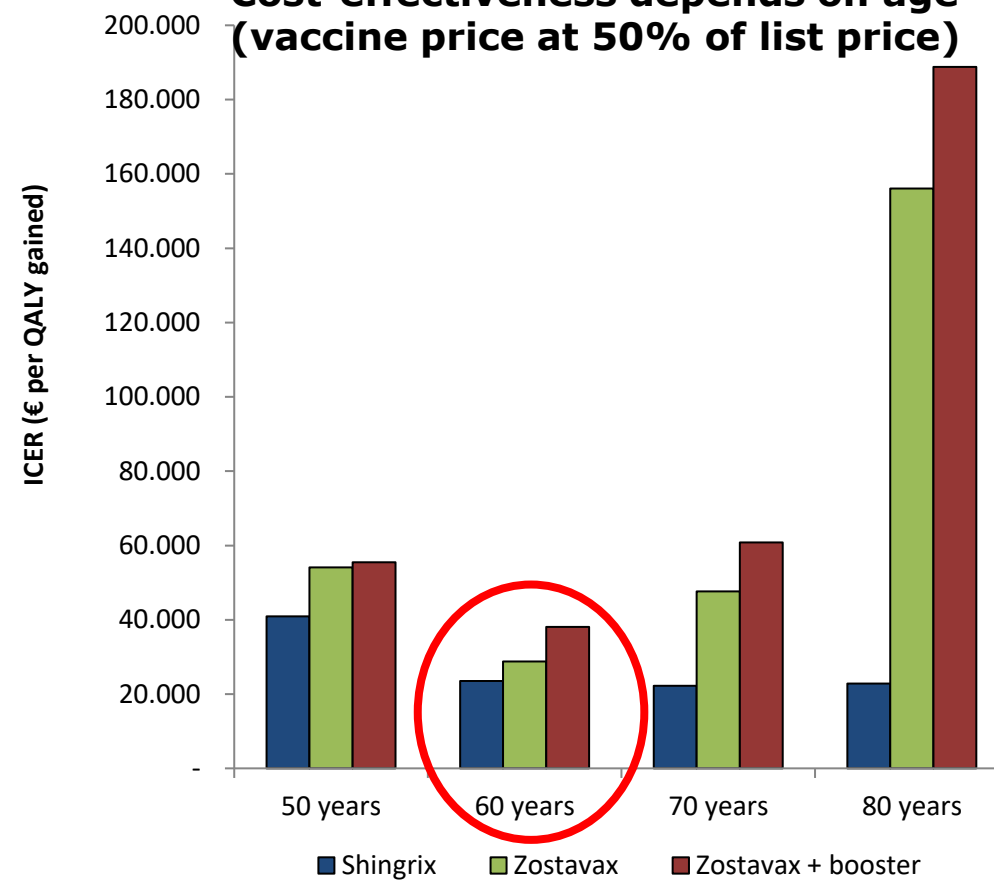


Effects and cost-effectiveness

Shingrix® superior in reducing HZ burden



Cost-effectiveness depends on age (vaccine price at 50% of list price)





RZV – cost-effectiveness

Information after Health Council advice

- › Recent review (2023) of publications of past 5 years
 - Conclusions:
 - Out of 18 selected studies, RZV vaccination against herpes zoster and post-herpetic neuralgia is cost-effective in 15
 - In the 15 studies establishing RZV cost-effectiveness, RZV is always cost-effective or frequently cost-saving in direct comparisons to ZVL
 - RZV was found cost-saving in several immune-compromised populations



Health Council advice (2019)

- > Positive advice regarding vaccination of elderly
 - Disease burden
 - Postherpes neuralgia
 - But disease burden lower compared to e.g. pneumococcal disease
 - High vaccine effectivity
 - Cost-effectiveness
 - Vaccinate 60-year olds (health benefits and cost-effectiveness)
 - Catch-up campaign
 - Troublesome but shortterm side effects -> give communication



Acknowledgement

Alies van Lier, Pieter de Boer, Caren van Roekel