Zoster in the Elderly

Benson Ogunjimi
Paediatric rheumatologist- immunologist

Center for Health Economics Research & Modeling Infectious Diseases (CHERMID) & Antwerp Center for Translational Immunology and Virology (ACTIV) – **Vaccine & Infectious Disease Institute** - UAntwerp

Antwerp Unit for Data Analysis and Computation in Immunology and Sequencing (AUDACIS) – UAntwerp

Division of Paediatric Rheumatology and Immunology – Antwerp University Hospital – UZB – ZNA

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University of Antwerp

Overview

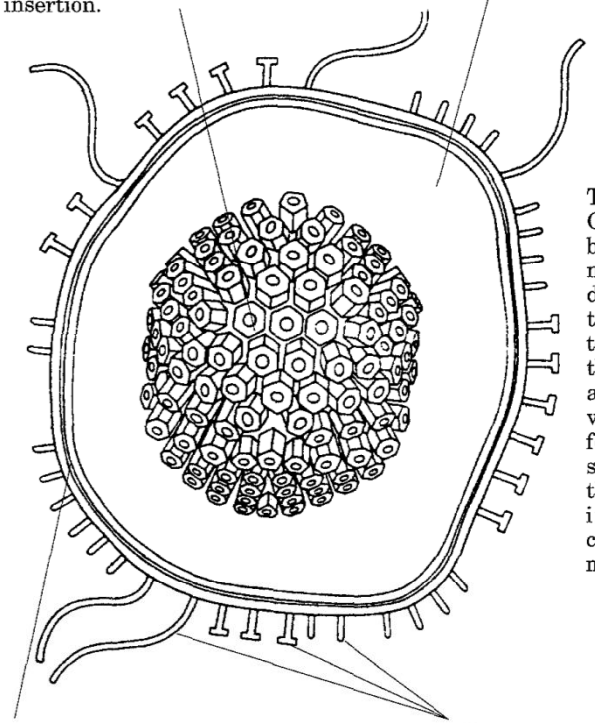
- Background on VZV
- HZ: burden of disease
- HZ: pathophysiology
- HZ: prevention

Background on VZV

- Varicella-zoster virus
- dsDNA virus
- Part of the (human) herpesvirus family (HSV1/2, VZV, EBV, CMV, HHV6/7/8)
  - Herpesvirus = latency!
- Immediate early, early, early-late and late genes

Capsid
Three forms have been observed in herpes viruses: A (empty), B (intermediate) and C (full). Structural and assembly proteins assemble into the inner and outer shells. The icosahedral outer shell is composed of 162 capsomers. After proteolytic cleavage of the inner shell proteins, the C capsids are formed by the insertion of the linear double-stranded DNA concurrent with the removal of the scaffolding proteins. A capsids are the result of inefficient DNA insertion.

Tegument
A complex, proteinaceous structure forming a shell around the capsid. It is the least well characterized part of the virion. Proteins present include the immediate early proteins which act as transcriptional regulators and a protein affecting host cell biosynthesis.



The virion
Overall size varies between 120 and 300 nm. The variation is due primarily to the thickness of the tegument. The state of the envelope may also affect the size of the virion. The hydrated forms appear to be spherical rather than the amorphous shape indicated by the conventional electron microscopy.

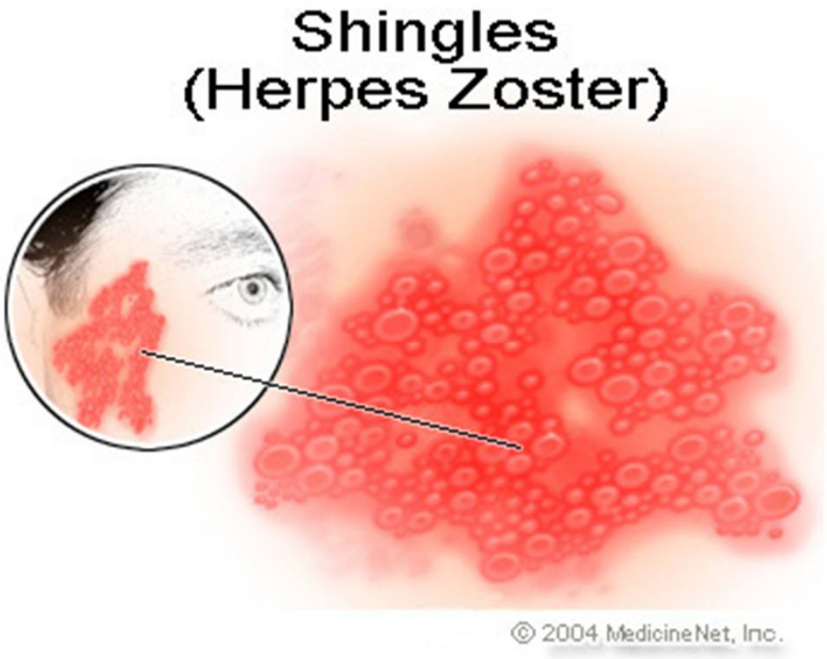
Envelope
A complex trilaminar entity thought to be derived from the cellular membranes of the *trans*-Golgi network.

Glycoprotein projections
Viral glycoprotein spikes (VZV gE/gI, gB, gH/gL and gC) project through the envelope and play an important role in the attachment of the virion to the host cell and in membrane fusion.

Varicella-zoster virus (VZV): some basics

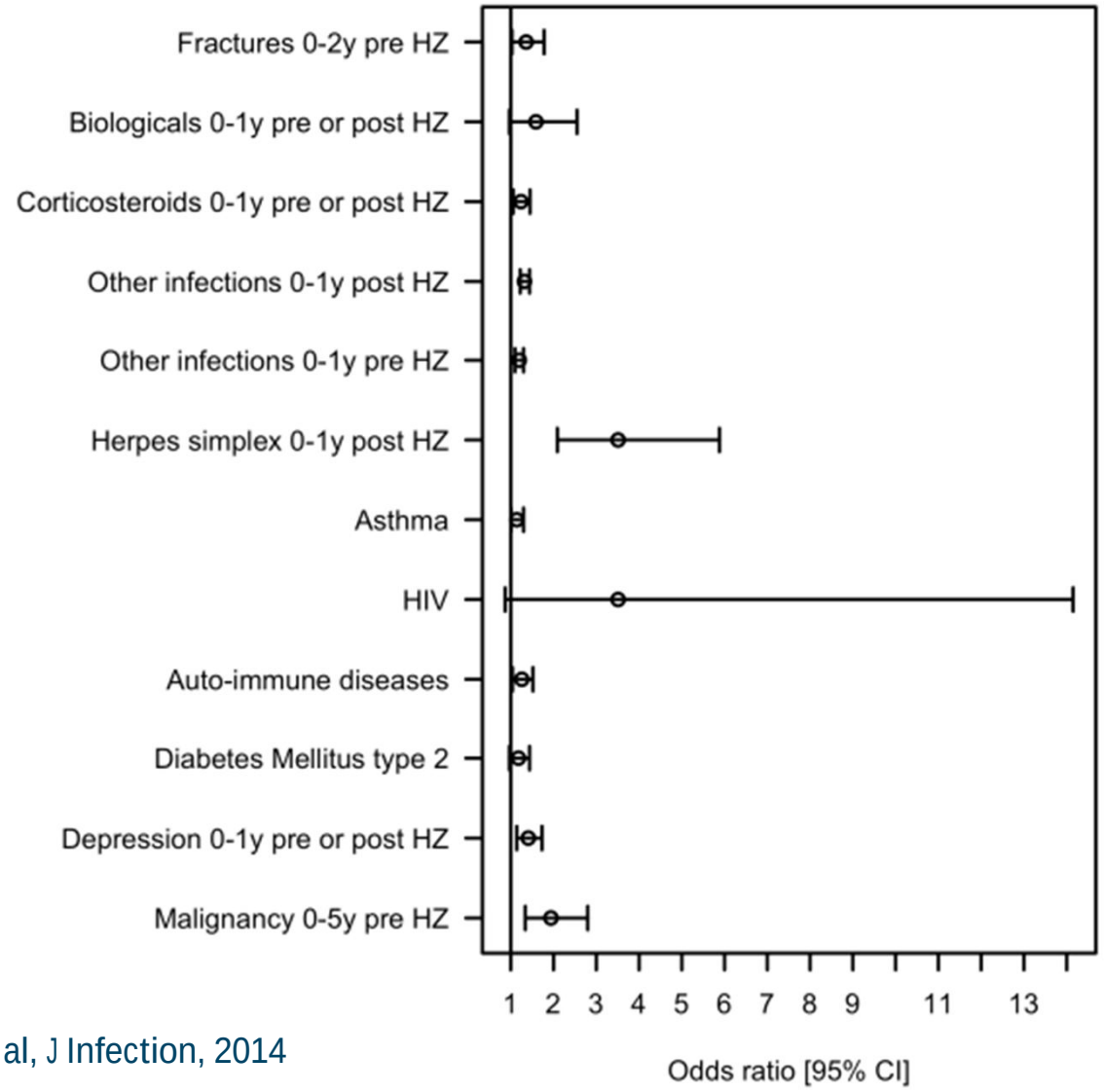
- Causes chickenpox after incubation period of 2w
- VZV remains latent/dormant in sensory, cranial and autonomic ganglia
- Reactivation can occur
  - Subclinical = without symptoms
  - Clinical → Herpes Zoster (HZ, zoster)

Zoster: serious morbidity (pain) & cost



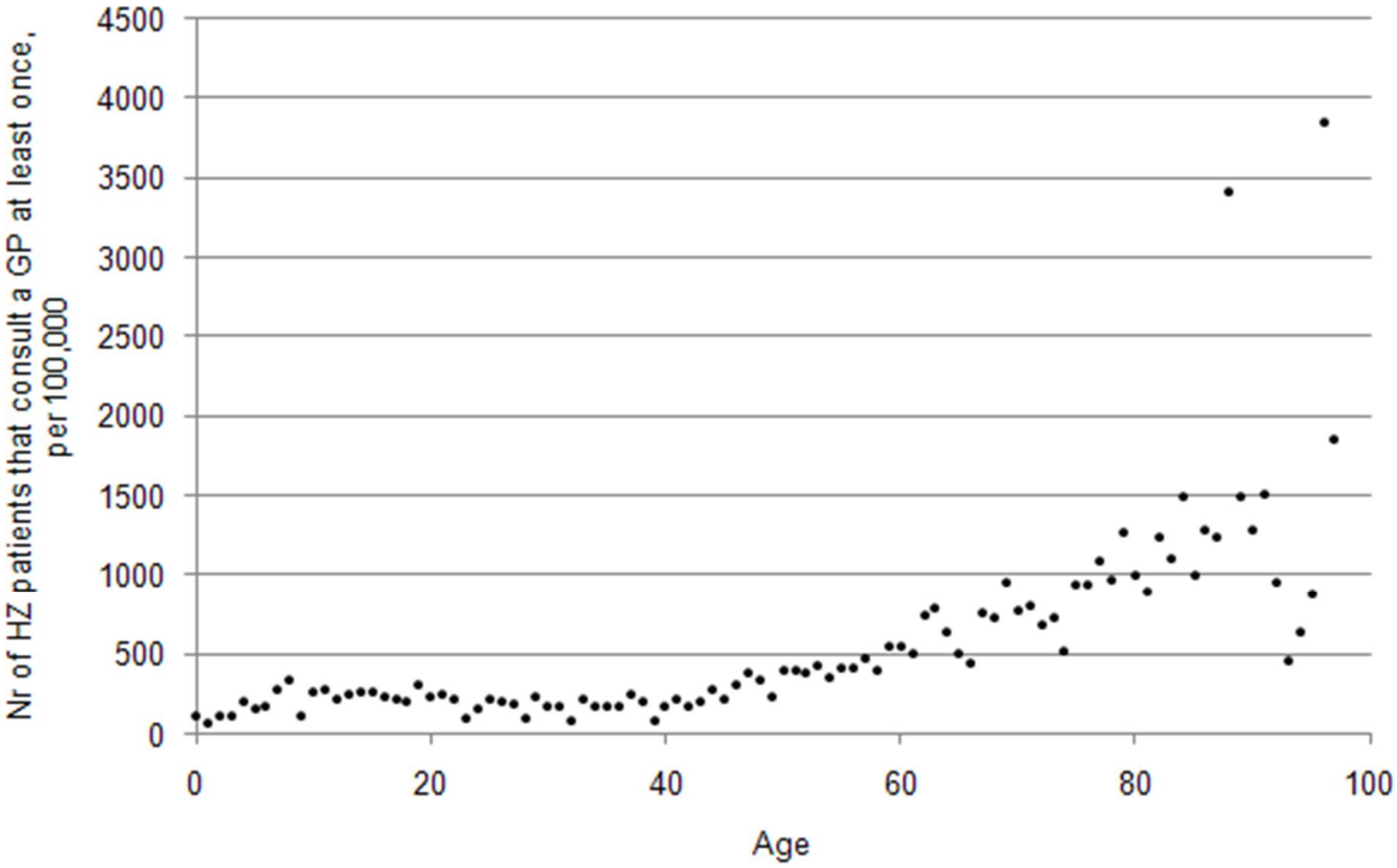
- About 40,000 consultations & 1,400 hospitalizations per year in Belgium (Bilcke, Ogunjimi et al, 2012)
- On average 6,000 EURO cost per HZ hospitalization & 250 EURO for ambulatory HZ
- Major complication → post-herpetic neuralgia

HZ – associations in Belgium



Ogunjimi et al, J Infection, 2014

Zoster incidence increases with age

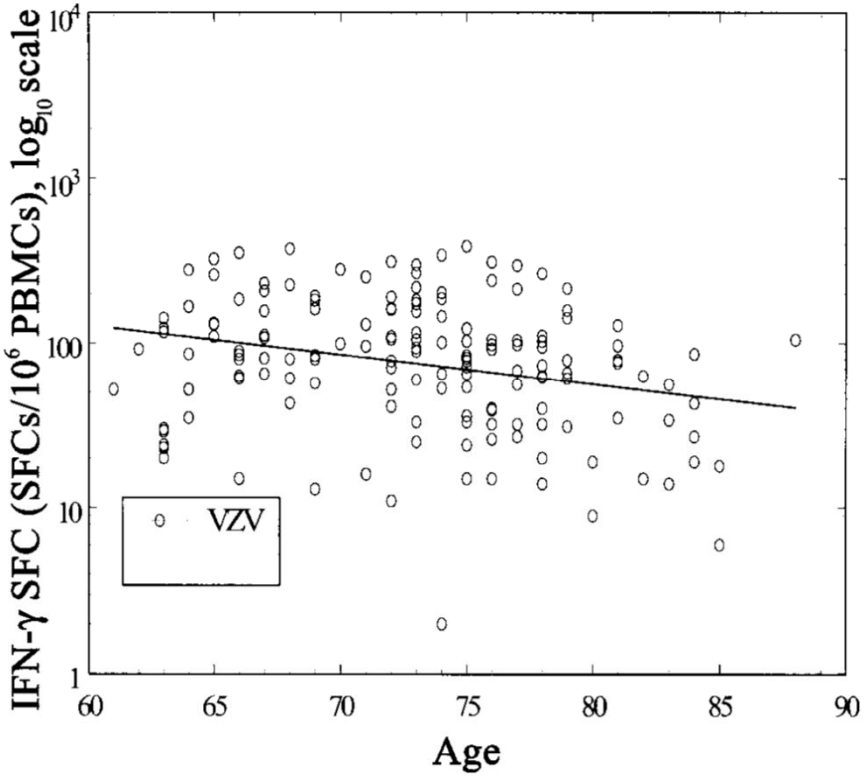


Bilcke, Ogunjimi et al, Epidem Infect, 2012

So, why does zoster occur?

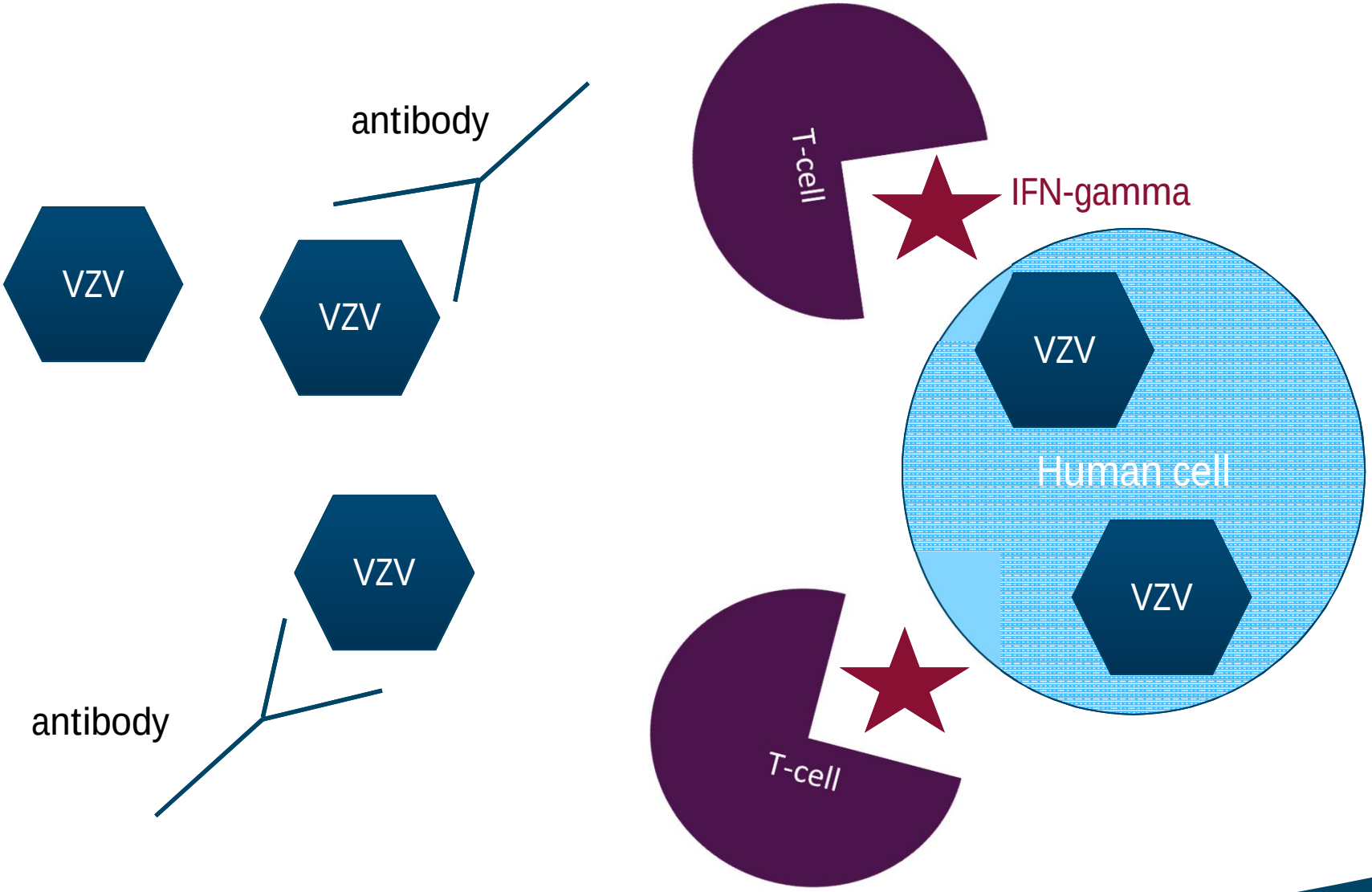
Decline in VZV-specific cellular immunity (VZV-CMI = T-cells)

- Immunocompromised individuals
  - Cancer
  - Chemotherapy
  - Corticosteroids
  - DMARDs/biologicals
  - Auto-immunity
- But also older individuals



Levin et al, J Infect Dis, 2003

Some basic virology & immunology

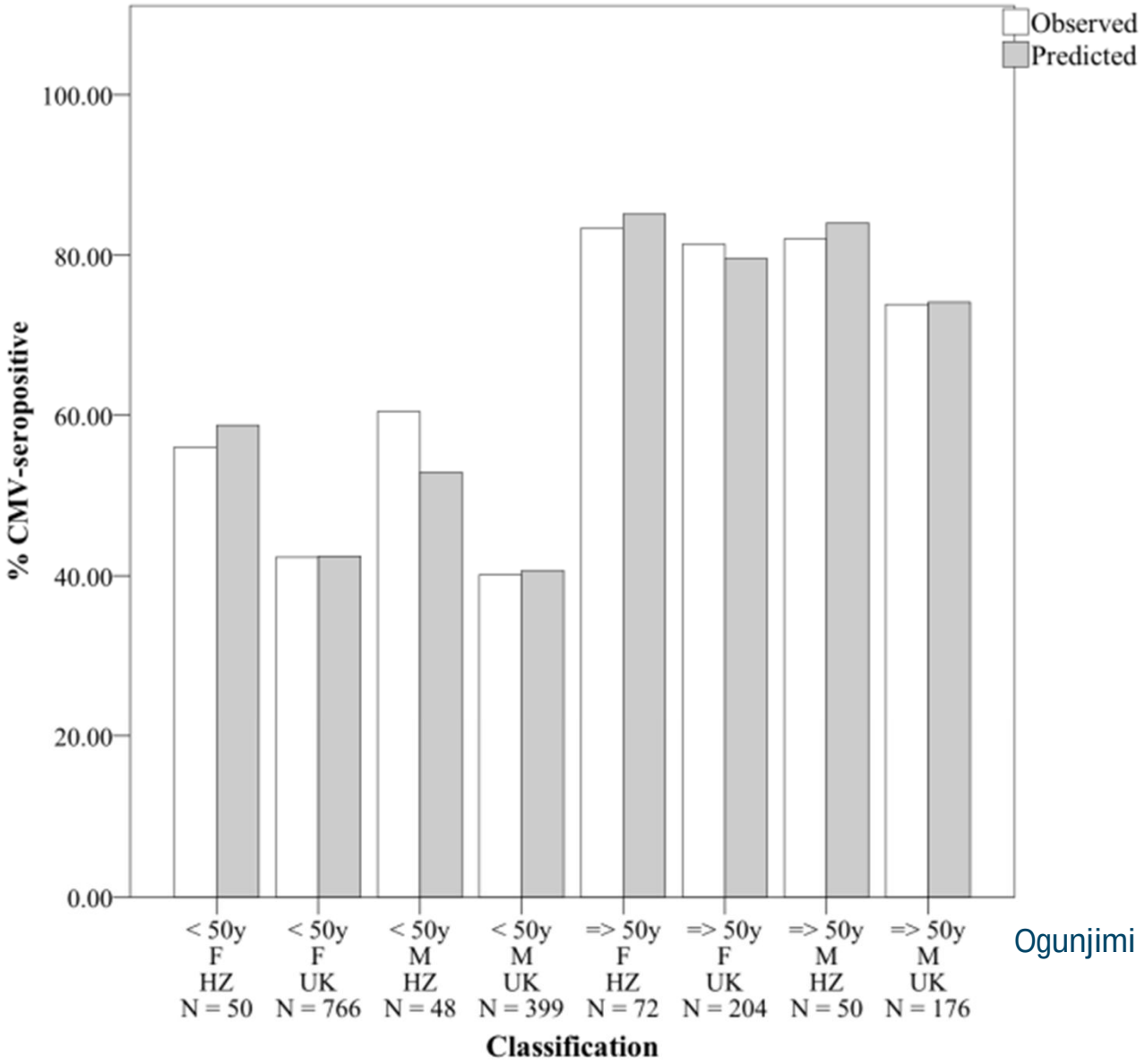


VZV-immunity pre-HZ

Time, immune assay	Clinical endpoint	Vaccine: Subjects, no.	Vaccine: Observed geometric mean (95% CI)	Placebo: Subjects, no.	Placebo: Observed geometric mean (95% CI)	P[a]
Before rash onset[c–e]						
RCF	Prerash- HZ	9	3.8 (2.1–6.9)	23	2.4 (1.3–4.4)	.006
	Matched control	58	6.5 (5.3–8.0)	169	5.6 (4.8–6.5)	
ELISPOT	Prerash- HZ	9	28.6 (7.1–114.2)	23	28.8 (17.2–48.2)	<.001
	Matched control	72	99.8 (80.8–123.2)	174	56.7 (47.3–68.0)	
gpELISA	Prerash- HZ	9	252.4 (126.1–504.9)	23	181.3 (122.3–268.8)	.030
	Matched control[d]	72	331.9 (267.8–411.3)	186	346.6 (301.3–398.6)	

Levin et al, J Infect Dis, 2008

HZ & Immunosenescence



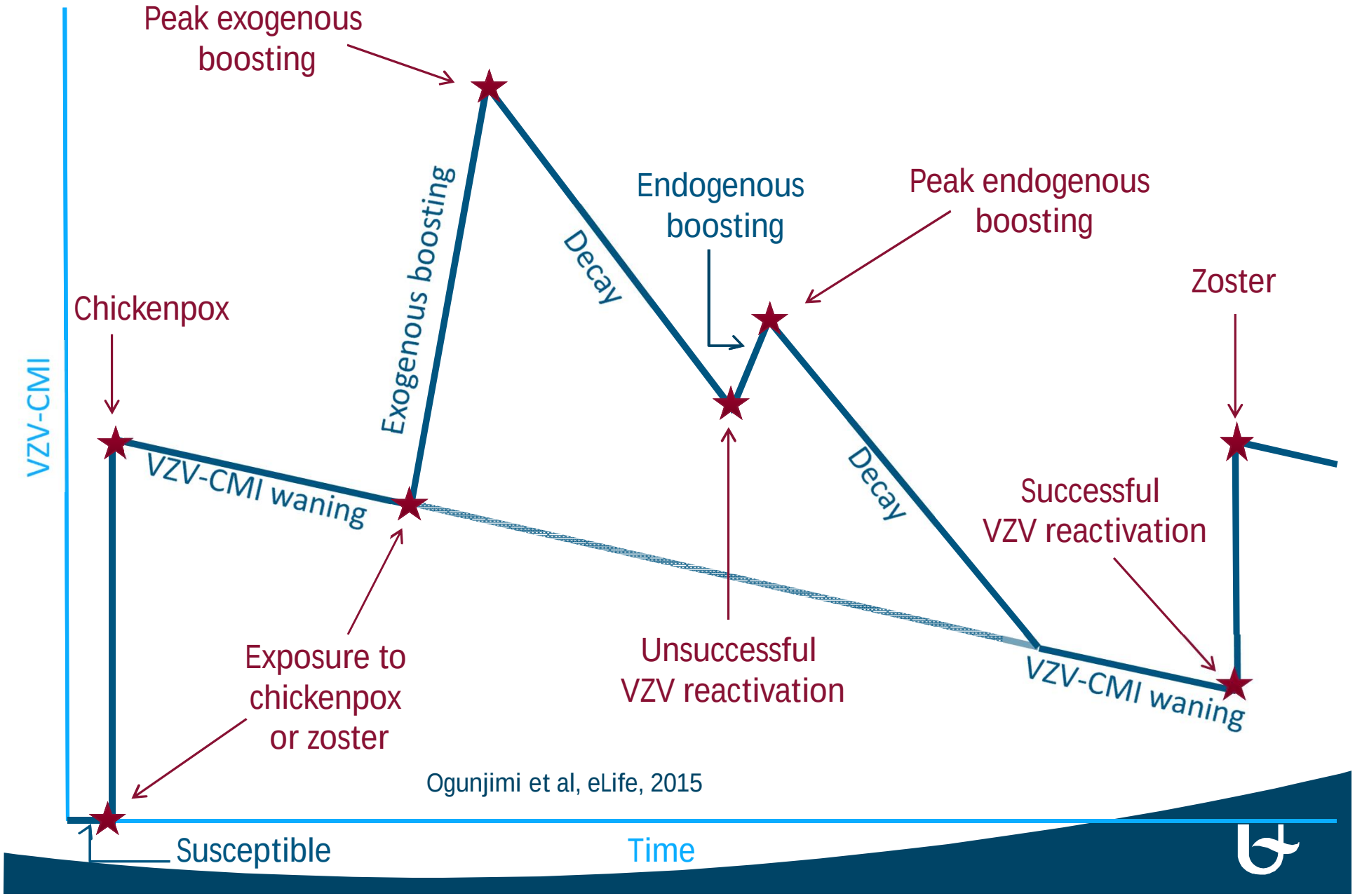
Ogunjimi et al, Hum Vaccin Imm, 2015

HZ – VZV re-exposure

- Hope-Simpson already proposed in 1965 that re-exposure to VZV (via chickenpox) would boost VZV-immunity, and therefore protect against HZ
  → exogenous boosting hypothesis

- Simulation models predict HZ increase when CP circulation would reduce

Hope-Simpson & exogenous boosting

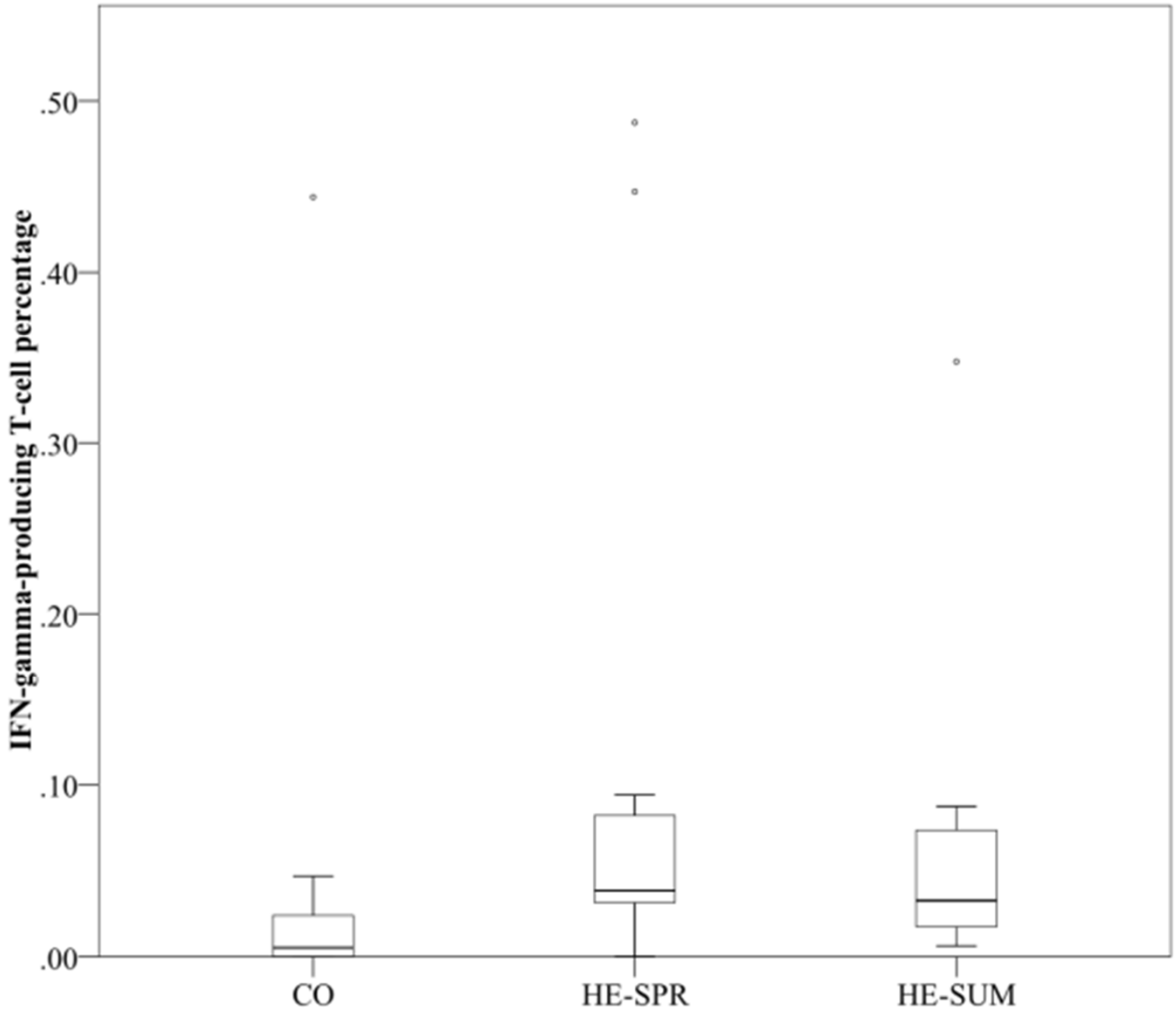


HZ in pediatricians

Table I. Questionnaire responses

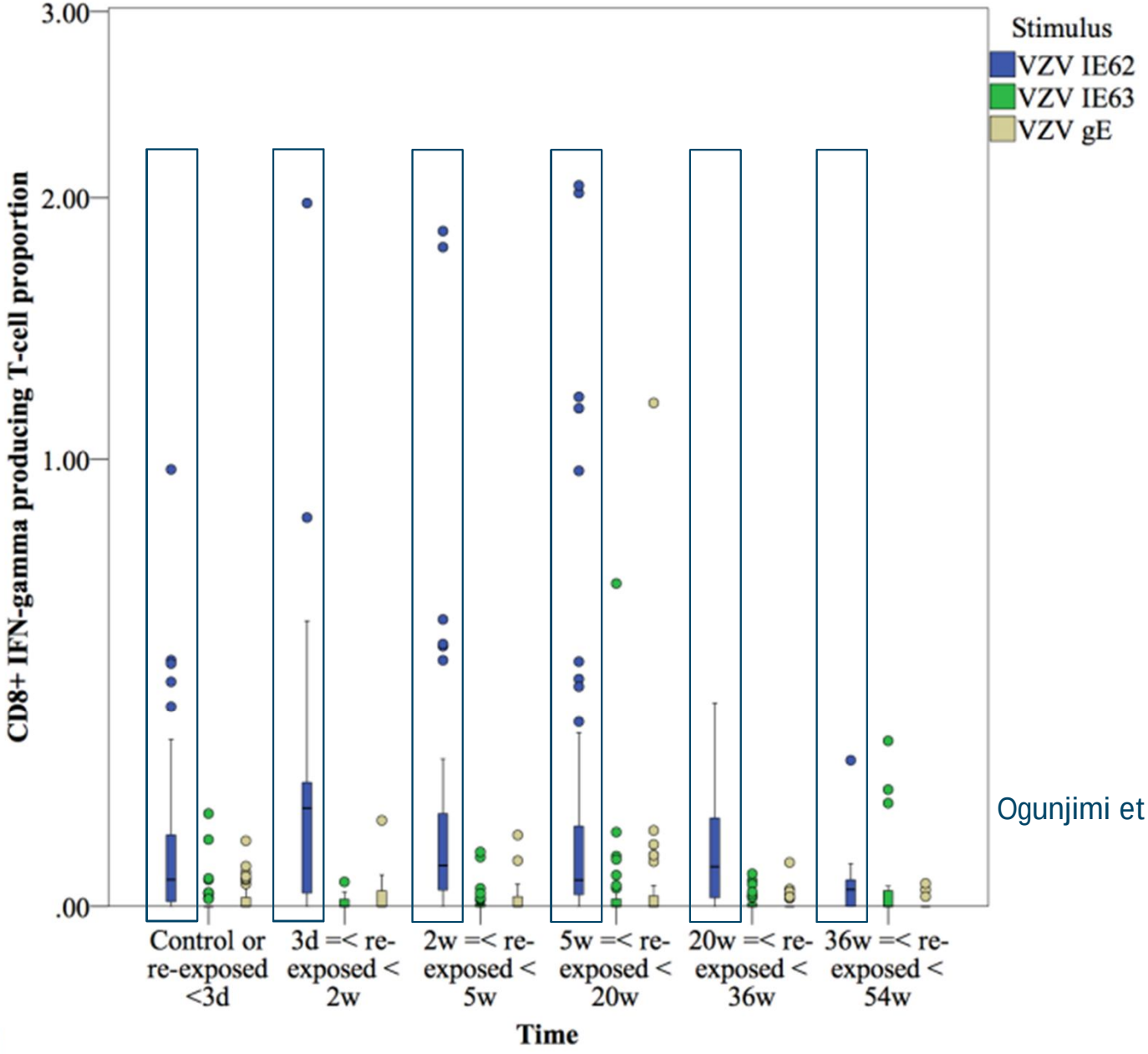
	Specialty		
	Dermatology	**Pediatrics**	**Psychiatry**
Sex (M:F) (%)	73:27	75:25	80:20
Positive history of primary VZV (%)	95	93	91
Physicians exposed to own children with VZV (%)	65	75	65
No. of patients with VZV contacted annually (%):			
Zero	4	0	55
1-5	8	12	35
6-12	30	11	10
13-24	34	15	0
25+	24	62	0
Incidence of herpes zoster (%)	9.27	5.95	10.82

VZV immunity increased in pediatricians



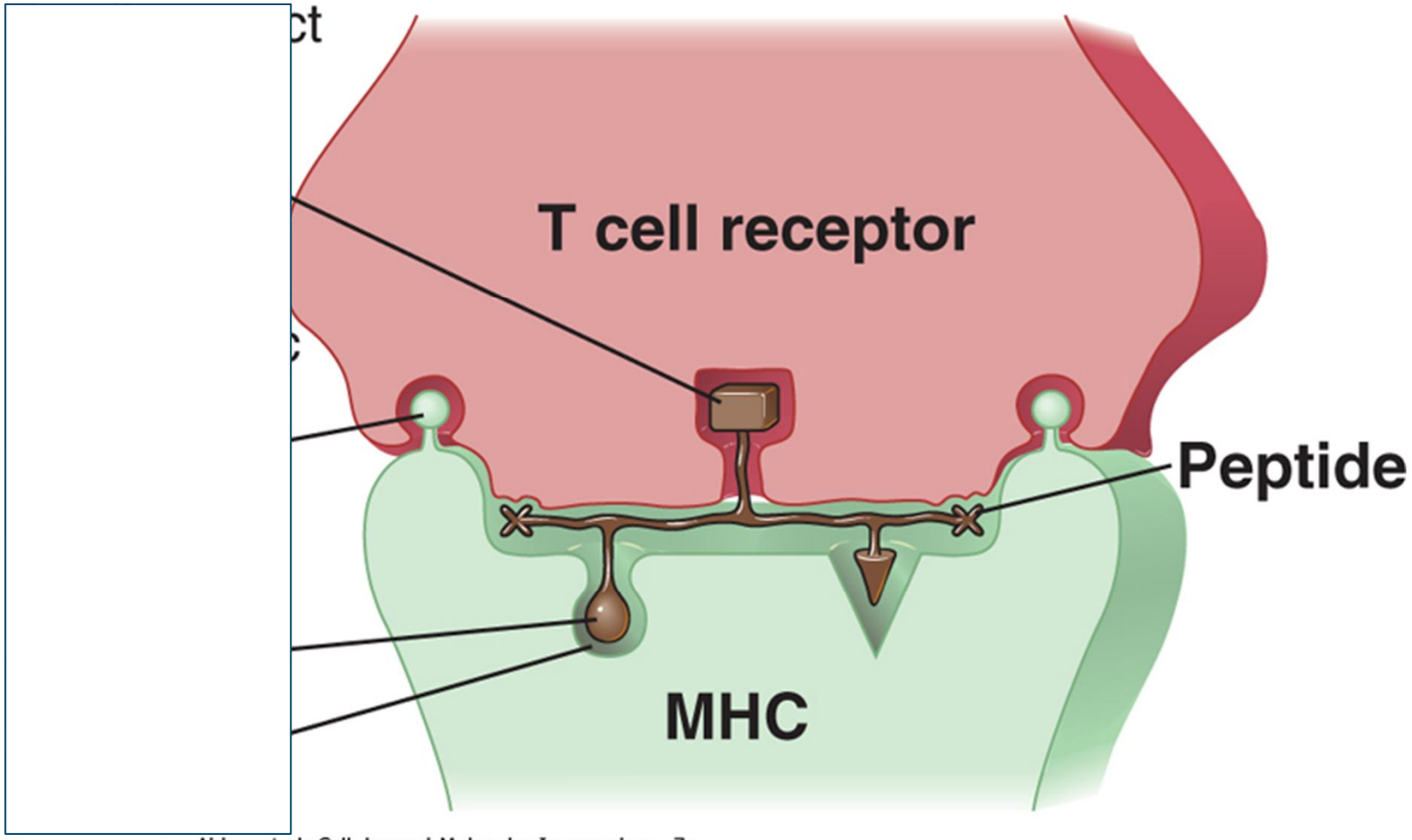
Ogunjimi et al, CVI, 2014

Limited exogenous boosting in grandparents



Ogunjimi et al, Scientific Reports, 2017

MHC – VZVpeptides - TCR



Abbas et al: Cellular and Molecular Immunology, 7e.

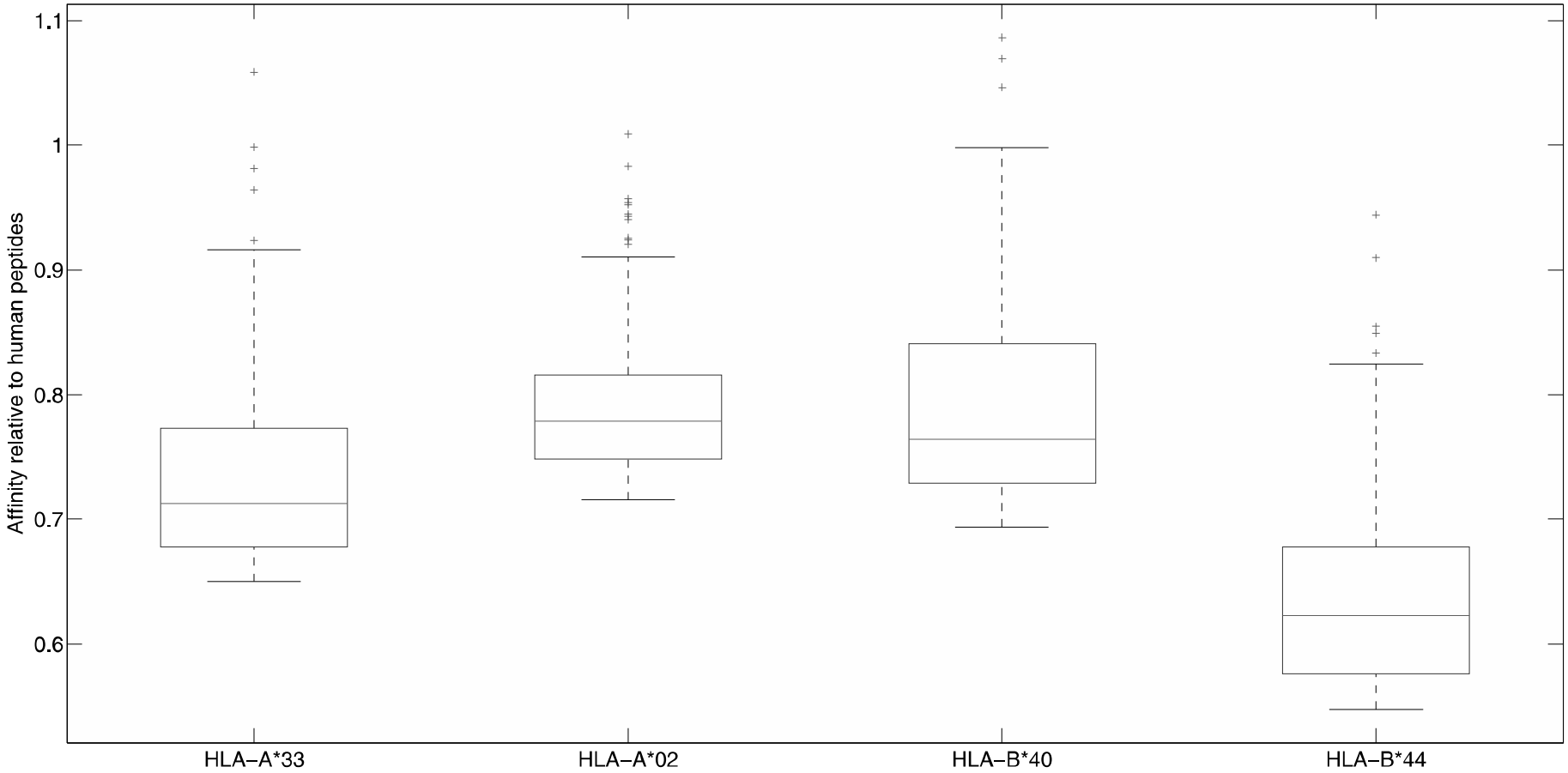
Population statistics for Japanese PHN & HZ patients

- PHN vs. controls
  - HLA A33 & B44 are enriched in PHN
  - HLA A02 is depleted in PHN
  - HLA-DRB1*13 is enriched in PHN

- PHN^+ vs. PHN^- HZ patients
  - HLA A33 & B44 are enriched in PHN^+
  - HLA B40 is depleted in PHN^+

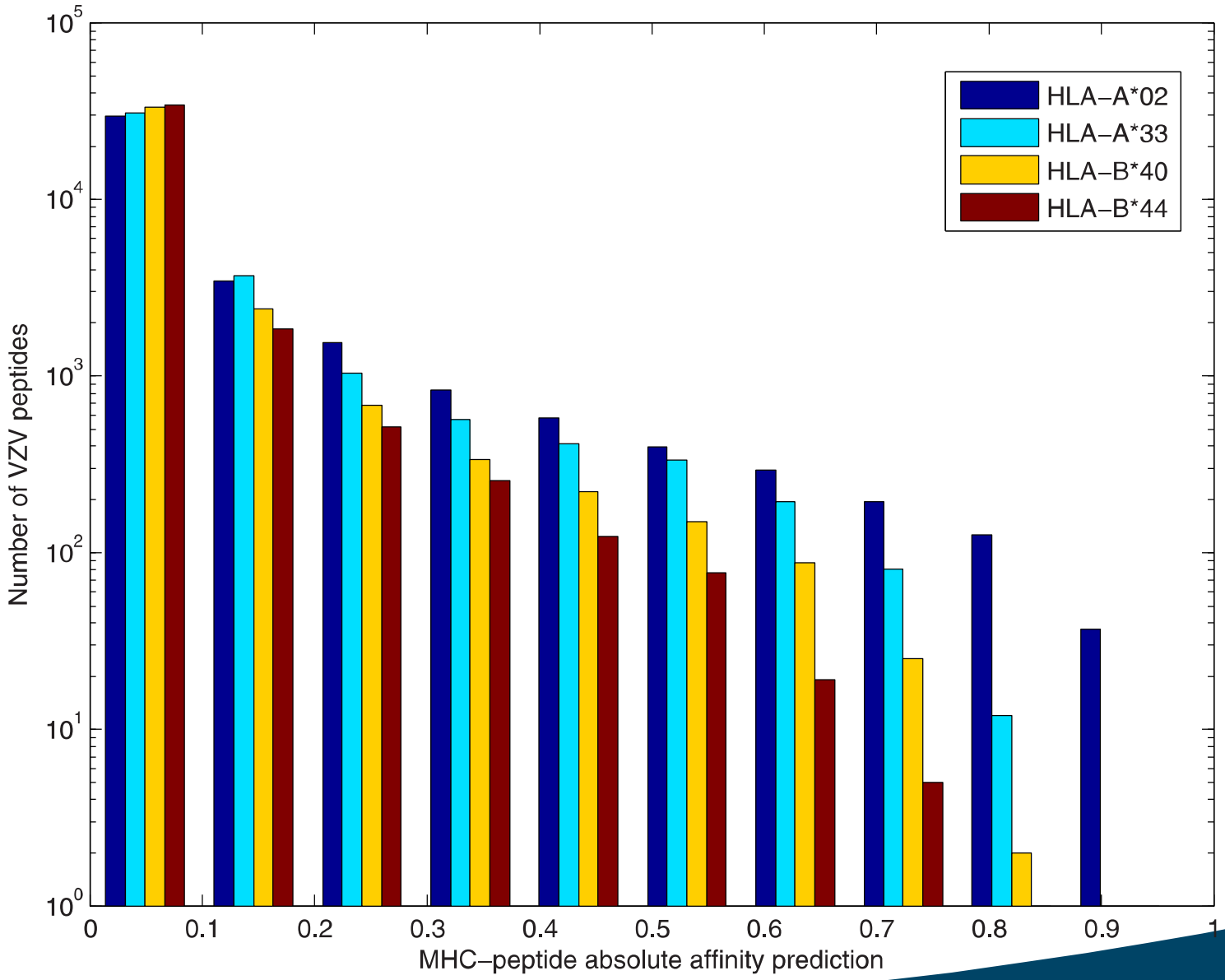
Meysman et al, J Virol, 2015

Box plots of the distribution of relative affinities for top 200 peptides

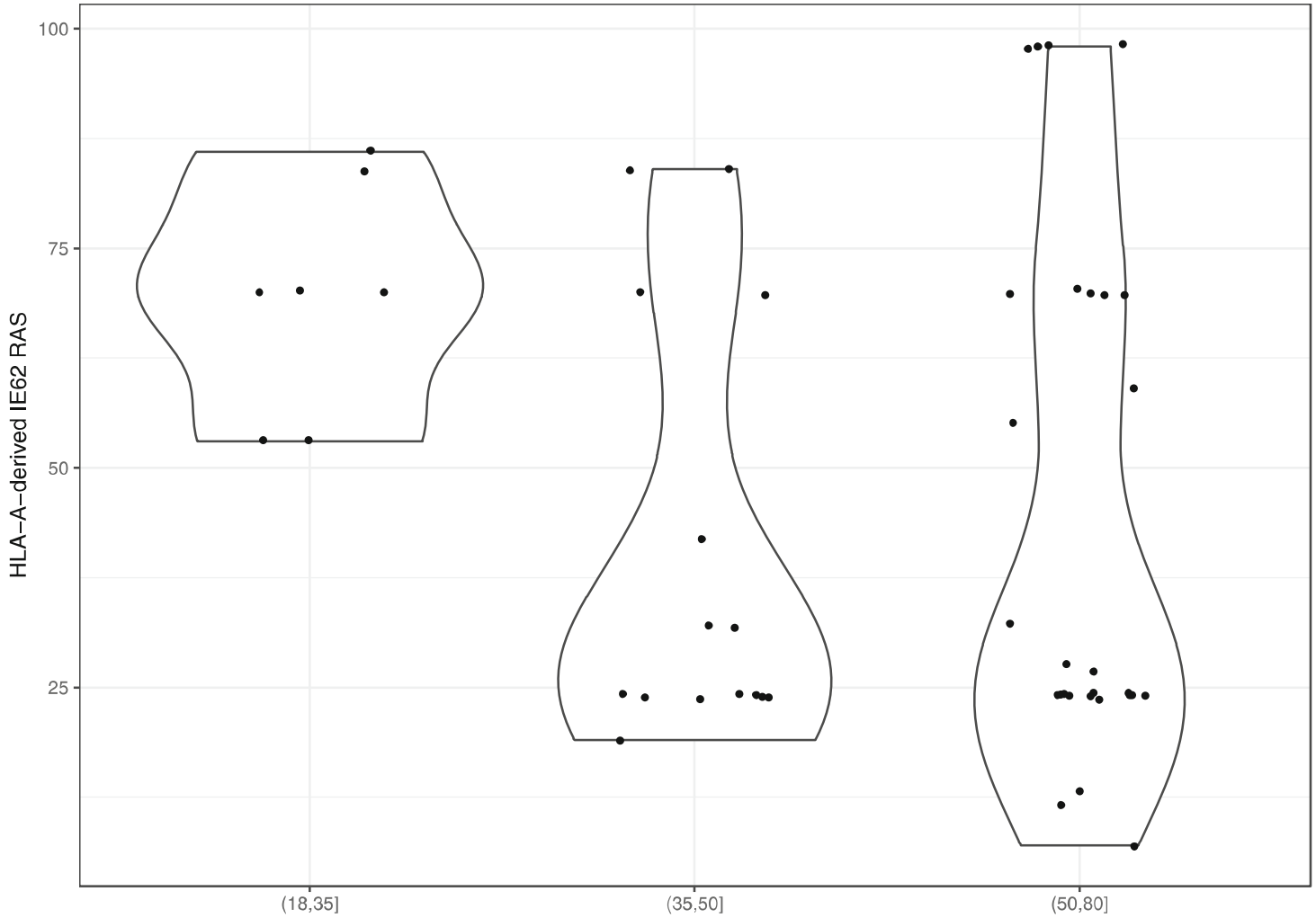


Meysman et al, J Virol, 2015

Bar plot of the affinity values



Age & VZVIE62 relation in Belgian HZ patients



Meysman et al, Immunogenetics, 2018

Preventive measurements against HZ

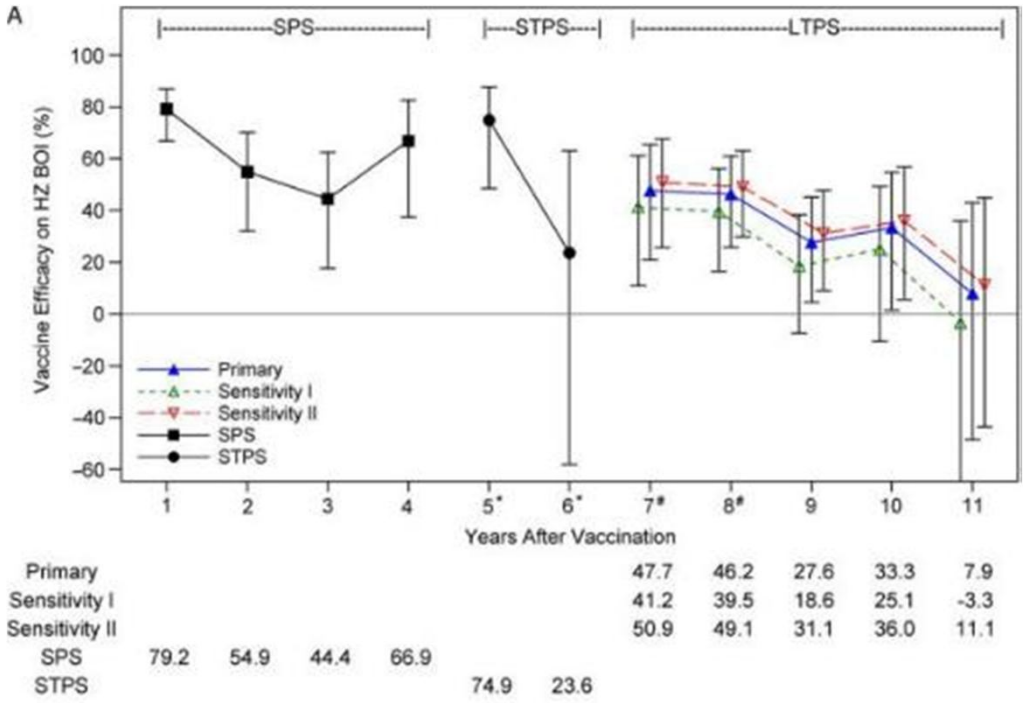
Zostavax (MSD)

- Live-attenuated virus
- Single dose (SC)
- Significant waning + age-depending response
  - Limited long-term protectiveness
- Registered in Belgium
- NOT for cellularly depressed individuals
- Co-administration ? (likely OK)
- 137,40 EURO

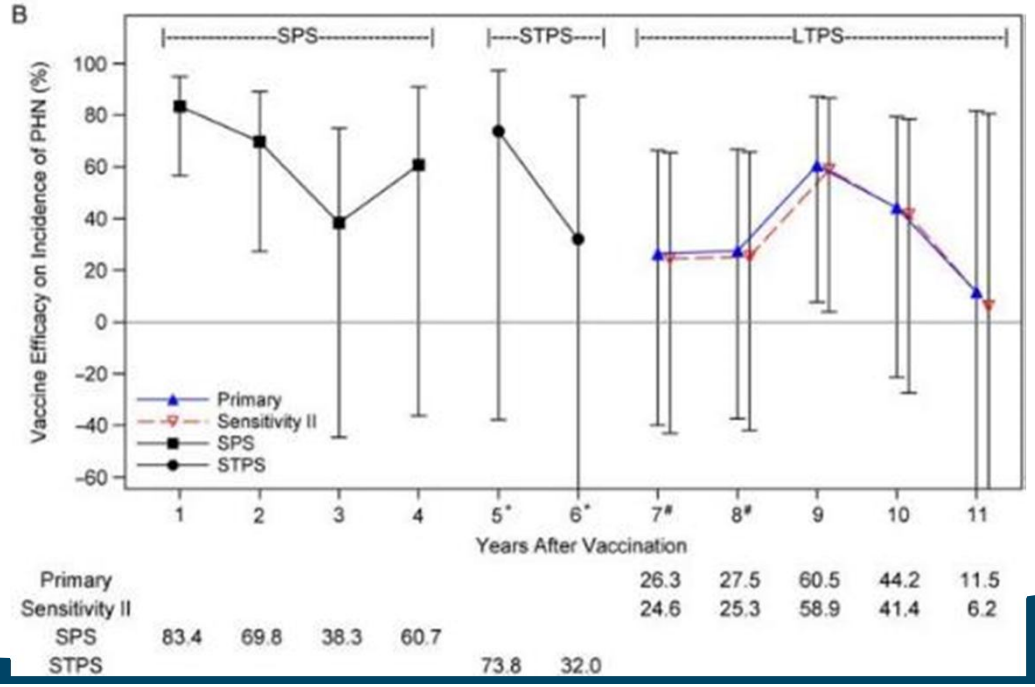
Shingrix (GSK)

- VZV gE subunit vaccine
- Two doses (2m apart, IM)
- Little waning due to very potent adjuvans
- Little/no effect of age on VE
- Not yet registered in Belgium
- No explicit CI

VE: Zostavax



Primary						47.7	46.2	27.6	33.3	7.9
Sensitivity I						41.2	39.5	18.6	25.1	-3.3
Sensitivity II						50.9	49.1	31.1	36.0	11.1
SPS	79.2	54.9	44.4	66.9						
STPS					74.9	23.6				

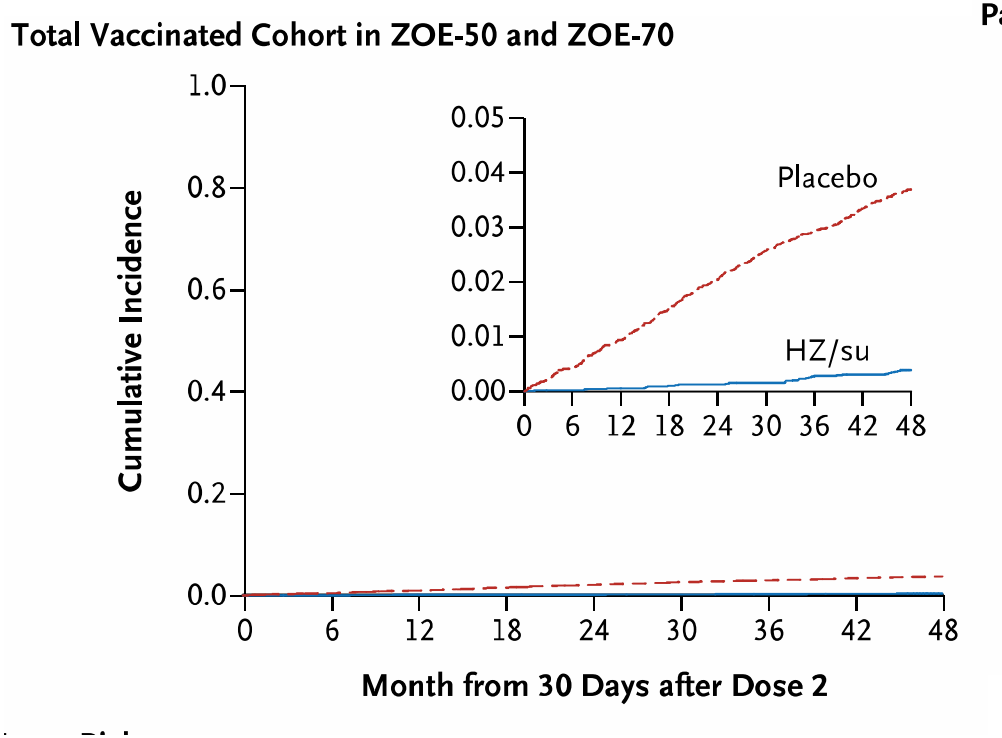


Primary						26.3	27.5	60.5	44.2	11.5
Sensitivity II						24.6	25.3	58.9	41.4	6.2
SPS	83.4	69.8	38.3	60.7						
STPS					73.8	32.0				

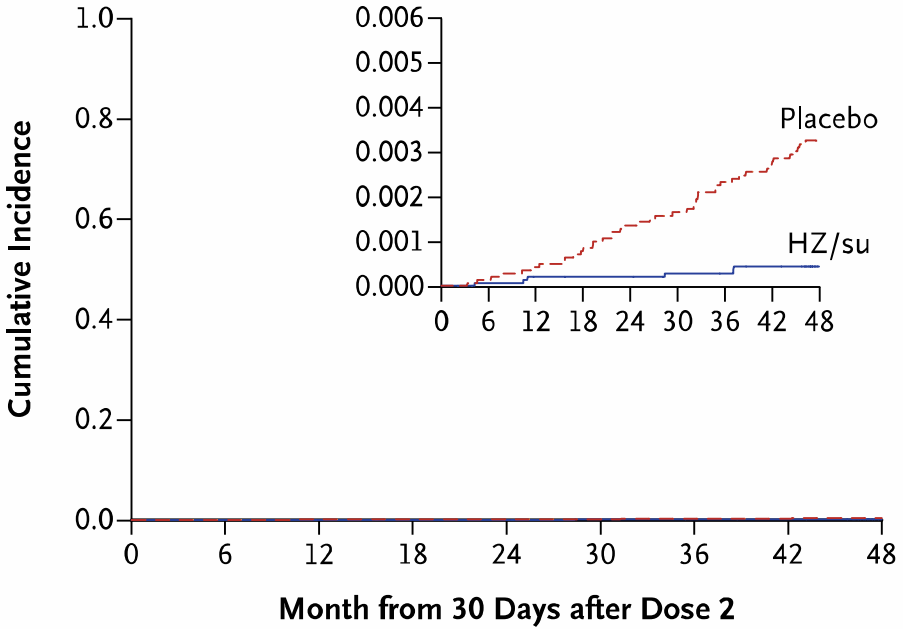
Morrison et al, CID, 2015

VE: Shingrix → VE > 88% (against HZ & PHN)

HZ

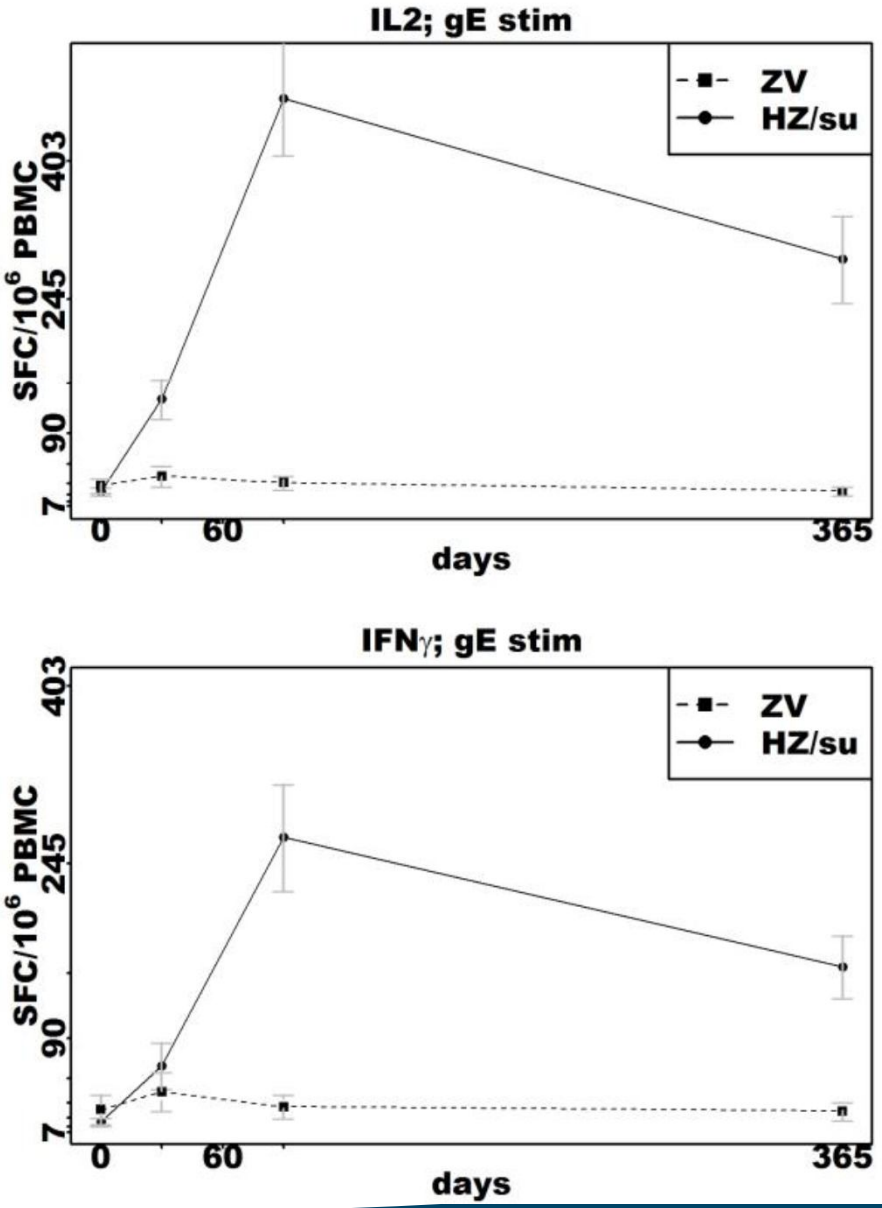


PHN



Cunningham et al, NEJM, 2016

Zostavax vs Shingrix – VZV-CMI



Levin et al, J Clin Invest, 2018

Safety

Zostavax & Shingrix

- Safe
- Minor injection-site related AE (pain, redness, swelling, itching)
- Headache
- No statistically significant increases in SAE

- Shingrix seems to cause more injection-site related AE

Superior Health Council recommendations (1)

- Herpes Zoster (HZ) has an important burden of disease in Belgium and ageing is a strong risk factor. Therefore, the SHC advises that Zostavax® might be considered for individuals aged over 65 years.
- There is uncertainty on the best age-window and vaccination can be considered on an individual basis, while the advantages of a population based vaccination programme needs further clarification.
- Persons should be vaccinated by means of a single dose of Zostavax®. They are no date supporting administration of a second dose.
- People with a prior history of HZ and with chronic conditions (e.g., diabetes mellitus, chronic renal failure, COPD, RA) may be vaccinated, unless the underlying condition is a contraindication such as cellular immunodeficiency.

Superior Health Council recommendations (2)

- A partial protection against HZ (Vaccine Efficacy [VE] of 52 %) and PHN (VE of 67 %) was demonstrated for 5 years after vaccination from 50 years to 79 years with the live- attenuated HZ Vaccine. However, protection is steadily decreasing over 10 years. After the age of 80 yrs there are no data on the efficacy.
- Zostavax® is not to be used in the treatment of acute HZ, the prevention of PHN in the event of acute HZ or the treatment of PHN. There is no need to enquire about a previous history of varicella or to carry out serological testing to verify the immunity status for varicella prior to administering Zostavax®.
- Taken all evidence in consideration, the SHC recommends that vaccination against HZ might be considered for all individuals between 65 and 79 years old.
  In case of immunosuppressive therapy, this vaccination could be considered from the age of 50 years old but if possible, at least 4 weeks before the start of the immunosuppressive therapy.

Thank you for your attention

Any questions?

benson@uantwerp.be