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Deutsches Rheuma-Forschungszentrum Berlin
Ein Institut der Leibniz-Gemeinschaft

Risk of herpes zoster in patients treated with biologicals

DANBIO 10th anniversary

Kopenhagen, 9th September 2011

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Outline

- Herpes zoster in general
- Herpes zoster in patients with rheumatoid arthritis
- Risk of herpes zoster under different treatments for RA
- Risk of herpes zoster in patients treated with biologics
- Prevention

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- **Herpes zoster in general**
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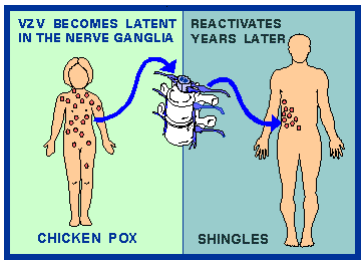
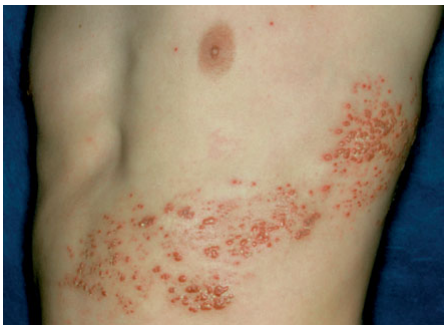
Herpes zoster

- a neurocutaneous disease
- with painful vesicular dermatomal rash
- resulting from reactivation of the varicella zoster virus





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Herpes zoster - Diagnosis

- Inspection: vesicular rash, (grouped vesicles), mostly unilateral distribution (1-3 adjacent dermatomes)

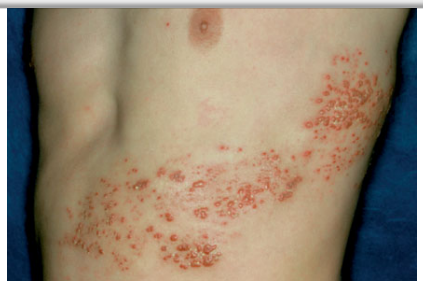
Prodromal phase: (4-14 days before) pain in the later on zoster-affected dermatome (intermittent or continuous, throbbing, sharp, stabbing, burning or shooting pain) sometimes with skin sensations (tingling or itching).

Malaise is a frequent element of the prodrome as well.

- Method of choice: PCR
  - direct fluorescence of antigen in vesicle scrapes

(EIA to detect VZV-specific immunoglobulins of classes IgG, IgM, IgA (only Germany)

Differentiation with laboratory diagnosis important in pregnant women and newborn infants, DD bullous dermatoses, in atypical infections of immunodeficient patients, and suspected VZV infection of the central nervous system



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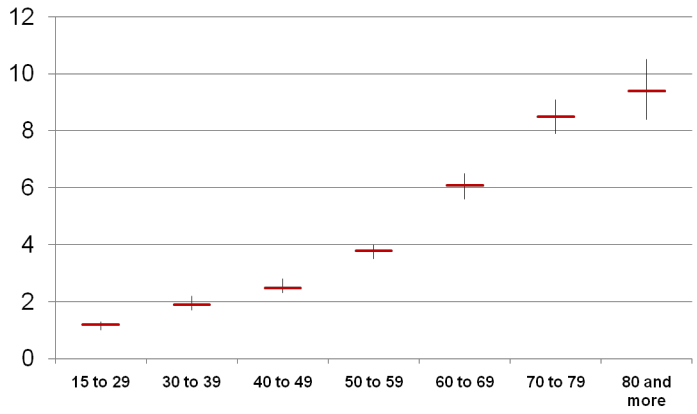
Incidence of Herpes zoster



Incidence of Herpes zoster per 1,000 person-years

Data from: *Insigna et al., J Gen Intern Med 2005; 20:748-753*

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Burden of disease

Variable; age group†	Time since onset of rash			
	0 days	30 days	90 days‡	180 days
No. (%) reporting pain				
50–60 yr	101 (100)	50 (49.5)	17 (16.8)	6 (5.9)
61–70 yr	78 (100)	49 (62.8)	19 (24.4)	11 (14.1)
> 70 yr	82 (100)	51 (62.2)	27 (32.9)	17 (20.7)
Total	261 (100)	150 (57.5)	63 (24.1)	34 (13.0)
Mean pain score (95% CI)§				
50–60 yr	5.9 (5.4–6.6)	3.1 (2.5–3.7)	3.1 (2.6–3.6)	3.2 (2.0–4.4)
61–70 yr	7.4 (6.7–8.1)	4.1 (3.5–4.7)	4.0 (3.6–4.5)	3.9 (2.9–4.9)
> 70 yr	5.7 (5.0–6.4)	4.2 (3.6–4.7)	4.2 (3.8–4.6)	4.2 (3.3–5.0)
Total	6.3 (5.9–6.7)	3.8 (3.4–4.1)	3.8 (3.5–4.1)	3.9 (3.3–4.5)

Drolet et al., CMAJ 2009; 182(16):1731-36

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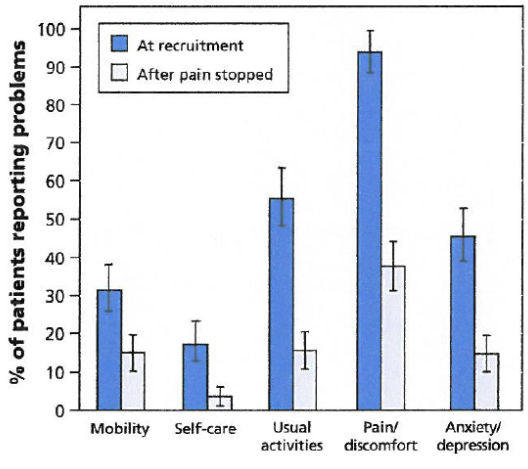
Health-related Quality of life

Percentage of patients with problems on the EuroQuOL EQ-5D domains (< 14 days after onset of HZ)



Drolet et al., CMAJ 2009; 182(16):1731-36

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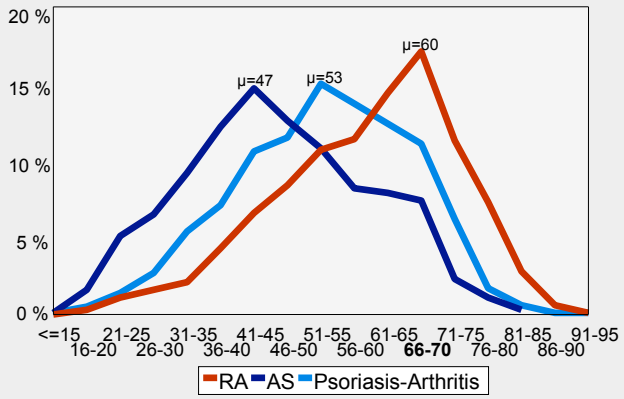
Rheumatoid arthritis (RA)

- **RA is a systemic inflammatory disease**
- **Patients with the disease are at higher age**

Mean age of arthritis patients observed in the german national database between 2005-2007 (n=13.924)



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Incidence of Herpes zoster in RA

Source	Country	N=	Years
NDB longitudinal study *	US	**10 614** RA patients w/o prev HZ, **1721** MSK, 33 825 PYRS FU	**01/02-06/05**
Pharmetrics claims database §	US	**122,272** patients with RA (at least one diagnose) included in the managed care db (incl. 61 health plans from the US); non-RA: **1 Mio.**	**1998-2002** mean f-u: RA 16.5 months non-RA 21.7
General § practitioner research db	UK	**38,621** patients with RA (at least one diagnose); non-RA: **500,000**	**1990-2001** mean f-u: RA 52 months non-RA 54
Veterans affaire health care db #	US	**20,357** patients followed in the Veterans Affaire Healthcare system and treated for RA	**10/98-06/05**

* *Wolfe et al., Rheumatology 2006; 45:1370-75*
§ *Smitten et al., Arthr Care Res 2007; 57: 1431-38*
\# *McDonald et al., Clin Infect Dis 2009; 48:1364-71*

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Incidence of Herpes zoster in RA

Source	Years	Country	CIR / 1,000 RA py	CIR/1,000 non-RA py	Adjusted HR RA vs. Non-RA (95% CI)
NDB longitudinal study *	01/02-06/05	US	13.2	14.6 MSK	1.0 (0.7-1.3)
Pharmetrics claims database §	1998-2002	US	9.8	3.7	1.94 (1.8-2.1)
General § practitioner research db	1990-2001	UK	10.6	4.1	1.7 (1.6-1.8)
Veterans affaire health care db #	10/98-06/05	US	9.96		

* *Wolfe et al., Rheumatology 2006; 45:1370-75*
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CIR = crude incidence rates; **HR** = hazard ratio

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Incidence of Herpes zoster in RA

→ increased in patients with RA (and MSK) compared to the general population

→ Possible causes:

- dysregulation of the immune system
- immunosuppressing/-modulating medication

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Treatment of RA

- **first line: methotrexate (MTX), glucocorticoids (prednisone), NSAIDs (selective and non-selective)**

2nd: leflunomide (LEF) or other DMARDs*
patients with high disease activity after failure of at least 2 DMARDs (incl. MTX) receive biologics (anti-TNFs, rituximab, tocilizumab, abatacept)

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HZ in RA – Hazard ratios for treatments

Source	Country	Traditional DMARDs	Biologics	Prednisone
NDB longitudinal study *	US	AZA 2.1 (1.3-3.3) LEF 1.4 (1.1-1.8) CyPh 4.2 (1.6-11.5)	INF 1.3 (1.1-1.7) ADA 0.4 (0.2-0.7)	1.6 (1.3-1.9)
Pharmetrics claims database §	US	1.4 (1.2-1.6)	1.5 (1.1-2.3)	2.5 (2.1-3.1)
General practitioner research db §	UK	1.3 (1.1-1.5)	--	1.5 (1.2-1.7)
Veterans affaire health care db #	US	Group 1 (HCQ, SAS, Auranofin, Penicillamin) < Group 2 (MTX, LEF, AZA, Cyclophos., Cyclosp., ANAK) **HR 1.34** < Group 3 (ETA, ADA, INF) **HR 1.38**		

* *Wolfe et al., Rheumatology 2006; 45:1370-75*
§ *Smitten et al., Arthr Care Res 2007; 57: 1431-38*
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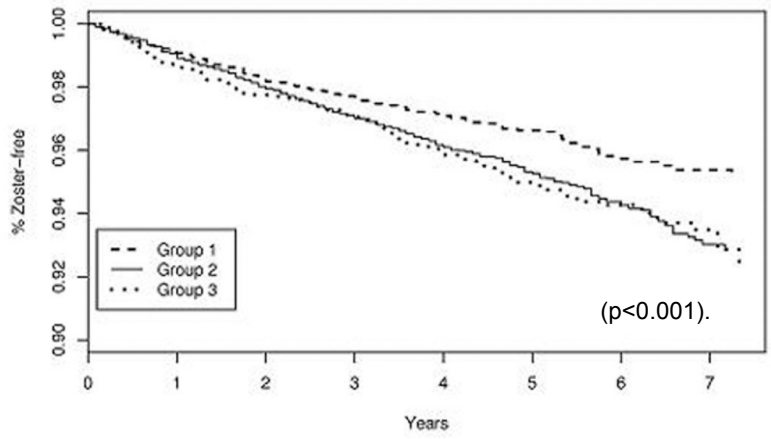
HZ in RA – Hazard ratios for treatments



Zoster-free survival in medication group 1, 2, and 3 adjusted for demographic data and comorbidities (p<0.001).

McDonald et al., Clin Infect Dis 2009; 48:1364-71

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Incidence and risk for HZ in biologics treated patients, register data

Source	Country	Incidence rates/ 1000 Pyrs	Hospitalisation rate / 100,000	SIR vs. Gen Pop
BIOBADASER* - only hospitalisations	Spain	**6.6** for all rheumatic diseases treated with biologics RA 55%, AS16%, PsA 15%	32 (14-78)	9 (3-20)
		only RA (n=2562):	44 (17-118)	10 (3-26)
CORRONA §	US	Incidence (n=7971): **12.9** MTX/TNF, **6.3** MTX, **12.2** TNF, **4.2** other DMARDs	A history of a prior infection was a significant predictor of a subsequent opportunistic infection	
RABBIT &	D	n=5040 Anti-TNF **10.1**, DMARDs **5.6**	142	-

* *Garcia-Doval et al., Ann Rheum Dis 2010; 69:1751-55*

§ *Greenberg et al., Ann Rheum Dis 2010; 69(2): 380-86.*

& *Strangfeld et al. JAMA 2009;301:737-44*

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HZ in RA – Incidence rates with diff. treatments

	Anti-TNF total	Controls#
Patientyears	6112	4291
Herpes zoster (total)	62	24
Incidence rates (/1000 pat.years)	**10.1***	**5.6**
Multidermatomal & ophthalmic zoster	15	4
Incidence rates (/1000 pat.yrs.)	**2.5**	**0.9**

In 14% of the cases hospitalisation was required

** p<0.05*

 # DMARD treated patients

Strangfeld et al. JAMA 2009;301:737-44

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Risk factors for Herpes zoster infections

Univariate Cox-regression

Baseline characteristics	HR	95% CI	p
Age (every 10-years)	**1.2**	1.0 – 1.5	**0.029**
DAS28	**1.4**	1.2 – 1.7	**0.0001**
Propensity score (high vs. low)	**1.9**	1.2 – 2.9	**0.0052**
Time varying variables			
Glukokortikoide < 5 mg vs. no	1.8	0.7 – 4.5	0.250
5 – 9 mg vs. no	**2.6**	**1.2 – 5.5**	**0.013**
≥ 10 mg vs. no	**2.9**	**1.2 – 6.7**	**0.016**
DAS28	**1.2**	**1.0 – 1.4**	**0.024**
TNF-Inhibitors vs. DMARD Controls	**1.9**	**1.3 – 3.1**	**0.013**
Etanercept vs. DMARD Controls	1.7	0.9 – 3.0	0.099
Infliximab/Adalimumab vs. DMARD Controls	**2.0**	**1.2 – 3.5**	**0.009**

Strangfeld et al. JAMA 2009;301:737-44

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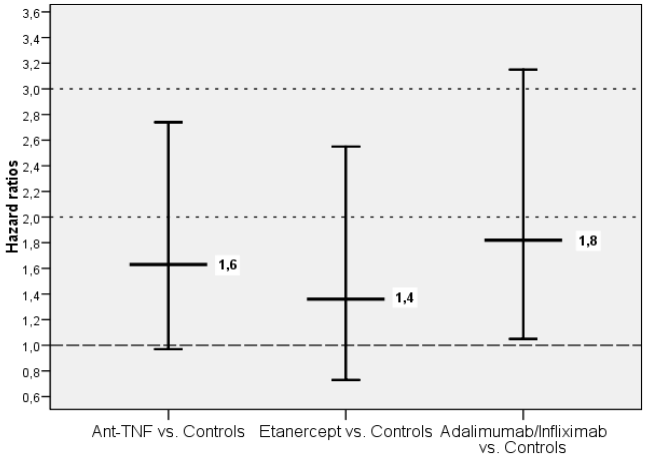
Adjusted Hazard Risk of Herpes zoster



adjusted for age, propensity score, treatment with steroids

Strangfeld et al. JAMA 2009;301:737-44

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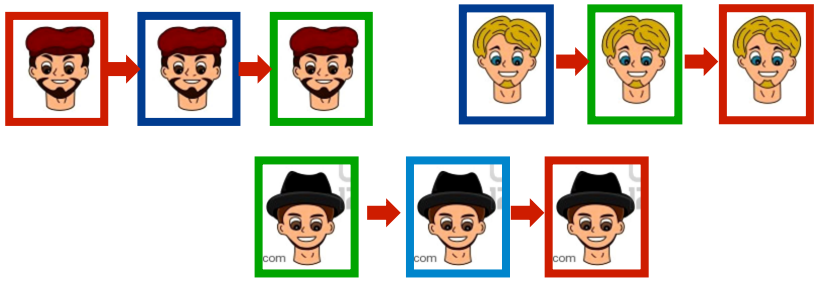
Problem with observational data

Selection bias!

→Solution: subsample of patients who switched treatment



Every patients was his own control in the other treatment group!

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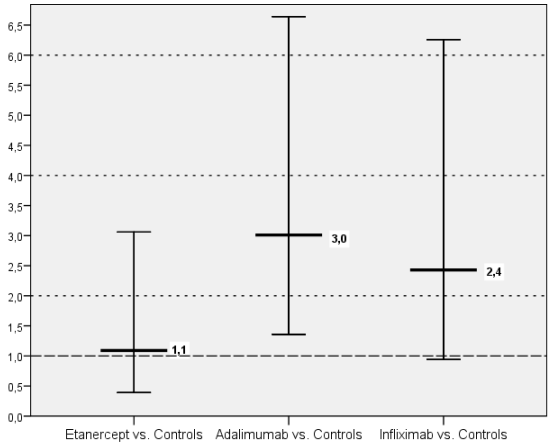
Risk in patients that changed treatment

N = 1.344

HRs adjusted for age, and propensity score

HZ events:
ETA 5, ADA 18, INF 8



* Controls = treatment periods with conv. ***DMARDs***

Strangfeld et al. JAMA 2009;301:737-44

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Herpes zoster - Prevention

Available vaccine since 2006: Zostavax ®
recommended for the use in all immunocompetent persons aged > 60 years

Vaccine guidelines for Immunosuppressed Patients:
Special concerns in immunosuppressed patients with live vaccines as they may not be able to control infections even with the attenuated strains.

Since 2008: recommend vaccination of patients with inflammatory disorders who are receiving
- **prednisone (≤ 20 mg/d) or short term (< 2 weeks) corticosteroids, topical or intra-articular corticosteroids**
- **‚low dose' methotrexate (≤ 0.4 mg/kg/week), azathioprin (≤ 3.0 mg/kg/day) or 6-mercaptopurine (≤ 1.5 mg/kg/day)**

The vaccine should not be given
- **with biologics treatments (esp. adalimumab, infliximab, etanercept)**
- **high dose corticosteroids ≥ 20 mg/day for more than two weeks….**

Cush, Kavanaugh, Calabrese, ACR Hotline August 2008 information on the alterations of the Centers for Disease Control Advisory Committee on Immunizations concerning the use of HZ vaccine.

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Herpes zoster - Prevention

Vaccine guidelines for Patients eligible for anti-TNF treatment:

- **Immunization schedule should be checked and missing vaccine administration given (travel plan? -> important for yellow fever!) before start of treatment**

All live vaccines (including Herpes zoster vaccine):

- **At least 3 weeks (F), preferably 4 weeks (UK, D) before start of anti-TNF therapy**
- **3 months after stopping immunosuppressive therapy (5 half-lives after anti-TNF, up to 6 months for infliximab)**

All contact persons (especially those in the same household) should be vaccinated against VZV and MMR!!

Duchet-Niedziolka et al. Joint Bone Spine 2007 (74): 563-5
Pham T. et al.,Club Rhumatismes et Inflammation, French Society of Rheumatology. Joint Bone Spine 2005.
British Society for Rheumatology (BSR). Vaccinations in the immunocompromised person: guidelines…..2002

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VZV vaccination in children under DMARDs

Study from Pileggi et al. Arthritis Care Res 2010, 62(7): 1034-9.

Vaccination with one dose (0.5mL) of **live-attenuated VZV** (BIKEN;*Sanofi Aventis), containing >1000 plaque-forming units of the VZV (Oka strain)* s.c. into right upper arm.

25 patients (2-19 years old, median 7.2 yrs): 17 JIA, 4 juv.dermatomyositis, 3 juvenile scleroderma, 1 with vasculitis.

All patients received MTX (10-27 mg/week; mean 16.4mg/m²/week),
13 prednisone (3-20 mg/d; mean 4.2 mg/d)
5 also received other DMARDs: 3 x cyclosporine (3-3.5mg/kg/day),
1 penicillamine (13.5mg/kg/day) and 1 leflunomide (10mg/day).

18 Healthy Controls (3-18 years)

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VZV vaccination in children under DMARDs

Study from Pileggi et al. Arthritis Care Res 2010, 62 (7): 1034-9.

Results
Positive VZV-IgG titers in 50% of the patients, and 72.2% of the controls.
Most of the patients (80%) maintained positive titers.
Three patients developed a mild self-limited varicella-like rash (few vesicular lesions 6-12) during the first 2 weeks post-vaccination. No other symptoms, rash lasted 5-7 days.

No increase in disease activity or flare after vaccination (during 3 months after vacc.).

16 patients had close contact to wild VZV (houshold, classmate).
2 patients developed chickenpox (both patients had been non-responders to VV).
One was using anti-TNF therapy at the time of the contact and developed severe varicella, complicated with pneumonia.

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VZV vaccination in adults

Study from Hata et al. N Engl J Med 2002; 347: 26-34.

Use of an **inactivated varicella vaccine** in 53 recipients of hematopoietic-cell transplants, compared with 58 patients that were not vaccinated (randomly assigned).

All patients were scheduled to undergo autologous hematopoietic-cell transplantation for non-Hodgkin's or Hodgkin's lymphoma.
Heat-inactivated, live attenuated varicella vaccine was given within 30 days before transplantation and 30, 60, and 90 days after transplantation.
The patients were monitored for zoster for 12 months.

Results

Zoster developed in 7 of 53 vaccinated patients (**13 %**)
and in 19 of 58 unvaccinated patients (**33 %**) (p=0.01).

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VZV vaccination in adults

Shingle Prevention Study, *Oxman et al.*

38 546 adults > 60 years of age

Randomized, double-blind, placebo-controlled trial of an live attenuated VZV vaccine.

95% of patients with complete follow up. Median of 3.1 years of surveillance for HZ.

Oxman et al. N Engl J Med 2005; 352(22): 2271-84

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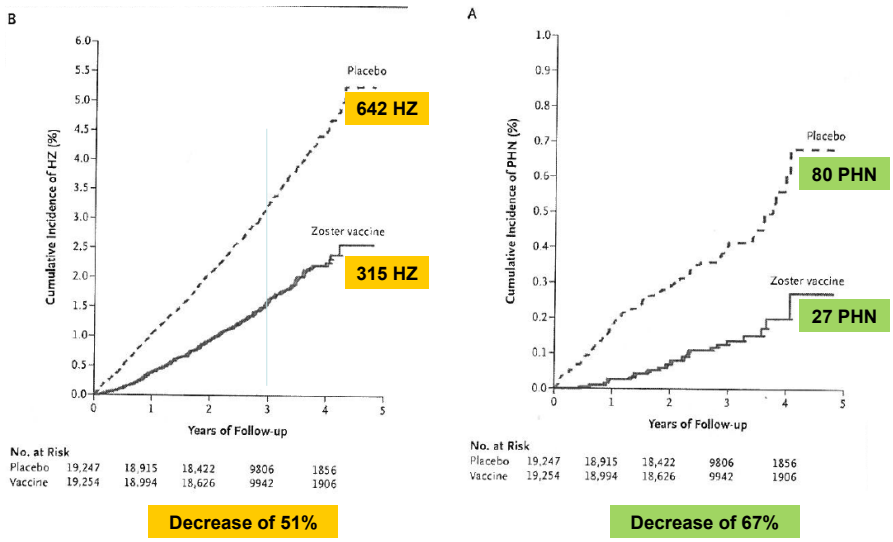
Incidence of HZ and PHN after vaccination



Decrease of 51%

Decrease of 67%

Oxman et al. N Engl J Med 2005; 352(22): 2271-84

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Conclusion

- the risk of Herpes zoster is increased in patients with RA (~ 2-fold compared to the general population)
- the risk is different under differing treatments, it seems higher under treatment with biologics (esp. monoclonal anti-TNFs)
- vaccination before the start of anti-TNF treatment is advisable and seems safe when recommendations are followed

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Happy birthday DANBIO!