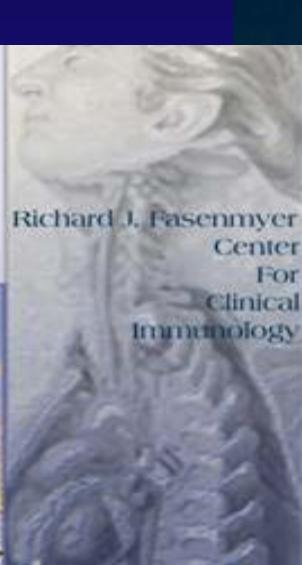
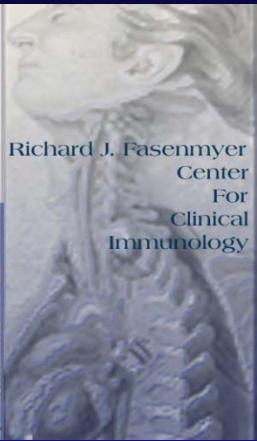




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Viral Infections as Etiology, Co-morbidities and Complications of Rheumatic Disease

Leonard H Calabrese D.O.

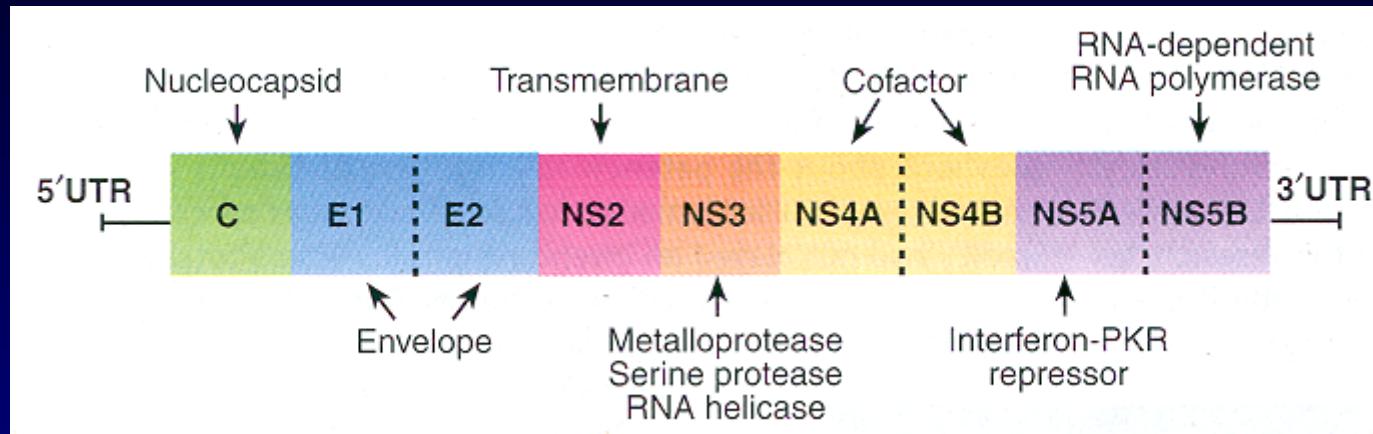
Department Rheumatic and
Immunologic Diseases

Cleveland Clinic

Virus - Host - Disease Interactions

- **Etiology**
 - *Pathology* . a. the study of the causes of diseases.
 - b. the cause or origin of a disease.
- **Comorbid**
 - **adjective (of medical conditions) present simultaneously in a patient:**
- **Complication**
 - *Pathology* . a concurrent disease, accident, or adverse reaction that aggravates the original disease.

Hepatitis C



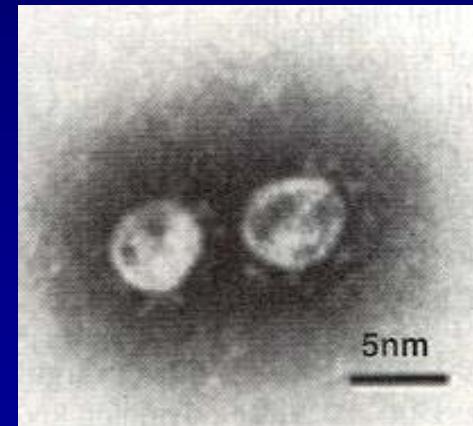
Flaviviridae

Single strand of RNA

3000 amino acids

10 encoded genes

100 strains - 6 genotypes



VIEWPOINT

For patients with rheumatic disease and hepatitis C infection: the end of interferon

Leonard H Calabrese,¹ Patrice P Cacoub^{2,3,4,5}

To cite: Calabrese LH, Cacoub PP. For patients with rheumatic disease and hepatitis C infection: the end of interferon. *RMD Open* 2015;0:e00008. doi:10.1136/rmdopen-2014-000008

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2014-000008>).

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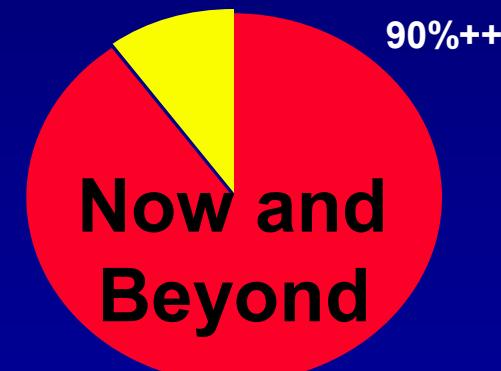
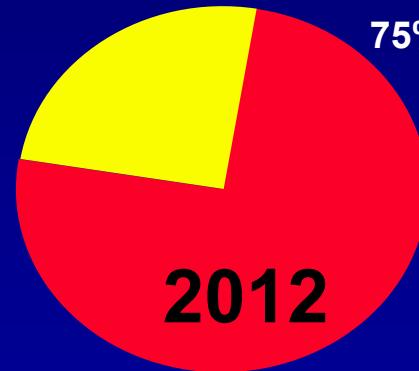
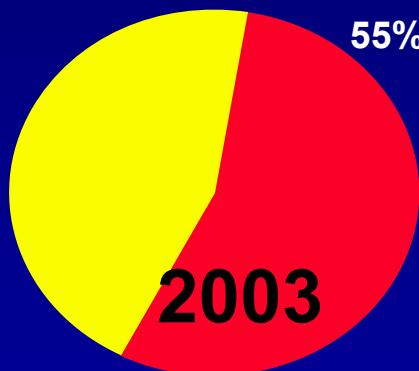
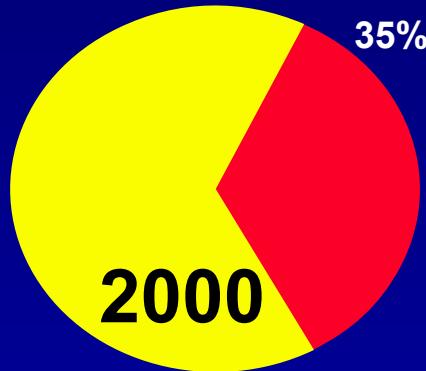
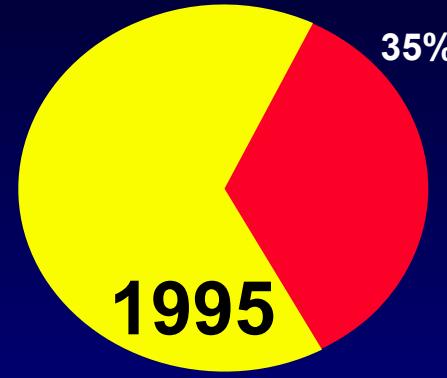
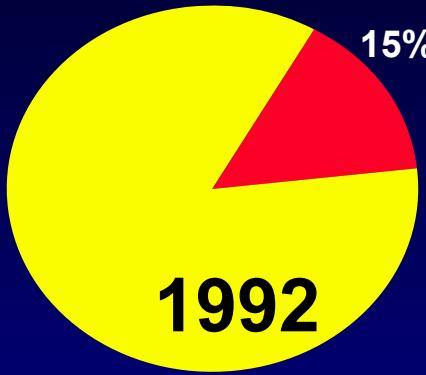
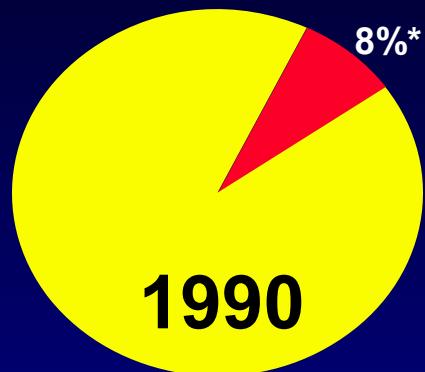
ABSTRACT

Hepatitis C virus (HCV) is a global pathogen and is the cause of rare but complex rheumatic complications but more commonly exists as a challenging comorbidity for patients with existing rheumatic diseases. Until recently, the standard of care of HCV has been the use of interferon-based regimens, which not only have limited effectiveness in curing the underlying viral illness but are poorly tolerated and in patients with rheumatic diseases especially problematic given their association with a wide variety of autoimmune toxicities. Numerous and other more effective and better tolerated regimens are rapidly emerging incorporating direct acting antiviral agents that do not require the use of interferon, that is, interferon free. The potential of interferon free treatment of HCV makes screening for this comorbidity more important than ever. Rheumatologists need to be knowledgeable about these therapeutic advances and partner with hepatologists to craft the most efficacious and toxicity-free regimes possible.

medicine, namely the prospects for curing HCV infection with short, well-tolerated oral regimes that are effective nearly 100% of the time; curing HCV infection will soon be totally devoid of the need to use interferon. This revolution is of particular relevance to rheumatologists and this commentary is designed to provide a brief background of this remarkable advance and guidance for approaching HCV in our practice.

The story of interferon therapy and, indeed, the common attitude towards interferon therapy for HCV, is one of resigned trepidation and deep concern. Introduced in the early 1980s as a mono therapy, it was found to be poorly tolerated and poorly effective with virological cure (sustained virological response or SVR) observed in about 6% of patients. Over time with different dosing regimens and pegylated formulations optimising its pharmacokinetics and then ultimately combining it with an

Progress in Anti-viral Therapy of HCV (1990-2015)



*Sustained virologic response

SPECIAL ARTICLE

2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis

JASVINDER A. SINGH,¹ DANIEL E. FURST,² ASEEM BHARAT,¹ JEFFREY R. CURTIS,¹ ARTHUR F. KAVANAUGH,³ JOEL M. KREMER,⁴ LARRY W. MORELAND,⁵ JAMES O'DELL,⁶ KEVIN L. WINTHROP,⁷ TIMOTHY BEUKELMAN,¹ S. LOUIS BRIDGES JR.,¹ W. WINN CHATHAM,¹ HAROLD E. PAULUS,² MARIA SUAREZ-ALMAZOR,⁸ CLAIRE BOMBARDIER,⁹ MAXIME DOUGADOS,¹⁰ DINESH KHANNA,¹¹ CHARLES M. KING,¹² AMYE L. LEONG,¹³ ERIC L. MATTESON,¹⁴ JOHN T. SCHOUSBOE,¹⁵ EILEEN MOYNIHAN,¹⁶ KAREN S. KOLBA,¹⁷ ARCHANA JAIN,¹ ELIZABETH R. VOLKMANN,² HARSH AGRAWAL,² SANGMEE BAE,² AMY S. MUDANO,¹ NIVEDITA M. PATKAR,¹ AND KENNETH G. SAAG¹

Contraindications for Initiating and Resuming Therapy

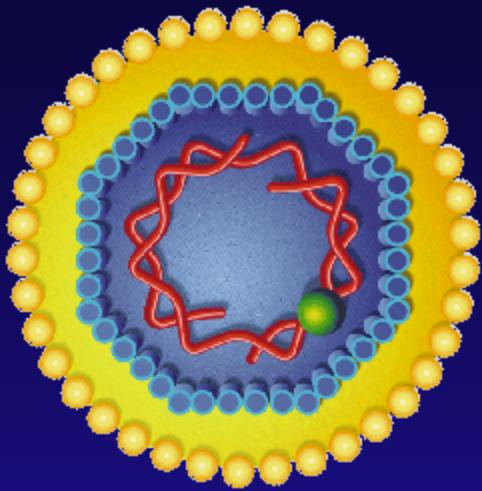
	MTX	LEF	Anti-TNF α	ABA	RIT
Active bacterial infection, TB, herpes zoster, or fungal infection	X	X	X		X
Low white blood cell or platelet count	X	X			
Moderate to severe heart failure			X		
Acute or Child-Pugh class B or C chronic hepatitis B or C viral infection	X	X	X	X	X
Renal insufficiency	X				
Pregnancy or breastfeeding	X	X			

MTX=methotrexate; LEF=leflunomide; ABA=abatacept; RIT=rituximab

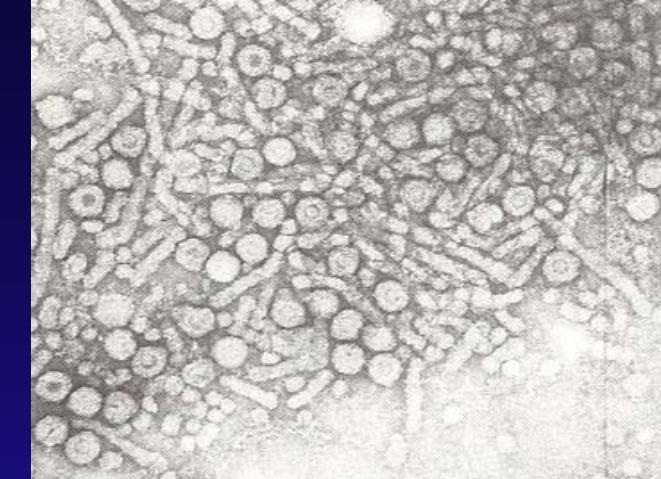
Saag K et al. *Arthritis Rheum.* 2008;59:762-784.

Treatment with Biologics with Co-morbid HCV

- According to ACR 2012 DMARD treatment guidelines (Singh Arth Care Res 64:625-639,2012) MTX and LFL are contraindicated. There are no data on abatacept in HCV and tocilizumab would be inappropriate based on prominent liver toxicity issues. In fact **etanercept** is recommended on the basis of weak evidence (C)



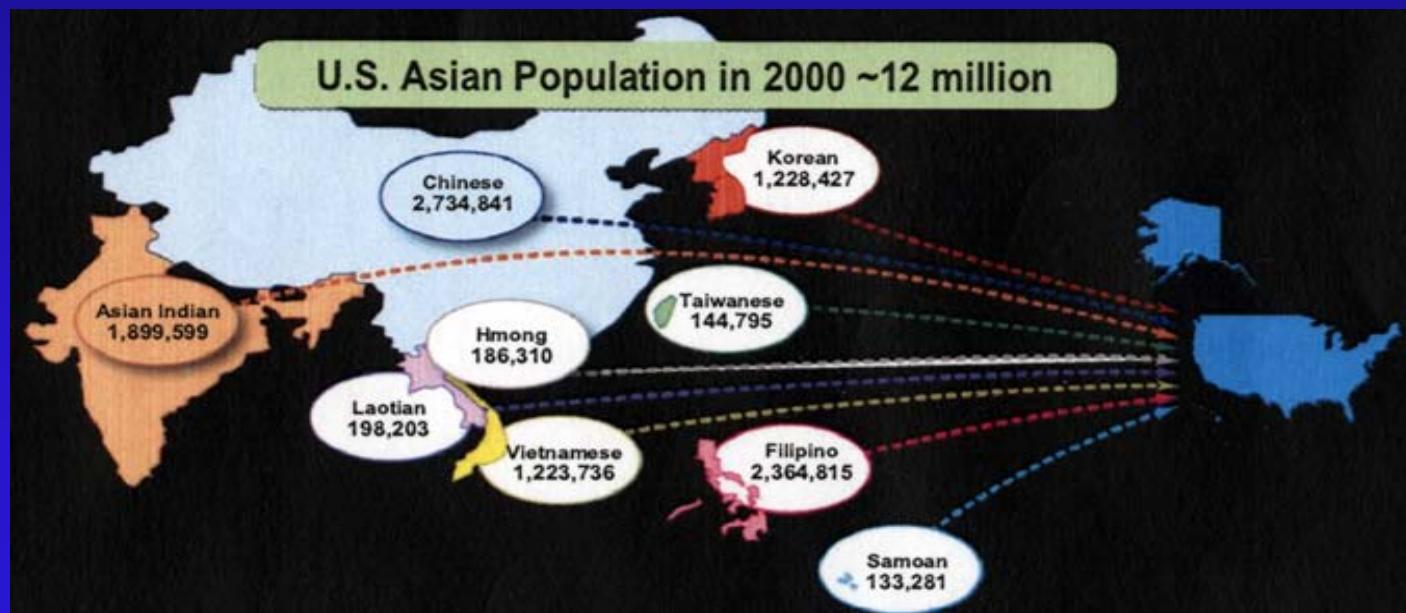
HBV



- Hepadnaviridae - small DNA
- 400-500 million world wide
- 1.25 million chronic cases in the USA
- HBV is a de-emerging pathogen as a cause of rheumatic disease
- Major changes in epidemiology and drug therapy make HBV reactivation a major concern

HBV Infection Represents a Vital Public Health Problem

- The Asian American community is projected to grow to 33.4 million people (or 8% of the total US population) by 2050
 - 68.9% of Asian Americans living in US are foreign-born
 - Asian Americans are 2.7 times more likely to develop hepatocellular carcinoma (HCC) and 2.4 times more likely to die from HCC than their white counterparts



U.S. Census bureau. <http://www.census.gov>; Lin SY, et al. Hepatology 2007;46:1034-40.

Extra-hepatic Complications of HBV

A De-emerging Pathogen

- **Arthralgia**
- **Arthritis**
- **Arthritis dermatitis**
- **PAN**
- **Nephropathy**
- **Others: aplastic anemia**
- **Overall occur in less than 1%**

Khasnis et al Sem Arth Rheum 2010

HBV reactivation and Immunosuppression

- Far more complex issue than HCV
- Major risk of HBV is not during but following immunosuppression where reactivation leading to severe/fatal hepatitis can occur
- Well reported to occur in RA and other conditions with conventional or biologic therapy (class warning anti-TNF, rituximab)

HBV Reactivation

Scope of the Problem

- “an abrupt increase in HBV replication in a patient with chronic or past HBV”
- A known complication of immunosuppressive therapy (cancer, transplant autoinflammatory diseases (Rheum, Derm ,GI, other)
- A syndrome that ranges from asymptomatic to liver failure and death
- Observed in patients with both chronic as well as ‘resolved’ HBV infection
- Largely preventable
- Unfortunately many physicians who regularly prescribe immunosuppressive therapies do not recognize this potential

Risks of anti rheumatic therapy in patients chronically infected with HBV

- Reactivation noted in patients treated with as little as prednisone (<10 mg/d) and MTX (7.5/w)
- Has been rarely described with all TNF inhibitors (Health Canada Jan 2006)
- Well described in association with rituximab (oncology) and abatacept
- Weak guidelines for screening other than ACR (MTX/LFL), infliximab and rituximab (high risk)
- Potentially fatal

HBV Reactivation and Rituximab

- Numerous cases reported in the oncology literature
- Flare occurred from .5 to 9 months after infusion
- Most, but not all with CHOP
- May be preventable with antiviral therapy
- OCT 2013 – New FDA Drug Safety Communication: Boxed Warning and new recommendations to decrease risk of hepatitis B reactivation with the rituximab

Tsutsumi et al Exp Opin Drug Safety 2005;4:599.

Aksoy S, et al. Leuk Lymphoma 2007;48:1307-12.

Reactivation of Hepatitis B During Immunosuppressive Therapy: Potentially Fatal Yet Preventable

Anna S.F. Lok, MD; John W. Ward, MD; Robert P. Perrillo, MD; Brian J. McMahon, MD; and T. Jake Liang, MD

Reactivation of hepatitis B virus (HBV) replication, an abrupt increase or reappearance of serum HBV DNA in a patient with chronic or past HBV infection, is a known complication of immunosuppressive therapy. This condition can lead to hepatocellular injury, elevated alanine aminotransferase levels, symptoms of acute hepatitis, liver failure, and even death (1). Many physicians who regularly prescribe immunosuppressive therapy unfortunately do not recognize this potentially fatal condition.

1 to 2 days. In the United States, all positive HBsAg test results must be confirmed before the result is reported. Commercially available anti-HBc assays claim to have diagnostic specificity and sensitivity of 99%. However, false-positive results may occur, particularly in low-prevalence groups. When anti-HBc is the only marker present, experts recommend confirmation with strength of the reaction in the anti-HBc test, repeated testing with a different assay, or testing for HBV DNA (11).

- **Stine et al Arth Care Res 2010**
- **RHEUMATOLOGISTS USA 2010**
 - 42% ‘routinely screen’ before non –biologic DMARD
 - 69% before Biologic DMARD
 - 7% observed reactivation event

Appropriate screening for HBV

- HBsAg
- Anti-HBcore (total)
- Anti-HBsAg

Arthritis Care & Research
Vol. 62, No. 5, May 2010, pp 585–589
DOI 10.1002/acr.20167
© 2010, American College of Rheumatology

EDITORIAL

Preventing Hepatitis B Reactivation in Immunosuppressed Patients: Is It Time to Revisit the Guidelines?

JINOOS YAZDANY¹ AND LEONARD CALABRESE²

Relative Risk of Reaction HBV

HIGHEST

LOWEST



CHRONIC HBV
INFECTION

HBs Ag+
High HBV DNA

INNACTIVE
CARRIER

HBs Ag +
Low
HBV DNA

RESOLVED
HBV

HBsAg neg
anti-HBc +
anti-HBs +

RESOLVED
HBV

Anti-HBc
alone

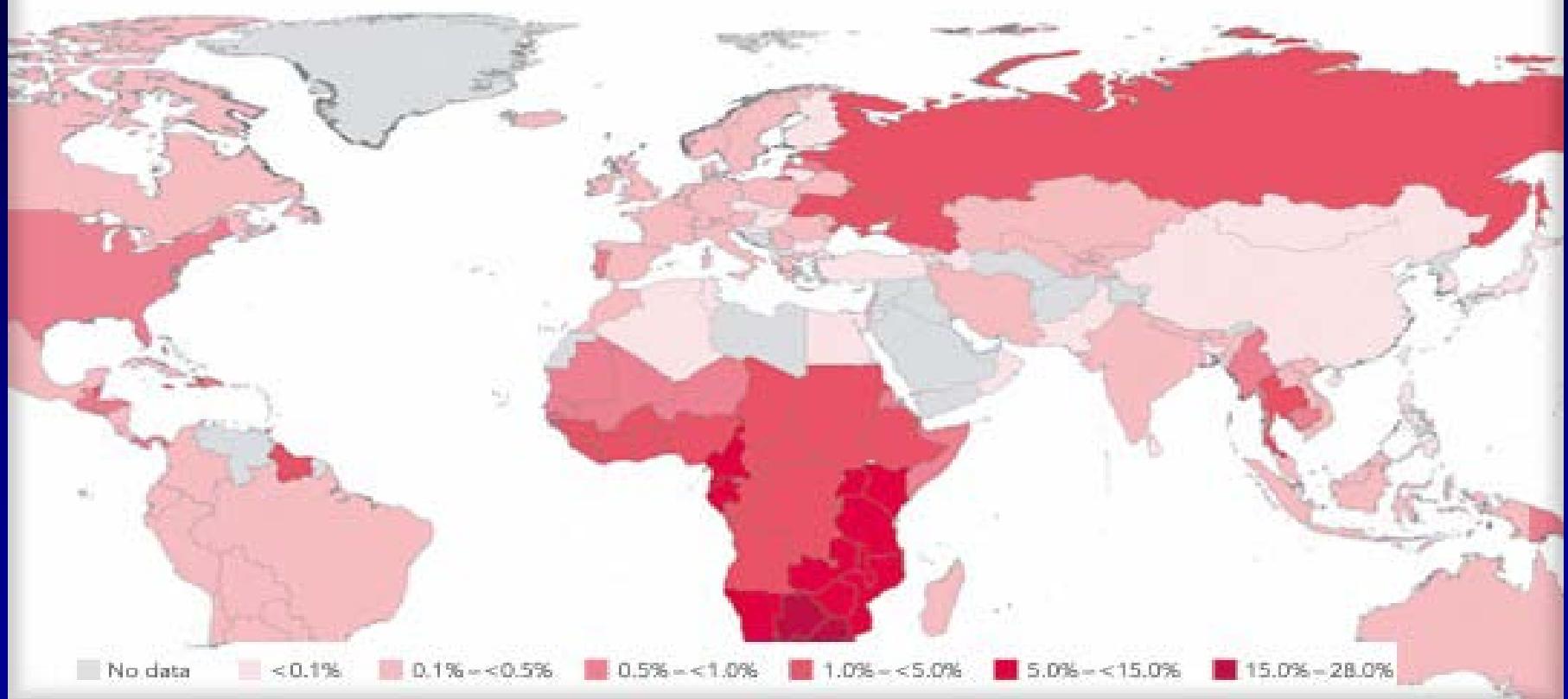
All patients with a past history of HBV are at some finite risk of reactivation
regardless of presence or absence of serologic markers

Reasonable Strategy in HBV infected patients requiring immunosuppression

- Screen all high risk patients (geographic origin, epidemiologic risks)
- Screen all patients going on immunosuppressives for HBV infection (HBsAg, anti-HBc, anti-HBsAb)
- Follow up with HBV-DNA in all positives
- Pre-emptive therapy in all HBsAg + and HBV-DNA + patients & careful monitoring in all isolated anti-HBc
- Refer to hepatology all patients candidate for anti-viral therapy

A global view of HIV infection

33.3 million people [31.4–35.3 million] living with HIV, 2009



HIV testing US 2012

- U.S. panel advises HIV tests for everyone ages 15 to 64
- The Preventive Services Task Force opens public comment on a recommendation of HIV tests for everyone 15 to 64.
- **November 19, 2012**
- **NEARLY EVERYONE AGES 15 TO 64 SHOULD BE SCREENED FOR HIV EVEN IF THEY'RE NOT AT GREAT RISK FOR CONTRACTING THE VIRUS, ACCORDING TO NEW GUIDELINES PROPOSED BY AN INFLUENTIAL PANEL OF MEDICAL EXPERTS. IF THE PANEL ULTIMATELY ADOPTS THOSE RECOMMENDATIONS, MEDICARE AND MOST PRIVATE HEALTH INSURERS WILL BE REQUIRED TO PAY FOR THE TESTS.**

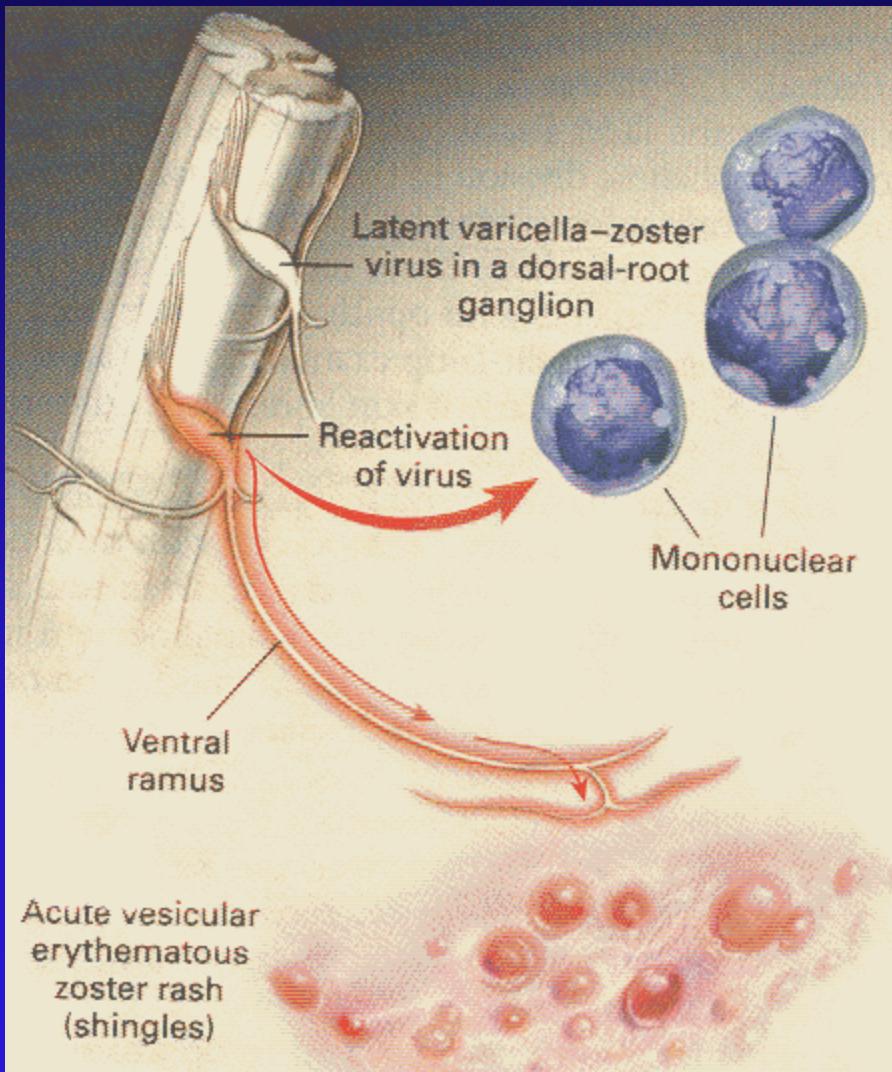
HIV Rheumatic Treatment “guidelines”

- No official recommendations
- In general drugs used for patients with HIV have the same cautionary notes as in the HIN non-infected population with several caveats.
- TNF inhibitors demonstrated reasonably safe CD4 > 200; HIV-VL non detectable
- Avoid glucocorticoids in patients on ritonavir

(Vasilopoulos & Calabrese Arth Res Ther 2008)



Pathogenesis and Natural History and Latency of VZV



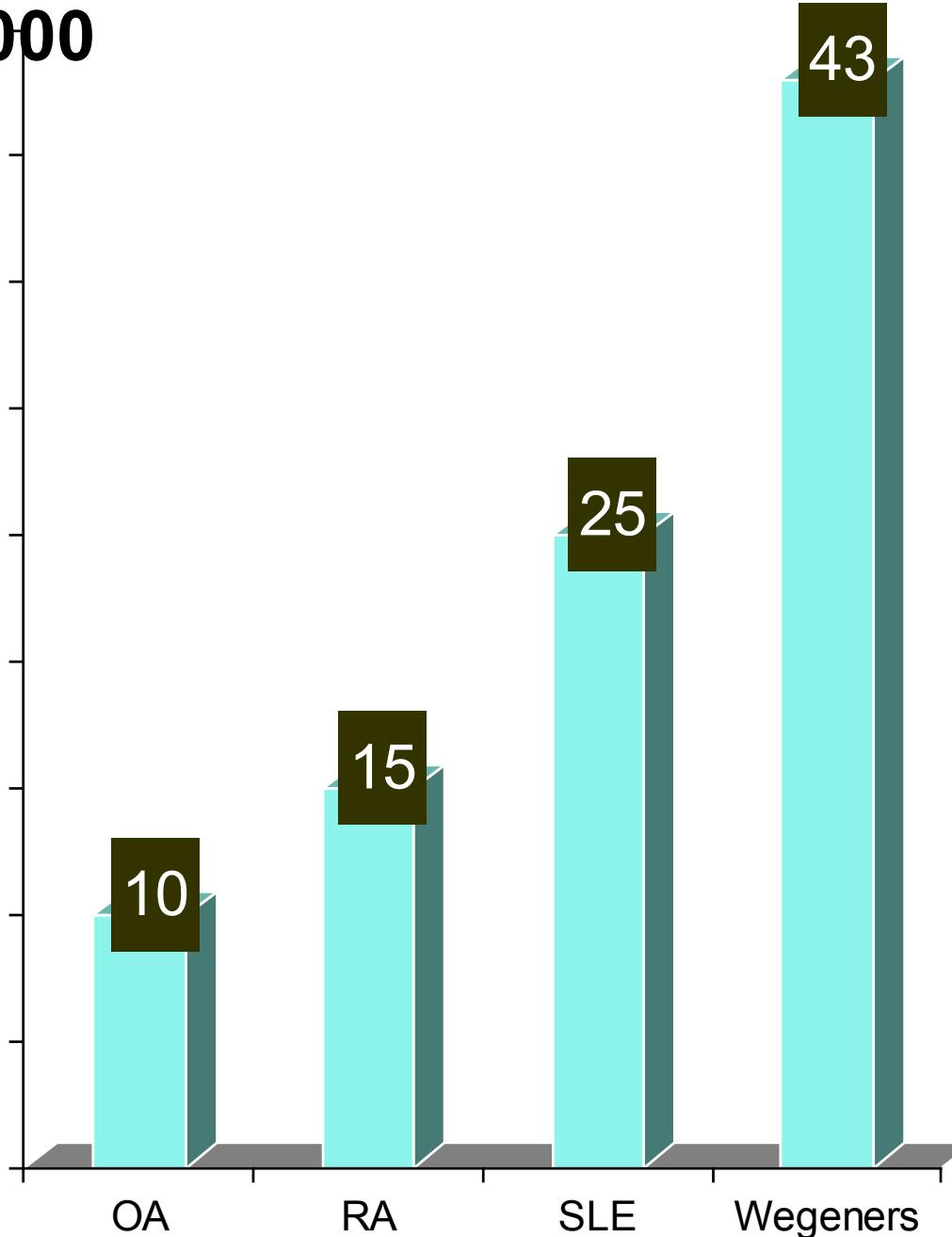
INCIDENCE RATES OF VZV IN RHEUMATIC DISEASES

CASES/100,000

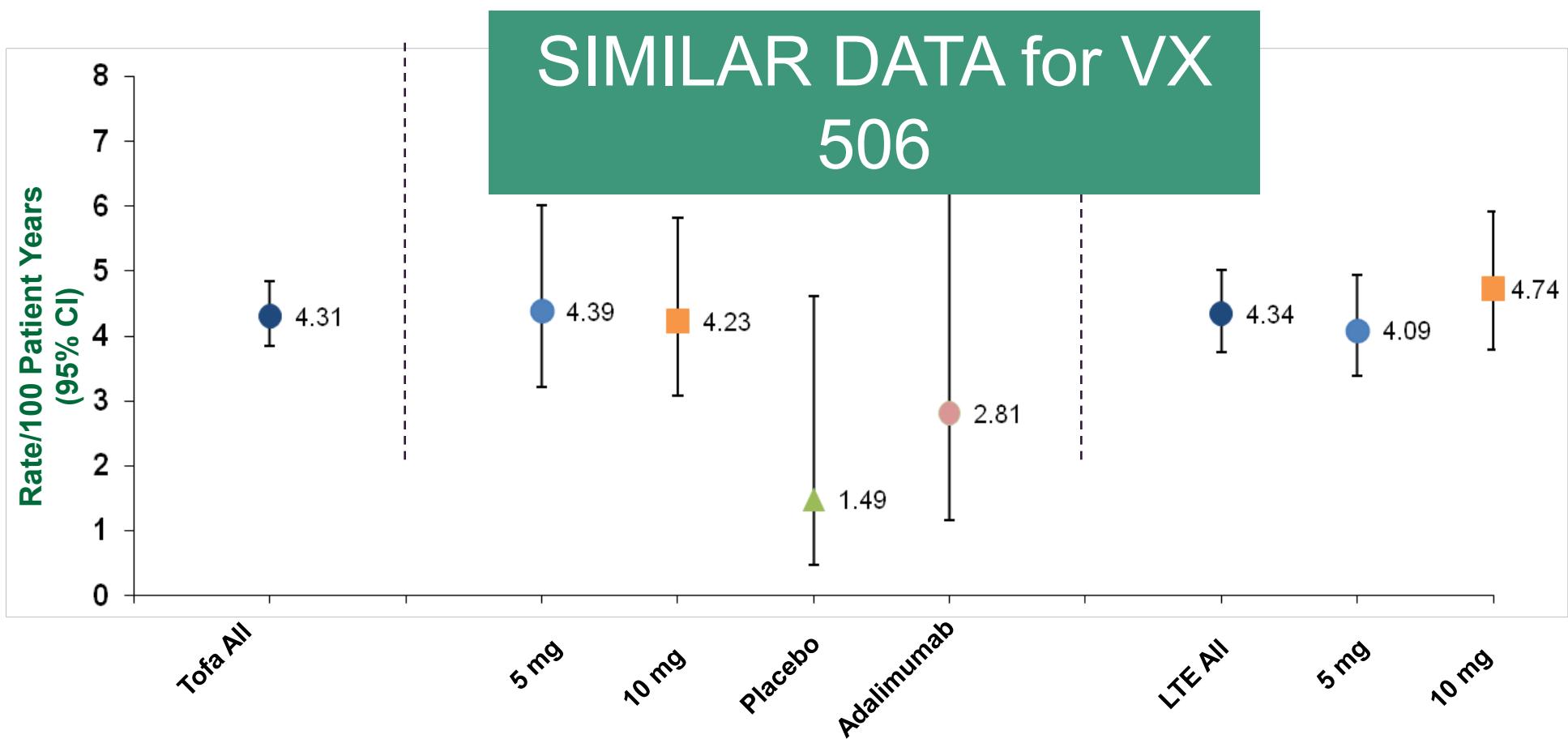
1/3 of
people
will get
VZV

1/2 of
those
surviving
to 85

US POPULATION
3.6/1000/yr



All Herpes Zoster (Non-Serious and Serious) Rates Across Dose Groups



Bars for CP indicate 95% Confidence Limits.

Incidence rate of patients per 100 pt-yrs

Tofa Phase 3

All LTE

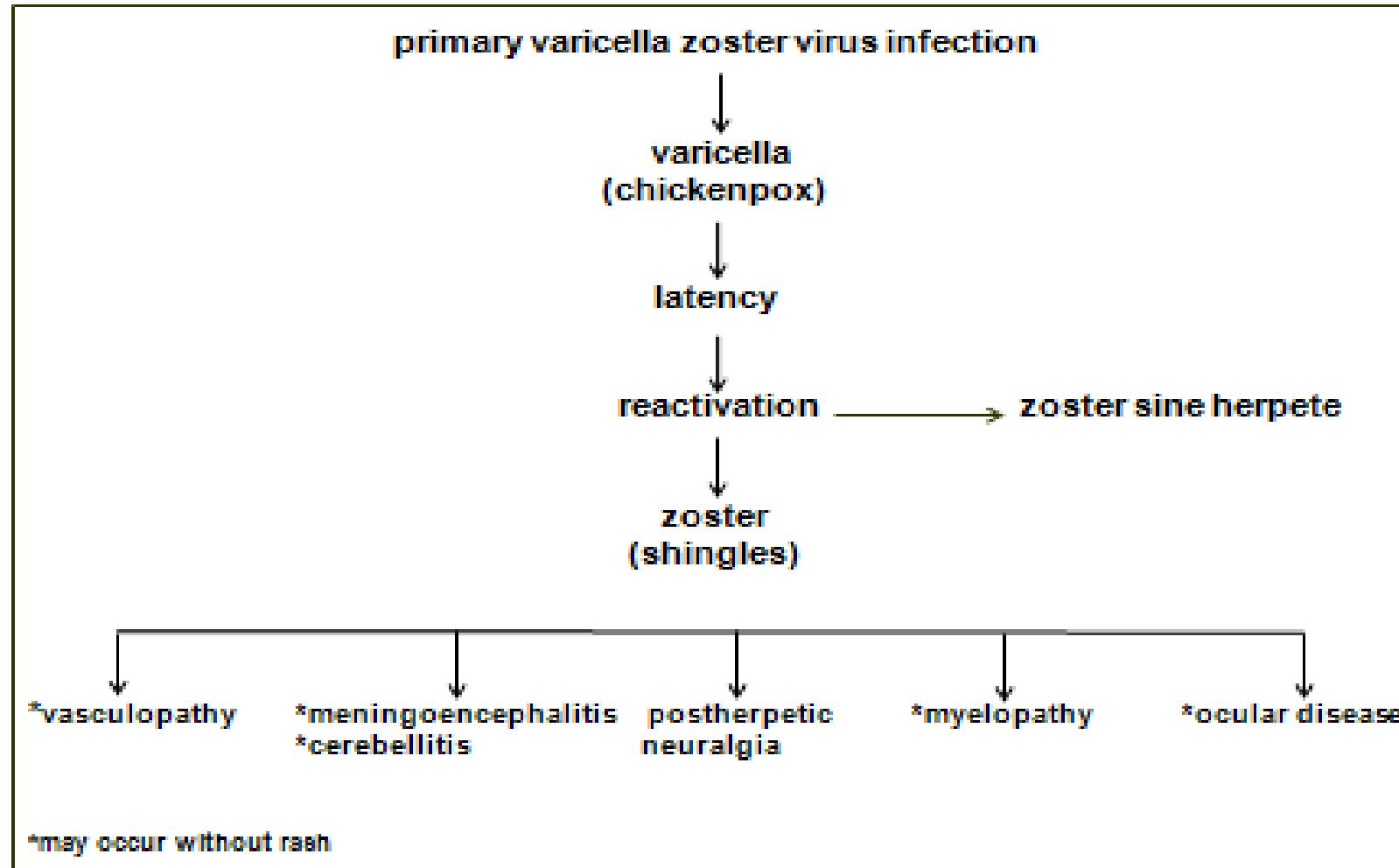


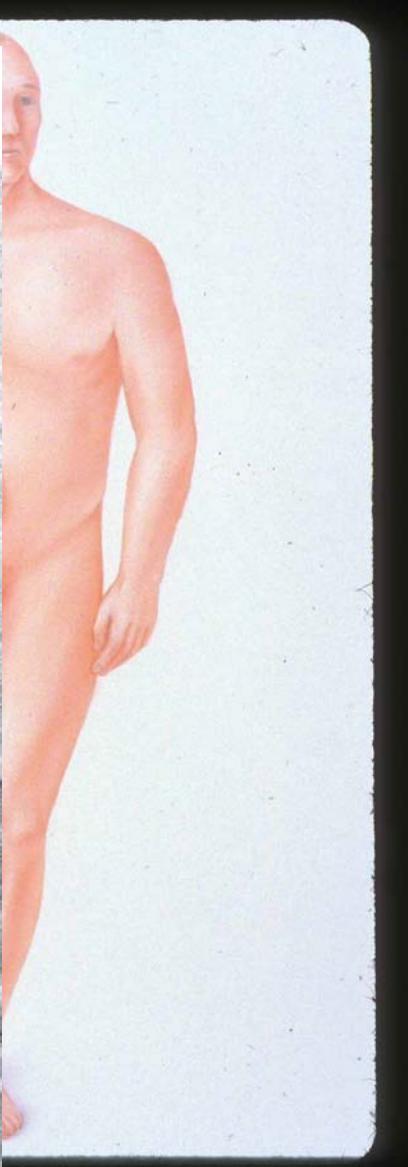
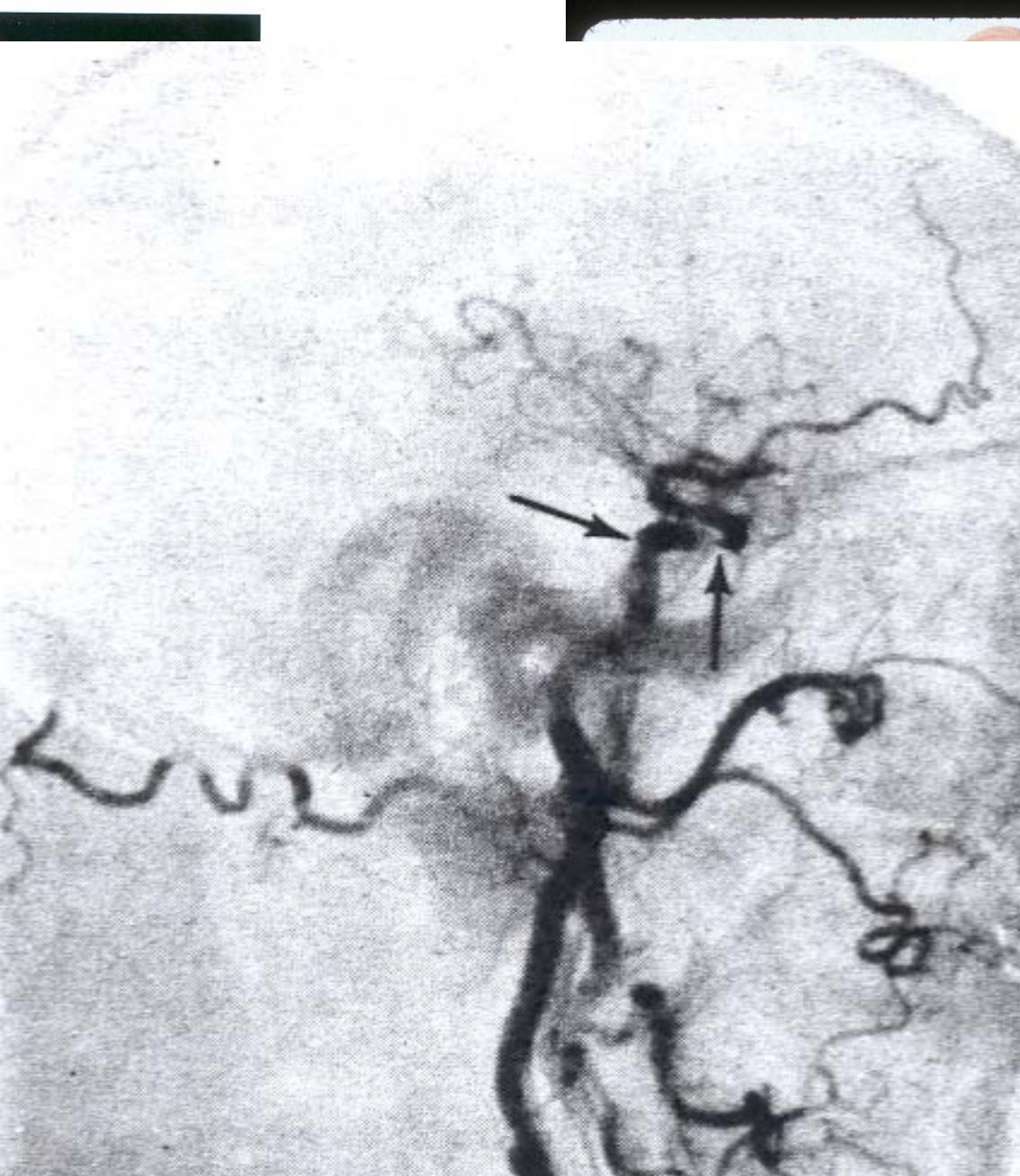
Why Do We Need a Strategy to Prevent Shingles?

- In immunocompetent persons, VZV is a common condition (esp. among elderly patients) and is associated with substantial morbidity
- Once herpes zoster develops, the available treatments (including antiviral therapy) do not prevent PHN in all patients
- The treatments for PHN are complicated, and not always effective
- Prevention is preferable to treatment



VZV as a vascular disease





VZV and Stroke

- Study of 7760 adults with zoster and 23,280 controls in Taiwan revealed 30% increase in risk of stroke over 1 year, 4x with HZO (Kang et al. *Stroke*. 2013;40:3443)
 - Danish registry of 4.6 million adults with 117,926 zoster patients treated with antivirals revealed a 126% increase in stroke within 2 weeks of zoster and a 17% increase from 2 weeks to 1 year (*PlosOne* 2013)
 - UK epidemiologic study of 106,661 VZV patients and 213,202 controls matched for age and sex revealed increased risk of TIA and MI (particularly for age<40) (Breuer et al. *Neurology*. 2014;82:206)
-

Risk of Stroke Following Herpes Zoster: A Self-Controlled Case-Series Study

Results. A total of 6584 individuals were included. Stroke rate was increased following zoster compared with the baseline unexposed period, then gradually reduced over 6 months: **weeks 1–4 (age-adjusted IR, 1.63; 95% CI, 1.32–2.02), weeks 5–12 (IR, 1.42; 95% CI, 1.21–1.68), and weeks 13–26 (IR, 1.23; 95% CI, 1.07–1.42)**, with no increase thereafter. A stronger effect was observed for individuals with zoster ophthalmicus, rising to a >3-fold rate 5–12 weeks after zoster

We have established an increased stroke rate within 6 months following zoster. Findings have implications for zoster vaccination programs, which may reduce stroke risk following zoster.



Clinical
Infectious
Diseases



Langana, Minassiana, Smeeth, Thomas. Clin Infect Dis. (2014) doi: 10.1093/cid/ciu098 First published online: April 2, 2014

From: Recommended Adult Immunization Schedule: United States, 2013*

Recommended Adult Immunization Schedule—United States • 2013

Note: These recommendations must be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

Figure 2. Vaccines that might be indicated for adults based on medical and other indications¹

VACCINE ▼	INDICATION ►	Pregnancy	Immuno-compromising conditions (excluding human immunodeficiency virus [HIV]) ^{4,6,7,10,11}	HIV infection (CD4+ T lymphocyte count) ^{4,6,7,10,14,15}	Men who have sex with men (MSM)	Heart disease, chronic lung disease, chronic alcoholism	Asplenia (including elective splenectomy and persistent complement component deficiencies) ^{10,14}	Chronic liver disease	Kidney failure, end-stage renal disease, receipt of hemodialysis	Diabetes	Health care personnel
Influenza ^{2,*}	Pregnancy		1 dose IIV annually	<200 cells/ μ L ≥200 cells/ μ L	1 dose IIV or LAIV annually			1 dose IIV annually			1 dose IIV or LAIV annually
Tetanus, diphtheria, pertussis (Td/Tdap) ^{3,*}		1 dose Td every 10 yrs			Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs						
Varicella ^{4,*}			Contraindicated					2 doses			
Human papillomavirus (HPV) Female ^{5,*}				3 doses through age 26 yrs				3 doses through age 26 yrs			
Human papillomavirus (HPV) Male ^{5,*}				3 doses through age 26 yrs				3 doses through age 21 yrs			
Zoster ⁶			Contraindicated					1 dose			
Measles, mumps, rubella (MMR) ^{7,*}			Contraindicated					1 or 2 doses			
Pneumococcal polysaccharide (PPSV23) ^{8,9}						1 or 2 doses					
Pneumococcal 13-valent conjugate (PCV13) ¹⁰						1 dose					
Meningococcal ^{11,*}						1 or more doses					
Hepatitis A ^{12,*}						2 doses					
Hepatitis B ^{13,*}						3 doses					

*Covered by the Vaccine Injury Compensation Program

- [Yellow Box] For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; Zoster vaccine recommended regardless of prior episode of zoster
- [Purple Box] Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)
- [White Box] No recommendation

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of January 1, 2013. For all vaccines being recommended on the Adult Immunization Schedule: a vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/pubs/acip-list.htm). Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.



**U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention**

The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), American College of Physicians (ACP), American College of Obstetricians and Gynecologists (ACOG), and American College of Nurse-Midwives (ACNM).

SAFETY OF VZV VACCINE IN RA PATIENTS

- Recent observational data suggests (4) that the effectiveness of the zoster vaccine in a large group of patients with autoimmune diseases, including RA and spondyloarthropathies, is comparable to that in healthy, older patients. In the same study, the vaccine was not associated with short term risks for zoster or varicella, even in patients exposed to biologics around the time they were vaccinated. However, in the absence of a prospective trial, this evidence should not be presumed to supersede the cautions above regarding live virus vaccines in biologic users.
- The duration of long-term immunity conferred by an episode of shingles or the zoster vaccine is not clear, so it may be reasonable to vaccinate even people who have had shingles in the past (e.g. \geq 5 years ago).

Abstract 1836

**SAFETY OF ZOSTER VACCINATION
ADMINISTRATION IN RHEUMATIC PATIENTS
ON CURRENT BIOLOGIC THERAPY**

Lindsey, Stephen



Safety of Zoster Vaccine in RA

- Background:
 - RA patients at higher risk for shingles
 - Vaccine FDA approved for all patients >50
 - Recommended for patients >60 by ACIP
 - ACIP and ACR do not recommend shingles vaccine in patients on biologics; however large database studies have not found an increase in shingles in patients inadvertently given the vaccine while on biologics.

Safety of Zoster Vaccine in RA

- 302 patients with RA, PsA or AS on biologic
 - 110 IV, 42 SubQ
 - Age >50, no allergies to components, no episodes of shingles in last 4 years, no pregnancy, disease activity stable, no active infection or malignancy
- Vaccine given at next interval scheduled dose of biologic; biologic HELD for that dose. MTX also held week of vaccine. Biologic restarted 2 weeks later.
- No patients in either group developed shingles within 6 weeks post vaccination.

Safety of Zoster Vaccine in RA: Conclusion

- Shingles vaccination in chronic RA, PSA or AS patients on current IV or subq biologic therapies appears safe using this protocol. No occurrence of disseminated HZ occurred. There was no increased incidence of HZ in the early post vaccination period.
- VERVE TRIAL
- Clinitrials.gov

2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

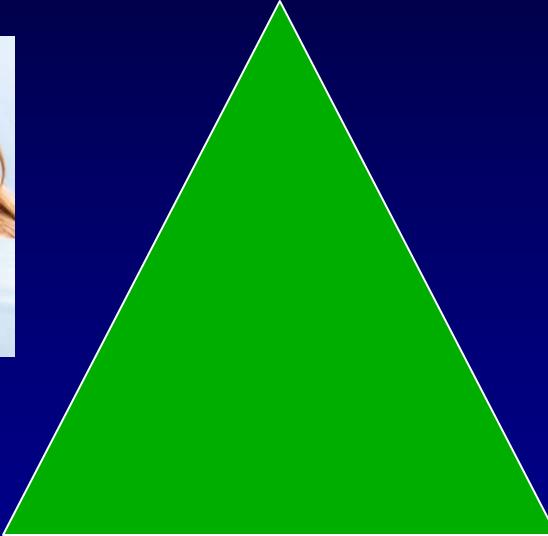
Lorry G. Rubin,¹ Myron J. Levin,² Per Ljungman,^{3,4} E. Graham Davies,⁵ Robin Avery,⁶ Marcie Tomblyn,⁷ Athos Bousvaros,⁸ Shireesha Dhanireddy,⁹ Lillian Sung,¹⁰ Harry Keyserling,¹¹ and Insoo Kang¹²

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An international panel of experts prepared an evidenced-based guideline for vaccination of immunocompromised adults and children. These guidelines are intended for use by primary care and subspecialty providers who care for immunocompromised patients. Evidence was often limited. Areas that warrant future investigation are highlighted.

Keywords. vaccination; immunization; immunocompromised patients; immunosuppression; asplenic patients; immunodeficiency patients

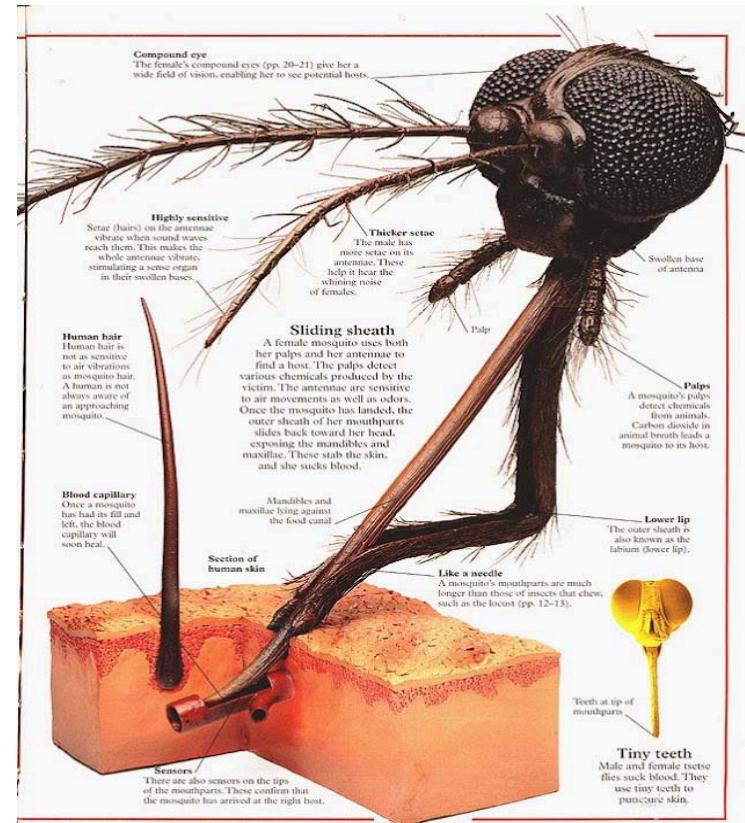
How to Prevent Infections in Immunocompromised Hosts Whose Job Is It ?



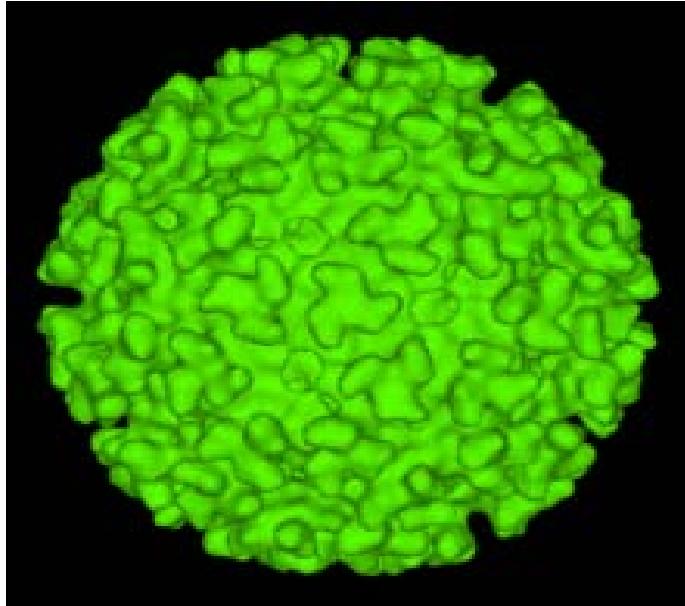
Systems Approaches to Improve Vaccination Rates

- Several abstracts describing various changes that were meant to improve vaccination rates:
 - 1344 & 1348 (UPMC): EMR-based best-practice alert (pneumovax and zoster)
 - 1346 (Northwestern): EMR best practice alerts (zoster, flu and pneumovax), quarterly vaccination rate reports to providers, information direct to patients
 - 1347 (Northwestern): Patient survey regarding barriers to vaccination.
 - 1349 (Mass General): Attach zostavax screening to prior authorization process
 - 1343 (Loyola): QI, educational sessions, pocket card (pneumovax)
 - 1345 (Dartmouth): Standing orders, education (pneumovax)
-





FAMILY TOGAVIRIDAE GENUS: ALPHAVIRUS



ARBOVIRIDAE

30 members

**OLD WORLD –
arthritogenic
NEW WORLD -
encephalopathic**



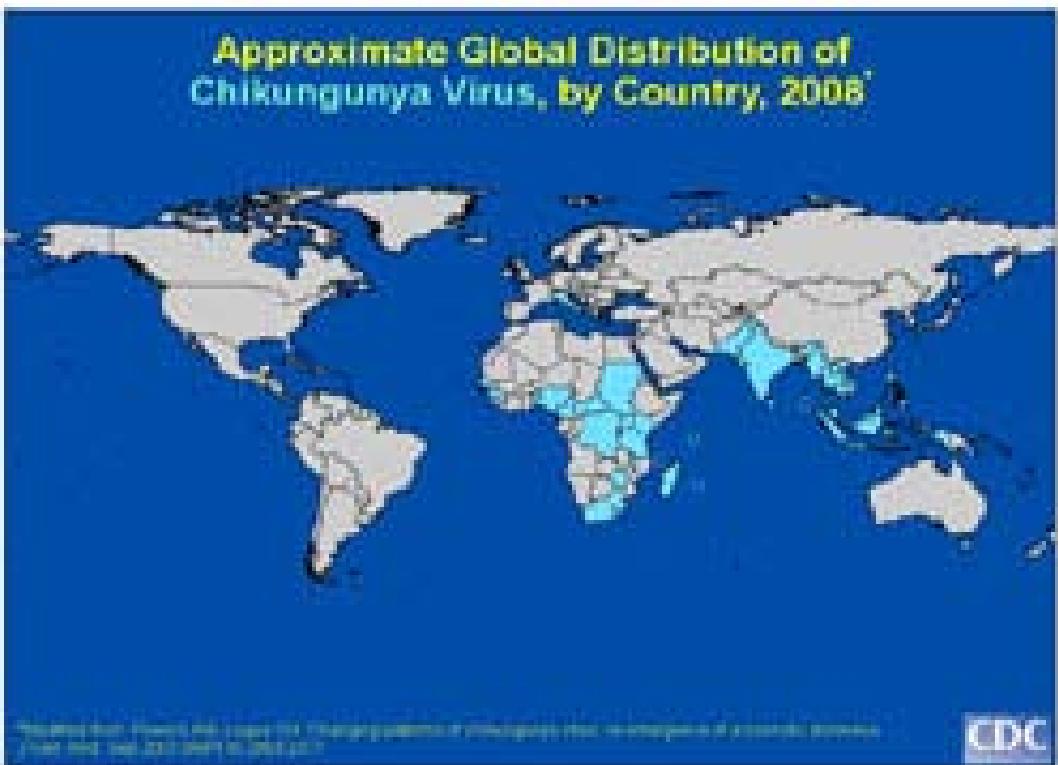


100 % fever

90% additive arrthritis

50% rash

Acute phase 1-2 weeks



Circa 2012

Courtesy Prof Sapan Pandaya

Vedanta institute of medical sciences, Navrangpura,

Chikungunya –'bend up'

RNA arbovirus Togaviridae

**Fever bodily pain,
headache, rash**

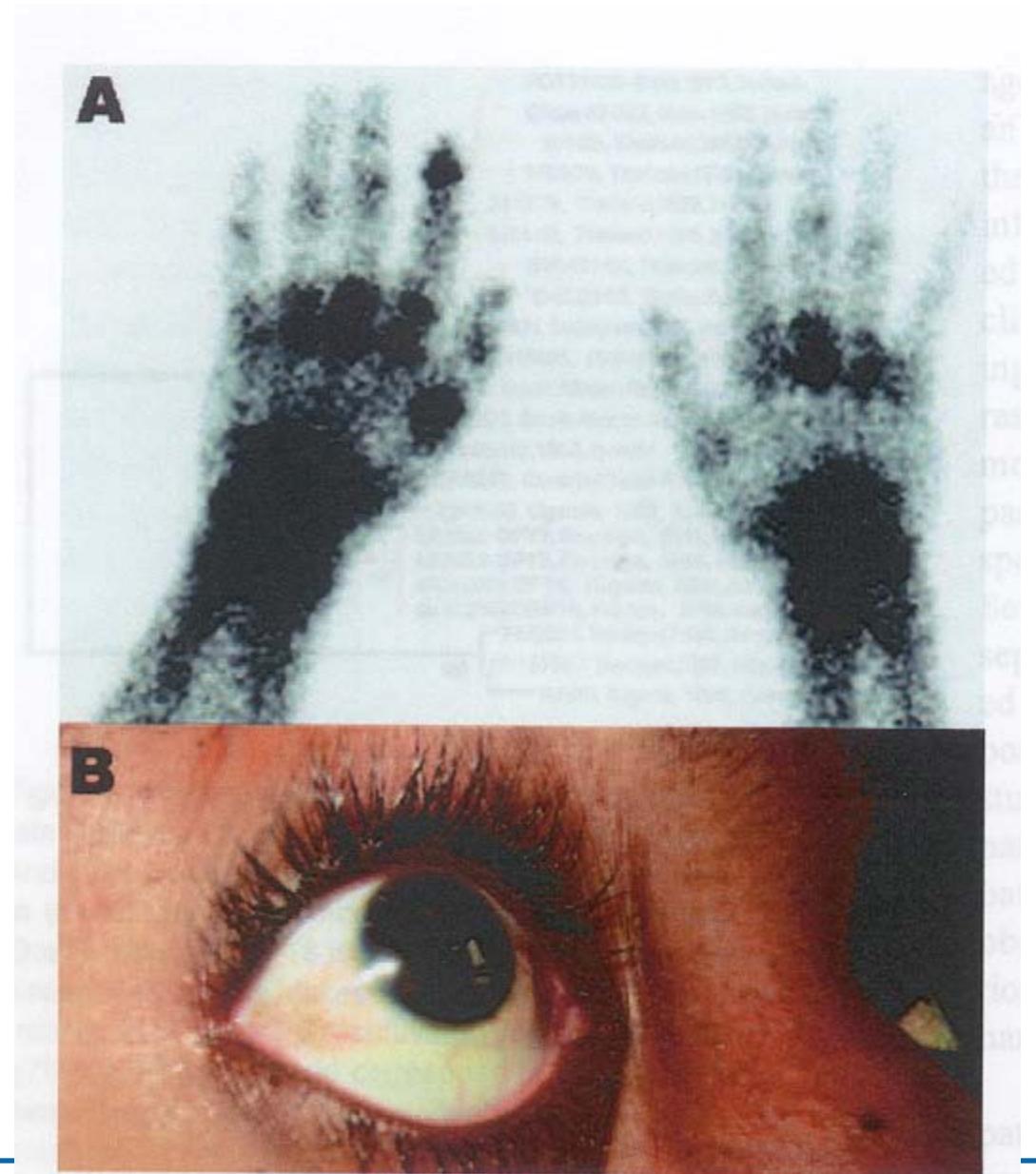
**Arthritis – severe,
knees>ankles>wrists>hands**

Last weeks to months

**LAB-anemia, leukopenia,
thrombopenia, elevated
APR**

+PCR

**IgM to IgG in
convalescence**



2014



> 1,000,000 cases



CHIK and Biologics

- Martinique (French West Indies)
 - >40,000 cases of CHIK as of mid-2014
- 22 patients with CHIK Jan-May 2014.
 - 19 women, 3 men
 - 5 SpA, 1 PsA, 2 SLE, 13 RA, 1 antisynthetase
 - 17 MTX, 3 HCQ, 2 AZA, 1 MMF, 2 CYC
 - 11 CS (mean dose 8.6 mg/d)
- No differences in symptoms, disease course or complications compared with general CHIK patients.

Arthralgia Following CHIK

- 14 adult Philippino CHIK patients followed at least 12 months (10 female, 4 male) post CHIK infection
- No preexisting arthralgias
- 8/14: arthritis x at least 6 weeks post-infection
- 7/14: persistent arthralgia
 - 5 intermittent, 2 continuous
- 2/14 recurrent chronic arthritis
- Arthralgia symmetric and polyarticular in all cases
- Previous study 2010 (Asia) 50% with symptoms at 15 months

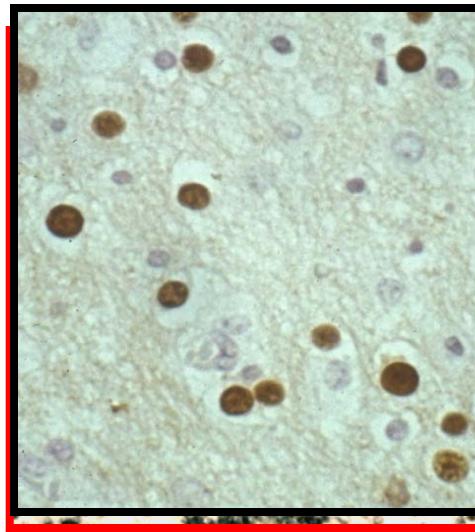
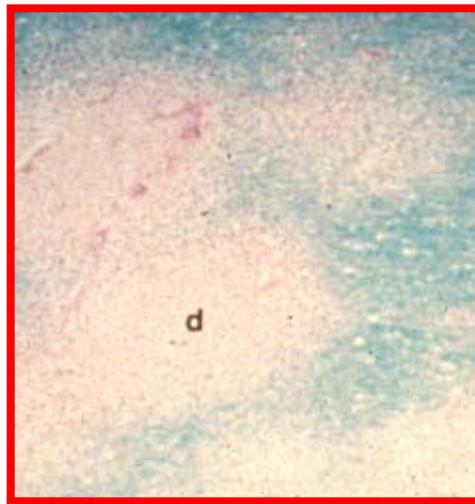
CHIK and Biologics: Conclusions

- CHIK does not seem to be deleterious in patients on DMARDs and/or biologics.
- CHIK does not seem to aggravate pre-existing disease.
- It does not seem necessary to modify the basic treatments of rheumatology patients in the setting of CHIK.
- CHIK does not seem harmful in patients receiving biologics.
- CHK can mimic idiopathic chronic inflammatory arthritis (RA etc)
- Travel history, febrile onset, rash are important features

Rheumatology and viral pathogens

- Rheumatologists are obliged to consider viral pathogens as etiology of a wide variety of conditions (traditional and non-traditional)
- Anti-rheumatic therapy must accommodate viral infections (active, latent and persistent) as co-morbidities
- Viral infections as complications of our diseases and therapies need to be diagnosed treated and most importantly prevented when ever possible

Progressive Multifocal Leukoencephalopathy



CHARACTERISTICS

- Demyelination by MR and neuropathology

JC induced demyelination

- only caused by *JCPyV replication*
- Demyelinating disease (*Lysis of oligodendrocytes*)
Diffuse and asymmetrical lesions (ill-defined edges)
- Relative axonal preservation and large bizarre astrocytes
- *No animal model*

Relevance to rheumatologists

- Alerts
 - Rituximab
 - Mycophenolate
 - Belimumab
- Inflammatory PML – differential dx of neurologic manifestations of rheumatic diseases and their therapy
- Affects patients/physicians' decisions re immunosuppressive therapies



Differential diagnosis of PML from other CNS rheumatic Diseases

- CNS vasculitis – MRI rarely respects gray/white matter borders, CSF> inflammatory
- NP SLE – can be similar in MR findings (T2 WML indistinct borders), PRES(and thus such patients must be approached with high index of must rule outs
- CNS SS – more NSWMLs i.e. multiple



Underlying Diagnosis

Case reports:

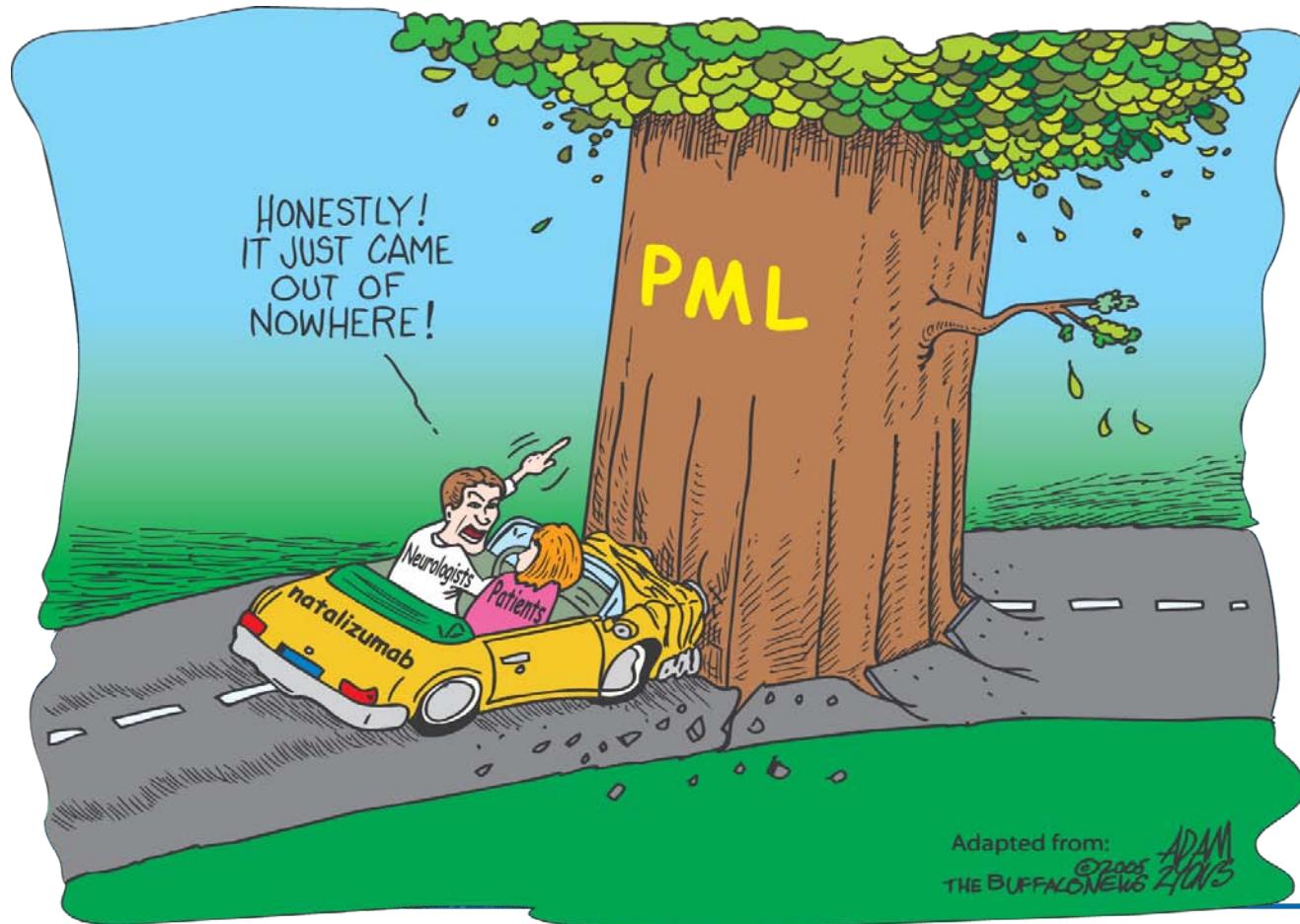
- Nonimmunosuppressed
- HIV-negative
- T-cell lymphopenia

Disease	% of PML cases*
AIDS	80%
Hematologic malignancies	13%
Transplant recipients	5%
Chronic inflammatory diseases	2%

*Series of 61 pts seen between 1996-2003

PML: Natalizumab

3/3,000 natalizumab recipients in clinical trials developed PML. Drug removed from market, returned in mid-2006 after extensive surveillance showed no additional cases. PML/natalizumab cases had all received either IFN-beta (MS) or other immunosuppressives (Crohn's)

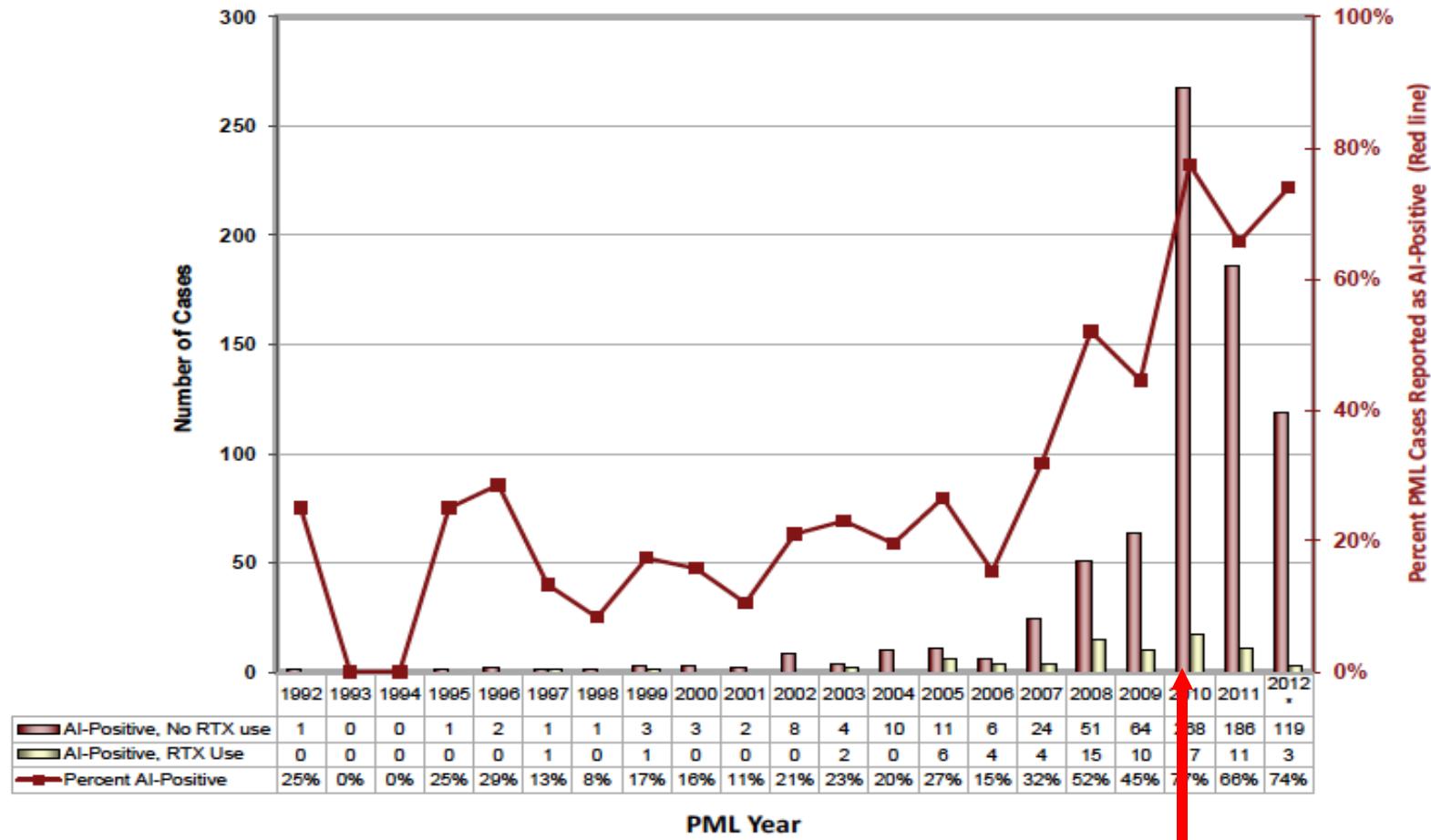


**NEVER DESCRIBED
IN MS!**

Drug Induced PML

- Refers to cases of PML where immunosuppression creates an environment where JC virus causes PML
 - An unfortunate term for physicians and patients
 - Does not imply any level of relative risk which may range from 1/90 to > 1/30,000
 - New proposal to weigh risks (Calabrese, Molloy & Berger – NAT REV RHEUM FEB 2015)
-

Autoimmune Disease Status of PML Cases Stratified by RTX Use



Therapeutic Agent	Autoimmune disease indication	Association with PML
CLASS 1 (HIGH RISK)		
Natalizumab >450 cases to date !!!!	Multiple sclerosis Crohn's disease	Risk ranges from ~ 1/90 to ~ 1/10,000 Varies with JC antibody status, prior immunosuppressives, duration of treatment
Efalizumab	Psoriasis	1/166 patients treated >3 years

Have been described in LOW/NO risk populations for PML

Clear evidence of latency >1-2 years

NOT RARE

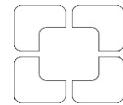
Therapeutic Agent	Autoimmune disease indication	Association with PML
CLASS 2 (LOW RISK)		
Rituximab	RA, AAV	~ 1/30,000 (RA) 8 reports of PML with off label use (5 SLE), denominator unknown
Belimumab	SLE	2 cases among ~ 18,000 pts treated
Cyclophosphamide	SLE, Vasculitis	Multiple cases, denominator unknown
Azathioprine	SLE, vasculitis	Multiple cases, denominator unknown
Mycophenolate mofetil	SLE, vasculitis	Multiple cases, denominator unknown
Methotrexate	RA, SLE, vasculitis	Multiple cases, denominator unknown



Therapeutic Agent	Autoimmune disease indication	Association with PML
CLASS		
Rituximab	Confounded by indication i.e. SLE and other CTDs	(5)
Belimumab		
Cyclophosphamide		
Azathioprine		
Mycophenolate mofetil		
Methotrexate		

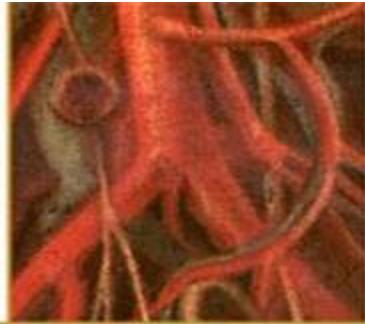
Therapeutic Agent	Autoimmune disease indication	Association with PML
CLASS 3 (VERY LOW RISK)		
Anti-TNF therapies	RA, JIA, AS, psoriasis, PsA, IBD	3 confirmed cases, denominator unknown, but likely >3 million patients
Abatacept	RA	No confirmed cases. 2 PML cases with belatacept, a closely related compound, in patients with solid organ transplantation
Tocilizumab	RA, JIA	No confirmed cases
Anakinra	RA, autoinflammatory disorders	No confirmed cases
Ustekinumab	Psoriatic arthritis, psoriasis	No confirmed cases
Tofacitinib	RA	No confirmed cases

Includes virtually any other immunosuppressive even in low doses including prednisone



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