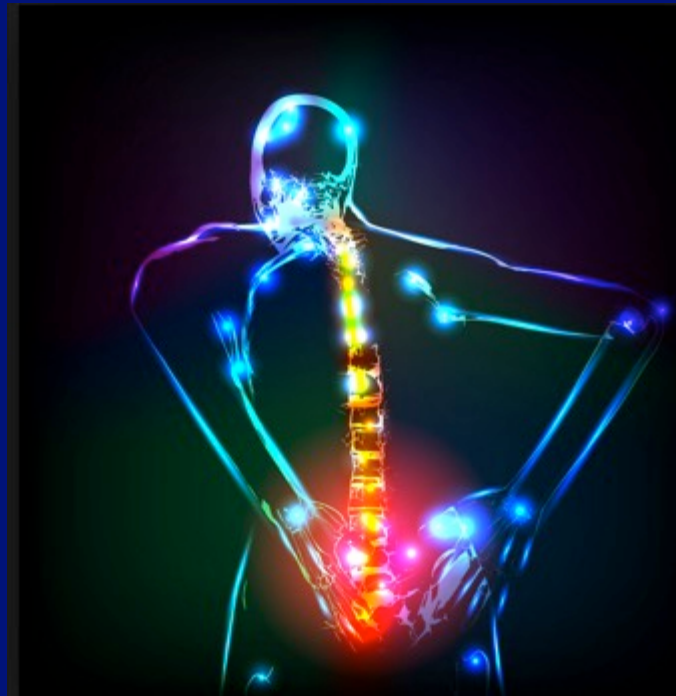


Infections & Vaccines in Rheumatology

Laurentian Rheumatology Conference – May 2016



arthritisbroadcastnetwork.org

Brian J Ward MDCM

JD MacLean Tropical Diseases Centre

Research Institute of the McGill University Health Centre



Potential Conflict of Interest Statement

(Last 5 years)

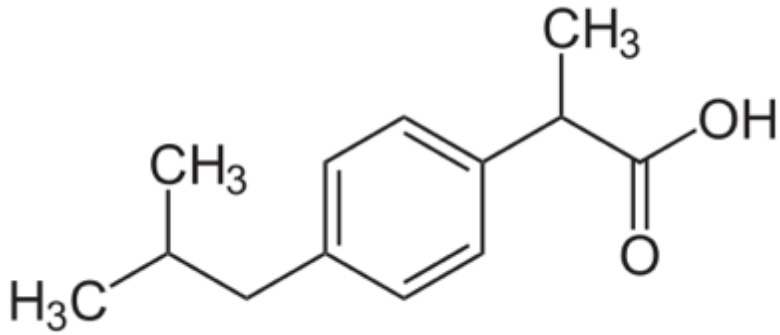
Position in Pharma	Medical Officer for Medicago Inc. (Oct 2011 - present)
Consulting and Advisory Committees	Pfizer, Merck, Novartis, GSK, Sanofi Pasteur MSSS, US Dept of Justice (Vaccine Compensation Programs) Provincial & Federal governments (Vaccine safety & use)
Contracts	Vaccine trials for virtually all companies
Shared Awards	Shared CIHR Team grant (Laval U, GSK) CIHR-Industry and MFEQ grants (Medicago) Shared CQDM grant (Medicago, Laval U, SNC Lavalin)
Occasional Speakers' Honoraria	Pfizer, Sanofi Pasteur, Novartis
Investments	(sadly) Nil

Outline

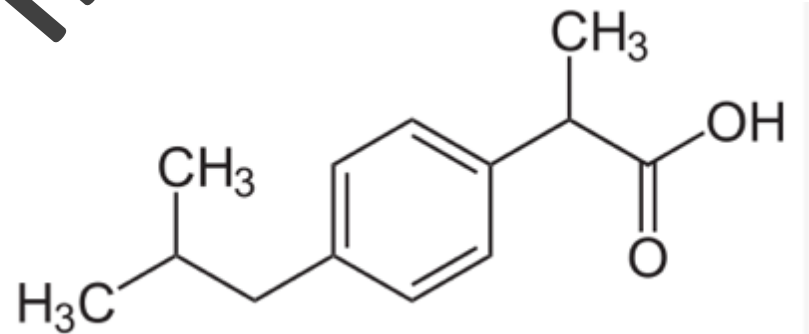
- Biologicals
- Infections
- Vaccines (in General)
- Vaccines & Infections
prior to and during Biologics Rx

Biologicals

Drugs versus Biologics

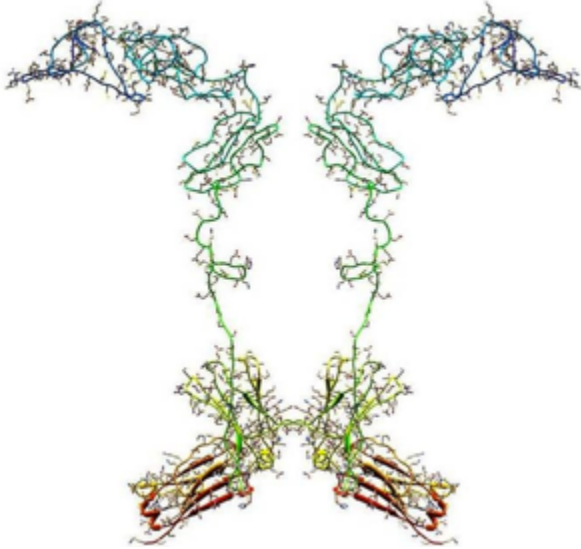


Patented Ibuprofen
(Advil™)



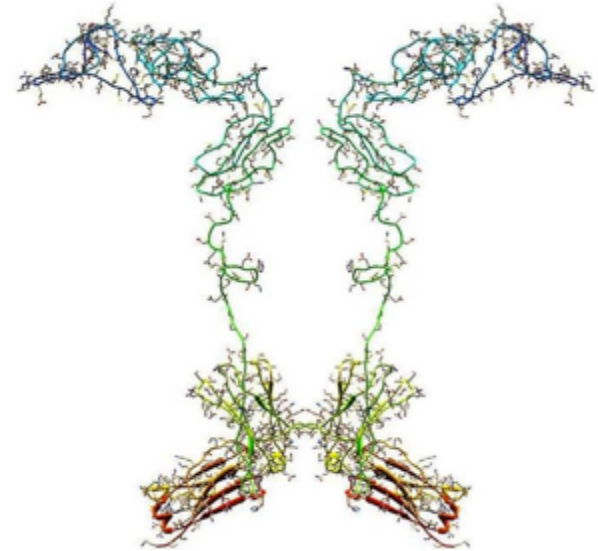
Generic Ibuprofen

BioSimilar/BioSuperiors



www.drugbank.ca

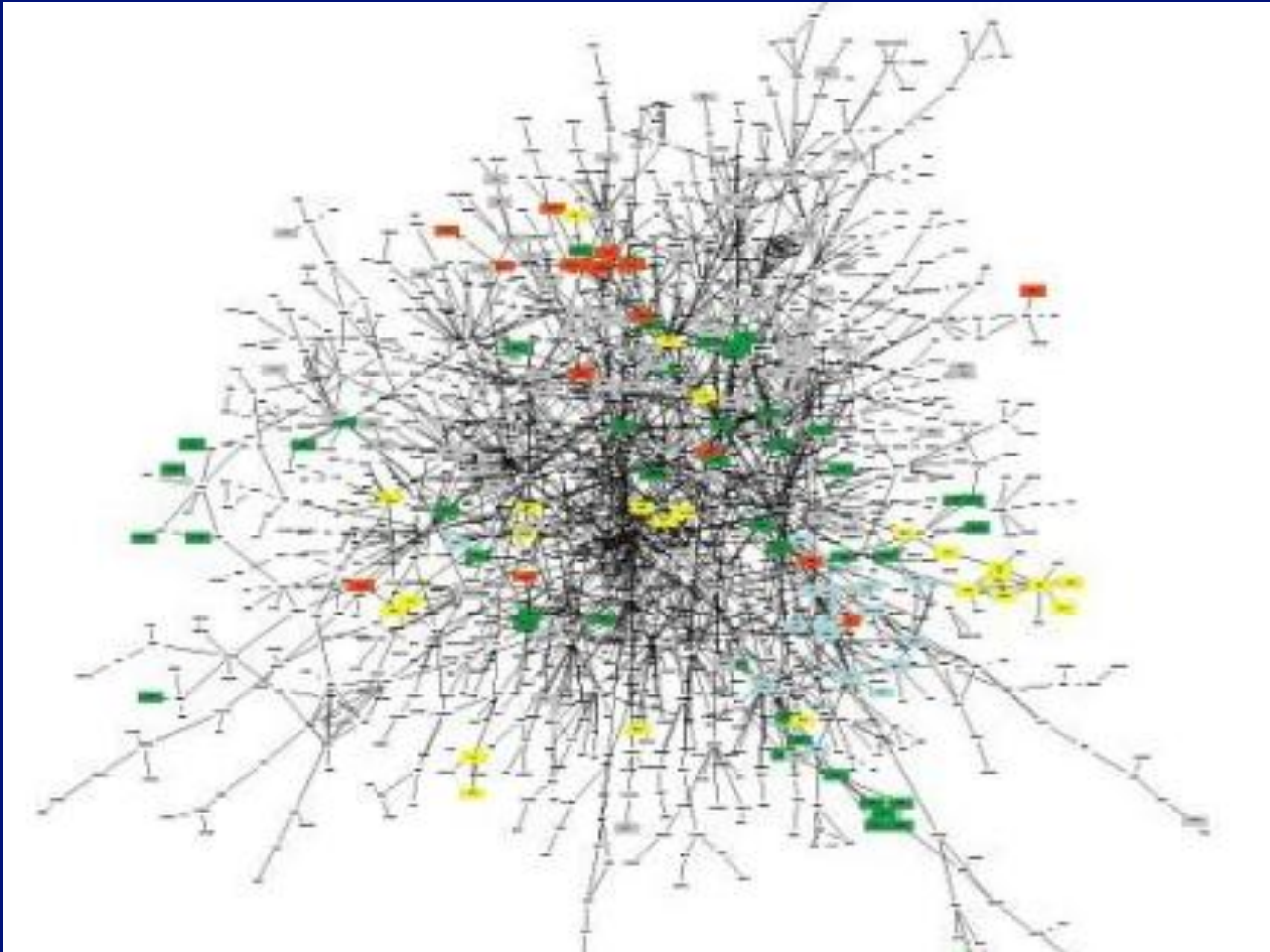
Patented Etanercept
(Enbrel™)



BioSimilar Etanercept
Etacept™ (India)

What Do They Target?

As many as 20,000 genes may be directly or indirectly involved in the human immune response.

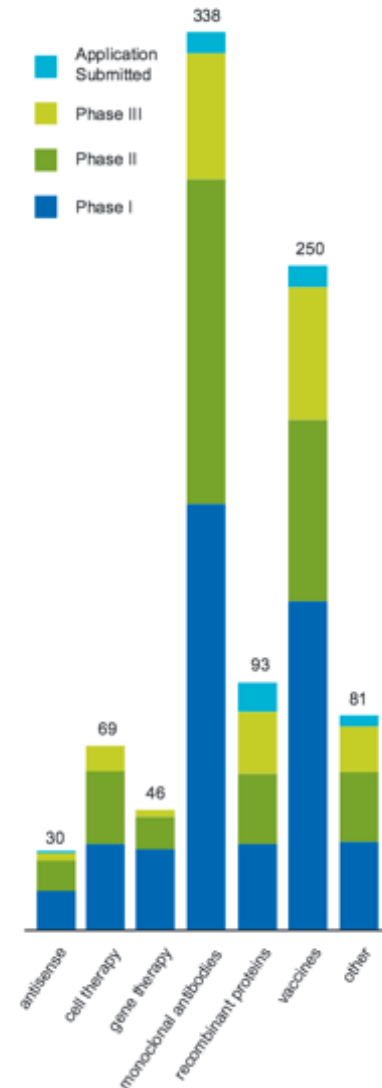


Landscape - 2013



Antisense (30)
Cell therapy (69)
Gene Therapy (46)
Monoclonal Antibodies (308)
Recombinant Proteins (93)
Vaccines (250)
Other (81)

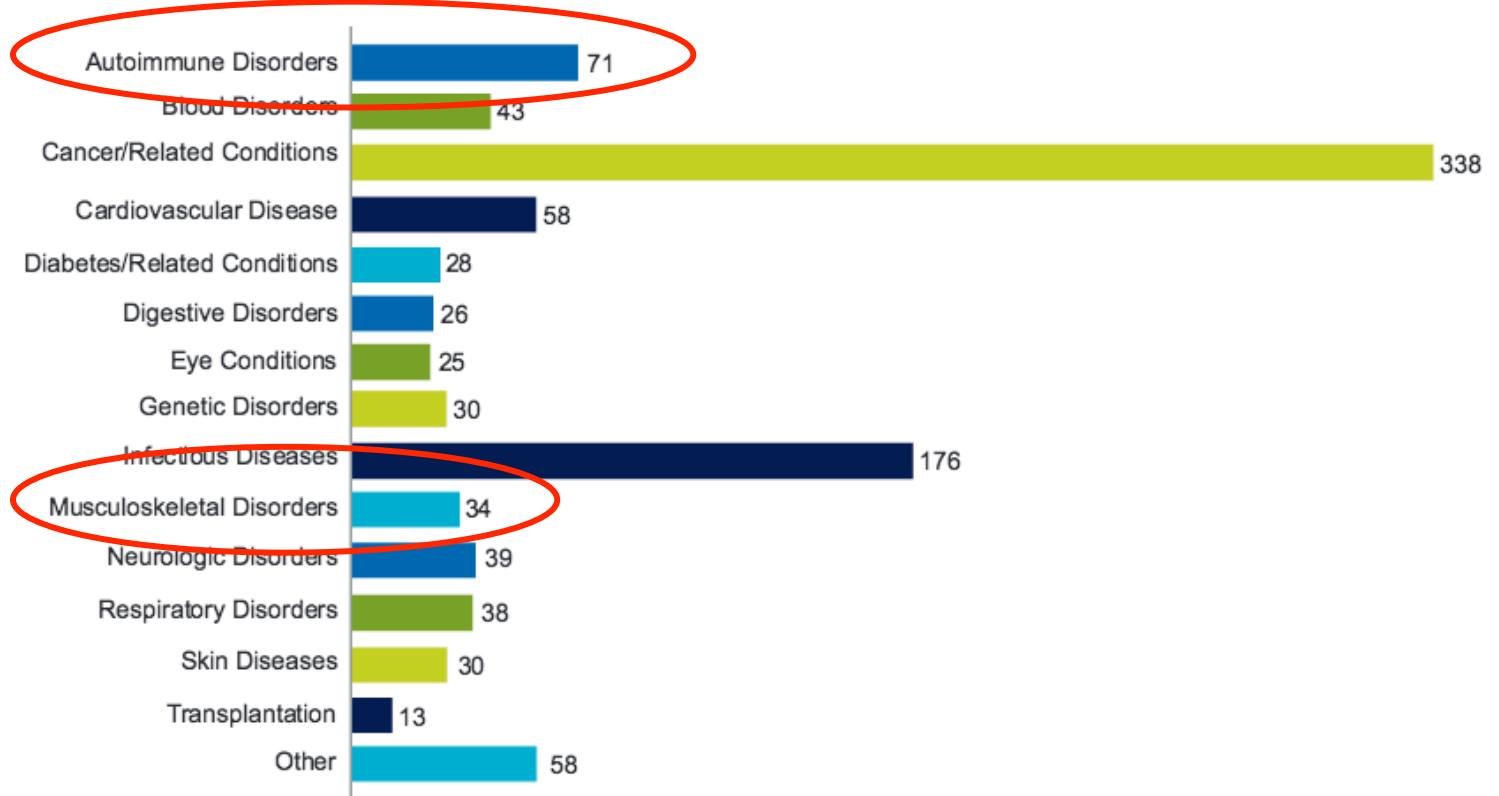
Biologics In Development
By Product Category and
Development Phase



Therapeutic Category

Biologic Medicines in Development—by Therapeutic Category

Some medicines are listed in more than one category



What Do They Target III?

Existing and Coming Therapies

Targeting the B Cell

Rituximab – mouse-human chimera anti-CD20

Ocrelizumab - humanized anti-CD20

Ofatumumab – human anti-CD20

Targeting the T Cell

- Block Inflammatory Cytokines (many)

Adalimumab – fully human IgG1 anti-TNF α

Etanercept – fusion protein TNF α R + IgG1

Infliximab – chimeric mouse-human) anti-TNF α

Golimumab – human IgG1k anti-TNF α

Certolizumab – humanized anti-TNF α

Onercept – recombinant human p55 TNF α binding protein

Tocilizumab – humanized anti-IL6

Anakinra – recombinant anti-IL1

What Do They Target?

Existing and Coming Therapies

Targeting the T Cell

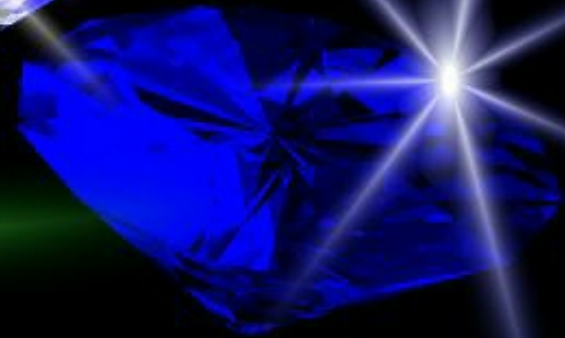
- Reduce the primary stimulation
 - Teplizumab – humanized/nonFc binding anti-CD3
 - OKT(R)cdr-4a – humanized anti-CD4
 - Zanolimumab – fully human anti-CD4
- Reduce Co-Stimulatory signals
 - Abatacept** – chimera of CD152 (CTLA4) + IgG1 Fc
 - Galiximab – anti-CD80
 - Alefacept – chimeria of LFA-3 + IgG1
 - Siplizumab – humanized anti-CD2
 - Efalizumab – humanized anti-CD1

What Do They Target II?

Existing and Coming Therapies

Targeting the T Cell

- Reduce T Cell Proliferation
 - Daciluzimab – humanized anti-CD25
 - Basiliximab – chimaric anti-IL2R
- Interfere with T Cell Differentiation (many)
 - Ustekinumab – fully human anti-IL12/23
 - Guselkumab – human IgG1 anti-IL23
 - Secukinumab – human IgG1 anti-IL17
 - Brodalmab – human IgG2 anti-IL17R
 - rhIL10 – recombinant human IL10



Top Anti-Cancer Rx in 2013

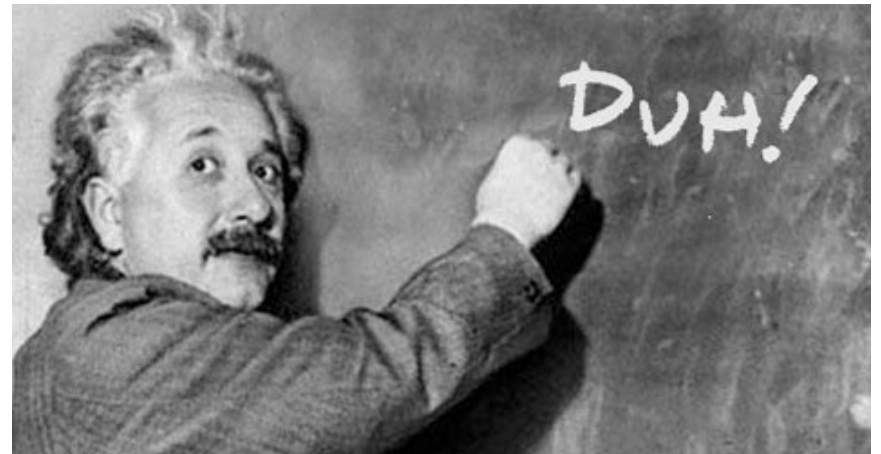
Table. Global Top 10 Selling Oncology Drugs in 2013

Drug	Sales (in billions)	Cancer Indications
Rituximab (<i>Rituxan/MabThera</i> , Genentech/Roche)	\$7.78	non-Hodgkin's lymphoma, chronic lymphocytic leukemia
Bevacizumab (<i>Avastin</i> , Genentech/Roche)	\$6.75	colorectal, lung, kidney, and glioblastoma
Trastuzumab (<i>Herceptin</i> , Genentech/Roche)	\$6.56	breast, esophageal, and gastric
Imatinib (<i>Gleevec</i> , Novartis)	\$4.69	variety of leukemias and gastrointestinal stromal tumors
Pegfilgrastim (<i>Neulasta</i> , Amgen)	\$4.39	febrile neutropenia
Lenalidomide (<i>Revlimid</i> , Celgene)	\$4.28	multiple myeloma, mantle cell lymphoma, myelodysplastic syndromes
Pemetrexed (<i>Alimta</i> , Eli Lilly)	\$2.70	lung
Bortezomib (<i>Velcade</i> , Takeda and Johnson & Johnson)	\$2.61	multiple myeloma, mantle cell lymphoma
Cetuximab (<i>Erbix</i> , ImClone and Merck)	\$1.87	colorectal, head and neck
Abiraterone (<i>Zytiga</i> , Johnson & Johnson)	\$1.70	prostate

Infections

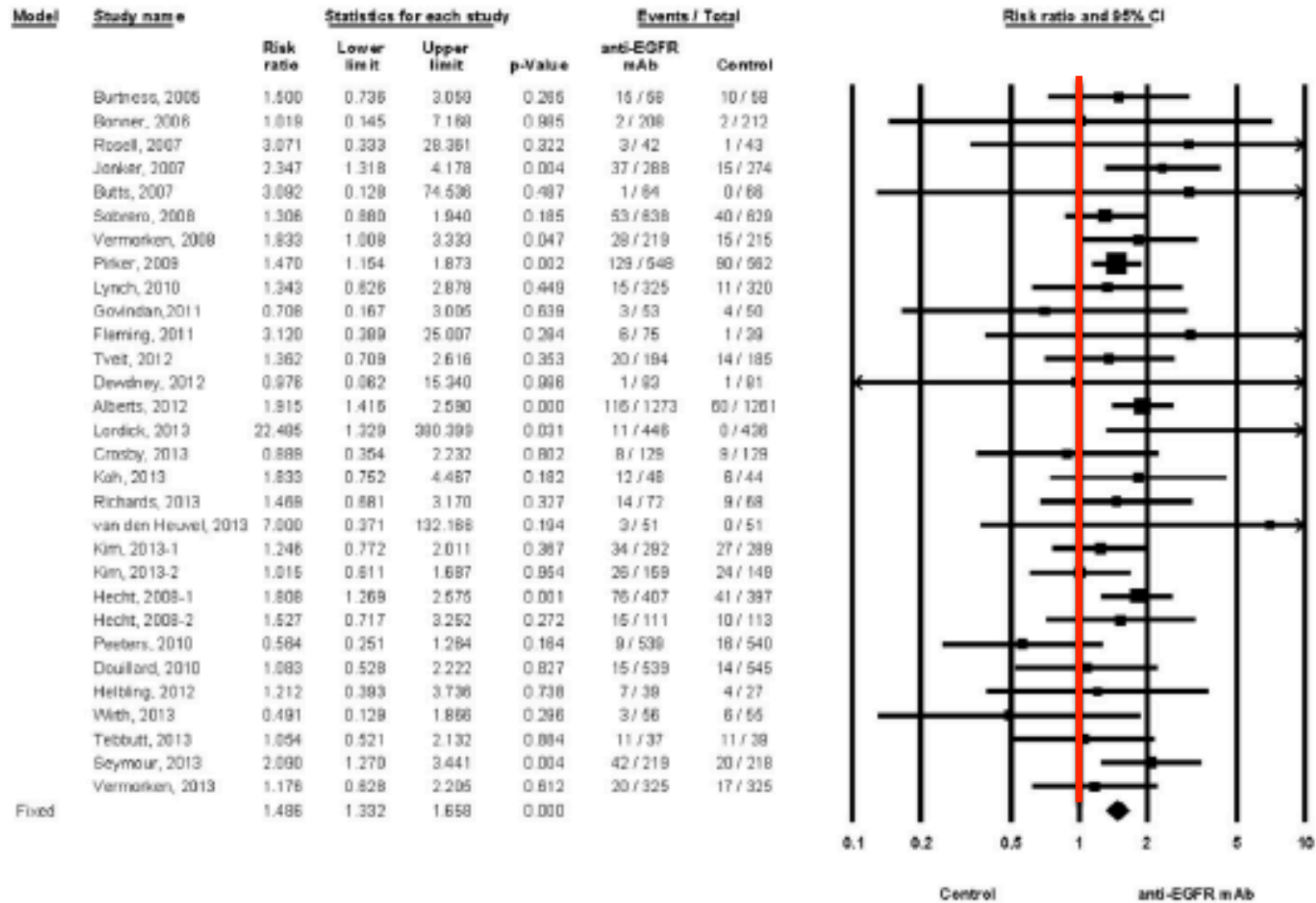
DMT and Infectious Diseases Risk

*Hmmm ... let's see ...
When you mess with
the immune systems
(surprise, surprise) ...
you get more infections*



Risk of High-Grade Infection with Anti-EGFR (cetuximab and panitumumab)

Infection



Routine versus 'Opportunistic' Infections

Routine (vary by age)

- Upper Respiratory
- Urinary Tract
- Skin & soft tissue
- Sexually-transmitted
- Pneumonia
- Varicella zoster
- others

Opportunistic

- Tuberculosis
- JC Virus
- Cryptococcosis
- Other mycobacteria
- Listeriosis
- others

What Is There to Worry About?

Frequency & Severity of Routine Infections

- Rheumatic patients **already** at elevated risk
- Respiratory, skin & soft tissues
- Bone & joint

Reactivation of Latent Infections

- Viral infections (Herpes zoster, HSV, hepatitis B/C, JCV)
- Bacterial infections (latent TB, listeriosis, legionellosis, salmonellosis, norcadial infection, non-TB mycobacteria)
- Others (*Pneumocystis jirovecii*, coccidiomycosis, histoplasmosis, aspergillosis)



Background Rates for Infections Higher in Many Rheumatology Patients?

Varicella Zoster Virus Reactivation

Life-time risk of reactivation (shingles) ~30%

Progressive increased risk with age

Risk in RA patients (without Rx) ~ 2x

Smitten AL et al. Arthritis Rheum 2007;57:1431

Progressive Multifocal Leukoencephalopathy (JC Virus)

General population 0.2/100,000

RA patients 0.4/100,000

Real risk with natalizumab (MS treatment)

Absolute risk with rituximab <1/30,000

Lahiri et al. Best Pract Res Clin Rheum 2015;29:290

Quantifying the Risk

Meta-Analysis of 106 trials of Standard DMARD & Biologics

Overall Risk of Serious Infection with Biological Rx

OR 1.31 (1.09-1.58) for Standard Dose

OR 0.93 (0.93-1.33) for Low Dose

OR 1.9 (1.5-2.39) for High Dose

Risk lowest in males, previously untreated

Absolute risk (vs background rates)

6/1000 PY (STD Rx)

55/1000 PY (combined biological Rx)

VZV and Biologics



www.shinglesexpert.org

Long history with corticosteroid use

2009 – RA subjects treated with >1 DMARDs

Several clear risks:

- age of subjects
- underlying autoimmune disease severity
- intensity of treatment (non-biologics and biologics)
- use of corticosteroids
- prior use (and length of use) of non-biologics

Estimates of risk vary but 1.7 (CI 1.1-2.7)

Most cases early (first 6 months)

Anti-TNF α drugs most clearly implicated (some variation in risk)

As data accumulates for other DMARDs – risks more obvious

Rates for tofacitinib + MTX 5-8/100 PY

Tuberculosis

1999 – first disseminated TB post-infliximab

Subsequently etanercept (all anti-TNF α)

Onset ~12 wks (rare after 6 months)

50-60% disseminated & extra-pulmonary

British/Swedish studies – 118/100,000 PY

Risk varies : Adalimumab > Infliximab > Rituximab

~~Screening can reduce but not eliminate risk~~

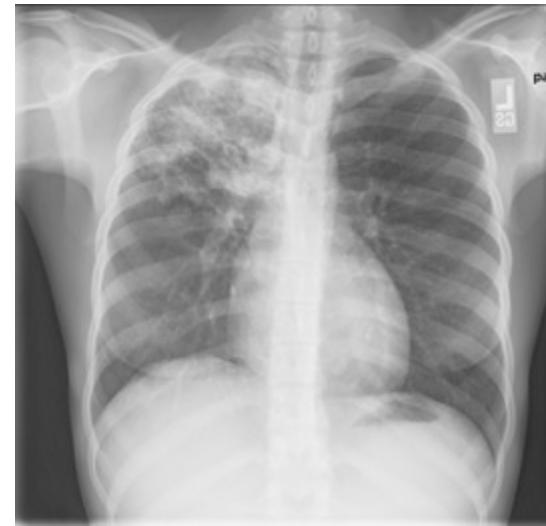
Swedish data on TB rates on biologics

2002-2006 89/100,000 PY

2007-2011 24.2/100,000 PY

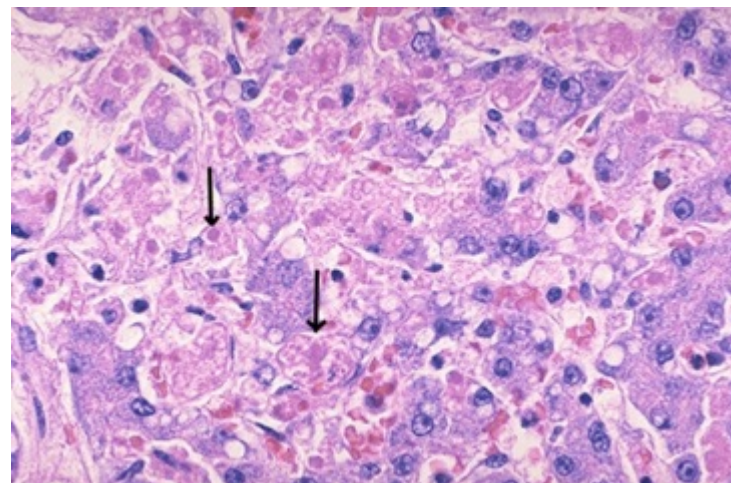
Median time to diagnosis also up 1.2 years (4 mo-5yr)

~~Risk with biological targeting other pathways less clear~~



radiopaedia.org

Hepatitis B



www.pathpedia.com

Resolved HBV (N=179) biologicals
(14 ritux, 146 anti-TNF α , 19 other)

No virologic reactivation but transaminases up

Barone M, et al. Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection *Hepatology*. 2015 Jul;62(1):40-6.

Risk of reactivation greatest in HBsAg + subjects

Small risk even in anti-HBsAg/anti-HBc positive

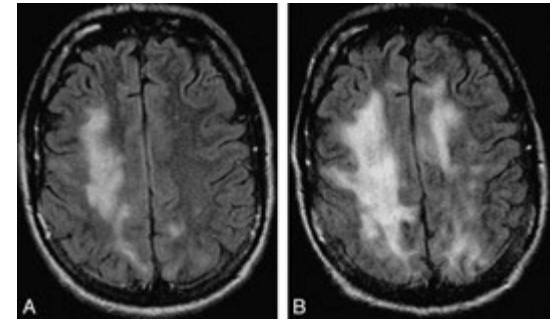
Risk increases with combined Rx, MTX, corticosteroids

Damage (clinical disease) most often occurs with reduced Rx

Viral load up then Rx reduction leads to immune attack

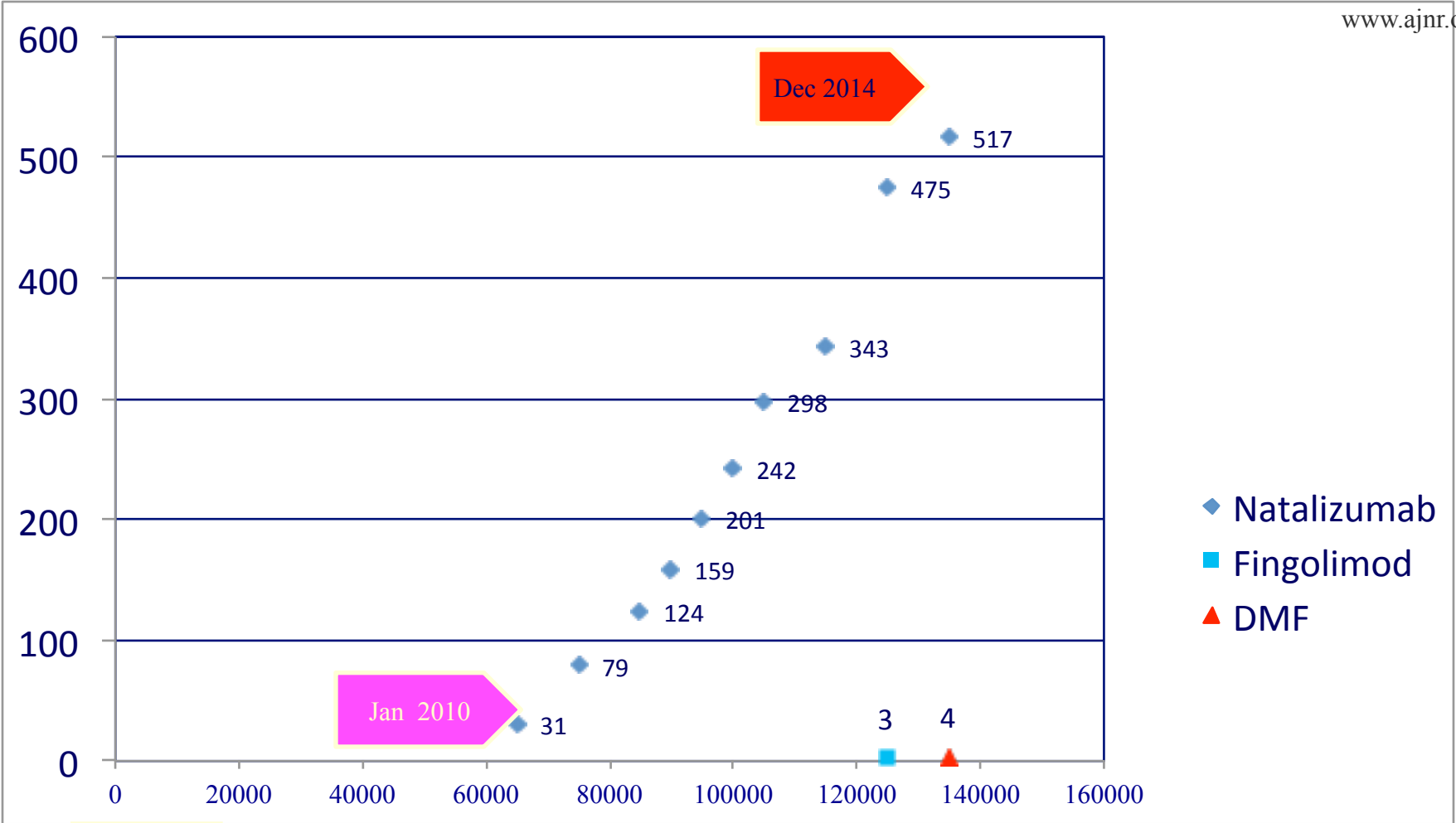
Nard FD, Todoerti M, Grosso V, Monti S, Breda S, Rossi S, Montecucco C, Caporali R.

Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologic treatment: Extending perspective from old to newer drugs. *World J Hepatol*. 2015 Mar 27;7(3):344-61.



JC Virus & PML in MS Patient

www.ajnr.org



July 2006

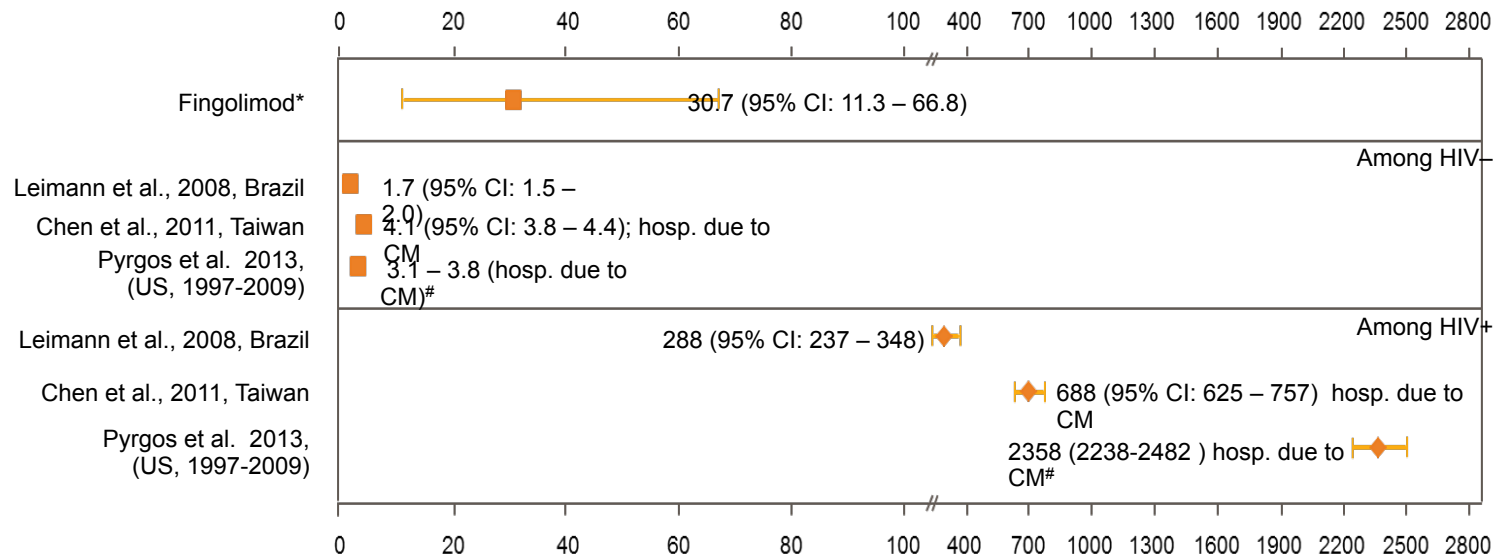
Cryptococcus species

Encapsulated yeast

Two common sp (*neoformans*, *gatti*)

Environment:

- Soil, particularly associated with bird droppings
- Eucalyptus trees



1. Novartis Data on File. Clinical Overview – Labelling Change (03-Feb-2015).

2. Pyrgos V et al. PLOS One. 2013;8:e56269.

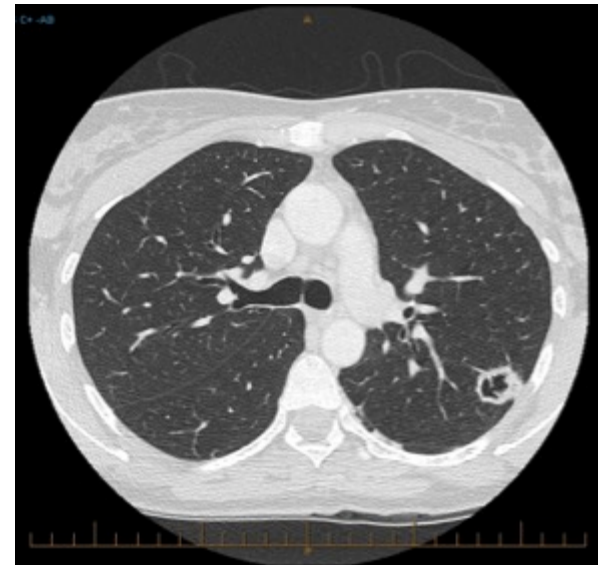
3. Chen Y et al. Neuroepidemiology. 2011;36:79–84.

4. Leimann BC et al. Cad Saude Publica. 2008; 24(11): 2582–2592.

* For fingolimod, reporting rates are presented
indicates range

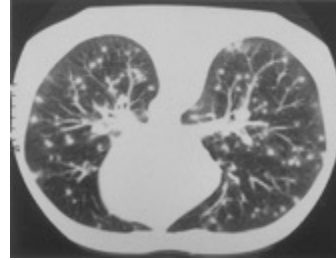
Cryptococcosis

Unusual Manifestations



Other Considerations as Biologics Applied to More Diverse Populations

Histoplasmosis



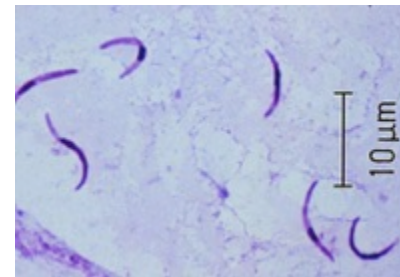
Leishmaniasis (Visceral & Cutaneous)



Chagas Disease



Malaria (*vivax*, *ovale*, *malariae*)



Strongyloides stercoralis



Local vs Systemic Adverse Events

Infection

Malignancy

Auto-Immunity

Table 1. Incidence of adverse events leading to withdrawal from biologic therapy

	Etanercept (n = 175)	Infliximab (n = 60)	Adalimumab (n = 134)	Ustekinumab (n = 176)	Total (n = 545)
Injection-site reaction	1.71 (3) 0.68	0 (0) 0	0 (0) 0	0 (0) 0	0.55 (3) 0.25
Infusion reaction	0 (0) 0	8.33 (5) 2.48	0 (0) 0	0 (0) 0	0.92 (5) 0.33
Infection	0 (0) 0	1.67 (1) 0	2.24 (3) 1.22	0.57 (1) 0.28	0.92 (5) 0.41
Malignancy	0.57 (1) 0.23	1.67 (1) 0.62	0 (0) 0	1.14 (2) 0.55	0.73 (4) 0.33
Tuberculosis reactivation	0 (0) 0	1.67 (1) 0.62	0 (0) 0	0 (0) 0	0.18 (1) 0.08
Lupuslike symptoms	0 (0) 0	1.67 (1) 0.62	0 (0) 0	0 (0) 0	0.18 (1) 0.08
Iritis	0 (0) 0	0 (0) 0	0.75 (1) 0.41	0 (0) 0	0.18 (1) 0.08
Cardiac	0 (0) 0	0 (0) 0	0 (0) 0	0.57 (1) 0.28	0.18 (1) 0.08
Neurologic	0 (0) 0	0 (0) 0	0 (0) 0	0.57 (1) 0.28	0.18 (1) 0.08
Total	2.29 (4) 1.13	15 (9) 4.96	2.99 (4) 2.38	2.84 (5) 1.38	4.04 (22) 1.97

Values are given as: percentage of patients with the adverse event leading to withdrawal of all patients on that biologic (number of patients with the AE) number of events/100 patient-years.

Vaccines

Mumps in the NHL 2014



www.cbc.ca

- At least 15 players on 6 teams
- At least 2 referees
- Fever, malaise, parotitis, orchitis
- No cases of encephalitis

2015 - The Magic (Measley) Kingdom

- 178 cases in outbreak
- 17 states + Mexico + Canada
- 82% unvaccinated



www.motherjones.com

McCarthy M. Measles outbreak linked to Disney theme parks reaches five states and Mexico. *BMJ*. 2015 Jan 23;350:h436.

Chikungunya

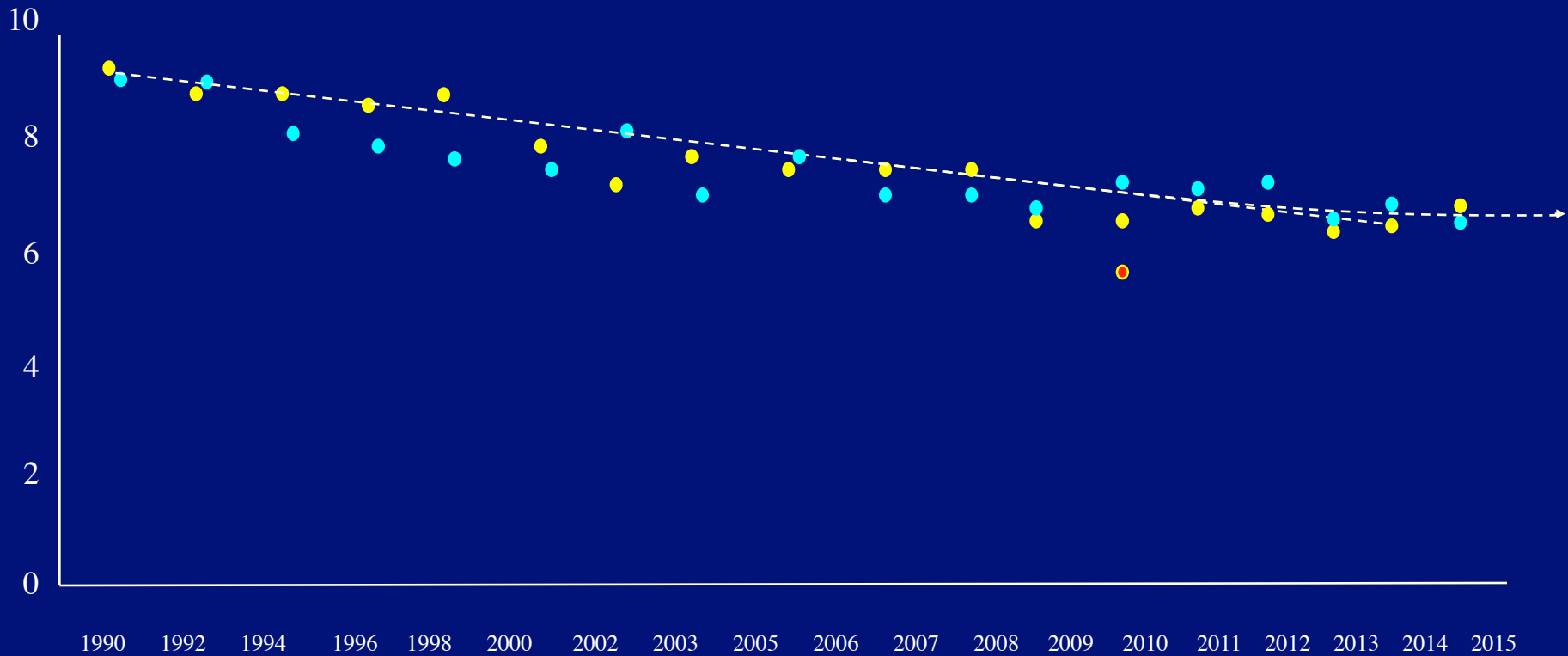
Ebola

Zika

(Soon)

*Anti-Vaccine
Sentiment Is Still
A Real Problem ...*

Vaccines are 'Good'



Vaccines are 'Bad'



Anti-Vaccine Sites are Becoming More Sophisticated ...

49 Doses of 14 Vaccines Before Age 6?
Before you take the risk, find out what it is.

Pregnancy	Birth	2 Months	4 Months	6 Months	7 Months	12-15 Months	18 Months	3 Years	4-6 Years
Influenza	Hepatitis B	Diphtheria Tetanus Pertussis Polio HIB PCV Rotavirus Hepatitis B	Diphtheria Tetanus Pertussis Polio HIB PCV Rotavirus	Diphtheria Tetanus Pertussis Polio PCV Rotavirus Hepatitis B Influenza	Influenza	HIB PCV Measles Mumps Rubella Varicella Hepatitis A	Diphtheria Tetanus Pertussis Hepatitis A Influenza	Influenza	Diphtheria Tetanus Pertussis Polio Measles Mumps Rubella Varicella Influenza (2)

Vaccine excipients or ingredients in trace or larger amounts depending on specific vaccine (partial list):
lab altered viruses and bacteria, aluminum, mercury, formaldehyde, phenoxyethanol, glutaraldehyde, sodium borate, sodium chloride, sodium acetate, monosodium glutamate (MSG), hydrochloric acid, hydrogen peroxide, lactose, gelatin, yeast protein, egg albumin, bovine and human serum albumin, antibiotics, unidentified contaminants.

National Vaccine Information Center
www.NVIC.org

Lab altered viruses and bacteria, aluminum, mercury, formaldehyde, phenoxyethanol, glutaraldehyde, sodium borate, sodium chloride, sodium acetate, MSG, hydrochloric acid, hydrogen peroxide, lactose, gelatin, yeast protein, egg albumin, bovine & human albumin, antibiotics, unidentified contaminants

... I Submit the Humble Twinkie™



Wheat Flour, **bleach**, enrichment Blend (Ferrous Sulfate and B Vitamins—Niacin, Thiamine Mononitrate (B1), Riboflavin (B2), Folic Acid), Sugar, Corn Sweeteners, Corn Syrup, Dextrose, Glucose, and High Fructose Corn Syrup, Corn Thickeners: Cornstarch, Modified Cornstarch, Corn Dextrins, Corn Flour, Water, Soy: Partially Hydrogenated Vegetable and/or Animal Shortening, Soy Lecithin, and Soy Protein Isolate, Eggs, Cellulose Gum, Whey, Leavenings, baking Soda, Phosphates (Sodium acid pyrophosphate and monocalcium phosphate), Salt, Mono and Diglycerides, Polysorbate 60, Natural and Artificial Flavors, Sodium Stearoyl Lactylate, Sodium and Calcium Caseinate, Calcium Sulfate, Sorbic Acid, Color (FD & C Yellow 5, Red 40)

People Are Still Saying Really Dumb Stuff



‘People that work for me, just the other day, 2years old, beautiful child went to have the vaccine and came back and a week later, got a tremendous fever, got very, very sick, now is autistic.’

‘You take this little beautiful baby, and you pump — it looks just like it’s meant for a horse.’

Aren't Patients Fully Vaccinated?

167 IBD patients and 47 GI docs

Vaccination History?

- 14% of GI docs stated that they took a full vaccination history
- 5.4% of patients recalled being asked about vaccines
- 0.6% (1/167) of patients recalled detailed questions about vaccine history

Not aware that live vaccines to be avoided?

- 23% of GI docs (43% didn't know which vaccines to be avoided)
- 47% of patients

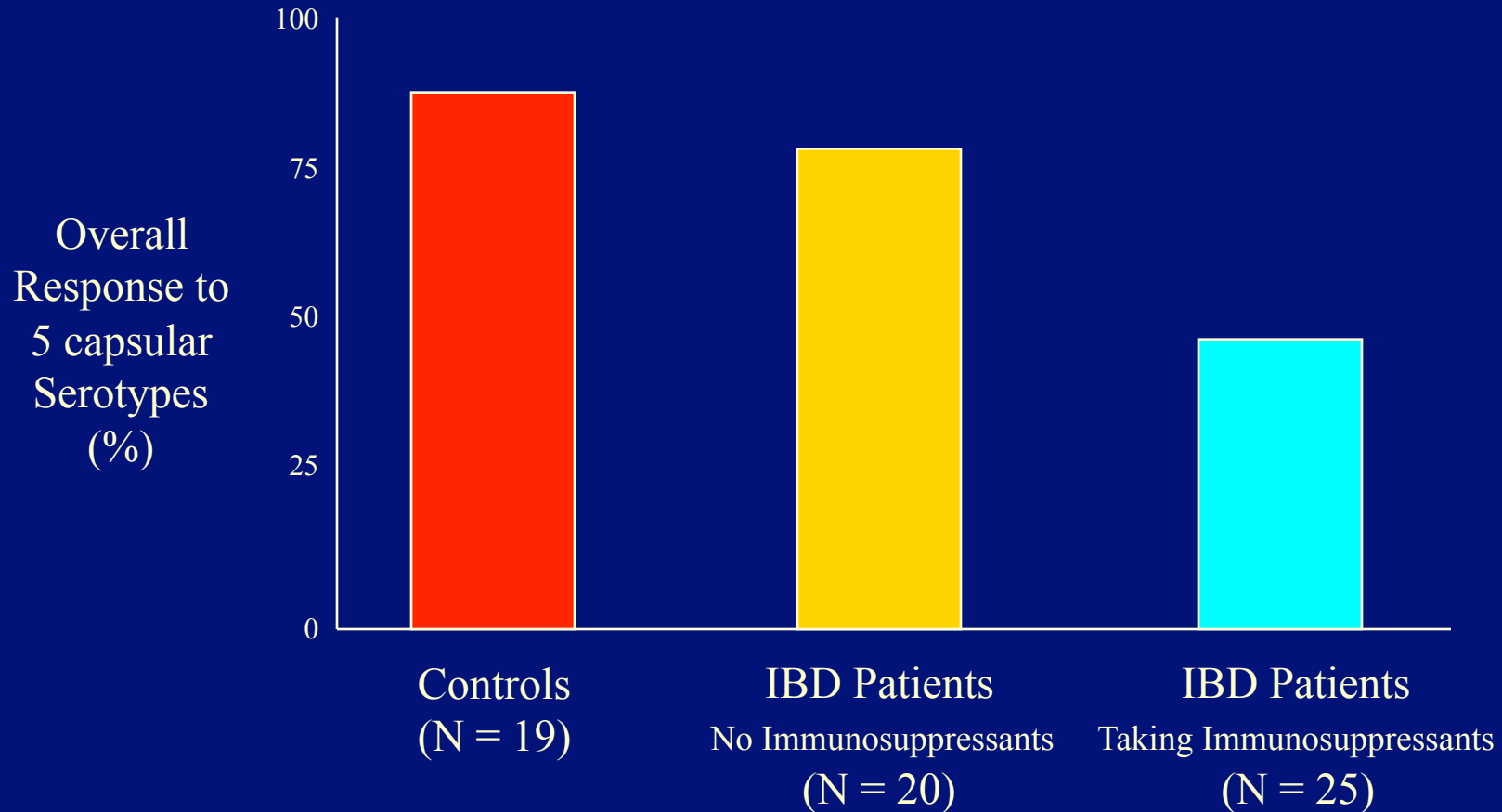
27% of patients had refused vaccines

19% of docs didn't know vaccines needed before Rx

*Don't Vaccines Cause
Exacerbations in
Autoimmune Patients?*

No

But Vaccines Don't Work in Autoimmune Patients ...



Melmed GY et al. Am J Gastroenterol. 2010 Jan;105(1):148-54.

Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease.

*But Live Vaccines Can Hurt
People on Immunosuppressants
(Even When Given to Family
Members) ...*

This one is actually true

Live Vaccines
in Canadian Universal Program

Two

Four

Six

Eight

Live Vaccines

and Potential for Spread in Families

Smallpox (Vaccinia)	—————→	+++
Measles	—————→	(?)
Mumps	—————→	(?)
Rubella	—————→	(?)
Varicella	—————→	+
Oral Poliovirus	—————→	+++
Rotavirus	—————→	+
Nasal influenza	—————→	+
Yellow fever	—————→	(?)
Japanese encephalitis (Chinese)	—————→	(?)
BCG	—————→	+++
Oral Typhoid	—————→	(?)

*Vaccines in
Preparation
for Biologic Rx*

Tropical Diseases Ctr - Pre-Biologics Screening

We Are Learning As We Go?

History

- autoimmune disease and Rx to date
- country of birth, travel and TB risk profile
- possible future travel patterns (pre-emptive vaccination)
- history of specific infections/risks (VZV, HBV/HCV)
- history of vaccines/vaccine record review

Investigations

- Latent TB (PPD or Quantiferon) +/- CXR
- HBV/HCV serology
- VZV serology

Vaccines

- Individualize schedule based on current Rx, age, plans, etc

Vaccines for Pre-Biologic Patients

Recommended whether taking Biologic Rx or not:

- single dose of dTaP in adulthood
- MMR if 2 doses not documented after 12 months of age and born after 1970
- polysaccharide pneumococcal vaccine (PPV23) if ≥ 65 yo or co-morbid condition(s)
- chickenpox vaccine if seronegative
- zoster vaccine if ≥ 60 -65 years of age
- HAV/HBV if risk factors: give 2 doses (eg: Twinrix or equivalent) before biologics

Recommended for those who will take Biologic Rx

- conjugated pneumococcal vaccine (PCV13) followed 8 weeks later by PPV23
- if < 30 yo, quadrivalent conjugated meningococcal vaccine + MenB4
- zoster vaccine if ≥ 45 yo

Travel vaccines to be considered prior to Biologics Rx

- Yellow fever vaccine
- HAV (give first dose before starting biologics)
- IPV (one dose as adult)
- others depending upon travel plans/hopes/dreams

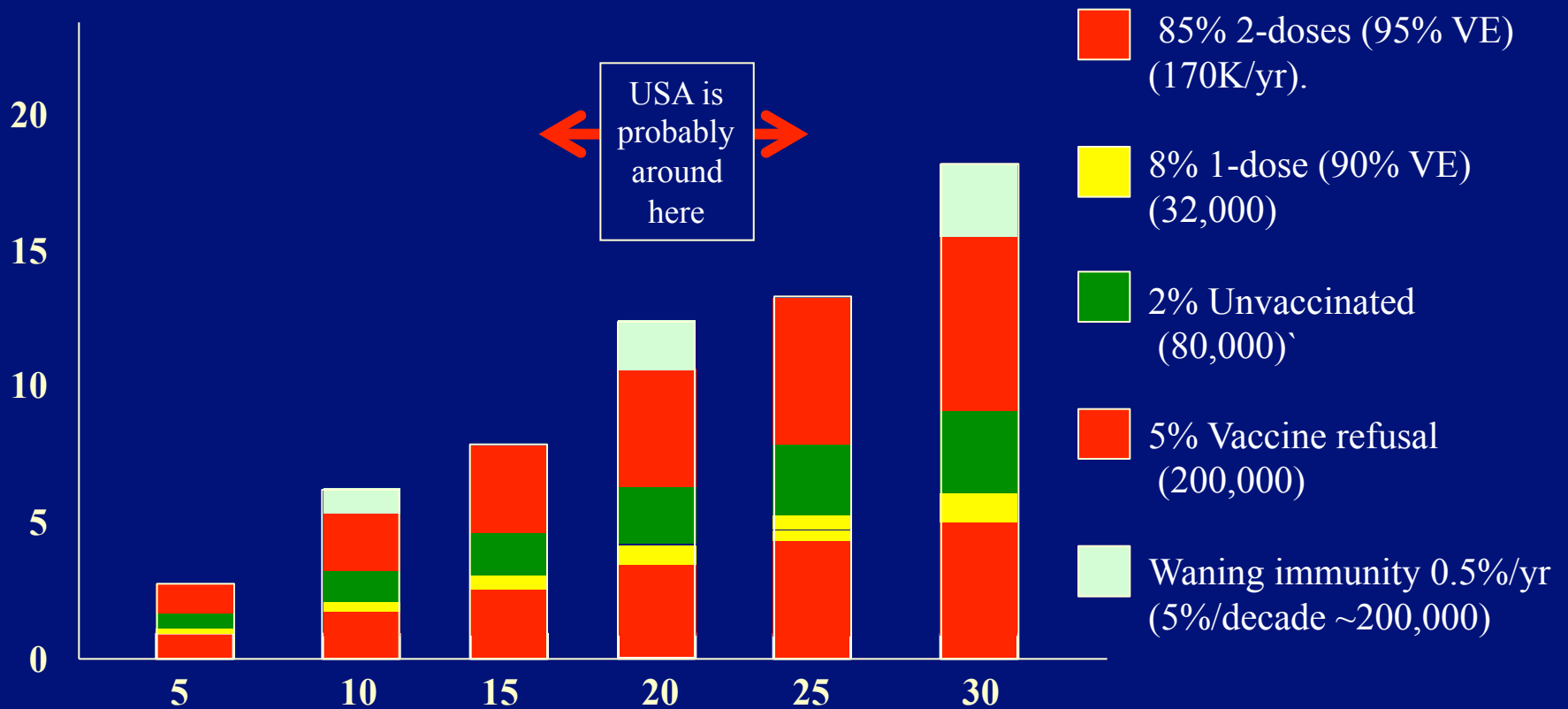
Measles



Accumulating Susceptibles

Millions

US birth cohort ~4 million/yr





www.nerdwallet.com

Extrapolations are Dangerous but ...

If 15 million people are susceptible in the USA,
and measles exposure is inevitable ... then
the country can expect:

- 2,250,000-3,000,000 hospitalizations
- 37,000 deaths
- 20,000-30,000 cases of encephalitis
 - 50% with permanent neurologic deficits
- 600-1650 cases of SSPE

MMR Rash - Semi-Immune



Influenza

- Influenza circulates year-round in tropics
- 'Northern' & 'Southern' formulations
- Life is getting more complicated
 - Live attenuated (nasal) best for kids
 - Adjuvanted \pm high dose best for elderly
 - ID delivery OK for adults
 - Quadrivalent (two As and two Bs)

- What vaccine should be used in rheumatology patients?
 - Don't know (I. Colmegna)



Hepatitis Vaccines



patient.info

Hepatitis A

Exposure in New Canadians

- Many countries experiencing epidemiologic transitions
- Dramatic impact on exposure to infectious diseases
- Hepatitis A antibodies (Dehli) in 50-60% of 15-35 year olds

Mathur P, Arora NK. Epidemiological transition of hepatitis A in India: issues for vaccination in developing countries. Indian J Med Res. 2008 Dec;128(6):699-704.



San Cristobal, Lima, Peru



[img177.imageshack.us/ img177/7531/54147499ea9.jp](http://img177.imageshack.us/img177/7531/54147499ea9.jp)



www.dcdiocese.org/.../MexicanFamily.JPG

Elderly Travellers Increasing



flyingcompanions.com.au



tctour.com



www.mirror.co.uk

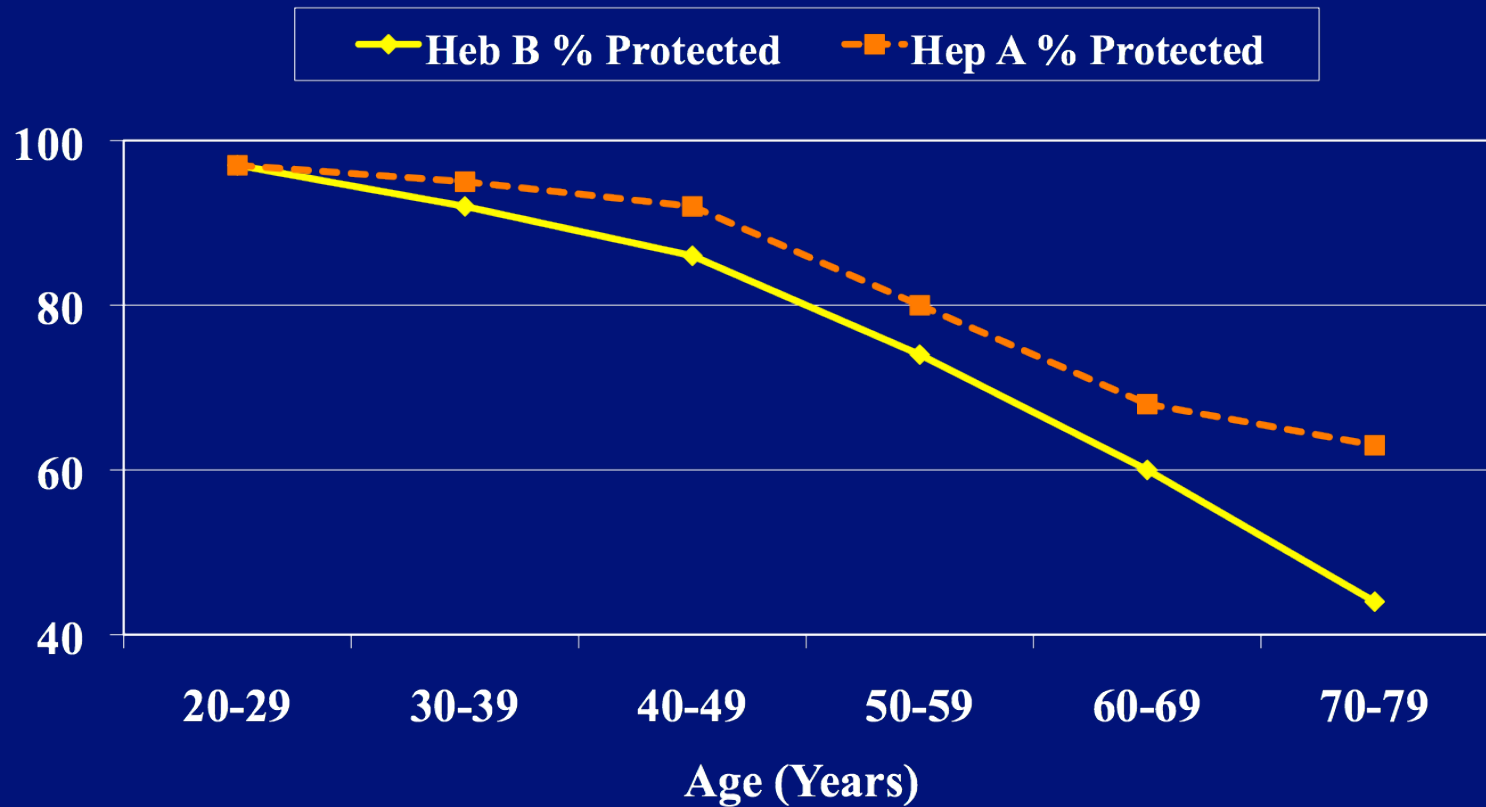
Hepatitis A in the News

Outbreak Associated with Costco Brand 'Organic' Berry Mix



- 11 cases so far in 3 provinces:
 - Ontario (8),
 - Quebec (2)
 - Newfoundland (1)
- Cases: February - March 2016

Age-related Declines in Efficacy for Hepatitis Vaccines

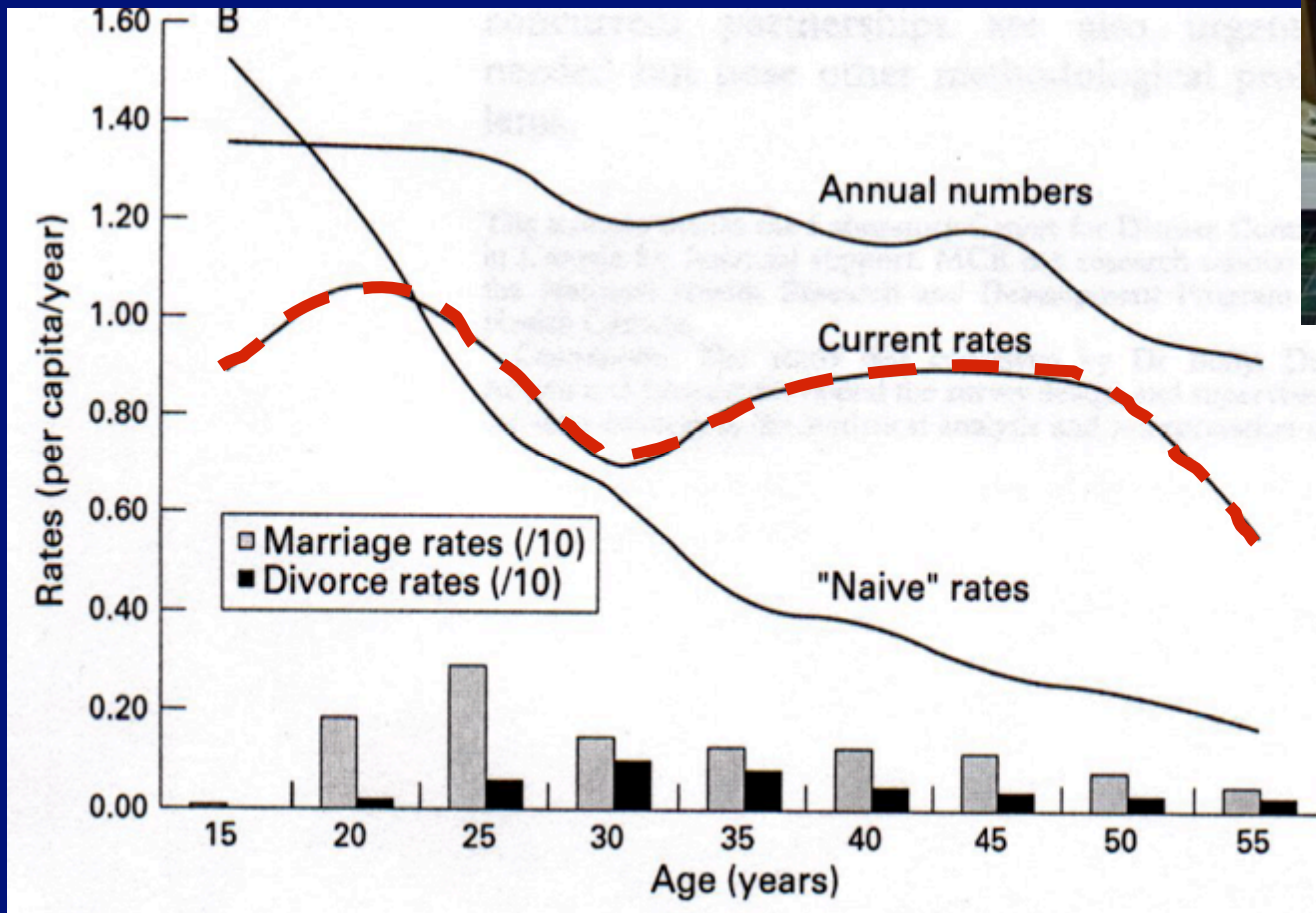


Sjogren MH, AJM 2005;118:34S-39S Fisman D, et al Clin Inf Dis 2002;35:1368-75

Meydani, et al. JAMA 1997; 277:1380-86 Wolters, et al. Vaccine 2003;21:3623-28

Hepatitis B

Sexual Partners by Age

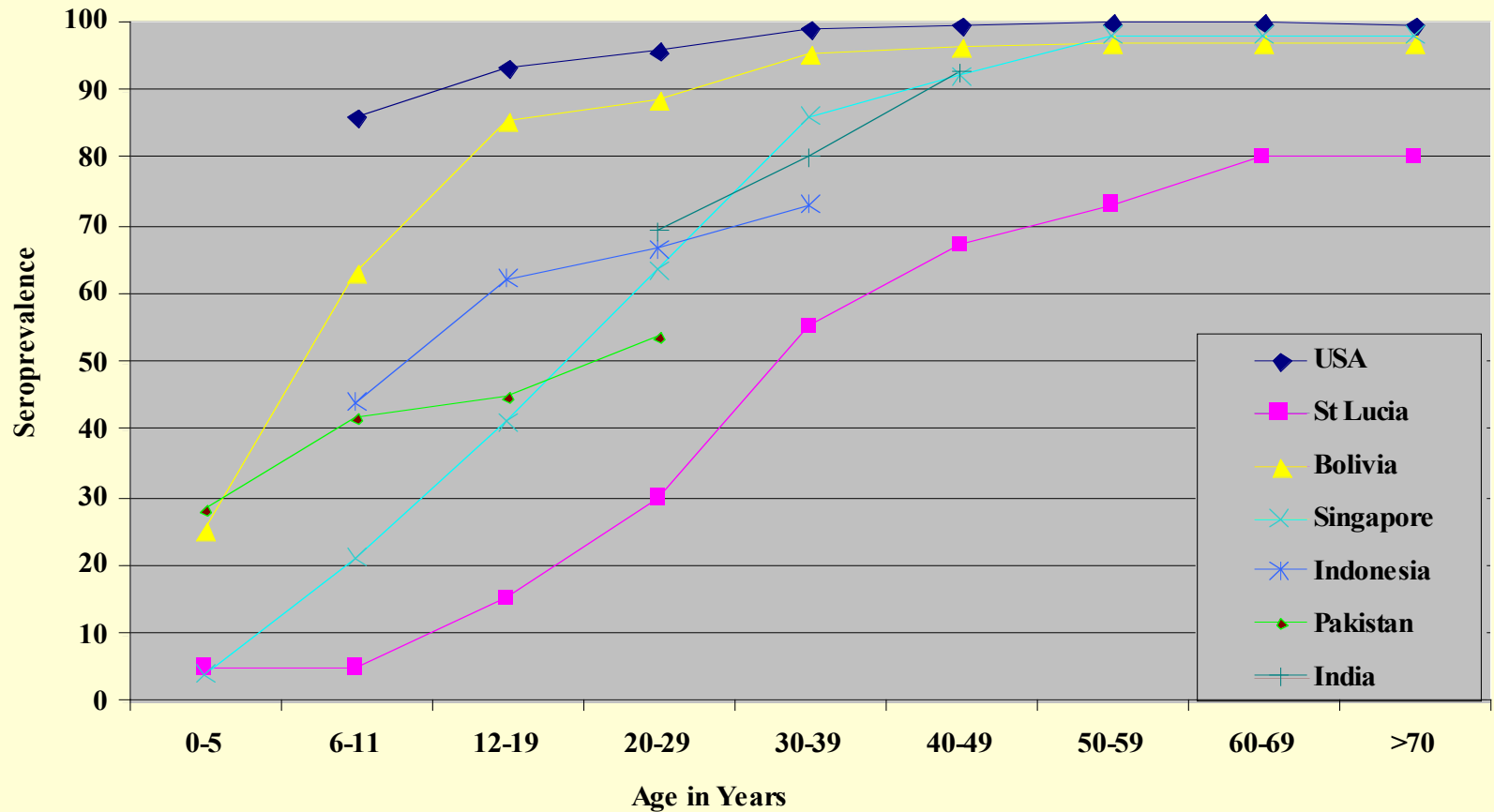


VZV & Shingles



Varicella

Seroprevalence by Age & Origin



2003 J Med Virol Kilgore, 1993 Epidemiol Infect, Garnett, 2002 Trop Med International Health Bartoloni,
2000 SE Asian J Trop Med Public Health Juffrie, 2000 SE Asian J Trop Med Public Health Akram, 1998 JID Mandal

Varicella Serostatus in 'Immigrant Cities'

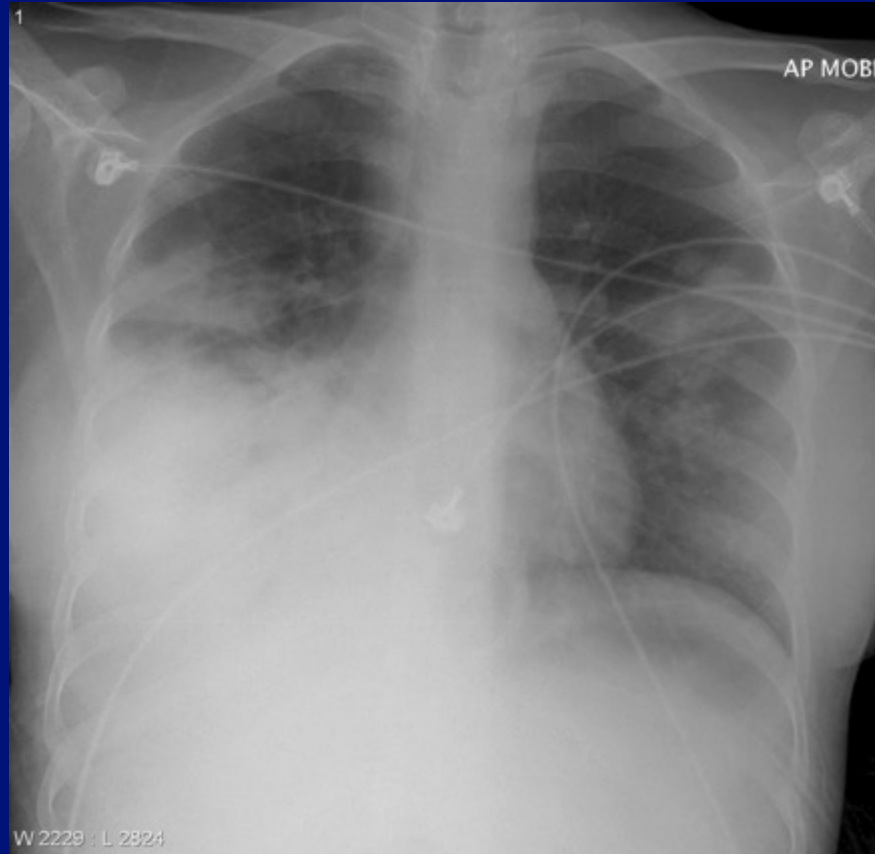


- Average 10-20% of immigrants >30 years susceptible
- Montreal seroprevalence data
 - 92% seropositive (~8% susceptible)
- Modeling suggests at least 2 cost-saving strategies
 - selective screening
 - mass screening

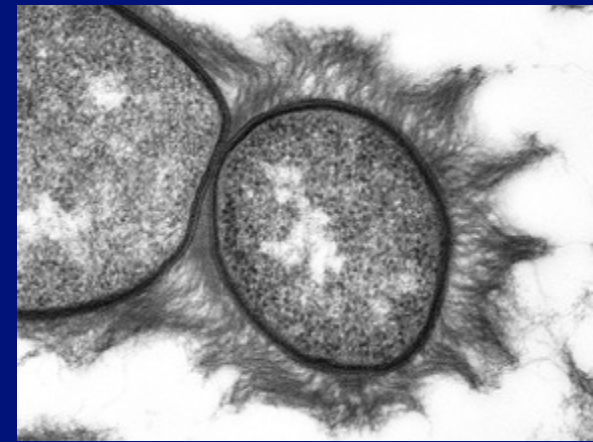
Merrett P, Schwartzman K, Rivest P, Greenaway C.

Strategies to prevent varicella among newly arrived adult immigrants and refugees: a cost-effectiveness analysis. Clin Infect Dis. 2007 Apr 15;44(8):1040-8.

Streptococcus pneumoniae



Streptococcus pneumoniae



rockefeller.edu

- Best approach
 - 13-valent (conjugate -PCV)
 - 23-valent (polysaccharide - PSV)
 - New data showing protection vs CAP for PSV (VE ~37%)
- Wiemken TL et al. The effectiveness of the polysaccharide pneumococcal vaccine for the prevention of hospitalizations due to *Streptococcus pneumoniae* community-acquired pneumonia in the elderly differs between the sexes: results from the Community-Acquired Pneumonia Organization (CAPO) international cohort study. *Vaccine*. 2014 Apr 17;32(19):2198-203.
- Kraicer-Melamed H et al. The effectiveness of **pneumococcal polysaccharide vaccine 23 (PPV23)** in the general population of 50 years of age and older: A systematic review and meta-analysis. *Vaccine*. 2016 Mar 18;34(13):1540-50.
- CAPITA study of PCV in adults (VE ~45% vaccine-strain CAP, 75% invasive disease)

Bonten MJ, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med*. 2015 Mar 19;372(12):1114-25.

Vaccine Timing & Booster(s)

Sequence is Important

- good evidence that PCV should be given first
- PSV followed by PCV can decrease responses

Wait at least 8 weeks after PCV before giving PSV

- Some advisory groups suggest 6-12 months

Boosters?

- Currently give 1 boost of PSV after 5 years
- PCV booster between 5-10 years probably useful
- Sequential PCV-PSV may change booster use

Meningococcus



carrington.edu

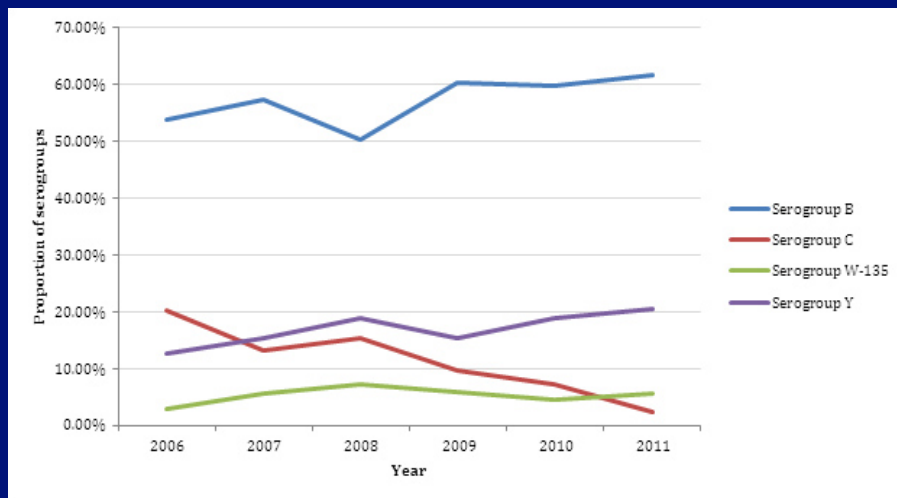
Meninigococcus B Conjugates

Tuumenba™

- lipidated factor H binding protein (fHBP) from subfamily A and B (A05 and B01 respectively)
- Three or two-dose schedules 0, 1 and 6 months or 0 and 6 months.

Bexsero™

- 2 recombinant fusion proteins (Neisseria heparin-binding antigen-GNA1030 and fHBP H-GNA2091), rec Neisserial adhesion A plus detergent-treated outer membrane vesicles from NZ98/254 strain (porin A 1.4 is immunodominant antigen)
- 2 dose schedule (at least 1 month apart)



In Conclusion

- Biologics are changing medicine
- Vaccines (in general) are under threat
- Biologics have infectious (and other) risks
- Some infectious risks can be mitigated prior to/during biological Rx

Thank you for your attention