

How Vaccines Cause Adverse Events

Neal A. Halsey

Institute for Vaccine Safety



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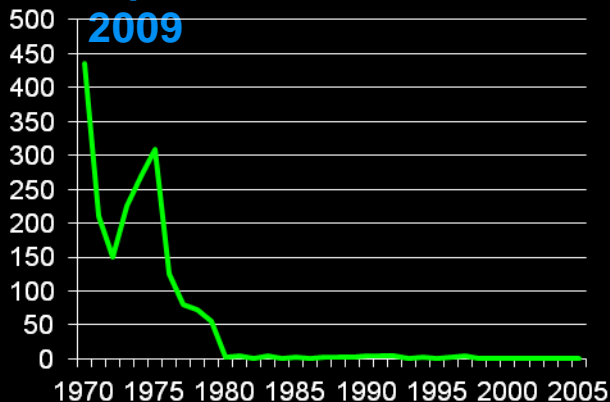
Other Vaccine Safety Sessions

1. Narcolepsy after influenza vaccine
2. Lessons and Causal assessment
3. Autoimmune and allergic diseases
4. Population-based surveillance
5. Immunization safety in developing country programs
6. Risk communication
7. Ethics
8. Vaccination in Immune compromised

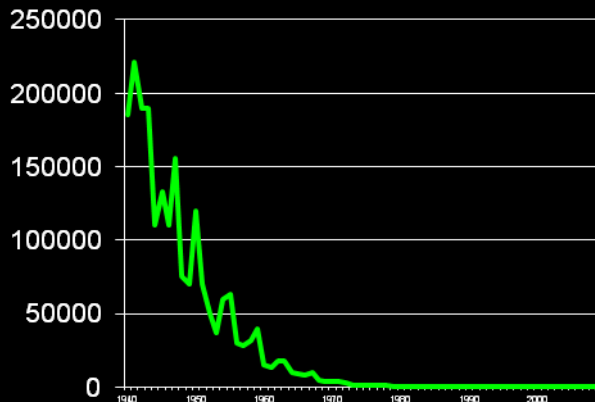


Vaccines Are Our Most Effective Tool to Control Infectious Diseases

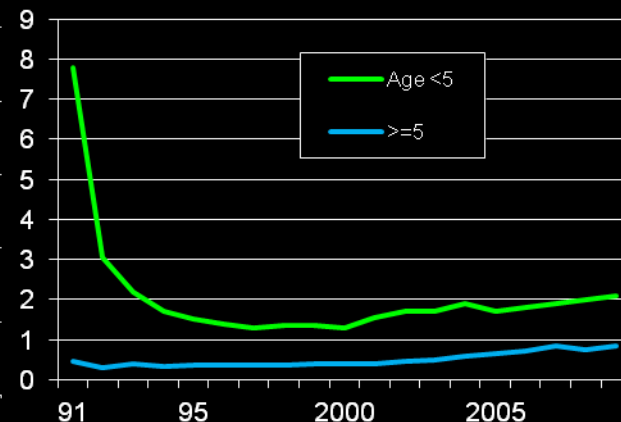
Diphtheria: 1970-2009



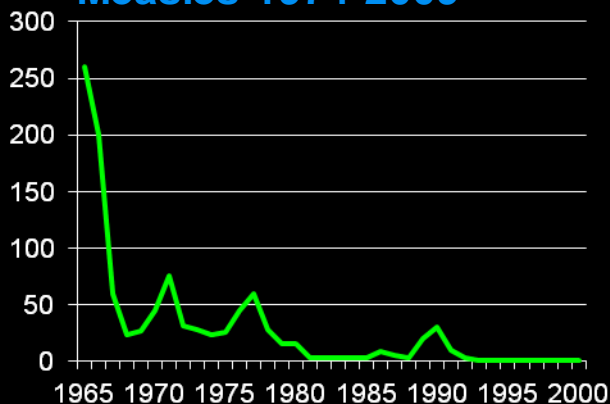
Pertussis: 1940-2009



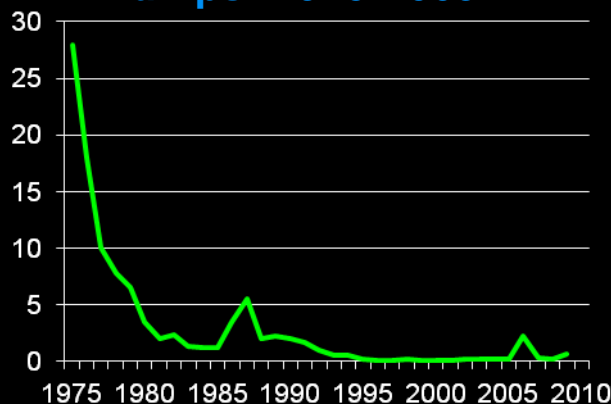
Hib: 1991-2009



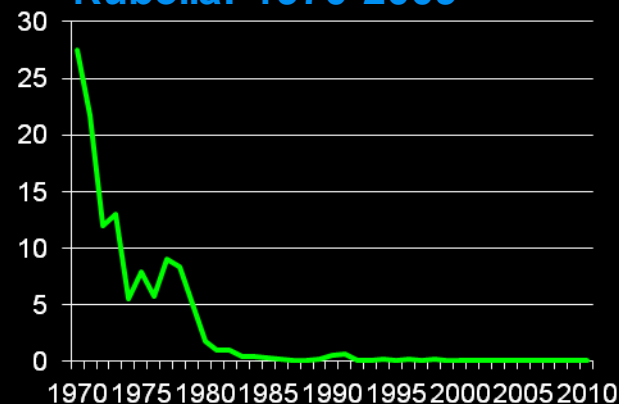
Measles 1974-2009



Mumps: 1975-2009



Rubella: 1970-2009



In



Vaccine Preventable Diseases That Were Once Common



Measles



Mumps



Congenital rubella



Diphtheria



Tetanus



Smallpox

But Vaccines do Cause Adverse Events

- Our responsibility is to make vaccination as safe as possible
- Understanding the pathogenesis of adverse events can lead to reductions in risk

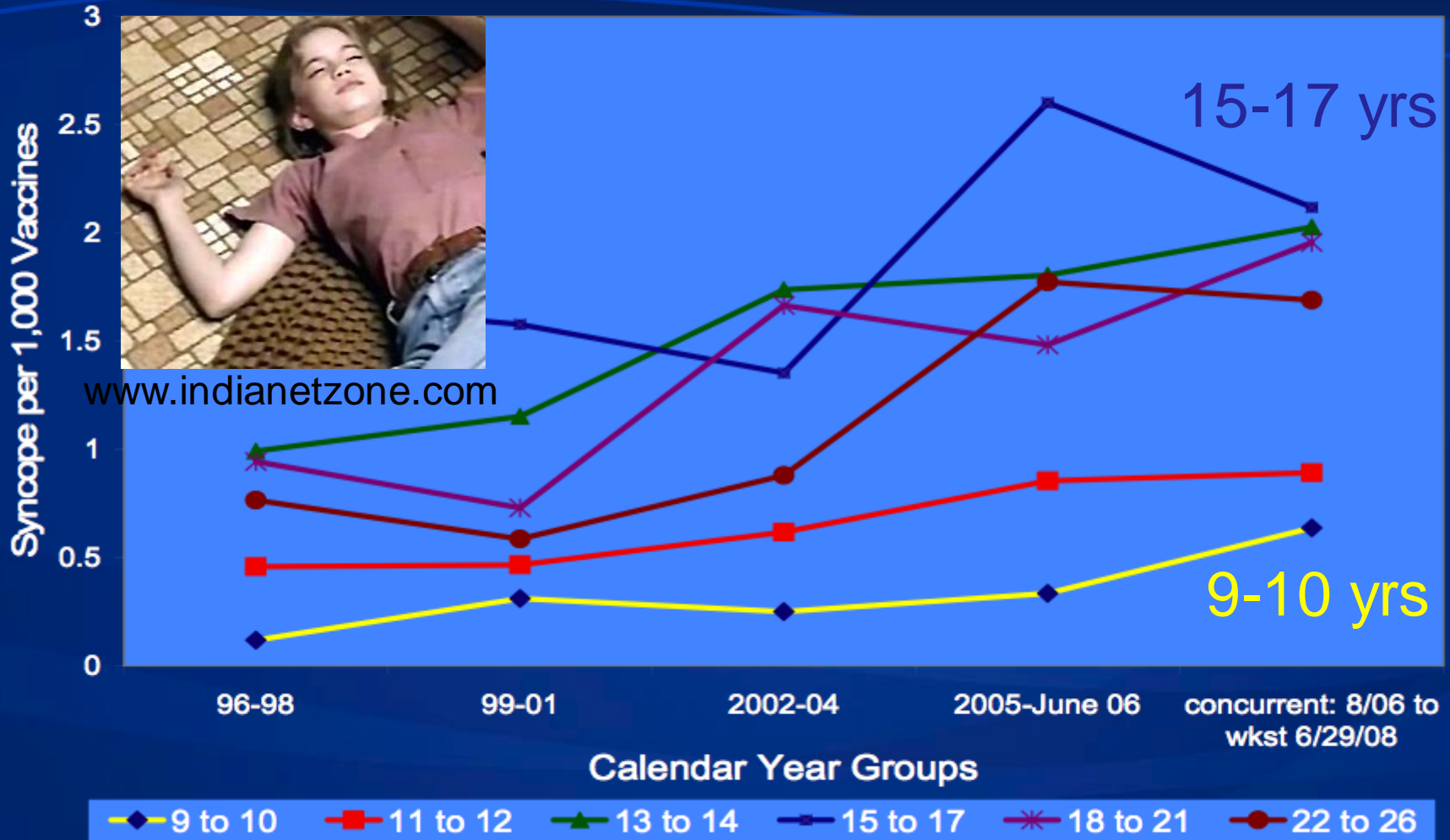


Pathogenesis of Adverse Events Caused by Vaccines

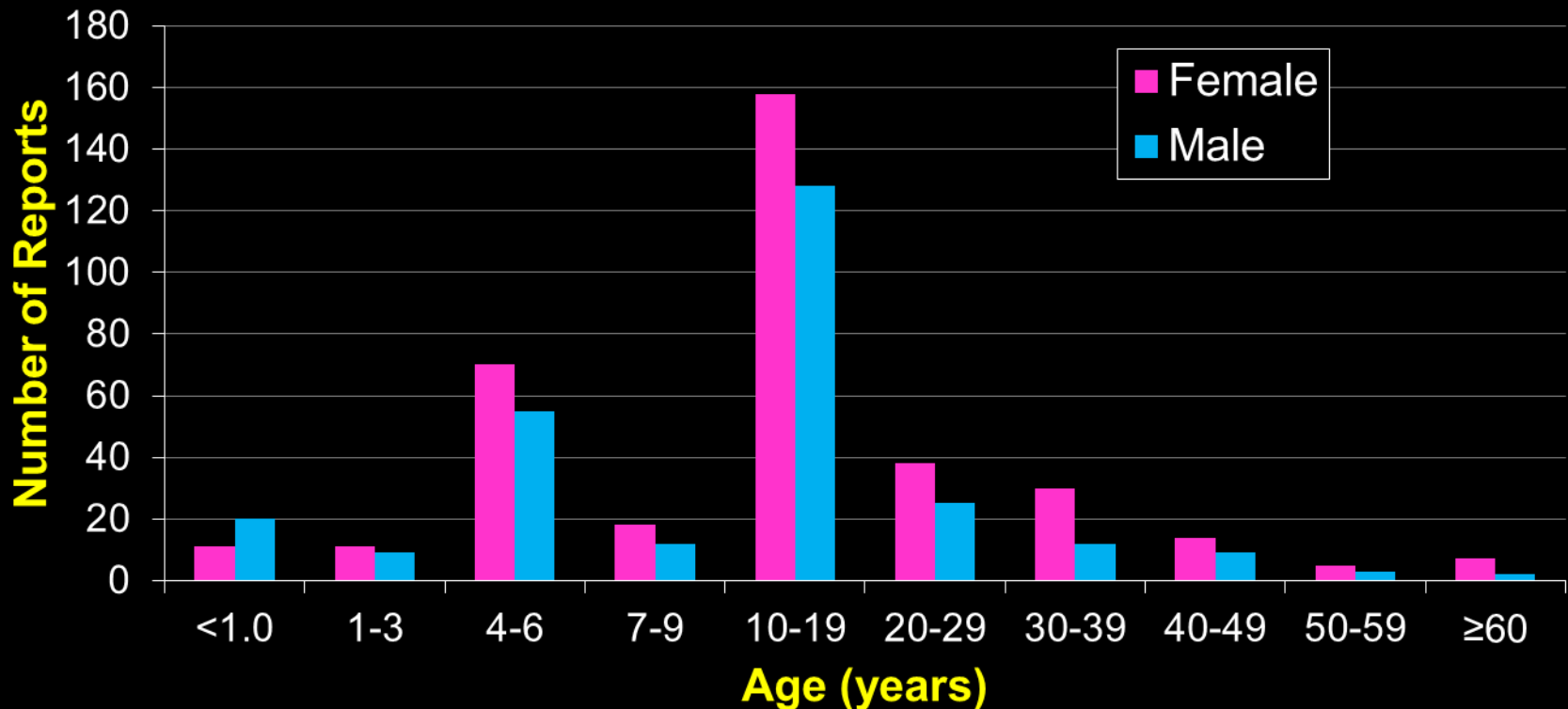
1. Injection process
2. Contamination
3. Replication of live agent
4. Direct effect of vaccine component
5. Host immune response to component
6. Unknown



Syncope per 1000 Vaccines Visits Following Td, Tdap, Menactra, and Varicella



Distribution of Syncope Cases by Age and Sex



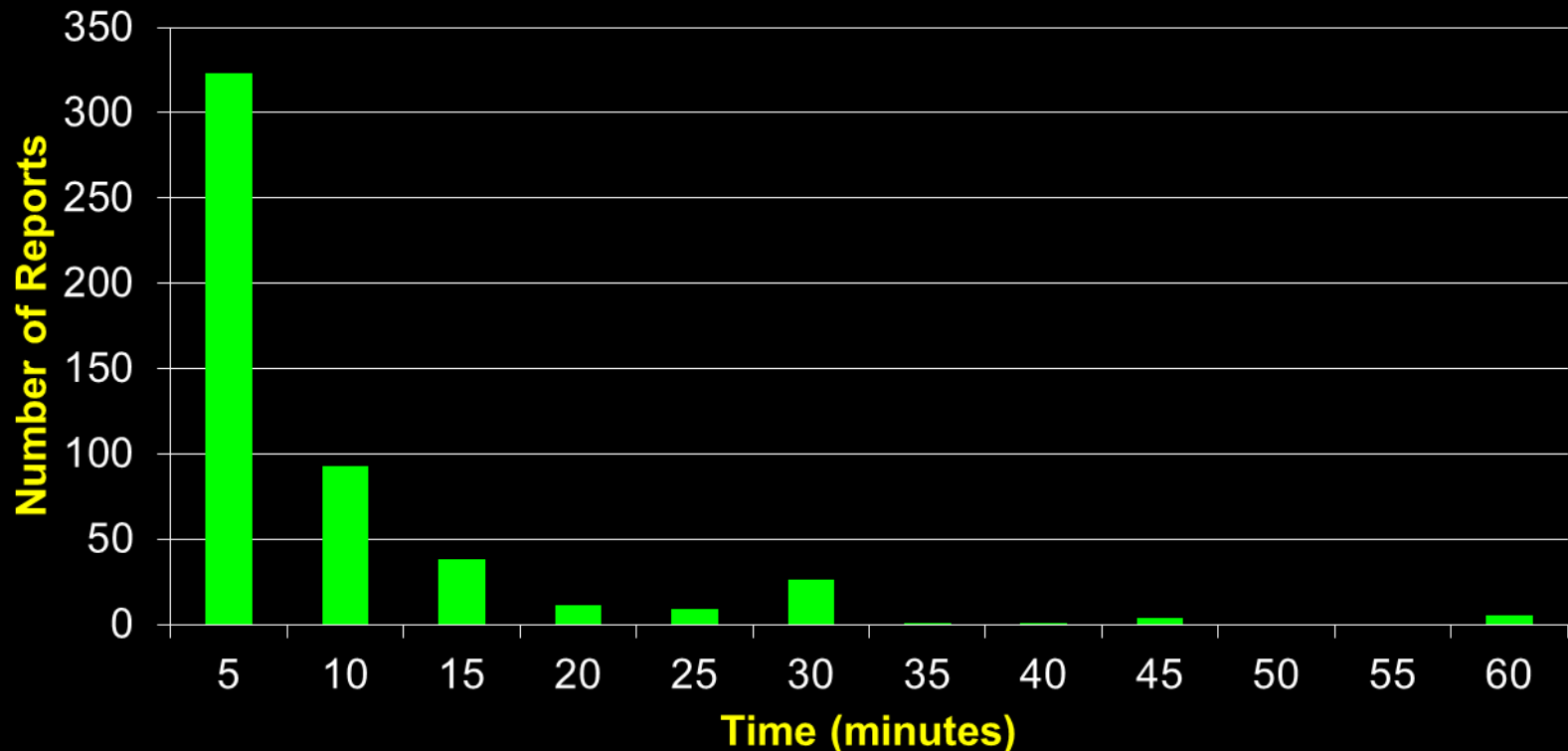
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Braun MM, et al. Arch Ped Adol Med 1997;151:255.

Time from Vaccination to Syncope for Syncope Occurring ≤ 1 Hour After Vaccination



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Braun MM, et al. Arch Ped Adol Med 1997;151:255.

Injection Related: Fainting

- Falls can lead to serious head injuries
- Neurologic sequelae, rare deaths
- Auto accidents
- Most are preventable: waiting 15 minutes



Incorrect Injection Site



**Nerve
damage
following
anthrax
Vaccine***

J. Salk

*Sever et al. *Pharmacoepidemiology and drug safety* 2002; 11: 189–202

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UNICEF Website 2007-9



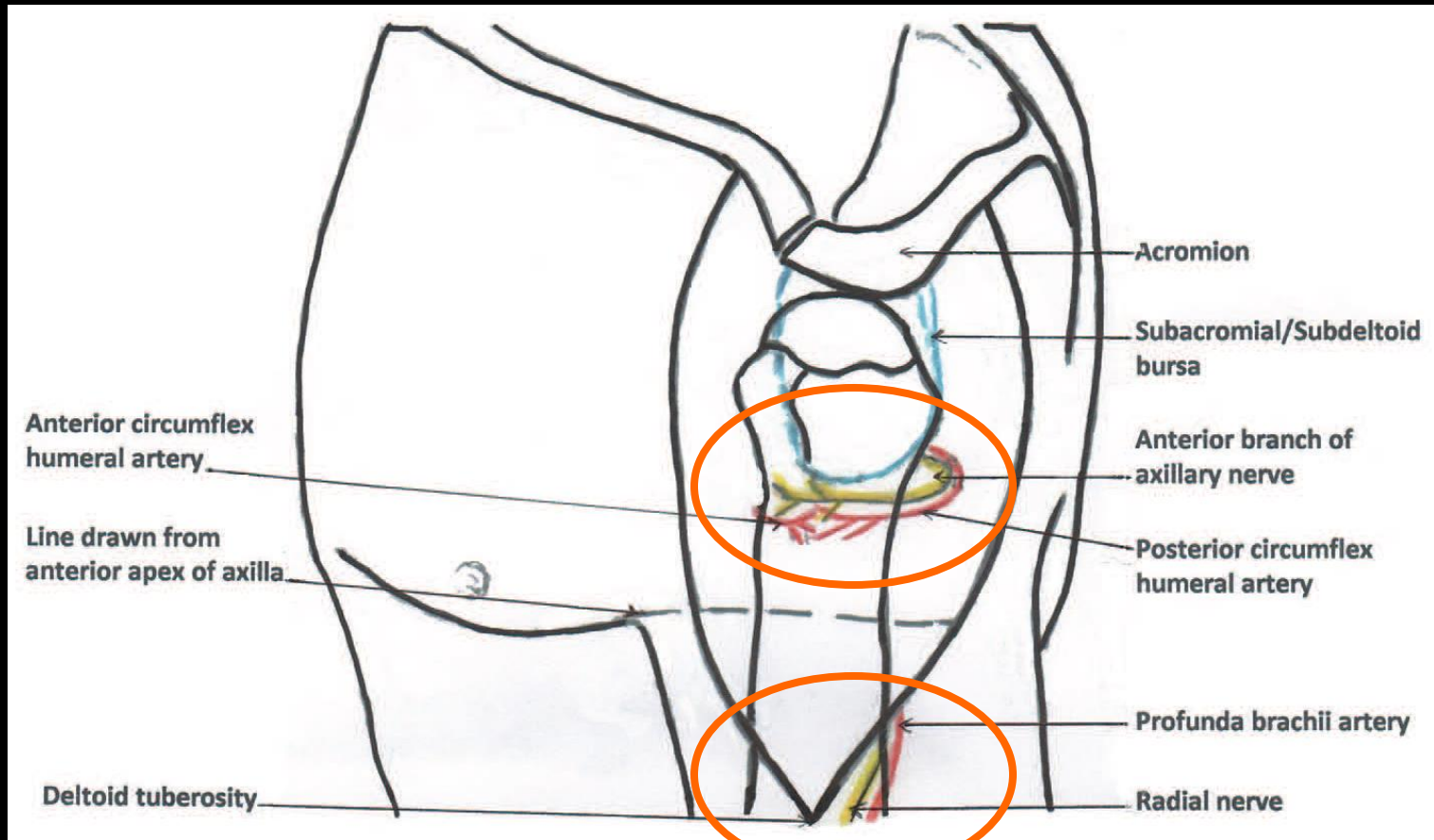
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Incorrect administration of TT –too low

Surface Landmarks And Structures Potentially Damaged By Intramuscular Injection In The Upper Limb



Shoulder injury related to vaccine administration (SIRVA)[☆]

S. Atanasoff^{a,*}, T. Ryan^a, R. Lightfoot^b, R. Johann-Liang^a

^a U.S. Department of Health and Human Services, Health Resources and Services Administration, National Vaccine Injury Compensation Program, United States

^b The Division of Rheumatology and Women's Health, University of Kentucky School of Medicine, United States

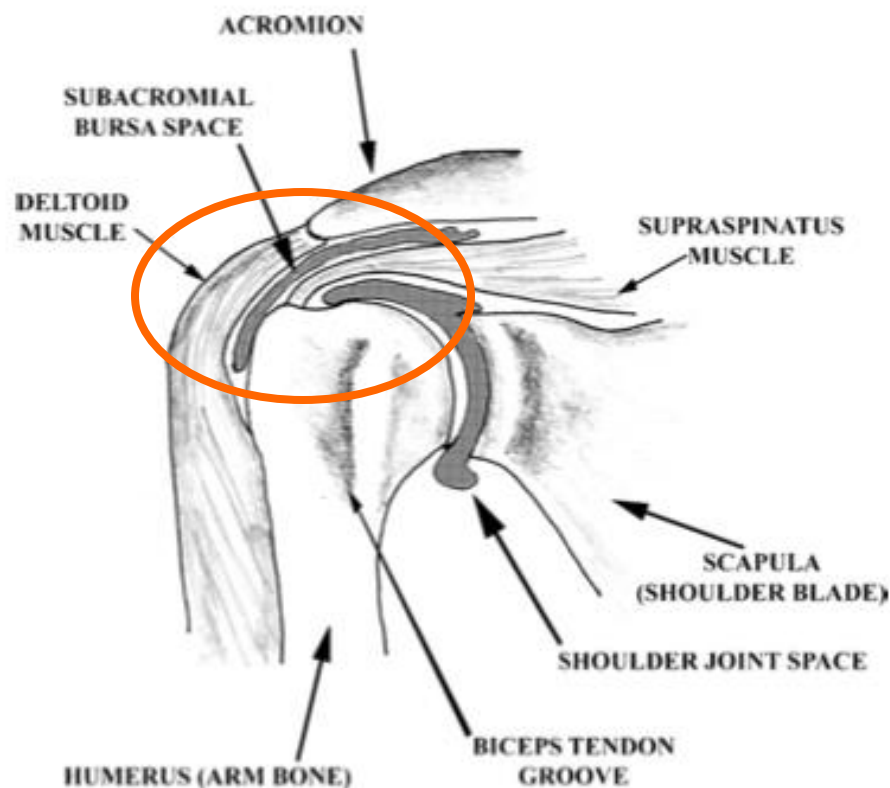


Fig. 1. Anatomy of the shoulder girdle. The relationships of the subdeltoid/subacromial bursa and shoulder joint space to the supraspinatus tendon and to the greater tuberosity on which it inserts.

13 patients:
persistent pain,
tendonitis

Safest Deltoid Muscle Injection

1. Hand on hip
 - Abduct 60°
 - Moves axillary nerve
2. Index finger on acromian process
3. Thumb on tuberosity
4. Inject at mid point



Appropriate IM Injection Sites

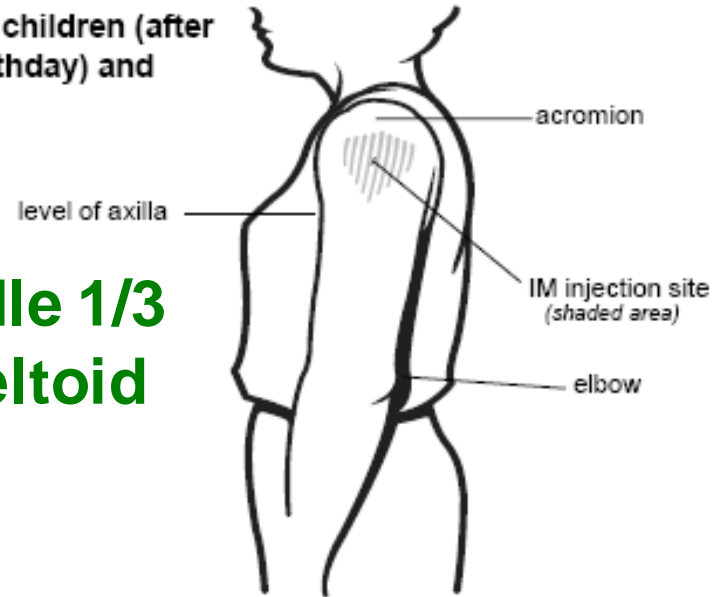


IM site for infants

IM injection site area
(shaded area)

Insert needle at a 90° angle into the anterolateral thigh muscle.

IM site for children (after the 1st birthday) and adults



**Middle 1/3
of deltoid**

Insert needle at a 90° angle into thickest portion of deltoid muscle— above the level of the axilla and below the acromion.

Adapted by the Immunization Action Coalition, courtesy of the Minnesota Department of Health

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2010 Edition!
Immunization
Techniques DVD
Award-winning training
video

www.immunize.org

Respiratory Arrest and Deaths Following Measles and BCG Vaccines

- Mexico, Kenya, Lesotho, other
- Paralyzing agents: Succinyl choline, Pavalon, or pancuronium bromide mistaken as vaccine diluent
- Diluent and drug vials identical size, color, and print type.
 - Stored together



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Weekly Epi Record 1996;71(32):239.

Bacterial Contamination of Measles Vaccines

Country	Year	Time to Onset	Outcome	Organism
Zaire	1994	'a few hours'	3 of 4 died	no information
Azerbaijan	1995	4-5 hours	4 of 5 died	S. aureus
India	1995	5 hours	All 3 died	'contaminated',
Kazakhstan	1995	4-7 hours	3 of 7 died	S. aureus



**Reuse of same syringe for
Reconstitution.
Storage > 6 hours.**

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Weekly Epi Record 1996;71(32):239.

Bacterial Contamination of Multi-dose vials Associated with Severe Disease

- Measles
- Yellow fever
- BCG
- DTP

Contamination by health care worker after opening the vial



Injection Related Serious Adverse Events

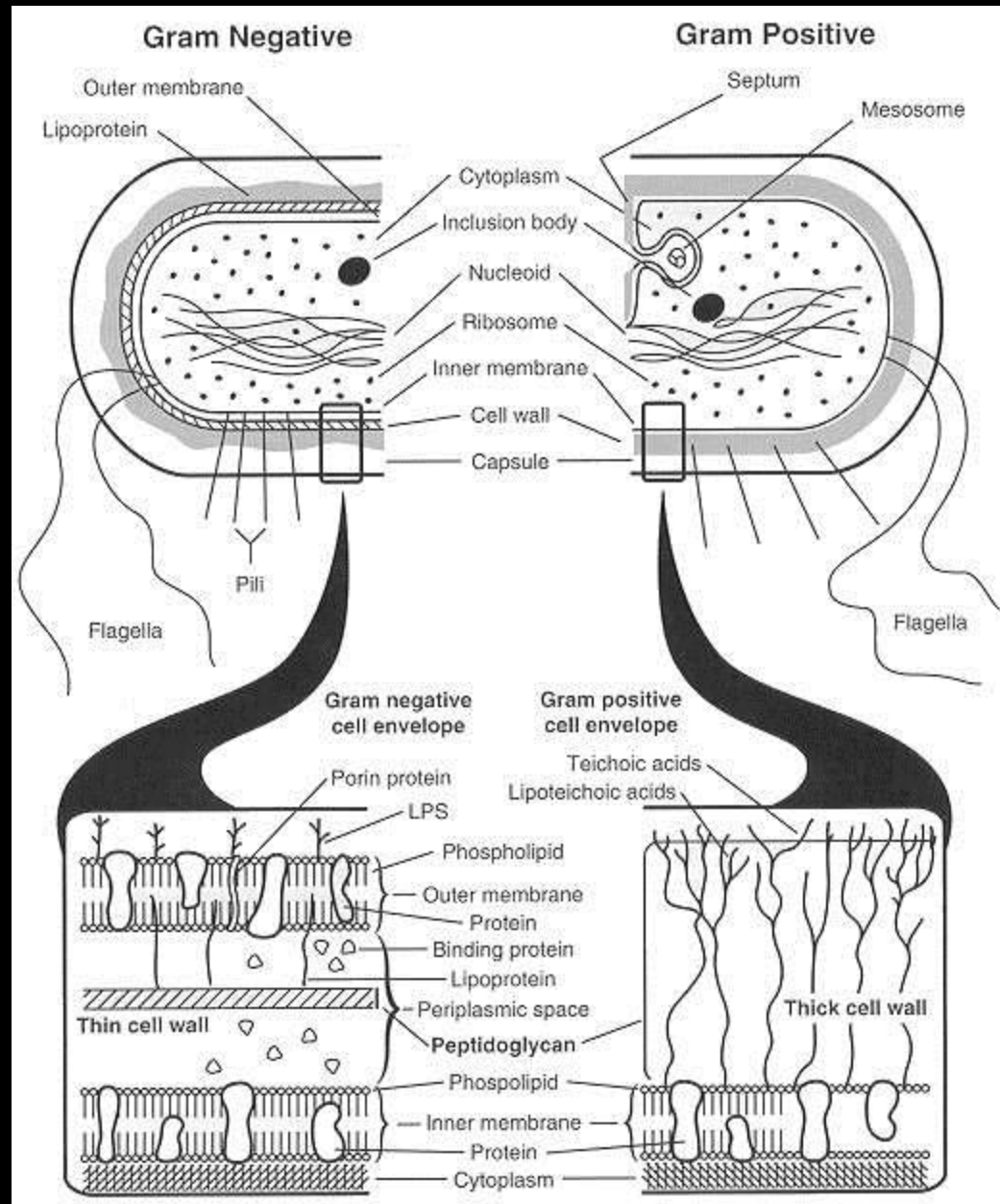
1. Fainting-head injury
2. Injury to tissue: e.g. Nerve, joint
3. Inappropriate diluents
4. Contamination of multi-dose vials
5. Bleeding
6. Transmission of blood-borne pathogens
 - Inappropriate reuse of needles and syringes
7. Provocation polio: incubating WT polio
 - Increased risk of paralysis in injected limb

Vaccine Factors Affecting the Risk of Adverse Events

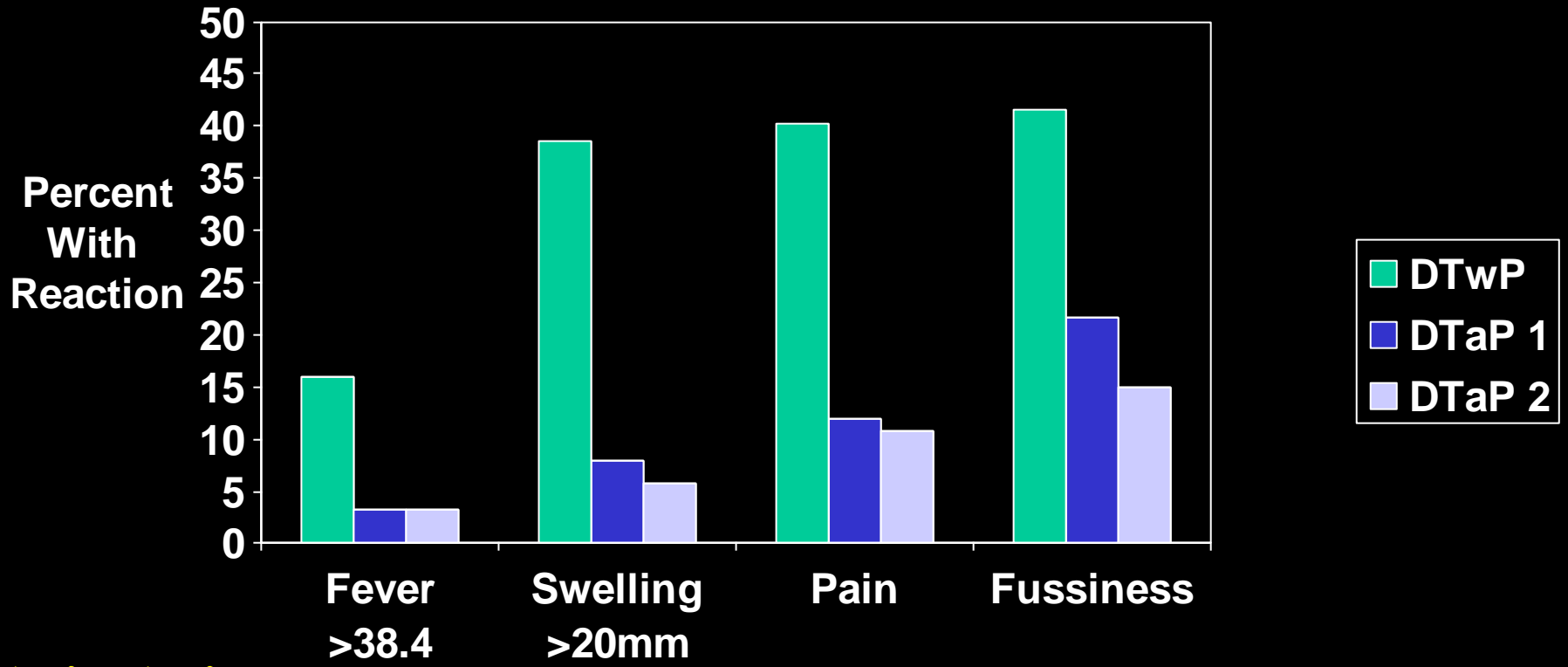
1. Type: live, killed, subcomponent
2. Strain
3. Attenuation
4. Dose
5. Adjuvants
6. Preservatives
7. Stabilizers
8. Purity
9. Route administered
10. Other vaccines simultaneously



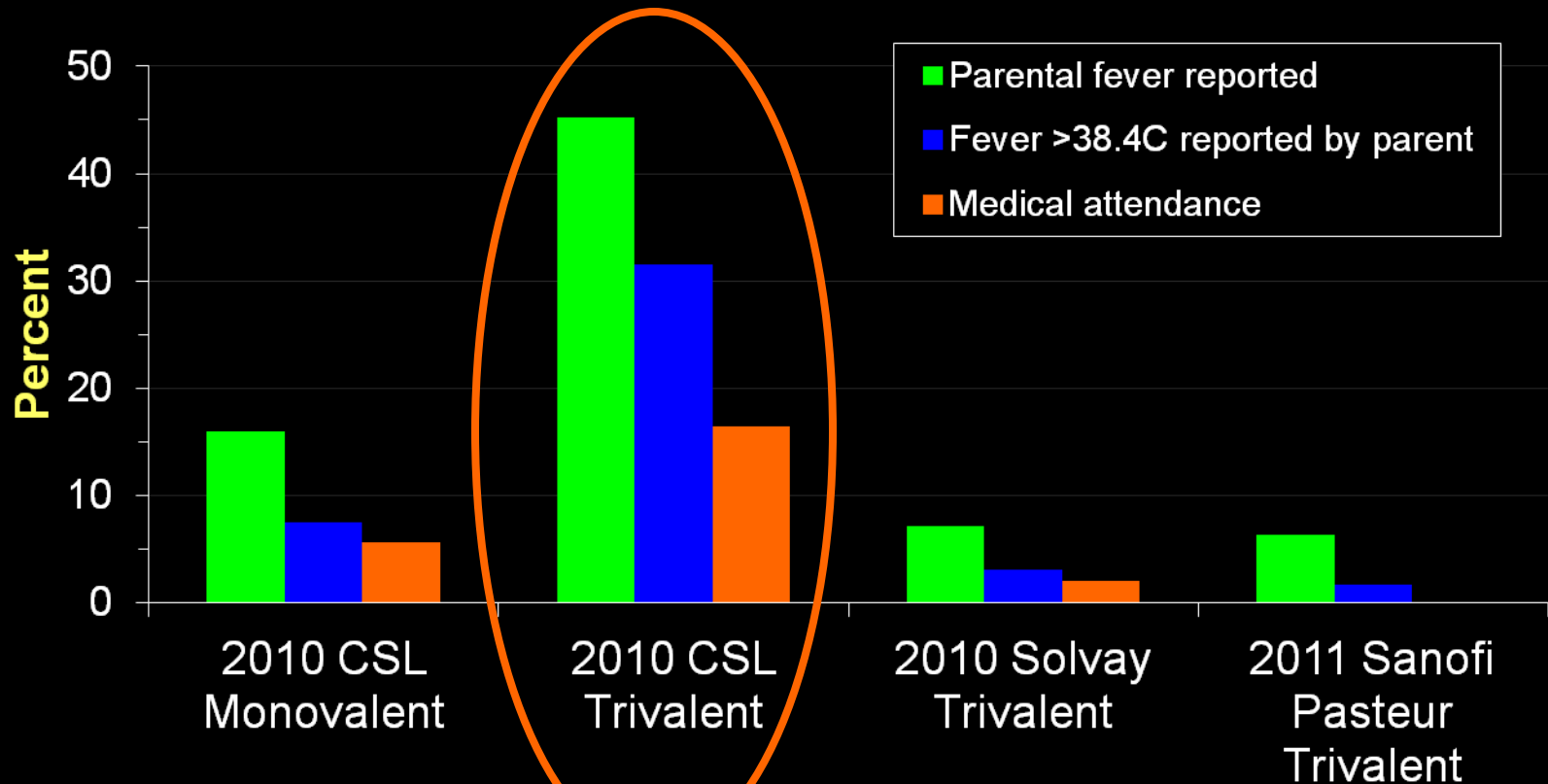
Bacterial Structure



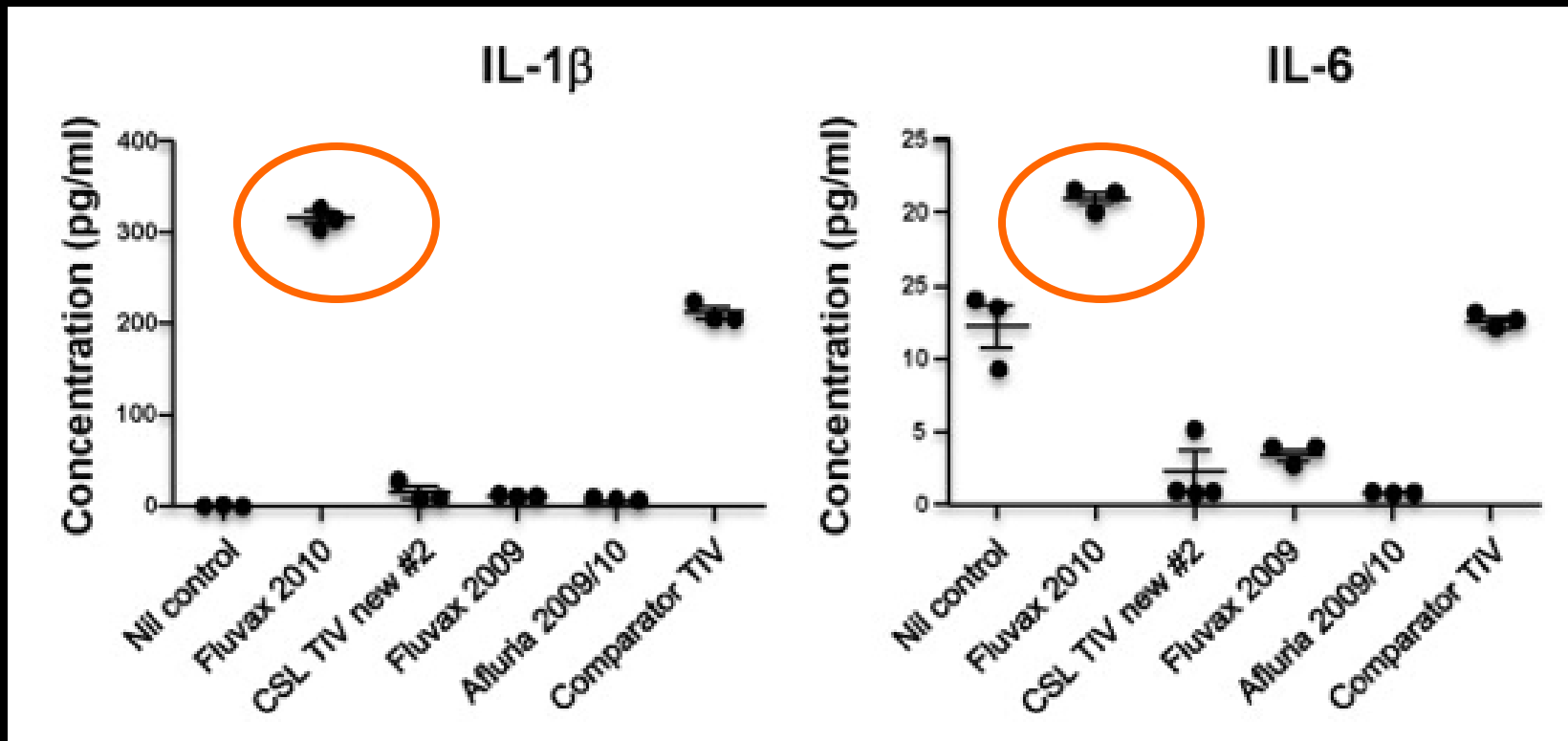
Adverse Events Following Whole Cell and Acellular Pertussis Vaccines Days 0-3 (DTwP vs DTaP)



Parental Report of Fever in Children <5yrs by Influenza Vaccine Type 2010 and 2011



CSL 2010 Vaccine Induced Higher Pro-inflammatory Cytokine Levels



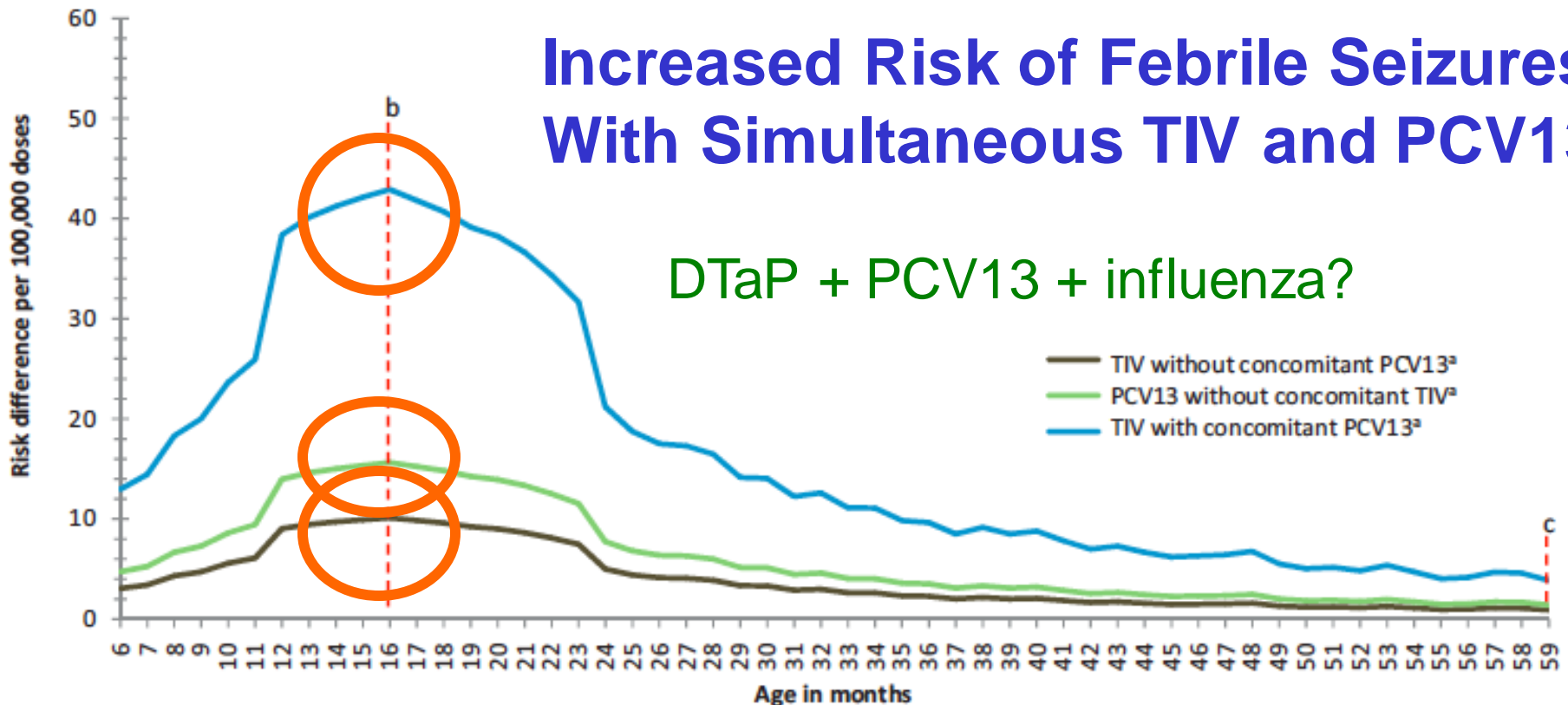
Higher Rates of Fever and Seizures with CSL vaccine

- Inadequate splitting
- Inactivation method
- Heat labile viral component
- Viral strain differences

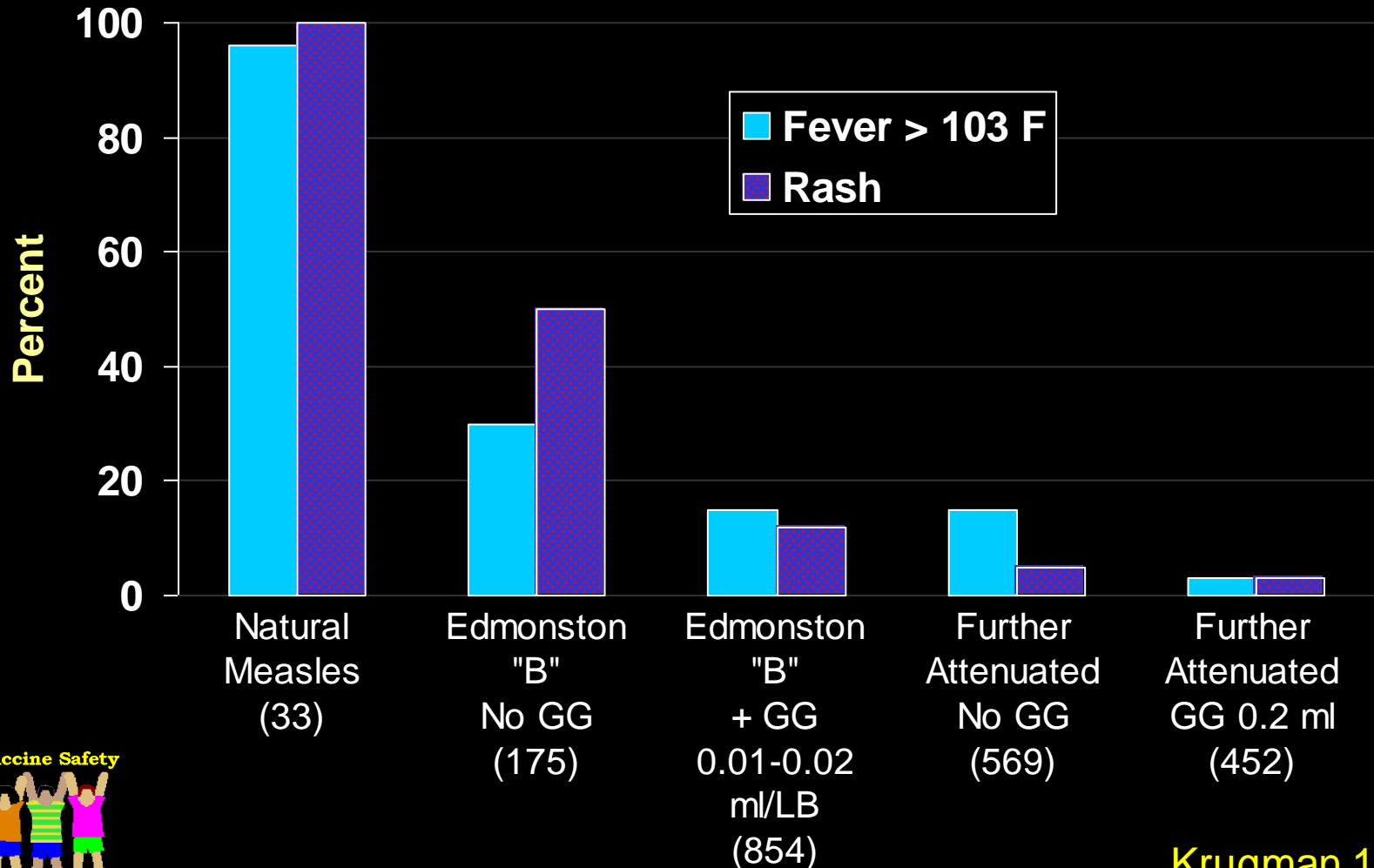


Risk of febrile seizures on days 0-1 vs 14-15 after TIV alone, PCV13 alone and simultaneous TIV and PCV13

A. Tse et al. / Vaccine 30 (2012) 2024-2031



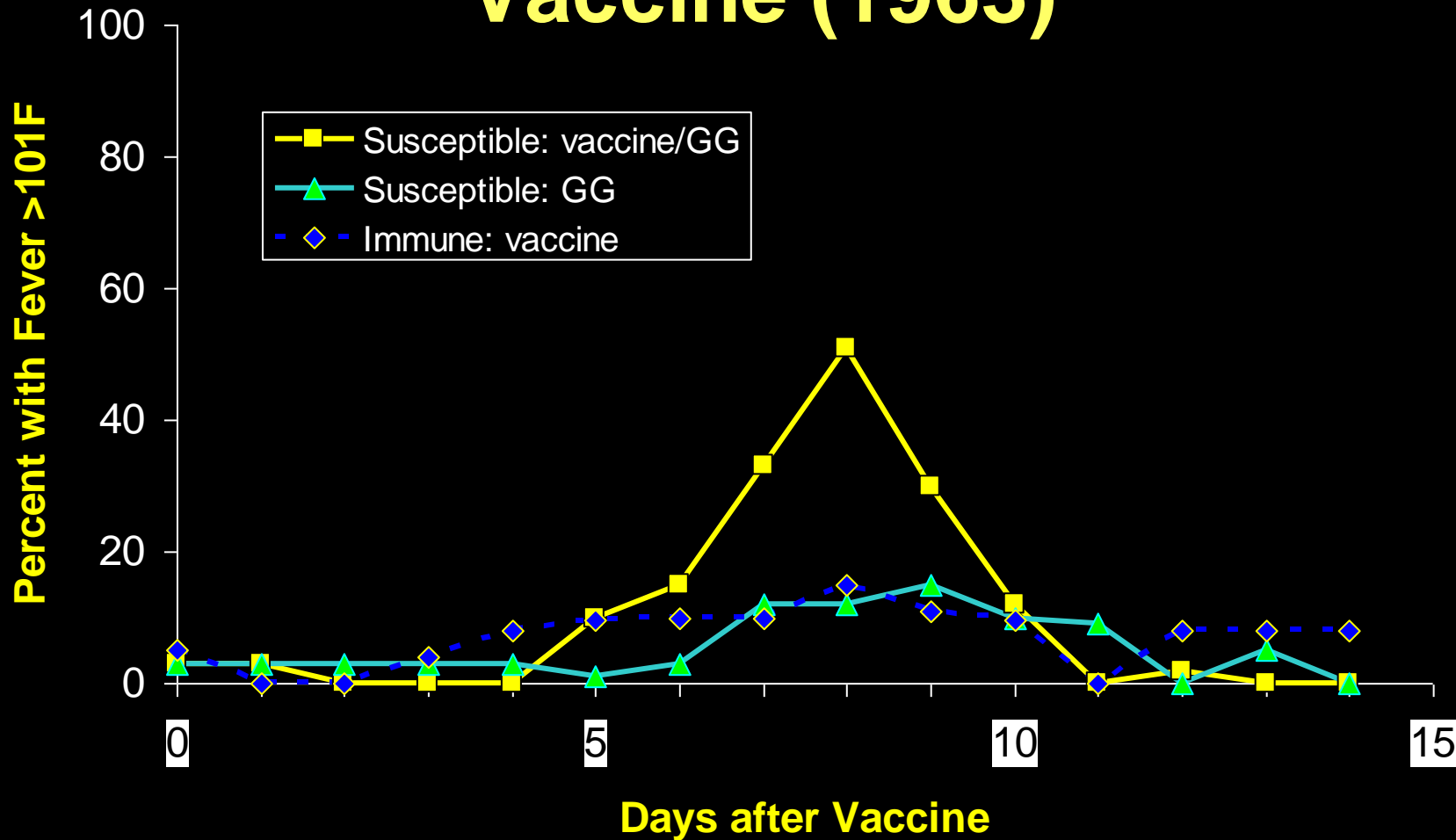
Fever and Rash Following Measles Vaccination With and Without Immune Globulin (GG)



Krugman 1965



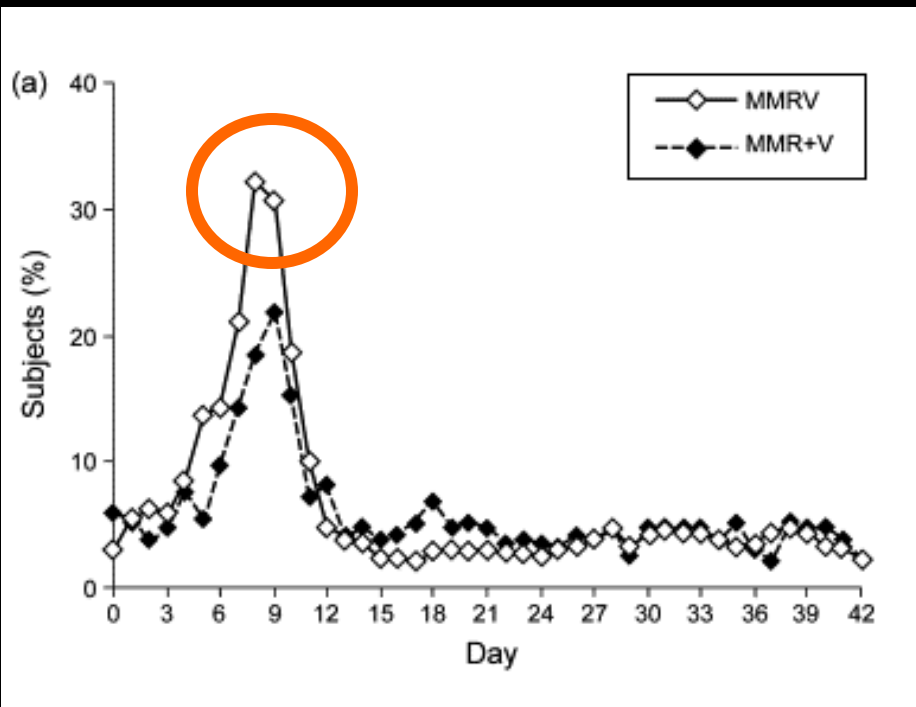
Percent of Children with Fever Following Edmonston B Measles Vaccine (1963)



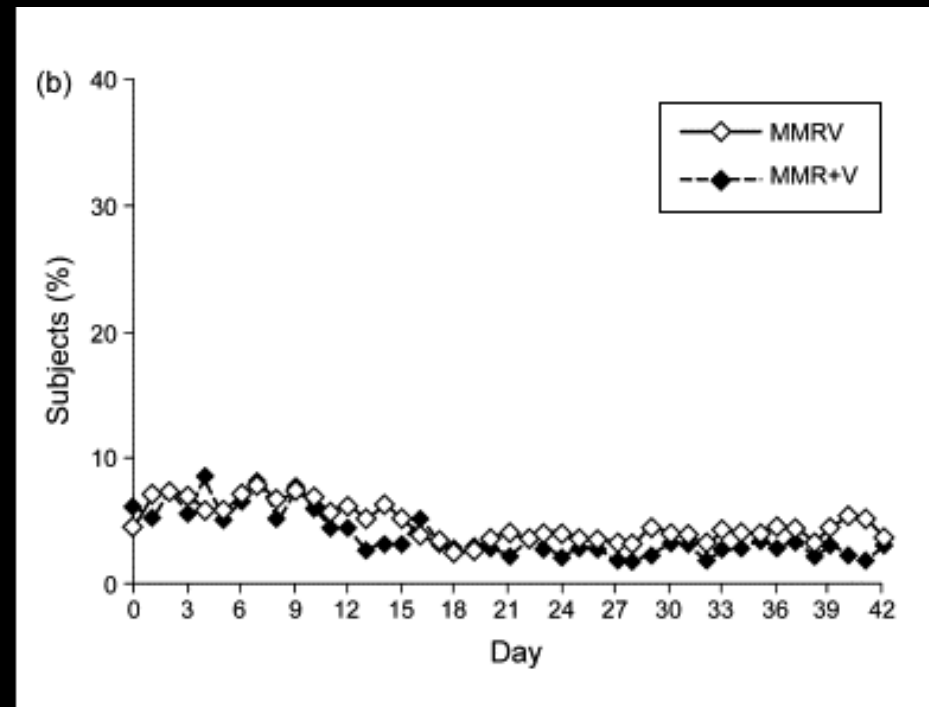
Adapted from Martin CM. Am J of Dis of Children 1963;106:270.

Prevalence of Fever After First Dose and Second Dose of MMRV

Fever after First Dose



Fever after Second Dose



Transient Arthritis/Arthralgia Associated With Rubella Vaccines in Women by Strain

Vaccine Strain

Joint Symptoms

~~HPV-77 Dog kidney~~

35-63%

~~HPV 77 duck embryo~~

27-33%

~~Condehill~~

8-10%

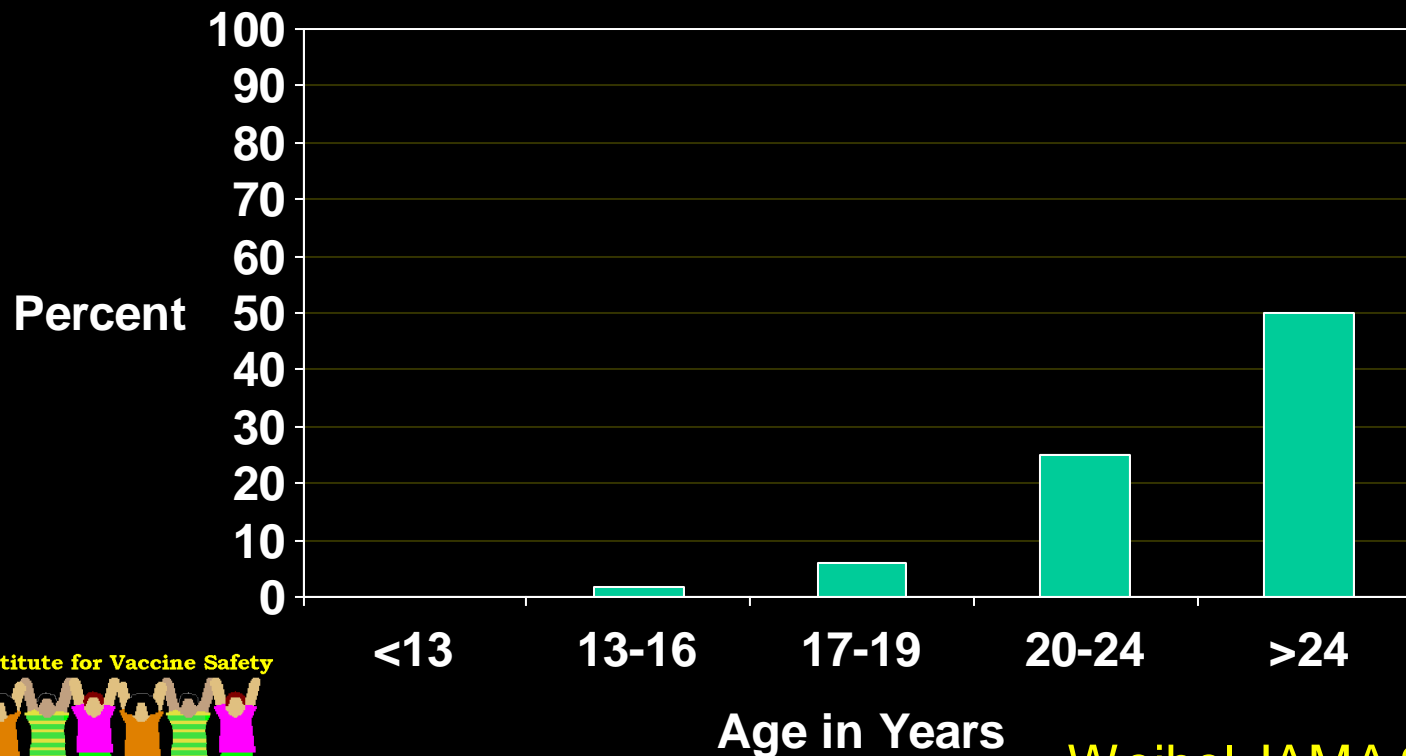
RA 27/3

13-15%



Host Factors

Joint Symptoms Associated With HPV-77 Rubella Vaccine in Females by Age



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Weibel JAMA 202:805;1972
Swartz Am J Epidem 94:246;1971

Arthritis Associated With RA 27/3 Rubella Vaccines by Gender

<u>Age(yrs)</u>	<u>Males</u>	<u>Females</u>
18-30	5%	20-25%

Arthralgia: females > males:

Anthrax

Lyme disease

Yellow fever vaccines



Pathogenesis of Joint Symptoms Following Rubella Vaccines

- HPV-77 vaccine virus in joint fluid
 - RA 27/3?
- Arthralgia pathogenesis?
 - Cytokine mediated?
 - Also with inactivated vaccines



Host Related Factors Associated With Adverse Events

- Age
- Gender
- Prior doses of vaccine
- Prior infection with agent
- Skin color
- Preexisting hypersensitivity
- Immune deficiency
- Genetics



Immediate Hypersensitivity Reactions

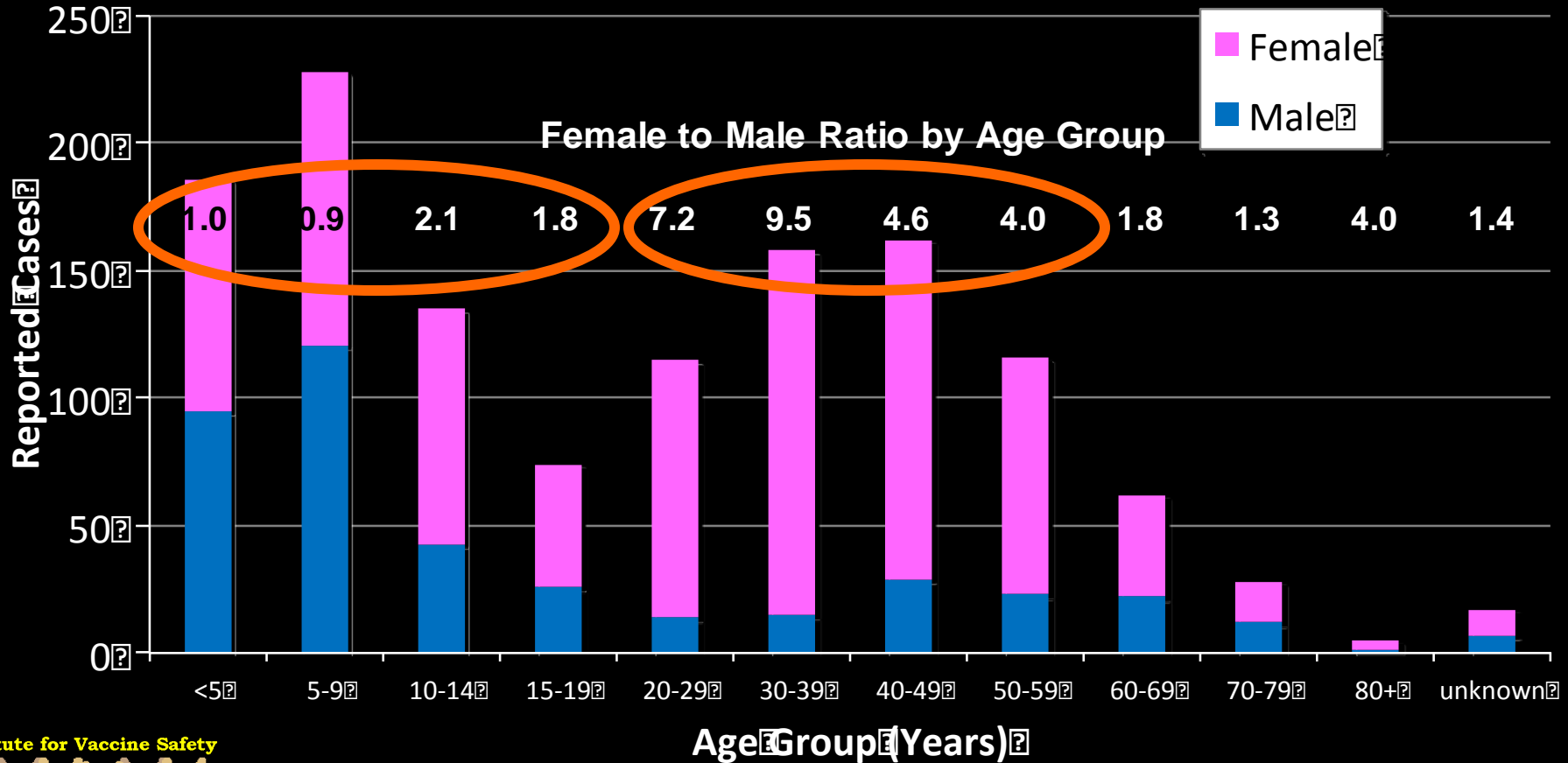


- Hives, angioedema, anaphylaxis
- IgE mediated
- Allergens in vaccines:
 - Media (e.g. egg in influenza or YF)
 - Gelatin
 - Antibiotics (neomycin, polymixin)
 - Yeast (hepatitis B, HPV)
 - Preservatives (thimerosal)

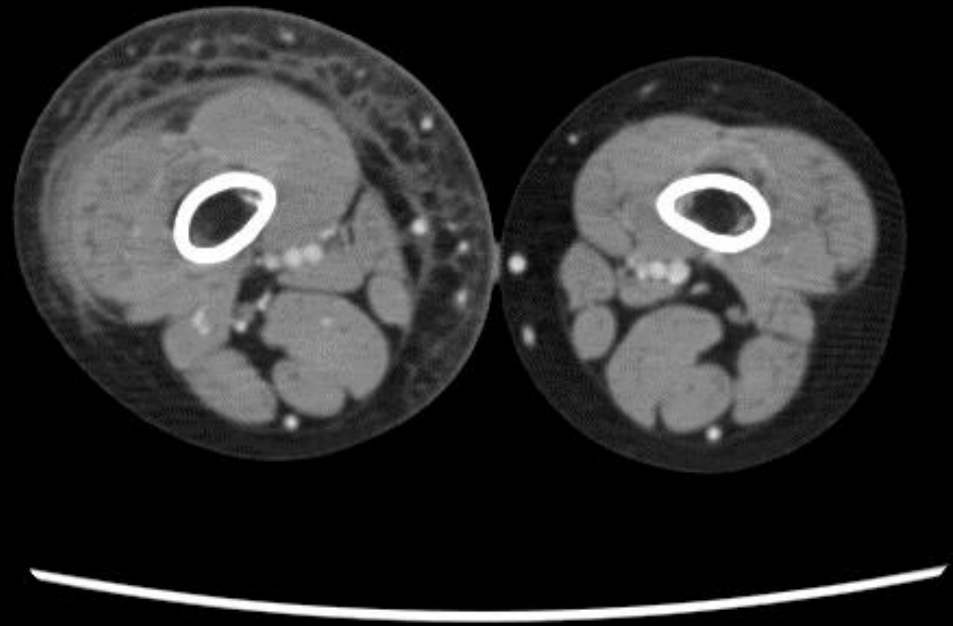
Why doesn't everyone develop these reactions?

www.vaccinesafety.edu/components-Allergens

1,286 Hypersensitivity VAERS Reports Following 2009 H1N1 Immunization by Age and Gender



Limb Swelling 3 Days After 4th Dose of DTaP Delayed Hypersensitivity Reaction?



High TH2 responders and high IgE to TT

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Sekaran NK, Edwards KM. *Pediatr Infect Dis J.* 2006 Apr;25(4):374-5.

Rowe J *Infect Immun.* 2005 Dec;73(12):8130-5

Large Local Reaction Following Second Dose of Influenza Vaccine: 8 yr old



Host and Vaccine Factors

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Delayed Hypersensitivity: Erythema Multiforme after Smallpox Vaccine



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Vincent A. Fulginiti, M.D.

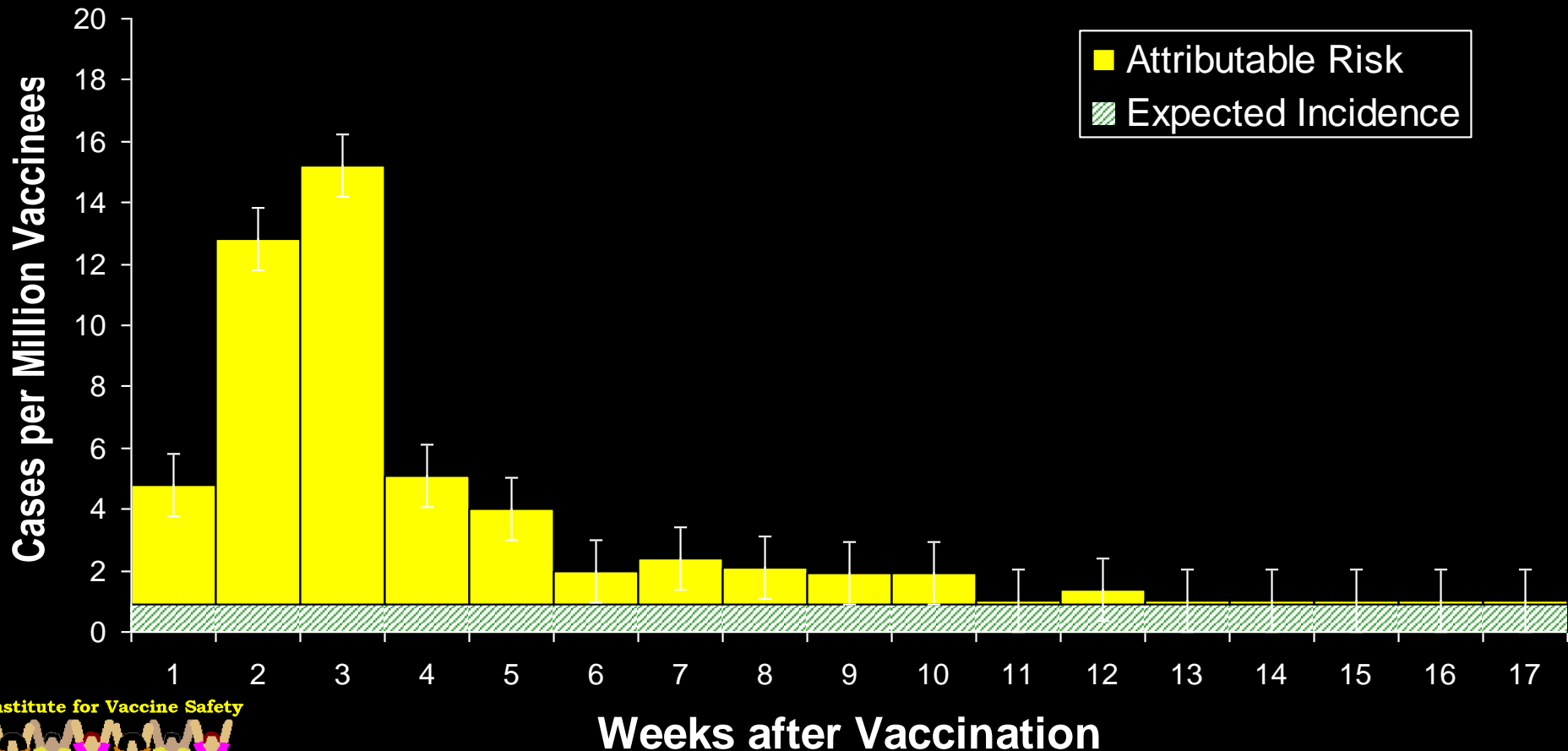
Do Vaccines Cause Autoimmune Diseases?

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Guillain-Barre syndrome relative risks for population over 17 years by week of onset after A/New Jersey influenza vaccination, US 10/3/76 - 1/29/77*



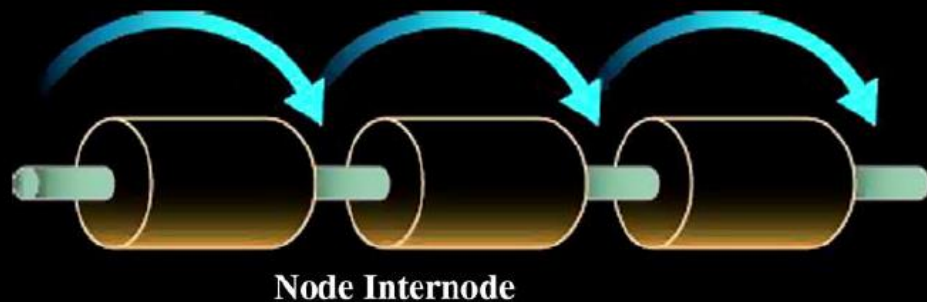
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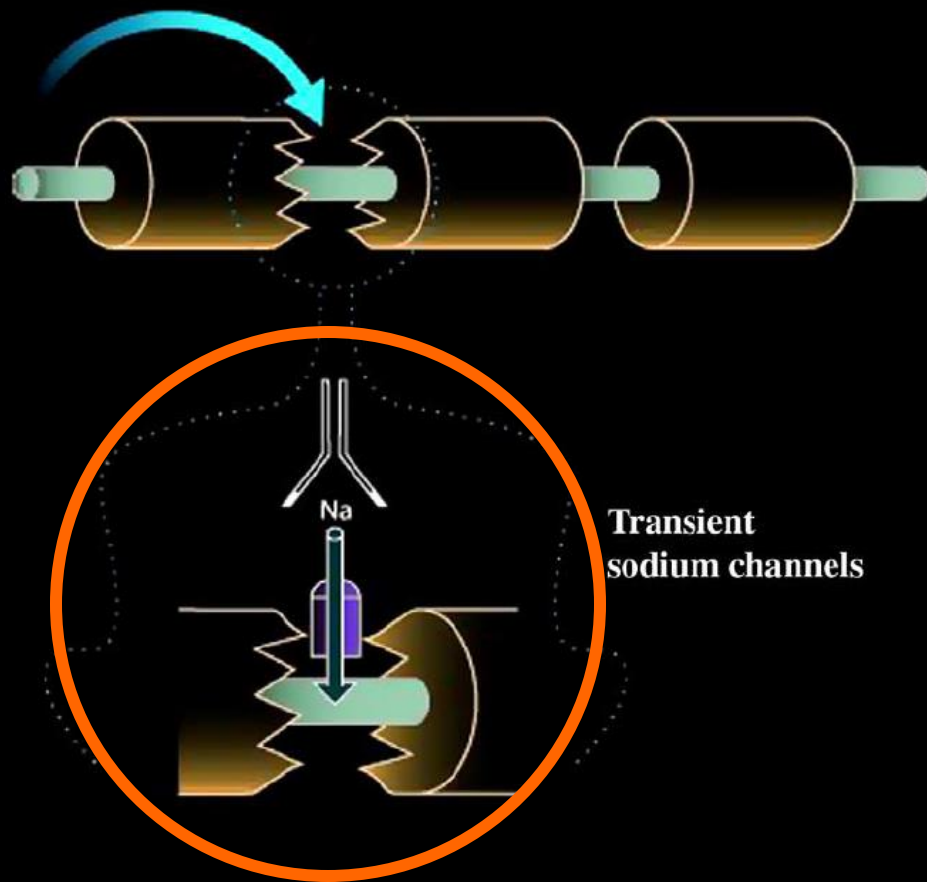
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- excluding AR, CT, DE, WA. Data for CA, FL, GA, MO, NC, NJ, NY
- and TX included for 10/3-12/18/76 only.

Action potentials propagated along the nerve fibre.



GBS: Demyelinating:
Axonal: antibodies
terminate action potential
propagation.



Attributable Risk of GBS following influenza vaccine in the U.S.

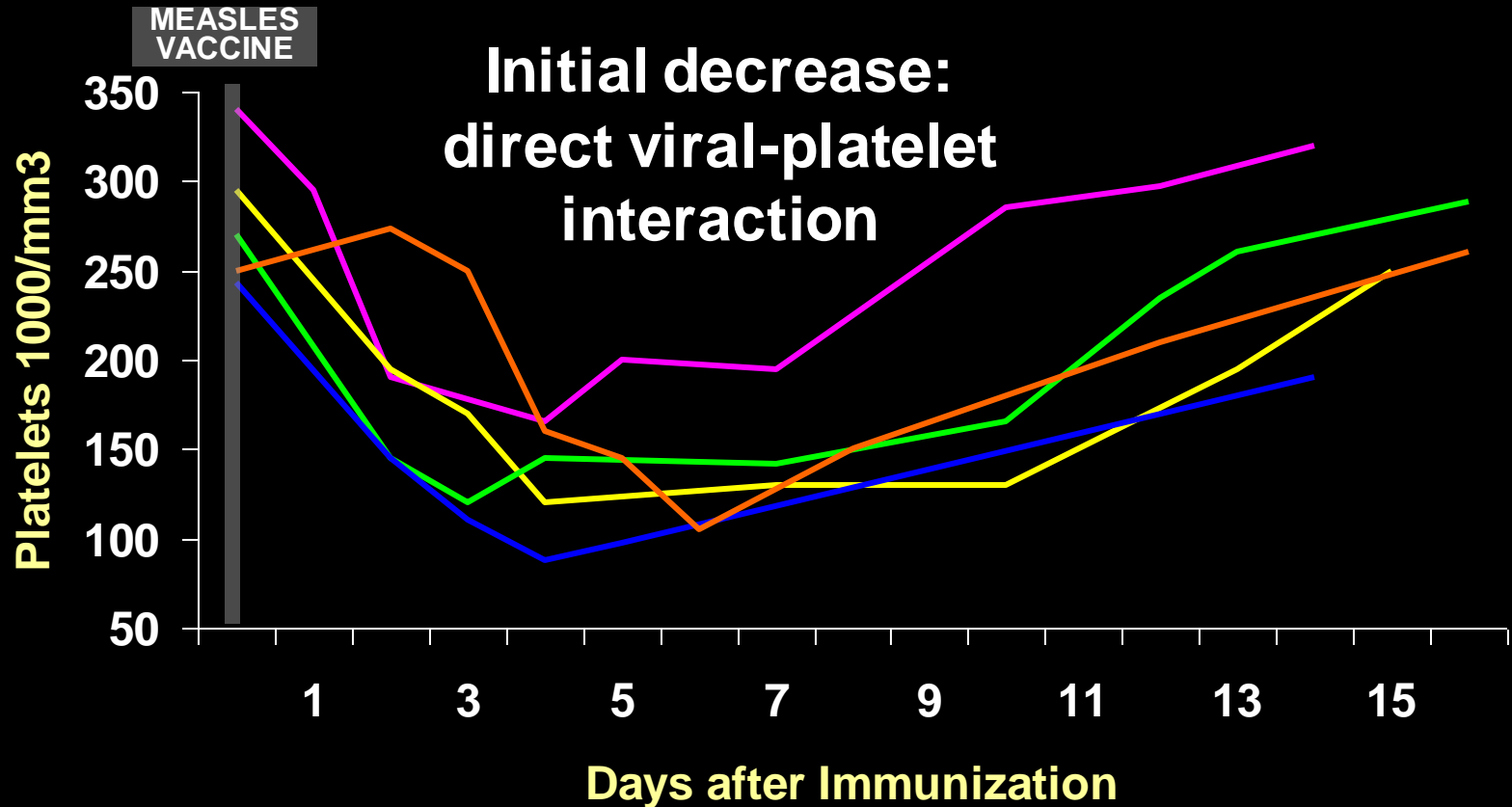
- 1976-1977 10 per million
- 1978-1991 0
- 1992-1994 ~1 per million
- 1995-2008 ?
- 2009-10 (H1N1) 1.6 per million

Salmon et al. Lancet 2013;381:1461

Yih AJE 2012; Wise AJE 2012

Greene AJE 2012; Haber Drug Saf 2009;32:309

Course of the Platelet Count after Measles Immunization in 5 Infants



Oski and Naiman. NEJM 1966;275(7):352.

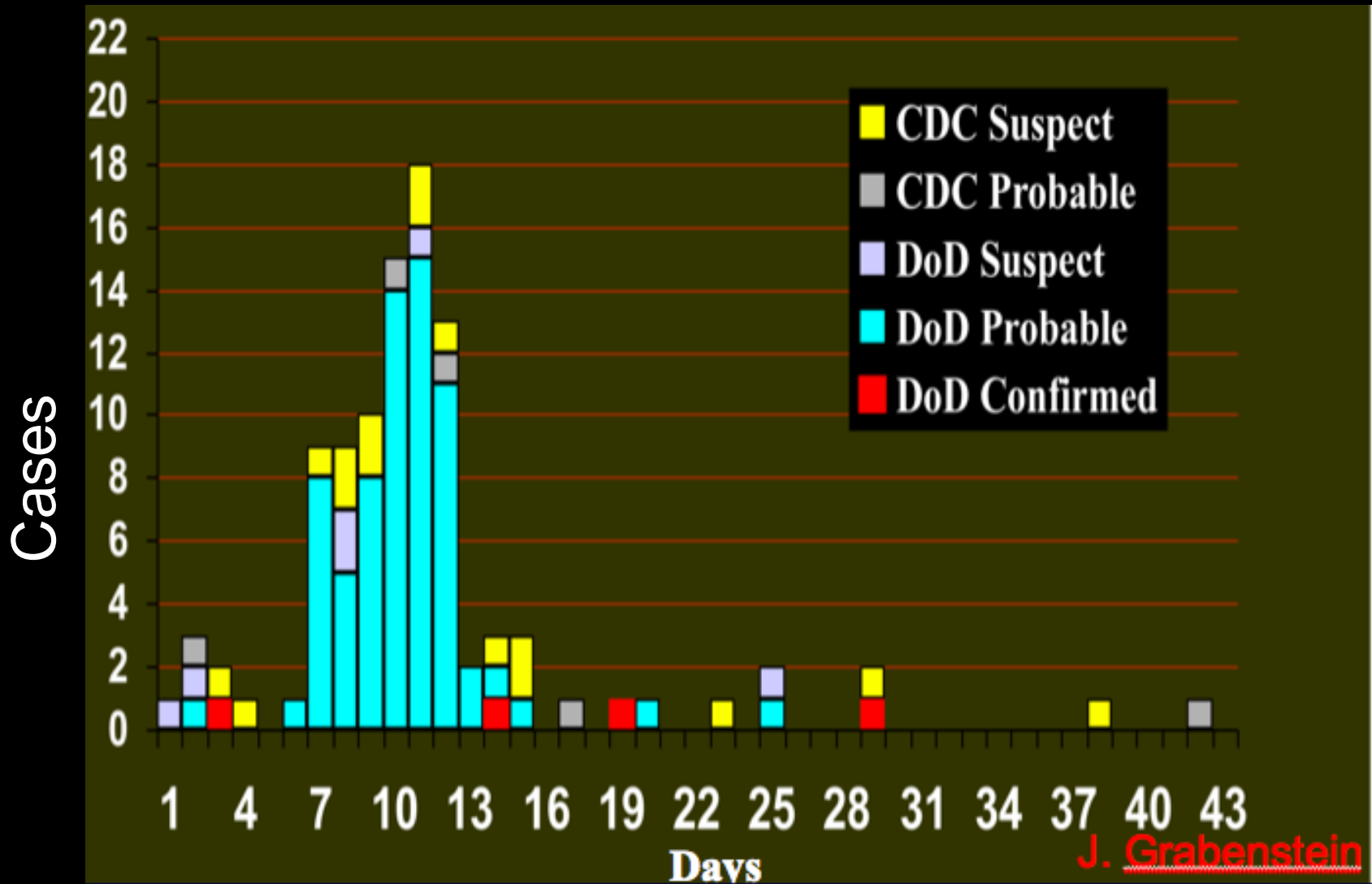
Clinical thrombocytopenia (ITP) ~1/30,000

Black C et al. Br J Clin Pharmacol. 2003;55(1):107-11.

Miller E et al. Arch Dis Child 2001 ;84(3):227-9.



Myo-pericarditis among Smallpox Vaccine Recipients (667,980) by day of onset Dec 2002 – Jun 2004



J. Grabenstein



Enhancement of the Target Disease

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Inactivated Respiratory Syncytial Virus Vaccine: 1960's

- Formalin inactivated
- Administered to infants
- Minimal reactions
- Induced neutralizing antibody



Enhanced RSV Disease 9-10 Months Following Inactivated RSV Vaccine

RSV Vaccine

No Vaccine

Pneumonia

9/13 (69%)

4/47(9%)

p< .001

RSV Vaccine

Paraflu Vac.

Hospitalization

80%

5%

p< .001

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**Kapikian AZ. Amer. J. Epid., 1969, 89:405-21
Kim HW et al 1969**

Formalin Inactivated (Killed) Measles Vaccine

- Licensed 1963
- Administered in 3 doses
- Induced HI antibody responses (protective)
- Protected against measles for up to 2 yrs



Atypical Measles in Child Who Received Killed Measles Vaccine 12 Years Earlier



Increased Rates of Pneumonia in Atypical Measles

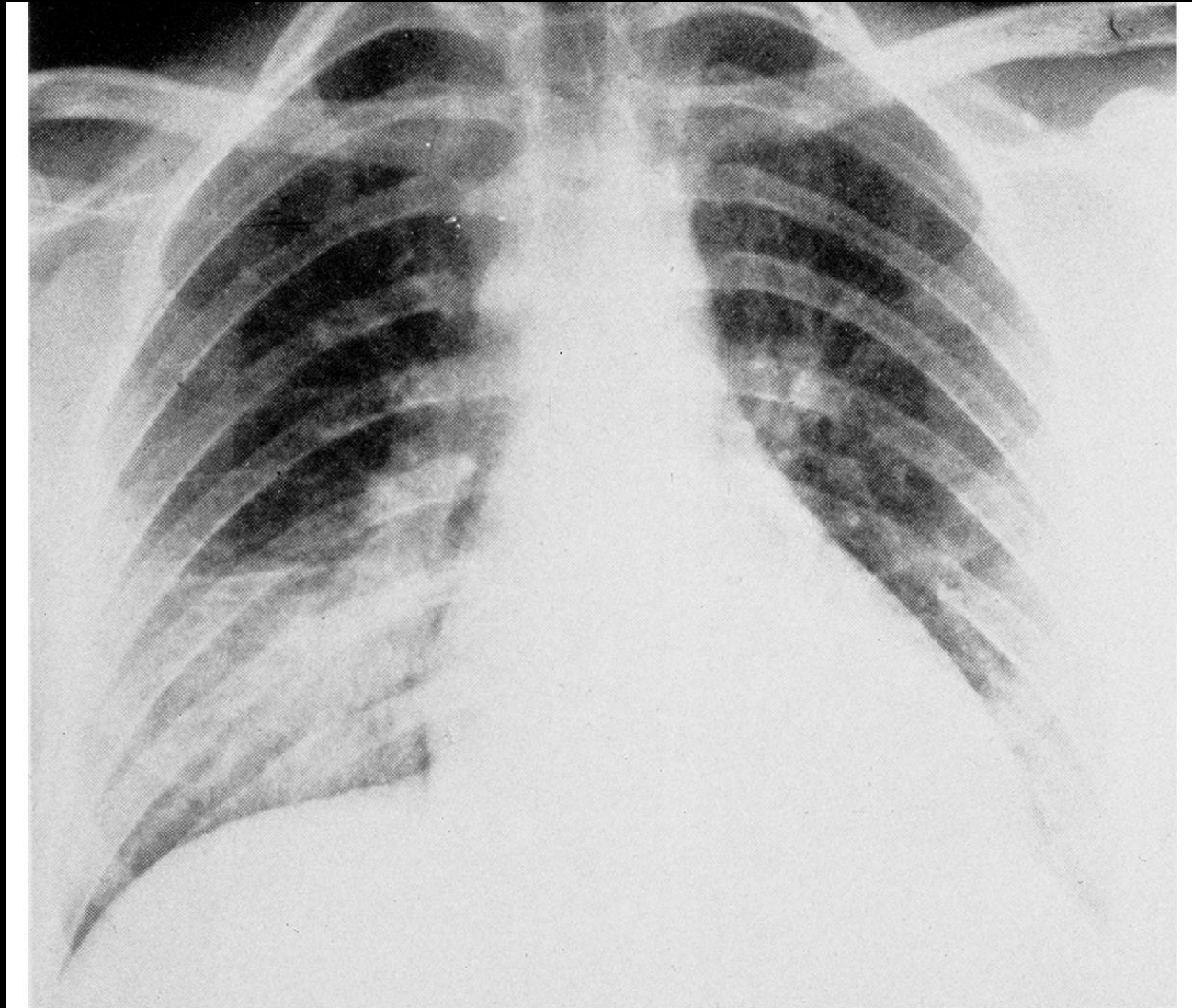


Figure 2. Chest roentgenogram of an 18-year-old boy (Patient 1) with atypical measles showing right lower lobe infiltrate and cardiomegaly.

Animal Model for Atypical Measles Rhesus Macaques

- Waning protection from neutralizing antibody following formalin inactivated vaccine
- No cytotoxic T-cell response
- Immune complexes and eosinophils in lungs of animals with atypical measles



Rotavirus Vaccines

- ~~Rhesus “Rotashield” (RRV)~~
- Bovine “Rotateq” (RV5)
- Human “Rotarix” (RV1)
- Others in development



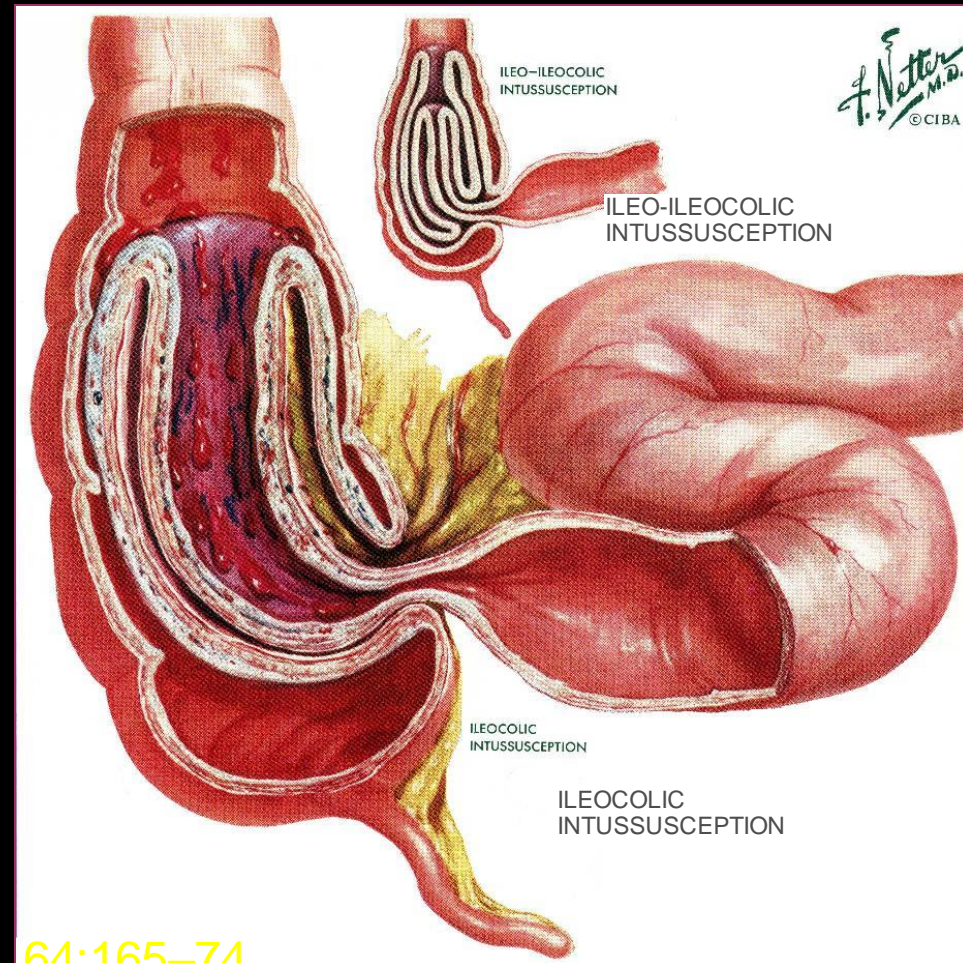
Intussusception after Rotavirus Vaccines

Pathogenesis unknown

Probable edema or
lymphoid hyperplasia

Intussusception/100,000:
Rhesus(Rotashield): 10-20
RV1 (Rotarix): 1-2*
RV5 (Rotateq) 1-2*

*in some populations



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Shaw Annu. Rev. Med. 2013. 64:165-74

Patel. Expert Rev Vaccines.
2009 Nov;8(11):1555-64.

Source: Netter. The CIBA Collection of
Medical Illustrations, Vol 3, 1962. pg134.

Live Vaccines: Unrecognized immune Deficiencies

- Age-related
- Defects in innate immune system
- B cell deficiency
- HIV infection
- Severe Combined Immune Deficiency

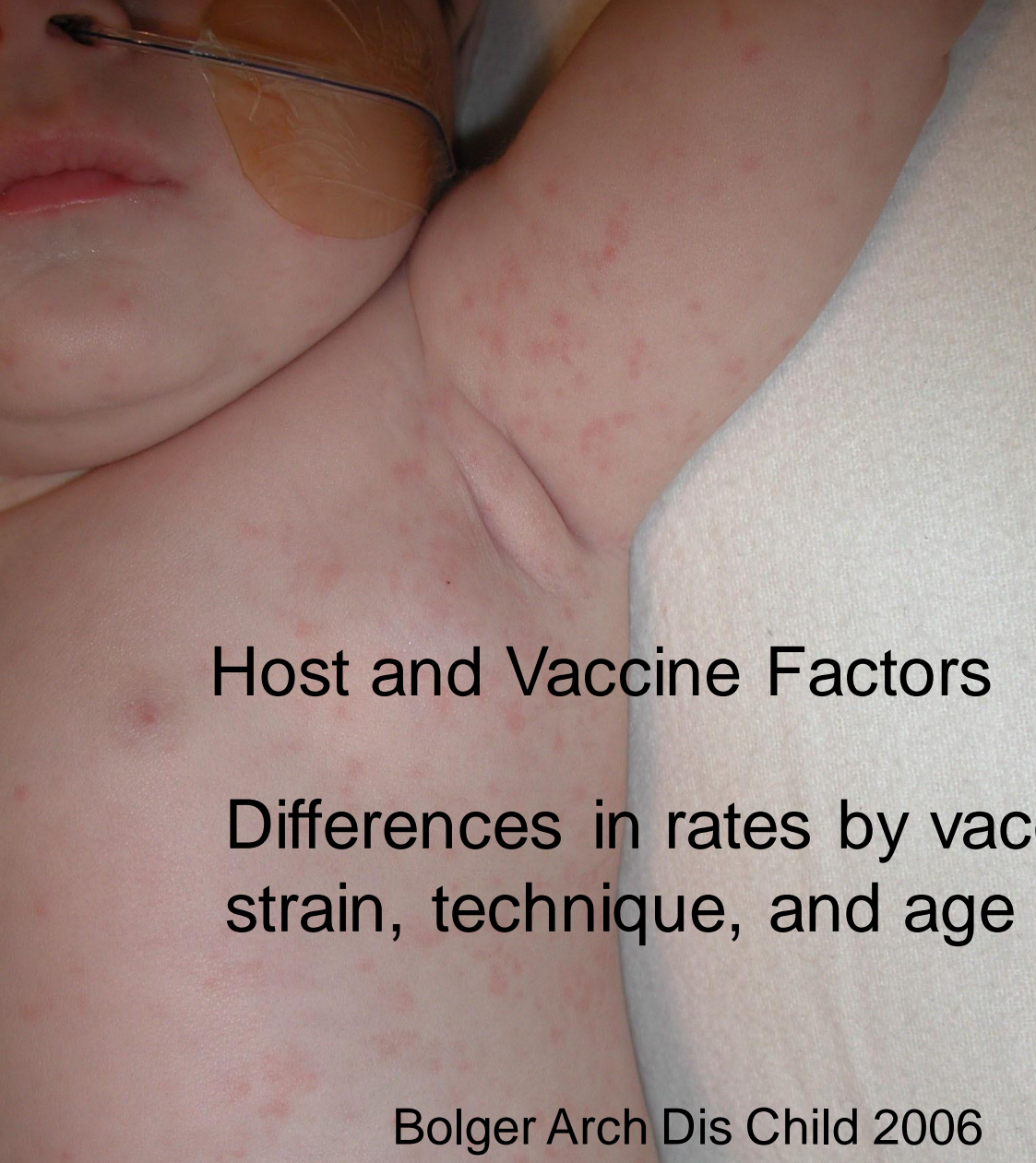


Lymphadenitis after BCG

Host and Vaccine Factors

Differences in rates by vaccine strain, technique, and age

Bolger Arch Dis Child 2006



Age-Specific Estimated Risks for Complications After Administration of BCG Vaccine

Incidence per 1 Million Vaccinations

Complication

Age <1 yr

Age 1–20 yr

Local subcutaneous abscess, regional lymphadenopathy.

387

25

Musculoskeletal lesions

0.39–0.89

0.06



Risk of Disseminated BCG

- **Infants:** ~ 1/million
 - IFN-gamma-receptor deficiency
 - Other undefined innate immunity defects?
- **HIV infected:** 1000-4000/million
 - >1000 fold increased risk
 - Often delayed several months



Areas of Risk for Yellow Fever Reported Cases and Vector Present



Source: HIIT

Increased Risk of Encephalitis from Yellow Fever Vaccine in Very Young Infants

<u>Age</u>	<u>Rate per million</u>
• ≥ 9 months	~1
• < 4 months	400-5000
– 1000 fold increase	



Yellow Fever Vaccine-Associated Viscerotropic Disease: Yellow Fever-like illness

- Onset 2-5 days post-vaccination
- Fever, myalgia, arthralgia
- Elevated liver enzymes & bilirubin
- Thrombocytopenia, lymphocytopenia
- Rhabdomyolysis
- Hypotension
- Renal failure
- Respiratory failure
- Case fatality >50%

Probable defect in
innate immune system,
thymus disorders,
age >60?
NK cells?



Delayed Onset of Severe Adverse Events Following Live Attenuated Measles Vaccines

- Pneumonia in children with leukemia or patient with AIDS: 3-9 mo.
- Inclusion body encephalitis: 5 wk - 6 mo.



Oral Polio Vaccine

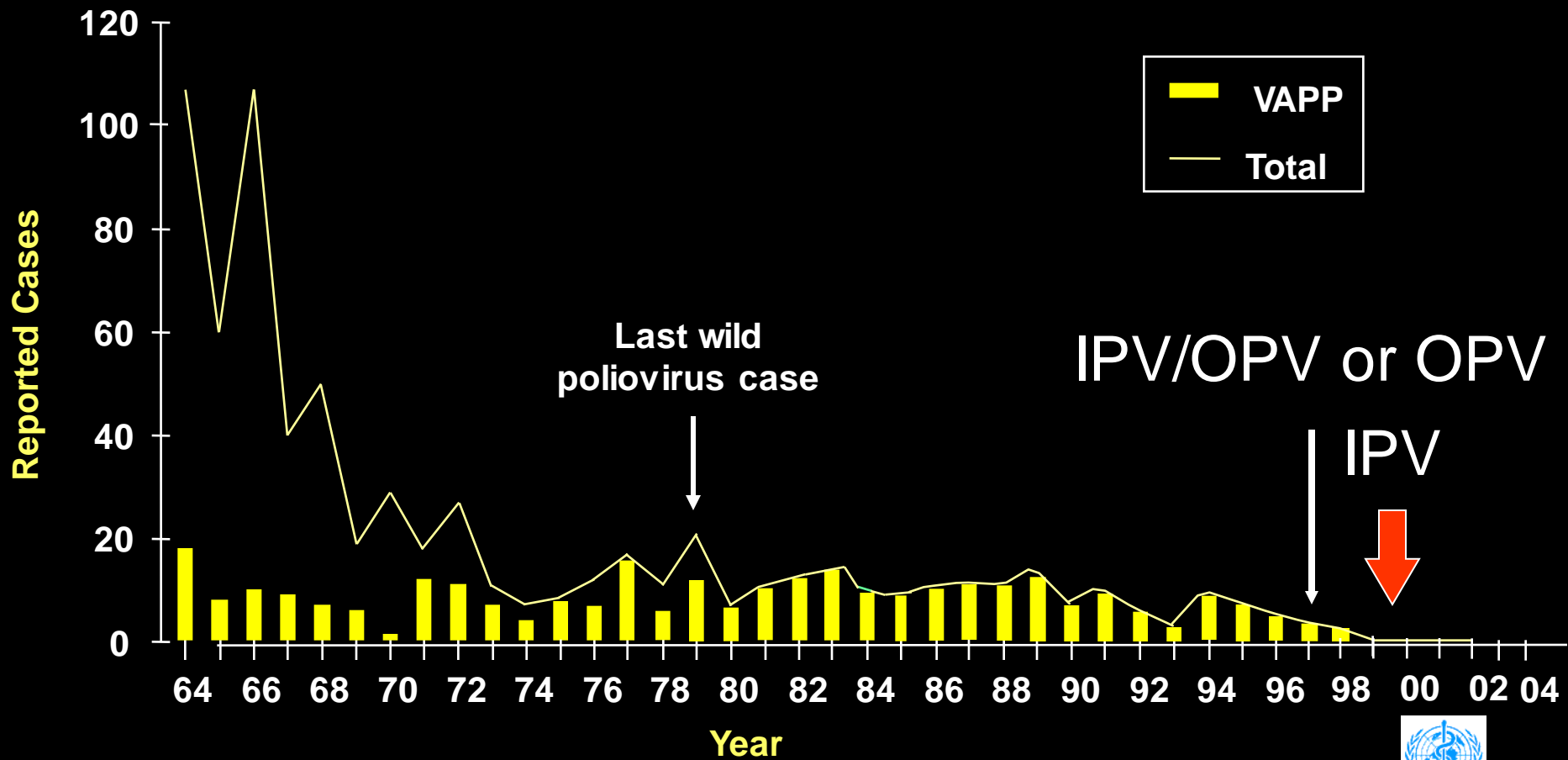


OPV-Associated Paralytic Poliomyelitis VAPP

- One case per 750,000 first doses
- Recipients and close contacts
- 250-500 cases per year globally
- Risk factors:
 - Age > 18
 - B cell immune deficiency
 - Multiple injections



Polio Incidence in USA, 1964-2004 and Vaccine Associated Paralytic Poliomyelitis (VAPP)



MMWR. 1997;46:79-83.
MMWR. 1998;47:676-677.

Polio Eradication



CDC

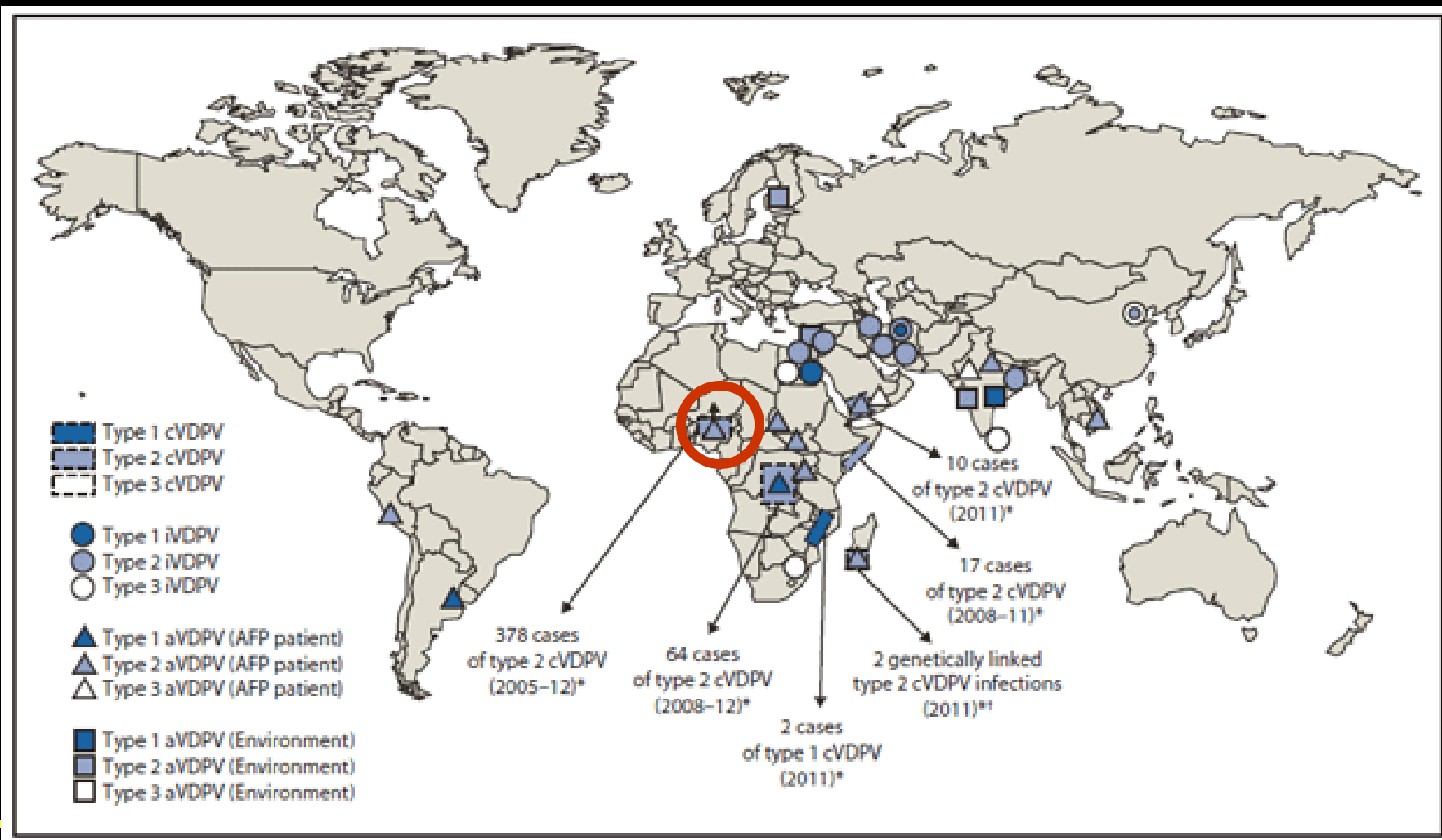
iVDPV Long Term poliovirus Excretors in immunodeficient

- >40 identified
- 39 countries
- Immune deficiency disorders
 - CVID
 - Agammaglobulinemia
 - XLA
 - SCID



Vaccine-derived Polioviruses

April 2011–June 2012



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MMWR 2012 / 61(37);741-746

Smallpox Vaccine



WHO

FETAL VACCINIA



Vincent A. Fulginiti, M.D.

Eczema Vaccinatum in Contact of Vaccinee



Vincent A. Fulginiti



Courtesy Mike Lane

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Underlying skin T cell disorder

Disseminated Vaccinia 1 Month after Vaccination in HIV Infected Recruit



Lesions during the first week of disseminated disease (day 5)

Extensive scarring of the resolving lesions after 9 weeks of passive immunotherapy.

Persistent Rotavirus Vaccine in Children With Severe Combined Immune Deficiency

- Present at 3-6 months of age
- Persistent diarrhea and growth failure

Catherine Yen ACIP Feb 2010

Werther et al. J Allergy Clin Immunol. 2009 Sep;124(3):600

Patel. J Allergy Clin Immunol (2009)

Uyungil. J Allergy Clin Immunol 2010 Jan; 125: 270-271

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Many Adverse Events are Preventable

The public needs
to know that
vaccines are made
as safe as possible



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