

Serious Adverse Events Associated with Unadjuvanted Influenza Vaccines

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**Adapted from ADVAC presentation
and Vaccine Development Course JHBSPH**

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
 - normal
 - aberrant

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Injection-related

1. Fainting – head injuries, mass hysteria
2. Incorrect site:
 - too high- bursa or joint
 - too low- ulnar nerve
3. Persistent pain syndromes
 - Brachial neuritis?
4. Inappropriate reuse of needles
 - Transmission of blood-borne pathogens
5. Provocation polio- WT or OPV



From Unicef Website 2007



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Incorrect administration of TT -wrong site

Appropriate IM Injection Sites

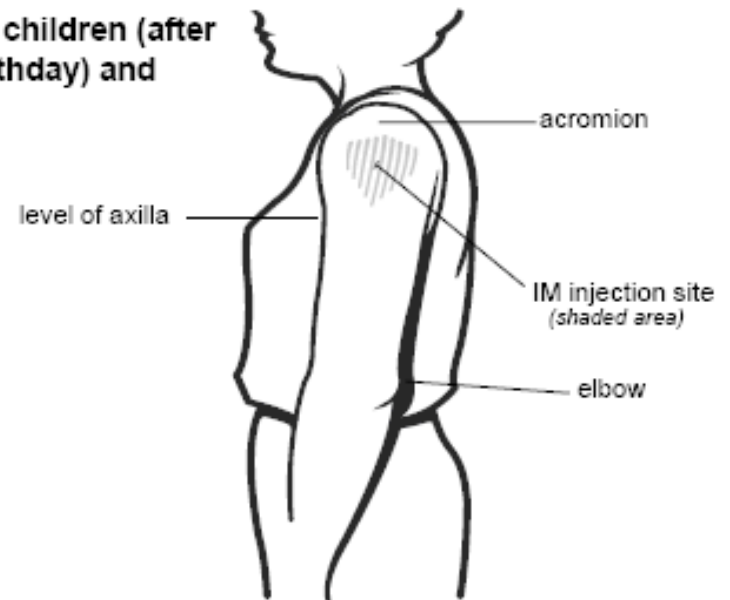


IM site for infants

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



level of axilla

acromion

IM injection site
(shaded area)

elbow

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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www.immunize.org

Potential for Contamination

- During production (2004)
- After initial use of multi-dose vials:
 - Not reported in the U.S. with flu vaccines
 - Group A strep with DTP
 - Staph aureus and enteric bacteria with measles

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Bernier et al Am J Dis Child. 1981 Sep;135(9):826-8.

Fever and Febrile Seizures in Children

- Fever:
 - Small increased rate of fever p TIV
 - Increased with whole virus vaccines
 - LAIV primarily first dose
- Febrile Seizures(usually benign):
 - 2-5% of all children in Europe and US have a febrile seizure by 5 years of age
 - 8-10% of Asian children
 - Uncertain if increased rate p flu vaccines
- Rare complex febrile seizures

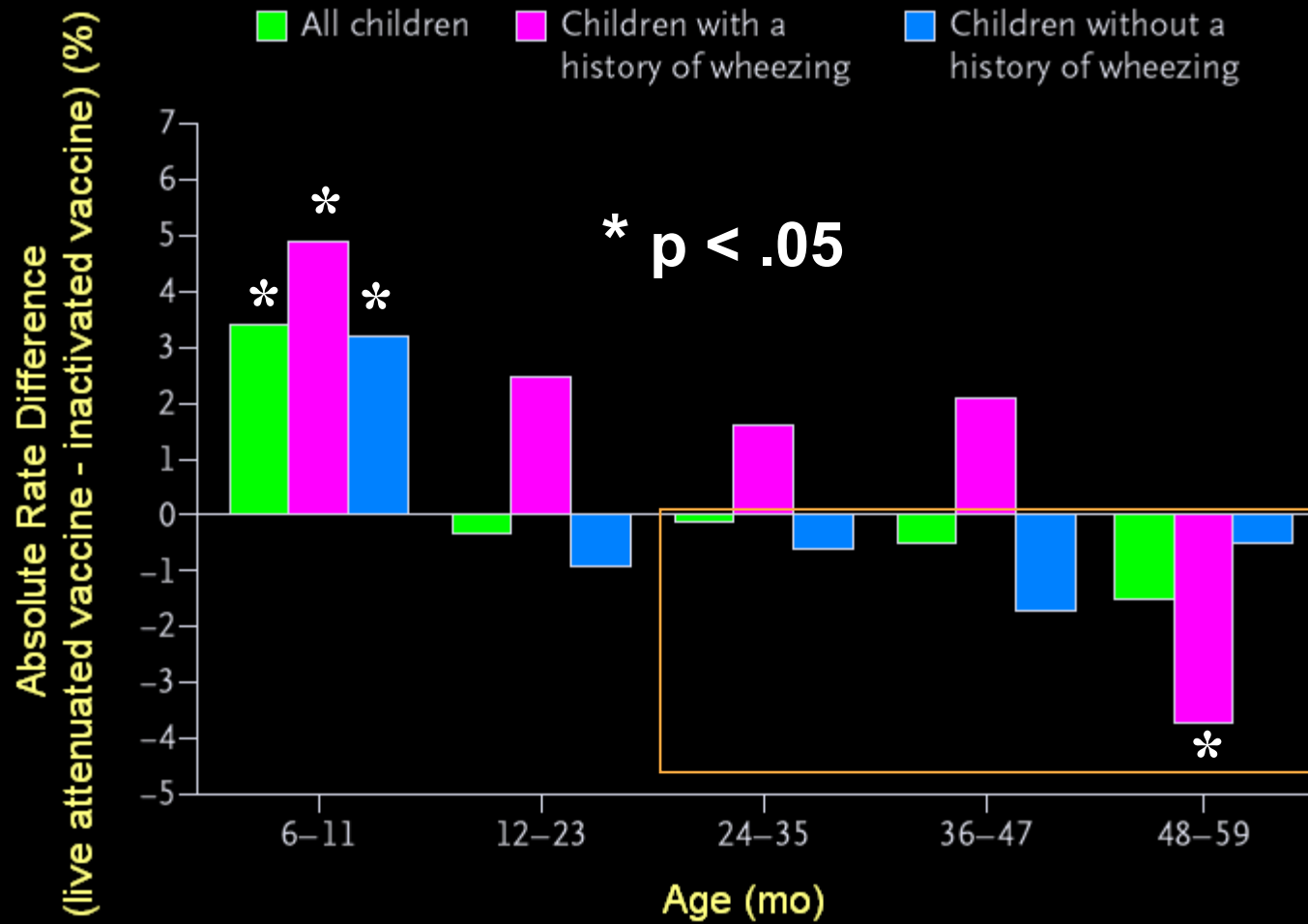
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Rosenberg M. Vaccine May 2009
ACIP Recommendations

Differences in Rates of Hospitalization between Live and Inactivated Vaccine by Age and History of Wheezing Illness before Vaccination



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Belshe RB et al. NEJM 2007;356(7):685.

Immediate Hypersensitivity Reactions



- Onset usually 0-4 hours p vaccine
- Hives, angioedema, anaphylaxis
- IgE mediated
- Allergens in influenza vaccines:
 - Egg(ovalbumin): 0.2-8.7 ug/ml*
 - Gelatin(2 vaccines in US)
 - Antibiotics(neomycin, polymixin)
 - Thimerosal

***Hugh Sampson**

Oculo-respiratory Syndrome

- Onset 2-24 hours after vaccination
 - Bilateral red eyes, Facial edema, or
 - Respiratory (wheezing, tightness, cough, difficulty breathing, sore throat), or
- Resolves in < 48 hours
- Recurrence rate? (5% or 34%)
- Pathogenesis?
- Canada rate decrease 46/100,000 to 9

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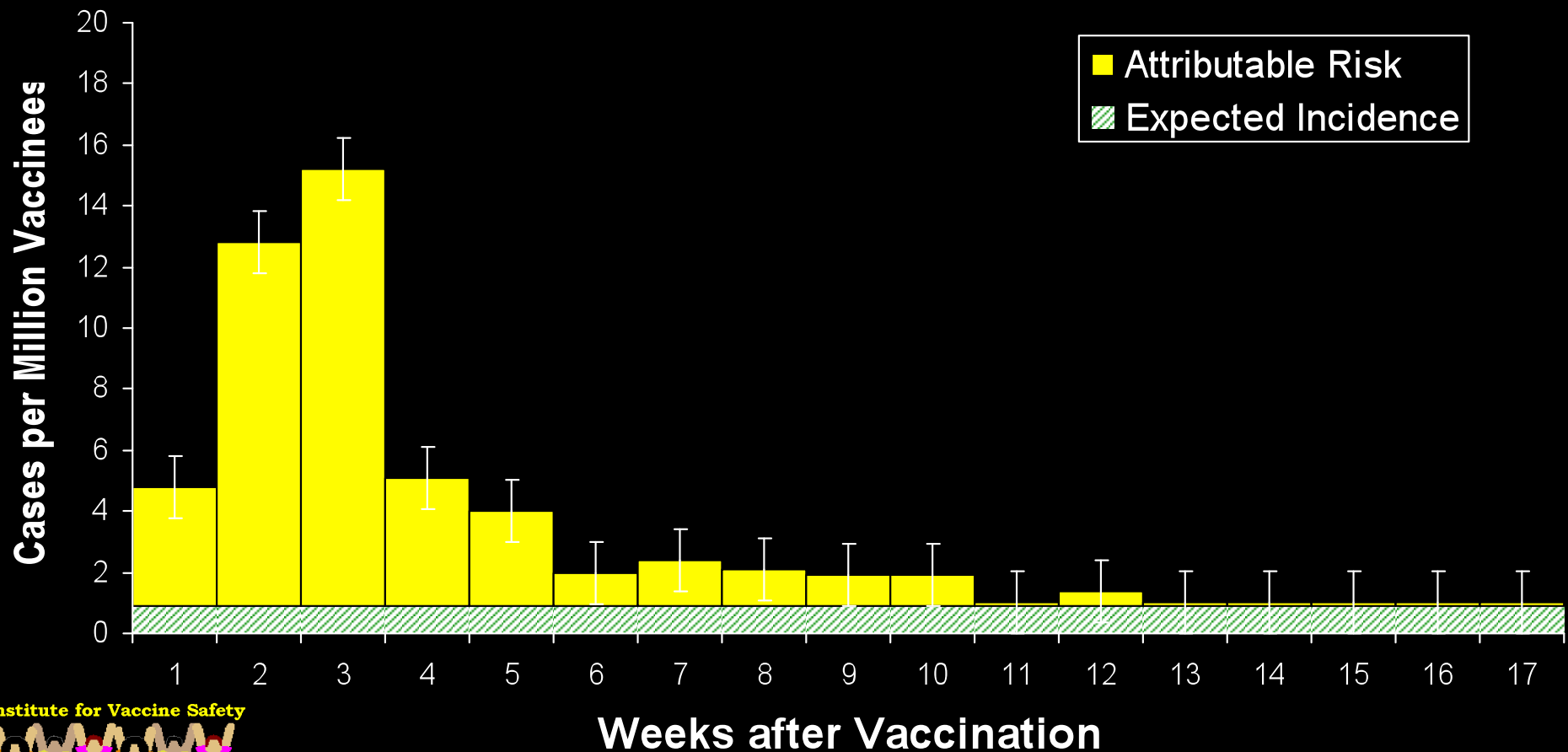
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De Serres Arch Int Med 2004;164:2266

Fredette CID 2003; 37:1136

De Serres Vaccine 2005; 23:3726

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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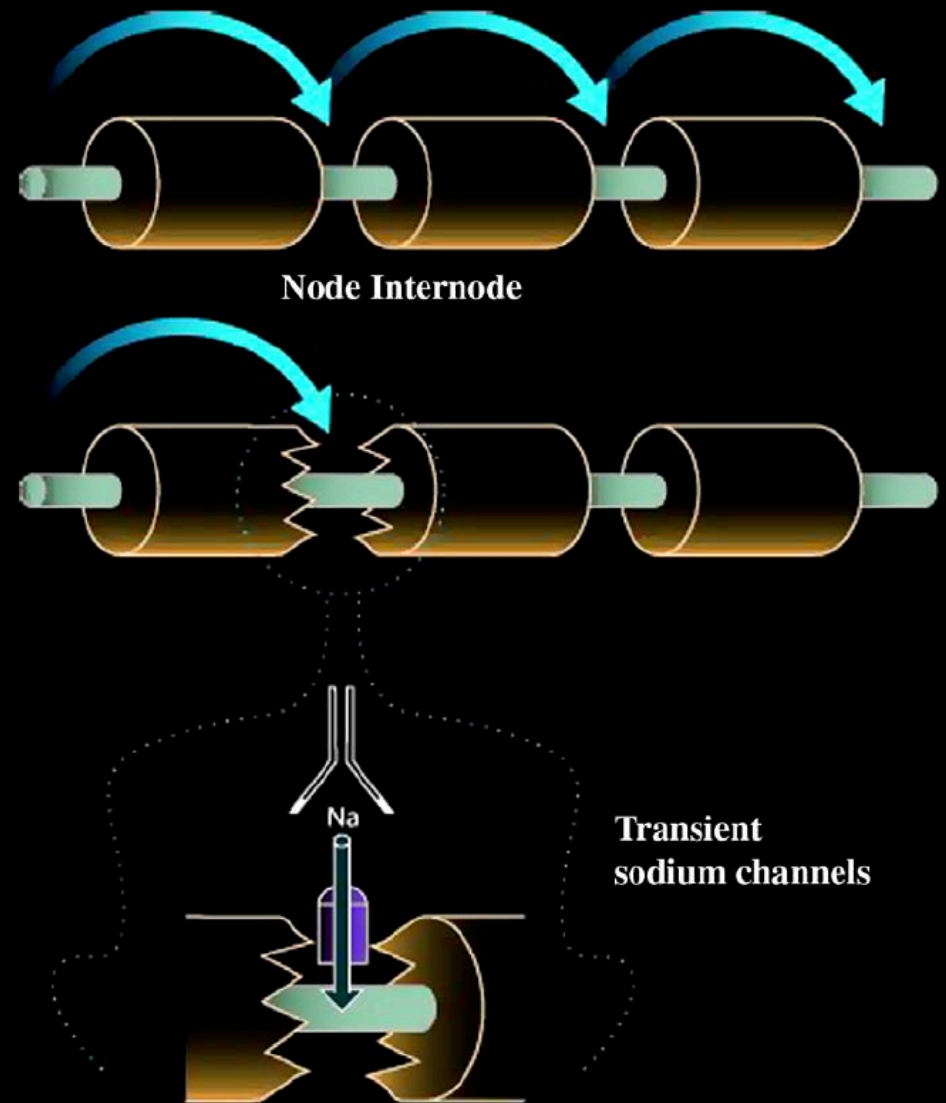
•excluding AR, CT, DE, WA. Data for CA, FL, GA, MO, NC, NJ, NY

•and TX included for 10/3-12/18/76 only.

Shonberger Am J Epidemiol 1979

Action potentials propagated along the nerve fibre.

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



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Vucic et al. *J Clin Neuro* 2009;16:741.

Attributable Risk of GBS following influenza vaccine

- 1976-1977 1/100,000
- 1978-1991 0
- 1992-1994 ~1/1,000,000
- 1995-2008 ?
- 2009 (H1N1) ?

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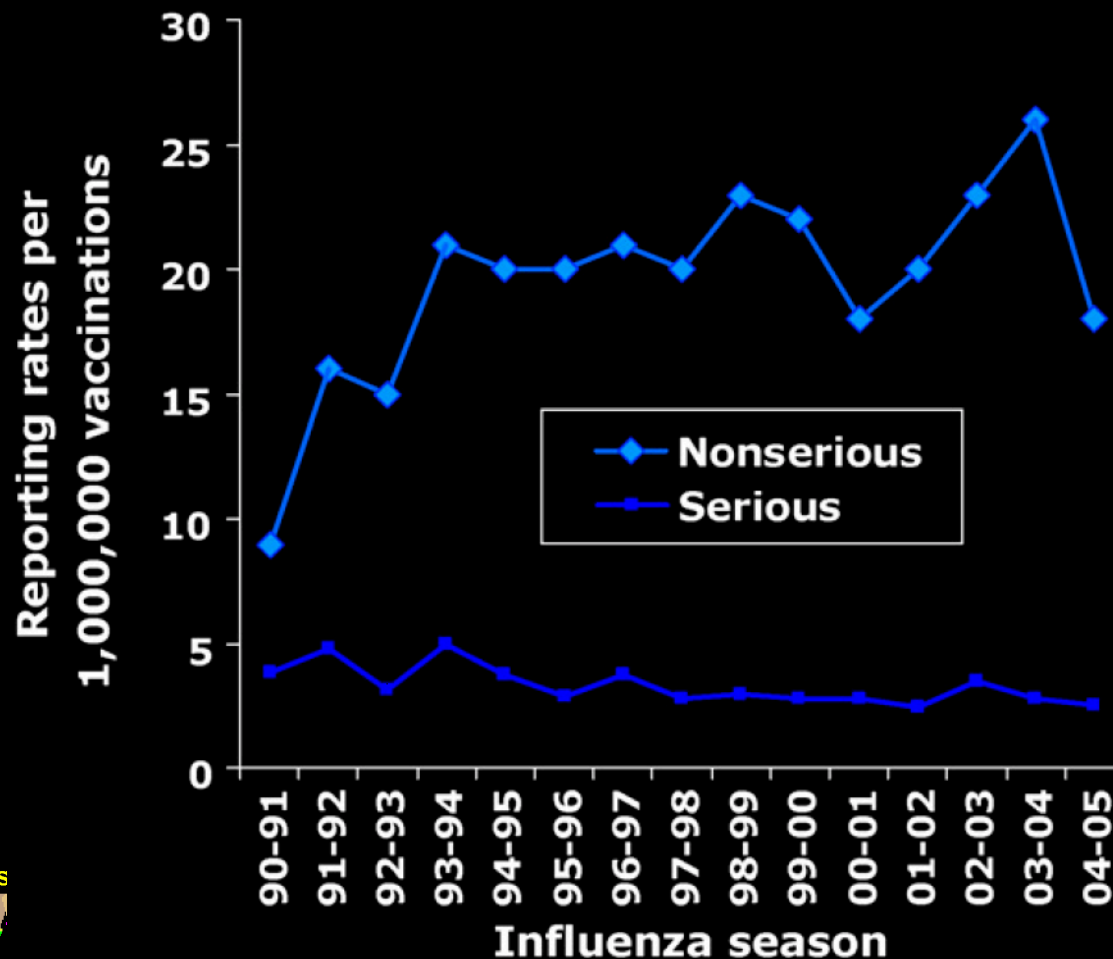


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Haber Drug Saf 2009;32:309

Serious and Nonserious Adverse Event Reports Following Trivalent Inactivated Influenza Vaccine

VAERS, July 1 1990 - June 30 2005 US



GBS reported
~0.70/million
doses distributed

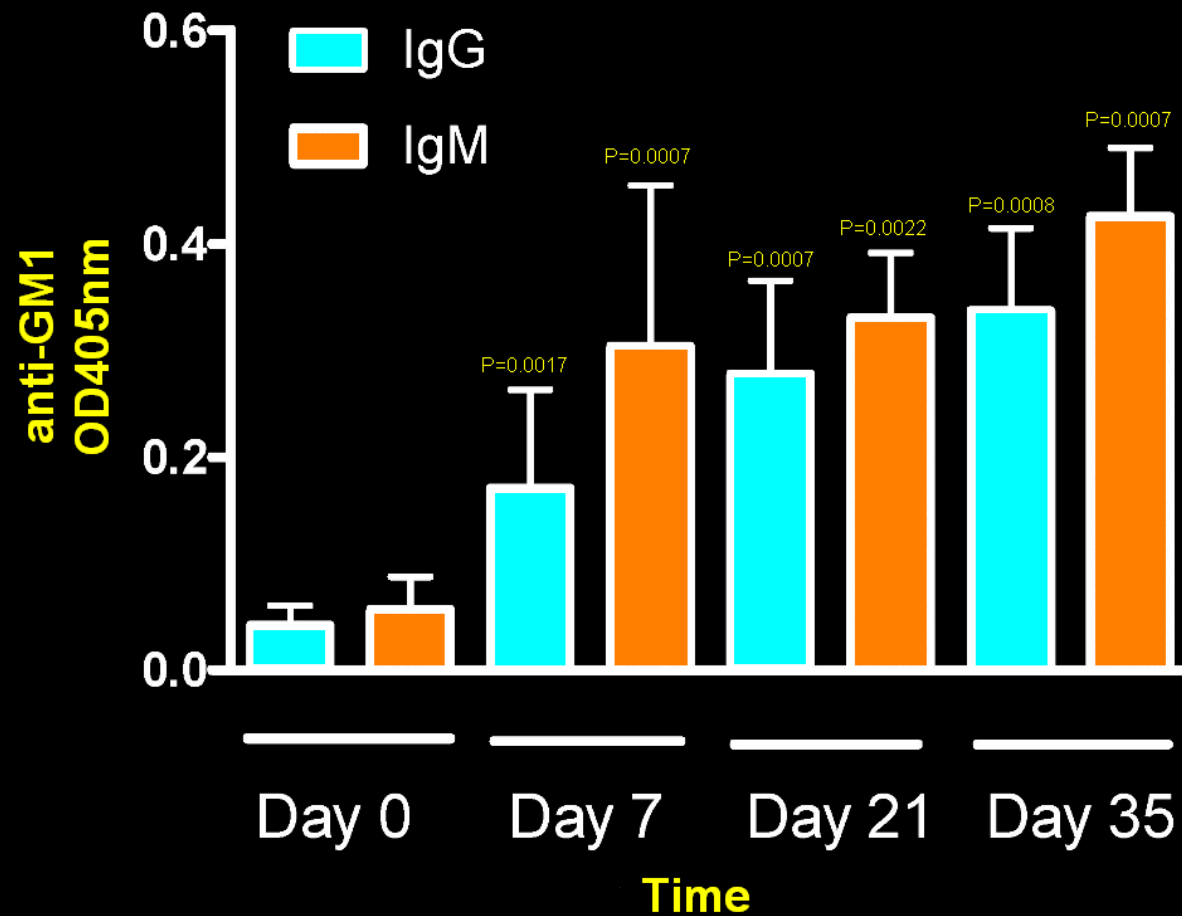
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Vellozzi et al. Vaccine 2009;27:2114.

IgG and IgM anti-GM₁ Antibody Response in Mice Immunized With Influenza A/NJ/1976 Vaccines on Days 0 and 21



1976 vaccine:
No evidence of
C. jejuni by PCR or
antibody response.

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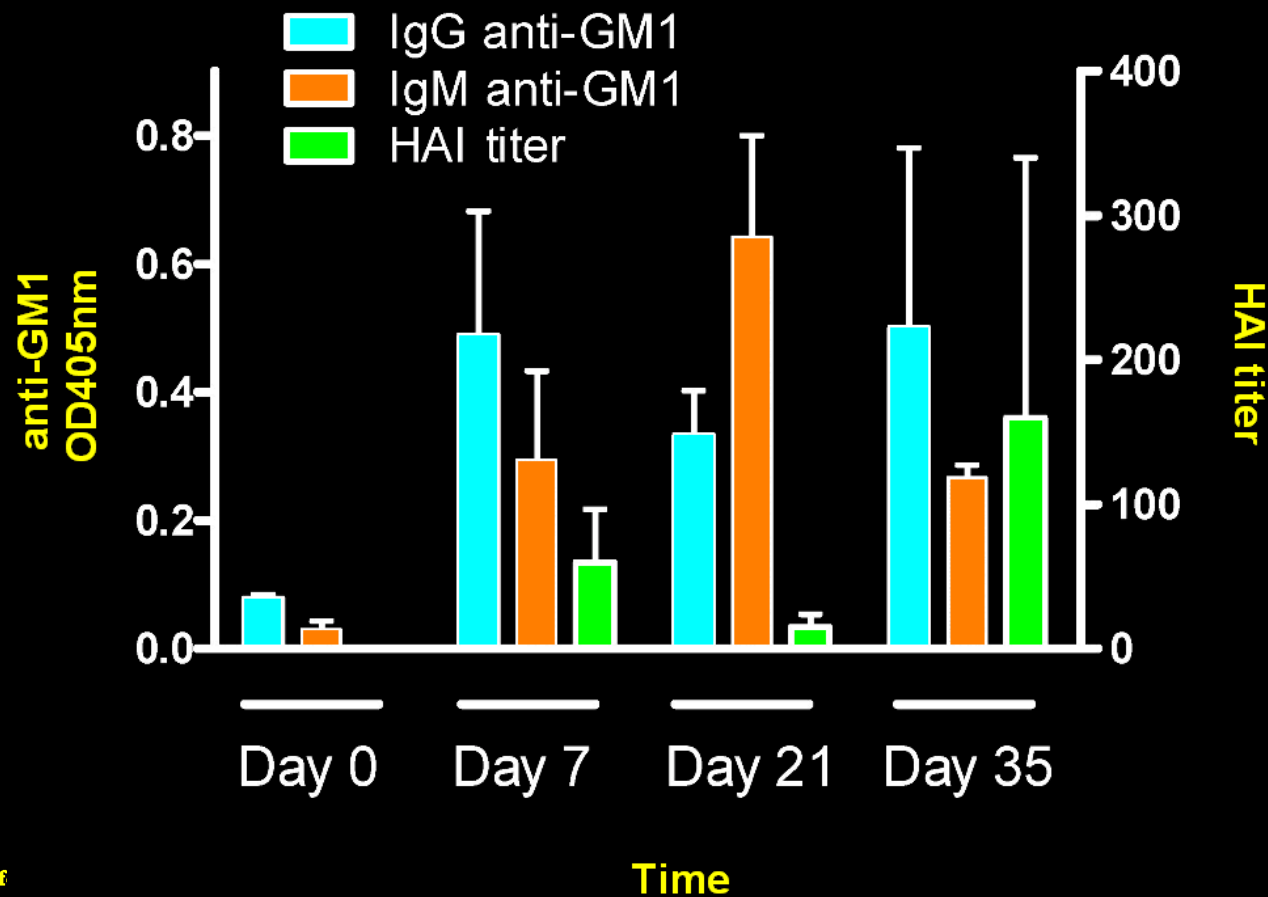
Bars represent mean optical density (OD) values for different groups of mice immunized with vaccine containing A/NJ/1976 from 11 vaccine lots.

Error bars indicate 95% confidence intervals.

P-values vs. day 0.

Nachamkin et al. JID 2008;198:226.

Anti-GM₁ Antibody and Hemagglutination Inhibition Responses in Mice Immunized with the Influenza Vaccines 1991-92



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Nachamkin et al. JID 2008;198:226.

ADEM and Transverse Myelitis Reported after Influenza Vaccines

- Some temporal clustering
- No convincing evidence of increased risk
- Neurologists and immunologists believe can be triggered by influenza vaccines

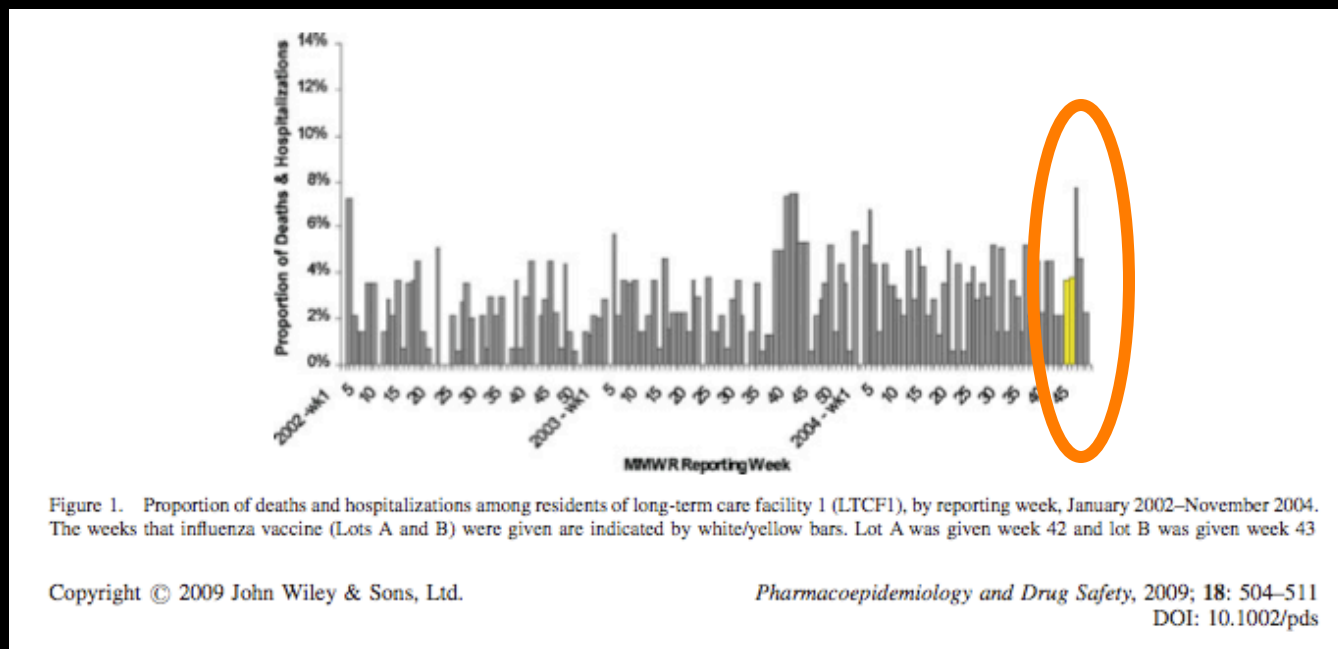
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Other Reported SAEs

- Serum Sickness (14 cases Thailand)
- Clusters of sudden death in adults:
 - Probably coincidence, disruptive (Israel)



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Apisarnthanarak A, Clin Infect Dis May 29, 2009

Rue-Cover Pharmacoepidemiol Drug Saf. 2009 Apr 16

Kokia ES Vaccine 2007;25:8557

Conclusions

1. Mass campaigns will result in temporal associations
2. Many coincidental adverse events will be reported
3. Some AEs with known causal relationships will occur
4. Determining higher than expected rates can be challenging

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