Assessing Safety of Influenza Vaccines

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Comprehensive Review

15,878 published articles identified through searches
6,001 some value for assessing causal relationships
Many Different Influenza Vaccines

• 108 vaccines produced last 10 years
• 47 Manufacturers, 27 countries
• Same or similar vaccines marketed under different names?
• Monovalent, bivalent, trivalent, quadrivalent
• Live, inactivated, whole, split-virion, adjuvants
  • Currently available vaccines differ
  • Caution when lumping all together
  • “influenza vaccines”
Factors affecting adverse event rates

• **Vaccine factors:** type, production method, adjuvants, other components, dose, route of administration, concomitant vaccines

• **Host factors:** age, gender, hypersensitivity, genetics, prior doses of vaccine
Adverse Events Caused by Inactivated Influenza Vaccines

- Pain, erythema and induration
- Shoulder injury
- Malaise, myalgia
- Fever and febrile seizures
- Syncope (head injury)
- Hypersensitivity (urticaria, anaphylaxis)
- Guillain-Barré syndrome
- Narcolepsy-one(two?) vaccine
13 patients: pain, bursitis, Injection in upper 1/3 of deltoid
Inactivated Vaccines Have Changed

1976: Whole vs Split-Virus Influenza Vaccines

Fever >37.8°C by Time in Hours After Vaccine

Whole virus vaccine: Febrile seizures in 3/42 children

Less fever with split virus and ½ dose in children

Figure 1. Frequency of maximal fever at various times after vaccination with whole-virus (MN, □, Merrell-National Laboratories, Cincinnati, Ohio; and MSD, △, Merck Sharp and Dohme, West Point, Pa.) or split-virus (PD ◊, Parke, Davis and Company, Detroit, Mich.; and W, ○, Wyeth Laboratories, Philadelphia, Pa.) influenza A/New Jersey/76 vaccine.

Study Variability in Methods Used for Detecting Fever

- “Feels warm”
- axillary
- oral
- rectal
- temporal artery
Variability in Reporting Fever

- Any fever: $\geq 37.1^\circ\text{C}$, $\geq 37.5^\circ\text{C}$, $\geq 37.8^\circ\text{C}$, $\geq 38.0^\circ\text{C}$, $\geq 38.3^\circ\text{C}$, $\geq 38.5^\circ\text{C}$, $\geq 39.0^\circ\text{C}$

- Days after vaccination:
  - 2, 3, 5, 7, 10, 21, 30

- Age groups: different groupings
  - 6 months to 1, 2, 3, 5, 8, 14, or 18 years
Whole vs. Split virus Vaccines in Children
Fever ≥38°C in Children 6 months to <5 years
AS03 Adjuvanted vs Whole Virus

Full Dose vs Half Dose
Some Vaccines No Increase in AEs
Adverse Events by Day 3 (Vaxigrip)

Some Vaccines Increase in Fever With Full Dose Only in Young Children

Fever ≥38.0°C within 21 Days after the First and Second Doses

H1N1 Vero cell Whole Virus Vaccine

Full Dose vs Half Dose Virosomal Vaccine in 6-35 month Old Children

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

Children < 5 years of Age With Febrile Convulsions

9 Perth, Australia Hospital ERs • January 1 – May 2 2010

CSL: 4.4/1000
Influvax: 0
P < .0001

CSL 2010 Fluvax Induced Higher Cytokine Responses

Maraskovsky E. et al, Vaccine 30 2012. 7400-7406
Increased Cytokine Response to 2010 CSL Vaccines

- Heat labile viral derived fragments
- Viral lipid-mediated delivery of fragmented RNA.
- Inadequate splitting of virions
  - sodium taurodeoxycholate
- Changes in the virus strains

CSL vaccines no longer recommended in children <4 or <5

Rockman, et al Vaccine 2014. 3869-3876
Differences in Production Methods for IIV Associated With Safety

• Splitting method:
  – Fever and febrile seizures: CSL vaccine Australia
  – Oculorespiratory syndrome in Canada

• Purification
  – Reduction in egg protein content for some
  – Reduction in endotoxin
Increase in Febrile Seizures Following IIV Administered With Pneumococcal Conjugate Vaccine

Febrile Seizures Days 0-1 vs 14-20 by Age in Months

206,174 Children 6-59 mo of age


<table>
<thead>
<tr>
<th>Vaccine Combination</th>
<th>Rel Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIV3 alone</td>
<td>1.4</td>
<td>0.54 – 3.61</td>
</tr>
<tr>
<td>IIV3 PLUS PCV13</td>
<td>5.25</td>
<td>1.87 – 1</td>
</tr>
<tr>
<td>IIV4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2013-14 and 2014-15 seasons
Influenza vaccines Contain Allergens That Can Cause Immediate Hypersensitivity Reactions

- Hives, angioedema, anaphylaxis
- Allergens in influenza vaccines:
  - Residual media
  - Antibiotics
  - Gelatin
  - Latex in stoppers and seals
  - Preservatives (thimerosal)

www.allergycapital.com  www.vaccinesafety.edu/components-Allergens
# Allergens in 2016/17 Influenza Vaccines

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Vaccine(s)</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin (Porcine)</td>
<td>Flumist Quad</td>
<td>Hydrolyzed, 2.00 mg</td>
</tr>
<tr>
<td>Gentamicin Sulfate</td>
<td>Flumist Quad, Fluarix Quad</td>
<td>&lt;0.015 mcg/mL, ≤0.15 mcg</td>
</tr>
<tr>
<td>Latex</td>
<td>Fludad, Fluvirin</td>
<td>The tip caps of the prefilled syringes contain natural rubber latex.</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Afluria, Fluarix Quad, Fluvirin</td>
<td>≤3 ng (Neomycin sulfate), ≤0.2 mcg, ≤2.5 mcg</td>
</tr>
<tr>
<td>Ovalbumin</td>
<td>Afluria, Fluarix Quad, Fluvirin</td>
<td>≤1 mcg, &lt; 0.4 mcg residual egg proteins, ≤ 0.05 mcg, ≤0.3 mcg, ≤ 1 mcg</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>Afluria, Fluvirin</td>
<td>≤0.5 ng, ≤3.75 mcg</td>
</tr>
<tr>
<td>Sodium Taurodeoxycholate</td>
<td>Afluria</td>
<td>&lt;10 ppm</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>Afluria, FluLaval Quad, Fluvirin, Fluzone Quad</td>
<td>24.5 mcg mercury in multi-dose vial, 25 mcg mercury in multi-dose vial, ≤1 mcg in prefilled syringe; 25 mcg mercury in multi-dose vial</td>
</tr>
</tbody>
</table>
### Reporting rate of Hypersensitivity Reactions following H1N1 By Manufacturer

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>No.</th>
<th>Doses</th>
<th>rate/10⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSL</td>
<td>27</td>
<td>3,451,900</td>
<td>7.8</td>
</tr>
<tr>
<td>Novartis</td>
<td>298</td>
<td>37,778,800</td>
<td>7.9</td>
</tr>
<tr>
<td>Sanofi pasteur</td>
<td>554</td>
<td>64,089,420</td>
<td>8.6</td>
</tr>
<tr>
<td>Medimmune</td>
<td>256</td>
<td>21,755,200</td>
<td>11.8</td>
</tr>
<tr>
<td>Unknown</td>
<td>151</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1286</td>
<td>127,075,320</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Medimmune vs Novartis p < .001, vs Sanofi pasteur p < .001, and vs. CSL p = .05.

Halsey et al. Vaccine 2013;31(51):6107-12
Anaphylaxis Following Influenza Vaccines

- Overall rate: 1-2 per million doses
- Females of child bearing age at higher risk
- Antigens responsible not usually identified

Halsey et al. Vaccine 2013;31(51):6107-12
Ovalbumin Content Influenza Vaccines


Additional final filtration

FIG 1. Ovalbumin levels reported for 2009-2010 (open diamonds) and tested in this study for 2010-2011 (solid circles). Each dot represents the ovalbumin content of 1 lot. The blue line at 1.2 μg/mL represents the historical level of ovalbumin content below which all patients with egg allergy in the study by James et al5 were safely vaccinated.
Large Local Reaction 3 Days Following Second Dose of Influenza Vaccine: 8 yr old
Adjuvants in Influenza Vaccines

- Alum (Aluminum Phosphate)
- MF59:
  - squalene, polyoxyethylene sorbitan monooleate (Tween™ 80) and sorbitan trioleate
- AS03:
  - squalene, DL-α-tocopherol, and polysorbate 80
- AF03(experimental):
  - Squalene, Montane 80, Eumulgin B1 PH
- Virosomes:
  - Lipids, hemagglutinin
### Switzerland: Bell’s Palsy Associated With Inactivated Intranasal Vaccine with *E. coli* toxin Adjuvant

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Case Patients (N=250)</th>
<th>Controls (N=722)</th>
<th>Adjusted Odds Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal inactivated influenza</td>
<td>63 (25.2%)</td>
<td>7 (1.0%)</td>
<td>84.0 (20.1-351.9)</td>
</tr>
<tr>
<td>Parenteral inactivated influenza</td>
<td>10 (4.0%)</td>
<td>41 (5.7%)</td>
<td>1.1 (0.6-2.0)</td>
</tr>
</tbody>
</table>

2009: Bell’s Palsy in 2/29 recipients of intranasal HIV or TB vaccines containing *E. coli* toxin adjuvant (Lewis 2009).

Bell’s Palsy After Influenza Vaccines

No increased risk:

• VSD no signal after IIV or LAIV (Greene 2010)
• Northern Kaiser (Rowhani-Rahbar 2012)
• 6 million claims based SCRI 0-42 vs 43-84 days
No increase H1N1 or TIV (McCarthy)

PRISM 0-42d vs prevaccination -56d to – 15 d

– 6mo- 24 yrs IRR of 1.65 (99%CI 1.03-2.64; p=0.006) (Yih 2012)
Reported cases of Guillain-Barre syndrome, by period between A/New Jersey influenza vaccination and onset of illness

US (including Puerto Rico) | Oct 1 1976-Jan 31 1977

Risk in > 18 years of age ~10/million
Similar risk for all vaccines
No data in children

Used by permission.

Risk of Guillain-Barre Syndrome associated with Influenza A (H1N1) 2009 Monovalent Inactivated Vaccine in U.S. Studies

Small circle represents the incidence rate ratio.
Vertical lines represent the 90% CI.
Horizontal lines represent the 95% CI.
VSD - Vaccine Safety Datalink
PRISM - Post-licensure Rapid Immunisation Safety Monitoring
EIP - Emerging Infections Programme

Attributable Risk of GBS per Million Increases With Age

Uncertain if there is any increase in risk in children

SCCS International Study of GBS and H1N1 Vaccine

- 471 cases from 15 countries
- Brighton level 1-3
- Days 1-42 RI 2.86: (95% CI 1.88-4.34)
- Age:
  - ≥ 65: 4.30 (2.18, 8.50)
  - 50–64: 2.78 (1.36, 5.68)
  - 19–49: 1.56 (0.51, 4.71)
  - <19: 0.73 (95% CI 0.16-3.46)

Meta-analysis of GBS 39 Studies
Seasonal and Pandemic Vaccines
Europe, USA, Canada, Australia, Taiwan

- Seasonal: RR = 1.22; 95% CI, 1.01–1.48
- Pandemic RR = 1.84; 95% CI, 1.36–2.50

GBS and Influenza Vaccines

- IIV
  - Adults small increased risk ~1-4/million
  - No evidence of different risk for different IIVs
  - Children? Insufficient data

- LAIV?
  - Insufficient data
Narcolepsy with Cataplexy
Hypocretin Deficiency

Silber M H, Rye D B Neurology 2001;56:1616-1618
<table>
<thead>
<tr>
<th>Country</th>
<th>Age Group (yrs)</th>
<th>Study Design</th>
<th>Definition of Onset</th>
<th>Follow up Period</th>
<th>Risk (RR/OR)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>4-19</td>
<td>RC</td>
<td>1. contact with HC</td>
<td>1/1/09 - 8/15/10</td>
<td>12.7</td>
<td>6.1 - 30.8</td>
</tr>
<tr>
<td>Sweden</td>
<td>≤19</td>
<td>RC</td>
<td>Date of dg G47.4</td>
<td>10/1/09 - 12/31/10</td>
<td>6.6</td>
<td>3.1-14.5</td>
</tr>
<tr>
<td>Ireland</td>
<td>&lt;20</td>
<td>RC</td>
<td>1. contact with HC</td>
<td>4/1/09 - 12/31/10</td>
<td>13.9</td>
<td>5.2-37.2</td>
</tr>
<tr>
<td>France</td>
<td>&lt;18 18+</td>
<td>CC 4/1/09 – 4/30/11</td>
<td>Date of Referral MSLT</td>
<td>4/1/09 – 4/30/11</td>
<td>6.5</td>
<td>2.1-19.9</td>
</tr>
<tr>
<td>Norway</td>
<td>4-19</td>
<td>RC Date of EDS by Patient</td>
<td>10/1/09 - 6/30/10</td>
<td>10-20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>4-18 Case-coverage</td>
<td></td>
<td></td>
<td></td>
<td>16.2</td>
<td>3.845</td>
</tr>
<tr>
<td>Canada</td>
<td>0.5-20</td>
<td>RC</td>
<td>Date of EDS by Patient</td>
<td>1/1/09 – 12/31/10</td>
<td>2.96</td>
<td>0.71-12.39</td>
</tr>
</tbody>
</table>
Narcolepsy: Decreasing Risk With Increase in Age

Hazard Ratios and 95% Confidence Intervals for Diagnosed Narcolepsy 2009-2011 by Age at Vaccination: Sweden

Proportion of Population with HLA Type Associated with Narcolepsy

DQB1*0602
Recent Review of Available Evidence

Meeting report

Where are we in our understanding of the association between narcolepsy and one of the 2009 adjuvanted influenza A (H1N1) vaccines?∗

K. Johansen a, D. Brasseur b, N. MacDonald c, H. Nohynek d, J. Vandeputte e, D. Wood f, P. Neels e, g, ∗, on behalf of the Scientific Committee

a Influenza and other Respiratory Viruses Disease Programme, Office of the Chief Scientist, European Centre for Disease Prevention and Control, Stockholm, Sweden
Overall the studies to date have produced consistent results for the risk following Pandemrix® despite various sources of data and study designs.
No Increase in Narcolepsy after Other H1N1 Influenza Vaccines

- No increase in Europe or the U.S. with other vaccines, including LAIV and MF59 adjuvanted
- Pathogenic mechanism for increased risk has not been determined.
  - The adjuvant? Novel antigen? Combination?

McCarthy, et al Vaccine 2013. 31:5975-5982
Johansen et al. Biologicals 44 (2016) 276e280
Good Evidence Current Influenza Vaccines Do Not Cause

- Immune Thrombocytopenia (ITP)
- Multiple Sclerosis (MS)
Acute disseminated encephalomyelitis (ADEM)

• 70+ case reports after vaccines (20+ influenza)
• 45+ reviews have concluded vaccines cause
  – Not based on evidence of increased risk
• Pathophysiology incompletely understood
• 1 epidemiologic study in Sweden after 2009-10 H1N1 vaccine (Persson J Int Med 2014)
  – HR 1.41 (95% CI 0.35-5.73)

The available evidence does not establish a causal relationship between influenza vaccines and ADEM, but the evidence does rule out the possibility of a small increased risk. (Halsey et al. Vaccine 2015)
“Studies have not found new, unusual, or unexpected patterns of serious acute events, adverse pregnancy outcomes, or congenital anomalies”

SAGE 2016: Reaffirmed recommendation for influenza vaccines at all stages of pregnancy

CBS News (Canada).

U.S. VSD study 2010-2011 and 2011-2012 seasons:
Increased SAB following IIV for women who had received an H1N1-containing vaccine the prior season.

Donahue ACIP June 2016

Safety of Immunization during Pregnancy
A review of the evidence

GAVCS 2014
Adverse Events Days 0-10 After LAIV vs TIV in 4245 Children 2-17 Years of Age in 7 Trials

LAIV vs. IIV: Small increase in rate of respiratory symptoms

Ambrose 2011
Differences in Rates of Hospitalization between Live and Inactivated Vaccine by Age and History of Wheezing Illness before Vaccination

Wheezing in the 6 Weeks After LAIV by Age

• 6-23 months 3.2% for LAIV vs 2.0% IIV adjusted risk difference = 1.18 (P = 0.076)

• No difference in all other age groups

(Belshe 2007)
No Increase in Wheezing for Persons With Past Wheezing

LAIV vs. IIV

Ambrose 2012
Will New Antigens Change Risk?

Fleishman et al. Science 2011
Theoretical Safety Issues With Universal influenza Vaccines

• Increased rates or severity of adverse events known to be caused by influenza vaccines
• Autoimmune disease
• Antibody mediated enhancement
• Other?
What Preclinical Safety Data Are Needed Before Human Trials?

Studies of small numbers of mice revealed no antibody mediated enhancement.

1. Which animal models should be studied?
2. Numbers? Strains?
3. What to monitor?
Clinical Trials

• What to monitor? Phase I, II, III, IV?
• Powered to detect which adverse events?
  – Which age groups? Can’t extrapolate
  – Which populations? Countries?
  – When to study pregnant women?
• Comparison with well characterized seasonal vaccines? or placebos?
### Sample Sizes Needed to Detect Rare Adverse Events and Impact

<table>
<thead>
<tr>
<th>Rates (%)</th>
<th>Sample Size *</th>
<th>US</th>
<th>Europe</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 vs. 0.2</td>
<td>50,000</td>
<td>4,000</td>
<td>5,100</td>
<td>23,000</td>
</tr>
<tr>
<td>0.1 vs. 0.3</td>
<td>17,500</td>
<td>8,000</td>
<td>10,200</td>
<td>46,000</td>
</tr>
<tr>
<td>0.05 vs. 0.1</td>
<td>100,000</td>
<td>2,000</td>
<td>2,550</td>
<td>11,500</td>
</tr>
<tr>
<td>0.01 vs. 0.02</td>
<td>500,000</td>
<td>400</td>
<td>510</td>
<td>2,300</td>
</tr>
<tr>
<td>0.01 vs. 0.03</td>
<td>175,000</td>
<td>800</td>
<td>1,020</td>
<td>4,600</td>
</tr>
</tbody>
</table>

*Two-arm trial, power 80%, alpha (2 sided) = 5%

** Entire birth cohort vaccinated

Source: Salmon and Halsey.
The Vaccine Book II. 2015

Births:
USA – 4 million (2014)
EU – 5.1 million (2014)
India – 23 million (2015)
PPC Safety Comments

• “The vaccine safety profile depends on the burden and severity of the disease being prevented.”
• Common sense
• Would we accept a vaccine that caused a 2X increase in adverse events that was more effective than current vaccines and protected for 5 years?
PPC: “Severe reactogenicity should occur at a rate similar to or less than current WHO prequalified vaccines.”

- Not possible to establish equivalence for rare events before widespread use.
- Evaluation requires very large numbers and infrastructure to capture and analyze AEs.
- Need to plan for large scale safety assessments in less developed countries.
Conclusions

• Influenza vaccines differ. Cannot extrapolate safety from one vaccine to all vaccines.
• We do not know which vaccine components are responsible for most adverse events.
• Many influenza vaccines have not been carefully studied for safety in children.
• Novel antigens or adjuvants could present new safety issues.
• Safety assessment is inadequate in many developing countries.