Influenza Vaccination
Myths & Reality

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Public Perceptions

- Influenza is not a serious disease
Figure 2
Cumulative numbers of deaths relative to the expected mortality by influenza season and age, influenza seasons 2006-7, 2007-8, 2008-9, 2009-10, pooled data from eight European countries*
USA data

• 200,000 people hospitalized w flu annually

• ~ 36,000 deaths
  – Most > 65 years of age

• Children < 2 yrs of age
  – ↑↑↑ risk to be hospitalized
Mortality surveillance network
Influenza 2010-11

Year and number of week

N of deaths
Clinical associations-Side effects

• The flu shot does not work
Clinical associations

• The truth is that *it protects from the flu*

• esp. when close antigenic match

  – between vaccine & circulating influenza strains

Improve vaccine efficacy

• We need to improve vaccine efficacy
<table>
<thead>
<tr>
<th></th>
<th>Adjusted VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H3N2)</td>
<td>41.9%</td>
<td>-67.1% - 79.8%</td>
</tr>
<tr>
<td>A (H1) pdm09</td>
<td>62.1%</td>
<td>-22.9% - 88.3%</td>
</tr>
<tr>
<td>B</td>
<td>78.2%</td>
<td>18% - 94.2%</td>
</tr>
<tr>
<td>A+B (target groups)</td>
<td>50.4%</td>
<td>-20.7% - 79.6%</td>
</tr>
</tbody>
</table>
### Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12

<table>
<thead>
<tr>
<th></th>
<th>Vaccine Effectiveness</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>31%</td>
<td>-21% - 60%</td>
</tr>
<tr>
<td>&lt; 65 yrs old</td>
<td>44%</td>
<td>-11% - 72%</td>
</tr>
<tr>
<td>&gt;65 yrs old</td>
<td>19%</td>
<td>-146% - 73%</td>
</tr>
<tr>
<td>Time Interval</td>
<td>Vaccine Effectiveness</td>
<td>95% CI</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------</td>
<td>------------</td>
</tr>
<tr>
<td>First 100 days</td>
<td>61%</td>
<td>5% - 84%</td>
</tr>
<tr>
<td>100-119 days</td>
<td>42%</td>
<td>-39% - 75%</td>
</tr>
<tr>
<td>&gt;119 days</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>
## Effectiveness of seasonal 2012/13 vaccine in preventing laboratory-confirmed influenza infection in primary care in the United Kingdom: mid-season analysis 2012/13

<table>
<thead>
<tr>
<th></th>
<th>Adjusted VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A &amp; B</td>
<td>51 %</td>
<td>27% - 68%</td>
</tr>
<tr>
<td>A</td>
<td>49 %</td>
<td>-2 % - 75%</td>
</tr>
<tr>
<td>B</td>
<td>52 %</td>
<td>23% - 70%</td>
</tr>
</tbody>
</table>
Low vaccine effectiveness against influenza A(H3N2) virus among elderly people in Denmark in 2012/13 – a rapid epidemiological and virological assessment

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<thead>
<tr>
<th></th>
<th>Adjust. VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-11 %</td>
<td>-41% - 14%</td>
</tr>
<tr>
<td>B</td>
<td>69 %</td>
<td>26% - 87%</td>
</tr>
</tbody>
</table>

K Bragstad¹,², H D Emborg²,³, T K Fischer¹, M Voldstedlund³, S Gubbels³, B Andersen¹, K Mølbak³, T G Krause (TGV@ssi.dk)³

Low vaccine effectiveness against influenza A(H3N2) virus among elderly people in Denmark in 2012/13 – a rapid epidemiological and virological assessment

K Bragstad1,2, H D Emborg2,3, T K Fischer4, M Voldstedlund3, S Gubbels3, B Andersen1, K Mølbak3, T G Krause (TGV@ssi.dk)3

Figure 2
Phylogenetic tree of 22 influenza A(H3N2) virus sequences coding for 520 amino acids of the viral haemagglutinin, Denmark, week 46 (14 November 2012) – week 2 (13 January 2013)

Low vaccine effectiveness against influenza A(H3N2) virus among elderly people in Denmark in 2012/13 – a rapid epidemiological and virological assessment

K Bragstad¹,², H D Emborg²,³, T K Fischer¹, M Voldstedlund³, S Gubbels³, B Andersen¹, K Mølbak³, T G Krause (TGV@ssi.dk)³

![Bar chart showing the number of trivalent influenza vaccines received vs. influenza A cases over weeks 39 to 52 of 2012 and weeks 1 to 4 of 2013.]

### Interim Adjusted Estimates of Seasonal Influenza Vaccine Effectiveness — United States, February 2013

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<tr>
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<th>Adjusted VE</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>A &amp; B</td>
<td>56 %</td>
<td>47 % - 63 %</td>
</tr>
<tr>
<td>A (H3N2)</td>
<td>47 %</td>
<td>35 % - 58%</td>
</tr>
<tr>
<td>B</td>
<td>67 %</td>
<td>58 % - 77%</td>
</tr>
</tbody>
</table>
Interim Adjusted Estimates of Seasonal Influenza Vaccine Effectiveness — United States, February 2013

<table>
<thead>
<tr>
<th>Age, (+) A H3N2</th>
<th>Adjusted VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mos – 17 yrs</td>
<td>58 %</td>
<td>38 % - 71 %</td>
</tr>
<tr>
<td>18 – 49 yrs</td>
<td>46 %</td>
<td>20 % - 63 %</td>
</tr>
<tr>
<td>50 – 64 yrs</td>
<td>50 %</td>
<td>15 % - 71 %</td>
</tr>
<tr>
<td>&gt;65 yrs</td>
<td>9 %</td>
<td>-84 % – 55 %</td>
</tr>
</tbody>
</table>
Improve vaccine efficacy

- Old vaccination may affect future vaccine efficacy
Recipients of Vaccine against the 1976 “Swine Flu” Have Enhanced Neutralization Responses to the 2009 Novel H1N1 Influenza Virus

Jonathan A. McCullers, Lee-Ann Van De Velde, Kim J. Allison, Kristen C. Branum, Richard J. Webby, and Patricia M. Flynn

A

% of sera achieving titer

No vaccine in 1976

Received 1976 vaccine

Seasonal H1N1

≥ 40

≥ 160

B

% of sera achieving titer

No vaccine in 1976

Received 1976 vaccine

Pandemic H1N1

≥ 40

≥ 160

*
Clinical associations-Side effects

• The flu shot can cause the flu
Does not cause the flu !!!

• Split-virion or subunit vaccines
  – Only surface proteins no infectious particles

• Misinterpretation
  – Chance of mild vaccine side effects
    • Mild fever, headache
  – Coincidental infection immediately post vaccination
Vaccination & Perceptions

- The side effects are worse than the flu

MYTH
Allergy to egg

• The majority of influenza vaccines in use
  – only trace amounts of ovalbumin (< 1 μg /dose)
  – can be safely given to most people w egg allergy

• Individuals w severe allergy to eggs
  – should seek specialist advice

Pregnancy

“Woe unto Them that are with Child”, Johnson, Lancet 1919

JAMA 1918, 1919
Pregnancy & breastfeeding

• Vaccination during pregnancy protects
  – mother
  – the offspring during first few months of life !!!

Seizures

- 2010 Fluvax “scare” in Australia
  - rate 1:100, acceptable background rate < 1:1000
  - Withdrawn from market, no other brand associated

- ↑ risk of sz when flu w PCV13 together
  - Additional 1.8 cases per 10,000 doses

Guillain Barre - A H1N1 pdm09

- 1 additional case for every 1 million people vaccinated against influenza

American Journal of Epidemiology 2012;175:1100-09, 1110-19, 1120-28, 1129-32
Multiple sclerosis

• There is definitive evidence against a substantial increased risk of MS exacerbation after influenza vaccine

Clinical associations-Side effects

• Immunocompromised people cannot be vaccinated
Vaccination with inactivated flu vaccine
Immunocompromised populations

- Can be administered safely
- Recommended annually
- Effectiveness might be suboptimal
  - Avoid vaccination during chemo or XRT
  - If vaccinated → Re-vaccinate 3 months post Rx d/c,
    HCT 4-6 months (1-2 doses)
- Vaccinate family, close contacts of patients!!!
**Rheumatoid Arthritis**

- Contradictory data on DMARDS
  - MTX / AZA modest effect on p immunization titers
  - 20-50% of pts --- no protection (flu)
    - ↓↓ response to FLU if MTX + TNF

- TNF blockers
  - mild inhibition of Ab response
  - can administer during Rx

---

Curr Opin Rheumatol 2008; 20:295
CID 2008; 46 :1459
British Society for Rheumatology 2010
Pharmacovigilance is necessary
Pharmacovigilance is necessary

In persons under 20 years of age Pandemrix, following link to very rare cases of narcolepsy in young people. Overall benefit-risk remains positive.
Flu vaccines for novel viruses

Human infection with a novel avian influenza virus, A(H7N9) – China

8 May 2013
WHO provisional recommendation on influenza A(H7N9) vaccine virus

31 May 2013

- An A/Anhui/1/2013-like* virus is used for the development of A(H7N9) vaccines for pandemic preparedness purposes.

* A/Shanghai/2/2013 is an A/Anhui/1/2013-like virus.
How long does it take to manufacture a new vaccine?

• It takes at least 5-6 months to produce a new influenza vaccine.
Seasonal flu vaccine

Virus Selection
- FDA advisory panel selects 3 strains
- CDC provides new strains of the seed virus to the FDA
- FDA distributes the 3 seed viruses to manufacturers

Production Begins

FDA Testing, Licensure
- Vaccine is filled into vials and syringes; packaged for distribution

Filling/Packaging
- Immunity develops approximately 2 weeks after vaccination

Product Release/Shipping

Vaccination Begins

http://www.niaid.nih.gov
Seasonal flu vaccine

THE PRODUCTION CYCLE
Rushing a swine flu vaccine is difficult; this timeline, using the United States as an example, illustrates how vaccine production takes at least six months from selecting a strain to producing the vaccine.

- WHO GISN*: Select strains
- WHO CC: Prepare reassortants
- WHO CC-CDC/FDA*: Standardize antigen
- FDA: Assign potency
- FDA: Review/license
- FDA: Formulate/test/package
- Manufacturers: Vaccinate

*World Health Organization Global Influenza Surveillance Network ¹WHO Collaborating Centres ²US Centers for Disease Control and Prevention ³US Food and Drug Administration

Source: CDC

http://www.niaid.nih.gov
• More than 20 countries have capacity to produce influenza vaccine
Countries currently producing seasonal vaccine

- Australia
- Canada
- France
- Germany
- Italy
- The Netherlands
- Switzerland
- The United Kingdom
- The United States
EXPERIENCE DURING 2009 PANDEMIC
WHO Global Influenza Surveillance Network (GISN)

Diagnostic kits made globally available: April
Vaccine strain recommendation: 2 May
Vaccine reassortants available: 26 May
Vaccine reassortants available: 27 May
Estimated Timeline of H1N1pdm Vaccine Development and Delivery in the U.S.

April
- CDC isolates H1N1 April 15
- WHO H1N1 vaccine virus recommendation April 27
- Vaccine virus reassortment started at CDC and NYMC April 25 and 28

May
- CDC ships high growth reassortant viruses to mfrs (X-179A and RG-15) May 26 and 27
- Working seed developed by vaccine manufacturers \(^(*)\) June 20-30
- Monovalent concentrate August \(^($)\)

June
- Test monovalent concentrate
- Pool monovalent concentrate
- CRER release, Sept 15 & 18 (N/sp)
- Filing September (at risk)
- September 30: Distribution
- Final September 30

July
- Final September 30

August
- FDA prepare potency test reagents: August 12, 2009

September
- 
- October 5: Start Vaccination

\(^(*)\) Manufacturers were transiently limited in their ability to develop seed viruses due to lack of facilities to grow virus in large volume at the required BSL3 biocontainment

\(^($)\) Production of monovalent inactivated vaccine is a continuous process

www.cdc.gov/H1N1flu
Timeline - 2009

- China, Oman
- Australia, Hungary
- USA
- Belgium, Italy, Sweden
- Denmark, Ireland, Israel, Qatar, Saudi Arabia, Singapore, Turkey
- Netherlands, Russian Federation, Switzerland, UAE
- Greece, Jordan, Spain
- Croatia, Cyprus, Romania
- Austria, Canada, Germany, Kuwait, Luxemburg, Portugal, Republic of Korea, Slovenia
- Albania, FYROM, Iran, Montenegro, Serbia

- 39 September
- 40 October
- 41 November
- 42 December
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53

UNICEF
World Health Organization
ESCMID Online Lecture Library
© by author
Estimated Pandemic vaccine coverage in entire populations 2009-10 (n=21)

- Sweden
- Finland
- Iceland
- Norway
- The Netherlands
- Spain
- Hungary
- Ireland
- Malta
- Romania
- Germany
- France
- Luxemburg
- Portugal
- Slovenia
- Italy
- Estonia
- Greece
- Cyprus
- Austria
- Czech Republic

Vaccination coverage %
# Data (Lab/ICU/Deaths) 
**Greece - 28 April 2011**

<table>
<thead>
<tr>
<th></th>
<th>Total 2009-10</th>
<th>Total 2010-11</th>
<th>Clinical high risk groups 2010-11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Samples tested</strong></td>
<td>18230</td>
<td>13072</td>
<td></td>
</tr>
<tr>
<td><strong>ICU - 28 April 2011</strong></td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Total ICU</strong></td>
<td>294</td>
<td>368</td>
<td>239 (64.9%)</td>
</tr>
<tr>
<td><strong>ICU bed demand- peak</strong></td>
<td>70</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td><strong>Total deaths</strong></td>
<td>149 (50.7%)</td>
<td>179 (48.6%)</td>
<td>144 (80.4%)</td>
</tr>
</tbody>
</table>
2010-2011 season

- 0.37 / 100,000
- 0.97 / 100,000
- 0.22 / 100,000
- 0.32 / 100,000
- 1.14 / 100,000
- 1.58 / 100,000
Vaccine received well despite scientific evidence

Over 300 million people have now been vaccinated against pandemic influenza and we have not seen any unusual safety events.
Vaccination coverage for seasonal influenza vaccine in older people (65 years and above) in EU and EEA countries

Latest seasonal available in spring 2009 - For Season 2007/8

Recommended 75% EU Target for 2014/15. Health Council 2009

Data available in spring 2008. Not available from: Austria, Cyprus, Czech Republic, Greece, Latvia

Vaccination & Perceptions

- People are afraid of the flu vaccine & other side effects
Rapid communications

Public perceptions in relation to intention to receive pandemic influenza vaccination in a random population sample: evidence from a cross-sectional telephone survey

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2. Opinion Marketing Research, Athens, Greece
3. First Department of Propaedeutic Medicine, Laiko General Hospital, Athens, University Medical School, Athens, Greece
4. Department of Psychiatry, Athens University Medical School, Athens, Greece
5. Department of Internal Medicine, University of Athens Medical School, Attikon University Hospital, Xaidari, Greece
6. Faculty of Political Science and Public Administration, University of Athens, Athens, Greece

This article was published on 10 December 2009.
Intention to receive pandemic vaccine

Figure 1
Trends in respondents’ intention to receive pandemic vaccine, Greece, 2009 (1,000 respondents per week)
Reasons for intention to decline pandemic vaccination as reported by 631 participants in week 44/2009 (multiple answers were allowed), Greece

- The vaccine might not be safe
- I do not believe the vaccine is effective
- The pandemic flu is mild
- I am not at risk of becoming ill with the pandemic flu
- I do not belong in the groups recommended for vaccination
- None of the above

Proportion of those intending to decline vaccination (%)
DATA FROM GREECE - HCW

• Nurses 2008 21.2%
  – Actual rates, 17 hospitals, 606 questionnaires
    » AJIC 2012 Apr;40(3):276-8

• 1ry care HCW 2008-09 22.8%
  – Mean vaccination rate - As low as 12%
    » Vaccine. 2010 Aug 23;28(37):5931-3

• HCW nationwide Oct 2009 21%
  – Intention to get vaccinated

• HCW Nov 2009 17%
  – Intention to get vaccinated
    » Eurosurveillance 2010 Feb
Less than 1/10 of HCW vaccinated

DATA FROM JOURNALISTS !!! - GREECE
Conclusions

• Influenza is a serious disease
• The flu vaccine remains the best way to prevent influenza
• It is safe, has minimal side effects & does not cause the flu
• We need to improve vaccine efficacy
• HCW are target group to ↑ vaccination rates
• Pandemic vaccination presents challenges