Current thinking about influenza vaccine efficacy and effectiveness
University of Otago, February 2012

Heath Kelly
Victorian Infectious Diseases Reference Laboratory
Australian National University
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  – James Fielding, Kristina Grant
## Key Events in Influenza Vaccine History in the United States

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1945</td>
<td>First military vaccine approved for routine use</td>
</tr>
<tr>
<td>1946</td>
<td>Civilian vaccine approved for use</td>
</tr>
<tr>
<td>1960</td>
<td>First recommendation for annual vaccination of civilians</td>
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<tr>
<td>1968</td>
<td>Split inactivated vaccine approved for use (akin to current inactivated vaccine)</td>
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<tr>
<td>1976</td>
<td>Swine flu vaccination effort</td>
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<tr>
<td>1977</td>
<td>Recognition of the value and role of US government in purchasing, delivering and administration of influenza vaccines</td>
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<tr>
<td>1978</td>
<td>Trivalent inactivated vaccine (TIV) usage became routine</td>
</tr>
<tr>
<td>1981</td>
<td>Antigen concentration of vaccine increased from 7 to 15 mcg</td>
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<tr>
<td>2003</td>
<td>Live attenuated influenza vaccine (LAIV) vaccine approved</td>
</tr>
<tr>
<td>2009</td>
<td>Monovalent H1N1 pandemic vaccine approved</td>
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<tr>
<td>2009</td>
<td>Fluzone® high-dose vaccine licensed (60 mcg)</td>
</tr>
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</table>
Vaccine efficacy/effectiveness: (both abbreviated as VE)

Concept introduced as ‘protective efficacy’ by Greenwood and Yule, 1915


Vaccine efficacy/effectiveness (VE)

- Percentage reduction in disease as a result of vaccination
- Compares disease outcome in vaccinated and unvaccinated
Vaccine efficacy and effectiveness

• Vaccine efficacy is also defined as
  – The proportion of persons in the placebo group of a vaccine trial who would not have become ill if they had received the vaccine

• \textit{Vaccine efficacy} is estimated from a trial

• \textit{Vaccine effectiveness} is estimated from an observational study \textit{Dictionary of Epidemiology}

• \textit{Efficacy} and \textit{effectiveness} studies of influenza should use influenza as the outcome
Hierarchy of Evidence

• Can it work? (Efficacy)
• Does it work? (Effectiveness)
• Is it worth it? (Cost effectiveness)

Professor Archie Cochrane
Pioneering Clinical Epidemiologist
Cochrane collaboration use of efficacy and effectiveness

- Cochrane review of influenza vaccine in adults aged 16-60 years
  http://summaries.cochrane.org/CD001269/vaccines-to-prevent-influenza-in-healthy-adults
- **Efficacy** is protection against laboratory confirmed influenza
  - Specific outcome
  - From trials or observational studies
- **Effectiveness** is protection against influenza-like illness (ILI)
  - Non-specific outcome
  - From trials or observational studies
- Non-standard use of *effectiveness*
  
  Kelly & Valenciano, *Lancet ID* 2011; October 26 online
Vaccine efficacy theoretical example

RCT of participants followed for one year

- 1,000 vaccinated
  - 80 with disease
- 1,000 unvaccinated
  - 800 with disease

- What is VE?
  - defined as the % reduction of cases among the vaccinated group
VE theoretical calculation

- 80/1000 vaccinated cases
- 800/1000 unvaccinated cases
- Denominators are the same, so can ignore
- Reduction of cases due to vaccination = 800 - 80 = 720
- Percent reduction = 720/800 cases
- VE = 90%
VE = 1 - RR from theoretical example

- 80/1000 vaccinated cases
  - symptomatic infection risk = 0.08
- 800/1000 unvaccinated cases
  - symptomatic infection risk = 0.8
- $VE = 1 - RR$
  
  $= 1 - \frac{0.08}{0.8}$

  $= 0.9$ (or 90%)
Study types and control selection

• Observational study designs used to estimate VE
• Control selection
### Observational study types used to measure VE

<table>
<thead>
<tr>
<th>Study type</th>
<th>Measure of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort – including household studies</td>
<td>Cumulative incidence (risk) ratio</td>
</tr>
<tr>
<td>Retrospective case control</td>
<td>Cumulative incidence (risk) odds ratio</td>
</tr>
<tr>
<td>Prospective case control</td>
<td>Incidence rate ratio</td>
</tr>
<tr>
<td>Case cohort</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>Test negative design</td>
<td>Risk ratio (?)</td>
</tr>
</tbody>
</table>
Control selection in a case control study

• Controls
  – usually without disease or with an unrelated disease
  – should be a (random) sample of the source population that gave rise to the cases
  – should represent the *person time* exposure of the source population
    • exposure is vaccination
    • exposure decreases risk of outcome
  – should theoretically be able to be chosen as a case if they had been subject to the same exposure as a case
Source population

Exposed

Unexposed

Sample

Cases

Controls:
Sample of the denominator
Representative with regard to exposure
The test negative design

- Derives its name from control selection
- Based on the case control design
- Can be retrospective or prospective
  - as is true for a case control study
- Cases have a clinical syndrome and test positive for the disease of interest
- Controls have the same clinical syndrome but *test negative* for the same disease
  - test specificity is critical

Brief remarks on methodological issues

- Immunogenicity is not VE
- Study endpoints
- Differences in vaccines by manufacturer
Immunogenicity is not effectiveness

• Immunogenicity
  – Quantification of immune response
  – For influenza vaccines, quantification is for humoral (not cellular) immunity usually by haemagglutination inhibition (HI) assay
  – Influenza vaccines are licensed annually on specific criteria
    • 70% of a sample of adults achieving 4-fold rise in titre or an HI titre of ≥40
    • HI titre of 40 shown to protect ~50% of volunteers in challenge studies from 1970s

• Immunogenicity is not effectiveness
Endpoint choice is critical

- VE studies need a specific outcome to monitor a specific intervention
  - PCR is preferred
  - More sensitive than culture and ~100% specific
- Serology will overestimate protection from inactivated vaccines
  - 166 rtPCR confirmed A(H3N2) cases over 3 years RCT
  - 90% placebo, 87% LAIV, 23% TIV infection confirmed by serology
  - Serology underdiagnoses cases in TIV recipients and hence overestimates VE

Vaccine types may not be interchangeable

- Licensed vaccine types
  - Trivalent or monovalent (pH1N1)
  - Inactivated
    - With/without adjuvant
    - Split vaccines
    - Sub-unit vaccines – H and N
  - Live attenuated vaccines

- Immunogenicity/effectiveness within vaccine type assumed similar for different manufacturers
- May not always be a valid assumption
  - Assumption proven not valid for safety

Influenza VE studies in Australia
WAIVE

- **Western Australia Influenza Vaccine Effectiveness** study
- Established to estimate VE as part of evaluation of state-wide influenza vaccine program for children 6-59 months in WA
- Implemented in 2008 after 3 deaths in 0-4 year olds associated with influenza in 2007
- General Practice (GP), Emergency Department (ED) and hospital inpatient components
- Test negative design in GP/ED
WAIVE 2008 VE

• Methods
  – Fully vaccinated = 2 doses >21 days apart and >14 days before symptom onset
  – Universal recruitment attempted
  – Logistic regression covariates: age-group, sex, pre-term birth, co-morbidities

• Results from ED/GP patients
  – 48 cases (29% vaccinated), 241 controls (47% vaccinated)
  – Crude VE = 54% (7 to 78)
  – Adjusted VE = 58% (9 to 81)
  – Adjusted VE = 68% (26 to 86) using children with other respiratory viruses detected as controls

  Kelly et al, PIDJ 2011; 29:6419-26
WAIVE 2009-2011

2009
• 431 patients, 79 with pH1N1
• Hospitalised patients
  VE =12% (-81 to 84) against pH1N1
• ED/GP patients
  VE = 36% (-18 to 66) against pH1N1

2010
• Vaccination program suspended because of increase in number of children with febrile convulsions following receipt of vaccine from a single manufacturer
  – Vaccine coverage ~16% before suspension of program
  – Vaccine coverage ~30% in 2008 and 2009

2011
• Mild influenza season with lower vaccine uptake
  – 2010 residual effect
FluCAN VE study design

- InFluenza Complications Alert Network
- 2010 VE study: 15 hospitals, all states
  - N = 182 cases and controls needed to estimate VE = 50% (vs VE = 0% with 90% power)
- Test negative design in hospitalised patients
  - Data on demographics, co-morbidities, previous seasonal influenza vaccine (5 years) and previous pneumococcal vaccine
  - Testing for influenza was physician dependent
FluCan VE 2010

- Vaccination status ascertained for ~70% cases and controls
- 302 cases (25% vaccinated) & 867 controls (54% vaccinated)
- VE = 32% (-9 to 57) against seasonal & pH1N1 influenza
- ~79% of cases were pH1N1
- Crude VE = 71% (54 to 82) against pH1N1
- Adjusted VE = 49% (13 to 70) against pH1N1
  - Adjusted for age>65, chronic illness and pregnancy

Chen et al, Vaccine 2011; 29:7320-5
FluCan VE 2011

- Vaccination status ascertained for ~45% cases and controls
  - Unanticipated problem with ethics at one site
- 129 cases (40% vaccinated) & 229 controls (55% vaccinated) with vaccination status known
- VE = 38% (-5 to 74) against seasonal & pH1N1 influenza

A/Prof Allen Chen, personal communication
Victorian Influenza Vaccine Effectiveness Audit (VIVEA)

- Test negative design using GP ILI surveillance data with laboratory testing since 2003
- Improved quality data from 2007 onwards
  - >90% vaccination status ascertained annually
- Methods
  - Testing at GP’s discretion
  - Data censored at 4 days between onset and testing
  - VE adjusted for age group, month of onset
  - Adjusted for co-morbidities and influenza vaccination in previous year only in 2011

Cases/controls sentinel surveillance 2007-2010

- Case: Data points
- Control: Data points

Significant differences at:
- 2008: p=0.020
- 2009: p=0.000
- 2010: p=0.030

Count of cases/controls
VIVEA results 2007-11

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude VE</th>
<th>Adjusted VE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>194</td>
<td>192</td>
<td>57%</td>
<td>59% (25 to 78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(27 to 75)</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>106</td>
<td>224</td>
<td>26%</td>
<td>9% (-96 to 58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-40 to 61)</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>267</td>
<td>476</td>
<td>19%</td>
<td>3% (-48 to 37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-20 to 45)</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>139</td>
<td>180</td>
<td>80%</td>
<td>79% (33 to 93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(39 to 93)</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>155</td>
<td>374</td>
<td>60%</td>
<td>57% (-11 to 83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(19 to 80)</td>
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</tbody>
</table>
VIVEA summary

- >67% of sentinel patients in age range 20-64 years
- For 20-64 year age group for 2007-11 excluding 2009 (pandemic)
  - VE = 64% (23 to 75) with additional adjustment for year
- Limitations of observational studies in general and TND in particular
  - Compare with Australian RCT
CSL vaccine trial

- RCT 2008-9, influenza vaccine vs placebo
- Multi centre trial, Australia & NZ until Nov 2009
- Healthy adults 18-64 years
- 9827 vaccine, 4907 placebo recipients
- Outcome: ILI due to lab confirmed influenza
- VE = 60% (44 to 72) when match was good
- VE = 42% (30 to 52) for both years
  - 2009 mostly pH1N1

## Australia VE summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design Setting</th>
<th>Age group</th>
<th>VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIVE</td>
<td>2008</td>
<td>TND GP &amp; ED</td>
<td>6-59m</td>
<td>68% (26 to 86) against all strains</td>
</tr>
<tr>
<td>FluCAN</td>
<td>2010</td>
<td>TND Hospital</td>
<td>≥18y</td>
<td>49% (13 to 70) against pH1N1</td>
</tr>
<tr>
<td>FluCAN</td>
<td>2011</td>
<td>TND Hospital</td>
<td>≥18y</td>
<td>38% (-5 to 74) against all strains</td>
</tr>
<tr>
<td>VIVEA</td>
<td>2007-11</td>
<td>TND Community</td>
<td>20-64y</td>
<td>64% (25 to 75) against all strains</td>
</tr>
<tr>
<td></td>
<td>not 2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSL</td>
<td>2008-9</td>
<td>RCT Community</td>
<td>18-64y</td>
<td>60% (44 to 72) against matched strains</td>
</tr>
</tbody>
</table>
Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis

Michael T. Osterholm, Nicholas S. Kelley, Alfred Sommer, Edward A. Belongia

Summary

Background  No published meta-analyses have assessed efficacy and effectiveness of licensed influenza vaccines in the USA with sensitive and highly specific diagnostic tests to confirm influenza.

Methods  We searched Medline for randomised controlled trials assessing a relative reduction in influenza risk of all circulating influenza viruses during individual seasons after vaccination (efficacy) and observational studies meeting inclusion criteria (effectiveness). Eligible articles were published between Jan 1, 1967, and Feb 15, 2011, and used RT-PCR or culture for confirmation of influenza. We excluded some studies on the basis of study design and vaccine characteristics. We estimated random-effects pooled efficacy for trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV) when data were available for statistical analysis (eg, at least three studies that assessed comparable age groups).

Findings  We screened 5707 articles and identified 31 eligible studies (17 randomised controlled trials and 14 observational studies). Efficacy of TIV was shown in eight (67%) of the 12 seasons analysed in ten randomised controlled trials (pooled efficacy 59% [95% CI 51-67]) in adults aged 16-65 years. No such trials met inclusion criteria for children aged 2–17 years or adults aged 65 years or older. Efficacy of LAIV was shown in nine (75%) of the 12 seasons analysed in ten randomised controlled trials (pooled efficacy 83% [93-99]) in children aged 6 months to 7 years. No such trials met inclusion criteria for children aged 8–17 years. Vaccine effectiveness was variable for seasonal influenza, as 17 analyses in nine studies showed significant protection against medically ascribed influenza in the contacts or household setting. Median monovalent pandemic H1N1 vaccine effectiveness in five observational studies was 69% (range 46-93).

Interpretation  Influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Evidence for protection in adults aged 65 years or older is lacking. LAIVs consistently show higher efficacy in young children (aged 6 months to 7 years). New vaccines with improved clinical efficacy and effectiveness are needed to further reduce influenza-related morbidity and mortality.

Funding  Alfred P. Sloan Foundation.

Introduction

The main strategy for prevention and control of seasonal and pandemic influenza for the past 60 years has been vaccination. The first population-scale use of an inactivated influenza vaccine was in US military personnel in 1945.1 In 1969, the US Surgeon General, in response to substantial mortality and mortality during the 1957–58 pandemic, recommended annual influenza vaccination for individuals with chronic debilitating disease, people aged 65 years or older, and pregnant women. This recommendation was made without data for vaccine efficacy or effects for these high-risk populations. Instead, it was made on the basis of studies showing efficacy in young, healthy military recruits with clinical illness or service-enlistment as primary measures of infection. In 1964, the Advisory Committee on Immunization Practices (ACIP) reaffirmed this recommendation but noted the absence of efficacy data, because of the longstanding public health recommendation of annual vaccination in the elderly and other high-risk groups, such patients have been excluded from placebo-controlled randomised clinical trials in the USA for the past 50 years. The ACIP supports the widely held view that influenza vaccination of individuals at high-risk of influenza in placebo-controlled trials would be unethical. In 2010, the ACIP established the first recommendation of national universal seasonal influenza vaccination.2 Vaccination every year is now recommended with trivalent inactivated vaccine (TIV) for all individuals aged 6 months or older, or live attenuated influenza vaccine (LAIV) for healthy non-pregnant people aged 2-49 years.3 In the USA, TIV has been used since 1978 and accounts for approximately 90% of influenza vaccines given at present.4 The LAIV was first approved for use in the USA in 2003 and accounts for approximately 9% of the vaccine given.5 The universal influenza vaccination recommendation came after a decade of incremental changes during which the ACIP expanded recommendations to include an ever-increasing proportion of the US population. Previous meta-analyses of TIV or LAIV efficacy and effectiveness have included studies that used diagnostic...
Summary of efficacy studies (trials) in adults

- Adults 18 to 64 years
  - TIV vaccine efficacy
    - 6/9 demonstrated efficacy (lower 95% CI >0%)
    - Meta-analysis, random effect:
      \[ VE = 59\% \text{ (51 to 67)} \]
    - Median: \( VE = 62\% \text{ (16 to 75)} \)
  - LAIV efficacy = 8%, 48% and 36%
    - 0/3 demonstrated efficacy (\( p<0.05 \))
- Adults \( \geq 65 \) years of age
  - Questionable evidence for LAIV and no evidence for TIV
Summary of efficacy studies (trials) in children

- Healthy children 6 months to 7 years of age
  - TIV efficacy = -7% and 66%
  - LAIV efficacy
    - MH, random effect = 83% (69 to 91)*
    - Median: 78% (57 to 93)

* Excluded Bracco Neto et al (2009)
Summary of effectiveness studies (observational)

Seasonal Influenza

- 6/17 (35%) demonstrated effectiveness
- VE for medically-attended influenza, adults
  - 2003-2008: median 44% (7 to 72)
- VE for medically-attended influenza, adults ≥ 65 years
  - 79% (-26 to 96) and 59% (15 to 80)
- VE for hospitalization adults ≥ 50 years of age
  - 1 study over 3 years without significant protection for any season
I-MOVE:
Monitoring IVE in EU and EEA Studies since 2008/9
Multi-centre case control
8 flu VE case-control studies in 2010/11 season
Very similar protocols pooled analysis:
- To obtain summary, preliminary VE measures
- To enable controlling for all covariates
Sample size for complete case and imputed datasets, multi-centre case control study, EU, 2010-11

Total records: 4410

No missing seasonal vaccination data: 4390

No missing data for covariates: 3254

Multiple imputation data: 4410

Complete case analysis
ILI influenza positive and negative cases, by week of symptom onset (N=4410), multi-centre case control study, EU, 2010-11

![Graph showing ILI cases by week of symptom onset for 2010 and 2011. The graph compares controls and any flu cases.](image-url)
VE of seasonal vaccine against all influenza, imputed analysis, multi-centre case control study, EU, 2010-11

* Study site in model as a fixed effect
‡ adjusted for 10 year age groups, sex, week of onset, chronic diseases and related hospitalisations, smoking, pandemic and seasonal influenza vaccination in 2009-10 and number of practitioner visits in the previous year
Conclusions from the meta-analysis

• Inactivated influenza vaccines can provide moderate protection (~60%) but such protection is greatly reduced or absent in some seasons

• RCT evidence for protection in those ≥ 65 years and ≤ 2 years is limited

• Based on a track record of substantial safety and moderate effectiveness in some seasons, influenza vaccines can play a role in reducing influenza morbidity
Discussion

• Future influenza vaccines that use the same or similar hemagglutinin antigen regardless of production methods may not provide any more protection than current vaccines
• We need a new generation of more highly effective and cross-protective vaccines that can be manufactured rapidly
• Observational study designs need continued improvement in order to monitor effectiveness of new generation vaccines when available