Do flu shots really work? Are they safe?

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DLSPH DOCTORAL SEMINAR SERIES

OCTOBER 31, 2013

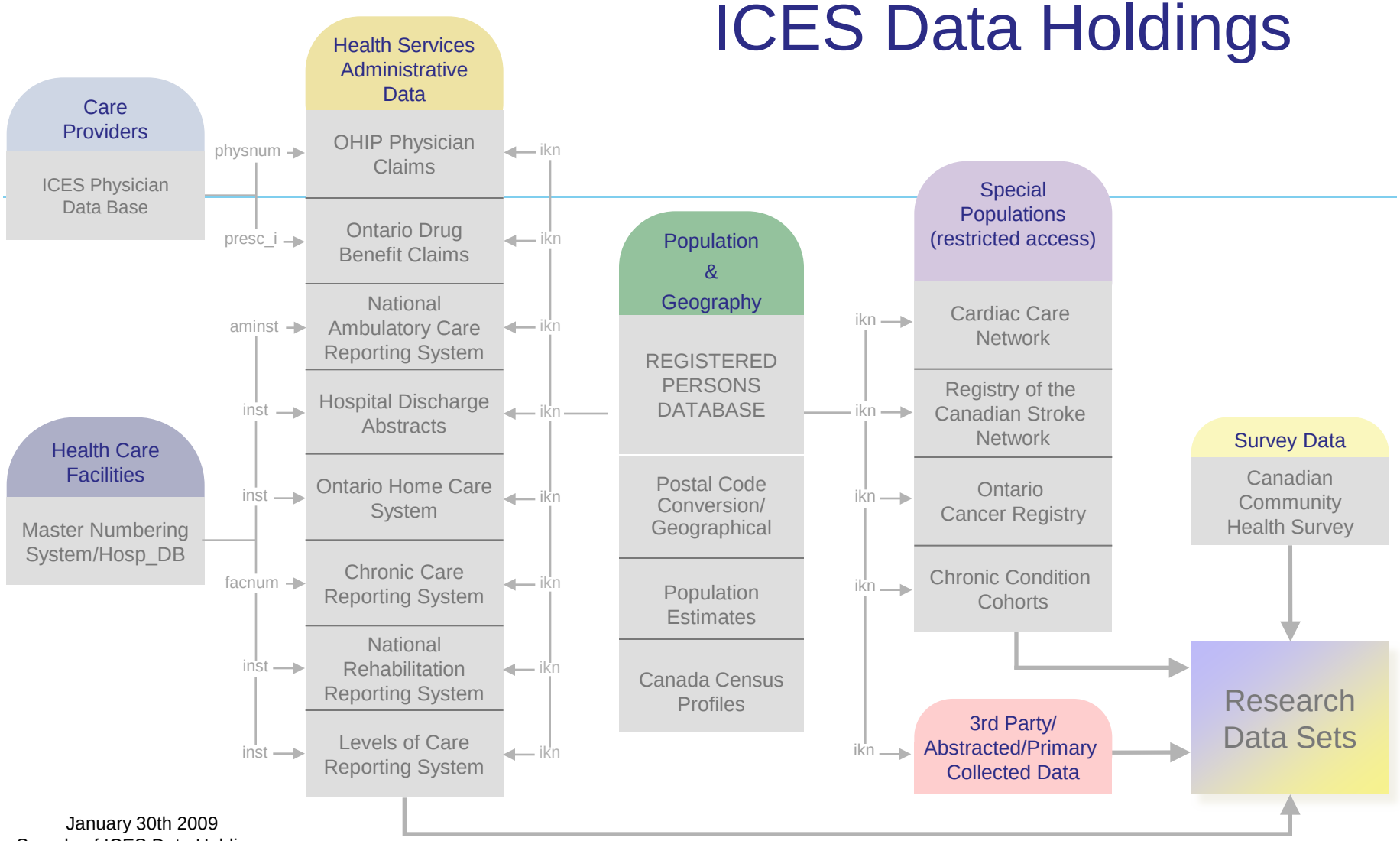
Learning objectives

- To understand some of the controversies related to influenza vaccine effectiveness in the elderly
- To learn about the safety of influenza vaccines
- To appreciate the indirect benefits of influenza vaccines

Institute for Clinical Evaluative Sciences

- ICES is an independent, non-profit research organization that evaluates health care services and delivery to meet the changing needs of the people of Ontario
- Funded by the Ontario Ministry of Health and Long-Term Care and peer-reviewed research grants from provincial and national organizations (e.g., Canadian Institutes of Health Research)
- ICES houses health administrative and other data for the province under strict privacy rules

ICES Data Holdings



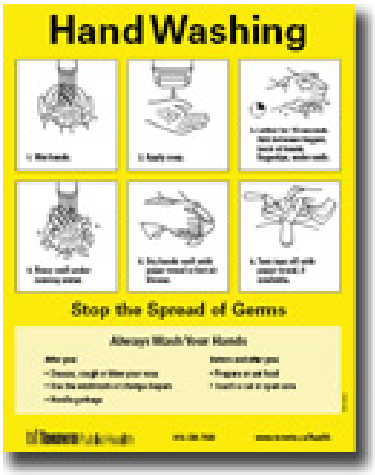
January 30th 2009
Sample of ICES Data Holdings

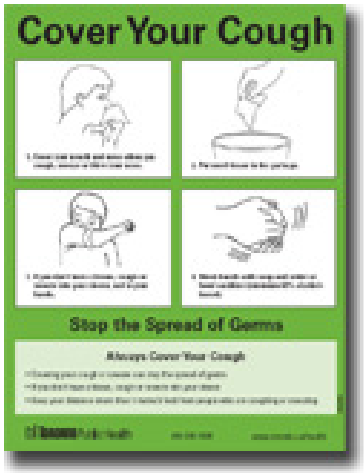
Burden of illness from influenza

- Annual influenza epidemics cause significant morbidity, mortality, and societal disruption
  - Annual age-specific incidence of 5-10%
  - Average ~4000 deaths in Canada annually
  - Elderly, young children, and those with chronic illnesses at higher risk of serious outcomes
  - Older children and working-age adults miss school or work

Protecting yourself and others

- Annual vaccination
- Hand hygiene
- Respiratory etiquette
- Social distancing





Do flu shots really work?

USA TODAY NEWS SPORTS LIFE MONEY TECH TRAVEL OPINION 85°

Flu vaccine barely worked in people 65 and older

2:28 p.m. EST February 21, 2013

Hospitalizations and deaths have been some of the highest ever recorded for the elderly.

(Photo: Timothy A. Clary, AFP/Getty Images)

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This season's flu vaccine was almost completely ineffective in people 65 and older, which could explain why rates of hospitalization and death have been some of the highest ever recorded for that age group, according to early estimates released Thursday by the Centers for Disease Control and Prevention.

For people under 65, getting vaccinated this season reduced the need to go to the doctor for the flu by one-half to two-thirds.

For those 65 and older, though, it helped in just 9% of cases, a number too low to be statistically significant, according to a report in the CDC's *Weekly Morbidity and Mortality Report* released

STORY HIGHLIGHTS

- Just 9% of people age 65 and older benefited from flu shots this year
- Under 65, it was much more effective
- Still, experts say a little protection is better than

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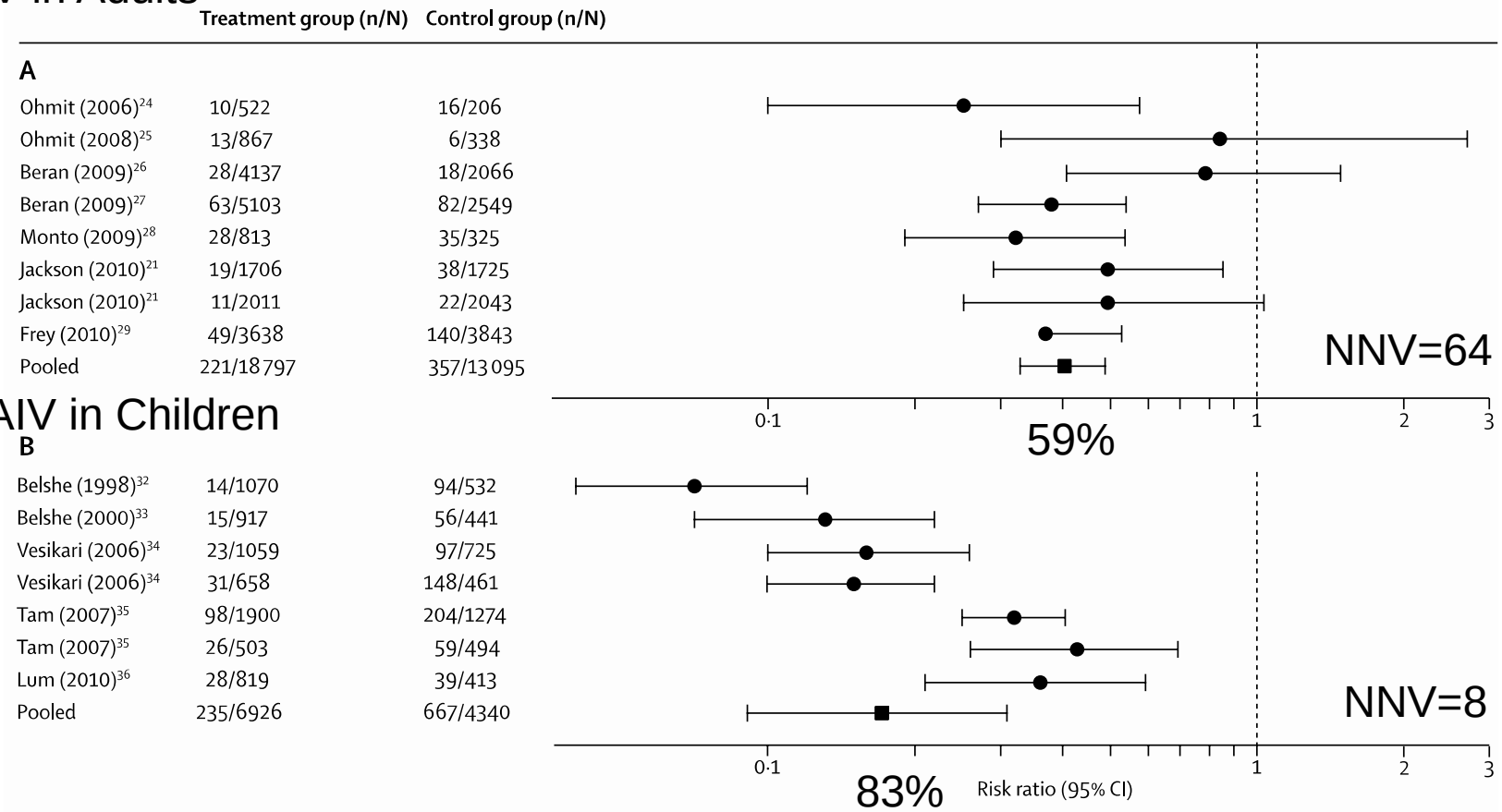
USA NOW

Twitter shuts down juror's USA NOW video

Jul 16, 2013

Influenza vaccines work for healthy adults & children

TIV in Adults



LAIV in Children

Osterholm MT, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet ID* 2012;12:36.

But doc, I still got sick last year even though I got the flu shot…

- Many other respiratory viruses circulate throughout the fall and winter:
  - Respiratory syncytial virus, adenovirus, parainfluenza viruses, coronaviruses, enteroviruses, rhinoviruses, human metapneumovirus, etc.
- Impossible to distinguish influenza from other respiratory viruses

Colds versus the Flu

Symptom	Cold	Influenza
Fever	Rare	Usual; high fever (102 ° F/39 ° C - 104 ° F, 40 ° C), sudden onset, lasts 3 to 4 days.
Headache	Rare	Usual; can be severe
Muscle aches and pains	Sometimes, generally mild	Usual; often severe
Tiredness and weakness	Sometimes, generally mild	Usual; severe, may last up to 2 to 3 weeks
Extreme tiredness	Unusual	Usual; early onset, can be severe
Runny, stuffy nose	Common	Common
Sneezing	Common	Sometimes
Sore throat	Common	Common
Chest discomfort, coughing	Sometimes, mild to moderate	Usual, can become severe.
Complications	Can lead to sinus congestion or infection, and ear aches.*	Can lead to pneumonia and respiratory failure, and become life-threatening. Can worsen a chronic condition.
Prevention	Frequent hand washing	Annual immunization and frequent hand washing

Influenza has a wide spectrum of illness

- Review of volunteer challenge studies
  - 56 studies with 1280 healthy participants
  - Viral shedding increases sharply 0.5-1 day after challenge, peaks on day 2; mean duration 4.8 days
  - Symptoms increase on day 1, peak on day 3
  - Symptomatic infection: 67% (95% CI, 58-75%)
  - Fever in 37% A/H1N1, 41% A/H3N2, 8% B

Carrat F, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *American Journal of Epidemiology* 2008;167:775-85.

Cold versus Flu (from the CDC website)

What is the difference between a cold and the flu?

The flu and the common cold are both respiratory illnesses but they are caused by different viruses. Because these two types of illnesses have similar flu-like symptoms, it can be difficult to tell the difference between them based on symptoms alone. In general, the flu is worse than the common cold, and symptoms such as fever, body aches, extreme tiredness, and dry cough are more common and intense. Colds are usually milder than the flu. People with colds are more likely to have a runny or stuffy nose. Colds generally do not result in serious health problems, such as pneumonia, bacterial infections, or hospitalizations.

How can you tell the difference between a cold and the flu?

Because colds and flu share many symptoms, it can be difficult (or even impossible) to tell the difference between them based on symptoms alone. Special tests that usually must be done within the first few days of illness can be carried out, when needed to tell if a person has the flu.

Do influenza vaccines work for the elderly?

- 2007 Cochrane Review: In community-dwelling elderly, well-matched vaccines prevent hospital admission for influenza or pneumonia (VE 27%) and all-cause mortality (VE 47%).

Vaccines for preventing influenza in the elderly (Review)

Rivetti D, Jefferson T, Thomas R, Rudin M, Rivetti A, Di Pietrantonj C, Demicheli V

But…

- Scarce RCTs, used immunogenicity or influenza infection (defined using serology) as the outcome
  - Govaert, 1994: VE 50% (35%-61%) for ≥60 years
- Bulk of evidence for serious outcomes (hospitalizations, mortality) based on observational studies
  - Non-specific outcomes
  - Selection bias and residual confounding

Influenza accounts for only 5% of all-cause mortality

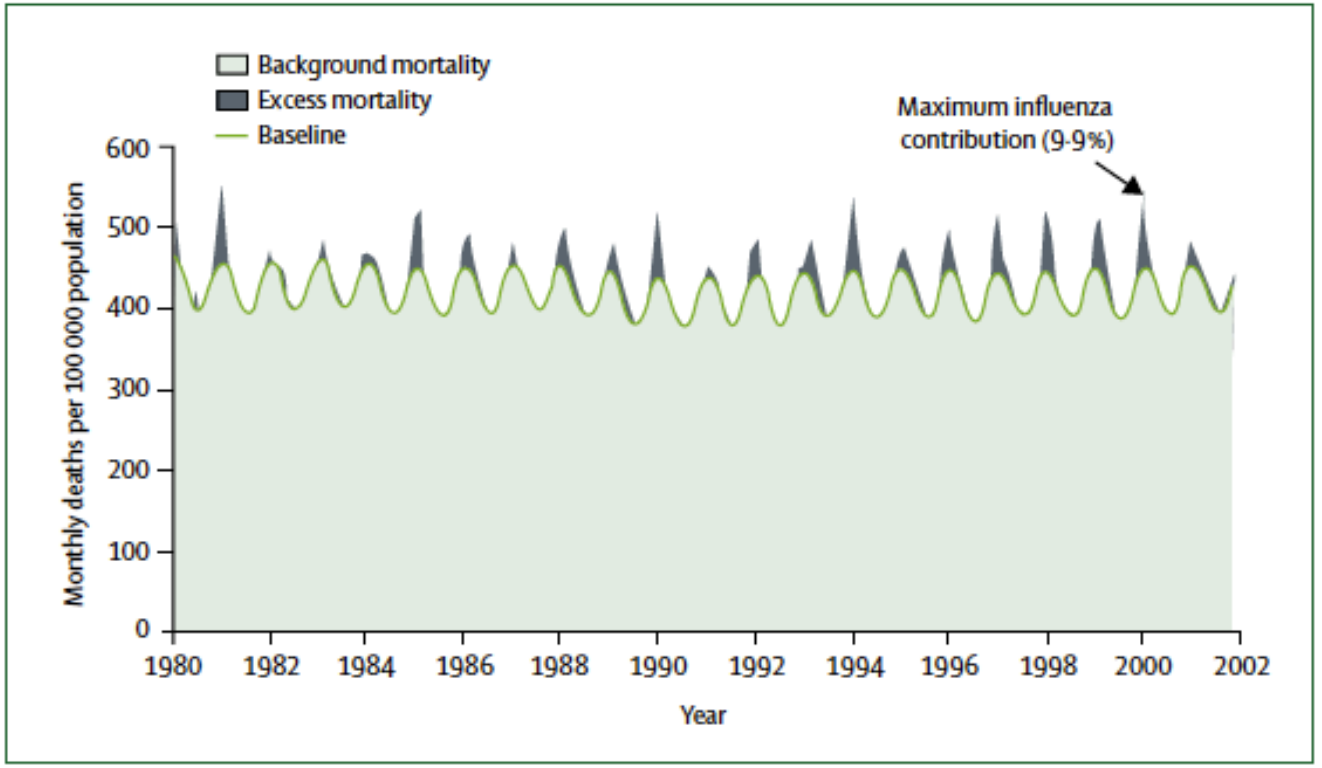
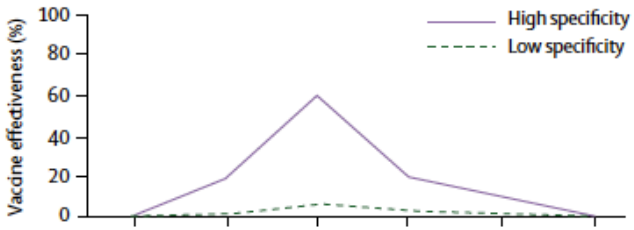


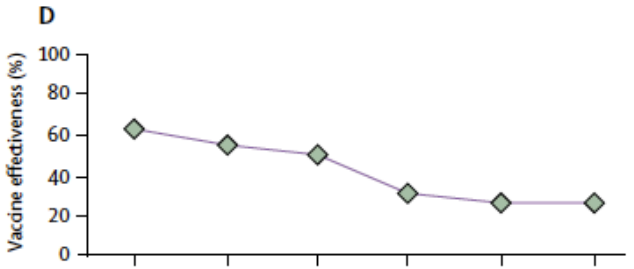
Figure 1: **Monthly national all-cause mortality rates in all US elderly people aged 65 years or more, 1980–2001**
The total winter-seasonal fraction of mortality attributed to influenza in national excess mortality studies averaged 5%, and was always less than 10%. Based on data from Simonsen et al.[6]

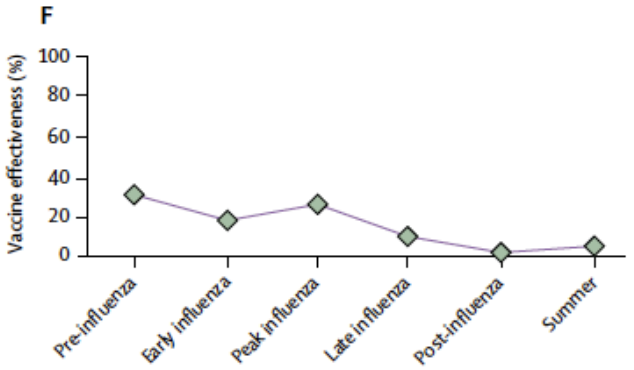
Simonsen, *et al*. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. *Lancet ID*. 2007. 7:658-66.

Using seasonality to detect bias in cohort studies

- Expected
- All-cause mortality (observed)
- Pneumonia and influenza hospitalizations (observed)







Data from Jackson LA, *et al*. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epi*. 2006. 35:337-44.

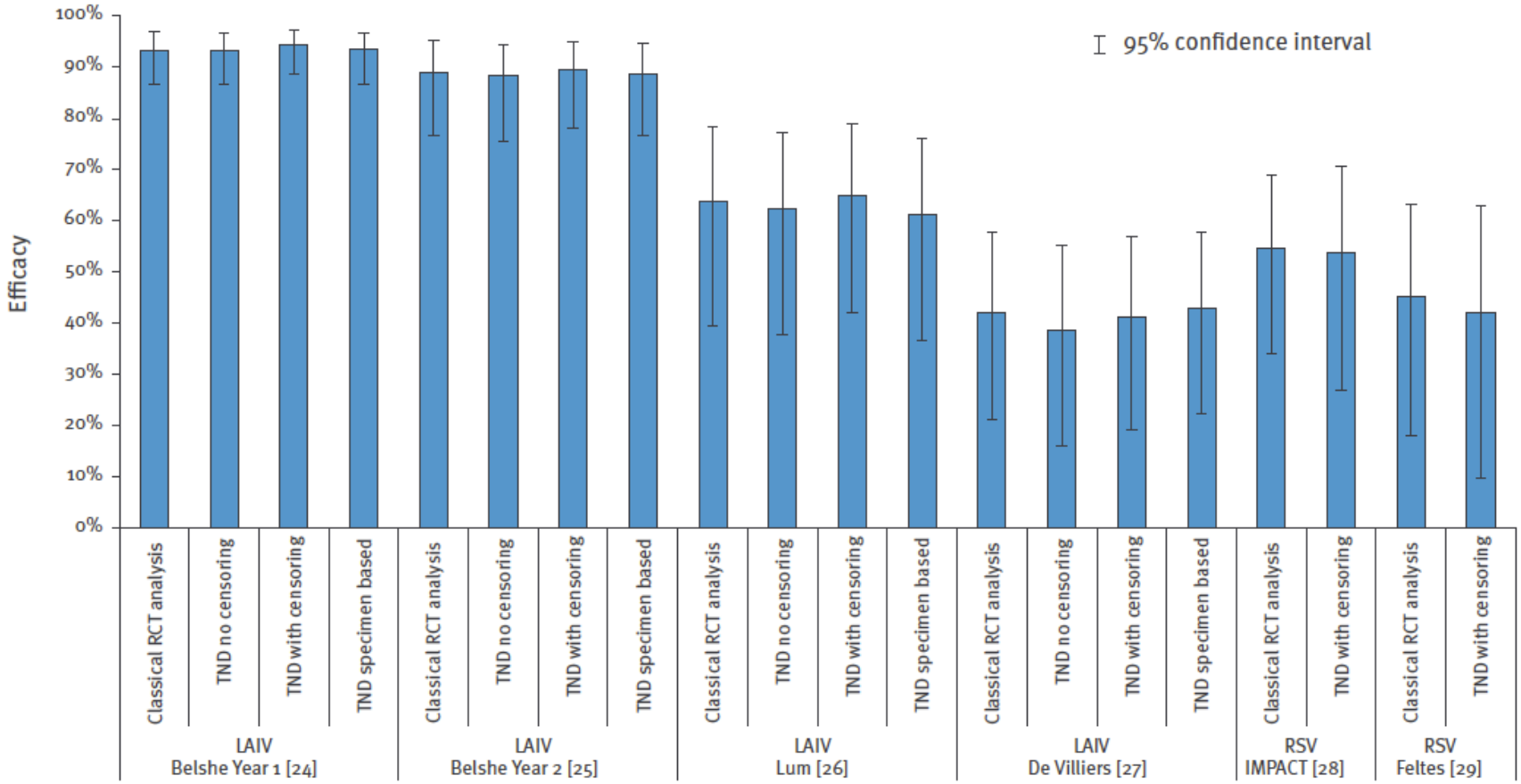
Vaccine effectiveness against laboratory-confirmed influenza hospitalizations among elderly adults during the 2010-11 season

Kwong JC, Campitelli MA, Gubbay JB, Peci A, Winter A, Olsha R, Turner R, Crowcroft NS. *CID*. 2013 Sep; 57:820-7.

Methods

- Test-negative design
- Linked 25,533 respiratory specimens tested for influenza by Public Health Ontario laboratories to ICES data
- Community-dwelling adults aged >65 years tested using NAAT for influenza during hospitalization – divided into test-positives and test-negatives
- Influenza vaccination determined from OHIP billing claims
- Used logistic regression to estimate VE (1 – adjusted OR) x 100%
- Adjusted for demographics, prior healthcare use, risk factors for influenza complications, and month of influenza test

Test negative design vs. RCTs



De Serres G, et al. The test negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomized placebo-controlled trials. Euro Surveillance 2013 Sept

Results (569 test-positives, 1661 test-negatives)

Analysis	Adjusted VE (95% CI)
Overall	42 (29-53)
By influenza subtype	
A/H3N2	40 (26-52)
A/H1N1	90 (51-98)
B	13 (−77-58)
By age group	
66-75 years	43 (16-61)
76-85 years	43 (22-59)
≥86 years	42 (12-62)

Results

Analysis	Adjusted VE (95% CI)
By outcome severity	
Hospitalization only	37 (20-51)
Needing ICU stay	52 (28-69)
Death within 90 days	46 (10-68)
By month of testing	
December 2010	51 (24-69)
January 2011	47 (27-61)
Feb/March/April 2011	34 (5-54)
Optometry assessments	−21 (−50-2)

Limitations

- Vaccines given outside of doctors' offices not captured by OHIP; non-differential under-ascertainment of influenza vaccination would bias estimates toward null
- Non-systematic testing of patients
- Possibility of residual confounding

Conclusions

- Receipt of 2010-2011 influenza vaccine associated with 42% (29%-53%) reduction in influenza hospitalizations in elderly
- Results consistent with previous test-negative studies of VE vs. influenza *infection*; first time significant estimate obtained for admissions in elderly
- Test-negative design believed to produce unbiased results
- Estimating influenza VE by linking routinely-collected administrative and lab data is feasible and inexpensive
- Using outcomes that are both highly specific and serious may better inform vaccine planning and decision-making

Next steps

- Awarded CIHR grant to link more specimens to admin data
  - Specimens tested by hospitals not submitting to PHO
  - 4 seasons (2010-11, 2011-12, 2012-13, 2013-14)
- Objectives:
  1. Determine risk of MI and stroke following laboratory-confirmed influenza infection
  2. Estimate influenza VE against laboratory-confirmed hospitalizations and deaths among elderly, young children, and those with chronic conditions (diabetes, COPD, asthma, heart disease, etc.)

Are flu shots safe?


MACKAY
BUT MOM, I WANTED TO BE THE SWINE FLU VIRUS THIS HALLOWEEN!
TRUST ME, YOU'RE MUCH SCARIER AS THE UNREGULATED ADJUVANT H1N1 VACCINE.

Safety of influenza vaccines

- Most common adverse events following influenza immunization among adults are local tenderness/erythema (NNH=3) and myalgia (NNH=42)
- But fear of serious adverse events, including Guillain-Barré Syndrome (GBS), may be one reason for suboptimal vaccine coverage

Guillain-Barré Syndrome

- Autoimmune, acute demyelinating peripheral neuropathy
- 0.62-2.66 cases per 100,000 annually (depending on age and sex)
- Commonly associated organisms: *Campylobacter jejuni*, EBV, CMV, *Mycoplasma pneumoniae* (molecular mimicry)
- Most require admission, 25% have respiratory failure
- Most recover, but 14% permanently disabled and 4% die

GBS after influenza vaccination

- First reported association after 1976 Swine Flu vaccination campaign in U.S.
  - 4-8x increased risk within 6 weeks of vaccination
  - Attributable Risk (AR) = 1 case per 100,000 vaccinated
- Studies of seasonal influenza vaccine since have shown weak or no association
  - Small sample sizes, suboptimal study designs
- A few recent studies found increased risk of GBS after influenza *illness*

Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza health-care encounters: a self-controlled study

Jeffrey C Kwong, Priya P Vasa, Michael A Campitelli, Steven Hawken, Kumanan Wilson, Laura C Rosella, Therese A Stukel, Natasha S Crowcroft, Allison J McGeer, Lorne Zinman, Shelley L Deeks

Self-controlled risk interval design

- Minimizes confounding by having each person serve as their own control
- Requires individuals who have a history of both the exposure (either influenza vaccination or influenza-coded healthcare encounter) and the outcome (GBS-coded hospitalization) within 42 weeks
- Looks for clustering of events in the risk interval (weeks 1-6) compared to the control interval (weeks 9-42)

GBS after influenza vaccination

Analysis	Relative Incidence (95% CI)
Primary (risk interval 6 weeks)	1.52 (1.17-1.99)
Narrower risk intervals	
Week 1	0.95 (0.47-1.92)
Week 2	1.76 (1.01-3.08)
Weeks 3 and 4	2.03 (1.39-2.97)
Weeks 5 and 6	1.22 (0.76-1.97)
Weeks 2-4	1.94 (1.41-2.68)
Adjusting for potential misclassification of GBS	1.84 (1.28-2.60)

GBS after influenza vaccination

Analysis	Relative Incidence (95% CI)
Primary (risk interval 6 weeks)	1.52 (1.17-1.99)
By age group	
<18 years	1.66 (0.46-6.03)
18-64 years	2.31 (1.55-3.42)
≥65 years	1.09 (0.74-1.61)
Non-vaccine injections	1.21 (0.80-1.82)

GBS after an influenza-coded healthcare encounter

Analysis	Relative Incidence (95% CI)
Primary (risk interval 6 weeks)	15.81 (10.28-24.32)
Narrower risk intervals	
Week 1	61.63 (39.25-96.75)
Week 2	14.57 (7.41-28.65)
Weeks 3 and 4	3.64 (1.51-8.80)
Weeks 5 and 6	2.43 (0.85-6.92)
Adjusting for potential misclassification of GBS	24.96 (16.02-38.73)
Acute respiratory infections	11.77 (10.38-13.35)

GBS after an influenza-coded healthcare encounter

Analysis	Relative Incidence (95% CI)
Primary (risk interval 6 weeks)	15.81 (10.28-24.32)
By age group	
<18 years	11.07 (4.74-25.87)
18-64 years	19.16 (10.34-35.51)
≥65 years	15.02 (6.32-35.74)
Dermatitis-coded visits	1.25 (0.84-1.86)
Periodic health examinations	1.32 (0.95-1.83)

Attributable risks of GBS

- 1.03 GBS admissions per million vaccinations
- 1 GBS admission per 971,567 vaccinations

- 17.2 GBS admissions per million influenza encounters
- 1 GBS admission per 58,108 influenza encounters

Limitations

- Validity of GBS diagnosis: relied on ICD coding to identify GBS cases (PPV=61%; led to underestimation of effects)
- Uncertain if milder or asymptomatic influenza infections carry same risk of GBS as illnesses leading to healthcare encounters
- Do not have dates of symptom onset for GBS cases or influenza infections
- Limited to influenza vaccines given in MD offices – may not be representative of all vaccine recipients

Conclusions

- Risk of GBS much greater after an influenza illness than after influenza vaccination, although both risks are small
- Greatest risk of GBS following influenza vaccination during weeks 2-4
- Greatest risk of GBS following influenza healthcare encounter is week 1 (delay from infection to seeking care)
- Likely trigger of GBS after influenza vaccination is influenza antigens in vaccine
- Patients should be informed of risks of GBS from both influenza vaccines and influenza illness, as well as the more substantial direct and indirect benefits from immunization

Will vaccinating children against influenza protect others?

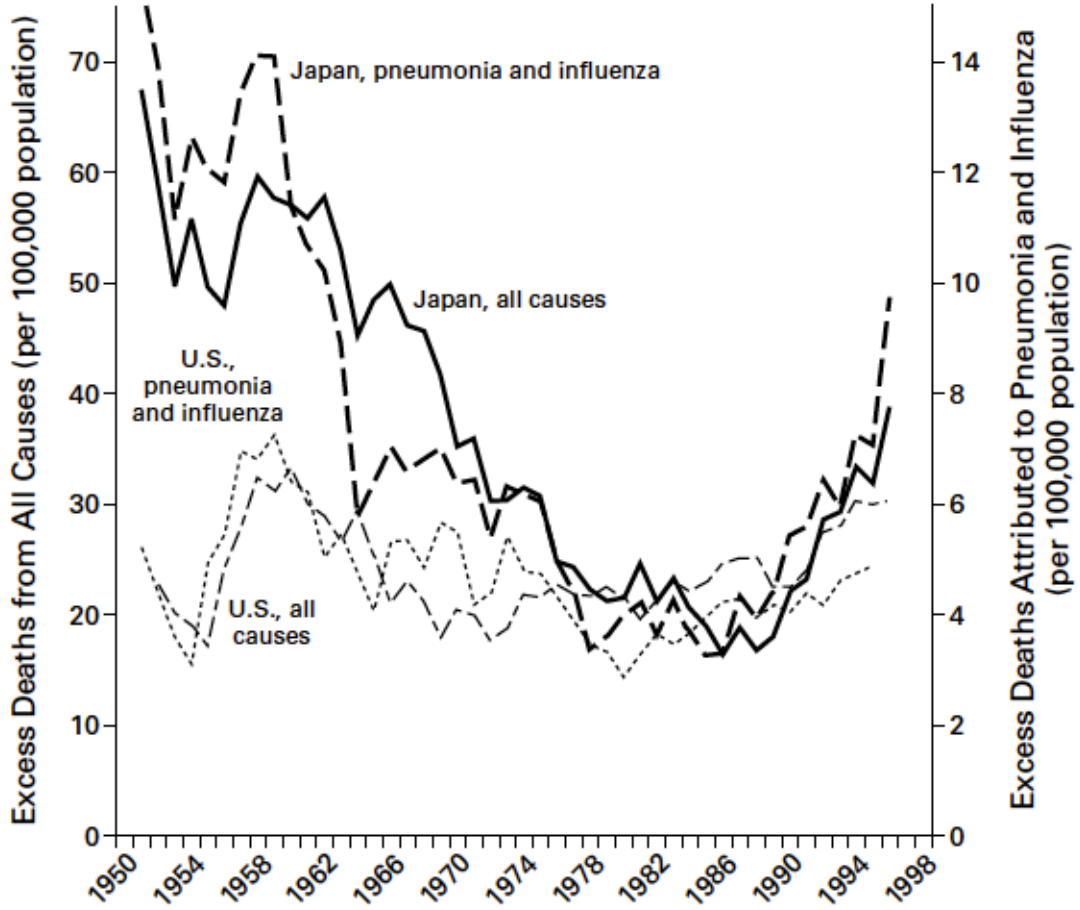
Paradox of influenza vaccination programs

- Targeting high-risk groups only confers direct protection to vaccinated individuals
- Individuals at greatest risk of influenza complications generally get the least protection from influenza vaccines
- School-age children have the highest rates of influenza infection, driving influenza epidemics by transmitting to peers and household contacts
- Vaccinating children to protect high-risk groups through herd immunity has been considered since the 1960s

Japanese experience

- Japan vaccinated schoolchildren against influenza between 1962 and 1994 (mandatory from 1977 to 1986)
- Obtained coverage of 50-85% in children
- High-risk groups not vaccinated

Mortality in elderly decreased during program



Reichert, *et al*. The Japanese experience with vaccinating schoolchildren against influenza. *NEJM* 2001. 344:889-96.

Hutterites

- Communal Anabaptists who live in communal colonies in rural Alberta, Saskatchewan, and Manitoba

Hutterite studies

- In 2008-09, 49 colonies were randomized to either influenza vaccine or hepatitis A vaccine for children aged 3-15 years
- Other colony members did not receive influenza vaccine
- Mean influenza vaccine coverage of 83% (range 53%-100%) among children associated with 61% (95% CI 8%-83%) reduction in PCR-confirmed influenza for non-recipient colony members

- Follow-up study comparing LAIV vs. TIV in progress

Loeb, *et al*. Effect of influenza vaccination of children on infection rates in Hutterite communities. *JAMA* 2010. 303:943-50.

But what about in the real world?

- **R**andomized **E**valuation of **L**ive **A**ttenuated vs. **T**rivalent **I**nactivated influenza **V**accin**E**s in **S**chools (RELATIVES)
- Pilot cluster-randomized trial comparing LAIV vs. TIV given through elementary schools during 2013-14 influenza season in Peterborough, Ontario
- Outcomes: vaccine coverage, acceptability, cost, direct and indirect effectiveness vs. PCR-confirmed influenza

PCIRN PHAC/CIHR Influenza Research Network | Public Health Ontario | Santé publique Ontario | Peterborough County-City HEALTH UNIT ...because health matters! | CIHR IRSC | Public Health Agency of Canada | Agence de santé publique du Canada

Take-home points

- Influenza vaccines generally work to protect against influenza infection and related complications
- Influenza vaccines are generally safe (at least no more dangerous than getting influenza infection)
- We should consider vaccinating school-age children against influenza
- Better influenza vaccines are needed

Questions?

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