Current thinking about influenza vaccine efficacy and effectiveness

University of Otago, February 2012

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Acknowledgements

- Center for Infectious Disease Research and Policy, University of Minnesota, USA
  - Professor Michael Osterholm, Dr Nicholas Kelley
- Epiconcept, Paris, France

  Dr Alain Moren, Dr Marta Valenciano,

  Dr Esther Kissling
- Epidemiology Unit, VIDRL, Melbourne, Australia
  - James Fielding, Kristina Grant

Key Events in Influenza Vaccine History in the United States

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

Vaccine efficacy/effectiveness: (both abbreviated as VE)

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

Proc Royal Soc Med 1915; 8 (part 2):113-94

Vaccine efficacy/effectiveness (VE)

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

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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
- *Vaccine efficacy* is estimated from a trial
- *Vaccine effectiveness* is estimated from an observational study *Dictionary of Epidemiology*
- *Efficacy* and *effectiveness* studies of influenza should use influenza as the outcome

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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

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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

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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%

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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- 0.08/0.8
  = 0.9 (or 90%)

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Study types and control selection

- Observational study designs used to estimate VE
- Control selection

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Observational study types used to measure VE

Study type	Measure of effect
Cohort – including household studies	Cumulative incidence (risk) ratio
Retrospective case control	Cumulative incidence (risk) odds ratio
Prospective case control	Incidence rate ratio
Case cohort	Risk ratio
Test negative design	Risk ratio (?)

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

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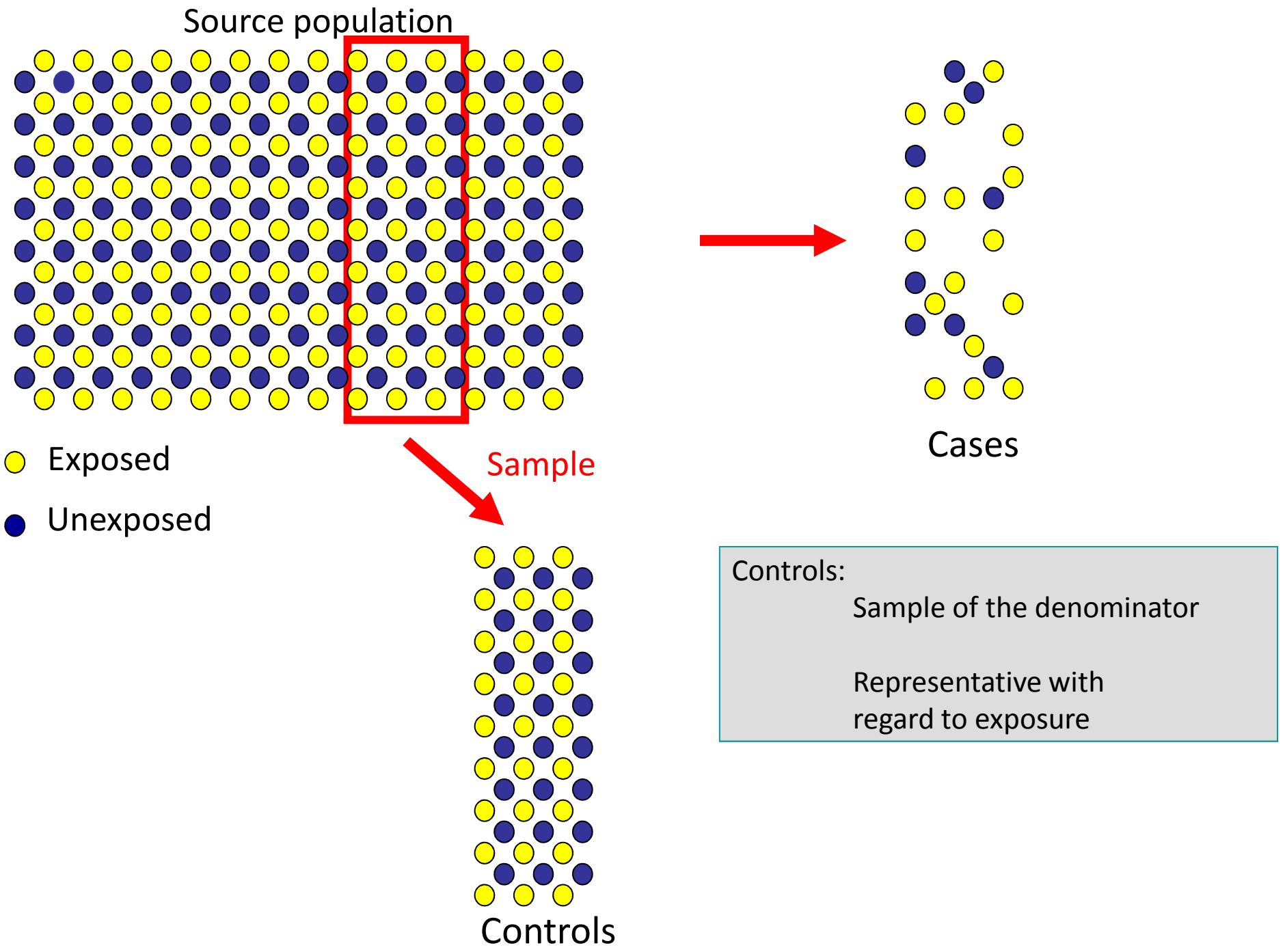
Source population
Exposed
Unexposed
Sample
Cases
Controls
Controls:
Sample of the denominator
Representative with
regard to exposure

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

Orenstein et al, *IJE* 2007; 36:623-31

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Brief remarks on methodological issues

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

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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 $\geq$40
    - HI titre of 40 shown to protect ~50% of volunteers in challenge studies from 1970s
- Immunogenicity is not effectiveness

Kelly & Barr, *Lancet* 2010; 375:6-9

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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 under diagnoses cases in TIV recipients and hence overestimates VE

Petrie et al, *JID* 2011; 203:1309-15

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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

Armstrong et al, *BMJ Open* 2011; 1:e100006

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Influenza VE studies in Australia

WAIVE

- **W**estern **A**ustralia **I**nfluenza **V**accine **E**ffectiveness 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

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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

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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

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FluCAN VE study design

- In**Flu**enza **C**omplications **A**lert **N**etwork
- 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

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FluCan VE 2010

- Vaccination status ascertained for ~70% cases and controls
- 302 cases (25% vaccinated) & 867controls (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

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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

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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

Fielding et al, *BMC ID* 2011; 11:170. Fielding et al, *EID* 2011; 17:1181-6. Kelly et al, *Vaccine* 2011; 29: 6419-26.

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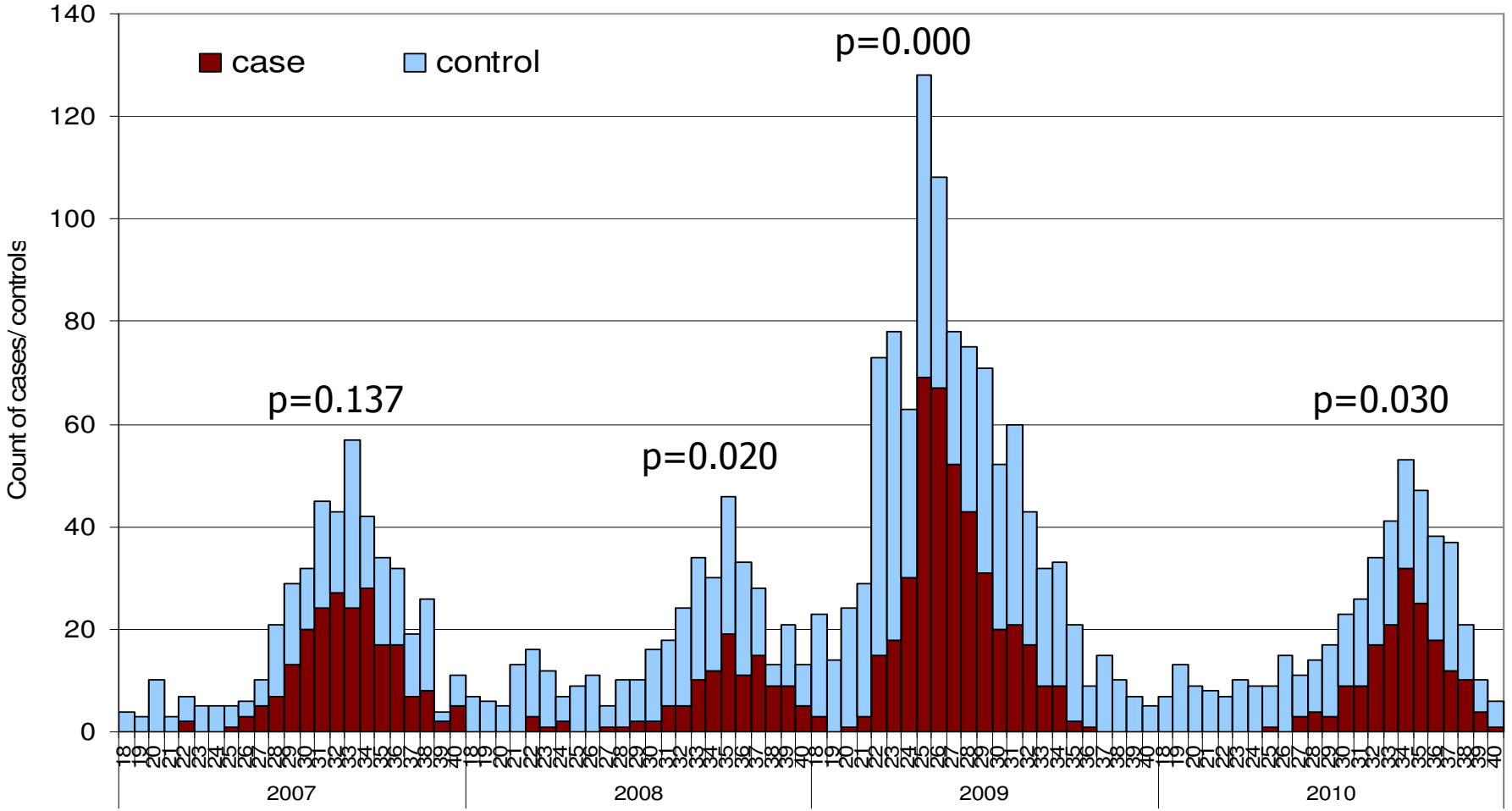
Cases/controls sentinel surveillance 2007-2010



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VIVEA results 2007-11

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

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

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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

http://clinicaltrials.gov/ct2/show/NCT00562484?term=CSL+influenza&rank=4

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Australia VE summary

Study	Year	Design Setting	Age group	VE
WAIVE	2008	TND GP & ED	6-59m	68% (26 to 86) against all strains
FluCAN	2010	TND Hospital	≥18y	49% (13 to 70) against pH1N1
FluCAN	2011	TND Hospital	≥18y	38% (-5 to 74) against all strains
VIVEA	2007-11 not 2009	TND Community	20-64y	64% (25 to 75) against all strains
CSL	2008-9	RCT Community	18-64y	60% (44 to 72) against matched strains

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 18–65 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% [69–91]) 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: six (35%) of 17 analyses in nine studies showed significant protection against medically attended influenza in the outpatient or inpatient setting. Median monovalent pandemic H1N1 vaccine effectiveness in five observational studies was 69% (range 60–93).

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 highest 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.

Published Online October 26, 2011 DOI:10.1016/S1473-3099(11)70295-X

See Online/Comment DOI:10.1016/S1473-3099(11)70289-4

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Introduction

The main strategy for prevention and control of seasonal and pandemic influenza for the past 60 years has been vaccination.[1,2] The first population-scale use of an inactivated influenza vaccine was in US military personnel in 1945.[3] In 1960, the US Surgeon General, in response to substantial morbidity 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.[4] This recommendation was made without data for vaccine efficacy or effectiveness 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 seroconversion as primary measures of infection. In 1964, the Advisory Committee on Immunization Practices (ACIP) reaffirmed this recommendation but noted the absence of efficacy data.[5] 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 inclusion of individuals at high-risk of influenza in placebo-controlled trials would be unethical.[3]

In 2010, the ACIP established the first recommendation of national universal seasonal influenza vaccination.[3] 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 vaccine given at present.[6] The LAIV was first approved for use in the USA in 2003 and accounts for approximately 9% of the vaccine given.[7,8] 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% (51 to 67)
    - Median: VE = 62% (16 to 75)
  - LAIV efficacy = 8%, 48% and 36%
    - 0/3 demonstrated efficacy ($p<0.05$)
- Adults ≥ 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)

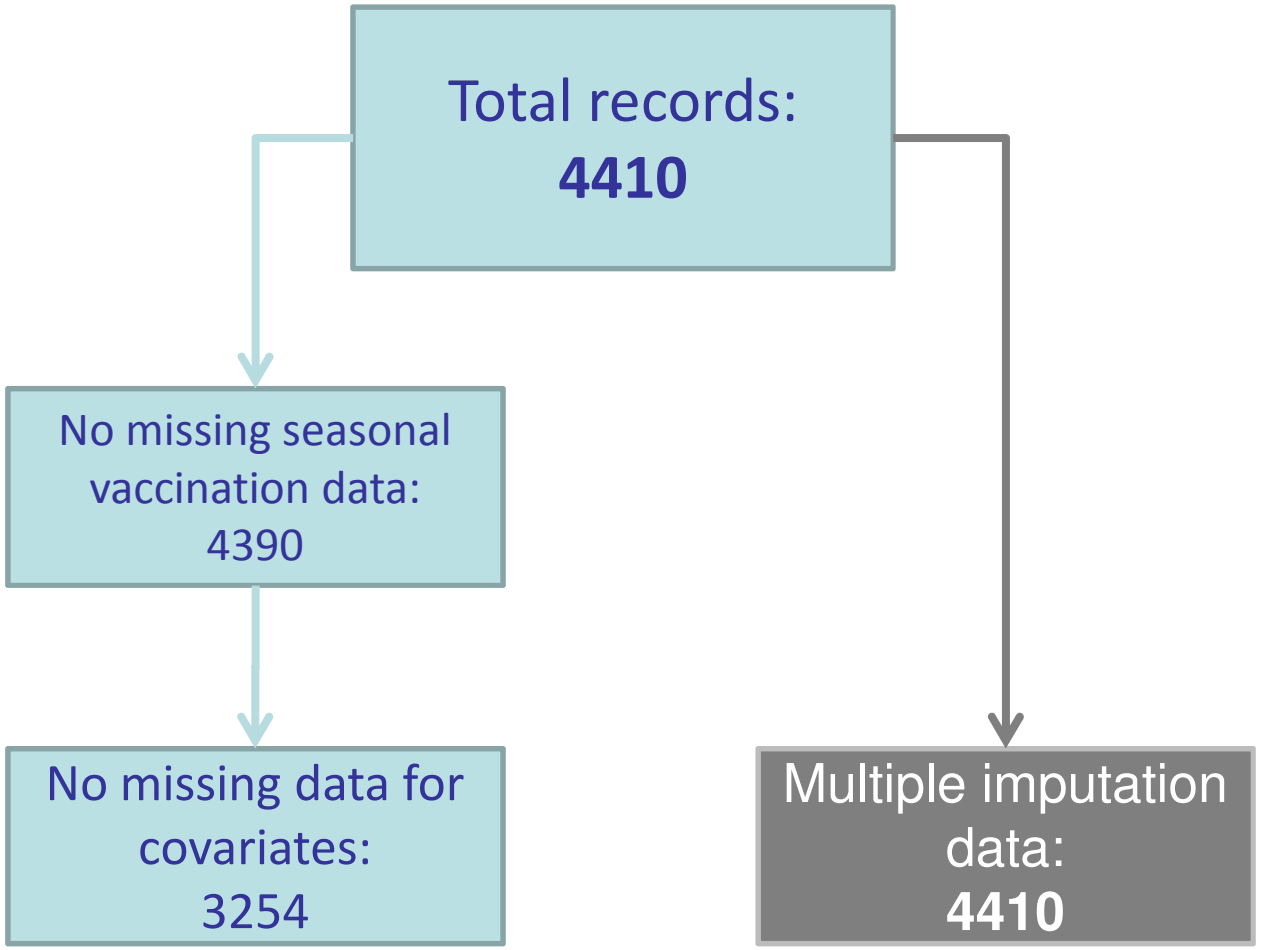
Seasonal Influenza

- 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

IMOVE

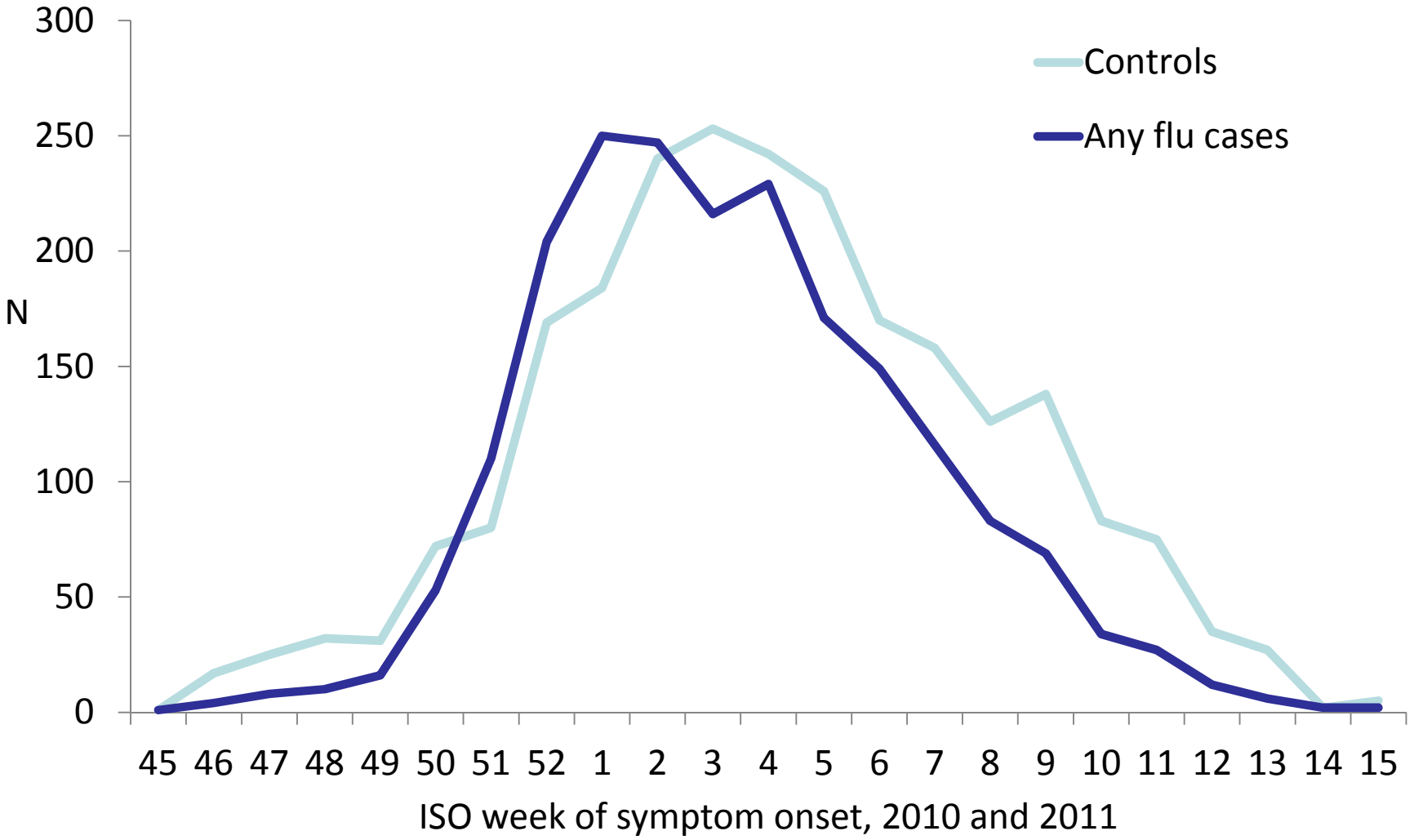
- **I-MOVE**:
  Monitoring IVE in EU and EEA
  Studies since 2008/9
- Multi-centre case control
  8 flu VE case-control studies
  in 2010/11 season
- Very similar protocols ⇒ pooled analysis
  - To obtain summary, preliminary VE measures
  - To enable controlling for all covariates

Sample size for complete case and imputed datasets, multi-centre case control study, EU, 2010-11

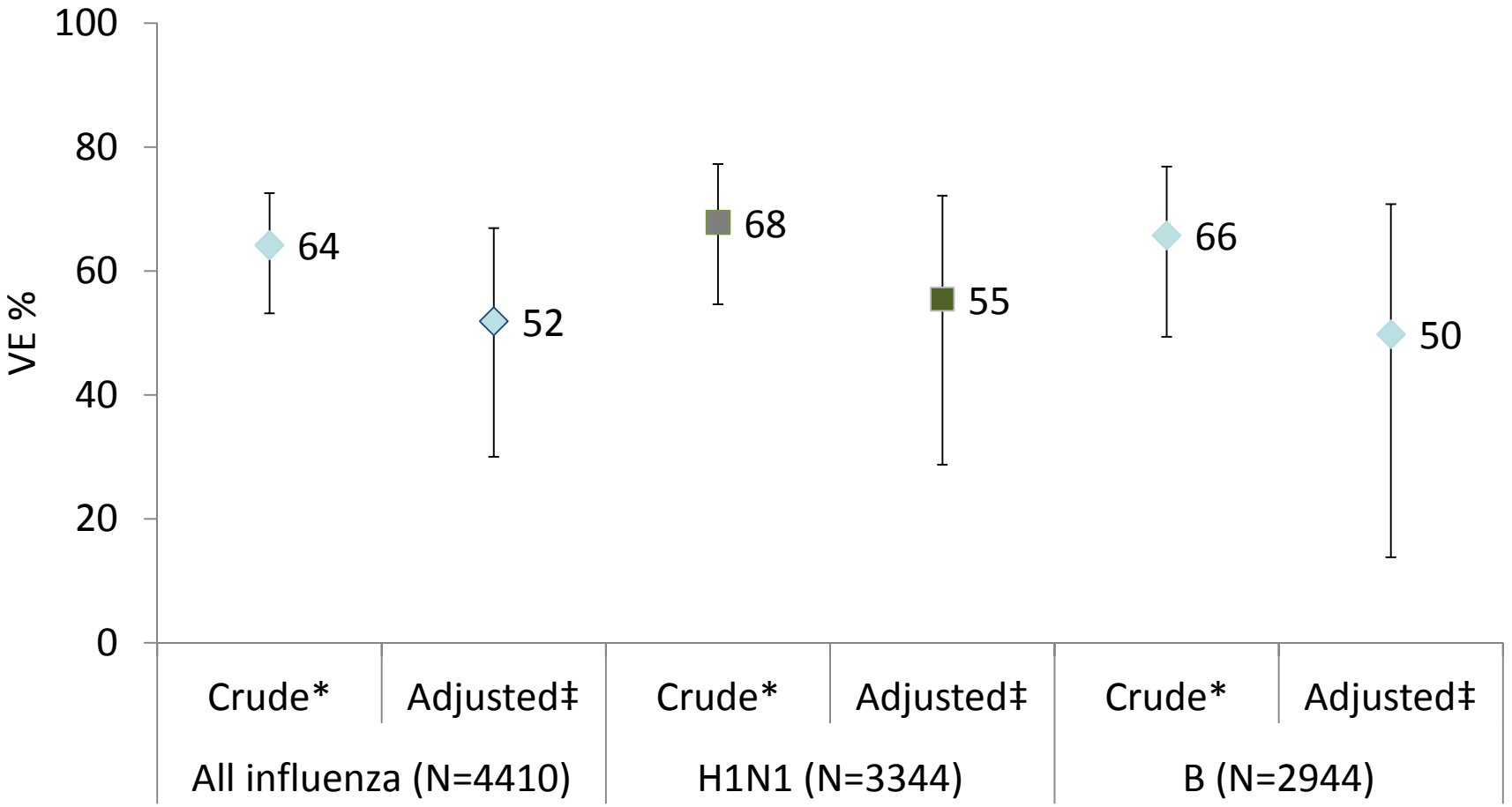


Complete case analysis

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



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

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