# Vaccine Effectiveness and New Vaccines

Ben Cowling

WHO Collaborating Centre for Infectious Disease Epidemiology and Control
School of Public Health, The University of Hong Kong, Hong Kong

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# Influenza vaccine efficacy and effectiveness

- **Vaccine efficacy**: proportional reduction of influenza in vaccinated group in a randomized placebo-controlled trial
- **Vaccine effectiveness**: ability of vaccine to prevent influenza in the "real world", estimated in observational studies.
  - Can vary from year to year and in different settings, and continuous assessment of VE is useful
  - Can be affected by factors such as
    1. timing of vaccination,
    2. age and other characteristics of the vaccine recipients, and
    3. the degree of matching between vaccine strains and prevailing strains in the community
  - VE now generally evaluated against laboratory-confirmed influenza outcomes.

# To measure influenza VE

- Randomized placebo-controlled trial (RCT)
  - Not logistically nor financially feasible to conduct on an annual basis, and may not be considered ethical in groups that are recommended to receive annual vaccination.
- Cohort studies and traditional case-control studies
  - Feasible in community setting
  - **BUT** may be susceptible to confounding by indication (healthcare seeking behaviour) and other biases
  - Implausible findings in some cohort studies

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doi:10.1093/ije/dyi274

# Evidence of bias in estimates of influenza vaccine effectiveness in seniors

Lisa A Jackson,[1,2]* Michael L Jackson,[1,2] Jennifer C Nelson,[1,3] Kathleen M Neuzil[4] and Noel S Weiss[2]

- The authors evaluated a cohort of 72,527 persons of older adults, followed up during an 8 year period
- Assessed risk of all cause mortality and hospitalization for pneumonia or influenza, in relation to influenza vaccination, in periods before, during, and after influenza seasons

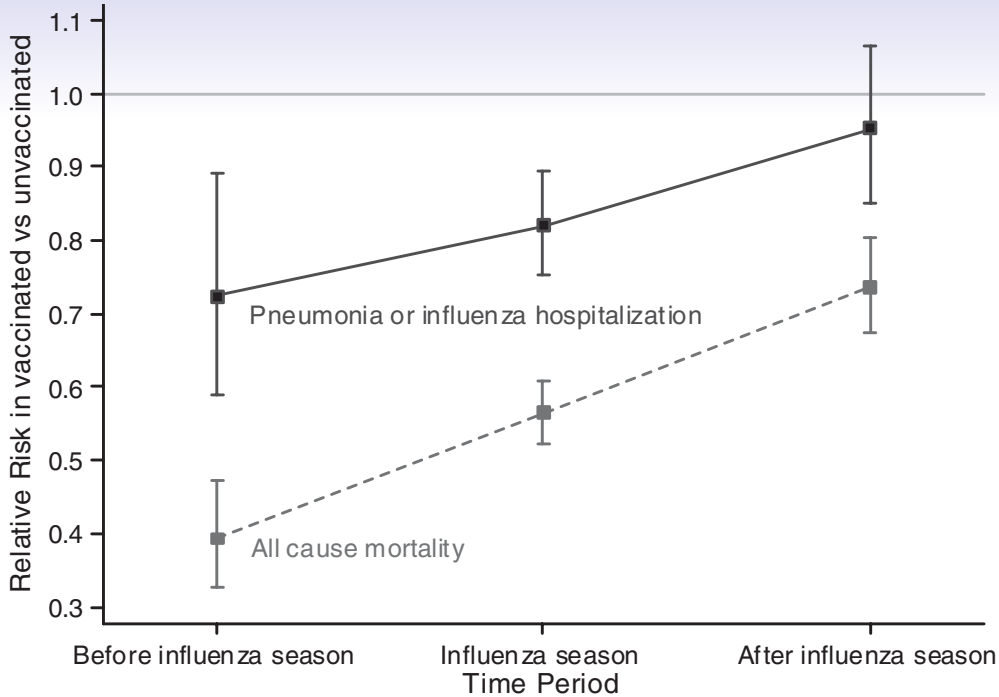



**Figure 1** Relative risk (and 95% CI) of all cause mortality and pneumonia or influenza hospitalization in vaccinated seniors compared with unvaccinated seniors, during periods before, during, and after influenza seasons, September 1995 through August 2003.

- Substantial reduction in risk before influenza season
  - Indicate preferential receipt of vaccine by relatively healthier participants, and uncontrolled confounding
  - Underlying differences between the vaccinated and unvaccinated groups are responsible for the 50% reduction in all-cause mortality, not influenza vaccination.

Jackson et al, Int J Epidemiol 2006

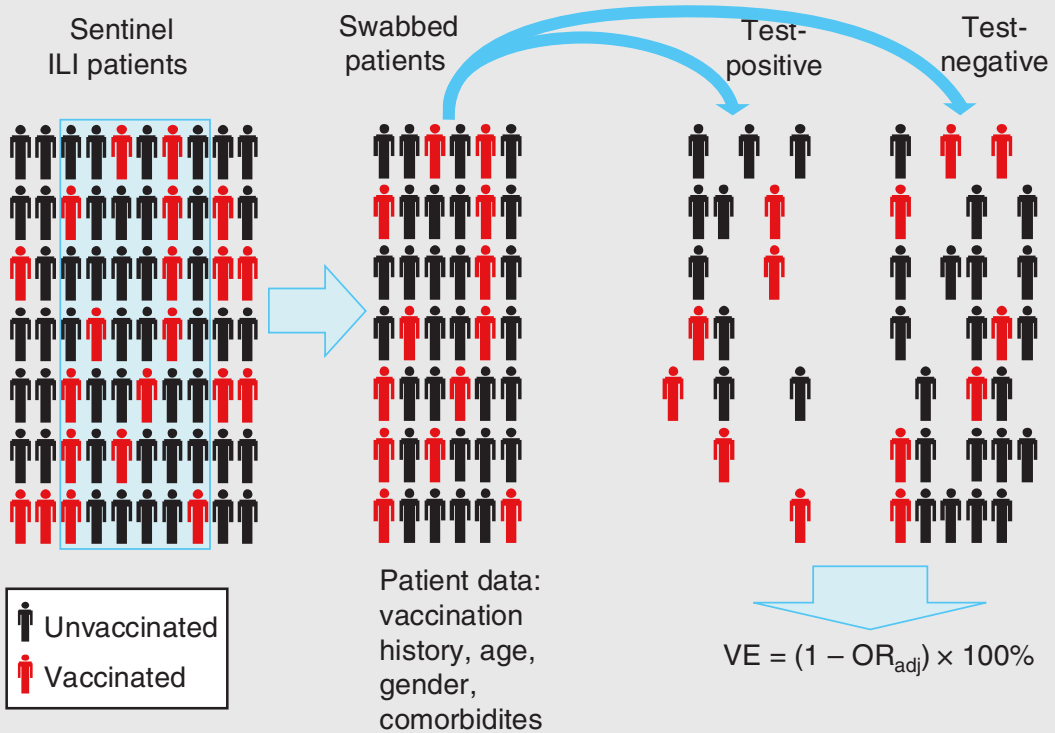
# Test-negative case-control study design (TND)

- New study approach for VE since 2005 by Canadian investigators[1]
- Has been employed in many locations for estimating VE[2]
- Thought to be a valid approach for estimation of influenza VE[3]
- Typical study – patients seeking healthcare for an acute respiratory illness (ARI) enrolled and have respiratory swabs tested for influenza by RT-PCR
- VE is calculated as $100\% \times (1 - \textit{odds ratio}[OR])$ for vaccine receipt in influenza cases versus test-negative controls, adjusting for confounders.


1. Skowronski DM, et al. Can Commun Dis Rep, 2005; 31:181-92.
2. Sullivan SG, Feng S, Cowling BJ. Expert Rev Vaccines, 2014; 13(12):1571-91.
3. Belongia EA, et al. Lancet Infect Dis, 2016; 16(8):942-51.

**Box 1. Estimating influenza vaccine effectiveness from the test-negative design.**

A selection of patients seeking care with influenza-like illness are swabbed and tested for influenza. Vaccination status is recorded, as well as additional patient data. The odds of vaccination among the test-positives is compared with the negatives by adjusted logistic regression, from which a vaccine effectiveness estimate can be calculated.




Sullivan SG, Feng S, Cowling BJ. Influenza vaccine effectiveness: potential of the test-negative design. A systematic review. Expert Review of Vaccines, 2014; 13(12):1571-91.

# Estimating VE using the test-negative study

- Feasible with reasonable cost in both inpatient and outpatient settings[1]
- Can account for 'confounding by indication' and selection bias – controls represent people who sought medical attention, *not* necessarily the general community.
- Efficient approach to assess influenza VE using available sentinel surveillance networks[1]
- VE estimates can be more accurate than traditional observational studies under realistic circumstances[2,3]

1. Feng S, Cowling BJ, Sullivan SG. Vaccine, 2016; 34(14):1672-9.
2. Orenstein EW, et al. International Journal of Epidemiology, 2007; 36(3):623-31.
3. Foppa IM, et al. Vaccine, 2013; 31(30):3104-9.

# Review of influenza VE estimates from TND studies

| | Pooled VE (%) | Pooled standard error | VE estimates (n)* | p value for heterogeneity | $I^2$ |
|---|---|---|---|---|---|
| **H3N2 by season** | | | | | |
| 2010–11 | 46% (30 to 58) | 0·131 | 5 | 0·368 | 26·1 |
| 2011–12 | 32% (23 to 40) | 0·063 | 9 | 0·626 | 0·0 |
| 2012–13 | 40% (32 to 46) | 0·059 | 6 | 0·644 | 0·0 |
| 2013–14 | 10% (–25 to 35) | 0·164 | 3 | 0·913 | 0·0 |
| 2014–15 | 7% (–32 to 34) | 0·179 | 3 | 0·051 | 74·3 |
| **H3N2 by antigenic similarity** | | | | | |
| Variant | 23% (2 to 40) | 0·126 | 6 | 0·081 | 55·6 |
| Similar | 33% (22 to 43) | 0·080 | 12 | 0·014 | 56·1 |
| **H1N1pdm09 by season** | | | | | |
| 2010–11 | 60% (54 to 65) | 0·071 | 12 | 0·894 | 0·0 |
| 2011–12 | 68% (50 to 80) | 0·239 | 3 | 0·541 | 7·2 |
| 2012–13 | 55% (41 to 66) | 0·142 | 6 | 0·930 | 0·0 |
| 2013–14 | 62% (52 to 70) | 0·117 | 6 | 0·260 | 35·2 |
| **Type B by season†** | | | | | |
| 2005–06 | 52% (25 to 70) | 0·231 | 3 | 0·648 | 0·0 |
| 2007–08 | 50% (29 to 64) | 0·172 | 5 | 0·235 | 41·2 |
| 2010–11 | 55% (48 to 62) | 0·080 | 11 | 0·554 | 0·0 |
| 2011–12 | 49% (0 to 74) | 0·343 | 7 | <0·0001 | 89·7 |
| 2012–13 | 55% (46 to 62) | 0·087 | 7 | 0·566 | 0·0 |

Data in parentheses are 95% CIs. VE=vaccine effectiveness. *Seasons with fewer than three VE estimates for a given subtype were not included. †2009–10 is not shown because only one estimate for type B during that season existed.

*Table 4:* **Pooled VE estimates by season and reported antigenic similarity of H3N2 viruses to the vaccine strain**

- Substantial protection against A(H1N1)pdm09 and B
- Reduced protection against A(H3N2)
  - Antigenic drift?
  - Vaccine manufacturing process generating egg-induced mutations in the haemagglutinin that affect antigenicity?

Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis, 2016;16(8):942-51.

# Review of influenza VE estimates from TND studies

| | Vaccine type | Pooled VE (%) | Pooled standard error | VE estimates (n) | p value for heterogeneity | $I^2$ |
|---|---|---|---|---|---|---|
| **Paediatric age groups*** | | | | | | |
| Type B | Seasonal | 56% (38 to 69) | 0·179 | 11 | 0·279 | 24·4 |
| H3N2 | Seasonal | 43% (28 to 55) | 0·119 | 10 | 0·251 | 28·2 |
| H1N1pdm09 | Seasonal | 69% (49 to 81) | 0·253 | 7 | 0·054 | 56·7 |
| H1N1pdm09 | Monovalent | 62% (–5 to 87) | 0·525 | 3 | 0·207 | 56·2 |
| **Working-age adults** | | | | | | |
| Type B | Seasonal | 54% (16 to 75) | 0·308 | 7 | 0·005 | 70·7 |
| H3N2 | Seasonal | 35% (14 to 51) | 0·146 | 9 | 0·078 | 48·4 |
| H1N1pdm09 | Seasonal | 73% (52 to 84) | 0·290 | 5 | 0·159 | 49·6 |
| H1N1pdm09 | Monovalent | 74% (44 to 88) | 0·391 | 3 | 0·852 | 0·0 |
| H1N1 (pre-2009) | Seasonal | 64% (29 to 82) | 0·343 | 4 | 0·541 | 3·2 |
| **Older adults†** | | | | | | |
| Type B | Seasonal | 63% (33 to 79) | 0·295 | 3 | 0·989 | 0·0 |
| H3N2 | Seasonal | 24% (–6 to 45) | 0·166 | 6 | 0·416 | 17·6 |
| H1N1pdm09 | Seasonal | 62% (36 to 78) | 0·267 | 3 | 0·906 | 0·0 |

VE=vaccine effectiveness. *Pooled VE was not calculated for two studies reporting VE against H1N1 (pre-2009) in paediatric age groups. †One VE estimate for monovalent vaccine in older adults is not shown.

*Table 3:* Pooled vaccine effectiveness in paediatric age groups, working-age adults, and older adults

- Pooled VE against A(H1N1)pdm09 and type B similar across age groups
- Pooled VE against A(H3N2) was highest in paediatric age groups and lowest in older adults

Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis, 2016;16(8):942-51.

# Review of VE estimates from inpatient and outpatient based TND studies

- We did a systematic review and meta-analysis of VE estimates in inpatient vs outpatient settings

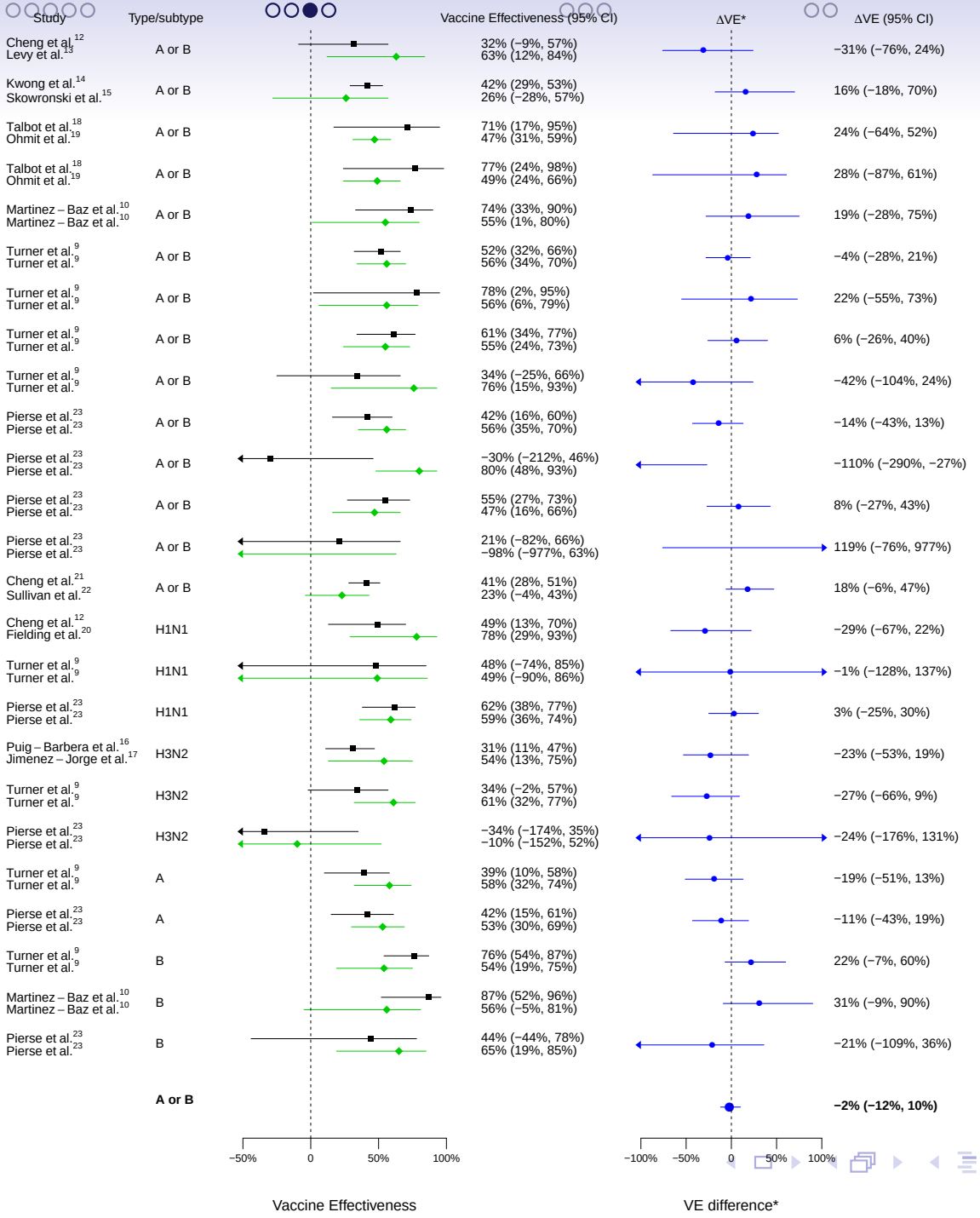
# Review of VE estimates from inpatient and outpatient based TND studies

- We did a systematic review and meta-analysis of VE estimates in inpatient vs outpatient settings
- We searched for pairs of test negative studies done in the same year, age group, and geographic location – one study done in inpatients and the other in outpatients
- We identified 25 pairs of estimates from 14 publications that were suitable for further analysis
- Included studies from Australia, Canada, New Zealand, Spain, and the US, in five influenza seasons from 2010 to 2014.

*Feng, Cowling, Sullivan, 2016, Vaccine*

# Review of VE estimates from inpatient and outpatient based studies

- The proportion of patients testing positive for influenza was 9.5%-33.3% in inpatient settings, and 14.0%-60.7% in outpatient settings, and usually higher in the outpatient studies in each pair.
- Vaccination coverage in the influenza-negative controls was generally higher among inpatients, and in 6 pairs the vaccination coverage in the inpatient control group was more than 20 percentage points higher than among the corresponding outpatient control group.


Study
Type/subtype
Vaccine Effectiveness (95% CI)
ΔVE*
ΔVE (95% CI)
Cheng et al.[12] Levy et al.[13] A or B 32% (−9%, 57%) 63% (12%, 84%) −31% (−76%, 24%)
Kwong et al.[14] Skowronski et al.[15] A or B 42% (29%, 53%) 26% (−28%, 57%) 16% (−18%, 70%)
Talbot et al.[18] Ohmit et al.[19] A or B 71% (17%, 95%) 47% (31%, 59%) 24% (−64%, 52%)
Talbot et al.[18] Ohmit et al.[19] A or B 77% (24%, 98%) 49% (24%, 66%) 28% (−87%, 61%)
Martinez – Baz et al.[10] Martinez – Baz et al.[10] A or B 74% (33%, 90%) 55% (1%, 80%) 19% (−28%, 75%)
Turner et al.[9] Turner et al.[9] A or B 52% (32%, 66%) 56% (34%, 70%) −4% (−28%, 21%)
Turner et al.[9] Turner et al.[9] A or B 78% (2%, 95%) 56% (6%, 79%) 22% (−55%, 73%)
Turner et al.[9] Turner et al.[9] A or B 61% (34%, 77%) 55% (24%, 73%) 6% (−26%, 40%)
Turner et al.[9] Turner et al.[9] A or B 34% (−25%, 66%) 76% (15%, 93%) −42% (−104%, 24%)
Pierse et al.[23] Pierse et al.[23] A or B 42% (16%, 60%) 56% (35%, 70%) −14% (−43%, 13%)
Pierse et al.[23] Pierse et al.[23] A or B −30% (−212%, 46%) 80% (48%, 93%) −110% (−290%, −27%)
Pierse et al.[23] Pierse et al.[23] A or B 55% (27%, 73%) 47% (16%, 66%) 8% (−27%, 43%)
Pierse et al.[23] Pierse et al.[23] A or B 21% (−82%, 66%) −98% (−977%, 63%) 119% (−76%, 977%)
Cheng et al.[21] Sullivan et al.[22] A or B 41% (28%, 51%) 23% (−4%, 43%) 18% (−6%, 47%)
Cheng et al.[12] Fielding et al.[20] H1N1 49% (13%, 70%) 78% (29%, 93%) −29% (−67%, 22%)
Turner et al.[9] Turner et al.[9] H1N1 48% (−74%, 85%) 49% (−90%, 86%) −1% (−128%, 137%)
Pierse et al.[23] Pierse et al.[23] H1N1 62% (38%, 77%) 59% (36%, 74%) 3% (−25%, 30%)
Puig – Barbera et al.[16] Jimenez – Jorge et al.[17] H3N2 31% (11%, 47%) 54% (13%, 75%) −23% (−53%, 19%)
Turner et al.[9] Turner et al.[9] H3N2 34% (−2%, 57%) 61% (32%, 77%) −27% (−66%, 9%)
Pierse et al.[23] Pierse et al.[23] H3N2 −34% (−174%, 35%) −10% (−152%, 52%) −24% (−176%, 131%)
Turner et al.[9] Turner et al.[9] A 39% (10%, 58%) 58% (32%, 74%) −19% (−51%, 13%)
Pierse et al.[23] Pierse et al.[23] A 42% (15%, 61%) 53% (30%, 69%) −11% (−43%, 19%)
Turner et al.[9] Turner et al.[9] B 76% (54%, 87%) 54% (19%, 75%) 22% (−7%, 60%)
Martinez – Baz et al.[10] Martinez – Baz et al.[10] B 87% (52%, 96%) 56% (−5%, 81%) 31% (−9%, 90%)
Pierse et al.[23] Pierse et al.[23] B 44% (−44%, 78%) 65% (19%, 85%) −21% (−109%, 36%)
A or B −2% (−12%, 10%)
−50% 0 50% 100%
−100% −50% 0 50% 100%
Vaccine Effectiveness
VE difference*

# Implications

- Low heterogeneity in IVE within each pair and pooled estimate of the difference in VE very close to 0
- Interpretation – hospital-based TND studies seem to give similar estimates of VE to outpatient-based TND studies

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- Low heterogeneity in IVE within each pair and pooled estimate of the difference in VE very close to 0
- Interpretation – hospital-based TND studies seem to give similar estimates of VE to outpatient-based TND studies
- One possible explanation from this ecologic comparison – vaccination (with TIV/QIV) does not provide additional protection against severe illness if a breakthrough infection occurs?

Feng S, Cowling BJ, Sullivan SG. Influenza vaccine effectiveness by test-negative design - Comparison of inpatient and outpatient settings. Vaccine, 2016; 34(14):1672-9.

# New ACIP recommendation against use of LAIV

- The US Advisory Committee on Immunization Practices (ACIP) has recently withdrawn the recommendation for use of live attenuated influenza vaccines (LAIV) in children in the US for the season 2016/17[1]
  - Mainly due to lower VE against A(H1N1)pdm09 in comparison to inactivated influenza vaccines in 2015/16
- However, VE studies conducted in Europe reported more reasonable VE[2]

1. Grohskopf L A, et al. MMWR Recomm Rep. 2016; 65(5):1-54.
2. Penttinen PM, et al. Eurosurveillance, 2016; 21(38):pii=30350.

**Table**

Comparison of study designs and populations assessing vaccine effectiveness of live attenuated influenza vaccine, northern hemisphere countries, United States, United Kingdom and Finland, influenza season 2015/16

| | CDC United States | DoD United States | ICICLE United States | PHE United Kingdom | THL Finland |
|---|---|---|---|---|---|
| **VE against A(H1N1)pdm09 (95%CI)** | **−21% (−108% to 30%)** | **15% (−48% to 51%)*** | **50% (−2% to 75%)*** | **41.5% (−8.5% to 68.5%)*** | **47.9% (21.6–65.4%)** |
| **Study design** | Test-negative case–control | Test-negative case–control | Test-negative case–control | Test-negative case–control | Cohort |
| **Source population / inclusion criteria** | Children and adolescents aged 2–17 years* | Children and adolescents (Military dependents) aged 2–17 years presenting to participating facilities | Children and adolescents aged 2–17 years | Children and adolescents 2–17 years of age | Children 24–35 months of age |
| **Inclusion criteria** | MAARI, including cough, and onset of illness≤7 days before enrolment | ILI (fever≥38 °C AND cough and/or sore throat of<72 hours duration) | ARI with fever≥100.0°F (37.8 °C), duration<5 days | ILI | Laboratory-confirmed influenza |
| **Assessment of vaccination status** | Current-season vaccination (at least one vaccine dose ≥ 14 days before illness onset; vaccine records obtained from electronic medical records and immunisation registries for children aged 2–8 years; with addition of reported vaccination for patients aged 9–17 years)* | Electronic medical records | Vaccination status was ascertained by medical record review and/or state or regional vaccine registries | Self-reported by patients to general practitioners | National immunisation registry |

Penttinen PM, Friede MH. Decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines: an observational bias or a technical challenge? Eurosurveillance, 2016; 21(38):pii=30350.

# Potential explanations

- Population or programme-specific effects
  - Comparatively high influenza vaccine coverage in children aged 6 months to 2 years in the US, before the age at which LAIV is given?
  - Repeat vaccination effect (blunted response)?
- Biological properties of the A(H1N1)pdm09 vaccine strain
  - Lower fitness of the A(H1N1)pdm09 strain?
  - Heat sensitivity and improper handling in supply chain?[2]
- Methodologic issues with VE assessment?

1. Penttinen PM, Friede MH. Decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines: an observational bias or a technical challenge?. Eurosurveillance, 2016;21(38):pii=30350.
2. Caspard H, Coelingh KL, Mallory RM, Ambrose CS. Association of vaccine handling conditions with effectiveness of live attenuated influenza vaccine against H1N1pdm09 viruses in the United States. Vaccine, 2016; 34(42):5066-72.

# Influenza in older adults

- Majority of influenza-associated hospitalizations and mortality are in older adults, particularly associated with H3N2
- Need for more potent vaccines in older individuals because of a weaker response to standard-dose inactivated vaccines due to immunosenescence or more historical infections/vaccinations[1]
- Concerns over waning immunity / duration of protection in locations where influenza seasons are longer or less predictable
- Vaccine mismatch remains an issue; need to have broader protection

1. Mosterín Höpping A, McElhaney J, Fonville JM, Powers DC, Beyer WE, Smith DJ. The confounded effects of age and exposure history in response to influenza vaccination. Vaccine, 2016; 34(4):540-6.

# Promising new vaccines for older adults

1. High-dose TIV: Higher efficacy and antibody titers and enhanced protection versus standard dose vaccine. Accelerated approval in the US. Response persists over 12 months
2. Adjuvanted TIV containing MF-59. Also underwent accelerated approval in the US, and also induced higher antibody titres than TIV
   - Improvement in H3N2 protection vs TIV
   - Appears to provide wider protection/better results in years of vaccine mismatch versus TIV

- Cannot as yet confirm which vaccine is better for older adults, but both appear to be superior to TIV

# Conclusions

- Annual evaluation of influenza VE is useful and can support policy decisions. The test-negative study design is now being widely used for monitoring VE
- Influenza VE tends to fall in the range 50% to 70% for A(H1N1) and B, but lower for A(H3N2)
- The high dose vaccine and the MF59-adjuvanted vaccine are promising new strategies for vaccination in older adults