Issues and challenges

Influenza vaccine effectiveness

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A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Outline

- Rationale for assessing influenza vaccine effectiveness (VE)
- Observational methods for assessing influenza VE
- The case test-negative design (TND)
- The Australian experience and recent data
- Influenza VE research questions arising from TND studies
- Recent northern hemisphere data
- Issues with A(H3N2) and newer vaccines

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Rationale for influenza vaccine effectiveness assessment

- Assess performance of vaccine in practice
  - Program evaluation
  - Contributes to disease impact assessment

- Ongoing assessment required
  - Vaccine strain composition changes from year-to-year
  - Emergence of difference vaccine brands & classes
  - Changes to at-risk/funded groups

- Clinical trials impractical for assessing vaccine efficacy
  - Observational studies conducted instead

Methods for estimating influenza vaccine effectiveness (VE)

- Accurate measurement of outcome & exposure

- Screening method
  - Uses vaccination status of cases and the population
  - Convenient, but least powerful of observational designs
  - Sensitive to selection & measurement bias

- Cohort studies
  - Compares influenza risk/incidence by vaccination status
  - Useful in outbreak or household study settings
  - Prospective, rare outcome: expensive & logistically challenging

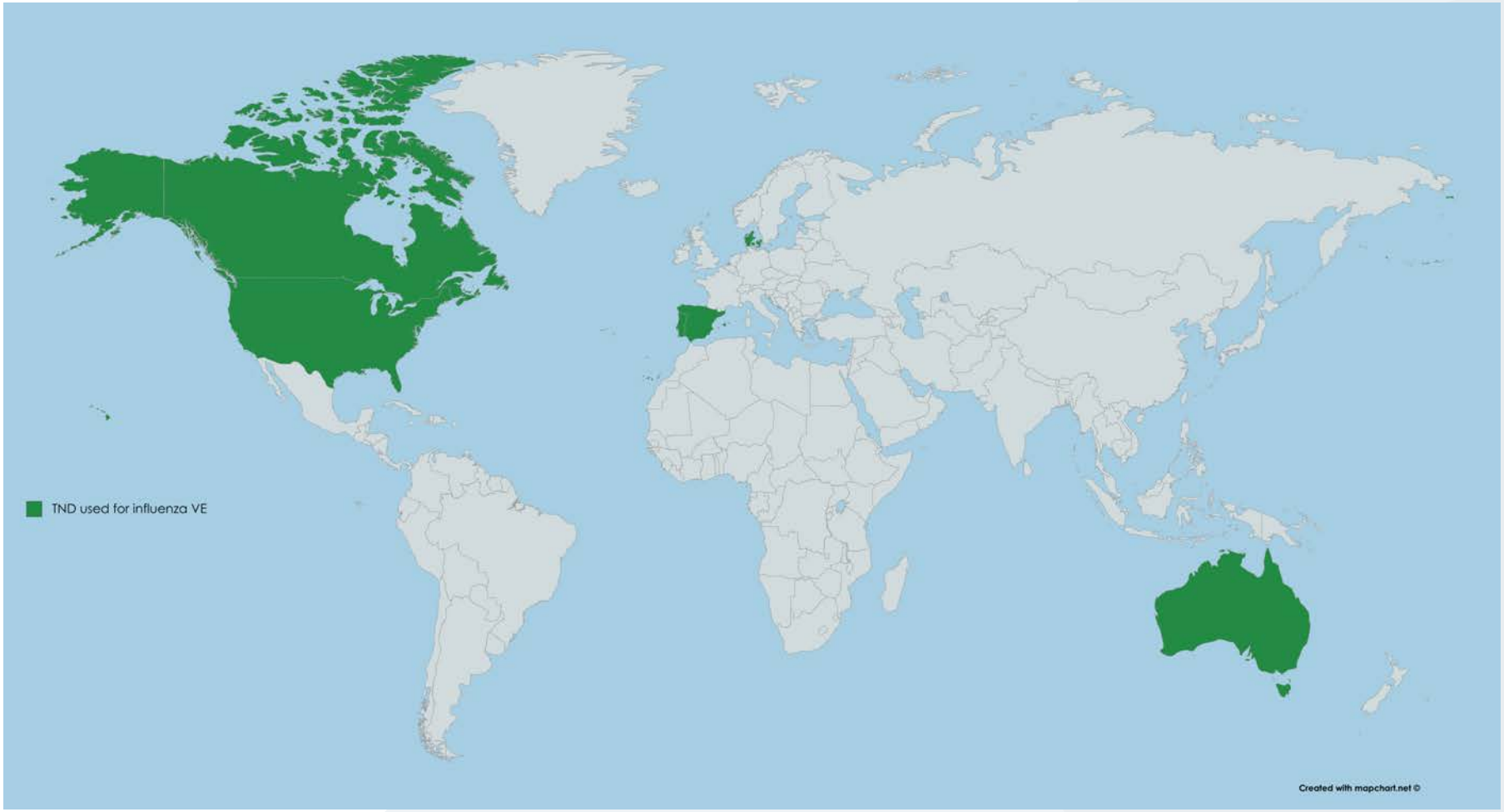
Methods for estimating influenza vaccine effectiveness

- Case control studies
  - Retrospectively compares odds of vaccination in cases and odds of vaccination in controls (influenza negative)
  - More efficient for study size than cohort studies
  - Challenges: misclassification of vaccination; selection bias in control recruitment

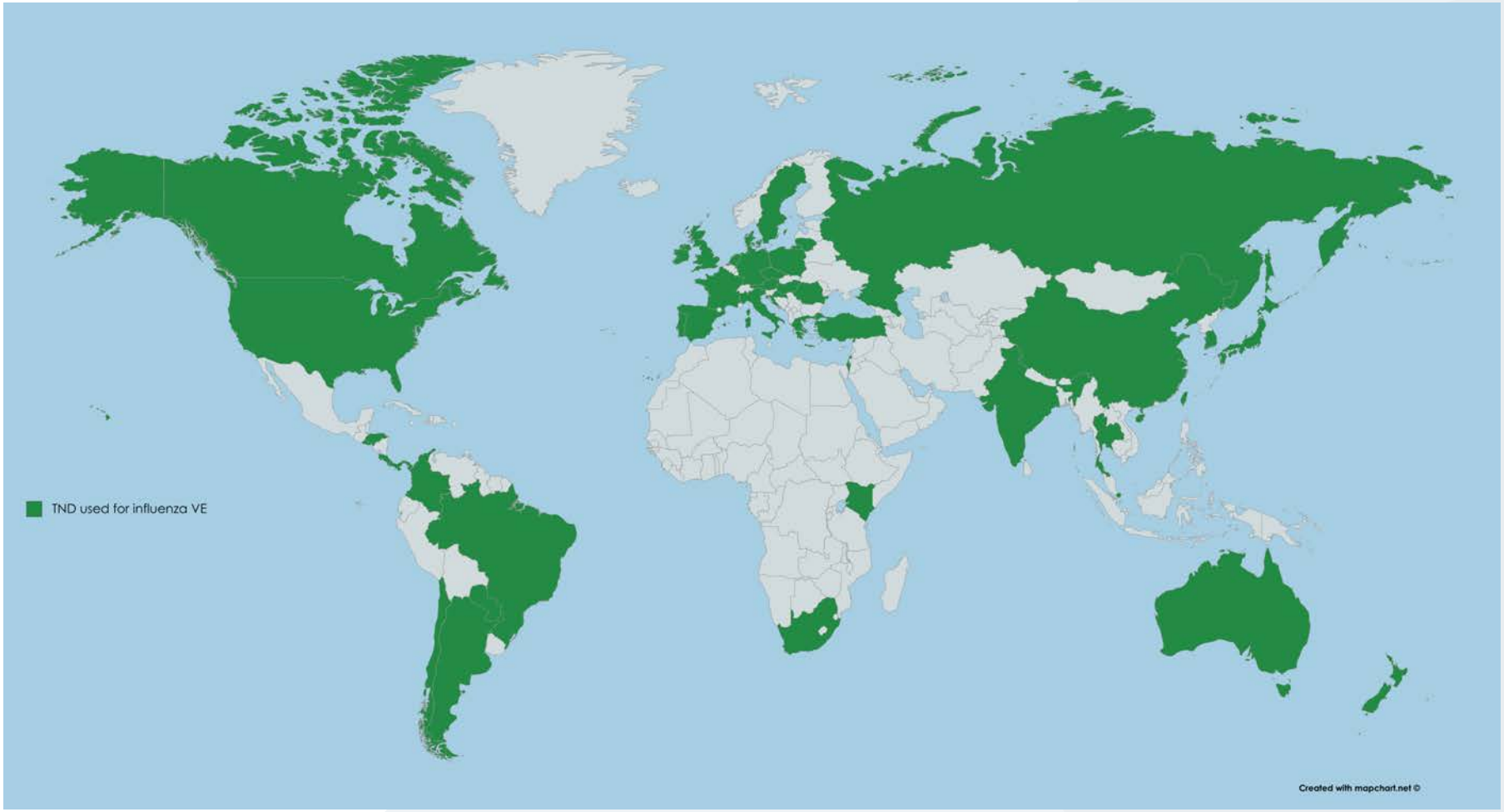
- Case test-negative design (TND)
  - Prospective variant of case control study
  - Increasingly adopted around the world

[WHO. Evaluation of influenza vaccine effectiveness: a guide to the design and interpretation of observational studies. WHO: Geneva; 2017]

Test-negative design for influenza VE in 2010



Test-negative design for influenza VE in 2018



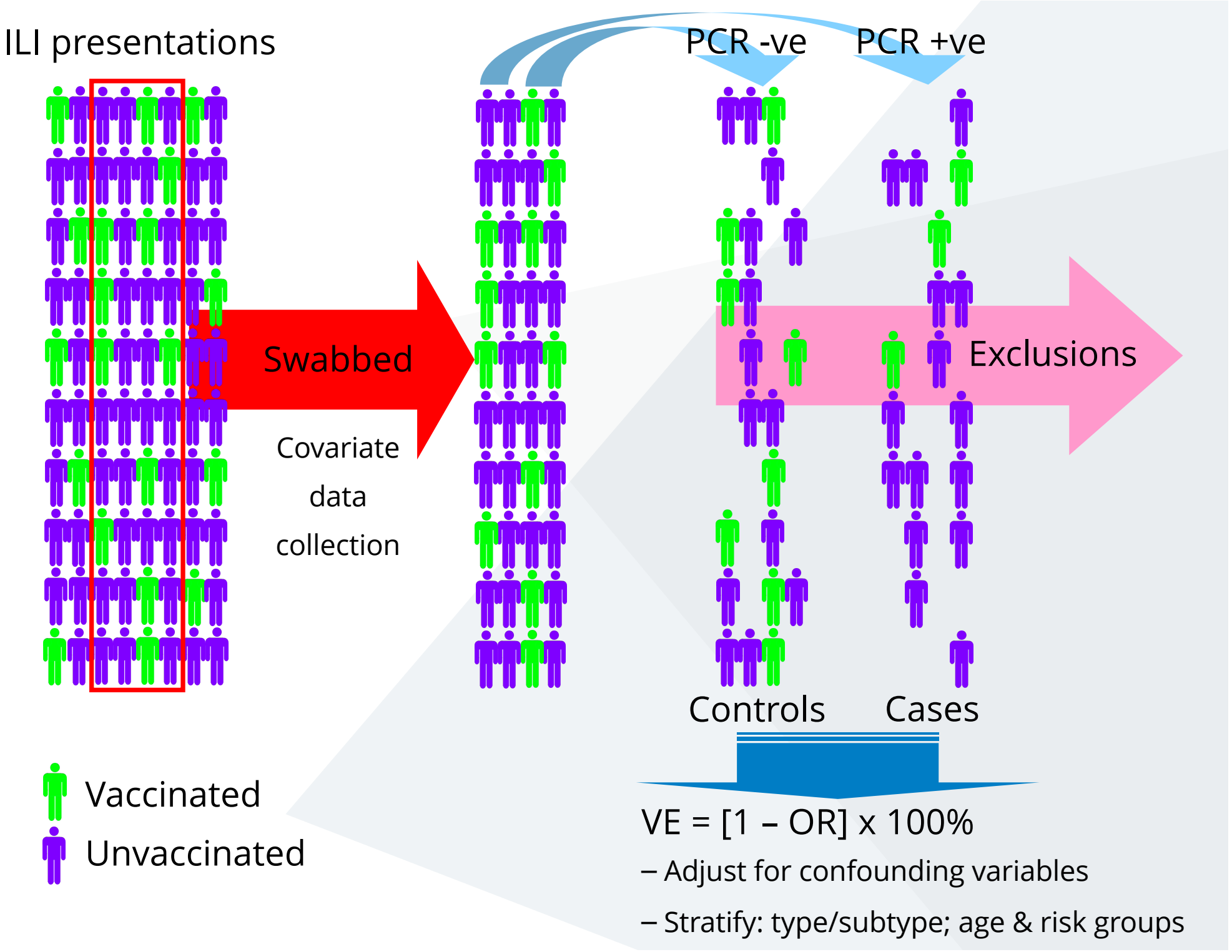
The case test-negative design

- Patients presenting with a defined acute respiratory illness (ARI) or influenza-like illness (ILI)
  - Outcome is unknown at recruitment

- Patients are tested for influenza
  - Those that test positive are cases
  - Those that test negative are 'controls'

- Vaccination & other covariate data collected

- $VE = (1 - O_{pos} / O_{neg}) * 100\%$

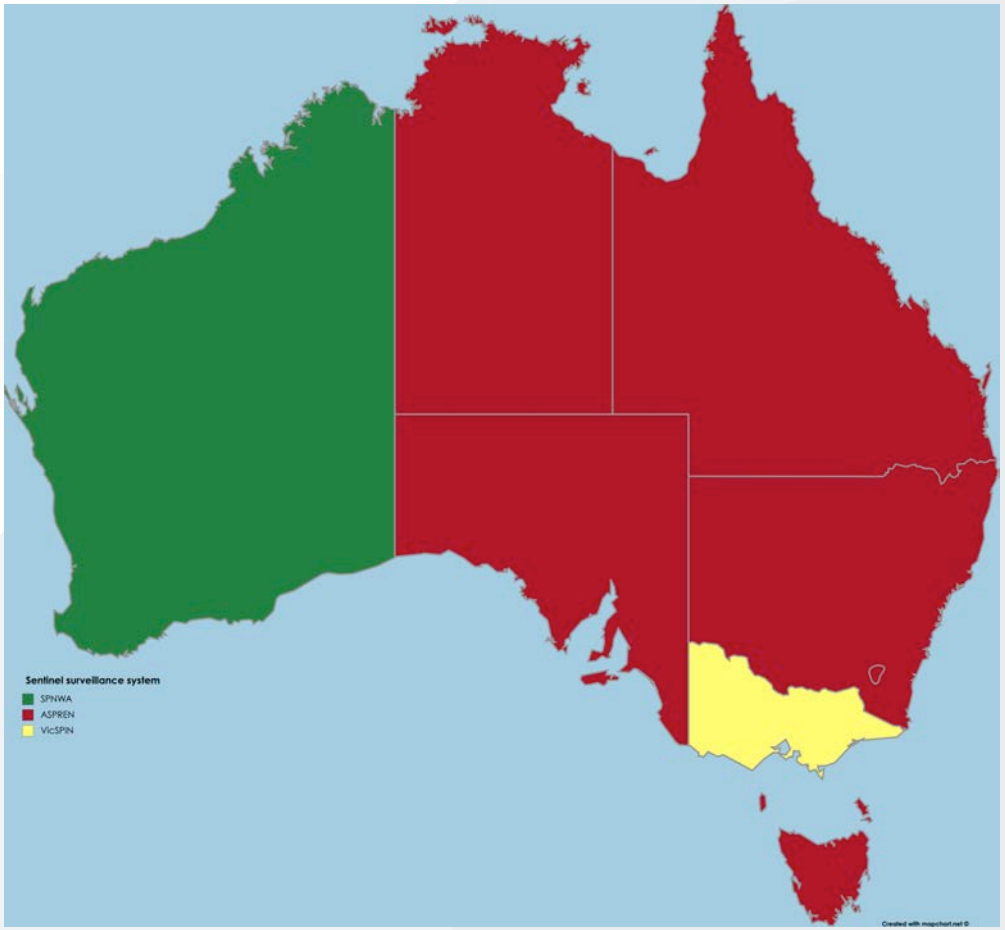

ILI presentations
PCR -ve
PCR +ve
Swabbed
Covariate
data
collection
Exclusions
Controls
Cases
Vaccinated
Unvaccinated
VE = [1 – OR] x 100%
– Adjust for confounding variables
– Stratify: type/subtype; age & risk groups

Advantages and challenges

- Easily applied to ARI/ILI surveillance systems
- Vaccination in non-cases estimate for community coverage
- Reduced selection & measurement bias
  - Cases & non-cases attend the same facilities
  - Cases & non-cases present with similar symptoms
  - Vaccination status collected at presentation prior to result being known reduces risk of misclassification
- Caution required for hospital settings/severe outcomes
- Heterogeneity of methods [Sullivan et al, *Expert Rev Vaccines*, 2014]

The TND experience in Australia

- First applied in Victoria in 2009 followed by Western Australia
- National pooled estimates for 3 systems from 2012
- Improved harmonisation of case definitions and data fields; greater antigenic & phylogenetic characterisation
- Precision of estimates limited, especially for children & elderly



Interim influenza VE results

- Prospective nature of TND allows 'real-time' VE calculations
- Value of interim VE estimates
  - High VE: encourage vaccination
  - Low VE: focus on other prevention measures
- Requires rapid analysis, writing and publication
- Review found ≤10% difference between interim & final VE in 18/33 study pairs
  - Some methodological inconsistencies found

[Leung et al, *Euro Surveill*, 2016]

Effect of repeated influenza vaccination on VE

- Concern repeated vaccination may result in lower VE
- Easier to assess with TND, but inconsistent findings observed
- Reviews of prior seasonal vaccination
  - Vaccination in both seasons associated with greater protection against H1N1 & B, but not H3N2
  - No difference between vaccination in both seasons & current season only for all sub/types
  - No evidence of harm from repeated vaccination
  - Doesn't account for previous infection or >2 seasons
- Multi-season clinical studies needed

[Belongia et al, *Expert Rev Vaccines*, 2017, Ramsay et al, *BMC Med*, 2017]

Systematic review and meta-analysis

- TND studies of influenza VE in outpatient settings 2004-14
- 56 studies included with: defined illness criteria; VE stratified by subtype; PCR confirmed outcome; age-adjusted
- Pooled VE
  - A(H3N2): 33% (95% CI 26-39)
  - A(H1N1)pdm09: 61% (95% CI 57-65)
  - B: 54% (95% CI 46-61)
- A(H3N2) VE lower for ≥60 years and if antigenic mismatch

[Belongia et al, *Lancet Infect Dis*, 2016]

Interim VE against influenza in the 2017/18 northern hemisphere season

Country/Region	Setting, population	Type/subtype	VE (95% CI)
Europe	Primary care, all ages	A(H1N1)	68 (42—83)
		A(H3N2)	-16 (-96—31)
		B	39 (19—54)
	Hospitalised, >65y	A(H3N2)	-1 (-93—47)
		B	34 (8—52)
Canada	Primary care, all ages	A(H3N2)	17 (-14—40)
		B	55 (38—68)
USA	Primary care, all ages	A(H1N1)	67 (54—76)
		A(H3N2)	25 (13—36)
		B	42 (25—56)
Hong Kong	Hospitalised, 6m–17y	A(HxNx)	66 (3—88)
		B	65 (40—80)

[Rondy et al, *Euro Surveill*, 2018]
[Skowronski et al, *Euro Surveill*, 2018]
[Flannery et al, *MMWR Morb Mortal Wkly Rep*, 2018]
[Chiu et al, *Euro Surveill*, 2018]

Low vaccine effectiveness against influenza A(H3N2)

- Ongoing problem since 2011-12
- Genetic changes in vaccine virus haemagglutinin arise during passage in eggs, as distinct from antigenic drift
  - Mutations at glycosylation sites alter structure of antigenic sites
- Difficult to characterise antigenically
  - High % of isolates not recovered from cell culture
- Studies needed to assess whether VE against A(H3N2) varies by vaccine type

New influenza vaccines

- High-dose unadjuvanted (trivalent)
- Adjuvanted standard-dose (trivalent)
- Cell-based flu vaccines (trivalent)
- Recombinant influenza vaccines (RIV) (quadrivalent)
- Live attenuated influenza vaccine (LAIV)
  - Not recommended in US in 2016-17 & 2017-18 due to low effectiveness against A(H1N1)pdm09

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