Factors contributing to influenza vaccine policy development and implementation

Vaccine effectiveness estimates

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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 our household study settings
  - Prospective, rare outcome: expensive & logistically challenging

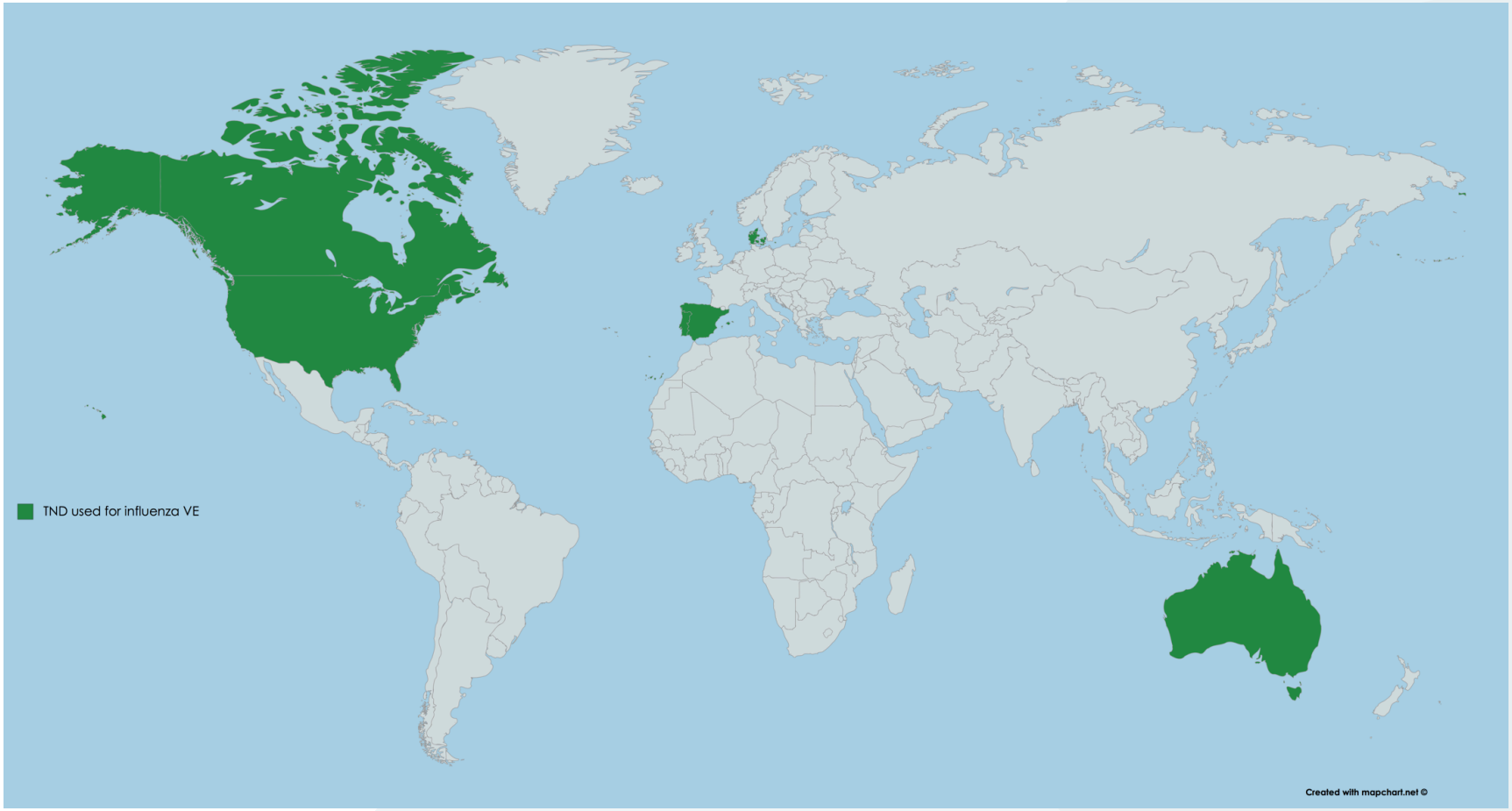
Methods for estimating influenza vaccine effectiveness

- 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

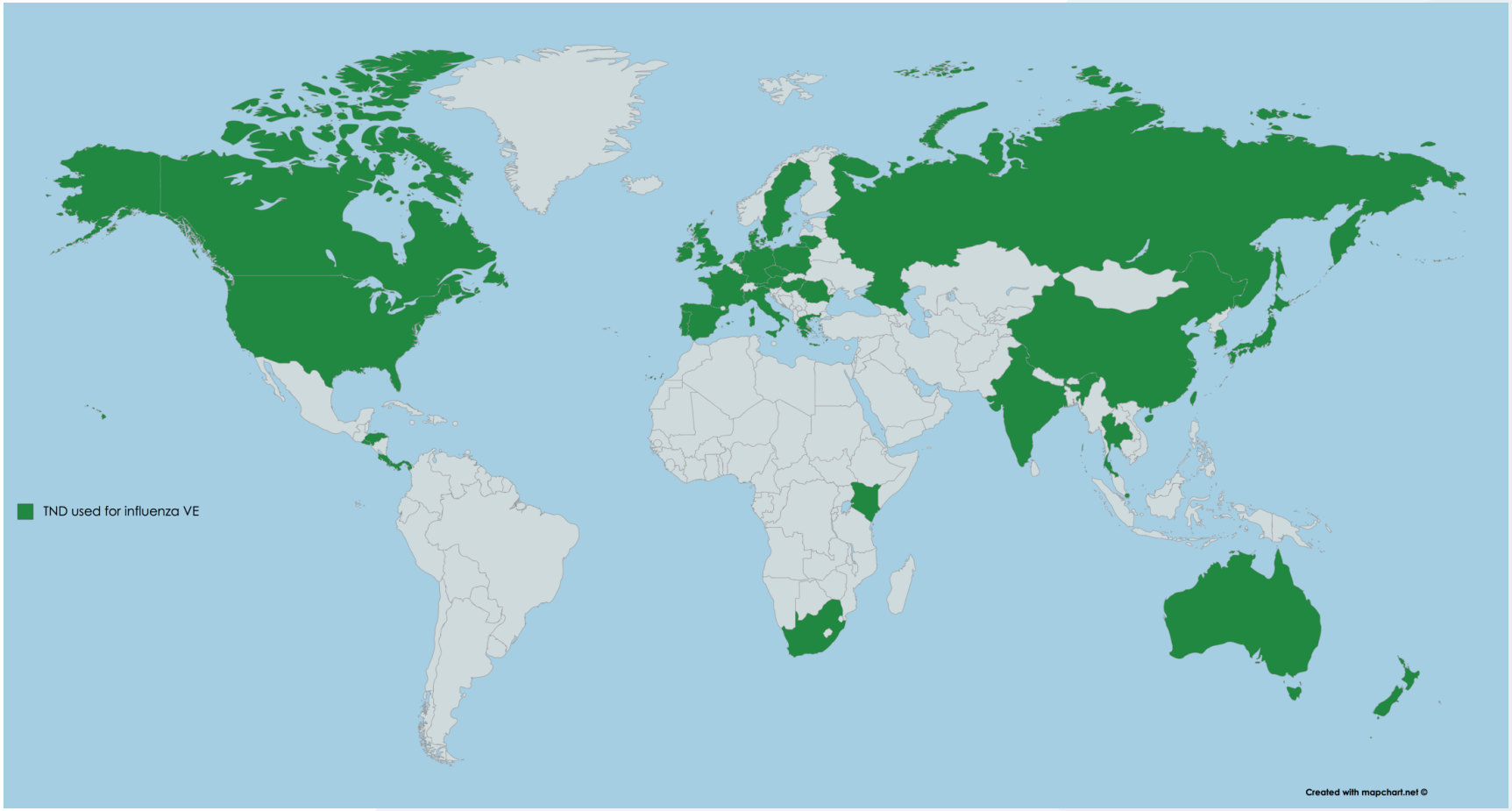
- Case test-negative design (TND)
  - Prospective variant of case control study
  - Increasingly adopted around the world

[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 2017



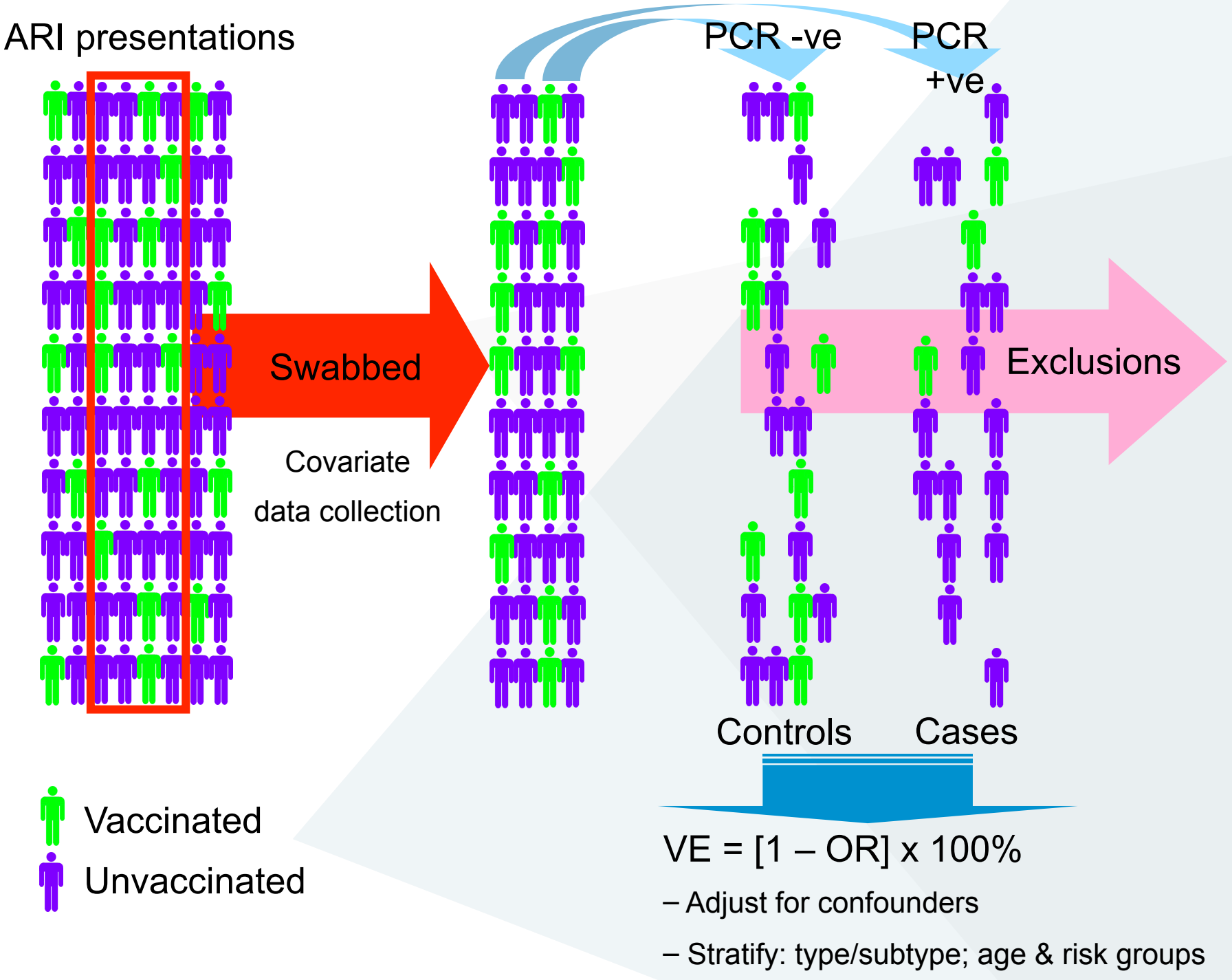
The case test-negative design

- 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

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


ARI presentations
Swabbed
Covariate
data collection
PCR -ve
PCR
+ve
Exclusions
Controls
Cases
Vaccinated
Unvaccinated
VE = [1 – OR] x 100%
– Adjust for confounders
– 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

Advantages and challenges

- Increasing use of TND
  - 40 papers in 2016
- Heterogeneity of methods
  - 85 studies used 68 unique statistical models
  - Harmonization can improve potential for pooling

[Sullivan et al, *Expert Rev Vaccines*, 2014]

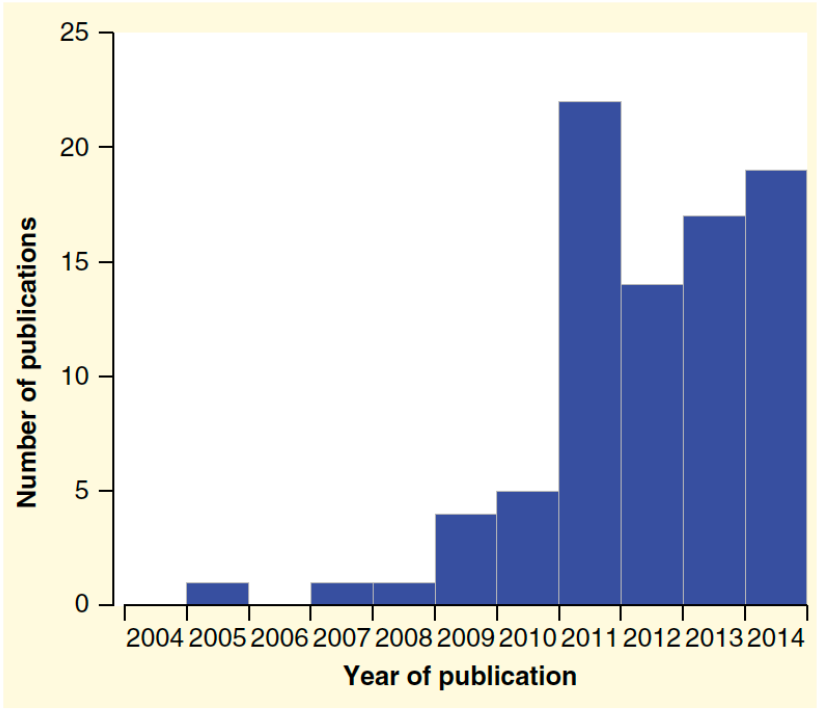
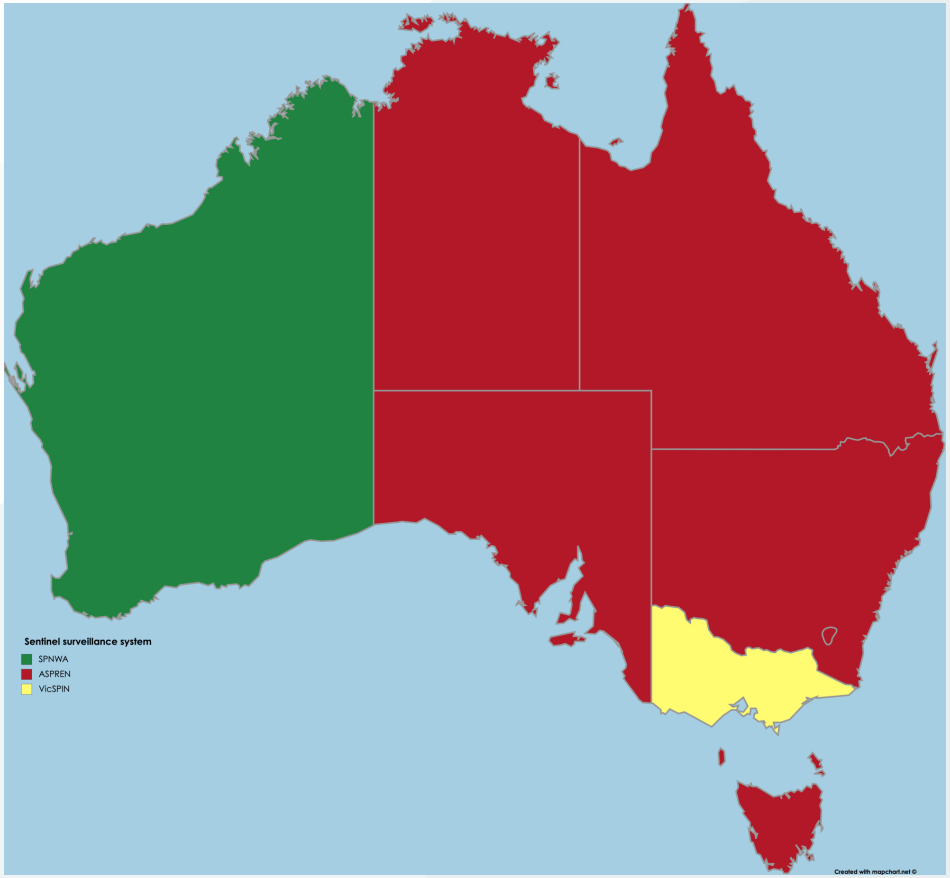


Figure 2. Number of published test-negative studies by year of publication. The bar for 2014 includes 19 studies published between January and August 2014.

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 antigentic & phylogenetic charcterisation
- 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

- Renewed interest following widespread use of TND
- Reliable vaccination histories difficult to collect
- Review of prior seasonal vaccination
  - Heterogeneity in effects within and between seasons and subtypes; most pronounced for A(H3N2)
  - VE may also be influenza by repeated vaccination across multiple seasons
- Multi-season clinical studies needed

[Belongia et al, *Expert Rev Vaccines*, 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 A(H3N2) in the 2016/17 northern hemisphere season

Country/Region	Influenza A(H3N2) VE (95% CI)
Canada	42% (18, 59)
USA	43% (29, 54)
Northern Spain	15% (-11, 35)
Europe (I-MOVE)	38% (21, 51)
Republic of Korea	-52% (-147, 6)

[Skowronski et al, *Euro Surveill*, 2017]
[Flannery et al, *MMWR Morb Mortal Wkly Rep*, 2017]
[Castilla et al, *Euro Surveill*, 2017]
[Kissling et al, *Euro Surveill*, 2017]
[Noh, *PLoS One*, 2017]

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