Flu – what to do about it?

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Influenza – interventions available

- Vaccination
- Antivirals (mainly oseltamivir)
- Non-pharmaceutical interventions

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- Antivirals (mainly oseltamivir)
- Non-pharmaceutical interventions
- Focus today is on vaccines

SAGE Position Paper on Influenza Vaccines – 2005

- In 2005:
  - Few countries with influenza vaccine programs
  - Supply of vaccines relatively limited
  - Data on need for vaccine and epidemiology of influenza mostly from high-income countries
- Recommendation: "In order of priority, the following groups **may be** targeted for vaccination..."
  1. Elderly and disabled residents of long-term care facilities
  2. Non-institutionalized elderly with chronic diseases
  3. All individuals $>$ 6 months of age with chronic diseases
  4. Elderly above a nationally defined age limit, irrespective of other risk factors
  5. **Other groups** defined on the basis of national data and capacities, such as contacts of high-risk people, pregnant women, health-care workers and others with key functions in society, as well as children 6-23 months of age

Situation in 2012

In 2012:

- Wealth of epidemiologic and surveillance data from low income and tropical countries
- Increased vaccine supply globally
- Increased appreciation of seasonal influenza vaccines
  - use of monovalent 2009 H1N1 vaccines in 2009/10
- More data on efficacy of flu vaccines in developing countries
  - Data on pregnant women
- Interest in pandemic readiness

SAGE Influenza Vaccine Recommendations, 2012

- Influenza vaccines are effective and safe and warrant increased use in all countries
- Five priority groups for countries using or considering introduction of seasonal influenza vaccines
  - Pregnant women (Highest priority group)
  - 4 other priority groups (not in order of priority)
    - Health-care workers
    - Children under 5 (particularly 6-23 months)
    - Elderly
    - Underlying health conditions
- Countries with existing influenza vaccination programs that target any of these subgroups should continue such programs
  - Consider incorporating pregnant women

Working Group's Assessment of Influenza Risk and Influenza Vaccine Characteristics in Various Risk Groups

Risk group	Feasibility of delivery	Disease severity	Vaccine effectiveness	Indirect Benefits
Pregnant women	++	+++	+++	++
Healthcare workers	++	+	+++	+
Children, 2-5 years	+	++	++	-
Children, < 2 years	++	+++	+	-
Elderly	+	+++	+	-
Underlying Health conditions	+	+++	+	-

SAGE influenza Vaccination Recommendations (continued)

- Countries should decide which other groups to target for influenza vaccination, based on:
  - Disease severity within individual risk group
  - Vaccine effectiveness in the risk group
  - Feasibility of delivery
  - Indirect effects
  - Cost-effectiveness
  - Opportunity cost
- Increased use of seasonal influenza vaccine globally supports enhanced influenza vaccine production capacity and thereby contributes to influenza pandemic preparedness

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 (e.g. see Jackson et al, Int J Epidemiol 2006)

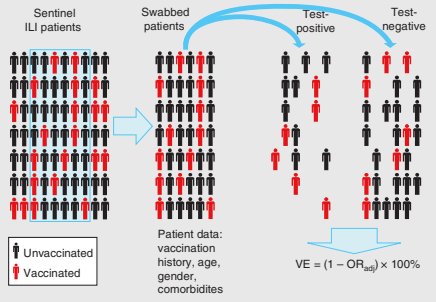
Test-negative design (TND)

- 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; 31:181-72.
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.

VE estimates by type/subtype 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.

VE estimates by age group 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.

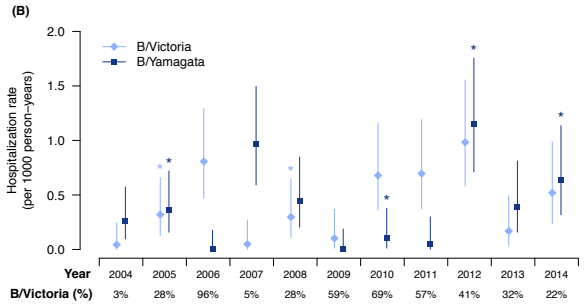
Importance of influenza B particularly in children >12m

Table: Number of detections of influenza virus and RSV in different age groups, 2004-14

Age group	No. of children	Influenza A	Influenza B	RSV
<6m	436	28 (6.4%)	4 (0.9%)	98 (22.5%)
6-12m	629	36 (5.7%)	7 (1.1%)	108 (17.2%)
>12m	4020	440 (10.9%)	210 (5.2%)	326 (8.1%)

Cowling et al. 2017 Clin Infect Dis

Annual incidence of influenza B by lineage, 2004-14



Annual hospitalization rates of pediatric patients infected with influenza B viruses identified as Victoria or Yamagata lineage in Hong Kong, 2004-14. An asterisk indicates years when there was an antigenic change. The bottom row reports local surveillance data for comparison.

Cowling et al. 2017 Clin Infect Dis

VE against influenza B by lineage

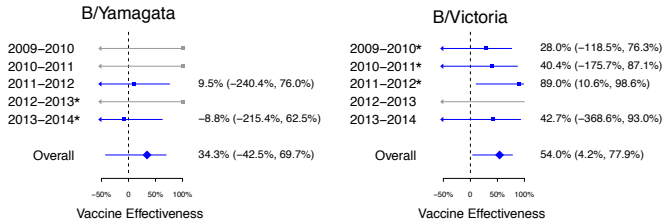


Figure: VE against influenza B hospitalization by lineage. Asterisks indicate the lineage included in the trivalent influenza vaccine.

Chiu et al. 2016 Vaccine

VE of TIV vs QIV in 2015/16

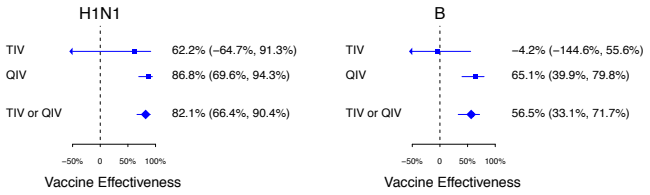


Figure: Estimated influenza vaccine effectiveness against hospitalization by type of vaccine among children in Hong Kong, October 2015 through August 2016. TIV included B/Yamagata strain only; Hong Kong had mixed activity of B/Victoria and B/Yamagata lineage viruses.

unpublished data

Comments

- Lineage-matched VE for B/Yamagata-like virus was poor and may be related to clade mismatch.
- Cross-lineage protection of TIV was not observed.
- QIV provided significantly better protection than TIV in 2015/16 when there was a lineage mismatch in the TIV.

Year-round circulation

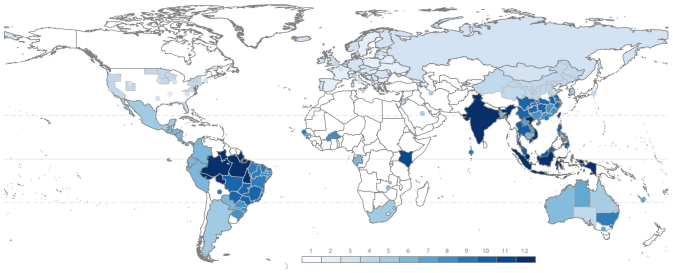


Figure: Number of months of influenza activity each year in 178 selected geographic locations, with darker colors indicating longer periods of activity in tropical and subtropical regions.

Cowling et al. unpublished

Changes in recommended vaccine strains

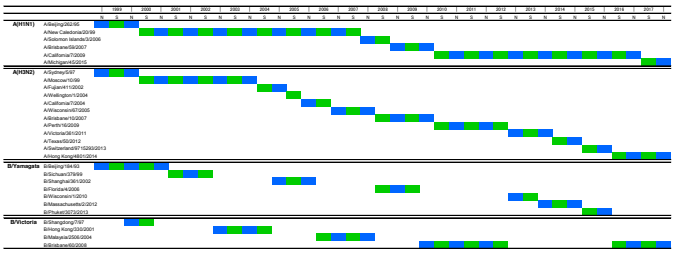


Figure: The vaccine compositions recommended by WHO for trivalent influenza vaccines to be used in northern hemisphere influenza seasons from 1998-99 through 2017-18 (blue) and those for southern hemisphere influenza seasons from 1999 through 2017 (green). There were 26 changes in 19 years.

Xu et al. 2017 Lancet Resp Med

Twice-annual vaccination?

- VE is slightly lower in older adults than younger adults
- Protection may not last for 12 months after vaccination because of (1) gradually declining antibody titers after vaccination, and (2) antigenic changes in circulating strains.
- Would vaccination every 6 months, with the most recent strains, improve protection in older adults, particularly in tropical and subtropical areas?
- Any limitations of repeated vaccination?

Xu et al. 2017 Lancet Resp Med

Repeated annual vaccination

- Conflicting results regarding the impact of repeated vaccination on influenza vaccine effectiveness (VE) may cause confusion regarding the benefits of receiving the current season's vaccine.
- We reviewed 20 articles including data on repeated vaccination
- Among those who **did not receive** vaccination last year, current year vaccination was beneficial for H1N1 (ΔVE = 61%; 95% CI, 50% to 70%), H3N2 (ΔVE = 41%; 95% CI, 33% to 48%), and B (ΔVE = 62%; 95% CI, 54% to 68%).

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- Among those who **received** vaccination last year, current year vaccination was beneficial for H1N1 (ΔVE = 26%; 95% CI, 15% to 36%) and B (ΔVE = 24%; 95% CI, 7% to 42%), but not H3N2 (ΔVE = 10%; 95% CI, -6% to 25%).

Ramsay LC et al. 2017 BMC Medicine

Conclusions

- SAGE recommendations (2012): pregnant women (highest priority), health-care workers, young children, elderly, underlying conditions.
- 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).

Conclusions (continued)

- Influenza B is a significant threat, causing considerable hospitalizations and deaths each year.
- QIV provides superior protection to TIV against the B lineage that is not included in the TIV
- Whether or not a person received vaccination last year, they will benefit from vaccination this year.