Influenza vaccine effectiveness in preventing out-patient visits, hospitalization and death in various population groups.

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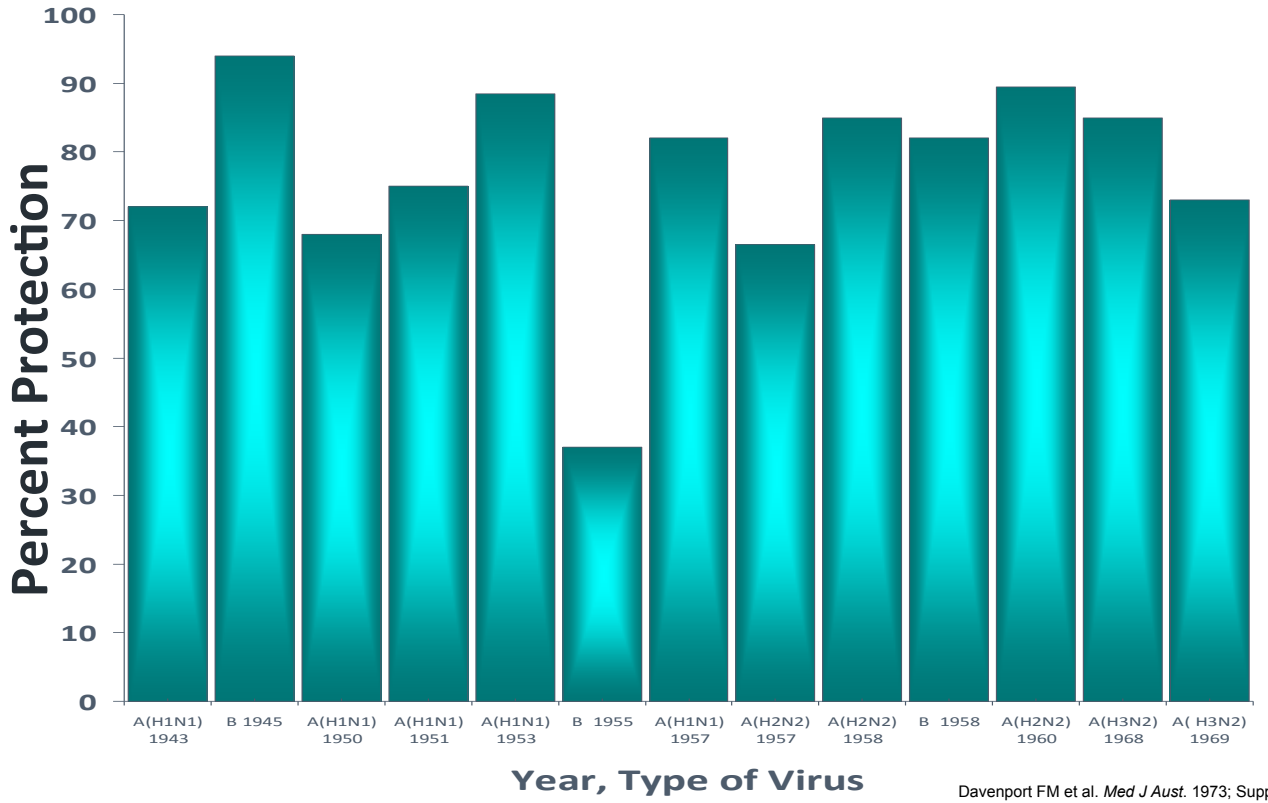
USA

Protective Efficacy of Inactivated Influenza Vaccines 1943-1969



Davenport FM et al. *Med J Aust.* 1973; Suppl 33-38

Issues in determining effectiveness of influenza vaccine

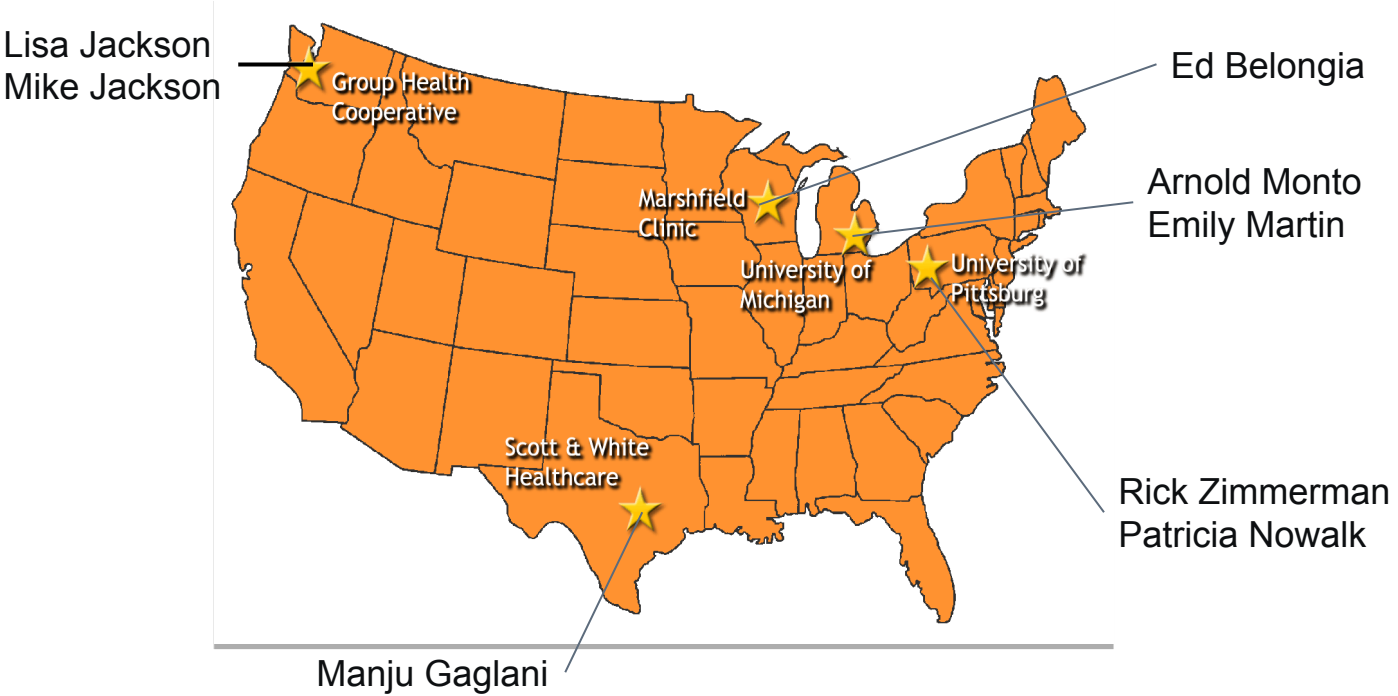
- Gold standard is a placebo controlled trial. However, this only applies to the year(s) the trial was conducted and the population that participated.
- Vaccine effectiveness (VE) varies by age group and other factors, such as past vaccination and underlying conditions.
- In some years, the virus circulating may not be similar to the one in the vaccine, resulting in lower VE.
- Observational studies are conducted to determine actual VE in real people.

Test-Negative Design

- Most commonly used observational design for estimating VE
- Study populations are generally drawn from patients seeking outpatient care for ARI or hospitalized for respiratory conditions
- RT-PCR confirmed outcomes
  - Cases: subjects testing positive for influenza
  - Controls: subjects testing negative for influenza
- Estimated ratios of the odds of influenza in vaccinated and unvaccinated subjects are used to calculate VE, adjusted to control for confounding factors.

Jackson et al. Vaccine 2013; 31:2165-8.
Foppa et al. Vaccine 2013; 31:3104-9.

US Flu VE Network: Five Study Sites and Principal Investigators



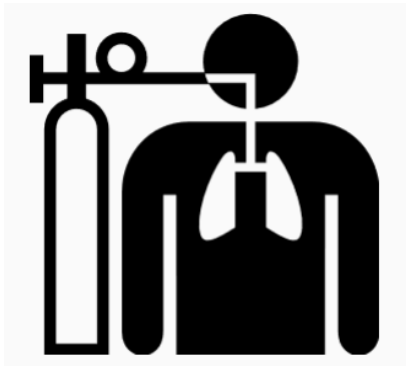
Priority groups for seasonal influenza vaccinatic

Highest priority

Pregnant women

Children aged 6-59 months

Elderly



Individuals with specific chronic medical conditions

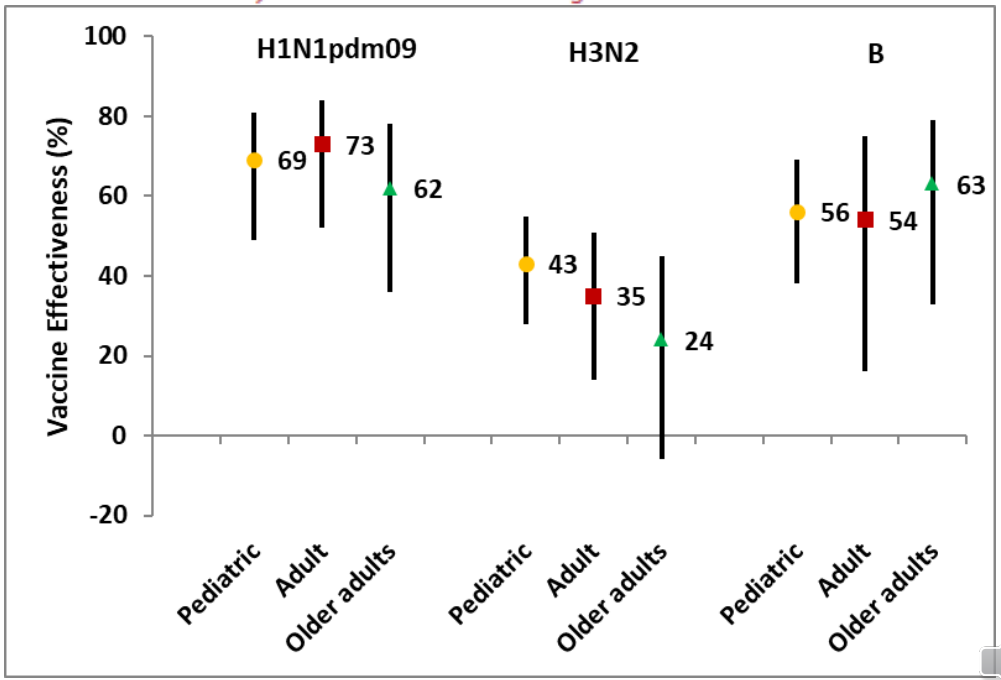
Health-care workers

Source: WHO, www.who.int; icons from www.thenounproject.com

Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies

Edward A Belongia, Melissa D Simpson, Jennifer P King, Maria E Sundaram, Nicholas S Kelley, Michael T Osterholm, Huong Q McLean

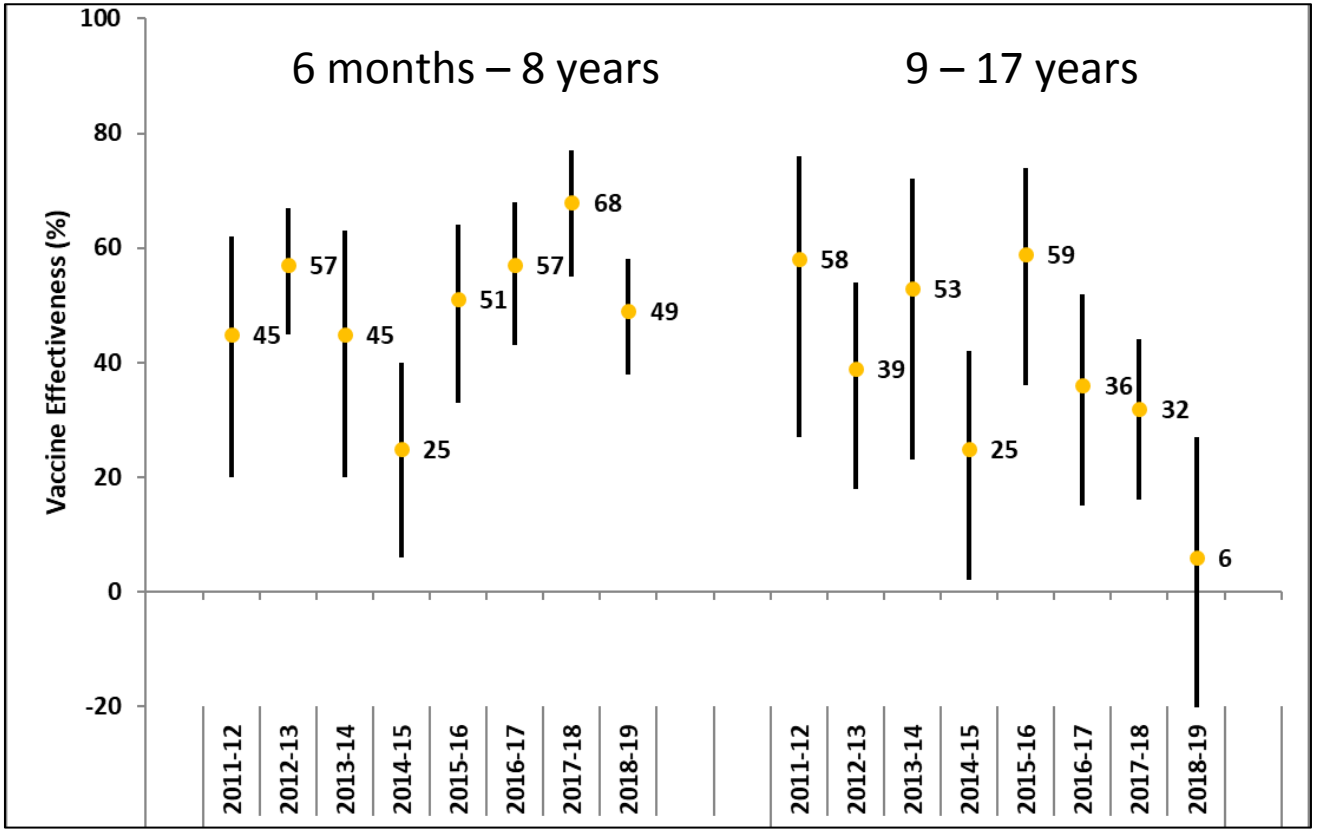
- 56 test-negative studies 2007 to 2014/15
- Lower pooled VE against H3N2 than H1N1pdm09 and B
- Pooled VE similar by age groups; decreasing trend for H3N2



Lancet Infect Dis 2016

Young children

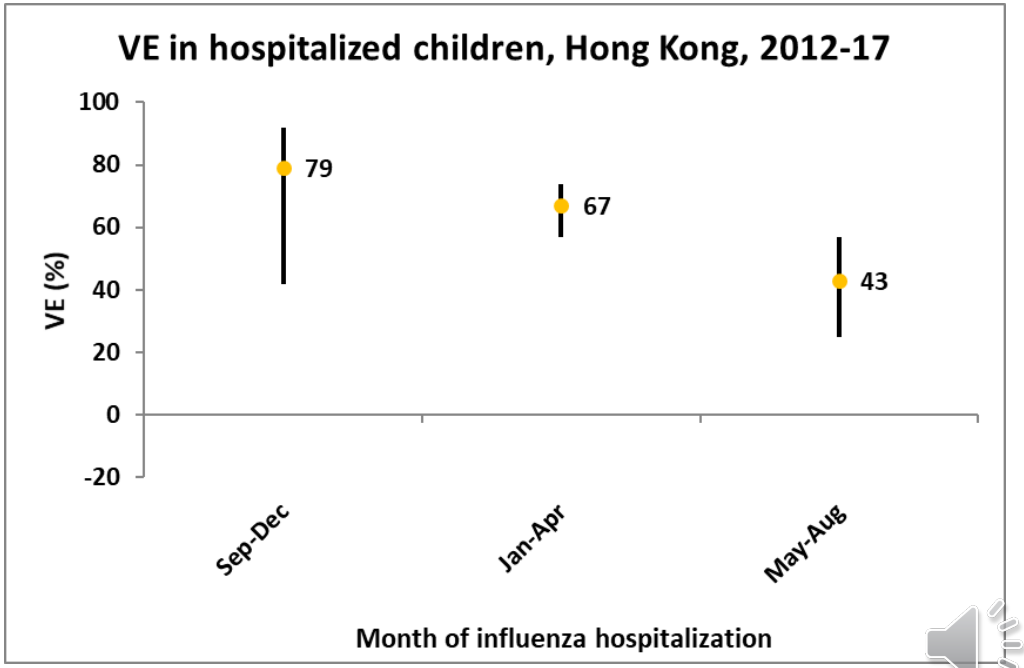
Effectiveness of influenza vaccination against medically attended influenza in children, US Flu VE Network, 2011-2019



Effectiveness of influenza vaccination on influenza-associated hospitalisations over time among children in Hong Kong: a test-negative case-control study

Shuo Feng, Susan S Chiu*, Eunice L Y Chan, Mike Y W Kwan, Joshua S C Wong, Chi-Wai Leung, Yiu Chung Lau, Sheena G Sullivan, J S Malik Peiris, Benjamin J Cowling*

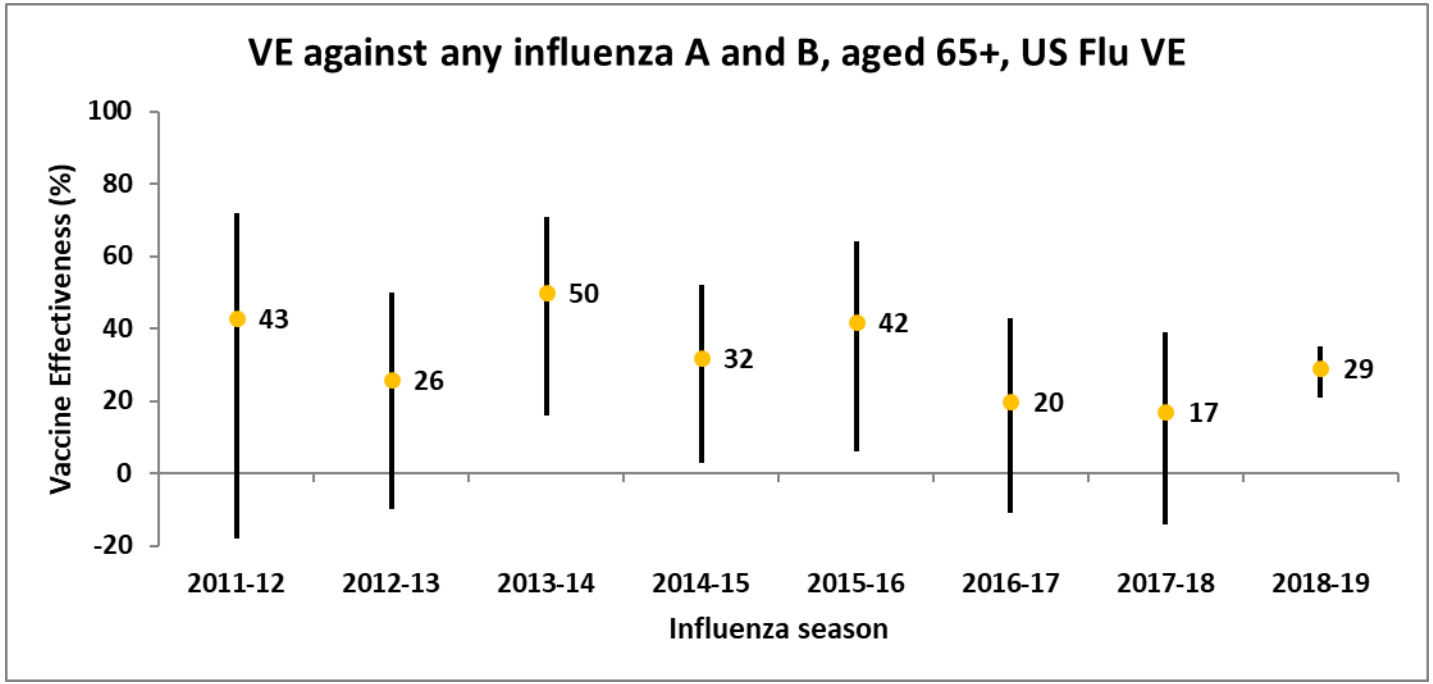
- Aged 6 months – 17 years
- 5 seasons, 2012-17
- Most vaccination by Dec
- Pooled VE declined with time since vaccination



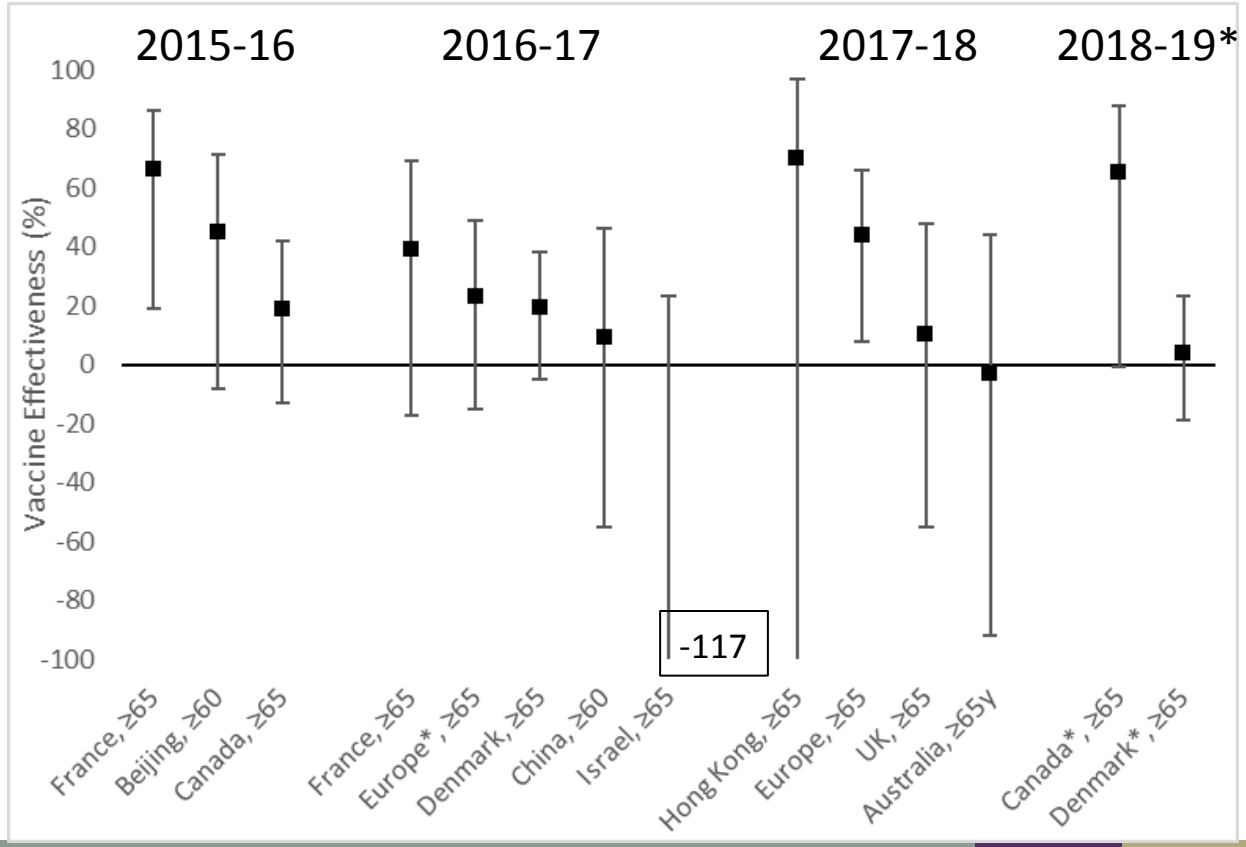
Lancet Resp Med 2018

Older adults

Influenza vaccine effectiveness against any influenza among US adults aged ≥65 years, Flu VE Network, 2011-2019



Ambulatory studies: Effectiveness of influenza vaccination against medically attended influenza in older adults, 2015-2019



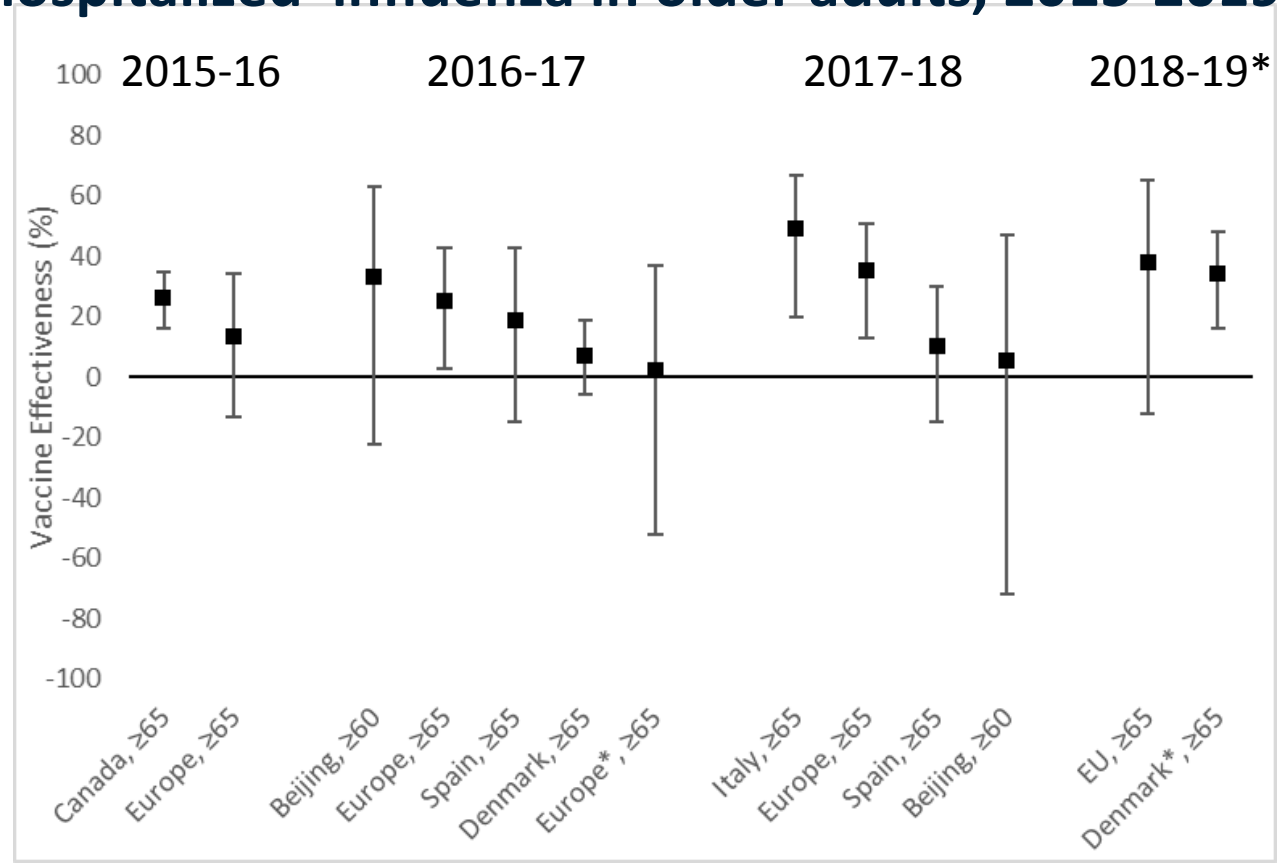
2015-16
Vilcu, 2018
Zhang, 2018
Kwong, 2019

2016-17
Regan, 2019
Shoubaki, 2018
Kissing, 2017*
Wu, 2018

2017-18
Rondy, 2018*
Coleman, 2018
Chan, 2018
Sullivan, 2017

2018-19
Skowronski, 2019*
Kissing, 2019*

Hospital studies: Effectiveness of influenza vaccination against hospitalized influenza in older adults, 2015-2019



2015-16
Chon, 2019
Pebody, 2016
Mohl, 2018
Zhang, 2018

2016-17
Regan, 2019
Shoubaki, 2018
Kissing, 2017*
Wu, 2018

2017-18
Rondy, 2018*
Coleman, 2018
Chan, 2018
Sullivan, 2017

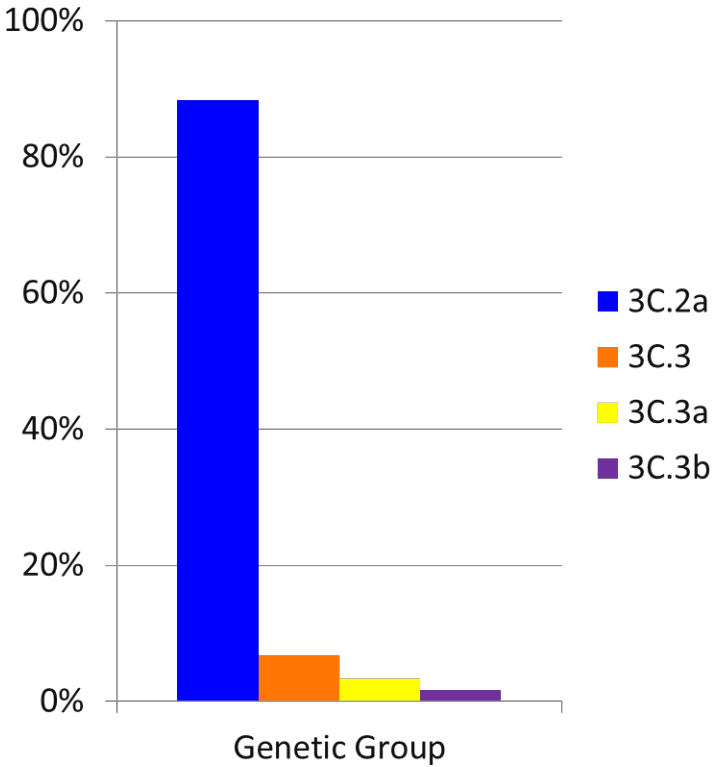
2018-19
Skowronski, 2019*
Kissing, 2019*

Study Hospital Sites

- University of Michigan Hospital
  - 550-bed adult tertiary care hospital
  - Ann Arbor, MI

- Henry Ford Hospital
  - 802 bed adult tertiary care hospital
  - Detroit, MI

Summary of A (H3N2) Virus Genetic Characterization



- Genetic group determined by pyrosequencing or Sanger sequencing
- The A (H3N2) virus included in the 2014-2015 influenza vaccine belongs to group 3C.3
- The 3C.2a genetic group was associated with antigenic drift from the vaccine virus.

Clin Infect Dis. 2016 ; 63:1017-25

Influenza Vaccine Effectiveness against Influenza Associated Hospitalization

Analysis Subset	Vaccinated N Flu/Total (%)	Unvaccinated N Flu/Total (%)	Unadjusted VE % (95% CI)	Adjusted VE % (95% CI)
All Influenza	66/430 (15)	50/212 (24)	41 (11 to 61)	47 (13 to 68)
Age 18-49 yrs	11/81 (14)	23/91 (25)	54 (-3 to 79)	59 (-3 to 84)
Age 50-64 yrs	22/169 (13)	13/73 (18)	31 (-46 to 67)	24 (-81 to 68)
Age ≥65 yrs	33/180 (18)	14/48 (29)	45 (-13 to 74)	55 (-14 to 83)
A (H3N2)	57/421 (14)	41/203 (20)	38 (4 to 60)	46 (7 to 68)
B Yamagata	3/152 (2)	6/74 (8)	77 (6 to 94)	82 (-3 to 97)

Models were adjusted for age in months (cubic spline), calendar time (categorical biweekly), sex, enrollment hospital (UM; HF), time from onset to specimen collection (days), frailty score (0-5), and Charlson score (categorical: 0, 1, 2, 3+).

Clin Infect Dis. 2016 ; 63:1017-25

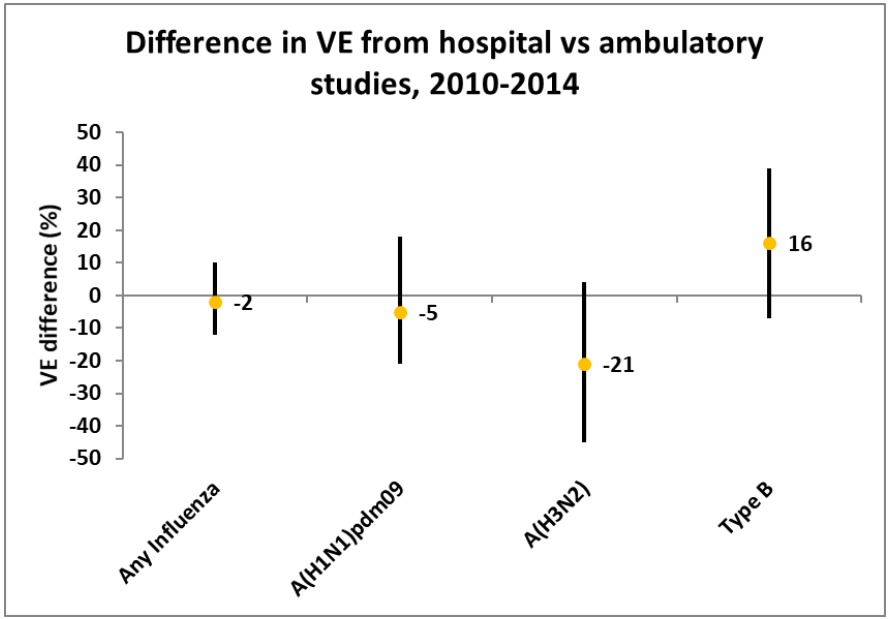
Ambulatory

Hospital

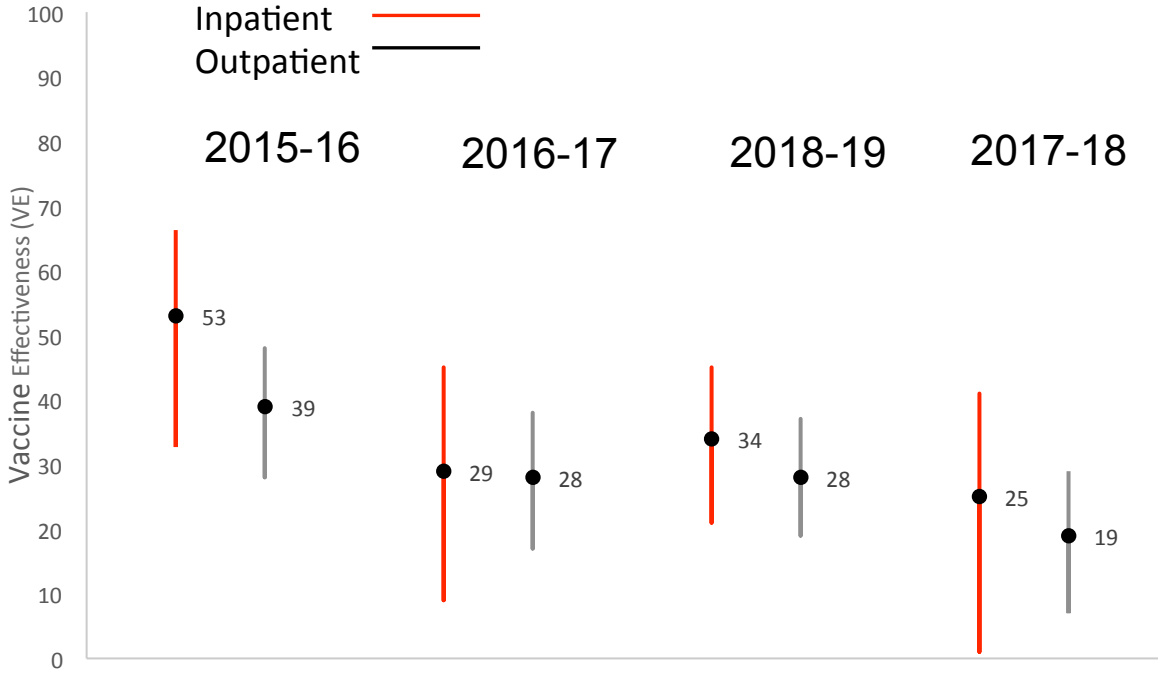
Influenza vaccine effectiveness by test-negative design – Comparison of inpatient and outpatient settings

Shuo Feng[a], Benjamin J. Cowling[a,*], Sheena G. Sullivan[b,c]

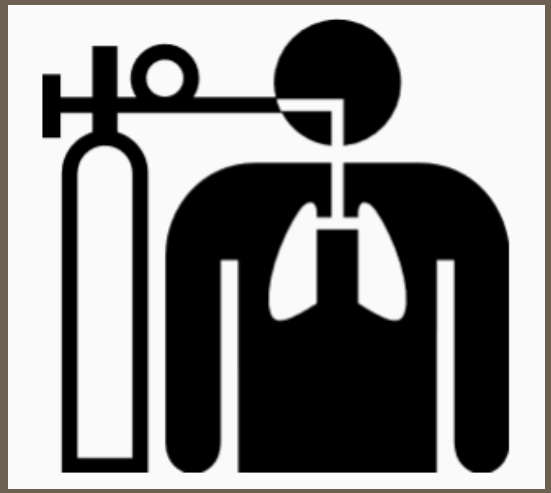
- 25 paired VE estimates from 14 hospital and ambulatory studies, 2010-2014
- Hosp. patients more likely to have high-risk conditions, vaccination
- Influenza positivity higher among ambulatory patients
- Compared differences in VE: ΔVE<0 if hospital VE<ambulatory



Comparison of influenza VE against any influenza A or B in inpatient vs outpatient setting, adults ≥18 years, USA

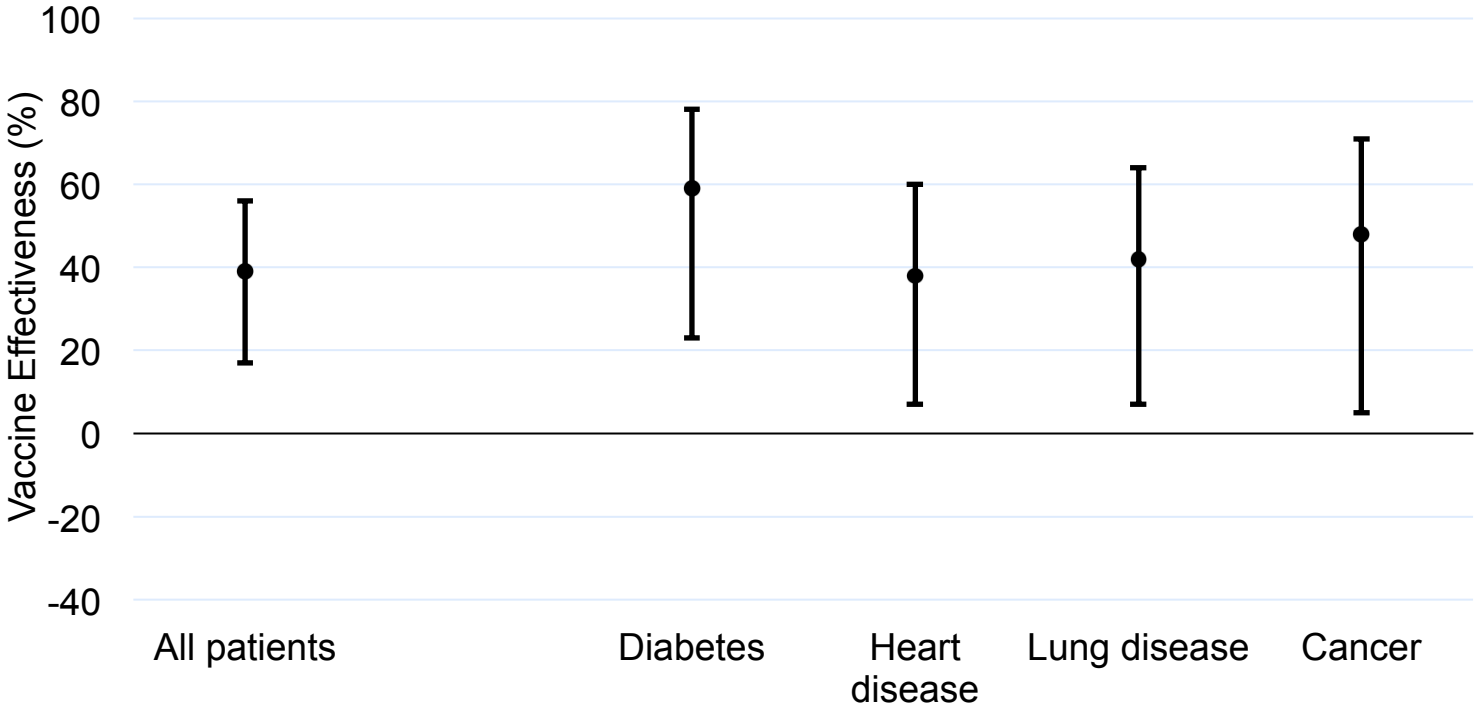


Tenforde, CID 2020 https://doi.org/10.1093/cid/ciaa407; CDC unpublished data

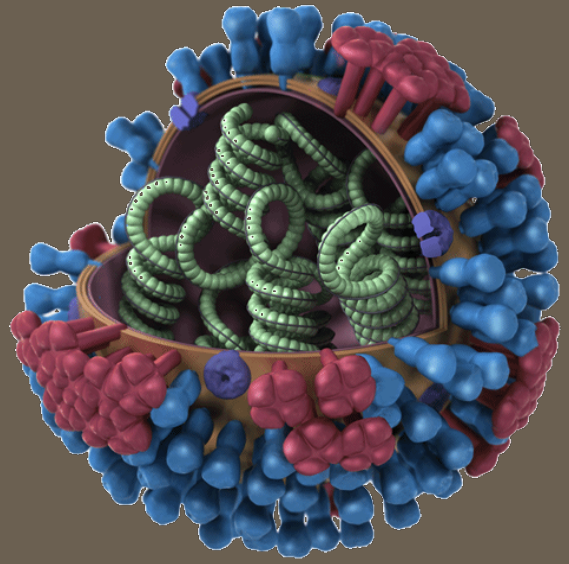


Persons with chronic medical conditions

Influenza vaccine effectiveness against hospitalized influenza A(H1N1)pdm09, persons aged ≥65 years, by risk groups, Europe, 2015-16



Source: Rondy, Eurosurveillance 2017



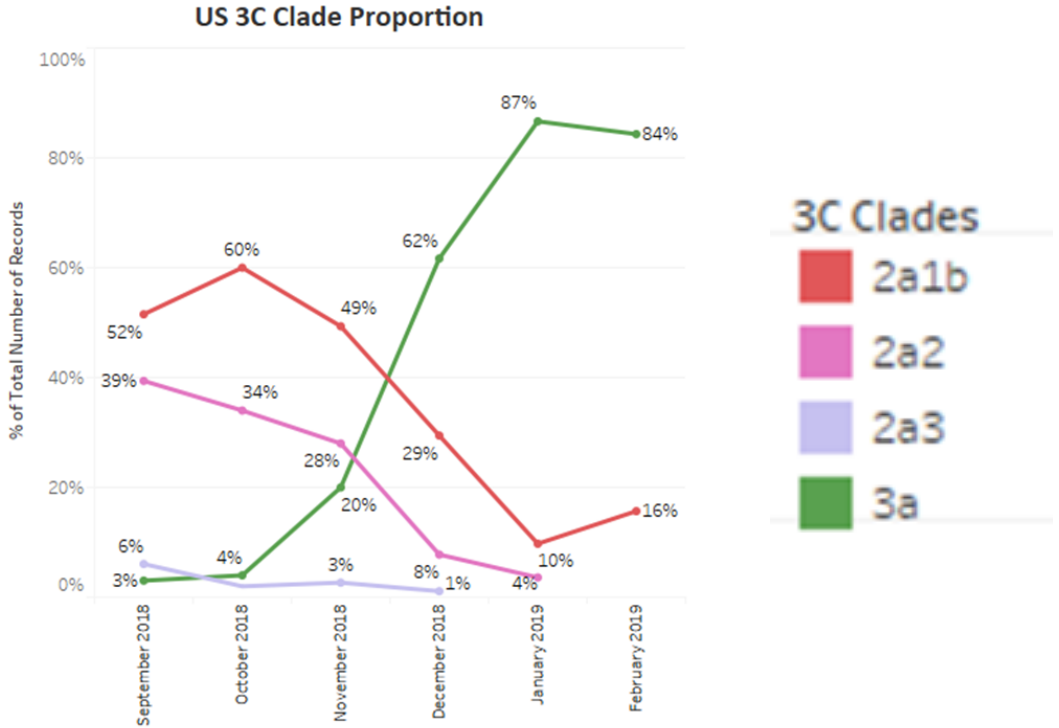
Clade-specific VE

Increasing use of Next Generation Sequencing to estimate VE against emerging influenza viruses

- US Flu VE network: platform for annual estimates of VE against medically attended influenza in the ambulatory setting

- Flu VE data presented to WHO Strain Selection Committee
  - VE against A/H3N2 clade 3C.3a (vaccine mismatch) in 2018-19
  - VE against emerging A/H1N1pdm09 subclade in 2019-20

Emergence of 3C.3a A/H3N2 viruses in the U.S., 2018–19



Adjusted vaccine effectiveness against influenza A/H3N2 by clade, US Flu VE Network, 2018–19 (seq. data as of 6/21/19)

	Influenza positive		Influenza negative		Vaccine Effectiveness			
					Unadjusted		Adjusted*	
	N vaccinated /Total	(%)	N vaccinated /Total	(%)	VE %	95% CI	VE %	95% CI
All Influenza A/H3N2								
All H3N2	710/1352	53	4065/7249	56	13	(3 to 23)	**9**	**(-4 to 20)**
A(H3N2) clade 3C.3a	372/709	52	4065/7249	56	14	(-1 to 26)	**11**	**(-6 to 26)**
A(H3N2) clade 3C.2a1	30/61	49	4065/7249	56	24	(-25 to 54)	**45**	**(5 to 68)**

* Multivariable logistic regression models adjusted for site, sex, race/ethnicity, self-rated general health status, interval from onset to enrollment, and calendar time.

Summary

- Observational studies are a real-world way of gaining evidence for influenza vaccine effectiveness in populations targeted for vaccination
- Effectiveness will vary by type and subtype, so overall effectiveness will change from year to year
- Estimates of vaccine effectiveness from ambulatory and hospital studies in often similar but may vary in favor of hospitalizations in some years.
- There is evidence of prevention of death in the older population, but the studies need to be much larger and are not laboratory confirmed.
- These studies have been repeated in different situations, validating the positive conclusions.