Influenza Vaccine Efficacy and Effectiveness

Arnold S. Monto
University of Michigan
School of Public Health
Ann Arbor, Michigan

Basic Issues

- Influenza vaccines were developed nearly 70 years ago, and much of the evaluation has been carried out in healthy adults.
- It is know that influenza vaccines vary in efficacy/effectiveness (VE) , based on the match between the viruses that circulate and those that were chosen for the vaccine.
- VE also varies by age, and is likely lower in older individuals and perhaps in the very young. There have been few randomized trials of vaccines in older individuals.

Key Definitions

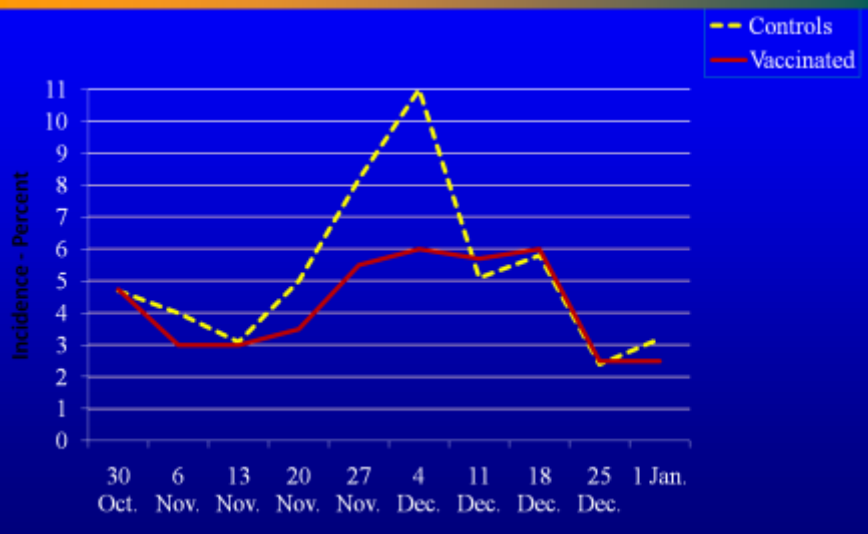
EFFICACY: The extent to which an intervention produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized controlled trial in which all intervention groups are similar.

EFFECTIVENESS: The extent to which an intervention when deployed , does what it is intended to do for a defined population. An observational study, in which groups may not be similar in characteristics.

Study of early influenza vaccine University of Michigan Military Service Unit, 1943

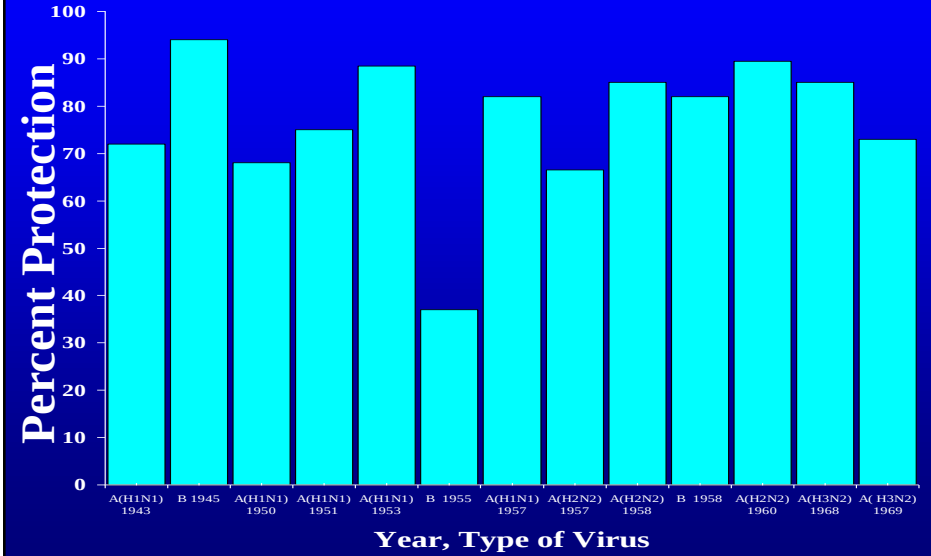
- Inactivated influenza vaccine containing two type A strains (PR8 and Weiss) and B/Lee
- Placebo controlled design
- HAI antibody pre and 14 days post vaccination
- Outbreak early – type A only. Combined endpoint – some virus identification

Incidence of respiratory disease in the University of Michigan A.S.T.P. unit, 1943-1944



Salk et al. *Am. J. Hyg.* 1945;42:57-93.

Protective Efficacy of Inactivated Influenza Vaccines 1943-1969



Davenport Med J Aust; 1973 ;suppl :33

VACCINE EFFICACY/ EFFECTIVENESS IN YOUNG ADULTS

Results 2004-2005:

- 32 (2.6%) participants had culture-confirmed symptomatic influenza.
  - 14 influenza A(H3N2) – A/California/07/2004-like (antigenically drifted)
  - 18 influenza B – seven B/Shanghai/361/2002-like [Yamagata lineage, vaccine strain] and eleven B/Hawaii/33/2004-like [Victoria lineage]
- 43 (3.4%) participants had PCR-confirmed symptomatic influenza
  - 28 influenza A(H3N2); 14 influenza B; 1 influenza A and B (two different illness episodes)

Efficacies of TIV and LAIV against type A and B influenza, Michigan, 2004-2005

Endpoint	Incidence of Influenza			Vaccine efficacy (95% CI)		
	TIV N=522	LAIV N=519	Placebo N=206	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV
Culture positive	7 (1.3)	13 (2.5)	12 (5.8)	77 (37 to 92)	57 (-3 to 82)	46 (-44 to 82)
Culture or PCR positive	10 (1.9)	21 (4.0)	16 (7.8)	75 (42 to 90)	48 (-7 to 74)	53 (-5 to 80)
Culture or serologic positive #	10 (2.7)	21 (5.8)	12 (8.2)	67 (16 to 87)	30 (-57 to 67)	53 (-4 to 80)

Numbers among per-protocol population (367 TIV, 363 LAIV, 146 placebo)

Ohmit et al. *NEJM*. 2006; 355:2513

Efficacies of TIV and LAIV against type A influenza, Michigan, 2004-2005

Endpoint	Cumulative Incidence of Influenza			Vaccine Efficacy (95% CI)		
	TIV (N=522)	LAIV (N=519)	Placebo (N=206)	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV
Culture positive influenza	4 (0.8)	4 (0.8)	6 (2.9)	74 (-11 to 95)	74 (-11 to 95)	1 (-434 to 81)
Culture or PCR positive cases	7 (1.3)	12 (2.3)	9 (4.4)	69 (7 to 90)	47 (-42 to 80)	42 (-60 to 81)

Ohmit et al. *NEJM*. 2006; 355:2513

Efficacies of TIV and LAIV against type B influenza, Michigan, 2004-2005

Endpoint	Cumulative Incidence of Influenza			Vaccine Efficacy (95% CI)		
	TIV (N=522)	LAIV (N=519)	Placebo (N=206)	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV
Culture positive influenza	3 (0.6)	9 (1.7)	6 (2.9)	80 (8 to 97)	40 (-103 to 81)	67 (-33 to 94)
Culture or PCR positive cases	3 (0.6)	9 (1.7)	7 (3.4)	83 (26 to 97)	49 (-61 to 83)	67 (-33 to 94)

Ohmit et al. *NEJM*. 2006; 355:2513

Results 2005-2006:

- 24 (1.2%) participants had culture-confirmed symptomatic influenza .
  - 23 influenza A(H3N2) – A/Wisconsin/67/2005-like.
  - 1 influenza B – B/Ohio/01/2005-like [Victoria lineage].
- 32 (1.6%) participants had PCR-confirmed symptomatic influenza.
  - 31 influenza A(H3N2); 1 influenza B.

Efficacies of TIV and LAIV against type A and B influenza, Michigan, 2005-2006

Endpoint	Incidence of Influenza			Vaccine efficacy (95% CI)		
	TIV N=867	LAIV N=853	Placebo N=338	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV
Culture positive	12 (1.4)	6 (0.7)	6 (1.8)	23 (-153, 73)	61 (-48, 89)	-95 (-539, 32)
PCR positive	12 (1.4)	14 (1.6)	6 (1.8)	23 (-153, 73)	8 (-194, 67)	16 (-96, 64)
Culture or PCR positive	13 (1.5)	14 (1.6)	6 (1.8)	16 (-171, 70)	8 (-194, 67)	9 (-110, 60)

Ohmit et al. *J Infect. Dis.* 2008; 198:312

Results 2007 - 2008:

- 119 (6.1%) participants had culture or PCR confirmed symptomatic influenza
  - All 107 type A (H3N2) viruses were genotypically A/Brisbane/10/2007
    - By HAI, some were high reactors to vaccine strain A/Wisconsin/67/2005, some low reactors
  - Only 1 type A (H1N1) virus identified, antigenically related to the vaccine virus, A/Brisbane/59/2007
  - All 11 type B viruses were from the B/Yamagata lineage while the vaccine virus was A/Victoria-like .

Monto et al. *NEJM.* 2009; 361:1260

Efficacies of TIV and LAIV against type A and B influenza, Michigan, 2007-2008

Endpoint	Incidence of Influenza			Vaccine efficacy (95% CI)		
	TIV N=813	LAIV N=814	Placebo N=325	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV
Culture positive	21 (2.6)	38 (4.7)	31 (9.5)	73 (51-85)	51 (19-70)	45 (3-69)
PCR positive	28 (3.4)	56 (6.9)	35 (10.8)	68 (46-81)	36 (0-59)	50 (20-69)
Positive culture or PCR	28 (3.4)	56 (6.9)	35 (10.8)	68 (46-81)	36 (0-59)	50 (20-69)

Monto et al. *NEJM.* 2009; 361:1260

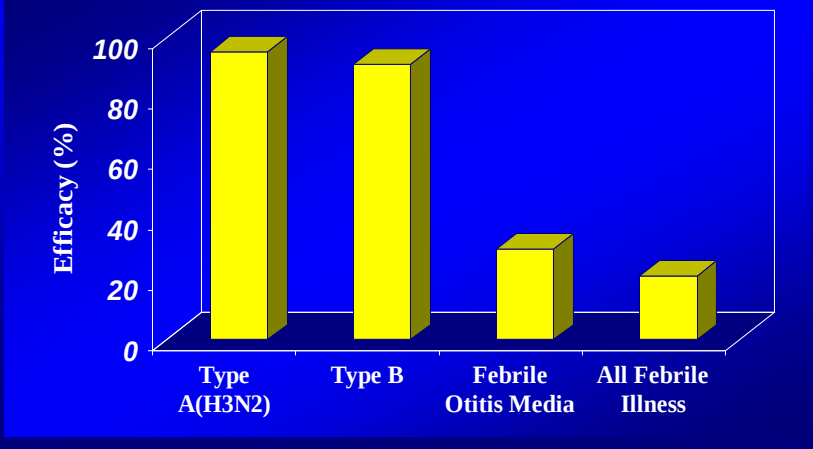
Efficacy of TIV and LAIV against type A and type B influenza viruses, Michigan, 2007-2008

Endpoint	Cumulative Incidence of Influenza			Vaccine efficacy (95% CI)		
	TIV N=813	LAIV N=814	Placebo N=325	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV
Influenza A						
Culture and/or PCR positive	22 (2.7)	55 (6.8)	31 (9.5)	72 (49 to 84)	29 (-14 to 55)	60 (33 to 77)
Influenza B						
Culture and/or PCR positive	6 (0.7)	1 (0.1)	4 (1.2)	40 (-189 to 86)	90 (-1 to 100)	-501 (-27530 to 27)

Monto et al. *NEJM.* 2009; 361:1260

VACCINE EFFICACY/ EFFECTIVENESS IN CHILDREN

Efficacy of LAIV (US) in Preventing Influenza and Complications in 15-71 month old Children, 1996-1997



*Adapted from Belshe et al., 1998.

Influenza attack rates in children 6-59 months of age, 2004-2005

Virus	Similarity to vaccine	LAIV (N=3916)		TIV (N=3936)		Reduction in attack rate with live vaccine
		Cases	Attack rate	Cases	Attack rate	
		no.	%	no.	%	% (95% CI)
	Well matched	53	1.4	93	2.4	44.5 (22.4, 60.6)
A/H3N2		0	0	0	0	--------
A/H1N1		3	0.1	27	0.7	89.2 (67.7, 97.4)
B		50	1.3	67	1.7	27.3 (-4.8, 49.9)
	Regardless of match	153	3.9	338	8.6	54.9 (45.4 , 62.9)
A/H3N2		37	0.9	178	4.5	79.2 (70.6, 85.7)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 , 97.4)
B		115	2.9	136	3.5	16.1 (-7.7, 34.7)

Belshe et al. *NEJM*. 2007; 356:685

Observational Study of TIV in Preventing Laboratory-Confirmed Illnesses in Pediatric Practices

Logistic Regression of Laboratory-confirmed Influenza by Vaccination Status, Adjusted for Risk Status & Health Care Usage

Parameter	Aged 6-59 mo		Aged 6-23 mo		Aged 24-59 mo	
	OR (95% CI)	VE, %	OR(95% CI)	VE, %	OR (95% CL)	VE, %
Fully vaccinated versus unvaccinated	**0.51 (0.4-0.7)**	**49**	**0.48 (0.3-0.8)**	**52**	**0.55 (0.3-0.9)**	**45**
Partially vaccinated versus unvaccinated	**0.76 (0.5-1.2)**		**1.7 (0.9-3.8)**		**0.35 (0.2-0.7)**	**65**
High health care usage	**1.6 (1.1-2.1)**		**2.5 (1.4-4.2)**		**1.2 (0.8-1.8)**	
High-risk conditions	0.9 (0.7-1.3)		1.0 (0.6-1.8)		0.9 (0.6-1.3)	

Shuler et al Pediatrics 2007; 119: e587

Multi-state case-control study of the effectiveness of inactivated influenza vaccine in preventing laboratory-confirmed influenza hospitalizations among children aged 6-23 months

David Shay and the CDC Emerging Infections Program

Preliminary VE for prevention of hospitalization, by immunization status

	Fully		Partially	
	VE	95% CI	VE	95% CI
Crude VE	64%	42% – 78%	33%	- 4% – 57%
Adjusted* VE	69%	45% – 82%	32%	-11% – 58%

*** Adjusted for high-risk conditions, very low birth weight, and lack of private insurance**

Shay , D et al. Unpublished data

VACCINE EFFICACY/ EFFECTIVENESS IN OLDER ADULTS

Influenza Vaccine Evaluation Observational Studies

Population: Residents > age 64 in Southern Michigan, USA

Design: Case control

Outcome: Cases of P & I identified by regional hospitals. Controls identified from comprehensive Medicare records

Vaccination History: Obtained from cases and controls

Analysis: Logistic regression controlling for confounding factors

Time period: 1989-1991 (Type A & B). Determined by active surveillance

Analysis by Logistic Regression of Predictors of P&I Hospitalization in a Case Control Study, Michigan, U.S.A., 1989-1990

Condition	Period of Peak Influenza		Period of Diminished Transmission	
	Odds ratio	95% Confidence interval	Odds ratio	95% confidence interval
Influenza vaccination,	0.55	0.36-0.86	0.79	0.48-1.31
Pneumococcal vaccination	1.22	0.79-1.88	1.55	0.93-2.57
Heart disease	2.04	1.37-3.04	1.11	0.68-1.79
Lung disease	7.20	4.46-11.60	8.20	4.62-14.55
Diabetes	0.97	0.53-1.77	1.56	0.81-3.00
Asthma	0.84	0.35-1.99	1.67	0.76-3.66
Anemia	1.96	0.96-4.01	2.01	0.80-5.05
Renal Disease	4.81	0.94-24.57	8.08	0.42-154.9
Smoking	1.24	0.68-2.28	.97	0.47-2.00

Influenza vaccine effectiveness (1-OR): peak period=45%, diminished activity period=21%.
Sample size: peak period=856, diminished acitivity period=598.

Foster et al. *Am J Epidemiol*. 1992; 136:296-307.

Summary Effectiveness for Inactivated Vaccine in Preventing Pneumonia and Influenza Hospitalization, Southern Michigan

Year	Predominant Virus	Effectiveness in peak season (95%CI)	Effectiveness in low season
1989-90	A(H3N2) (100%)	45% (15-64%) p=0.009	21% p=0.4
1990-91	B (82%)	31% (4-51%) p=0.026	2% p=0.9
1991-92	A(H3N2) (80%)	32% (7-50%) p=0.016	-10% p=0.5

Foster DA, et al. *Am J Epidemiol*. 1992; 136:296-307.
Ohmit SE and Monto AS. *Int J Epidemiol*. 1995; 24:1240-8.

Influenza Vaccine Evaluation Controlled Trial

Population: Mainly non-high risk persons = 60 years of age

Design: Randomized, double-blind assignment. Stratified by underlying condition

Outcomes: Clinical illness, confirmed by antibody change

Analysis: Direct calculation of efficacy

Time period: 1991-92. Netherlands

Efficacy of Vaccination in Participants With Influenza or Influenza-like Illness Diagnosed According to Different Criteria

Influenza or Influenza like illness according to	Vaccine group, No. (%) (n=927)	Placebo group, No. (%) (n=911)	Relative risk (95% CI)	Efficacy (%)
Sentinel stations	62 (7)	89 (100)	0.69 (0.50-0.87)	36
Family physician	17 (2)	31 (3)	0.53 (0.39-0.73	48
Serology	41 (4)	80 (9)	0.50 (0.35-0.61)	50
Serologically confirmed influenza	16 (2)	34 (4)	0.42 (0.23-0.74)	58

Govaert TM et al. *JAMA*. 1994;272:1661-5

Pandemic vaccine effectiveness: US Flu Effectiveness Network

- Observational study to determine effectiveness of influenza vaccine on an annual basis
- Four sites: Marshfield, WI; Nashville. TN; Rochester, NY; SE Michigan
- Medically attended illnesses identified. Individuals with ILI tested for presence of influenza viruses.
- Vaccination frequency in those influenza positive (cases) compared to frequency in influenza negatives (controls), adjusted for potential confounders.
- Study of pandemic vaccine complicated by timing of vaccine arrival and 2009 fall pandemic peak.

Pandemic vaccine effectiveness in those vaccinated > 14 days before illness onset. US Flu Network

Age (years)			
	Inactivated Pandemic Vaccine		
All	1.0 (10/999)	15.0 (826/5504)	61.7 (24.9, 80.5)
0.5—9	1.3 (5/373)	22.8 (376/1647)	31.6 (-91.9, 75.6)
10 —49	0. 2 (1/528)	9.9 (208/2096)	88.6 (15.2, 98.5)
≥50	4.1 (4/98)	13.7 (242/1761)	-5.9 (-230.9, 66.1)
	Live Attenuated Pandemic Vaccine		
2—49	0.6 (5/860)	7.3 (214/2931)	39.9 (-56.4, 76.9)
2—9	0.3 (1/330)	13.3 (130/977)	54.8 (-269.5, 94.5)
10—49	0.8 (4/530)	4.3 (84/1954)	-1.0 (-196.5, 65.6)

Moving forward

- Current influenza vaccines are efficacious/effective in all population groups but higher VE is desirable.
- New generation influenza vaccines with higher VE are being developed and introduced.
- These vaccines may also be less affected by antigenic drift and may have longer duration.
- It will not be possible or perhaps ethical to do randomized trials in key target populations, particularly the elderly.
- There is a need to carry out well designed observational studies to determine VE in various population groups and conditions, especially as new vaccines are introduced.