Influenza Vaccine Efficacy and Effectiveness: A Comprehensive Review

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Influenza Vaccine Efficacy and Effectiveness: A Comprehensive Review

- An overview of the CIDRAP Comprehensive Influenza Vaccine Initiative (CCIVI)
- Background on influenza vaccine efficacy/effectiveness
- Vaccine efficacy
- Vaccine effectiveness
- Comments on the Cochrane Collaboration Reviews of influenza vaccines
- Next steps

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CIDRAP Comprehensive Influenza Vaccine Initiative (CCIVI)

- **Goal:** A rational and practical blueprint for producing and using a 21st Century Influenza Vaccine(s)
- Financial support for this effort is provided by the Alfred P. Sloan Foundation
- The final report will be available Spring 2011
- 14 member Expert Advisory Group, chaired by Alfred Sommer, MD, MHS
- Hosted two expert working group meetings over summer.
- Reviewing basic R&D, financing, manufacturing, efficacy, effectiveness, safety, regulatory issues, procurement, distribution, vaccine usage, public education, consumer acceptance, and public policy for influenza vaccines

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CCIVI Expert Working Group Meetings

- July 2010 focused on R&D, vaccine efficacy/effectiveness, manufacturing and financing
  - 37 experts in these fields including senior leadership from all five current manufactures of US licensed influenza vaccines and five companies using promising new approaches to influenza vaccine, senior academic researchers and science/policy leaders from the US Government
- September 2010 focused on vaccine safety, distribution, procurement, risk communication, and public acceptance
  - 31 experts in these fields including the chairs of all four committees that advise the US Government on the licensing and use of influenza vaccines.

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Influenza Vaccine Efficacy and Effectiveness: A Comprehensive Review

- Efficacy/effectiveness
- Availability
- Safety
- Acceptance
- If one of these is lacking, then the public health impact will be too!!

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Factors Related to the Public Health Impact of Vaccines

- Efficacy/effectiveness
- Availability
- Safety
- Acceptance
- If one of these is lacking, then the public health impact will be too!!

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Key Events in Influenza Vaccine History in the United States

Year	Event
1945	First military vaccine approved for routine use
1946	Civilian vaccine approved for use
1960	First recommendation for annual vaccination of civilians
1968	Split inactivated vaccine approved for use (akin to current inactivated vaccine)
1976	Swine flu vaccination effort
1977	Recognition of the value and role of US government in purchasing, delivering and administration of influenza vaccines
1978	Trivalent inactivated vaccine (TIV) usage became routine
1981	Antigen concentration of vaccine increased from 7 mcg to 15 mcg
2003	Live attenuated influenza vaccine (LAIV) vaccine approved for use
2009	Monovalent H1N1 pandemic vaccine approved for use
2009	Fluzone® high-dose vaccine licensed (60 mcg)

Populations Recommended to Receive an Annual Vaccination Against Seasonal Influenza in the US

Year	Additions to Recommendation
1960 (US Surgeon General)	Persons aged 65 and older Person with chronic medical conditions that make them more likely to have complication from influenza Pregnant women in 2nd or 3rd trimester
1984	Healthcare Workers "Influenza-control options should also be made available to individuals who wish to reduce their chances of acquiring influenza infection or to reduce the severity of disease"
1987	Household contacts and out of home caregivers of individuals in identified high-risk groups
2000	Adults 50 and older
2004	Children aged 6-23 months Household contacts and out of home caregivers of children aged 0-23 months Women who will be pregnant during influenza season
2006	Children aged 6-59 months Household contacts and out of home caregivers of children aged 0-59 months
2008	All children aged 6 months – 18 years, if feasible
2009	All children aged 6 months – 18 years.
2010	All healthy non-pregnant adults aged 18-49 years

Outcome Endpoints In Interpreting Influenza Vaccine Efficacy/Effectiveness

- Endpoints
  - Influenza-like illness
  - Death
  - Serologic response (HAI)
  - Virus culture
  - RT-PCR

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Understanding Influenza Vaccine Efficacy/Effectiveness and Vaccine Match

- It really is “rocket science”
- Performance and virus match:
  - Vaccine strain
  - Incidence of influenza
  - Proportion of circulating isolates antigenically similar to vaccine strain
  - Time
  - Location

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Hierarchy of Evidence

- Can it work? (Efficacy)
- Does it work? (Effectiveness)
- Is it worth it? (Cost effectiveness)

Professor Archie Cochrane
Pioneering Clinical Epidemiologist

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Influenza Vaccine Efficacy Studies

- 5,707 publications in English on influenza (human) and vaccine indexed in PubMed between January 1, 1967 and February 15, 2011
  - 992 identified as cohort studies, case-control studies, clinical trials, randomized control trials (RCTs)
  - 202 (20%) potentially eligible studies;
    - 97 were RCTs

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Inclusion Criteria for Trivalent Inactivated Vaccine (TIV) and Live Attenuated Influenza Vaccine (LAIV) Efficacy Studies, 1967- 2011

Efficacy
A published blinded randomized controlled trial indexed by Medline Reported the overall vaccine efficacy against all circulating influenza strains by season Outcome defined as viral culture and/or RT-PCR confirmation of influenza infection Comparison group received placebo or vaccine other than influenza Inactivated influenza vaccines as were licensed at the time of study or as eventually licensed in the US and antigen concentrations reported as mcg of hemagglutinin. Similarly, live attenuated influenza vaccines as were licensed at the time of study or as eventually licensed in the US and active virus reported as tissue-culture infective doses (TCID) of 10^6 and 10^8.

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Influenza Vaccine Efficacy Studies

- Based on the inclusion criteria,16 studies (3 studies evaluated both vaccines) have been identified since 1967
  - 9 using TIV
  - 10 using LAIV
  - 58,494 participants from twenty-three countries
- Represents 23 “vaccine trial seasons”
  - 11 TIV “vaccine trial seasons”
  - 12 LAIV “vaccine trial seasons”

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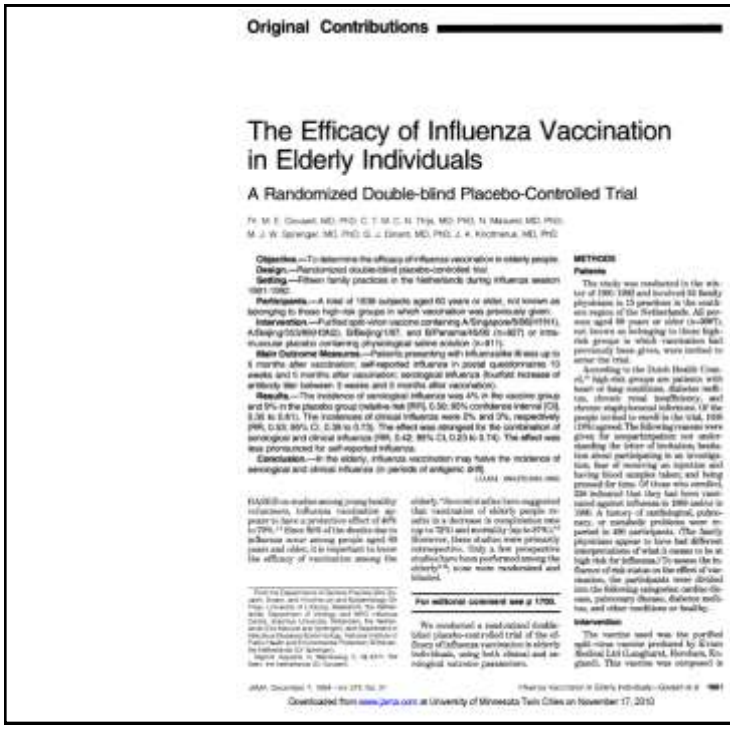
RCT of TIV in Healthy Adults (≥ 65 Years of Age)

Study	Population and Season	No. Subjects Randomized	Vaccine Efficacy (95% CI)	Vaccine Match
Adults ≥ 65 Years of Age				
None				



Original Contributions

The Efficacy of Influenza Vaccination in Elderly Individuals

A Randomized Double-blind Placebo-Controlled Trial

RCTs of TIV in Adults (18-64 Years of Age)

Study	Population and Season	No. Subjects Randomized	Vaccine Efficacy (95% CI)	Vaccine Match
		Adults 18 to 64 Years of Age		
Ohmit et al (2006)	Healthy adults 18 to 46 years old 2004-05	1,247	**75%** (42% to 90%)	H3N2 and B strains antigenically distinct
Ohmit et al (2008)	Healthy adults 18 to 48 years old 2005-06	2,058	**16%** (-171 to 70)	Isolates were antigenically distinct
Beran et al (2009a)	Healthy adults 18 to 64 years old 2005-06	6,203	**22%** (-49% to 59%)	76% of isolates were antigenically distinct
Beran et al (2009b)	Healthy adults 18 to 64 years old 2006-07	7,652 ★	**62%** (46% to 73%)	87% of isolates were antigenically similar
Monto et al (2009)	Healthy adults 18 to 49 years old 2007-08	1,952	**68%** (46% to 81%)	52% of H3N2 antigenically similar B lineage mismatch
Jackson et al (2010)	Healthy adults 18 to 49 years old 2005-06	3,428	**50%** (14% to 71%)	B lineage mismatch
Jackson et al (2010)	Healthy adults 18 to 49 years old 2006-07	4,054	**50%** (-3% to 75%)	B lineage mismatch
Frey et al (2010)	Healthy adults 18 to 49 years old 2007-08	11,404 ★	**63%** (1 sided 97.5% lower limit, 47%)	69% of isolates were antigenically distinct
Madhi et al (2011)	HIV infected adults 18 to 55 years old 2008-09	506	**76%** (9% to 96%)	Partial drift in dominate strain

RCT of TIV in Healthy Children (6 Months to 17 Years of Age)

Study	Population and Season	No. Subjects Randomized	Vaccine Efficacy (95% CI)	Vaccine Match
Children 2 to 17 Years of Age				
None				
Children 6 to 23 Months of Age				
Hoberman et al (2003)	Healthy children, 6 to 24 months 1999-2000	411	**66%** (34% to 82%)	Isolates well matched
Hoberman et al (2003)	Healthy children, 6 to 24 months 2000-2001	375	**-7%** (-247% to 67%)	Isolates well matched

RCT of LAIV in Adults ≥60 Years of Age

Study	Population and Season	No. Subjects Randomized	Vaccine Efficacy (95% CI)	Vaccine Match
Adults ≥ 60 Years of Age				
De Villiers et al (2010)	Community-dwelling ambulatory adults ≥60 2001-02	Total	**42%** (21% to 57%)	H3N2 and B strains antigenically similar
		60 to 69 yrs of age (n=1,821)	**31%** (-3% to 53%)	
		≥70 yrs of age (n=1,315)	**57%** (29% to 75%)	

RCTs of LAIV in Healthy Adult (18-55 Years of Age)

Study	Population and Season	No. Subjects Randomized	Vaccine Efficacy (95% CI)	Vaccine Match
Adults 50 to 59 Years of Age				
None				
Adults 18 to 49 Years of Age				
Ohmit et al (2006)	Healthy adults 18 to 46 years old 2004-05	1,247	**48%** (−7 to 74)	H3N2 and B strains antigenically distinct
Ohmit et al (2008)	Healthy adults 18 to 48 years old 2005-06	2,058	**8%** (-194 to 67)	Isolates were antigenically distinct
Monto et al (2009)	Healthy adults 18 to 49 years old 2007-08	1,952	**36%** (0% to 59%)	52% of H3N2 antigenically similar B lineage mismatch

RCTs of LAIV in Healthy Children (6 Months to 17 Years of Age)

Study	Population and Season	No. Subjects Randomized	Vaccine Efficacy (95% CI)	Vaccine Match
Children 8 to 17 Years of Age				
None				
Children 6 Months to 7 Years of Age				
Belshe et al (1998)	Healthy children 15 to 71 months of age 1996-97	1,602	**93%** (88% to 96%)	H3N2 and B strains antigenically similar
Belshe et al (2000)	Healthy children 26 to 85 months 1997-98	1,358	**87%** (78% to 93%)	B lineage mismatch
Vesikari et al (2006)	Healthy children 6 to <36 months of age attending day care 2000-01	1,616	**84%** (74% to 90%)	Isolates were antigenically similar
Vesikari et al (2006)	Healthy children 6 to <36 months of age attending day care 2001-02	1,090	**85%** (78% to 90%)	Partial drift in B strain
Bracco Neto et al (2009)	Healthy children 6 to <36 months of age 2000-01	2,821	**72%** (62% to 80%)	Isolates were antigenically similar
Tam et al (2007)	Healthy children 12 to <36 months of age 2000-01	3,174	**68%** (59% to 75%)	Isolates were antigenically similar
Tam et al (2007)	Healthy children 12 to <36 months of age 2001-2002	3,174	**57%** (30 to 74)	B lineage mismatch
Lum et al (2010)	Healthy children 11 to <24 months of age 2002-03	1,233	**64%** (40% to 79%)	60% of H3N2 isolates were antigenically distinct

Number of Trivalent Inactivated Vaccine (TIV) and Live Attenuated Influenza Vaccine (LAIV) Randomized Control Trials Demonstrating Significant Efficacy* by Age, 1967-2011

TIV		LAIV	
Age	**No.**	**Age**	**No.**
6 - 23 mo	1	6 mo - 7 yr	8
2 - 17 yr	0	8 -17 yr	0
18 - 64 yr	6	18 - 49 yr	0
≥ 65 yr	0	50 – 59 yr	0
Total	7	≥ 60 yr	1
		Total	9

* $p < 0.05$

Summary of Efficacy Studies

- Adults ≥ 65 years of age
  - Questionable evidence for LAIV and no evidence for TIV
- Healthy adults 18 to 64 years of age
  - Evidence does not support VE of 70-90%
  - TIV vaccine efficacy:
    - 6/9 demonstrated efficacy ($p<0.05$)
    - MH, random effect: 59% (51% to 67%)
    - Median: 62% (16% to 75%)
  - LAIV efficacy: 8%, 48% and 36%
    - 0/3 demonstrated efficacy ($p<0.05$)

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Summary of Efficacy Studies
Continued

- Healthy children 6 months to 7 years of age
  - TIV efficacy: -7% and 66%
  - LAIV vaccine efficacy:
    - MH, random effect: 83% (69% to 91%)*
    - Median: 78% (57% to 93%)

* Excluded Bracco Neto et al (2009)

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RCTs of TIV using Novel Manufacturing Platforms in Healthy Adults

Study	Population and Season	No. Subjects Randomized And Dose	Vaccine Efficacy (95% CI)	Vaccine Match
Adults 18 to 64 Years of Age				
VRBPAC (2009) Baculovirus	Healthy adults 18 to 49 years old 2007-08	4,648 45µg	**44.6%** (18.8% to 62.6%)	Significant H3 and B mismatch (>70%)
Frey et al (2010) MDCK Cell-culture	Healthy adults 18 to 49 years old 2007-08	11,404 15µg	**69.5%** (1 sided 97.5% lower limit, 55.0%)	31% of viruses isolates were matched to vaccine strains
Barrett et al (2011) Vero Cell-culture	Healthy adults 18 to 49 years old 2008-09	7,250 15µg	**71.5%** (54.7% to 82.1%)	Well match to vaccine strains

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  - 202 (20%) potentially eligible studies;
    - 105 were observational

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Inclusion Criteria for Trivalent Inactivated Vaccine (TIV) and Live Attenuated Influenza Vaccine (LAIV) Effectiveness Studies, 1967- 2011

Effectiveness
A published case vs test negative control, case cohort, or prospective cohort study design indexed by Medline Vaccine effectiveness reported for individual seasons and adjusted (as necessary based on study design) for age and calendar time (week or month of enrollment). Interim or partial season estimates were excluded. Testing of eligible patients based on systematic sampling using defined clinical criteria without regard to vaccination status. Studies allowing enrollment of patients based on clinical judgment were excluded to minimize selection bias. Vaccination status determined by self report, medical record review, or immunization registry Cases had influenza confirmed by RT-PCR and/or viral culture Controls had a negative RT-PCR and/or viral culture for influenza (test negative control design) or had no ILI (community controls or cohort design)

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Influenza Vaccine Effectiveness Studies

- Based on the inclusion criteria, 12 studies have been identified since 1967
  - 4 evaluated the effectiveness of pH1N1 vaccine
- Represents 27 “influenza seasons”
- TIV, primary vaccine assessed

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Vaccine Effectiveness (VE) of Seasonal Influenza Vaccine Meeting Inclusion Criteria

Study	Population and Season	No. Subjects	VE Against Medically Attended Influenza (95% CI)
Eisenberg et al (2008)	All patients between the ages of 6 to 59 months hospitalized, seen in ED or by primary care physician for acute respiratory illness 2003-2005	2003-04 (n=927) 2004-05 (n=1,502)	**44%** (-42% to 78%) **57%** (28% to 74%)
Szilagyi et al (2008)	All patients between the ages of 6 to 59 months hospitalized, seen in ED (inpatient/ED) or by primary care physician (outpatient) for acute respiratory illness 2003-2005	2003-04 Inpatient/ED cohort (n=4,760) Outpatient cohort (n=696) 2004-05 Inpatient/ED cohort (n=4,708) Outpatient cohort (n=742)	**12%** (-120% to 60%) **52%** (-100% to 90%) **37%** (-50% to 70%) **7%** (-80% to 50%)
Heinonen et al, (2011)	Cohort of patients enrolled in a RCT for antivirals between the ages of 6 to 35 months presenting with ILI 2007-2008	340	**72%** (35% to 88%)
Kelly et al, (2011)	All patients between the ages of 6 to 59 months presenting with ILI 2008	289	**68%** (26% to 86%)

Vaccine Effectiveness (VE) of Seasonal Influenza Vaccine Meeting Inclusion Criteria

continued

Study	Population and Season	No. Subjects	VE Against Medically Attended Influenza (95% CI)
Belongia et al (2009)	Residents recommended for vaccination by ACIP with acute respiratory illness 2004 – <24 months of age, ≥65 yrs of age, or high risk condition 2005 - <24 months of age, ≥50 yrs of age 2006 - <59 months of age, ≥50 yrs of age, or high risk condition	2004-05 (n=818) 2005-06 (n=356) 2006-07 (n=932)	**10%** (-36% to 40%) **21%** (-52% to 59%) **52%** (22% to 70%)
Savulescu et al, (2010)	All patients ≥65 yrs of age presenting with ILI 2008-2009	103	**79%** (-26% to 96%)
Kissling et al, (2009)	All patients ≥65 yrs of age presenting with ILI 2008-2009	292	**59%** (15% to 80%)
Study	**Population and Season**	**No. Subjects**	**VE Against Hospitalization (95% CI)**
Talbot et al (2011)	Adults aged > 50 yrs hospitalized with respiratory symptoms or nonlocalizing fever 2006-2009	2006-07 (n=168) 2007-08 (n=68) 2008-09 (n=181)	**57%** (-44% to 87%) **56%** (-63% to 88%) **73%** (-15% to 94%)

Vaccine Effectiveness (VE) of pH1N1 Vaccine Meeting Inclusion Criteria

Study	Population	No. Subjects	VE Against Medically Attended Influenza (95% CI)
Andrews et al (2011)	All patients hospitalized with ILI or patients presenting to GP with in the critical risk group	2,153	All **60%** (27% to 78%) 6 mo – 24 yrs **80%** (32% to 94%) 25+ yrs **1%** (-156% to 62%)
Valenciano et al (2011)	Patients presenting with to sentinel primary care practitioners.	2,902	All **66%** (24% to 84%) <15 yrs **100%** (N/A) 15-64 yrs **66%** (12% to 87%)
Hardelid et al (2011)	Patients presenting with to sentinel primary care practitioners.	5,985	All **72%** (21% to 90%)
Study	**Population**	**No. Subjects**	**VE Against Hospitalization (95% CI)**
Puig-Barberà et al (2010)	Hospitalized patients with suspected pH1N1	349	All **90%** (48% to 100%)

Summary of Effectiveness Studies

Seasonal Influenza

- Vaccine effectiveness: Medically-attended influenza
  - 2003-2008: Median 44% (7% to 72%)
- Vaccine effectiveness: Medically-attended influenza adults ≥ 65 years of age
  - 79% (-26% to 96%) and 59% (15% to 80%)
- Vaccine effectiveness: Hospitalization for adults ≥ 50 years of age
  - 1 study over 3 years without significant protection for any season

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Summary of Effectiveness Studies

- pH1N1(2009-2010)
  - Vaccine effectiveness: Medically-attended influenza 60%, 66% and 72%
  - Vaccine effectiveness: Hospitalization 90%,
  - All adjuvanted vaccines
  - No study had the ability to measure VE for adults ≥ 65 years of age
  - Monovalent pH1N1 vaccine was closely matched to the circulating pandemic strain

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CCIVI Review Compared to Cochrane Reviews

- Significant difference in review endpoints
  - CCIVI high specificity (RT-PCR or viral culture)
  - Cochrane varied:
    - Influenza diagnosis by multiple means: serology or serology and limited viral culture
    - RT-PCR confirmation only used in 4 studies in pediatric review
- CCIVI search methodology identified studies not included in Cochrane reviews

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CCIVI Identified Studies Eligible for Inclusion in Cochrane but Excluded

Vaccines for preventing influenza in healthy adults
Literature review by Cochrane current through June 2, 2010

Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. New England Journal of Medicine. 2006;355(24):2513.

Ohmit S, Victor J, Teich E, et al. Prevention of Symptomatic Seasonal Influenza in 2005–2006 by Inactivated and Live Attenuated Vaccines. J Infec Dis. 2008;198(3):312-317.

Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. New England Journal of Medicine. 2009;361(13):1260.

Belongia E, Kieke B, Donahue J, et al. Effectiveness of Inactivated Influenza Vaccines Varied Substantially with Antigenic Match from the 2004–2005 Season to the 2006–2007 Season. J Infec Dis . 2009;199(2):159-167.

Jackson LA, Gaglani MJ, Keyserling HL, et al. Safety, efficacy, and immunogenicity of an inactivated influenza vaccine in healthy adults: a randomized, placebo-controlled trial over two influenza seasons. BMC Infectious Diseases. 2010;10(1):71.

Vaccines for preventing influenza in healthy adults (Review)

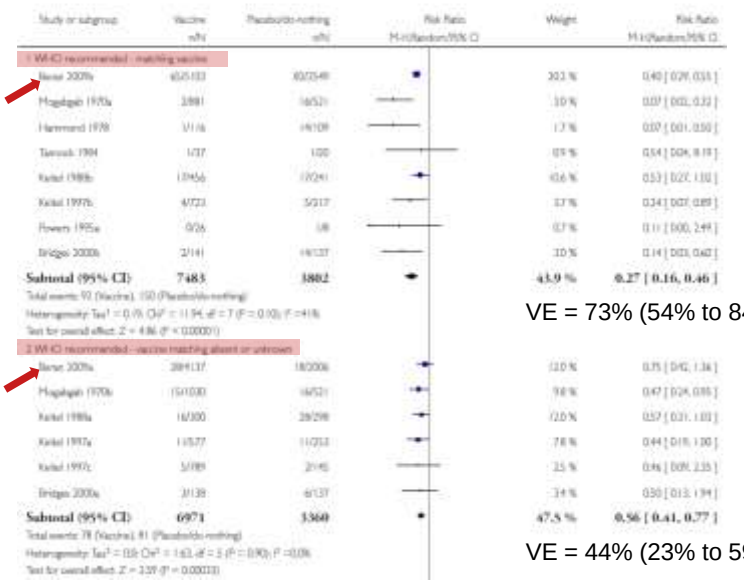
Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer GA, Al-Ansary LA, Ferroni E

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 7

http://www.thecochranelibrary.com

Analysis 1.2. Comparison 1 Inactivated parenteral vaccine versus placebo or do-nothing, Outcome 2 Influenza.



VE = 73% (54% to 84%)

VE = 44% (23% to 59%)

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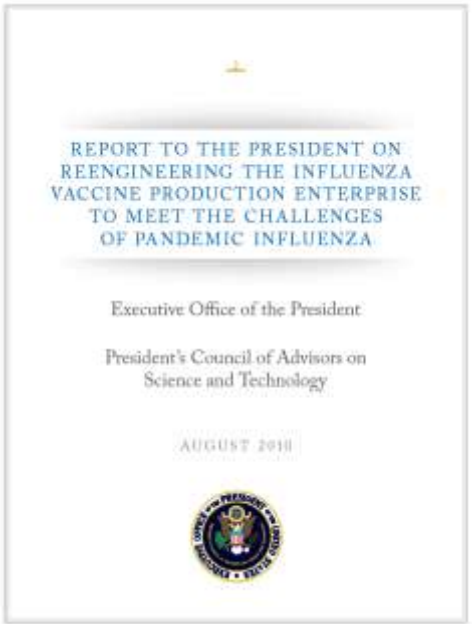

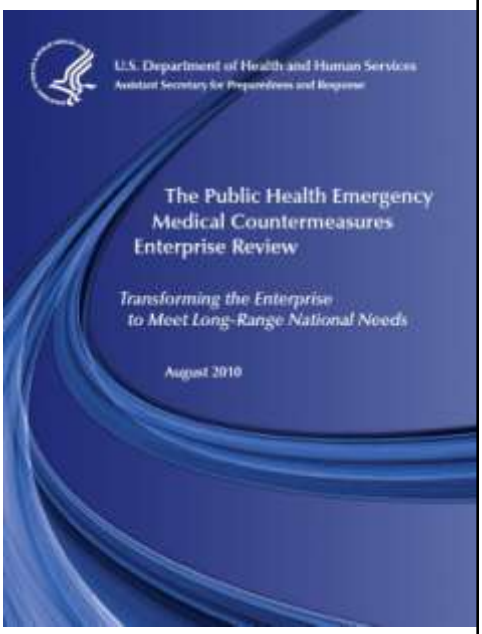

THE NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Influenza Vaccines for the Future

Linda C. Lambert, Ph.D., and Anthony S. Fauci, M.D.

From the Division of Microbiology and Infectious Diseases (L.C.L.) and the Office of the Director (A.S.F.), National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD. Address reprint requests to Dr. Lambert at the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, 6610 Rockledge Dr., Bethesda, MD 20892, or at llambert@mail.nih.gov.

N Engl J Med 2010;363:2036-44

EACH YEAR, SEASONAL EPIDEMICS OF INFLUENZA CAUSE SERIOUS ILLNESS and death throughout the world. In the United States, the annual burden of disease is estimated to be 25 million to 50 million cases of influenza, resulting in an average of 225,000 hospitalizations. Over the past three decades, the estimated number of influenza-associated deaths per year in the United States has ranged from 3349 to 48,614. The majority of deaths (>90%) occur among elderly persons, usually those with chronic underlying health conditions.[1-3] The World Health Organization uses these estimates to extrapolate a likely global disease burden from influenza of up to 1 billion infections, 3 million to 5 million cases of severe disease, and between 300,000 and 500,000 deaths annually.[4] Pandemics of influenza with varying rates of illness and death have occurred throughout history; the most notable was the 1918–1919 pandemic, which claimed an estimated 50 million to 100 million lives worldwide.[5]

First isolated from humans in 1933,[6] influenza viruses contain 8 single-stranded RNA segments encoding 11 proteins (Fig. 1). There are three types of influenza viruses: A, B, and C, with types A and B causing annual human epidemics. A key feature of the influenza virus is its error-prone polymerase, which results in an accumulation of genetic mutations that are selected for in hemagglutinin (HA) and to a lesser extent neuraminidase (NA) — the major surface glycoproteins of the virus. This antigenic drift of the HA protein renews our susceptibility to influenza viruses and is the basis for frequent updating of the composition of seasonal influenza vaccines. Protection after natural infection is primarily mediated by HA-specific antibodies in serum and mucosa, with the presence of antibodies against NA, conserved influenza proteins, and T-cell responses correlating with reduced disease severity.

A novel virus can emerge in humans either through direct interspecies transmission or as a result of molecular exchanges between influenza viruses that already infect humans. Because the influenza virus genome is segmented, coinfection of a single host cell with two or more different influenza viruses can result in a reassortment or shuffling of their genetic material. The antigenic shift can lead to a pandemic if the resulting progeny virus contains an HA protein to which humans have no preexisting immunity, if it has an efficient replication-competent set of internal genes, and if it can readily spread from human to human — as was the case with the 2009 H1N1 virus.

Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine

Gary J Nabel & Anthony S Fauci

The immune system normally responds to influenza virus by making neutralizing antibodies to regions of the viral spike, the hemagglutinin, that vary year to year. This natural response protects against circulating subtypes but necessitates production of new vaccines annually. Newer vaccine approaches have succeeded in eliciting broadly neutralizing antibodies to highly conserved yet vulnerable regions of the hemagglutinin and suggest potential pathways for the development of universal influenza vaccines.

In the struggle between viral infection and immune protection, influenza viruses have perfected the art of evasion. As humans develop immunity to the current circulating viruses, the virus evolves variants through genetic mutation, leading to antigenic drift in humans or other influenza-susceptible species. These new strains evade neutralization and give rise to new seasonal influenza viruses that claim the lives of more than 250,000 people worldwide each year. Current influenza vaccination campaigns rely on a well-honed process every year, a new vaccine is prepared that aims to match the strains predicted to circulate in the coming flu season. For more than 65 years, this pragmatic approach has saved lives and benefited public health. Yet the preparation of new influenza vaccines costs $2–4 billion yearly. In addition, a vaccine prepared for an upcoming influenza season does not always completely match the actual strains that circulate in that season. More importantly, as witnessed in the 2009 H1N1 outbreak, completely new strains can unexpectedly emerge against which contemporary vaccines provide little or no protection. The emergence of completely new strains is potentially devastating, because most of the world's population lacks adequate background immunity that might have come from other natural exposure or vaccination. This potential vulnerability underscores the need to advance a universal influenza vaccine as a means to address a serious public health concern.

The strategic approach to influenza vaccine development is typical of all licensed vaccines: the aim is to mimic natural exposure to the virus using inactivated or attenuated viruses that provoke immune recognition without causing disease. Protection is conferred by the antibody response that neutralizes the influenza virus, measured by the hemagglutination inhibition assay. This laboratory test serves as the baseline predicting the efficacy of new vaccines and for licensing them. However, with influenza, the process of vaccine development needs to be repeated annually, as influenza outbreaks predictably occur each year and viruses usually drift or change their hemagglutinin (HA) enough from year to year that infection or vaccination with strains from a particular year often does not provide adequate protection against those circulating in the subsequent year. An enigma for the field of influenza vaccinology is the fact that despite repeated exposures to influenza, most humans do not ultimately develop universal protection against any emerging influenza strain. One potential explanation for this is that in natural infection, the virus does not readily expose to the host immune system those components of its structure that do not vary from strain to strain, because immune responses to such components would probably protect against drifting strains. Hence, the predominant components of the virus that the immune system adequately sees upon infection are those that change with each emerging strain, reducing the likelihood of universal protection induced by prior infection. Because currently employed vaccination strategies use killed or attenuated influenza viruses that mimic these causing natural infection, the same constraints hold true for influenza vaccination.

Two areas of investigation have emerged that provide opportunities to improve upon the traditional approach to influenza vaccination. They are based on understanding natural immunity to influenza and the structure of the virus. Some individuals are immune to subtypes of influenza virus to which they have not previously been exposed through natural infection or immunization. This protection, termed heterosubtypic immunity, suggests that regions of the virus shared by different strains can be recognized by the immune system[7–9]. These common regions of vulnerability that serve as the basis for natural cross-protective immunity have not been well defined. It has been proposed that certain components of either HA, the nucleoprotein (NP) or M2 protein of the virus may be the targets for heterosubtypic immunity (reviewed in ref. 4). Indeed, some vaccine efforts have aimed to elicit antiviral CD8+ T cell responses by gene-based immunization with the highly conserved NP and M2 proteins.

A possible explanation for cross-protective immunity has arisen from an understanding of the molecular targets of broadly neutralizing monoclonal antibodies directed to the viral

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Conclusions

- The CCIVI review found that the currently available influenza vaccine can provide moderate protection against infection and illness.
- Based on a track record of substantial safety and moderate efficacy in some seasons, the influenza vaccine can play a role in reducing influenza morbidity.
- However, during some influenza seasons, and especially among some age groups, it is questionable if our current influenza vaccines provide even moderate protection.

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Conclusions
continued

- Future influenza vaccines that use the same or similar hemagglutinin antigen regardless of production methods may not provide any more protection than current vaccines.
- We can no longer rely on current influenza vaccines to mitigate the threats of either seasonal or pandemic influenza, even if such vaccines can be produced quicker or in far greater quantity.

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Influenza Vaccine Availability

- Global availability of seasonal and pandemic vaccines is severely limited
  - Majority of the world does not have routine access to an influenza vaccine
- Manufacturing process is based on 50 year old technology
  - Numerous problems with seasonal vaccine availability in the past 10 years
- 2009 pandemic vaccine availability was “déjà-vu all over again”

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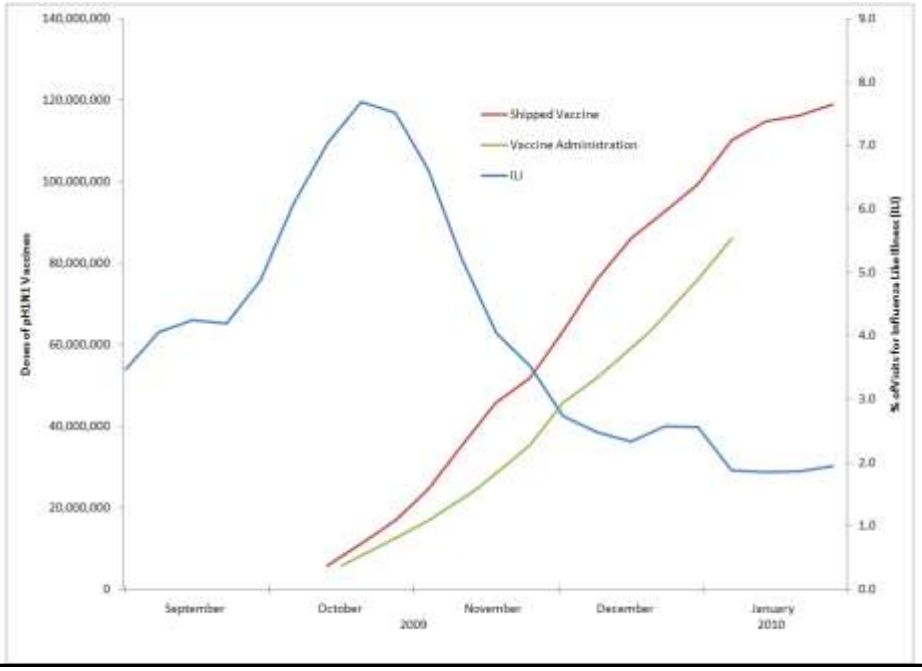
Seasonal Influenza Vaccine Production and Issues, US, 1999-2009

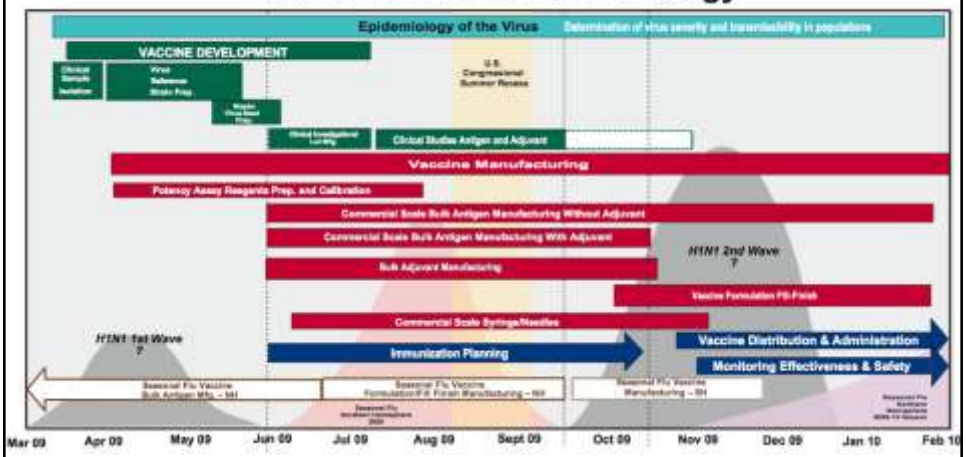
	99-00	00-01	01-02	02-03	03-04	04-05	05-06	06-07	07-08	08-09
Doses Produced (million)	77.2	77.9	87.7	95	86.9	61	88.5	120.9	140.6	135.9
Doses Distributed (% produced)	76.7 (99)	70.4 (90)	77.7 (89)	83.5 (88)	83.1 (96)	57 (93)	81.5 (92)	102.5 (85)	112.8 (80)	113 (83)
Production Issues^^	No	**Yes**	**Yes**	No	No	**Yes**	**Yes**	**Yes**	No	No
Shortages Reported	No	**Yes***	**Yes***	No	**Yes**	**Yes**	**Yes**	**Yes***	No	No
Rationing of Vaccine	No	No	No	No	No	**Yes**	**Yes**	No	No	No

^^issues manufacturing the vaccine (i.e. slow viral growth, low potency, Good Manufacturing Practice (GMP) violations)
*Vaccine became readily available later than anticipated, resulting in supply not meeting demand, which were reported as shortages.

2009 Pandemic Vaccine Response



U.S. 2009-H1N1 Vaccine Strategy



Influenza Vaccine and the Past Three Pandemic Responses

Year	Identification of new strain	Strain released to manufactures	Vaccine orders placed	First lot released	Amount of vaccine release by pandemic wave peak
1957-58	4/57	5/12/57	7/2/57	8/12/57	48.8 million doses* – 11/9/57
1968-69	8/68	9/9/68	9/24/69	11/15/68	15.3 million doses – 1/3/69
2009-10	4/21/09	5/27/09	5/22/09	10/14/09	11.2 million doses – 10/22/09

*these vaccines were approximately half the dose of the 1968-69 vaccine.