Influenza Vaccination: Successes and Failures

Walter A. Orenstein, MD
Professor of Medicine, Epidemiology, Global Health, and Pediatrics
Emory Department of Medicine
Associate Director, Emory Vaccine Center, Atlanta, GA

I, the undersigned, declare that neither I, nor any immediate member of my family, have a financial arrangement or affiliation with any corporate organization offering financial support or grant monies for this continuing medical education activity. In addition, I do not intend to include information or discuss investigational or off-label use of pharmaceutical products or medical devices.

Emerging Infections Program (EIP)
Atlanta, GA
March 27, 2015

EMORY UNIVERSITY SCHOOL OF MEDICINE

EMORY VACCINE CENTER | EMORY UNIVERSITY
Where Science Meets Hope

Influenza hospital, Philadelphia, 1918

Purpose of presentation and topic to be covered:

- Clinical aspects of influenza
- Assessing the burden of influenza
- Current vaccine recommendations and coverage including herd immunity and new vaccines
- Scientific challenges to prevention
- Evolving strategies for influenza prevention
- Health benefits of vaccinating pregnant women
- Prospects for a universal influenza vaccine

Classic Clinical Illness

- Abrupt onset fever, chills, muscle aches, fatigue
- Cough, sore throat, runny nose
- Gastrointestinal symptoms in about 10% of children
- Incubation period 1-4 days
- Infectious period
  - 24 hours prior to onset
  - Potentially up to 7 days after onset
  - Maximum contagiousness in first 1-3 days of illness

Major Causes of Death from the Influenza Virus

- Primary viral pneumonia
- Secondary bacterial pneumonia
- Exacerbation of underlying illness
- Encephalitis
- Myocarditis
- Acute respiratory distress syndrome from "Cytokine Storm"

Comparison of Symptoms and Signs of Influenza Positive and Negative Patients, Paris, 1995-1996[+]

Symptom or Sign	Influenza A+ (%) n=158	Influenza – (%) n=442	P value
Chills	82.9	74.9	0.04
Moderate or severe fatigue	74.7	61.8	0.003
Headache	84.2	73.8	0.008
Sneezing	50.0	41.0	0.05
Cough	83.5	71.5	0.003
Pain on deep breath	34.8	23.3	0.005
Rhinorrhea	78.5	67.7	0.01
Expectoration of sputum	29.8	21.3	0.03
Lacrimation or conjunctival infection	39.2	29.2	0.02

[+]Carrat F et al. Clin Infect Dis 1999; 28:283-290.

Table 1: Influenza Virus Testing Methods

Method[1]	Types Detected	Acceptable Specimens[2]	Test Time	CLIA Waived[3]
Viral cell culture (conventional)	A and B	NP[4] swab, throat swab, NP[2] or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days	No
Rapid cell culture (shell vials; cell mixtures)	A and B	As above	1-3 days	No
Immunofluorescence, Direct (DFA) or Indirect (IFA) Antibody Staining	A and B	NP[4] swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	No
RT-PCR[5] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays	A and B	NP[4] swab, throat swab, NP[2] or bronchial wash, nasal or endotracheal aspirate, sputum	Varied (Generally 1-6 hours)	No
Rapid Influenza Diagnostic Tests[6] (antigen)	A and B	NP[4] swab, (throat swab), nasal wash, nasal aspirate	<30 min.	Yes/No

1. Serologic (antibody detection) testing is not recommended for routine patient diagnosis.
2. Ref: Leland, et al. 2007, *Clin Micro Rev* 20: 49-78. Approved respiratory specimens vary among FDA cleared influenza assays.
3. Ref: http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html
4. NP = nasopharyngeal
5. Reverse transcriptase polymerase chain reaction, including FDA-approved test systems, reference laboratory testing using ASR or lab-developed reagents
6. Chromatographic- and/or fluorescence-based lateral flow and membrane-based immunoassays

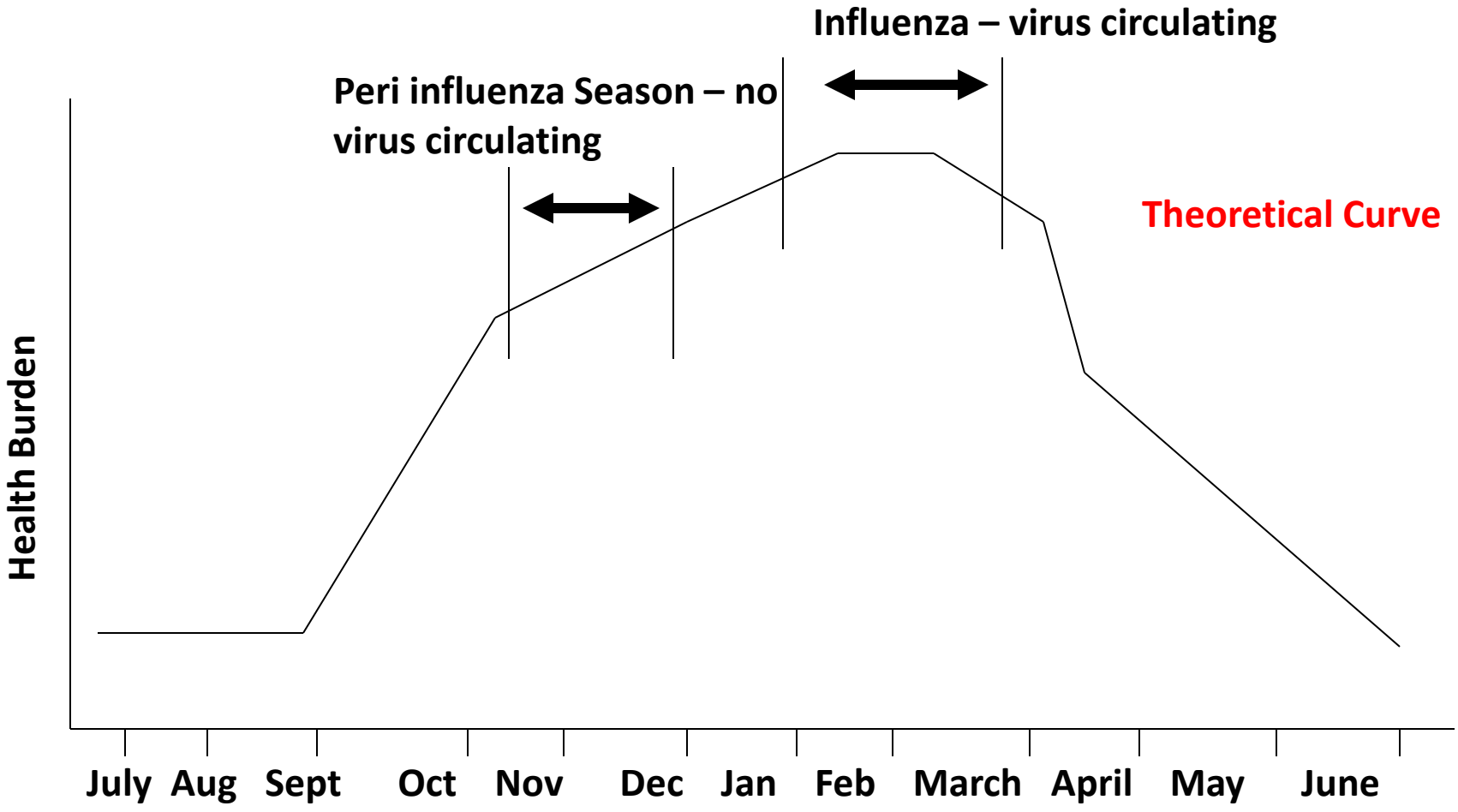
http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table

Rapid Diagnostic Tests *

- Sensitivity
  - 50-70% with culture or RT-PCR as gold standard
- Specificity 90-95%
- Sensitivity best when specimens collected within 4-5 days of symptom onset
- CDC lists 15 rapid tests on its website
  - Some detect A only, some B only
  - Most A and B but some cannot distinguish among the viruses

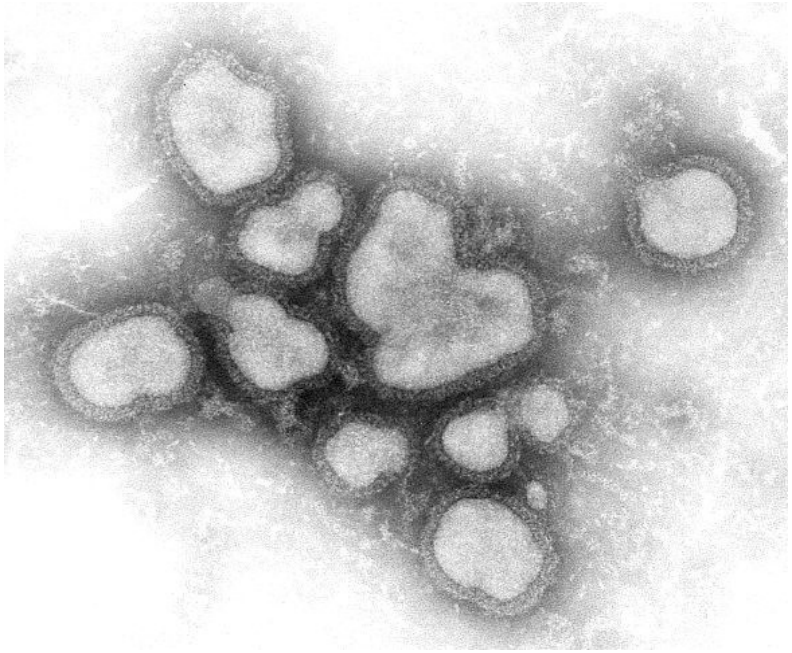
http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table

Assessing the Health Burden of Influenza



Influenza is a Serious Disease

From 1976-2007, influenza caused an average of 23,000 deaths, annually. 90% of the deaths occurred in adults > 64 years of age



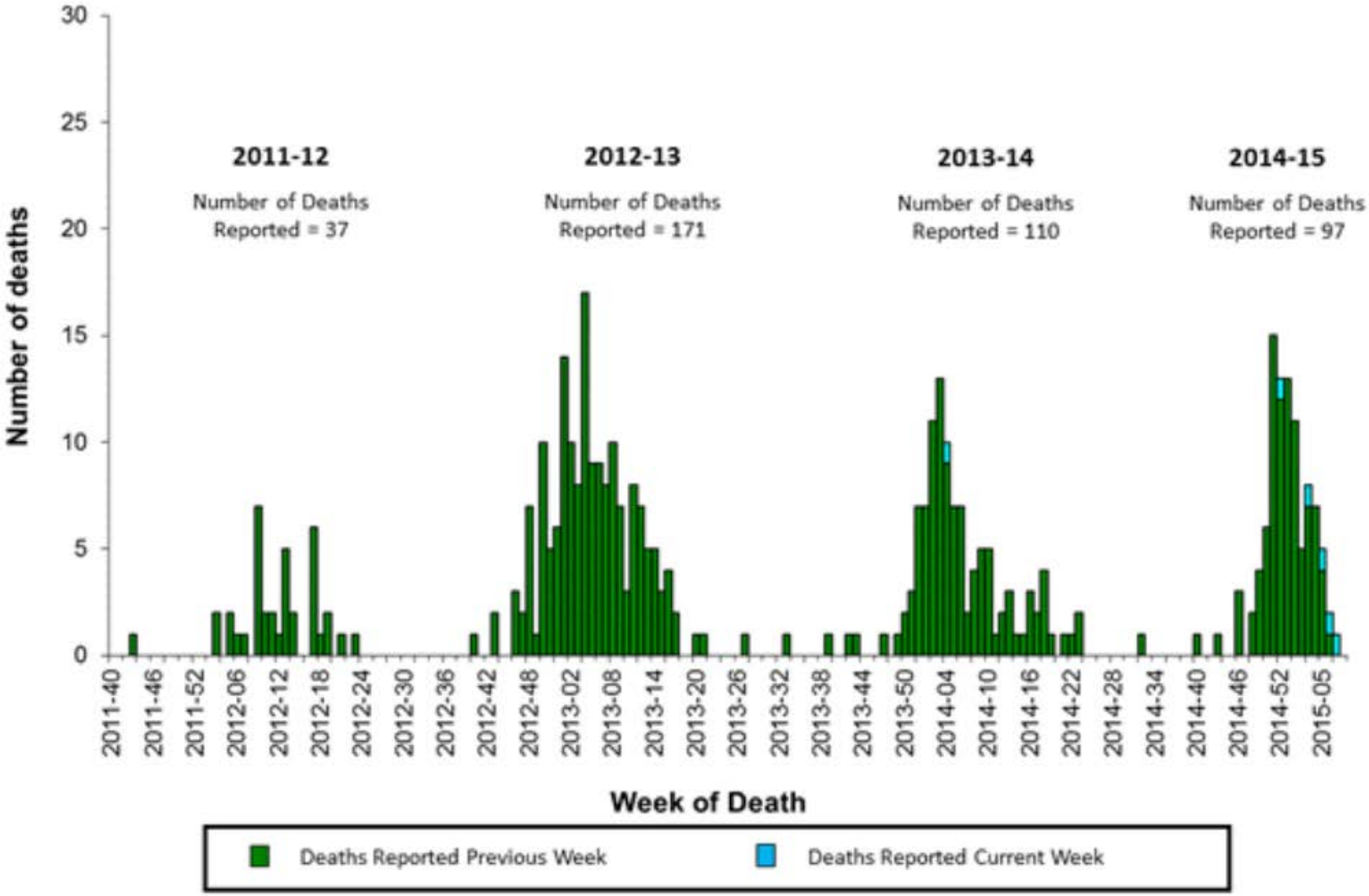
From CDC. MMWR 2010;59:1057-1062

Estimated Influenza Hospitalizations by Age Group (United States †)

Age group (yrs)	Hospitalizations †	Hospital Rate/100,000
<5	20,031	107.9
5 – 49	34,867	20.8
50 – 64	29,447	83.8
≥ 65	141,709	189.7-1194.9

From: Thompson WW et al, JAMA 2004; 292:1333-1340

Number of Influenza-Associated Pediatric Deaths by Week of Death: 2011-12 season to present



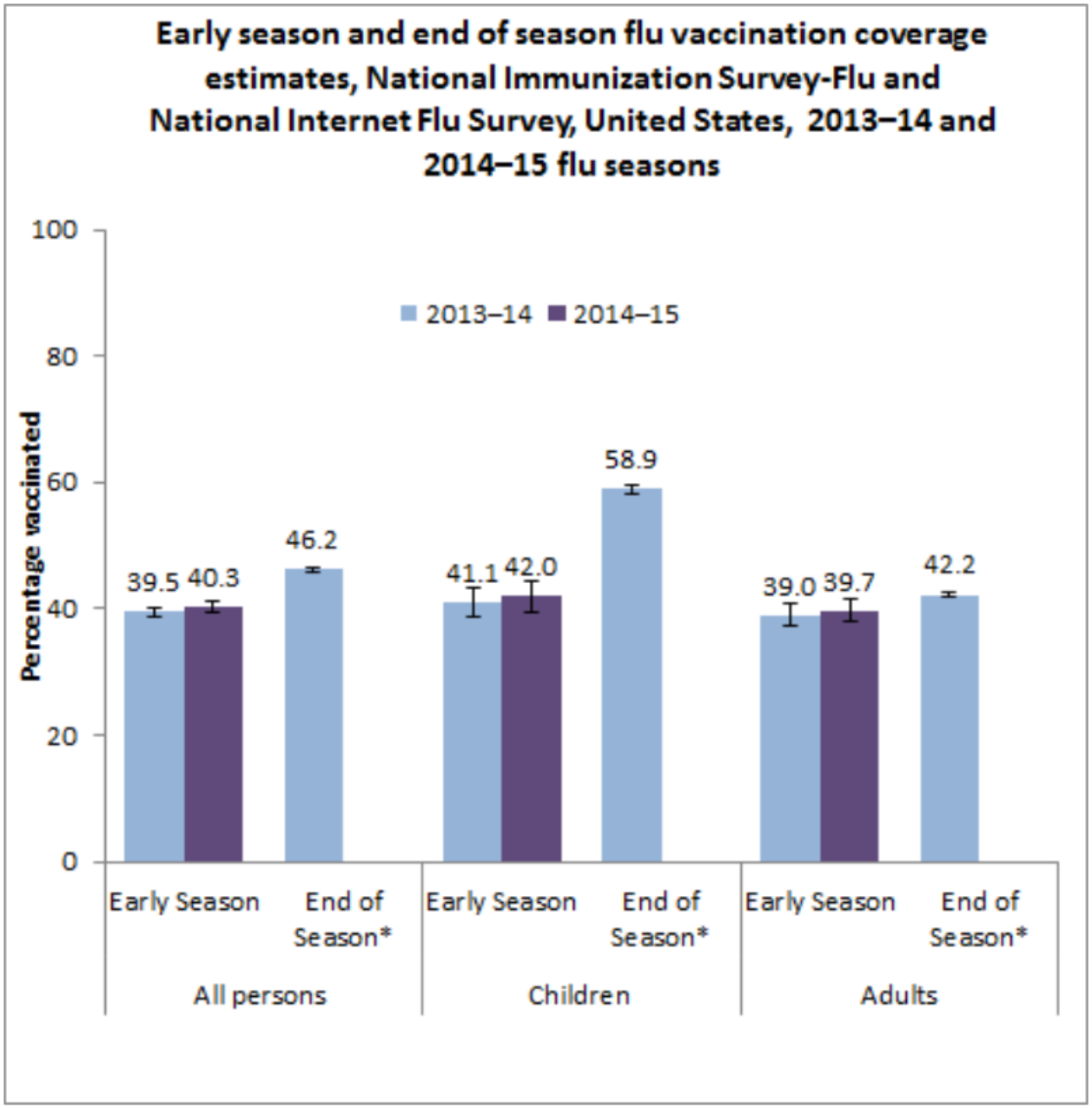
http://www.cdc.gov/flu/weekly/index.htm, accessed 3-9-15

Groups Recommended for Vaccination

- Annual influenza vaccination is recommended for all persons aged 6 months and older

- Groups considered at higher risk for severe illness:
  - Children 6 mos through 4 yrs, (particularly those <2); adults 50 years and older
  - Adults and children who have:
    - chronic lung disease, including asthma
    - heart disease
    - blood, endocrine, liver, kidney, and metabolic disorders
    - neurological and neurodevelopmental conditions
    - weakened immune systems due to disease or medication including diabetes
    - people younger than 19 years old who are receiving long-term aspirin therapy
    - pregnant women
    - severely obese patients
    - Alaska Natives / American Indians

Adapted from http://www.cdc.gov/flu/protect/whoshouldvax.htm#annual-vaccination accessed 3-9-15

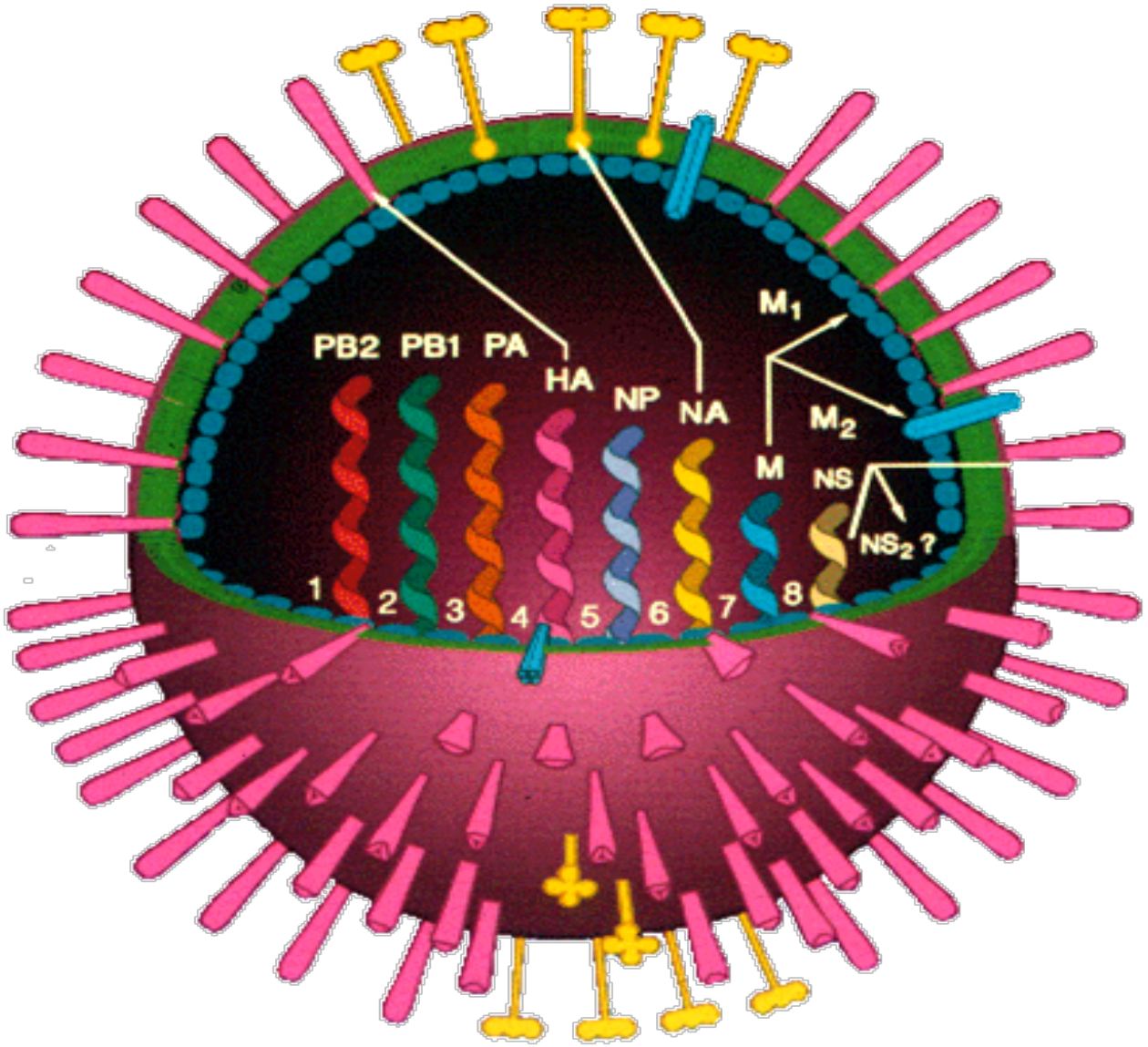


From: http://www.cdc.gov/flu/fluvaxview/nifs-estimates-nov2014.htm, accessed 3-9-15

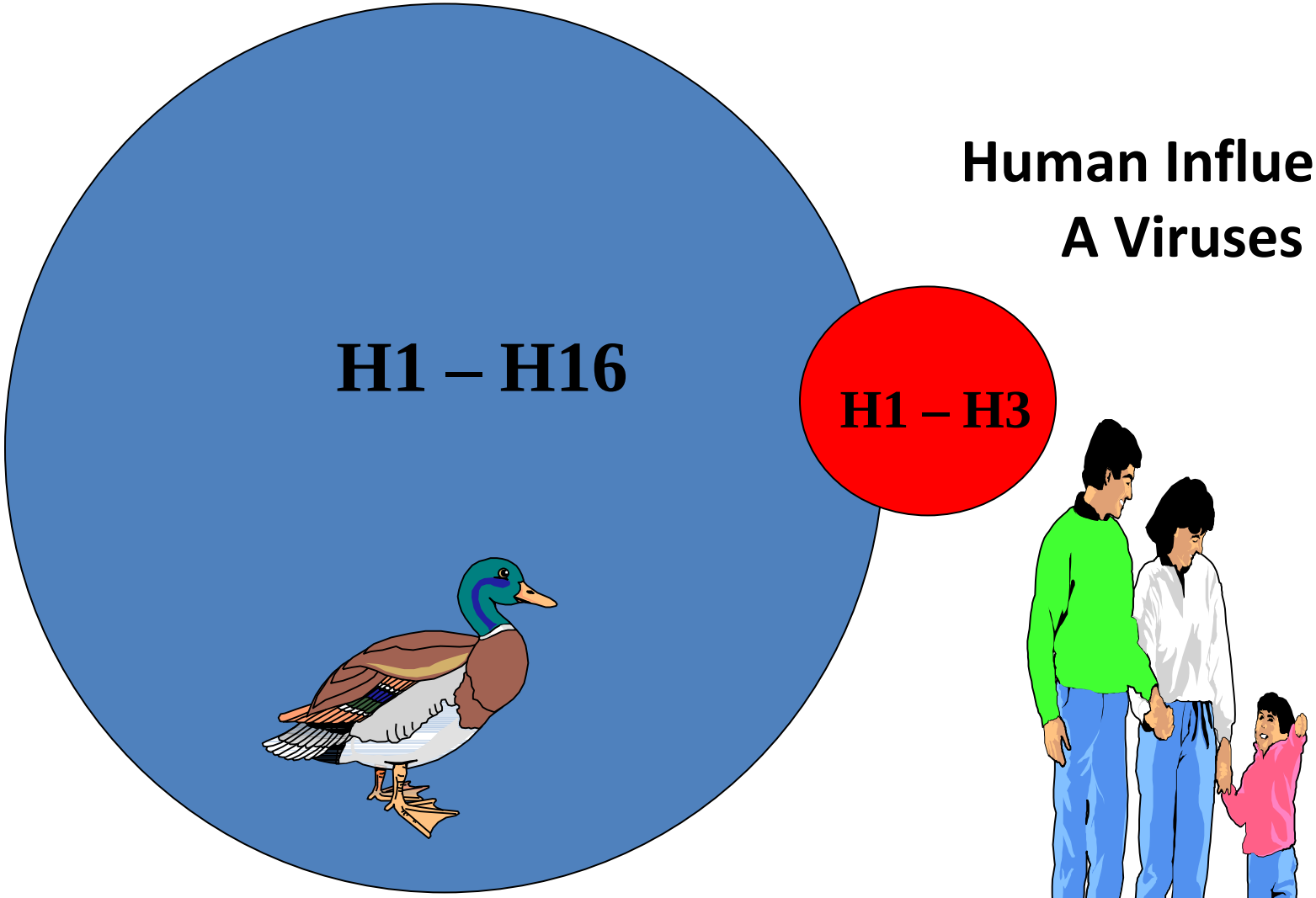
Scientific Challenges to Influenza Prevention

- Changing viruses
- Changing vaccines
- Complexity of vaccine production

Influenza Virus



Avian Influenza A Viruses



Footnote: H17 & H18 isolated from bats

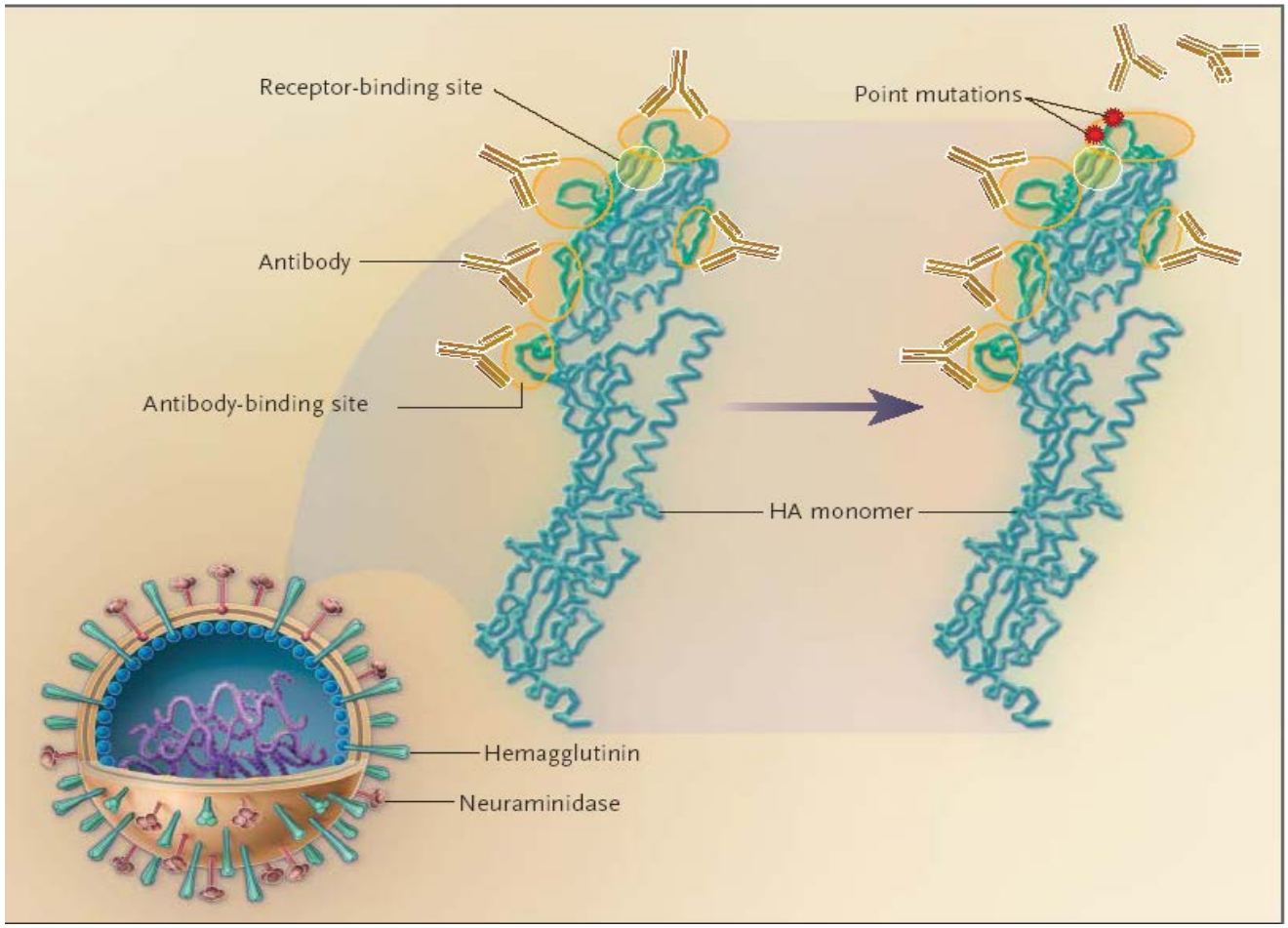
Molecular Determinants of Human Infection

- Host cell receptor for hemagglutinin
  - Avian N-acetyl sialic acid linked to galactose with α 2, 3, linkage
  - Human linkage with α 2, 6
  - Epithelial cells in human trachea primary α 2, 6
  - Duck trachea and intestines α 2, 3
  - Pigs both

Antigenic Change

- Antigenic ‘drift” occurs in HA and NA
  - Continual development of new strains secondary to genetic mutations/seasonal epidemics
  - A viruses >> B viruses
- Antigenic “shift” occurs in HA and NA
  - Associated with pandemics
  - Appearance of novel influenza A viruses bearing new HA or HA & NA

Structure of a Hemagglutinin Monomer and Location of the Five Known Antibody-Binding Sites in the HA1 Subunit



J Treanor, N Engl J Med 2004; 350: 218-220

	Population (dates)	Patients randomly allocated to receive TIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Adults (18–64 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	728	75% (42 to 90)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1205	16% (–171 to 70)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Beran et al (2009)[26]	Healthy adults aged 18–64 years (2005–06)	6203	22% (–49 to 59)	Type A: similar H3N2 and H1N1; type B: lineage mismatch
Beran et al (2009)[27]	Healthy adults aged 18–64 years (2006–07)	7652	62% (46 to 73)	Type A: similar H3N2; type B: lineage mismatch
Monto et al (2009)[28]	Healthy adults aged 18–49 years (2007–08)	1139	68% (46 to 81)	Type A: drifted H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2005–06)	3514	50%† (14 to 71)	Type A: similar H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2006–07)	4144	50%† (–3 to 75)	Type A: similar H3N2; type B: mixed lineage
Frey et al (2010)[29]	Healthy adults aged 18–49 years (2007–08)	7576	63% (one-sided 97·5% lower limit of 47%)	Type A: mixed strains; type B: lineage mismatch
Madhi et al (2011)[30]	Adults aged 18–55 years with HIV infection (2008–09)	506	76% (9 to 96)	Type A: drifted H1N1; type B: not reported
Children (6–24 months)				
Hoberman et al (2003)[31]	Healthy children aged 6–24 months (1999–2000)	411	66% (34 to 82)	Type A: similar H3N2 and H1N1; type B: not reported
Hoberman et al (2003)[31]	Healthy children aged 6–24 months (2000–01)	375	–7% (–247 to 67)	Type A: similar H3N2 and H1N1; type B: lineage match

No studies were available for adults aged 65 years or older or children aged 2–17 years. *One other study by Loeb and colleagues[23] met inclusion criteria and contained data for all age groups. †Our calculation.

Table 2: Randomised controlled trials of trivalent inactivated vaccine (TIV) meeting inclusion criteria*

* Pooled estimate 18-65 years – 59% (95% CI 57 to 61)

From: Osterholm MT, et al. Lancet Infect Dis 2012; 12:36-44

Types of Influenza Vaccines Available 2014-2015 Season

- Trivalent vs Quadravalent
- Inactivated
  - Subvirion or split virus
    - Standard dose (15mcg): ≥ 6 months
    - Intrademal (9mcg): 18-64 years
    - High dose (60mcg): ≥ 65 years
  - Cell based – Flucelvax: ≥18 years
  - Recombinant influenza vaccine: 18-49 years
- Live attenuated influenza vaccines: 2-49 years

Adapted from Grohskopf LA et al. ACIP Recommendation for Influenza Vaccine – 2014-15 Season. MMWR 2014; 63:691-697

Characteristics of Specific Influenza Vaccines

- Trivalent – A/H1N1, A/H3N2, and one influenza B strain (Victoria or Yamagata)
- Quadrivalent – A representative of both influenza B lineages
  - No ACIP preference
- Severe egg allergies such as anaphylaxis
  - Recombinant influenza vaccine (RIV3) for 18-49 year olds
  - Flucelvax (ccIIV3) has <50 femtograms of total egg protein

Efficacy of High Dose Influenza Vaccine versus Standard Dose Influenza

Vaccine in persons ≥ 65 years of age [++]

Protocol Defined Influenza-like Illness [+]	TIV – HD N=15, 990	IIV – SD N=15, 993	Relative Efficacy (%)
Influenza A	228 (1.4)	301 (1.9)	24.2 (9.7 – 36.5)
A/H1N1	8 (<1)	9 (0.1)	11.1 (-159.6 – 70.2)
A/H3N2	171 (1.1)	223 (1.4)	23.3 (6.0 – 37.5)
B	38 (0.2)	51 (0.3)	25.5 (-15.7 to 52.4)

[+] Respiratory illness with sore throat, cough, sputum production, wheezing, or difficulty breathing with one or more of: temperature >37.2C, chills, tiredness, headaches or myalgia

[++] Assuming 50% VE for SD, VE for HD would be 62%

[+++] Diaz Granada CA, et al. N Engl J Med 2014; 37(1):635-45

Measurement of Influenza Vaccine Effectiveness (VE)

VE (%) = (1 – RR) x 100

where RR = (ARV/ARU)

Traditionally measured in cohort studies of vaccinees and non-vaccinees

VE (%) = (1 – OR) x 100

where Odds Ratio is the ratio of odds a case is vaccinated divided by the odds a control is vaccinated

Controls – Community

– Test-negative

Vaccine Effectiveness

	Cases	Controls
Vaccinated	a	c
Unvaccinated	b	d

$$Odds\ Ratio = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{ad}{bc}$$

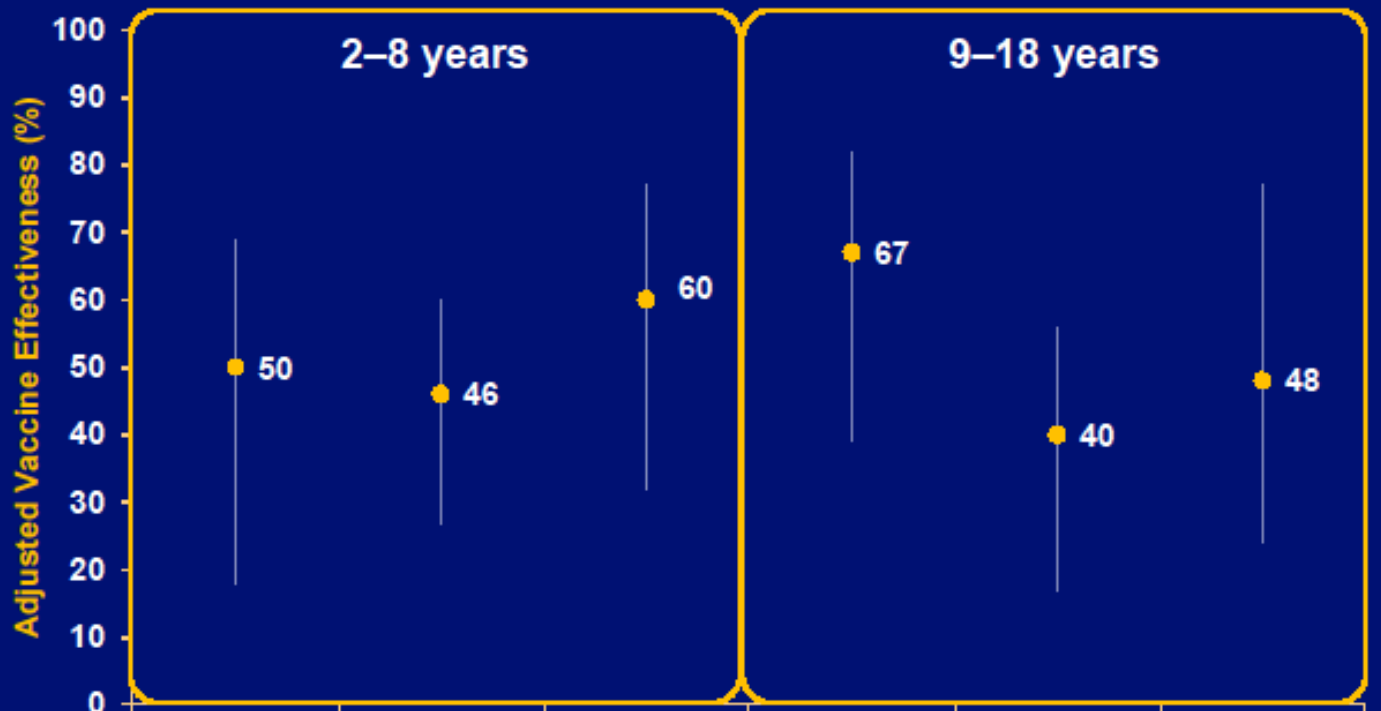
Table 1 Differences between true vaccine effectiveness and calculated vaccine effectiveness by using three observational study methods as true vaccine effectiveness varies

True vaccine effectiveness (%)	Calculated vaccine effectiveness		
	Cohort (%)	Case-control (%)	Test negative (%)
90	71.6	74.7	72.6
70[a]	55.7	59.5	57.0
50	39.8	43.6	41.1
30	23.9	26.8	24.8
10	8.0	9.2	8.4
5	4.0	4.6	4.2

[a]Base-case assumptions: $VE_{true} = 70\%$, $AR_{flu} = 15\%$, $AR_{nonflu} = 30\%$, sensitivity = 80%, specificity = 90%.

From: Orenstein EW, et al. Int J. Epidemiol. 2007; 36(3):623-31.

IIV effectiveness against medically-attended influenza, by season and age category



	2011-12	2012-13	2013-14	2011-12	2012-13	2013-14
Total, Flu +	155	466	124	112	412	103
IIV, Flu +	29	110	21	18	91	16

From Flannery B. Slide 14 from ACIP presentation 10/14/14

Interim adjusted VE against vaccine-like vs drifted A(H3N2) among patients aged ≥6 months, for ≥1 dose of 2014-15 seasonal influenza vaccine

	Influenza cases	% vaccinated	Influenza-negative	% vaccinated	Adjusted VE*	(95% CI)
Any influenza A (H3N2)	1415	53%	3281	57%	18%	(6 to 29)
A(H3N2), vaccine-like (group 3C.3/3C.3b)	115	39%	3281	57%	49%	(18 to 69)
A(H3N2), low-reactor (group 3C.2a)	624	55%	3281	57%	15%	(-5, 30)
A(H3N2), low-reactor (group 3C.3a)	25	60%	3281	57%	-14%	(-177, 53)

* Vaccine effectiveness was estimated as 100% X (1 – odds ratio [ratio of odds of vaccination among flu-positive cases to odds of vaccination among flu-negative controls]) using logistic regression. Multivariate models adjusted for study site, age category, sex, race/Hispanic ethnicity, self-rated health status, days from illness onset to enrollment, and calendar time (biweekly intervals).

From Flannery S, ACIP Presentation February 24, 2015

Table 71–2 Approximate Basic Reproduction Numbers (in Developed Countries) and Implied Crude Herd Immunity Thresholds (*H*, Calculated as $(1 - 1/R_0)$) for Common Vaccine-Preventable Diseases[1,12]*

Infection	Basic Reproduction Number (R_0)	Crude Herd Immunity Threshold, *H* (%)
Diphtheria	6–7	85
Influenza†	1.4–4	30–75
Measles‡	12–18	92–94
Mumps	4–7	75–86
Pertussis	12–17	92–94
Polio§	2–15	50–93
Rubella	6–7	83–85
Smallpox	5–7	80–85
Tetanus	Not applicable	Not applicable
Tuberculosis¡	?	?
Varicella¶	8–10?	?

*It should be emphasized that the values given in this table are approximate, and that they do not properly reflect the tremendous range and diversity among populations. Nor do they reflect the full immunologic complexity underlying the epidemiology and persistence of these infections. See text for further discussion.
†R_0 of influenza viruses probably varies greatly between subtypes.
‡Herd immunity thresholds as low as 55% have been published.
§Complicated by uncertainties over immunity to infection and variation related to hygiene standards.
¡Protective immunity not defined.
¶Immunity not sterile, herd immunity threshold not defined.

Source: Fine PEM, et al. Community Immunity in Plotkin SA, Orenstein WA, Offit PA, Vaccines 5th edition, Elsevier, 2008, pp 1573-1592

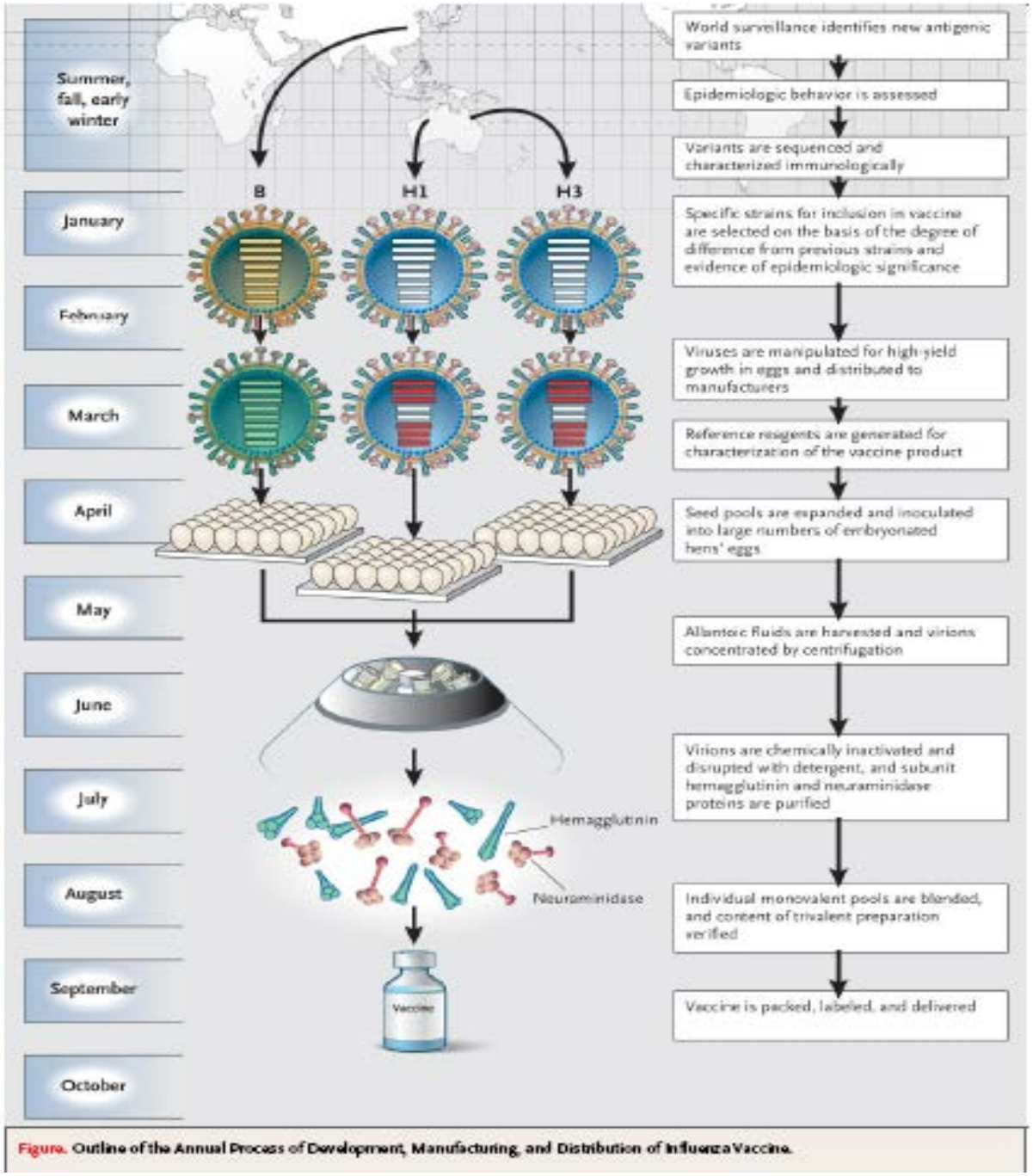


Figure. Outline of the Annual Process of Development, Manufacturing, and Distribution of Influenza Vaccine.

From: Treanor J. New Eng J Med Volume 351 (20), 11 November 2004, pp 2037-2040

Clinical Effectiveness of maternal vaccination on laboratory: confirmed Influenza in infants through 6 months of age †, † †, † † †

	Effectiveness (%)	Risk Difference
Respiratory illness with fever	28.9 (6.9-45.7)	-28.1 (-48.2 to -8.0)
Clinical visits for respiratory illness with fever	42.0 (15.2-58.8)	-24.5 (-39.5 to -9.5)

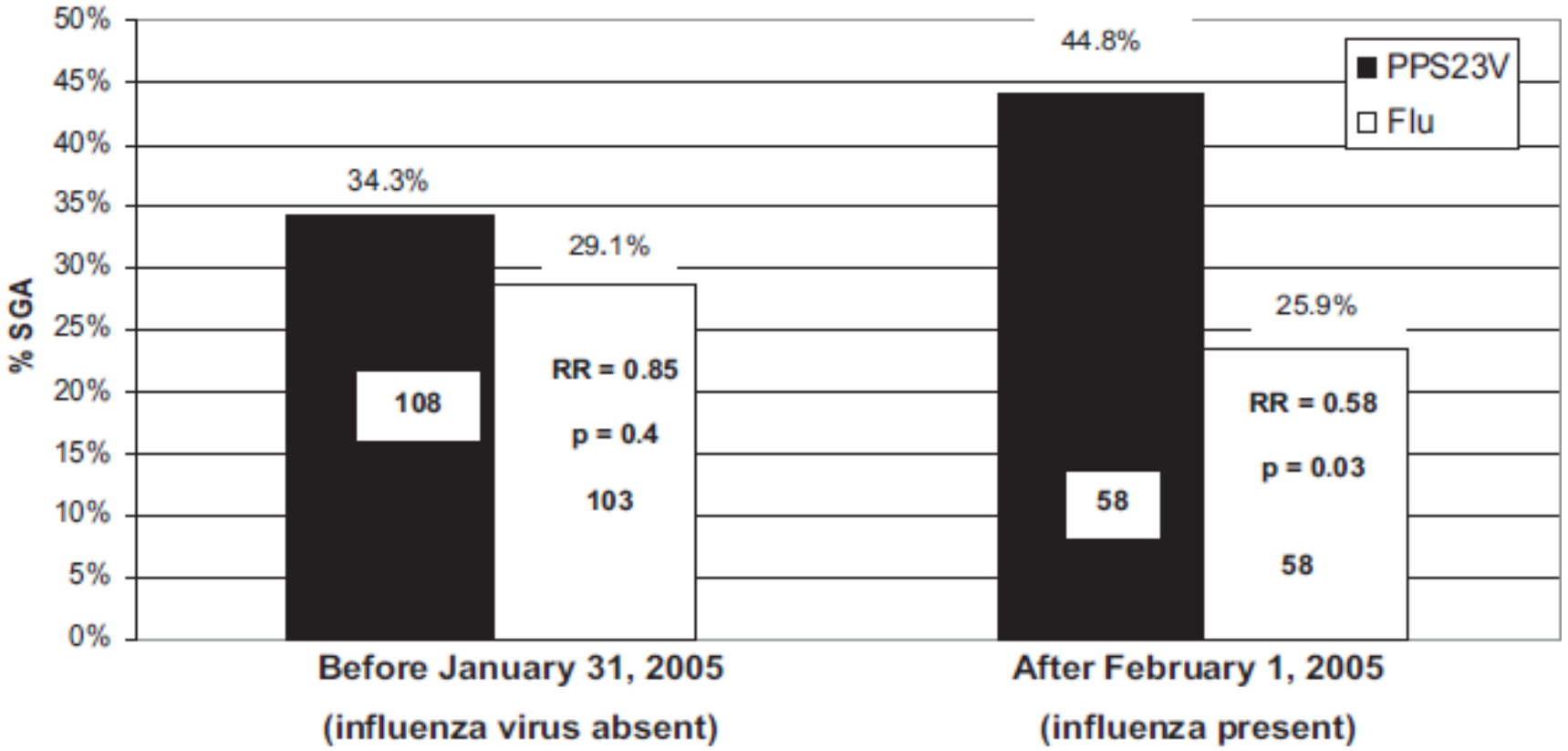
† control mothers 168, Vaccine Mothers 172

† † Risk difference = difference in incidence per 100 subjects at 6 months control group = mothers who received pnuemococcal polysaccharide vaccine

† † † Zaman K et al. NEJM 2008; 359: 1555-64

FIGURE 1

Percent SGA births by study interval, by vaccine[11]

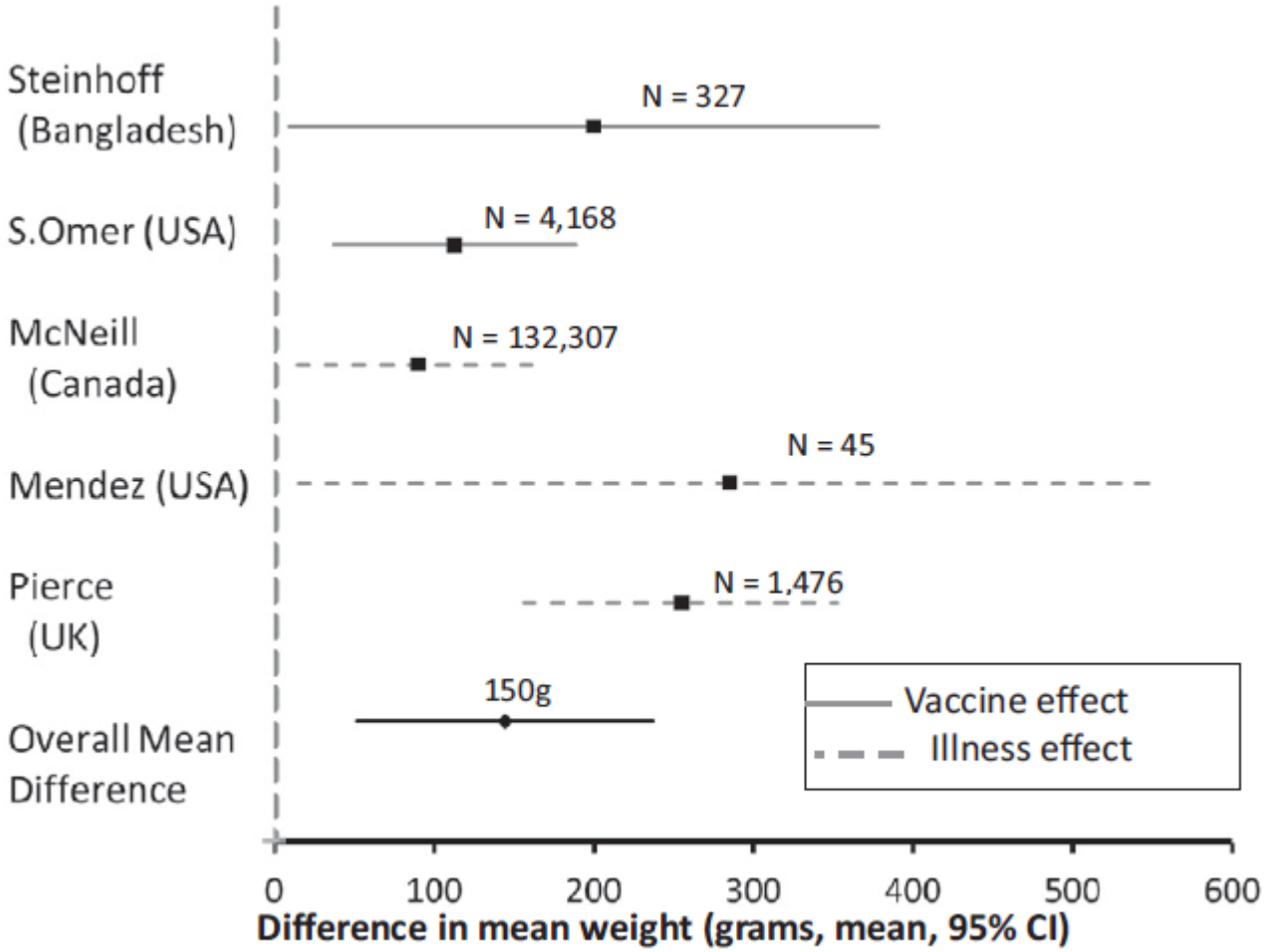


Flu, influenza; *PPS23V*, pneumococcal polysaccharide 23 valent vaccine; *RR*, relative risk; *SGA*, small-for-gestational-age.

Steinhoff. Antenatal influenza Immunization. Am J Obstet Gynecol 2012.

FIGURE 4

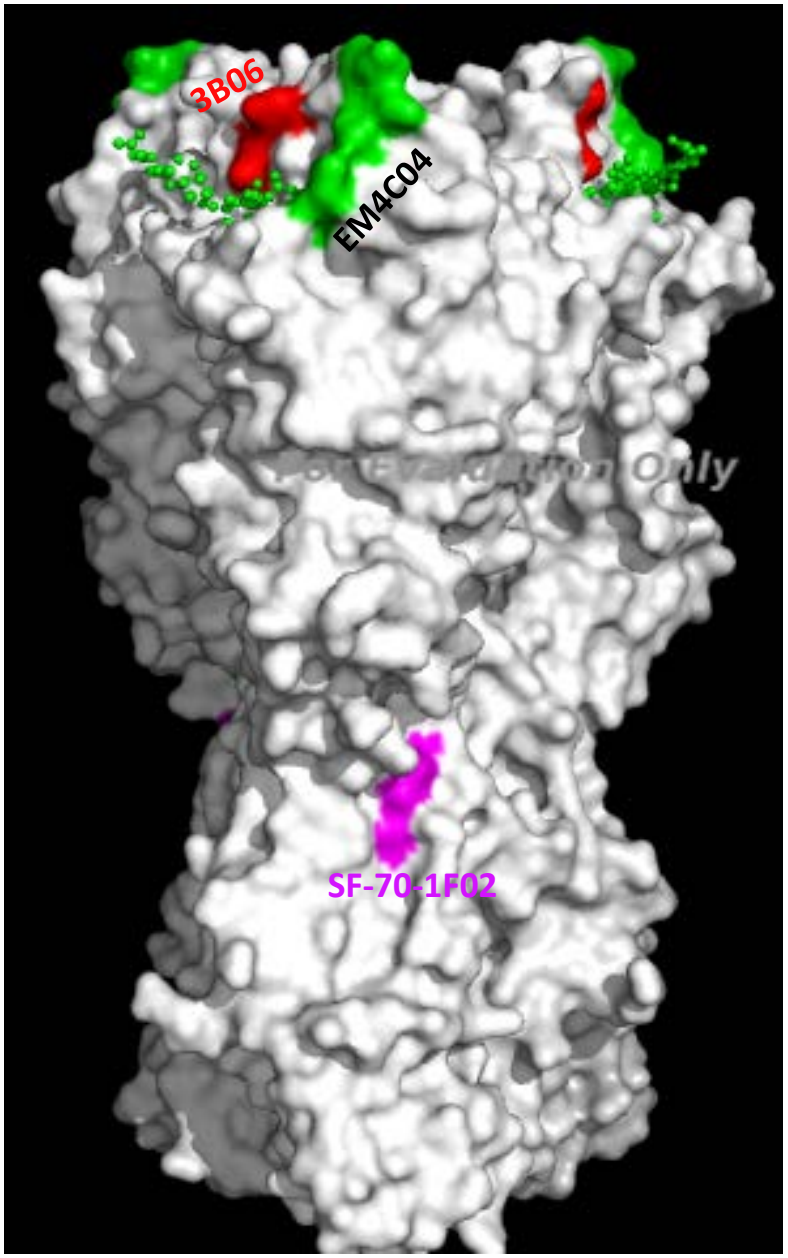
Difference in mean birthweights associated with maternal influenza vaccination or illness status



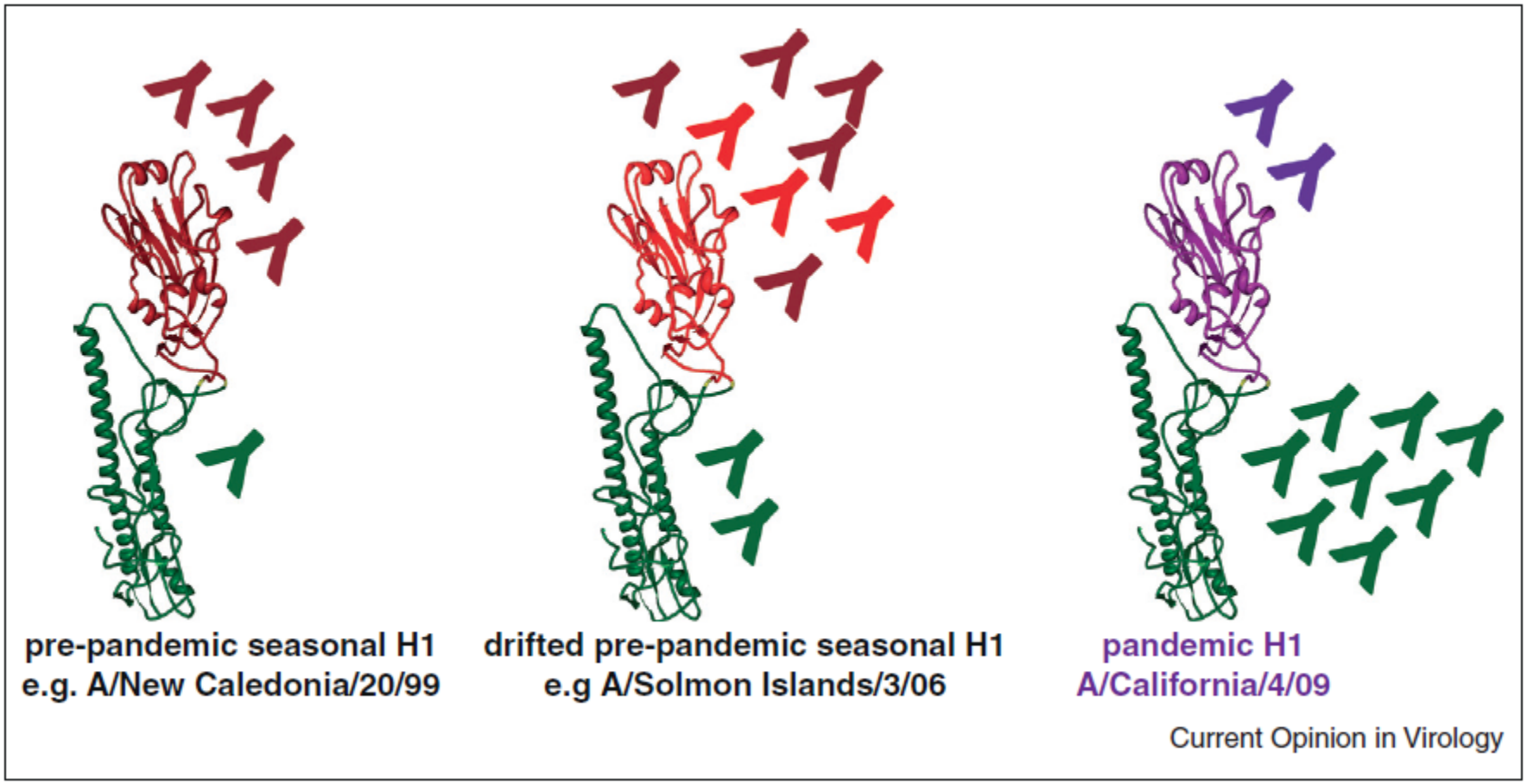
CI, confidence interval.

Steinhoff. Antenatal influenza Immunization. Am J Obstet Gynecol 2012.

Epitope mapping



From Jens Wrammert,
via email 4-4-13



Krammer F, Palese P. Current Opinion in Virology, 2013; 3:521-530

Summary I

- Influenza is a common infection
- Health impact usually most serious in the elderly
- Children likely to be major transmitters
- Epidemiology and health burden in low and middle income countries unclear
- Influenza vaccines most effective way to protect against influenza
- Annual vaccination of children being implemented in US both for individual protection and potential herd immunity
- There is promise of development of a “universal” influenza vaccine targeting the conserved stem region of the hemagglutinin