Considerations for Influenza Policy

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Objectives

- To understand the complexity of influenza vaccine policy
  - Unique characteristics of the vaccine
  - Delivery challenges
- To discuss tools and strategies that might facilitate better influenza prevention.

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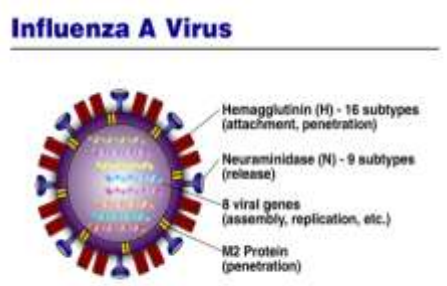
Why is delivering influenza vaccine so challenging?

- Influenza vaccine given every year.
- Influenza vaccine given on a seasonal schedule.
- Three different types of influenza vaccines licensed in US: TIV, LAIV, high-dose
- Vaccine supply and distribution: timing and availability of influenza vaccine uncertain.
- Need 2 doses in children the first year they receive vaccine.
- No vaccine licensed for children younger than 6 months
- Public perception.



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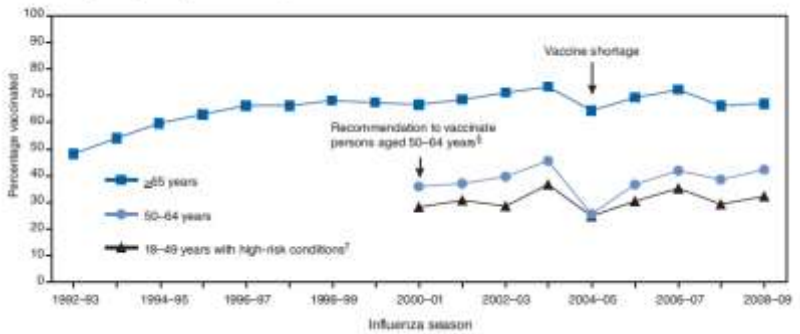
Delivery challenges: low vaccination rates

FIGURE. Estimated influenza vaccination coverage among persons aged ≥18 years — United States, Behavioral Risk Factor Surveillance System (BRFSS), 1992–93 through 2008–09 influenza seasons*



CDC. Influenza Vaccination Coverage Among Children and Adults — United States, 2008–09 Influenza Season. MMWR 2009;58:1091-5

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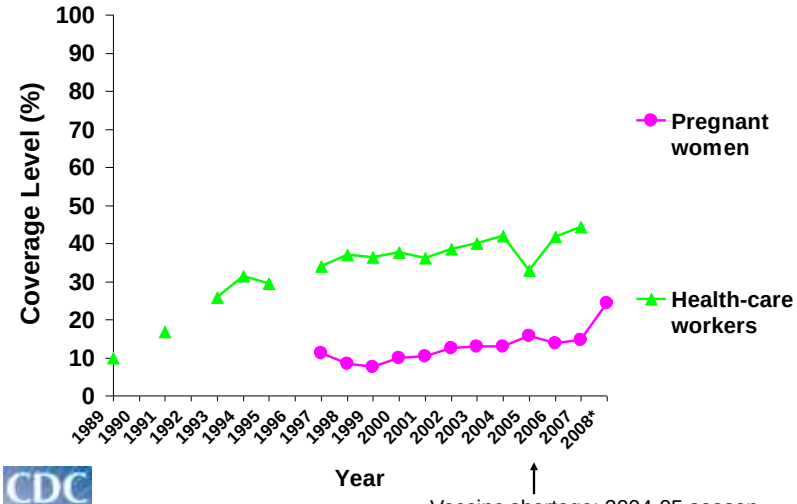
Self-Reported Influenza Vaccination Coverage Levels Among Selected Priority U.S. Adult Populations, 1989-2008*, National Health Interview Survey



Source: CDC, NHIS. http://www.cdc.gov/flu/professionals/vaccination/pdf/vaccinetrend.pdf

*Preliminary data from 2007-08 influenza season

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Goal: To prevent influenza virus infection and its complications

Need to consider factors related to disease, vaccine and implementation.

- Disease burden.
  - Absolute measure.
- Vaccine effectiveness
  - Relative measure.
- Vaccine safety
- Cost-effectiveness.
- Vaccine supply.
- Feasibility of sustained implementation.

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How can improved influenza prevention be accomplished?

- New strategies (e.g. higher coveragae)
- New tools (e.g. better vaccines)

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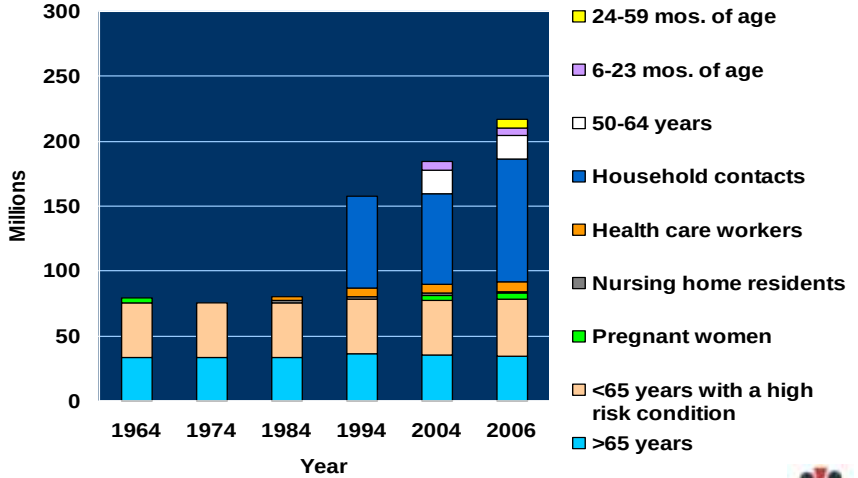
Estimated size of ACIP-recommended groups



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Evolution of seasonal influenza vaccination recommendations

Pre-2000:	Persons aged 65 or older
	Persons with chronic medical conditions that make them more likely to have complications of influenza
	Pregnant women in the second or third trimester
	Contacts (household and out of home caregivers) of the above groups
	Health care workers
2000:	Adults 50 and older
2004:	Children aged 6 through 23 months
	Contacts (household and out of home caregivers) of children aged 0 through 23 months
	Women who will be pregnant during influenza season
2006:	Children aged 6 through 59 months
	Contacts (household and out of home caregivers) of children aged 0 through 59 months
2008:	All children 6 months through 18 years, if feasible
2009:	All children 6 months through 18 years
2010:	All persons 6 months and older

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Decision to vaccinate young children

- Influenza is a nonspecific clinical disease.
- Manifestations and impact vary by age and risk group.
  - Youngest children at highest risk for serious disease.
  - Older children have significant outpatient illness, antibiotic use, missed school.
- Deaths are rare in children, but do occur.
- Efficacy is moderate in the youngest age groups.


Flu hits region's kids hard

Early wave of severe cases brings call for children's vaccination

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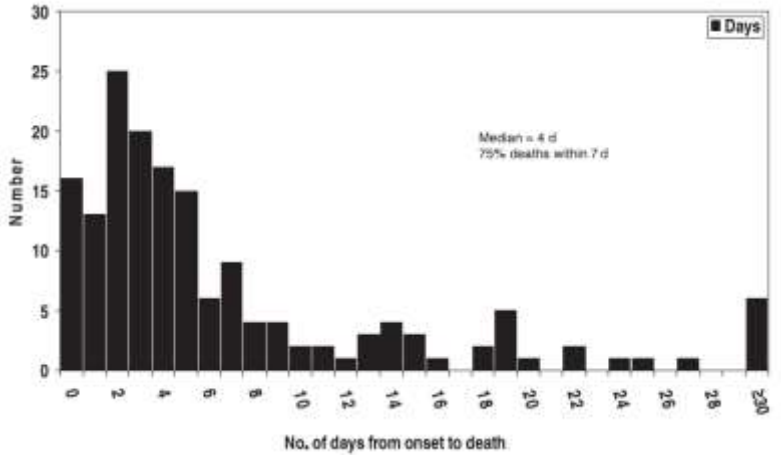
Number of days from influenza onset until influenza-associated death: United States, 2004-2007



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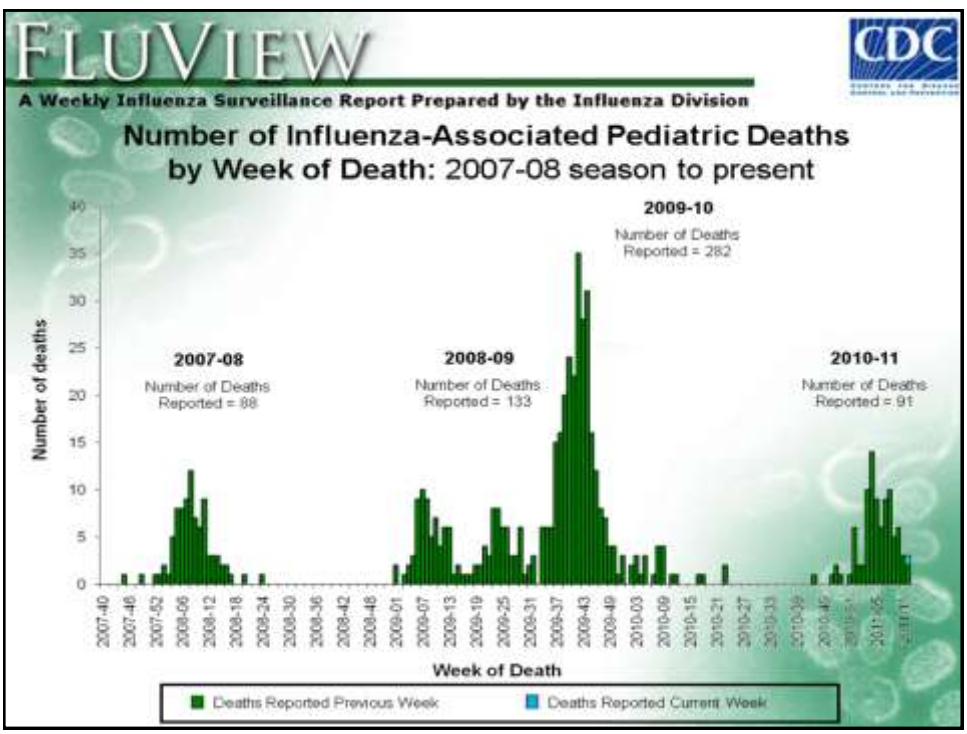
Finelli et al. Pediatrics 2008; 122, 805.



New Recommendations, 2004-2006 Advisory Committee on Immunization Practices

Program	Age Group	$/QALY*
Rotavirus	Infants	Cost saving
Pertussis	Adolescents	20,000
HPV	Adol girls	24,000
Influenza	2-4 yrs, non-high-risk	25,000
Hepatitis A	2 yrs	27,000
Varicella 2nd dose	5 yrs	105,000
Meningococcal	Adolescents	126,000

*Converted to 2003 dollars

Slide source L Prosser, 2007.
Reference: Emerg Infect Dis, 2006

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Influenza vaccination recommendations — 2007

- Annual vaccination against influenza is specifically recommended for:
  - Persons at increased risk for severe complications (hospitalizations and death) from influenza.
    - Risk groups added as evidence became available — pregnant women, children aged 6-23 months, children with neurologic disorders.
  - "Or at higher risk for influenza-associated clinic, emergency department or hospital visits" (MMWR 2007):
    - Children through 4 years of age.
  - Persons who live with or care for persons at high risk of complications from influenza.
- Routine vaccination is also "permissive" for the general population.

***Presented at ACIP meetings 2006-07**

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Limitations of risk-based recommendations

- The recommendations are complicated.
- Risk groups can be difficult to remember – in 2007, there were 12 specific influenza vaccination target groups.
  - More difficult for health care providers to identify patients by risk than by age.
  - More difficult for patients to self-identify based on risk conditions.
  - Coverage levels among the target groups vary, but in general are low.

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Gulf Between Recommendations and Reality

- 220 million persons (73% of the population) should get vaccinated annually
- Fewer than 100 million get vaccinated

***Presented at ACIP meetings 2006-07**

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Potential Time-Frame for Modifying Influenza Vaccination Recommendations*

- **2007-2008**: Consider expanding recommendations to include school-age children
- **2010-2011**: Consider expansion of recommendations to include household contacts and caregivers of school-aged children
- **2012-2013**: Consider expansion to universal vaccination

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***Presented to ACIP meetings 2006-07**

Summary: Vaccinating school-age children against influenza*

- **Vaccine supply:** Adequate and improving, although local distribution issues remain problematic.
- **Vaccine safety:** Established, but need for continued vigilance and long-term studies.
- **Cost effectiveness:** Higher than many currently-recommended vaccines, but models do not fully account for potential indirect effects.
- **Disease burden:** Highest rates of influenza, but severe outcomes less common than in older or younger age groups.
- **Vaccine effectiveness:** Effective in reducing influenza illness, and increasing evidence for indirect effects.
- **Feasibility of sustained implementation:** Uncertain, but comprehensive efforts to vaccinate this large cohort are not likely to be established until a recommendation is made.

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Based on CDC/CSTE consultation, September 2007.
***Presented at February 2008 ACIP meeting.**

2008:
Universal pediatric recommendation

The Atlanta Journal-Constitution

THURSDAY, FEB. 28, 2008

ONLINE AT AJC.COM | 50¢

Flu: Give vaccine to almost all kids, panel says

▶ Continued from A1

country.

If adopted, the recommendation would represent one of the largest expansions of flu vaccinations in U.S. history.

The vaccine is already recommended for people considered to be at highest risk of death or serious illness from the flu, including children ages 6 months to 5 years, adults 50 and older and people with weakened immune systems.

The panel said that list should be expanded to include children up to age 18.

Harrison, the Tandy Springs physician, said he would like to see flu shots become mandatory for children to get into school.

Dr. Joel Gay, a pediatrician at West Atlanta Pediatrics in Dallas, also celebrated the news, saying many more kids may now be spared fever, chills and body aches.

"I'd rather have them crying from a shot than have them to four days of high fever," Young said.

He said immunized children can still get sick, but they tend not to have as high a fever and "think out their parents as much."

Children ages 6 to 18 get flu at higher rates than other age groups, but they tend not to get as sick. Of the 36,000 estimated annual deaths attributed to the flu, only 15 to 50 occur in children in that age bracket, CDC officials said.

But children who stay home sick from school cause parents to stay home, reducing the illness in this group should cut down days of lost work, some experts said.

Experts believe giving flu shots to more children may prevent the illness in adults and the elderly, although studies haven't clearly established that.

Shots are not the only option. A nasal spray vaccine, FluMist, is approved for healthy people ages 2 to 49.

Panel members waffled a bit on whether to make the recommendations kick in immediately. Some public health professionals pushed them to make the clearest endorsement possible of the flu vaccine, concerned that the public is losing faith in flu shots because this year's vaccine was not well matched to circulating viruses.

Meanwhile, vaccine makers said they expect to be able to produce enough doses next season to accommodate an extra 30 million children, but panel members had concerns about how the doses would be given to so many.

No other vaccine is given to nearly all kids every year. Most schools aren't set up to do it, and physicians groups said they weren't sure if doctors are ready to handle a flood of children seeking vaccinations.

Maybe they shouldn't worry. Some experts noted that only a fraction of people recommended to get flu vaccinations actually get them.

Dr. Michael Cortina, a pediatrician at Northside Pediatrics, has high hopes for

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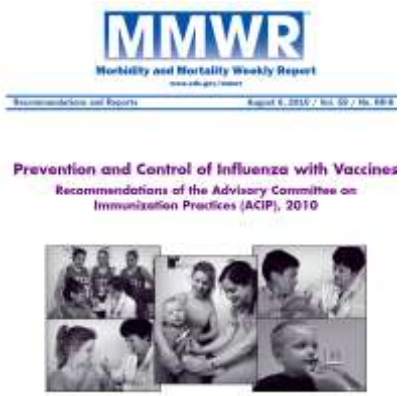
Highlights of 2010 Influenza Vaccine Recommendations

- Influenza vaccine recommended for all persons 6 months and older
- Number of doses needed in children 6 months through 8 years
- Licensure of High-Dose Fluzone



MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports

Prevention and Control of Influenza with Vaccines

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010

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Risk factors for complications of or severe illness with 2009 H1N1 virus infection

Risk Factor	Examples and Comments
Age <5 yr	Increased risk especially for children <2 yr of age; highest hospitalization rates among children <1 yr
Pregnancy	Risk of hospitalization increased by a factor of 4 to 7, as compared with age-matched nonpregnant women, with highest risk in third trimester
Chronic cardiovascular condition	Congestive heart failure or atherosclerotic disease; hypertension not shown to be an independent risk factor
Chronic lung disorder	Asthma or COPD, cystic fibrosis
Metabolic disorder	Diabetes
Neurologic condition	Neuromuscular, neurocognitive, or seizure disorder
Immunosuppression	Associated with HIV infection, organ transplantation, receipt of chemotherapy or corticosteroids, or malnutrition
Morbid obesity†	Suggested but not yet proved to be an independent risk factor for complications requiring hospitalization or ICU admission and possibly for death
Hemoglobinopathy	Sickle cell anemia
Chronic renal disease	Renal dialysis or transplantation
Chronic hepatic disease	Cirrhosis
Long history of smoking	Suggested but not yet proved to be an independent risk factor
Long-term aspirin therapy in children	Risk of Reye's syndrome; drugs containing salicylates should be avoided in children with influenza
Age ≥65 yr	Highest case fatality rate but lowest rate of infection

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Source: N Engl J Med. 2010 May 6;362(18):1710

Healthcare Personnel Influenza Vaccination

- Prevent transmission to patients
  - Transmission of influenza in HC settings occurs; vaccination of patients and HCP reduces risk
  - Vulnerable populations with suboptimal response to vaccine
- Reduce risk that HCP will be infected with influenza
- Maintain critical workforce
- Set an example for the importance of vaccination for every person

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Infect Control Hosp Epidemiol 2010; 10: 987.

New “tools” are needed

- Efficacy
  - Suboptimal, particularly in young children, elderly, immunocompromised
- Limited cross-protection
- Annual administration
- Cumbersome manufacturing process
- Supply and distribution

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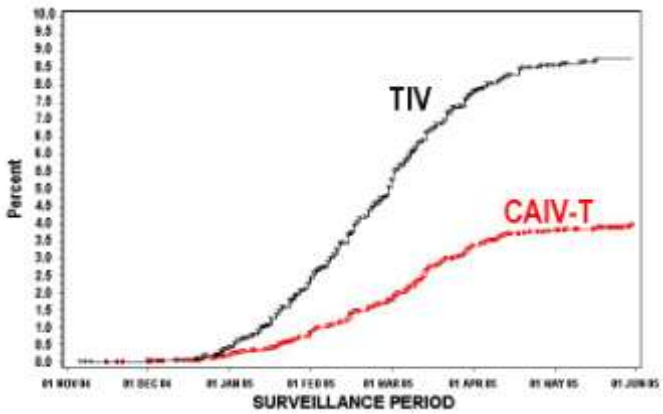
But translating to policy could be complicated…LAIV vs TIV

Laboratory-confirmed influenza illness by vaccine type, 6-59 months



Belshe, et al. NEJM 206; 355:2512.

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Efficacy of influenza vaccine in young, healthy college students, 2007-2008

Table 2. Estimated Absolute and Relative Efficacies of the Trivalent Inactivated and Live Attenuated Influenza Vaccines.*

Confirmation of Symptomatic Influenza†	Cumulative Incidence of Influenza			Relative Risk (95% CI)			Percent Reduction (95% CI)‡		
	TIV (N=813)	LAIV (N=834)	Placebo (N=325)	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV	Absolute Efficacy, TIV vs. Placebo	Absolute Efficacy, LAIV vs. Placebo	Relative Efficacy, TIV vs. LAIV
	no. of participants (%)								
Positive culture	21 (2.6)	38 (4.7)	31 (9.5)	0.27 (0.15–0.49)	0.49 (0.30–0.81)	0.55 (0.31–0.97)	73 (51–85)	51 (19–70)	45 (3–69)
Positive PCR	28 (3.4)	56 (6.9)	35 (10.8)	0.32 (0.19–0.54)	0.64 (0.41–1.00)	0.50 (0.31–0.80)	68 (46–81)	36 (0–59)	50 (20–69)
Positive culture, positive PCR, or both	28 (3.4)	56 (6.9)	35 (10.8)	0.32 (0.19–0.54)	0.64 (0.41–1.00)	0.50 (0.31–0.80)	68 (46–81)	36 (0–59)	50 (20–69)

* The study population included all 1952 enrolled participants who were randomly assigned to a vaccine or a placebo group and who actually received vaccine or placebo. The trivalent inactivated influenza vaccine (TIV) used was Fluzone (Sanofi Pasteur), and the trivalent live attenuated influenza vaccine (LAIV) used was FluMist (MedImmune). The placebo was physiologic saline administered as an intramuscular injection or as an intranasal spray. Exact 95% confidence intervals (CI) were calculated.

† Case-eligible episodes of symptomatic influenza-like illness were confirmed by culture, real-time polymerase-chain-reaction (PCR) assay, or both. Confirmation by culture was defined as isolation of virus by cell culture and subsequent identification by fluorescence antibody assay.

‡ The percent relative reduction in vaccine efficacy was defined as (1 − relative risk) × 100.

Monto et al. N Engl J Med 2009;361:1260-7.

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How do we protect children younger than 6 months? Effectiveness of maternal influenza immunization in mothers and infants

- **Study participants and design:**
  - Bangladesh, 2004-05.
  - Randomized controlled trial.
  - 340 pregnant women received either influenza vaccine or pneumococcal polysaccharide vaccine (control) during third trimester.
  - Follow-up through pregnancy and first 6 months after birth.
- **Outcomes:**
  - Febrile respiratory illness among infants and mothers.
  - Lab-confirmed influenza among infants.

ICDDR,B - Matlab, July 2006.

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Influenza vaccine reduced disease in mothers and babies

Table 2. Clinical Effectiveness of Influenza Vaccine in Infants and Mothers.*

Variable	Episodes		Clinical Effectiveness (95% CI)†	Risk Difference (95% CI)‡
	Control	Influenza Vaccine		
	no.		%	
Infants				
Person-months	870	881		
Respiratory illness with fever				
Any fever	151	110	28.9 (6.9 to 45.7)	−28.1 (−48.2 to −8.0)§
Temperature >38°C	77	56	28.1 (−4.6 to 50.6)	−13.7 (−28.0 to 0.5)
Diarrheal disease	138	137	1.9 (−30.0 to 26.0)	−1.6 (−22.1 to 18.9)
Clinic visit	92	54	42.0 (18.2 to 58.8)	−24.5 (−39.5 to −9.5)§
Influenza test ordered	79	41	48.7 (25.4 to 64.7)	−24.4 (−38.0 to −10.8)§
Influenza test positive	16	6	62.8 (5.0 to 85.4)	−6.4 (−12.2 to −0.5)§
Mothers				
Person-months	1076	1089		
Respiratory illness with fever				
Any fever	77	50	35.8 (3.7 to 57.2)	−14.2 (−25.5 to −2.9)§
Temperature >38°C	33	19	43.1 (−9.0 to 70.3)	−7.3 (−14.5 to −0.1)§
Diarrheal disease	60	49	19.3 (−24.6 to 47.8)	−5.9 (−16.4 to 4.5)
Clinic visit	25	19	24.9 (−43.9 to 60.8)	−3.2 (−9.8 to 3.4)

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High-dose influenza vaccine in adults 65 years and over

- A multicenter, randomized, double-blind controlled study was conducted to compare HD vaccine (which contains 60 mcg of HA per strain) with the licensed standard-dose (SD) vaccine (which contains 15 mcg HA per strain) in adults 65 years of age.
- HD vaccine was administered to 2575 subjects, and SD vaccine was administered to 1262 subjects.
- The immunogenicity of HD vaccine was assessed in terms of rates of seroconversion and ratio of GMTs for each virus strain, relative to the values obtained for the SD vaccine.

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Table 2. Comparison of responses to high-dose (HD) and standard-dose (SD) influenza vaccine.

Response, by antigen	HD vaccine recipients[a] (n = 2576) Subjects with valid serologic result, no.	HAI GMT (95% CI)	SD vaccine recipients[a] (n = 1276) Subjects with valid serologic result, no.	HAI GMT (95% CI)	HAI GMT ratio for HD and SD vaccine, (95% CI)
GMT					
A/H1N1					
Day 0	2553	28.5 (27.4–29.7)	1267	29.4 (27.7–31.1)	...
Day 28	2543	115.8 (111.4–120.3)	1262	67.3 (63.7–71.1)	1.7 (1.6–1.8)
A/H3N2					
Day 0	2552	74.6 (70.3–79.2)	1268	74.7 (68.6–81.4)	...
Day 28	2544	608.9 (583.5–635.3)	1262	332.5 (310.4–356.1)	1.8 (1.7–2.0)
B					
Day 0	2551	19.3 (18.6–20.1)	1267	19.0 (17.9–20.0)	...
Day 28	2542	69.1 (66.6–71.6)	1262	52.3 (49.5–55.3)	1.3 (1.2–1.4)
Seroconversion[b]		Subjects, % (95% CI)		Subjects, % (95% CI)	Percentage difference in rate (95% CI)
A/H1N1	2531	48.6 (46.6–50.5)	1249	23.1 (20.2–25.6)	25.4 (22.4–28.5)
A/H3N2	2531	69.1 (67.3–70.9)	1248	50.7 (47.9–53.5)	18.4 (15.1–21.7)
B	2529	41.8 (39.8–43.7)	1249	29.9 (27.4–32.6)	11.8 (8.6–15.0)
Seroprotection[c]					
A/H1N1	2543	89.9 (88.7–91.0)	1252	76.8 (74.3–79.1)	13.1 (10.5–15.8)
A/H3N2	2544	99.3 (98.9–99.6)	1252	96.5 (95.3–97.4)	2.8 (1.7–3.9)
B	2542	79.3 (77.6–80.3)	1252	67.6 (64.9–70.2)	11.7 (8.7–14.7)

NOTE. Superiority was demonstrated if the lower limit of the 95% confidence interval for the difference in seroconversion rates (i.e., HD vaccine minus SD vaccine) was >10%, and noninferiority was shown if the lower limit was >−10 %. The ratios of the hemagglutination inhibition (HAI) geometric mean titers (GMT) for HD vaccine and SD vaccine were assessed for all vaccine strains. Superiority was demonstrated if the lower limit of the 95% confidence interval for the ratio was >1.5, and noninferiority was defined as an HAI GMT ratio value >0.67. For HD vaccine to be considered superior to SD vaccine overall, for each measure it was required to demonstrate superiority for at least 2 of the 3 vaccine strains without demonstrating inferiority for any strain. CI, confidence interval.

[a] n values are the number of subjects used for the immunogenicity analysis (i.e., the counts of subjects as randomized rather than as actually vaccinated; see figure 1A).

[b] Paired samples with prevaccination (day 0) HAI titer <1:10 and postvaccination (day 28) titer ≥1:40 or a ≥4-fold increase from day 0 to day 28.

[c] Postvaccination samples with HAI GMT ≥1:40

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Falsey et al. JID 2009:200 (15 July).

Vaccine efficacy of adjuvanted TIV against all strains and vaccine matched strains in Year 2 (6 to < 72 month old subjects)

Analysis	Cases / Vaccinated	VE% (2-sided 80% CI)	Target	Assessment
Vaccine Efficacy (VE) Against All Strains				
ATIV vs. Non-Influenza Controls	13/1937 vs 47/983	86 (74 - 93)	Lower CI ≥ 40	Met
TIV vs. Non-Influenza Controls	50/1772 vs 47/983	43 (15 - 61)	N/A	N/A
ATIV vs. TIV	13/1937 vs 50/1772	76 (55 - 87)	Lower CI ≥ 10	Met
Vaccine Efficacy Against Vaccine Matched Strains				
ATIV vs. Non-Influenza Controls	9/1937 vs 41/983	89 (79 - 95)	Lower CI ≥ 40	Met
TIV vs. Non-Influenza Controls	44/1772 vs 41/983	45 (16 - 64)	N/A	N/A
ATIV vs. TIV	9/1937 vs 44/1772	80 (59 - 90)	Lower CI ≥ 10	Met

Of the total of 105 FLU case isolates in year 2:
- 91 were A/Brisbane/10/2007(H3N2)-like viruses;
- 5 were B/Brisbane/60/2008-like viruses;
- 4 were A type viruses of unknown subtype;
- 2 were B type viruses of unknown lineage.
- No H1N1 viruses were detected.

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Vesikari et al., IDSA 48th Annual Meeting, Vancouver, Canada, October 21-24, 2010.

Summary

- Influenza causes substantial morbidity and mortality in many different populations; vaccine is cornerstone of influenza prevention
- Vaccine efficacy is only one of many considerations in making policy decisions
  - Burden of disease is critical
  - Absolute as well as relative prevention is important
  - Practical considerations
- The landscape of influenza vaccine development is rapidly evolving; policymakers will also need to be flexible