HHS/CDC Update: 2010-11 Flu Season and Universal Vaccine Recommendations

Clinician Outreach and Community Activity (COCA) Conference Call

August 30, 2010

Office of Public Health Preparedness and Response
Division of Emergency Operations

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Influenza Update for 2010-2011

August 30, 2010

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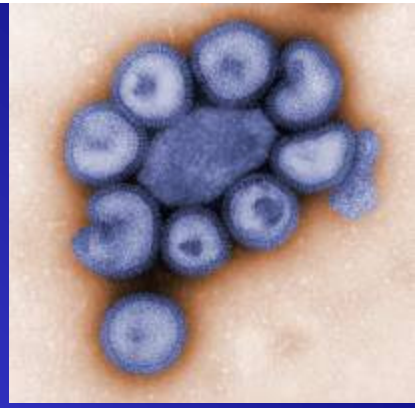
Information and opinions provided in this presentation are those of the author and does not necessarily reflect the position of the CDC

Influenza



- Contagious respiratory illness caused by influenza viruses
- Seasonal influenza causes yearly winter epidemics
- Pandemics are sporadic, unpredictable
  - Caused by novel influenza A viruses
    - Spread from person to person and cause human illness
    - Most of the population is susceptible
- Hallmark of influenza viruses is their ability to undergo change
  - Drift – gradual changes through point mutations acquired during virus replication
  - Shift – exchange of entire gene segments

Influenza Virus Symptoms and Complications

- Acute febrile respiratory infection characterized by
  - Abrupt onset fever, chills, muscle aches, headache, fatigue
  - Cough, sore throat, runny nose
  - GI symptoms more often in children
  - Sepsis-like syndrome in infants
- Complications
  - Primary viral pneumonia
  - Secondary bacterial pneumonia
  - Worsening of underlying illness, e.g. asthma, CHF
- Definitive diagnosis, when testing indicated, requires testing by rRT-PCR or culture
- Rapid influenza test sensitivity suboptimal
- Clinical spectrum varies with different influenza viruses

Influenza Clinical Pathogenesis For Seasonal Influenza

- Incubation period 1-4 days, median 2 days
- Duration of virus shedding
  - Begins day prior to illness onset
  - Most outpatients with shedding through day 5 from onset
    - Most done with shedding after 7 days, some longer
    - Longer shedding in hospitalized persons and immune compromised – up to 10 days to months for most severely immune deficient
- Little if any shedding in stool – only rare cases detected
  - Some 2009 H1N1
- Viremia thought to be rare
- Pathogenesis may differ for human infections with animal-origin influenza viruses, such as avian and swine influenza viruses

Seasonal Influenza Impact in U.S.

- Vary substantially from year to year
- Difficult to predict severity or timing
- 5% - 20% of US population infected
  - highest illness rates in children
  - highest complication rates in elderly
- Range of 3,349-48,614 (average 23, 607) influenza-related deaths
  - 2.7 times higher when H3N2 prominent
  - ~90% among 65 and older
  - Recently updated 1976-2007 in MMWR (Aug 20, 2010)
- Annual average of 220,000 hospitalizations
  - About 50% in 65 and older

CDC Estimates of 2009 H1N1 Cases and Related Hospitalizations and Deaths from April 2009-April 30, 2010, By Age Group

Outcome and age group	Mid-level Range	Estimated Range
Illnesses		
0-17 years	20,000,000	14 -28 million
18-64 years	35,000,000	25 - 52 million
65 and older	6,000,000	4 - 9 million
Total illnesses	61,000,000	43 - 89 million
Hospitalizations		
0-17 years	87,000	62 - 128 thousand
18-64 years	160,000	114 - 235 thousand
65 and older	27,000	19 - 40 thousand
Total hospitalizations	270,000	195 - 403 thousand
Deaths		
0-17 years	1,280	910 - 1880
18-64 years	9,570	6,800 – 14,040
65 and older	1,620	1,160 - 2,380
Total deaths	12,470	8,870 - 18,300

Estimated number and proportion of deaths in persons <65 years of age in the United States for seasonal and pandemic influenza*

Pandemic/season	Total Estimated Deaths*	% deaths <65 years*
1918 H1N1 Pandemic (b)	546,000	99%
1957-58 H2N2 Pandemic (b)	66,000	36%
1968-69 H3N2 Pandemic (b)	36,400	48%
1976-2007 Seasonal (c)	23,607	10%
2009-10 H1N1 Pandemic (d)	12,470	87%

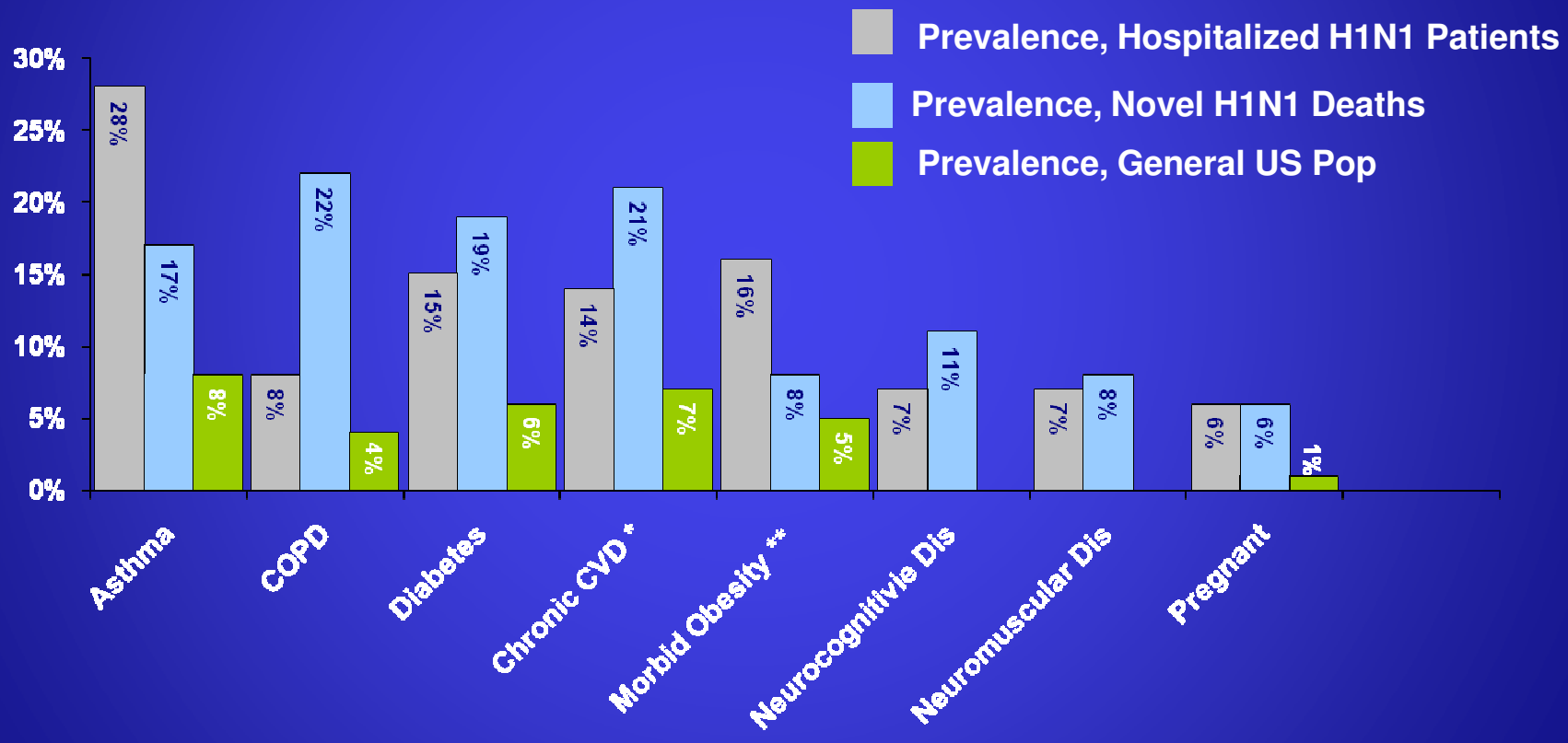
*[a]The methods of estimating influenza deaths between pandemics and for seasonal influenza varied considerably. Estimates are not directly comparable, but are included to illustrate the wide range in potential impact.
[b]Estimated excess pneumonia and influenza deaths attributed to influenza.
[c]Estimated excess respiratory and circulatory deaths attributed to influenza.
[d]Estimated 2009 pandemic H1N1 influenza attributable deaths. Available at: http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm

Groups at Increased Risk of Severe Influenza

Those at higher risk for flu complications include:

- Children younger than 5 years old, but especially children younger than 2 years old
- Adults and children who have:
  - asthma
  - neurological and neurodevelopmental conditions
  - chronic lung disease, including asthma
  - heart disease
  - blood disorders
  - endocrine disorders, such as diabetes
  - kidney, liver, and metabolic disorders
  - weakened immune systems due to disease or medication
  - people younger than 19 years old who are receiving long-term aspirin therapy
  - pregnant women
  - people aged 65 years or older
  - severely obese persons

Underlying conditions among hospitalized patients and those who died from H1N1 compared to the general population



Obesity a New Risk Factor for Severe Illness due to 2009 H1N1

- Disproportionate number of obese, particularly morbidly obese, among severely ill during 2009 H1N1 pandemic
- Morbid obesity (BMI≥40) was associated with hospitalization, and possibly death, due to 2009 H1N1 infection among adults without chronic medical conditions
- Additional studies with larger samples of patients and appropriate comparison groups are needed

Morgan OW, et al. PLOS ONE, 2010

Age-adjusted and Season-specific pH1N1 Influenza-related Hospitalization Rates (per 100,000) by race & ethnicity – Emerging Infections Program, 2009-10 (Preliminary Unpublished Data)

Race/Ethnicity	Influenza Season	
	2009*	2009-10**
White, non-Hispanic	3.0	16.3
Black, non-Hispanic	10.9	29.7
Hispanic	8.2	30.7
Asian/Pacific Islander	8.1	12.5
American Indian/Alaska Native	4.1	32.7

*2009: April 15 - August 31, 2009
**2009-10: September 1, 2009 - January 26, 2010

Key Recent Vaccine Studies

- Loeb, et al. A Cluster Randomized Trial of Vaccinating Children in Hutterite Colonies against Influenza. JAMA 2010
  - Blinded study
  - Assessed the effects of influenza vaccination of children on influenza in the children and among unvaccinated contacts
    - Colonies randomized to vaccinating school aged children 3-15 yo with either influenza vaccination or hepatitis A vaccine
    - Nurses made weekly visits to colonies to collect swabs from ill persons of any age for RT-PCR testing

Results from Loeb, et al

- 46 of 187 colonies randomized
  - 22 to influenza vaccine, 24 to hepatitis A vaccine
- 947 children received a study vaccine
  - 502 flu vaccine, 445 hepatitis vaccine
- 2,326 others in the colonies evaluated for indirect effect
- Study vaccination rate: 83% influenza, 79% hepatitis
- 294 received flu vaccine outside of the study
  - Two were 3-15 years
  - 292 of 2326 (12.6%) of non-school aged children vaccinated
- Among *non-study vaccine* participants
  - 3% PCR + in flu vaccine group vs 8% PCR + in hepatitis A vaccine group
  - VE 61% (8-83%) after adjusting for vaccination rates among non-school children population and for cluster randomized design
- Among the 3-15 year olds, VE 55% (-21% - 84%)

Study Strengths/Conclusions

- Confirms results from Monto Tecumseh study from 1968 pandemic
  - Influenza vaccination of children to high levels results in indirect protection to others in the community
  - Both obtained similarly high vaccination rates in children target group (about 80%)
  - Large differences between control and intervention group vaccination rates
- Vaccine with similar VE (though not SS) in vaccinated children as in the community
- Two additional years data forthcoming
  - 2009-11 influenza seasons
  - Did not randomize 2009 H1N1 vaccine

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 3rd trimester
  - Follow-up through pregnancy and first 6 months after birth

- Outcomes
  - Febrile respiratory illness among infants
  - Lab-confirmed influenza among infants
  - Febrile respiratory illness among mothers

* K Zaman et al. N Engl J Med 2008

Cumulative Cases of Lab-Confirmed Influenza among Infants, by Receipt of Influenza Vaccine, Bangladesh, 2004-05

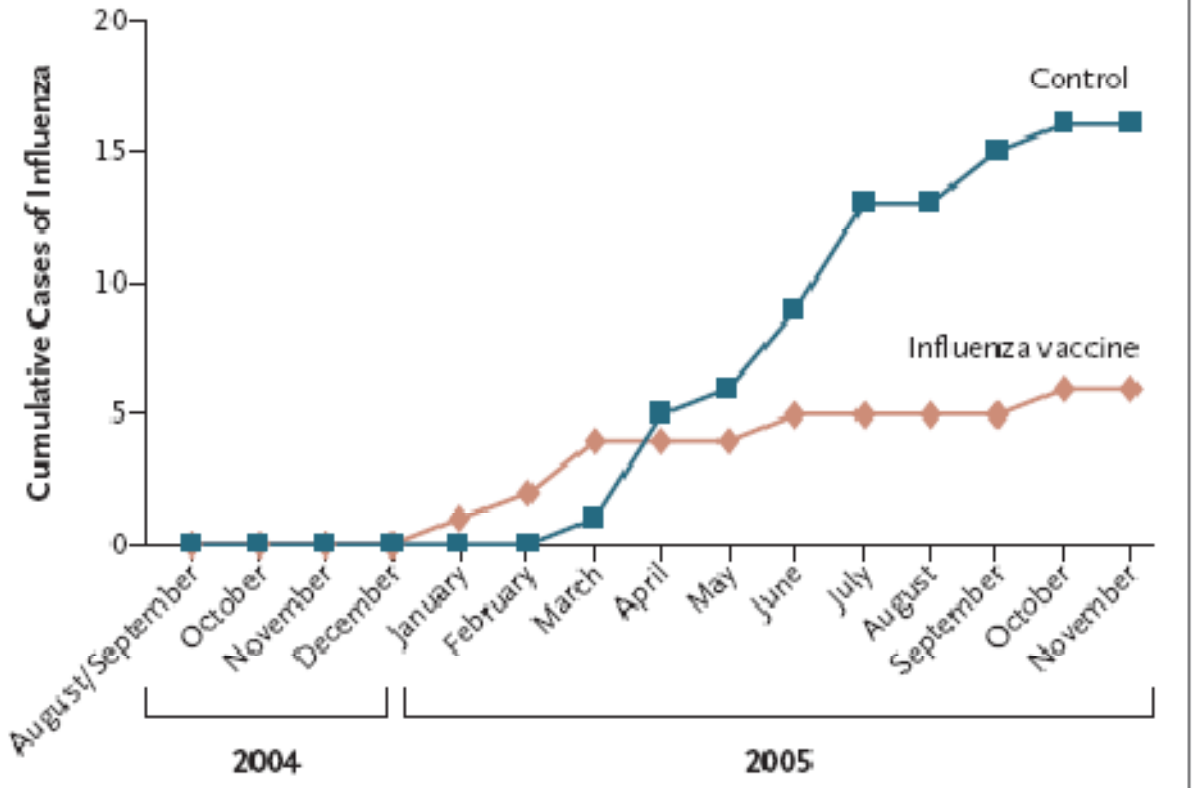


Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.

Testing for influenza antigen was performed from December 2004 to November 2005.

* K Zaman et al.
N Engl J Med 2008

Cumulative Cases of Lab-Confirmed Influenza among Infants, by Receipt of Influenza vaccine, Zaman et al, Bangladesh, 2004-05

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	153	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)

Influenza Vaccine

Influenza Vaccine

- Primary means to prevent influenza and its complications
- Seasonal influenza vaccination recommended for all persons 6 months of age and older
- Primary means to protect <6 months is vaccination of household members and out-of-home caregivers
- Yearly updated vaccine strains and recommendations
- Recommendation for vaccination by a healthcare provider is a key factors in patients' decisions to get vaccinated

Types Influenza Vaccines

- Inactivated vaccines
  - Intramuscular injection
  - First approved for used in 1945 in U.S.
  - Used in persons ≥6 months old
  - Different manufactures, including 1 with a high dose vaccine for adults 65 years and older
- Live, attenuated vaccines (LAIV)
  - Licensed in U.S. 1999
  - Approved for healthy non-pregnant persons 2-49 years
    - Persons at high risk of influenza-complications are not recommended to receive LAIV
  - Health care personnel and contacts of high risk *can* take FluMist
  - Only contraindicated in persons working with those who are so immune suppressed as to require a protected environment
- Both types
  - Updated annually, yearly vaccination needed

Seasonal Vaccine Safety

- Inactivated vaccine
  - Mild reactions most common: redness and soreness at injection site
  - Uncommon: body aches and fever, occulo-respiratory syndrome
  - Rare: Guillian Barre Syndrome
    - Estimated risk in some years 1-2 per million vaccinees
- Live, attenuated vaccine
  - Children – rhinnitis, cough, fever, heachache/muscle aches, occassional wheezing, abdominal pain or vomitting
  - Adults – rhinnitis, sore throat, cough, chills, headache
- All US licensed vaccines are egg-derived
  - Contraindicated for persons with severe egg allergies
- Severe allergic reactions rare with either vaccine
- Safety monitored every year through Vaccine Adverse Events Reporting System (VAERS) and other systems
- Covered by the National Vaccine Injury Compensation Program (VICP)

2010-11 Influenza Vaccine Composition

- Only one vaccine this year, not two
- First year: all 6 months and older recommended for annual vaccination
- Vaccine strains:
  - A/California/7/2009-like H1N1
    - Same strain as 2009 monovalent vaccine
  - A/Perth/16/2009-like H3N2
    - New H3N2 strain for Northern Hemisphere
  - B/Brisbane/60/2008
    - Was in 2009-10 seasonal vaccine
- This summer, all 3 strains identified in US and internationally

ACIP: Influenza Vaccination Recommendation Changes for the US Over Time

2006:

- Children aged 6 months through 59 months
- Contacts (household and out-of-home caregivers) of children aged 0 months through 59 months

2008:

- All children aged 6 months through 18 years

2010:

- All persons 6 months of age and older

In 2009-10 season, ~85% of population had an indication for vaccination.

Rationale: Recommendation to vaccinate all people ages 6 months or older

- **Annual influenza vaccination is a safe and effective prevention measure that provides a potential benefit for people in all age groups**
- **Morbidity and mortality occurs in all age groups, including among adults aged 19-49**
  - **Already 50% had a recommendation, and 85% overall**
- **Some persons who have influenza complications**
  - **have no previously identified risk factors,**
  - **have risk factors but are unaware that they should be vaccinated, or**
  - **might be at risk due newly identified risk factors, such as morbid obesity or race/ethnicity**
- **A recommendation that all people ages 6 months or older receive an annual influenza vaccination**
  - **eliminates the need to determine whether each person has an indication for vaccination**
  - **emphasizes the importance of preventing influenza across the population spectrum**
  - **reduces potential barriers to increasing the number of persons protected from influenza, including lack of awareness about vaccine indications among persons at higher risk for influenza complications and their close contacts.**

Seasonal Influenza Vaccines United States, 2010-11 Season

TABLE. Influenza vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) for different age groups — United States, 2010–11 season

Vaccine	Trade name	Manufacturer	Presentation	Mercury content (mcg Hg/0.5 mL dose)	Age group	No. of doses	Route
TIV*	Fluzone	sanofi pasteur	0.25mL prefilled syringe	0	6–35 mos	1 or 2†	Intramuscular§
			0.5 mL prefilled syringe	0	≥36 mos	1 or 2†	Intramuscular§
			0.5 mL vial	0	≥36 mos	1 or 2†	Intramuscular§
			5.0 mL multidose vial	25.0	≥6 mos	1 or 2†	Intramuscular§
TIV	Fluvirin	Novartis Vaccine	5.0 mL multidose vial	25.0	≥4 yrs	1 or 2†	Intramuscular§
			0.5 mL prefilled syringe	<1.0			
TIV	Agriflu	Novartis Vaccine	0.5 mL prefilled syringe	0	≥18 yrs	1	Intramuscular§
TIV	Fluarix	GlaxoSmithKline	0.5 mL prefilled syringe	0	≥3 yrs	1 or 2†	Intramuscular§
TIV	FluLaval	GlaxoSmithKline	5.0 mL multidose vial	25.0	≥18 yrs	1	Intramuscular§
TIV	Afluria¶	CSL Biotherapies	0.5 mL prefilled syringe	0	≥9 yrs	1	Intramuscular§
TIV High-Dose**	Fluzone High-Dose	sanofi pasteur	0.5 mL prefilled syringe	0	≥65 yrs	1	Intramuscular§
LAIV††	FluMist§§	MedImmune	0.2 mL sprayer, divided dose	0	2–49 yrs	1 or 2†	Intranasal

* Trivalent inactivated vaccine

Expected number of doses for 2010-11 season is approximately 160 million.

Young children and pandemic 2009 H1N1 antigen, 2010-11 season

Children entering 2010-11 season have a variety of immunologic profiles

- Susceptible
- Immune after natural infection
  - Miller et al – London, UK (Lancet 2010)
    - 21% seroconversion among <5 year olds
    - 42% among 5-14 year olds
  - Ross et al, Pittsburgh area (PLoS Currents 2010)
    - 28% seropositivity among 0-9 year olds
- Immune after 2 doses of monovalent vaccine
- Immune response after 1 dose of monovalent vaccine is less certain

Immunogenicity of influenza A(H1N1) 2009 monovalent vaccines, 1 versus 2 doses

- After 1 dose of 2009 pandemic H1N1 monovalent vaccine, hemagglutinin inhibition (HI) titers considered to be protective (≥40) develop in
  - 81% of adults 65 years and older
  - 90%-97% of older children and adults
  - 44%-93% of children 3 years -- 9 years
  - 19%-92% of children ages 6 months---35 months
- Responses after 1 dose of children < 9 years old vary across studies
  - Some children who are currently recommended to receive 1 seasonal 2010-11 dose, AND who received no monovalent vaccine doses, might benefit from 2 doses of 2009 H1N1 antigen
- After 2 doses, 73-100% of infants and young children develop HI titers considered to be protective
  - No increase in reactogenicity with second dose

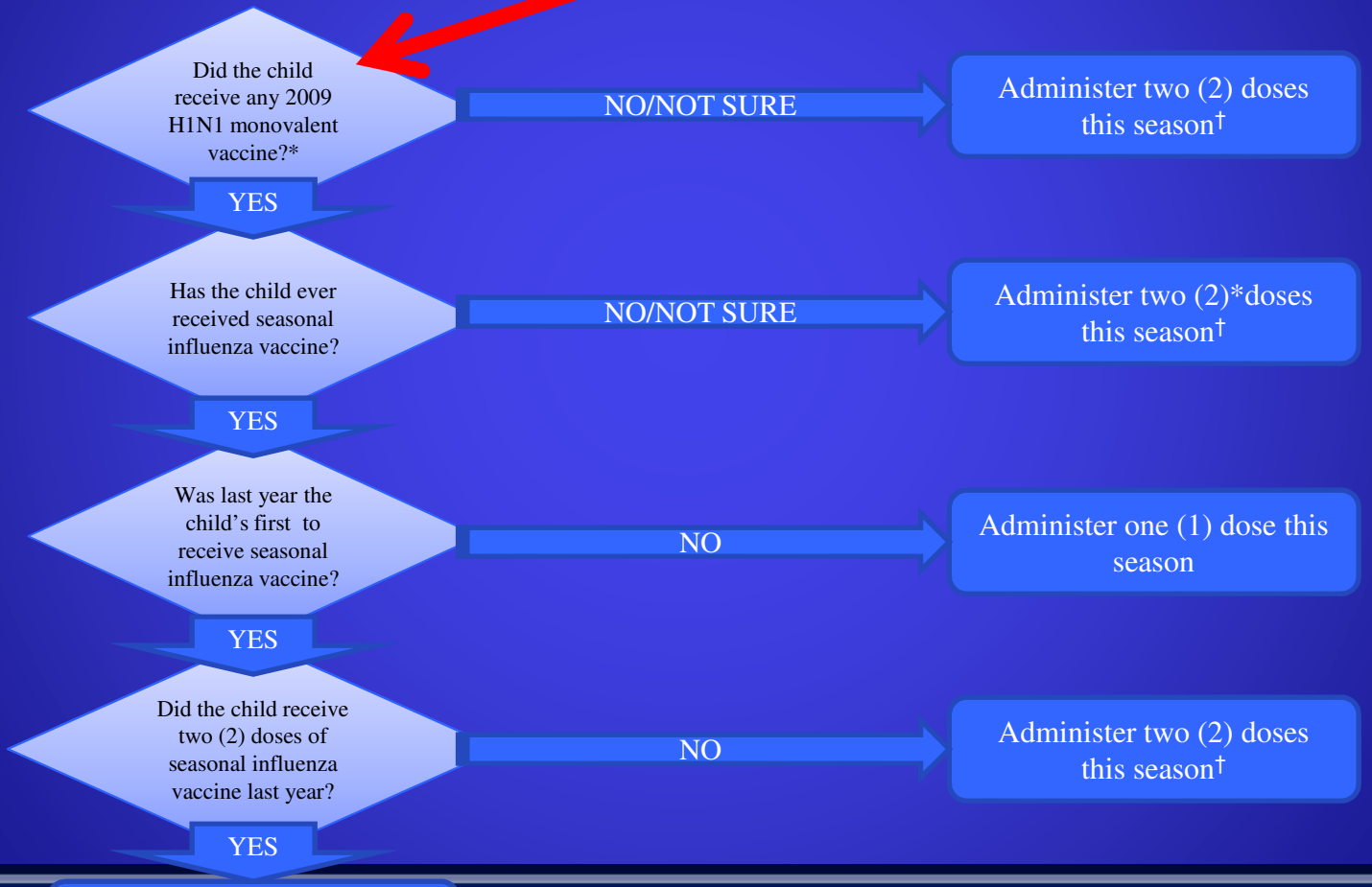
*Walter et al. Pediatrics 2006

Doses Needed in Children Younger than 9 years

- Children aged 6 months--8 years whose vaccination status is unknown or who have never received seasonal influenza vaccine before (or who received seasonal vaccine for the first time in 2009--10 but received only 1 dose in their first year of vaccination) as well as children who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine regardless of previous influenza vaccine history should receive 2 doses of a 2010--11 seasonal influenza vaccine (minimum interval: 4 weeks) during the 2010--11 season.

Number of 2010-2011 Seasonal Influenza Vaccine Doses Recommended For Children

Infants under 6 months of age	**No influenza vaccine**
Children 6 months through 8 years of age	**Follow algorithm below**
Children 9 years of age and older	**One (1) dose**



Vaccines with Higher Doses of Hemagglutinin (HA) Antigen

High-Dose vs Standard-Dose Influenza Vaccine

- Higher antibody titers compared with standard-dose vaccine in all studies
  - significantly higher antibody responses to influenza A vaccine strains vs standard-dose TIV vaccine for people ≥65 years of age with or without underlying medical conditions[1]
- With an increased dose, there was an associated increase in injection-site reactogenicity
  - Most injection-site and systemic reactions were mild and resolved within 72 hours
- *Fluzone High Dose* (sanofi-pasteur)
  - US FDA approval – December 2009
  - Option for US adults 65 years and older

1. Falsey A, et al. *J Infect Dis*. 2009;200:172-180.

Recommendations for use of CSL Afluria brand vaccine in US Children

- Background
  - April 2010: Vaccination of children <5 yo suspended in Australia due to reports of febrile seizures during a mass vaccination campaign
  - Also noted higher reports of fever in children 5-8 years
  - No prior years with similar incidence
  - Studies conducted in Australia and New Zealand found increase risk only associated with FluVax and Fluvax Jr. brands of CSL vaccine, but not with other manufacturers' vaccines
  - Febrile seizures (FS) occurred median of 7 hours after vaccination
  - Australian estimated risk FS in <5 yo 9/1000 vaccinees
  - Antigenically equivalent trivalent vaccine approved in US

Interim Findings, June 1, 2010, Australian Government; Therapeutic Goods Administration, Australia, July 2, 2010

Investigations to Date

- Potency: Pass
- Endotoxin: Pass
- Rabbit Pyrogenicity: Pass
- Inactivation of Virions: Pass
- Disruption of Virions: Pass
- Ongoing investigations to evaluate processes/reagents related to disruption of whole virions

August 2010 Recommendations of ACIP

- Afluria should not be used in children aged 6 months through 8 years*
- Other age-appropriate, licensed seasonal influenza vaccine formulations should be used for prevention of influenza in children aged 6 months through 8 years
- *However, if no other seasonal TIV is available, use in children aged 5 years through 8 years old who are at high risk of influenza related complications may be considered

Afluria Vaccine Formulations for US and Vaccine Package Insert

- **Afluria (CSL/Merck) was approved by FDA in November 2009 for use in persons ≥6 months**
- **Only the single dose 0.5ml vaccine will be marketed in US this year**
  - **Neither the 0.25 ml pediatric single dose preparation nor the 5.0ml multi-dose vials will be marketed in the US**
- **Afluria package insert changes for 2010-2011**
  - Added information to Sections 5: Warnings and Precautions section, 6: Adverse Reactions, and 8: Use in Specific Populations

5.1 Fever and Febrile Seizures: "Administration of CSL's 2010 Southern Hemisphere influenza vaccine has been associated with increased postmarketing reports of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years."

Afluria package insert, July 30, 2010

Antiviral Medications

Influenza Antiviral Medications

- Antiviral medications are an adjunct to influenza vaccine
- Two classes
  - Adamantanes – rimatadine and amantadine
    - *Currently not recommended for use due to high levels of resistance among circulating viruses*
  - Neuraminidae inhibitors
    - Oseltamivir and zanamivir
    - Activity against both influenza A and B
    - <1% isolates resistant
- Can be used for treatment or for prophylaxis
- Treatment should begin as soon as possible after symptom onset for optimal effect
    - Ideally within first 2 days of illness

www.cdc.gov/h1h1flu/antivirals

Neuraminidase Inhibitors

- Reduces duration of influenza symptoms by average of 1-1.5 days when administered within 2 days of illness onset
  - Recent observational studies from seasonal and 2009 H1N1 show benefit even when treatment started >48 hours after onset
- Reduces lower respiratory tract complications, pneumonia, hospitalization, and death
  - Seasonal influenza and 2009 H1N1
- Given suboptimal sensitivity of rapid tests for influenza
  - Treatment, if indicated, should be initiated empirically, even if test results negative if testing is done

Antiviral Treatment Recommendations

- Clinical judgment is an important factor in treatment decisions for patients presenting with influenza-like illness.

- Prompt empiric antiviral treatment with influenza antiviral medications is recommended while results of definitive diagnostic tests are pending, if testing is done, for patients with clinically suspected influenza illness who have:
  - Illness requiring hospitalization,
  - Progressive, severe, or complicated illness, regardless of previous health status, and/or
  - Patients at increased risk for severe disease.

Antiviral Resistance and Treatment

- Before the pandemic, a major gap data was the safety and effectiveness of antiviral medications in pregnant women and children <1 year old.
- Substantial experience gained in using these medications during the pandemic
  - Investigations extended amount of information indicating treatment benefits in decreased risk of severe disease and death
  - Benefits for those hospitalized even up to 96 hours after illness onset
  - Medication well tolerated for pregnant women and infants

Impact on Pregnant Women and Use of Antiviral Treatment

- Pregnant women were at higher risk of hospitalization and death from 2009 H1N1
  - 1% of US population, but 6% of 2009 H1N1 hospitalizations
  - 50% with additional high risk (HR) condition
  - 22.6% admitted to ICU, 63% with HR condition
  - 5% died, 78% with a HR condition
- Compared with early antiviral treatment (<3 days)
  - Intermediate treatment (3-4 days) associated with 2.4X increase risk of ICU if hospitalized (9% vs 23%), 10X increase risk of death (0.5% vs 5%)
  - Late treatment (>4 days) associated with 6.6X increase risk ICU (57%) , and 54X increase risk of death (27%)

Siston, et al JAMA 2010

Questions?

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www.cdc.gov/flu

Thank You

- **Please e-mail additional questions to: coca@cdc.gov**
  - If you have a question for a specific speaker please indicate their name in the subject line of your e-mail.
- **For COCA Call materials and resources please visit: http://emergency.cdc.gov/coca/callinfo.asp**
- **COCA Website: http://emergency.cdc.gov/coca/**
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