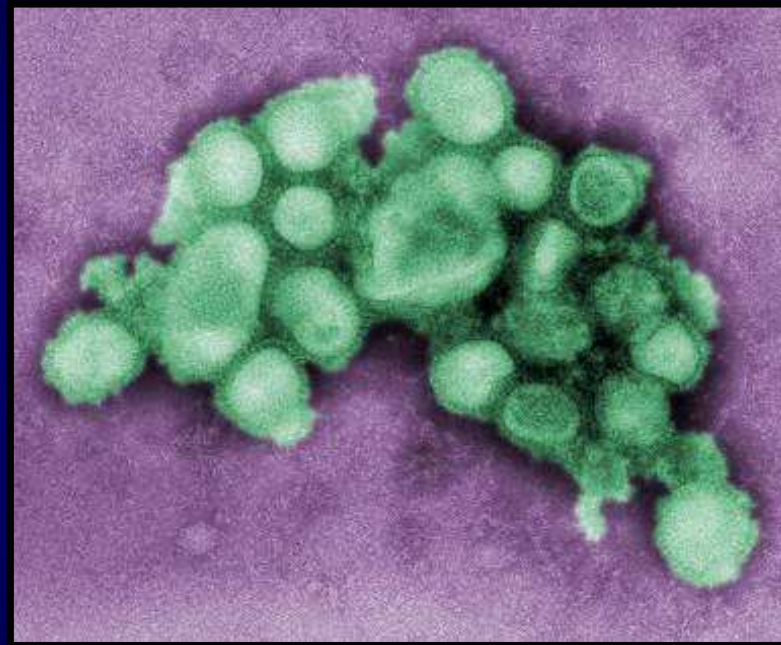


Clinical Issues

Pandemic Influenza A (H1N1) Virus Infection



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US Centers for Disease Control and Prevention



www.pandemicflu.gov

www.cdc.gov/flu



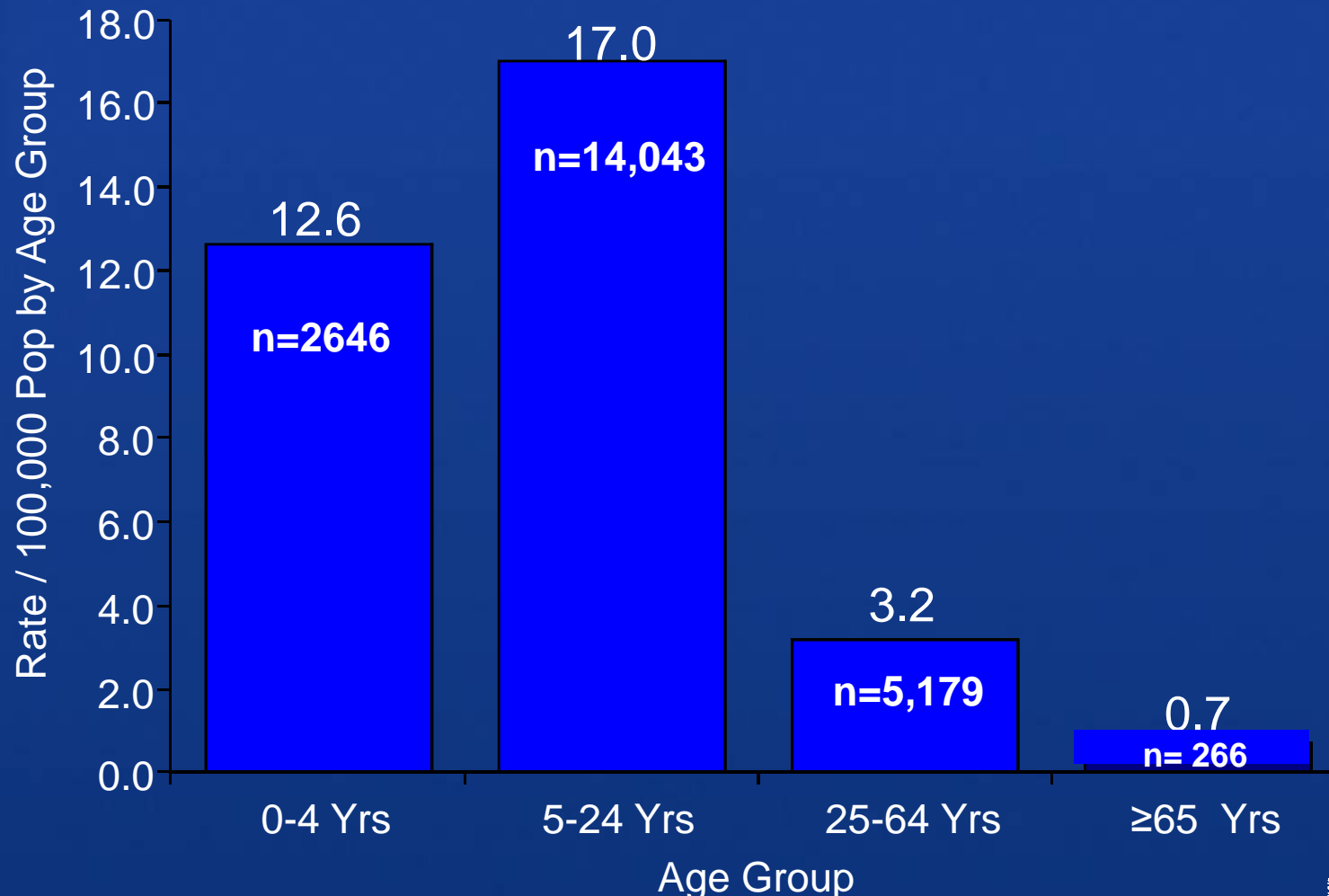
U.S. Cases Reported to CDC

- **Confirmed/Probable** **27,717**
 - Median age: 12 years
- **Hospitalizations*** **3,065**
 - Median age: 20 years
- **Deaths:** **127**
 - Median age: 37 years

*Current priority for testing



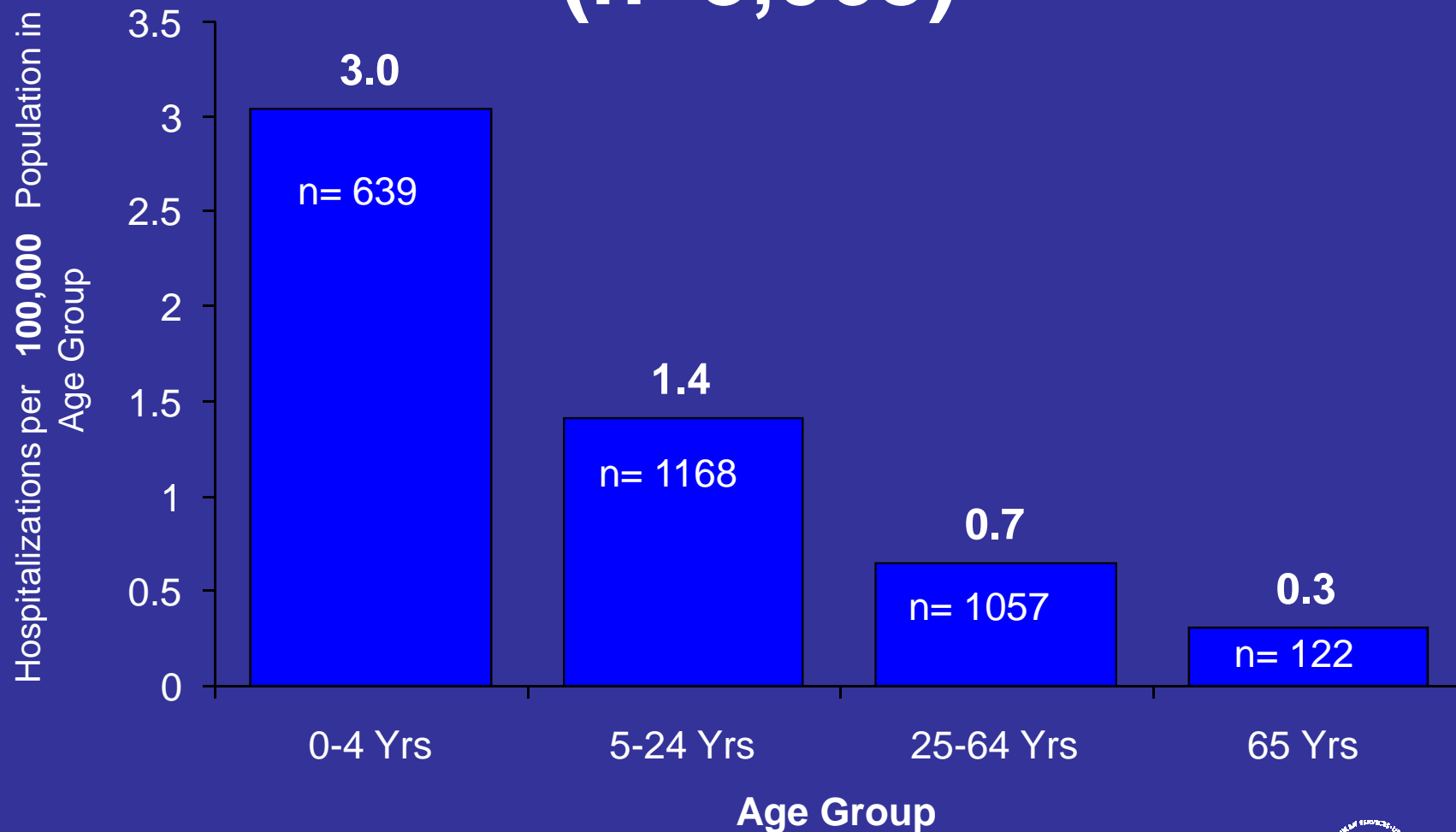
Pandemic H1N1 Case Rate/100,000 population by age group



*Excludes 5,582 cases with missing ages. Rate / 100,000 by Single Year Age Groups: Denominator source: 2008 Census Estimates
U.S. Census Bureau at: <http://www.census.gov/popest/national/asrh/files/NC-EST2007-ALLDATA-R-File24.csv> (n=22,134**)



Pandemic H1N1 Hospitalization Rates* by Age Group (n=3,065)



*Hospitalizations with unknown ages are not included (n=79)

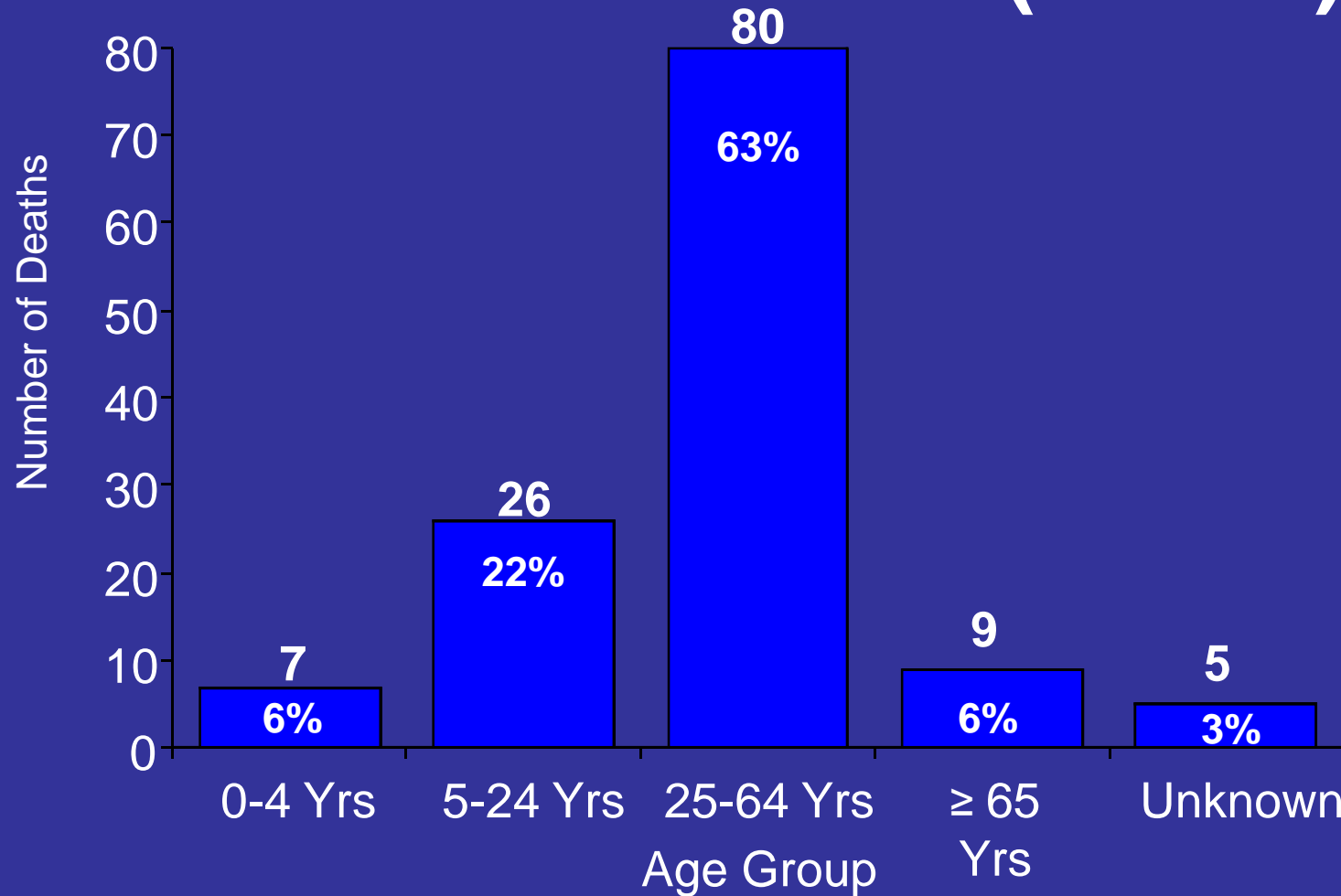
*Rate / 100,000 by Single Year Age Groups: Denominator source: 2008 Census Estimates, U.S. Census Bureau at:

<http://www.census.gov/popest/national/asrh/files/NC-EST2007-ALLDATA-R-File24.csv> as of 25 Jun 2009



Pandemic H1N1 Deaths by Age Group

As of 25 JUN 2009 (n=127)



States:

- AZ - 8
- CA - 16
- CT - 5
- FL - 2
- IL - 12
- MA - 1
- MD - 1
- MI - 2
- MN - 1
- MO - 1
- NJ - 6
- NY - 35
- OK - 1
- OR - 3
- PA - 3
- RI - 1
- TX - 10
- UT - 10
- VA - 1
- WA - 3
- WI - 4



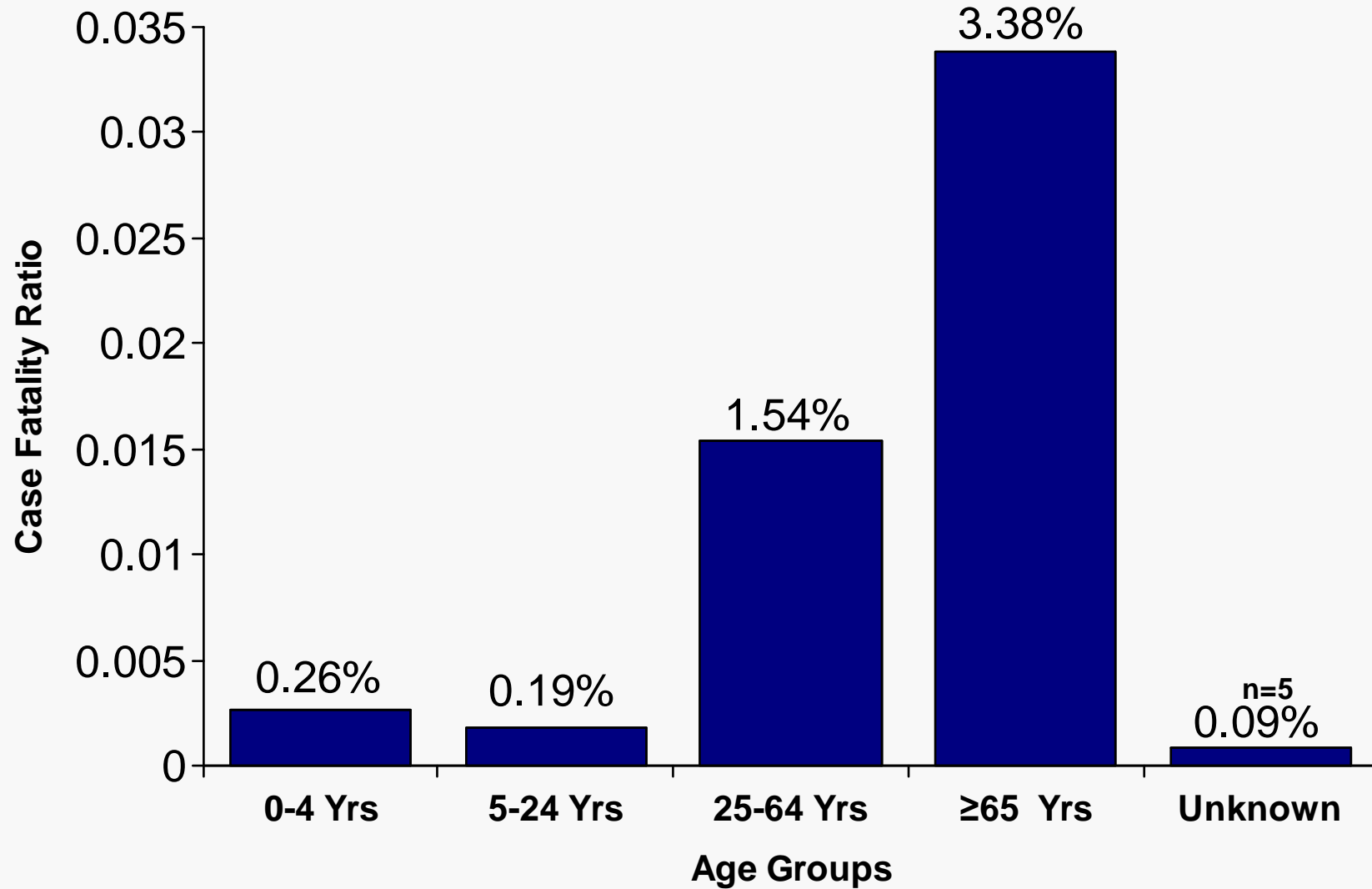
<>Data are provisional and will not be officially released by the CDC until 1100 EDT <>

Internal Use Only (FIUO)---For Official Use Only (FOUO) NOT FOR FURTHER DISTRIBUTION -Sensitive But Unclassified (SBU)



Pandemic H1N1 Case Fatality Proportion by Age Group

Data reported as of 18 JUN 2009 (n=87)



Serologic Investigations

- Pre and Post vaccination sera evaluated
- Microneutralization (MN) and hemagglutination inhibition (HI) assays performed at CDC
 - Among 79 children (6 months to 9 years), little evidence of preexisting cross-reactive antibodies to novel A/California/04/2009 (H1N1) virus
 - Sera from persons >60 years old had some cross-reactive antibodies against novel H1N1
 - Suggests some immunity for infection/illness in older persons, but not <60 years



Katz J et al MMWR May 21, 2009



Transmission Dynamics (U.S.)

- **Secondary attack rate in household contacts:**
 - Acute respiratory illness: 19%
 - Influenza-like illness: 8-12%
 - Higher attack rates observed in schools
- **Serial interval:**
 - Acute respiratory illness: 2.0-3.1 days
 - Influenza-like illness: 2.4-3.1 days
- **Estimated $R_0 = 1.4-1.7$**



Pandemic H1N1 Diagnostic Testing of Respiratory Specimens

- Best respiratory specimen to detect pandemic H1N1 virus infection: not yet known
 - Nasopharyngeal (swab, aspirate)
 - Nasal swab
 - Throat swab
 - Combined specimens
 - Lower respiratory tract specimens (intubated patients)



Pandemic H1N1 Diagnostic Testing of Respiratory Specimens

- **Antigen Detection**

- **Rapid influenza diagnostic tests**

- Sensitivity: 51% (compared to rRT-PCR, QuickVue Influenza A+B)*
 - Sensitivity: 10-40% (compared to Luminex PCR, Binax NOW, 3MA+B)**
 - Cannot distinguish between seasonal influenza or pandemic H1N1 virus infection
 - Positive and Negative results need interpretation

- **Immunofluorescence**

- Sensitivity: 47%** (compared to Luminex PCR Resp Viral Panel)
 - Cannot distinguish between seasonal influenza or pandemic H1N1 virus infection
 - Positive and Negative results need interpretation



*Faix et al., NEJM 2009; **Ginocchio JC Virol 2009

Pandemic H1N1 Diagnostic Testing Respiratory Specimens

- **Detection of viral RNA (preferred method)**
 - **Real-time reverse transcription polymerase chain reaction (rRT-PCR)**
 - Highest sensitivity, highly specific
 - CDC primer-probes for specific detection of pandemic H1N1 distributed throughout the U.S and worldwide
 - Use of seasonal influenza primer-probes will be positive for influenza A, but negative for seasonal H1, H3 subtypes
 - **Isolation of virus**
 - **Viral tissue cell culture**
 - High sensitivity, highly specific



Clinical Spectrum of Influenza Virus Infection

- **Asymptomatic infection:**
 - Occurs with seasonal influenza virus infection
 - Serological investigations pending
- **Uncomplicated mild-moderate illness**
 - Upper respiratory tract symptoms without fever
 - Influenza-like illness (ILI)
 - Fever, headache, non productive cough, rhinorrhea, sore throat, myalgias
 - ILI with vomiting, diarrhea
 - More frequent than with seasonal influenza



Clinical Spectrum of Influenza Virus Infection

Seasonal Influenza - Expect with Pandemic H1N1

- **Mild to moderate complications:**
 - Otitis media, sinusitis, bronchitis
- **Moderate to severe complications:**
 - Exacerbation of chronic illness (e.g. cardiac, pulmonary)
 - Lower respiratory tract disease
 - Pneumonia (viral, bacterial co-infection)
 - Bronchiolitis, croup
 - Cardiac: myocarditis
 - Musculoskeletal: myositis, rhabdomyolysis
 - Neurologic: encephalopathy, encephalitis
 - Toxic shock syndrome
 - Severe dehydration



CRX Findings at Admission

- Evidence of pneumonia in 40-50% cases
- Bilateral or unilateral infiltrates
- Patchy, diffuse, alveolar, interstitial infiltrates
- Multilobar or single lobe involved



Hospitalized Pandemic H1N1 Cases, U.S.

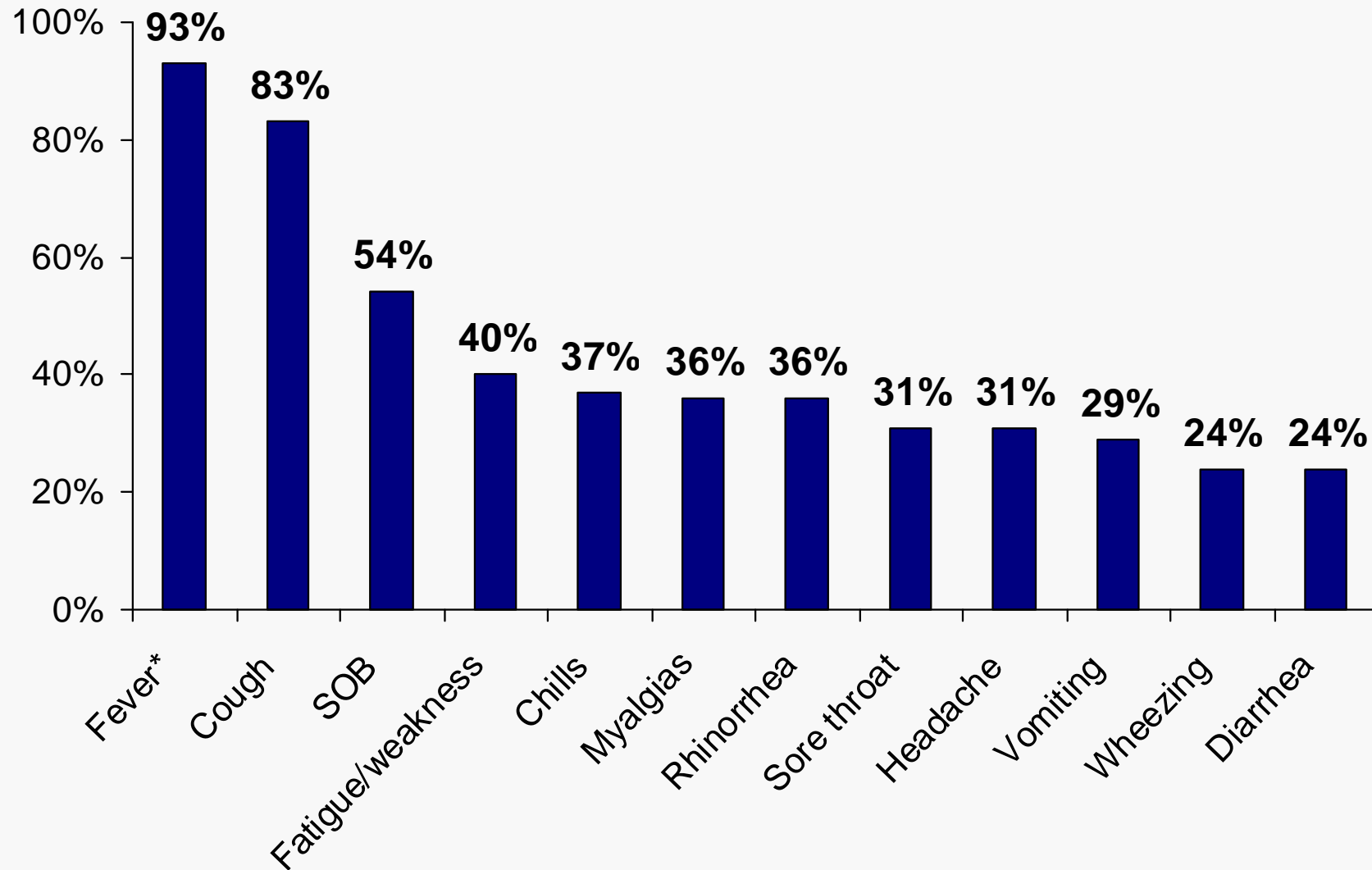
(N = 268)

- Median time from onset to admission
 - **3 days (range 1-14 days)**
- Median length of stay
 - **3 days (range 1-59)**
- Median age
 - **22 years (range 21 days-86 years)**
- 128 female (48%), 140 male (52%)
- **71% with underlying co-morbidities**
- 21% admitted to ICU
- 13% required mechanical ventilation
- 17 deaths (6.3%)





Pandemic H1N1 Hospitalizations Reported to CDC Clinical Characteristics at Admission (n=268)

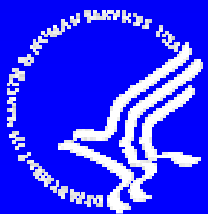


as of 19 JUN 2009

Novel Influenza A (H1N1) Hospitalizations, U.S. (n=268)

- Median age: 22 years (range 21 days-86 years)

Age Groups	Hospitalized No. (%)
0-23 months	24 (9)
2-4 years	20 (8)
5-9 years	28 (10)
10-17 years	55 (20)
18-49 years	95 (35)
50-64 years	31 (12)
≥65 years	15 (6)



Underlying Conditions among 268 Hospitalized Patients With Novel Influenza A (H1N1) Reported to CDC Compared to US Prevalence

Condition	Prevalence, hospitalized H1N1 patients	Prevalence, General US Population
Asthma or COPD	32%	8% (asthma) 4% (COPD)
Diabetes	15%	6%
Immunocompromised	13%	
Chronic cardiovascular disease*	14%	7%
Current Smoker	10%	18%
Chronic Renal Disease	9%	17%
Neurocognitive disorder	7%	
Neuromuscular disorder	7%	0.03%
Pregnant	6%	1%
Seizure disorder	6%	1%
Cancer	3%	4%
Obesity	8%	27%

*Excludes hypertension



Pandemic (H1N1) Deaths Reported to CDC by States as of 25 JUN 2009

- **Limited data available on 99/111 deaths in 20 states**
- **49 Female (53%), 44 Male (47%)**
- **Median time from illness onset to death**
 - **7.5 days (range 0 - 40 days)**



Pandemic (H1N1) Deaths Reported to CDC by States (24 JUN 2009)

- N=87
- Median age: 37 years (range 2 months-72 years)

Age Group	No. (%)
0-23 months	5 (6%)
2-4 Yrs	0 (0%)
5-9 Yrs	7 (8%)
10-17 Yrs	10 (11%)
18-29 Yrs	11 (13%)
30-49 Yrs	35 (40%)
50-64 Yrs	18 (21%)
≥65 Yrs	1 (1%)



Pandemic (H1N1) Deaths Reported to CDC by States as of 25 JUN 2009 (n=99)

- 12 (12%) persons with **no** underlying conditions
- **82% with underlying conditions** - may overlap for individual cases

Condition	Percent Deceased Cases with Condition
Asthma	11%
Other Pulmonary disease	24%
Diabetes	13%
Chronic cardiovascular disease	14%
Neurocognitive disorder	15%
Neuromuscular disorder	11%
Pregnant	8%
Seizure disorder	7%
Morbid obesity	11%
Obesity	34%
Other serious (hepatic, cancer, immunosuppressed)	13%

Possible Pathogenesis in Severe Disease

- **Unknown to date - data needed**
- **Fulminant pneumonia**
 - **Suggests viral infection of lower respiratory tract**
 - **Possible high viral replication triggering cytokine dysregulation (similar to highly pathogenic avian influenza H5N1 virus infection?)**
 - **Acute lung injury, rapid progression to ARDS**
 - **Refractory ARDS**
 - **Invasive bacterial co-infection**
 - **Multi-organ failure, septic shock**
 - **Muscle inflammation**
 - **Potential for extrapulmonary dissemination**
 - **Viremia, fecal shedding, etc.**



Clinical Management*

- **Early antiviral treatment with neuraminidase inhibitors (Oseltamivir, Zanamivir)**
- **Oxygen therapy - ensure adequate oxygenation**
- **Advanced respiratory support - mechanical ventilation - follow guidelines for sepsis-associated ARDS**
- **Antibiotic treatment following evidence-based guidance for community-acquired pneumonia**
- **Corticosteroids: no routine use**
 - **Low dose for septic shock requiring vasopressors and have adrenal insufficiency**
- **No aspirin or aspirin-containing products for <18 years**



*WHO Clinical Management Guidance May 2009



Infection Control

- **WHO Guidance**
 - Isolation of patients
 - Standard, Droplet precautions
 - Aerosol-generating procedures
 - N95 or FFP2 respirator, eye protection, gowns, gloves, airborne precaution room with natural or mechanically ventilation per WHO guidance
- **CDC Guidance**
 - Isolation of patients
 - Standard, Droplet, Eye precautions, fit-tested N95 respirator, gowns, gloves, when providing care
 - Aerosol-generating procedures - negative pressure room



Summary

- Most pandemic H1N1 disease is mild-to moderate self-limited influenza-like illness
- Severe and fatal disease has occurred, and will continue to occur
 - Expect a wide range of clinical syndromes, not just pneumonia cases
- Hospitalizations and deaths have occurred in children and adults <65 years old
 - Most have had underlying co-morbidities
- Data on severe disease pathogenesis are needed
- Clinical and virological data are needed to inform clinical guidance **{we need to learn together!}**



Thank you for your attention!

