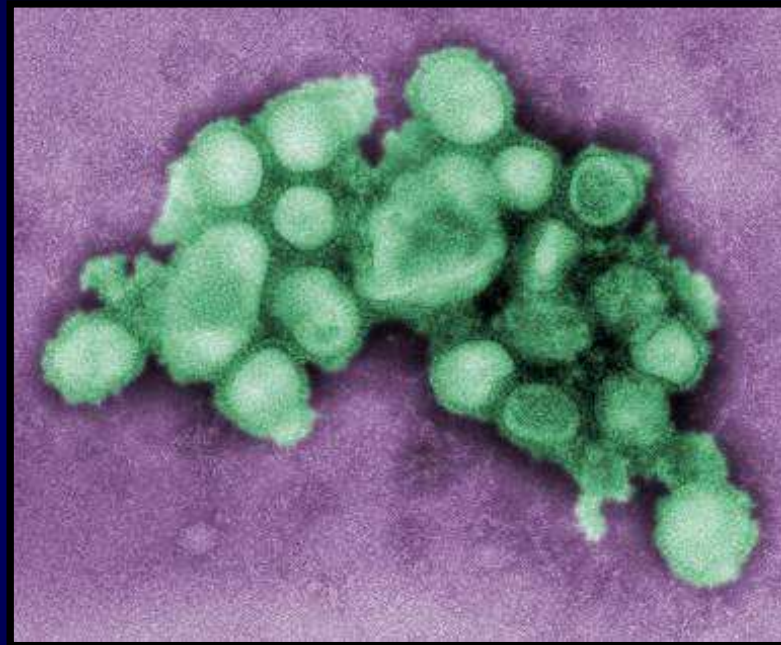


Clinical Issues

Pandemic Influenza A (H1N1) Virus Infection



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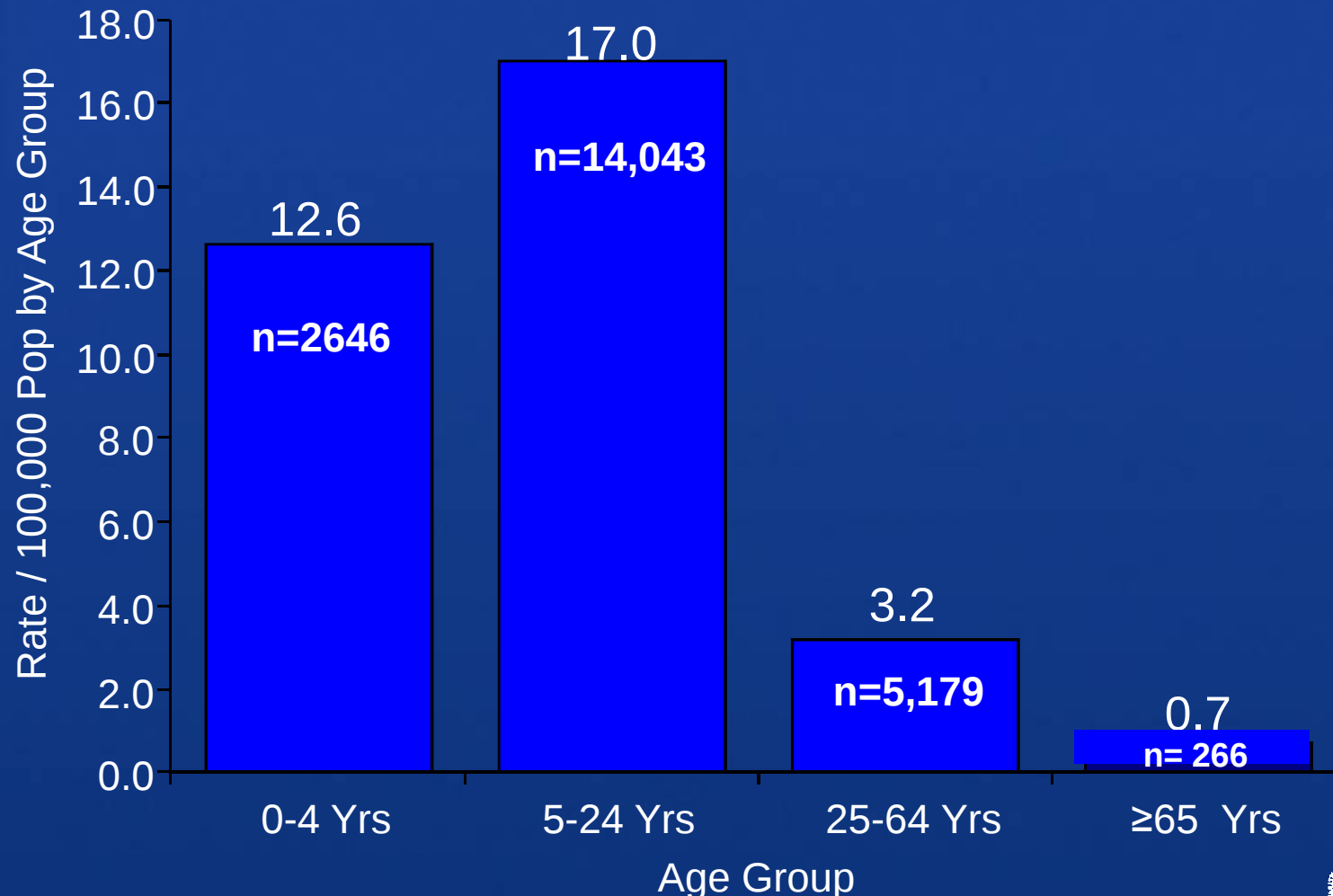


www.pandemicflu.gov

www.cdc.gov/flu



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

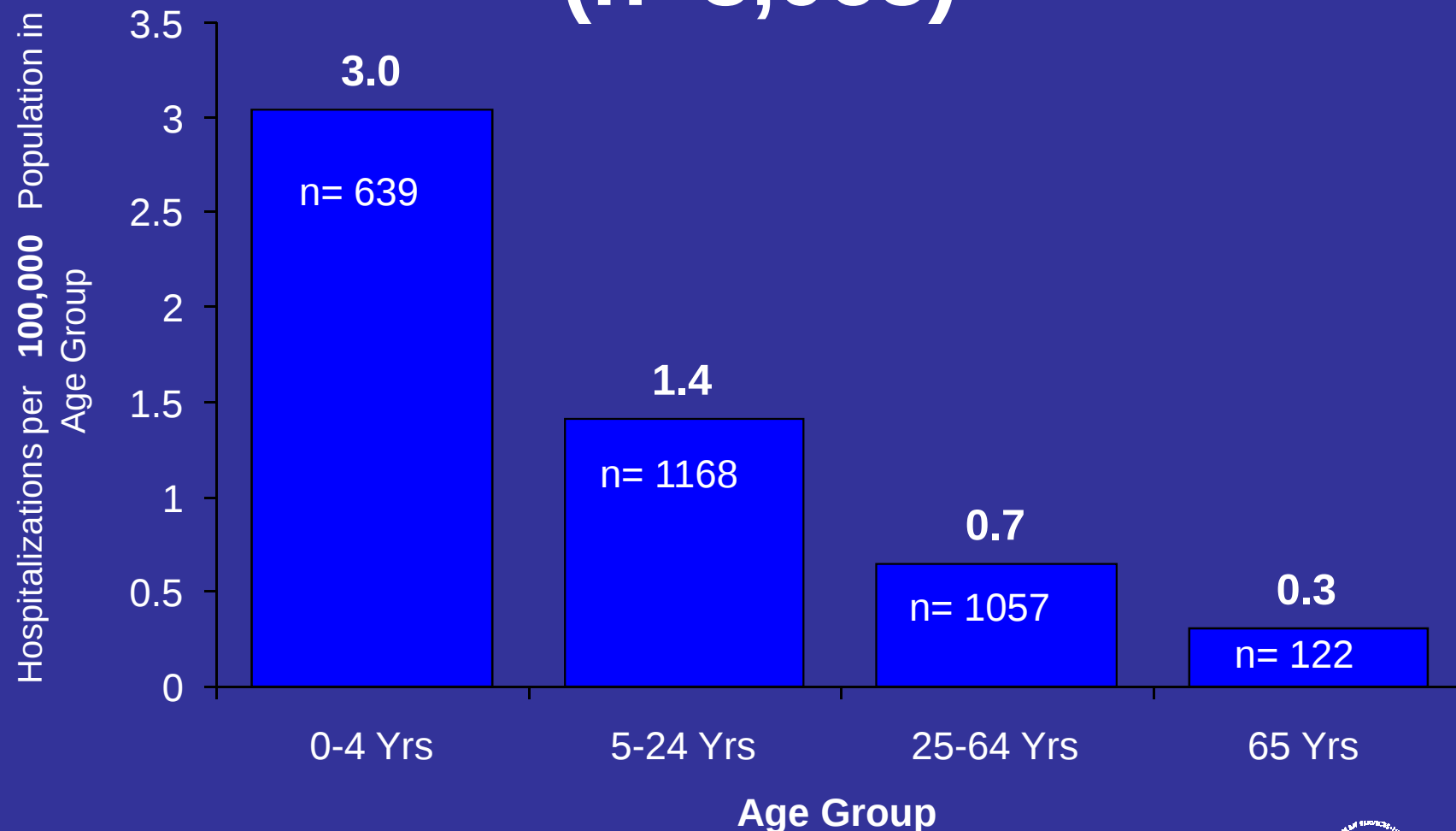


*Excludes 5,582 cases with missing ages. Rate / 100,000 by Single Year Age Groups: Denominator source: 2008 Census Estimates

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)



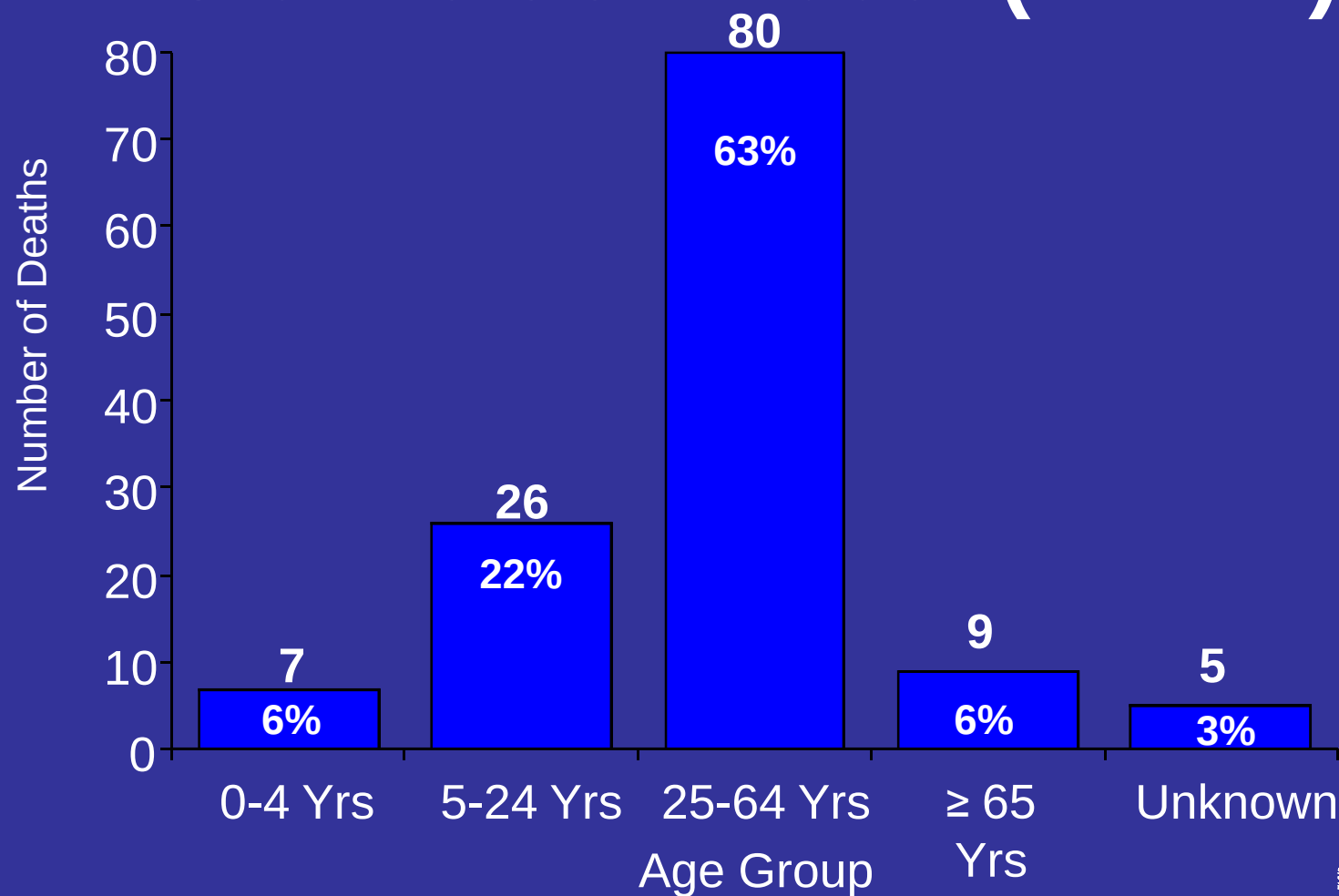
*Hospitalizations with unknown ages are not included (n=79)

*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)

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 $R_0 = 1.4-1.7$



Diagnostic Testing of Respiratory Specimens

- **Antigen detection misses many infections**
 - Rapid diagnostic tests: Sensitivity: 10-51%
 - Immunofluorescence: Sensitivity: 47%
 - Cannot distinguish between seasonal influenza or pandemic H1N1 virus infection
 - Positive and Negative results need interpretation
- **Detection of viral RNA (preferred method)**
 - **Real-time reverse transcription polymerase chain reaction (rRT-PCR) using specific primers, probes against pandemic H1N1 virus**
- **Isolation of virus**
 - Important for virologic analyses, surveillance, viral shedding studies (viable virus)



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



Clinical Spectrum of Pandemic H1N1 Virus Infection

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



Clinical Spectrum of Pandemic H1N1 Virus Infection Observed or Expected

- **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)
 - Rapid progression to respiratory failure, ARDS
 - Cardiac: myocarditis
 - Musculoskeletal: myositis, rhabdomyolysis
 - Neurologic: encephalopathy, encephalitis
 - Severe dehydration



Hospitalized Pandemic H1N1 Cases, U.S.

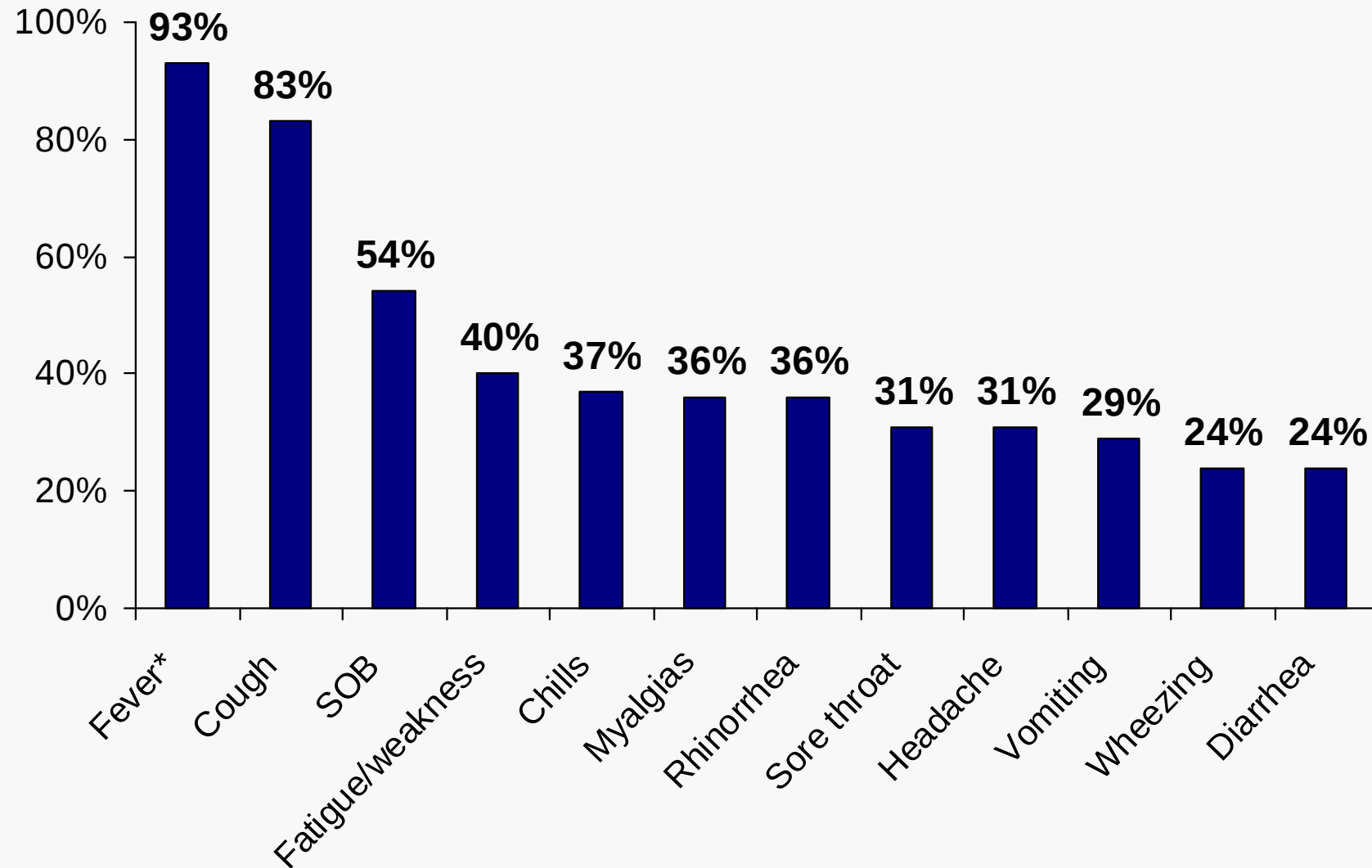
(N = 268)

- 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)

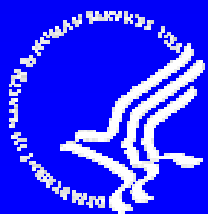


as of 19 JUN 2009

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

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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

- **Limited human and animal model data**
- **Rapid progression of 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 observed**
- **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); treatment of hospitalized and high-risk;
 - **Consider higher dosing, longer duration of treatment for severely ill**
 - **Pandemic H1N1 virus resistant to amantadine, rimantadine**
 - **Three reports of Oseltamivir-resistance in pandemic H1N1**
- **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 with adrenal insuff
- No aspirin or aspirin-containing products for <18 years



*WHO Clinical Management Guidance May 2009



Summary

- Most pandemic H1N1 disease is mild-to moderate self-limited influenza-like illness
- Severe and fatal disease has occurred
 - Median age of fatal cases older than in hospitalized cases
 - Expect a wide range of clinical syndromes, not just pneumonia cases
 - Most hospitalizations and deaths have occurred in children and adults <60 years old
 - Most have had underlying co-morbidities
- Clinical and virological data are needed to inform clinical treatment **{we need to learn together!}**
 - **Many unanswered questions**



Thank you for your attention!

