Clinical Lessons Learned During the H1N1 Pandemic

Jonathan A. McCullers, M.D.
Associate Member
Department of Infectious Diseases
St. Jude Children’s Research Hospital
Memphis, Tennessee
The ecology of influenza viruses
Timeline of viruses in humans and pigs


- H1N1
- H3N2
- H2N2
- H1N2
- H1N1
- Novel H1N1
Emergence of a pandemic strain

“Triple reassortant” novel pandemic H1N1 influenza virus
Pandemics in the last century

1918 – fully avian H1N1 virus enters humans and pigs simultaneously, 40-50 million deaths worldwide, endemic in pigs

1957 – reassortant virus takes H2N2 surface proteins and PB1 from avian sources, other genes from human H1N1, ~ 2 million deaths worldwide

1968 – reassortant virus takes H3 and PB1 from avian sources, other genes from human H2N2, ~ 1 million deaths worldwide

[1977 – H1N1 related to 1950 strain “re-emerges” from frozen source, has circulated together with H3N2 since]

2009 – “triple” reassortant H1N1 emerges from pigs, “novel H1N1”
Clinical features of influenza

- Sudden onset of symptoms

- Incubation period 1 to 7 days, typically 2-3 days

- Infectious period varies by age:
  - Adults shed virus typically 1 day before through 4-5 days after onset of symptoms
  - Children shed virus longer, typically 2-3 days before (and up to 6) through 7-10 days (and up to 21) after onset of symptoms

Clinical manifestations of influenza

<table>
<thead>
<tr>
<th></th>
<th>Infants</th>
<th>Children</th>
<th>Adults</th>
<th>Novel H1N1 *</th>
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</thead>
<tbody>
<tr>
<td>Fever</td>
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<tr>
<td>Cough</td>
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<td>Myalgias</td>
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<td>Sore throat</td>
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<td>Headache</td>
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<td>Diarrhea</td>
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<tr>
<td>Vomiting</td>
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<td>Rhinitis</td>
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<td>Malaise / lethargy</td>
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<td>Neurologic symptoms</td>
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</tbody>
</table>

- rare, + uncommon, ++ common, +++ very common

*Represents children and adult data combined

Each episode of influenza may result in:

- **7 to 15 days** of illness
- **5 to 6 days** of restricted activity
- **3 to 4 days** of bed rest
- **3 days** of missed work or school

Toll of disease from influenza in the U.S.

Deaths:
~41,000¹ (primarily in the elderly)

Hospitalizations:
~334,000¹

Physician visits:
~31 million¹

Infections and illnesses*:
~95 million²

Economic costs:
~$87.1 billion¹

Complications occur at extremes of age

Hospitalizations per 100,000 persons

Age in Years

MMWR 2001, 50:RR4
Patient groups at risk for complications

- Children < 2 years old

ACIP, MMWR, 2007;56:1-54.
Patient groups at risk for complications

- Children < 2 years old
- Children and adults with chronic conditions
  - chronic pulmonary, renal, metabolic, or CV disorders
  - neurological or neuromuscular disorders
  - hemoglobinopathies
  - immunosuppression, including HIV infection

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- Persons > 50 years of age

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- Pregnant women
- Persons > 50 years of age
- Residents of chronic care facilities

ACIP, MMWR, 2007;56:1-54.
ACIP vaccination recommendations

- Universal vaccination now recommended in the US

- Mandatory vaccination of health care workers should be strongly considered

Influenza is a disease of children

Monto & Sullivan, Epidemiol Infect 1993;110:145-60
Burden for school-aged children

- For every 1000 children influenza accounts for an estimated:
  - 280 primary illness episodes, 220 secondary
  - 630 missed school days, 200 days missed work
  - 50-95 outpatient clinic visits
  - 0.9 hospitalizations

- 10-20% of outpatient clinic visits are due to influenza at peak times of circulation

- CDC began collecting data on pediatric influenza-related deaths in 2003-2004

- 153 influenza-associated deaths among children <18 yo reported to CDC from 9/03 to 5/04 (46-74 last 3 yrs)
  - 37% of the children were 5 to 17 years of age
  - 47% of the children had no high-risk medical conditions (only 33% had an ACIP-defined high risk condition)
  - 24% died from secondary bacterial infections

Children transmit influenza

Other children ↔ Family members

Daycare, preschool, and school-age children

Community including high risk populations

Mortality

Naïve immune systems = Higher replication = Increased transmission
Age Distribution of 2009 H1N1

Reichert TA.....McCullers JA. BMC Inf Dis 2010.
Rationale for universal vaccination

- Influenza is a vaccine-preventable disease
  - influenza has not been brought under control using strategies targeting high risk groups alone
  - healthy school-age children are often major transmitters of influenza
  - substantial morbidity and some mortality in children
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Broader vaccination strategies are expected to reduce influenza morbidity and mortality. Increased vaccination of preschool and school-age children may provide benefits to their close contacts and the community at large.

Rationale for universal vaccination
HA (hemagglutinin)
NA (neuraminidase)
M1 (matrix protein)
M2 (ion channel)
NP (nucleoprotein)
RNA (negative sense)
Polymerase complex (PA, PB1, PB2)
Lipid envelope (host-derived)

Non-structural proteins
- NS1
- NEP
- PB1-F2

RNP Complex

11 proteins on 8 (-) strand RNA gene segments
(≈ 14 kb)
Antivirals for influenza

M2 inhibitors
- block the M2 ion channel preventing viral uncoating
- Amantadine (Symmetrel) and Rimantadine (Flumadine)
- problems with resistance and side effects

Neuraminidase inhibitors
- block the neuraminidase enzyme and prevent viral budding and spread through the respiratory tract
- Zanamivir (Relenza) and Oseltamivir (Tamiflu)
- may prevent secondary bacterial pneumonia and otitis media

Antivirals for influenza

- Significant resistance to M2 inhibitors last several years (> 95% of all strains)

- Little resistance to oseltamivir now seen in the US

- There have been post-marketing reports of children taking oseltamivir having delirium and abnormal behavior, sometimes leading to injury, but unclear if from influenza itself or the drug - FDA has recommended child warning label disclosing this
Treatment of novel H1N1

- Novel H1N1 viruses are susceptible to neuraminidase inhibitors (NAIs; oseltamivir, zanamivir) but resistant to adamantanes (amantadine, rimantadine) – limited published experience with treatment outcomes

- Prophylaxis has been undertaken with NAIs to prevent spread to close contacts

- Development of resistance in this clinical scenario has been documented (H275Y mutation), but these strains have not spread widely

WHO
Diagnosis of novel H1N1

- Currently used antigen tests have 40-60% sensitivity for novel H1N1 compared to RT-PCR

- Most available RT-PCR assays cannot distinguish novel H1N1 from seasonal strains

- Targeted antiviral use will require development and widespread utilization of PCR based assays that can distinguish type (A vs. B), subtype (H3N2 vs. H1N1), and strain (seasonal vs. pandemic)

- Sequencing based methods for rapid antiviral resistance determination could also be employed

MMWR 2009 / 58(30);826-829
Risk factors for severe disease

- Overall, similar to risk factors for seasonal influenza

- Chronic medical conditions including cardiopulmonary disease and immunosuppression

- Pregnancy

- Neurodevelopmental delay

- Obesity (this is not recognized as a risk factor for seasonal influenza)

- Extremes of age have not been a risk factor for novel H1N1
Complications of novel H1N1

- Viral pneumonia – most common cause of death
- Most severe disease in persons with no underlying risk factors has been in older children and young adults – immunopathology?
- Bacterial super-infections – otitis media, pneumonia, sinusitis – are being found more commonly with novel H1N1

- Few reports of bacterial superinfections in initial descriptions of severe pandemic related disease

- However, most critically ill patients were treated with broad spectrum antibiotics, and invasive assays (e.g., pleural taps) were not commonly done

- Several pathology series have shown 30-50% of all fatal cases had evidence of bacterial super-infection (S. aureus, S. pneumoniae, Group A Streptococcus)

- All vaccines are trivalent and contain the same strains
  - vaccine composition provides protection from the 3 most likely wild-type virus infection in a given year
  - vaccine strains are A (H3N2), A (H1N1), and B
  - usually 1 or 2 vaccine strains are changed annually
- Recommendations are based on previous circulation patterns, expert opinion, and last decade experience

**Annual influenza vaccine composition**

- Influenza type: A
- Isolate number: Fujian/411/2002
- Year of isolation: 2002
- Hemagglutinin subtype: H3N2
- Geographic source
- Neuraminidase subtype: \( \backslash \)

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Vaccines against H1N1 influenza

- Standard vaccines targeting H1N1 were made and tested by same process we use every year

- The vaccines were extremely safe and no problems were reported

- Although plenty of vaccine was made, distribution problems limited access

- Children, young adults, pregnant women, first responders, and persons with chronic illnesses were first priority

- Novel H1N1 has replaced seasonal H1N1 in the trivalent vaccine for 2010-2011
Conclusions

The 2009 H1N1 pandemic shared several common features with past pandemics, it:
- had a high clinical attack rate due to lack of immunity
- transmitted easily enabling worldwide spread
- caused severe disease in some risk groups (but fortunately was milder than was anticipated)

Children occupied a central role in the pandemic:
- highest clinical attack rate
- main vectors of transmission
- most severe disease in patients without chronic medical conditions
Conclusions…continued

- All influenza strains predicted to circulate in the US in 2010-2011 are susceptible to oseltamivir but resistant to adamantanes

- Antigen tests have low sensitivity – only trust PCR

- Universal vaccination is now recommended

- The vaccine is safe and the best means of protection against severe outcomes such as pneumonitis and bacterial pneumonia
THANKS!