H1N1 Clinician Update
September 2009

Paul Lewis, MD
Deputy Tri-county Health Officer
Clackamas, Multnomah, Washington Counties
Desired Outcomes

1. Understand the clinical implications of the H1N1 Influenza pandemic
2. Understand likely H1N1 Influenza scenarios
3. Be aware of the Public Health response
4. Be familiar with protocols and response specific to your organization
5. Have questions answered or acknowledged
Status as of: 23 August 2009

http://gamapserver.who.int/h1n1/cases-deaths/h1n1_casesdeaths.html
WHO VIEW OF H1N1
- Rapid, global, spread April-June 2009
- Declared ‘Pandemic’ June 2009
- Overall severity mild
- Shift in severe disease to younger ages
- Virus susceptible to neuraminidase inhibitor drugs

Likely Origin Winter 2009

Timeline (22 July 2009 onwards)
Pandemic (H1N1) 2009 laboratory confirmed cases
And number of deaths as reported to WHO

Status as of: 23 August 2009

Cumulative deaths
- 1 - 10
- 11 - 50
- 51 - 100
- 101 and more

Country/territory/area with confirmed cases

Chinese Taipei has reported two deaths associated with pandemic (H1N1) 2009.
Lab-confirmed, hospitalized H1N1 symptoms (n=642 USA)

- Fever: 94%
- Cough: 92%
- Sore Throat: 66%
- Diarrhea: 25%
- Vomiting: 25%

Lab findings/complications of H1N1

- WBC
- AST, ALT, CK, creatinine sometimes

Known complications
- respiratory failure
- dehydration
- bacterial pneumonia

Anticipated complications
- cardiac
- neurologic
- systemic

Influenza requiring hospitalization
H1N1 (2009) vs seasonal (07–08)
Influenza requiring hospitalization
H1N1 (2009) vs seasonal (07-08)

H1N1 2009
~40% under 18 years
Median age 20 years
Highest rate < 4 yrs

MMWR August 21, 2009 / Vol. 58
Pandemic H1N1 deaths in younger people, US

Median 37 years

Source Oregon Public Health Division, August 2009
Risk for severe H1N1 disease is (mostly) similar to seasonal flu

- WHO reports minority and indigenous populations at increase risk of severe disease\(^3\)
- 117 (65%) of 179 hospitalized had traditional risk\(^1\)

- Hospital cases in CA\(^2\)
  - Chronic lung 37%
  - Immune 20%
  - Cardiac 17%
  - Obesity 13%
  - Diabetes 13%
  - Pregnant 17%
  - Seizures 10%

\(^1\) http://www.cdc.gov/mmwr/pdf/rr/rr5810.pdf
\(^2\) http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5819a6.htm
\(^3\) http://www.who.int/csr/disease/swineflu/notes/h1n1_second_wave_20090828/en/index.html
H1N1 Deaths under 18 yrs
US, April-August 2009

• 36 (7.5%) of 477 deaths reported
• 24 (67%) of 36 had high-risk condition
  – 22 (92%) of these 24 neurodevelopmental
• 10 (43%) of 36 had bacterial co-infection
• 6(100%) of 6 who lacked high-risk and
  were >5 yrs had bacterial co-infection
  – S. pyogenes, S. pneumoniae, S. aureus
    (mostly MRSA)
H1N1 Clinical Take-home Points

• Typical influenza symptoms, complications
• Most cases recover uneventfully
• Typical risk factors for severe disease
  – Substantial minority without ‘risk factor’
• SHIFT TO YOUNGER AGES FOR HOSPITALIZATION AND DEATH
• Anticipate acute care, ED, ICU surge in demand
• Understand your organization’s protocols
• Anticipate concern among the well and mildly ill
Generation of New Influenza A Virus Subtypes with Pandemic Potential

Gene Segments, Hosts, and Years of Introduction

- PB2, PA → ~1998 → PB2, PA
- PB1 → ~1968 → ~1998 → PB1
- HA, NP, NS → ~1918 → HA, NP, NS
- NA, M → ~1979 → NA, M

Triple Reassortant

Classical Swine

Eurasian Swine

2009 A(H1N1)
Take-home Points H1N1 Biology

• New virus to humans 2009
  – Genetically stable so far
  – Those under 65 yrs have little immunity
  – Currently susceptible to neuraminidase antiviral drugs

• Origin of virus complex
  – Relation to human H1N1 from 1918-1957 may explain observed protection of older folks
  – No known genetic markers for high virulence
Public Health Response

• Objectives
  – Prevent illness and death
  – Gather and share information
  – Ensure access to care for the ill

• Strategies
  – VACCINATION
  – COMMUNICATION
  – ACCESS TO CARE
  – SURVEILLANCE
  – MITIGATION
Regional Health Coordination

• Goal: Consistent health policies and practices in Portland metropolitan area
• Foci:
  – Regional coordination of public health policies, operations protocols, and clinical practice guidelines
  – Regional prioritization of scarce resources
Outline of the Annual Process of Development, Manufacturing, and Distribution of Influenza Vaccine

H1N1 Vaccine Rapidly produced by 5 manufacturers

- Clinical Trials on-going, results Sept/Oct
- Production quantity vaccine October/November
  - 45 million doses initially
  - 20 million doses weekly thereafter
- Distribution via McKesson (up to 90,000 sites nationally)
- Liability protection for producers and dispensers
- Considered simple ‘strain change’ by FDA
- Risk of Guillane-Barre expected to be minimal but surveillance planned
- Can give injectable H1N1 vaccine at same time as seasonal
  - LAIV seasonal and H1N1 must be separated
- Unresolved: Dose (15 vs 30 ug), Doses (1 vs 2)

The NEW ENGLAND JOURNAL OF MEDICINE
ACIP H1N1 2009 Vaccine
Recommendations
(not in order of priority)

- Pregnant women
- Live with or care for infants < 6 mo old
- Healthcare/EMS with direct contact with patients or infectious material
- Persons 6 mo-24 yrs
- Persons 25-64 yr with high-risk medical conditions

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5810a1.htm
ACIP H1N1 2009 Vaccine Recommendations
(not in order of priority)

• Pregnant women
• Live with or care for infants < 6 mo old
• Healthcare/EMS with direct contact with patients or infectious material
• Persons 6 mo-24 yrs
• Persons 25-64 yr with high-risk medical conditions

~50% Of USA

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5810a1.htm
Local Vaccination Planning

Unprecedented prevention opportunity

• Identify healthcare vaccination partners* for…
  – Pregnant women
  – Healthcare/EMS personnel
  – Contacts of infants
  – Children < 5yrs
  – Those with high-risk medical conditions who have access to care

• Public vaccinations campaigns to for…
  – K-12
  – Higher education
  – Persons without medical home
  – General public
Communication

• Public Information
  – Regional Public Information Officers collaborating on pre-event education and media response

• Clinician communication
  – Oregon Public Health uses blast fax
  – Medical Society of Metropolitan Portland is surveying clinicians for their preference (email, fax, US mail, direct to website)
  – What do you prefer?
Vaccine Recommendations

if initial supply inadequate

- Pregnant women
- Live with or care for infants < 6 mo old
- Healthcare/EMS with direct contact with patients or infectious material
- Kids 6 mo-4 yrs
- Kids 5 yr-18 yr with high-risk medical conditions

Defer if initial supplies inadequate

- Persons 5 -24 years
- Persons 19-64 years with high-risk medical conditions
Antiviral Drugs for H1N1 (2009)

- Initial H1N1 isolates susceptible to neuraminidase inhibitors, resistant to adamantanes
  - Drugs effective in RCTs for seasonal influenza
  - Few side effects
  - Little value after 36-48 hours after symptom onset
  - 8 reports of NI resistance in H1N1 as of August 2009, mostly in prophylaxis recipients

- Availability
  - Commercial
  - Strategic National Stockpile (80 million treatments for US; ~550,000 for Oregon)

- Distribution? TBA

- Strategy for use
  - Treatment >> prophylaxis
Neuraminidase Inhibitor Mechanism
Impact of Time from Symptom Onset on Oseltamivir Treatment Outcomes

Analysis of 10 Oseltamivir Placebo controlled blinded randomized trials
(3564 subjects, age range 13-97 yr) Kaiser Arch Int Med 2003

• Outcomes
  – LRT infection requiring antibiotics occurring >48 hrs after study rx began
  – Hospitalization, URT complications, overall antibiotic use

• Among subjects infected with influenza
  – Matched well for age (median 44 placebo, 40 oseltamivir), gender, influenza type, duration of illness before medication (24 hrs)
  – More placebo recipients were elderly or chronically ill (38% vs 27%, p<<0.01 noted only in text!)
## Confirmed Flu Antibiotic Use

<table>
<thead>
<tr>
<th>LRTC</th>
<th>Placebo N=1063</th>
<th>Oselt N=1350</th>
<th>Placebo N=662</th>
<th>Oselt N=982</th>
<th>Placebo N=401</th>
<th>Oselt N=368</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>10.3%</td>
<td>4.6%</td>
<td>5.3%</td>
<td>1.7%</td>
<td>18.5%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Bronc</td>
<td>8.2%</td>
<td>3.9%</td>
<td>3.8%</td>
<td>1.5%</td>
<td>15.5%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Pnx</td>
<td>1.8%</td>
<td>0.7%</td>
<td>1.4%</td>
<td>0.2%</td>
<td>2.5%</td>
<td>1.9%</td>
</tr>
</tbody>
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All p<0.001 comparing Placebo:Oseltamivir
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<tr>
<td>All</td>
<td>18</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Bronc</td>
<td>23</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Pnx</td>
<td>91</td>
<td>83</td>
<td></td>
<td></td>
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<td>166</td>
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### Confirmed Flu Hospitalization

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</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>18(1.7%)</td>
<td>9(0.7%)</td>
<td>5(0.8%)</td>
<td>3(0.3%)</td>
<td>13(3.2%)</td>
<td>6(1.6%)</td>
</tr>
<tr>
<td>At Risk</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ILI related</td>
<td>12(1.1%)</td>
<td>6(0.4%)</td>
<td>3(0.5%)</td>
<td>1(0.1%)</td>
<td>9(2.2%)</td>
<td>5(1.4%)</td>
</tr>
<tr>
<td>All cause</td>
<td>18(1.7%)</td>
<td>9(0.7%)</td>
<td>5(0.8%)</td>
<td>3(0.3%)</td>
<td>13(3.2%)</td>
<td>6(1.6%)</td>
</tr>
</tbody>
</table>

**P=0.02**

**P=0.17**
Wholesale/Local Health Hybrid Model

Federal SNS

State Warehouse

Wholesale Distributor

Local Health Department Storage

Primary Distribution

Hospitals Retail Pharmacies Institutions

Back-up Distribution

PODS Dispensing Physicians Other

Alternative Distribution
Surveillance

• Focus on severe disease and deaths
  – Use existing systems
  – Hospitalizations – confirmed influenza
    hospitalization is NOW REPORTABLE TO PUBLIC HEALTH
  – Deaths from influenza
  – Voluntary school absenteeism reporting
Oregon Influenza Surveillance, 2008-09

Kaiser ILI* Outpatient visits per 1,000 members (right y-axis)

Outpatient ILI* Surveillance Network Percent patients with ILI* (right y-axis)

Number of Pediatric and Adult Lab-Confirmed Hospitalizations† (left y-axis)

Number of positive flu specimens at OSPHL‡ (left y-axis)

* ILI = influenza-like illness
† Clackamas, Multnomah, and Washington Counties only
‡ Oregon State Public Health Lab
FIGURE 3. Number of influenza viruses identified, by type — New Zealand, week ending May 3 through week ending August 2, 2009

General practitioner sentinel surveillance system*

![Bar chart showing the number of viruses identified by week and type.]

- A (not subtyped)
- B (not typed)
- Seasonal A
- Seasonal A (H3N2)
- Seasonal A (H1N1)
- 2009 pandemic (H1N1)
How bad is it?

July, 2009

‘H1N1 is a new virus, . . . illness may be more severe and widespread as a result.’

July, 2009

“disease is mild in most cases, severe in some and moderate overall” –
US Pandemic Severity Scale

Anticipated range of H1N1 severity during 2009-2010

Case Fatality Ratio

Projected Number of Deaths*
US Population, 2006

Category 5: >2.0% - >1,800,000
Category 4: 1.0 - <2.0% - 900,000 - <1,800,000
Category 3: 0.5 - <1.0% - 450,000 - <900,000
Category 2: 0.1% - <0.5% - 90,000 - <450,000
Category 1: <0.1% - <90,000

Assumes 30% illness rate and unmitigated pandemic without interventions
Mitigation of Pandemic Influenza

- Isolation of ill
- Voluntary quarantine of exposed
- Cancellation of educational classes
- Social distancing of adults
<table>
<thead>
<tr>
<th>Interventions* by Setting</th>
<th>1</th>
<th>2 and 3</th>
<th>4 and 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Home</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voluntary isolation of ill at home (adults and children); combine with use of antiviral treatment as available and indicated</td>
<td>Recommend†‡</td>
<td>Recommend†‡</td>
<td>Recommend†‡</td>
</tr>
<tr>
<td>Voluntary quarantine of household members in homes with ill persons‖ (adults and children); consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient</td>
<td>Generally not recommended</td>
<td>Consider‖</td>
<td>Recommend‖</td>
</tr>
<tr>
<td><strong>School</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child social distancing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- dismissal of students from schools and school based activities, and closure of child care programs</td>
<td>Generally not recommended</td>
<td>Consider: ≤ 4 weeks††</td>
<td>Recommend: ≤ 12 weeks§§</td>
</tr>
<tr>
<td>- reduce out-of-school social contacts and community mixing</td>
<td>Generally not recommended</td>
<td>Consider: ≤ 4 weeks††</td>
<td>Recommend: ≤ 12 weeks§§</td>
</tr>
<tr>
<td><strong>Workplace / Community</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult social distancing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings)</td>
<td>Generally not recommended</td>
<td>Consider</td>
<td>Recommend</td>
</tr>
<tr>
<td>- increase distance between persons (e.g., reduce density in public transit, workplace)</td>
<td>Generally not recommended</td>
<td>Consider</td>
<td>Recommend</td>
</tr>
<tr>
<td>- modify postpone, or cancel selected public gatherings to promote social distance (e.g., postpone indoor stadium events, theatre performances)</td>
<td>Generally not recommended</td>
<td>Consider</td>
<td>Recommend</td>
</tr>
<tr>
<td>- modify work place schedules and practices (e.g., telework, staggered shifts)</td>
<td>Generally not recommended</td>
<td>Consider</td>
<td>Recommend</td>
</tr>
</tbody>
</table>

National Policy
National Public Information
National Guidelines
National assets (vaccine, PPE etc)
Funding for state/local efforts

Statewide policy
Statewide Public Information
State guidelines if different
Statewide resources/assets
Statewide surveillance

Local policies/community stds
Local Public Information
Local resources/access to care
H1N1 vaccination campaigns
Surveillance
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H1N1 Influenza non-Public Health Response

• Continuity of Operations (COOP)
  – How will your organization carry out its critical operations in the face of possible 20-50% peak absenteeism?

• Human Resources Support
  – Are policies and procedures in place to manage absenteeism?
  – Will people be supported in following instructions to “stay home if you’re sick”?
Influenza Virus Nomenclature

Multiple RNA Segments

Type of Nuclear Protein

Hemagglutinin

Neuraminidase

A/USSR/90/77 (H1N1)

Virus Type
Geographic Origin
Strain Number
Year of Isolation
Virus Subtype

NIH web conf
Influenza A viruses in humans this century

H1N1 → H2N2 → H3N2 → H1N1

Spanish Influenza
Asian Influenza
Hong Kong Influenza

1918 ➔ 1957 ➔ 1968 ➔ 1977

Influenza A reservoir

15 HA subtypes
9 NA subtypes
The Two Mechanisms whereby Pandemic Influenza Originates.

Belshe, NEJM 2005
So what is the big deal with a new H1N1; haven’t we seen it before?

- The H1 proteins of 2009 Swine H1N1 and 2009 Human seasonal H1N1 share common ancestors, BUT
- H1N1(Swine) 2009 has changed little in 90 years—’stasis’
- Seasonal H1N1 has drifted far from its origin
How did two H1 proteins become so different?

Change

Continuous Drift

Near ‘stasis’

1920  2009

Time
Antigenic Drift and Shift of H and N

- Drift: continuous small RNA mutations
  - H and N evolve during and between seasons
  - Vaccine requires frequent modification to be effective
  - Over many years a specific H or N-type can become much different from its origin
Antigenic Drift and **Shift** of H an N

- **Drift**: continuous small RNA mutations
- **Shift**: major changes
  - Non-human virus infecting humans
  - Reassortment of RNA segments between human and animal strains
  - Pandemic requirement

Earthquake fault, New Zealand
Health Emergency Management, NZ
Bird, Pig, and Human origin of novel H1N1 Influenza

Note: H1 and N1 Are from north American and Eurasian swine respectively

NEJM July 16, 2009
Duration of infectivity; how long do cases need isolation/furloughs etc

- Duration of shedding unknown for H1N1
- Seasonal flu can be detected shortly before symptom onset to days after resolution
- Children and immune compromised shed longer
- Interim recommendation
  - 7 days for HCW
  - 24 hours after last fever (without anti-pyretics) for others
H1N1 non-Public Health Response

- Can your organization support large scale Public Health operations if needed? (e.g., mass vaccination, flu evaluation centers)
- How will we all maintain good public service and a compassionate perspective in the face of widespread illness?
- How will we emerge with trust in our community intact?
Personal Protective Equipment

**Interim H1N1 Recommendations, Oregon**

- **All patients** → **Standard Precautions**
  - **Direct Patient care**
  - **Proven or suspected influenza** → **Droplet**
    - (surgical mask)
  - **Aerosol-generating procedures**
  - **Proven or suspected influenza** → **Airborne**
    - (N-95 or PAPR)
    - eye protection

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H1N1 vaccination campaigns
Surveillance
Engagement with partners
Testing, Treatment, Infection Control

• Testing
  – Specific H1N1 testing capacity limited and slow
  – Rapid tests have mediocre sensitivity (~40-70%)\(^1\)
  – Clinicians need to make point of care decisions

• Antiviral treatment for high-risk groups
  – Best if started <48 hr after onset
  – Resistance possible if drugs overused
  – Limited prophylaxis indications

• Infection Control
  – Administrative, environmental, personal protection

\(^1\) [http://www.cdc.gov/mmwr/PDF/rr/rr5810.pdf](http://www.cdc.gov/mmwr/PDF/rr/rr5810.pdf)
Antivirals in Children

• Modest RCT efficacy data for oseltamivir similar to adults
  – Shorter illness, fever, OM, antibiotic Rx, viral shedding if started early
  – Few serious adverse events (vomiting 14% in oseltamivir vs 8% placebo)
    • Concern over neuropsych side-effects from Japan
    • Estimated risk 1:10,000 to 1:100,000
  – Use in children < 1 yr covered by FDA emergency use authorization see http://cdc.gov/h1n1flu/recommendations.htm

• Zanamivir also efficacious
  – Caution in those with bronchospasm
H1N1 Infection Control

• Administrative
  – Scheduling, cohorting, respiratory etiquette
  – Furlough for ill health workers - 7 days

• Environmental
  – Clinic set-up
  – Virus can survive for hours on surfaces BUT EASILY KILLED BY SOAP AND DISINFECTANTS

• Personal Protection
  – Hand-hygiene
  – Lack of national consensus on respirators (e.g. N-95, PAPR)
  – Anticipate new CDC recommendations
  October 2009
Insert Organization specific info here

- Testing protocols (rapid vs cx vs PCR)
  - Which patients
  - Turn-around
  - Decision-making
- Institution specific treatment protocols
- Institution specific infection control
- Institution specific incident management structure etc