Influenza: Nomenclature
- Influenza A and B are human pathogens
- Subtypes of Influenza A classified by surface antigens H and N
  - H1N1, H2N3, H2N2
  - H5N1 (avian)
- Scheme used for naming strains
  - A/Sydney/5/93(H1N1)
  - Type/Origin/strain sequence/year/H/N

Influenza: Biology
- Segmented viral RNA – 8 segments
- Infection with one or more different strains (pig, avian, human) leads to new viruses with RNA segments from different sources.
- Hemagglutinin (cell entry) and Neuraminidase (cell escape) are surface antigens.
  - Antibody against these antigens confer immunity.
  - Immunity is short not long lived
  - Mutation in the H and N antigens occurs frequently (antigenic shift and drift)

What is the origin of the new pandemic strain?

Garten RJ et al. Science 2009;325: 197
H1N1 Epidemiology/Incidence

- 8,843 H1N1 influenza hospitalizations in 2009
  - 556 total deaths
- 110 pediatric deaths since Sept. 28, 2008
- 42 pediatric deaths from H1N1 2009
- WHO reports 209,438 lab-confirmed H1N1 cases
  - 2,185 deaths
- Probably undercounts cases 20-50 fold with apparent overestimate of mortality rate
  * CDC August 28, 2009

H1N1 Epidemiology/Outcomes

- Total hospitalizations similar to seasonal flu
- Mortality rate similar to seasonal
- Both seasonal and novel expected to circulate
  - Currently all viruses in US are novel H1N1
  - Some circulation of the seasonal flu in Southern Hemisphere
- No significant mutational change in Southern Hemisphere virus

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[Image of a weekly flu activity map from CDC]

---

[Image of a chart showing number of influenza-associated pediatric deaths]

---

[Image of a chart showing cumulative hospitalization rates]

---

[Image of a chart showing influenza positive tests reported to the CDC by WHO/INREVS Collaborating Laboratories, National Summary, 2008-09]
Transmission of Influenza

- Person to person
- Large droplets fall out within 3 feet
- Fomites persist until drying 8-48 hrs
  - Self-inoculation of conjunctivae and nasal mucosa is efficient
- Incubation Period 18 hrs - 5 days (usually 2-3 days)

Clinical Signs and Symptoms

Clinical Symptoms
- Fever 371/394 (94%)
- Cough 365/397 (92%)
- Sore Throat 242/367 (66%)
- Diarrhea 82/323 (25%)
- Vomiting 74/293 (25%)

- NEJM 360:2605, 2009

Diagnostic Testing for Influenza

- Rapid Antigen Detection Tests on nasopharyngeal secretions are highly specific, but lack sensitivity (30-70%).
- PCR testing is more sensitive (95%) but costly ($100). PCR is a rapid lab test but often 1-5 days if sent to reference lab.

Diagnostic Testing: Conclusions

- No testing of healthy outpatients
- Very selective testing of chronically ill or immune compromised patients. Test only if it will change management
- Seriously ill patients (ICU on ventilator)
- Hospitalized patients if it will change management

Antiviral Susceptibility

<table>
<thead>
<tr>
<th></th>
<th>Amantadine</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
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<tbody>
<tr>
<td>Seasonal A H1N1 -</td>
<td>Susceptible</td>
<td>Resistant</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Novel A H1N1 -</td>
<td>Resistant</td>
<td>Susceptible</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Seasonal A H3N2 -</td>
<td>Resistant</td>
<td>Susceptible</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Seasonal B -</td>
<td>Resistant</td>
<td>Susceptible</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>

Anti-Viral Medication: Who to Treat

- Seriously ill, hospitalized patients
- Patients with serious underlying disorders
- Pregnant women
- Children younger than 2 years
- Treat within 48 hours
- Expense: Treatment of adults for 5 days ~ $100
**Efficacy of Antiviral Treatment in Children**

- Oseltamivir given within 48 hours shortens illness 36 hours, fever 22 hours
  - *Pediatrics* 120:127, 2001
- Zanamivir given within 36 hours shortens illness 1.25 days
  - *Pediatrics* 116:110, 2000
- Retrospective analysis of Oseltamivir treatment of children with various chronic medical conditions 1-17 years reduced hospital admissions, otitis media and respiratory conditions other than pneumonia.
  - Pediatrics 124:170, 2009
- 10 day course of prophylaxis was associated with an 8% decrease in in confirmed symptomatic influenza.
  - NNT =13
  - *BMJ* 339:b3172, 2009

**Anti-Viral Medication: Prophylaxis**

- Household contacts, infants < 6 months
- Pregnant women
- Patients with serious underlying disorders
  - **BUT**…
- How many courses of prophylaxis will we give?
- How many will be exposed multiple times?

**H1N1 Vaccination: An Evolving Picture**

Matthew F. Daley, MD
Assoc. Professor, Pediatrics
University Colorado at Denver
September 16, 2009

Children's Outcomes Research Program
The Children's Hospital, Aurora, Colorado

Department of Pediatrics
University of Colorado Denver
School of Medicine

**Disclosures**

No relevant financial relationships with any commercial interests are present

Novel influenza A (H1N1) vaccine is not currently licensed by the Food and Drug Administration (FDA); therefore this talk will reference the use of medications not currently licensed by the FDA

H1N1 vaccination is a constantly changing topic; all organizations and healthcare providers should seek updated information for as long as H1N1 infections persist in the community

**H1N1 Immunity and Seasonal Influenza Vaccine**

- Limited data from serologic studies indicates seasonal influenza vaccines will not provide protection against novel H1N1 infection
- In persons vaccinated with seasonal vaccine, percent with adequate antibody against H1N1:
  - 18-64 years old: 6-9%
  - >60 years old: 33%
  - Children: 0%


**Influenza A (H1N1) 2009 Monovalent Vaccine**

- H1N1 vaccination likely to be best way to prevent H1N1 infection and its consequences
- H1N1 vaccines being produced using methods similar to those used to make seasonal vaccine
- Licensure based on same standards used for seasonal vaccines

**H1N1 Vaccine**
- Both inactivated (injectable) and live, attenuated (intranasal) H1N1 vaccines will be available
- No adjuvants will be used (no adjuvants in seasonal vaccine either)
- If vaccines with adjuvants are available later in season, will be under different scenario (public health threat; special documentation)


**H1N1 Vaccine Dosing**
- Number of doses required for immunity not known at this time
- Possibly 2 doses will be required
- Whether 1 vs. 2 doses needed may vary by age
- Interval between 1st and 2nd dose not known (range could be >21 days, >28 days, or longer)
- Vaccine should not be “held in reserve” for those needing 2nd doses


**Seasonal and H1N1 Influenza Vaccine: Simultaneous Administration**
- Inactivated (injectable): simultaneous admin. of seasonal and H1N1 vaccines permissible if different anatomic sites used
- Live attenuated (intranasal): simultaneous admin. of seasonal and H1N1 vaccines not recommended
- Give seasonal as soon as available


**Anticipated H1N1 Vaccine Supplies**
- 45-55 million doses by mid-October
- 20 million doses weekly after that
- Up to total of 190 million doses nationwide
- Volume distributed on a proportional basis by state
- However, these estimates based on many assumptions (production, trials, licensure)


**Vaccine Distribution**
- A “blended” model of public and private
- Distribution centralized through vaccine distributors
- Similar to process used to ship vaccines through routine childhood immunization program
- Private providers need to sign up
- Minimum order (~100 doses?)


**Recommendations for H1N1 Vaccine Use**
- ACIP recommends 5 targeted groups for initial H1N1 vaccination, based on risk of complications, or risk of contact and spread
- Targeted groups:
  - Pregnant women
  - Persons caring for infants <6 months of age
  - Healthcare personnel
  - Persons 6 months-24 years of age
  - Persons 25-64 years of age with chronic medical conditions (same definition as used for seasonal)

If H1N1 Vaccine Supplies Initially Limited

- Not anticipated, but may occur if demand exceeds supply
- Targeted while local supplies limited:
  - Pregnant women
  - Persons caring for infants <6 months of age
  - Healthcare personnel with direct patient contact
  - Persons 6 months-4 years of age
  - Persons 5-18 years of age with chronic medical conditions

Expanding Vaccination Efforts

- Decisions should be made at local level
- Once vaccination programs and providers meeting demand for 5 targeted groups
- Expand vaccination to all persons 25-64 years of age
- Local areas can consider vaccinating all persons ≥65 years, after reassessing supply and demand

Financing and Billing

- All H1N1 vaccine will be paid for by the federal government
- Patients/insurers should not be charged for vaccine itself
- Admin. fee can be billed; should be reimbursed at the rate set by Medicare for seasonal influenza vaccine administration
- H1N1-specific vaccination codes have been established (both the vaccine codes, and the administration codes)

Monitoring the Safety of Influenza A (H1N1) 2009 Monovalent Vaccine

Novel H1N1 Influenza Teleconference
September 16, 2009

Simon J Hambidge, MD, PhD
Director, General Pediatrics, Denver Health
Investigator, Vaccine Safety Datalink, Kaiser Colorado
Associate Professor of Pediatrics, University of Colorado School of Medicine

Claudia Vellozzi, MD, MPH
Immunization Safety Office, CDC

Background

- When seasonal influenza vaccines are administered according to licensed indication and usage information they are safe.
- It is anticipated that the safety profile of licensed influenza A (H1N1) 2009 monovalent vaccine (2009 H1N1 vaccine) will be similar to seasonal influenza vaccines.
  - Serious adverse events after vaccination are uncommon.
- Vaccine safety monitoring is an important component of the pandemic (H1N1) 2009 influenza response
Components of H1N1 Vaccine Safety Monitoring

- VAERS
- Vaccine Safety Datalink (VSD)
- Vaccine Analytic Unit
  - Collaboration with DoD/CDC/FDA
  - Utilizes Defense Medical Surveillance System
  - U.S. military personnel (~1.5 million active duty personnel)
- Real Time Immunization Monitoring System
  - Automated web-based active surveillance for certain sub-populations of vaccinees (CDC & Johns Hopkins)
- Other

Using the Vaccine Adverse Event Reporting System (VAERS) during the Pandemic (H1N1) 2009 Influenza Response

Beth Hibbs RN, MPH
Angela Calugar MD, MPH
Immunization Safety Office, CDC

VAERS Background

- US post licensure vaccine safety surveillance
  - Collects voluntary reports of adverse events following immunization
  - Co-managed by CDC and the Food and Drug Administration (FDA)
- Healthcare providers are encouraged to report clinically significant adverse events after vaccination
  - Anyone can submit a report to VAERS
- Receives ~23,000 reports per year (2005-2008 average)
- Data publicly available

VAERS Strengths

- Can detect very rare adverse events
- Generates hypotheses
  - Helps identify new and/or rare adverse events following immunization
  - Helps determine if further investigations are needed
- Monitors trends of already known adverse events
- Monitors vaccine lot safety

VAERS Limitations

- Risk of underreporting
- Stimulated reporting due to media attention and other factors
- Possibly incomplete or inaccurate data on report form
- Lack of availability of denominator data
  - No information on number of persons vaccinated
  - No information on background rates of adverse events in the population
- VAERS generally cannot determine if an adverse event was coincidental or caused by a vaccine

VAERS “Non-Serious” Reports

92% of VAERS reports are “non-serious”

Most frequent adverse events (based on 91,000 VAERS reports received 2005 – 2008):
- Local reactions
- Fever
- Rashes or itching
- Headache
- Dizziness
**VAERS definition of “Serious” Reports***

- Death
- Life-threatening illness
- Hospitalization
- Prolonged existing hospitalization
- Persistent or significant disability
- Certain other medically important conditions

*Code of Federal Regulations Title 21 (21CFR 314.80)

**What to Report to VAERS**

- Report any clinically significant adverse event following immunization ([www.vaers.hhs.gov](http://www.vaers.hhs.gov))
  - Adverse event of concern to the healthcare provider or vaccinee/caregiver or other VAERS reporter
- The National Childhood Vaccine Injury Act of 1986 mandates that healthcare providers report specific adverse events that occur after immunization for some vaccines.
  - Events listed in the vaccine package insert
  - [http://vaers.hhs.gov/pdf/ReportableEventsTable.pdf](http://vaers.hhs.gov/pdf/ReportableEventsTable.pdf)
  - No events are listed in the table for seasonal influenza vaccines
  - The National Childhood Vaccine Injury Act does not apply to 2009 H1N1 vaccines

**What to Report to VAERS (cont.)**

- Submit reports of adverse events, even when not sure whether the vaccine caused the adverse event
- Include as much information as possible in the report (vaccination location, date, vaccine type, lot number and dose number)
  - Reports with incomplete information accepted
- Report as soon as possible but no time limit on reporting

**How to submit a VAERS report:**

1) Online via a secure website at [https://vaers.hhs.gov](https://vaers.hhs.gov)
   Fax a completed form: 877-721-0366
   Mail a completed VAERS form to VAERS, P.O. Box 1100, Rockville, MD, 20849

To request a reporting form or for VAERS assistance: call 800-822-7967 or email: info@vaers.org

**VAERS Follow-up**

- Follow-up conducted for reports of serious adverse events or for vaccines or adverse events designated for enhanced surveillance
  - Medical records
  - Autopsy reports
- Letter sent to reporters to check recovery status for all reports with “no” or “unknown” recovery listed on initial VAERS form (60 days and 1 year)

**Other Safety Monitoring Plans: Enhanced 2009 HINI Vaccine Safety Surveillance System (timely identification and rapid evaluation)**

- Collaboration with the CDC and the FDA to increase the capacity to monitor vaccine safety in real-time
- Link exposure data (vaccine registry data) to outcome data available in large health care plans in selected states
**Other Safety Monitoring Plans:**
- Clinical Immunization Safety Assessment (CISA) Network
  - Collaboration between CDC and 6 academic centers with vaccine safety experts
  - Provide vaccine safety clinical expertise in the evaluation of serious adverse events following 2009 H1N1 vaccination (e.g., assist with review of complex serious cases reported to VAERS)
- Field investigations as needed
  - In collaboration with state/local health departments if CDC assistance is requested

**Vaccine Safety Monitoring in Pregnant Women after 2009 H1N1**
- Rapid Assessment
  - VAERS
  - VSD (selected outcomes)
  - Real-time Immunization Monitoring System
- Prospective study
  - Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) will be used to monitor seasonal and 2009 H1N1 vaccine safety in pregnant women and their infants
  - Office of the Biomedical Advance Research and Development Authority

**Guillain-Barré Syndrome (GBS)**
- Immune-mediated acute demyelinating polyneuropathy affecting the peripheral nervous system
- Estimated annual incidence rate: 1 case per 100,000 population
- In 1976, a type of influenza vaccine was causally associated with GBS (Institute of Medicine)
  - 1 additional case per 100,000 persons vaccinated
- Subsequent studies of influenza vaccines have found small or no increased risk of GBS
  - If there is a risk of GBS from seasonal influenza vaccines, it would be no more than ~1 additional case per million people vaccinated

**GBS Active Case-Finding**
- Emerging Infections Program
  - Active case finding (other adverse events as necessary)
  - Ascertainment of vaccination status
  - Identify risk factors for GBS (e.g., antecedent infection)
  - 10 states
- American Academy of Neurology (AAN)
  - Increase VAERS awareness to enhance GBS reporting
  - Active case finding is an option
- Provisional Brighton Collaboration GBS case definition being used*


**Summary Systems and Strategies for Monitoring 2009 H1N1 Vaccine Safety**

<table>
<thead>
<tr>
<th>Objective</th>
<th>System/Strategy</th>
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<tbody>
<tr>
<td>Timely identification of adverse event</td>
<td>- Vaccine Adverse Event Reporting System (VAERS)</td>
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<td>- Vaccine Safety Datalink (VSD)</td>
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<td></td>
<td>- Vaccine Analytic Unit (VAU)</td>
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<td></td>
<td>- Real time immunization monitoring system (RTIMS) and Enhanced Safety Surveillance System</td>
</tr>
<tr>
<td>Rapid evaluation of serious adverse events</td>
<td>- VSD, VAU, and RTIMS, Enhanced safety surv.</td>
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<tr>
<td></td>
<td>- Clinical Immunization Safety Assessment Network</td>
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<td></td>
<td>- Special studies and field investigations in collaboration with states as indicated</td>
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<tr>
<td>Evaluation of GBS</td>
<td>- Case finding through the Emerging Infections Program and American Academy of Neurology</td>
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<tr>
<td></td>
<td>- VSD</td>
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<tr>
<td>Communication</td>
<td>- Communications materials; partnerships and collaborations</td>
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**Summary 2009 H1N1 Vaccine Safety Monitoring**
- Established vaccine safety infrastructure will be utilized, enhancements planned
- New collaborations being developed
- CDC to provide support to states and territories during 2009 H1N1 vaccination program
- Vaccine risk communication is an important component of the vaccine safety monitoring effort.
Vaccine Safety Risk Communication During the Pandemic (H1N1) 2009 Influenza Response

Abbigail Tumpey, MPH CHES
Assoc. Director for Communications Science
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention

Jason M. Glanz, PhD
Investigator, Vaccine Safety DataLink
Institute for Health Research, Kaiser Colorado

The Landscape
- Concept of being a well educated parent
- Encouraged to be critical consumers of healthcare
- More information than ever available 24/7
- More virtual peer-to-peer interactions
- General distrust of government, pharmaceutical companies, and others
- Healthcare system that might not allow time for communication and relationship-building

Perception of Risk

Less Risk Perceived
- Voluntary
- Personal control
- Familiar
- Natural origin
- Reversible
- Endemic
- Generated by trusted institution

More Risk Perceived
- Involuntary
- Controlled by others
- Exotic
- Manmade
- Permanent
- Epidemic
- Generated by a mistrusted institution

Perceived Safety Concerns: 2009 H1N1 Vaccine
- Vaccine hesitancy driven by safety and disease threat
- Ingredients (e.g., thimerosal)
- Safety testing concerns
- Special populations (e.g., pregnant women, children)
- What is the government doing
- Where to find accurate information

CDC’s Communication Response: Guiding Principles (1)
- Acknowledge uncertainties and the unpredictable nature of influenza, including 2009 H1N1
  - recognize the amount of uncertainty is more than everyone would like
  - trust the public to tolerate incomplete and potentially upsetting information
  - do anticipatory guidance even in the face of uncertainty

CDC’s Communication Response: Guiding Principles (2)
- Share challenges and dilemmas
- Address fears and concerns (vs. attempting to minimize them)
- Maintain transparency and communicate early and frequently
- Utilize multiple channels and partners to increase reach and visibility of recommendations and messages
Available Communication Resources
PandemicFlu.gov
- Crisis & Emergency Risk Communication (CERC) Training – CDC
- Pandemic Influenza Pre-Event Message Maps – CDC
- Effective Media Communication during Public Health Emergencies - WHO
- WHO Outbreak Communications Guidelines
- Communicating in a Crisis: Risk Communication Guidelines for Public Officials - SAMSA

Crisis and Emergency Risk Communications Training
Crisis and Emergency Risk Communication Training
- Module available Online
- In-person trainings
- Web site: http://emergency.cdc.gov/cerc/
- Email: cercinfo@cdc.gov

Lessons Learned from Vaccine Refusing Parents & Their Doctors
- Don’t patronize or act defensively
- Show empathy – acknowledge that parents’ fears are real – do not dismiss them
- Parents want doctors to present both sides – it is important for providers to be honest and describe the risks of vaccination – no medication is 100% safe
- If comfortable, discuss your own children – it’s powerful when concerned parents know you vaccinated your own children
- Don’t just use data, use anecdotes, especially around your own experiences caring for children with vaccine-preventable diseases

Lessons Learned from Vaccine Refusing Parents & Their Doctors (cont’d)
- $ - some parents think doctors are paid for each vaccine administered. It is important to communicate that vaccines are not a profitable business and the motivation behind vaccination is to protect children even if it means losing money.
- Community Benefit (Herd Immunity): immunizing helps to protect the community, particularly children too young to be vaccinated.

H1N1 Vaccine Delivery & Coordination
Nancy Gilbert
Emergency Preparedness Manager
Colorado Community Health Network

Region VIII H1N1 Vaccine State Contact Information
- Colorado
  http://www.cdphe.state.co.us/epr/h1n1.html
  Colorado Immunization Program
  303-692-2650
- Montana
  Not yet identified
- North Dakota
  Molly Sanders
  800-472-2180 or 701-328-3386
  msander@nd.gov
Region VIII H1N1 Vaccine State Contact Information

- South Dakota
  Not yet identified
- Utah
  Linda Abel
  801-538-9450
  label@utah.gov
- Wyoming
  www.immunizewyoming.com
  Immunization Section
  307-777-7952

Federal Plans for H1N1 Vaccine Distribution

- McKesson will distribute the H1N1 vaccine
- Providers interested in distributing the vaccine need to register with their state
- Providers will also receive:
  - Needles
  - Syringes
  - Alcohol Wipes

H1N1 Vaccine State and Local Plans

- Plans are still being developed
- At this time vaccine will be sent to providers
- Some states/counties are still considering setting up points of distribution (PODs)
- Maintain connections with local health departments for new developments

Administration & Documentation

- Storage and Handling
- Administration of the Vaccine
- Documentation

Additional H1N1 Information Resources

- For posters, flyers and other immunization information:
- Good resource for up to date guidance for providers on testing, medications, and vaccines:
  http://www.cdc.gov/
- Web site dedicated to flu information for the US. A source for archived flu briefings:
  http://www.flu.gov/

Thank You!

- Please complete the online evaluation form so we can review our goals and topics for future presentations.
- If you are requesting CME credit, 1.5 credits is available through the AAFP.
- You MUST complete the evaluation and the CME questions to receive CME credit.
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