H1N1 Influenza: Are We Ready For A Pandemic?

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## Influenza Pandemics

Mortality with 20th century pandemics

<table>
<thead>
<tr>
<th>Year</th>
<th>Type of Flu</th>
<th>Deaths</th>
<th>Virus Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918-19</td>
<td>Spanish flu</td>
<td>30M deaths</td>
<td>A(H1N1)</td>
</tr>
<tr>
<td></td>
<td>worldwide</td>
<td>worldwide</td>
<td></td>
</tr>
<tr>
<td>1957-58</td>
<td>Asian flu</td>
<td>1 M deaths</td>
<td>A(H2N2)</td>
</tr>
<tr>
<td></td>
<td>worldwide</td>
<td>worldwide</td>
<td></td>
</tr>
<tr>
<td>1968-69</td>
<td>Hong-Kong flu</td>
<td>800,000 deaths</td>
<td>A(H3N2)</td>
</tr>
<tr>
<td></td>
<td>worldwide</td>
<td>worldwide</td>
<td></td>
</tr>
</tbody>
</table>

- Pandemics occur every 10 to 40 years
- Affect up to 50% of population worldwide
- Huge death toll

Swine Influenza Virus (SIV)
Swine influenza Virus (SIV)

- Highly contagious respiratory disease in pigs caused by one of several SIV type A
- Bivalent SIV vaccines for animals
- Transmission to humans is uncommon
  - via contact with infected pigs or contaminated environments
- Infected human can spread the virus via coughing or sneezing
H1N1 Influenza Pandemic

Initially called "swine flu" the H1N1 flu strain
• Brought the international pandemic alert to one of its highest levels
• Shut down hundreds of schools
• Threat of a new pandemic overnight
• Took front-page headlines beginning in April
Historically

- Outbreaks of swine flu in humans dates back to investigation of the 1918 Spanish influenza pandemic
- Infected 1/3 of the world’s population (500 million people)
  - caused 50 million deaths
- Cause of human influenza & links to avian and swine influenza was not understood
- Answers began to emerge in 1930
1918 Influenza Virus

- 1918 virus
  - viral constructs w/ 1918 hemagglutinin gene pathogenic mouse model
- Infects the entire lung
- Elicit high levels of chemokines/cytokines ⇒ severe inflammation & hemorrhage
SIV in Humans

- 1976 outbreak in NJ, 200 cases, 1 death
- *Fear of an influenza pandemic in 1976 led to a national immunization campaign in the US*
- 1988 healthy 32 y pregnant pt died in Wisconsin
- 1958-2005, 37 cases, 6 deaths, 44% with exposure to pigs
- Cases reported in the U S, Czechoslovakia, the Netherlands, Russia, Switzerland, and Hong Kong
- 2005-2009, 12 human cases in the US
  - None were fatal

Myers KP. Clin Infect Dis. 2007 15;44:1084-8
1976, 40 M people received the A/NJ/1976/H1N1 vaccine (swine flu vaccine)

- Immunization halted ⇒ strong association with Guillam-Barre syndrome (500 cases, 25 deaths due to pulm complications)

- Subsequent influenza vaccines did not have this association

- Mice experiments with influenza vaccines:
  - 1976 swine flu
  - 1991-1992
  - 2004-2005

- Production of antibodies to antiganglioside (anti-GM1), (associated with GBS)

Current H1N1 Influenza Outbreak

- March 18, 2009, cases of influenza like illness first reported in Mexico
- Outbreak confirmed as H1N1 influenza A
- By May 5, 600 cases in Mexico with 25 deaths
  - 97 confirmed as Influenza A/H1N1

In the US

- April 17, 2009: CDC 2 children from California
- April 26: US Department of Health & Human Services declared it a national public health emergency (affects national security)
- June 25: 27,717 lab-defined cases
- September 1: 9,000 hospitalizations, 550 attributed deaths
- Outbreak spread rapidly to Canada, and throughout the world as a result of airline travel
- As of October 4, 2009, over 378,000 laboratory-confirmed cases

http://www.cdc.gov/h1n1flu/surveillanceqa.htm
WHO Stand

- June 11: WHO raised pandemic alert level to phase 6 (global pandemic)
  - North America, Australia, UK, Argentina, Chile, Spain, Japan
- September 1: WHO reported 200,000 people in ≥100 countries & 2185 confirmed deaths

Virus with sustained community-level outbreaks in ≥ 1 other country in another WHO region
WHO Focus

- Focus has shifted to:
  - Following trends of illness rather than individual cases in countries with widespread disease
  - Close monitoring of cases only in newly affected countries
Analysis of the Pandemic “H1N1 Flu"

- Virus is transmitted more efficiently (22 to 33%) but is less lethal than past pandemic viruses (1918). Fatality rate is ~0.4%
- Cases outside of Mexico occurred most commonly in countries with highest volume of travelers from Mexico
- Attack rates are higher in 5-24 y of age then 0-4 (highest hospitalization rates)
- Highest mortality rates among individuals aged 25 to 49 y
- High M&M in pregnant pts
- Individuals born before 1950 had preexisting antibody titers ≥80 against pandemic H1N1 influenza

http://www.cdc.gov/h1n1flu/surveillanceqa.htm
Conflicting Mortality Data

- Of 45 fatal cases in Mexico, 24 (54%) occurred in previously healthy individuals
- Most of the deaths outside of Mexico occurred in individuals with underlying health problems
Origin of the Virus

The A/H1N1 virus
An unusual cocktail of avian, swine and human viruses

Bird flu
Human flu

Swine flu
Pigs may harbour several flu viruses simultaneously. The pathogens may mix to create a new viral strain

Transmission
Pig to human
By inhaling viral particles (there is no risk from eating cooked pork)

Symptoms
Human to human
By inhaling viral particles

High fever
Coughing, sneezing
Breathing difficulties
Loss of appetite
Genetic Studies, Quadruple Reassortment

- Derived from 4 strains:
  - 2 swine (1 since 1918)
  - 1 avian
  - 1 human
- Genetic similarity between Mexico and US
- Classic SIV circulating in swine populations
- Ag profile drifted so that vaccines would be ineffective
- Susceptible pig cells have receptors for avian & human influenza allowing for reassortment if a pig cell is infected with $\geq 1$ strain

Neumann G. Nature 2009; 459:931
Garten RJ. Science 2009; 325:197
H1N1 Influenza in Lebanon

- May 22/2009: 22 Lebanese from Spain exposed to H1N1 influenza
- May 30: 3 confirmed cases
- July 10: 60 cases, 42 of them came from abroad
- Aug 18: 568 confirmed cases mostly local contacts
- Aug 27: 15 hospital admissions and 2 deaths
H1N1 Influenza in Lebanon

- MOH: Surveillance system and awareness campaigns, obligatory reporting, PCR testing (RHUH), hotline
- July 30: declared not a lethal pandemic
- No more routine testing
- Testing of high risk groups (as per WHO memo 117)
  - Hospitalization
  - Comorbidities
  - Pregnancy
  - Close contact with pts with severe disease
- Estimated cases of several thousand
- Continue to see cases in Oct
For How Long Is H1N1 Flu Contagious?

- Pts shed virus:
  - 1 d before to 7 d after the onset
  - Children for 10 d
  - IS pts for wks or months
- Via large droplets from sneezes or coughs
  - Droplets are propelled (within 6 feet) and deposited on mucous membranes
- Touching contaminated secretions
- Other bodily fluids (eg, diarrheal stool)
Clinical Manifestations of H1N1 influenza

- Incubation period 1-4 d, up to 7 d
- Acute respiratory illness
- Similar to seasonal influenza
- ≥2 of:
  - Rhinorrhea, nasal congestion
  - Sore throat
  - Dry cough
  - Extreme tiredness
  - Sudden onset of high grade fever
- Other typical symptoms
  - Body aches
  - Headache
  - Chills
  - **Diarrhea and vomiting** (mostly in children)

Symptoms in Virologically Confirmed Cases

- Outbreak of H1N1 in NY high school, sample of students (median age, 15 y)
  - Cough 98%
  - Subjective fever 96%
  - Fatigue 89%
  - Headache 82%
  - Sore throat 82%
  - Abdominal pain 50%
  - Diarrhea 48%
  - Dyspnea 48%
  - Joint pain 46%

http://www.cdc.gov/swineflu/identifyingpatients.htm
Range of Illness Severity

- In infants and young children:
  - Apnea, tachypnea, dyspnea, cyanosis, dehydration, altered MS, and extreme irritability
- Young children are at risk for complications
- Many cases may be mild or even asymptomatic
- Most recent cases in the US have been mild
- In Mexico
  - Much more severe
  - Presented in young adults
  - Caused pneumonia, respiratory failure, ARDS, and death
Complications of the Current pandemic

- ~ 0.3 % required hospitalization
  - Mostly for pneumonia and dehydration
- 29% of fatal cases had bacterial superinfection
- Most common risk factors for complications (553 American pts):
  - Chronic lung disease (37%)
  - Immunosuppression (17%)
  - Cardiac disease (17%)
  - Pregnancy (17%)
  - Diabetes mellitus (13%)
  - Obesity (13%)
Complications of H1N1 Influenza

- Exacerbation of underlying chronic disease
- Complications related to upper airways
  - Sinusitis, otitis
- Pulmonary complications
  - Bronchitis
  - Asthma: status asthmaticus
  - AECB
  - Pneumonia: viral and bacterial
- Cardiac
  - Myocarditis and pericarditis
- Myositis, rhabdomyolysis
- CNS complications
  - Encephalopathy, encephalitis, seizures
- Toxic shock syndrome
How Should H1N1 Flu Be Diagnosed?
Diagnosis

Respiratory specimen
- Nasopharyngeal aspirate
- Nasal wash
- Combined nasal swab with an oropharyngeal swab
  - Dacron nasal swabs (decrease aerosolization)
  - Swabs with a synthetic tip and an aluminum or plastic shaft
    - cotton tips and wooden shafts, calcium alginate not recommended
- Specimens placed in a 4°C refrigerator (not freezer) or immediately placed on ice or cold packs for transport
Tests for Detection of H1N1 influenza

- Most important is the RT-PCR
- DFA require expertise and fluorescence microscope
  - take 1-4 h, sensitivity 93% and a NPV 96%
- Rapid influenza diagnostic tests commonly used
  - Provide results in < 30 min
  - Can distinguish between influenza A and B
  - None of them are adequate to exclude 2009 influenza A (H1N1)
  - Sensitivity of 40-79%
- Viral culture

Pollack NR, Clin Infect Dis. 2009;49:e66-e68
October 2009: Who Should Be Tested?

- Acute febrile RTI and sepsis syndrome
- Atypical presentation
  - Old pts
  - Infants
  - IS
- Hospitalization
- High risk for severe disease and complications
Treatment of Influenza: Seasonal and Pandemic
Influenza Surface Proteins

Neuraminidase inhibitors

Neuraminidase

Hemagglutinin

RNA

M₂ protein
(only on type A)

Adamantanes
Available Drugs for Influenza

**M2 inhibitors: Adamantanes**
- Only active against influenza A
- Prevent viral replication by blocking M2 protein ion channel, preventing fusion of the virus and host-cell membranes
  - Amantadine
  - Rimantadine

**Neuraminidase inhibitors (NI)**
- Zanamivir: Inhalation (Not available in Lebanon)
- Oseltamivir: oral form
- Peramivir :IV administration
Neuraminidase Inhibition

Virus is engulfed into cell

RNA replicates virus in nucleus

Neuraminidase facilitates release from cell

Neuraminidase inhibitor prevents release of virus
Two Placebo-Controlled, Double-Blind Clinical Trials

- **US and ROW**: (Europe, China, Canada) (N = 1355)
- Influenza virus present in community
  - Fever $\geq 38^\circ\text{C}/100^\circ\text{F}$
  - At least 1 respiratory symptom
    - Cough, sore throat or nasal symptoms
  - At least 1 systemic symptom
    - Myalgia, chills/sweats, malaise, fatigue, or headache
- Oseltamivir 75 mg or 150 mg twice $\times$ 5 d vs placebo
- Rx started within 36 h of symptom onset
- Unrestricted access to antipyretic medication
Symptom Duration

US Study (N = 253)

Symptom Duration, h (median) (95% CI)

- Cough: Placebo (n = 129) 55 h, Tamiflu 75 mg bid (n = 124) 31 h, 45% decrease
- Myalgia Symptoms: Placebo 28 h, Tamiflu 16 h, 43% decrease
- Fever: Placebo 23 h, Tamiflu 10 h, 57% decrease

Treanor JJ. JAMA. 2000;283:1016-1024
IMPACT Study
IMmediate Possibility to ACcess Oseltamivir Rx

- Investigate the relationship between time to intervention and maximum Rx benefit with oseltamivir
- Prospective, open-label, multicenter study, 1999-2000
- 1426 subjects: 13 to 70 y presenting within 48 h of sudden onset of fever ($\geq 37.8^\circ C/\geq 100^\circ F$) and $\geq 2$ of the following:
  - Cough, sore throat, coryza, myalgia, headache, fatigue, and chills/sweats
- Oseltamivir 75 mg given twice daily for 5 d

Aoki F. JAC, 2003;55:123
Earlier Rx Maximizes Clinical Benefits

Modeled time to treatment $P < 0.0001$

Aoki F. JAC, 2003;55:123
Secondary Complications

- Pooled analysis of 10 double-blind, placebo-controlled phase III trials in 3564 subjects from 97-2000
- ↓ in bronchitis and pneumonia in influenza confirmed cases
- ↓ LRTC by 34% in the at risk pts and by 67% in the healthy population
- ↓ in influenza related hospitalization
### Oseltamivir Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea*</td>
<td>40 (5.6)</td>
<td>72 (9.9)</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>21 (2.9)</td>
<td>68 (9.4)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15 (2.1)</td>
<td>17 (2.3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (0.8 )</td>
<td>8 (1.1)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>4 (0.6 )</td>
<td>7 (1.0)</td>
</tr>
</tbody>
</table>

*↓ when taken with food and resolved with continuation of medication

Postmarketing: rare but serious neuropsychiatric events in children

Aoki F. JAC, 2003;55:123
Treanor JJ. JAMA. 2000;283:1016-1024
Concerns About Resistance
Emergence of Resistance to Oseltamivir in Seasonal Influenza

- Prior to 2007: 1-5% resistance rates
- Late 2007: resistant H1N1 isolates emerged in Europe
- In 2007-08 resistance rates to oseltamivir in H1N1 isolates:
  - Europe: 20% (67% in Norway)
  - Canada: 26%
  - US: 11%
  - Japan: 3%
  - *Pts had not been taking oseltamivir → resistant virus can be transmitted between individuals*
- Oct 08-Jan 09:
  - 185/190 isolates (97%) from 30 US states were R to oseltamivir (S to zanamivir, amantadine, and rimantadine)
  - South Africa: 100%, Australia: 93%, Philippines: 91%
Mechanisms of Resistance

- Neuraminidase
  - Frameshift mutations
    - Glu119 (\rightarrow Gly, Ala, Asp, Val)
    - **His274 (\rightarrow Tyr)**
    - Reduces susceptibility to oseltamivir by > 400-fold
  - Catalytic site mutations
    - Arg292 or Arg152 (\rightarrow Lys)

- Hemagglutinin
  - Mutations near receptor binding site

Jackson HC. Clin Drug Invest 2000;20:447
Resistance of 2009 H1N1 Influenza to Oseltamivir

- Reported in 7 isolates in the US and cases from Japan, Canada, China, Denmark, and Hong Kong
- 2 IS pts in Seattle with H275Y mutation
- Zanamivir only therapeutic option in such cases
  - contraindicated in pts with lung disease or asthma

MMWR. 2009;58:893-896
http://www.cdc.gov/swineflu/recommendations.htm
Implications of NI Resistance

- *In vitro* and animal models: R strains may be less fit than wild-type
- *Human data: mutated virus is transmissible and retains pathogenicity*
- Clinical features similar to oseltamivir-S H1N1 influenza
- Also observed in influenza B viruses
- Use of oseltamivir in children with influenza promotes R
- IS pts: R may result from prolonged viral shedding despite antiviral Rx

Jackson HC. Clin Drug Invest 2000;20:447
Pt Management Issues

- Routine Rx for all symptomatic pts not appropriate
- ↑ drug availability to public ⇒ ↑ rates of inappropriate use ⇒ ↑ risk of viral R
- Uncontrolled use of NI may do more harm than good
- Recent meta-analysis results
  - Overall ↓ in median time of symptoms in healthy adults by 0.57 d with zanamivir, 0.55 d with oseltamivir, 0.98 d in high risk pts
- Recommend Rx to people at ↑ risk of influenza-related complications
- **When treatment is indicated**, it should be started within 48 hrs or less of onset of symptoms

“When treatment of influenza is indicated in a patient with suspected influenza, health care providers should initiate empiric antiviral treatment as soon as possible. Waiting for laboratory confirmation of influenza to begin treatment with antiviral drugs is not necessary. Patients with a negative rapid influenza diagnostic test should be considered for treatment if clinically indicated because a negative rapid influenza test result does not rule out influenza virus infection”

“clinical judgment should be the ultimate guide in making antiviral treatment decisions for ……….”
CDC Health Advisory: October 19, 2009

- Pts requiring hospitalization
- Pt with lower respiratory tract illness or clinical deterioration regardless of previous health or age
- Children < 2 y
- Adults ≥ 65 y
- Pregnant women
- Persons with the following conditions:
  - Chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), or metabolic disorders (including diabetes mellitus)
  - Disorders that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders)
  - Immunosuppression, including that caused by medications or by HIV
  - Persons younger than 19 y receiving long-term aspirin therapy, because of risk for Reye syndrome
Prevention of Influenza
Prevention of Spread

- Basic hygiene measures
  - Cough etiquette
  - “Sneeze in your sleeve"
  - Hand hygiene
  - Face mask
  - Consider all body secretions as potentially infectious
Prevention of Spread

- Stay home until afebrile for 24 h
  - Initial CDC recommendation to stay home for 1 w
- If it is necessary to leave the house wear a facemask
- Avoid visitors
- Use "phone visits"
Infection Control Precautions in Healthcare Settings?

- At beginning of pandemic: airborne isolation N95 facemask, negative pressure room or Hepa filtered
- Currently Pts to be placed in a single room with door closed
- Pt should wear a mask when outside the room
- Standard, droplet, and contact precautions maintained by HCW for 7 d after the illness onset or until symptoms have resolved
Options for Influenza Prevention

- Chemoprophylaxis with antiviral agents
- Vaccination: 2 wks required for antibody response
Antiviral Chemoprophylaxis

- Postexposure: prophylaxis for ≥7 d after exposure to influenza-infected individual
- Seasonal: during community outbreak prophylaxis for entire influenza season
- Postvaccination: prophylaxis for 2-4 wks after vaccine
- Outbreak control: prophylaxis in institutional settings after influenza confirmed as present

Welliver R JAMA. 2001;285:748-754
Who should take Chemoprophylaxis?

- CDC recommends it for 7 d after the last known exposure to a confirmed case to:
  1. Household close contacts who are at high risk for complications of influenza (persons with certain chronic medical conditions, elderly)
  2. School children who are at high risk for complications with close contact (face-to-face)
  3. Travelers to Mexico who are at high risk for complications of influenza
  4. HCW or public health workers who have had unprotected close contact
  5. Outbreaks in institutions

- Antiviral prophylaxis is not recommended for healthy children or adults exposed in community, school, camp, or similar settings
Seasonal Influenza Vaccination

- Efficacy depends on match with circulating strains and pt’s immune status
- Efficacy:
  - Young adults or healthy elderly: 70%
  - Elderly in nursing homes: 30-40%
- Inactivated vaccine
- FluMist: live attenuated virus
  - Not to be used in IC pts, or <5 or >49 yrs
  - HCW: do not work with severely immunocompromised pts x 7d

MMWR. 2001;50(RR-4):5,8.
Does the Seasonal Flu Vaccine Protect Against H1N1?

- Analysis of the pandemic influenza strain with strains in the H1N1 vaccine: 72%-73% aa congruence with hemagglutinin. (97%-98% sequence identity for seasonal flu)
- CDC: seasonal flu vaccine will **not** provide any protection for the pandemic strain
- 2 influenza vaccines required for this year
  - Standard seasonal influenza vaccine
  - Pandemic H1N1 vaccine
    - *Both may be taken at the same time*
H1N1 Influenza Vaccine: Obligation or Option?

- US FDA selected strain A/California 07/2009 (H1N1)
  - Inactivated strain in single-dose and multiple-dose vials
  - Live attenuated product provided as an inhaler sprayer

- In US initial federal vaccine order was for 195 million doses at a cost of more than $1 billion

- Current projections are for 45 million doses by Oct

- Suppliers for the US product
  - AstraZeneca
  - CSL Biotherapeutics
  - GlaxoSmithKline
  - Novartis
  - Sanofi-aventis
Vaccine Response: Preliminary Results

- Vaccine was well tolerated and induced a "strong immunologic response" with a single, unadjuvanted 15-µg dose was given to healthy adults

Response rate:
- Sanofi-aventis
  - 96% in 18-64 y
  - 56% in ≥ 65 y
- CSL Biotherapeutics
  - 80% in 18-64 y
  - 60% in ≥ 65 y
Response After Single-Dose Monovalent Vaccine

- Vaccine from CSL with virus NYMC X-179A
- 15 µg and 30 µg with thimerosal given to 240 subjects
- A titer of ≥ 1:40 considered protective
- Results in 120 recipients

<table>
<thead>
<tr>
<th>Age</th>
<th>18-49 yr</th>
<th>50-64 yr</th>
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</thead>
<tbody>
<tr>
<td>Baseline titer ≥ 1:40</td>
<td>33%</td>
<td>34%</td>
</tr>
<tr>
<td>Day 21 Titer ≥ 1:40</td>
<td>100%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Local reactions at injection site in 46% and systemic symptoms in 45%

Greenberg ME. N Enl J Med. 2009 Sep 10. [Epub ahead of print]
Vaccination Priorities

- Advisory Committee on Immunization Practices (ACIP) at CDC:
  1. Pregnant women
  2. Household contacts of babies < 6 m
  3. HCW and emergency medical workers
  4. Children and young adults aged 6 m-24 y
  5. Persons 25-64 y with chronic medical conditions: chronic pulmonary or CV disease; high BP; renal, liver, neurologic, hematologic, and metabolic conditions, diabetes, IS

- High-priority list:
  1. 1-3. Risk categories above
  2. Children 6 m-4 y
  3. Children and adolescents 5 to 18 y with the risks defined above
Drugmakers, Doctors Rake in Billions Battling H1N1 Flu

Swine Flu Is Bad for Victims, But Good for Businesses That Cater to Expanding Market

“Americans are still debating whether to roll up their sleeves for a swine flu shot, but companies have already figured it out: vaccines are good for business. Drug companies have sold $1.5 billion worth of swine flu shots, in addition to the $1 billion for seasonal flu they booked earlier this year. These inoculations are part of a much wider and rapidly growing $20 billion global vaccine market. "The vaccine market is booming," says Bruce Carlson....."It's an enormous growth area for pharmaceuticals at a time when other areas are not doing so well," he says, noting that the pipeline for more traditional blockbuster drugs such as lipitor and nexium are drying”
How Accurate is the Data Collected To Justify this Global Vaccination Campaign?
Change in Reporting!!!!

- In Britain, the transition has been from:
  - "confirmed cases" (lab confirmation) ⇒ "suspected cases" (established by health professional, not requiring testing) ⇒ "self categorization"
- Enter name into the system over internet or phone, allows pts to collect anti-viral medication and categorize them as a suspected or probable case
- The question is: what is being reported by the countries? How does one ascertain that the reported cases are H1N1 as opposed to seasonal influenza?
Unanswered Questions?

Fatality rate only 0.4%

- Does the data justify a Worldwide public health emergency including a $40 billion vaccination program (benefit to pharmaceutical companies)?

- Is this public health emergency diverting public opinion from the real crisis affecting the World (economic and social)??
Contradictory Messages!

- WHO predicts with authority:
  
  "As many as 2 billion people could become infected over the next 2 y, nearly 1/3 of the world population"

- Creating an atmosphere of fear and insecurity, pointing to an impending global public health crisis

- WHO has acknowledged:
  
  "The underlying symptoms are moderate and most people will recover from swine flu within a week, just as they would from seasonal forms of influenza"

WHO statement, quoted in the Independent, August 22, 2009
Contradictory Messages!

- Without systematic lab confirmation, it is impossible to differentiate.
- Statistical manipulation creating an atmosphere of panic.
- In the UK, coupled with announcements:
  - "mass graves are being set up to deal with a rising death toll"
- In Massachusetts contemplating obligatory vaccination against penalty and jail.
- FDA cleared manufacturers of vaccine from future liability!
“The dramatic causes and consequences of the "real crisis" which in real sense threaten the future of humanity must remain unheralded. Both the Economic Crisis and the Middle East Central Asian war are the object of routine and persistent media distortion and camouflage. In contrast, the H1N1 swine flu --despite its relatively mild and benign impacts-- is depicted as major "Save the World" endeavor”

Michel Chossudovsky, Director of the Centre for Research on Globalization, Montreal
At AUBMC Team Work

- Infection Control and Prevention Program
- Emergency Department
- University Health Services
- Nursing Services
- Laboratory Services
- Administration
- Outpatient Clinic Services
At AUBMC Team Work

- Several hundred pts seen at AUBMC ER and clinics
- Messages sent to all employees
- Influenza Ag test performed by nasal wash
- Specimens referred to RHUH for confirmation by PCR
  - Sensitivity of Ag around 78%
- Posters distributed all over hospital
- Masks and antiseptic hand solutions available at various points
- Walk-in clinic established to accommodate influx of pts to ER

AMERICAN UNIVERSITY OF BEIRUT
MEDICAL CENTER

DEAR VISITORS / PATIENTS

If you have any of the following symptoms:
- Fever more than 38º
- Sore throat
- Cough
- Runny nose
- Headache or body aches
- Vomiting or Diarrhea

Kindly follow these special precautions before entering the Hospital/Emergency Department/Laboratories:
1. Rub your hands with the alcohol based hand solution
2. Put the protective mask

Your Safety Is Our Concern
At AUB A Team Work

Multidisciplinary taskforce
- UHS
- Administration
- Safety
- ICPP
- Public health
- Office of publications
- Others
Pathology of Influenza Infection

A. Hemagglutinin binds to sialic acid

B. Virus is engulfed into cell

C. RNA replicates virus in nucleus

D. Neuraminidase facilitates release from cell
A Constantly Mutating Virus

Type A

H1N1  H2N2  H3N2  H5N1
Case Presentation
Case Presentation

- 28 year old previously healthy ♀ living in Africa, developed for 2 d:
  - High grade fever
  - Pleuritic chest pain
  - Non-productive cough
  - Dyspnea
- Presented to the AUBMC ER on August 2, 2009
- PE was unremarkable
- WBC 6700, 76% neutrophils
- Influenza Ag -ve
CXR ⇒ Infiltrates in the medial segment of the RML
Case Presentation

- Was sent home on levofloxacin 750 mg PO Q24h
- August 4(d3 of illness) she presents back to the ER
  - Persistent fever, non responsive to antipyretics
  - Left pleuritic chest pain
  - SOB
- History:
  - No sick contacts
  - Last history of AB intake 2 m earlier (clindamycin post D&C)
- P.E: stable vital signs
  - ↓ breath sounds in RML, and RLL
Case Presentation

- WBC: 5800 /cu.mm (69% PMNs), Hct 32, Plts 248,000/mm³
- Oxygen saturation 94%
- No atypical lymphocytes
- LFTs nl
- HIV –ve
- Malaria smear –ve

- Pt was admitted and started on
  - Oxygen
  - IV hydration
  - Levofloxacin and ceftriaxone
CT Angiogram

- Large bilateral lower lobe consolidations containing air bronchograms with small bilateral pleural effusions
- Small nodular opacities in both upper lobes and right middle lobe
- Mild diffuse soft tissue thickening surrounding the carina and extending to the bifurcation
Case Presentation

- Bronchoscopy done on August 5
  - Showing purulent discharge from RLL
  - BAL sent for cytology, PCP stain, cultures, Influenza Ag

- Urine Legionella Ag –ve
- BAL results unrevealing

- 7 August, 2009: D6 levofloxacin and D4 ceftriaxone
  - Pt afebrile, clinically asymptomatic
  - Pt was sent home on cefpodoxime
Case Presentation

Repeat CXR showed clear lungs
Case Presentation

- After discharge
- PCR for influenza H1N1 +ve (RHUH)
- Cured without antiviral treatment

- Hundreds of cases with H1N1 influenza at AUBMC
- Most are mild and self limited
Efforts AT AUB
**Illness Duration**

![Bar chart showing duration of illness comparison between Placebo, Oseltamivir 75 mg bid, and Oseltamivir 150 mg bid in US and ROW populations.](chart)

- **US (N = 374)**
  - Placebo: 103.3 hours (95% CI)
  - Oseltamivir 75 mg bid: 71.5 hours (95% CI, *P < 0.001)
  - Oseltamivir 150 mg bid: 69.9 hours (95% CI, †P = 0.006)

- **ROW (N = 475)**
  - Placebo: 116.5 hours (95% CI)
  - Oseltamivir 75 mg bid: 87.4 hours (95% CI, ‡P < 0.017)
  - Oseltamivir 150 mg bid: 81.8 hours (95% CI, §P = 0.007)

*P < 0.001.
†P = 0.006.
‡P < 0.017.
§P = 0.007.

Treanor JJ. JAMA. 2000;283:1016-1024
Seasonal Vaccine Indications

- High risk: >50 yrs, residents of chronic care homes, chronic pulmonary/cardiac disease, chronic illness (diabetes, renal failure, IS, sickle cell)
- Pregnancy: during 2nd/3rd trimesters
- Household member of high risk pts
- HIV
- Travelers: high risk pts to tropics (all yr), or to southern hemisphere in April-September
- Anyone who wants it
- HCW

Contraindications to IM vaccine: allergy to eggs or prior severe allergic reaction, or fever > 40 °C

CDC guidelines: MMWR 2005;54:1
HCWs

- The ACIP has identified HCWs as a high priority for influenza vaccine since 1984
- Concurred by SHEA
- To protect HCWs, families, and pts
- Risk to pts is demonstrated by high rates of nosocomial infections due to provider-to-patient transmission
- Up to 76% of HCWs continue to work when they have a flulike illness

Lester RT. Infect Control Hosp Epidemiol. 2003;24:839-844
No Need To Kill the Pigs

- There is no risk of becoming infected with influenza virus from eating pork
Levels of Adamantane Resistance Among Influenza A (H3N2): US, 2005-06

- 38,932 specimens tested for influenza viruses
- 4.0% tested positive
  - 96.3% influenza A
- Subtyping of influenza A viruses:
  - 99.3% H3N2
  - 0.7% H1N1
- Of 120 influenza A (H3N2) viruses tested: 91% were resistant to amantadine and rimantadine
- Recommendations against the use of adamantanes in favor of NI

MMWR Morb Mortal Wkly Rep 2006;55:44
Resistance to M2 Inhibitors

- Resistance can occur spontaneously or emerge on Rx 2-3 d after drug initiation
- Single point mutation of the M2 protein can confer cross-resistance to both amantadine and rimantadine
- Resistant viruses are genetically stable, virulent, and transmissible

MMWR Morb Mortal Wkly Rep 2006;55:44