AVIAN INFLUENZA

“The pandemic influenza clock is ticking. We just don’t know what time it is.”

Laurene Mascola, MD, MPH, FAAP
Acute Communicable Disease Control Program
OUTLINE

- Background on Influenza A
- Impact of influenza
- Pandemics
- Avian influenza A viruses
- Human infections with avian influenza A viruses since 1997
- H5N1 Asia 2005
BACKGROUND: HUMAN INFLUENZA

- Acute febrile respiratory illness
  - Symptoms, signs may differ by age
- Etiology: infection with human influenza viruses (infect upper respiratory tract epithelial cells)
  - 2 major surface glycoproteins
    - Hemagglutinin, Neuraminidase
    - 8 gene segments code for 10 proteins
- Types A and B viruses cause substantial illness and death among humans yearly
Epidemiology

- Short incubation period, usually 1-4 days.
- Spread by respiratory droplets—person-to-person, direct contact, rare aerosol
- Highly contagious; infectious period:
  - Adults: 1 day prior to symptoms thru 5 days post illness
  - Children: >10 days
  - Immune compromised shed virus for weeks to months
- Virus 1st detectable just before symptom onset. Usually not detectable after 5-10 days
**KEY INFLUENZA VIRAL FEATURES**

Surface proteins (major antigens)

- **Hemagglutinin (HA)**
  - Site of attachment to host cells
  - Antibody to HA is protective

- **Neuraminidase (NA)**
  - Helps to release virions from cells-oseltamivir works here
  - Antibody to NA can help modify disease severity

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IMPACT OF INFLUENZA

- Seasonal epidemics in temperate regions
  - U.S., Canada, Europe, Russia, China, Japan, Australia, Brazil, Argentina

- Year-round activity in tropical climates
  - Equatorial Africa, Southeast Asia

- U.S. impact
  - Average of >200,000 influenza-related hospitalizations/year
  - Average of >36,000 influenza-related deaths/year

- 3 global pandemics in the 20th century
INFLUENZA PANDEMICS
20TH CENTURY

1918: “Spanish Flu”
A(H1N1)
20-40 m deaths
675,000 US deaths

1957: “Asian Flu”
A(H2N2)
1-4 m deaths
70,000 US deaths

1968: “Hong Kong Flu”
A(H3N2)
1-4 m deaths
34,000 US deaths

Credit: US National Museum of Health and Medicine

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INFLUENZA A VIRUSES

- Subtypes based on surface glycoproteins
  - Hemagglutinin (HA) and Neuraminidase (NA)
  - Current human influenza A virus subtypes:
    - H1 (H1N1, H1N2)
    - H3 (H3N2)

- Cause epidemics and pandemics

- Infect multiple species
  - Humans
  - Birds (wild birds, domestic poultry)
  - Other animals: pigs, horses, dogs, marine mammals (seals, whales)
NATURAL RESERVOIR FOR NEW HUMAN INFLUENZA A VIRUS SUBTYPES: WATERFOWL (AQUATIC DUCKS)

Avian Influenza A Viruses
H1 - H16
N1 - N9

Human Influenza A Viruses
H1 - H3

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Antigenic “drift”: Point mutations in the hemagglutinin gene cause minor antigenic changes to HA

- Continuous process
- Immunity against one strain may be limited
- Vaccine strains must be updated each year
  - 6-8 month process
  - Targeted at high-risk (inactivated); healthy (LAIV)

Antigenic “drift” causes seasonal epidemics
Antigenic "shift": Emergence of a new human influenza A virus subtype (new HA subtype +/- NA) through:

- Genetic reassortment (human and animal viruses)
- Direct animal (poultry) to human transmission
Because there is little or no immunity to a novel virus, a pandemic can occur if:

- Efficient and sustained virus transmission occurs among humans (sustained person-to-person spread)

A pandemic can result in:

- Widespread morbidity and mortality worldwide
- High proportion of deaths among young adults
DEFINITION OF PANDEMIC

- Isolation from humans of a novel influenza A virus
- Little or not immunity in the population
- Demonstrated ability of the virus to replicate and cause disease
- Efficient person to person transmission
- May have increased mortality with higher proportion in younger persons
WHO ALERT PHASES

PANDEMIC ALERT PERIOD
Where we are now

Phase 3: Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact

www.dh.gov.uk/pandemicflu
DOES AVIAN FLU = PANDEMIC FLU

- NO!
- Current impact of highly pathogenic avian influenza (HPAI) viruses on human health is small
- Only since 1997, and in 2003 till present do we see human infections
- Current A/H5N1 viruses are poorly adapted to human species-rare human to human transmission, rare to no mild or asymptomatic infection
Antigenic “Shift” Pandemic

Avian virus

Goose/Guangdong/1/96 (H5N1)

Quail/HK/G1/97 (H9N2)

Teal/HK/W312/97 (H6N1)

Avian virus

Reassortment in swine

Human virus

Model of the emergence of a pandemic influenza virus

Reassortment in humans

A/HK156/97 (H5N1)

Avian-human pandemic reassortant virus

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Migratory water birds

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PANDEMIC STRAIN REASSORTMENT IN HUMANS

Migratory water birds

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AVIAN INFLUENZA FROM BIRDS TO HUMANS

Migratory water birds

Domestic birds

- Hong Kong 1997, H5N1
- HK, China 1999, H9N2
- Netherlands 2003, H7N7
- Hong Kong 2003, H5N1
- Viet Nam and Thailand, 2004 H5N1

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ESTIMATED IMPACT OF A FUTURE INFLUENZA PANDEMIC IN THE U.S.

- Deaths: 89,000-207,000
- Hospitalizations: 314,000-734,000
- Outpatient visits: 18-42 million
- Additional illnesses: 20-47 million
- Economic impact: $71.3-166.5 billion
- Population affected: 15-35%
- U.S. population: 290 million


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D12: Avian Flu.ppt  No. 20
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IMPACT ON HEALTH SERVICES

- Likely to place great pressure on health and social services
- Increased numbers of patients requiring treatment
- Depletion of the workforce due to illness and other disruption

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IMPACT ON BUSINESS

- 25% of the UK workforce will take 5-8 working days off over a three-month period
- Estimates suggest that during the peak absenteeism will double in the private sector and increase by two-thirds in the public sector

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IMPACT ON SCHOOLS AND SERVICES

- Likely to spread rapidly in schools and other closed communities
- Impact on all services including police, fire, the military, duel supply, food production, distribution and transport, prisons, education and business

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Past experience teaches us that following the emergence of a new pandemic virus:

- More than one wave of influenza is likely
- The gaps between the waves may be weeks or months
- A subsequent wave could be worse than the first

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BIRD FLU
Is Asia hatching the next human pandemic?
AVIAN INFLUENZA A VIRUSES

- Infect respiratory and gastrointestinal tracts of birds
  - Usually do not cause disease in wild waterfowl
  - Genetic re-assortment occurs frequently
  - Can cause morbidity and mortality in domestic poultry
  - Is a vet problem

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“There is no evidence that any human cases of avian influenza have been acquired by eating poultry products.” — CDC, February 24, 2004

“To date there is no epidemiological information to suggest that the disease can be transmitted through contaminated food or that products shipped from affected areas have been the source of infection in humans.” — WHO, January 24, 2004
Highly Pathogenic Avian Influenza viruses (HPAI)

- May not cause illness in wild birds
- High mortality in domestic poultry
- Subtypes: H5, H7
- Molecular and pathogenicity criteria for determining HPAI
INTER-SPECIES TRANSMISSION AND PANDEMICS

- Many reports of transmission animal influenza viruses to humans that do not result in pandemic
  - E.g. Swine Flu 1976
    - 230 infected, 13 hospitalized, 1 death
    - No sustained transmission
- But, because pandemics may be so devastating, vigilance and planning critical
HUMAN INFECTIONS WITH HPAI AVIAN INFLUENZA (1)

- H5N1, Asia
  - 1997: Hong Kong (18 cases, 6 deaths)
  - Risk factor: visiting live poultry market
  - 2003: Hong Kong (2 cases, 1 death)
  - 2004: February 2, 2005, Vietnam, Thailand, Cambodia (55 cases, 42 deaths)
  - Overall case fatality rate 65%
HUMAN INFECTIONS WITH HPAI AVIAN INFLUENZA (2)

- **H9N2, 1999 and 2003**
  - 3 cases Hong Kong, 6 cases China, no deaths
- **H7N7, 2003 Netherlands** (89 cases, 1 death)
- **H7N3 2004 Canada** (2 cases, 0 deaths)
- **H7N2 2003, US**
  - Virginia (1 case, no deaths)
  - New York (1 case, no deaths)

Carolyn Bridges, MD

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H7N3 (British Columbia, Canada, Feb.- Apr. 2004)

- Highly pathogenic H7N3 detected in chicken farms
- 2 persons involved in H7N3 poultry outbreak culling activities (mild illness and conjunctivitis; conjunctivitis and headache)
  - H7N3 isolated
  - One worker was not wearing eye protection
  - One worker was wearing glasses
  - Oseltamivir treatment given, full recovery

Tweed SA et al. EID Dec. 2004
### Human Cases of H5N1 (2003 - 2006*)

<table>
<thead>
<tr>
<th>Country</th>
<th>Total cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>93</td>
<td>42</td>
</tr>
<tr>
<td>Thailand</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Cambodia</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>China</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Turkey</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Iraq</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Egypt</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>207</strong></td>
<td><strong>115</strong></td>
</tr>
</tbody>
</table>

* 12/26/03 through 5/5/06

HUMAN H5N1 CASES 2003-2006

- Most cases had direct contact with sick/dead poultry
- Majority of cases: children, young adults
- Reports of possible person to person spread, not sustained
  - Also seen during 1997 H5N1 Hong Kong outbreak and 2003 H7N2 Netherlands outbreak
H5N1 ISSUES

- Viruses circulating widely among poultry in several Asian countries, now Europe
  - Cannot be eradicated anytime soon
  - Activity may increase during cooler months
  - Viruses continue to evolve
- Can infect cats; has infected tigers, leopards (Thailand, China)
- Has infected pigs (China)
- Ducks may be infected without illness

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AVIAN INFLUENZA

- Highly pathogenic avian flu (A/H5N1) currently circulating in poultry in Asia
- Strain of avian flu has shown ability to transmit from poultry to people
- Fear that humans infected with avian flu could also be infected with “ordinary” flu
- Exchange of genes could lead to emergence of a potentially pandemic strain

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AVIAN INFLUENZA

ALTERNATIVELY

- Avian flu strain could evolve into a potentially pandemic strain with greater affinity for people and acquire ability to pass easily from person to person

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THE WORLD HAS CHANGED

- Global population in 18th century was <1 billion vs. 6 billion today
- Intercontinental travel is in hours rather than months and in millions rather than hundreds
- Human crowding has increased
- Population health has improved
- Animal husbandry has changed
- Interdependence had increased

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OPPORTUNITIES FOR VIRUS EMERGENCE AND SPREAD

- Modern pig and poultry production create conditions for mass animal influenza outbreaks
- Proximity of humans and animals in many markets create potential of virus recombination
- Human crowding and travel present opportunities for virus spread

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KEY H5N1 ISSUES

- Resistance to antivirals amantadine and rimatidine in many isolates
- Surveillance for disease in poultry, humans and virus changes critical
- Planning for H5N1-related pandemic and non-H5N1 pandemics essential to reduce impact
  - Including vaccine development
PANDEMIC SPREAD AND VACCINE AVAILABILITY

▶ Spread of a pandemic
  ✓ Months to reach U.S. for prior pandemic strains
    1918 – 0; 1957 – 4-5; 1968 – 2-3; 1977 – 3-4
  ✓ Next pandemic: earlier entry from air travel
    may be offset by international surveillance

▶ Availability of vaccine
  ✓ Optimally, first doses available ~4 months
    after reference strain is developed
  ✓ Weekly delivery of ~3-5 m doses from U.S.
    production
No current evidence of sustained person-to-person transmission of avian influenza A viruses, all avian genes

Avian influenza viruses continue to evolve and have the potential for genetic reassortment

The key to preventing human infections with avian influenza A viruses is to control poultry outbreaks of avian influenza
ANTI VI RAL ISSUES (1)

- Single manufacturer for world supply
  - US production expected 2006
- Limited courses in stockpile (2 million) and in pharmacies (1.5 million prior to 2005 season)
  - Short shelf life 3-5 years
ANTIVIRAL ISSUES (2)

- Treatment vs. prophylaxis (>5 times as much)
  - Treatment can reduce symptoms and complications
- Resistance may develop
  - Current H5N1 strain resistant to adamantanes
POSSIBLE PRIORITY GROUPS FOR VACCINE AND ANTIVIRAL DRUG USE

Define goals: Reduce health impacts or maintain infrastructure

- Hospital health care workers
- Outpatient health care workers
- Public health and public safety workers
- Hospital in-patients
- Decision makers
- Persons admitted to hospital
- High-risk outpatients
- Long-term care facilities
PRIORITIZATION

- Optimally federal decision for consistency
- States or local jurisdiction will act in absence of federal leadership
- High degree of specificity is needed
  - Clearly state objectives
  - Definition of groups, e.g., direct patient care or essential service worker
  - Sub-prioritization of “high risk”
- Cannot avoid ethical issues
Effectiveness doubtful

- Transmission characteristics not favorable
- Likely to be implemented early (public, political and professional pressures to “buy time”)
- Lower impact as pandemic becomes more widespread
MEASURES TO CONTROL INFLUENZA PANDEMIC (1)

- Measures to reduce risk that cases transmit infection
  - Confinement
  - Face masks (symptomatic, exposed, seeking care)

- Measures to reduce risk that contacts transmit infection
  - Follow-up of contacts
  - Quarantine of healthy contacts
  - Antiviral prophylaxis- only in specific situations
MEASURES TO CONTROL INFLUENZA PANDEMIC (2)

Measures to increase social distance

- Isolation of ill
- Closures
- Masks—???CDC says unlikely to help
LESSONS FROM PAST PANDEMICS

- Occurs unpredictable, not always in winter
- Great variations in mortality, severity of illness and pattern of illness or age most severely affected
- Rapid surge in number of cases over brief period of time, often measured in weeks
- Tend to occur in waves – subsequent waves may be more or less severe

Key lesson - unpredictability

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OTHER CONTAINMENT MEASURES

- Influenza more difficult than SARS or smallpox
- Measures would vary as pandemic develops
  - Isolation of ill persons (yes)
  - Quarantine of exposed persons (initially-avian)
  - Contact tracing (initially-avian)
  - Cancellation of events (school, public meetings, etc)
  - Steps to reduce individual exposure to virus (yes)
    - Masks
    - Hand washing
  - Public will adopt their own measures
## PANDEMIC INFLUENZA

### ESTIMATES FOR CALIFORNIA

<table>
<thead>
<tr>
<th>CDC Estimates of Percent of Population Affected by the Next Pandemic*</th>
<th>Number Affected in California (pop. 36,363,502)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>15% to 35% become ill with flu</td>
<td>5.4-12.7 Million</td>
</tr>
<tr>
<td>8% to 19% require out-patient visits</td>
<td>2.9-6.9 Million</td>
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<tr>
<td>0.2% to 0.4% require hospitalization</td>
<td>72-145 Thousand</td>
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<tr>
<td>0.04% to 0.1% die of flu-related causes</td>
<td>14-36 Thousand</td>
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</tbody>
</table>

*Estimates from FluAid 2.0, CDC [www2.cdc.gov/od/fluaid/default.htm](http://www2.cdc.gov/od/fluaid/default.htm)

**California Department of Finance Pop. Projections for 2003

Backer H, MD

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### LAC PANDEMIC ESTIMATES*

<table>
<thead>
<tr>
<th>Influenza Pandemic Impact</th>
<th>Weeks</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<th>10</th>
<th>11</th>
<th>12</th>
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<tbody>
<tr>
<td>Hospital Admission</td>
<td>Weekly admission</td>
<td>458</td>
<td>1,834</td>
<td>3,209</td>
<td>4,585</td>
<td>5,960</td>
<td>6,877</td>
<td>6,877</td>
<td>5,960</td>
<td>4,585</td>
<td>3,209</td>
<td>1,834</td>
<td>458</td>
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<td></td>
<td>Peak admission/day</td>
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</tr>
<tr>
<td>Hospital Capacity</td>
<td># of flu patients in hospital</td>
<td>458</td>
<td>1,834</td>
<td>3,209</td>
<td>4,585</td>
<td>5,960</td>
<td>6,877</td>
<td>7,226</td>
<td>6,734</td>
<td>5,746</td>
<td>4,371</td>
<td>2,995</td>
<td>1,620</td>
<td></td>
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<tr>
<td></td>
<td>% of hospital capacity used</td>
<td>2%</td>
<td>7%</td>
<td>12%</td>
<td>17%</td>
<td>22%</td>
<td>25%</td>
<td>27%</td>
<td>25%</td>
<td>21%</td>
<td>16%</td>
<td>11%</td>
<td>6%</td>
<td></td>
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</tr>
<tr>
<td>ICU Capacity</td>
<td># of flu patients in ICU</td>
<td>69</td>
<td>306</td>
<td>606</td>
<td>906</td>
<td>1,206</td>
<td>1,438</td>
<td>1,517</td>
<td>1,488</td>
<td>1,275</td>
<td>1,000</td>
<td>706</td>
<td>413</td>
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<td></td>
<td>% of ICU capacity used</td>
<td>4%</td>
<td>18%</td>
<td>36%</td>
<td>54%</td>
<td>72%</td>
<td>86%</td>
<td>91%</td>
<td>89%</td>
<td>76%</td>
<td>60%</td>
<td>42%</td>
<td>25%</td>
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<tr>
<td>Ventilator Capacity</td>
<td># of flu patients on ventilators</td>
<td>34</td>
<td>153</td>
<td>303</td>
<td>453</td>
<td>603</td>
<td>719</td>
<td>758</td>
<td>744</td>
<td>637</td>
<td>500</td>
<td>353</td>
<td>207</td>
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<tr>
<td></td>
<td>% usage of ventilator</td>
<td>2%</td>
<td>8%</td>
<td>15%</td>
<td>23%</td>
<td>30%</td>
<td>36%</td>
<td>38%</td>
<td>37%</td>
<td>32%</td>
<td>25%</td>
<td>18%</td>
<td>10%</td>
<td></td>
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</tr>
<tr>
<td>Deaths</td>
<td># of deaths from flu</td>
<td>88</td>
<td>351</td>
<td>615</td>
<td>878</td>
<td>1,142</td>
<td>1,317</td>
<td>1,317</td>
<td>1,142</td>
<td>878</td>
<td>615</td>
<td>351</td>
<td>88</td>
<td></td>
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<tr>
<td></td>
<td># of flu deaths in hospital</td>
<td>61</td>
<td>246</td>
<td>430</td>
<td>615</td>
<td>799</td>
<td>922</td>
<td>922</td>
<td>799</td>
<td>615</td>
<td>430</td>
<td>246</td>
<td>61</td>
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</tbody>
</table>

*D Assumes 35% attack rate

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D Bagwell: CDC FluSurge
## Medical Care for Severe Influenza Infections

### Supportive Therapy
- Supplemental oxygen
- Intubation/ventilation
- Fluid management
- Nutrition

### Specific Therapy
- Antiviral drugs
- Antibiotics for bacterial superinfection
CHALLENGES TO MAINTAINING QUALITY MEDICAL CARE

- Ability to effectively triage patients
- Ability to care for ill outpatients
  - Delivery of medical care, medications, and food
- High demand for inpatient services
  - Estimated >25% increase in demand for inpatient beds, ICU beds, & ventilators for a mild pandemic
  - Staff absenteeism
  - Limited availability of critical resources
- Surge capacity for inpatient care
UNKNOWN AND UNCERTAINTIES

- When will a pandemic occur?
- How bad will it be?
- Will there be major societal impacts beyond health?
- Who will be at greatest risk of disease and death?
- How much vaccine or antiviral drug will be available and who will get it?
- Will the health care system be able to cope with the increased demands?
- What control measures will be implemented to decrease spread in the community?
PANDEMIC INFLUENZA SUMMARY

- Limited antivirals
- Limited vaccine
- Limited benefit of isolation and quarantine
- Limited excess capacity in health care system

What are we supposed to do?
Thanks to Tim Uyeki, Carol Bridges, and Ben Schwartz (CDC) and Howard Backer from CADHS for assistance with developing this presentation.
More information can be found at:
http://lapublichealth.org/acd/flu.htm
QUESTIONS AND ANSWERS
Good Bye
Have a Nice Day