Pandemic Influenza Preparation Update

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Force Health Protection and Readiness
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Agenda

• Current status of H5N1
• Antivirals
  – Resistance
  – National plan
  – DoD plan
• Modeling
  – Vaccine
  – Antivirals
OIE confirmed H5N1 Activity in Poultry and Wild Birds in 2007

- Afghanistan
- Bangladesh
- Cambodia
- China
- Czech Republic
- France
- Germany
- Ghana
- Hong Kong
- Hungary
- India
- Japan
- Republic of Korea
- Kuwait
- Laos
- Malaysia
- Myanmar
- Pakistan
- Russia
- Saudi Arabia
- Thailand
- Togo
- Turkey
- United Kingdom
- Vietnam
**The Year in Birds – H5N1 Activity for 2007**

<table>
<thead>
<tr>
<th>JAN</th>
<th>FEB</th>
<th>MAR</th>
<th>APR</th>
<th>MAY</th>
<th>JUN</th>
<th>JUL</th>
<th>AUG</th>
<th>SEP</th>
<th>OCT</th>
<th>NOV</th>
<th>DEC</th>
</tr>
</thead>
</table>

Germany, Myanmar, Pakistan, an outbreak in poultry
UK and Kuwait report first findings in poultry and previously reported wild birds
Hong Kong, Japan, Hungary, Vietnam, ROK, Thailand
- Poultry

Bangladesh becomes the 57th country to report its first outbreak (poultry)
Pakistan, Vietnam, Malaysia, Thailand (reported previously in poultry)

Ghana reports 17th outbreak due to H5N1 (previously in poultry)

Now 59 Countries

Bangladesh, Myanmar, Pakistan, Vietnam, Cambodia
- Poultry

Vietnam
- Five more poultry outbreaks
Myanmar
- New outbreak

Saudi Arabia reports 4 outbreaks

Russia, China, Germany, Vietnam, Malaysia, poultry outbreaks

Germany, Myanmar, Pakistan, further outbreaks in poultry

France
- Wild birds

Germany, Bangladesh, Vietnam, Togo, Myanmar
- Poultry

India becomes the 25th country in 2007 to report poultry outbreak

Germany, Myanmar, Pakistan further outbreaks in poultry

France outbreak in wild birds

India, Vietnam, Germany, Bangladesh, Kuwait
- Poultry

Russia, China, Germany, Vietnam, Malaysia, poultry outbreaks

Now 60 Countries

Ghana, Vietnam, Myanmar, Malaysia, Turkey, Indonesia, poultry outbreaks

Global Count – 60 Countries

Germany
- Wild Bird Outbreak
Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO in 2007 as of 12 November 2007

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Egypt</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>China</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cambodia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Indonesia

- Remains a hot spot with the highest number of new cases for 2007
- Sole source of new cases of Clade 2.1 disease
- GOI continues to refuse to share samples
- Mitigation measures continue to be hampered due to decentralized government (public health system)
Egypt

- Second highest case rate
- Clade 2.2
- Lowest mortality rate
- Effective control measures in place
  - Pandemic plan a model for the area
  - Extensive communication program facilitates early recognition and treatment and improved survival
  - Effectively addressing backyard poultry without changing cultural practices
Human Cases H5N1 2003-2007*

* WHO November 14, 2007
Antivirals

I thought you brought the Tamiflu!
### Adamantane Resistance Among H5N1 Viruses

<table>
<thead>
<tr>
<th>Genetic Group</th>
<th># Resistant</th>
<th># Tested</th>
<th>% Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clade 1</td>
<td>Vietnam-like</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Clade 2.1</td>
<td>Indonesia-like</td>
<td>61</td>
<td>71</td>
</tr>
<tr>
<td>Clade 2.2</td>
<td>Qing Hai-like</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Clade 2.3</td>
<td>Anhui-like</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>91</td>
<td>161</td>
</tr>
</tbody>
</table>
Neuraminidase Resistance

- Represents 8% of samples tested
- Resistance emergence (H274Y) or reduced susceptibility (N294S in Egypt)
- Uncertain of clinical significance
- Molecular markers not well defined
- Differences in NAI susceptibility among A(H5N1) isolates
  - IC$_{50}$s: clade 1 is 6 fold $<$H1N1$ < 3-5$ fold clade 2
New Neuraminidase Inhibitors in H5N1 viruses

• Novel mutations at
  – 136 (human)
  – 150 (avian)

• Potential resistance to
  – Oseltamivir
  – Zanamivir
  – Peramivir

Nature 443, 45-49(7 September 2006)
doi:10.1038/nature05114
Oseltamivir & Hospitalized Patients

- Hospitalized with laboratory confirmed influenza
- 327 adults
  - Median age 77 (15-98)
  - 51% male
  - 75% chronic underlying disease
  - 59% presented to ER within 48hr of symptoms
  - 16% ICU
  - 8.3% died
  - 89% received antibacterial therapy
  - 32% received oseltamivir
  - Treatment with oseltamivir associated with a significant reduction in mortality (OR 0.21 95% CI 0.06 – 0.80)

Antiviral Therapy and Outcomes of Influenza Requiring Hospitalization in Ontario, Canada Allison McGeer, Karen A. Green, Agron Plevneshi, Altnay Shigayeva, Nilofar Siddiqi, Janet Raboud, Donald E. Low, and for the Toronto Invasive Bacterial Diseases Network
Draft National Antiviral Strategy

• Proposes:
  – Increase stockpile to 200M treatment courses (current target 81M now at 37M)
  – Outbreak prophylaxis in certain health care settings
  – Outbreak prophylaxis for emergency services
  – Household post exposure prophylaxis

• Now in public/stakeholder engagement process

• US production capacity 80M/yr
  – If adopted will take a few years to meet goal
• Increases oseltamivir stockpile to 4 million treatment courses
• Establishes local stockpiles to = 30% of population at risk for each GeoCOCOM
• Initiates post exposure prophylaxis mitigation strategy
• Maintains treatment and selected outbreak/operational prophylaxis strategies
Modeling Efforts
NIH Sponsored Modeling Efforts Indicate:

- Being a member of a household containing an influenza case is the largest single risk factor for being infected.
- Antiviral post-exposure prophylaxis of household contacts is effective in reducing attack rates by 1/3 and peak attack rates by 50%.
  - Requires a robust stockpile
- Unless treatment can be initiated on day 1 there is little impact on community infection rates.
- Non-Pharmaceutical Interventions alone may reduce attack rate by ½ to 1/3.
DoD Modeling Efforts

• DTRA model that addressed impact of pandemic influenza vaccine
  – Impact of 0 vs 100% vaccination rate
  – 30% attack rate, vaccine with 30% effectiveness

• Rural installation:
  – 32% infected without vaccine
  – 17% infected with 100% vaccine coverage

• Urban installation:
  – 28% infected without vaccine
  – 15% with 100% immunization

• Lower rates if sequestration is employed

• No herd immunity – only those vaccinated are protected
HA Modeling

- Using basic DTRA computational methods
- Estimates derived with the following variables:
  - Attack Rates of 30, 20, 10%
    - Three assumptions: no, limited and effective community mitigation
  - Vaccine Effectiveness of 30, 50, 80%
    - Reflects unadjuvanted unmatched vaccine, unadjuvanted matched vaccine and adjuvanted vaccine or matched vaccine after priming
Effect of Variable Vaccination Rates on Number and Percent Infected

Population of 4M, 20% Attack Rate and 50% Vaccine Effectiveness
Effect of Variable Vaccination Rates on Number and Percent Infected

Population of 4M, 20% Attack Rate and 80% Vaccine Effectiveness

Vaccination Rate

Number Infected

Percent Infected

0
20
40
60
80
100

0
2
4
6
8
10
12
14
16
18
20

200,000
400,000
600,000
800,000

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Impact of Vaccine with Variable Effectiveness and Attack Rates

- As attack rates (AR) decreases so does the number of cases prevented with vaccine.
- As vaccine effectiveness (VE) increases greater reduction in % infected.

<table>
<thead>
<tr>
<th>Decrease in % infected for every 20% vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>30% VE</td>
</tr>
<tr>
<td>50% VE</td>
</tr>
<tr>
<td>80% VE</td>
</tr>
</tbody>
</table>
30% Vaccine Effectiveness
Effect of Variable Attack Rates (AR) and Vaccination Rate on Proportion of the Population Infected

Percent Vaccinated
Proportion Infected

30% AR
20%AR
10%AR

20%  40%  60%  80%  100%

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50% Vaccine Effectiveness
Effect of Variable Attack (AR) and Vaccination Rates on the Proportion of the Population Infected

![Graph showing the effect of variable attack rates and vaccination rates on the proportion of the population infected. The graph illustrates how different attack rates (30%, 20%, 10%) and vaccination rates (0% to 100%) affect the proportion of the population infected, with lines indicating a decrease in infection proportion as vaccination rate increases.]
80% Vaccine Effectiveness
Effect of variable Attack (AR) and Vaccination Rates on the Proportion of the Population Infected

Fraction Infected

Percent Vaccinated

30% AR
20% AR
10% AR
Antiviral Modeling

- Basic modeling using projected impact of a variety of strategies on DOD population
- Explored a number of existing models
- Used pre-existing modeling developed for Australia and applied DOD baseline data
- Universal findings:
  - Treatment alone will not halt the pandemic
  - Post exposure prophylaxis may blunt or halt the progression of a pandemic
Impact of Variable Antiviral Strategies on a population of 4.7 Million

The diagram illustrates the impact of different antiviral strategies on the number of infected individuals. The strategies include:

- **TX Only**
- **NPI & TX**
- **PEP & TX**
- **NPI & TX & PEP**

The chart shows the number of infected individuals (blue bars) and antiviral TC (red bars) for each strategy.
<table>
<thead>
<tr>
<th>Requirement</th>
<th># Infected</th>
<th># of TC available for outbreak prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP+TX+NPI</td>
<td>1,566,000</td>
<td>3,033,670</td>
</tr>
<tr>
<td>PEP + TX</td>
<td>4,700,000</td>
<td>Exhausts Stockpile</td>
</tr>
<tr>
<td>TX + NPI</td>
<td>940,000</td>
<td>3,600,000</td>
</tr>
<tr>
<td>TX</td>
<td>1,410,000</td>
<td>3,190,000</td>
</tr>
</tbody>
</table>
SEIR Modeling

- Used an existing model developed for the Australian Department of Health
- Population defined as
  - Susceptible
  - Exposed
  - Infectious
  - Removed (immune or dead)
- We added the variables of:
  - Population 4.7 Million
  - Variable infectivity ($R_0$ 1.2 - 2.4)
  - 30, 50, 80% provided post exposure prophylaxis
  - 80% treatment of those infected
Unmitigated Pandemic $R_0 = 1.2$

Number of Infectious People
($R_0 = 1.2$, No Interventions)

Time (Months)

Number of People

0 10000 20000 30000 40000 50000 60000
Unmitigated Pandemic $R_0$ 2.4

Number of Infectious People
($R_0 = 2.4$, No Interventions)
Effect of variable post exposure prophylaxis $R_0$ 1.2

Number of Infectious People
(Ro = 1.2, 80% of Receive Treatment,
Varied % of Contacts Who Receive Prophylaxis)

![Graph showing the number of infectious people over time with different prophylaxis rates.](image-url)
Effect of 80% treatment and variable post exposure prophylaxis R₀ 2.4

Number of Infectious People
(Ro = 2.4, 80% of Receive Treatment, Varied % of Contacts Who Receive Prophylaxis)

Time (Months)

Number of People

30% of Contacts get Prophylaxis
50% of Contacts get Prophylaxis
80% of Contacts get Prophylaxis
Do other models tell the same story

- PEP stops the pandemic
- PEP reduces hospitalizations
- PEP has a synergistic effect with other measures
The effective reproduction number achieved by using antivirals for treatment and post exposure prophylaxis. Assumes a basic reproduction of 1.5 and that individuals are isolated 2 days after the development of symptoms.

Taken from: Becker NG et al. Using Mathematical Models to Assess Responses to an Outbreak of an Emerged Viral Respiratory Disease. The Australian National University, National Centre for Epidemiology and Population Health April 2006
Cases in need of hospitalization over time from a baseline attack rate of 50% for three antiviral strategies (no antivirals, treatment alone, post exposure prophylaxis)

Taken from Becker NG et al. Using Mathematical Models to Assess Responses to an Outbreak of an Emerged Viral Respiratory Disease.
Additive effect of various interventions on daily incidence of infection assuming a compliance rate of 50%.

Modeling Summary

- Unadjuvanted vaccine will have a modest impact on mitigation
- Adjuvanted or other more effective vaccines will have a substantial effect on pandemic mitigation
- Antiviral use limited to treatment will not result in substantial reductions in overall impact on the DOD community
- Addition of an antiviral post-exposure prophylaxis strategy, combined with infection control and social distancing measures may halt a pandemic
Questions?

She’s coming to your next meeting...

PRACTICE SOCIAL DISTANCING!