The Impact of Pandemic Influenza on Public Health

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Part Five of Six

Interventions
Influenza Vaccine Development

1. Clinical study
   - Vaccine release
   - Standardizing reagents
   - Vaccine manufacturing

2. New variant virus
   - Cell culture isolate
   - Egg isolate
   - Development of HGR vaccine virus

3. Remove avian pathogenicity
   - Early harvest of eggs??
   - Cell culture production??

Other steps:
- WHO diagnostic test kit
- Post-vaccination serum/trials

Source: WHO Global Influenza Program
Vaccine Production

Lag between pandemic strain detection and full scale vaccine production

- Vaccine prototype development: 1-2 months
- Clinical batch production & Testing: 1-2 months???
- Optimistic Projection: Today
- Vaccine production: 2 month ~ 360 million?

Source: WHO Global Influenza Program
Key “Bottlenecks”

1. “Purity” of strain
2. Production requirements
   - Production system “EGG”
   - Bio-security
3. Clinical data allowing increase in vaccine availability

Clinical data allowing increase in vaccine availability

Clinical Trials

Source: WHO Global Influenza Program
Vaccine Production Capacity

- 70% of global vaccine production located in Europe (5 companies)
  - 50% of that production is exported outside of Europe

Source: EVM Press Release 30 April 2004

Source: WHO Global Influenza Program
Vaccine Consumption, 2000

Source: WHO Global Influenza Program
Vaccine

- Challenges
  - H5HA is poorly immunogenic as compared to H3N2 or H1N1 viruses
    - To date vaccines against H5 have required two doses or an adjuvant to induce a necessary level of neutralizing antibodies
  - Influenza virus has a high error rate making it evolve continuously
  - There are already two clades of HPAI H5N1 virus circulating
  - Manufacturing capacity is limited and licensing requirements are stringent
Vaccine

- September 16th, 2005—HHS
- News headlines
  - U.S. DHHS [is] buying $100 million worth of avian vaccine
  - Vaccine has not been approved by FDA
  - Proper dosage [is] being determined
    - Protection for two to twenty million Americans
Vaccine

- **Inactivated vaccine candidate:**
  - Sanofi Pasture has developed an unadjuvanted, inactivated H5N1 vaccine candidate
  - Prospective, randomized, double-blind trials (~450 adults, 18-64 years) established the need for two doses (neutralizing titer 1:40)
  - Now being tested in children and the elderly

- **Live, attenuated vaccine candidate:**
  - MedImmune (under U.S. contract) will develop at least one vaccine for each of the 16 HA
  - Candidate vaccine has been developed for H5 and H9 (phase one clinical trials)
Sanofi Pasture has developed an unadjuvanted, inactivated H5N1 (virus isolated in Southeast Asia in 2004) vaccine candidate

Reported in NEJM

- The higher the dosage of vaccine, the greater the antibody response produced
- Of the 99 people evaluated in the 90-mcg, high-dose group, 54 percent achieved a neutralizing antibody response to the vaccine at serum dilutions of 1:40 or greater
- Only 22 percent of the 100 people evaluated who received the 15-mcg dose developed a similar response to the vaccine
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- Generally, all dosages of the vaccine appeared to be well tolerated
- Almost all reported side effects were mild
- The second dose of the vaccine did not cause more local or systemic symptoms than the first
- Systemic complaints of fever, malaise, muscle aches, headaches, and nausea occurred with the same frequency in all dosage groups as in the placebo group
- Lab tests did not reveal any clinically significant abnormalities
A new genetically engineered vaccine, created by scientists at the CDC, is egg-independent and adjuvant-independent


A similar vaccine, adenovirus-based influenza A virus vaccine directed against the hemagglutinin (HA) protein of the A/Vietnam/1203/2004 (H5N1) (VN/1203/04) strain isolated during the lethal human outbreak in Vietnam from 2003 to 2005

Chemotherapy

- Prevent membrane fusion (M2 Inhibitors)
  - Amantidine (Symmetrel)
  - Remantidine (Flumadine)
- Neuraminidase inhibitors
  - Zanamivir (Relenza)
    - U.S. is buying $2.8 million (could treat 84,300 people)
  - Oseltamivir (Tamiflu)
  - Peramivir (more potent in vitro)?
Chemotherapy

- Relenza
  - Reduced the incidence of the disease in both young and older populations
  - First study—in participants 18 years of age or older, the proportion of people who developed symptoms confirmed to be the flu was 6.1% for the placebo group and 2.0% for the Relenza group
  - The second community study—enrolled people 12 to 94 years of age (56% of whom were older than 65 years)
    - In this trial, the percentage of people who developed symptoms confirmed to be the flu was reduced from 1.4% of the participants on placebo to 0.2% for those who used Relenza
Types of Protective Masks

- **Surgical masks**
  - Easily available and commonly used for routine surgical and examination procedures

- **High-filtration respiratory mask**
  - Special microstructure filter disc to flush out particles bigger than 0.3 micron
  - These masks are further classified:
    - Oil proof
    - Oil resistant
    - Not resistant to oil
  - The more a mask is resistant to oil, the better it is
  - The masks have numbers beside them that indicate their filtration efficiency
  - For example, a N95 mask has 95% efficiency in filtering out particles greater than 0.3 micron under normal rate of respiration
Types of Protective Masks

- The next generation of masks are called Nanomasks.
- These boast of the latest technologies like 2H filtration and nanotechnology, which are capable of blocking particles as small as 0.027 micron.
Do N95 Respirators Provide 95% Protection?

- AJIC paper by Balazy, et al.
- Recent study in AJIC by Balazy, et al., looked at respiratory protection devices used to protect the wearers from inhaling particles suspended in the air
- Filtering face piece respirators are usually tested utilizing non-biologic particles, whereas their use often aims at reducing exposure to biologic aerosols, including infectious agents such as viruses and bacteria
The investigators studied the performance of two types of N95 half-mask, filtering face piece respirators and two types of surgical masks. The collection efficiency of these respiratory protection devices was investigated using MS2 virus (a non-harmful stimulant, of several pathogens). The virions were detected in the particle size range of 10 to 80 nm.
Do N95 Respirators Provide 95% Protection?

- AJIC paper by Balazy, et al.
- The results indicate that the penetration of virions through the National Institute for Occupational Safety and Health (NIOSH)-certified N95 respirators can exceed an expected level of 5%
- The tested surgical masks showed a much higher particle penetration because they are known to be less efficient than the N95 respirators.
- The two surgical masks, which originated from the same manufacturer, showed tremendously different penetration levels of the MS2 virions—20.5% and 84.5%, respectively, at an inhalation flow rate of 85 L/min.
Do N95 Respirators Provide 95% Protection?

- AJIC paper by Balazy, et al.
- This study concluded that . . .
  - N95 filtering face piece respirators may not provide the expected protection level against small virions
  - Some surgical masks may let a significant fraction of airborne viruses penetrate through their filters, providing very low protection against aerosolized infectious agents in the size range of 10 to 80 nm.
  - It should be noted that the surgical masks are primarily designed to protect the environment from the wearer, whereas the respirators are supposed to protect the wearer from the environment (Am J Infect Control 2006; 34: 51-7)
There are six manufactures of N95 respirators in the U.S.
As of March 2006, the two largest U.S. manufacturers are at full capacity running 24/7.
Both of these played a large roll in filling the U.S. government’s order for approximately 100,000,000, N95 masks.
Lead time on certain styles is as long as five months.
U.S. inventory of unsold N95s changes on an hourly basis
   - The inventory is also at a record low quantity.
Capacity

- Other shortages now surfacing for the first time are for the following:
  - Influenza field tests kits
  - Hand sanitizers
  - Protective coveralls
  - Booties
- Pricing on N95 respirators with out escalation value is inching up
- The market is clearly on a first come first serve basis
- Smaller sizes have all but disappeared due to Asian demand
Food Safety

- Conventional cooking (temperatures at or above 70°C in all parts of a food item) will inactivate the H5N1 virus
- Properly cooked poultry meat is therefore safe to consume
- The H5N1 virus, if present in poultry meat, is not killed by refrigeration or freezing
- Home slaughtering and preparation of sick or dead poultry for food is hazardous—this practice must be stopped
- Eggs can contain H5N1 virus both on the outside (shell) and the inside (whites and yolk)
- Eggs from areas with H5N1 outbreaks in poultry should not be consumed raw or partially cooked (runny yolk); uncooked eggs should not be used in foods that will not be cooked, baked, or heat-treated in other ways
There is no epidemiological evidence to indicate that people have been infected with the H5N1 virus following consumption of properly cooked poultry or eggs.

The greatest risk of exposure to the virus is through the handling and slaughter of live infected poultry.

Good hygiene practices are essential during slaughter and post-slaughter handling to prevent exposure via raw poultry meat or cross contamination from poultry to other foods, food preparation surfaces, or equipment.
The World Health Organization recommends that environmental surfaces be cleaned by the following:

- Disinfectants such as sodium hypochloride, 1% in-use dilution, 5% solution to be diluted 1:5 in clean water, for materials contaminated with blood and body fluids
- Bleaching powder seven grams per liter with 70% available chlorine for toilets and bathrooms
- 70% alcohol for smooth surfaces, tabletops, and other surfaces where bleach cannot be used
- Environmental cleaning must be done on a daily basis
The FDA has approved a new laboratory test developed by the CDC to diagnose H5 strains of influenza in patients suspected to be infected with the virus. The product—the Influenza A/H5 (Asian lineage) Virus Real-time RT-PCR Primer and Probe Set provides preliminary results on suspected H5 influenza samples within four hours once a sample is tested. If the presence of the H5 strain is identified, then further testing is conducted to identify the subtype. If clinicians suspect a patient may be infected with an avian influenza virus, they should contact their state or local health department. For more information: