Challenges of Meeting Global Demand for Pandemic Flu Vaccine

David S. Fedson, MD
Sergy Haut, France
dfedson@wanadoo.fr
Influenza Vaccination in 71 Vaccine-producing and Non-producing Countries, 2002-2005

Vaccine-producing

Non-producing

Doses of influenza vaccine distributed / 1000 population

MIVSG 2007
Implications of the MIVSG Findings for Pandemic Vaccination

• Global vaccine distribution increased from 292 M doses in 2003 to >329 M in 2005
• ~95% of all doses are still produced in 9 countries
• In 2005, these 9 countries had 12% of the world’s population and used 59% of doses of vaccine
• Steady growth in vaccine use continues in non-vaccine-producing countries outside Western Europe, Canada and the US
Implications of the MIVSG Findings for Pandemic Vaccination

- Non vaccine-producing countries import virtually all of their vaccines from five Western European countries
- UN System Coordinator reports that almost 100 countries will want to be supplied with pandemic vaccines
- Prohibiting the export of pandemic vaccines from producing countries will lead to a global political as well as public health crisis
A Political Crisis Has Emerged Before the Pandemic

• In February 2007 Indonesia announced it would no longer share its H5N1 viruses with WHO unless it could have access to affordable pandemic vaccine
• World Health Assembly resolution in May attempted to address this problem
  - transfer production technology to six developing countries
  - create international stockpile of pandemic vaccines
  - establish mechanism for vaccine financing
  - renegotiate ‘terms of reference’ for virus sharing
• As of September 2007, the impasse between Indonesia and WHO over virus sharing had not been resolved
Estimated Global Mortality of a 1918-like Pandemic in 2004

- Excess mortality estimates in 1918-1920 varied > 30-fold across countries
- > 50% of this variation was explained by per capita income
- A similar pandemic in 2004 would have killed 62 million (51-81 million) worldwide
- A pandemic with a case fatality rate of H5N1 would have caused a far greater number of deaths
- 96% of deaths would have occurred in developing countries

Why We Should Worry

• Avian (H5N1) influenza in humans has killed ~60% (2004-2007) of those infected

• Recent population die-offs in mammals
  - early 1980s, avian (H7N7) influenza killed 20% of the harbour seals along the North Atlantic coast
  - early 1990s, distemper killed ~ 1/3 of the lions in E Africa
  - early 2000s, Ebola virus has killed ~ 50 % of the gorillas and chimps in several regions of Central Africa

• Human beings are bystanders; our disappearance would not affect the survival of the influenza virus in nature
The Pandemic Threat

“Influenza experts agree that another influenza pandemic is inevitable and may be imminent. … The world will be in deep trouble if the impending pandemic strikes this week, this month or even this year.”

Webby RJ, Webster RG.
Science 2003; 302;1519-22.
Pascal’s Wager and the Pandemic Threat

- Blaise Pascal - 18th Century French philosopher and mathematician
- Pascal’s wager - “Do you believe in God?”
  
  If you say God exists and he doesn’t, you haven’t lost anything
  If you say God does not exist and she does, you’re in trouble
  The sensible response is to say, “God exists.”

- Do you believe the next pandemic is imminent?
  The sensible response is to say,
  “Yes, the pandemic is imminent.”
Confronting an Imminent Pandemic: Vaccines, Antivirals or Other Agents?
Vaccination for an Imminent Pandemic

Basic Assumptions

• The pandemic is imminent (Pascal’s wager)
• A global estimate of vaccine demand and existing production capacity is essential
• Pandemic vaccines must be:
  – antigen sparing
  – acceptably immunogenic for populations, not optimally immunogenic for individuals
  – development must be supported by public funding
• The scientific challenges can be managed, but the logistical and political challenges for vaccine development, production and delivery are more difficult and much more important
Antigen Sparing Pandemic Vaccines

“When two doses of adjuvant vaccine are given ..., a phenomenal economy can be effected in the requirement of antigen.”

Clinical Trials of Inactivated H5N1 Vaccines in the United States

- Until 2006, FDA would not register adjuvanted influenza vaccines without efficacy trials, so NIAID tested only a nonadjuvanted vaccine
- Two doses @ 90 μg HA were moderately immunogenic
- Six months’ domestic production would be enough to vaccinate < 5% of the US population
- A national vaccination program using this vaccine would be socially and politically unsustainable
- FDA no longer requires efficacy trials for adjuvanted vaccines, but two years were wasted!
Clinical Trials of Adjuvanted H5N1 Vaccines in Other Countries

- Sanofi Pasteur (France) and CSL (Australia) - 2 doses alum adjuvanted, split virus @ 30 μg HA
- Sinovac (China) @ 10 μg HA and 4 Japanese companies @ 5 μg HA - 2 doses alum, whole virus
- GSK (Germany) and Baxter (Austria) - 2 doses alum- and ASO3-containing split or whole virus @ 3.75 μg HA
- Six months’ production of these *adjuvanted* vaccines would be enough to vaccinate with two doses:

<table>
<thead>
<tr>
<th>Number of people (million)</th>
<th>Global production</th>
<th>EU production</th>
<th>US production</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 μg HA →</td>
<td>~ 265</td>
<td>~ 175</td>
<td>~ 53</td>
</tr>
<tr>
<td>3.75 μg HA →</td>
<td>~ 700</td>
<td>~ 470</td>
<td>~ 140</td>
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</tbody>
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A Regulatory Dilemma: Pandemic Vaccination for an Individual or a Population?

<table>
<thead>
<tr>
<th>µg HA per dose</th>
<th>Individual</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% with neut Ab ≥ 1:40</td>
<td>Number of people Vaccinated</td>
</tr>
<tr>
<td>90</td>
<td>54</td>
<td>100</td>
</tr>
<tr>
<td>45</td>
<td>43</td>
<td>200</td>
</tr>
<tr>
<td>15</td>
<td>22</td>
<td>600</td>
</tr>
<tr>
<td>7.5</td>
<td>9</td>
<td>1200</td>
</tr>
</tbody>
</table>

Registering Adjuvanted Pandemic Vaccines: US and European Criteria

- FDA: clinical efficacy trials are no longer necessary
  “… the immune response elicited by the adjuvanted antigen (should be) significantly better than that elicited by the same antigen alone.” (Draft, March 2006)
- A two-fold increase in HI antibody or a 15% increase in seroconversion rate will be considered a meaningful difference
- FDA final criteria are more general but they are still focused on the individual, not the population
- EMEA - all three CHMP criteria

When supplies are limited and demand is great, pandemic vaccines that meet the needs of populations become essential
A Lesson from History: Swine Flu Vaccine Development in the US in 1976

Within 4-5 months of isolating the swine influenza virus, publicly funded vaccine trials were completed

- 6200 children, younger and older adults
- 4 different vaccines
- 3 dose levels
- one and two doses

In immunologically naïve subjects, very large doses of whole virus vaccine were required, and two doses were better than one
The Public Response to the Threat of an Imminent Pandemic

Pandemic influenza vaccines
- WHO estimated need (2006) - $10 B
- UN System response (2005-08) - < $3.4 B
- US domestic response - < $7.2 B
- US international response - > $400 M
- EU influenza research - < €100 M

Clinical trials of H5N1 vaccines
- US government funding generous
- Western European countries very little
The Public Response to Financial and Economic Crises

Financial crises - international loan guarantees
- Mexico (1995) - $38 billion (US, IMF, BIS)
- SE Asia (1997) - $120 billion (IMF, international)
- Brazil (1998) - $52 billion (IMF, international)


Economic crisis - US Strategic Petroleum Reserve
- 688.5 million barrels (December 1, 2006)
- Value at $60 per barrel - $41.3 billion

[www.spr.doe.gov/reports/dir.htm](http://www.spr.doe.gov/reports/dir.htm)
The WHO Response to the Pandemic Threat

WHO press conference 23 May, 2007

“The world is not prepared for a pandemic … We don’t have enough vaccine”… (we can cover only 1.5 billion people), and it will be “…a five year maximum before we believe we will have enough vaccine to begin to talk about equitable sharing.”

WHA resolution follow up

- 40-60 M dose vaccine stockpile will cover only HCWs and VIPs

WHO press statement on 16 May

- four-year $58 M program for yellow fever vaccination for 48 million people in West Africa. Yellow fever accounts for 30,000 deaths in this region each year.
Summary: Current Status of Inactivated H5N1 Vaccine Development

- The global demand for pandemic vaccines will be > 4-8 billion doses
- Demand for seasonal vaccine will increase too slowly
- H5N1 RG-engineered viruses give poor yields of HA
- Egg- and cell-based production capacity will not increase substantially within the next 3-5 years
- Each company is making conservative decisions in developing its own adjuvanted H5N1 vaccine
- Government funding for clinical trials is limited, except in the US, and almost non existent in Western Europe
- Almost all new technologies (better adjuvants, ID delivery, dermal patches, DNA vaccines, etc.) will take many years to develop
The inability to see the worst was “a mistake embedded in the banality of organizational life and facilitated by an environment of scarcity and competition, elite bargaining, uncertain technology, incrementalism, patterns of information ...(and) ... organizational structures ... that normalized signals of potential danger and re-aligned action with organizational goals.”

A Lesson from Childhood

“Then he shut the Things in the box with a hook. And the cat went away with a sad kind of look. “That is good,” said the fish. “He has gone away. Yes, but your mother will come. She will find a big mess! And this mess is so big and so deep and so tall, we can not pick it up. There is no way at all!”

Dr. Seuss
“The Cat in the Hat”
The Pandemic Threat: Is a Global Response Possible?

• Vaccination - need truly antigen sparing vaccines
  high growth reverse genetics seed strain
  inexpensive universally available adjuvant
  formulation suitable for populations
  government funding of vaccine development
  rapid production of huge amounts of antigen
  government organization and management of production, financing and distribution

• Antivirals -
  greater promise of efficacy
  greatly expanded production capacity
  much lower cost
  international commitments to stockpile
Can We Count On Using Inactivated Vaccines for an Imminent Pandemic?

- The technical limitations for vaccine production are significant, but the political, organizational and logistical limitations are even greater.
- Global vaccination will require an elaborate international organization and be such a nightmare to manage that it is not even being contemplated.

*Pandemic vaccination will not be a realistic possibility for > 85% of the world’s people who live in countries that don’t have vaccine companies and it will be difficult even for those who do.*
New Approaches to Confronting and Imminent Pandemic

- Live-attenuated vaccine
- Recombinant hemagglutinin vaccine
- Anti-inflammatory/immunomodulatory agents that modify the host response to influenza virus infection
Live-attenuated H5N1 Vaccine

Live-attenuated influenza vaccine (LAIV) for seasonal intranasal vaccination is licensed (MedImmune)

LAIV for H5N1 are being developed
  - broad cross-protection in mice and ferrets
  - one-dose, needle-free administration

Pre-pandemic use not possible, although vaccine could be stockpiled

LAIV production capacity is limited, but highly efficient
  - 180-fold increase in number of doses per egg
  - 100-fold increase if produced in cell culture

Existing human and animal vaccine production facilities are being considered; regulatory hurdles formidable

Potential to produce billion of doses in a few months
Recombinant HA (rHA) Vaccine

- rHA seasonal vaccine is safe and immunogenic
- Efficacy is ~100% against culture-proven influenza, 54% against ILI, despite vaccine/circulating virus mismatch
  
  \[ J \text{ Infect Dis} \ 2006; \ 193: \ 1223-8, \ JAMA \ 2007; \ 297: \ 1577-82 \]
- FDA will review of seasonal rHA vaccine in the US in 2007
- Adjuvanted rHA H5 vaccine could be developed, but is not receiving company or government support

\[ \text{rHA pandemic vaccines could be produced in pharmaceutical bioreactors, and the existing global bioreactor capacity is very large (2 million liters)} \]
### Number of People Vaccinated With Egg-based or rHA Adjuvanted Pandemic Vaccines

<table>
<thead>
<tr>
<th>No. of months of production</th>
<th>Egg-based vaccine</th>
<th>rHA vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 μg HA</td>
<td>44 M</td>
<td>425 M</td>
</tr>
<tr>
<td>3.75 μg HA</td>
<td>117 M</td>
<td>1.1 billion</td>
</tr>
<tr>
<td>Three</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 μg HA</td>
<td>132 M</td>
<td>1.25 billion</td>
</tr>
<tr>
<td>3.75 μg HA</td>
<td>350 M</td>
<td>3.4 billion</td>
</tr>
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Responding to the Pandemic Threat

‘Top-down’ approach - pandemic vaccination

- involves only scientific, company and governmental elites
- slow, complex and difficult to organize and manage

‘Bottom-up’ approach

- uses ordinary people and existing health care systems
- uses abundant supplies of inexpensive generic medications
- would be available worldwide on the first day of a pandemic
A Bottom-up Alternative to Vaccines and Antivirals: The Underlying Rationale for Statins

• Influenza causes heart attacks, congestive heart failure and strokes
• Influenza vaccination prevents these events
• Influenza increases levels of pro-inflammatory cytokines (e.g., TNFα, IL-6), especially H5N1
• Statins decrease these cytokine levels
• Statins decrease mortality in patients with bacterial sepsis and severe pneumonia, illnesses associated with elevated pro-inflammatory cytokines
• No published data from laboratory studies, although anecdotal comments report no efficacy in murine models (no concomitant antiviral treatment)
• No studies in ferrets or non human primates

PPAR\(\alpha\) Agonist Gemfibrozil Increases Survival in Mice with H2N2 Influenza

- BALB/c mice infected with H2N2 virus
- Treatment  - gemfibrozil 60 µg, days 4-10 (46)
  - untreated controls (50)
- Survival (~12 days)  - controls 26%
  - gemfibrozil 52%
- Statistical significance  - \(p = 0.0026\) (log rank test)
  - hazard function 0.46 (95% CI 0.26-0.76)
- Treated mice lost less weight
- Simvastatin not effective in this model (no data)

Statins, Fibrates and Influenza
Possible Mechanisms of Action

Direct antiviral effects
- alter microdomains on lipid rafts $\rightarrow$ ↓virus assembly and budding
- alter intracellular signaling pathways needed for virus replication

Non antiviral effects that improve endothelial and epithelial cell function
- ↓NF-κB and ↓AP-1 $\wedge$ ↓cytokines, chemokines, cellular adhesions molecules; modify caspase activation and apoptosis
- ↑eNOS $\wedge$ ↑NO,↑vasodilatation, ↓oxidative stress;
- alter actin cytoskeleton and intracellular tight junctions $\wedge$ ↑lung barrier function, ↓vascular leak
Could Statins and Fibrates Be Useful for Pandemic Treatment and Prophylaxis?

• The public health need for effective agents to complement vaccines and antivirals is profound

• Inexpensive generic are produced in developing countries
  - simvastatin by almost 100 companies, more than 50% located in China and India
  - fibrates by many companies, including some in India and China

• Generic agents produced in developing countries are inexpensive (five-day course)
  - simvastatin - $1; fibrates - ~ $3-5 or less

• Experimental, clinical and epidemiological evidence suggests statins and fibrates might be protective, but more research is needed
The Pandemic Threat: Is a Global Response Possible?

- Anti-inflammatory and immunomodulatory agents that modify host response
  - persuade influenza scientists and governments to accept the concept
  - define specific antiviral effects, if any, in vitro
  - animal studies in mice, ferrets and NHPs
    treatment and prophylaxis with and without antivirals, acute pharmacokinetics, combination treatment
  - observational studies of their effectiveness against influenza-related illness
  - define global production capacity and prices
  - determine logistical requirements for managing global distribution and use
The Pandemic Threat: Can We Meet The Global Demand For Vaccine?

“'It is not enough to say, 'We are doing our best.' You have got to succeed in doing what is necessary.'”

Winston Churchill