



**John R. La Montagne Memorial Symposium on
Pandemic Influenza Research: Meeting
Proceedings**

Planning Group on the John R. La Montagne Memorial
Symposium on Pandemic Influenza Research

ISBN: 0-309-65376-2, 214 pages, 8 1/2 x 11, (2005)

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**JOHN R. LA MONTAGNE
MEMORIAL SYMPOSIUM
ON
PANDEMIC INFLUENZA RESEARCH
Meeting Proceedings**

Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This study was supported by Contract No. N01-OD-4-2139, Task Order No. 159 between the National Academy of Sciences and the National Institutes of Health. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museum in Berlin.

*“Knowing is not enough; we must apply.
Willing is not enough; we must do.”*
—Goethe



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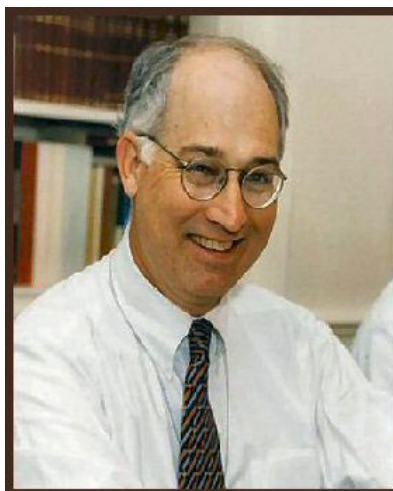
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JOHN R. LAMONTAGNE
1943-2004

This symposium is dedicated to the memory and legacy of John R. LaMontagne, Deputy Director of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health.

As a quiet but tireless champion, he helped to spearhead some of the most important recent global efforts to fight infectious diseases and to improve the health of children and adults everywhere. For nearly 30 years, John's thoughtful demeanor and even-handed approach led the way in tackling some of nature's greatest challenges to humankind. His influence has been incalculable on both national and international programs related to the development of vaccines for pertussis, rotavirus, AIDS, influenza, and malaria; new drugs for tuberculosis; and, more recently, biodefense research. In all of his work, John brought the human and public health dimensions to the efforts of laboratory research. He served the nation and the world immeasurably well, and we are better for it.

For the leadership, wise counsel, humor, and friendship that he shared with us and so many others, we are deeply grateful.

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1

INTRODUCTION

**JOHN R. LA MONTAGNE MEMORIAL SYMPOSIUM
ON PANDEMIC INFLUENZA RESEARCH**

The Institute of Medicine (IOM) of the National Academies of Science held a symposium, in memory of Dr. John R. La Montagne on April 4-5, 2005, to discuss the current state of the art of research on pandemic influenza and to identify gaps in research. The symposium serves as a first step of discussion towards a combined and coordinated research effort among Department of Health and Human Services agencies, other governmental agencies, international partners and the private sector. The statement of task that guided the Symposium agenda included these specific questions:

1. What is the current state of the science on pandemic influenza research?
2. What are the pressing unmet scientific questions and technical issues?
3. What administrative, logistic or legal impediments exist that block progress towards the development of interventions to respond to pandemic influenza?
4. How can collaboration among Global Health Security Action Group nations be strengthened to address unmet scientific questions and technical issues related to research on pandemic influenza?
5. What do experts believe are the most important next steps to take to advance research on pandemic influenza?

The Symposium was funded by the Department of Health and Human Services, Office of Public Health Emergency Preparedness, the Vaccine Program Office, and the National Institute of Allergy and Infectious Disease, National Institutes of Health.

Dr. Harvey Fineberg, President of the Institute of Medicine moderated the workshop, which included plenary presentations from leading experts. Following the plenary sessions, symposium participants engaged in working group discussions on a number of topics.

Day 1

| |
|---|
| 1. Influenza Virulence and Antigenic Change |
| 2. Controlling Animal Influenza and Decreasing Animal-to-Human Transmission |
| 3. Influenza Diagnostics for Surveillance |
| 4. Treatments and Immunotherapies – Antivirals and Non-Specific Approaches |

Day 2

| |
|--|
| 1. Immunology, Assay Standardization, and Correlates of Protection |
| 2. Pandemic Vaccines – Assessment, Development and Production Strategies |
| 3. Strategies to Contain Outbreaks and Prevent Spread |
| 4. Virus Transmission: Understanding and Predicting Pandemic Risk |

Each working group was directed to:

- identify research needs broadly in the topic area;
- select the highest priority activities that should be accomplished in the immediate term (1-2 years), short term (5 years), long-term (10 years); and
- provide input on approaches and potential timelines to address those priority needs.

An expanded list of specific questions for each workgroup was also provided.

A chairperson, topic briefer, and rapporteur, were assigned to each working group to facilitate the discussion. The working group briefer provided an overview of the state-of-the art (what is known) and the gaps (what is not known) in the working group area to frame the discussion. The rapporteur synthesized the discussion and provided an oral presentation of the working group's research priorities to the plenary.

The *Proceedings of the John La Montagne Memorial Symposium on Pandemic Influenza Research Gaps* represents a slightly edited transcript of the plenary presentations, rapporteur presentations, plenary discussion and presentation slides. It is not an official report of the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine, or the National Research Council (the "National Academies"). Opinions and statements included in the transcript are solely those of the individual persons or participants at the workshop, and are not necessarily adopted or endorsed or verified as accurate by the National Academies.

Appendix A contains short biographies of plenary speakers and Appendix B provides a list of the individuals who attended the symposium. The Symposium agenda follows.

JOHN R. LAMONTAGNE MEMORIAL SYMPOSIUM
 ON PANDEMIC INFLUENZA RESEARCH
 April 4-5, 2005
 INSTITUTE OF MEDICINE

Day 1- April 4, 2005

| | | | |
|-------|-------|--|--|
| 8:30 | 8:45 | Welcome and Introduction | Dr. Harvey Fineberg President, Institute of Medicine |
| 8:45 | 9:00 | Welcome | Honorable Michael O. Leavitt Secretary, U.S. Department of Health and Human Services |
| 9:00 | 9:15 | Meeting Objectives | Dr. Bruce Gellin Director, National Vaccine Program Office |
| 9:15 | 9:45 | Current Status of Avian Influenza and Pandemic Threat | Dr. Julie Gerberding Director, Centers for Disease Control and Prevention |
| 9:45 | 10:15 | Meeting the Challenge of Pandemic Vaccine Preparedness: An FDA Perspective | Dr. Jesse Goodman Director, Center for Biologics Evaluation and Review U.S. Food and Drug Administration |
| 10:15 | 10:45 | Global Pandemic Preparedness Research Efforts | Dr. Klaus Stohr Global Influenza Programme, World Health Organization |
| 10:45 | 11:00 | Discussion | Dr. Harvey Fineberg |
| 11:00 | 11:30 | The Role of NIH Research in Pandemic Influenza Preparedness | Dr. Anthony Fauci Director, National Institute of Allergy and Infectious Disease, National Institutes of Health |
| 11:30 | 3:30 | Concurrent break-out groups 1-4 (with working lunch) | |
| | | Group 1 (NAS Room 150): | Influenza Virulence and Antigenic Change |
| | | Group 2 (NAS Board Room): | Controlling Animal Influenza and Decreasing Animal-to-Human Transmission |
| | | Group 3 (NAS Lecture Room): | Influenza Diagnostics for Surveillance |
| | | Group 4 (NAS Members Room): | Treatments and Immunotherapies – Antivirals and Non-Specific Approaches |
| 3:30 | 5:30 | Working group 1,2,3,4 reports to the plenary | Dr. Harvey Fineberg |
| 6:00 | 9:00 | Reception in the Great Hall | |

JOHN R. LAMONTAGNE MEMORIAL SYMPOSIUM
 ON PANDEMIC INFLUENZA RESEARCH
 April 4-5, 2005
 INSTITUTE OF MEDICINE

Day 2-April 5, 2005

| | | | |
|-------|-------|---|--|
| 8:30 | 9:00 | Modeling and Pandemic Preparedness | Professor Neil Ferguson Professor of Mathematical Biology School of Medicine Imperial College of London |
| 9:00 | 9:30 | Clinical trials of potential pandemic vaccines-key issues | Dr. John Treanor Associate Professor of Medicine, and of Microbiology and Immunology University of Rochester Medical Center |
| 9:30 | 10:00 | Research Issues in Animal Surveillance | Dr. Robert Webster Professor and Chair, Department of Infectious Diseases, St. Jude's Children's Research Hospital |
| 10:00 | 10:15 | Break | |
| 10:15 | 2:30 | Concurrent break-out groups 5-8 with working lunch | |
| | | Group 5 (NAS Board Room): | Immunology, Assay Standardization, and Correlates of Protection |
| | | Group 6 (NAS Room 150): | Pandemic Vaccines – Assessment, Development and Production Strategies |
| | | Group 7 (NAS Members Room): | Strategies to Contain Outbreaks and Prevent Spread |
| | | Group 8 (NAS Lecture Room): | Virus Transmission: Understanding and Predicting Pandemic Risk |
| 2:30 | 4:30 | Working group 5,6,7,8 reports to the plenary | Dr. Harvey Fineberg |
| 4:30 | 6:00 | Preparation for Pandemic Influenza: Filling the Gaps in Knowledge and Understanding | Dr. Harvey Fineberg |

MEETING OPENING REMARKS

Dr. Harvey Fineberg, President, Institute of Medicine

Good morning and thank you for joining me for this Pandemic Influenza Research Symposium dedicated to the memory and legacy of John R. LaMontagne. John was a giant in infectious disease and vaccine research. He made extraordinary contributions to the development of swine flu vaccine, the whooping cough vaccine and vaccines against childhood diarrheas and pneumonia. He was a dedicated public servant and mentor to many. In all of his work, John brought the human and public health dimensions to the efforts of his research. He served the nation and the world immeasurably well, and we are better for it.

I know for many of you, the memory of John and his quiet but tireless efforts to fight infectious diseases and to improve the health of people everywhere has brought you here to give of your time and intellectual efforts to advance his work. As you know, fighting influenza was one of John's passions. He recognized influenza as a constant challenge to the health of our nation and the world and that the possibility of a pandemic outbreak related to new influenza strains, to which there is little immunity in the population, is as an ever-present threat. It is that threat that brings us here today to take stock of where we are and where we need to be in order to be better prepared to respond when that threat becomes a reality.

Over the next two days you will discuss in the working groups the current state of the art of research on pandemic influenza and identify gaps in research on influenza virology, immunology, diagnostics, antiviral drugs, surveillance/transmission, vaccines and their production, and strategies to contain outbreaks and prevent spread. We are seeking in the workshops to develop and refine everyone's best thinking on the most glaring research gaps for each topic and develop ideas for how to progress in closing those gaps in the short and long term. While we will not adopt any formal recommendations, we intend for each participant from the public or private sector to emerge with a clearer idea of the constructive roles they can play in influenza research and preparedness.

The success of this Symposium will rely upon candid, open discussions among the range of experts present. In this spirit, I would like to note that we are joined by a few members of the press who have continually followed the ongoing topic of pandemic flu preparations. Because we wish to encourage free and unfettered discussions throughout the symposium, we have stipulated that all remarks made during the plenary sessions and individual working groups must be considered on background only and not for quotation or attribution. Of course, any individual participant who wishes to engage in one-on-one interviews with reporters on the record may do so.

It is now my pleasure to introduce the Honorable Michael O. Leavitt Secretary of the Department of Health and Human Services.

PLENARY SPEAKERS, DAY 1

OPENING REMARKS

The Honorable Michael Leavitt, Secretary of the Department of Health and Human Services

Thank you, Harvey, for that kind introduction (Harvey Fineberg, President of the Institute of Medicine).

This meeting is a tribute to a man who was a friend to many in this room, Dr. John La Montagne. You all know how his brilliant work helped save people from many diseases. While working on one of these projects, he told a colleague, "It's good that we're doing this. But if anything is going to get us, it will be the flu."

I am also especially pleased to have the opportunity to share the podium with Dr. Fineberg this morning. Because, as he knows, I have learned many lessons from his excellent book: *The Epidemic that Never Was: Policymaking and the Swine Flu Scare*.

I know that many of you have dedicated your careers to this field. In the short time that I have been Secretary of Health and Human Services, I have become acutely aware of the disastrous public health impact that an influenza pandemic could have throughout the world. This is one of the most urgent health challenges we face, and I've made it a top HHS priority. Recently, I increased my briefing frequency on the flu to daily.

While much of our attention is focused on the H5N1 virus in Asia, I know very well that it is not the only flu threat we face. Many of the lessons that we learn from it will prepare us for annual influenza as well as for other potentially pandemic influenza viruses that may emerge in the future.

President Bush also understands the gravity of our situation. In fact, the United States government has made significant progress on pandemic influenza since he took office. We have increased spending on influenza tenfold over the past 5 years. We have added flu vaccine and flu drugs to the stockpile and made influenza part of regular public health discussions.

In order to increase our readiness against a pandemic strain of influenza, last Friday, on my recommendation, President Bush added pandemic influenza to the list of quarantinable events. This gives HHS the authority to take steps to prevent people with a new or reemerging influenza virus from infecting others by stopping them at our borders.

As we learned from CDC in last week's Morbidity and Mortality Weekly Report, there was a silver lining in last season's influenza vaccine situation. Despite the fact that we lost nearly half of our expected influenza vaccine supply, careful management of the available supply allowed this vaccine to be directed to the most vulnerable members of our population. We also sought out additional vaccine produced by foreign manufacturers and made arrangements to use

it if needed. I applaud the remarkable effort that this took, and the close working relationship between our agencies, the vaccine companies, state and local health officials, and healthcare providers that made it possible.

In spite of such challenges as that one, we've made great progress on influenza preparedness over the past few years. Flu preparation is an international responsibility, and I know many of you are involved in projects around the world.

My study of this matter has been short in duration but intensive, and the best in the world. Flu virus is a networked enemy. We must fight it with a networked army.

The United States will take precautions necessary to protect this country but we know our success is dependent on others protecting their own countries.

When you fight a networked enemy, a mainframe response will not do. Let me just mention a few steps we've taken here in the United States:

- HHS is working to bring more influenza vaccine manufacturers into the domestic market through the joint efforts of CDC, FDA, NIH, our National Vaccine Program Office (NVPO), and the Office of Public Health Emergency Preparedness.
- We're working to accelerate the development of new influenza vaccine formulation and production techniques that will allow us to have a flexible surge capacity to make the doses of vaccine that we would need in a pandemic.
- We're devoting an unprecedented amount of resources to vaccine research, development, and procurement, and we want to increase the routine seasonal use of influenza vaccine for all who would benefit from it.
- On Friday, I was delighted to announce a contract with Sanofi Pasteur for the development of an influenza vaccine produced in cell culture rather than eggs.

We're doing all we can to ensure that Americans are healthy and protected against the flu. And everything we do to improve our approach to seasonal influenza prepares us to respond to an influenza pandemic.

In the past century, the world experienced three global outbreaks, or pandemics, of influenza. The recent emergence and persistence of a new influenza virus in birds in Asia and its infection of a limited number of humans with a high mortality rate has raised concern among scientists and public health professionals about the possibility of another pandemic influenza.

Dr. Julie Gerberding will talk more about this situation later this morning.

I am sure that most of you have seen the HHS draft Pandemic Influenza Preparedness and Response Plan we released last August, and I know that many of you have submitted comments. We're grateful for all of your input. I expect we will have the next revision out in the next few months. I am hopeful that the discussions and deliberations at this important meeting will feed into this effort.

And as part of our commitment to preparedness against the possibility of a pandemic, I am pleased to report that NIH has very recently begun clinical trials of a vaccine specifically designed against the H5N1 strain of avian influenza that is currently circulating in Asia. We have also gone ahead and produced 2 million doses of this vaccine in bulk. You will hear more about these efforts from Dr. Fauci later this morning.

Since we don't know where or when a pandemic may originate, we have enhanced our surveillance network across the globe, but especially in east and southeast Asia, where we at HHS have people on the ground who are working with local researchers, clinicians, and governments. We are also in daily contact with the World Health Organization Secretariat in Geneva and its regional offices in Manila and New Delhi. We at HHS have experts on short- and long-term assignments to W.H.O. headquarters and the W.H.O. Country Office in Vietnam.

I've begun meeting with health ministers and ambassadors from affected countries, and soon I will begin to visit their countries. In May, I will also travel to the World Health Assembly, where pandemic influenza preparedness is on the agenda; I am convening a special meeting of health ministers from affected and donor countries to coordinate planning on influenza, followed by a technical meeting of experts the next day. Influenza will continue to be an important topic in all my discussions with my counterparts.

Needless to say, I've gained a much greater appreciation for how important your work is. We have learned so much in recent years about how to assess and respond to flu outbreaks, but we also have much more work to do. I am glad that all of you are engaged in these research and public health activities, and glad that you've come together today to compare notes and help us reexamine and reset the direction of our collective efforts.

While pandemics have happened several times in the past, never before have we had all of the tools of today. Never before have we possessed the wealth of knowledge on the problem and the ability to prepare. The challenge is immense, but so is our will to protect and preserve.

The outcome of this conference will be extremely important and will help guide us all in our work toward improving our ability to prepare ourselves. I look forward to being able to present a brief report on this symposium to my fellow health ministers when we meet at the World Health assembly next month.

MEETING OBJECTIVES

Dr. Bruce Gellin, Director, National Vaccine Program Office

As you just heard from Secretary Leavitt, the Department of Health and Human Service is devoting unprecedented focus on pandemic influenza preparedness. In addition to our work and the many activities that you'll hear about during this meeting, other countries and international organizations are also stepping up to the plate. As individual nations and as a global public health community, we are now better prepared to detect and respond to an influenza pandemic, but we clearly have to do more.

Secretary Leavitt also reminded us that the draft pandemic influenza plan issued last summer is now being revised to more clearly articulate the roles and responsibilities at each stage of an emerging pandemic and provide clearer guidance to state and local health departments, the healthcare sector and the public. In addition, the updated plan will conform to the new format proposed by the World Health Organization (WHO) which will facilitate international communication before and during a pandemic.

Like the pandemic influenza plans of many countries, our plan has had a long incubation period. In 1995, under John La Montagne's leadership, the National Institutes of Health convened an international meeting to examine available data, identify critical scientific issues, and frame research questions to address gaps in knowledge vital to controlling pandemic influenza. Many of you participated in that meeting in December 1995, and much has happened since, but it is worth reviewing a few of the nearly 20 recommendations as they appeared in the 1997 supplement to the *Journal of Infectious Disease (JID)*:

- Improve or sustain international surveillance efforts, particularly in Asia and the Pacific Rim.
- Improve our understanding of the role of humeral, cellular and mucosal immunity in protection against exposure to influenza, especially in immunologically naive populations.
- Determine immunologic correlates of protection for live attenuated influenza virus vaccines.
- Improve our understanding of the molecular basis of pathogenesis of pandemic strains.
- Manufacture and clinically test new, inactivated vaccines made from selected novel influenza viruses that have pandemic potential.
- Evaluate the effectiveness of using less than 15 micrograms of the current inactivated vaccine.

In addition to the specific research priorities was the overarching recommendation to establish a mechanism to facilitate collaboration among international laboratories -- to share reagent strains and new technological advances and to enhance overall capacity and capability. Some of those ideas that helped us respond to severe acute respiratory syndrome (SARS). The international composition of this meeting acknowledges the need for a coordinated global response.

By the time the proceedings of that 1995 NIH symposium were published in 1997, we were facing the outbreak of H5N1 in Hong Kong that was challenging some existing assumptions. We expect that the road ahead will include additional twists and turns.

Before turning our attention to the task ahead over the next two days, I would like to offer one final quote from Dr. La Montagne that appeared in the 1997 JID supplement. "The ability to initiate the tasks outlined above is beyond the responsibility and resources of the NIH or any single government agency. This scope of action requires international organizations and the vaccine and pharmaceutical companies."

Acknowledging the need for a coordinated global response, HHS and WHO organized this meeting to refocus our collective efforts on the scientific underpinnings of preparedness. Within this venue of the National Academy of Sciences, and with Institute of Medicine (IOM) president Dr. Fineberg presiding, we have assembled the top scientific leaders to seek your individual and collective input on critical scientific and epidemiological questions.

The goals of this meeting are to describe the state of the sciences relevant to pandemic influenza, identify and prioritize scientific and technical questions that will have the greatest impact on our ability to identify and respond to a pandemic, and develop an action plan for addressing those gaps. This meeting also provides an opportunity set a course that will strengthen our international collaborations. For this we will need your input, and have constructed the meeting with substantial time for breakout sessions that focus on specific scientific areas.

Last fall, Dr. John La Montagne speculated to a small group of us that pandemics might not necessarily be the virologic equivalent of the Big Bang, wherein a spark instantly becomes a raging fire. Rather, he hypothesized, that our strengthened surveillance systems and new diagnostic tools allow us to watch pandemics slowly unfold. If that is the case, then now is the time to advance our preparedness, because the only thing that is more difficult than planning for an emergency is explaining why you didn't. We have a large task ahead.

CURRENT STATUS OF AVIAN INFLUENZA AND PANDEMIC THREAT

Dr. Julie Louise Gerberding, Director, Centers for Disease Control and Prevention

Secretary Leavitt, in his opening remarks, used a metaphor—the network model—that is absolutely appropriate for this meeting. CDC is a highly connected hub in the network of disease preparedness and response, and we are here to exchange ideas and information with our colleagues from the Department of Health and Human Services, (DHHS), the Department of Defense, the Department of State, other federal agencies, state and local agencies, private sector organizations, academics, and our key global partner, the World Health Organization. We thank Dr. Fineberg and IOM because you are also a highly connected node in this network, and much of the scientific work we do would not happen without your facilitation.

Every time I have been in this room in the last four years, it has been in the context of some horrifying public health threat—anthrax, smallpox, SARS, and now influenza. Anthrax, smallpox, and SARS are threatening situations where the risk calculation is relatively low yet the terror threat is high. In the case of influenza, the risk calculation suggests that we will certainly experience a pandemic sooner or later, yet most people perceive a very low threat. How do we prepare our society and the world for a likely threat amid growing complacency?

The fact that we are here today speaks to growing scientific recognition that influenza is an urgent menace, and that the time for action is now. I'm going to talk about we know about avian influenza, highlight what we don't we know, and mention a few steps we are taking to do something about it.

One thing we know for sure is that influenza epidemics and pandemics do happen—the three large pandemics in the last century attest to that. But as Mike Osterholm will tell you, many other influenza pandemics have also occurred throughout recorded history, some as large if not larger than the 1918–1919 epidemic. It doesn't take a scientist to appreciate that the clock is ticking, and that another pandemic is due.

We also have some understanding of how antigenic shift occurs in influenza viruses, and why pandemics may emerge. There are at least two mechanisms. One is through reassortment of viruses—typically avian and human viruses in swine, which create a new strain which can infect people who lack immunity to the new antigens. The second mechanism, direct avian-to-human transmission, may also have accounted for some of the past pandemics.

The picture becomes more complicated in the context of the current avian influenza outbreak, because we also have the possibility of an avian virus and a human virus reassorting in people and/or other host species. We need to know much more about influenza virus strain evolution before we can predict whether any of these mechanisms would allow this or any other avian strain to emerge and become more efficiently transmitted to people.

We also know that pandemics are brutal on their impact on human mortality. The spike in mortality in 1918 and 1919 is a sober reminder of what happened when global connectivity was unusually high, given the movement of people that occurred at the end of the world war. But that situation was nothing compared with the connectivity and complex global networks in which we

live and move today, and the increasing connectivity between humans and animal reservoirs of influenza viruses.

We have only to think about SARS, as it moved from “Hotel M” in Hong Kong to global distribution in just a few short weeks, to be sobered by how quickly a problem in one corner of the world can reach other backyards literally overnight. So while we can be optimistic about advances in medical care and vaccine development, the potential for a pandemic with high mortality in this very small world is great.

We know of avian influenza have been identified in people living in Thailand, Vietnam, and Cambodia. Why haven't we seen human cases in other countries? Is this surveillance bias? Is it virologically determined? Is it host determined? What exactly is the explanation for the relative paucity of infections among people, given that the virus is much more prevalent in avian species than these human cases would suggest? What is the full spectrum of illness? We must do more research to understand the relationships among the virus, its virulence factors, the host's immune response, and the clinical outcomes of infection.

We know that the people with H5N1 influenza reported to the WHO in the current outbreak have a high mortality rate. To date, 74 cases and 49 deaths in Asia have been reported to the WHO, yielding case fatality rate of 66 percent. We don't know if this fatality rate is accurate. Does it represent detection bias—in that sicker people are being diagnosed? Is the reported number of cases the tip of the iceberg, in that many less severe or asymptomatic cases have gone unrecognized? We do not know why so many young people died from influenza in 1918–1919. Certainly the stereotypical explanation has cited complications—particularly bacterial complications, although a 1976 review in the *New England Journal of Medicine* suggests that they might not have been the reason for so many deaths. Case reports, a review of the pathology literature, and recent experiments with influenza virus constructs containing genes from that pandemic strain suggest other potential explanations for the high incidence of shock and death associated with that pandemic.

Most of the affected individuals in the current epidemic have been young and healthy. Why young and healthy people? Does this reflect exposure bias or a susceptibility in young people that perhaps reflects lack of prior exposure? Does age, ethnicity, nutrition status, or viral strain affect the case mortality rate? We need to address these very important questions about the clinical presentation and outcome of avian influenza through careful epidemiologic, laboratory, and clinical investigations.

We also lack information on the relationship between treatment and the outcome of these infections. We know that the avian viruses currently causing human infections are resistant to amantadines and susceptible to neuraminidase inhibitors, and that some of the patients who succumbed had been treated. But whether treatment, alone or in combination of antivirals, offers any virologic or outcome advantage is unknown.

We know that exposure to infected birds is a major source of infection among people, but what are the specific modes of transmission? Recent case reports suggest exposure to contaminated water and eating uncooked chicken could be risks as well. If we look back at the H5N1 influenza virus outbreak in Hong Kong in 1997, some information could direct us to the studies that we need to do today. We learned from case-control studies that the primary risk factor in the last outbreak was exposure to live poultry, and that the prevalence of the virus in chickens was very high. The prevalence of antibody to H5 in a cohort of the exposed population

was about 10 percent, and those who butchered high risk birds were at higher risk for seropositivity. Targeted research—designed to understand the relationship between exposure, transmission modes, immunity, and disease outcome, as well as opportunities for intervention in environmental, occupational, household, and healthcare settings—is critical in affected countries. We must conduct these studies and many others in people, birds, swine, other mammals, as well as water and other potential environmental reservoirs to develop a comprehensive understanding of the epidemiology of this infection.

Although we know that avian H5N1 influenza virus is widespread in Asia today, some places are not represented in the surveillance network or have very weak connectivity, and those weak links create vulnerability. Research needs to address how to strengthen the network and obtain information from these missing nodes on the network.

Other critical questions include: Are all virus isolates among the poultry strains alike, and are they evolving? If so, what selection pressures are encouraging that evolution? Where are the carriers of these viruses from one country to another or one population to another or one species to another? How does the ecology of avian influenza virus affect its mobility to other parts of the world through migratory bird vectors or other movements of people, animals, birds, or fish?

Unlike the 2003 isolates, which were homogeneous, these H5N1 influenza viruses now circulating in Asia are expressing some degree of heterogeneity. We don't know how immunogenic these viruses are. We also don't know what implications heterogeneity will have for vaccine development. We need a much more comprehensive understanding of the differences between the human and the avian isolates and their geographic distribution.

Given the relative paucity of what we know compared with what we need to know, what are we doing about it? At DHHS, Secretary Leavitt received a comprehensive briefing on influenza even before his Senate confirmation, and CDC has since had several face-to-face briefings with the DHHS team as well as a daily update. We could not have better departmental leadership and commitment. Besides our support for WHO as the lead for international preparedness, we are also investing resources in specific Asian countries to improve their ability to detect emerging influenza strains and transport them to laboratories for reliable evaluation. Our other regional activities include our International Emerging Infections Program in Thailand and our collaboration with the US Naval Medical Research Unit laboratories of the U.S. Department of Defense (DOD) in Jakarta and Cairo.

Our laboratory and epidemiologic scientists are hard at work to study the genetic determinants of pathogenicity and transmissibility, the genomic bases of drug resistance and binding properties, tracking and monitoring the antigenic evolution of virus isolates in time and place, and understanding the epidemiology of the current epizootic in more detail. This meeting will undoubtedly incubate other scientific questions.

We are taking steps to enhance communication between public health and veterinary agencies. Dr. Lonnie King, former dean of the College of Veterinary Medicine at Michigan State University, is heading CDC's Office of Strategy and Innovation. Dr. King is forging better connectivity between CDC and the veterinary community—both domestically and internationally—and the academic animal health community.

Through investments in influenza preparedness as well as global detection of emerging threats, CDC is building a comprehensive international health protection network to connect all

relevant capabilities and assets. The private sector is a key partner that we have engaged through our global roundtable of senior business leaders to understand how the international business community can benefit from our preparedness efforts and provide relevant information as another hub in our preparedness and response network.

Secretary Leavitt mentioned that President Bush has authorized us to use our quarantine powers, if needed, for a novel or re-emergent strain of influenza with the potential to cause a pandemic. We are also moving domestically to expand our capacity from 8 quarantine stations to 30. Those are important steps, but they also highlight the fact that preparedness takes time – and time is of the essence if we hope to optimize quarantine and isolation capacity on a global scale. We had some practice with SARS. That experience taught us that with the right framework, people can do the seemingly impossible. But SARS was a relatively easy problem compared with the global challenges that an influenza virus strain with a high reproductive number (R_0) would create. We need to investigate the human aspects of isolation and quarantine, and what we need to do to prepare people and engage our leaders and our population in appropriate isolation and quarantine responsibilities.

Anthrax and SARS taught us that we need solid communication science if we are going to have any hope of managing a major influenza outbreak. That science needs to address the content and credibility of communication to diverse populations. That effort isn't just about translating science into messages that ordinary people can understand. It's about translating ordinary messages into hopeful and helpful information that people of multiple cultural and linguistic backgrounds can use, and about transmitting information through a variety of channels on which we do not usually rely in the Western Hemisphere. I would urge this meeting not to lose sight of the human side of the research agenda, and to grapple with the communication sciences that are essential to our ability to prepare for and respond to an influenza outbreak or pandemic.

The biggest lesson we have learned from other public health threats is that the most important enemy is complacency. I do not know how to develop a research agenda around preventing complacency, but I would submit that doing so is urgent. My fear is that although the lens may be shining on avian influenza right now, if the H5N1 strain does not become more transmissible to people, we will falsely assume that the threat is over. Worse, we could be accused of inappropriately revving up our preparedness efforts without a scientific basis. I do not believe we have done that, but it reminds us about the importance of credible communication so that the public understands the need to prepare and what is at stake if we don't. We must strike the right balance between action and reassurance. The stimulus to effective research that this conference promises to foster is an essential step toward evidence-based policy decisions, effective public health action, and credible communication in the context of this global threat.

Plenary Presentation Slides-Dr. Julie Louise Gerberding

| <p style="text-align: center;">Dr. Julie Louise Gerberding Director Centers for Disease Control And Prevention</p> <p style="text-align: center;">Current Status of Avian Influenza and Pandemic Threat</p> <p style="text-align: center;">Presentation To IOM, April 2005</p> | <p style="text-align: center;">Influenza Pandemics Happen!</p> <p style="text-align: right;">2</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|--|----------------|---------|----------------------|-----------------|----------------|------------------|---------------|-----------|----------------------|----------------|--------------|----------------------|---------------|--------------|---|------|-----------|------|------|-------|------|------|-------|------|------|-----------|-----------|------|-------------|------|
| <p style="text-align: center;">Mechanisms of Antigenic Shift</p> <p style="text-align: right;">3</p> | <p style="text-align: center;">Infectious Disease Mortality in the United States 1900 - 1996</p> <p style="text-align: right;">4</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p style="text-align: center;">Bacteriologic Findings among Patients with Influenzal Pneumonia 1918-1919</p> <table border="1"> <thead> <tr> <th></th> <th>Sputum</th> <th>Blood</th> </tr> </thead> <tbody> <tr> <td><i>S. pneumoniae</i></td> <td>1230/1609 (76%)</td> <td>78/1507 (4.9%)</td> </tr> <tr> <td><i>S. aureus</i></td> <td>133/1485 (9%)</td> <td>0/1535</td> </tr> <tr> <td>Beta-hemolytic strep</td> <td>254/2077 (12%)</td> <td>32/1587 (2%)</td> </tr> <tr> <td><i>H. influenzae</i></td> <td>436/729 (60%)</td> <td>1/1400 (.1%)</td> </tr> </tbody> </table> <p style="text-align: left; font-size: small;">Stevens KM. NEJM 1978; 1363-66</p> <p style="text-align: right;">5</p> | | Sputum | Blood | <i>S. pneumoniae</i> | 1230/1609 (76%) | 78/1507 (4.9%) | <i>S. aureus</i> | 133/1485 (9%) | 0/1535 | Beta-hemolytic strep | 254/2077 (12%) | 32/1587 (2%) | <i>H. influenzae</i> | 436/729 (60%) | 1/1400 (.1%) | <p style="text-align: center;">Potential Causes of Influenza-related Shock and Death</p> <ul style="list-style-type: none"> • Exacerbation of undiagnosed underlying conditions • Coincidental occurrence of an unrelated problem • Influenza pneumonia • Secondary bacterial pneumonia • Toxic shock syndrome / endotoxemia • Hypersensitivity response • Myopericarditis • Cytokine-induced shock syndrome <p style="text-align: right;">6</p> | | | | | | | | | | | | | | | |
| | Sputum | Blood | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <i>S. pneumoniae</i> | 1230/1609 (76%) | 78/1507 (4.9%) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| <p style="text-align: center;">Avian Influenza is Emerging</p> <p style="text-align: right;">7</p> | <p style="text-align: center;">Outbreaks of Highly Pathogenic Avian Viruses Before 2004</p> <table border="1"> <thead> <tr> <th>Avian subtype</th> <th>Country</th> <th>Year</th> </tr> </thead> <tbody> <tr> <td>H5N3</td> <td>U.S.</td> <td>1983</td> </tr> <tr> <td>H7N7</td> <td>Australia</td> <td>1985</td> </tr> <tr> <td>H5N2</td> <td>Mexico</td> <td>1995/95</td> </tr> <tr> <td>H7N3</td> <td>Pakistan</td> <td>1995</td> </tr> <tr> <td>H5N1</td> <td>Hong Kong</td> <td>1997</td> </tr> <tr> <td>H5N2</td> <td>Italy</td> <td>1997</td> </tr> <tr> <td>H7N1</td> <td>Italy</td> <td>1999</td> </tr> <tr> <td>H5N1</td> <td>Hong Kong</td> <td>2001-2003</td> </tr> <tr> <td>H7N7</td> <td>Netherlands</td> <td>2003</td> </tr> </tbody> </table> <p style="text-align: right;">8</p> | Avian subtype | Country | Year | H5N3 | U.S. | 1983 | H7N7 | Australia | 1985 | H5N2 | Mexico | 1995/95 | H7N3 | Pakistan | 1995 | H5N1 | Hong Kong | 1997 | H5N2 | Italy | 1997 | H7N1 | Italy | 1999 | H5N1 | Hong Kong | 2001-2003 | H7N7 | Netherlands | 2003 |
| Avian subtype | Country | Year | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H5N3 | U.S. | 1983 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H7N7 | Australia | 1985 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H5N2 | Mexico | 1995/95 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H7N3 | Pakistan | 1995 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H5N1 | Hong Kong | 1997 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H5N2 | Italy | 1997 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H7N1 | Italy | 1999 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H5N1 | Hong Kong | 2001-2003 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H7N7 | Netherlands | 2003 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| <p>Situation Report: Confirmed Human H5N1 Cases Updated April 3, 2005</p> <table border="1"> <thead> <tr> <th>Country</th> <th>H5N1 cases</th> <th>Deaths</th> <th>Case fatality</th> </tr> </thead> <tbody> <tr> <td>Thailand</td> <td>17</td> <td>12</td> <td>71%</td> </tr> <tr> <td>Vietnam</td> <td>55</td> <td>35</td> <td>64%</td> </tr> <tr> <td>Cambodia</td> <td>2</td> <td>2</td> <td>100%</td> </tr> <tr> <td>Total</td> <td>74</td> <td>49</td> <td>66%</td> </tr> </tbody> </table>  <p>CDC 9</p> | Country | H5N1 cases | Deaths | Case fatality | Thailand | 17 | 12 | 71% | Vietnam | 55 | 35 | 64% | Cambodia | 2 | 2 | 100% | Total | 74 | 49 | 66% | <p>Risk Factors for Human H5N1 Illness in 1997</p> <ul style="list-style-type: none"> • Case control study primary risk factor for H5N1 illness <ul style="list-style-type: none"> • Exposure to live poultry in poultry stall or market in the week prior to illness • Studies on poultry workers in Hong Kong markets <ul style="list-style-type: none"> • 20% chickens infected with H5N1 • Seroprevalence for H5 antibody = 10% • Seroprevalence in general population = 0% • Occupational risk factors for poultry workers: <ul style="list-style-type: none"> • Butchering • Exposure to sick birds <p>CDC 10</p> |
|---|---|------------|---------------|---------------|----------|----|----|-----|---------|----|----|-----|----------|---|---|------|-------|----|----|-----|--|
| Country | H5N1 cases | Deaths | Case fatality | | | | | | | | | | | | | | | | | | |
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| Total | 74 | 49 | 66% | | | | | | | | | | | | | | | | | | |
| <p>1997 H5N1 Field Studies</p> <ul style="list-style-type: none"> • Most cases likely contracted influenza after exposure to infected poultry <ul style="list-style-type: none"> • Human-to-human transmission occurred but was uncommon • Groups with greatest risk of H5-antibody <ul style="list-style-type: none"> • Household contacts and poultry workers • Although poultry workers had highest antibody rate, none found ill with H5 <ul style="list-style-type: none"> • May have been protected based on prior exposures to avian H5 <p>CDC 11</p> | <p>Avian Influenza Poultry Outbreaks, Asia, 2003-04</p>  <p>CDC 12</p> | | | | | | | | | | | | | | | | | | | | |
| <p>Situation Report: Avian Influenza 2005</p> <ul style="list-style-type: none"> ✓ H5N1 enzootic of unprecedented size and complexity now established <ul style="list-style-type: none"> – Poultry outbreaks in 9 or more countries – Ongoing poultry outbreaks and human cases – Substantial economic and social impact – Continuing risk of emergence of a pandemic <p>CDC 13</p> | <p>Situation Report: Avian Influenza 2005</p> <ul style="list-style-type: none"> ✓ H5N1 seasonal pattern for avian flu in Asia <ul style="list-style-type: none"> – Expect increased activity in winter months ✓ Ongoing human cases <ul style="list-style-type: none"> – Most in young and healthy – Extremely high apparent case-fatality – No sustained person-to-person transmission <p>CDC 14</p> | | | | | | | | | | | | | | | | | | | | |
| <p>Situation Report: Avian Influenza 2005</p> <ul style="list-style-type: none"> ✓ Human isolates (Vietnam, Cambodia & Thailand and 1 group of Vietnamese avian isolates) <ul style="list-style-type: none"> – Resistant to adamantane drugs – Sensitive to oseltamivir ✓ Probable human-to-human transmission in Thailand; family clusters in Vietnam <ul style="list-style-type: none"> – ? increasing ✓ Antigenic heterogeneity among current H5N1 viruses (unlike 2003 Hong Kong H5N1 virus) <ul style="list-style-type: none"> – How variable are the 2005 H5N1 viruses? – How immunogenic? – Must compare human and avian isolates <p>CDC 15</p> | <p>WHO Collaborating Centers for Influenza</p>  <p>CDC 16</p> | | | | | | | | | | | | | | | | | | | | |

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|--|---|
| <p>HHS Response: Partnership with WHO</p> <ul style="list-style-type: none"> ✓ Support Global Influenza Pandemic Preparedness ✓ Enhance Collaboration with Animal Influenza Health Authorities ✓ Enhance Global Influenza Surveillance ✓ Training - Laboratory, epidemiology, and biosafety  <p>17</p> | <p>HHS / CDC Contributions to Preparedness and Response in Asia: HHS/CDC</p> <p>A \$5.5 M initiative to build surveillance capacity</p> <ul style="list-style-type: none"> - Surveillance networks with bilateral funding to 9 countries in Asia - WHO HQ and Western Pacific Regional Office - CDC's IEIP in Thailand and NAMRU-2 in Jakarta - WHO's Animal Influenza Network - Communications between public health and veterinary agencies - Shipment of isolates and specimens  <p>18</p> |
| <p>Enhancing Influenza Surveillance: HHS/CDC</p>   <p>19</p> | <p>Global Biosurveillance: International Health Protection Network</p>   <p>20</p> |
| <p>Quarantine Authorization</p> <ul style="list-style-type: none"> • Public Health Service Act (Title 42 U.S. Code 264(b), Section 316 of the Public Health Services Act amended -- "(c) Influenza caused by novel or reemerging influenza viruses that are causing, or have the potential to cause, a pandemic." • Quarantine and isolation tools were last used during the SARS 2003 outbreak • Quarantine duration of one incubation period  <p>21</p> | <p>CDC's Research Priorities</p> <ul style="list-style-type: none"> • Genetic determinants of pathogenicity and transmissibility • Testing for antiviral resistance, receptor binding properties, etc. • Tracking antigenic changes in the circulating viruses to facilitate appropriate vaccine development • Epidemiology of the current H5N1 epizootic <ul style="list-style-type: none"> - Why did it spread so rapidly? - How many people have been infected? - What is the extent of asymptomatic infection? - What is the actual death rate?  <p>22</p> |
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(Slides available on accompanying CD)

MEETING THE CHALLENGE OF PANDEMIC VACCINE PREPAREDNESS: AN FDA PERSPECTIVE

**Dr. Jesse Goodman, Director, Center for Biologics Evaluation and Review
U.S. Food and Drug Administration**

My presentation will focus on how FDA can and is approaching meeting the challenges of pandemic vaccine preparedness including the more applied science needed to support assessment of safety and efficacy as well as quality in manufacturing. I will also focus on steps to increase manufacturing diversity and capacity. While the drivers for investment are primarily economic, FDA can help by developing and defining the needed and efficient pathways and regulatory processes to speed vaccine development, assessment and availability. Assuring safety and public confidence is absolutely critical as a pandemic vaccine will impact millions of individuals. Finally, and perhaps most important, I also want to touch briefly on the idea of considering whether there are pathways to prevent a pandemic, such as incorporating preparedness into routine immunization, and to emphasize the need for thinking and working globally. I'm not going to emphasize antivirals, as doing so would require an entire workshop, but I do think they have a role to play.

The Secretary and Dr. Gerberding made analogies to bioterrorism threats, and I want to reiterate that pandemic flu poses similar and equally serious challenges and demands some of the same kinds of approaches. As a result, we are not treating this as business as usual. We have had extensive interactions with sponsors to encourage them to develop new products, and have turned things around very rapidly. We have taken proactive trips to look at manufacturing facilities and have participated in multiple product development teams to ensure expedited reviews. We used such approaches to combat last year's supply problems with flu vaccine. These approaches are appropriate for pandemic preparedness.

Markets—that is demand and sales—are the main drivers of manufacturing. No one is going to build factories just for a possible pandemic. In the last two or three years, growing yearly vaccine use in the United States—prompted by CDC and its public health partners—has helped to stimulate interest in the U.S. vaccine market among global manufacturers. This past year's problems at Chiron in producing flu vaccine, and the growing concerns about, and investments in, pandemic preparedness, have also accelerated commercial interest and the development plans of potential manufacturers.

Our interactions with industry to respond to the problems this past year included extensive review of clinical and manufacturing data and multiple facility inspections of foreign manufacturers, which made an additional 5 million doses of investigational vaccine potentially available if needed in 2004. I'm proud of the contributions of the people in our department, and appreciative of the cooperation of manufacturers, although fortunately we did not experience a bad flu season. Several manufacturers have expressed interest in becoming licensed to supply flu vaccine to the U.S. market, and, as I will discuss, FDA has defined an accelerated approval mechanism that can help speed their availability to meet this important public health need.

Several of the most important lessons learned regarding the manufacturing infrastructure for flu vaccine are relevant to other critical vaccines, many of which also have only one or a few

manufacturers and an overall fragility in their supply. While many vaccines can be stored from year to year, this is not the case for influenza vaccine, which changes in composition almost every year. We should not lose this opportunity to teach our colleagues in the policy arena more about the fragility of vaccines—and steps that can be taken to support the infrastructure, an area where IOM has provided leadership.

We now have a global pharmaceutical marketplace as well as a global disease marketplace—we are fully globalized on both ends of the equation. FDA has realized the need for better international information sharing, much as CDC has recognized the need for better surveillance. We have therefore completed new confidentiality and information-sharing agreements with regulatory authorities in other countries, so that we can obtain or share important product manufacturing and safety information both pre- and post-licensure. I have also been trying for some time to encourage global plans to develop vaccines: why develop a vaccine for just one country? Regulatory cooperation and harmonization will help, and we are starting to see companies develop vaccines for a global market.

Also in response to last year's flu vaccine shortfall, FDA has decided to move from biannual inspections of flu manufacturers to annual inspections in the hope of catching problems sooner or, even better, wherever possible encouraging the prevention of problems through robust quality systems and high quality manufacturing processes. The full swing of manufacturing of flu vaccine occurs in summer. If problems develop then, we may not detect them early enough to respond. We want to address these issues, consistent with FDA's good manufacturing practices (GMP) initiative to strengthen the communications with companies around vaccine GMPs.

I would like to talk a bit about how we handle annual availability of flu vaccine in the United States. Each year, any of the three strains that made up the previous year's vaccine can be replaced with a new strain. We base the determination on surveillance, working with CDC, WHO, and our advisory committees, among others. We do not view this as a major change to the vaccine, so we require a manufacturer with an existing license for inactivated influenza vaccine to submit only a prior-approval manufacturing supplement, which basically describes the strain and its characteristics—a routine, straightforward process. We do not require licensed manufacturers of inactivated influenza vaccine to provide clinical data to gain approval of these annual supplements.

To meet current deficits in capacity and to make licensure of other flu vaccines faster and more efficient, we have turned to our accelerated approval authorities. Accelerated approval can be used to approve a product that provides a meaningful therapeutic benefit for a serious or life-threatening condition when there is a lack or shortage of available alternative therapies. We determined that influenza vaccines qualify for accelerated approval, as the number of individuals who could benefit and for whom vaccination is recommended far exceeds the current supply. For pandemic strains as well, we would certainly find an unmet medical need, in that no vaccines currently exist for those strains. Accelerated approval allows approval of a product under a surrogate endpoint—a marker reasonably likely to predict clinical benefit—rather than requiring completion of all clinical efficacy studies before licensure. Clinical endpoint studies would later confirm this benefit.

Considering flu vaccine to be in short supply, we have stated that we consider hemagglutinating inhibiting anti-HA antibody levels as a likely surrogate marker for efficacy. We commonly approve vaccines based on proven surrogate markers such as hepatitis-B anti-

surface antibody levels, but this would be the first or one of the first accelerated approvals based on likely markers.

We have thus told manufacturers that they can seek accelerated approval based on immunogenicity-provided validated assays are used, and complete manufacturing data and control, and satisfactory safety data are provided, followed by post-approval studies of efficacy. In considering the vaccines that other manufacturers offered or expressed interest in bringing to the U.S. market—vaccines licensed in other countries with competent regulatory authorities—we have said that well performed clinical trials and data from use under foreign licensure can contribute to U.S. licensure. At least two firms, GSK and ID Biomedical, have indicated they will seek U.S. licensure for their flu vaccines under this approval mechanism. We believe we have shortened the time to approval by one to two years.

The kind of immunogenicity data we are looking for can also be useful when we try to bridge efficacy of flu vaccine to other populations. For example, these data could help us allow a manufacturer to look at immune response in different populations as a surrogate for efficacy in those populations, making it easier to perform certain clinical studies. The information obtained from immunogenicity studies will also be important in looking at and establishing appropriate dosing for novel strains such as pandemic strains.

How can we facilitate the rapid availability of vaccine needed to prevent or respond to a pandemic? First, we will view a pandemic strain used in a licensed manufacturing process as a strain change. Biologically, a new hemagglutinin antigen is just that: another hemagglutinin antigen such as we use in a routine strain change. For licensed manufacturers using licensed processes, we wouldn't treat this as a new vaccine but as a supplement. This will significantly reduce unneeded costs and speed availability. However, having some clinical data are important because of the differences in immunogenicity in a naive population are likely to affect the doses needed to protect the population and because there should be assurance that the vaccine has the excellent safety profile typical of routine flu vaccines. We also have no problem with the use of recombinant or cell-culture-based technologies, including reverse genetics, in strain production, as long as manufacturers use adequate controls and characterization. We don't want to immunize potentially billions of people with a vaccine strain if there is any substantive concern about its origin or safety.

Conducting the needed clinical studies for candidate pandemic vaccines during the inter-pandemic period is very important, and real progress is being made here. Studies by the National Institute of Allergy and Infectious Diseases (NIAID) of H5N1 will provide critical information on dose and schedule. However, it is important not to get too overconfident. Just when we think we understand something, it changes, and right now we don't have the experience to generalize from one pandemic strain to another.

Whenever we undertake important public health programs, ensuring product safety to the extent we can and engaging in effective communication are critical, as is full transparency about the potential risks and uncertainties of a pandemic vaccine versus the pandemic itself. Where time permits, we think it is a good idea to obtain an additional safety database on several thousand individuals before licensure and wide use of the pandemic vaccine, even though there is no particular reason to suggest that the vaccine should behave differently. Establishing a system for surveillance and reporting of adverse events before the use of such a product is important, as is public communication that we are taking that step.

Applied science, such as the preparation of qualified seed strains representing major known and evolving pandemic antigens, can facilitate vaccine manufacturing and availability a The flu community, including CDC, academic researchers, WHO, and our regulatory and public health counterparts around the world, have done a great job, but we need more such efforts, and they need to be well supported and coordinated.

We also need much more information on the biological basis for strain cross-protection among evolving pandemic types, and on whether we can predict whether one vaccine strain will be protective against another without extensive studies. We also need to prepare in advance reagents for manufacturing, such as antigens and antisera. Our lab and others have been very engaged in that, but the needs of a pandemic are an order of magnitude greater. We need to not only evaluate and standardize assays but also consider new approaches to improve assays of potency, antibodies, and sterility to speed the regulatory and manufacturing processes.

Many people have noted that even if we had a decent interpandemic vaccine infrastructure and supply, manufacturing capacity will still most likely be inadequate to meet U.S. needs in a pandemic—if we needed a higher antigen dose or multiple doses, for example. And, it is very clear that inadequate global vaccine capacity currently exists to meet global needs.

Many questions have therefore been asked about adjuvants and whether they could reduce the requirements for antigen used in each dose and therefore enable us to stretch supplies in a pandemic. There have been some promising reports and if safe adjuvants could reduce dose requirements and/or enhance vaccine immunogenicity, they could play an important role in pandemic preparedness. However, it is important to recognize that both published and unpublished results have been conflicting. We need adequate studies before we assume adjuvants will be effective and, if they are, to determine how best to use them. These studies should be a very high priority and are now being undertaken with HHS support.

Such an approach would be considered a new product because it would require different formulation and manufacturing, and we would need to assess the safety and efficacy of the product. The simplest adjuvant would be aluminum, with which we have extensive experience and safety records in licensed vaccines. Early studies should demonstrate significant increases in immunogenicity with an acceptable safety profile. More novel adjuvants, especially any with reactogenicity or safety signals in early use, would obviously require more safety data. If proof of concept and other studies are favorable—and recent informal and published presentations have suggested potential benefits from adjuvant approaches—researchers should pursue controlled studies in the inter-pandemic period. Accelerated approval mechanisms could be used, so long as adequate safety and immunogenicity data were provided.

Other potential antigen-sparing strategies for vaccine delivery should be on the table. The simplest change—as indicated in provocative papers in the *New England Journal of Medicine* in the last year—might include intradermal vaccines using needle and syringe, but this raises practicality and delivery issues. Other means of intradermal or transdermal delivery are also available. Again, safety and efficacy would need to be determined, especially immunogenicity in the population using the vaccine. Immune stimulators, such as patches with added cytokines or other stimulants, also look promising in small numbers of patients, but again we would need data before adopting such measures on a public health basis.

Non-egg-based technologies such as cell culture and recombinant vaccines offer very significant potential advantages, such as flexibility, potential for rapid scale up and production of

large quantities, and the fact that they could be primarily sterile processes from the start. Despite problems, egg-based manufacturing has been successful and cost-effective, and other technologies have not been widely used or marketed yet despite early promise.

We have licensed other cell-culture–derived and recombinant vaccines, and we have no special regulatory concerns with those technologies if used for flu. We are working hard to help people with development processes, though the scientific and technical challenges have not been trivial. For cell-based vaccines, these include the usual assessment of tumorigenicity, advantageous agents, and residual DNA. These are critical but addressable scientific issues for a vaccine that, as stated before, could be given to hundreds of millions or billions of people. FDA is providing guidance for manufacturers on cell lines and adventitious agents. However, the biggest hurdle has been obtaining enough yield, manufacturing scale, and cost-effectiveness. Still, there is no reason in the long-term or even medium-term why a cell culture-based technology couldn't succeed. With recombinant vaccines, some of these issues are less pressing. However, in that case we have to address antigenicity and ensure that the immune response elicited to a recombinant protein is indeed a protective one.

Other new technologies worth considering include vaccination with potentially cross-protective antigens to build immunity against influenza strains in the population more generally, and live attenuated vaccines, one of which is licensed. The latter provide multiple immunogens, some of which may offer some cross-protection. They may also enhance more rapid development of immunity, and potentially require only a single dose, an advantage especially in the immune naive, but they raise potential containment issues, at least in the pre-pandemic period.

Can we consider other pathways to pandemic preparedness, and other approaches to how we use vaccines? Obviously, for a pandemic to occur, not only does the viral strain need to be lead to transmissible and virulent, but, by definition, the population must lack immunity. Can we conceptualize pandemic preparedness as routine prevention rather than as something that must occur only during a crisis? Some of the tremendously challenging public health communication problems that occurred around the swine flu, anthrax, and smallpox reflected a crisis mode of communications and intervention. Should we consider building immunity against evolving virulent pandemic-threat strains through more routine and earlier immunization against those strains? Should we produce and make vaccine against pandemic threat strains available before a pandemic? Should we even integrate antigens protective against pandemic threat strains into routine influenza immunization? What are the risks and benefits? Transparency and public dialogue would be essential in considering such approaches.

We are acting locally, but we should also be acting globally. CDC is taking the initiative to work with global partners in surveillance, as is WHO, and FDA is similarly work with industry worldwide to build vaccine capacity.

Regulatory cooperation can facilitate the potential transnational use of vaccines in both pandemic and inter-pandemic settings. We, as a global community, should also consider vaccinating people at geographic sites of evolving virulent pandemic strains. Such an approach could save lives at the sites of pandemic strain emergence and, potentially, help slow or halt a pandemic. Antivirals could also play a role in such settings, even before widespread human-to-human spread, to slow or halt a pandemic.

To summarize, we are working with partners, many of whom are in this room, to help diversify and strengthen manufacturing and provide flexible, rapid regulatory pathways. I think

we are making progress. Pandemic vaccines licensed as supplements rather than new vaccines can help speed and reduce the burden and cost of pandemic response, but we need to ensure that the vaccines are high quality.

Advance preparation and improvement of strains, reagents, assays, and standards would be beneficial. Many here are engaged in that, but we can do more. We can best address scientific needs, create manufacturing capacity, and evaluate the safety and effectiveness of antigen-sparing new vaccines and delivery methods as well as non-egg-based technologies before a pandemic. Those studies are now under way and should be expanded and accelerated as results indicate.

Finally, we need to consider the risks and benefits of earlier intervention against virulent potential pandemic strains, including potentially integrating them into routine medical and public health preparedness as we do for annual influenza. Can we learn from experiences such as that with swine flu and still meet the challenge of pandemic preparedness? Enhanced surveillance and increased awareness along with improved vaccine and antiviral manufacturing capacity and global regulatory and public health infrastructure and cooperation, can provide mankind with the potential opportunity to effectively intervene to prevent or reduce the catastrophic consequences of the inevitable, the next influenza pandemic.

Plenary Presentation Slides-Dr. Jesse Goodman

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|---|--|
| <p>Meeting the Challenge of Pandemic Vaccine Preparedness: FDA Perspectives</p>  <p><i>Jesse L. Goodman, MD, MPH</i> Director Center for Biologics Evaluation and Research (CBER)</p> | <p>Or: If pigs (or chickens) can fly – can we be prepared?</p>  |
| <p>Not Business as Usual</p> <ul style="list-style-type: none">• Since 9/11, CBBER has adapted to extraordinary circumstances through extraordinary efforts<ul style="list-style-type: none">– These include proactive measures w/ sister agencies and industry such as:<ul style="list-style-type: none">• Meetings to encourage developing new products• Early and intensive interactions w/ sponsors• Collaboration and rapid turnaround on INDs, EUA• Proactive trips to inspect facilities• Participation in multiple product development teams• Expedited reviews of key product apps.– Such approaches were also used in the 2004 flu season and are appropriate, where needed, for pandemic preparedness  | <p>Meeting the Pandemic Vaccine Challenge: Overview and Actions</p> <ul style="list-style-type: none">✓ Increasing manufacturing diversity and capacity✓ Developing needed pathways and regulatory processes to speed vaccine availability✓ Assuring safety and public confidence✓ Facilitating vaccine manufacturing and availability<ul style="list-style-type: none">– scientific and related technical needs– enabling both current and evolving technologies;✓ Considering pathways to prevent a pandemic✓ Thinking and working globally |
| <p>Increasing manufacturing diversity and capacity</p> <ul style="list-style-type: none">• Markets (demand and sales) are main driver• In last 2-3 years, increasing vaccine stimulating interest of global manufacturers in US market• 2004 shortage further accelerated interest• FDA and industry interactions helpful:<ul style="list-style-type: none">– Intensive interactions to assure potential access to vaccine under IND for 2004-5 season; data reviews and facility inspections made 5 mill doses avail, if needed– Several manufacturers have expressed interest in US licensure and FDA is interacting proactively with them– CBBER providing accelerated approval mechanism | <p>Lessons Learned Lead to Other FDA Steps to Strengthen Supply</p> <ul style="list-style-type: none">• Globalization:<ul style="list-style-type: none">– Information sharing agreements and relationships both completed and being developed<ul style="list-style-type: none">• Pre and post-licensure– Encouraging global vaccine development plans and regulatory cooperation/harmonization• Annual inspections of flu manufacturers• GMP initiative<ul style="list-style-type: none">– Increased communications and enhanced preventive approaches including on vaccine GMPs |

Pathways to Speed Availability: Annual US Influenza Vaccine

- Each year, any of the previous three vaccine strains may be replaced with a new strain
- Strain changes based on evaluation of circulating wild-type strains
- Only submission and review of a prior approval manufacturing supplement is needed for strain changes to an existing license
- *FDA does not require clinical data for approval of these annual supplements for licensed manufacturers of inactivated flu vaccine*

Basis for Use of Accelerated Approval Authorities

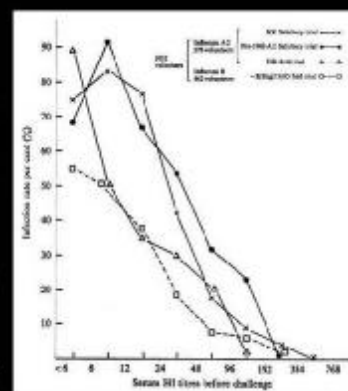
- 21 CFR 601.40
 - Meaningful therapeutic benefit
 - Serious or life-threatening conditions
 - Lack of available alternative therapies
 - Influenza vaccine shortage applicable
 - CDC population of benefit – 185 million doses
 - For pandemic strains, unmet medical need per se
- 21 CFR 601.41
 - Surrogate endpoints
 - Reasonably likely to predict clinical benefit
 - Clinical endpoint studies to confirm

Pathways to Speed Availability: Accelerated Approval for Inactivated Flu Vaccines

- FDA considers there to be a short supply
- CBER will consider HI anti-HA antibody levels as a likely surrogate marker for efficacy
- Therefore, accelerated approval can be sought based on immunogenicity provided:
 - validated assays
 - post-approval studies of clinical efficacy
 - complete manufacturing data, controls & inspections
 - satisfactory safety data, clinical trials and data from experience with same vaccine under foreign licensure can contribute

Potential Surrogate: Infection Rate of Volunteers Challenged with Influenza Viruses in Relation to Pre-Challenge HI Titers

From: Hobson et al
J Hyg, Camb 1972



Pathways to Speed Availability: Accelerated Approval for Inactivated Flu Vaccines II.

- GSK and ID Biomedical have, to date, each indicate that they will seek licensure under this accelerated approval mechanism (others may in future) – shortening time to potential approval by 1-2 years
- Immunogenicity data can also be useful:
 - to bridge efficacy data to additional populations and to evaluate manufacturing changes
 - to determine HA dose and number of doses needed for a novel strain (e.g. For pandemic strains)

Need for Valid and Standardized Methods: Comparison of HI Titers for H1N1 Flu in Two Labs with Same Sera

| Lab | Serum Source | Pre % >40 | Post % >40 | Pre GMT | Post GMT | 4 Fold Rise |
|-----|--------------|-----------|------------|---------|----------|-------------|
| A | EU | 13 | 88 | 9 | 195 (3) | 83 |
| B | | 4 | 58 | 7 | 25 (3) | 58 |
| A | USA | 68 | 96 | 46 | 202 (2) | 27 |
| B | | 20 | 75 | 11 | 39 (2) | 40 |
| A | AUS | 50 | 100 | 20 | 216 (1) | 79 |
| B | | 17 | 88 | 7 | 68 (1) | 83 |
| A | JAP | 50 | 92 | 34 | 93 (4) | 25 |
| B | | 16 | 32 | 7 | 16 (4) | 48 |

Pathways to Speed Availability: Licensure of Pandemic Vaccines

- FDA views a pandemic strain used in a licensed manufacturing process as a strain change
 - Biologically, a new HA antigen is just that, another HA antigen, such as used in routine strain changes
 - For licensed manufacturers using licensed processes, would not be treated as a *new vaccine* but as a supplement with *some clinical data important*
- Either a wild type or a reassortant virus (including virus derived by reverse genetics) can be used
 - FDA has no problems with use of recombinant or cell culture based technologies in strain production so long as adequate controls and characterization

Pathways to Speed Availability: Licensure of Pandemic Vaccine; II

- Conduct clinical studies for pandemic vaccine during interpandemic period to extent possible
 - NIAID studies (e.g. of H5N1) will provide critical information on dose and schedule
 - Future generalizability of such data to other strains unclear; immunogenicity of various pandemic strains may differ
- Assuring safety and public confidence
 - Clear communication: full transparency and continuing discussions re: risks/uncertainties of pandemic vs. vaccine safety/effectiveness
 - Where time permits, obtain additional safety database on several thousand individuals pre-licensure
 - Facilitate AE reporting & surveillance through VAERS & other databases

Thinking ahead: facilitating manufacturing and availability of licensed pandemic vaccines

- Preparation of qualified seed strains and high growth reassortants representing major known and evolving pandemic antigens
- Studies of strain cross-protection in H2A types, methods to predict based on sequence analysis
- Advance preparation of needed reagents for manufacturing: e.g. antigens & antisera
- Evaluation of existing assays and consideration of development of new technological approaches (e.g. to potency, Abs, sterility) that may speed manufacturing and regulatory review

Thinking Ahead: Enabling New Approaches and Technologies: Overview

- Even with aggressive and successful efforts to diversify and strengthen US inter-pandemic production, capacity may still be inadequate for true widespread pandemic in US, and, almost certainly, for global needs
- Antigen sparing and other new technologies should be evaluated before a pandemic

Enabling New Technology - Scientific Needs

- Addition of adjuvant to vaccine formulation
 - Results (published and unpublished) in past have been conflicting: adequate studies are needed before adopting
 - Would be considered a new product (requiring BLA)
 - Safety and efficacy (immunogenicity) data required
 - Simplest - aluminum (extensive experience in licensed vaccines)
 - Early studies should demonstrate rationale (e.g., significant increases in immunogenicity with acceptable safety profile) and determine dose
 - Novel adjuvants or those with previous safety signals would require more safety data
 - Supporting manufacturing and product information also needed
 - If proof-of-concept and other studies favorable, Phase 3 studies should be pursued in interpandemic period

Antigen Sparing Strategies

- Changing route of vaccine delivery
 - Simplest change might be i.d. using needle and syringe but raises practicality issues
 - Safety and efficacy (immunogenicity) data needed
 - Other delivery methods promising: need data
- Use of immune stimulators, (e.g. use of patch with heat-labile toxin).
 - Safety and efficacy data required
 - Such strategies are in relatively early development; lack of experience will require safety testing

Enabling New Technologies: Cell Culture & Recombinant Vaccines

- There are significant potential advantages in flexibility afforded by non-egg based technologies
 - Despite problems, egg based manufacturing has been successful & cost effective and, to date, other technologies have not been marketed or widely used
 - FDA has licensed other cell culture derived and recombinant based vaccines and has no special regulatory concerns with these technologies for flu
 - We encourage their development and provide intensive interactions with sponsors
 - Scientific/technical challenges include:
 - Cell based: usual safety issues (i.e. tumorigenicity, adventitious agents), sufficient yield, manufacturing scale & cost
 - Recombinant: Antigenicity and protective immune response

Other New Technologies

- Cross-protective antigens
- Live attenuated vaccines
 - Provide multiple immunogens, some may be cross-protective
 - May enhance more rapid development of immunity
 - May raise potential containment issues for public health and agriculture

Considering Potential Future Pathways to Preparedness?

- For a pandemic to be a pandemic a prerequisite is the lack of population immunity
- Can we conceptualize pandemic preparedness in a routine prevention rather than crisis mode?
- Should we consider earlier building of immunity against evolving virulent pandemic threat strains?
- Should we consider the potential for integration of such preparedness into more routine influenza immunization, as we do for emerging epidemic strains?
- Transparency, public dialogue, a non-crisis environment, and acceptance/demand would be important for any such approaches to be considered

Thinking globally and acting both locally and globally

- Work with public health and industry partners to facilitate building global vaccine capacity – benefits all
- Regulatory and other cooperation to facilitate potential sharing and transnational use of vaccines
 - Payoffs in both pandemic and inter-pandemic settings
- Potential to vaccinate at geographic site(s) of evolving virulent pandemic strain transmission threat, even prior to widespread human to human spread
 - May slow or halt pandemic – modeling may be helpful
 - May allow better understanding and additional modeling of unique scientific and non-scientific challenges in early intervention against pandemic threat strains

Summary

- FDA is working with partners to diversify and strengthen influenza vaccine manufacturing, and providing flexible rapid regulatory pathways – *progress has been made*
- FDA views pandemic vaccines made using licensed processes as supplements rather than new vaccines – *this can speed & reduce the burden and costs of pandemic response*
- Further advance preparation and improvement of strains, reagents, assays and standards would be beneficial
- Scientific needs in manufacturing and in evaluating safety and effectiveness of antigen sparing approaches, and of new vaccines as well as of non-egg based technologies is best addressed before a pandemic – key studies are beginning
- Pathways exist to allow consideration of benefits and risks of early intervention against virulent potential pandemic strains, including potential integration into public health preparedness, as we do for annual influenza strains.

"The roosters of America are ready to do their duty"

Secretary of Agriculture (Knobel or Baiz) quoted in Neustark and Fineberg – "The Swine Flu Affair" USDHEW, 1978



Are we?

Can we learn from the Swine Flu experience and still work to meet the challenge of pandemic preparedness?

We welcome your ideas and input....

(Slides available on accompanying CD)

GLOBAL PANDEMIC PREPAREDNESS RESEARCH EFFORTS

Dr. Klaus Stöhr, Project Leader, Global Influenza Programme, World Health Organization

I would like to thank the Department of Health and Human Service and the Institute of Medicine for their vision and leadership in organizing this meeting—not only because it is 10 years since the National Institutes of Health and the World Health Organization convened a meeting in Washington to figure out what would happen in a 1918-style pandemic, a meeting that John La Montagne was critical in organizing, but also given the evolving situation in Asia and the need to consider strategies to reduce morbidity and mortality from the next pandemic.

Medical and public health interventions must be built on the best science and evidence. But the world is changing, and that includes the influenza world. The current situation requires a thorough understanding not only of the research landscape but also of the most important public health and research priorities that inform policy. I regard research as generating knowledge for action.

From the perspective of an ever-changing world, influenza has been extremely interesting over the last few years. I hope that the influenza virus will slow down a bit and make fewer changes. On the other hand, it is certainly exciting to live and work during this extraordinarily dynamic time.

WHO collaborates with many partners world wide. I would like to particularly mention colleagues at HHS, CDC, NIH, FDA, and many academic institutions with which we have the privilege to work so closely. I would like to thank them for not only the direct support they provide to WHO but also for their international leadership.

I was asked to talk today about global pandemic preparedness efforts. I would like to look at only a small fraction of pandemic preparedness and research during this inter-pandemic period. We will have to confront a pandemic at some point, and then we will return to the next inter-pandemic period. I hope that we do not have to find out during the next pandemic that complacency during the current inter-pandemic period slowed our preparations. I would like to look at medium-term applied research linked to medical and public health interventions, addressing current needs, especially the situation in Asia. I would also like to cover two smaller areas that can make a profound difference in our ability to reduce morbidity and mortality from the next influenza pandemic.

In my view, we are all overwhelmed with responding to the current situation and have not yet had time to prepare for the research necessary DURING the next pandemic. For targeted public health interventions during the next pandemic we will have to understand the natural history of the disease and the risk groups. We do not yet know the incubation period of the new virus or the duration of infectivity. We are considering quarantining, but how long will we quarantine someone if we don't know how long he or she is going to excrete the virus? We have to develop standardized protocols for the next pandemic to obtain a critical mass of knowledge to react very quickly and precisely.

We have to inform policy, and that will be impossible unless we can assess the medical impact of the disease. Many interventions that we are recommending now are based on the best science, but that science may be limited. The evidence may have come from good studies conducted many years ago, perhaps with viruses that are different from those now circulating or that might cause the next pandemic. That caveat also applies to vaccines and antivirals. We have to anticipate the economic impacts of the next pandemic and consider how can we convince people that strengthening the communicable disease infrastructure now, makes sense and is economically sound.

We certainly need to do virologic research. Because a pandemic virus will change very rapidly, we must better understand the factors that influence the genetic and antigenic evolution of influenza viruses. Preparing not only for control and response during a pandemic but also for the research needed to inform policy will require vision, leadership, and the ideas of the participants in the symposium over the next two days.

I consider research during the pandemic and pre-pandemic phase as deserving particular attention, along with risk assessment and communication. Medical interventions—vaccines, antivirals, treatment with antimicrobials—as well as non-pharmaceutical interventions are also critical. The combination of these measures will vary within countries. Many potential interventions such as vaccines and antivirals will be only suboptimally effective or not available.

We consider risk assessment very important. There are intense efforts from a global perspective to control—and possibly even eradicate—the disease in animals. This will require long-term control measures and an enormous investment. The government of Thailand has invested \$120 million to compensate farmers for sacrificing chickens infected with bird flu. That country can afford such an effort and is capable of doing it because it is the fourth largest poultry exporter, and poultry production is critical to its gross national product. On the one hand we are encouraging considerable investments by the agricultural industry for the control of H5N1 in animals. On the other hand, we can not precisely quantify the pandemic risk from H5N1. As an example, we have not seen evidence of reassortment since 2004, even though the virus is widespread and has been transmitted thousands of times to humans. We are certainly seeing only the tip of the iceberg in Vietnam and Thailand: many more cases are likely occurring.

The question that needs to be answered fast is: what is the likelihood and the outcome of a reassortment between an H5N1 and human as well as perhaps pig viruses? One-third of the pig population in China has human H3 influenza viruses. This might be a good time to look at pig viruses, as we have no understanding of whether H5N1 has already gained a foothold in pigs, because studies have not yet even begun to assess this. Fortunately, CDC has embarked on a laboratory project to assess outcome of reassortment. These studies are now in the second phase, and a second laboratory from Europe might join these activities.

There is certainly a need to conduct studies on the H5N1 infection rate in the general population of an affected country. Experiences from studying other diseases show that such research can be relatively simple and inexpensive. Such research would help us understand the true prevalence of mild and severe H5N1 infection in the general population against the background noise of 100 of thousand influenza-like- illnesses every year and help assess epidemiological significance of the few severe cases that turn up in hospitals.

The second area with numerous opportunities for researcher is the control of pathways of transmission. Laboratory data and recent studies from Thailand and Vietnam suggest that ducks

are a potent reservoir for highly pathogenic avian influenza for a relatively short period of time. H5N1 has an increased pathogenicity in poultry and mice and is found in a growing number of mammalian species. But what is the role of these animals and birds in the epidemiology of influenza viruses of pandemic potential? Vector studies in domestic and wild animals and birds are very important and could be of relatively low cost. A few colleagues are conducting such serological and biological studies, and some funding agencies are supporting them, but the research is too limited to provide the knowledge necessary to guide policy decisions. Another area for research in countries now affected by H5N1 and which have developed control strategies in response to this outbreak in animals, would be the assessment of the effectiveness of the interventions.

Case management and control of infections in hospitals also present opportunities for research. For rapid detection of the emergence of a pandemic virus, the number of reported cases is less important than immediately investigating every suspicious case in Vietnam, Thailand, and elsewhere in Asia. If we do not make such an effort, the narrow window of opportunity to stop an emerging pandemic virus or virus with greater human-to-human transmissibility will close.

We have seen only very few publications on the clinical course of H5N1. We still have very little understanding of H5N1 key clinical epidemiological and virological parameters, incubation period, duration of infectivity, duration of transmission, and excretion kinetics. And we are talking about a disease that has been around for a relatively long period of time. We have decent data on the usefulness of antivirals, and we are finding out more about the duration of treatment and size of dose, but how will we use that knowledge?

We need coordinated clinical research and case management, as well as a network of hospitals in affected countries, not only for avian influenza but also for emerging infectious diseases. Such a mechanism for coordinating clinical research, exchanging samples and information can enable affected countries to rely on standardized treatments and research protocols and support effective communication. NIH is supporting an initiative to establish an international clinical research network on emerging infectious diseases in Asia. We believe this is vitally important so we can investigate diseases in a standardized way at a very early stage.

Doing so will not only strengthen national capacity and resources but will also facilitate international collaboration and exchange. With NIH, WHO has developed a concept paper on such a network, and we have identified international research and funding partners. The next step is to engage national partners and enroll hospitals. It's not going to be easy sailing, but we believe this is a step in the right direction.

For the first time we have the possibility of detecting a pandemic virus early, and of stockpiling H5N1 vaccines as well as antivirals. But could massive prophylactic use of antivirals and possibly vaccines in and around an epicenter extinguish an emerging new subtype, or at least buy time, is another unanswered question.

Modeling of a pandemic is ongoing, and we will hear the first results at this meeting. We have also looked at data from other groups, and they are very encouraging. However, we need to take conditions in developing countries into account and review the applicability of the models.

We also have to factor in the time it would take to detect a pandemic virus. Today a diagnosis and possible field investigation of an individual case takes more than 20 days. We also have to look at the accessibility of populations in developing countries, particularly in remote

areas. More than 80 percent of the territory in Vietnam may only be reached by four-wheel drive. We have also to look at the challenges of enforcing control measures, such as quarantine time, over large areas in developing countries.

We certainly need more research on an H5N1 vaccine stockpile, which could make a difference for countries that could afford one. A stockpile could be a complementary tool in a large armamentarium of pandemic interventions, allowing vaccination of certain critical groups before a pandemic virus arrives. A stockpile would also provide an incentive for pharmaceutical companies to invest in a pandemic vaccine, although clinical trials are not complete. WHO is looking forward to receiving data from the modeling, because without them it is difficult to think about the appropriate size of a possible international stockpile of antivirals and the intensity with which we should be pursuing this strategy.

If antigen-sparing strategies and low-antigen dosage for stockpiled vaccines are chosen, will they remain fully effective after storage over 6 or 10 months, when the vaccines may have degraded? We also need to investigate vaccination liability before a pandemic starts.

WHO has developed recommendations for slowing down local spread and using non-pharmaceutical measures at international or national levels during different phases of an influenza pandemic. They are built on the best available science, but assessing their potential impact is difficult. We will need a research protocol during a pandemic, or we will be relying on incomplete data generated during the last pandemic.

One incompletely understood area is the pathways of transmission of seasonal influenza virus and their relative importance. Patients in Asia now excrete large amounts of H5N1 virus in stool, perhaps even enough to infect other persons or chickens. We don't know the infectious dose for humans. What role would fomites play in transmitting this disease now, and perhaps in the future? How should we change hospital infection control, knowing that there are different pathways of transmission?

There is also a need to establish permanently the immunogenicity of the available H5N1 vaccine against newly emerging H5N1 strains. Although that will not tell us everything on the expected effectiveness of available H5N1 vaccines against the future pandemic virus, up-dating of the antigen content will contribute to increased vaccine effectiveness.

Global production capacity of normal seasonal vaccines over eight months is roughly 3 million doses of a trivalent vaccine with 15 micrograms of antigen. This information is based on an estimate prepared by the Influenza Vaccine Supply Task Force of the International Federation of Pharmaceutical Manufacturers Association. Manufacturers could produce three times that amount of a monovalent vaccine. Manufacturers could produce even more whole-virus vaccine, because splitting the virus and developing a subunit eliminates some of the virus in the original liquid. Vaccine output could be further increased, perhaps up to four times, if immuneenhancers are used. Under such circumstance, the global daily vaccine production capacity could be in the range of 13 million doses. Smart vaccine design and use of immuneenhancers could thus make a big difference—not only for one country but for the world population. Such an effort would require coordination of vaccine research. WHO will organize a meeting in November for all pharmaceutical companies to compare data and recommend next steps.

Since November 2004, two companies are working on the preparation of clinical trials in the United States. Ten more companies in Australia, Canada, France, Germany, Japan, and the

United States will have begun or finished clinical trials before the end of the year. All will use antigen-sparing strategies, which is very encouraging. Every company which wants to start pandemic vaccine production rapidly after the begin of a pandemic—whether it uses H5 or another strain- will have to license a pandemic vaccine beforehand.

If a pandemic virus were to emerge today, companies would require about two months to prepare their production sites, although some might need more time and some less time. Manufacturers would require another two months for pilot production. By that time a pandemic virus emerging in Asia might already have reached Europe or Australia. Clinical testing would require another two months, and by then the virus might be globally distributed. That means that vaccine production might start only after the virus had already circumvented the globe—a scenario we all would consider inappropriate in view of expected morbidity and mortality. Companies need to update and test vaccines now so they can begin production much more quickly.

Another problem is that manufacturers have little or no surge capacity for seasonal and pandemic influenza vaccine. We need to look now at improving existing production systems and devising alternative systems. Dr. Goodman has already mentioned cell-culture vaccine and recombinant vaccine—a very promising development. Improved antigen harvest from eggs is also a possibility. None of these options is going to be a silver bullet—each is only one component.

The epidemiology, natural history, and public health risk of emerging avian and mammalian influenza viruses are very difficult to evaluate. Surveillance in animals and constant characterization of viruses would be ideal, as they would allow us to better determine whether these emerging strains pose a public health risk. Then we would not need to invest into outbreak response from an H7 virus in a given country, because we could tell from the beginning that a highly pathogenic strain had little or no pathogenicity for humans.

The determinants of human pathogenicities of animal and bird influenza viruses and the role of migratory birds are not well understood. We also need studies of the ecology and molecular biology of animal influenza viruses, to understand the genetic foundation for specificity and pathogenicity. And we certainly need virological and serological studies on the prevalence and molecular evolution of influenza viruses in animals and birds. That would require a long-term investment which will be profoundly important in anticipating the next pandemic.

About 40 countries use seasonal influenza vaccine in humans. Most have vaccination policies, this means that at the end it is tax payers money that governments or health care providers are investing in disease control. Many countries can not afford influenza vaccines. Per capita spending on health in Vietnam is \$3. The wholesale price of influenza vaccine in South America might be \$3; perhaps in some countries it is lower. In the United States it's much more than \$10, depending on the vaccine.

Global expenditures on influenza vaccine are considerable. If we assume 300 million doses per year at a wholesale price of \$7.50, and a 5 percent increase over time, we can expect annual expenditures on influenza vaccine of around \$3 billion per year in 2015. So over the next 10 years, public health institutions will spend at least \$28.3 billion to buy vaccine to reduce the impact of seasonal influenza. That represents a considerable amount of money. If we could invest only 5 percent of those funds on research or add 5 percent, after 10 years, we would have \$1.4 billion to invest in research for a vaccine that could fundamentally change the landscape of

influenza control. Such a vaccine would be cross-subtype specific, could be stockpiled, might not need to be given annually, and would be affordable for developing countries.

In 10 years' time, many of us may look back and say, yes, we have made a big difference. I know many of you might be raising your eyebrows and shrugging your shoulders, thinking about insurmountable obstacles. But we must try to find solutions to address both pandemic and epidemic dilemmas. I would also remind you that the estimated global investment in the antiviral stockpile exceeds already by far \$2 billion, and 23 countries have orders in. Such spending might not be necessary if we had a vaccine.

Prioritizing research is very important, but that does not equal international coordination of research efforts. That should come next. This meeting is very important in that regard, and will provide us with better insight into priorities for influenza research. Some research projects already exist, initiated by governments, academia, national research and philanthropic institutions, the U.N. Food and Agriculture Organization, and Office International des Epizooties (OIE). The WHO Global Influenza Network, including the WHO Animal Influenza Network, has been supporting operational research and also providing direct support to influenza control efforts. However, we have to think more about coordinating research in addition to identifying research priorities.

WHO is also seriously considering organizing an international meeting to coordinate international support for surveillance and control of avian influenza in Asia. That will be a donor meeting, bringing together everyone who is interested in investing in influenza control in Asia, as well as everyone who has already invested. A meeting to coordinate research and identify the gaps could accompany such an event.




In summary, urgent, short-term research needs to include risk assessment for possible reassortment of H5N1 viruses with other circulating influenza A viruses. Assessing the effectiveness of non-pharmaceutical interventions is becoming increasingly important. We have also overlooked preparing for research during a pandemic. Regarding long-term research, we believe the best bang for the buck will come from investing in a subtype-specific influenza vaccine with long-lasting immunity.

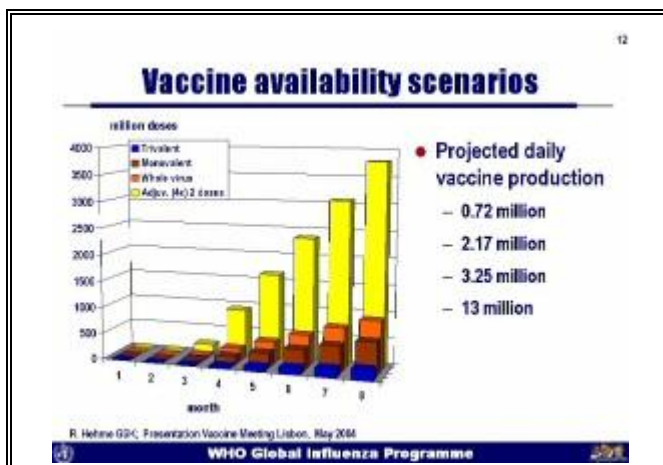
One major priority is rapid exchange of information during operational research, and the time to think about stronger international coordination is now. As an example, last August, WHO received a telephone call from a colleague in this room who said that ducks might play a much greater role in the epidemiology of the disease. That finding has shaped global as well as national intervention policies. Many countries since have embarked on control programs in ducks, as field investigation has confirmed the laboratory results. If this scientific group had held on to that information and we had delayed developing control strategies, many more people would have been infected, and many more would probably have died. We need to create an environment for translating scientific evidence into immediate public health action without negative consequences for scientists.

More research will initially cost money, but we will save lives and money in the end. And fundamental research is the foundation for any applied research. If we do not want to invest now in research, let's put money aside to spend when the disease comes.

Plenary Presentation Slides-Dr. Klaus Stöhr

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|   <h2 style="text-align: center;">Global Pandemic Preparedness Research Efforts</h2> <p style="text-align: center;">Klaus Stöhr</p> <p style="text-align: center;">WHO Global Influenza Programme</p> | <h2 style="text-align: center;">Today</h2> <ul style="list-style-type: none"> • Focus on applied research on interventions during influenza pandemics that will reduce/minimize <ul style="list-style-type: none"> - morbidity and mortality during influenza pandemics - economical impact - societal interruption <p style="text-align: center;">WHO Global Influenza Programme</p> |
| <h2 style="text-align: center;">Today</h2> <ul style="list-style-type: none"> • Medium-term applied research linked to medical and public health interventions addressing the current pandemic situation in Asia <ul style="list-style-type: none"> • Natural history • Medical impact • Effectiveness of interventions <ul style="list-style-type: none"> - Vaccines; antivirals; non-pharmaceutical • Economic impact • Virological research  <p style="text-align: center;">Research to address long-term inter-pandemic and pandemic challenges</p> <p style="text-align: center;">WHO Global Influenza Programme</p> | <h2 style="text-align: center;">Priority Public Health Interventions International</h2> <ul style="list-style-type: none"> • Generic <ul style="list-style-type: none"> - Research during pandemics and pre-pandemic phase - Risk assessment and communication • Medical interventions <ul style="list-style-type: none"> - Several - Sub-optimally effective - Antiviral accessible in time - Treatment of viral and secondary bacterial pneumonia (antimicrobials) • Non-pharmaceutical interventions <ul style="list-style-type: none"> - Opportunities for research - Slowing down local spread of pandemic virus → package of activities to reduce local transmission/infection rate - Avoidance of pandemic → package of activities aiming at eliminating a new subtype with increasing fitness <p>→ Combination might vary</p> <ul style="list-style-type: none"> - Reducing morbidity or mortality or economical implications or societal interruption <p style="text-align: center;">WHO Global Influenza Programme</p> |
| <h2 style="text-align: center;">Priority Public Health Interventions International</h2> <ul style="list-style-type: none"> • Generic <ul style="list-style-type: none"> - Surveillance - Research during pandemics and pre-pandemic phase - Risk assessment and communication • Medical interventions <ul style="list-style-type: none"> - Vaccines - Antivirals - Treatment of viral and secondary bacterial pneumonia (antimicrobials) • Non-pharmaceutical interventions <ul style="list-style-type: none"> - Slowing down local spread of pandemic virus → package of activities to reduce local transmission/infection rate - Avoidance of pandemic → package of activities aiming at eliminating a new subtype with increasing fitness <p>→ Combination might vary</p> <ul style="list-style-type: none"> - Reducing morbidity or mortality or economical implications or societal interruption <p style="text-align: center;">WHO Global Influenza Programme</p> | <h2 style="text-align: center;">Priority Public Health Interventions International</h2> <ul style="list-style-type: none"> • Generic <ul style="list-style-type: none"> - Surveillance - Research during pandemics and pre-pandemic phase - Risk assessment and communication • Medical interventions <ul style="list-style-type: none"> - Vaccines - Antivirals - Treatment of viral and secondary bacterial pneumonia (antimicrobials) • Non-pharmaceutical interventions <ul style="list-style-type: none"> - Slowing down local spread of pandemic virus → package of activities to reduce local transmission/infection rate - Avoidance of pandemic → package of activities aiming at eliminating a new subtype with increasing fitness <p>→ Combination might vary</p> <ul style="list-style-type: none"> - Reducing morbidity or mortality or economical implications or societal interruption <p style="text-align: center;">WHO Global Influenza Programme</p> |

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| <p style="text-align: right;">6</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">1. Risk assessment</h4> <ul style="list-style-type: none"> ● New developments <ul style="list-style-type: none"> - 1997: direct transmission of avian influenza virus to humans - 2004: No reassortment despite <ul style="list-style-type: none"> • long + widespread presence of new influenza type of known human pathogenicity • multiple transmission to humans with co-circulation of human influenza virus ● What is the likelihood and outcome of reassortment between H5N1 and currently circulating human or pig influenza A viruses? <ul style="list-style-type: none"> - Lab trials (appropriate biosafety): viable reassortants; pathogenicity and transmissibility ● Studies on the infection rate in the general population in affected countries  <p style="text-align: center;">WHO Global Influenza Programme</p> | <p style="text-align: right;">7</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">2. Control of source and pathways of transmission</h4> <ul style="list-style-type: none"> ● New developments <ul style="list-style-type: none"> - Domestic ducks are (a potent?) reservoir for HPAI - H5N1 with increased pathogenicity in poultry and mice and found in <ul style="list-style-type: none"> • Pigs • Wild birds • Mammals (felines) ● What is the role of various animal/bird species in the epidemiology of influenza viruses of pandemic potential? <ul style="list-style-type: none"> - Vector and reservoir studies (domestic and wild animals/birds); <ul style="list-style-type: none"> • Serological/virological studies in various animal/bird species in H5N1 affected/non-affected countries ● What are the best disease control options in animals in the currently affected countries?  <p style="text-align: center;">WHO Global Influenza Programme</p> |
| <p style="text-align: right;">8</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">3. Case management and hospital infection control</h4> <ul style="list-style-type: none"> - 74 cases; 49 deaths (VTN: 55/35) <ul style="list-style-type: none"> • Two publications on the clinical course of the disease.... - Very little understanding of key clinical, epidemiological and virological parameters of H5N1 infection in humans <ul style="list-style-type: none"> • Risk groups, ICP, Ab kinetics, excretion patterns; duration of infectivity • Efficacy of antiviral drugs; adapted diagnostic tests/protocols ● Coordinated clinical research and case management <ul style="list-style-type: none"> - Network of linked laboratories in affected countries; standardized treatment and study protocols; mechanism of sample and information exchange; complementary analyses - International clinical research network on emerging infectious diseases in Asia (WHO and NIH initiative) <ul style="list-style-type: none"> • Strengthen national capacity and resources and facilitate international collaboration and exchange • Concept paper developed; international partners/funding institution identified; next step: engagement of national partners and enrollment of hospitals <p style="text-align: center;">WHO Global Influenza Programme</p> | <p style="text-align: right;">9</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">4.1 Aversion of a pandemic</h4> <ul style="list-style-type: none"> ● New developments <ul style="list-style-type: none"> - Possibility of early detection of new subtype with increasing transmissibility - Antiviral and H5N1 vaccine stockpile feasible ● Could massive prophylactic use of antivirals (vaccines) in/around an epi centre extinguish an emerging new subtype or at least buy time? <ul style="list-style-type: none"> - Modelling very foundation for any decision making - Particular large number of assumptions. ● Research on H5N1 vaccine stockpile ● Could an international stockpile of respective size(?) be established and maintained? <p style="text-align: center;">WHO Global Influenza Programme</p> |
| <p style="text-align: right;">10</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">4.2 Slowing down local spread</h4> <ul style="list-style-type: none"> ● New developments <ul style="list-style-type: none"> - Recommendations available on non-pharmaceutical measures at the international and national level during different phases of an influenza pandemic - Built on best available science ● What effectiveness will non-pharmaceutical interventions have? <ul style="list-style-type: none"> - Research package necessary <ul style="list-style-type: none"> • during pandemics ● What are the pathways of transmission of influenza viruses? <ul style="list-style-type: none"> - incompletely understood and their relative importance unknown. - Hospital infectious control; case management; non-pharmaceutical interventions <p style="text-align: center;">WHO Global Influenza Programme</p> | <p style="text-align: right;">11</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">5. Clinical research on the immunogenicity of pandemic vaccines</h4> <ul style="list-style-type: none"> ● New developments <ul style="list-style-type: none"> - Pandemic vaccine prototype strain available since April 2004 - Vaccine stockpile feasible ● Establish immunogenicity of H5N1 vaccines from currently circulating strain and implement antigen sparing strategies  <p style="text-align: center;">WHO Global Influenza Programme</p> |

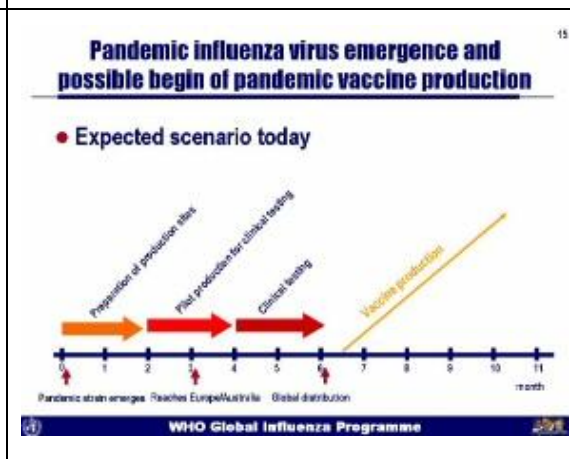
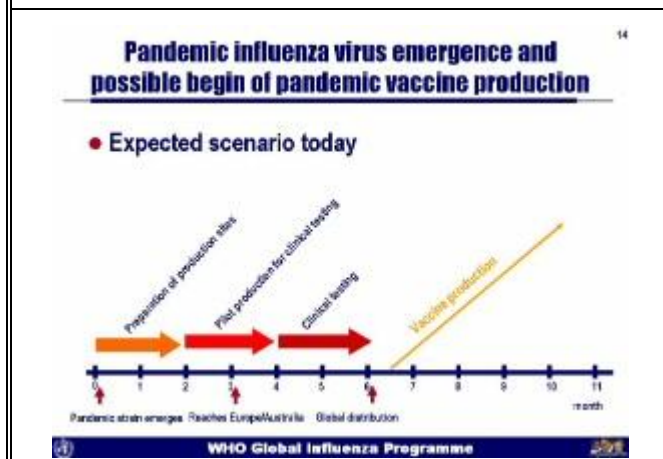


Opportunities for research

5. Clinical research on the immunogenicity of pandemic vaccines

- **New developments**
 - Pandemic vaccine prototype strain available since April 2004
 - Vaccine stockpile feasible
- **Establish immunogenicity of H5N1 vaccines from currently circulating strain and implement antigen sparing strategies**
 - **Requires**
 - research coordination between countries and companies to avoid duplication
 - Public funds to compensate for lack of commercial interest
 - **Current status**
 - Promising progress since Nov 2004
 - 2 clinical trials started (USA)
 - 10 more companies in Australia, Canada, France, Germany, Japan, USA before the end of the year (all antigen sparing)
- H5N1 registration=pandemic vaccine registration

WHO Global Influenza Programme



Opportunities for research

6. Vaccine production: surge capacity

- **Current problems**
 - Little to no surge capacity for seasonal and pandemic influenza vaccines
- **What alternative production systems exist and how could existing ones be improved?**
 - Cell-culture; recombinant vaccines
 - Improved Ag harvest from eggs

→ Should be assessed as part of a package of an complete pandemic preparedness concept.

WHO Global Influenza Programme

Opportunities for research

7. Epidemiology and natural history: mid-long term

- **Current problems**
 - Public health risk of emerging avian and mammalian viruses very difficult to assess and to predict.
 - Determinants for human pathogenicity of influenza viruses ill understood
 - Role of migratory birds as vector/reservoir of HPAI unclear
- **Studies on the ecology and molecular biology of animal influenza viruses**
 - Genetic foundation for host specificity and pathogenicity
 - Molecular studies on the genetic determination of pathogenicity and host specificity
 - Laboratory trials on the susceptibility of domestic animals
 - Virological/serological studies on the prevalence and molecular evolution of influenza viruses in animals/birds

WHO Global Influenza Programme

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| <p style="text-align: right;">18</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">8. Vaccines: long-term</h4> <ul style="list-style-type: none"> ● Current problems <ul style="list-style-type: none"> - Pandemic vaccines <ul style="list-style-type: none"> • Stockpiling not possible for all subtypes as current vaccines confer protection only against small number of variant viruses • Surge capacity - Seasonal vaccines <ul style="list-style-type: none"> • Annual revaccination costs  <p style="text-align: center;">WHO Global Influenza Programme</p> | <p style="text-align: right;">18</p> <h3 style="text-align: center;">Annual vaccine costs to health</h3> <ul style="list-style-type: none"> ● Annual seasonal vaccine production <ul style="list-style-type: none"> - 300 million doses - Assumptions <ul style="list-style-type: none"> • WS price 7.5 USD • 5% increase ● Costs by 2015: 28.3 billion ● If only 5% was taken/added for research: 1.41 billion.  <p style="text-align: center;">WHO Global Influenza Programme</p> |
| <p style="text-align: right;">20</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">8. Vaccines: long-term</h4> <ul style="list-style-type: none"> ● Current problems <ul style="list-style-type: none"> - Pandemic vaccines <ul style="list-style-type: none"> • Stockpiling not possible for all subtypes as current vaccines confer protection only against small number of variant viruses • Surge capacity - Seasonal vaccines <ul style="list-style-type: none"> • Annual revaccination costs ● Cross-subtype specific influenza vaccines which confer long-lasting immunity <ul style="list-style-type: none"> - Would address both pandemic and epidemic dilemmas <p>→ Estimated global investment into antiviral stockpiling</p> <ul style="list-style-type: none"> - 1.4 billion USD  <p style="text-align: center;">WHO Global Influenza Programme</p> | <p style="text-align: right;">21</p> <h3 style="text-align: center;">Opportunities for research</h3> <ul style="list-style-type: none"> ● Urgent short-term Short- to mid-term <ul style="list-style-type: none"> - Risk assessment - Control of source and pathways of transmissions (research at the human-animal interface) - Case management and hospital infection control - Non-pharmaceutical interventions <ul style="list-style-type: none"> • Aversion of pandemic: avian of new subtype with increasing fitness • Slowing down spread of pandemic virus - Clinical research on immunogenicity of pandemic vaccines ● Mid-and long-term <ul style="list-style-type: none"> - Vaccines - Epidemiology and natural history of influenza - Antivirals... <p style="text-align: center;">WHO Global Influenza Programme</p> |
| <p style="text-align: right;">22</p> <h3 style="text-align: center;">Research prioritization and coordination</h3> <ul style="list-style-type: none"> ● Identification of research priorities does not equal international coordination of research efforts ● Several research projects already initiated <ul style="list-style-type: none"> - Many individual projects <ul style="list-style-type: none"> • Governments, academia, national research and philanthropic institutions. - WHO Global Influenza Network including WHO Animal Influenza Network: operational research and direct support to control efforts - Several loose ends <p>→ Need for an meeting on coordination of international support to avian influenza surveillance and control in Asia (donor meeting with gap analyses)</p> <ul style="list-style-type: none"> - Coordination meeting on research?! <p style="text-align: center;">WHO Global Influenza Programme</p> | <p style="text-align: right;">22</p> <h3 style="text-align: center;">Opportunities for research</h3> <h4 style="text-align: center;">Summary</h4> <ul style="list-style-type: none"> ● Major needs for research exist <ul style="list-style-type: none"> - Urgent short-term research <ul style="list-style-type: none"> • Risk assessment/reassessment • Assessment of the effectiveness of non-pharmaceutical interventions • Preparation of research during pandemic - Long-term research <ul style="list-style-type: none"> • Hetero-subtype specific influenza vaccine with long-lasting immunity <ul style="list-style-type: none"> - "Best bang for the bug." ● Need for international coordination!? ● Creating the environment for translating scientific evidence in immediate public health action <p style="text-align: center;">WHO Global Influenza Programme</p> |

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- **Research will initially cost money**
 - **And will save lives and money!**
 - will also apply to fundamental research



If you think research is expensive - try disease. Mary Lasker 1901-1994

WHO Global Influenza Programme

(Slides available on accompanying CD)

THE ROLE OF NIH RESEARCH IN PANDEMIC INFLUENZA PREPAREDNESS

**Dr. Anthony S. Fauci, Director, National Institute of Allergy and Infectious Disease,
National Institutes of Health**

I am going to talk about one component of pandemic influenza preparedness: the role of NIH research endeavors in complementing the activities of CDC, FDA, and other U.S. agencies as well as international collaboration.

As this is the John La Montagne Symposium, I would like to remind us not only of the extraordinary loss we all felt when John passed away on November 2, 2004, but also of his extraordinary impact at both a scientific level and at the level of human interactions throughout the international and national community. As many of you know, John died at the airport in Mexico City, the city of his birth. John loved Mexico and Mexico City. He had returned there for one of the important meetings at which he so well represented not only NIH but the U.S. Government.

I could probably use my entire time to talk about his accomplishments, but I would like to point out some highlights of his career, most importantly in vaccinology. He loved vaccinology. He loved global health, and he played a major role personally and administratively in the development of vaccines for acellular pertussis, in supporting malaria initiatives with international colleagues, and in leading research endeavors in pneumococcus, rotovirus, influenza, and TB.

He was an advisor to virtually every important international organization, and he had a special interest in the Children's Vaccine Initiative. He was a major player in the U.S.-Japan Program. He was our representative on the Multilateral Initiative on Malaria (MIM), and he enticed Harold Varmus, when he was director of NIH, to become heavily involved as well.

John's greatest love, as we all know, was influenza research. John had been talking for many years about the dangers not only of seasonal flu but also the potential for a pandemic influenza that we are discussing here. He also focused on emerging infectious diseases and the threat of bioterrorism—all long before they became fashionable.

However, as important as his scientific and administrative accomplishments was the fact that John was one of the finest individuals I have ever met. He was the most self-effacing, highly competent person that I have dealt with in my professional career. When I called then-Secretary of Health and Human Services, Tommy Thompson the morning after I had learned in the middle of the night that John had died, Secretary Thompson said something that all of us feel: that John was a true public health hero whose leadership—especially in the realm of infectious diseases—truly left the world a healthier place. I am very pleased that we have the opportunity to dedicate this symposium to such an extraordinary scientist, science administrator, and human being.

Let me move on now to pandemic influenza preparedness. In the United States, CDC heads a multiagency endeavor that encompasses surveillance, detection, training, maintaining the stockpile, and importantly, disease control and prevention. FDA guides us through the regulatory approval process for vaccines, therapeutics, and diagnostics. NIH is involved not only in basic research but also in developing medical interventions and conducting clinical trials. HHS's

Office of Public Health Emergency Preparedness, under the leadership of Stewart Simonson, coordinates all of these efforts.

The HHS commitment and allocation of resources to influenza has grown dramatically over the past several years, starting with about \$41 million in the 2001 Budget and rising to \$430 million in the President's request for the FY 2006 budget. Of NIAID's 2005 budget of \$4.4 billion, the agency is spending over \$1 billion on vaccine research—about 27 percent of its endeavors. Funding for influenza research has similarly risen from about \$20 million in 2001 to about \$120 million in the President's 2006 budget request.

NIH divides those funds into several components. Although the main player in surveillance and epidemiology is CDC, some of our grantees monitor the molecular evolution of bird and other animal influenza viruses as they evolve into viruses that can infect humans. Our basic research looks at the pathophysiology of viral diseases, in this case influenza. We are building not only physical but also intellectual research capacity by training people in the development of countermeasure: diagnostics, therapeutics, and vaccines.

In the influenza surveillance component, one of our main players is Robert Webster at St. Jude's Children's Research Hospital. He pursues the surveillance of animal influenza in Asia, and plays a major role in generating candidates for vaccines against a pandemic influenza strain, as well as studying emerging strains that are infecting swine in Asia. He is playing a key role in generating the H5N1 vaccine reference virus now being used by both Sanofi Pasteur and Chiron. He has also collaborated with others to study the spectrum of the host range of H5N1 influenza virus. One important resulting observation was the fact that ducks can serve as a silent reservoir for H5N1.

Basic research provides the fundamental matrix for developing countermeasures. The NIH portfolio includes a substantial effort to understand the pathogenesis of pandemic influenza viruses, including virulence factors, and the transmissibility of H5N1 among different animal species as well as the molecular evolution that allows for the host range to expand. Our research also includes studies on the mechanisms of animal-to-human transmission and the development and propagation of animal models to study pandemic influenza viruses.

Also important are attempts to understand better the extraordinary pathogenicity and virulence of the 1918 pandemic flu, known as H1N1. Current studies include sequencing the 1918 influenza viral genes, trying to identify signature sequences responsible for the virulence, determining the molecular mechanisms that led to the emergence of this virus, and understanding the contribution of the hemagglutinin and the neuraminidase genes to the unprecedented clinical virulence. Four important papers have probed the pathogenicity, immunogenicity, and virulence of this very important viral strain, as we are obviously concerned about the possibility of a repeat of this phenomenon.

Other basic research and applied research involves the growing use of reverse genetics, whereby we eliminate some of the uncertainty when trying to develop a seed virus for our vaccine. Generally, researchers would put two different viruses together in culture and wait for the inevitable reassortment of genes between them. In this case, we would co-cultivate either an H5 or an H7 influenza virus with a familiar strain such as the Puerto Rico strain, which we use regularly in our egg-based cultures. Reverse genetics, in contrast, deliberately takes the relevant genes from each strain, and actually creates the hybrid virus strain that expresses the H and N from the potentially pandemic virus together with the 6 other influenza genes from the benign

and easy-to-grow strain. This approach has been used to develop the seed virus for the H5N1 vaccine, which has just recently entered clinical trials.

Multiple HHS agencies, including CDC, as well as some of our grantees and pharmaceutical and biotechnology companies are also doing research to develop a sound, consistent, cell-culture-based capability. The goal is to take some of the uncertainty out of egg-based culture and to give us greater surge capacity so we can have the year-round capability to produce vaccine. These cell-culture-based strains are also important because if we confront a virulent influenza strain that might prove lethal to chicken embryos, we can use reverse genetics to splice out the virulence factor. Also, a vaccine that is not grown in eggs is important to individuals who have allergies to egg proteins.

Another important project that NIAID supports is the influenza genome project in collaboration with CDC, the New York State Department of Health, the National Center for Biotechnology Information, St. Jude's Hospital in Memphis, and others. This project collects the full genomic sequences of a large number of isolates of influenza from humans and, in some cases, animals. The goal is to make these sequences available for basic as well as applied researchers, so that they may be helpful in the development of drugs, vaccines, and diagnostics.

As of a couple of days ago, we have released the sequences of about 93 human isolates—an important research resource for our grantees and collaborators.

What about antiviral therapies? Four separate anti-influenza antivirals are available. Among these, only Oseltamivir (Tamiflu) is adequate for treatment of H5N1 influenza. We are putting about 2.3 million treatment courses of Tamiflu into the national stockpile,

NIAID and NIH research projects are developing and testing long-acting, next-generation neuraminidase inhibitors. We need targeted antiviral efforts like those for other disease such as HIV/AIDS, for which we have made remarkable advances, with more than 20 separate antiviral drugs now available.

Animal studies are examining the effectiveness of combination therapies—a new approach for influenza. Other non-traditional pharmacological approaches include inhaled polyclonal IgG as an immunoprophylactic and the evaluation of new targets—not just the M protein and the neuraminidase, but also viral entry, replication and maturation.

Protocols for the use of oseltamivir in infants are evolving. Oseltamivir is licensed for individuals older than 1 year, but we do not have enough information on people 1–2 years of age or younger to feel totally confident in the use of this drug in these subjects. That is why we are developing protocols to try to identify the optimal use of oseltamivir, particularly in children.

Our main weapon in the armamentarium against influenza is a vaccine. As we have done in developing other countermeasures, particularly in the arena of biodefense, we are collaborating with at least two companies to develop a new vaccine for H5N1.

Last spring we signed contracts with Sanofi Pasteur and Chiron to develop an H5N1 vaccine, as well as with Chiron for an H9N2 vaccine. Progress has been quite good. In fact, for H5N1, we contracted to produce pilot lots of 18,000 doses—10,000 from Chiron and 8,000 from Sanofi Pasteur—for a phase I-II clinical trial. The trial of the Sanofi product, which has accrued about 450 individuals thus far, will examine safety and immunogenicity first in healthy adults, then in the elderly population, and ultimately in the pediatric population.

We are also contracting for 2 million doses of the H5N1 vaccine from Sanofi Pasteur for the strategic national stockpile. We also have an H9N2 vaccine, and one might ask why we would want that. Although it is not now as important as the H5N1 virus in Asia, particularly in Vietnam and Thailand, we need to learn more about the body's immune response and the safety of the vaccines that are derived avian viruses. The H9N2 has also started its clinical trial. The live attenuated version of both vaccines is very important. Studies on that version are taking place in the NIAID intramural laboratory of Brian Murphy and Kanta Subbarao, but other individuals in the outside community are also looking at this.

We all know from experience with live attenuated vaccines that this approach induces a broader range of serum and local mucosal antibodies. It induces cellular immune responses as well as humeral, and immunity develops rapidly, usually with a single dose. This is important because there is a question of whether we will have to use multiple doses of the killed H5N1 vaccine.

The attenuated vaccine has a wider breadth of cross-reactivity, as do most live attenuated vaccines. This becomes critical when dealing with H5N1. If it mutates to become much more efficient in its transmissibility from human to human, will that mutation affect the ability of the vaccine to protect against it? Not necessarily, but broader cross-reactivity would be very helpful. The other advantage is that such a vaccine does not require needle injection, and it is more effective in infants and children than are inactivated virus vaccines.

Vaccine clinical trials traditionally occur in our vaccine and treatment evaluation units. The three involved in the H5N1 vaccine are located in Los Angeles, Baltimore, and Rochester, New York, but other units will also be involved in the second and third components of the clinical trial.

I want to finish by commenting on the fragility of the vaccine enterprise in general, but particularly the influenza vaccine enterprise, and the role of the research enterprise in addressing this fragility. We all were faced with a rude awakening when we discovered the contamination of half of the U.S. supply of influenza vaccine last year. However, other nations that rely on influenza vaccine have also experienced delays. For example, Australia found that one of the influenza strains in a vaccine was not present in as great a concentration as required, which created somewhat of an analogous situation to the one that we experienced last fall.

How can we strengthen the fragile vaccine enterprise? One approach is by targeting research resources. I have already mentioned several research efforts, such as the use of reverse genetics to add consistency and reproducibility to our ability to obtain a seed virus. We can also gradually transition to cell-based vaccines and the use of recombinant-DNA technologies to express hemagglutinin and neuraminidase and other proteins. Developing a perennial vaccine based on conserved epitopes is particularly problematic with influenza, because humans are continually infected each year, yet we do not seem to have adequate cross-protection against small changes in connection with the yearly antigenic drifts.

We also lack dose-sparing strategies. Toward that end NIH is looking at using intradermal vaccines, and comparing intradermal with intramuscular vaccines. A clinical protocol to compare intramuscular to intradermal approaches in H5N1 vaccination is in preparation. We are also discussing production of an adjuvant-aided H5N1 vaccine with manufacturers, although the trial that has just started is not adjuvant-aided.





Because this is the John La Montagne symposium, I want to mention that one of his last scientific efforts was to co-author with me an invited commentary in the *New England Journal of Medicine*, which was published on November 3, 2004, the day after his death. He was hired as one of our first influenza program officers, and his last scientific publication was on influenza.

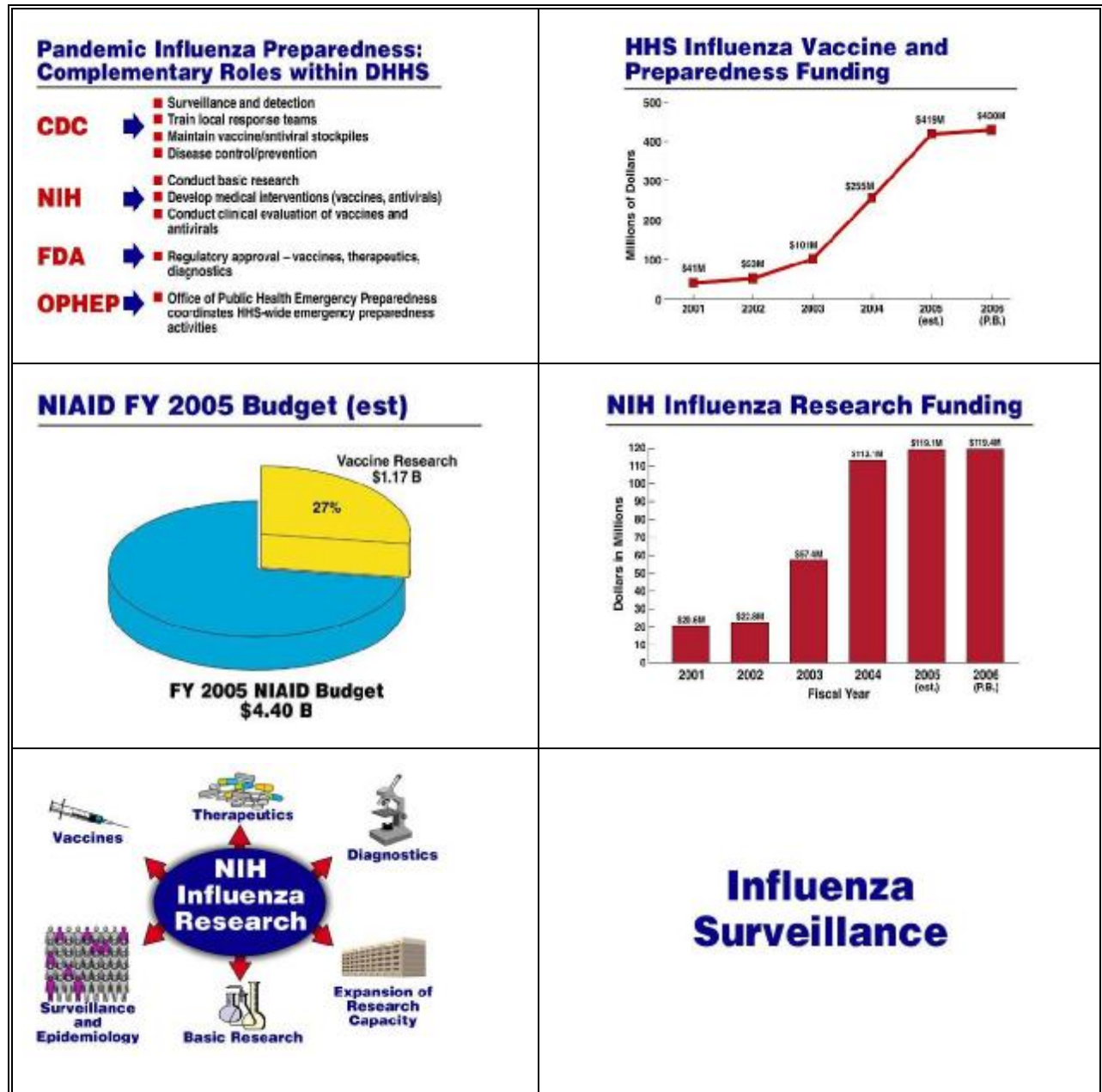
The fragility of the influenza enterprise is real, and we must address it with incentives to industry as well as with basic research that improves the process of vaccine development. Potential incentives are now being discussed at HHS. NIAID is also trying to help industry make products that might supplement our normal supply of influenza vaccine—that is, to obtain the necessary information for as rapid FDA approval as possible. Such efforts are occurring with GlaxoSmithKline's inter-pandemic Fluarix vaccine. One of the most rapidly accrued trials that we have ever experienced—it enrolled almost 1,000 people in 5 days—began in December 2004. People were interested in getting into the trial given the shortage of influenza vaccine. We are expecting the results shortly.


I want to close by mentioning that when we deal with emerging diseases, we see the extraordinary capability of pathogens to persist, emerge, and reemerge. None does it better than influenza. To address this threat, we must balance public health measures, biomedical research, and technological advances. Staying on top of what could be an extraordinary public health problem is extraordinarily important.

John was co-author of a review of the last such meeting in 1995, published in the *Journal of Infectious Diseases*, called "Pandemic Influenza: Confronting a Re-emerging Threat." What he said then holds true today. Success in controlling a pandemic will benefit from new advances by the scientific community, which provides the pool of solutions to combating emerging threats.

Plenary Presentation Slides-Dr. Anthony S. Fauci

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| <p>John R. La Montagne Memorial Symposium on Pandemic Influenza Research April 4-5, 2005 Institute of Medicine National Academies</p> <p>The Role of NIH Research in Pandemic Influenza Preparedness</p> <p>Anthony S. Fauci, M.D. Director National Institute of Allergy and Infectious Diseases National Institutes of Health April 4, 2005</p>   |  <p>John R. La Montagne, Ph.D. 1943-2004</p> |
| <p>John R. La Montagne, Ph.D. Selected Career Highlights</p> <ul style="list-style-type: none">■ Vaccinology<ul style="list-style-type: none">- Vaccines for acellular pertussis, malaria, pneumococcus, rotavirus, influenza, tuberculosis- Advising WHO and others on immunization and vaccines- Children's Vaccine Initiative■ Fostering International Collaboration<ul style="list-style-type: none">- e.g. US-Japan Program, Multilateral Initiative on Malaria■ Influenza<ul style="list-style-type: none">- Long-standing vision of importance of preparedness■ Emerging Diseases, including Bioterrorism<ul style="list-style-type: none">- Recognized importance long before it became "fashionable" |  |
| <p><i>"Dr. John La Montagne was a true public health hero whose leadership, especially in the realm of infectious diseases, left the world a healthier place."</i></p> <p>- HHS Secretary Tommy G. Thompson, Nov. 3, 2004</p> | <p>Pandemic Influenza Preparedness</p> |



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| <p>NIAID Pandemic Preparedness in Asia Contract</p> <ul style="list-style-type: none"> ■ PI: Robert Webster, St. Jude's Children's Research Hospital ■ Activities include: <ul style="list-style-type: none"> - animal influenza surveillance in Asia - generating vaccine candidates against pandemic influenza strains - studying newly emerging influenza strains infecting swine in the U.S. ■ Generated a 2004 H5N1 vaccine reference virus using the 8-plasmid system; NIAID has provided this reference virus to both Sanofi Pasteur and Chiron. | <p>October 29, 2004: WHO announced a new study by St. Jude's Children's Research Hospital that showed "... that domestic ducks might now be acting as a 'silent' reservoir for the H5N1 virus..."</p>  <p>Source: WHO</p> |
| <p style="text-align: center;">Basic Research</p> | <p>NIAID-Supported Influenza Research Activities Basic Research</p> <ul style="list-style-type: none"> ■ Pathogenicity of pandemic influenza viruses: virulence factors ■ Transmission of H5N1 influenza viruses among different animal species ■ Mechanisms of animal to human transmission ■ Animal models to study pandemic influenza viruses |
| <p>NIAID-Supported Research on 1918 Pandemic H1N1 Influenza Virus: Current Studies</p> <ul style="list-style-type: none"> ■ Complete sequence of 1918 influenza virus genes ■ Identify signature sequences responsible for virulence ■ Determine molecular mechanisms leading to emergence ■ Understand contribution of 1918 HA and NA genes to unprecedented virulence | <p style="text-align: center;">Recent Findings</p> <ul style="list-style-type: none"> • Pathogenicity and Immunogenicity of Influenza Viruses with Genes from the 1918 Pandemic Virus (Proceedings of The National Academies, T Tumepey et al, 2004) • Enhanced Virulence of Influenza A Viruses with the Haemagglutinin of the 1918 Pandemic Virus (Nature, D Kobasa et al., 2004) • The Structure and Receptor Binding Properties of the 1918 Influenza Hemagglutinin (Science, SJ Gamblin et al., 2004) • Transmissibility of 1918 Pandemic Influenza (Nature, CE Mills et al., 2004) |

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| <h3>Influenza Seed Virus for Inactivated Virus Vaccine Production Using a Reverse Genetics System</h3> <p>Highly pathogenic H5 or H7 Allworte FluA/B04 (H1N1)</p> <p>Removal of additional basic amino acids</p> <p>Vaccine approved cell line</p> <p><small>Source: Webster et al. Vaccine 20(2195) (2002); Science 302(1519)(2003)</small></p> | <h3>Influenza Vaccine Production: Cell Culture as an Alternative to Chicken Eggs</h3> <p>Identify target influenza strains</p> <p>Provide target viruses to vaccine manufacturers</p> <p>Egg-based</p> <p>Cell culture-based</p> |
| <h3>Potential Advantages of Cell Culture-Based Influenza Vaccines</h3> <ul style="list-style-type: none"> ■ Allows greater flexibility for surge capacity. ■ Provides opportunity for year-round vaccine production. ■ Requires less manufacturing space. ■ Circumvents possible problems presented by highly virulent influenza strains (i.e., lethality to chicken embryos). ■ Tolerated by people with egg allergies. | <h3>NIAID Influenza Genome Project</h3> <p>Avian and Human Influenza Viral Strains</p> <p>HAIID NYSDOH NCBNLM CDC St. John's Children's Hospital Others</p> <p>Strain Selection Sample Preparation</p> <p>NIAID Microbial Genome Sequencing Center TIGR</p> <p>Flu Sequence Data Publicly Accessible: GenBank/NIAID Bioinformatics Research Center</p> <p>As of Nov. 31, 2005, full genomic sequences of 93 human isolates released</p> <p>Basic Research: How flu virus evolves/ spreads/causes disease</p> <p>Applied Research: Drugs/Vaccines/Diagnostics</p> |
| <h2>Antiviral Therapies</h2> | <h3>Antiviral Therapies for Influenza</h3> <p>Hemagglutinin (H)</p> <p>Neuraminidase (N)</p> <p>M2 Protein</p> <p>Oseltamivir Zanamivir</p> <p>Amantadine Rimantadine</p> |

| <p>Antiviral Drugs in Strategic National Stockpile</p> <table border="1"> <thead> <tr> <th></th> <th>Number of Treatment Courses</th> </tr> </thead> <tbody> <tr> <td>Tamiflu (capsules and suspension)</td> <td>2,269,624</td> </tr> <tr> <td>Rimantadine (tabs and syrup)</td> <td>5,054,720</td> </tr> </tbody> </table> <p>Not effective against H5N1</p> <ul style="list-style-type: none"> Roche is the single supplier of Tamiflu (oseltamivir) Currently single production facility in Switzerland <p><small>Source: US Dept. Health & Human Services</small></p> | | Number of Treatment Courses | Tamiflu (capsules and suspension) | 2,269,624 | Rimantadine (tabs and syrup) | 5,054,720 | <p>Antivirals: NIAID-funded Projects</p> <ul style="list-style-type: none"> Development/testing of long-acting next-generation neuraminidase inhibitor Animal studies to assess effectiveness of combination antiviral therapy Development of inhaled polyclonal IgG as immunoprophylactic Evaluation of novel drug targets (viral entry, replication, HA maturation) |
|--|--|-----------------------------|-----------------------------------|-----------|------------------------------|-----------|--|
| | Number of Treatment Courses | | | | | | |
| Tamiflu (capsules and suspension) | 2,269,624 | | | | | | |
| Rimantadine (tabs and syrup) | 5,054,720 | | | | | | |
| <p>Antivirals</p> <p>Use Profile of Oseltamivir in Infants</p> <ul style="list-style-type: none"> Currently licensed for treatment of individuals ≥ 1 year old (chemoprophylaxis ≥ 13 years old) Animal study to further characterize safety profile of oseltamivir in infants Safety protocol to administer oseltamivir to children < 2 years with confirmed influenza A infection in the setting of an H5N1 outbreak Goal: Identify the optimal use of oseltamivir | <p>Pandemic Influenza Vaccine</p> | | | | | | |
| <p>NIH Role in Influenza Vaccine Development</p> | | | | | | | |

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| <p>H5N1 Vaccine Contracts</p> <ul style="list-style-type: none"> ■ NIAID awarded contracts to Sanofi Pasteur and Chiron to produce H5N1 pilot lots of inactivated vaccine for Phase I/II clinical trials ■ >8,000 doses delivered from Sanofi Pasteur: trial has begun ■ 10,000 doses to be received from Chiron: trials to begin late fall 2005 ■ Initial Trial: Safety/Immunogenicity in healthy adults with possible expansion to elderly and pediatric populations |  <p>HHS News U.S. Department of Health and Human Services www.hhs.gov/news</p> <p>FOR IMMEDIATE RELEASE Tuesday, September 21, 2004</p> <p>HHS Orders Avian Flu Vaccine Doses as Preventive Measure</p> <p>HHS Secretary Tommy G. Thompson announced today the awarding of a contract to Aventis Pasteur Inc. to manufacture and store 2 million doses of avian influenza H5N1 vaccine, an important initial acquisition to better prepare the nation for an influenza pandemic.</p> |
| <p>H9N2 Vaccine Contracts</p> <ul style="list-style-type: none"> ■ NIAID task order to Chiron for production of an investigational inactivated vaccine based on an H9N2 strain ■ Chiron produced a total of 40,000 doses of vaccine formulated with and without MF59 adjuvant ■ Initial Trial: Safety/Immunogenicity in healthy adults ■ Trial has begun; results expected late summer/early fall | <p>Live Attenuated Cold-Adapted Pandemic Influenza Vaccine</p> <p>H5N1:</p> <ul style="list-style-type: none"> ■ 3 vaccine candidates made and compared ■ Clinical lots to be generated from best candidate ■ Clinical trials planned for 2005/2006 <p>H9N2:</p> <ul style="list-style-type: none"> ■ Clinical lot produced ■ Clinical trials (70 subjects) planned for summer 2005 |
| <p>Potential Advantages of a Live Attenuated Influenza Virus Vaccine</p> <ul style="list-style-type: none"> ■ Induces both serum and local mucosal antibodies ■ Induces both antibodies and cellular immune protective mechanisms ■ Induces immunity rapidly, usually following one dose ■ Has wider breadth of cross-reactivity with related influenza virus strains ■ Does not require a needle injection ■ More effective in infants and children than inactivated virus vaccines | <p>NIAID's Network of Vaccine and Treatment Evaluation Units (VTEUs)</p>  <p>Los Angeles Houston St. Louis Nashville Cincinnati Baltimore Rochester</p> |
| <p>Fragility of the Influenza Vaccine Enterprise</p> | <p>U.S. Flu Vaccine Supply Halved</p> <p>Health Officials Face Record Shortage as Britain Shuts Down Supplier</p> <p>Americans' supply of flu vaccine was cut in half Tuesday as Britain abruptly shut down a major supplier just as flu season is about to begin. Facing a record shortage, U.S. health officials scrambled to reserve remaining shots for the elderly and others at highest risk from influenza.</p> <p>Associated Press, Oct 2004</p> |

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| <p style="text-align: center;">Delays in Australian Flu Vaccine Likely This Year</p> <p>Australia's chief medical officer today warned there could be delays in obtaining the flu vaccine this year...because one of the influenza strains in the vaccine was not present in as great a concentration as required... Sanofi pasteur was contracted to supply 35 per cent of the government's vaccine supplies...</p> <p style="text-align: center;">Money Plans, March 2005</p> | <p style="text-align: center;">Addressing the Fragile Vaccine Enterprise</p> <ul style="list-style-type: none"> ■ Research resources: developing and sharing new technologies, e.g. <ul style="list-style-type: none"> - reverse genetics - cell culture-based vaccines - recombinant DNA technologies - "perennial" vaccines based on conserved epitopes - dose-sparing strategies |
| <p style="text-align: center;">Vaccine Dose-Sparing Strategies</p> <ul style="list-style-type: none"> ■ Intramuscular (IM) vs. Intradermal (ID): Clinical protocol to compare IM vs. ID H5N1 vaccine is in preparation. ■ NIAID is in discussions with manufacturers concerning production of an alum-adjuvanted H5N1 vaccine. | <div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"> <p>"These studies raise the possibility of using alternative routes of immunization (e.g., intradermal as opposed to intramuscular, administration) with smaller doses of vaccine as a means of "stretching" available doses of influenza vaccine in times of shortages."</p> </div> <p style="text-align: center;">Intradermal Influenza Vaccination: Can Less Be More? John R. La Montagne and Anthony S. Fauci The New England Journal of Medicine, November 2004</p> |
| <p style="text-align: center;">Addressing the Fragile Vaccine Enterprise <i>(continued)</i></p> <ul style="list-style-type: none"> ■ Incentives to industry, e.g. <ul style="list-style-type: none"> - regulatory relief - guaranteed purchases and fair pricing - liability protection - research resources and clinical trials capacity - tax incentives - ensure demand through public education on health benefits of vaccination | <p style="text-align: center;">GSK Clinical Trial</p> <p>NIAID rapidly initiated a Phase III trial to evaluate safety and immunogenicity of GSK's inter-pandemic Fluarix® vaccine in healthy adults:</p> <ul style="list-style-type: none"> - Trial began in Dec. 2004 - 952 subjects enrolled in 5 days - Trial conducted through VTEUs - Results expected Q2 2005 |



(Slides available on accompanying CD)

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MORNING PLENARY DISCUSSION, DAY 1 (APRIL 4, 2004)

Moderator: Dr. Harvey Fineberg

**Panel Participants:
Dr. Bruce Gellin, Dr. Julie Gerberding,
Dr. Jesse Goodman, Dr. Klaus Stöhr,
Dr. Anthony Fauci**

DR. FINEBERG: I would like to invite this morning's speakers to join us here on stage for a half-hour of questions and comments.

PARTICIPANT: I have two comments, one rather general and one very specific. First, in all the articles published on H5N1 and its potential, particularly its introduction into people, I have not seen any evidence of a rigorous study of the neuraminidase antibody concentration in a population that must have some N1 immunity. This is particularly important if we are facing inapparent infections and wondering about the sporadic occurrence of lethal or very severe diseases. I am wondering whether those cases have been cautiously and deliberately investigated with respect to their neuraminidase antibody response.

Before that question is answered, I would like to make a comment about intradermal versus subcutaneous inoculation. In comparisons of intradermal and subcutaneous routes of inoculation, an important control is often omitted—namely, the comparison of equal doses of vaccine delivered by the two routes. We are beginning to create new studies for comparing small doses of flu vaccine and larger doses of flu vaccine as a second injection. In these studies we do not compare apples and oranges, we give the same amount of virus—namely one-tenth of an mL—by both subcutaneous and intradermal routes. Very few studies have been done using equal amounts of virus. We gave one-tenth mL intradermally, and we gave five-tenths mL intramuscularly, and the response is about the same. Perhaps this is because we are usually dealing with a primed population.

DR. GERBERDING: We have not been able to do a comprehensive serologic assessment of any of the antigens in the H5N1 immune response because those studies have been difficult to start. They are obviously very important. We need field investigations that would allow us to do sampling on a population basis in several regions that are experiencing infection.

DR. STOHR: Yes, I think it would be quite interesting—because it is so difficult to assess the significance of the immune response—to try to better understand the effectiveness, or at least the immunogenicity, of vaccines in non-human primates, which could be vaccinated with a vaccine with an N1 component irrespective of its HA component. We can then see if the vaccine provides any cross-protection against the H5N1, and the significance of that cross-protection.

Many people have thought about doing that, but it's a very costly exercise, and nobody has tried it. Such a study requires a considerable number of non-human primates as well as a better understanding of the infectious dose.

DR. GERBERDING: It is not so much science as samples that are rate-limiting.

DR. FINEBERG: The second question concerned intradermal immunization or route of administration more generally.

DR. FAUCI: Yes, I agree with you completely. If we consider whether we could stretch out supply, and give a half a dose intradermally versus the full dose intramuscularly, we could prove the concept that we could get relatively equivalent protection. Another question is: what happens if you give an equivalent dose intradermally to intramuscularly in elderly individuals who generally have poorer antibody response? I would be interested, from an immunological standpoint, as to whether we can boost the relatively poor immunological response in people 65 years of age and older toward a relatively normal response by using intradermal dosing but relying on the dose that we would use intramuscularly.

DR. FINEBERG: If I understood, your point was also that the immunologic memory might enhance responsiveness to an intradermal dose of lower intensity, and therefore could mask what might happen in a population that was immunologically naive.

DR. GELLIN: Both those questions highlight the need for international collaboration. Dr. Stohr, I hope you hold the meeting you mentioned, because based on what we have seen here, I think there is going to be tremendous interest. If we continue to compare apples to oranges we are going to be in trouble, because we are going to have a range of data points that we don't know how to put together. We need international collaboration to understand who is doing these studies and how they are advance the science in this area.

PARTICIPANT: In response to the previous question about the apples and oranges of intradermal versus subcutaneous: In preparing for tomorrow's workshop, I found a number of studies that used the same dose intradermally and subcutaneously.

Back in 1949, Bruin et al. found that, using the same doses, geometric mean titers were higher intradermally than subcutaneously in both adults and children. Still, when the antigen mask was small, intradermal did better. When the antigen dose quantity was higher, subcutaneous did better. More recently, in 1969 in the Canadian Journal of Public Health, Davies found that giving the same dose intradermally or subcutaneously with jet injectors for both routes produced a higher response intradermally, but the result was not significant.

PARTICIPANT: Our biotech company, founded less than two years ago under the National Biodefense Program, focuses on developing novel therapeutics and prophylaxis for influenza. I agree that a fundamentally new approach against influenza is greatly needed, because as Dr. Fauci pointed out, even cross-reactive vaccines are very difficult to generate because the natural infection doesn't offer long-lasting cross-protection. In light of this, we have developed a new molecule that is sialidase based and is designed to tether to the human receptor epithelium. Our lead works by eliminating the sialic acid used as a receptor for all strains of influenza viruses. The strain works by making the host inaccessible to influenza viruses. With the help of NIAID, we have done some very successful in vitro studies, and now multiple animal studies, showing that this approach holds great promise, not only as a prophylaxis but as a

therapeutic as well. Even 48 to 72 days after the viral challenge, we still get very significant therapeutic effects.

A novel approach like ours would not be possible without the support of the national biodefense effort and NIAID. We are several months from filing an investigational new drug application, and we are hoping to go to clinical trials quickly. Our scientists are working day and night, but the limiting factor is still funding. I'm here to urge continued public-sector funding because private-sector funding is hard to come by. When we talk about pandemics, the market is not there.

Companies like ours can do such research with many fewer resources. With less than \$14 million, we believe we can take the drug all the way through phase III clinical trials. So, important progress is being made with public funding.

PARTICIPANT: Dr Gerberding alluded to the fact that we are exploring an expanded surveillance effort in Southeast Asia, with partnering between DOD and CDC. DOD has a fairly significant global surveillance system for emerging infections, with laboratories in Cairo and Jakarta, Peru, Thailand, and elsewhere around the world. Our folks in Jakarta commented on the opportunity after the tsunami to greatly enhance surveillance efforts in Vietnam and Cambodia with modest funding.

Specific suggestions for the types of studies that need to be done would be very helpful. We are certainly willing to partner with others, including with WHO and Dr. Stohr, to expand this effort. We have some funding that we could apply right away, but we need to know what we need to do.

PARTICIPANT: Several speakers touched on the stockpiling of antivirals. It is very difficult to know when we should pull items out of the stockpile and start shipping them for use in the field. Tamiflu is under patent from Roche. It costs about \$3 a pill to buy the drug in bulk. Under the World Trade Organization's TRIPS agreement [trade-related aspects of intellectual property rights], a country can issue a compulsory license during a public health emergency to allow other companies to manufacture the drug. I am interested at what point the panelists think the United States should evoke the TRIPS agreement to start producing its own Tamiflu. And at what point should we deploy non-vaccine interventions?

DR. GELLIN: I think all countries are grappling with that issue. As you said, a single manufacturer now has a patent, and it is the only feasible player in a pandemic setting. Unlike the H5 vaccine, which is still being evaluated, anyone can purchase that product today. The question is how nations handle that on a public health basis. Nobody knows how much of the drug to buy and exactly when to pull the TRIPS trigger. I hope this workshop will shed light on how to refine the models so we can understand some of these trigger points more precisely. I don't have the answer, but clearly how much of the drug we buy and how we deploy it are issues of great importance, given that there will not be enough vaccine to go around.

DR. STOHR: The international trigger point for WHO would be the emergence of a virus with effective human-to-human transmission. In the next couple of days WHO will publish a new pandemic preparedness plan that will not only recommend what countries should do during different phases of a pandemic but also clearly outline what countries can expect from WHO during those phases. The plan will include trigger points for national use of antivirals from a

national stockpile, but, as Bruce said, the modeling data are just not available at this stage for use with an international stockpile.

The TRIPS agreement is a powerful tool that can be used when a global health emergency would require increased access to a certain drug. That powerful tool is accessible to every nation in the world. Hopefully, nations will think twice before they use that tool, as doing so would encourage others to use the same tool for other drugs and circumstances. A country has to balance the advantage of gaining access to one drug against what might happen if other countries use the agreement to gain access to patented drugs made in the first country.

DR. GERBERDING: One of the early triggers for the use of antivirals would clearly be the need to initiate prophylaxis to continue the initial rounds of replication and outbreak. Another important other aspect is the scalability of our use of these countermeasures. And at least with antivirals, the stockpile exists, and we have conceptualized the idea that we will deploy it under certain circumstances to obtain the biggest public health benefit for the amount of drug we have. But we haven't effectively researched the deployment step. The U.S. public health system is working to deliver countermeasures to a population within a short timeframe, but research does not tell us the best strategy.

How do you mobilize effectively? What models of distribution actually work? We did learn some lessons from distributing flu vaccine this year. But we can also consider provocative ideas such as pre-event deployment and home storage of countermeasures. We need to be open to all possibilities and then do the studies to figure out the best models for specific circumstances.

DR. GOODMAN: I think it is very important to obtain more knowledge of antivirals and their impact, particularly in treatment and containment. They are likely to be effective prophylactically, but the amount of drug needed on any scale beyond a very small population would be daunting. On the treatment end, perhaps the working group on antivirals will consider studies that—relying on the NIH and WHO clinical trial networks—would tell us rather quickly about the safety and effectiveness of antivirals in a pandemic threat. Assumptions should not go unquestioned.

As with vaccines, the time to assess production needs and build a manufacturing infrastructure is before the pandemic. Making a high-quality, complex pharmaceutical that is safe and effective in a crisis situation would be difficult. We need to understand better how we to use these drugs and prepare for those uses.

PARTICIPANT: One issue raised in recent biodefense discussions is what would happen with a limited supply of countermeasures given an international outbreak of disease. Everyone hoped to deal with that question later. Well, this may be later. Domestic versus international law poses a particular problem, in that U.S. officials have a congressional mandate to protect the American people with whatever measures are necessary.

Given the fact that Tamiflu supplies are limited and no vaccine is available, how will we decide which countermeasures to retain for domestic purposes and which to make available for international use, given an outbreak in another country? That question is especially important given that the use of countermeasures internationally is often the best way to protect a domestic population. On the other hand, if a disease were not contained, a country would be obligated to use the countermeasure to the maximum possible extent domestically. I can see borders all over the world closing to the transfer of countermeasures.

DR. FINEBERG: This and the previous question raise important ethical aspects of research as well as preparedness strategy.

DR. GELLIN: While I cannot give you a comprehensive and definitive answer regarding what would be done in a given situation, the comment highlights the importance of on-the-ground surveillance. If we look only under the street lamp, we may miss important developments.

DR. GOODMAN: We could well argue that the appropriate use of interventions on a global level will benefit both U.S. citizens and residents of other countries. We need to consider global response plans rather than pitting one country versus another. Maybe we can help our policymakers to come to the same conclusion.

DR. GERBERDING: We need to emphasize economic as well as international health motives. Multinational corporate interests are likely to be more involved in addressing these problems than in the past.

DR. STOHR: The question has a political as well as a technical component. The political component must be addressed at a relatively high level: we are talking about multinational treaties and agreements between heads of states. We should continue raising the issues at that level. At the same time, we need to continue to invest in technical solutions like antigen-sparing strategies that will give countries without production capacity access to vaccines and antivirals as well as knowledge when they are most needed. We should not put all our eggs in one basket.

DR. FAUCI: If ever there were a need for international agreements on what countries will do if and when a crisis occurs, this is certainly one such situation, because if individual countries make conflicting policy decisions, we will have chaos. We need an international agreement before we get into a crisis.

PARTICIPANT: We are talking about the availability of new technologies and new approaches. While on the science side that makes a great deal of sense, we are overlooking the supply side. Can we actually provide the new technologies, and what is the surge capacity per item? Given all the orders for antivirals, it's going to be years before they are actually going to be filled. Today two companies own 80 percent of the market for N95 masks and have no surge capacity. The United States also lacks surge capacity for mechanical ventilators. The country has 105,000 ventilators, and in any one day 70,000 are in use; during flu season 100,000 are in use. Unless we are prepared to spend money to create capacity that will not be used except during a crisis, we can develop all the technologies we want, but our actual ability to bring a stockpile to market is going to be limited.

During the anthrax situation, the biggest problem many of us in the states faced concerned reagents for testing for bacillus anthracis—they just did not exist. We couldn't make them fast enough. Even though scientists might come up with wonderful diagnostics for influenza, I question how many will be available during a crisis. Wonderful new technology tools may have little applicability if they are not available.

DR. GERBERDING: I agree but this also speaks to the need for communication, because we have to make hard decisions about how to spend our dollars. Business figured out a long time ago that just-in-time delivery was the most cost-effective approach. We are moving in the opposite direction by stockpiling and investing large quantities of resources in items we might never use. But that's the role of leadership and the federal government.

People must understand that readiness will be expensive, that funding might never be used, and that capacities are in reserve. That's a tough message to communicate, and a tough position for politicians to be in, given so many competing priorities. We are lucky to have leaders who are willing to take those steps, but we need to do more, and we need to do it faster.

DR. GOODMAN: We may have rare opportunities for win-win approaches. For example, progress in the inter-pandemic use of flu vaccine with current technologies will increase the capacity and ability to respond during a pandemic.

DR. STOHR: Perhaps we need dress rehearsals for the delivery of vaccines and antivirals, which would enable us to see what is missing and what is needed. We have not mentioned syringes or the whole downstream need for vaccine packaging, such as multi-dose containers. If one link is missing in the chain, all our preparatory work may be in vain.

DR. FINEBERG: As we begin to discuss research priorities in detail, we clearly have to consider the total preparedness strategy, including communication among scientists, across cultures and political boundaries, with the public at large, and with policymakers. All of that will affect the success of a flu preparedness strategy

WORKING GROUPS, DAY 1

WORKING GROUP 1 INFLUENZA VIRULENCE AND ANTIGENIC CHANGE

Chairperson—Robert Webster

Briefer—Peter Palese

Rapporteur—Robert Lamb

Charge: The charge of this working group is to define research priorities associated with understanding influenza virulence, with tracking and predicting antigenic change, and with defining which antigenic changes may be associated with increased virulence, risk of transmission, and pandemic potential.

Potential issues to consider:

1. What studies are needed to define the genetic loci for pathogenicity in avian and human influenza virus strains?
2. What studies are needed to affirm the hypothesis that incremental acquisition of genetic changes can lead to influenza pandemics as compared with the sudden emergence of previous pandemics?
3. What studies are needed to track the rate of antigenic change in avian and human influenza virus strains and to predict changes that may occur?
4. What studies are needed to determine whether pandemic risk can be predicted by virulence factors and/or antigenic characteristics?

REPORT TO PLENARY

Rapporteur—Dr. Robert Lamb

One question concerned how we would define the loci for pathogenicity with influenza virus. We know at the molecular level the importance of the hemagglutinin's cleavage site. It is required to be cleaved to HA1 and HA2 which activates the molecule for fusion..

We know that if we have a multi-basic residue at the HA cleavage site, it has the potential to be cleaved in the trans-Golgi network, and that correlates directly with high pathogenicity of viruses in many cases. If that cleavage site has only a single basic residue, it very often correlates with low pathogenicity. We know that the ability of neuraminidase to bind the protease plasminogen is a determinant of pathogenicity, because binding plasminogen then causes cleavage of the hemagglutinin, such as found for the WSN strain.

We know that the presence of carbohydrate sites around the cleavage site of HA are important for pathogenicity. We know that certain mutations in the NS1 protein affect cytokine production in some viruses. And we know that mutations that affect replication and decrease replication—such as in the cold-adapted virus and the so-called PB2 627 mutation found in many of the H5 viruses—lead to a difference in pathogenicity in the mouse.

One important consideration is that the very same residue makes no difference when the studies are done in ferrets. Researchers are now using mice, ferrets, and chickens as animal models. The use of non-human primates for influenza virus studies is somewhat questionable. Although mice are obviously the smallest and cheapest animal, there are major questions about the use of inbred mice, particularly the popular strains that lack the MX1 gene, as those do not produce the induction of a normal antiviral state. The best model animal system is probably the ferret: it requires no adaptation for human viruses. However, we do need to agree internationally on one strain of ferret, because British ferrets and Japanese ferrets and American ferrets are not all the same.

Another problem is that very few immunological reagents exist for the ferret. How would we study a cytokine response? We need a ferret DNA sequence genome project, like those under way for another 11 or so organisms, from zebra fish to mouse, and of course humans before that. We also need to increase the number of ferrets. That doesn't just mean ordering a few more. We need a very large breeding colony—the approach taken with the breeding of woodchucks for hepatitis-B studies. We should also determine if other small animal models would work, such as hamsters and mini-pigs. An underlying need is for biological containment facilities for both tissue-culture work and animal work.

We need to determine the genes needed for both transmission and pathogenicity, which we would do by making reassortments using reverse genetics—the so-called 6 plus 2, 5 plus 3, etc combinations of 8 genes. We would then study the genetic basis underlying transmission, virulence, and pathogenicity in terms of the function of proteins, the structure of proteins at the atomic level, and how proteins go together to make complexes such as polymerase. We do not completely understand the components of what can be reassorted from one strain versus another. The suggestion is there are incompatibilities among proteins—that not all P proteins can go together.

We were asked whether incremental changes in the genome lead to pandemics. We know that from 1997 to 2005 the H5N1 virus gained the ability to kill ducks, and that it has transferred to cats and killed them. We need studies where a series of viruses have changed in virulence pathogenicity.

We need to obtain the genome sequences of all these viruses and post them on public databases. The new NIAID-NIH-sponsored public database with The Institute of Genome Research (TIGR) sequencing genomes of human viruses is a start, but we need such an approach for other viruses as well. We also need reverse genetics working for all of these viruses. And when we have all those components in place, we can then show that mutations are sufficient and necessary for the property of pathogenicity being examined.

The third question we were asked was whether studies are needed to track the rate of antigenic change in avian and human strains, and to predict the changes that occur. As background, note that only three hemagglutinin subtypes—H1, H2 and H3—cause major human disease

We know, as Dr. Palese has often pointed out, that the 1918 virus caused a W-shaped death rate. That is, if we plot the number of deaths on the Y-axis and the age groups that died on the X-axis, we find that young people died early on, and then there was a gap, and older people died much later. People between 30 and 60 years of age presumably had prior exposure to an H1-like virus. We should add that it is thought that H3 and H1 both circulated before 1918, and that there is no evidence that H5, H7, H9, or any of the highly pathogenic viruses in avian species were found in humans in those earlier times.

A question about viral archeology inevitably comes up—the sort of studies that Dr. Jeff Taubenberger has done. Such investigation is very difficult because tissues were not preserved before 1900. His work was done on formalin fixed tissues. The question was raised whether we could examine tombs in churches for examples of antibodies, but we felt that would be extremely difficult.

At the theoretical level we can continue to predict changes and the effect on antigenic epitopes. An example is the paper in the Proceedings of the National Academies of Science by evolutionary biologist Dr. Simon Levin and his group, who predicted HA clusters and antigenic evolution. Such studies should continue.

Surveillance of influenza viruses—now occurring throughout the world—should also continue, as should nucleotide sequencing of viral genomes. Ideally, we need better immunological markers. We point out that hemagglutinin inhibition tests are insensitive, and that they don't work on H5 viruses.

Question 4 addressed the studies needed to determine pandemic risk associated with antigenic characteristics. We need to determine the extent of antigenic variation that yields a pandemic strain. We need both human and animal studies to follow how much variation can occur in a strain and still lead to disease and pandemic potential.

We would like to know whether preexisting antibody to one subtype can have an effect on infection with another subtype. That is, we can look at the ability of viruses of different subtypes to infect animals such as ferret that already have antibody levels to common human viruses. If we already have some antigenic determinants to a component of any one of those viruses, might that provide some benefit against infection with another influenza virus?

Lastly, Dr. Purnell Chopin and others asked whether we need studies that ask whether human genetic changes increase or decrease susceptibility to influenza virus infection. Could such studies be coupled to the NCI cancer genome project? For the mouse, such work could easily be coupled with the huge forward genetics projects occurring at five centers in the United States for mutagenizing the mouse on a total random basis and mapping any genetic changes. Could we use those leftover mice to determine if their susceptibility to influenza had increased or decreased? Although the mouse may not be a very good model, those projects provide an avenue of research.

Our workshop's first priority is to determine the sequences of human, animal, and avian isolates within an epidemiological framework. We want to stress the latter, because just having the sequences doesn't help. We need to know the clinical data from human cases to accompany the sequences.

Our second major recommendation is to determine the genes and their function for transmission and pathogenicity in ferrets using qualified reagents. That one sentence

encompasses several needs. Such an effort will require ferrets—lots of them. We are talking about determining not just which genes are involved but also their function. That will require a lot of basic research.

**Research Recommendations
Priorities**

- Determine sequences of human, animal and avian isolates within an epidemiological framework.
- Need for clinical data from human cases.
- Determine the genes and their function for transmission and pathogenicity in ferrets using qualified reagents

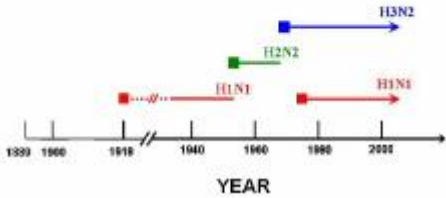
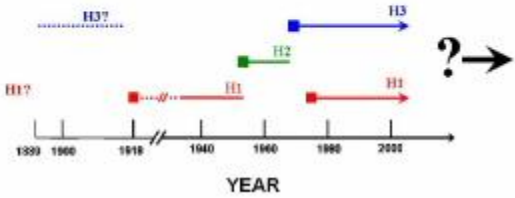
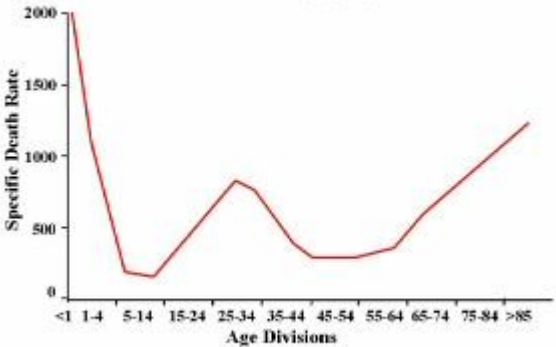
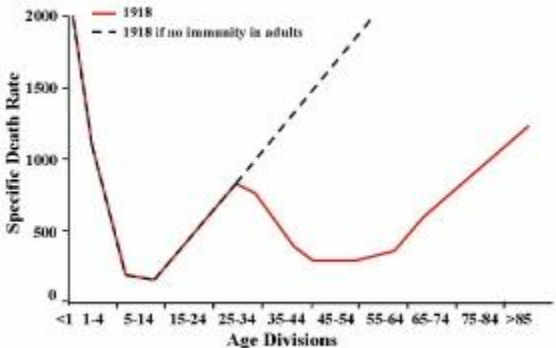
**Working Group 1 Presentation Slides: Influenza Virulence and Antigenic Change
 -Dr. Lamb, Rapporteur**

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| <p style="text-align: center;">John R. LaMontagne Memorial Symposium on Pandemic Influenza Research April 4-5, 2005 Institute of Medicine</p> <p style="text-align: center;">Working Group One: Influenza Virulence and Antigenic Change</p> <p style="text-align: center;">Research Recommendations</p> | <p style="text-align: center;">Defining the host for pathogenicity (Combined Q1 and in part Q4)</p> <p>Known: HA cleavage site, NA binding plaminogen, CD134 sites around cleavage site, NS1 mutations affecting cytokine production, mutations that affect replication (e.g. cold-adapted virus PB2 527 mutation, more but not ferrets).</p> <p>Suitable animal model – currently microferrets/chickens Non-human primates quest onable. Major questions about use of inbred mice: lacking Mx gene (ant-viral site) Ferrets: no adaptation required for human viruses. Problems with ferret model: need to use one agreed upon strain of ferret Few immunological reagents, how to do cytokine response, a ferret DNA sequence genome project would help</p> <p>To do: Determine genes needed for both transmission and pathogenicity (reverse genetic reassortments). Study genetic basis that underlies transmission, virulence and pathogenicity. Increase number of ferrets. Need lg, breeding colony of ferrets Ferret reagents: Test ferrets and pigs: Need containment facilities</p> |
| <p>Q2: Do incremental changes in genome lead to pandemics?</p> <p>From 1997 to 2005 H5N1 virus gained ability to kill ducks and it transmits and kills cats</p> <p>Need series of viruses where a change in virulence/pathogenicity has occurred</p> <p>Need sequences of all of these genomes of all of these viruses and posted to public database</p> <p>Need reverse genetics working for each of these viruses</p> <p>Need appropriate animal model systems</p> <p>Show mutations are sufficient and necessary for property being examined</p> | <p>Q2? Do incremental changes in genome lead to pandemics?</p> <p>From 1997 to 2005 H5N1 virus gained ability to kill ducks and it transmits and kills cats</p> <p>Need series of viruses where a change in virulence/pathogenicity has occurred</p> <p>Need sequences of all of these genomes of all of these viruses and posted to public database</p> <p>Need reverse genetics working for each of these viruses</p> <p>Need appropriate animal model systems</p> <p>Show mutations are sufficient and necessary for property being examined</p> |
| <p>Q3: Studies needed to track the rate of antigenic change in avian and human strains and to predict the changes that occur.</p> <p>Note: Only 3 HA subtypes caused major disease in humans H1, H2 and H3 Note: 1918 "W"-shaped death rate: Presumably prior H1 exposure for older population (H3 and H1 thought to circulate before 1918 – not H5A/7/H9).</p> <p>Note: Viral archeology – difficult: No preservation of tissues before 1900.</p> <p>Continue predictions of changes and effect on antigenic epitopes – e.g. Simon Levin's PNAS paper on prediction of HA sequence clusters and antigenic evolution.</p> <p>Continue surveillance.</p> <p>Continue nucleotide sequencing of viral genomes</p> <p>Ideally need better immunological markers – HAI tests are insensitive and do not work on H5</p> | <p>Q4 in part: Studies needed to determine pandemic risk associate with antigenic characteristics.</p> <p>Determine the extent of antigenic variation to give a pandemic strain. Need both human and animal studies.</p> <p>Does pre-existing antibody to one subtype have an effect on infection with another sub-type?</p> <p>Look at ability of viruses of different subtypes to infect animals (ferrets) that already has antibody levels to common human viruses (H1N1, H2N2, H3N2).</p> <p>Question 5: NEW</p> <p>Are there human genetic changes that increase/decrease susceptibility to influenza virus infection. Coupling to Cancer Genome Project?</p> |

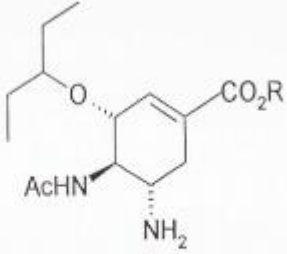
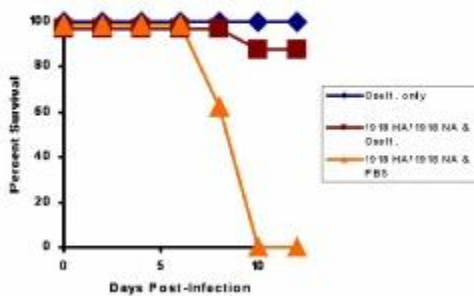
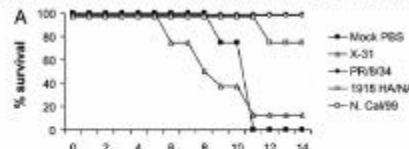
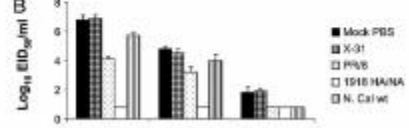
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| <p>Priorities</p> <ol style="list-style-type: none">1. Determine sequences of human, animal and avian isolates within an epidemiological framework.2. Need for clinical data from human cases.3. Determine the genes and their function for transmission and pathogenicity in ferrets using qualified reagents. | |
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(Slides available on accompanying CD)

**Working Group 1 Briefing Slides: Influenza Virulence and Antigenic Change-
 Dr. Palese, Briefer**

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| <p>WORKING GROUP 1 Influenza Virulence and Antigenic Change</p> <p>Chairperson – Robert Webster Briefer – Peter Palese Rapporteur – Robert Lamb</p> | <p>INFLUENZA A VIRUS SUBTYPES IN THE HUMAN POPULATION</p>  |
| <p>INFLUENZA A VIRUS SUBTYPES IN THE HUMAN POPULATION</p>  | <p>1918 influenza mortality by age in the U.S.</p>  |
|  | <p>Potential issues to consider:</p> <ul style="list-style-type: none"> What studies are needed to define the genetic loci for pathogenicity in avian and human influenza virus strains? Identification of relevant strains Better and different animal models Use of reverse genetics to study strains/mutants Transmission studies |

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| <p>2) What studies are needed to affirm the hypothesis that incremental acquisition of genetic changes can lead to influenza pandemics as compared with the sudden emergence of previous pandemics?</p> | <p>INFLUENZA A VIRUS SUBTYPES IN THE HUMAN POPULATION</p> <p>1889 1900 1918 1940 1960 1980 2002</p> <p>YEAR</p> |
| <p>HYPOTHESES</p> <p>ONLY REASSORTANTS BETWEEN HUMAN AND ANIMAL (AVIAN) STRAINS CAN "MAKE IT"</p> <p>GRADUAL/INCREMENTAL CHANGES IN AN ANIMAL STRAIN CAN RESULT IN A NEW PANDEMIC VIRUS</p> | <p>3) What studies are needed to track the rate of antigenic change in avian and human influenza virus strains and to predict changes that may occur?</p> <p>Better immunological markers are needed Sequencing of strains is appropriate</p> |
| <p>Proc Natl Acad Sci U S A. 2002 Apr 30;99(9):6263-8.</p> <p>Hemagglutinin sequence clusters and the antigenic evolution of influenza A virus.</p> <p>Plotkin JB, Dushoff J, Levin SA.</p> <p>Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08540, USA. plotkin@ias.edu</p> | <p>THE NEW ENGLAND JOURNAL OF MEDICINE Volume 352:686-691 February 17, 2005</p> <p>Fatal Avian Influenza A (H5N1) in a Child Presenting with Diarrhea Followed by Coma</p> <p><i>Menno D. de Jong, M.D., Ph.D., Bach Van Cam, M.D., Phan Tu Qui, M.D., Vo Minh Hien, M.D., Tran Tan Thanh, M.Sc., Nguyen Bach Hue, M.D., Marcel Beld, Ph.D., Le Thi Phuong, M.D., Truong Huu Khanh, M.D., Nguyen Van Vinh Chau, M.D., Tran Tinh Hien, M.D., Do Quang Ha, M.D., Ph.D., and Jeremy Farrar, F.R.C.P., D.Phil.</i></p> |

| <p>4) What studies are needed to determine whether pandemic risk can be predicted by virulence factors and/or antigenic characteristics?</p> | <p style="text-align: center;">Acknowledgements</p> <p><u>Mount Sinai School of Medicine</u> Adolfo Garcia-Sastre, PI Christopher F. Basler Peter Palese</p> <p><u>CDC, Atlanta</u> <u>University of Washington</u> Terrence M. Tumpey Michael Katze</p> <p><u>Southeast Poultry Research Laboratory</u> David E. Swayne</p> <p><u>Armed Forces Institute of Pathology</u> <u>TSRI</u> Jeffery K. Taubenberger Ian Wilson</p> | | | | | | | | | | |
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| <p style="text-align: center;">FDA-approved Antiviral Drugs against Influenza</p> <table border="0" style="width: 100%;"> <thead> <tr> <th style="text-align: left;"><u>Generic/(Trade Name)</u></th> <th style="text-align: left;"><u>Route</u></th> </tr> </thead> <tbody> <tr> <td>• Amantadine</td> <td>ORAL</td> </tr> <tr> <td>• Rimantadine</td> <td>ORAL</td> </tr> <tr> <td>• Oseltamivir/(Tamiflu)</td> <td>ORAL</td> </tr> <tr> <td>• Zanamivir/(Relenza)</td> <td>Inhalation</td> </tr> </tbody> </table> | <u>Generic/(Trade Name)</u> | <u>Route</u> | • Amantadine | ORAL | • Rimantadine | ORAL | • Oseltamivir/(Tamiflu) | ORAL | • Zanamivir/(Relenza) | Inhalation | <div style="text-align: center;">  <p>Oseltamivir/Tamiflu</p> </div> |
| <u>Generic/(Trade Name)</u> | <u>Route</u> | | | | | | | | | | |
| • Amantadine | ORAL | | | | | | | | | | |
| • Rimantadine | ORAL | | | | | | | | | | |
| • Oseltamivir/(Tamiflu) | ORAL | | | | | | | | | | |
| • Zanamivir/(Relenza) | Inhalation | | | | | | | | | | |
| <p style="text-align: center;">Oseltamivir Protects Mice from a Lethal Challenge with 1918 HA/1918 NA Virus</p>  <p style="text-align: right;">Tumpey et al. PNAS, 99,13849,2002</p> | <p style="text-align: center;">H1N1-INACTIVATED VACCINE PROTECTS AGAINST LETHAL CHALLENGE WITH 1918 HA/NA INFLUENZA VIRUS</p> <div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 10px;"> <p>A</p>  </div> <div> <p>B</p>  </div> </div> <p style="text-align: center; font-size: small;">Tumpey, Terrence M. et al. (2004) Proc. Natl. Acad. Sci. USA 101, 3166-3171</p> | | | | | | | | | | |

| <h2 style="margin: 0;">AVIAN INFLUENZA THE NEXT PANDEMIC?</h2> <p style="font-size: 2em; margin: 20px 0;">MAYBE NOT</p> | <p style="text-align: center;">Table 7. Serological Evidence for Human Exposure to Avian Influenza Viruses in the Hypothetical Influenza Epicenter and Occurrence of these Viruses in Domestic Ducks There</p> <p style="text-align: center;">Percent Seropositivity of Human Sera From:</p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th>HA Subtype</th> <th>Pearl River Delta (n = 400)*</th> <th>Jiangsu Province (n = 300)</th> <th>Taichung Taiwan (n = 150)</th> <th>Urban Hong Kong (n = 100)</th> <th>Percent Isolation Rate From Domestic Ducks</th> </tr> </thead> <tbody> <tr><td>H1</td><td>NT</td><td>19</td><td>NT</td><td>NT</td><td><1</td></tr> <tr><td>H2</td><td>NT</td><td>58</td><td>NT</td><td>NT</td><td>1</td></tr> <tr><td>H3</td><td>47</td><td>46</td><td>48</td><td>45</td><td>25</td></tr> <tr><td>H4</td><td>11</td><td>4</td><td>10</td><td>2</td><td>29</td></tr> <tr><td>H5</td><td>2</td><td>7</td><td>2</td><td>0</td><td>4</td></tr> <tr><td>H6</td><td>12</td><td>1</td><td>13</td><td>1</td><td>22</td></tr> <tr><td>H7</td><td>5</td><td>38</td><td>4</td><td>0</td><td><1</td></tr> </tbody> </table> <p style="font-size: 0.8em;">K.F. Shortridge. <i>Seminars in Respiratory Infections</i>, 7, 11, 1992</p> | HA Subtype | Pearl River Delta (n = 400)* | Jiangsu Province (n = 300) | Taichung Taiwan (n = 150) | Urban Hong Kong (n = 100) | Percent Isolation Rate From Domestic Ducks | H1 | NT | 19 | NT | NT | <1 | H2 | NT | 58 | NT | NT | 1 | H3 | 47 | 46 | 48 | 45 | 25 | H4 | 11 | 4 | 10 | 2 | 29 | H5 | 2 | 7 | 2 | 0 | 4 | H6 | 12 | 1 | 13 | 1 | 22 | H7 | 5 | 38 | 4 | 0 | <1 |
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| H3 | 47 | 46 | 48 | 45 | 25 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H4 | 11 | 4 | 10 | 2 | 29 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| H6 | 12 | 1 | 13 | 1 | 22 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H7 | 5 | 38 | 4 | 0 | <1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p style="text-align: center;">Table 7. Serological Evidence for Human Exposure to Avian Influenza Viruses in the Hypothetical Influenza Epicenter and Occurrence of these Viruses in Domestic Ducks There</p> <p style="text-align: center;">Percent Seropositivity of Human Sera From:</p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th>HA Subtype</th> <th>Pearl River Delta (n = 400)*</th> <th>Jiangsu Province (n = 300)</th> <th>Taichung Taiwan (n = 150)</th> <th>Urban Hong Kong (n = 100)</th> <th>Percent Isolation Rate From Domestic Ducks</th> </tr> </thead> <tbody> <tr><td>H1</td><td>NT</td><td>19</td><td>NT</td><td>NT</td><td><1</td></tr> <tr><td>H2</td><td>NT</td><td>58</td><td>NT</td><td>NT</td><td>1</td></tr> <tr><td>H3</td><td>47</td><td>46</td><td>48</td><td>45</td><td>25</td></tr> <tr><td>H4</td><td>11</td><td>4</td><td>10</td><td>2</td><td>29</td></tr> <tr><td>H5</td><td>2</td><td>7</td><td>2</td><td>0</td><td>4</td></tr> <tr><td>H6</td><td>12</td><td>1</td><td>13</td><td>1</td><td>22</td></tr> <tr><td>H7</td><td>5</td><td>38</td><td>4</td><td>0</td><td><1</td></tr> </tbody> </table> <p style="font-size: 0.8em;">K.F. Shortridge. <i>Seminars in Respiratory Infections</i>, 7, 11, 1992</p> | HA Subtype | Pearl River Delta (n = 400)* | Jiangsu Province (n = 300) | Taichung Taiwan (n = 150) | Urban Hong Kong (n = 100) | Percent Isolation Rate From Domestic Ducks | H1 | NT | 19 | NT | NT | <1 | H2 | NT | 58 | NT | NT | 1 | H3 | 47 | 46 | 48 | 45 | 25 | H4 | 11 | 4 | 10 | 2 | 29 | H5 | 2 | 7 | 2 | 0 | 4 | H6 | 12 | 1 | 13 | 1 | 22 | H7 | 5 | 38 | 4 | 0 | <1 | <p style="font-size: 0.8em;">* Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi. 1999 Jun 30; 13(2): 105-8. Related Articles.</p> <p style="font-size: 1.2em; margin: 5px 0;">[Discovery of men infected by avian influenza A (H9N2) virus]</p> <p style="font-size: 0.8em;">[Article in Chinese] Guo Y, Li J, Cheng X. China National Influenza Center, Institute of Virology, Chinese Academy of Preventive Medicine, Beijing 100052.</p> <p style="font-size: 0.8em;">OBJECTIVE: To understand whether the avian influenza A(H9N2) virus can infect men or not. METHODS: Seroepidemiological surveys for avian (H9N2) virus in human, chickens and pigs were conducted. The specimens for viral isolation were taken from throat of patients with influenza like disease, as well as from chickens, then the specimens were inoculated into embryonated chicken eggs. Afterward, the isolates were identified with HI and NI tests. Meanwhile, the patients who would be studied individually were found to carry H9N2 virus. RESULTS: Approximately 19% of human had antibody to H9N2 virus with HI titers > or = 20. 5 strains of influenza A (H9N2) virus were isolated from the patients. CONCLUSION: Avian influenza A(H9N2) virus can infect men.</p> |
| HA Subtype | Pearl River Delta (n = 400)* | Jiangsu Province (n = 300) | Taichung Taiwan (n = 150) | Urban Hong Kong (n = 100) | Percent Isolation Rate From Domestic Ducks | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H1 | NT | 19 | NT | NT | <1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H2 | NT | 58 | NT | NT | 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H3 | 47 | 46 | 48 | 45 | 25 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H4 | 11 | 4 | 10 | 2 | 29 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H5 | 2 | 7 | 2 | 0 | 4 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H6 | 12 | 1 | 13 | 1 | 22 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| H7 | 5 | 38 | 4 | 0 | <1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p style="font-size: 1.2em; margin: 0;">Nature Medicine 10, S82 - S87 (2004)</p> <p style="font-size: 1.5em; margin: 10px 0 0 0;">Influenza: old and new threats</p> <p style="text-align: center; margin: 10px 0 0 0;">Peter Palese</p> <p style="margin: 10px 0 0 0;">Department of Microbiology, Mount Sinai School of Medicine, New York, New York 10029, USA.</p> | <p style="font-size: 1.5em; margin: 0;">IT'S TOUGH TO MAKE PREDICTIONS, ESPECIALLY ABOUT THE FUTURE</p> <p style="margin: 20px 0 0 0;">Yogi Berra</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

(Slides available on accompanying CD)

WORKING GROUP 2 CONTROLLING ANIMAL INFLUENZA AND DECREASING ANIMAL-TO-HUMAN TRANSMISSION

Chairperson—David Halvorson

Briefer—David Swayne

Rapporteur—Bruce Innis

Charge: The charge to this group will be to define research needs related to strategies for controlling the spread of influenza among animals and decreasing the risk of spread from animals to people. Specific research areas may include assessing the role and impacts of vaccine in animals; environmental modifications and precautions to decrease the spread of infection within and between farms; optimal approaches to culling animal populations; and prevention or management of exposure to infected animals by people.

Specific Questions:

1. What studies are needed to determine whether the circulating avian influenza H5N1 virus in Southeast Asia is likely to cause a human pandemic?
2. What studies are needed to assess the effectiveness of strategies to control animal influenza?
3. What studies are needed to assess optimal approaches to use and to assess impact of avian influenza vaccines?
4. What effective cross-cutting technologies for control of animal influenza are translatable to human pandemic scenarios?

Report to Plenary

Rapporteur: Dr. Bruce Innis

We selected several objectives for the intermediate 5-to-10-year horizon. The highest priority is to focus resources on country-specific epidemiological studies targeted at understanding both disease and transmission in animals and in humans.

We focused principally on avian influenza. The countries now affected in Southeast Asia do not have a unitary system of poultry production. Thus it is important to look not only at industrial settings but also at village farms, where much bird raising occurs, and also at live markets, and to remember that animals are raised for recreational uses and captivity.

It is also important to investigate the epidemiology of humans who care for these animals—we are dismayed that more is not being done on that front. We would like to know where transmission is taking place. Why are people who apparently are exposed not becoming sick? And in many cases, why are they not becoming infected?

Immediate: Epidemiology

- Country specific epidemiological studies – both animals and humans
 - Conduct surveillance in industrial settings, village farms, markets (also captive birds)
 - Conduct studies to identify risks for humans
 - Where are humans acquiring infections?
 - Why don't these individuals become sick (or infected)
 - Develop a more accessible serology method; micro-NT necessary (standardization ongoing)
 - Complement epi studies by evaluating pathogenesis in affected bird species – domestic, captive and wild birds

We recognize that the serological method is a barrier to such investigation: no easily accessible tool such as an ELISA test is available. Most such investigation is based on micro-neutralization, and even that is not yet standardized.

We would like to complement epidemiological studies by evaluating pathogenesis in the affected bird species, looking at both domestic and captive birds, and at wild birds as a lower priority.

We would also like to perform reverse genetic studies to identify avian influenza genes from specific strains with the greatest interspecies transfer potential. Of course, caution needs to be exercised to contain these strains, and there would still be a gap once we developed these resorted viruses, as we lack methods to realistically assess their person-to-person transmission potential. A tool for doing so needs to be developed in parallel.

Immediate: Reverse Genetics

- Perform reverse genetic studies to identify avian influenza genes from specific strains with greatest interspecies transfer potential
 - Caution should be exercised as to the appropriate biosafety level for re-assortant studies to generate a potentially pandemic strain by reverse genetics
 - Develop methods to assess person to person transmission potential

We also prioritized identifying control measures optimized for conditions in developing countries, although some U.S. communities raise birds under the conditions used in Asian villages. As many as 100,000 people in Southern California are raising small poultry flocks with 10 birds or more in their backyards, for example. We would like to see an assessment of creative

solutions for such small flock holders. What kinds of educational approaches would work? What economic incentives can be used? What changes in agricultural systems should be employed?

5-yr: Identify control measures

- Identify control strategies optimized for conditions in Developing Countries
 - Assess creative solutions for smallholders: education, economic incentives, changes in agricultural systems
 - Perform knowledge, attitude, practice studies
 - Assess all strata (recreational vs village vs industry)
 - Assess what interventions are practiced
 - Leverage local pathways for communication
 - Leverage public education system to introduce better practices
 - Perform operational research to assess impact of interventions such as education including baseline surveys

We view studies of knowledge, attitude, and practice at recreational, village, and industry levels of bird rearing as very important. We need to assess what interventions are being practiced now, and leverage local pathways of communication and public education systems to introduce better practices and ensure that the people who own these animals and their children are aware of the objectives and risks of control. As a complement, operational research needs to assess the impact of interventions such as education. That is predicated on baseline surveys, which should be done now.

Although many animals are vaccinated, we need improved standards for vaccine purity, safety, and especially potency, particularly for avian influenza. Research needs to improve procedures for lot release that assess potency. We need to have to better understand vaccine potency and how to measure it, and we need greater regulatory oversight. Although that is usually a national responsibility, international dialogue is also important. This isn't a topic for research, but it is certainly a topic for discussion.

5-yr: Technologies to better regulate animal influenza vaccines

- Improve standards of purity, safety & potency of AI vaccines
 - Research to improve procedures for lot release (potency): what is it and how should it be measured?
 - Greater regulatory oversight (internationally)
- Studies to confirm efficacy of AI vaccines in chickens and also ducks, geese and other minor poultry species
 - Need effectiveness studies to monitor product
 - Particularly in Asia if vaccines will be used for AI control
 - Develop vaccines for domestic ducks and geese

Besides improving animal vaccines, field studies need to assess their effectiveness, particularly in Asia. If vaccines will be used to control avian influenza, then studies need to






assess their impact. Although domestic ducks may be a very important reservoir, we know almost nothing about the effectiveness of these vaccines or their suitability for ducks and geese. We need to develop vaccines for these waterfowl.

In the long-term, various efforts could improve veterinary vaccines. Cell culture might be used to produce influenza vaccine antigens to be combined with new adjuvant systems. The usual adjuvant system for veterinary vaccines is an oil and water emulsion. Birds that have been vaccinated and retain oil are not considered suitable for sale, so we need oils that serve as an adjuvant that can be more rapidly metabolized. We also need to develop vaccines that not only maintain a flock's economic viability but also reduce transmission. The need for techniques for mass-delivery of vaccines is also great.

Lastly, we prioritized the development of animals to predict and understand the potential for circulating animal influenza viruses, including H5N1 Asian viruses, to infect humans, and to be transmitted from human to human.

| |
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| <p style="text-align: center;">10-yr: Improve Vaccines</p> <ul style="list-style-type: none">▪ Cell culture production▪ New adjuvant systems▪ Oils which can be metabolized▪ Vaccines which reduce transmission (Sterilizing immunity is unachievable)▪ Mass delivery techniques |
| <p style="text-align: center;">10-yr: Animal Models</p> <p>Develop animal models to predict & understand potential for circulating animal influenza viruses including H5N1 Asian viruses to infect humans and be transmitted from human to human</p> |

Working Group 2 Briefing Slides: Controlling animal Influenza and Decreasing Animal-to-Human Transmission-Dr. Swayne, Briefer

| | |
|--|--|
| <h3 style="text-align: center;">Controlling Animal Influenza and Decreasing Animal-to-Human Transmission</h3> <hr style="border: 1px solid red;"/> <div style="display: flex; justify-content: space-around; align-items: center;">  <div style="text-align: center;"> <p>David E. Swayne Southeast Poultry Research Laboratory Agricultural Research Service U.S. Department of Agriculture Athens, Georgia</p> </div> </div> | <h3 style="text-align: center;">Questions</h3> <hr style="border: 1px solid red;"/> <ul style="list-style-type: none"> • Studies to assess effectiveness of strategies to control animal influenza • Studies to assess optimal approaches to use and to assess impact of AI vaccines • What cross-cutting technologies for control of animal influenza are translatable to human pandemic scenarios • Studies to determine whether the circulating AI H5N1 virus in Asia is likely to cause a human pandemic |
| <h3 style="text-align: center;">1. Animal Influenza Control Strategies</h3> <p style="text-align: center;">No single poultry production system in SE Asia – vary by country</p>  <p style="font-size: small;">Thus control will vary with each country & their specific agricultural systems</p> | <h3 style="text-align: center;">1. Animal Influenza Control Strategies</h3> <p style="text-align: center;">Epizootic – S. Korea</p>  <p style="font-size: small;">Thus control will vary with each country & their specific agricultural systems</p> |
| <h3 style="text-align: center;">1. Animal Influenza Control Strategies</h3> <p style="text-align: center;">Epizootic – Malaysia</p>  <p style="font-size: small;">Thus control will vary with each country & their specific agricultural systems</p> | <h3 style="text-align: center;">1. Animal Influenza Control Strategies</h3> <p style="text-align: center;">Epizootic – Thailand (1st wave)</p>  <p style="font-size: small;">Thus control will vary with each country & their specific agricultural systems</p> |

1. Animal Influenza Control Strategies

Epizootic – Thailand (2nd wave)

Thus control will vary with each country & their specific agricultural systems

Household Income.

Source: UNDP (2003).

| Country | % Households below poverty line | |
|-----------|-----------------------------------|---------------------|
| | < US\$ 1/capita/day | < US\$ 2/capita/day |
| Indonesia | 7.2 | 55.4 |
| Lao PDR | 26.3 | 73.2 |
| Thailand | 2.0 | 32.5 |
| Vietnam | 17.7 | 63.7 |
| Cambodia | 36.1% below National Poverty Line | |

Dolberg – FAO Study

Many households have poultry – few are commercial

Dolberg – FAO Study

- * In all countries the large majority of rural households have poultry – even in Thailand.
- * How to formulate strategies that have them co-exist with commercial units?
- * Up to 80% no services

Duck systems

- Of interest because of the ducks' roles as silent carriers of the virus, but limited data
- Ducks are 10-15% of the poultry population in the five countries
- Three systems:
 - Commercial
 - Migrating, seasonal and large flocks: rice fields, large water bodies
 - A household system with a few ducks mixed with chicken – frequency not known

Dolberg – FAO Study


The market

- Played a role in spreading the disease
 - Farmers sell sick animals
 - Women keep birds in more than one household as a safety measure for "a bad day".

Dolberg – FAO Study

1. Animal Influenza Control Strategies

- Veterinary infrastructure
- Adequate GDP
- Low rural population in animal agriculture
- Education on disease control
- Financial incentives to seek control
- Successes (eradication): Japan, S. Korea, Malaysia, (Taiwan)
- Successes in management: Hong Kong, China, (Thailand)

| | |
|--|---|
| <h3>1. Animal Influenza Control Strategies</h3> <ul style="list-style-type: none"> • Country specific epidemiological studies – FAO, OIE, EU, and others • Surveillance: agricultural systems, captive birds and wild birds • Understanding pathogenesis in affected bird species – domestic, captive and wild birds • Could pigs play a future role in pandemic virus generation? • Creative solutions for smallholder: education, economic incentives, changes in agricultural systems <p style="text-align: right; font-size: small;">ICM/NSAR 2001</p> | <h3>2. Animal-to-Human Transmission</h3> <p>Potential Modes of Transmission to Humans</p> <ul style="list-style-type: none"> • Inhalation: <ul style="list-style-type: none"> • Contaminated dust from farming operations • Fine water droplets generated during slaughtering, defeathering, eviscerating and preparing • Contact with oral/nasal mucus membrane or conjunctiva: <ul style="list-style-type: none"> • Hand-transplantation of virus from contaminated surface (poultry feces, respiratory secretions or other contaminated products) • Direct oral exposure in cleaning fighting cocks? • Consumption of raw products? <ul style="list-style-type: none"> • Duck blood pudding & internal organs • No epidemiological evidence at this time |
| <h3>2. Animal-to-Human Transmission</h3> <ul style="list-style-type: none"> • Exposure Risks for Infection: Assessment of H5N1 HPAI - human cases [HK 1997, Vietnam & Thailand early 2004] (Mounts et al., J. Inf. Dis. 180:505-508, 1999; Tran et al., NEJM 350 [12]:1179-88, 2004; Chotpitayasunondh et al., EID 2005 11(2):201-9) <ul style="list-style-type: none"> – Risk: exposure 1 week before illness to live poultry, direct contact w/sick poultry – Not a risk: travel, preparing or eating poultry meat, or exposure to human AI cases – Not involved in organized culling or large poultry farms – Cases were associated with Village (smallholder) poultry or Live Poultry Market | <h3>2. Animal-to-Human Transmission</h3> <ul style="list-style-type: none"> • Occupational risk for exposure & infection (HK 1997): poultry farmers, depopulation crews & processors (Bridges et al., J. Inf. Dis. 188:1005-1010, 2002). • Some suspected limited human-to-human transmission – family clusters • January 2004 cases in Hanoi (Liem et al., EID 2005 11(2):210-5): no health careworker cases • Needs: <ul style="list-style-type: none"> – Timely epidemiological studies and sharing of data with veterinary medical sector which will assist in focusing control efforts in animal agricultural sector |
| <h3>3. Disease Control Basics</h3> <ul style="list-style-type: none"> • Strategies for dealing with poultry disease are developed to achieve one of 3 goals or outcomes: <ul style="list-style-type: none"> – <i>Prevention</i>: preventing introduction – <i>Management (Control)</i>: reducing losses by minimizing negative economic impact through management practices – <i>Eradication</i>: total elimination • These goals are achieved through various strategies developed using universal components: <ul style="list-style-type: none"> – Biosecurity (exclusion and inclusion) including quarantine – Diagnostics and surveillance – Elimination of AI virus infected poultry – Decreasing host susceptibility to the virus (vaccines and host genetics) – Education <p style="text-align: right; font-size: small;">ICM/NSAR 2001</p> | <h3>Avian Influenza Vaccines: Poultry</h3> <ul style="list-style-type: none"> • Vaccination not routine in most of the world • No single vaccine for AI viruses • Anti-HA antibodies are protective, but NA also protective, less effective • Types of Vaccines <ul style="list-style-type: none"> – Inactivated whole AI virus (C,E) – Recombinant live virus vectors: Fowl Pox (C), VEE (E), ALV (E), Vaccinia (E), ILT (E), NDV (E) – Subunit AI proteins (E) - HA, NA: Baculovirus, Yeast, Bacterial, Plant – Naked DNA vaccines (E) • Critical: safety, purity, potency & economy  <p style="text-align: right; font-size: small;">ICM/NSAR 2001</p> |

| <h3 style="text-align: center;">Vaccines in AI Control</h3> <ul style="list-style-type: none"> ▪ LPAI outbreaks - <ul style="list-style-type: none"> • Waterfowl – origin viruses: Meat Turkeys (Minnesota: 22 million doses over 20 years) – • Swine influenza (H1N1, H1N2, H3N2): Turkey Breeders (2.6 million USA 2001); other subtypes in world used • H7 & H5 in Italy – use in areas high risk since 2000 • H9N2 Middle East and Asia: billions (?) doses • Layers - rare use USA (inactivated H6N2 & H7N2) ▪ HPAI – outbreaks <ul style="list-style-type: none"> • Mexico (1995-2001) - H5N2: >1.3 billion doses inactivated & >1 billion doses Fowlpox recombinant • Pakistan (1995-04) - H7N3: inactivated (? Doses) • Hong Kong (2002-04) – H5N1: inactivated; China & Indonesia for unknown period (2 billion doses) <p style="text-align: right; font-size: small;">ICM-NSAB 2001</p> | <h3 style="text-align: center;">Avian Influenza Vaccines in Asia</h3> <ul style="list-style-type: none"> • Inactivated vaccine strains: <ul style="list-style-type: none"> ▪ A/turkey/England/73 (H5N2) LPAIV ▪ A/chicken/Mexico/94 (H5N2) LPAIV ▪ A/chicken/Indonesia/03 (H5N1) HPAIV ▪ A/turkey/Wisconsin/68 (H5N9) LPAIV ▪ Infectious clone: H5 & N1 genes of A/goose/Guangdong/96, 6 internal genes PR8 • Fowlpox recombinants with cDNA inserts of AI viral genes <ul style="list-style-type: none"> ▪ H5 gene - A/turkey/Ireland/83 ▪ H5 & N1 - A/goose/Guangdong/96 <p style="text-align: right; font-size: small;">ICM-NSAB 2001</p> | | | | | | | | | | | | | | | |
|---|--|-------------------------------------|-----------|-------------------------------------|--|-------------------|-------------------|---|-------------------|-------------------------|---------|-------------------|-------------------------|--|-------------------|-------------------|
| <h3 style="text-align: center;">Components of Effective Inactivated AI Vaccines</h3> <ul style="list-style-type: none"> ▪ Proper adjuvant system (major) ▪ High antigen mass in each dose (major) ▪ Proper transportation, storage & administration in high proportion of population to get effective immunization (major) ▪ Proper vaccine strain – homologous hemagglutinin and sufficient sequence similarity (minor contribution) <p style="text-align: right; font-size: small;">ICM-NSAB 2001</p> | <h3 style="text-align: center;">Priorities for Vaccination</h3> <h4 style="text-align: center;">Decreasing Order of Priority</h4> <ol style="list-style-type: none"> 1. High risk situations; e.g. in an outbreak zone as ring or suppressor vaccination 2. Valuable genetic stock such as pure lines or grandparent stocks whose individual value is high 3. Rare captive birds 4. Long-lived birds, such as egg layers or parent breeders 5. Meat birds <p style="text-align: right; font-size: small;">ICM-NSAB 2001</p> | | | | | | | | | | | | | | | |
| <h3 style="text-align: center;">Properly Used AI Vaccines</h3> <h4 style="text-align: center;">Protection</h4> <ul style="list-style-type: none"> ▪ Increase resistance to AIV infection ▪ Prevent clinical signs and death ▪ Reduced shedding of field virus when infected ▪ Prevent or reduce contact transmission ▪ Provide long protection from single vaccination ▪ Protect against high exposure dose of field virus ▪ Protect against a changing virus, but vaccine strains will have limited life span ▪ NO STERILIZING IMMUNITY outside the laboratory <p style="text-align: right; font-size: small;">ICM-NSAB 2001</p> | <h3 style="text-align: center;">Recombinant Fowlpox & Inactivated H5N9 AI Vaccine Protection Against H5N1</h3> <p style="font-size: x-small;">Chickens vaccinated SQ 1d with fowlpox-AIV-H5 recombinant* or inactivated whole AIV vaccine** and IN challenged at 3 wks with low challenge dose ($10^{3.5}$ EID₅₀ of HPAIV A/chicken/South Korea/2003 [H5N1]).</p> <table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <thead> <tr> <th style="font-size: small;">Vaccine Group</th> <th style="font-size: small;">Morbidity</th> <th style="font-size: small;">Mortality (Mean Death Time in days)</th> </tr> </thead> <tbody> <tr> <td style="font-size: x-small;">Fowlpox recombinant (10^4 TCID₅₀)*</td> <td style="font-size: x-small;">0/12^a</td> <td style="font-size: x-small;">0/12^a</td> </tr> <tr> <td style="font-size: x-small;">Fowlpox recombinant (10^4 TCID₅₀)**</td> <td style="font-size: x-small;">1/12^a</td> <td style="font-size: x-small;">1/12^a (6.0)</td> </tr> <tr> <td style="font-size: x-small;">Diluent</td> <td style="font-size: x-small;">9/10^b</td> <td style="font-size: x-small;">9/10^b (4.7)</td> </tr> <tr> <td style="font-size: x-small;">TW/68 Oil Emulsified (2-3 µg HA protein)**</td> <td style="font-size: x-small;">0/12^a</td> <td style="font-size: x-small;">0/12^a</td> </tr> </tbody> </table> <p style="font-size: x-small;">* H5 gene of A/turkey/Ireland/83 ** A/turkey/Wisconsin/68 (H5N9) Swazye, Develop. Biol. 119:219-228, 2004</p> <p style="text-align: right; font-size: small;">ICM-NSAB 2001</p> | Vaccine Group | Morbidity | Mortality (Mean Death Time in days) | Fowlpox recombinant (10^4 TCID ₅₀)* | 0/12 ^a | 0/12 ^a | Fowlpox recombinant (10^4 TCID ₅₀)** | 1/12 ^a | 1/12 ^a (6.0) | Diluent | 9/10 ^b | 9/10 ^b (4.7) | TW/68 Oil Emulsified (2-3 µg HA protein)** | 0/12 ^a | 0/12 ^a |
| Vaccine Group | Morbidity | Mortality (Mean Death Time in days) | | | | | | | | | | | | | | |
| Fowlpox recombinant (10^4 TCID ₅₀)* | 0/12 ^a | 0/12 ^a | | | | | | | | | | | | | | |
| Fowlpox recombinant (10^4 TCID ₅₀)** | 1/12 ^a | 1/12 ^a (6.0) | | | | | | | | | | | | | | |
| Diluent | 9/10 ^b | 9/10 ^b (4.7) | | | | | | | | | | | | | | |
| TW/68 Oil Emulsified (2-3 µg HA protein)** | 0/12 ^a | 0/12 ^a | | | | | | | | | | | | | | |

Recombinant Fowlpox & Inactivated H5N9 AI Vaccine Protection Against H5N1

Chickens vaccinated SQ 1d with fowlpox-AIV-H5 recombinant* or inactivated whole AIV vaccine** and IN challenged at 3 wks with low challenge dose ($10^{3.2}$ EID₅₀ of HPAIV A/chicken/South Korea/2003 [H5N1]).

| Vaccine Group | Virus Isolation, 2 days Post-challenge (Log ₁₀ EID ₅₀ titer/ml) | |
|--|---|--------------------------|
| | Oral swab | Cloacal swab |
| Fowlpox recombinant (10^8 TCID ₅₀) [*] | 3/5 ^{AI} (1.67) | 0/5 ^A (<0.97) |
| Fowlpox recombinant (10^6 TCID ₅₀) [*] | 0/5 ^A (<0.97) | 0/5 ^A (<0.97) |
| Diluent | 4/5 ^D (3.06) | 4/5 ^D (1.98) |
| TW/68 Oil Emulsified (2-3 µg HA protein) ^{**} | 0/5 ^A (<0.97) | 0/5 ^A (<0.97) |

*H5 gene of A/turkey/Ireland/83 Swayne, Develop. Biol. 119:219-228, 2004
 ** A/turkey/Wisconsin/68 (H5N9) JOM 05/08 2009

Vaccine Protection Against Asian H5N1

Chickens vaccinated SQ 3 wks with inactivated whole AIV vaccine and IN challenged 3 wks later with $10^{5.5}$ EID₅₀ of HPAIV (A/chicken/Indonesia/7/2003 [H5N1])
 • 1994 North American vaccine virus
 • 1986 Eurasian vaccine virus

| Group | Vaccine | Morbidity (3-4) [*] | Mortality (MDT) ^{**} | Virus Isolation, 2 DPC (Log ₁₀ EID ₅₀ titer/ml) | |
|-------|--|------------------------------|-------------------------------|---|---|
| | | | | oral | cloacal |
| 1 | Nobilis Hepatitis + ND Inac (Control) | 10/10 ^A | 10/10 ^A (2.2) | 10/10 ^A (6.16 ⁺) | 10/10 ^A (5.82 ⁺) |
| 2 | Nobilis I.A. Inactivated H5N2 (Mexican Strain) | 0/10 ^B | 0/10 ^B | 0/10 ^B (1.21 ⁻) | 3/10 ^B (1.00 ⁻) |
| 3 | Nobilis influenza, H5N2 (European Strain) | 1/10 ^B | 1/10 ^B (2.0) | 6/10 ^B (1.78 ⁻) | 3/10 ^B (1.33 ⁻) |

HAI A.A. similarity with challenge virus, Mexican Strain 84.8% & European 91.5%
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Protect Against a Changing Virus

- Fowl pox with H5 AIV gene insert
- Different challenge viruses (87.3-100% aa sequence similarity)

* challenge viruses (Swayne et al., Vaccine 18:1088-1095, 2000) JOM 05/08 2009

Fowlpox Recombinant Virus: Protection Against Changing Virus

| Vaccine Virus | HA A.A. Similarity | Fowlpox controls | Fowlpox-AI HA [*] |
|----------------------|--------------------|------------------|----------------------------|
| TK/Ireland/83 | 100% | 10/10 | 0/10 |
| TK/England/91 | 94.2% | 10/10 | 0/10 |
| Tem/S Africa/59 | 93.1% | 10/10 | 0/10 |
| CK/Scotland/59 | 92.0% | 9/10 | 0/10 |
| Hong Kong/156/97 | 90.2% | 8/10 | 0/10 |
| CK/Queretaro/1488/95 | 89.3% | 10/10 | 0/10 |
| TK/Ontario/77322/66 | 89.1% | 9/10 | 0/10 |
| Emu/TX/39992/4/93 | 88.8% | 7/10 | 0/10 |
| CK/PA/1370/83 | 87.3% | 10/10 | 0/10 |

*Fowlpox-AI HA had TK/Ireland/83 as insert (Swayne et al., Vaccine 18:1088-1095, 2000) JOM 05/08 2009

Protection in the Face of Changing AIV

- 100% protection from clinical signs and death
- Variable reduction in shedding of challenge virus

Oropharyngeal Swabs - Peak Shedding
r_s = 0.783, P = 0.009

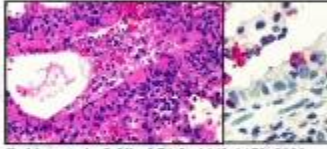
Cloacal Swabs - Peak Shedding
r_s = -0.106, P = 0.789

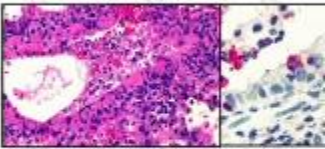
(Swayne et al., Vaccine 18:1088-1095, 2000) JOM 05/08 2009

Broad and longer-term protection efficacy of poultry AI vaccines

- Proprietary oil-emulsion-adjuvant technology → intense & long-lived immune response
- AI virus immune response in poultry appears to be broader than in humans
- Greater genetic homogeneity in poultry gives more consistent immunity
- Young, healthy poultry population are immunized verses in humans with emphasis on population at highest risk of severe illness and death
- Limit to how long a vaccine strain can be used – evaluated biennially

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| <h3 style="text-align: center;">Limitations and Disadvantages of Avian Influenza Vaccines</h3> <ul style="list-style-type: none"> • Best protection is in experimental studies with specific pathogen free chickens • Field protection less than in laboratory <ul style="list-style-type: none"> • High challenge exposure • Improper vaccination technique • Reduced vaccine dose • Immunosuppressive viruses • Improper storage & handling of vaccines • Unable to vaccinate 100% of poultry population <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | <h3 style="text-align: center;">Cross Protection of Commercially Vaccinated Birds to Different LPAI Challenge</h3> <ul style="list-style-type: none"> • Mexico: use of vaccination to control both LPAI and HPAI started in 1995 using killed and in 1998 using recombinant Fowl poxvirus (TK/Ireland/83 H5 gene insert) • Has field strain drifted from vaccine? Is protection still adequate? <table border="1" style="width: 100%; text-align: center;"> <thead> <tr> <th rowspan="2">Challenge virus</th> <th rowspan="2">DPF*</th> <th colspan="2">Oropharyngeal Viral Titers</th> </tr> <tr> <th>Vaccinated</th> <th>Control</th> </tr> </thead> <tbody> <tr> <td>Vaccine strain</td> <td>3DPI</td> <td>1.66 (5/10)</td> <td>4.5 (5/5)</td> </tr> <tr> <td>Jalisco Lineage</td> <td>5DPI</td> <td>0.98 (4/10)</td> <td>3.1 (5/5)</td> </tr> <tr> <td rowspan="2">CK/AG/124/3705/98 Lineage A</td> <td>3DPI</td> <td>4.44 (10/10)</td> <td>4.2 (5/5)</td> </tr> <tr> <td>5DPI</td> <td>2.14 (8/10)</td> <td>2.4 (5/5)</td> </tr> <tr> <td rowspan="2">CK/Guatemala/194573/02 Lineage B</td> <td>3DPI</td> <td>4.86 (10/10)</td> <td>4.9 (5/5)</td> </tr> <tr> <td>5DPI</td> <td>3.62 (10/10)</td> <td>3.4 (5/5)</td> </tr> </tbody> </table> <p style="text-align: center;"><small>(Lee et al., J. Virol. 78:8372-8381, 2004)</small></p> <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | Challenge virus | DPF* | Oropharyngeal Viral Titers | | Vaccinated | Control | Vaccine strain | 3DPI | 1.66 (5/10) | 4.5 (5/5) | Jalisco Lineage | 5DPI | 0.98 (4/10) | 3.1 (5/5) | CK/AG/124/3705/98 Lineage A | 3DPI | 4.44 (10/10) | 4.2 (5/5) | 5DPI | 2.14 (8/10) | 2.4 (5/5) | CK/Guatemala/194573/02 Lineage B | 3DPI | 4.86 (10/10) | 4.9 (5/5) | 5DPI | 3.62 (10/10) | 3.4 (5/5) | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---------------------|------------|----------------------------|-----|------------|---------------------|----------------|---------------|-------------|-----------|-----------------|------------|----------------|-----------|-----------------------------|------|--------------|-----------|---------------|-------------|-----------|----------------------------------|------|--------------|-------------------------|------|---|-----------|---|---|-----------------|--|--|--|--|--|-------------------------|---|---|---|---|---|---|---|---|---|---|---|------------------------|---|---|---|---|---|--|
| Challenge virus | DPF* | | | Oropharyngeal Viral Titers | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Vaccinated | Control | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Vaccine strain | 3DPI | 1.66 (5/10) | 4.5 (5/5) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Jalisco Lineage | 5DPI | 0.98 (4/10) | 3.1 (5/5) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| CK/AG/124/3705/98 Lineage A | 3DPI | 4.44 (10/10) | 4.2 (5/5) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 5DPI | 2.14 (8/10) | 2.4 (5/5) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| CK/Guatemala/194573/02 Lineage B | 3DPI | 4.86 (10/10) | 4.9 (5/5) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 5DPI | 3.62 (10/10) | 3.4 (5/5) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <h3 style="text-align: center;">4. Will the H5N1 Be the Next Pandemic Virus?</h3> <ul style="list-style-type: none"> • Lesion distribution and infection in mice similar to humans <table border="1" style="width: 100%; text-align: center;"> <thead> <tr> <th>Virus</th> <th>Mice</th> <th>%AIV</th> </tr> </thead> <tbody> <tr> <td>Italy/97</td> <td>0/8</td> <td>-3</td> </tr> <tr> <td>Scot/59</td> <td>0/8</td> <td>5</td> </tr> <tr> <td>Eng/91</td> <td>1/8</td> <td>-18</td> </tr> <tr> <td>Q20/95</td> <td>0/8</td> <td>-2</td> </tr> <tr> <td>HK/156</td> <td>8/8</td> <td>-26</td> </tr> <tr> <td>HK/220</td> <td>8/8</td> <td>-25</td> </tr> <tr> <td>HK/728</td> <td>6/8</td> <td>-10</td> </tr> <tr> <td>Shen</td> <td>0/8</td> <td>7</td> </tr> </tbody> </table>  <p style="text-align: center;"><small>Dybing et al., J. Virol 74(3):1443-1450, 2000</small></p> <ul style="list-style-type: none"> • Experimentally, some AIV cause infection and disease in mice, but not all AIV do! • Value of Ferret and Primate models <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | Virus | Mice | %AIV | Italy/97 | 0/8 | -3 | Scot/59 | 0/8 | 5 | Eng/91 | 1/8 | -18 | Q20/95 | 0/8 | -2 | HK/156 | 8/8 | -26 | HK/220 | 8/8 | -25 | HK/728 | 6/8 | -10 | Shen | 0/8 | 7 | <h3 style="text-align: center;">Limitations and Disadvantages of Avian Influenza Vaccines</h3> <ul style="list-style-type: none"> • Must be able to differentiate infected from vaccinated animals (DIVA): <ul style="list-style-type: none"> • Must detect "silent" infections and eliminate immediately • All vaccinated flocks must have surveillance <ul style="list-style-type: none"> • Specific serological tests, or • Unvaccinated sentinel animals – serology and virus detection, and • Virus detection (virus isolation or RT-PCR) on dead birds <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Virus | Mice | %AIV | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Italy/97 | 0/8 | -3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Scot/59 | 0/8 | 5 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eng/91 | 1/8 | -18 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Q20/95 | 0/8 | -2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HK/156 | 8/8 | -26 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HK/220 | 8/8 | -25 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HK/728 | 6/8 | -10 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Shen | 0/8 | 7 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <h3 style="text-align: center;">Interference of AI Vaccination with Surveillance</h3> <table border="1" style="width: 100%; text-align: center;"> <thead> <tr> <th rowspan="3"></th> <th colspan="5">Serological Test</th> </tr> <tr> <th rowspan="2">NP/M (AGP/ELISA)</th> <th rowspan="2">HA (HI)</th> <th colspan="2">Homo. Hetero.</th> <th rowspan="2">NS</th> </tr> <tr> <th>NA (NI)</th> <th>NA (NI)</th> </tr> </thead> <tbody> <tr> <td>AI Field Virus</td> <td>X</td> <td>X</td> <td>X</td> <td>-</td> <td>X</td> </tr> <tr> <td>Homologous NA</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td> inactivated AIV vaccine</td> <td>X</td> <td>X</td> <td>X</td> <td>-</td> <td>-</td> </tr> <tr> <td>Heterologous NA</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td> inactivated AIV vaccine</td> <td>X</td> <td>X</td> <td>-</td> <td>X</td> <td>-</td> </tr> <tr> <td>Recombinant Fowlpox, subunit HA & DNA HA vaccines</td> <td>-</td> <td>X</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>Unvaccinated sentinels</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> </tr> </tbody> </table> <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | | Serological Test | | | | | NP/M (AGP/ELISA) | HA (HI) | Homo. Hetero. | | NS | NA (NI) | NA (NI) | AI Field Virus | X | X | X | - | X | Homologous NA | | | | | | inactivated AIV vaccine | X | X | X | - | - | Heterologous NA | | | | | | inactivated AIV vaccine | X | X | - | X | - | Recombinant Fowlpox, subunit HA & DNA HA vaccines | - | X | - | - | - | Unvaccinated sentinels | - | - | - | - | - | <h3 style="text-align: center;">Needs in Vaccines and Vaccination</h3> <ol style="list-style-type: none"> 1. Standards in purity, safety & potency of AI vaccines 2. Studies to confirm efficacy of AI vaccines in ducks, geese and other minor poultry species 3. Effective vaccines that can be applied by mass immunization method 4. Metabolizable oil adjuvant systems 5. Sterilizing immunity? 6. Effective DIVA strategies that will be used to identify infected flocks for elimination 7. Periodic evaluation of vaccine strains for efficacy against predominate circulating strains <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> |
| | | Serological Test | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | NP/M (AGP/ELISA) | HA (HI) | Homo. Hetero. | | NS | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | NA (NI) | | | NA (NI) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| AI Field Virus | X | X | X | - | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Homologous NA | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| inactivated AIV vaccine | X | X | X | - | - | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heterologous NA | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| inactivated AIV vaccine | X | X | - | X | - | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Recombinant Fowlpox, subunit HA & DNA HA vaccines | - | X | - | - | - | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Unvaccinated sentinels | - | - | - | - | - | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| <h3>4. Will the H5N1 Be the Next Pandemic Virus?</h3> <p>• Lesion distribution and infection in mice similar to humans</p> <table border="1"> <thead> <tr> <th>Virus</th> <th>Mort.</th> <th>NaIVV</th> </tr> </thead> <tbody> <tr> <td>Italy/97</td> <td>0/8</td> <td>-3</td> </tr> <tr> <td>Scot/59</td> <td>0/8</td> <td>5</td> </tr> <tr> <td>Eng/91</td> <td>1/8</td> <td>-18</td> </tr> <tr> <td>Q20/95</td> <td>0/8</td> <td>-2</td> </tr> <tr> <td>HK/156</td> <td>8/8</td> <td>-26</td> </tr> <tr> <td>HK/220</td> <td>8/8</td> <td>-25</td> </tr> <tr> <td>HK/728</td> <td>6/8</td> <td>-10</td> </tr> <tr> <td>Shenn</td> <td>0/8</td> <td>7</td> </tr> </tbody> </table>  <p>Dybing et al., J. Virol 74(3):1443-1450, 2000</p> <p>• Experimentally, some AIV cause infection and disease in mice, but not all AIV do!</p> <p>• Value of Ferret and Primate models</p> <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | Virus | Mort. | NaIVV | Italy/97 | 0/8 | -3 | Scot/59 | 0/8 | 5 | Eng/91 | 1/8 | -18 | Q20/95 | 0/8 | -2 | HK/156 | 8/8 | -26 | HK/220 | 8/8 | -25 | HK/728 | 6/8 | -10 | Shenn | 0/8 | 7 | <h3>Not all Asian H5N1 AIV have same potential to infect and cause disease in humans</h3> <p>Three H5N2 HPAIV in intranasally inoculated BALB/c mice</p> <table border="1"> <thead> <tr> <th>Virus</th> <th>Mortality</th> <th>Lung Lesions</th> <th>Virus location</th> </tr> </thead> <tbody> <tr> <td>220/97</td> <td>100%</td> <td>33-80%</td> <td>lung, trachea, brain, kidney</td> </tr> <tr> <td>317.5/01</td> <td>0-10%</td> <td>20-33%</td> <td>lung, trachea</td> </tr> <tr> <td>Anyang/01</td> <td>22-33%</td> <td>0-10%</td> <td>lung, trachea</td> </tr> </tbody> </table> <p>(Tumpey et al., J. Virol. 76:6344-6355, 2002)</p> <p>• 2003-2004: Cases only in Thailand, Vietnam and Cambodia, but not other Asian countries with H5N1 poultry cases</p> <ul style="list-style-type: none"> • Differences in virus strains • Exposure differences <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | Virus | Mortality | Lung Lesions | Virus location | 220/97 | 100% | 33-80% | lung, trachea, brain, kidney | 317.5/01 | 0-10% | 20-33% | lung, trachea | Anyang/01 | 22-33% | 0-10% | lung, trachea | | | | | | | | | | | |
|--|--|------------------------------|------------------------------|-----------|------------------------------|-------------------------|---------|---------------|---|--------|-----------------------|-----|--------|-----------|------------------------------|--------|-----------|------------------------------|--------|-----|-----|---------|------|-----|---------|------|---------|---|-------|-----------|--------------|----------------|--------|--------------------|--------|------------------------------|----------|-------|--------|---------------|--------------------|--------|-------------------------|-------------------------|-----|-----|-----|------------------|-----|-------------------------|-------------------------|-----|-------------------------|-------------------------|---|
| Virus | Mort. | NaIVV | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Italy/97 | 0/8 | -3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Scot/59 | 0/8 | 5 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eng/91 | 1/8 | -18 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Q20/95 | 0/8 | -2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HK/156 | 8/8 | -26 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HK/220 | 8/8 | -25 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HK/728 | 6/8 | -10 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Shenn | 0/8 | 7 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Virus | Mortality | Lung Lesions | Virus location | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 220/97 | 100% | 33-80% | lung, trachea, brain, kidney | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 317.5/01 | 0-10% | 20-33% | lung, trachea | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Anyang/01 | 22-33% | 0-10% | lung, trachea | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <h3>Do LPAIV have the potential to infect and cause disease in humans?</h3> <table border="1"> <thead> <tr> <th rowspan="3">Groups</th> <th colspan="6">Mouse Strain</th> </tr> <tr> <th colspan="3">BALB/c (Mx1-)</th> <th colspan="3">CAST/EI (Mx1+ & Mx1-)</th> </tr> <tr> <th>Mortality</th> <th colspan="2">Virus Isolation^b</th> <th>Mortality</th> <th colspan="2">Virus Isolation^b</th> </tr> <tr> <td></td> <td></td> <td>Trachea</td> <td>Lung</td> <td></td> <td>Trachea</td> <td>Lung</td> </tr> </thead> <tbody> <tr> <td>Control</td> <td>0/2</td> <td>0/2</td> <td>0/2</td> <td>0/2</td> <td>0/2</td> <td>0/2</td> </tr> <tr> <td>PA/11787/97 (H7N2)</td> <td>0/5</td> <td>1/2(10^{6.5})</td> <td>0/2</td> <td>0/5</td> <td>0/2</td> <td>0/2</td> </tr> <tr> <td>PA/19241/97 (H7N2)</td> <td>0/5</td> <td>2/2(10^{6.5})</td> <td>2/2(10^{6.5})</td> <td>0/5</td> <td>0/2</td> <td>0/2</td> </tr> <tr> <td>HK/156/97 (H5N1)</td> <td>5/5</td> <td>2/2(10^{6.5})</td> <td>2/2(10^{7.2})</td> <td>5/5</td> <td>2/2(10^{6.5})</td> <td>2/2(10^{7.2})</td> </tr> </tbody> </table> <p>(Henzler et al., Avian Diseases 47:1022-1036, 2003)</p> <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | Groups | Mouse Strain | | | | | | BALB/c (Mx1-) | | | CAST/EI (Mx1+ & Mx1-) | | | Mortality | Virus Isolation ^b | | Mortality | Virus Isolation ^b | | | | Trachea | Lung | | Trachea | Lung | Control | 0/2 | 0/2 | 0/2 | 0/2 | 0/2 | 0/2 | PA/11787/97 (H7N2) | 0/5 | 1/2(10 ^{6.5}) | 0/2 | 0/5 | 0/2 | 0/2 | PA/19241/97 (H7N2) | 0/5 | 2/2(10 ^{6.5}) | 2/2(10 ^{6.5}) | 0/5 | 0/2 | 0/2 | HK/156/97 (H5N1) | 5/5 | 2/2(10 ^{6.5}) | 2/2(10 ^{7.2}) | 5/5 | 2/2(10 ^{6.5}) | 2/2(10 ^{7.2}) | <h3>Human Pandemic Influenza</h3> <p>• Which one of the avian influenza viruses could contribute genes to the next human pandemic virus?</p> <ul style="list-style-type: none"> • LP versus HPAI as contributor of genes • Asian H5N1 HPAI • Asian H9N2 LPAI • H7N3 HPAI • H7N7 HPAI • H7N2 LPAI • H2N2 – the old nemesis? <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> |
| Groups | | Mouse Strain | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | BALB/c (Mx1-) | | | CAST/EI (Mx1+ & Mx1-) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Mortality | Virus Isolation ^b | | Mortality | Virus Isolation ^b | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Trachea | Lung | | Trachea | Lung | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Control | 0/2 | 0/2 | 0/2 | 0/2 | 0/2 | 0/2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PA/11787/97 (H7N2) | 0/5 | 1/2(10 ^{6.5}) | 0/2 | 0/5 | 0/2 | 0/2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PA/19241/97 (H7N2) | 0/5 | 2/2(10 ^{6.5}) | 2/2(10 ^{6.5}) | 0/5 | 0/2 | 0/2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HK/156/97 (H5N1) | 5/5 | 2/2(10 ^{6.5}) | 2/2(10 ^{7.2}) | 5/5 | 2/2(10 ^{6.5}) | 2/2(10 ^{7.2}) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <h3>Needs: Determine What AI Virus(es) Have Greatest Potential to be the Next Pandemic Virus!</h3> <ol style="list-style-type: none"> 1. Develop, evaluate and use animal models to predict and understand human infection and transmission potential for circulating AI viruses including H5N1 Asian viruses 2. Determining in vitro anti-viral susceptibility and in vivo vaccine protection against circulating H5N1 AI viruses as prelude to human prevention 3. Reverse genetic studies to identify avian genes from specific strains with greatest pandemic potential (reassortants) - Caution should be exercised as to the appropriate biosafety level for reassortant studies to generate a potentially pandemic strain by reverse genetics <p style="text-align: right;"><small>ICM/NIAS 2001</small></p> | <p style="text-align: center; font-size: 1.2em;">Thank you for your attention!</p> <hr/> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

(Slides available on accompanying CD)

WORKING GROUP 3 INFLUENZA DIAGNOSTICS FOR SURVEILLANCE

Chairperson –Richard Webby

Briefer – Nancy Cox

Rapporteur – Alan Hay

Charge: The charge of this working group is to define research needed to improve influenza surveillance through improved diagnostics and surveillance methods in clinical settings and in animals.

Specific Questions to address:

1. What studies are needed to assess and improve the specificity, sensitivity, and robustness of current diagnostic methods in influenza surveillance?
2. What studies are needed to assess diagnostic methods that are more rapid, cheaper, easier to handle and transport or that have additional capabilities such as detecting subtype or antiviral resistance?
3. What studies are needed to define or assess new epidemiological approaches to surveillance that will be more sensitive in detecting novel influenza strains and their extent in a region to provide data on possible pandemic candidates as early as possible?
4. What studies are needed to assess diagnostic approaches that may be of value in resource poor areas where laboratory facilities are not readily available and issues of specimen handling and transport are potential barriers to surveillance?
5. What studies are needed to address diagnostics in animal populations?

Report to Plenary

Rapporteur-Dr. Alan Hay

As you heard this morning, influenza is a very networked enemy, and combating it also requires a network approach. The issues are complicated by different circumstances in different parts of the world, such as how we would apply diagnostics to emergencies such as that in Southeast Asia.

Research Priorities—Immediate (1-2 years)

- Strengthen and extend the global network with immediate emphasis on national and regional laboratories in SE Asia,
 - Ensuring resources for the availability and distribution of diagnostic tests
 - Public health and private sectors should be involved
 - Network would provide financial and technical capacities required
 - Organization and management structure
 - WHO and other organizations would play a significant role

Our first priority is the urgent need to gain much more information about the viruses circulating in avian and animal populations in Southeast Asia, the extent of infections in human beings, the relationship in terms of sporadic infections, and the nature of infections that occur in clusters. Are the latter also sporadic avian-to-human infections, or do they represent a greater degree of human-to-human transmission?

We obviously need to know much more about the progression of H5N1 disease in individuals, and how to apply diagnostic tests most efficiently. But the highest priority is to strengthen and extend the WHO global network, with an immediate emphasis on establishing an effective network of national and regional laboratories in Southeast Asia. We also need to ensure that resources are available for distributing diagnostic tests. These clearly need to be inexpensive and simple to use, and much effort should go into studies to evaluate the tests in underdeveloped settings. We further need interaction between public health and private-sector interests regarding the avian situation, and effective dialogue between public health and veterinary people.

The network will clearly need enough financial and technical capacity as well as an effective organization and management structure. WHO and other organizations would play a significant role.

Research Priorities—Immediate (1-2 years)

- Rapid, inexpensive, uncomplicated and sample stable diagnostic tests for typing and sub-typing, and optimization of specimen collection and shipment
- High throughput analyses; micro-arrays
- Establish an epidemiological strategy and tools (e.g. clinical case definitions, syndromic surveillance)

Our other priority concerned research to develop rapid, inexpensive, uncomplicated, and sample-stable diagnostic tests for typing and subtyping. We need tests that will actually diagnose H5N1 infections and distinguish them from other influenza infections. We also need research on optimizing sample collection and distribution. Many point-of-care diagnostic tests have been developed. We heard this morning about the limitations of those, and we clearly need an environment that encourages both small and larger private interests to develop those tests so they would be available now but also in a pandemic situation. We also need to develop high-throughput analytical procedures for diagnosing viral infections and developing therapies. An effective microarray technology is particularly important.

We need to establish an epidemiological strategy and create the tools—including clinical case definitions and syndrome surveillance—to support those studies, to understand the nature of the infections in Southeast Asia and the risks they pose. In a five-year timeframe, we considered integrating studies in humans and animals and developing the most suitable sampling strategies to determine the populations to focus on. We also suggested developing a real-time database of all available information. We further need to develop strategies to diagnose disease, so we can understand the nature of an infectious agent as quickly as possible. That entails developing syndromic surveillance techniques.

Research Priorities-Intermediate term (5 Years)







- Sampling strategies for animals and humans (who to study in a population, sample size)
- Development of a real-time database
- Develop strategies to diagnose the disease before you have the diagnostic tests (syndromic surveillance)









Our 10-year priorities include understanding the biological and epidemiological dynamics of respiratory pandemics, focusing on flu but also the nature of influenza in relation to other agents. We would also like to understand multi-pathogen population-based systems so we can better evaluate the most suitable interventions.

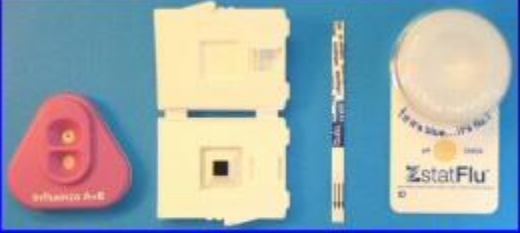

Research Priorities- Long Term (10 years)

- Understand the biological and epidemiological dynamics of respiratory pandemics
- Multi-pathogen population-based system (evaluate interventions)



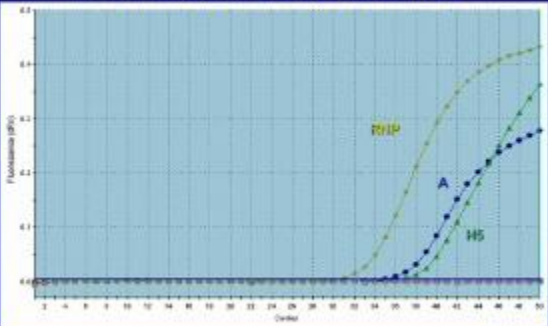




Working Group 3 Briefing Slides: Challenges and Strategies for Detection and Characterization of Influenza Viruses: Surveillance and Diagnosis-Dr. Cox, Briefer

| | |
|--|---|
| <p>Challenges and Strategies for Detection and Characterization of Influenza Viruses: Surveillance and Diagnosis</p> <p>Nancy J. Cox, Ph.D. Chief, Influenza Branch Director, WHO Collaborating Center for Influenza Centers for Disease Control and Prevention</p>  | <p>Laboratory Surveillance for Influenza</p> <p>Many respiratory outbreaks have characteristic "influenza-like" symptoms</p> <p>H5 influenza + SARS suspect case definition similar</p> <p>Effective laboratory testing for influenza necessary to rapidly "rule-in" or "rule-out" influenza</p>  |
| <p>Laboratory Quality Assurance</p> <p>Successful diagnosis depends largely on the quality of the specimen and the conditions for transport and storage of the specimen before testing.</p> <p>Antigenic tests</p> <ul style="list-style-type: none">- detection of viral protein <p>Genetic tests</p> <ul style="list-style-type: none">- detection of viral nucleic acid  | <p>Types of Specimens for Influenza Testing</p> <p>Respiratory specimens:</p> <ul style="list-style-type: none">• bronchoalveolar lavage• tracheal aspirates• sputum• nasopharyngeal or oropharyngeal aspirates or washes• nasopharyngeal or oropharyngeal swabs• Swab specimens should be collected on swabs with a Dacron tip and an aluminum or plastic shaft. <p>Specimens should be collected within first 1-5 days after onset of clinical symptoms</p>  |
| <p>Specimen Transport</p> <ul style="list-style-type: none">• Specimens for direct detection of viral antigens by immunofluorescent staining of infected cells should be kept on ice and processed within 1 - 2 hours.• Specimens for virus isolation should be refrigerated immediately after collection and inoculated into susceptible cell cultures as soon as possible.• If the specimen cannot be processed within 48 - 72 hours, the specimen should be kept frozen at or below -70°C.  | <p>Diagnostic Virology Options for Diagnostic Testing</p> <ul style="list-style-type: none">• Virus Culture<ul style="list-style-type: none">- Conventional- Centrifugation-enhanced• Direct Antigen Detection<ul style="list-style-type: none">- Immunofluorescence- Rapid commercial tests• Molecular Techniques• Serology• Future technology•  |

| <h3 style="text-align: center;">Virus Isolation</h3> <ul style="list-style-type: none"> • Highly sensitive (“gold standard”) • Allows quantity enough for further antigenic and genetic characterization • Labs must maintain several cell lines for different respiratory pathogens • Influenza <ul style="list-style-type: none"> • Madin-Darby canine kidney (MDCK) cells • Primary monkey kidney (PMK) cells • Embryonated eggs • Disadvantage – requires several days • Very important for vaccine selection  | <h3 style="text-align: center;">Viral Isolation</h3> <ul style="list-style-type: none"> • Madin - Darby Canine Kidney (MDCK) • Embryonated chicken eggs, 10 days old   | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|--|--------------------------|--------|------|-----|-----------|---------|---------|--------|------|-----|---------|------|----|----|----|-----|---------|----|------|----|----|----|--------------|-----|-----|-----|-----|-----|-------------|-----|-----|----|------|----|------------|------|----|----|----|----|----|------------|------|----|----|-----|-----|----|------------|-----|-----|-----|----|-----|-----------|------------|-----|-----|-----|-----|-----|-----------|------------|------|----|----|----|----|----|------------|-----|------|----|----|-----|----|------------|-----|------|----|-----|----|----|------------|-----|-----|-----|-----|-----|-----------|--|
| <h3 style="text-align: center;">HA/HAI test</h3> <p>Advantages</p> <ul style="list-style-type: none"> ➢ General subtyping to detailed antigenic characterization ➢ “Gold standard” for vaccine selection <p>Disadvantages</p> <ul style="list-style-type: none"> ➢ Cultured virus with high titres necessary ➢ Immune sera necessary ➢ Time consuming/ labor intensive  | <h3 style="text-align: center;">WHO Influenza Detection Kit</h3> <ul style="list-style-type: none"> • Antigens • Serology Antigens • Antisera • Monoclonals produced in ascites fluid or TC • RDE • Negative Control   | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <h3 style="text-align: center;">WHO Kit - HAI Test</h3> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2">Antigens</th> <th colspan="5">Reference Sheep Antisera</th> </tr> <tr> <th>A(H1N1)</th> <th>A(H3N2)</th> <th>B/Sich</th> <th>B/HK</th> <th>Neg</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>5120</td> <td>40</td> <td>10</td> <td>10</td> <td><10</td> </tr> <tr> <td>A(H3N2)</td> <td>40</td> <td>5120</td> <td>40</td> <td>10</td> <td>10</td> </tr> <tr> <td>B/Sic/379/99</td> <td><10</td> <td><10</td> <td>160</td> <td><10</td> <td><10</td> </tr> <tr> <td>B/HK/339/01</td> <td><10</td> <td><10</td> <td>40</td> <td>5120</td> <td>10</td> </tr> <tr> <td>Isolate #1</td> <td>1280</td> <td>10</td> <td>40</td> <td>20</td> <td>10</td> <td>01</td> </tr> <tr> <td>Isolate #2</td> <td>2560</td> <td>20</td> <td>10</td> <td><10</td> <td><10</td> <td>01</td> </tr> <tr> <td>Isolate #3</td> <td><10</td> <td><10</td> <td>160</td> <td>40</td> <td><10</td> <td>01/02/200</td> </tr> <tr> <td>Isolate #4</td> <td><10</td> <td><10</td> <td><10</td> <td>320</td> <td><10</td> <td>01/02/200</td> </tr> <tr> <td>Isolate #5</td> <td>5120</td> <td>40</td> <td>40</td> <td>20</td> <td>20</td> <td>01</td> </tr> <tr> <td>Isolate #6</td> <td><10</td> <td>5120</td> <td>40</td> <td>20</td> <td><10</td> <td>01</td> </tr> <tr> <td>Isolate #7</td> <td><10</td> <td>2560</td> <td>40</td> <td><10</td> <td>10</td> <td>01</td> </tr> <tr> <td>Isolate #8</td> <td><10</td> <td><10</td> <td><10</td> <td>320</td> <td><10</td> <td>01/02/200</td> </tr> </tbody> </table>  | Antigens | Reference Sheep Antisera | | | | | A(H1N1) | A(H3N2) | B/Sich | B/HK | Neg | A(H1N1) | 5120 | 40 | 10 | 10 | <10 | A(H3N2) | 40 | 5120 | 40 | 10 | 10 | B/Sic/379/99 | <10 | <10 | 160 | <10 | <10 | B/HK/339/01 | <10 | <10 | 40 | 5120 | 10 | Isolate #1 | 1280 | 10 | 40 | 20 | 10 | 01 | Isolate #2 | 2560 | 20 | 10 | <10 | <10 | 01 | Isolate #3 | <10 | <10 | 160 | 40 | <10 | 01/02/200 | Isolate #4 | <10 | <10 | <10 | 320 | <10 | 01/02/200 | Isolate #5 | 5120 | 40 | 40 | 20 | 20 | 01 | Isolate #6 | <10 | 5120 | 40 | 20 | <10 | 01 | Isolate #7 | <10 | 2560 | 40 | <10 | 10 | 01 | Isolate #8 | <10 | <10 | <10 | 320 | <10 | 01/02/200 | <h3 style="text-align: center;">Immunofluorescence</h3> <ul style="list-style-type: none"> • Do not need viable virus; can perform culture on + specimens • Rapid (~ 20 minutes to ~ 2 hours) • Can assess quality of specimen • Subjective reading – reader expertise is needed • Limited to laboratories with IF capability • Variable sensitivity and specificity  |
| Antigens | | Reference Sheep Antisera | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | A(H1N1) | A(H3N2) | B/Sich | B/HK | Neg | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| A(H1N1) | 5120 | 40 | 10 | 10 | <10 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| A(H3N2) | 40 | 5120 | 40 | 10 | 10 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| B/Sic/379/99 | <10 | <10 | 160 | <10 | <10 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| B/HK/339/01 | <10 | <10 | 40 | 5120 | 10 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Isolate #1 | 1280 | 10 | 40 | 20 | 10 | 01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Isolate #2 | 2560 | 20 | 10 | <10 | <10 | 01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Isolate #3 | <10 | <10 | 160 | 40 | <10 | 01/02/200 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Isolate #4 | <10 | <10 | <10 | 320 | <10 | 01/02/200 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Isolate #5 | 5120 | 40 | 40 | 20 | 20 | 01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Isolate #6 | <10 | 5120 | 40 | 20 | <10 | 01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Isolate #7 | <10 | 2560 | 40 | <10 | 10 | 01 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Isolate #8 | <10 | <10 | <10 | 320 | <10 | 01/02/200 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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| <h3>Immunofluorescence Staining of Infected Cell Cultures (IFA)</h3> <ul style="list-style-type: none">• Rapid and sensitive• Monoclonal antibodies available (WHO Kits)<ul style="list-style-type: none">• Typing (A, B), subtyping (H1, H3, H5)• Can be used for staining smears of clinical specimens directly<ul style="list-style-type: none">• Preferable in cell culture• Quality of isolate, specificity of reagents used, experience of staff are essential  <p>Anti-H5 Anti-H3 Anti-A/NP Anti-B</p>  | <h3>Rapid Diagnostic Kits Advantages</h3> <ul style="list-style-type: none">• Rapid – results in ~15-30min• Simple• On-site testing• Test clinical material or grown virus <p>Useful for clinical settings and outbreak investigations</p>  |
| <h3>Rapid Diagnostic Kits Disadvantages</h3> <ul style="list-style-type: none">• Less sensitive than viral culture or RT-PCR<ul style="list-style-type: none">- False negatives and positives• Some kits cannot type (A/B)• Cannot subtype (H3, H1, H5?)• Cost (\$12 - \$20+/test)  | <h3>Role of Genetic Characterization in Influenza Surveillance</h3> <p>Influenza surveillance is based primarily on antigenic characterization of virus isolates for vaccine selection</p> <ul style="list-style-type: none">• Supplement & facilitate biological characterization• Rapid detection from clinical specimens or unknown virus cultures• Provide data for epidemiological studies• Characterization - genetic typing/subtyping of atypical viruses, mixed populations, "non-growers"  |
| <h3>Rapid Test Result Indicators</h3>  <p>Directigen Fu A + B FLU OIA QuickVue ZstatFlu</p>  | <h3>Molecular Techniques</h3> <ul style="list-style-type: none">• RT-PCR (single or multiplex)• Restriction Fragment Length Polymorphism (RFLP)• Nucleic Acid Sequence Based Amplification• Oligonucleotide hybridization Probes• Microarray• Heteroduplex mobility  |

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| <h3 style="text-align: center;">Genetic Analysis of Influenza virus</h3> <div style="text-align: center;"> <pre> graph TD vRNA --> RT-PCR_S[RT-PCR (Sequence Analysis)] vRNA --> RT-PCR_D[RT-PCR (Detection/Characterization)] RT-PCR_S --> RT-PCR_D </pre> </div> <div style="display: flex; justify-content: space-around;"> <div style="width: 45%;"> <ul style="list-style-type: none"> • % Similarity/Difference • Blast/Fasta Query • Phylogenic analysis • Identify amino acid changes that correlate with antigenic/biological characterization • genome composition </div> <div style="width: 45%;"> <ul style="list-style-type: none"> • gel electrophoresis • RFLP • probe hybridization • Real-Time RT-PCR • MicroArray • RT-PCR-ELISA </div> </div> <p style="text-align: right;"></p> | <h3 style="text-align: center;">Role of Genetic Characterization in Influenza Surveillance</h3> <p>Influenza surveillance is based primarily on antigenic characterization of virus isolates for vaccine selection</p> <ul style="list-style-type: none"> • Supplement & facilitate biological characterization • Rapid detection from clinical specimens or unknown virus cultures • Provide data for epidemiological studies • Characterization - genetic typing/subtyping of atypical viruses, mixed populations, "non-growers" <p style="text-align: right;"></p> |
| <h3 style="text-align: center;">Detection of H5N1 Influenza Viruses by RT-PCR</h3> <p>Advantages</p> <ul style="list-style-type: none"> • Rapid • Sensitive* • Specific* • Low Biocontainment - BSL2 • High Throughput <p>Disadvantages</p> <ul style="list-style-type: none"> • Expensive • Cross-contamination <p style="text-align: right;"></p> | <h3 style="text-align: center;">Detection and Characterization of Influenza by RT-PCR</h3> <ul style="list-style-type: none"> • Detection <ul style="list-style-type: none"> • Sensitivity • Broad reactivity will allow detection of all influenza viruses • Target conserved internal genes (M) • Characterization <ul style="list-style-type: none"> • Specificity • Subtyping of surface antigens (HA/NA) <p style="text-align: center;">PRIMER DESIGN IS CRITICAL</p> <p style="text-align: right;"></p> |
| <h3 style="text-align: center;">Design Strategy for RT-PCR Primers</h3> <ul style="list-style-type: none"> • Similar T_m to allow for simultaneous reactions and possibly multiplex reactions • Multiple primer sets to allow for rapid reassessment/redesign • Allow for future developments/technologies <p style="text-align: right;"></p> | <h3 style="text-align: center;">Detection vs Characterization</h3> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p style="text-align: center;">Detection</p> <p style="text-align: center;">All Type A influenza viruses (M gene)</p> <p style="text-align: center;">Subtype (HA/NA)</p> <p style="text-align: center;">Genotype</p> <ul style="list-style-type: none"> - host specific differences - lineage/sublineage specific differences - nucleotide specific differences (drug resistance, antigenic correlates) </div> <div style="width: 45%; text-align: right;"> <p style="text-align: center;">Characterization</p> </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div style="width: 45%; text-align: center;"> <p>↑ sensitivity</p> <p>low</p> </div> <div style="width: 45%; text-align: center;"> <p>↓ specificity</p> <p>high</p> </div> </div> <p style="text-align: right;"></p> |

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| <h3>Real-Time RT-PCR</h3> <ul style="list-style-type: none">> Simplified Protocol<ul style="list-style-type: none">• Lower risk of technician error• Lower risk of contamination> Universal assay<ul style="list-style-type: none">• Comparable results with different platforms, chemistries, etc.> No processing of amplified DNA<ul style="list-style-type: none">• Low risk of "carry-over" contamination  | <h3>Realtime RT-PCR for Influenza</h3> <ul style="list-style-type: none">> Virus detection – type A/B> Subtyping – H1, H3, H5, etc.> Specimen quality control> Estimate virus load  |
| <h3>Real-Time RT-PCR for Influenza</h3>  <p>The graph shows fluorescence (RFU) on the y-axis (0.0 to 0.5) and Cycle on the x-axis (1 to 50). Three curves are shown: RNP (green), A (blue), and H5 (red). RNP shows the earliest amplification, followed by A, and then H5.</p>  | <h3>Respiratory Panel for Real-Time RT-PCR diagnosis</h3> <ul style="list-style-type: none">• Influenza A (Flu A)• Influenza B (Flu B)• Human metapneumovirus (hMPV)• RSV• Adenovirus (Adeno)• SARS  |
| <h3>Serology</h3> <ul style="list-style-type: none">> Both acute and convalescent sera are useful but not necessary for suspect avian influenza cases.> HI not effective for detecting H5 neutralizing Ab in sera from human cases.> Neutralization test is more effective for detection of antibodies to avian viruses<ul style="list-style-type: none">• Technically difficult, requires live virus, BSL3+ containment, confirmation by Western blot desirable.> ELISA often demonstrate high level of nonspecificity  | <h3>Future of Detection & Identification of Influenza</h3> <p>Need for simple, inexpensive, low-tech methods for screening for respiratory pathogens in the field (typing and subtyping of influenza included)</p> <p>Genetic (RT-PCR based)</p> <ul style="list-style-type: none">• Conventional• Real-time (SYBR[®] green, dual-labeled probes, molecular beacons, etc.)• RT-PCR-ELISA• Luminex/Bioplex bead array• Micro array  |

(Slides available on accompanying CD)

**WORKING GROUP 4
ANTIVIRALS AND NON-SPECIFIC APPROACHES,
TREATMENTS AND IMMUNOTHERAPIES**

Chairperson – Richard Whitley

Briefer – Fred Hayden

Rapporteur – Charles Hackett

Charge: This working group will identify research priorities related to the development, evaluation, and use of antiviral drugs and immunotherapies. Issues to consider include studying the impacts of currently available antiviral drugs and strategies to increase their effectiveness or efficiency; studies of other licensed products that may have benefit in treatment or prevention of influenza; studies of drugs in the development pipeline; and studies of immune therapies and biologicals. Research needed to predict, identify, evaluate, and decrease antiviral resistance also is relevant

Specific Questions:

1. What studies are needed to identify the optimal strategies for use of currently available antiviral drugs?
2. What studies are needed to evaluate licensed agents that may moderate the occurrence or severity of influenza?
3. What new antiviral agents are being developed and what research is needed to evaluate these agents or to identify new drug treatment or prevention options?
4. What potential immunotherapeutics could be developed and what research is needed for their evaluation?
5. What studies can help in prediction, identification, assessment, and prevention of antiviral drug resistance?
6. What studies on the pathophysiology of influenza can offer insights for prevention?

Report to Plenary

Rapporteur: Dr. Charles Hackett

At the top of our list are clinical trials for antivirals and immunotherapeutics. One of the main priorities is to develop pandemic protocols now. We reflected on experience with SARS, where public health authorities faced difficult decisions on which of many different possible courses of action they could take unless they had determined ahead of time which protocols to put in place.

We need to obtain data on the virologic course and immune responses following pandemic influenza infection, as well as response to therapy following human H5 infections and other potential pandemic infections. A major priority is safety and tolerability of available drugs—oseltamivir pharmacokinetics (PK)—especially in infants less than 1 year old. We also need to determine the PK and tolerability of parenteral drug use, and to assess the long-term (12–20 weeks) tolerability of oseltamivir in inhaled zanamivir prophylaxis.

We also need to look at high-priority/high-risk populations, such as pregnant women and immuno-compromised hosts. We need data on these populations, because we need to resolve questions about safety and efficacy of treatments before using them in a pandemic.

We also need to study emergence of H5N1 resistance in animal models, and strategies for preventing it. Animal models seem to be the best vehicle for obtaining good data. We need to assess the probability of licensure for orally inhaled zanamivir for disease prophylaxis, because oseltamivir resistance was uncovered and because well-controlled studies show that this approach may work.

The short-term priority is to accelerate drug development and discovery programs, including assessment of orphan drugs. We want to support operational infrastructure research. We decided that the strength of our group is to recommend research that will go hand-in-hand with policy development. Thus we see the need for clinical trials of drugs administered more than 48 hours after viral infection, and data on differences in sites of care and drug deployment and response time.

We need research on physician prescription of antiviral drugs, because many physicians are not geared up to prescribe such drugs. That would have to change if antiviral drugs were a major cornerstone of a pandemic treatment. That effort should start now, and would dovetail with policy development.

We need to test systematic approaches to influencing inflammatory expression and disease. We drew that lesson from looking at SARS, where inflammation damages lungs and steroids were used for treatment, even though steroids have unintended and longer-term consequences. We need to look at other ways of controlling inflammation as a priority.

In the medium term, we pointed to accelerated clinical trials of antivirals. We need to test oseltamivir monotherapy versus combination with an M2 inhibitor or ribavirin or other novel therapies in high-risk populations. We also need to test therapeutic efficacy of parenteral peramivir in hospitalized influenza patients, and to test prophylactic efficacy and tolerability of topical long-acting neuraminidase inhibitors.

We need to develop a contemporary virus challenge pool or pools for studies of experimental human influenza. This is an important piece of the puzzle, but obtaining the appropriate challenge virus that will provide the characteristics of the disease that we need to test takes time. We also need to use those to test candidate immunomodulators and antivirals in healthy challenge patients.

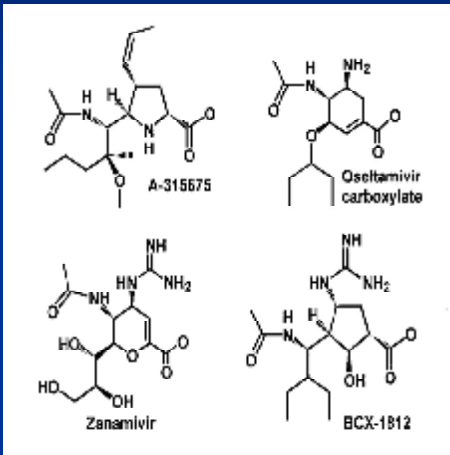
We need to develop immune-based therapies such as monoclonal antibodies, polyclonal antibodies, and polyclonal antibodies for therapy and prophylaxis, including monoclonal antibodies that target multiple proteins, so the virus will not escape by mutation of the targeted epitope.

We also need to consider polyclonal antibodies. New developments in polyclonal antibodies from animals with humanized immune systems might provide a passive therapy for pandemic influenza.

This slide shows examples of potent and specific inhibitors of neuraminidase of various viruses, influenzas A and B. They have different potencies according to the viral subtypes. Some are available and some are investigational. Thus there is a pipeline of long-acting neuraminidase

inhibitors, including conjugated sialidase, HA inhibitors, polymerase inhibitors including siRNA, and protease inhibitors. However, the pipeline must be developed.

Inhibitors of Influenza A and B Virus Neuraminidases









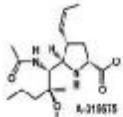
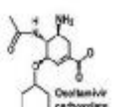
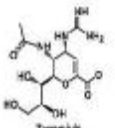
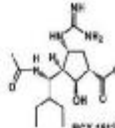
- Potent and specific inhibitors of influenza NAs in nM range
- Varied potencies for NAs of different types (A and B) and subtypes
- Zanamivir (Relenza™) and oseltamivir (Tamiflu™) are commercially available
- Peramivir (BCX-1812, RWJ - 270201) and A-315675 are investigational.

The longer-term goal is to support ongoing small molecule discovery programs. One with promise is siRNA as a systemic or topical antiviral; siRNA holds potential as a novel approach toward new antiviral targets, such as polymerases. We also need to address incentives for industrial partners, as it is very difficult for a drug company to suddenly pursue another antiviral.

Over the longer-term, innate immune effector molecules need development both as specific antiviral molecules, and also for general innate immune activation as a strategy for broad prophylaxis. We need to promote the development of innate-immune system based modulators of inflammatory cascades as alternatives to steroids.

What should we be doing now? One suggestion was to create a clinical trial infrastructure for therapeutics, including a uniform protocol for development and data capture. Some trials could be done in Southeast Asia. To develop a public health policy, we also need research on transmission and treatment factors. Such an effort would include operational research to define the optimal infrastructure for developing, stockpiling, and distributing efficacious antiviral agents as quickly as possible.

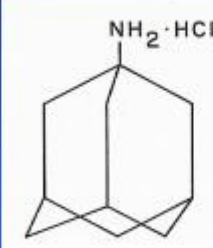
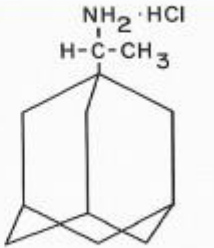
Working Group 4 Presentation Slides: Antivirals and Non-Specific Approaches, Treatments and Immunotherapies-Dr. Hackett, Rapporteur

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| <p style="text-align: center;">John R. LaMontagne Memorial Symposium on Pandemic Influenza Research April 4-5, 2005 Institute of Medicine</p> <hr/> <p style="text-align: center;">Working Group Four: Antivirals and Non-Specific Approaches, Treatments and Immunotherapies Research Recommendations</p>  | <p style="text-align: right;"></p> <p>Research Priorities: Short-term (1-2 Years)</p> <ul style="list-style-type: none"> • Clinical trial development for antivirals and immunotherapeutics <ul style="list-style-type: none"> • Develop pandemic protocols: now • Obtain data on virologic course, host immune responses, and response to therapy following human H5 infections and other potential pandemic infections • Safety and tolerability of available drugs: <ul style="list-style-type: none"> • Oseltamivir PK + tolerance in infants <1 yr • Determine PK and tolerability of IV/IM peramivir (parenteral drug) • Assess long-term (12-20 weeks) tolerability of oseltamivir and inhaled zanamivir prophylaxis • High risk patient populations: pregnant women, IC Hosts |
| <p>Research Priorities: Short-term (1-2 Years)</p>  <ul style="list-style-type: none"> • Study H5N1 resistance emergence in animal models and strategies for prevention • Assess probability of licensure for orally inhaled zanamivir for disease prophylaxis (because of oseltamivir resistance and two well controlled published studies) | <p>Research Priorities: Short Term (Years 1-2)</p>  <ul style="list-style-type: none"> • Accelerate drug development and discovery programs, including assessment of orphan drugs • Support Operational Infrastructure Research: <ul style="list-style-type: none"> • Clinical trials of drugs administered > 48 hours • Site of care • Drug deployment and response times • Research on physician use of antiviral agents • Test systemic approaches to influencing inflammatory cytokine expression in disease |
| <p>Research Priorities: Mid-term (2-5 Years)</p>  <ul style="list-style-type: none"> • Accelerated clinical trials of antivirals: <ul style="list-style-type: none"> • Test oseltamivir monotherapy vs combination with M2 or ribavirin or other novel therapies in high-risk population • Test therapeutic efficacy of parenteral peramivir in hospitalized influenza patients • Test prophylactic efficacy and tolerability of topical LANI • Develop contemporary virus challenge pools for studies of experimental human influenza <ul style="list-style-type: none"> • Test candidate immunomodulators and antivirals • Development of immune based therapies (mab's, polyclonal antibodies, etc.) for therapy and prophylaxis | <p>Inhibitors of Influenza A and B Virus Neuraminidases</p>  <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;">  <p>A-315675</p> </div> <div style="text-align: center;">  <p>Oseltamivir carboxylate</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: flex-start; margin-top: 20px;"> <div style="text-align: center;">  <p>Zanamivir</p> </div> <div style="text-align: center;">  <p>BCX-1812</p> </div> </div> <ul style="list-style-type: none"> • Potent and specific inhibitors of influenza NAs in nM range • Varied potencies for NAs of different types (A and B) and subtypes • Zanamivir (Relenza™) and oseltamivir (Tamiflu™) are commercially available • Peramivir (BCX-1812, RWJ-270201) and A-315675 are investigational |

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| <p>Investigational Anti-Influenza Agents</p> <ul style="list-style-type: none">● Neuraminidase (NA) inhibitors<ul style="list-style-type: none">- Peramivir (oral/IV), A-315675 (oral)● Long-acting NA inhibitors (LANI)<ul style="list-style-type: none">• R-118958 (topical), Flunet[®] (topical)● Conjugated sialidase<ul style="list-style-type: none">• Fludase[™] (topical)● HA inhibitors- cyanovirin-N● Polymerase inhibitors<ul style="list-style-type: none">• siRNA; ribavirin (aerosol/IV/PO)● Protease inhibitors<ul style="list-style-type: none">• Aprotinin | <p>Research Priorities: Longer-term (5-10 Years)</p> <ul style="list-style-type: none">● Support ongoing small molecule discovery programs<ul style="list-style-type: none">• siRNA as a systemic or topical antiviral• New antiviral targets and agents (e.g., polymerase)• Address incentives for industrial partners● Support innate immune effector molecule development:<ul style="list-style-type: none">• Surfactants• Mannose-binding lectins• Defensins● Support innate immune activation molecules<ul style="list-style-type: none">• TLR-3, 4, 7, 8, 9 agonists• NOD receptors● Promote the development of modulators of inflammatory cascades |
| <p>What Should Be Done NOW?</p> <ul style="list-style-type: none">● Clinical trial infrastructure for therapeutics<ul style="list-style-type: none">• Conduct studies in SE Asia now• Protocol development, data capture● Research on transmission and treatment factors to develop public health policy● Operational research to define the optimal infrastructure for distribution of drug, etc.● Stockpile oseltamivir or other efficacious agents● Develop antiviral agents as quickly as possible | |

(Slides available on accompanying CD)

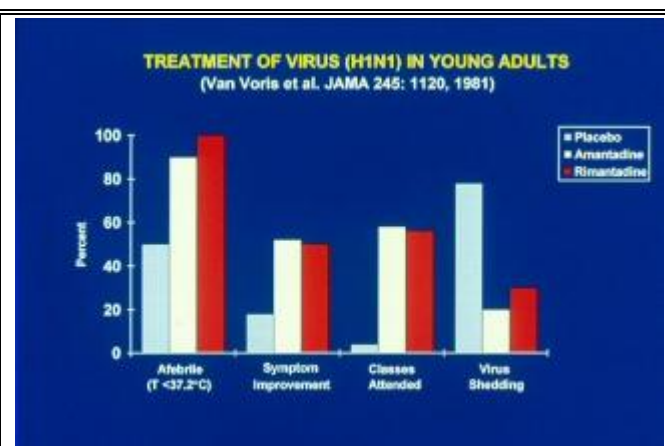
Working Group 4 Briefing Slides: Antivirals and Non-Specific Approaches, Treatments and Immunotherapies-Dr. Hayden, Briefer

| <p style="text-align: center;">ANTIVIRALS and IMMUNOTHERAPIES in PANDEMIC INFLUENZA</p> <p style="text-align: center;">IOM Briefing</p> <p style="text-align: center;">April 4, 2005</p> <p style="text-align: center;">Frederick G. Hayden, M.D. Division of Infectious Diseases and International Health University of Virginia School of Medicine</p> | <p style="text-align: center;">Antiviral Agents for Influenza</p> <table border="1"> <thead> <tr> <th>Class/agent</th> <th>Brand name</th> <th>Route</th> </tr> </thead> <tbody> <tr> <td colspan="3">M2 inhibitors</td> </tr> <tr> <td>Amantadine</td> <td><i>Symmetrel</i></td> <td>PO</td> </tr> <tr> <td>Rimantadine</td> <td><i>Flumadine</i></td> <td>PO</td> </tr> <tr> <td colspan="3">NA inhibitors</td> </tr> <tr> <td>Zanamivir (GG167)</td> <td><i>Relenza</i></td> <td>Inhaled</td> </tr> <tr> <td>Oseltamivir (GS4104)</td> <td><i>Tamiflu</i></td> <td>PO</td> </tr> <tr> <td>Peramavir (RWJ-270201)*</td> <td></td> <td>PO</td> </tr> </tbody> </table> <p>*Investigational in USA</p> | Class/agent | Brand name | Route | M2 inhibitors | | | Amantadine | <i>Symmetrel</i> | PO | Rimantadine | <i>Flumadine</i> | PO | NA inhibitors | | | Zanamivir (GG167) | <i>Relenza</i> | Inhaled | Oseltamivir (GS4104) | <i>Tamiflu</i> | PO | Peramavir (RWJ-270201)* | | PO | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|----------------------------------|---------------------|---------------------|----------------------|----------------|-----------|-----------------|------------------|-----------|-------------|----------------------|--------|----------------------|-----|----------------------|-------------------|----------------|---------|-------------------------------------|----------------|----|-------------------------|------------|--------|-----|--------|---------------|----------|-----|-----|---|-------------|-----|-------------|----------|-------------------|-----|-----|----|----|-----|---------|----|-----|-----|---------------------|----------|-----|-----|----|--------------------|
| Class/agent | Brand name | Route | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| M2 inhibitors | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Amantadine | <i>Symmetrel</i> | PO | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Rimantadine | <i>Flumadine</i> | PO | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NA inhibitors | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zanamivir (GG167) | <i>Relenza</i> | Inhaled | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oseltamivir (GS4104) | <i>Tamiflu</i> | PO | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Peramavir (RWJ-270201)* | | PO | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>AMANTADINE</p> </div> <div style="text-align: center;">  <p>RIMANTADINE</p> </div> </div> | <p style="text-align: center;">Amantadine Prophylaxis During Pandemic Influenza</p> <table border="1"> <thead> <tr> <th rowspan="2">Pandemic</th> <th colspan="2">Protective efficacy</th> </tr> <tr> <th>Influenza A Illness</th> <th>Seroconversion</th> </tr> </thead> <tbody> <tr> <td>1968 H3N2</td> <td>59-100%</td> <td>28-52%</td> </tr> <tr> <td>1977 H1N1</td> <td>31-71%</td> <td>19-39%</td> </tr> </tbody> </table> <p>Hayden. J Infect Dis 176:S56, 1997</p> | Pandemic | Protective efficacy | | Influenza A Illness | Seroconversion | 1968 H3N2 | 59-100% | 28-52% | 1977 H1N1 | 31-71% | 19-39% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pandemic | Protective efficacy | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Influenza A Illness | Seroconversion | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1968 H3N2 | 59-100% | 28-52% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1977 H1N1 | 31-71% | 19-39% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p style="text-align: center;">Chemoprophylaxis of Epidemic Influenza</p> <table border="1"> <thead> <tr> <th rowspan="2">Strategy</th> <th colspan="3">Efficacy (vs placebo or no drug)</th> </tr> <tr> <th>AM/RM</th> <th>ZNV</th> <th>OSEL</th> </tr> </thead> <tbody> <tr> <td colspan="4">Seasonal</td> </tr> <tr> <td>Non-immunized adults</td> <td>85-91%</td> <td>84%</td> <td>84%</td> </tr> <tr> <td>Immunized NH elderly</td> <td>58-75%</td> <td>?</td> <td>92%</td> </tr> <tr> <td colspan="4">Post-contact / post-exposure</td> </tr> <tr> <td>Households</td> <td>3-100%</td> <td>82%</td> <td>67-89%</td> </tr> <tr> <td>Nursing homes</td> <td>Variable</td> <td>Yes</td> <td>Yes</td> </tr> </tbody> </table> <p>?= No placebo-controlled study or not reported</p> | Strategy | Efficacy (vs placebo or no drug) | | | AM/RM | ZNV | OSEL | Seasonal | | | | Non-immunized adults | 85-91% | 84% | 84% | Immunized NH elderly | 58-75% | ? | 92% | Post-contact / post-exposure | | | | Households | 3-100% | 82% | 67-89% | Nursing homes | Variable | Yes | Yes | <p style="text-align: center;">Oseltamivir PEP in Households: Reduction in Influenza Illness, 2000-01</p> <table border="1"> <thead> <tr> <th>Contact Age</th> <th>No.</th> <th>Observation</th> <th>Osel PEP</th> <th>Efficacy (95% CI)</th> </tr> </thead> <tbody> <tr> <td>13+</td> <td>373</td> <td>8%</td> <td>2%</td> <td>74%</td> </tr> <tr> <td>1-5 yrs</td> <td>20</td> <td>36%</td> <td>22%</td> <td>39% (-211%, 88%)</td> </tr> <tr> <td>6-12 yrs</td> <td>109</td> <td>22%</td> <td>9%</td> <td>61% (-19%, 87%)</td> </tr> </tbody> </table> <p>Note: All index cases influenza-positive and treated with oseltamivir (ITT) Hayden et al. JID 189:440, 2004</p> | Contact Age | No. | Observation | Osel PEP | Efficacy (95% CI) | 13+ | 373 | 8% | 2% | 74% | 1-5 yrs | 20 | 36% | 22% | 39% (-211%, 88%) | 6-12 yrs | 109 | 22% | 9% | 61% (-19%, 87%) |
| Strategy | | Efficacy (vs placebo or no drug) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | AM/RM | ZNV | OSEL | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Seasonal | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Non-immunized adults | 85-91% | 84% | 84% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Immunized NH elderly | 58-75% | ? | 92% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Post-contact / post-exposure | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Households | 3-100% | 82% | 67-89% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nursing homes | Variable | Yes | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Contact Age | No. | Observation | Osel PEP | Efficacy (95% CI) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 13+ | 373 | 8% | 2% | 74% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1-5 yrs | 20 | 36% | 22% | 39% (-211%, 88%) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 6-12 yrs | 109 | 22% | 9% | 61% (-19%, 87%) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

AMANTADINE TREATMENT OF INFLUENZA A/HONG KONG/68 ILLNESS

| | Amantadine (n=72) | Placebo (n=81) | P-value |
|--------------------------------|-------------------|----------------|---------|
| Mean age, yrs | 37.4 | 39.1 | NS |
| Mean duration of fever, hrs | 46.6 | 75.1 | <0.01 |
| Mean duration of symptoms, hrs | 102.7 | 111.7 | >0.1 |
| > 5-fold rise HAI titers, % | 76.3 | 74.4 | NS |

Amantadine dose = 100 mg q12h for 7 days
 Galbraith et al. Lancet II:113, July 17, 1971



Antiviral Treatment of Influenza

| Outcome | AM/RM | ZNV | OSEL |
|----------------------------------|---------|-----|--------|
| Symptom relief | Yes | Yes | Yes |
| Prevention of complications | ? | Yes | Yes |
| Decrease antibiotic use | ? | 28% | 24-40% |
| Decrease hospitalizations | ? | ? | ~50% |
| Treatment of viral complications | ? | ? | ? |
| Reduction in transmission | ? (30%) | ? | ? |

? = No placebo-controlled study or not reported

Oseltamivir Treatment: Effect on Hospitalizations

| | Hospitalizations | | % Reduction |
|---------------------|-----------------------|----------------------|----------------------|
| | Placebo | Oseltamivir | |
| Healthy adults | 5/662 (0.8%) | 3/982 (0.3%) | 60% |
| High-risk + elderly | 13/401 (3.2%) | 6/368 (1.6%) | 50% |
| Total | 18/1063 (1.7%) | 9/1350 (0.7%) | 59% (P=0.019) |

Kaiser et al. Arch Intern Med 163:1667, 2003

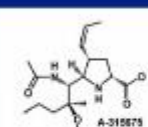
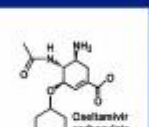
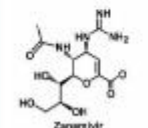
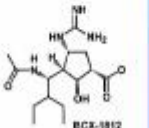
Oseltamivir and Complications: Retrospective Cohort Study, USA

| Outcome | Exposed | Unexposed | Adj. Hazard Ratio (95% CI) |
|------------------|-------------------|-------------------|----------------------------|
| Age 1-12 | (n=596) | (n=17,888) | |
| Pneumonia | 4 (0.7%) | 453 (2.5%) | 0.34 (0.13, 0.90) |
| Hosp. | 1 (0.2%) | 120 (0.7%) | 0.29 (0.04, 2.07) |
| Age 13-59 | (n=10,848) | (n=47,007) | |
| Pneumonia | 138 (1.3%) | 885 (2.1%) | 0.81 (0.68, 0.97) |
| Hosp. | 99 (0.9%) | 510 (1.2%) | 0.75 (0.60, 0.93) |
| Age 60+ | (n=952) | (n=1,388) | |
| Pneumonia | 8 (1.7%) | 290 (8.8%) | 0.41 (0.20, 0.82) |
| Hosp. | 10 (2.2%) | 163 (4.9%) | 0.55 (0.29, 1.05) |

Nordstrom et al. 44th ICAAC, abstr no. V-1260, 2004

Anti-Influenza Agents: Adverse Drug Reaction Profiles

| Agent | ADR | Severity | Freq | Dose-related |
|-------------|---------------|----------------|---------------|--------------|
| Amantadine | CNS | Mild- severe | 10-30% | Yes |
| | GI | Mild | Common | Yes |
| Rimantadine | CNS | Mild- moderate | <10% | Yes |
| | GI | Mild | Common | Yes |
| Zanamivir | Broncho-spasm | Mild- severe | Very uncommon | No |
| Oseltamivir | GI | Mild | Common | Yes |

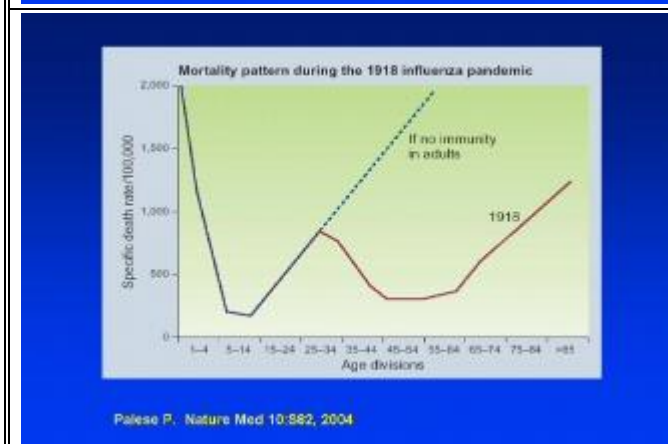
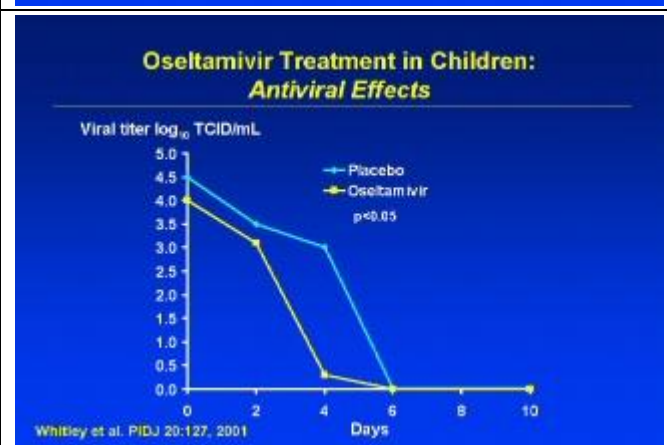
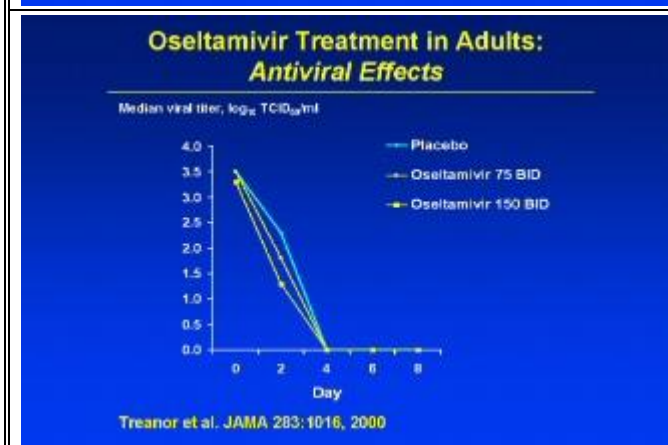
| <h3 style="text-align: center;">Influenza Antivirals: Pregnancy Risks</h3> <table border="1"> <thead> <tr> <th>Drug</th> <th>Embryo-toxicity*</th> <th>Terato-genicity*</th> <th>Pregnancy category</th> <th>Breast milk excretion</th> </tr> </thead> <tbody> <tr> <td>Amantadine</td> <td>Yes</td> <td>Yes*</td> <td>C</td> <td>Yes</td> </tr> <tr> <td>Rimantadine</td> <td>Yes</td> <td>Yes</td> <td>C</td> <td>Yes</td> </tr> <tr> <td>Oseltamivir</td> <td>No</td> <td>No</td> <td>C</td> <td>Yes*</td> </tr> <tr> <td>Zanamivir</td> <td>No</td> <td>No</td> <td>C</td> <td>Yes*</td> </tr> <tr> <td>Ribavirin</td> <td>Yes</td> <td>Yes</td> <td>X</td> <td>?</td> </tr> </tbody> </table> <p>* Animal models * Case reports in humans</p> | Drug | Embryo-toxicity* | Terato-genicity* | Pregnancy category | Breast milk excretion | Amantadine | Yes | Yes* | C | Yes | Rimantadine | Yes | Yes | C | Yes | Oseltamivir | No | No | C | Yes* | Zanamivir | No | No | C | Yes* | Ribavirin | Yes | Yes | X | ? | <h3 style="text-align: center;">Drug Resistance in Influenza A Viruses</h3> <table border="1"> <thead> <tr> <th></th> <th>M2 Inhibitor</th> <th>Oseltamivir</th> </tr> </thead> <tbody> <tr> <td>Magnitude of resistance</td> <td>High</td> <td>High</td> </tr> <tr> <td>Primary resistance</td> <td>1-2.5%</td> <td>No</td> </tr> <tr> <td>Frequency during therapy</td> <td>High</td> <td>Low</td> </tr> <tr> <td>Rapid development</td> <td>Yes</td> <td>Variable</td> </tr> <tr> <td>Person-person transmission</td> <td>Yes</td> <td>Not-to-date</td> </tr> <tr> <td>Pathogenicity</td> <td>Yes</td> <td>Reduced*</td> </tr> <tr> <td>Competition with wild-type</td> <td>Yes*</td> <td>Reduced*</td> </tr> </tbody> </table> <p>*Animal models</p> | | M2 Inhibitor | Oseltamivir | Magnitude of resistance | High | High | Primary resistance | 1-2.5% | No | Frequency during therapy | High | Low | Rapid development | Yes | Variable | Person-person transmission | Yes | Not-to-date | Pathogenicity | Yes | Reduced* | Competition with wild-type | Yes* | Reduced* |
|--|---|------------------|--------------------|-----------------------|-----------------------|------------|-----|------|---|-----|-------------|-----|-----|---|-----|-------------|----|----|---|------|-----------|----|----|---|------|-----------|-----|-----|---|---|--|--|--------------|-------------|-------------------------|------|------|--------------------|--------|----|--------------------------|------|-----|-------------------|-----|----------|----------------------------|-----|-------------|---------------|-----|----------|----------------------------|------|----------|
| Drug | Embryo-toxicity* | Terato-genicity* | Pregnancy category | Breast milk excretion | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Amantadine | Yes | Yes* | C | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Rimantadine | Yes | Yes | C | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oseltamivir | No | No | C | Yes* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Zanamivir | No | No | C | Yes* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ribavirin | Yes | Yes | X | ? | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | M2 Inhibitor | Oseltamivir | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Magnitude of resistance | High | High | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Primary resistance | 1-2.5% | No | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Frequency during therapy | High | Low | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Rapid development | Yes | Variable | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Person-person transmission | Yes | Not-to-date | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pathogenicity | Yes | Reduced* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Competition with wild-type | Yes* | Reduced* | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <h3 style="text-align: center;">NEURAMINIDASE INHIBITORS: Resistance Mechanisms</h3> <ul style="list-style-type: none"> • HA mutations <ul style="list-style-type: none"> – Mutations near receptor binding site – ↓ affinity of HA for sialic acid – ↓ dependence on NA for release • NA mutations- vary by type/subtype and drug <ul style="list-style-type: none"> – Framework- variable cross-resistance <ul style="list-style-type: none"> • Glu119 (→Gly, Ala, Asp, Val), His274Tyr, Asp198Asn – Catalytic site <ul style="list-style-type: none"> • Arg292Lys, Arg152Lys | <h3 style="text-align: center;">Antiviral and Immunotherapy Research Topics in Pandemic Influenza</h3> <ul style="list-style-type: none"> • Current agents <ul style="list-style-type: none"> – Decreased/increased dose and duration – Other risk populations; infants, pregnant women, immunocompromised, hospitalized – Delayed treatment benefit (>48 hr) • Parenteral route of administration • Resistance prevention and management • Combinations of antivirals • New antiviral targets | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <h3 style="text-align: center;">Oseltamivir Resistance In N1 Neuraminidase</h3> <ul style="list-style-type: none"> • Single nucleotide substitution (His274Tyr) <ul style="list-style-type: none"> → ↓ oseltamivir susceptibility (≥ 400-fold) • Frequency drug therapy <ul style="list-style-type: none"> – Children: 16% (7/43) – Adults: 4% (2/50) • Reduced replication in cell culture (≥ 2.0 log₁₀) <ul style="list-style-type: none"> – ↓ infectivity in mouse (1,000-fold) and ferret (100-fold) – Variable ↓ pathogenicity in ferret • Transmissible in ferret model <p>Ives et al. Antiviral Res 5:307, 2002 Herlocher et al. JID 190:1627, 2004</p> | <h3 style="text-align: center;">Inhibitors of Influenza A and B Virus Neuraminidases</h3> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  <p>A-315675</p> </div> <div style="text-align: center;">  <p>Oseltamivir carboxylate</p> </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 20px;"> <div style="text-align: center;">  <p>Zanamivir</p> </div> <div style="text-align: center;">  <p>BCX-1812</p> </div> </div> <ul style="list-style-type: none"> • Potent and specific inhibitors of influenza NAs in nM range • Varied potencies for NAs of different types (A and B) and subtypes • Zanamivir (Relenza™) and oseltamivir (Tamiflu™) are commercially available • Peramivir (BCX-1812, RWJ-270201) and A-315675 are investigational. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

NA Inhibitor Resistance Profiles

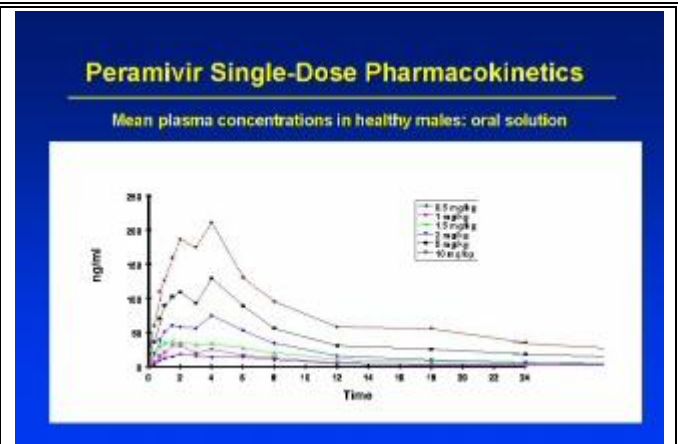
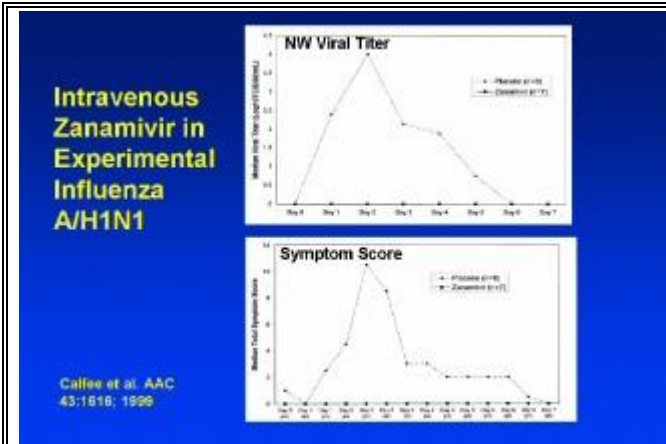
| NA mutation | NA type/subtype | Susceptibility in the NAi assay (fold Δ) | | | |
|-------------|-----------------|--|------------|-----------|----------|
| | | Oseltamir | Zanamivir | Peramivir | A-315675 |
| E119V | A/N2 | R (>50) | S (1) | S | S |
| R292K | A/N2 | R (>1000) | S (4-25) | R (30) | S (8) |
| H274Y | A/N1 | R (900) | S (1) | R (40) | S (3) |
| R152K | B | R (>30-750) | R (10-100) | R (>500) | R (150) |

Gubareva LV. *Virus Res* 103:199, 2004; Wetherall et al. *AAC* 41:742, 2003

- ### Antiviral and Immunotherapy Research Topics in Pandemic Influenza
- Current agents
 - Decreased/increased dose and duration
 - Other risk populations; infants, pregnant women, immunocompromised, hospitalized
 - Delayed treatment benefit (>48 hr)
 - Parenteral route of administration
 - Resistance prevention and management
 - Combinations of antivirals
 - New antiviral targets



- ### IV Zanamivir in Experimental Influenza A
- Double-blind, randomized, placebo-controlled
 - Healthy adults with serum HAI titers ≤ 1:8
 - IV zanamivir 600 mg q12 hr or saline starting 4 hr before intranasal inoculation with 10⁵ TCID₅₀ A/Texas/36/91(H1N1)
 - Nasal wash ZNV median 10-12 ng/ml
 - Outcomes (saline [n=8] vs ZNV [n=7]):
 - Infection- 100% vs 14%, P<0.005
 - Virus shedding- 100% vs 0%, P<0.005
 - URI- 100% vs 0%, P<0.005
- Calfee et al. *Antimicrob Agents Chemother* 43:1618, 1999



Absence of Interferon in Lungs from Fatal Cases of Influenza

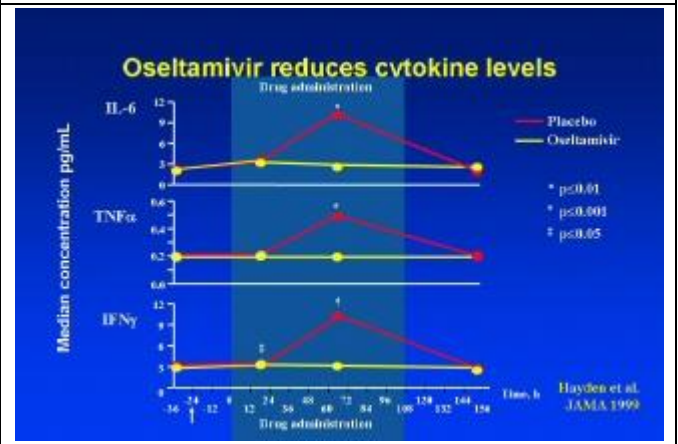
National Institute for Medical Research, Mill Hill, London

Interferon and Influenza, S Baron and A Isaacs, January 1962

Peramivir Phase 3 Treatment: Quantity of Viral Shedding

| Treatment Group | Days-log TCID ₅₀ /ml | P Value |
|-------------------|---------------------------------|----------|
| Placebo | 5.61 | |
| Peramivir 800/400 | -1.38 | P=0.0003 |
| Peramivir 800 | -1.92 | P<0.0001 |

- ### Potential Immunomodulatory Therapies
- Replacement of deficient responses
 - Stimulation of protective innate immune responses
 - TLR-4 agonists*
 - Modulation of immunopathologic host responses
 - Pro-inflammatory cytokines/chemokines/NO
 - Anti-TNF*, corticosteroids
 - Statins, fluoroquinolones, macrolides
 - Reactive oxygen species
 - N-acetylcysteine, allopurinol*, superoxide dismutase*
 - Potentiation of viral replication → combined antiviral and anti-mediator therapies
- *Beneficial in murine models of influenza



| | |
|---|---|
| <p>Research Priorities: Short-term (1-2 Years)</p> <ul style="list-style-type: none">• Obtain data on virologic course and host immune responses in human H5 infections• License orally inhaled zanamivir for prophylaxis• Study oseltamivir PK + tolerance in infants <1 yr• Determine PK and tolerability of IV/IM peramivir• Assess long-term (8 –12 weeks) tolerability of oseltamivir and inhaled zanamivir prophylaxis<ul style="list-style-type: none">– Trial in risk populations in SE Asia• Study H5N1 resistance emergence in animal models and strategies for prevention | <p>Research Priorities: Mid-term (2-5 Years)</p> <ul style="list-style-type: none">• Test oseltamivir monotherapy vs combination with M2 or ribavirin in high-risk population• Develop contemporary virus challenge pools for studies of experimental human influenza<ul style="list-style-type: none">– Test candidate immunomodulators and antivirals• Test therapeutic efficacy of IVIM peramivir in hospitalized influenza patients• Test prophylactic efficacy and tolerability of topical LANI• Trial combination of antiviral and immunomodulator therapy |
| <p>Research Priorities: Longer-term (5-10 Years)</p> <ul style="list-style-type: none">• siRNA as systemic or topical antiviral• New antiviral agents (eg, polymerase)• Innate immune effector molecules<ul style="list-style-type: none">– Surfactants– Mannose-binding lectins– Defensins• Innate immune activation<ul style="list-style-type: none">– TLR-3, 4, 7, 8, 9 agonists– NOD receptors• Modulation of inflammatory cascades | |

(Slides available on accompanying CD)

AFTERNOON DISCUSSION: REACTION TO RAPPORTEURS, DAY 1

DR. FINEBERG: I will introduce one question to get us started, and it relates to the opportunities for studies of pathogenicity, and the degree to which those studies can be conducted in a sense, on viruses free of hosts, or whether those studies have to be conducted always from the beginning, thinking about a particular virus and particular host.

When I was hearing the first group's discussion about pathogenicity and the studies of viral genome, it was not clear to me what the strategy would be vis-à-vis variety of hosts. And since it is evident in nature that different hosts, for the same virus, have different pathogenicity, how is it possible to study pathogenicity without automatically thinking of it in terms of the combination of a virus and a host?

So, that is the question. And if the presumption is correct, what does that imply about the complexity of a research strategy to investigate pathogenicity? So, let me put that on the floor and ask anyone who would like to comment.

PARTICIPANT: If I can just summarize very quickly, in Group 1 I think this was discussed. I think other people from Group 1 can chime in; it was discussed quite a bit. And there was certainly a feeling among a few physicians in the audience that it was hard to understand pathogenicity for human disease without humans somewhere in the process other than doing the experiment. We debated what model was the best model. After some debate, it was felt that the ferret model was everybody's bet as the best model--given no model is perfect

DR. FINEBERG: Could you say just a word about why immunologically or otherwise, the ferret seems to be a preferred model as a small animal for human study?

PARTICIPANT: I am not a ferret expert. I think what was said in the meeting was that by and large, virulence factors co-segregated between humans and ferrets, so that viruses that tended to have a phenotype in humans, also tended to have that in ferrets more than in other models. I think there was the acknowledgement that some models, for example pigs, hadn't been tested to the degree to know whether they might be better than ferrets. But by and large, it was felt that ferrets were more reflective than say mouse. And there was also a strong feeling in the meeting that mice, which lacked the Mx system, that part of their immune response, and specifically their innate immune response, was quite distinct from what goes on in humans. And that might really throw things out of kilter.

PARTICIPANT: I was also in Group 1, another point that I would make is that I think we all agreed on is that any sequencing data and attempts to correlate sequence with virulence need to be accompanied by very careful and detailed clinical histories of the individuals from whom these samples were obtained. So, there was an epidemiologic link to the genomics was very important to all of us.

PARTICIPANT: I wanted to make a comment to kind of drive us away from the pathogenicity discussion. In regards to the third and fourth presentations, which I think were the

fourth and third groups, both of them touched on something that I thought was incredibly important, and in some ways I wish they had gone further with it.

The third group talked about operational infrastructure research. And the fourth group talked about animals, the need for surveys of knowledge, attitude and practice among people who raise poultry, the development of economic incentives, and the development of educational programs all of which are subject to research. I think that as part of our long-term research strategy, we should be putting much more effort than we have into the non-biologic aspects of a pandemic, because there are factors that strongly influence the spread of a virus, and the ability to control the spread of a virus that really have very little to do with pathogenicity and with hosts and molecules and all those areas that we, as scientists, drawn to. I also think that if a pandemic emerges, we will not lose so many people to Tamiflu resistance as we will to the fact that they did not understand the importance of basic hygiene or they did not have access to personal protective equipment. I think those are factors that determine how a pandemic flows.

I also think that the type of research that we need to do will have to draw much more heavily on some people who we do not usually partner with. We need to talk to the people who know about immune modulators, but also the people who know about health education, and the people who know about international trade law, the people who know about organizational dynamics, some of the factors in getting these drugs out to the field, getting the supply chain, which we heard about earlier today.

Those are issues that we have not spent the time researching. It is a much more basic set of questions that we have. In contrast, we have gone very, very far with research on some of the biologic questions.

PARTICIPANT: I would like to return to the previous discussion, if we could, and maybe ask the group if there is any information that we can glean from historical perspectives of pandemics. Over the past few months I have been trying to understand the future of the pandemics, and have gone back and pulled out a lot of the original work or writing that have been done. But I think there has been a lot of what I would call also folklore around previous pandemics. And when you really start to peel the onion and look at what's there, it is clear that 1918 was not unique. It looks like 1830-1832 had a very similar picture of deaths primarily between 20 and 35 year olds, and a very classic W shaped curve again, just like we saw in 1918. Whereas, if you get into the 1880, you get into the other ones, there are at least 10 in the last 300 years; they really fall into two camps, those that had the classic accelerated or exaggerated Y shaped curve, and those that had the W shaped curve. Which would suggest to me, that there are several mechanisms for pandemics to occur?

The underlying necessary cause of a pandemic is a new virus for which there is a lack of overall population-based immunity. Pathogenicity is by definition, the virus' ability to cause disease. Virulence defines the virus' ability to cause severe disease. The virulence factors may determine which type of pandemic it is.

In other words, is it one of the W shaped curve, or the accelerated or exaggerated Y shaped curve? The answer has tremendous implications for how we deal with it, because one is probably more of a secondary bacterial pneumonia type picture and the other not. I think that this area needs a lot more research because we have artificially lumped all pandemics under one category, when in fact they may be of a common origin, but not of common outcome or cause. Perhaps an historian in this area could comment on it.

PARTICIPANT : One of the problems with deciding whether there will be another 1918 or not is that there will never be another 1918, because 1918 was a year replete with secondary bacterial pneumonia in many of these victims. We talk about the high mortality in that year. It was also true that 98 percent of the population had ordinary three day fever and flu. In addition, the summer of 1918 was an unusually cold one, in which case there would be more people indoors and the possibility for more abundant transmission and so forth. Another point about another 1918 is again, it is not 1918. We have learned a great deal. We know how to make vaccines. We know what kind of virus is causing this; we have antivirals.

PARTICIPANT: I think these points are really good. The point that I would make to that is that I think we really have to consider in a sense each pandemic as a unique event. And if you have a unique circumstance--when a unique virus emerges that can circulate in humans--that is going to be different from one pandemic to another in terms of what has happened in the past, what kind of other strains have circulated in the past, and what the immunity in the population by different ages would be. So, I think that we should not generalize. It is clear going back to the molecular biology, looking at the genetics of the 1918 virus versus the 1957 or 1968 virus is clearly where we are seeing differences by which pandemics may emerge, and clearly that is a useful model.

Another difficulty, however, is that even just looking at 1918, with all the work that has been done for 80 years on this virus; we are still missing so much of the primary data that we really need to understand what happened. We have no pre-1918 human samples to study. We have no sera collected before 1918; we are never going to have those data. And if we are not going to have data before 1918, it is going to be very, very difficult to go back to what happened in the very distant past. So, we have the epidemiologic evidence that exists, and we can use that data to sort of tease out hypotheses. But the problem is that going back in the past is going to be extremely difficult to develop experimental models.

DR. FINEBERG: It seems that the fundamental problem in one sense is that the time horizon for an observation--a pandemic--goes back centuries to obtain a handful of type of observations. And in our lifetimes, where we are accustomed to looking at organisms that turn over in the hours, rather than units of observation that take decades or centuries to become apparent, we are not accustomed to thinking as cautiously as you are now advising us about generalizing from such a paucity of real observation. And I think that is a pretty important caution. At the same time, the premise of all of our work on thinking of a research strategy has to be that we believe what we learned from the past can help us in the future. And so, being modest about it, and being properly qualified I hope at the same time will not deter us from making the effort that we are all engaged in today. And I know you certainly wouldn't want that to be the case.

PARTICIPANT: I think a very important point was made, and was made very quickly, and that is about the usefulness of having challenge strains available, contemporary challenge strains of virus. Economically, this can be very cost effective to do this, because instead of having to go to complicated and very costly and dangerous clinical trials, it means that you could develop at least attenuated strains of contemporary viruses to have those available. I say this with feeling, because I have recently been through an experience with a clinical trial where an up-to-date strain was not available. So, we came away with the conclusion that we could not affect enough of a control population to come up with any kind of answer. So, I think cost effectively, this would be very important.

DR. FINEBERG: Let me ask a question of the group who were reporting on the development of antivirals. The timeframes of that set of studies struck me that one would really have to look quite concretely and specifically at the state-of-science for each line of activity that one is thinking about. I wonder if anyone in that group could comment to help us understand where, if the group did discuss this, the most promising direction of development might rest today, and where things were still at a much more speculative stage across that list that we saw arrayed.

PARTICIPANT: As everybody is aware, there is a relative -- and I just say relative paucity of drugs in the pipeline that are unique and different for the treatment of influenza infection. There are several that are available, but they have not been studied appropriately in high risk patient populations. We have tried to emphasize that, and quite honestly, it can be done immediately. That includes evaluating drugs like oseltamivir in infants less than 1 year of age.

There is a fundamental problem that we have, and that is the pre-clinical animal toxicity data would imply that oseltamivir is toxic for the newborn brain in a rat model. We have to understand how we can circumvent that problem. And if we can not, we have to find a back-up drug such as peramivir. Peramivir has gone through phase 3 studies. It is not orally bioavailable. It can be given parenterally. It is available for a group to develop as quickly as possible. After that, then it becomes a question of the long acting neuraminidase inhibitor applied topically, or alternative strategies. But there are clearly two or three clinical protocols that could be developed and implemented within a short period of time.

PARTICIPANT: These drugs are available and could be studied in next influenza season. There are other possible approaches that presumably in the next year or two could be undertaken with regard to looking at resistance emergence strategies to reduce the combination therapies with antivirals. Another point of discussion within our group was the need to start studies of the available drugs to determine their impact, and their dose-related impact on some of the important outcomes in H5 disease in South Asia.

DR. FINEBERG: Yes, I thought that point was really quite telling, as well as some of the others that emphasized the importance of proactive planning for clinical protocols at the time outbreak would occur. We learned the lesson from SARS on how valuable it would have been to have had those protocols in place, accepted and ready to go across a whole spectrum of geographic locations. I think that is something that could definitely be done in a short timeframe, and in preparation for the next flu season.

There is relatively little, as one looks at the list that we have arrayed so far, that actually would have a bearing on something that happens in the next 12 months. And I think the reality of all of us in thinking about the importance of a research strategy is ultimately to work it back to what we can do in what timeframe to provide the kind of preparation, preventive and ameliorative strategies that we all know are going to be needed.

The discussion that we have had is of course premised on the great worry of the grand pandemics. But a lot of what we are talking about truly is going to be relevant year after year to endemic influenza that is still underappreciated as a significant source of mortality and morbidity in countries all around the world. So, I think there will be a true value coming out of this discussion, even if we are fortunate to not experience for some time, any of the greatest threats that worry us.

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PLENARY SPEAKERS, DAY 2

MODELING AND PANDEMIC PREPAREDNESS,

**Professor Neil Ferguson, Professor of Mathematical Biology,
Faculty of Medicine, Imperial College of London**

I am not going to cover the whole gamut of modeling related to pandemic influenza, as the list of potential modeling questions is long. I will focus principally on whether can we contain pandemics at their source. In this case, the principal threat is an H5N1-based pandemic emanating from Southeast Asia. Models can address many other questions with the right sort of data. A particularly relevant question, given recent experience with SARS, is whether restrictions on people's movements—such as on international travel—can delay the international spread of a pandemic. I will touch on that topic at the end.

In thinking about preparedness, we might ask how fast a pandemic strain might spread within a country. What will the health care burden be? How can we best use antivirals to reduce mortality and morbidity, protect key personnel, reduce social disruption given significant mortality, and reduce disease attack rates while we prepare a vaccine? More difficult to model than the impact of antivirals is the role of measures to increase “social distance”—such as closing schools or limiting travel within a country—in slowing the spread of disease or reducing attack rates. Models clearly need to capture the logistical constraints and resource limits that always affect such policies. Because we will not know the characteristics of a given influenza strain until a pandemic occurs, we also need real-time techniques for refining model estimates, and potentially even public policies, once a pandemic starts.

What do we need to contain a pandemic at its source? That ambitious goal will require early detection of a pandemic strain along with well-planned and rapidly executed responses. Containment is probably feasible only if we detect the emerging pandemic at its earliest stages—for instance, after a cluster of a few cases has emerged in a village in rural Vietnam or Thailand, for instance..

Containing a potential pandemic at its earliest stages is perhaps made more feasible with the knowledge that transmissibility of a pandemic strain may evolve incrementally, requiring many additional changes after the initial reassortment or mutation event. If the pandemic strain which emerges initially has a value of R_0 (the reproduction number) which only slightly exceeds the critical threshold of 1—that is, only one secondary case ensues from each primary case—then spread, while inevitable, will be slow, giving us time to respond.

What are our options? Compared with the past, there are more possibilities. In particular, prophylactic use of antiviral drugs is a potentially key measure to reduce spread. Vaccination will also clearly play a key role if vaccine is available. Other public health measures include those that increase social distance. Here I focus on identifying combinations of control measures

capable of controlling the earliest stages of a pandemic, assessing how sure we can be of the outcome of a containment strategy, and quantifying the resources which would be necessary to deliver these measures.

We have undertaken modeling to address such questions as part of a study called Models of Infectious Disease Agents Study, (MIDAS), funded by the National Institute of General Medical Sciences in NIH. The project includes three basic research groups, one at Virginia Tech led by Dr. Steve Eubank, one at Emory led by Dr. Ira Longini, and one at Johns Hopkins led by Dr. Donald Burke. I am part of the latter study, which includes researchers at Imperial College. I will talk about the work I have been doing with Don's group in modeling pandemic spread in Thailand. Ira Longini has been working on the same topic, and we hope that both these studies will be published in the next few months.

I will talk a bit about the structure of our model and its frailties and assumptions. A key difference between this model and many infectious disease models in the past is its scale. Our approach is to simulate entire countries as realistically as possible, so our computationally intensive simulation models a population of over 85 million. We tried to capture social structure by modeling individuals and households, because—as with many other infectious diseases—households are key location for transmission of influenza. Transmission of influenza also occurs within peer groups at schools and workplaces, and a separate component of the model captures those. We also know that community-based journeys to shops and other locations in the country are key to the longer-range spread of the pathogen. The model captures those by modeling a random contact process between individuals in the population that depends on distance.

We can think of the population as a set of individuals residing within households, in which adults travel to workplaces and children attend schools. An important aspect of this model is data we have collected on how far people in a household typically travel to schools or work. Thus the model tries to capture both the social structure and the real geography of populations—both of which are key to understanding and predicting the spatial and geographic spread of an emergent strain.

How do we simulate the population? We use probably the most detailed dataset available on global population density, called Landscan, which is now being used in Iraq and was used for the tsunami relief effort. This dataset, prepared by Oak Ridge National Laboratory, gives sub-kilometer data on population density globally. We clearly do not know precisely how many people live on every square kilometer of the planet, but the Landscan predicted density figures have been validated using remote-sensing as well as census data. One output of the simulation model we have constructed is maps of population density, which use colour to represent reas of the modeled region in which infection is present or treatment being undertaken..

Capturing age and household structure are also critical for realistically modeling influenza transmission, and the model incorporates data we have collected for Thailand. We chose Thailand not because we felt it was the country of highest risk for emergence of a pandemic, but because it is representative of Southeast Asia, and data on population structure and movements in that country are available. However, we intend to generalize the model to examine Vietnam, among other countries.

The model also incorporates school and workplace demographics, including the distribution of school and workplace sizes. Dr. Derek Cummings at Johns Hopkins collected these data, which are also important for realistically describing disease transmission.

Most critical is capturing the movement of people. To do so, we use data from the Thai national migration survey, which asked a sample of people the distance they travel to work. The cumulative probability distribution function for those data is typical of many countries: most people travel a very short distance to work, but the distribution includes a fat tail—some people travel tens of kilometers or even 100 kilometers. The distribution of individuals going to school includes a distance cutoff, as students clearly do not travel quite so far to school as adults do to work. Although sample size is limited, the curve is similar to that seen in other countries, so we have some confidence in it. The model also captures the proportion of the population that is working.

The transmissibility of the pathogen will determine the outcome or feasibility of containment policies for pandemic influenza. To investigate this, we are aided by work done by Dr. Mark Lipsitch's group led by Dr. C.E. Mills in 2004, which tried to quantify the transmissibility of pandemic influenza in 1918 and came up with a range of 2 to 3 for R_0 . Our later work noted that this assumes a serial interval for influenza—the delay between one generation of infections and the next—of about 3.5 days. This value was also assumed by many other past publications, but relatively few data exist with which to back up the figure.

Reanalyzing the available data on the incubation period of influenza and the duration of infectiousness reduces that figure to perhaps 2.5 days, which paradoxically drops estimates of R_0 . Our revised estimates of R_0 for the pandemic waves in the United Kingdom in 1918 and 1919 peak at 1.8, and are considerably less most of the time. However, those adjustments do not mean that pandemic influenza will spread more slowly, because the doubling time of these epidemics remains the same. That is, if we reduce the serial interval and the reproduction number, then the overall rate of spread can remain constant.

The model tries to capture the natural history of influenza as realistically as possible. We are using current H3 and H1 influenza as our principal model. We are well aware that the H5-based pandemic may not show the same natural history parameters, and so are undertaking sensitivity analyses, but we felt it was best to root the model in what we know about human influenza. We are using data published by Moser et al. on the distribution of latent periods of the disease, which average about 1.5 days. The model also incorporates data on the distribution of infectiousness, and we tried to match the model to previous age-dependent attack rates of pandemics.

We base our assumptions on the effect of antiviral drugs on parameters estimated by Dr. Fred Hayden and by Dr. Ira Longini. Our baseline assumptions are that prophylaxis of uninfected individuals reduces their susceptibility by about 30 percent, and the infectiousness of infected people by 60 percent for as long as they are on therapy. A treated person also sees a 65 percent drop in the chance of becoming a clinically diagnosable case.

We assume that only about half of infections result in clinically identifiable disease. That means that should a pandemic strain of H5 emerge through reassortment, its virulence will be less than what we are now seeing. However, if the current human virulence of the avian H5N1 virus remained unchanged for an emergent pandemic H5 strain, severe clinical disease would actually occur in a much higher proportion of cases. Our assumption of the 50 percent clinical case rate is thus quite pessimistic from the perspective of case ascertainment. Our assumption that treatment reduces someone's chance of becoming a case by 65 percent reduces the average infectiousness of infected individuals still further.

A simulation model can examine almost any policy. We concentrated on a combination of three: treatment of cases and prophylaxis of households; prophylaxis of schools and workplaces; and prophylaxis of everyone within a certain number of kilometers of a diagnosed case. The model can incorporate delays, detection thresholds, and limits on drug use, as well as the impact of measures to increase social distance. Currently I am less satisfied with our estimates of the latter, so I will not present results here.

All these assumptions yield a simulation of uncontrolled pandemic spread in Thailand. We assume that a pandemic will start with a single case in a randomly selected rural area—a reassortment or mutation event in an individual which will increase transmissibility and thus give rise to a growing cluster of cases. At a reproduction number of 1.5, we predict that the epidemic in Thailand will peak within about 120 days. The spatial spread is very fast. After a few hundred cases, we are almost certain to see cases emerging in Bangkok. Once the disease reaches Bangkok, it spreads to the rest of the country very rapidly, because Bangkok is highly connected to all other locations through travel.

The key results from this modeling exercise show the probability of containment as a function of the reproduction number of the pathogen. This analysis does not assume any particular level of transmissibility. Rather, it asks: what is the threshold level of transmissibility beyond which containment will be impossible, or below which containment is feasible? The results indicate that an perfectly implemented policy could achieve containment with a production number of 1.8 or less. As I showed before, that is a feasible range for what we now think the reproduction number of pandemic influenza might be. By perfect implementation, I mean a policy which is started 7 days after the first case of a pandemic strain, and where 90 percent of cases are detected and treated on the day they develop symptoms, 90 percent of their households are treated, 90 percent of their schools and workplaces are treated, and 90 percent of the general population within 10 kilometers of those cases is treated.

If antiviral containment is effective, it reduces the size of the outbreak to a small number of cases—a few hundred at most. The treatment course lasts 5 days, and the prophylaxis course at half the dose lasts 10 days. On average, containment is feasible with an average of under 1 million courses of drug. Even in the worst cases, the pandemic is containable with fewer than 3 million courses. Note that results are averages of a large number of runs of the model. Every run is different, so we have to run it many times to characterize the average behavior.

Perfect implementation is clearly an unrealistic best case, so I will show you briefly what happens when we start relaxing some of our perfect assumptions. One key issue is when we would recognize when a pandemic was potentially starting: that is, when a new cluster of cases in which efficient human-to-human transmission was occurring would be detected. We calculated the probability of containment as a function of whether we have detected the cluster after 0, 10, 20, or 30 cases. What is encouraging is that even if we require a single cluster of 30 cases to realize that the virus has changed, we still see about 95 percent containment under reproduction number (R_0) of 1.7, and 100 percent containment under R_0 of 1.6.

Some elements are critical to an effective policy. These elements do not include how quickly we identify the first cluster (given that the number of cases is somewhat limited, and that we detect the cluster within a month of the first identified case), but rather that once we start a policy we pursue it effectively. We identify new cases, treat them, and perform prophylaxis rapidly. The model also shows the impact of varying the time required to treat cases and perform

prophylaxis of the case's contacts. A two-day delay yields considerably less containment, and a four-day delay even less. For four days, we can contain the strain only up to an R_0 of about 1.2 (though despite the reduced effectiveness we still only need an average of under 1 million courses of treatment if the policies succeed). That's because for such a long delay, a whole generation of transmission has been missed, so we are constantly one or two generations of infection behind the pandemic. If we can reduce the delays to two days or less, we are treating people who have just been infected and prophylaxing on their contacts. Remember, I'm assuming a relatively short serial interval for this pandemic strain—about 2.5 days. If the pandemic strain has a much longer incubation and infectious period (as human cases of infection with the avian H5N1 virus currently have), policy effectiveness would be less dependent on very rapid case detection and prophylaxis.

We can also relax many of the assumptions at once and still see a policy that is capable of some degree of containment. One alternative shows a more realistic (but perhaps still optimistic) policy of a 14-day delay to initiation, 75 percent of cases detected, 80 percent of cases treated, 90 percent of households treated, and 90 percent of schools and workplaces treated. Given a two-day delay in all such treatment after a case is detected, we could still contain a pandemic with a reproduction number up to about 1.3 or 1.4.

Remember that I'm modeling purely an antiviral containment strategy. In reality, we would expect to combine that strategy with other measures, especially those that increase social distance. We can improve containment further by adding social distance measures to a prophylaxis-based policy. One example is a quarantine zone. That is, we restrict movement in and out of those areas where we are treating everyone. If we assume that such a policy could reduce traffic in and out of the treatment zone by 80 percent, then we could contain pandemics up to about a R_0 of 1.6. Importantly, such a measure makes containment more robust to uncertainty in key model parameters, including the proportion of transmission that occurs in schools and workplaces versus randomly in the community.

If that a containment policy succeeds, it does so by containing the disease in a relatively small geographic area, typically a small rural community in Thailand. We may see the occasional case further afield, but spread is generally quite tightly contained geographically. Thus the results from this modeling give some optimism in assessing the feasibility of containing a pandemic.

These results do assume that policies are transnational; i.e. implementation can cross borders. If a pandemic spark occurred at the center of Thailand, that wouldn't necessarily need to be the case for containment to succeed. However, if the original cluster arises in a border region, spread occurs rapidly across the border, meaning a containment policy which is implemented in one country only is doomed to failure. This reinforces the need for a concerted international response—probably with teams on the ground chasing cases.

While a pandemic will spread across land borders, air traffic will be probably be the most important mechanism for international spread in the next pandemic. Compared with 1918, travel capable of transmitting infection over long distances has grown 100-fold to 1,000-fold, and that trend is accelerating. As SARS showed last year, the increasing volume of international air traffic poses clear risks for the rapid spread of novel pathogens. Within a week of the arrival of the index case of SARS at the Metropole Hotel in Hong Kong, the disease had spread to multiple countries around the world.

We have been using a variety of models—both simple and complex—to examine the effectiveness of international restrictions and travel advisories on different pathogens. The conclusions, I have to say, are somewhat pessimistic. For influenza well as SARS, our analysis shows that we would need to reduce traffic by more than 99 percent to have a significant effect on the international spread of an emerging influenza pandemic. This is because when once 100 or 200 cases appear, there is a very high probability that at least one will be exported, owing to the international connectivity in these populations. Even if we reduce that connectivity by 90 percent, we would still need only about 1,000 cases in a source region before being reasonably certain that some export of infection will occur. And an influenza pandemic could entail tens of thousands of cases in the source country if containment is not successful. So while international restrictions might play a small role at the very earliest stages of a pandemic, when only a few dozen cases have appeared, such restrictions become almost irrelevant after a very short period of time. The source country will have so many cases and the world is so connected that we can delay the spread of disease by a week or two at most.

We are using expanded versions of the models of pandemic containment to quantify and predict rates of international spread. We are not quite at the level of global scale simulations, although we are discussing that. Instead, we are using a variety of simpler models to investigate global spread – in particular patch models, which divide the world into small areas and then model traffic between them. People often ask why pandemics emerge in China and Southeast Asia. The Landsat dataset map showing areas of high population density offers some insight into this.

Besides quantifying the international spread of influenza, the MIDAS initiative and various projects funded by the European Union are modeling pandemic preparedness options within the continental United States and Europe. These efforts are starting to address some of the questions about the optimal use of antiviral resources to limit mortality and morbidity. We hope preliminary results will be available this summer.

To conclude, our work indicates that a policy of antiviral prophylaxis combined with social distance measures is potentially capable of containing the early stages of a pandemic, but with some caveats. The reproduction number of the virus must be relatively low—less than about 1.8. However, we think that is realistic—particularly if transmissibility evolves incrementally—given our new estimates of the reproduction number of past pandemics.

We need to quickly identify the original cluster where efficient human-to-human transmission occurs. And we need to deliver treatment rapidly to a large proportion of the rural population. That is arguably the area most in need of development. Frankly, I'm skeptical about whether such an approach is possible right now. However, that is not necessarily a reason to rule out containment as a strategy, but rather a spur to improve the public health infrastructure. We also need enough courses of drug—perhaps as many as 3 million. If we end up using more than that, it is likely a containment policy will not succeed in any case, according to this model. We also need excellent case detection and rapid implementation of prophylaxis once the first cluster is identified. That implies that we can ramp up surveillance once a pandemic situation is declared. And we need policies to be transnational.

The policy modeled here entails many logistical hurdles. But given the potentially huge human and economic cost of a pandemic, those hurdles represent challenges to us to make a containment strategy feasible, not reasons to dismiss the strategy outright.

PLENARY SPEAKERS DAY 2

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(Slides not available)

CLINICAL TRIALS OF POTENTIAL PANDEMIC VACCINES: KEY ISSUES

**Dr. John Treanor, Associate Professor of Medicine and Microbiology and Immunology,
University of Rochester Medical Center**

One of the key features of pandemic planning is trying to prepare potentially effective vaccines. I'm going to briefly review what we have learned about evaluating such vaccines.

The most straightforward approach for controlling pandemic influenza remains the use of inactivated vaccines, because they have several potential advantages. This is a proven technology that has been used successfully to control pandemic influenza, and abundant efficacy data are already available from both pandemic and inter-pandemic years. A large safety database is also available, as these vaccines have been used in hundreds of millions of people. Thus we have a good idea of what we might expect in the way of side effects if such a vaccine were deployed on a very large scale.

Manufacturing capacity is also already in place. It clearly would not be sufficient to make enough vaccines for everyone in the world, but it is a very large. And, as mentioned yesterday, licensing such a vaccine—using a process already employed for conventional vaccination—would be relatively straightforward compared with some other approaches.

The inactivated vaccine approach does have disadvantages. It is unlikely to induce mucosal immunity, for example, and might therefore not be as effective at preventing transmission as some other strategies. The protection might also be fairly strain specific. Such a vaccine would be likely to induce little, if any, cellular immune responses, and would probably require at least two doses to prime a naive population.

Manufacturing capacity for the current egg-based vaccine strategies is also limited by the availability of eggs. And the facilities that make egg-based vaccines are fairly specialized. Cell-culture technologies would be one way around that, and we clearly need to pursue those vigorously.

Recent clinical evaluations have told us a bit about what future studies of inactivated vaccines should pursue. I'm going to describe them briefly. The strategies used recently have included the Duck Singapore. We have looked at recombinant baculovirus-expressed HAs, and a variety of studies are looking at both whole virus and split virus for H2N2 and H9N2.

Some of the first data came from Karl Nicholson and his group in England, who looked at egg-grown Duck Singapore as a potential vaccine for H5 influenza when the first outbreak was noted in Hong Kong in 1997. Duck Singapore is an antigenically-related H5 virus that does not have the highly cleavable hemagglutinin, and therefore could be used for vaccine production without the need for biocontainment.

One aspect noticed early on was that this vaccine is not particularly immunogenic. So Karl and his group looked at the Duck Singapore formulated as a subunit vaccine in doses of 7.5, 15, or 30 micrograms. They found very little response when looking at a neutralization of the H3N3 virus in microneutralization assay. Two doses of as much as 30 micrograms did not produce any significant response in neutralizing the vaccine virus. The finding that the addition of the adjuvant MF59 did result in significant increases was encouraging, although they are

relatively low titer. And for reasons that are still not completely clear, lower doses seemed to be slightly more immunogenic than higher doses when combined with MF59.

The other interesting finding was that the response was relatively strain specific. Because of containment issues, neutralization tests against the A-Hong Kong H5 were not done directly. Investigators looked instead at the radial hemolysis test. The vaccine did have a tendency—when adjuvanted with MF59—to induce antibody with much greater ability to recognize the Duck Singapore virus than the Human Hong Kong virus, which would be the target of the vaccine program. This is just an example of the observation that inactivated vaccines in an unprimed population are likely to stimulate an immune response that will be fairly specific for the actual antigen in the vaccine.

With Karl, Ian Stevenson recently noted a very interesting finding: despite the fact that these responses were relatively minimal and short-lived, significant responses occurred when these individuals were revaccinated 16 months later. The investigators revaccinated everyone in the study who agreed to that with the same vaccine formulation they had received in the first dose. The MF59 group, in particular, saw an increase in neutralizing antibody that was essentially gone 16 months later. But when these individuals received a single additional dose at 16 months, a very significant response occurred by neutralization against the H5N3 virus. This is a very encouraging finding from the point of view of strategies to provide a priming dose before beginning a vaccination campaign.

Those studies taught us about the need to develop standardized and validated surrogate markers of protection. We also learned that the responses to inactivated pandemic vaccines are likely to be strain specific. Adjuvants may play an important role in dose-sparing strategies for an inactivated vaccine. And the use of a pre-pandemic priming dose could generate a more rapid response in the face of an emerging pandemic. Particularly for MF59, the dose-response relationships may not be obvious, and may be more related to the relative ratio of MF59 in antigen than to the total dose of antigen.

At the same time, we did studies looking at recombinant hemagglutinin expressed in a baculovirus system as a vaccine. These were actually the first human trials of a vaccine for H5 in response to the 1997 outbreak in Hong Kong. These studies were possible because of the relative ease of expressing the hemagglutinin—even of a highly pathogenic virus using the baculovirus vector. The great advantage of this kind of approach is the speed with which we can come up with new antigens.

This very complicated study attempted to look at many things at the same time, including the dose of vaccine as well as whether administering the two doses 21, 28, or 42 days apart made any difference. We found that this vaccine was fairly effective in inducing antibody that recognized the baculovirus-expressed hemagglutinin in an ELISA system, although there was a clear-cut dose response, with the highest levels of response seen in individuals who received 90 micrograms. We also looked at as a dose-sparing strategy of giving a large priming dose and then boosting with a smaller dose. That did not work as well as two doses of 90 micrograms in inducing ELISA antibody. Jackie Katz performed these neutralization tests in a containment laboratory—an extremely tedious and difficult way to test lots of sera.

However, none of these vaccines were as effective as we had hoped in generating antibody that could actually neutralize the Hong Kong virus. Two doses of 90 micrograms generated, on average, neutralizing titers on the order of 1 to 32. Those are good but not great

titers, and that is encouraging, but that is a very large amount of antigen. Again, a 90-microgram dose followed by 10 micrograms was somewhat effective, and there was a clear-cut dose relationship in terms of the total amount of hemagglutinin and antigen used—the factor that largely determined the responses.

A very complicated algorithm was necessary for trying to decide whether someone had actually responded, because of the difficulties of doing the assay in the first place. This resulted in a very complex definition of a response: a 4-fold or greater increase in titer, to a titer of 1 to 80 or greater by neutralization, confirmed with a positive Western blot. Using those criteria, we found that even two doses of 90 micrograms resulted in a sera response rate of only slightly more than 50 percent of the subjects. The tests did show that immunization is possible but not particularly efficient.

We found that the interval—whether we measured antibody by ELISA or neutralization—did not appear to play an important role in the ultimate response. We saw just as good a response when two doses were separated by 21 days as when they were separated by 28 or 42 days. I can confirm that this vaccine appears to have 100 percent efficacy, because we have not noticed a single case of H5 influenza in any of the vaccine recipients! So that is encouraging news.

But again, this pointed out the technical struggles of doing the assays, and the fact that we have no way of knowing whether these vaccines would have been protective. There is a critical need for any clinical trial to develop well-validated and high-throughput assays, as we anticipate that we will be running many people through trials of candidate H5 vaccines. Getting a better handle on some of the immune responses and how to measure them is one of the critical needs in the field.

We found, however, that interval does not appear to be important, with the proviso that we did not look at the duration of antibody. It is possible that the interval could have had more of an effect on the duration of the antibody response or the development of immune memory. Future trials should probably evaluate those aspects. The expressed hemagglutinin looked like a promising approach, but that is not a validated strategy for influenza control. Pandemic planning should thus confirm whether this approach is actually effective in preventing conventional influenza.

One issue that the Duck Singapore studies and our studies have raised is whether there is something special about the H5 hemagglutinin that makes it intrinsically less immunogenic. I have no idea what the explanation for that would be, but we have noticed poor responses in human trials, and others have reported less-than-expected responses in some scenarios in animals. However, experience so far in humans has been extremely limited, and it is probably premature to conclude that we will not be successful with other vaccine trials with H5 viruses. Still, there might be something about the H5 that makes it intrinsically less immunogenic. I leave it to the immunologists to figure out what that would be, but I think that's an important question to answer.

Norm Hehme and others at GlaxoSmithKline have looked at vaccines for H2N2 viruses, because the next pandemic is likely to be an H2 virus, given previous human history. Those investigators examined two important issues. One is the immunogenicity and safety of a whole virus vaccine—not because it would be more immunogenic, but because it is more efficient to produce, and the yield might therefore be greater without the need for additional purification

steps. Another important issue is whether the addition of alum would help, given that it has been used for influenza vaccines in the distant past and is a readily available and widely used adjuvant for other vaccines.

The study design compared a 15-microgram dose of hemagglutinin in a split product or subunit vaccine formulation against lower doses of hemagglutinin administered with alum. When the researchers used HAI antibody against the H2 virus as the outcome, they found that responses to relatively low doses of hemagglutinin with alum approached but did not equal those seen with the 15-microgram dose. Adjuvant studies need to include truly comparable groups to determine whether the adjuvant itself is increasing the response.

When this group also did a similar study with H9 vaccines, they found that low-dose vaccine with alum appeared to induce responses comparable to those seen with unadjuvanted high-dose vaccine. More recently, Ian Stevenson and his group looked at whole virus and split unit vaccines for H9, and found that whole virus vaccines, particularly at lower doses, might be modestly more immunogenic. The interesting finding in that study was the difference in responses between older and younger individuals, with those over the age of 35 manifesting much better responses—particularly to the first dose of both whole virus and subunit vaccine. Those investigators found a very significant difference in the presence of pre-vaccination antibody against the H9 virus between people born before 1968 and those born after 1968.

Maria Zambon and her group did an extensive series of studies with reassortants to show that this specifically was antibody related to the H2, not a neuraminidase effect. This very interesting phenomenon might be relevant to other potential pandemic viruses.

We learned from this study that dose-sparing roles of adjuvants need to be evaluated by direct comparisons. We also need to consider whether further studies should consider the potential production advantages of whole virus vaccines. And we need to be aware of the potential impact of prior exposure on whether people may respond to a single dose.

The current study that Dr. Fauci alluded to yesterday entails an H5 inactivated vaccine. The goal is to use a virus generated using a process that would be considered a strain change, using a licensed production process. There are two candidate vaccines manufactured using as a seed virus the genetically engineered A-Vietnam strain produced by Dr. Richard Webby and Dr. Robert Webster. The first product is from Sanofi-Avantis and second is from Chiron. Both manufacturers used a production facility to produce subunit vaccines that are very similar in principle to the vaccines that these manufacturers are licensed to produce for conventional influenza.

Our study design is very detailed, because we want to be very clear about the safety of these vaccines before proceeding further. We screen individuals for clinical history and normal laboratory results prior to immunization. They are then randomized to receive either placebo or various doses of the inactivated vaccine, ranging from 7.5 micrograms to 90 micrograms. Although a 90-microgram dose might not be practical for pandemic control, we are hoping that by pushing the dose up, we can root this in the entire dose curve and ensure that at least some people manifest a meaningful response to vaccination.

Serum is obtained before and after vaccination, and clinical evaluation occurs 7 days after vaccine, along with safety labs. That information will be fed to a data safety monitoring board. If

the vaccine meets pre-specified safety rules, the second dose of vaccine will be administered on day 28, with the same type of follow-up in this preliminary group.

An additional cohort of subjects will be enrolled if the vaccine proves safe in the first cohort. The second cohort will be randomized to the same levels of vaccine but will not have laboratory safety. This will give us a total enrollment of 100 subjects in each group at each dose level, plus 50 placebo recipients. The latter are being added mostly to blind the laboratory in assessing the H5 antibody. Based on whether the vaccine is well tolerated, and which doses appear to be effective in generating an immune response, we will do further studies in both elderly subjects and children using the lowest dose that appears to be immunogenic in adults.

Overall, the goal in evaluating an inactivated vaccine is to find the lowest dose that results in a potentially protective immune response in the greatest proportion of people with an acceptable level of safety. Another important goal is to gain experience with the logistical challenges involved in producing a pandemic vaccine. Many of these challenges have in fact come up and have been solved. This learning process has been very important.

Going forward, we need to look at the potential advantages of a whole virus versus subunit vaccines, and to compare egg-grown vaccines with those made using cell culture or other substrates. Evaluating the dose-sparing capacity of adjuvants is critical, and alum and MF59 are the first candidates, because those are the two adjuvants licensed for use with influenza vaccine. We should also look at the schedule and route of administration, including not only inactivated vaccine but also intranasal, transcutaneous, and intradermal administration, again trying to reduce the dose.

We have looked a bit at intradermal vaccines for conventional influenza vaccines, using a clever device made by Becton Dickinson that nurses were able to use very effectively to deliver vaccine intradermally. That study was sponsored by GlaxoSmithKline.

The results—published by Dr. Robert Belshe in the *New England Journal of Medicine*—showed that an intradermal dose of 6 micrograms of hemagglutinin gave antibody responses in young adults very similar to those seen with an intramuscular dose of 15 micrograms. So essentially half the dose of vaccine given intradermally produced a response in terms of the geometric mean titer (GMT) of H1 antibody to both H1, H3, and type B influenza virus that was very similar to that seen with full-dose vaccine. Actually, the response rate was slightly less in those receiving the intradermal vaccine, and the titer was a little bit less. In individuals over 60, who interestingly did not manifest significant local inflammatory responses to the intradermal vaccine, this difference was more marked, and the intradermal approach did not appear to be as effective.

In interpreting this information, bear in mind that healthy adults respond well to low doses of vaccine administered intramuscularly. So it is premature to conclude that the intradermal approach is necessarily an advantage—that needs to be tested. In healthy adults, intramuscular doses of 7.5 micrograms and 15 micrograms do not produce markedly different results. So we need to look at these dose-sparing strategies again using comparable groups.

So, what have we learned in the process of doing these studies? We have learned that the assays for H5 antibody are insensitive, and that we need better assays. It is important to evaluate these vaccines in multiple groups—not just healthy adults but also children and the elderly. And we have to think about an acceptable level of safety, given that this vaccine is designed to protect

against a potentially extremely serious disease but will also be used on a very broad scale. What is an acceptable level of safety for a pandemic vaccine? Should we think about this in the same way as a conventional vaccine, or accept a broader safety profile, particularly in terms of local side effects? Considering local toxicity is important, because although whole virus, alum, and MF59 offer advantages in the studies done so far, all are associated with a significantly increased risk of local side effects, which could factor into the vaccine's safety profile.

I am going to talk only briefly about other potential approaches. They have not been tested yet in humans, so we have much less experience in designing studies. But we clearly need to consider live vaccines, for several reasons. One is that they are highly immunogenic in susceptible populations. Studies in unprimed, naive children show that these vaccines are extraordinarily immunogenic because individuals are susceptible to infection, and thus those vaccines could be used in highly diluted form. For example, a live vaccine approach could significantly increase the number of doses obtained per egg or per fermenter, because of the potential to use a much lower dose—probably just 10⁵ to 10⁶ PFU. These vaccines are clearly more effective at inducing mucosal immunity, and that might play an important role in their ability to reduce transmission.

What do we need to know? We need to know the correlates of immunity, particularly for live vaccines. We need to look at administering a full range of potential doses with live vaccines. It would be useful to use the live vaccines to develop a form of human challenge model for pandemic influenza, similar to the models that have been so useful for conventional influenza. This type of model would be especially important as we try to get an early signal as to whether candidate vaccines would in fact protect against protection and shedding. The live approach might also induce a broader and more cross-protective response against other antigenic variants within the same subtype—so-called heterosubtypic immunity. That issue needs to be investigated in both inactivated and live vaccines.

A problem with live vaccines is that they are not now licensed in all populations, for a variety of reasons. Facilitating licensure of attenuated vaccines for conventional influenza in a broader population, particularly children, would be extremely useful. We clearly need to obtain additional safety data in children, and to define correlates of immunity that could be extended to the elderly, given that these vaccines are not now licensed in that age group.





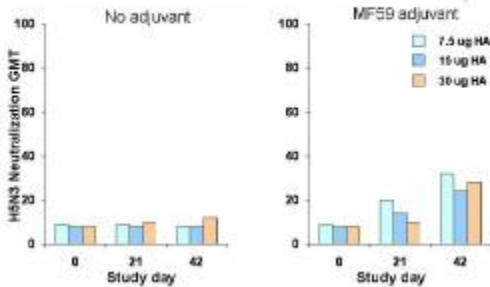
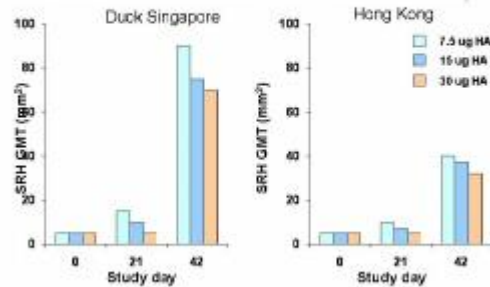
There are some concerns regarding transmission and reassortment. We need to clearly define the conditions of deployment, the expected shedding patterns, and the biological behavior of potential reassortants, to assess whether this is a real or perceived risk of a live vaccine.

Investigators are evaluating a number of more experimental approaches to combating influenza. Some, including universal vaccines and vaccines with cross-protective epitopes, have potential advantages for fighting pandemic viruses. Clinical evaluations should proceed, but we are further from knowing whether those vaccines will work, so I regard them as a long-term goal for pandemic preparedness. They will require extensive safety evaluation, as they are now in phase I: we do not know very much about them. For some, we will need to develop specific markers of efficacy, which may differ from those we use for hemagglutinin-based vaccines. And each will require an individualized development strategy.

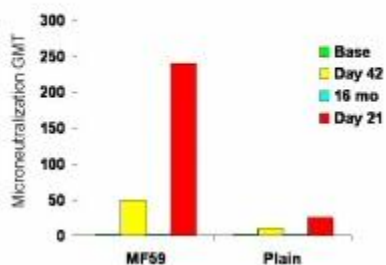
Devising a cohesive clinical development plan applicable to every vaccine will thus be difficult. However, it's useful to get early indications of whether these vaccines offer potential advantages over conventional approaches, so we can focus on those that are most worthwhile.

We need to take that step as soon as possible, potentially using the human challenge model as an early indicator of whether these vaccines have promise.

Plenary Presentation Slides-Dr. John Treanor

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| <h2 style="text-align: center;">Clinical Trials of Pandemic Vaccines: Key Issues</h2> <p style="text-align: center;">John Treanor University of Rochester Rochester, NY</p>  | <h3>Inactivated vaccine approach</h3> <ul style="list-style-type: none"> • Proven technology <ul style="list-style-type: none"> • Used successfully in 1957 and 1968 • Abundant efficacy data in both pandemic and interpandemic years • Very safe, with large safety database • Manufacturing capacity exists in potentially large scale • Licensing would be relatively straight-forward  |
| <h3>Inactivated vaccine approach</h3> <ul style="list-style-type: none"> • Unlikely to induce mucosal immunity <ul style="list-style-type: none"> • May be less effective in preventing spread • Protection may be strain specific <ul style="list-style-type: none"> • Little if any cellular immune response • Requires multiple doses • Manufacturing capacity limited by availability of eggs and capacity for expansion limited <ul style="list-style-type: none"> • Cell culture strategies might circumvent this problem  | <h3>Recent clinical evaluations of potential pandemic viruses</h3> <ul style="list-style-type: none"> • Duck Singapore/97 (H5N3) as a vaccine for Hong Kong/97 • Recombinant, baculovirus-expressed HA of A/Hong Kong/156/97 (H5) • Whole virion A/Singapore/1/57 (H2N2) and A/Hong Kong/1073/99 (H9N2) • Whole virion and subunit A/Hong Kong/1073 (H9N2)  |
| <h3>Egg-grown Duck/Singapore</h3>  <p>Nicholson et al/Lancet 357:1937, 2001</p> | <h3>Egg-grown Duck/Singapore</h3>  <p>Nicholson et al/Lancet 357:1937, 2001</p> |

Reimmunization with Duck/Singapore

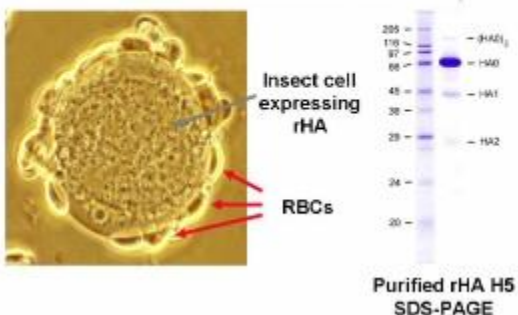


Stephenson et al, Vaccine 21:1627, 2003

Key issues [1]

- Development of standardized, validated surrogate markers of protection
- Responses to inactivated vaccines may be very strain specific – evaluation of strategies to broaden responses
- Adjuvants should be evaluated. Ratio of antigen to adjuvant may be important
- Pre-pandemic priming dose with heterologous variants should be explored
- Dose responses relationships may not be obvious

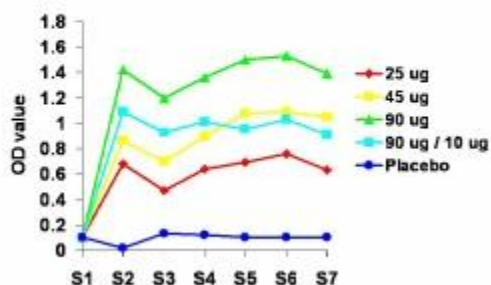
Recombinant rHA H5 Vaccine



Phase I evaluation of rH5

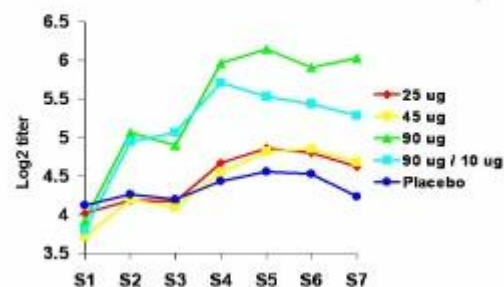
- Randomized to interval between doses (21, 28, or 42 days) and then to dose groups (90 ug, 45 ug, 25 ug, 90/10 ug, placebo) - Total of 15 groups
- Vaccine or placebo administered in total of 1 mL by i.m. injection
- Sera before and 14 days after dose 1, and before and 7, 14, 21, and 28 days after dose 2

ELISA vs. A/HK/156 virus

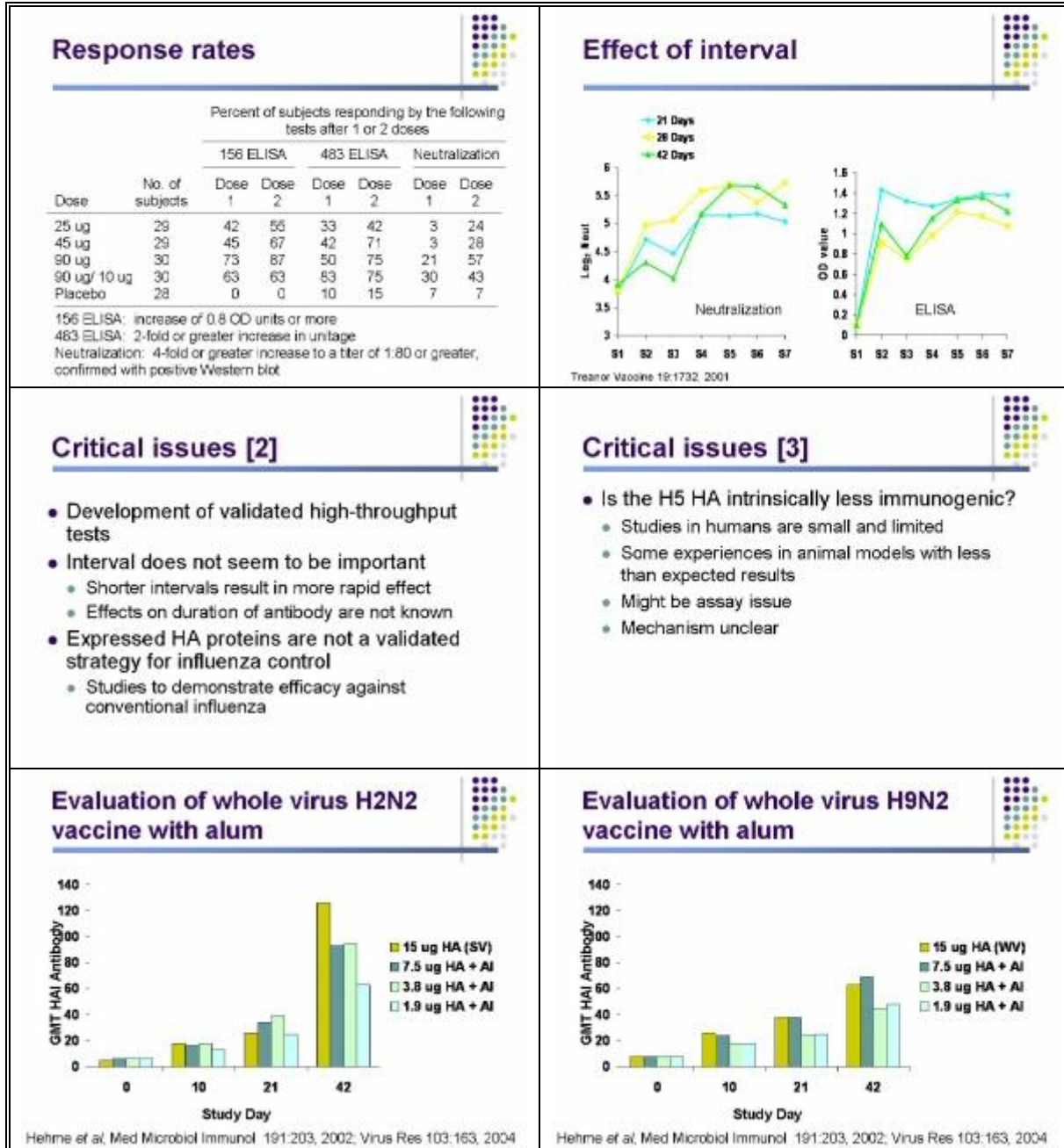


Treanor Vaccine 19:1732, 2001

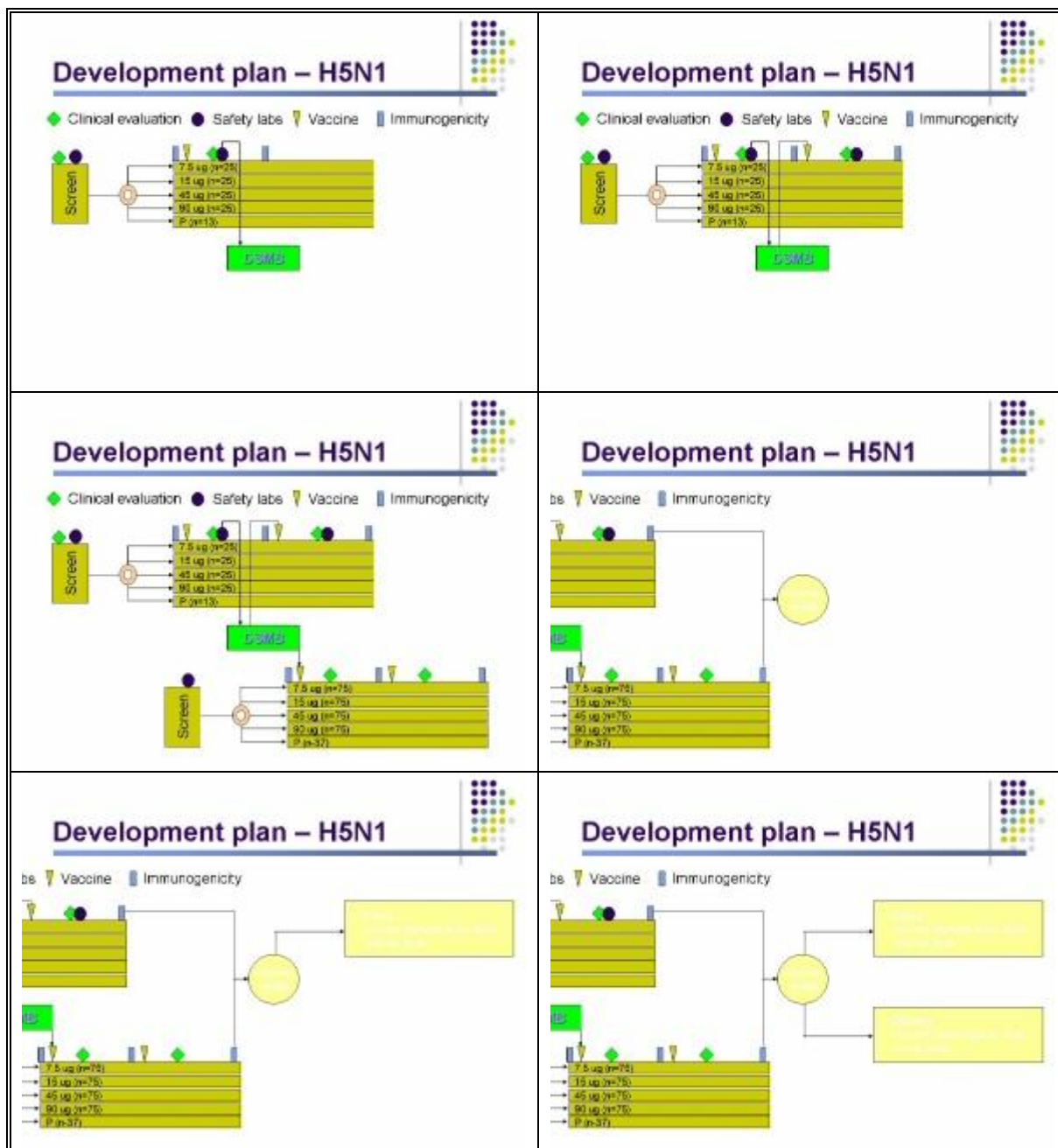
Neutralization titers



Treanor Vaccine 19:1732, 2001



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| <h3>Geometric mean 50% MN (H9N2) antibody titres to WV and SU vaccines</h3> <p>Stephenson Lancet 362: 1959, 2003</p> | <h3>Age effect on GMT HI responses</h3> |
| <h3>Effect of H2N2 exposure on H9N2 neutralizing antibody</h3> <p>Stephenson Lancet 362: 1959, 2003</p> | <h3>Critical issues [4]</h3> <ul style="list-style-type: none"> • Dose-sparing role of adjuvants should be evaluated by direct comparison of adjuvanted and non-adjuvanted vaccine • Do potential production advantages of WV vaccine warrant further evaluation? • Impact of prior exposure to related HA should be considered • Optimal testing strategy and results may differ between subtypes |
| <h3>Current H5 vaccine candidates</h3> <ul style="list-style-type: none"> • Seed virus reverse genetically engineered A/Vietnam • Manufactured by Sanofi Aventis and Chiron • Subunit vaccine • Represent new strain manufactured with licensed manufacturing | <h3>Development plan – H5N1</h3> |



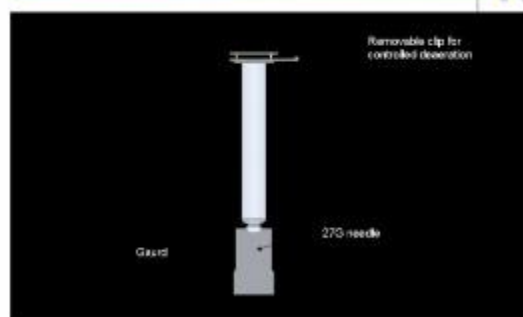
Evaluation of inactivated vaccines: Objectives

- Determine the lowest dose resulting in a potentially protective immune response in the greatest proportion of people with an acceptable level of safety.
- Gain experience with the logistical issues involved in producing a pandemic vaccine

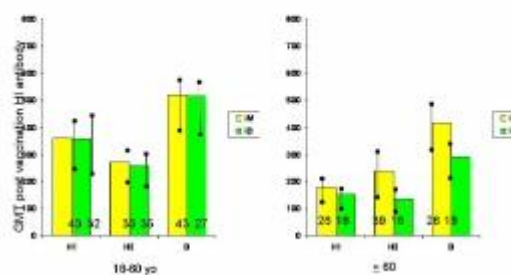
Find the lowest dose

- Whole virus vs. subunit
- Egg grown vs. cell culture or other substrates
- Adjuvants
 - Alum and MF59 are currently licensed
- Schedule and route of administration
 - Intradermal, transcutaneous, intranasal

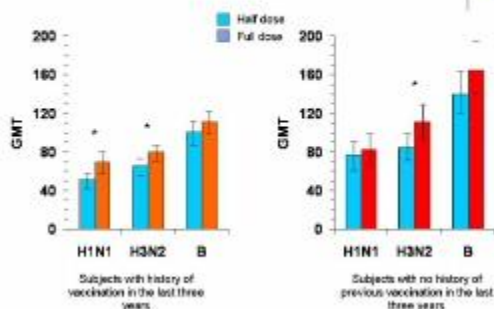
Device for intradermal vaccination



Intradermal vaccination: post vaccination GMT and response rate (%)



Responses to 15 ug or 7.5 ug IM in adults



Determine the immune response

- Assays: HI assay insensitive for avian viruses
 - Neutralization
 - SRH
- Protective levels not defined
- Role of mechanisms other than serum antibody are unknown

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| <p>Protect the greatest proportion of people</p> <ul style="list-style-type: none">• Majority of studies will be done in healthy adults• Safety and immunogenicity may be different in children• Evaluation of priming strategies• Need to evaluate pandemic vaccines in groups that respond poorly to conventional vaccine | <p>Acceptable level of safety</p> <ul style="list-style-type: none">• Defining acceptable safety parameters• Considerations of sample size related to detection rates for rare events• Safety considerations may favor conventional (licensed) approaches• Tolerability may be different in different populations |
| <p>Evaluation of live attenuated vaccines (CAIV)</p> <ul style="list-style-type: none">• Highly immunogenic in susceptible populations<ul style="list-style-type: none">• Critical need to define correlates of immunity• Potential use of low doses<ul style="list-style-type: none">• Studies should evaluate full range• Induction of mucosal immunity might reduce transmission<ul style="list-style-type: none">• Development of challenge models | <p>Evaluation of live attenuated vaccines (CAIV)</p> <ul style="list-style-type: none">• Potential cross protection<ul style="list-style-type: none">• Evaluate responses to range of antigenic variants• Not licensed in all populations<ul style="list-style-type: none">• Critical need to expand safety database• Define correlates of immunity that could be extended to elderly• Concerns regarding transmission and reassortment<ul style="list-style-type: none">• Clearly define conditions of deployment, expected shedding patterns, and biologic behavior of reassortants |
| <p>Experimental Approaches</p> <ul style="list-style-type: none">• Nasal inactivated vaccines• Cross protective peptides/epitopes• Virus-like particles• Alternative live vaccines• Vectored approaches• DNA Vaccines | <p>Considerations for alternate approaches</p> <ul style="list-style-type: none">• Validation in clinical studies• Extensive safety evaluation• Specific markers of efficacy• Individualized development strategy• Need for early determination of potential advantages against conventional approaches |

(Slides available on accompanying CD)

RESEARCH ISSUES IN ANIMAL SURVEILLANCE

Dr. Robert Webster, Professor and Chair, Department of Infectious Diseases, St. Jude's Children's Research Hospital

I would like to thank the organizers for the invitation to speak on this auspicious occasion in honor of John La Montagne. John was my first project officer; he came to Memphis for a site visit when we were preparing the reference antisera to influenza subtypes that are now in the NIAID bank. John held the old goat while I bled it. He was a fine human being.

I want to speak about surveillance. Surveillance in each of the regions with an H5N1 problem is critical. At the time of the meeting, we have recorded 70 human cases and 47 deaths—33 in Vietnam, 12 in Thailand, and 2 in Cambodia. This is an unprecedented event in the history of influenza, and we must contain this virus.

The difficulty of surveillance lies in obtaining the necessary viruses for analysis. We now know that the outbreaks of H5N1 occurred before 2004 in some of the affected countries, although they were not reported at first. The question of rapid reporting of H5 and H7 must be addressed. One barrier is trade embargoes: if a country reports cases of H5N1, it can hurt its poultry trade. Another factor is national pride: countries want to characterize their own influenza viruses as much as possible. We also need to build surveillance infrastructure in countries such as Lao and Cambodia so that viruses become available for analysis.

The different missions of the Food and Agricultural Organization (FAO), the World Organization for Animal Health (OIE), and WHO also pose challenges. Even today these organizations are not talking to each other in a satisfactory fashion—they are not fully sharing viruses or information. They must sit down together and harmonize their approaches.

H5N1 first occurred in Hong Kong in 1997. That city developed a strategy for dealing with the virus, and it has not seen H5N1 influenza in humans or poultry in 2004 or 2005. The rest of the world largely ignored Hong Kong's approach, which is part of the problem.

What did Hong Kong do to cope with the virus in 1997? It had limited infrastructure at the time—one small laboratory. The government quickly flew in the brightest young people from all over Asia as well as laminar flow hoods, and established a temporary isolation laboratory. The staff stayed on the ground to characterize those viruses, and continue to do so today. No infections occurred in any of these staff members. And the agriculture department, the health department, the university, and WHO collaborated successfully to control H5N1 influenza.

After SARS and the laboratory infection of humans, the advice given to countries that lack adequate infrastructure is: do not attempt to isolate viruses. In other words, Hong Kong should not have been isolating H5N1 viruses in 1997 but instead should have been using molecular techniques and reverse transcription-polymerase chain reaction, or sending samples to experts around the world. I think that advice is a mistake. We should have been building infrastructure in these affected countries from the word go.

What did Hong Kong do to achieve the continued absence of H5N1? The country made very simple changes in its agricultural and marketing systems. It banned ducks and geese from live markets, and after Daniel Perez found that quail were capable of replicating every strain of

flu, they were also banned. The country also introduced two clean days per month when all live bird markets were empty and cleaned. They also have instituted the use of inactivated H5 vaccine on poultry farms and have included nonvaccinated sentinel birds in each flock to monitor any virus spread. The result is no H5N1.

Why hasn't this system been copied throughout Asia? The response I usually get is that it's too expensive. Hong Kong can afford to take that approach, but other countries can't. It is too expensive to ban the sale of ducks, geese, quail in these live markets across Asia? Of course it's not. Such stalling indicates a lack of political will, and a reluctance to accept agricultural vaccines. International agencies have failed to promote very simple measures such as keeping ducks, geese, and quail out of live markets. Countries could still take these simple yet profound measures.

Let's turn to agricultural vaccines. We have been talking about vaccines for some time. The problem is that there is a double standard for vaccines. Human vaccines are standardized for antigen content, but agricultural vaccines are not. They are required to induce an HI antibody in poultry, and as a result there are good and bad agricultural vaccines.

Which vaccines are available at the moment, and which have been used in poultry? In Hong Kong, the commercial vaccine in use is based on A/Chicken/Mexico/1994 (H5N1). The homology in the hemagglutinin between this virus and the H5 currently circulating is about 94 percent, so the difference is large, but the vaccine is still effective. China is still using an old virus from 1973, H5N2. Indonesia is using an inactivated highly pathogenic strain, which is a dangerous practice.

Asia is seeing new developments in poultry vaccines. China has developed a fowl pox-based H5, and the United States has developed one as well. These are efficacious. China is developing a reverse genetic H5N1 on an H9N2 backbone, and in the U.S. we have developed a reverse genetic H5N3 on the PR8 backbone.

Good poultry vaccines provide protection despite the antigenic difference. The mechanism of this protection without close homology is not really understood, and we need to pursue this. Is chicken immunology different from human immunology?

These poultry vaccines do not provide sterilizing immunity. Maybe that is because of the lack of antigenic match. However, they can reduce viral load below the level of transmission. In Hong Kong, agricultural researchers have clearly shown that the vaccines now available reduce the load so that transmission does not occur.

Bad vaccines provide protection against disease signs. In other words, the chickens and ducks look fine in the markets, but the birds are shedding high levels or transmissible levels of virus. They thus promote the spread of virus as well as antigenic drift. The lack of regulation is disturbing.

The missing information on the spread of H5N1 in Asia, particularly in Vietnam, is the role of the domestic duck. Let's look at some of the information about ducks in Vietnam. Some 60 million ducks are now raised in Vietnam. Many are free range: these ducks don't go to a home every night; they move from one paddy field to another as rice is harvested, picking up residue grain. The peak numbers of free-range ducks in Vietnam occur in May and October, corresponding to the rice harvest. The plan is to reduce the number of ducks from 60 million to

40 million by banning commercial hatching. However, hatching will likely continue in backyard flocks.

We now know that duck raising increases the risk of H5N1 in both Vietnam and Thailand. Eight percent of households in Vietnam that raised only chickens were infected with serological evidence of H5N1, while 67 percent of households that raised only ducks were infected. Households that raised both ducks and chickens had a 70 percent infection rate. Thus households that raise ducks have infection rates that are eight times higher.

A similar figure has been established in Thailand. However, we should complement the Thais on their great success in containing the second and the third waves of the virus. In October 2004, 39 percent of duck flocks in Thailand tested positive for H5N1, but by February only 2 infected flocks were found. In March, none were detected.

What did Thailand do differently? As we heard yesterday, Thailand could afford to pay compensation to farmers, so it pursued an aggressive program to stamp out the virus. Perhaps the outside world should pay Vietnam to adopt the same strategy.

H5N1 has continued to evolve in ducks in Asia, incrementally increasing its most worrisome biological properties. In November 2002 the virus acquired the ability to kill waterfowl in Hong Kong. All the waterfowl in Kowloon Park in central Hong Kong, including flamingoes and other decorative birds, were susceptible and died of neurological infection.

In 2003 the majority of the H5N1 isolates around Asia were the so-called Z genotype, and they were highly pathogenic in ducks. By 2004, many of the duck isolates were non-pathogenic. Studies by Diane Hulse in my lab in Memphis established some of the key information—which was released immediately—showing that in ducks there is long-term shedding of influenza viruses despite the passage of antibody. Some of the ducks shed virus for up to 17 days. During this period non-pathogenic viruses became dominant in the ducks, but they retained high pathogenicity for chickens; we do not know whether they were pathogenic to humans.

These non-pathogenic H5N1 duck viruses also transmitted naturally to other ducks put into the cage. These properties are very disturbing. The duck is pushing the virus back toward the non-pathogenic state, which naturally occurs with influenza in ducks but these viruses retain high pathogenicity for chickens and presumably humans.

We decided to use Dr. Eric Hoffman's reverse genetic strategy to generate a vaccine and determine whether it is efficacious in the duck, because we need a vaccine if we want to avoid culling all the ducks. That strategy is the standard eight plasmid system, modified hemagglutinin, that we heard about yesterday. We put on an N3 neuraminidase so we could distinguish between vaccinated and infected birds; these viruses replicate to very high titers.

The strategy was to vaccinate ducks at 2 weeks, boost them at 5 weeks, and challenge them with an H5N1 at 8 weeks—all, of course, in biosafety level 3 containment facilities. The doses of vaccine were surprisingly small: 0.25 to 1.2 micrograms of HA per dose.

We failed to put in a small-enough dose because all the doses of vaccines induced high levels of antibody after one shot, pre-boost HI titers ranged from 500 up to 5,000, and all the ducks were protected from challenge. We are now reducing the dose. So the good news is that the vaccines are efficacious in ducks, and that a very small dose is sufficient to protect them from H5N1 challenge.

What about the lethality of these viruses for ferrets—the models we were talking about yesterday? The human viruses caused severe disease in the ferrets, with central nervous system symptoms and death. The viruses from ducks caused only extremely small numbers of severe cases: one in ferrets, none in chickens. These numbers are too small to mean much, but they indicate that the ferret is an excellent model for determining pathogenic potential in humans.

Duck populations have been increasing rapidly since the early nineties, corresponding to the time when these problems began to occur. The Thais did a back-of-the-envelope calculation that Asia is home to some 2 billion domestic ducks—10 to 100 times the number of wild ducks. Is the wild duck—the true migrating duck—involved in spreading this virus? Our view is that the true migrating bird was not responsible for the initial spread in Hong Kong. The virus did spread locally in wild ducks and other wild birds. What is the situation now, after two seasons? Are wild ducks infected? We desperately need to know, because birds that are breeding in Siberia will spread to other areas, including continental Europe.

North Korea has just seen an outbreak of highly infectious disease in poultry. We don't know yet what caused the outbreak—maybe H5N1, maybe not. It was characterized as a non-pathogenic H7N7 virus. Thailand, Japan, and South Korea have stamped out the virus, but what will come across the border from Lao or Cambodia to Thailand? We don't know, nor will we know what will cross the border in China, given the use of vaccine there.


I would like to end with suggestions. The immediate issue is to reduce the likelihood of human-to-human transmission by reducing the viral load in poultry. And we can do that: the international agencies must come aboard to reduce the ducks in live markets and standardize agricultural vaccines.


Stamping out is effective if countries can afford it: Thailand is showing that it can be done. However, the government realizes that it must consider vaccination of the poultry population, including ducks, because this virus will not go away. We desperately need a quality vaccine for poultry right now.


The unresolved issues are many. Why hasn't H5N1 transmitted more freely to mammals including humans? The molecular basis of its pathogenicity still needs to be resolved. Is the Asian human genome special for susceptibility to influenza, given that Asia is the epicenter for these pandemics?



I would like to conclude by acknowledging NIAID, which has supported this program at St. Jude's Children's Research Hospital, in Hong Kong, and in other Asian countries. I would also like to acknowledge the group in Memphis, and particularly the group in Hong Kong, including Malik Peiris and Yi Guan, as well as collaborators in Indonesia, Thailand, and Vietnam.

Plenary Presentation Slides-Dr. Webster

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|---|---|
|  <p>Research Issues in Animal Surveillance and Pandemic Planning</p> <p>Robert G. Webster, PhD Division of Virology Department of Infectious Diseases St. Jude Children's Research Hospital</p> | <p>SURVEILLANCE</p> |
| <p>Spread of H5N1 Influenza in Asia 2004</p>  <p>100s of millions of birds culled</p> <p>Human Cases: 70 Human Deaths: 47</p> <p>Vietnam: 33 deaths Thailand: 12 deaths Cambodia 2 deaths</p> | <p>The Difficulty of Obtaining Avian H5N1 Viruses</p> <ul style="list-style-type: none">• Trade embargos• National pride• Intellectual property• Different missions for FAO, OIE and WHO• Absence of infrastructure |
| <p>The Hong Kong Model</p> <p><i>No H5N1 influenza in poultry or humans in 2004, 2005</i></p> | <p>The 1997 H5N1 Outbreak in Hong Kong</p> <p>FIRST BUILD THE INFRASTRUCTURE</p> <p>Nov. 1997 1 small lab, 1 ancient hood</p> <p>Dec. 1997</p> <ul style="list-style-type: none">• The brightest and best trained young virologists flown in• Laminar flow cabinets flown in• Temporary isolation lab established• Staff stay on the ground <p>No human infections: virus availability</p> <ul style="list-style-type: none">• Collaboration Agriculture, Health Department, University, WHO |

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|--|---|--------------------------------|----------------------------|-------|------------|-----------------------------|-----------|--|--------------------------------|---|--------------|--|-----------|-------------|---------------|-------|-------------|--------------|----|
| <p>Current Advice to Countries with Poor Infrastructure</p> <ul style="list-style-type: none"> • After SARS and laboratory infection of humans <ul style="list-style-type: none"> – Do not attempt to isolate viruses – Use molecular analysis – RT PCR – Send samples to expert laboratories | <p>Changes in Poultry Marketing in Hong Kong</p>  <ul style="list-style-type: none"> • Two clean days per month • Inactivated H5N1 vaccine <ul style="list-style-type: none"> – Sentinel birds • No H5N1 2004, 2005 | | | | | | | | | | | | | | | | | | |
| <p>Why is the Hong Kong H5N1 Control Strategy Not Copied?</p> <ul style="list-style-type: none"> • Too expensive! • Reluctance to accept agricultural vaccines • Lack of promotion by international agencies • Lack of political will | <p>Agriculture Vaccines</p> <ul style="list-style-type: none"> • Not standardized for antigen content • Required to induce HI antibody in poultry • There are good and bad agricultural vaccines | | | | | | | | | | | | | | | | | | |
| <p>Vaccines for use in Poultry (Traditional)</p> <table border="0"> <tr> <td>Hong Kong</td> <td>Commercial</td> <td>A/CK/Mexico/232/94 (H5N2)*</td> </tr> <tr> <td>China</td> <td>Commercial</td> <td>A/DK/England/N-28/73 (H5N2)</td> </tr> <tr> <td>Indonesia</td> <td></td> <td>A/CK/Indonesia/03 (H5N1) [H.P]</td> </tr> </table> <p>*Homology of HA ≈ 94% with current H5/04</p> | Hong Kong | Commercial | A/CK/Mexico/232/94 (H5N2)* | China | Commercial | A/DK/England/N-28/73 (H5N2) | Indonesia | | A/CK/Indonesia/03 (H5N1) [H.P] | <p>Recent Developments in Poultry Vaccines</p> <table border="0"> <tr> <td>Fowlpox – H5</td> <td></td> <td>China, US</td> </tr> <tr> <td>r.g. – H5N1</td> <td>H9N2 backbone</td> <td>China</td> </tr> <tr> <td>r.g. – H5N3</td> <td>PR8 backbone</td> <td>US</td> </tr> </table> | Fowlpox – H5 | | China, US | r.g. – H5N1 | H9N2 backbone | China | r.g. – H5N3 | PR8 backbone | US |
| Hong Kong | Commercial | A/CK/Mexico/232/94 (H5N2)* | | | | | | | | | | | | | | | | | |
| China | Commercial | A/DK/England/N-28/73 (H5N2) | | | | | | | | | | | | | | | | | |
| Indonesia | | A/CK/Indonesia/03 (H5N1) [H.P] | | | | | | | | | | | | | | | | | |
| Fowlpox – H5 | | China, US | | | | | | | | | | | | | | | | | |
| r.g. – H5N1 | H9N2 backbone | China | | | | | | | | | | | | | | | | | |
| r.g. – H5N3 | PR8 backbone | US | | | | | | | | | | | | | | | | | |

| <h3 style="text-align: center;">Poultry Vaccines (The Good Ones)</h3> <ul style="list-style-type: none"> • Provide protection despite antigenic drift • Mechanism unresolved • Do not provide sterilizing immunity • Can reduce virus load below level of transmission | <h3 style="text-align: center;">Poultry Vaccines (The Bad Ones)</h3> <ul style="list-style-type: none"> • Protect against disease signs • Birds shed transmissible levels of virus • Promotes spread of virus in live markets and antigenic drift | | | | | | | | | | | | | | | | |
|--|--|------------|--------|------|--------|---|---|---|------|---|---|---|---------|---|---|---|--|
| <h2 style="text-align: center;">Missing Information</h2> <p style="text-align: center;"><i>The role of domestic ducks</i></p> | <p style="text-align: center;">Vaccine – Reverse Genetics Hoffmann 8 Plasmid System</p> | | | | | | | | | | | | | | | | |
| <h3 style="text-align: center;">Lethality of H5N1/04 Viruses for Ferrets</h3> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Isolated from</th> <th style="text-align: center;">No. Tested</th> <th style="text-align: center;">Severe</th> <th style="text-align: center;">Mild</th> </tr> </thead> <tbody> <tr> <td>Humans</td> <td style="text-align: center;">4</td> <td style="text-align: center;">4</td> <td style="text-align: center;">0</td> </tr> <tr> <td>Duck</td> <td style="text-align: center;">3</td> <td style="text-align: center;">1</td> <td style="text-align: center;">3</td> </tr> <tr> <td>Chicken</td> <td style="text-align: center;">4</td> <td style="text-align: center;">0</td> <td style="text-align: center;">4</td> </tr> </tbody> </table>  | Isolated from | No. Tested | Severe | Mild | Humans | 4 | 4 | 0 | Duck | 3 | 1 | 3 | Chicken | 4 | 0 | 4 | <h3 style="text-align: center;">Trends in Duck Populations (FAOSTAT 2001)</h3> |
| Isolated from | No. Tested | Severe | Mild | | | | | | | | | | | | | | |
| Humans | 4 | 4 | 0 | | | | | | | | | | | | | | |
| Duck | 3 | 1 | 3 | | | | | | | | | | | | | | |
| Chicken | 4 | 0 | 4 | | | | | | | | | | | | | | |

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| <h3>Duck Population -- Asia</h3> <p>~ 2 BILLION domestic ducks 10 to 100 times more domestic than wild ducks</p> | <h3>N. Korean Poultry Industry Could be Wiped Out</h3> <p>An outbreak of deadly bird flu in North Korea could wipe out its fledgling chicken breeding industry and deprive the impoverished country of its main source of animal protein, animal experts said yesterday</p> <p>South China Morning Post, Asia Pacific, Tuesday, March 29, 2005</p> |
|  | <h3>Summary</h3> <p><i>The immediate issue</i></p> <ul style="list-style-type: none">• Reduce the likelihood of human to human transmission by reducing virus load in poultry<ul style="list-style-type: none">– Stamping out– Vaccination– Quality vaccines for poultry needed |
| <h3>Summary</h3> <p><i>Unresolved issues</i></p> <ul style="list-style-type: none">• Transmissibility• Pathogenicity• The Asian Host |  <h3>Acknowledgements</h3> <p>Support: NIH/NIH/NIH, NIAD, ALSAC</p> <p><i>St. Jude Children's Research Hospital</i> Richard Webby, Elena Govorkova, Eric Hoffmann and the Influenza Support Staff</p> <p><i>Hong Kong University</i> Dr. Y. Guan, K. Pei, L. Pei, L. Y. Yuen, Influenza Research Group</p> <p><i>Indonesian Ministry of Research & Technology</i> Dr. Ann Soewandono</p> <p><i>Vietnamese Ministry of Agriculture and Rural Health Development</i> Dr. Th Nguyen</p> <p><i>Thailand Street of Disease Control and Veterinary Services</i> Dr. Chantana Boonpradit</p> |

(Slides available on accompanying CD)

MORNING PLENARY DISCUSSION, DAY 2 (APRIL 5, 2005)

Moderator: Dr. Harvey Fineberg

**Panel Participants:
Dr. Ferguson, Dr. Treanor, Dr. Webster**

DR. FINEBERG: I invite Professor Ferguson and Dr. Treanor to join Dr. Webster on stage for questions and comments.

PARTICIPANT: Professor Ferguson, yesterday Dr. Gerberding told us that CDC planned to expand the number of quarantine stations from 8 to 30. Could you comment—based on your modeling insights—on whether you think quarantine stations are an effective component of containment?

PROF. FERGUSON: If we are not quarantining individual cases, I predict such an approach will have a fairly limited impact, because by the time cases are diagnosed, viral shedding is already occurring, although the extent depends on the characteristics of the virus. If the virus resembled human influenza, then quarantining arguably would have limited effect, because viral shedding would have declined. If the virus resembled avian H5, quarantining might have a greater effect. In any case, people who are very sick pose less risk of transmission, because they are not moving about the community. So I do not think quarantining would be the principal element of a control program.

PARTICIPANT: I have a couple of comments on the theme that history can lead us to ask certain questions. First, in the seventeenth century, when crossing the ocean took at least 6 weeks and sometimes 10 to 12 weeks, influenza made it from England to the colonies. Those were small ships. One would have thought that in a population as small as 50 and no more than 250, the virus would have burned itself out on that voyage. Information on the population of the ship that carried the disease and the exact duration of the voyage might be useful to your modeling.

The other point is that in the 1889–1890 pandemic, the third wave was the most lethal wave. In researching 1918, I found that public health officials were concerned about that. New York City was the only major city I know of that did not close its schools, but it did quarantine cases. Unlike practically everywhere else in the world, New York experienced peaks in the second and third wave, yet the killing was much more level. Philadelphia had less than one-third the population of New York City yet experienced a higher peak death toll. On a per capita basis, the death toll for Philadelphia and New York was almost identical, but the fact that the peaks were so different, and that the virus moved to the latter city so much more slowly, may be worth investigating. I can not imagine that the quarantine was effective enough to account for the lower peak death toll. Perhaps the fact that fear, prompted people to stay off the streets and normal traffic dropped significantly brought movement below a critical mass.

PROF. FERGUSON: We are very interested in looking at the latter phenomenon. I did not use my model to predict the impact of social distance measures because we regard past pandemics through the filter of intrinsic behavioral adjustments in the population. That is, people decrease their social distance spontaneously, whether by closing schools or through fear, and that was particularly true for 1918.

One of my hypotheses for why three waves occurred in some but not all locations in 1918 was that density-dependent adjustment of contact rates occurred. People did not contact each other during the pandemic, and that reduced transmission rates. The disease went away temporarily and came back multiple times. Other hypotheses to explain the waves exist, but we are trying to correlate transmission and mortality patterns with quantitative data on social distance measures such as school closures.

Our models of international travel do account for journey time and numbers of people, which is why I talked about effective epidemiological contact rates rather than absolute numbers of individuals traveling. But I agree: a 6-week journey with 50 people is a bit of a paradox.

PARTICIPANT: Is it possible that the H5 we now observe in poultry reflects better surveillance in Asia? I am referring to a paper by Ken Shortridge from 1990, which showed that about 7 percent of the rural population had H5 antibodies. If 500 million people live in rural China, this would mean that 35 million people had been infected by H5 before the 1997 outbreaks. Is the situation today truly different, or do higher infection rates simply reflect the fact that we have better ways of detecting the virus?

Dr. Webster: Surveillance in Hong Kong has certainly improved. However, if deaths had previously occurred, they would have been noticed. This virus has undoubtedly changed. Before 1997, the H5N1 viruses did not have the capacity to infect humans, as they do today. That is a learned capacity, with incremental changes then allowing the virus to kill the duck population, to transmit to cats, and so on. This virus is continuing to evolve, and we are probably creating the conditions that allow that to happen. This epidemic began just as Asian countries began to move from backyard flocks to huge chicken houses and pig-raising facilities. So no--current infection rates do not simply reflect better skills.

PARTICIPANT: Could you apply your models to try to block the annual epidemic, using antivirals, vaccines, and measures to reduce social distance, instead of waiting for a pandemic? That is, can we test the modeling and predictions in real time, rather than continue to model until we have a pandemic?

PROF. FERGUSON: I think that would be feasible, and one of my research priorities is to initiate another community study, perhaps equivalent to the Tecumseh study, where we attempt to influence transmission in isolated communities. Blocking seasonal influenza epidemics is probably infeasible, but we don't need to do that. We simply need to demonstrate the impact of control measures on transmission to be fairly sure we are exerting some influence.

Complete blocking is impractical because of the sheer weight of infectious burden on a particularly community. We are not going to treat the whole country, so the infection is constantly challenging the treated population from outside. But we certainly could use well-designed studies to refine the values of our model's parameters in advance.

Participant: Some of the studies that Ian Stevenson and the group at CDC have done lately, with neutralization antibodies to the Duck Singapore vaccine, suggest significant

heterosubtypic immunity. My question is: what would be the effect of using an H5N1 or an H5N3 vaccine in the affected areas to induce heterosubtypic immunity, to protect against more severe disease and non-sterilizing immunity? Modeling can look at this in terms of the increased likelihood that an antiviral strategy in a population with partial immunity might affect further spread.

DR. TREANOR: Whether we can induce antibody to neutralize viruses other than the vaccine needs to be evaluated. I question whether an inactivated vaccine can do that, but finding out is critical. We could model a less-than-perfect vaccine and try to figure out how much of an effect it would have.

PROF. FERGUSON: Ira Longini's group has looked at the combination of limited-efficacy vaccines and antivirals. These produce a synergistic impact, and the overall effectiveness of the combined control policy is considerably greater than that of just one measure.

Participant: I agree with Dr. Webster that there are good veterinary vaccines and bad ones. However, I would like to comment on regulatory authority in the U.S. and the European Union, which exerts very strong control of manufacturing of vaccines. The production facilities and quality control of multinational companies such as Meriel Intervet, Lohman Animal Health, and even Biomune are very good, so the quality of the vaccines they manufacture is very high. However, one study Dr. Webster did about six years ago showed that quality control in developing countries without a strong regulatory authority is not very good, so vaccines made there show huge batch-to-batch variation. Some are very bad.

Dr. Webster also showed that veterinary vaccines, especially those for poultry, use a lower antigen content to give optimal immunity and proper protection. Vaccine studies show that the challenge dose has a huge impact on viral reduction and shedding. Thus a poor-quality vaccine used to immunize birds looks very good, but if we give the birds a challenge dose of the same vaccine, the results are not very good. Could Dr. Webster comment on how adjuvanted proteins affected the reassortment of the virus and the challenge virus dose he gave in his duck study?

DR. FINEBERG: Dr. Webster, could you also clarify the term "bad vaccine"? I understood you to mean more than poor manufacturing practice.

DR. WEBSTER: The bad vaccines I was referring to were those made in developing countries without adequate regulation. We see this problem throughout Central America and in China. We need to pay attention to unregulated companies. My message is particularly directed at people from Thailand and Vietnam, who are trying to ensure that vaccines are available when these viruses reappear. Those countries would be very wise to emphasize the quality of vaccines and ask for testing of the batches.

PARTICIPANT: There is an old adage about models: all are wrong, but some are useful. I was happy to see that Neil's model fell into the latter category—that models can help articulate many different assumptions and put them in perspective. One of the key parameters used in your model was the (R_0 reproducibility number) of approximately 2, which might well be much greater than 2 if we calculate the reproductive rate based on mortality rates rather than infection rates. Can you comment on the fact that the R_0 of a pandemic strain is about 2, while that of epidemic strains is much higher? I thought that influenza is one of the most highly communicative diseases, like measles and varicella.

PROF. FERGUSON: I, too, always thought of influenza having an R_0 similar to that of measles and other such diseases. However, a detailed analysis of inter-pandemic flu—particularly household transmission rates—shows that the virus is not that transmissible. The inter-pandemic R_0 is probably about the same as the pandemic R_0 .

The question is what is the R_0 of influenza? The study undertaken by Mills et al., and other historical studies of transmissibility based on mortality data, show that whether we measure mortality or infection rates does not matter as long as the ratio of one to the other remains constant. I do not believe the measures are affected by the fact that we are looking at deaths rather than infections.

The one caveat regarding inter-pandemic transmission rates is that multiple strains are circulating. The accumulated reproduction number of all the strains in circulation at a particular point in time is probably somewhat higher than that of a single strain. However, it's probably no more than 3–4, which is considerably less than that of either varicella or measles.

8

WORKING GROUPS, DAY 2

**WORKING GROUP 5: IMMUNOLOGY, ASSAY STANDARDIZATION,
AND CORRELATES OF PROTECTION**

Chairpersons—Ann Arvin and Brian Murphy

Briefer—Brian Murphy

Rapporteur—Ann Arvin

Focus: The focus of this group will be research needed to improve understanding of the immune response to influenza infection or vaccination; to enhance comparability of results between laboratories; and to identify correlates of protection that will facilitate testing and licensure of candidate vaccines.

Specific Questions:

1. What studies are needed to better assess the role of antibody to neuraminidase in protection against influenza disease or its complications?
2. What studies are needed to assess the importance of cellular immunity following influenza disease or the potential importance of cellular immunity in response to vectored vaccines?
3. What research is needed to develop, validate, and standardize immunological assays to facilitate vaccine evaluation and licensure?
4. What research is needed to evaluate the immune response to influenza vaccine delivered by different routes of administration?
5. What studies are needed to better define or validate proposed immune correlates of protection for different influenza strains and in different populations?
6. What research is needed to better understand mucosal immunology and influenza?

Rapporteur Report—Dr. Ann Arvin

A key priority is to develop, validate, and standardize serologic tools for pandemic preparedness. We focused on improving neutralization assays for antibodies against avian strains; standardizing protocols; engineering an inoculum so it could be used in a Biosafety lab 2 setting; and boosting automation, which might include robotics but also new reagents such as fluorescentated or luciferase tagged inocula.

Improving HAI methods for detecting H5 antibodies is also important.. Developing ELISA methods for a variety of HA subtypes is considered important and includes developing standardized, purified, or recombinant HA and NA proteins, as well as reference serum panels to facilitate the development and use of ELISA-based assays.

We recommend efforts to develop and standardize assays for antibodies to NA, and to evaluate and correlate the subtype ELISAs with a gold standard functional assay, e.g. a neuraminidase inhibition method.

Sero-epidemiology research is important for pandemic preparedness. Such research should include studies to understand pre-pandemic antibody levels in human populations in key areas to HA and NA proteins, and investigating potential cross-protection provided by human anti-HA or anti-NA antibodies against the avian strains.

A longer-term goal is to develop simpler serologic assays for field use. It seems most prudent and practical to do this work on assay development and standardization in centralized reference laboratories, but we ultimately need to develop techniques that can be transferred to field laboratories.

We discussed the need to investigating immune correlates of protection extensively. A much broader and deeper understanding of the human immune response to flu infection in general, as well as to vaccines is needed, based on using modern immunologic techniques. Examples include subtype-specific ELISAs and new assays, focusing on trying to better understand protection and cross-protection by antibodies to these proteins; and the role of IgG and IgA in serum and mucosal sites that have specificity for these proteins in protection.

We conclude that it is important to use the many new methods now available to probe human immune responses against primary and secondary flu infections with non-pandemic strains. These studies would give us a repertoire of methods to apply immediately to evaluate host responses in a pandemic setting. Examples of this kind of work include better characterizing flu-specific memory T cells and B cells, and aspects of trafficking of immune cells that can be studied now, such as lung trafficking and trafficking to mucosal epithelium. What is the role of cross-protective immunity by T cells that recognize various flu proteins? We can now study all of these questions in new ways.

Applying new immunologic assays to understand protective immunity requires their use in the context of prospective studies, using clinical endpoints and viral shedding to define a true correlate of protection, as opposed to just to measuring an immune response in the absence of information about viral replication.

We recommend efforts to improve understanding of the consequences of antigenic drift in H5 strains. New tools should be used to better understand the immunopathogenesis of complex and fatal flu infections, not just in the pandemic setting, where obtaining samples may be difficult, but also during annual epidemics. New tools and a better network for sharing patient samples for testing would enable us to better analyze the mechanisms that lead to these unusual situations.

Additional research to evaluate flu vaccine immunity is necessary. This work should be based on some of the same concepts discussed for assessing the response to natural infection and defining protective immunity. In this case, the goal should be to develop a panel of standardized immunologic assays that can be used as background information for designing pandemic vaccines that would engender the best repertoire of immune responses in the shortest time after vaccination.

In this context, we recommend comparing the capacities of existing inactivated, live attenuated, and vectored vaccines for inducing humoral and cellular and mucosal immunity,

during primary and secondary vaccination, and with varying routes of administration of the vaccines.

These studies should focus on immunogenicity and efficacy in populations at the extremes of age, especially infants and the elderly, including the very elderly. The interval required to induce a protective immune response after immunization is key to understanding the best vaccine for a pandemic setting. Responses that are reliably associated with reduced viral shedding must be defined and persistence of the immune response is another important factor.

Finally, it is important to generate experience with multiple pandemic vaccines to assess reactogenicity, immunogenicity, optimal dose, and route of administration. In our final analysis, gaining a broad understanding of the immune response to both natural infection and vaccines for as many different HA and NA viruses is a priority, as is looking not just at the standard serologic responses but also at cellular immune responses.

Working Group 5 Presentation Slides: Immunology, Assay Standardization, and Correlates of Protection-Ann Arvin, Rapporteur

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| <p>John R. LaMontagne Memorial Symposium on Pandemic Influenza Research April 4-5, 2005 Institute of Medicine</p> <p>Working Group Five: Immunology, Assay Standardization, and Correlates of Protection</p> <p>Research Recommendations</p> | <p>Develop, validate and standardize serologic tools for pandemic preparedness (1-2 yr)</p> <ul style="list-style-type: none"> • Improve neutralization assays for avian strains: Standard protocols, engineered inoculum (BSL-2), automation • Improve HAI for detection of H5 antibodies • Develop ELISA methods for HA subtypes • Develop standardized purified/recombinant HA and NA proteins and reference serum panels • Develop and standardize assays for anti-NA <ul style="list-style-type: none"> - Correlate subtype ELISA with 'gold standard functional' inhibition (NI) method |
| <ul style="list-style-type: none"> • Seroepidemiologic research related to pandemic preparedness <ul style="list-style-type: none"> - Assess pre-pandemic antibodies to HA and NA - Investigate potential cross-protection provided by human anti-HA or anti-NA against avian strains • Longer term goal: <ul style="list-style-type: none"> - Simpler serologic assays for field use | <p>Investigate immune correlates of protection Goal: Characterize the human immune response to flu infection and vaccines using modern immunologic techniques Examples</p> <ul style="list-style-type: none"> - Subtype-specific ELISA and neutralization assays for HA and NA to improve understanding of protection and cross-protection - Role of IgG/IgA in serum or at mucosal sites with specificity for HA or NA in protection - Use new methods for probing human immune responses to primary and secondary flu infection with non-pandemic strains in order to develop methods that can be applied immediately to studies in a pandemic setting <ul style="list-style-type: none"> - Characteristics of flu-specific memory T cells and B cells - Trafficking of immune cells to lung, mucosa, etc. - Cross-protective immunity by T cells against flu proteins |
| <ul style="list-style-type: none"> • Apply new immunologic assays in prospective studies using clinical endpoints + viral shedding to define correlates of protection • Improve understanding of consequences of antigenic 'drift' in H5 strains • Use new tools to better understand immunopathogenesis in complex/fatal flu infection (epidemic and pandemic cases) | <p>Additional research to evaluate flu vaccine immunity (2-5 yr) Goal: Develop panel of standardized immunologic assays for use in designing pandemic vaccines</p> <ul style="list-style-type: none"> • Compare capacities of inactivated, live attenuated and vectored vaccines to induce humoral, cellular and mucosal immunity, with primary and secondary vaccination and with varying routes of administration <ul style="list-style-type: none"> • Immunogenicity and efficacy in infants, children, adults and the elderly • Time to induction of protective response • Persistence of immune response • Generate experience with multiple pandemic vaccines to assess reactogenicity, immunogenicity, optimal dose and route of administration |

(Slides available on accompanying CD)

Working Group 5 Briefing Slides: Immunology, Assay Standardization, and Correlates of Protection-Dr. Brian Murphy, Briefer

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| <p><i>I Direct correlation between level of virus replication and clinical response</i></p> <ul style="list-style-type: none"> • fever index vs. peak virus titer (Illness correlates with peak virus titer) • titers 10² to 10³ = asymptomatic or URI • titers of 10⁷ = 104-105°F fever • peak titer achieved early after infection • job of immune system is to keep peak titer < 10³ • live att vaccines replicate to < 10³ | <p><i>II Rapid rate of replication in humans</i></p> <ul style="list-style-type: none"> • Single cycle growth curve = 8 hrs. • Illness with titers >10⁵ shed by 24 hrs after giving 10⁵ pfu of wt virus. • Immune responses on board at time of exposure major players in resistance • Immune factors, either cellular or humoral, generated from memory that require infection to be initiated make minor contributions to peak titer achieved |
| <p><i>III Lessons learned from experiments of nature</i></p> <ul style="list-style-type: none"> • 1977 H1N1 – long duration of HA specific immunity • Antigenic drift – virus selected based on ability to escape antibody • 1968 – level of serum antibody to NA correlated with illness/peak virus titer • 1957 - Severe disease despite multiple exposures to wild type H1N1 viruses – weak contribution of immunity to conserved genes | <p><i>IV Lessons learned from experimental challenge of humans with wt or att viruses</i></p> <ul style="list-style-type: none"> • Immunological correlates largely defined • four major contributors to immunity <ul style="list-style-type: none"> serum IgG Ab to HA – major player in LRT mucosal IgA to HA – Major player in URT serum IgG to NA mucosal IgA to NA (assumed) • moderate players in immunity <ul style="list-style-type: none"> transudated IgG Ab to HA on mucosal surface of URT IgM Ab to HA and NA (from IgA deficient and mouse data) • weak players in immunity <ul style="list-style-type: none"> cell-mediated immunity memory B-cell immunity antibodies to M2 • No one correlate of immunity-Immunity is the sum of the individual contributions of the four major player indicated above- high serum IgG without mucosal IgA = protection; no serum IgG but high mucosal IgA = protection Dream of a single correlate of immunity is in large part a fantasy |

(Slides available on accompanying CD)

WORKING GROUP 6: PANDEMIC VACCINES—ASSESSMENT, DEVELOPMENT AND PRODUCTION STRATEGIES

Chairperson—John Treanor
Briefer—Harry Greenberg
Rapporteur—Regina Rabinovich

Focus: The focus of this group will be to identify research needed to improve the production, evaluation, and use of existing in an influenza pandemic; to improve their immunogenicity; and to decrease the amount of antigen needed per dose through alternative formulations or routes of administration. This group also will define research needs associated with development and evaluation of new vaccines, new approaches to vaccine production, and potential new antigens to target in influenza vaccines such as conserved structural viral proteins.

Specific Questions:

1. What research is needed to better define the potential for common antigen vaccines against heterologous strains including avian influenza strains and for the optimal approach to their development?
2. What studies are needed to identify and study adjuvants that may provide an antigen-sparing effect with influenza vaccines?
3. What studies are needed to assess intradermal administration as an immunogenicity enhancing or antigen sparing measure?
4. What research is needed to develop and assess new devices or strategies for vaccine administration intradermally, transcutaneously, or intranasally?
5. What research is needed to develop and assess new vaccine production strategies?
6. What technologies hold promise and what studies are needed to evaluate candidate influenza vaccines or vaccination strategies?

Rapporteur Report-Dr. Regina Rabinovich

A central theme of the discussion is that a pandemic vaccine needs to use technologies, tools, and processes that are integrated into inter-pandemic influenza vaccines. Otherwise, there is no market for such vaccines, and thus no surge capacity. Improving the efficacy, effectiveness, ease of administration and production, and routine use of all influenza vaccines is the technical framework for influenza pandemic preparedness.

An immediate and long term need is broad access to critical reagents (some which may involve management of intellectual property and know-how), such as influenza isolates, validated assays, serum panels, or platform technologies. Whether collected by government, academic researchers, or developed by the private sector, delayed access to these for either business or academic reasons can slow the development of new influenza vaccines. But much of the funding for collecting and creating these tools comes from the public sector, and we need to ensure their access by the global community. Respect for intellectual property surrounding

platform technologies, a keystone of the U.S. pharmaceutical industry, is not incompatible with this goal, but negotiated agreements to manage this may be necessary.

If we take access to these tools as given, pandemic planning requires a quiet revolution in influenza vaccines, and making the case for industry involvement in manufacturing these vaccines is critical. This effort requires a research program that actually yields a usable product rather than a special vaccine that sits in the freezer awaiting deployment during a pandemic. If it does not, pandemic flu will be akin to orphan diseases such as malaria, where the market is limited and the drivers for investing in the technologies that the research community is developing are somewhat mysterious. A specific concern in pursuing development of novel vaccines along with manufacturing of annual supply is competition between inter-pandemic and pandemic vaccine development and manufacturing, in some instances even at the pilot lot level, because production will require the same facilities and there are relatively few players. Research and product development for influenza need to be managed and integrated. And global challenges in scale and implementation—that is, universal access to some sort of vaccine-based intervention—are the 900-pound gorilla.

In terms of priorities, our first is to improve production. Enhanced understanding of the molecular factors that influence viral growth in any substrate is needed. In the short term, improved egg manufacturing yield and capacity may be possible – although there are clearly enormous regulatory barriers to changing manufacturing processes for licensed vaccines - with greater use of influenza vaccine in the inter-pandemic period as the market driver.

Our medium-term priority is a cell-culture vaccine, which would be a new vaccine from a regulatory perspective and thus would require safety and efficacy data. A cell-culture approach to vaccine production has been plagued by low yields and the technology is still unproven. We identified a couple of cell substrates that are perhaps furthest ahead. One is MDCK, whose safety issues could be evaluated based on specific scientific criteria. Regulatory barriers to using new cell lines for production have apparently been overcome by one European company, with plans to license and produce an influenza vaccine based on MDCK cells in 2006. Data to support this claim were not reviewed.

In the long-term column is a totally new way of producing influenza vaccine based on processes used for other vaccines. A second long-term priority is improving immunogenicity. This goal could include increasing vaccine potency through the use of adjuvants; and new routes, mechanisms, and tools for different formulations and routes of delivery. Achieving this goal will require head-to-head testing of existing vaccines.

Another priority is to generate full dose-response curves for both intradermal and intramuscular delivery, because it is not clear that these that flu vaccine has been optimized for immunogenicity. We also need clinical evaluation of alternate routes that may be dose-sparing, as well as of nearer-term adjuvants and other approaches in the early stages of development. Developing novel adjuvants and formulations is not a minor endeavor, and thus is a medium-term priority.

We also need to improve immunogenicity by improving heterosubtypic potency. One approach that is furthest off and highest risk—but potentially high payoff—is the common protein vaccine, with clinical data from one candidate pending. We also discussed what we know and don't know about heterosubtypic protection following cold-adapted influenza vaccine. An existing trial will probably be informative.

Questions that could be answered in the short-term include more knowledge of the immune response to wild-type H5. Precious samples from that virus are not available, and collecting them needs to become a priority, because we are missing opportunities to evaluate them.

We also discussed the potential of DNA vaccines, vectors, and expressed flu proteins. Recombinant-DNA, protein-based vaccines, which can copy a viral protein without changes, or some new technology could be viable. DNA vaccines deserve special mention because of the mouse data from Margaret Liu, and because they offer so many advantages in yield and the ability to deal with pandemic flu if we can make them work in humans.

Finally, we need to improve clinical evaluation by performing challenge models and head-to-head comparisons, and by improving criteria and methods for assessing safety, efficacy, and immunogenicity. A priority is to create the infrastructure for the human challenge model using pandemic HAs and NAs on the challenge virus, including finding locations, critical reagents, and funding for these studies. We also see validating surrogate markers as a priority, particularly in the context of a priming dose for a population.

Working Group 6 Presentation: Pandemic Vaccines-Assessment, Development and Production Strategies, Dr. Rabinovitch, Rapporteur

General Issues

- A “pandemic vaccine” needs to use technologies, tools and processes that will have to become integrated into interpandemic influenza vaccinology and vaccines.
- Access to critical IP and know-how –
- Platform technologies: reverse genetics, adjuvants, delivery systems
- Shared tools: isolates, shared/validated assays, reagents, serum panels
- Processes for manufacturing
- Clinical trial tools...
- As a result, true pandemic planning requires a quiet revolution in influenza vaccines.
- Making the case for industry involvement to manufacture is critical if research is designed to result in a product - closer to malaria if considered solely for pandemic flu
- There will be competition between interpandemic and pandemic vaccine development and manufacturing capacities
- Global challenges in scale and implementation are a quiet 900 lb gorilla.
- Research and product development enterprise needs management and integration

TABLE 1 Research Priorities for Vaccine Assessment, Development, and Production

Research Areas

1. Improved Production of Vaccines—general issues

Increased growth

Cell substrate

Eggs vs. cells

Limits to eggs

PER.C6 or MDCK

Rapidly identify the appropriate flu isolate in accepted cell line

Short term research priorities - < 2 year

- Research to enhance understanding of the molecular factors that influence viral growth in any substrate
- Research to improve egg manufacturing yield or capacity – lack of diversity or assurance of supply of eggs
 - greater use of influenza vaccine in inter-pandemic years would be a market driver
 - Eggs vs. cells – a “no brainer” but...
 - Cells still have low yield – yet unproven
 - European cell based influenza vaccine in 2006 (MDCK)

Medium term research priorities – 3 -10 year

- Research to develop a cell culture vaccine. This would be a “new vaccine” and would require a body of safety and efficacy (could use surrogate) research to support licensure in the US
 - Cell substrates (such as PER.C6 or MDCK)
 - Others have advantages of being approved but are not as good candidates than these 2 above
 - MDCK – safety of cell substrate – can develop scientific criteria rather than a generalized concern
- Research to facilitate evaluation of characterized cell line in context of new understanding of factors that influence growth

Long term research priorities- >10 years

- **Research to develop a totally new way of producing influenza vaccine (i.e., e coli)**
-

2. Improve Immunogenicity – general issues

Increased potency

adjuvant

route (intradermally/intramuscularly)

formulations

head-to-head cold adapted influenza virus (CAIV) vs. trivalent influenza vaccine (TIV)

Short term research priorities - < 2 year

- **Research that generates full dose response curves - flu vaccine has never been optimized for immunogenicity at the currently accepted dose; (some are ongoing; need to be done for both intradermal (ID) and intramuscular (IM)).**
- **Research on the clinical evaluation of alternate routes for dose-sparing - should be done up front.**
- **Evaluate alum and MF59 and other late stage adjuvants.**

Medium term research priorities – 3 -10 year

- Research to develop novel adjuvants are longer term, particularly for US where only alum is licensed in flu vaccine.
 - Research to develop novel formulations (such as adjuvanted patch)
-

3. Improve Immunogenicity: Understanding Heterosubtypic Potency.

Increase heterosubtypic potency

Mechanisms for crossreaction

Cold adapted influenza virus (CAIV) vs. trivalent influenza vaccine (TIV)?

Common ag

T cell immunity vs. Ab to HA/NA

Pre-prime pop with heterosubtypic H5/H9/etc?

Short term research priorities - < 2 year

- Research to document that heterosubtypic protection does happen post CAIV – analysis of ongoing trial may suffice.
- Research to determine if there is a fundamental difference between H5 and H3 or H1. How much of the response is the virus and the immune response?
- Urgent Research: Need to know more about immune response to wild type H5
- Research on role of other proteins in pathogenesis

Long term research priorities- >10 years

- Common protein vaccine
 - Existing preclinical data more related to severity/death than prevention of infection
 - lower priority for public sector
 - Would benefit from reviewing all potential proteins for systematic analysis particularly if role in pathogenesis is not understood
-

4. Research on Totally New Influenza Vaccines—general issues

DNA vaccines

Vectors

Expressed flu proteins or peptides

Short term research priorities - < 2 year

Issues around anti-vector immunity?

rDNA protein based vaccines can copy viral protein – without changes to surface antigens that may be relevant

Medium term research priorities – 3 -10 year

rHA has been in humans and not

DNA vaccine on gold bead: remains a viable approach as a vaccine, new data deserves review – will be a new vaccine

Long term research priorities- >10 years

Same as above?

Vector: some advantages

5. Improved Clinical Evaluation—general issues

Create infrastructure for human challenge models

Comparisons head-to-head

Criteria and methods for safety, efficacy, and immunogenicity

Short term research priorities - < 2 year

- Create infrastructure for challenge model – using pandemic HAs/NAs on the challenge virus. Could evaluate new candidates.
 - Places—finding locations
 - critical reagents
 - Readouts
 - funding \$\$
- Research to validate surrogate markers
- Research to determine the immunologic surrogate for a priming dose for a population
- Evaluate logistics for vaccination with different approaches above.

Working Group 6 Briefing Slides: Pandemic Vaccines-Assessment, Development and Production Strategies-Dr. Harry Greenberg, Briefer

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| <p style="text-align: center;">Smallpox and Influenza</p> <p>"In early 1962 long queues attended any clinic in Birmingham offering vaccination, because three patients with smallpox were in the isolation hospital. At this time over 100 people a week were dying in Birmingham of ... (influenza) ... ; but this caused no great public agitation."</p> <p style="text-align: right;">T. H. Flewett Introduction to 'Symposium on Influenza in Hospital and Elsewhere', <i>Postgrad Med J</i> 1963; 39: 563.</p> | <p style="text-align: center;">IOM Pandemic Flu Meeting: working group 6</p> <p style="text-align: center;">Specific Questions:</p> <ol style="list-style-type: none"> 1) What research is needed to develop/ assess new vaccine production and clinical trial strategies 2) What research is needed to define the potential for common antigen vaccines against all Flu including avian influenza strains? 3) What studies are needed to identify/ study adjuvants that can provide antigen-sparing effects for Flu vaccines? 4) What studies are needed to assess ID/TD/IN administration as an immunogenicity enhancing/ antigen sparing measure? 5) What research is needed to develop/ assess new devices/ strategies for vaccine administration ID/TD/IN? 6) What studies are needed to assess the feasibility of novel vaccines (conserved proteins, etc.) for pandemic influenza preparedness? |
| <p style="text-align: center;">IOM Pandemic Flu Research Meeting – Working Group 6 Improve Production (Question 1)</p> <p>A. Cell substrate for production of existing vaccines</p> <ol style="list-style-type: none"> 1. What is current best (eggs vs. cells)? Do we know which cells? 2. What is future best (eggs vs. cells)? How do we determine? 3. Is it possible to be prepared with egg based production? 4. If current best cells are PER.C6 or MDCK, what are research needs? <p>B. Improve Growth yield of existing flu vaccine</p> <ol style="list-style-type: none"> 1. Via increased viral growth (reassortants/ reverse genetics/other)? <p>C.) Rapidly identify the appropriate flu isolate for use in pandemic vaccine</p> <ol style="list-style-type: none"> 1. Substrate used for isolation (cell/eggs/reverse genetics/avian issues) 2. Ensure high yield of vaccine (reverse genetics, other) 3. Manufacturing safety (reverse genetics, other) | <p style="text-align: center;">IOM Pandemic Flu Research Meeting – Working Group 6 Improve Immunogenicity (Questions 2,3,4,5)</p> <p>A. Increased Potency of Existing or New Vaccines (not heterosubtypic)</p> <ol style="list-style-type: none"> 1. Adjuvant (MF59, alum, others)- How to design/ choose new adjuvants? 2. Alternate routes (ID, TD, IN), new delivery devices, other – What's needed? 3. Alternate formulation of existing vaccines: WCI/ Split Product/ Subunit 4. Alternative existing vaccine types – TIV vs. CAIV – Is one more immunogenic in the immuno-naïve setting? <p>B. Increased Heterosubtypic Potency of New or Existing Vaccine</p> <ol style="list-style-type: none"> 1. What is basic and molecular mechanism for cross reactivity? 2. CAIV vs. TIV- are they different, if so, why? 3. Common Antigen (M2, other), is this approach feasible? 4. T Cell immunity vs. Antibody to HA/NA, is T cell approach feasible? 5. Pre-prime pop. with heterosubtypic H5/H9/etc. Advantages vs. problems <p>C. Speed of Onset</p> <ol style="list-style-type: none"> 1. One dose vs. 2 or 3 doses (TIV/ CAIV/other)- is this different than potency? |
| <p style="text-align: center;">IOM Pandemic Flu Research Meeting – Working Group 6 Totally New Flu Vaccines (Question 6)</p> <p>A. Expressed Flu Proteins Administered as Proteins or Peptides (HA/NA/M2) – Protein Folding/ Peptide Immunogenicity problems</p> <p>B. Expressed Flu Proteins Administered as DNA – How to Improve?</p> <p>C. Expressed Flu Proteins Administered via Viral/Bacterial Vectors Which Vector / Route? Pandemic specific vs. general approach?</p> <p>D. Other?</p> | <p style="text-align: center;">IOM Pandemic Flu Research Meeting – Working Group 6 Improve Clinical Evaluation of Existing/ New Vaccines (Question 1)</p> <ol style="list-style-type: none"> A. Can we develop informative human challenge models for pandemic flu? B. Are there methods to compare distinct candidates head to head, if not? C. How to evaluate safety/ reactogenicity/ immunogenicity for a pandemic candidate? Are criteria the same or different? D. When do we need to move testing to infants /elderly in the evaluation? |

WORKING GROUP 7: STRATEGIES TO CONTAIN OUTBREAKS AND PREVENT SPREAD

Chairperson – Harvey Fineberg

Briefer – Neil Ferguson

Rapporteur – Nicole Lurie

Focus: The focus of this group will be research priorities to define better strategies that may contain an initial outbreak of disease caused by a novel influenza strain or to decrease the spread of infection if containment fails. Issues to consider include priorities related to mathematical modeling; to analysis of existing data from interventions that have been implemented to control the spread of influenza or other infectious diseases; and prospective studies that could be implemented and evaluated in the context of annual influenza outbreaks.

Specific Questions:

1. What research is needed to develop and assess models for pandemic influenza and how can these models be used to identify optimal containment and/or intervention strategies or approaches to decreasing spread of disease? What are the most important questions a model or strategy must answer in containing an influenza outbreak?
2. What are the most important model assumptions that must be made and what research is needed to make the assumptions reliable?
3. What research is needed to assess the relative role of model building based analyses of previous epidemics (SARS, previous influenza outbreaks) and non-model based analyses (communication mobilization, training of health workers, stockpiling of antivirals and vaccines) for strategies to prevent spread?
4. What research is needed to assess the relative effectiveness and interdependence of different control strategies (isolation and quarantine, travel restrictions, physical barriers, masks, use of antivirals , vaccines)?
5. What studies are needed to better assess whether a population focus if any (children, elderly, sing, military and other clustered populations) is most important for containing spread?
6. What prospective studies are high priorities to conduct that will help in defining strategies to decrease the spread of influenza? These may include studies of vaccine strategies (e.g., vaccination of children) or use of antiviral agents.
7. What studies can be done to evaluate available data on decreasing the spread of influenza of other viral respiratory infections where results may be applicable to influenza?

Rapporteur Report—Dr. Nicole Lurie

We talked a lot about the promise and perils of models, as well as their assumptions and the need to test those assumptions. We agreed that modeling is most useful in helping us understand gaps in the assumptions and which data we need to fill them. Modeling can also take options for intervention off the table or put them on the table quickly, enabling us to prioritize them differently.

We focused on modeling not only human disease but also the agricultural epidemic, to understand the tradeoffs between “upstream” and “downstream” strategies. Should we put more money, time, and energy into trying to identify and eradicate virus in poultry in Southeast Asia now, and consider the use of antivirals or other strategies, or apply those strategies when until a pandemic hits or the disease spreads to other areas?

We need to caution policymakers not to overuse the numbers that come out of models, as precision can outpace accuracy. Mathematical models make their assumptions much more explicit than some of the mental models.

We also discussed the tradeoffs involved in inputs for the models. Some participants felt that interventions that are not socially practical or acceptable are not worth modeling, with quarantine an example. Other participants felt that if we could better understand the implications of these interventions, those results might drive policymakers and the public to regard those interventions as more doable. Because planning continually shifts during a pandemic, modeling will have a role throughout, and the assumptions underlying the model will also have to change during the pandemic.

We need to be clear that one model can't do it all, and that modeling can serve very different functions. These include not only disease transmission and control but also the vaccine supply chain, helping us understand the consequences of just-in-time delivery, for example.

We also need to model the social consequences of different interventions. For example, what are the implications of closing schools for parents' ability to work and other social functions? If policymakers instruct people to stay home, how will they obtain food and medicine? A model can address only factors we can conceive of in advance. One aspect we cannot anticipate terribly well is how a pandemic might alter international relations.

This discussion led us to focus on the data we need to better model different outbreak and containment strategies. We recommend more comprehensive community surveillance in the inter-pandemic period, and more studies. We also need to beef up international surveillance and initiate well-placed field trials this season and next to help us both model and understand a future pandemic.

Modeling linear or additive combinations of public health measures is fairly easy, but we don't really understand what synergies among those measures may occur. Creating a good evidence base on these strategies is very important. We also need to better understand human and population behavior during a pandemic.

We wondered whether we could calibrate influenza models to SARS, and determine whether they would predict that we could contain SARS with the strategies that we actually used. Even more important is learning from the social isolation measures used to contain SARS, and from experience with anthrax, smallpox, and other infectious diseases. How do stigmatized populations who don't trust government react to such measures? What happens when different sectors of our government, including civilian and defense agencies, respond differently?

In the short-term we need better data, and people need to share their knowledge and information with modelers so they can create better models. Input from colleagues in Vietnam and other Asian countries could prove especially valuable. Another priority is designing studies for seasonal influenza, to help us establish research protocols and clarify the kinds of data we

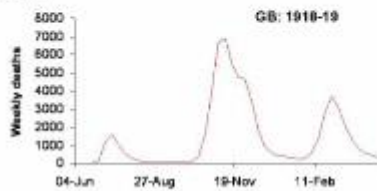
want to collect before a pandemic hits. Widespread use of antivirals and vaccines will require a slightly longer timeframe.

Media hype will ensure major consequences from a pandemic even if it is not the worst in history, and we need to understand the role of media in affecting the outcome. We also urgently need to connect policymakers and public health experts. We would make a plea for a trusted communicator along the lines of C. Everett Koop, who gave the public the straight scoop.

Working Group 7 Presentation Slides: Strategies to Contain Outbreaks and Prevent Spread-Dr. Nicole Lurie, Rapporteur

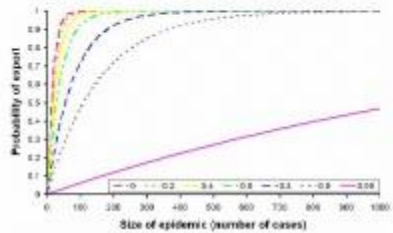
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| <p>Working Group 7: Strategies to Contain Outbreaks and Prevent Spread</p> <p>Outbreak and Containment Strategies</p> | <p>Modeling</p> <ul style="list-style-type: none"> • Mostly focused on caveats of modeling <ul style="list-style-type: none"> – Calibration – Assumptions that go into models—how do you test the assumptions and decide if they are right or things you have confidence in – Relevance of past vs real time data • Useful to help us understand what gaps are and what data are needed to fill them, and which options or intervention points are most useful to consider • Modeling agricultural epidemic • Help us to understand tradeoffs—eg in leveraging upstream vs downstream • Need to be really careful not to impel policy makers to overuse numbers—predict can outpace accuracy. However, at least mathematical modeling makes the assumptions explicit. |
| <p>Modeling</p> <ul style="list-style-type: none"> • Input tradeoffs: socially practical/feasible • Planning continually shifts throughout pandemic—so modeling has a role throughout • Lots of different models—need to be clear that one can't do it all—transmission vs supply chain efforts vs social consequences <ul style="list-style-type: none"> – Modeling, or at least considering, social consequences is important • A model can only deal with things you can conceive of in advance <ul style="list-style-type: none"> – Including stability of international relations | <p>Data Needs</p> <ul style="list-style-type: none"> • More studies like Tecumseh • Comprehensive community surveillance in inter-pandemic period • International surveillance and well placed field trials now • Effectiveness of public health measures <ul style="list-style-type: none"> – Mask use—N-95 vs surgical, community vs HC setting effectiveness – Travel restrictions – Social distance practices – Disinfection effectiveness – Combination strategies • Understand more about human/population behavior • Protocols now for use in pandemic <ul style="list-style-type: none"> – eg. route of transmission, attack rates etc, reproductive rate and generation time – Relationship of disease vs shedding vs transmissibility • Role of immunologic preparedness |
| <p>Lessons</p> <ul style="list-style-type: none"> • Calibrating models to SARS—would current models predict that you could contain SARS with strategies that were used • Lessons learned from social isolation in SARS • Other challenges lessons learned from anthrax and smallpox and others <ul style="list-style-type: none"> – Trust, stigmatized populations – When different sectors have different response <ul style="list-style-type: none"> • Eg civilian and DoD | |

**Working Group 7 Briefing Slides: Strategies to Contain Outbreaks and Prevent Spread-
 Dr. Neil Ferguson, Briefer**

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| <p>Imperial College London</p> <p>WG 7: Strategies to Contain Outbreaks and Prevent Spread</p> <hr/> <p>Neil Ferguson</p> <p>Dept. of Infectious Disease Epidemiology Faculty of Medicine Imperial College</p> <p><small>© All material copyright Neil Ferguson 2005. No reproduction without prior written permission</small></p> | <p>Imperial College London</p> <p>Are we attempting the impossible</p> <hr/> <p>Is containment of a respiratory pathogen feasible?</p> <p>Never been achieved previously</p> <p>Or has it...</p>  <p>GB: 1918-19</p> |
| <p>Imperial College London</p> <p>Topics to cover!</p> <hr/> <p>What are our objectives? Containment: what does it take? What do we need to know? Transmission dynamics & modeling How transmissible is influenza? How fast does it spread? Is seasonality important? Data needs – household & cohort studies. Data needs – school/workplace transmission. Data needs – ‘community’ transmission. Data needs – antivirals & vaccines. Data needs – population/movement data ‘Social distance’ measures – did they have an effect in past pandemics?</p> | <p>Imperial College London</p> <p>What are our objectives?</p> <hr/> <p>‘Containment’ = eradication or dramatic slowing of spread. Probably only feasible at source (SE asia?) For other countries, objectives are more varied:</p> <ul style="list-style-type: none"> ➢ Minimizing mortality/morbidity. ➢ Maximizing societal resilience. ➢ Minimizing economic impact. ➢ ‘Keeping it out’ (e.g. GB). ➢ Slowing spread until the cavalry arrive. <p>Tensions can exist between objectives. Need clearer policy guidance.</p> |
| <p>Imperial College London</p> <p>Containment – what does it take (in theory)?</p> <hr/> <ul style="list-style-type: none"> • The spread of an infectious pathogen is characterised the basic reproduction number R_0 – the average number of secondary cases generated by a single case in an entirely susceptible population. • Control policies optimally reduce transmission so that $R_0 < 1$ – since at that level an epidemic cannot sustain itself. • Hence control policies need to eliminate a fraction $1-1/R_0$ of transmission – i.e. 33% for $R_0 = 1.5$, 50% for $R_0 = 2$, 75% for $R_0 = 4$. • This can be achieved by: <ul style="list-style-type: none"> ➢ Reducing contact (quarantine, increasing social distance). ➢ Reducing susceptibility (vaccination, antiviral prophylaxis). ➢ Reducing infectiousness (antiviral treatment). • Key issues are who is targeted, how much effort is needed, and how fast do we need to act. | <p>Imperial College London</p> <p>What do we need to know?</p> <hr/> <ul style="list-style-type: none"> • Aetiology (avian- or ILI-like) • How transmissible the virus is. • Major contexts of transmission (home, school, workplace, random contacts). • Risk groups for severe disease. • The effect of specific control measures on transmission rates. • Quality and timeliness of surveillance (ascertainment). • Logistic constraints on control measures. |

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| <p>Imperial College London</p> <h3>Transmission dynamics and modelling</h3> <p>Epidemiological analyses aim to gain quantitative insight into:</p> <ul style="list-style-type: none"> • Disease transmission route(s). • Heterogeneities and risk factors for disease spread. • The effectiveness of disease-control/risk-reduction policies. <p>Mathematical epidemic models precisely represent knowledge and assumptions about disease transmission.</p> <p>Statistical methods allow key parameters to be estimated from epidemiological data, hypotheses to be tested and robust predictions (with confidence bounds) to be made.</p> <p>Integrating the two increases power of analysis, but is more difficult.</p> | <p>Imperial College London</p> <h3>Transmissibility: R_0</h3> <ul style="list-style-type: none"> • Mills et al 2004 – $R_0=2-3$ • But this assumes serial interval of 3+ days (on the basis of little data). • Probably closer to 2 days – gives reduced estimates <2. |
| <p>Imperial College London</p> <h3>How fast will it spread?</h3> <ul style="list-style-type: none"> • Depends on R_0 and average interval between 'rounds' of infection • Data on generation time very limited. • Historical estimates are more assumptions than data-based • Incubation: mean ~1.5 days (Moser et al) • Infectiousness profile (Cauchemez 2004 etc): mean ~2.4 days. | <p>Imperial College London</p> <h3>Seasonality</h3> <ul style="list-style-type: none"> • Known to be important for inter-pandemic flu in temperate countries. • Degree of variation in transmission unclear though. • Could seasonality slow pandemic spread? • Research priority <p>UK lab-confirmed isolates (biased sample)</p> |
| <p>Imperial College London</p> <h3>Data needs :household transmission</h3> <ul style="list-style-type: none"> • Longini et al. compiled household data set from family cohort study data.. • Cauchemez (Statist. Med. 23:3469-87, 2004) analysed newer French data • Data allows household transmission rates to be approximately estimated, but more data needed (a new Tecumseh?) <p>Matching household data fixes ratio of within- to between-household spread.</p> | <p>Imperial College London</p> <h3>Data needs: school/workplace transmission</h3> <p>Limited data – children known to be most at risk of inter-pandemic flu, but no robust quantification of transmission in school.</p> <p>Can approximately quantify non-household transmission, but difficult to partition.</p> <p>Age specific attack rate data is only partly informative.</p> <p>Some work underway attempting to quantify drop in transmission during school holidays.</p> <p>Better data on this critical to obtain reliable estimates of the effect of school closure.</p> |

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| <p>Imperial College London Data needs: age-specific attack rates</p> <p>• Limited data, and not all agrees.</p> | <p>Imperial College London Data needs: effect of antivirals/usage options</p> <p>• Rough estimates (Hayden, Longini & Halloran) can be derived from clinical trial data:</p> <ul style="list-style-type: none"> ➢ Uninfected individual on prophylaxis has 30% drop in susceptibility. ➢ Infected person has 60% drop in infectiousness. ➢ Additionally, a treated infected person has 65% reduction in chance of becoming a 'case'. ➢ However, these estimates are for H3N1 – not H5 <p>• Policy options:</p> <ul style="list-style-type: none"> ➢ treatment of risk groups/essential personnel. ➢ treatment of all cases. ➢ + prophylaxis of households, schools, workplaces. ➢ + blanket spatially targeted usage (everyone within x km) |
| <p>Imperial College London Data needs: effect of vaccines</p> <p>• Effectiveness of vaccines on current flu strains reasonably well quantified (both in terms of clinical effectiveness and protection against infection, reduction in infectiousness).</p> <p>• No data on pandemic vaccine effectiveness, however.</p> | <p>Imperial College London Data needs: detailed population data</p> <p>Need both population data (density, age, household).</p> |
| <p>Imperial College London Data needs: population movements</p> <p>• To model global or continental spread, need data on travel (frequency/distance) – both local (travel to school/work), and long-range (flights).</p> <p>• Need systematic exercise to collate this (sensitive) data.</p> <p>• Population behaviour during pandemic?</p> | <p>Imperial College London Research issues relating to social distance measures</p> <ul style="list-style-type: none"> • Almost certain that it can have a significant effect. • Probably happened in previous pandemics (spontaneously?). • Hence if we use estimates of R_0 derived from 1st wave attack rates, possible that these already include the effect of school closure etc. • How do we avoid such 'double-counting'? • Also, how do the rates of other types of contact change when school or workplaces are closed? • This makes any prediction of the impact of school/workplace closure highly speculative. • Quantifying effect medium-long range movement restrictions (area quarantine) less difficult. |

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| <p>Imperial College London</p> <h3>International movement restrictions</h3> <ul style="list-style-type: none">Recent analysis indicates travel restrictions would have to be >99% effective to gain any significant delay in spread from source country to unaffected country.  <p>Probability of export</p> <p>Size of epidemic (number of cases)</p> | <p>Imperial College London</p> <h3>Key data needs/modelling assumptions</h3> <ul style="list-style-type: none">Need to know where transmission occurs to develop targeted, efficient interventions.<ul style="list-style-type: none">Currently just have rough estimates partitioning transmission between households and 'other'Models therefore have to make informed guesses about school, workplace & 'community' transmission.How valid are these for new pandemic strains?Population behaviour during a pandemic???Basic natural history parameters (infectiousness through time)Disease severity (morbidity/mortality)How good is surveillance (depends on severity of disease)? |
| <p>Imperial College London</p> <h3>Ongoing UK research</h3> <ul style="list-style-type: none">Can restrictions on international travel delay the spread of a pandemic?How fast will a pandemic strain spread within a country?What will the healthcare burden?How can antivirals best be used to:<ul style="list-style-type: none">reduce mortality/morbidity?protect key personnel/reduce social disruption?slow spread/reduce attack rates?What use do social distance measures (school closure, movement restrictions) have in:<ul style="list-style-type: none">slowing spread?reducing attack rates?Logistical constraints/economic costs.Need a flexible strategy – to be able to respond to a pandemic with 0.01%, 0.1%, 1% or even 10% population mortality. | |

(Slides available on accompanying CD)

VIRAL TRANSMISSION: UNDERSTANDING AND PREDICTING PANDEMIC RISK

Working Group 8

Chairperson – Richard D. Slemons

Briefer – Daniel Perez

Rapporteur – Peter Palese

Focus: The focus of this working group is to define research needed to better understand the genetic and environmental factors responsible for animal to human and human to human influenza transmission.

Potential issues to consider:

1. What further studies are needed to define the genetic loci important for virus transmission between species?
2. What studies are needed to determine whether changes in the viral RNA polymerase play a role in virus transmission?
3. What studies are needed to define environmental factors that contribute to virus transmission and how they interact with genetic factors?
4. What studies can be done to provide measures to predict intraspecies changes in virus transmission?
5. What studies are needed to identify what measures, if any, can alter intraspecies virus transmission and what the effects of these measures?
6. What studies are needed to determine whether transmission changes can be used to predict pandemic risk?

Rapporteur Report--Dr. Peter Palese

The ability of influenza viruses to be transmitted from animal to animal, from animal to human and from human to human is determined by the genome of the virus as well as by the host.

In the past, animal influenza viruses—or at least genes from animal influenza viruses—have jumped into humans. One example was the 1957 H2N2 virus, where three genes, likely from an avian source, jumped into a human H1N1 virus. This virus, possessing a novel hemagglutinin (H2), neuraminidase (N2) and a new PB1 gene circulated for 11 years in the human population. In 1968, only the hemagglutinin and the PB1 gene came from an avian virus, resulting in the new H3N2 virus. In these two cases, essentially a human virus was spiked with genes from an avian virus and the new viruses were easily transmitted from humans to humans. We don't know the precise origin of the 1918 virus but it could also have come from birds (at least the hemagglutinin gene appears to derive from an animal influenza virus strain).

The hemagglutinin clearly helps to determine the host range and tissue tropicity. We know a lot about the receptor specificity of influenza viruses: sialic acid which is bound in 2-3 linkage to galactose is preferentially present in avian cells and a 2-6 linkage, in which the sialic acid is bound to the six position of galactose, is the more common structure for receptors of human influenza viruses. Hemagglutinins from avian viruses thus preferentially recognize 2-3

sialic acid receptors and those from human viruses preferentially bind to 2-6 linkages. However, this specificity is not absolute, since most hosts possess cells which carry both receptors. Thus, an avian virus may bind cells in the human host which also carry 2-3 receptors. Furthermore, one (or only a few) amino acid changes may change an avian hemagglutinin into one which recognizes 2-6 sialic acid (human) receptors.

We understand that influenza virus proteins interact with signal transduction pathways such as the interferon pathway. A virus may be able to effectively block the interferon response in one species (and thus grow to high titers) but not do it well in another host species. Thus, many different factors come together to determine the transmissibility (from one species to the other) of influenza viruses.

Given this short introduction, we examined our first question: What further studies do we need to define the genetic loci important for virus transmission between species? Because the hemagglutinin is probably very important, surveillance of the receptor specificity of viruses is an important aspect of understanding viral transmission. But we also need to understand the receptors in the cell. As strange as it may sound to some colleagues, we still don't know exactly which cell protein or glycolipid is the best (the natural) receptor for influenza viruses. They must contain sialic acid, but which carbohydrate-containing glycoprotein or glycolipid is the "real" receptor is still not clear. Some of the specific cells we see in some quail and chicken may actually contain both 2-3 and 2-6 receptors, so one cell may actually be a mixing vessel (for the infection of a human and an avian virus).

Other important studies would look at the molecular changes associated with adaptation. Here we are referring to all of the genes, as they may all contribute to the properties of a virus. Except for the hemagglutinin and the interferon antagonist NS1, there is probably not a good reason to single out one gene over another. We will need to employ classic virologic methods in these studies to identify the gene(s) responsible for transmission, but sequencing will also be important. The NIH is pursuing an influenza virus genome sequencing project, as is the CDC and many other groups, and those studies will prove important in defining the genetic mutations contributing to transmissibility.

We need to use different animal models to try to understand transmission. Mice have been very helpful so far, but ferrets provide another model, and we should not forget about simple systems such as organ cultures, which can shed light on which cells become infected. We can now make influenza viruses that express a green fluorescing protein, so studying animal infections with these reporter viruses will be very important. We feel that it is critical to immediately initiate such studies, although some will be more long-term than others. Human organ culture experiments, for example, are certainly more easily performed than animal studies.

Our third question concerns what studies we need to do in order to define the environmental factors which contribute to virus transmission and how genetic factors weigh in. We clearly need more studies on the environmental survival of different strains. Different viruses may have different stabilities, and some may be transmitted more effectively than others. The duration of shedding may vary among viruses, and modes of transmission may also vary, extending beyond aerosol transmission. Dr. Kilbourne reminded us that the Balb/c mouse is an important animal system for answering some of these questions because it can be standardized from one lab to another. However, we should not forget that the human is basically the best animal model we have. Prospective clinical studies are long-term and expensive, and they require excellent laboratory support. However, human studies will be invaluable in answering questions such as: Are some patients super shedders of influenza viruses? Which influenza virus

strains transmit more easily from one patient to another? At the present time, we do not have enough data to answer such questions.

What studies can provide measures to predict intra-species changes in virus transmission? We will need multiple transmission models. Ferrets are obviously the most advanced model, but other models may also be useful in reducing spread. This aspect has not received much attention, but principles gleaned from intra-species transmission should help us understand inter-species transmission.

Our fifth question—concerning what studies we need to identify measures that can alter intra-species virus transmission, and the possible side effects or consequences of these measures—was probably the most hotly debated. Some colleagues felt that social controls among both animals and humans would be quite useful in reducing spread, while others felt that they would be less effective. One important measure in preventing viral spread is educating small farmers to minimize contact with birds and rely on certain techniques for raising these animals.

Hopefully, better and cheaper vaccines will become available. One consequence will clearly be the need to study whether antigenic changes of strains are selected by the widespread use of vaccination.


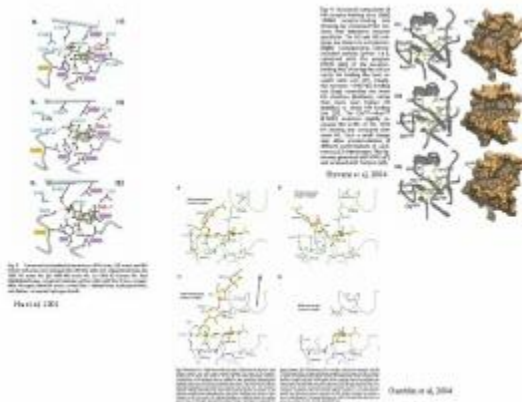
Our last question was: what studies are needed to determine whether transmission changes can be used to predict pandemic risk? We were not comfortable giving a definitive answer. One colleague suggested that we will find out only during the next pandemic. As a philosopher in New York (Yogi Berra) said, it's tough to make predictions, especially about the future.

DR. FINEBERG: I understand that Niels Bohr said something very similar, and it sounds so much more elegant coming from him than from Yogi Berra. But the sentiment is exactly right: prediction is always risky. On the other hand, if we do not make the effort, we certainly will not be prepared. The question is how to make the most cogent, effective, and promising effort.

Working Group 8 Presentation Slides: Viral Transmission: Understanding and Predicting Pandemic Risk-Dr. Peter Palese, Rapporteur

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| <p style="text-align: center;">Working Group 8 Viral Transmission: Understanding and Predicting Pandemic Risk Chairperson – Richard D. Slemons* Briefer – Danie Perez* Rapporteur – Peter Palese*</p> <p style="text-align: center;">FOCUS: The focus of this working group is to define research needed to better understand the genetic and environmental factors responsible for animal to human and human to human influenza transmission.</p> | <p style="text-align: center;">Viral Transmission: Understanding and Predicting Pandemic Risk</p> <p>1) What further studies are needed to define the genetic loci important for virus transmission between species?</p> <ul style="list-style-type: none"> • Surveillance of receptor specificity of viruses and study of receptors in cells (eg 2,3 and 2,6 in the same cell?) • Identify molecular changes associated with adaptation – classical virology, reverse genetic and influenza genomic sequencing project • Different animal models (in addition to mice and ferrets) as well as organ cultures will have to be used to study specific strains |
| <p style="text-align: center;">Viral Transmission: Understanding and Predicting Pandemic Risk</p> <p>3) What studies are needed to define environmental factors that contribute to virus transmission and how they interact with genetic factors?</p> <ul style="list-style-type: none"> • Environmental survival of different strains, duration of shedding, different modes of transmission. • A standardized model such as the Balb/c mouse might serve us well. • Prospective clinical studies with excellent laboratory support (the idea being humans are the best animal model). Supershedders? | <p style="text-align: center;">Viral Transmission: Understanding and Predicting Pandemic Risk</p> <p>4) What studies can be done to provide measures to predict intraspecies changes in virus transmission?</p> <ul style="list-style-type: none"> • Multiple transmission models will have to be used (ferrets, other models?). • Principles gleaned from intra-species transmission may be applicable for inter-species transmission |
| <p style="text-align: center;">Viral Transmission: Understanding and Predicting Pandemic Risk</p> <p>5) What studies are needed to identify what measures, if any, can alter intraspecies virus transmission and what the effects are of these measures?</p> <ul style="list-style-type: none"> • Social controls should be studied to find out whether they are effective. Education leading to prevention of viral spread. • Vaccination is possible in domestic animals (better vaccines). • Will antigenic changes be selected by widespread vaccination? | <p style="text-align: center;">Viral Transmission: Understanding and Predicting Pandemic Risk</p> <p>6) What studies are needed to determine whether transmission changes can be used to predict pandemic risk?</p> |

Working Group 8 Briefing Slides: Viral Transmission: Understanding and Predicting Pandemic Risk-Dr. Daniel Perez, Briefer

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| <p>John R. LaMontagne Memorial Symposium on Pandemic Influenza Research</p> <p>Working Group 8</p> <p>Virus Transmission: Understanding and Predicting Pandemic Risk</p> | <p>Molecular basis for interspecies transmission and pathogenesis. Influenza A virus host range is polygenic</p>  <p>Receptor specificity is a major factor</p> |
| <p><u>What we know</u></p> <p>•Pandemic Human influenza A viruses contain genes from the avian reservoir</p> <ul style="list-style-type: none"> •1918 "Spanish" flu H1N1: avian? virus that killed >20,000,000 people. •1957 Asian flu H2N2: reassortant between avian H2N2 and human H1N1 -> 3 avian genes: HA, NA, and PB1. •1968 Hong Kong flu H3N2: reassortant between avian H3N2 and human H2N2 -> 2 avian genes: HA and PB1. •Influenza viruses that circulate in terrestrial poultry have the potential to cross to humans (H5, H9) •Pigs could be potential intermediate hosts. <ul style="list-style-type: none"> •Evidence of H3N2 in pigs in or around 1968, with H3 having α2,3 receptor specificity (Kida et al. 1988) | <p><u>What we know</u></p> <p>•Influenza viruses that have established permanent lineages in humans have altered receptor specificity</p> <ul style="list-style-type: none"> •H1 viruses until 1957 have dual receptor specificity, contemporary H1 viruses bind α2,6 receptors preferentially (Rogers et al. 1989; Matrosovich et al. 2000; Gamlin et al. 2004; Stevens et al. 2004). •Glycosylation can affect the virus binding properties to receptors (Aytay & Schulze, 1991). •H3 viruses recognize α2,6 receptors almost exclusively (some of them do not grow in chicken eggs). •H5 and H9 viruses have altered receptor specificities (Matrosovich et al. 1999 & 2000). |
|  | <p><u>What we know</u></p> <p>•The internal genes limit the virus' host range</p> <ul style="list-style-type: none"> •Some internal gene constellations limit replication and transmission of influenza in humans (Snyder et al. 1997; Clements et al. 1992). •A single amino acid change in PB2 (627) is responsible for host range (Guibereau et al. 1993; Hatta et al. 2001). <ul style="list-style-type: none"> •Avian; Glutamic •Human; Lysine •Incompatibility between polymerase genes of viruses from human and duck origin (Hata et al. 2002). |

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| <p><u>What we know</u></p> <p>•The internal genes limit the virus' host range</p> <p>•Interactions between replication complex and host factors</p> <ul style="list-style-type: none"> ◦Interaction of NS1 with... <ul style="list-style-type: none"> Human U6 snRNA...disrupts binding of U6-U2 and U6-U4 during RNA splicing (Gietal, 1995) NS1-I, a human homolog of the porcine 17beta-estradiol dehydrogenase precursor protein (Kulfer et al, 1996) PABP1 and eIF4G1 (Aragon et al, 2000) 30 kDa subunit of CPSF, inhibits 3'end formation of cellular pre-mRNAs (Nemeroff et al, 1998; Chen et al, 1999; Neat et al, 2003) Interferes with interferon pathways (Garcia Sastre, et al, 1999 a&b; Bergmann et al, 2000; Taton et al, 2002; Wang et al, 2000; Tumpey et al 2004) | <p><u>What we know</u></p> <p>•The internal genes limit the virus' host range</p> <ul style="list-style-type: none"> ◦Interaction of the polymerase complex with... <ul style="list-style-type: none"> PA and hCLE a potential transcription factor (Huante et al, 2001) ◦Interaction of NS2 with... <ul style="list-style-type: none"> Nuclear export pathway (O'Neill et al, 1998; Neumann et al, 2000; M1 (Akarsu et al, 2001) ◦Interaction of NP with... <ul style="list-style-type: none"> RAF-2p48/NPI-5/BAT1/UAP56 (Morosio et al, 2001) NPI-, NPI-3 (O'Neill & Pateso, 1995; Wang et al, 1997) Polymerase complex (Sikwas et al, 1998) Nuclear export pathway (Silan et al, 2001) |
| <p><u>What we know</u></p> <p>•Some animal species may promote the emergence of novel influenza strains</p> <ul style="list-style-type: none"> ◦Quail and other terrestrial birds as potential intermediate hosts (Makarova et al 200; Perez et al, 2003) ◦Changes on the globular heads of HA and NA, as well as changes in the internal genes modulate transmission and pathogenicity (Hulse et al 2004) ◦Presence of α2,3 and α2,6 receptors in terrestrial birds | <p><u>What we do not know</u></p> <p>•Intermediate hosts that participate and the molecular features that render a virus potentially pandemic</p> <ul style="list-style-type: none"> ◦The host that resulted in the emergence of the 1918, 1957, and 1968 pandemic viruses. ◦If pigs were really involved in the emergence of each one of these pandemics. <ul style="list-style-type: none"> ◦Circumstantial evidence of H1N1 in pigs in 1918 ◦No evidence of H2N2 in pigs prior, during, or after the 1957 pandemic |
| <p><u>What we do not know</u></p> <p>•How the known interactions with host factors modulate virus replication in different species</p> <p>•If additional interactions exist with other cellular factors that may promote host restriction</p> <p>•The exact molecular mechanism for incompatibility among some replication complexes from different species</p> <p>•Whether different animal species favor certain molecular changes during adaptation</p> | <p><u>What we do not know</u></p> <p>•Whether alteration in receptor specificity is required to jump to other species, including humans</p> <p>•Whether any of the known interactions with the internal proteins are involved in host range</p> |
| <p><u>What needs to be done</u></p> <p>•Hypothesis: Pandemic influenza is the result of a complex process involving an expansion of the host range of one or more avian influenza viruses followed by a contraction with selection of one strain that transmits readily in humans.</p> <ul style="list-style-type: none"> ◦Identify molecular changes associated with adaptation in different animal species <ul style="list-style-type: none"> ◦Classical virology and reverse genetics are instrumental to accomplish this goal. | <p><u>What needs to be done</u></p> <p>•Changes associated with adaptation of influenza viruses to terrestrial birds and other potential intermediate hosts.</p> <ul style="list-style-type: none"> ◦Are pathways of adaptation in different animal species random? ◦Or is there a pattern of changes that are more favored than others? |

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| <p>What needs to be done</p> <ol style="list-style-type: none">1. What further studies are needed to define the genetic loci important for virus transmission between species?2. What studies are needed to determine whether changes in the viral RNA polymerase play a role in virus transmission?3. What studies are needed to define environmental factors that contribute to virus transmission and how they interact with genetic factors?4. What studies can be done to provide measures to predict intraspecies changes in virus transmission?5. What studies are needed to identify what measures, if any, can alter intraspecies virus transmission and what the effects of these measures?6. What studies are needed to determine whether transmission changes can be used to predict pandemic risk? | |
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(Slides available on accompanying CD)

PREPARATION FOR PANDEMIC INFLUENZA: FILLING THE GAPS IN KNOWLEDGE AND UNDERSTANDING

Moderator—Dr. Harvey Fineberg

DR. FINEBERG: The premise of this meeting is about research gaps and developing new knowledge needed to prepare better for pandemic flu, with a minimum time horizon of one to two years. Let me invite others, to share their thought about this meeting or what may have been missing from the meeting.

PARTICIPANT: There have been some excellent representatives of industry who have attended this meeting, but noticeably absent are the large pharmaceutical firms, who have a vested interest in the well being of the public health of our country. This issue is very fundamental. As a group of academic scientists, we can have grand designs about producing drug X or drug Y; however, it is actually the industry that is going to have to produce the drugs. The hurdles that we have talked about in terms of public health delivery or in terms of the academic challenges are not as insignificant as they would be for producing the drug that is going to be required by our society. In the future as these meetings continue, the senior management of the large pharmaceuticals who really do want to participate in this effort should be invited and should have a seat at the table.

PARTICIPANT: I think there are some more industry representatives which I was glad to see. I think partnership is the theme of the times. And I think back over three decades of looking at it from both sides. If we think about partnership 30 years ago, it was there. We were doing it, but it is much more so now. I think there is a sincere interest and belief that partnership is not only the way to go, but it is essential, and I think that is happening. I think as we look around, we see that the academic-government-industry partnership is working. It is high maintenance. It is a ton of work, and it can be exhausting, and there can be partnerships that simply do not work, but that is the way we are going.

I think we need to see some innovation in looking at how these things work, especially on the funding side. Simple grants and contracts are not going to do it anymore, and I think the question of how to pay for stockpiles is a good example. Clearly, stockpiling in one sense is something that companies want to do. They want to make stuff for stockpiles. On the other hand, let me remind everyone that the last thing companies want is inventory. Inventory is evil in all its forms, as they say in the industry. And the stockpile is the ultimate inventory. So, rather than say we need to have a ton of capacity, we have got to find ways to do that without -- and novel ways to fund it. For example, the payment may not be for the drug or the device in the stockpile. It may be for maintaining the inventory and different ways to do that.

I think the issue of indemnity remains an important one, and we have to wrestle with that. I do not believe it has been answered, and it comes up all the time. It came up yesterday; we need to deal with that issue. We are in a time when novel approaches are welcome, and I think the door is open.

PARTICIPANT: I think it is a little unrealistic to ask industry to increase capacity to the surge that would be needed for a pandemic, especially when we have to recognize that we are not controlling inter-influenza now. I think the burden on us is to increase demand. Right now the ACIP recommendations include 185 million people. And you know how much vaccine we regularly distribute here. So, if we were distributing anywhere near the amount that we recommend, a lot of that supply problem would be taken care of. The same goes for antivirals. I do not think we are using antivirals nearly as effectively as we could to supply vaccine. And if we were doing that, recognizing flu in the community has occurred, and treating it appropriately, we would increase the demand, and therefore increase the supply. So, I think that is something we need to work on, and help industry work toward the goals that we have for pandemic preparedness.

DR. FINEBERG: Do you think it is imaginable that there could be an experimental demonstration, or does it just have to happen gradually across the country? Could there be a state or a region which said we are going to take this seriously. We are going to get our professional groups, we are going to get industry, we are going to get the public health authorities, we are going to have a community education program, we are going to make sure every family knows how important this is, et cetera, could that be imaginable?

PARTICIPANT: I think it is not only imaginable, I think that is what we are trying to do now. And I would just like to have more support and other groups to join us.

PARTICIPANT: I have actually seen a number of pharmaceutical people here, more than I thought might be here. I've seen leaders from GSK, Chiron, and Merck. I am really glad for the opportunity to be here and be part of this dialogue.

I just wanted to say even though we do not currently have a flu vaccine on the market, we certainly did have one in the past. Our interest in influenza has never waned, whether it is a vaccine or the antiviral efforts. And there are different roles for different aspects of the industry.

I do not know that it is the best thing at this time to be a contract manufacturer for egg-based vaccines. Certainly in an emergency we will do whatever needs to be done. What we focused on, particularly in the last decade in the 15 years among other things, is trying to come up with new ways of making better flu vaccines and getting broader immunity is really the goal of our work. That may or may not be something that is going to be feasible in our lifetimes, but certainly there is unmet need there, and that is something the world needs. And we are looking for ways to not only continue our efforts; we are looking for support and communication with groups like this one to do a better with this.

DR. FINEBERG: Thank you for your comment. I think you also in these remarks, highlight the transitions in capacities and interests that are represented I would say in universities, as in industry and in government increasingly as well. And thinking afresh about the relative contributions that can be made I think is a very important reminder, and a very welcome one.

PARTICIPANT: I would just like to highlight a theme that has been mentioned several times in the course of these meetings, but perhaps one that needs emphasis. And that is, this is an international event with which we would be dealing for this. And certainly one of the issues that needs a top priority, if not in terms of resource commitment, at least in terms of policy evaluation is if there is indeed a limited supply of antivirals, and that is possessed by the more developed countries, what is that commitment to the developing world? Because this is where at least most

people feel the initial outbreak is likely to occur. That is something that should be worked out very early in the course of this.

The second point is with respect to modeling. I would encourage you to go beyond the national borders when you consider modeling. Look at the downstream effects of this, not only in terms of who takes care of the kids that are no longer in school, but going across international borders, what is the effect on this on our commerce, of our agriculture, of our energy supply? How does this come back to affect this country or the world in a fairly short-term perspective?

DR. FINEBERG: Thank you for your comment. If I may, I think your remarks focused on modeling but apply with equal force to our general discussion about research strategy. That is defining the research strategy also can benefit from looking at it from a global or different country perspective, as well as from any one national perspective. And I think the force of those comments apply equally to all of our thinking about research strategy.

PARTICIPANT: Just to follow-up on the issue of funding and how we are going to do this. I personally think that we have exhausted the situation of trying to get what we need on inter-pandemic flu preparedness. If you extrapolate the line of increase, it will be about 90 years from now that we will reach some kind of moderate worldwide capability of producing flu vaccines and antiviral drugs. I think we have to take a step back, because we are talking about an issue of international security and economic consequences that are unlike anything that humankind has seen. And you can say, well, do not say that, because you will scare people. I think we have to be willing today to say we are not going to say it is H5N1, but a pandemic influenza situation is going to occur unless somebody is convinced that water now flows uphill. It is Mother Nature. It has been there. It is going to happen. We have already discussed you do not need an H5N1 in a world of 6.5 billion people today to create economic chaos for 12-18 months.

As a world, we invest all the time in things that are insurance policies. Today, some of the best funded fire departments in this United States exist in our major metropolitan airports; airports that have not had a plane crash in 50 years. Airports that have incredible equipment, and never can leave the airport compound, because they have to be there. And we pay for that day in and day out, because we have made a decision if it ever does happen, you have to be able to respond in the force that is equivalent for a plane crash. We do that with our federal oil reserves. We have spent billions of dollars stockpiling oil in the salt domes of the Gulf States. I think we have to change our mind set to say that this is an insurance policy that we are not going to sit here and try to scare you and say this H5N1, although many of us think that still is a real possibility, but it is going to happen. And we need a Manhattan-like project that encompasses many of the issues that have been discussed here today; it is going to be an economic insurance policy.

To follow-up on the previous comment about the international piece, I would remind people that if we totally protected ourselves, if we had 300 million doses or 600 million, depending on the two dose regimen in the United States, we would still be devastated, because the economic consequences of a worldwide pandemic minus the United States would still have incredible implications. We saw it during SARS. The computer industry of this country shut down, because no one realized that 95 percent of the computer chips in the world were made in the Kwong Dong province of China. And when they couldn't travel, nothing else traveled. And if you start looking at the consequences here, we can demonstrate to our policymakers that this is in fact a very wise use of resources.

And so, I would urge us to take a step back, get away from this idea that if we could just keep expanding inter-pandemic flu, not that no one does not want to do that, because that is like motherhood and apple pie. But I think we are ready for a sea change. We are at a point where if we do not do it now, we are not going to it.

And then I would just add one last piece. I have absolutely no doubt about it, and all of you in this room will be part of it, there will be a post 9/11-like commission one day that will ask the questions why we did not do what we could have done, when we could have, because people were afraid that we would scare people, or that somehow we would be seen as scare mongers, that we have not put it together.

And I guarantee you, just as many of the very fine people who pre-9/11 said I wish I had done more, ended up being identified and well documented in that 9/11 commission report. There will be post-pandemic flu commission, make no doubt about it and the people in this room are going to be the people who are on the front line. So, it is time that we either make a decision that we are going to actually not live for another 20 or 30 years, whenever the pandemic occurs, trying to do this, and actually for once set out an international policy that says to our world leaders you can not afford not to do this.

PARTICIPANT: In terms of things that we are missing from the meeting, I did think that more of a focus on what the economic impacts of a pandemic might be would be something that would strengthen the overall case. A study of the economic impacts of disease, emerging disease in particular is being done. There has already been about a \$10-12 billion impact on Southeast Asia as a result of H5N1, which is a significant impact. It compares to what we estimate to be a \$30-50 billion direct impact from SARS, so it is getting there.

I wrote an op-ed piece which did not get published several months ago about H5N1 in which I pointed out that if you did have an influenza pandemic, the economic impact would be utterly unlike anything we have ever seen before. And the analogy that I used that I think would be powerful is an analogy to the first world oil price shock. You will remember back in the 1970s we had been in a sustained period of relative calm and low prices in oil, and then we had a shock to the system which created an enormous concern about our vulnerability to oil prices. Now, it took the shock to make the International Energy Agency happen, but it did happen, and there was a sort of Manhattan-like project organized internationally around the paucity of information that existed, and standardized information and data on in this case, energy and energy statistics.

I would suggest, after having gone through the exercise of trying to find good data on the economic impact of emerging infectious diseases over the past 30 years, the data is terrible. There is no standard data out there. There are no standard metrics. And it would not be a bad idea for the world community to take seriously the idea that there needs to be a collaborative approach to gathering standard surveillance data sets, as well as other data sets that could be tremendously important in the event that we did get an emergence.

The final comment is just that in a practical sense, for the last six months I have been trying to bring together major corporations, including the pharmaceutical industry, but also the biotechnology industry, and many other sectors of the economy to take seriously the idea of planning or thinking ahead about the potential impacts of an avian influenza pandemic. And I can tell you that it is fascinating, because when we began this work really around SARS, at that time major corporations really did not take the possibility of disease emergence as being a

serious business issue. It was something that maybe there was a chief medical officer who worried about disease emergence from the point of view of what should I tell my human resources people about our travel policy, or something like that, or how does it affect my insurance? But it was not seen as fundamentally a business disruption issue. SARS changed that fundamentally. GE, for example, just hired a global security officer to be a bridge between the chief medical officer and the business planning people, a similar thing is going on for at Kraft Food, or any one of a number of other Fortune 500 or Fortune 1,000 companies. My suggestion is that we involve not only the chief medical officers, but also people who are increasingly tasked inside these major companies with the job of understanding what the business impacts are going to be.

DR. FINEBERG: Thank you. I think that point about the interest and willingness of industry to support this work also gets to the question of mobilizing the kind of political movement that would lead to public decision-making, because it goes hand-in-hand, one with the other.

PARTICIPANT: I would just like to second the comment about engaging politicians. I have spoken in this National Academy many times to the choir, if you like. And I am encouraged that I am speaking now to some of the politicians who can influence what is being done on the Hill. This is a very important step forward, because over the past five years we have seen the scientists have pushed this field forward. We have got good antivirals. We have got strategies to make vaccines. We can make any influenza virus we wish now for good or for bad. And we have to keep that in mind, for good or for bad. And so, I am encouraged that the science is in place, but there are many questions that are not in place. They are all man made -- liability, the willingness to stockpile, how to use these things. I am very encouraged by the meeting today, the modeling, and the modeling of the use of the antivirals that I pushed for in this room many times, to see this put in place is most encouraging.

This is a monumental event as far as I am concerned, one of the grandfathers of this whole business. And so, I compliment you and Mike and the others for making this take place.

I also come back to having just returned from Hong Kong, I was in Hong Kong, at the time, May, when the SARS was at its peak. I came through Hong Kong, and those that know Hong Kong, I was the only person from overseas entering Hong Kong. I had the luxury of sleeping in the Mandarin. There was no food available in the Mandarin. I met with the chief executive, he said, tell me one thing that I can do. The economy is in a tail spin. Just one thing, I will do anything to turn this economy around. The economy was in disaster. How many people died of SARS? A handful, compared with what would happen whether it is H5N1 or H9N2 or H2N2. It is going to happen, we know that, sooner or later.

And so, yes, do put a plan in place, because going back to Hong Kong, there has just been a commission in Hong Kong looking at why SARS was not correctly handled in Hong Kong. And the senior people have lost their jobs. So, yes, take this opportunity and finish the job that you are just beginning.

PARTICIPANT: My introduction into influenza was in 1957, when the first pandemic came along, and we had no flu surveillance program at CDC. And so, I was charged with setting that up, and following that epidemic along through the summer, and then along came autumn.

A lot of work was being done to develop a vaccine, and indeed through the summer things were relatively quiet. About the 15th of September all hell broke loose, and we had a huge epidemic that went across the country. The vaccine finally began arriving, as I recall at that time, about the 1st of November. The epidemic ended toward the end of November. And as I look at it today, we are not much better shape today. If we got the strain today at about the same time we did in 1957, we would be getting the vaccine pretty close to the same time. We had a wake up call in 1968, with the next pandemic, and I know there is a lot of enthusiasm about getting on and doing something, a spasm of interest. Things disappeared, and we came up to 1978. I think that was my first major influenza meeting. Much was said, many thoughts were there about what we could and couldn't do, and another spasm of interest. Tissue cell culture was just around the corner, two to three years. I remember that very well. And that is something I think is repeated at every meeting I have ever been. Then we had the swine flu affair, which certainly again stimulated a tremendous amount of interest, activity, what have you, pledges to do something, et cetera, et cetera.

Then as we come up to this year, or last year and you look at the amount of money going into research in influenza even as recently as just two years ago, a year ago, it was pretty slim. It was not really until the H5N1 began spreading in South Asia that I think we really began to get increasingly concerned. I know Stewart Simonson and others in HHS were really deeply concerned about this, and managed to obtain quite an increase in funding for it, although certainly far from what I think is needed.

Well, again, we have a great deal of interest and concern about pandemic flu. I think we all pretty much would agree that we are going to have a pandemic at some point. Is it going to be H5N1? That is hard to say, but if it were, I think it would be really serious. And we have never had anything quite like this H5N1 experience before, so it is a little hard to read at this point in time.

I think, if there is anything that I felt was missing at this point in time, I just do not have the sense from the meeting that there is a sense of compelling concern about moving ahead with some sort of deliberate and fairly vigorous activity to at least prepare for the next pandemic ASAP, not somewhere down the road. So, I think for me this has been a great meeting in terms of outlining a lot of needs that we have in the research field. And I think a lot of people have very thoughtfully examined a real agenda out for 10 years. What I really have missed is a sense of urgency that maybe we ought to be doing something really serious, maybe more than we are doing now, and laying out an agenda which is going to take us down the road for 6 months from now, for 18 months from now if indeed H5N1 remains quiet. So, I would hope this is not another spasm, and that we all go back to our laboratories and that is it. But I hope we keep up something very vigorous at this point. I think we need it.

PARTICIPANT: It is been a privilege to be a part of the discussions that have gone on over the last two days. And I undoubtedly share the views on urgency; I think urgency needs to be writ large in all of this. I have one question and I think one comment. The question really relates to the synthesis of what has happened over the last two days. The science has been highly informed, most interesting. I have learned. I am sure it is been very valuable to many people. The question that I have, is this going to be a portfolio that develops from all of this discussion that is a managed portfolio? Or is it business as usual, with some great ideas that need to be developed, and science will go its usual way in finding solutions? I hope it is clear which my preference

would be, and my preference is that this would be a very clearly managed process that delivers outcomes in the shortest possible time.

My comment builds onto that. Those of us who work in policy development and implementation are already working pretty hard towards how we will deliver antivirals to treat people, and how we will deliver vaccines to prevent any further harm to our societies. My plea is that the research that is taken forward is supportive of those requirements and perhaps the excitement of the science may be just bridled a little so that questions that will answer the difficult issues that we will have to face are those that come to the fore.

PARTICIPANT: I think for me, pandemic planning is important, but what would be more important is to prevent a pandemic from happening. And I have heard a lot of good ideas I think at this meeting which could help doing that. For example, trying to contain the disease in the place where it is.

Dr. Webster this morning clearly indicated to us that if you would be able to provide economic support to the people that are actually holding all these birds that are infected, or ducks that are infected, that you might be able to control in that place.

The modeling that we have seen also indicates very clearly that you can do things to contain disease in certain areas by making antivirals available at the place where they need to be available. Another idea that I heard, and I really hope that that is going to get some very clear attention is to proactively add antigens to the licensed vaccine. I am thinking we have for five years been putting H1 New Caledonia in this vaccine. It wouldn't hurt so much for one year to put for example, H2 in there, of which I would be more concerned, because it has shown us that it can transfer very well from humans to humans. But then the next year put H5 in there. I have heard that a lot of people have suggested this. But I am very much afraid, because so many ideas have been posted here, that nothing really happens with, those ideas that deal with prevention of pandemics. And I am wondering who is doing what to make sure that somebody actually takes action?

DR. FINEBERG: I will not take that as a purely rhetorical question, because it is central indeed to a number of the commentators. I would just say on that last point that what we hope to accomplish out of the discussion is to assemble the principal ideas. And I think one of the principal ideas which was just articulated is the need for a coherent strategy that is not nearly, if you will, an eclectic collection of whoever happens to think of a good idea that might be then supported, but rather a more concerted strategy.

The question for me is what is it that we will do from a research point of view that will put us in a position in two to five years that is different than the position that we are in today, quite in addition to the very compelling and important messages we have heard about the need to prepare today for the possibility of the outbreak and the pandemic even in the coming season, much less before we have made any of these additional changes.

When I said earlier that it is in a sense up to us to do things, I mean that quite literally, and not merely figuratively; those of us here, and those that we can influence. And I think that this will be an important consequence of this activity if indeed we carry it through. If we fail, then we will be subject rightly to the criticism of those who will look after and look back and see those who could have done more and failed to do it.

PARTICIPANT: I have a comment and a request, and that is I found this meeting to be very enriching. I think a lot of great ideas have come through this. But I would like to echo the comments about that we know something is coming, and we ought to have a sense of urgency to start doing something about it. It would be very helpful to the industry to know what our role would be in case a pandemic happens in a year or two or five years. Therefore, I would like to see a meeting similar to this that looks really at preparing for a pandemic in practicalities. For example, if you are going to vaccinate 600 million people in the US, do you have the distribution infrastructure to do that? It is hard enough to try and get 80 million or 100 doses annually distributed. I heard through the grapevine that WHO might be organizing such a meeting, and I would urge them to do that rather urgently.

DR. FINEBERG: I do not know if Klaus is still here. Do you want to comment on the plans, which I think you alluded to, Klaus, in your own comments?

DR. STOHR: Well, I am not sure if I can give a good answer to your question, I think, which was very good. I believe that there are different partners who have different responsibilities. Without any doubt, however, for the delivery of a safe and effective vaccine in time for a pandemic requires a very strong partnership between the public health institutions and the industry.

You may know that in November last year we invited the industry to come to the WHO to discuss at least as view it, the slow progress in vaccine development. We had a very good response by the industry. November of last year there were two companies which are considering the development of clinical batches of pandemic vaccine for testing, now there are 12 companies I think in 8 countries. So, I do believe a very strong partnership is necessary. In the end we have to look how we can jointly create an environment which is conducive towards insuring that at the right point of time a safe and effective vaccine is going to be available.

DR. FINEBERG: Thank you very much, Klaus.

PARTICIPANT: I also found this to be a terribly interesting and enriching meeting. And just thinking about your last comment, Harvey, about the synthesis, and thinking I guess also about your question about what kinds of things are missing, I am really struck by the fact that preparedness requires sort of a balanced portfolio if you will, of the kinds of research that we have been talking about today, planning, and figuring out not only how we are going to make a plan, but how we are going to operationalize it, which takes a lot of practice. It takes a lot of exercise. It takes understanding why we have not had traction on this, despite all the multiple efforts we have heard about before. And so, the other pieces that I just would like to put on the table in terms of research that need get done are really the kinds of questions about how do you best operationalize the plan? How do you best practice so that you can keep getting better? How do we answer the questions about if when we have vaccine, what are the more efficient ways to deliver it? And a whole variety of other questions that I think cross preparedness for lots of kinds of infectious diseases, and potentially other kinds of events. But we have not talked very much about a research agenda there. We talked a little bit in our group about issues related to population and human behavior, about trust, about stigmatized populations. All of those things I think are still not on the table to the degree that they should be.

And then finally, something I do not think we talked about much at all is maybe getting some help from some political science types or others to answer the question about why so many people have been at this meeting so many times, and there has not been traction. Are there other

lessons learned about the political system that would help us be able to move forward in the future? It can not be one or the other, but I think we need to balance the portfolio of the hope of many of the exciting discoveries and innovations we talked about today with some really practical, now, on the ground stuff.

DR. FINEBERG: Thank you. It may be that those who commented on what is missing also were expressing what they think was most important, but I also would like to invite those who had thoughts about what they took away as a most important lesson from the two days that they would like to share with the group, that this would be a good time to do it. So, the floor is now open for any discussion of lessons, take homes that you would like to offer to share with everyone here.

PARTICIPANT: I would like to respond to the request for doing something now about something that might happen very soon. I do not know what the next pandemic strain is. I do not have the crystal ball that everybody else seems to have.

Since 1969, I have been advocating that we make high yield reassortment viruses against all the existing known HA subtypes. It would not have to be put into storage, but certainly seed viruses can be made. They could be preliminarily tested and so forth.

Every planning commission that has come up since has endorsed this recommendation. I do not know what really is going to have to be done to implement it, but I am making one final plea, that this very simple operation, if anything occurs in the next five years, it is going to be chick embryo derived inactivated vaccine in all probability. All the elegant work with reverse genetics, and the DNAs and so forth should proceed apace, and I hope very rapidly. But in practical terms, that is what is going to be available to us. So, I think that we can at least get a hold of H14 and H10 and so forth and so on, that thus far have not caused any trouble, and simply add those to a stockpile of seed vaccines ready to go. It would save us months when the trigger is pulled, and we know what actually the next pandemic virus is, if there ever is one.

PARTICIPANT: We are starting a program to do this for developing live attenuated virus vaccines. We have been listening to you, but only part of what you are saying. We are very interested in developing live attenuated virus vaccines, because we think that they are going to be especially useful in the time of pandemic for the reasons that Dr. Fauci put up on the screen during his talk.

The point I want to make is that I think that one of the problems that we have now, is that for the existing technology for making subunit vaccines--for inactivated or non-living vaccines--the results were terribly disappointing in terms of their immunogenicity. What we are doing now is we are disrupting a virus and finding out that for the H5 antigen, it is not terribly immunogenic unless we now put back in an adjuvant, which we do not have a lot of experience with, and then hopefully get it up to levels that are barely associated with resistance. I think one of the reasons that there has not been an awful lot of enthusiasm is that we really have not developed a coherent strategy for exactly what is the goal in this situation. And I think one of the real important things that we need to come out of this particular meeting is making a simple decision. Do we want a whole virus vaccine that we do not have to disrupt and then use an adjuvant, rather than a subunit vaccine? Because right now, most of the manufacturers I think are making the opposite, making the subunit type vaccine. And that is a simple decision. That would not be a bad decision to come up early on, because the other decision has complications. So, I just think we need to really decide on a strategy. And then I think Ed is absolutely right. We need to not just get the vaccines

made, but make experimental lots of sets of experimental vaccines to find out whether H4s through H15s are indeed immunogenic in humans. How immunogenic are there? We need to find out what kind of generalities can you make by using these particular immunogens. That information does not exist right now. It is absolutely essential in order to say if a new virus comes, are we going to be able to successfully use a strategy which we think is going to work. Right now we are finding it is not very successful for the H5.

So, I think there is a lot of very, very important stuff that needs to come out of this. And I would agree that we need to make vaccines, decide on strategies, get lots of experience with multiple HAs, both live, inactivated formats. There are even some vector strategies that need to be considered, and make progress along these lines.

PARTICIPANT: Well, I think my favorite moment is where we start thinking about what is in pandemic preparedness for countries with limited resources. For example, why should a resource poor country be engaged in pandemic planning when it is unlikely they will ever get a slash of the vaccines or the antivirals?

And I thought with Neil Ferguson's presentation for example, that the incredible importance in getting there early, partnering, and actually having something in terms of incentives to offer to those countries that are actually engaging and contributing, that is really, really important and key from this whole meeting.

PARTICIPANT: I would like to pick up on some earlier comments about the reasons why we find ourselves here every few years. And I think we have a problem of a law of the commons. All of us here have private interests as well as public interests, and we share the same public interest about doing something for the global public good for public health measures for influenza. However, there are also commercial, academic and public agencies who are seeking also their own incentives, whether it is for funding or credit for the future, or other types of incentives. And it brings up an issue about in this country we have no national institute of public health in effect, that funds global collective goods. And getting the type of collaboration, whether it be for the magnitude that we are seeing ourselves dealing with, this is a magnitude of proportions that mankind sees perhaps a few times a century, but yet we all need to act together collaboratively. Dr. Gerberding pointed that out very succinctly in her slide.

But again, the incentives of our individual provide settings do not necessarily allow that collaboration to take place. So, that is why I think we find ourselves here every 10 years, seeing the same problem. And we come back again when H5 resurfaces and have a few meetings. We had a meeting here in June, a similar meeting, but yet hopefully this perhaps will be different. I do not know how it could be different.

We talked about data sharing. There are a number of new mechanisms that were created. The NIH has NLM, which has GenBank which puts out data in the public domain. We have a sequencing unit now that will sequence all data. I do not know if that will be successful, if people will share their strains. That's data that can be modeled, that can help to prevent and predict potential strain drift and shift.

There are other types of IPR technologies which companies have, and I am not sure whether or not there are commercial incentives which will allow them to share it or not. Again, these are issues that are very valid, because everyone has their own private and public incentives.

That is the way society is set up. But once again, are we dealing with an issue of significant magnitude that will invite a collaborative spirit that we have not seen before?

PARTICIPANT: I want to just support what others have said about this being a serious problem. I would like to harken back to something I mentioned when I talked, and that I have thought a lot about, which is sort of like whether this particular avian flu is Chicken Little, and we said the sky is falling, and it does not fall, or it is Chicken Big. The issue really is that pandemic preparedness has to be addressed for the short- and long-term. This perspective ties in with this preparedness portfolio. As we move new technologies further along, and understand better what interventions we make, we also have to be focused on public health preparedness.

I want to return to the comment that I made earlier. There are studies of immunogenicity of novel strains. Further, the studies that have just begun that were described here by some of the funders and participants will be informative. If we do see substantive immunogenicity in any of the regimens, one could consider: Can we incorporate immunologic preparedness for pandemic strains into influenza preparedness in general? And we will then have some vaccine, and a way to give it. And one could conceivably make more. I am not saying it is just building immunologic memory in the population. It is evaluating this whole portfolio critically. But that is something that I think we do not have to wait forever, and can help build the kind of capacity we need.

PARTICIPANT: I would like to thank the organizers for supporting me to come here from Thailand. I feel badly for other countries like Vietnam or Cambodia that did not have the chance to come here.

In Thailand we have had a few meetings to discuss similar issues that are being discussed here. So, we appreciate that you recognize the problem in our area. When I heard the modeling of a pandemic presentation, and it was said that it could take about two to four months for the pandemic to spread around the world. I thought that in reality, if we had a pandemic, we would have no chance in my country. To have access to tamiflu at the time of outbreak is difficult, it was difficult in the past with the two outbreaks that have occurred.

In Thailand we believe that other countries will have their own stockpile of drugs or vaccine for their people. But how many people or countries will think about getting vaccine to the hot spot where the outbreak occurs. We would like to plan to be self sufficient—to stand by our own. But we do not we have the factory to produce vaccines, why? The technology is difficult for us acquire. We would like the WHO or other international organizations to help support vaccine production in our countries. Similar support is given to us for work on HIV research. We have a NIS laboratory to support us with the reagent, the serum, and the peptides. I would like to see something like this for pandemic flu. It is difficult to send materials out of the country. You need a special channel for transporting infectious material out and to communicate to with the international organizations, it takes time. If an international organization can help us get access to materials-- reagents so we can take care of ourselves from the beginning. We can then give you preliminary data at the time that the material is being shipped to your lab.

PARTICIPANT: My comment follows-up on an earlier comment, what was missing was social science research linked to all the research that was presented and discussed here-- the more basic infectious disease immunology and virology research. When a plan or strategies for the implementation phase is developed, you need to know the recipients of these strategies very well. There could be some near-term research that would look at how you reach different kinds

of people in different settings; this research would be helpful for any public health emergency, not just this one.

We have had experience here, for example, the African American community in our country, which is not represented here, had a really hard time accepted preventive measures for HIV infection. It took a long time, because the public health community really did not understand what the concerns were, what their beliefs were, and how to reach people who had credibility in that community. So, whatever strategies are developed, be they for prevention, for prophylaxis, for management, for dealing with an emergency, maybe there is already research out there that I do not know about, but the linking of the social science research that would help in the implementation of whatever these other areas come up with I think would be helpful.

PARTICIPANT: I spent a lot of time trying to make the case for investments in diseases that are very far away and neglected. And I am struck by the disparity and the reality, and how we are looking at it. And I do not know if that is social science, anthropology, or what the field that is required here. We have a disease here creates 36,000 excess deaths every year. And it is really different than malaria, where it is very far away, and it happens to children, and it is unseen, and there is not an advocacy group. So, I think we have in the context of a number of anthrax cases that caused sheer panic in this country; we have the basis for thinking that this is an important disease every year. And yet, we are unable to communicate that beyond the in community that works on influenza and works on vaccines and thinks that this is important. This abject failure to translate what are real, countable deaths and then the fear of the next pandemic when it strikes is really astonishing, and one that deserves some analysis that goes beyond the tools that we probably have at this table.

PARTICIPANT: I just wanted to follow-up on the very good point about the social research agenda and what is going on here. I think this is a very important point. One of the areas that public health today is really short strapped in attempting to try and prepared for this kind of issue, and they obviously have been boosted to some degree by the recent funding that has come out relative to post-9/11. But what very few people realize is that while those dollars were coming from the federal government, state governments were cutting that amount or more in many states because of state budget issues. Many of the state health departments are not really much better prepared today in terms of infrastructure, planning, and so forth. You need look no further than what happened last fall when we had the vaccine shortage. Nobody was prepared in the public health or health care delivery system to figure out how to allocate vaccine in this drop of a dime when there was suddenly a shortage. And the fact that we did not even have that worked out I think goes to the point that was being made about we have a lot of work to do here. So, I think that agenda should be there very, very definitely, and that that is part of the research.

It is as horrible to consider, but being prepared is as straightforward as how do we deal with bodies? We had one experience in this country in 1995 in Chicago when we had the heat wave, where they could not process bodies fast enough and had to put them in refrigerated semi-trucks, which created a psychological situation in itself, which was there. We have done the calculations. Even a mild pandemic today in this “just in time” delivery model of even funeral services and burial could not handle a slight increase in the number of bodies that would need to be processed. So, I think that is again, a social science issue as much as it is actually a technology issue. So, I think many of us would urge that that be part of the research agenda.

PARTICIPANT: If you go on to the Department of Health in London's Web site, there is a public information leaflet that tells you and your family what you need to know about pandemic flu. The point about this is that this has been researched. And just as it is important to be doing the research on all of the things we have heard about in the last two days, this simple piece of writing and leaflet has been researched with the public. It is been redrafted and re-researched. This is part of the operational research and the infrastructure research that is every bit as important as the rest of the science. If you cannot communicate the issues, there is not much point to actually doing the science. So, we already have this communication piece. It is in place, and it is available. But this type of research is a part of the research agenda that we have not talked about in the last two days. It is every bit as important.

DR. FINEBERG: Thank you for that reinforcement. This has been a remarkably hardworking group. I must say, the fact that you have been willing to attend so faithfully not only the plenary sessions, but to throw yourselves into the workshops to work so creatively, I would say so abundantly with the ideas that will give us a lot to work with in trying to craft the proceedings of this discussion that does justice not only to the ideas, but to the convictions and the drive that is behind so much of this discussion.

I think that it is inevitable that a research strategy must begin from a vantage point of asking why we are starting on this research. And if we do that, and if we start from a vantage point of protecting the public, if we start from a vantage point of protecting the individual patient, if we start from a vantage point of solving mysteries of biology that apply to flu and to others, if we ask ourselves the question of what is important in one country, and what is important from another country's vantage point.

If we are willing to take multiple perspectives, I think we are going to be able to define a convergent research strategy that is going to depend upon many actors working in a way, at a degree of coherence, and a degree of collaboration, and a degree of coordination that is unprecedented in the flu field, and maybe unprecedented in preparation in advance for any natural disaster. I am hopeful that this deliberation, this set of discussions can contribute materially to the ability of ourselves, our nation, our world to accomplish that kind of increased coherence for research.

I want to ask each of you who are here if you have thoughts afterward that are result of further reflection, or perhaps you have not felt moved to come to a microphone, and would like to share some additional ideas bearing on these questions that we have discussed over the two days, we welcome them. We urge you to share them.

I want to say personally how much of a thrill it is been for me to be able to be part of the discussions, to be with so many who have done so much over such a long time for public health, for influenza, for research, for the care of patients, for the advancement of science as it bears on all of these concerns. I am truly grateful to all of you for your participation. I want to thank the presenters, the briefers, the chairs, the rapporteurs, and all those who have contributed so much through the course of these discussions, and helping to plan it, and helping to carry it through.

I look forward very much to our continued work together toward the goals that we have outlined. I want to thank all of you for being part of the program. And please join me in also thanking especially the staff, Dr. Rose Marie Martinez and others who have been so valuable through the course of these days in making our discussions come to life.

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SPEAKER BIOGRAPHIES

Anthony S. Fauci, M.D.

Dr. Fauci received his M.D. degree from Cornell University Medical College in 1966. He then completed an internship and residency at The New York Hospital-Cornell Medical Center. In 1968, Dr. Fauci came to the National Institutes of Health (NIH) as a clinical associate in the Laboratory of Clinical Investigation (LCI) at the National Institute of Allergy and Infectious Diseases (NIAID). In 1974, he became Head of the Clinical Physiology Section, LCI, and in 1980 was appointed Chief of the Laboratory of Immunoregulation, a position he still holds. In 1984, Dr. Fauci became Director of NIAID, where he oversees an extensive research portfolio of basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, illness from potential agents of bioterrorism, tuberculosis, malaria, autoimmune disorders, asthma and allergies. In addition, he serves as one of the key advisors to the White House and Department of Health and Human Services on global AIDS issues, and on initiatives to bolster medical and public health preparedness against possible future bioterrorist attacks.

Harvey V. Fineberg, M.D., Ph.D.

Dr. Fineberg is President of the Institute of Medicine. He served as Provost of Harvard University from 1997 to 2001, following thirteen years as Dean of the Harvard School of Public Health. He has devoted most of his academic career to the fields of health policy and medical decision making. Dr. Fineberg helped found and served as president of the Society for Medical Decision Making and also served as adviser and consultant to the US Centers for Disease Control and the World Health Organization. At the Institute of Medicine, he has chaired and served on a number of panels dealing with health policy issues, ranging from AIDS to vaccine safety. He is the author, co-author, and co-editor of numerous books and articles on such diverse topics as AIDS prevention, tuberculosis control, assessment of new medical technology, clinical and public health decision making, and understanding risk in society.

Neil Ferguson, D. Phil.

Professor Ferguson holds the chair in Mathematical Biology at the Dept. of Infectious Disease Epidemiology, Imperial College. He uses mathematical and statistical models to investigate the processes shaping infectious disease pathogenesis, evolution and transmission. A key practical focus is advising on disease control policies in public health, clinical and veterinary contexts. As well as basic theoretical work on evolutionary and epidemiological dynamics, Professor Ferguson also applies his work to a range of pathogens, including influenza, SARS, BSE/vCJD, HIV, foot-and-mouth disease and smallpox. He was educated at Oxford University, held a Royal Society University Research Fellowship at Oxford, then a readership at the University of Nottingham before moving to Imperial College. He was awarded an OBE (a UK 'honour') by the British government in 2002 for "services to epidemiology and the control of infectious disease",

for his contribution to advising on the control of the foot-and-mouth epidemic in the UK in 2001. His current research focus is on the use of models as contingency planning tools for emerging infections (pandemic influenza in particular) and bioterrorism.

Bruce Gellin, MD

Dr. Gellin is the Director of the National Vaccine Program Office (NVPO) in the US Department of Health and Human Services. Before joining the NVPO, Dr. Gellin was the director of the National Network for Immunization Information, an organization he founded to be a resource for up-to-date, authoritative information about vaccines and immunizations. Dr. Gellin has had broad experience in public health aspects of infectious diseases and has held positions at the National Institute of Allergy and Infectious Diseases (NIAID), the Centers for Disease Control and Prevention (CDC), the Rockefeller Foundation, and the Johns Hopkins University School of Public Health.

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Dr. Gerberding is the Director of the Centers for Disease Control and Prevention (CDC) and the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR). Before becoming CDC Director and ATSDR Administrator, Dr. Gerberding was Acting Deputy Director of National Center for Infectious Diseases (NCID), where she played a major role in leading CDC's response to the anthrax bioterrorism events of 2001. She joined CDC in 1998 as Director of the Division of Healthcare Quality Promotion, NCID, where she developed CDC's patient safety initiatives and other programs to prevent infections, antimicrobial resistance, and medical errors in healthcare settings. Prior to coming to CDC, Dr. Gerberding was a University of California at San Francisco (UCSF) faculty member and directed the Prevention Epicenter, a multidisciplinary research, training, and clinical service program that focused on preventing infections in patients and their healthcare providers. Dr. Gerberding is an Associate Clinical Professor of Medicine (Infectious Diseases) at Emory University and an Associate Professor of Medicine (Infectious Diseases) at UCSF.

Jesse Goodman, MD.

Dr. Goodman serves as the Director of FDA's Center for Biologics Evaluation and Research (CBER). Dr. Goodman joined FDA's Office of the Commissioner in 1998, where he directed the U.S. government's Interagency Task Force on Antimicrobial Resistance. He later moved to CBER, where he has been active in a wide variety of clinical and public health issues including bioterrorism preparedness and response, product development, human subject protection, and blood and vaccine safety. He is a virologist who is board certified in internal medicine, oncology, and infectious diseases. Educated at Harvard, he earned an M.D. from Albert Einstein, and did residency and fellowship training at the University of Pennsylvania and UCLA.

Honorable Michael O. Leavitt

Secretary Leavitt was sworn in as the 20th Secretary of the U.S. Department of Health and Human Services on January 26, 2005. As secretary, he leads national efforts to protect the health of all Americans and provide essential human services to those in need. He manages the largest civilian department in the federal government, with more than 66,000 employees and a budget that accounts for almost one out of every four federal dollars. Prior to his current service,

Secretary Leavitt served as Administrator of the U.S. Environmental Protection Agency and Governor of Utah. While at EPA, Administrator Leavitt signed the Clean Air Diesel Rule, implemented new, more-protective air quality standards for ozone and fine particle pollution and organized a regional collaboration of national significance to clean and protect the Great Lakes. Sec. Leavitt is widely recognized as a health care innovator and welfare reformer, and his record of achievement in Utah bears this out. He was chosen by the nation's governors to represent the states in Congress on welfare reform, Medicaid and children's health insurance. As Secretary of Health and Human Services he is committed to unleashing the power of technology to improve the quality of care, reduce mistakes and manage costs.

Klaus Stöhr, D.V.M.

Dr. Klaus Stöhr is the Project Leader for World Health Organization Global Influenza Programme. Dr. Stöhr trained as a veterinarian in East Germany and later became an expert in diseases that are transmitted from animals to people. He joined the WHO in 1992. More recently he played a crucial role in the WHO investigation of SARS and now is leading the WHO's efforts to prepare for an influenza pandemic.

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Dr. Treanor received his MD degree from the University of Rochester in Rochester NY and Internal Medicine internship and residency training at the University of Vermont, in Burlington, Vermont. He then did clinical and research training in Infectious Diseases at the University of Rochester and in the Laboratory of Infectious Diseases, NIH, Bethesda MD. Since 1988 Dr. Treanor has been a member of the Infectious Diseases Unit at the University of Rochester, where he directs the Vaccines and Treatments Evaluation Unit (VTEU). Dr. Treanor's primary research interests include clinical virology and clinical trials, especially related to clinical evaluation of novel vaccines for influenza. Current projects are related to candidate pandemic vaccines, approaches to intranasal vaccination using live or inactivated vaccines, and use of expressed recombinant proteins as vaccines.

Robert Webster, Ph.D., F.R.S.

Dr. Webster is the Rose Marie Thomas Chair of the Virology Division of the Department of Infectious Diseases at St. Jude Children's Research Hospital in Memphis, Tenn. In addition to his position at St. Jude, he is Director of the U.S. Collaborating Center of the World Health Organization (WHO), dealing with the ecology of animal influenza viruses. The center is the world's only laboratory designed to study influenza at the animal-human interface. Dr. Webster's interests include the structure and function of influenza virus proteins and the development of new vaccines and antivirals; the importance of influenza viruses in wild birds as a major reservoir of influenza viruses and their role in the evolution of new pandemic strains for humans and lower animals.

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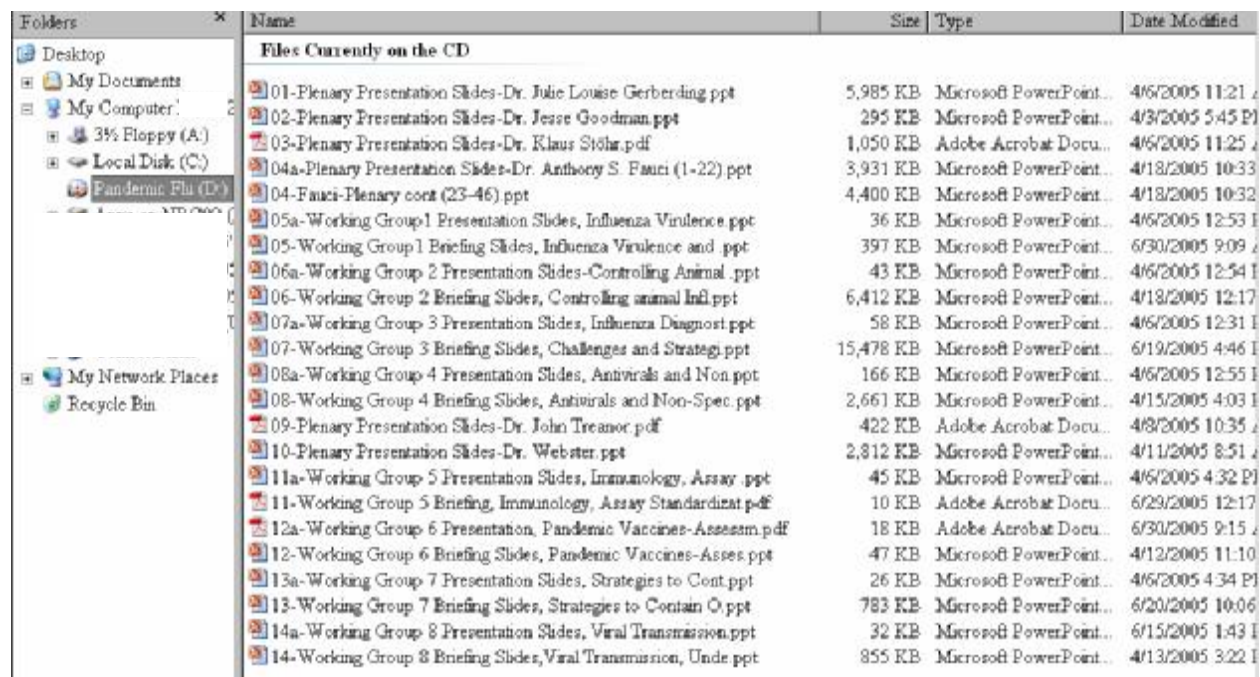
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- 06-Working Group 2 Briefing Slides, Controlling animal Influenza and Decreasing Animal-to-Human Transmission-Dr. Swayne, Briefer
- 07a-Working Group 3 Presentation Slides, Influenza Diagnostics for Surveillance

- 07-Working Group 3 Briefing Slides, Challenges and Strategies for Detection and Characterization of Influenza Viruses, Surveillance and Diagnosis-Dr. Cox, Briefer
- 08a-Working Group 4 Presentation Slides, Antivirals and Non-Specific Approaches, Treatments and Immunotherapies-Dr. Hackett, Rapporteur
- 08-Working Group 4 Briefing Slides, Antivirals and Non-Specific Approaches, Treatments and Immunotherapies-Dr. Hayden, Briefer
- 09-Plenary Presentation Slides-Dr. John Treanor
- 10-Plenary Presentation Slides-Dr. Webster
- 11a-Working Group 5 Presentation Slides, Immunology, Assay Standardization, and Correlates of Protection-Ann Arvin, Rapporteur 139
- 11-Working Group 5 Briefing Slides, Immunology, Assay Standardization, and Correlates of Protection-Dr. Brian Murphy, Briefer
- 12a-Working Group 6 Presentation, Pandemic Vaccines-Assessment, Development and Production Strategies, Dr. Rabinovitch, Rapporteur
- 12-Working Group 6 Briefing Slides, Pandemic Vaccines-Assessment, Development and Production Strategies-Dr. Harry Greenberg
- 13a-Working Group 7 Presentation Slides, Strategies to Contain Outbreaks and Prevent Spread-Dr. Nicole Lurie, Rapporteur
- 13-Working Group 7 Briefing Slides, Strategies to Contain Outbreaks and Prevent Spread-Dr. Neil Ferguson, Briefer
- 14a-Working Group 8 Presentation Slides, Viral Transmission, Understanding and Predicting Pandemic Risk-Dr. Peter Palese, Rapporteur
- 14-Working Group 8 Briefing Slides, Viral Transmission, Understanding and Predicting Pandemic Risk-Dr. Daniel Perez, Briefer