



Pandemic Influenza Vaccines Workshop: Building a Platform for Global Collaboration

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Beijing



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On January 28-30, 2007, 80 leaders from policy, public health, science, and industry convened in Beijing to clarify critical problems and facilitate cross-border collaboration, both regional and international, on vaccine R&D, manufacturing, and delivery. The goal was to take a step in the direction of building a platform for global collaboration on pandemic influenza vaccines. This report provides a summary of the workshop discussions that took place.

“In China it is not a question of “when”—we are already faced with low incidence and high mortality.”

—Weidong Yin, Sinovac

The Chinese Centers for Disease Control and Prevention (CDC) and the Center for Health and Aging at The National Bureau of Asian Research (NBR) co-presented the Pandemic Influenza Vaccines: Building a Platform for Global Collaboration workshop with sponsorship from the Bill & Melinda Gates Foundation and Wellcome Trust. In June, the Pacific Health Summit will focus on these topics and incorporate the workshop findings into the Summit process.

Challenges

- Vaccination may be our best defense against pandemic influenza and other emerging infectious disease threats, but barriers to progress in vaccine R&D include: the misalignment of incentives for collaboration and transparency, as well as insufficient access to strain and sequence databases.
- Lack of demand for existing seasonal influenza vaccines contributes to an underdeveloped manufacturing capacity for pre-pandemic and pandemic vaccines.
- Patchwork global distribution infrastructure and uncertainties about pre-pandemic vaccine storage and dosage also represent significant barriers to ensuring access to effective vaccines.
- Timing is a critical concern. Although streamlined production and regulatory processes could conceivably shrink testing, manufacturing, and paperwork time to three months, the estimated time for a pandemic to reach full scale is less than two months.

The scientific and research community, academia, international organizations, private sector organizations, and governments alike have all made significant efforts to communicate and identify a more collaborative path forward, but many issues remain unresolved.

Without a clear, effective mechanism to address persistent challenges, we could lose our opportunity to act early and respond successfully to a pandemic influenza outbreak. The problem is not simply a lack of money; indeed, the scientific community is barely able to absorb all the money currently directed toward pandemic influenza research. Rather, our dilemma starts with the inefficient distribution of resources and insufficient information-sharing, strategic direction, capacity, communication, and collaboration.



Plenary Sessions

I. Where We Are Now?

Epidemiology, Status of Preparedness, and R&D Update

II. Evolving Diseases, Evolving Processes

Approval and Regulation

III. Collaboration and Fair Engagement

Information Sharing and Utilization: Access to Strain and Sequence Databases

IV. Building Preparedness and Capacity

Pandemic Influenza Vaccine Manufacturing

Special Presentation

Looking Ahead: Strategies for Building a Platform

V. From Bench to Bedside

Dissemination and Application: A Vision for the Future

VI. Call to Action

Brainstorming for a Global Collaboration Platform

A Vietnamese man transporting chickens on his motorcycle. Many in Vietnam, as well as other countries, continue to live among poultry, as they have for centuries.

Scientific Challenges

Until scientists identify the precise strain of pandemic influenza, the development and production of pre-pandemic vaccine candidates remains critical both to boost human immunity and build capacity and infrastructure to prepare for a pandemic. The challenge derives from the uncertainty about the strain of influenza we need to identify and from the very nature of vaccine development.

The goal of pre-pandemic vaccines is to protect populations against possible pandemic disease strains. The production, stockpiling, and distribution of pre-pandemic vaccines also helps manufacturers, policymakers, and other stakeholders understand the kind of infrastructure and capacity that would help support the production of pandemic vaccines. Unfortunately, depending on the level of cross protection and the match between the stockpiles and the emergent pandemic strain, manufacturers may have to develop entirely new vaccines. Whatever happens, we need flexibility to adapt to an evolving threat and integrate new technologies.

Participants from science, research, academia, and industry reminded their colleagues in policy and public health about the working-level scientific challenges involved in creating pre-pandemic and pandemic influenza

vaccines. Key questions include: Which type of vaccine is ideal—live attenuated, killed, whole virus or split-pooled, viral-vectored, or nucleic acid? Which adjuvants are safe and effective? Is a single dose pandemic influenza vaccine even possible? Should we abandon the egg-based method and adopt a cell culture approach? Moreover, apart from concerns about safety and effectiveness, scientists must take into account the significant regulatory implications each scientific decision carries.

Finally, since the pre-pandemic strains of influenza are zoonotic viruses, collaboration among human and animal health experts, as well as specialists in the fields of virology, epidemiology, pathology, ecology and agriculture will be necessary to ensure that we are developing the most effective human and animal vaccines. Stakeholders must also prioritize and facilitate new research that integrates knowledge of different disciplines on human and animal influenza.

“A vaccine’s antigen match may be just as important as the speed of deployment.”

—Ruben Donis, U.S. CDC

According to a February 2007 WHO document, 16 manufacturers from 10 countries are currently developing pre-pandemic vaccines against the H5N1 avian influenza virus strains. Five of these manufacturers are also involved in the development of vaccines against other avian viruses.



Field workers pushing bicycles in Quilin, China. One major challenge is how to deliver pandemic influenza vaccines effectively to rural areas.

We Must Answer Tough Questions

- Even if we are able to create an effective pandemic vaccine, how do we distribute it?
- Who pays?
- How do we coordinate distribution?
- Who ensures that delivery is safe and effective in a pandemic situation, when public health delivery systems may not be functioning?
- How do we reach high-infection areas with already-feeble health infrastructure?

Information-Sharing

Access to strain and sequence information is essential to producing vaccines that match emerging dominant strains. Unfortunately, misaligned incentives contribute to reluctance among some governments, researchers, institutions, and companies to share data. Nevertheless, the threat of pandemic flu has brought forth notable collaboration that continues to grow.

Because countries like Thailand, Vietnam, and Indonesia carry a disproportionate burden of the risk associated with the emergence of new disease threats, they usually have first access to new virus strain and sequence information. While all are interested in joining forces to prevent a pandemic, many in these countries fear that the drugs and vaccines produced using the information they provided would ultimately be unaffordable to their populations—the very populations most likely to bear the initial brunt of a pandemic outbreak.

While manufacturers invest significant capital in vaccine R&D and manufacturing, these countries also contribute essential data to the development of pre-pandemic vaccine—at the expense of human lives. While the controversy over Indonesia's MOU with Baxter Healthcare Corporation emerged

after this workshop took place, participants anticipated these kinds of tensions, acknowledging the dilemma that countries like Indonesia face.

Considering the huge potential losses at stake, all participants agreed that manufacturers, governments, and researchers must come together to overcome intellectual property issues for pandemic influenza vaccines, create more incentives for sharing, and empower existing international databases. Participants also considered different incentive strategies that might encourage more information sharing, including arrangements whereby manufacturers and international organizations could provide vaccines, technology, and other interventions in exchange for strain and sequence information from affected countries.

“These are not theoretical needs—reality is telling us where to go.”

—Keiji Fukuda, WHO



Henk Bakedam and Keiji Fukuda



David Nabarro outlining strategies for building a platform for global collaboration.

Manufacturing Capacity

At present, manufacturing capacity for influenza vaccines can meet only a small fraction of expected demand, should a pandemic virus emerge. For this reason, many countries and manufacturers are exploring ways to increase production capacity. But ultimately, demand drives supply—Who will pay for the ramp-up?

In order for the populations who live in or close to the epicenter of a pandemic outbreak to have the appropriate interventions, manufacturers will need to ramp up production of safe, effective vaccines without delay. Arming these countries with the most effective response mechanism is in the interest of every other country in the world, as a 21st century trade and travel ensure the rapid spread of highly infectious diseases.

Yet there is currently a limited flat market for seasonal flu vaccine, making an increase in production of pre-pandemic vaccines very difficult. Although pandemic vaccines will be different from seasonal vaccines, they will be produced in the same facilities, and demand for latter drives production of the former. Since seasonal flu vaccines are expensive or not covered by health insurance in most countries, demand remains low. In many Asian countries for example, people pay out-of-pocket for seasonal flu vaccines, making the immunization a non-option for those who cannot afford it. Who should take on the cost?

As we move toward building a global platform for collaboration, we must remember

that public demand drives the vaccine industry. It takes between 12–15 years to bring a new drug to market at a cost of \$900 million, with nearly 45% of this cost accrued during the clinical trial phase.

Without sufficient demand for the product, manufacturers are hesitant to increase production. A potential over-supply of vaccine now might hurt the market in the future if companies find themselves stuck with surplus stocks. If stakeholders can find a way to encourage the general population's use of seasonal flu vaccine, we can stimulate further production of pre-pandemic vaccines, readying capacity for the production of pandemic vaccines when the pandemic virus strain emerges.

On top of manufacturer concerns, many governments face real trade-offs between investments in manufacturing versus research and development. While ramping up production of seasonal influenza vaccine would help increase the capacity for pandemic vaccine production, limited resources, regulatory burdens, and complex review processes for pandemic vaccine will still pose many challenges.



Su Lin, discussing the importance of demand in seasonal influenza vaccine supply.

“An evaluation of current global manufacturing capacity would help illustrate to policymakers how to invest, how to cooperate, and where to build capacity.”

—Martin Friede, WHO



Plenary Session I: “Where are we now”? In the center (from left to right): Donglou Xiao, Yuelong Shu, Ruben Donis, and Keiji Fukuda. To the far right: Jianguo Li and Henk Bakedam.

Vaccine Approval and Regulation

Vaccine patenting, funding, licensing, indemnity, and protection are just a few issues which pose serious barriers to capacity building. Global regulatory harmonization could streamline development and expand production capacity.

For some countries, the research, development, and production of pandemic vaccine comprise one national project, funded entirely by the government and conducted through national manufacturing silos. One department is usually responsible for R&D and another for approval and licensure. Several “fast-track pathways” for priority (i.e., pre-pandemic and pandemic) vaccines exist, but public plans for national manufacturers to export vaccine internationally are rare.

Other countries use public funding to develop pre-pandemic vaccines but may rely on public-private partnerships with international vaccine manufacturers for production. With such partnerships, the cost burden largely falls on manufacturers, and a lack of regulatory flexibility for pre-pandemic vaccines can create tension among stakeholders. Additionally, the use of the reverse genetics technique that pre-pandemic and pandemic influenza vaccines require can complicate the licensing process in some countries, especially in the EU, which considers these products genetically modified organisms, and as a result requires manufacturers to make certain facility upgrades for safety. Such upgrades are costly and time-consuming.

Despite variations in each country’s regulatory processes, most stakeholders agree that international collaboration is critical in fast-tracking the approval process for effective pre-pandemic and pandemic influenza vaccines. These actions will also help all stakeholders navigate through the issues that will arise with proprietary adjuvants and commercialization.

Each country, especially those in which vaccines are typically manufactured, must re-evaluate existing regulations and policies regarding clinical trials, approval, commercialization, and indemnification for pre-pandemic and pandemic vaccines. The investigation of immunological responses to pre-pandemic vaccines and studies of the levels of clinical protection during an actual pandemic, as part of post-market conditions will also require new authorization processes. Collaboration between national licensing agencies, international organizations, and industry is necessary now if we want to produce anything close to an adequate supply of pre-pandemic and pandemic vaccines in time to reduce the human and financial cost of disease. Streamlining these processes requires action by all—for the self interest of every country.

- In China, the SFDA passed a special fast-track approval process targeted at pandemic influenza vaccines at the end of 2005.
- In the United States, the FDA’s Emergency Use Authorization (EUA), is applicable to pandemic flu vaccines during emergency situations.



Plenary Session IV: “Building Preparedness and Capacity.” From left to right: Bing Zeng, Su Lin, Bing Li, and John Tam



Photo by Kaleb Brown/lew

A Hmong village in northern Thailand. Currently, Thailand has no pandemic influenza vaccine manufacturing capacity.

Call to Action: Building a Platform for Global Collaboration⁶

Convincing stakeholders to take action is not necessary; political commitment exists in full force in almost all countries, even in the absence of daily media headlines. The challenge is to define the kind of action we each must take.

Participants acknowledged that no single global champion will be able to address every challenge. Instead, a harmonized, collaborative process between all stakeholders is the only way the global community can succeed in taking full advantage of the time and resources that are available now to prepare for a pandemic. Governments cannot leave pandemic preparedness and response to vaccine manufacturers or international organizations, and the work of the latter cannot be accomplished without the support of each government.

The challenge is to provide authorities with decision making tools that illustrate realistic scenarios at home and abroad—tools that also help them make realistic choices about resource allocation. Computational modeling and simulation can help address the former, but policymakers need more information to support difficult investment decisions.

In the event of a pandemic, decisions might be more clear-cut. But risks will be greater and choices few. Now is the time, when most people feel relatively safe—when we have the most opportunity to make a real difference—to address challenging investment decisions and clarify a “way forward.” Stakeholders should re-examine incentives for information-sharing and governments can re-evaluate and harmonize their regulatory and licensing policies.

Manufacturers understand that while demand must drive supply in order for their businesses to survive, they cannot approach this situation with good business as the

only driver. Millions of lives are at stake. Increased collaboration with governments could help manufacturers build capacity and extend the reach of live-saving vaccines.

We must recognize that many organizations are already providing significant leadership in many areas of vaccine research, development, dissemination, and regulation. Unfortunately, there are some gaps in sharing information and barriers to effective collaboration by the critical players. By linking previously silo-ed industries and departments we can create more awareness about the mechanisms that currently exist to help improve preparedness. For example, by removing barriers between animal and human health for pandemic preparedness we can open doors to new discovery and innovative approaches. Moreover, by linking public health and clinical services in some countries we can improve service delivery and increase infrastructural capacity to support vaccine delivery in the event of a pandemic.

Call to Action Participant Suggestions

- Establish an “International Fund for Pandemic Influenza” to help direct the currently disjointed resources for preparedness and response.
- Launch a “Human Pandemic Influenza” project (modeled after the Human Genome Project) to set the stage for more international collaboration and information-sharing.
- Develop country-specific impact analyses to help policymakers understand investment options in their respective states vis-à-vis preparedness and response.
- Examine the limitations of IP policies currently in place and study of the benefits of technology transfer in exchange for strain and sequence information in order to help address tensions surrounding information sharing.
- Launch an international drive to boost subsidized or free seasonal flu vaccinations in order to increase immunity and augment manufacturing capacity for pre-pandemic and pandemic vaccines.

The *WHO Global Action Plan to Increase Access to Pandemic Vaccines* provides:

- Comprehensive analyses of existing problems
- A global overview of generic solutions
- A strategic basis for a new initiative

http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.13_eng.pdf

Featured Participants

Donald Burke

Dean
Graduate School of Public
Health, University of
Pittsburgh

Wuchun Cao

Deputy Director
Beijing Institute of
Microbiology and
Epidemiology

Xu-li Chen

*Director of Strategy and
Planning,*
Department of Science,
Technology, and Education,
Chinese Ministry of Health

Martine Denis

Director
Influenza Vaccine Projects
Strategy, GlaxoSmithKline

Vincent Deubel

Professor
Institut Pasteur of Shanghai,
Chinese Academy of Sciences

Xiaoping Dong

Director
Office of Science and
Technology, Chinese CDC

Ruben Donis

*Chief, Molecular Virology and
Caccines*
Branch Influenza Division, U.S.
CDC

Jeremy Farrar

Professor
Ho Chi Minh City Hospital for
Tropical Diseases

Zijian Feng

Director
Office of Disease Control and
Emergency Response, Chinese
CDC

Martin Friede

Scientific Officer
World Health Organization

Keiji Fukuda

*Coordinator, Global Health
Influenza Programme*
World Health Organization

Fu Gao

Director and Professor
Institute of Microbiology,
Chinese Academy of Sciences

John Grabenstein

Senior Director
Scientific Affairs, Merck
Vaccine Division

Frank Gray Handley, Jr.

Associate Director
International Research Affairs,
U.S. National Institute of
Health

Alan James Hay

*National Institute for Medical
Research*
Medical Research Council

Douglas Holtzman

Senior Program Officer
Bill & Melinda Gates
Foundation

Jacqueline Khor

Associate Director
Rockefeller Foundation

Bing Li

*Commercial Development
Director*
GlaxoSmithKline

Dexin Li

Professor and Director
National Institute for
Viral Disease Control and
Prevention, Chinese CDC

Felix Li

Associate Director-General
CDC, Public Health Agency of
Canada

Ian Lipkin

Professor and Director
Jerome L. and Dawn Greene
Infectious Disease Laboratory,
Columbia University School of
Public Health

David Nabarro

*UN System Coordinator for
Avian and Human Influenza*
United Nations Development
Group Office

Thi Hong Hanh Nguyen

*Medical Doctor and Deputy
Director*
Vietnam National Institute of
Hygiene and Epidemiology

Albert Osterhaus

Head
Department of Virology,
Erasmus Medical Center

Duanthanorm

Promkhatkaew
Senior Medical Specialist
Thai Ministry of Public Health

Bruce Ross

Health Attaché
U.S. Embassy in China

Yiming Shao

Chief Expert on AIDS
National Center for AIDS/STD
Control and Prevention,
Chinese CDC

Klaus Stöhr

Director
Influenza Franchises, Novartis
Vaccines and Development

Bhagirath Singh

Scientific Director
Institute of Infection and
Immunity, Canadian Institute
for Health Research

John Siu Lun Tam

Vice President
Vaccine Far East Clinical
Research Strategy, Wyeth
Vaccine Research

Frederick Vogel

Project Director
R&D, Sanofi Pasteur

Junzhi Wang

Deputy Director
National Institute for the
Control of Pharmaceutical and
Biological Products

Weizhong Yang

Deputy Director
Chinese CDC

Weidong Yin

General Manager
Sinovac Biotech

Bing Zeng

Vice President
China National Biotech Group

Kai Zhao

Professor
Beijing Institute of Biological
Products

Workshop Co-Chairs

Michael Birt

Director
Center for Health and Aging,
The National Bureau of Asian
Research

Yu Wang

Director
Chinese Center for Disease
Control and Prevention

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