# Trilateral Seminar on R&D Policies Related to Emerging and Re-emerging Infectious Diseases

# Section I ─ Executive Summary

## A. Rationale

In 1969, the U.S. Surgeon General, William H. Stewart, enthused by success against typhoid, cholera and smallpox, told the U.S. Congress that it was time to close the book on infectious diseases. Within a few years, public health officials throughout the world had increasingly come agree with Stewart's assessment that severe epidemics of infectious diseases had become–or soon would become–relics of the past, at least in developed and middle-tier countries. Smallpox had been virtually eradicated, as had poliomyelitis in many countries. Efficacious vaccines for common childhood infections had become available and were being widely used.

Within a very few years these experts were obliged to reexamine their confident prediction. HIV/AIDS emerged in many countries as a newly identified and severe infectious disease. Reemerging infections such as drug resistant variants of tuberculosis and malaria appeared and rapidly spread around the world. SARS emerged suddenly in late 2002 and by the following spring as it spread to several countries in Southeast Asia, it came to be recognized not only as a serious infectious disease, but the source of a severe social and economic crisis as well. The appearance of SARS in Canada emphasized the fact that because of the increasing frequency and speed of international travel, no country could consider itself safely immune from a serious outbreak of an infectious disease in any other country. Although an outbreak of avian influenza with 18 human cases occurred in Hong Kong in 1997, it was only during the early months of 2004 that the health authorities and the public in many countries began to be aware of the potential for a major global pandemic of the disease. It was of increasing concern when, a year later, the virus that was responsible for the so-called Spanish influenza epidemic of 1918-19 was genetically characterized and was shown to have characteristics that resembled the H5N1 virus responsible for the more recently identified cases of avian influenza.

Several factors have combined to increase the likelihood of major infectious disease pandemics. In addition to the previously noted increased frequency and speed of international travel, these factors include the population increases and particularly the growth of so-called megacities outside of the developed world, with their increased

crowding and frequently sub-standard sanitation. The proximity of humans and animals in many rural areas, the lack of potable water, and poor nutrition are also contributing factors, as are lack of sufficient understanding of elemental precautions required to ensure health among large segments of the general public. Global warming has led to a number of contributing environmental changes affecting, for example, the migration patterns of wild birds and bringing them into closer proximity with domestic poultry. Microorganisms leading to severe infectious diseases are exhibiting an uncanny ability to evolve rapidly into drug-resistant strains and strains permitting human-to-human transmission. The possibility that infectious pathogens could be deliberately released in a bioterrorism attack further underlines the complexity and urgency of the issues associated with infectious diseases.

By the early 1990s governments in many countries had begun to recognize that since the serious consequences of emerging and re-emerging infectious diseases could no longer be ignored, steps needed to be taken to strengthen their respective public health systems. A decade later as SARS spread from Asia to North America, it became clear that increased global efforts to coordinate the activities of national public health systems and to arrange for information exchange, technology transfer, and assistance on a timely basis were essential.

If the emergence of SARS served to illustrate how the medical and public health communities can be taken by surprise by a hitherto unknown infection, it also served as a wake up call to the leadership in many countries. The fact that SARS was eventually contained and did not assume global epidemic proportions has also provided some encouragement that measures to contain at least some infectious diseases can, in fact, be effective. Unfortunately, experts provide no assurance that an avian influenza pandemic could be contained. To the contrary, they caution that even if avian influenza fails to achieve the dubious status of a pandemic, potentially serious outbreaks of diseases caused by currently unknown or unidentified pathogens will almost certainly occur periodically. For that reason, steps currently underway or under consideration to try to minimize the effects of a serious outbreak of avian influenza should be regarded as efficacious even if an avian influenza pandemic itself fails to materialize.

Because emerging and re-emerging infectious diseases are a global threat, international cooperation at many levels has become increasingly indispensable.

## B. Organization

Against this background, the **National Natural Science Foundation** of China (NSFC), the **Korea Science and Engineering Foundation** (KOSEF), and the U.S. **National**

**Science Foundation** (NSF), sponsored a trilateral seminar on R&D Policies Related to Emerging and Re-emerging Infectious Diseases at Boston University, Boston Massachusetts, December 14-16, 2005. This seminar brought together a total of 40 participants: physicians, scientists, and public health officials and practioners from the three countries, as well as representatives from the three sponsoring organizations[1].

**Themes and Issues.** Themes and issues considered throughout all sessions of the seminar included:

- National and international institutional structures to deal with emerging infections diseases, including past successes, failures and lessons learned.
- Opportunities/limitations to common international agenda setting.
- Expediting the generation of new scientific knowledge and its translation into technological capacity and action.
- Science policies, including research, training and education.
- Accountability and transparency; security vs. openness.

**Plenary Sessions.** The seminar was organized into four plenary sessions, with session descriptions agreed upon in advance by the Chinese, Korean, and U.S. seminar co-chairs, as follow:

> **Plenary Session I. Surveillance:** This session reviewed existing and potential local and national mechanisms for the early detection and diagnosis of new or emergent infectious diseases as well as approaches for international collaboration in surveillance. There was a special emphasis on respiratory infections, notably SARS and influenza. Factors contributing to past successes and failures were considered along with feasible means for improving the relevant mechanisms. Presentations dealt primarily with the three national programs; a three member panel elaborated on how these programs translate into operations at city and/or local or regional levels.
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> **Plenary Session II. Modeling and Simulation:** Emerging and re-emerging infectious diseases occur in the context of uncertainty with regard to their control. However, data from past or similar experiences can be integrated to formulate decision-support models. Quantitative variables that describe biological properties (microbial niche, transmission dynamics, natural history with hosts, population immunity profiles), intervention effectiveness (isolation of patients, social spacing, vaccines,

1. A list of participants and their affiliations appears as Appendix A.

therapeutics) and operational/logistical response to implement population based controls, can help describe the impact of an emerging disease and possible response scenarios. Speakers and panelists in this session described how some of these modeling tools have been used to inform decision making in both real time and for future planning. Issues covered included the use and limits of models; collaborations to facilitate data collection/collation; and how to address uncertainty.

**Plenary Session III. Products and Technologies:** This session considered two aspects of product development for emerging infectious diseases: drugs and vaccine on the one hand, and tools for surveillance, rapid diagnosis and determination of virulence and drug resistance profiles on the other. Discussion covered the technical, development, testing and safety challenges associated with designing and manufacturing drugs and vaccines for these agents, which may be locally important and limited in capacity to spread widely or rapidly to counter diseases pandemic in nature. The second topic was the need for faster development and dissemination of new and rapid technologies for epidemiological and clinical use to identify and characterize emerging infectious agents, whether in the environment, in reservoir hosts, or in individual patients. Issues such as sensitivity, specificity, cost and availability were considered. The potential for and barriers to international collaboration in the development of products and diagnostic technologies were highlighted.

**Plenary Session IV. Implementation of Effective Policies:** This session, based in part on lessons learned from past experience, considered how to put in place feasible national policies and institutional mechanisms for dealing effectively and rapidly with specific threats associated with the spread of infectious diseases. Short range measures intended to deal with infectious diseases that may emerge within the next five years, as well as longer-term measures were discussed. The latter, long-term measures include areas where additional research should be emphasized, as well as education and career paths for the next generation of scientists and policy specialists.

**Presentations by Distinguished Speakers.** The opening session of the seminar on December 15 featured a keynote address by **P. FREDERICK (FRED) SPARLING**, University of North Carolina entitled, *Control of Emerging and Re-emerging Infectious Diseases: Lessons from the Institute of Medicine Forum on Microbial Threats*.

During a working lunch on December 15 **LAURIE GARRETT**, Council on Foreign Relations, gave a presentation entitled, *It's All about Infrastructure*.

The working dinner on December 15 featured an address by **JOUNG SOON KIM**, Seoul National University, entitled, *Epidemiological Transition of Communicable Diseases, and Contributions of Academia to the National Communicable Disease Program in Korea.*

**ZENG YI**, Chinese Center for Disease Prevention and Control, presented his remarks on *Lessons Learned from the SARS Epidemic in China* during a working lunch on December 16.

**Related Activity.** On December 14, the day preceding the first full day of the trilateral seminar, several participants attended and/or made presentations at a symposium organized by Boston University with support from Merck Research Laboratories, Boston, entitled Preparing for the Inevitable: Emerging and Reemerging Infectious Diseases. The agenda for this symposium appears in these proceedings as Appendix D. Texts of papers presented at the symposium may be accessed at http://www.bu.edu/ghi/index.html.

**Continuity and Auspices.** The December 2005 trilateral seminar was the seventh in an approximately annual series of **Sino-U.S. Science Policy Dialogues**, which have been supported jointly by the **National Natural Science Foundation of China** and the U.S. **National Science Foundation** since October 1999. This seminar was the second of these dialogues to include participants from a third country, the previous occasion being the December 2003 **Seminar on Science, Society and the Internet**, in Honolulu, Hawaii, which included a group of Japanese participants whose travel was supported by the **Japan Society for the Promotion of Science**.

The respective chairs of the Chinese, Korean and U.S. delegations to the December 2005 seminar were: **WU GUANLING**, Nanjing Medical University; **HAE-KWAN CHEONG,** Sungkyunkwan University; and **GERALD KEUSCH**, Boston University.

The seminar was supported in part by a grant from the U.S. **National Science Foundation** to **George Mason University's National Center for Technology and Law, J. THOMAS RATCHFORD**, Distinguished Visiting Professor of Technology and Law, Principal Investigator, the principal U.S. organizer of all Sino-U.S. Science Policy Dialogues since October 1999. A detailed description of the George Mason U.S.-China program appears as Appendix D. Proceedings of all previous seminars in addition a list of references and including links to recent literature on Chinese science and technology can be accessed at: http://www.law.gmu.edu/nctl/stpp/us_china.php.

## C. Presentations by Distinguished Speakers

Special presentations were made by four distinguished speakers during the two full days of the seminar. **P. FREDERICK (FRED) SPARLING** from the University of North Carolina delivered a keynote address entitled *Control of Emerging and Re-emerging Infectious Diseases: Lessons from the Institute of Medicine Forum on Microbial Threats* during the opening session on December 15. **LAURIE GARRETT** from the Council on Foreign Relations and **JOUNG SOON KIM** from Seoul National University gave presentations respectively entitled *It's All about Infrastructure*; and *Epidemiological Transition of Communicable Diseases, and the Contributions of Academia to the National Communicable Disease Program in Korea*, during a working lunch and during dinner on December 15. **ZENG YI** from the Center for Disease Control, China, delivered his presentation entitled *What Lessons We Have Learned from the SARS Epidemic in China?* during the course of a working lunch on December 16.

**SPARLING** led into the substance of his presentation with a series of photographs taken in what appear to be the pristine conditions in the Canadian Arctic, including several of animals and of the Inuit people who are native to the region (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/Keynote-Sparling.ppt). He then posed what he referred to as the Arctic paradox: The traditional diet of Inuits in Canada and Greenland exposes them to dangerous levels of pollutants, even though they live far from the sources of the toxins. These include very high levels of organic pesticides, industrial pollutants, and mercury. Birds appear to be a main source of pollutants carried north from developed countries and deposited in massive guano piles that find there way into the food chain

Based upon this example, **SPARLING** emphasized that what we do in one place affects all of us. For example, global warming is upon us, even though some are unwilling to face up to the problem. Infectious diseases are no exception. Infections always have demonstrated their capacity to travel, but the pace has quickened. Emerging, novel infections seemed to have boomed world wide in the past 30 years.

The H5N1 virus, the source of avian influenza, is spreading into new species and across land barriers.

We all remember SARS. Although there were relatively few cases, SARS had dramatic effects world-wide, on public health, global commerce and international relations. One lesson learned was that public health measures, particularly patient isolation, could be most effective. Fortunately, the disease has not recurred but the causative organism still persists in some wild animals.

**SPARLING** went on to list a number of emerging infectious diseases which originated in many different parts of the world. Additionally, old infections re-emerge and new problems associated with their emergence appear. Malaria and tuberculosis are increasing, while antimicrobial resistance to the organisms that cause these diseases (in particular, malaria) is also increasing.

What can we do to protect ourselves? It does no good to ignore the problem. Antibiotics and antimicrobials will not make the problems disappear. Vaccines help but they are hard to develop, in short supply, and expensive. Most important, according to **SPARLING**: we need to understand the nature of the problems and do what we can to mitigate them. To this end, the U.S. Institute of Medicine (IOM) has responded by creating two ad-hoc committees: the first of these, which focused on problems in the United States, issued a report in 1992 entitled, *Emerging Infections Microbial Threats to Health in the United States*. The second committee adopted a more global perspective in its 2003 report entitled, *Microbial Threats to Health Emergence: Detection and Response.*

The 2003 IOM report considered a number of factors contributing to the re-emergence of infectious diseases, namely: microbial adaptation, change; climate and weather; changing ecosystems, land use; human demographics and behavior; international travel and commerce; technology and industry; breakdown in public health; poverty and social inequality; war and famine; lack of political will; and intent to harm (i.e., bioterrorism). These interrelated factors converge to create the microbial "perfect storm" scenario. Rather than once in a lifetime, the microbial perfect storm threatens to recur because the factors persist with few prospects for change.

In addition to these two ad-hoc IOM committees, since 1996 public health practioners in the United States have created a set of Forums on Microbial Threats which aim to improve communications between the public and private sector on specific problems. These forums are composed of representatives of federal agencies, academia, private foundations and societies and the pharmaceutical industry. They are supported by grants and donations. They do not make recommendations but do issue publications with summaries of the issues and discussions of solutions. Their audience includes the U.S. Congress as well as the educated public.

**SPARLING** concluded by stressing the need for extension of such discussions to include more participants from around the world. Such a global expansion could improve sharing data and problems, and improving systems for surveillance and disease control, including evaluation of new drugs and vaccines.

**GARRETT** opened her presentation by reminding participants that following the end of the Cold War and, again, after 9/11, the U.S. national security establishment recognized a

clear need for new, fresh thinking. But does U.S. security or that of any nation hinge on transnational threats that have no direct relationship to guns, bullets, or bombs? She proposed an operational definition that: national security policy operates to secure primary public goods that are at the heart of the social contract between the people and its government; economic prosperity; governance continuity; ideological sustainability military capability; population well-being; and territorial integrity. Within the context of this definition, the aftermath of the December 2004 Indian Ocean Tsunami and responses to Hurricane Katrina in August 2005 illustrate disparities in the capabilities of the U.S. government to respond to such threats to national security. In the former case, the U.S. armed forces were first responders, arriving in Aceh, Indonesia, within 24 hours of the tsunami. In contrast, four days were required for the military to mobilize along the Gulf Coast in the aftermath of Katrina.

Emerging infectious diseases represent an obvious and serious non-violent, global threat to U.S. national security and the security of all nations, due in part to increased international travel and increasing population growth and crowding. The UN Population Fund estimates that by 2015 there will be 23 megacities in the world (that is, urban areas with populations in excess of 10 million): 14 in Asia, 6 in India alone, but only four in the developed world.

The H5N1 virus, responsible for avian influenza, first emerged in Hong Kong in 1996 or 1997. More than 150 million chickens have been culled thus far, or have died. H5N1 is 100 percent fatal to chickens: an unheard-of mortality rate. Tigers fed dead chickens developed H5N1 flu. More than 50 percent died of it. The virus in the meat is transmissible. Domestic cats fed H5N1 contaminated meat succumb. In October 2005, it was discovered that asymptomatic chickens in Indonesia can carry the virus.

Can serious outbreaks of avian influenza be contained? For how long? A network of laboratories around the world routinely hunts for H5N1 and other influenza strains. But laboratories in the first-responder nations, such as Vietnam, are woefully inadequate and confirmation time from patient diagnosis to World Health Organization (WHO) reporting often exceeds six weeks.

If an epidemic of H5N1 occurred today, airline unions would refuse to fly so that all global transport would come to a halt. Tamiflu is made in one factory in Switzerland and could not be transported, except if a national security emergency were declared and the U.S. Air Force carried it. There is an analogous problem with Chiron vaccine, made in the UK. WHO would corral its resources, perhaps having 150-200 responders, but no committed budget. The organization estimates that in the event of an avian influenza pandemic, it would have a maximum of 30 days to implement a containment strategy. Notification by countries takes from eight to 80 days. Assuming the best case scenario,

WHO would have about two weeks. The G-8 nations would most probably use their wealth to save their populations, but not the rest of the world. China, not a G-8 partner, would be on its own. Global mechanisms of response would almost certainly fail, and lack of any effective global infrastructure or coordinated international response strategy could lead to a diplomatic crisis.

**GARRETT** reminded participants of the panic atmosphere in China during the SARS outbreak in early 2003. Information and rumors were circulated by text messaging and 24-hour television coverage. The crisis period was characterized by censorship, lies, cover-up, lack of government credibility, and fear of government oppression.

Turning to HIV/AIDS, she presented data showing that between 1991 and 2000, both the prevalence and incidence of HIV among Russian army conscripts have increased steadily. The life expectancy at birth has decreased sharply since 1995 in 12 sub-Saharan African countries due to HIV/AIDS. By 2020, orphans will account for 15 to 20 percent of the population in 12 countries. However, HIV/AIDS is only one of several serious conditions afflicting populations, particularly children, in these countries.

The sharp decrease in AIDS mortality rates in the United States since 1996 is not due to a decrease in HIV infections, but to the increased availability of combination antiretroviral drugs. **GARRETT** concluded by suggesting that all state strategies for the use of anti-HIV drugs must strive to minimize the emergence of drug-resistant strains. All states have an interest in ensuring that these imperfect drugs retain their utility until alternative therapies are affordably available.

**KIM** opened her presentation with data on some current health indicators in the Republic of Korea, then presented data on several factors underlying changes in those indicators during the past few decades (her presentation is available at http://law.gmu.edu/nctl/stpp/-pubs/Dinner-Kim_000.ppt). These included; 1) population growth; 2) growth in Gross Domestic Product; 3) life expectancy by sex; 4) percent of death by infectious diseases; chronic degenerative diseases, and external causes by year; 4) proportion of the population with sanitary water supply; and 5) proportion of the population with education above high school graduation. She then provided data on occurrences of several types of infectious diseases in the country: 1) newly identified diseases, including legionnaire's disease, leptospirosis, and scrub typhus (1980s), and tularemia (1990s); 2) re-emerging diseases, particularly malaria (1994); and 3) imported diseases, most significantly, HIV/AIDS (1980).

The Korean government has responded to the threats posed by these new, re-emerging, and imported infectious diseases by: 1) amending the Communicable Disease Control

Act; 2) re-enforcing the communicable diseases surveillance system; 3) strengthening epidemiologic investigation activities and the capacity of public health laboratories; and 4) establishing the Korea Center for Diseases Control and Prevention in 2004. **KIM** provided data illustrating how these government actions had facilitated responses to a measles epidemic in the late 1990s, to SARS and to the threat of an avian influenza pandemic.

The Korean Society of Epidemiology was established in 1978. Its members are mainly faculty teaching epidemiology, statistics, demography, and genetics in graduate schools of public health, medical schools, nursing schools, colleges of nursing, and colleges of public health. According to **KIM**, this society has played an important role in stipulating the concept and practice of epidemiology suitable to the Korean situation by: 1) organizing epidemiology teachers workshops sponsored by the WHO; 2) holding biannual symposia and publishing their proceedings in special editions of the society's journal; 3) the education and training of competent epidemiologists; 4) conducting epidemiologic field investigations; and 5) engaging in a variety of advisory activities to the Korean government.

**ZENG** began by noting that by the end of the 1970s, many international experts were confident that serious epidemics of infectious diseases were – or soon would be – relics of the past. Within a few years they were forced to reassess their position as re-emerging infections such as drug resistant variants of tuberculosis and malaria appeared rapidly spread around the globe. HIV/AIDS emerged as a previously unknown disease which spread rapidly in the world and has already killed tens of millions and infected more than 400 million.

By the spring of 2003, the Chinese government had come to recognize that SARS was not only a serious infectious disease, but was also resulting in a severe social and economic crisis. In response, government leadership in areas associated with public health has been strengthened, as has China's public health surveillance and control system. Funding for public health has been significantly increased.

The Chinese leadership and public health system are taking these lessons learned from SARS into account in addressing the potentially disastrous outbreak of Avian Influenza.

## D. Plenary Session I: *Surveillance*

The first plenary session of the seminar was chaired by **D.A. HENDERSON**, University of Pittsburgh.

Prepared presentations were given by **WANG NING**; Chinese National Center for AIDS/STD Prevention and Control; **OK PARK**, World Health Organization and Korean Center for Disease Control; and **RUTH BERKELMAN**, Emory University

**HYUN-SUL LIM**, Dongguk University, **MARCELLE LAYTON**, New York City Health Department, and **XU JIANGUO**, Chinese Center for Diseases Prevention and Control, served as discussants/panelists.

**HENDERSON** opened the session by noting that public health surveillance is one of the most critical functions of a health system but still in an early stage of development in many countries. Surveillance involves the on-going monitoring of the occurrence of disease, the prompt and regular reporting of such information to responsible health authorities, the analysis of these reports and the implementation of needed action.

Over recent years, the importance of surveillance has been dramatized by the emergence of increasing numbers of new diseases. What is being done or should be done to detect and characterize newly emergent diseases is of universal concern. Also important is international cooperation and the prompt exchange of information regarding the epidemiological and clinical characteristics of the diseases and in discovering vaccines or therapeutic products. He looked forward to learning about practical experiences in operating surveillance programs in China, Korea and the United States during the session.

**WANG** began his presentation entitled, *HIV/AIDS Surveillance System in China*, with data on the status quo of HIV/AIDS in China: since 1985 and through the end of July 2005, the cumulative total of HIV-infection cases has been 126,990, amongst which a total of 30,786 cases of AIDS, has been reported in all 31 provinces, municipalities and minority autonomous regions in the country (his presentation is available at http://law.gmu.edu/-nctl/stpp/pubs/PresentationI-Wang.ppt). Currently, the HIV-infected population living in China is 840,000, amongst which the estimated number of AIDS patients is 80,000. The sexual, blood, and mother-to-child modes of transmission all exist[2].

China's current, comprehensive HIV/AIDS surveillance program dates from 1999, although surveillance itself dates from 1985. According to the concept of comprehensive

2. The epidemiological data presented were in accordance with the 2003 estimation written into the *Joint Chinese HIV/AIDS Control & Prevention Assessment, 2004*, published by the People's Republic of China State Council HIV/AIDS Control & Prevention and the United Nations Theme Groups on HIV/AIDS in China. In the *Estimation of HIV/AIDS Epidemic and Control & Prevention Work Assessment, 2005*, jointly published by the PRC Ministry of Health, the World Health Organization and the Joint United Nations Program on HIV/AIDS (UNAIDS) in January, 2005, the accumulative total of reported HIV infections in China, that of AIDS incidences, the estimated size of the population living with HIV, and the estimated size of AIDS patients have been updated, as of the end of November, 2005, to 141,241, 32,244, 650,000 with a range between 540,000 and 760,000, and 75,000 with a range between 65,000 and 85,000, seriatim.

surveillance presented by WHO and UNAIDS, the behavior of special populations at greatest risk as well as those of the general population are monitored and investigated, and the dynamics of HIV/AIDS epidemic are tracked. A principal mode of obtaining these types of information is the country's sentinel surveillance system in which data are collected twice each year at posts throughout the country from sample populations of a variety of high risk populations. Epidemiological, serological, and behavioral data are collected. China's sentinel surveillance system needs to be improved in terms of: sample coverage and the categorization of risk groups, and the variation and deviation of operational quality from site to site. Additionally, there is insufficient data analysis and application capacity.

According to **WANG**, the challenges to the HIV/AIDS surveillance program in China include: a lack of epidemiological data on the development patterns from new HIV infections to AIDS incidence, and eventually to death; a more comprehensive and frequently updated surveillance database; and better estimates of the size of various high risk groups. The goals of he and his colleagues are: to 1) improve the quality of data to make it more current and complete by incorporating the mechanism into the existing infectious disease reporting system; 2) improve the comprehensive surveillance network by expanding the coverage of sentinel sites; 3) strengthen the quality control and management of surveillance work; and 4) build better data analysis and application capacity

**PARK** opened her presentation entitled, *Surveillance System for Emerging Infectious Disease in Korea*, by noting that the country has experienced sporadic cases or outbreaks of emerging and re-emerging infectious diseases since the early 1980s (her presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PresentationI-Park.ppt). The range of emerging and re-emerging diseases pose serious public health threats to the public. Thus, since the late 1990s the Korean government has been striving to build the capacity to detect and respond to these infectious diseases threats in a timely manner. To this end, the government has revised the Communicable Disease Prevention Law, reorganized its structure for communicable disease control, and developed human resources through field epidemiology and various other training programs.

Revision of Korea's Communicable Disease Prevention Law has resulted in: 1) the reclassification of notifiable diseases; 2) refinements in case classification criteria for notifiable diseases; 3) an expedited reporting process for notifiable diseases; 4) introduction of an electronic data interchange system,; 5) a data management program and a statistical program; 6) development of a website for information sharing and communication; 7) establishment of various surveillance systems; 8) enhancement of analysis and feedback and collaboration with the private sector; and 9) training of health

care workers at local government levels.

According to **PARK**, gaps in the existing system include: 1) insufficient capacity for disease surveillance and response for emerging infectious disease by local governments; 2) insufficient operation of various surveillance systems; 3) insufficient integration among surveillance systems; and 4) low participation rate for notification from physicians. Future plans consist of the establishment of a web-based reporting system; integration of field and laboratory surveillance systems; extension of the electronic reporting system to the private sectors; continuous human resources development to build capacity; and enhancement of collaboration with the private sector.

**BERKELMAN** focused her presentation entitled, *Public Health Surveillance for Respiratory Diseases in the United States*, predominantly on domestic public health surveillance, with some attention to systems supported by the United States in other countries. She began by quoting **HENDERSON**: surveillance "represents organically the brain and the nervous system in a management process." There is a wide variety of surveillance systems used by the United States to supplement the domestic notifiable disease surveillance system and to support surveillance outside the country.

The United States has relied on routine reporting of cases of notifiable diseases by states since 1925 as the backbone of infectious disease surveillance. States have the legal authority for determining what diseases are notifiable in their jurisdiction. This population-based system has numerous strengths. However, studies show that most diseases are not completely reported. There are also problems with reporting of diagnosed cases. Physicians may believe that the laboratories will report or vice versa, and few physicians are likely to contact their public health professionals directly. The notifiable disease system is useful for a few respiratory conditions such as tuberculosis and drug-resistant invasive infections, but less so for most acute respiratory infections. Established almost 10 years ago, the Emerging Infections Programs conduct intensive population-based surveillance in 10 states and/or metropolitan areas. They were initiated, in part, to enhance surveillance and to address the problems of incomplete reporting of diagnosed cases, and incomplete data submission on case reports. Of note, more attention has recently been paid to monitoring disease in animals that may result in human infection. Veterinarians and departments of agriculture are working with public health professionals in a number of states on infectious disease monitoring.

There are a number of sentinel systems for respiratory disease surveillance which have the advantage of being relatively inexpensive, with the disadvantages of a lack of adequate geographic coverage and inability to calculate incidence and prevalence rates. Notifiable disease surveillance does not cover common viral respiratory or enteric

infections, and, partially to address this deficiency, the National Respiratory and Enteric Virus Surveillance System (NREVSS) was established in 1982 by the Center for Disease Control (CDC). It is a voluntary, laboratory-based surveillance system of 87 clinical and public health laboratories in 40 states. For influenza surveillance, a sentinel system has been long established with family practitioners who volunteer to be part of a reporting system for influenza-like-illness. Currently, about 1000 providers are included in the system.

Many syndromic surveillance systems have also been established throughout the United States in the past decade by various governmental and non-governmental entities. These systems examine such records as absenteeism, ambulance dispatch calls, pharmacy records, and chief complaints of persons presenting themselves at emergency departments.

Most public health surveillance for respiratory disease is conducted by the local and state health departments in collaboration with CDC. Separately, the Department of Defense conducts ongoing febrile respiratory disease surveillance at eight military training sites. In addition, in the past 10 years, the Department of Defense has established a Global Emerging Infections Surveillance system (GEIS) at its five overseas laboratories in Egypt, Indonesia, Kenya, Peru, and Thailand. GEIS includes influenza surveillance among its core activities for all sites. CDC has recently established international emerging infections programs (IEIPs) in Thailand and Kenya, and is planning another in Egypt.

The Program for Monitoring Emerging Diseases (ProMED) is an Internet-based reporting system. It is operated under the auspices of the International Society on Infectious Diseases and dedicated to rapid global dissemination of information on outbreaks of infectious diseases and acute exposures to toxins that affect human health**.** A second system resulting from advances in computer technology is the Global Public Health Intelligence Network (GPHIN) directed by Health Canada. It is a unique multilingual system that gathers and disseminates relevant information on disease outbreaks and other public health events by monitoring global media sources such as news wires and web sites.

**LIM**, the first of the three discussants/panelists in the session, opened his description of the evolution of Korea's infectious diseases surveillance system by presenting historical data on several emerging and infectious diseases in Korea, including leptospirosis, HIV/AIDS, tsutsugamushi disease, rotavirus, hepatitis C, hantaan virus, and coxsackie virus A24, as well as re-emerging diseases such as malaria, hepatitis A, shigellosis, mumps, and salmonellosis (his presentation is available at http://law.gmu.edu/nctl/-stpp/pubs/PanelI-Lim_000.ppt). The surveillance system for infectious diseases has

become more inclusive and rigorous during the past decade. However, there are still problems including: 1) low reporting rates; 2) lack of representativeness of reports 3) lack of participation; and 4) poor utilization of reports. The country's public health authorities have taken cognizance of these problems in their plans for the future.

The Korean National Institute of Health started laboratory surveillance for influenza virus in 1968 in collaboration with the WHO. The Korean Government extended influenza surveillance by launching the Korean Influenza Surveillance Scheme (KISS) nationwide from the 2000-2001 season. KISS incorporates both clinical and laboratory surveillance components, both of which rely heavily on voluntary reporting from the country's public and private hospitals and clinics. **LIM** then reiterated some of the principal causes of the worldwide emergence and re-emergence of infectious diseases, including: 1) alteration of the environment and climatic changes; 2) increasing numbers of people living and moving in the world; 3) overcrowding in cities with poor sanitation; 4) increased international trade in food, mass distribution of food and unhygienic food preparation practices; 5) increased exposure of humans to disease vectors and reservoirs in nature; and 6) and abuse of antibiotics. Coordination of public health surveillance systems on an international level is an essential prerequisite for dealing with infectious diseases.

**LAYTON** opened her commentary entitled, *Infectious Disease Surveillance in Practice−New York City*, by emphasizing that traditional local surveillance for infectious diseases depends on effective partnerships between public health officials and physicians, infection control practitioners, laboratorians, medical examiners, and veterinarians (her presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelI-Layton.ppt). The 1999 West Nile Virus outbreak in New York City highlights both the operation of the city's traditional surveillance system and lessons learned from that outbreak. Animal diseases are now reportable to the New York City Department of Health. The department engages in active outreach to clinical veterinarians, wildlife specialists, and the city's parks departments Her department is attempting to address the challenge in doing surveillance for nonspecific clinical syndromes through a syndromic surveillance program involving real-time public health surveillance by: 1) using clinical data that is routinely collected for other purposes; 2) does not rely on physician reporting; 3) is immediately computerized; and 4) is population-based, geographically representative, and categorized by clinical syndrome. Alert thresholds can be established by means of this system. It has also established a veterinary health alert system. Syndromic surveillance has been useful in the detection of annual citywide outbreaks of norovirus, rotavirus, and influenza, and in detecting citywide increases in diarrhea after the August 2003 power blackout. Although it has been less useful for detecting localized outbreaks, it offers reassurance when there are no citywide signals, as was the case for anthrax in 2001 and SARS in 2003.

**LAYTON** concluded her presentation with a quotation from a 1992 Institute of Medicine report: *As the human immunodeficiency virus (HIV) epidemic surely should have taught us, in the context of infectious diseases, there is nowhere in the world from which we are remote and no one from whom we are disconnected.* This is particularly true for New York City, which experiences 210,000 non-commuter arrivals each day.

**XU** began his presentation entitled, *Infectious Disease Laboratory Surveillance Network: a Powerful Tool for Investigation of Infectious Disease Outbreak*, by highlighting key elements of any program to deal with outbreaks of infectious diseases (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelI-Xu.ppt). The infectious diseases electronic reporting system in China is good, as is the country's laboratory-based surveillance system for single diseases. Data comparability remains poor; however, standardized methods are on the way. PulseNet China is a new concept for infectious diseases control and prevention which involves identical equipment, identical reagents, identical protocols, identical software for data analysis, trained personnel, remote data analysis and data sharing. It is based on new technology which: 1) assures that there is no experimental variation in results; 2) allows direct inter-laboratory comparisons; 3) offers precise information on strain relatedness; 4) takes advantage of declining costs of DNA sequencing technology; 5) simplifies subtype data production and analysis; 6) provides improved strain discrimination; and 7) reduces response times for outbreak investigation and other public health issues.

**HENDERSON** opened the general discussion by emphasizing that knowing someone is there to help is an essential attribute to effective utilization of any infectious disease surveillance system. **DAVID CHALLONER** was struck by the fact that all presentations had emphasized the importance of physicians to effective surveillance systems. Feedback and rewards to participating physicians are essential. **LAYTON** agreed, admitting that much that public health officials are doing with respect to discussion of surveillance systems is to advertise the importance of public health. **XU** reiterated the importance of training physicians in timely and complete reporting, particularly in rural areas.

**JOUNG SOON KIM** noted that during the Japanese occupation, disease reporting in Korea was very bad, since households were convinced that there would be significant penalties if it were known that they harbored serious diseases. The situation improved markedly after 1945 with the adoption of a U.S. surveillance model and the involvement of the Korean Medical Association.

**WEN YU-MEI** emphasized that an effective, general reporting system is now in effect in China for influenza and HIV/AIDS. But these are special exceptions. Shanghai is better

than the rest of the country. Like the situation **LAYTON** described in New York City, Shanghai has a great deal of experience with timely and complete reporting. For example, all physicians must go to one-day training courses on pediatric influenza.

**GERALD KEUSCH** spoke about the need to differentiate voluntary from non-voluntary reporting systems. Countries often weigh the economic consequences of reporting vs. non-reporting. The international public health community needs to devise better ways to reward governments for reporting infectious diseases.

Taking up this theme, **XU** stated that since China is a large country, it experiences problems with reporting. Since SARS, the central government no longer tries to hide infectious disease epidemics, but some provinces need better education about the need for timely and accurate reporting. Currently for avian influenza the system has improved. The provinces are reporting faster. In some cases information is released within a month, and very often faster.

**LAURIE GARRETT** noted that there are frequent disincentives to reporting. This is true to a large extent for managed care systems in the United States. In China, local officials may not want physicians to report probable emerging infectious diseases, since they don't want bad news to reach Beijing.

In response to a question about the extent of knowledge of infectious diseases in North Korea, **LIM** responded that the situation is largely a black box. Some years ago South Korea experienced an upsurge in malaria which was traced to soldiers who had been stationed in the demilitarized zone. The South Korean government offered direct assistance. When that was refused, assistance had to come by way of WHO. **PARK** noted that the South Korean government is attempting to obtain information from North Korea in exchange for in-kind assistance. The government has also offered to provide money to medical associations in North Korea in exchange for discussions on communicable disease reporting.

**HENDERSON** closed the session by remarking that principal prerequisite to a more effective international surveillance system is to build greater confidence and better relationships between scientists, institutions and governments. How can rewards be offered to governments? Attitudes have changed since SARS, but too slowly. The problem of effective rewards remains complicated.

## E. Plenary Session II: *Modeling and Simulation*

The second plenary session of the seminar was chaired by **MARK MILLER**, National Institutes of Health.

Prepared presentations were given by **CAO WUCHUN**, Academy of Military Medical Sciences, Beijing; and **BYUNG-CHUL CHUN**, Korea University.
**MORAN KI**, Eulji University, **WU HAIWEI**, Nanjing Medical University, and **MARC LIPSITCH**, Harvard University School of Public Health served as discussants/panelists.

**MILLER** opened the session by noting that reductionism of complex biological systems to their constituents is relatively new in the field of public health. Currently, computational biology and mathematical modeling is undergoing further development and is being applied from the genomic- to the macro-levels in public health. A variety of models can contribute to how we can potentially plan a public health response. Many of these models are intuitive. However, the process of articulating them within a framework of a tested range of assumptions provides support to policy decisions. While models by their nature are all oversimplified views of reality and therefore wrong, they can be useful by providing insight into strategies and highlighting the most relevant and important parameters for focus. He suggested that there is a need for greater recognition of the value of an interdisciplinary approach of biological, engineering, social, and political sciences to help predict interaction of zoonotic hosts, microbes, human interaction, and incentives for personal and population control. When outcomes are linked to monetary resources they can immediately inform policy in that they become economic analyses which can translate biological phenomena to a common currency that decision makers/policy makers can use to help formulate policy.

**CAO**'s paper entitled, *Modeling SARS Transmission Dynamics and Control Efforts*, focused on a review of modeling work and different approaches to analyzing SARS data, then highlighted a number of problems that remain unresolved. He began by defining three key parameters commonly used to model the transmission dynamics of infectious diseases: the effective or net reproduction number ($R_t$), the mean serial interval (S), or the time from the onset of symptoms in one case to the onset of symptoms in a subsequent case, and the incubation period, the interval between infection and the onset of symptoms. Estimating $R_t$, the mean number of secondary cases generated by an infectious case, is more difficult than for the other two parameters. He highlighted contrasting approaches to this problem used by authors of two of the first papers published on the 2003 SARS epidemic. Both papers sought to estimate the impact of control measures on reducing $R_t$, in Hong Kong, Vietnam, Singapore and Canada. These and subsequent papers using different methodologies have yielded remarkably similar estimates for $R_t$. Control

measures also appeared to be similarly effective at reducing $R_t$ to below one in different countries.

Other modeling work has addressed the international spread of SARS, and demonstrated that air traffic volumes between countries are able to explain much of the international variation in numbers of SARS cases.

**CAO** concluded his presentation by observing that mathematical models and new statistical techniques to fit these models to data have yielded much greater understanding about SARS transmission dynamics and control efforts, and provide valuable information to inform control policies. Nonetheless, there remain some important gaps in our knowledge. There is a need for a more detailed understanding of the relative roles of hospital and community transmission and the relative effectiveness of different control measures in each setting. It would be useful to assess the importance of household transmission in community spread. It would also be useful to estimate how transmissibility varies during the course of infection, and to see how well this correlates with viral shedding data. To address these questions detailed data giving times of onset, hospitalization, isolation and quarantine; and type, timing, location and duration of exposures (ideally, even amongst those not acquiring SARS) would be of great value.

**CHUN**, whose paper was entitled, *Epidemic Modeling and its Applications in Emerging Infectious Diseases and Bioterrorism in Korea*, highlighted two examples of epidemic models and their use that he and his colleagues developed in 2004 and 2005 (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PresentationII-Chun.ppt). The first example was a model of new influenza pandemic to estimate the number of cases and deaths; the shortage of medical resources; and the effect of intervention like isolation and vaccination. The second example modeled a smallpox epidemic as a likely result of a bioterrorist attack to determine how fast the epidemic would spread in the population of a single Korean city and to evaluate the intervention effects.

In the first example, the required parameters of the epidemic were set, considering the examples of pandemic that have actually occurred in history, especially the 1918 Spanish influenza pandemic. The model forecasts the number of patients and the dead in case of a pandemic; the necessary medical resources; and the effects of medical treatment and isolation of patients. Based on this model, a scenario was developed as a basis for a table-top exercise carried out in several Korean cities and provinces. Approximately 150 people from 14 central government agencies and from the 16 cities and provinces participated in this series of exercises. The exercise included the disease team's provision of attack scenario, the response team's preparation of their response plan, and the disease team's evaluation of the response plan. The Korean National Security Council Secretariat

has announced that it will fully reflect the exercise into the national level crisis management model that will be conducted in the future. Also, it will construct the decision-making system and the cooperation system among related government agencies to define the role of each organization.

Smallpox was selected for the second bioterrorism model because it is one of the agents of greatest concern (Category A) for use as a biological weapon. The modeling work was required to develop a smallpox response plan to determine effective control measure strategies. On the basis of this work, **CHUN** and his colleagues concluded that to control a smallpox epidemic, the early start of vaccination and fast coverage are more important than the vaccine coverage rate itself in reducing the numbers of cases and deaths. If the infected were isolated effectively to reduce 50 percent of transmission, and the vaccination started within 30 day of the epidemic, the smallpox epidemic size would be minimized. How to detect an epidemic in its earliest phase and how fast the population can be vaccinated are keys to preparing for a smallpox epidemic.

According to **CHUN**, these two examples provide convincing evidence of the usefulness of epidemic modeling in Korea.

**KI** began her commentary with a review of several types of modeling: analytical modeling, historical modeling, and predictive modeling, noting that a combined approach blending all three methods of modeling can inform control policy implementation (her presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelII-Ki.ppt). Review of data for the effectiveness of anti-viral therapy (ART) in South Korea indicates that despite widespread use of ART, the incidence of HIV/AIDS in the country has actually increased. In addition to intervention therapy for HIV/AIDS and other infectious diseases, we need to consider other interventions, such as behavioral change and combination therapy; cost-effectiveness; and treatment vs. other interventions. The efficacy of these and other factors can be estimated by means of modeling and simulation.

She then raised several questions about the two invited presentations given earlier in the session:

- Will a SARS epidemic return? If so, would it be similar to the 2003 outbreak? Are there any models or simulations of any new epidemic of SARS in China? What are the most important lessons learned from SARS in China?

- With regard to avian influenza: what options for avoiding or lessening the spread of a pandemic are available – e.g. prophylactic vaccination (if H5 trial vaccine is

available); antiviral (NAI) prophylaxis; increasing social distance (school /workplace closure, movement restriction, isolation)?

Key modeling questions drawn from these examples include:

- Is any combination of these actions capable of controlling a pandemic?
- What resources are required?
- Can we be more certain of the utility of our models?

**KI** concluded by suggesting that many needs have to be fulfilled in order to improve the utility of infectious diseases modeling and, therefore, effective public policies with regard to infections diseases. These needs include: 1) effective information systems (laboratory and clinical data) for communicable disease control as a permanent infrastructure; 2) closer collaboration between academic scholars and service providers on new developments in communicable disease control; and 3) enhanced monitoring of veterinary infections and 'minor' zoonoses, particularly in resources poor settings.

**WU** opened her commentary by emphasizing that modeling and simulation can provide a way of understanding dynamic complexity (her presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelII-WuHaiwai.ppt). She then proceeded to explore issues underlying modeling and simulation with reference to a project in which she is engaged entitled, *A Novel Sero-epidemiology Approach to the Identification of Target Population for Chemotherapy in Schistosomiasis Japonica Control.* The study is being conducted in four provinces in China. She listed several problems with strategies for shistosomiasis control: 1) almost all assays of both antibody and antigen detections are performed more poorly in the field in terms of sensitivity and specificity than in the laboratories where they were developed; 2) one of the available immuno-diagnostic assays has been improved sufficiently enough to offer an alternative to stool exams; 3) antibody-based serological assays cannot distinguish active infections from previous infection or re-infection; and 4) antigen-based assays are also not as valuable as expected.

The principal aim of her project is to develop a novel diagnostic system for schistosomiasis involving: 1) application software for modeling and target identification; 2) sampling; 3) data input and antibody distribution analysis, emphasizing "dual peak" model construction; and 4) the most appropriate antibody detection assay. **WU** concluded by suggesting a number of issues for research in schistosomiasis control in China and, by implication, control of other infectious diseases: 1) China's rapidly developing economy will result in changes for schistosomiasis transmission; 2) population migration is also a significant factor; and 3) the mechanization of agriculture is reducing bovine contamination.

Simulation, according to **WU**, provides a method for checking our understanding of the world around us and helps produce better results faster. A search of the Chinese literature on modeling and simulation of infectious diseases in the country indicates that more attention needs to be focused on these areas. Interdisciplinary collaboration, and particularly international collaboration should be emphasized.

**LIPSITCH's** point of departure for his commentary entitled, *Containment of an Emerging Influenza Pandemic: How Much Time Can We Buy?* was a summary of modeling work that he and his collaborators have conducted on factors determining the spread of avian influenza[3]. The elevated risk of an avian influenza epidemic is indicated by: 1) increased frequency of contact between birds and humans; 2) growing populations; and 3) closer proximity between vulnerable populations (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelII-Lipsitch.ppt). How likely are multiple inceptions? Historical data suggest that: 1) no pandemic-capable strain has been contained; 2) genetic heterogeneity might suggest multiple inceptions; and 3) no inference can be made in the absence of heterogeneity.

He emphasized that any efforts to contain a pandemic must expect containment to fail eventually. The success probability of containment efforts is not 100 percent, and we have limited ability to undertake repeated attempts. On the other hand, modeling work by **LIPSITCH** and his colleagues indicate that containment may "buy time." For most realistic scenarios, the expected gain in trying to control the spread of a potential pandemic disease is small. But if the hazard is high, it is important to "buy time" to develop a sufficient lead time to develop an action plan between the first event and the onset of a possible pandemic. Containment alone is unlikely to prevent a pandemic. Rather, a multipronged strategy is essential, including: 1) risk reduction; 2) modification of animal practices, including bird-human contact; 3) local containment; 4) antiviral stockpiling and increased surveillance in Asia; 4) global transmission prevention; 5) social distance measures; 6) vaccines; 7) harm reduction; and 8) provision for surge capacity, including antivirals and vaccines.

Following these three commentaries, **LAURIE GARRETT** remarked that she had heard nothing during the presentations about either genetic factors or behavioral changes being included in models of infectious diseases. **MILLER** responded that many models do incorporate such factors, while noting that models can only be as good as the data used. He closed the session by reiterating some of the points he had made when he opened it. Any model can be put into an economic framework by expressing health outcomes and the resources needed for interventions in monetary terms. When this is done, models can

3. Lipsitch's collaborators are Christina Mills and James Robins of the Harvard University School of Public Health, and Carl Bergstrom of the University of Washington.

influence public policies. While all models by their nature are wrong, some are useful. The strength of a model is dependent on the data input that help to parameterize the model and emphasize the importance of data sharing.

## F. Plenary Session III: *Products and Technologies*

The third plenary session of the seminar was chaired by **JIN-HAN KANG**, the Catholic University, Seoul.

Prepared presentations were given by **WEN YU-MEI**, Shanghai Medical College, Fudan University; and **GERALD KEUSCH**, Boston University

**XU JIANGUO**, Chinese Center for Disease Prevention and Control, **BAIK-LIN SEONG**, Yonsei University, and **MARK KLEMPNER**, Boston University served as discussants/ panelists.

**WEN,** whose presentation was entitled, *Strategies for Developing Novel Types of Vaccines to Combat Emerging Infectious Diseases*, began by reminding particpants that vaccination has the potential to produce major changes in disease epidemiology by its direct effects on those who were vaccinated, and by affecting herd immunity through those who were unvaccinated (her presentation is available at http://law.gmu.edu/nctl/-stpp/pubs/PresentationIII-Wen.ppt). However, the evaluation process of a newly developed vaccine is a long-term study which complicates the development of effective vaccines for new emerging diseases. One of the strategies for developing vaccines for emerging infectious diseases is to support basic and applied research projects in vaccines that already have been used and have high implications in the development of possible forthcoming infectious diseases.

She then shared her thoughts on three strategies for developing novel types of vaccines or biological products:

- A vaccine for stimulating innate immune responses might be considered for emergency use to block disastrous outbreaks of an infectious diseases caused by a new biological agent that has not been characterized.

- The idea of a "first-aid" vaccine is to develop an inactivated microbial vaccine or vaccine-like biological products for immediate prevention during an outbreak of acute emerging infectious disease. Once the etiology of the emerging disease has been identified, and this microbe can be grown or propagated in cultures to a high concentration, inactivation of the specific microbe with a well-established

traditional method would be able to produce a "first-aid" vaccine within a short period of time.

- In cases where the hosts are unable to develop effective immune responses to clear the antigens, one may regard these persistent infections as immune tolerance of hosts against the microbes or versus their specific antigens. An effective strategy could be to modify the pathway of antigen processing and presentation of the tolerogen to convert it into an immunogen, which can then be recognized by the hosts as "non-self" and induce effective host immune responses.

In his presentation entitled, *Security and Intellectual Property Constraints on Emerging Infectious Diseases Research*, **KEUSCH** dealt with two potentially serious, non-scientific types of obstacles to the development of effective strategies for combating emerging infections diseases (his presentation is available at http://law.gmu.edu/nctl/stpp/-pubs/PresentationIII-Keusch.ppt). He began by asking whether it is possible to balance the legitimate social goals of security and academic freedom in a time of crisis. Debate over this issue is not new in the United States. In 1759, Benjamin Franklin wrote that "they that can give up essential liberty to obtain a little safety deserve neither liberty nor safety." Within two years of the entry of the United States into World War II, the Association of American University Professors issued a statement emphasizing that, "academic freedom is one facet of intellectual freedom; other aspects of that larger concept - freedom of speech, freedom of the press, and freedom of religion - are among the avowed objects for which this war is being fought."

There are four primary areas of academic freedom: freedom to conduct research, freedom to publish, freedom to teach, and freedom to speak. The law has long criminalized "giving aid and comfort" to the enemy, which entails, for example, trading with or providing financial support. Confined within proper bounds, such measures need not pose a threat to civil liberties in general or to academic freedom in particular. However, we have learned from experience that in the passion of war, and in the hands of those who may be properly zealous for its successful prosecution, the boundaries can blur. Information the body politic vitally needs to maintain oversight of public affairs has been made secret, and classification has sometimes been imposed solely to save the classifying entity from accountability and embarrassment. Although the actions of private groups may affect the climate of a campus, the government is necessarily held to a different standard, since it has the capacity not only to preach, but also to act. There is a deep philosophical debate about how much we value academic freedom. Since 9/11 there have been attempts to: 1) categorize and restrict some research as "sensitive" (and therefore subject to control); 2) implement export control laws and select agent regulations; 3) limit the publication of research findings; 4) prohibit certain foreign nationals from

collaborating with U.S. researchers and receiving education and training in U.S. universities; and 5) restrain faculty free speech. The debate has only begun. Can the debate itself be shut down by the government?

Turning to intellectual property-related issues, **KEUSCH** noted that of estimated total $105 billion in world expenditures for health-related R&D in 2001, almost 50 percent was spent by the private-for-profit sector, 97 percent of it in high income countries. Increasing public attention is being paid to global disparities in access to health care. But the media portrayals of complex issues are often framed simplistically: e.g., as rich vs. poor, big pharmaceutical companies vs. sick people, or insensitive bureaucracies vs. caring relief organizations. However, although the private sector owns much of the health care-related intellectual property, **KEUSCH** suggested that patents are not a primary cause of global health disparities. The U.S. government has the authority, contained in provisions of the Bayh-Dole and Stevenson-Wydler Acts of 1980, to compel the pharmaceutical industry to produce vaccines and market these and other drugs at a relatively low price in times of crisis. However, this authority has rarely if ever been used. (The Bayh-Dole Act extends intellectual property rights to non-government organizations performing federally-sponsored research, including universities and small business. The Stevenson-Wydler Act provides the same rights and benefits to government scientists.)

Two provisions of the Bayh Dole Act ensured that the government retains the rights to meet future needs and to protect the public against non-use or unreasonable use of inventions. These provisions are still debated by intellectual property specialists and still provoke anxiety in academia and the private sector. Because the Act expressed Congress' view that the use of discoveries supported by public funds to improve health was clearly in the public interest, even if it must be carried out by government action, the question remains when and with what justification would the clauses be invoked by the government?

**KEUSCH** concluded by emphasizing that there are economic, legal, and policy barriers to resolving disparities in health care. The main economic barrier is the high cost of developing a product from a basic discovery. The main legal barrier is the complex ownership system in place to protect the interest of those who invest in research and development, and to maintain incentives to continue such investment. The main policy barrier is the difficulty to balance the competing interests−scientific community, consumers, and industrial development−that vie for advantage in the potentially lucrative world of commercialized health products.

**XU** began his presentation entitled, *Technology for Identification of Emerging and Re-emerging Pathogens,* by emphasizing that outbreaks and transmission of emerging and re-emerging infectious diseases is testing how effective our diagnosis and surveillance is performed (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelIII-Xu.ppt). If the diagnosis or surveillance fails to address the needs of public and policy-makers, it is likely that there will be loss of confidence. However, it is difficult to detect or identify emerging pathogens in a country where reliable methodology, requisite technology, or experienced personnel are not available. Detecting such events relies on good data collection, comparative background data, reference pathogen strains or materials, and diagnostic serum.

**XU** suggested that one of the keys to dealing with emerging infectious diseases globally is by developing collaboration, technology exchange and information sharing among involving countries. Global efforts to deal with emerging infectious diseases should include: 1) technology transfer for the detection of emerging infectious diseases; 2) workshops for training personnel; and 3) sharing reagents, materials, and relevant technologies.

**SEONG** began his presentations by reminding participants of the recent WHO *Guidelines on the Use of Vaccines and Antivirals during an Influenza Pandemic*, which include guidelines for both therapeutic intervention and vaccine development (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelIII-Seong.ppt). Pandemic preparedness from a Korean perspective includes contingency planning for vaccine shortages, including: 1) an independent vaccine production facility; 2) a cell culture production facility (Celltrion; CMO); and 3) development of an independent vaccine strain, based on lessons learned from the 1997 Hong Kong Asian Influenza outbreak. The Pandemic Influenza Consortium, Korea (PICK) for the Prevention and Control of Pandemic Influenza in the Asia Pacific Region has a budget equivalent to $500 million and a duration of five years. PICK has four project goals: 1) development of a high-yielding H5N1 vaccine strain; 2) development of recombinant and genetic vaccines; 3) development of a "needle free" vaccine for mass immunization; and 4) improving the requisite research infrastructure by establishing a Vaccine Center of Excellence and a regional BSL3 biocontainment laboratory.

**SEONG** noted that funding for research associated with emerging infectious diseases in the United States is heavily weighted towards bioterrorism defense. He concluded from this that it is necessary to secure R&D funds from competing activities such as bioterrorism or stem cell research. "All we want is that a pandemic does not occur at all. Therefore, there is a need to develop a global strategy to minimize lost opportunity costs."

**KLEMPNER**'s presentation on, *The Emerging Infectious Diseases and Biodefense Network in the United States of America,* opened with a description of the program of 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs) which have been funded by the National Institute of Allergy and Infectious Diseases (NIAID) since 2003 for a total of $350 million over five years (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelIII-Klempner.ppt). NIAID has also funded a total of 13 Regional Biocontainment Laboratories (RBLs) at the BSL 2 and 3 levels for a total of $260 million, subject to matching institutional funding. Two National Biocontainment Laboratories (NBLs) with facilities at the BSL 2, 3 and 5 levels have also been funded for a total of $240 million from NIAID. RBLs and NBLs are available to assist national, state, and local public health officials in the event of bioterrorism or infectious disease emergencies.

Boston University Medical Center has been awarded funds from NIAID (with matching funds from the university) to construct (beginning in spring 2006) and operate a National Emerging Infectious Diseases Laboratory. Its mission is to: 1) conduct basic and clinical research on emerging infectious diseases, including category A, B, and C agents aimed at developing diagnostic tests, treatments and vaccines to promote the public's health; 2) provide training in these areas of research; and 3) support a national response in the event of a biodefense emergency. Issues which the Emerging Infectious Diseases and Biodefense Network in the United States must address include: 1) safety and construction standards; 2) research priorities; 3) collaborative research projects; 4) collaborative funding; 5) global stockpiles: where and under what auspices?; and 6) distribution of centers, their oversight, and logistics.

**FRED SPARLING** opened the discussion portion of the session by stating that he is impressed that there is so much money in the United States for research on emerging infectious diseases. He suggested that in the spirit of international cooperation, a way should be found to use part of it to create a fund to do collaborative research, including bringing people from China and Korea to use our BSL-3 labs, such as the one at Boston University which will be available in about 18 months.

In response to a question from **HYUN-SUL LIM** about who produced the anthrax bacteria released in limited quantities in the fall of 2001? **KEUSCH** responded that he would also like to know. However, the U.S. government's investigation remains secret. A critical question is how do we track such matters in the future? How do we strike a balance between national security and public information?

**WEN** asserted that there is a critical need for an international consensus regarding standards of high security biological laboratories and training for personnel working in

those facilities. A proposed BSL-3 laboratory at Fudan University in Shanghai has been pending for almost two years, but the government approval has yet to be forthcoming about when or even if it will be approved. An international agreement on safety standards could help a great deal.

**RUTH BERKELMAN** noted that the United States and the European Union have been discussing such safety standards. Perhaps any agreement they reach could be extended to principal countries in Asia as well. **CHEN XIANYI** noted that since the SARS epidemic, the Chinese government has been overly cautious about approving new high security BSL facilities, which no doubt accounts for much of the delay experienced by **WEN** and her colleagues at Fudan University. **KLEMPNER** emphasized that requests for licensing and running BSL facilities in the New England area by private universities, including the new BSL-3 facility at Boston University, have also experienced significant hurdles.
**OK PARK** asked what kind of regulations are in place in the United States about distribution of pathogens to foreign organizations by private companies? **BERKELMAN** stated that oversight of such transactions has deteriorated during the past few years, but that the Center for Disease Control (CDC) is now examining the situation.

**SPARLING** and several other U.S. participants suggested that although the National Institutes of Health (NIH) has substantial funds to support research related to epidemic diseases pathogens, most of these are directed to so-called Category A pathogens that could be used for weapons by bioterrorists. There is a clear need to broaden the range of pathogens that qualify for NIH funding.

**D.A. HENDERSON** responded by highlighting the history of biodefense funding in the United States. The U.S. government showed no interest in this issue until about 1997 when a major Soviet bioweapons program came to light. For 1998, the Clinton administration raised the Department of Health and Human Service's budget for biodefense to $170 million. Information exchange in the area of public health was woefully inadequate at the time. It has gotten better, but is still not nearly as good as it could be. Following 9/11 Congress, for 2002, appropriated $3 billion for biodefense. While these funds are focused on biodefense, they can also be used more broadly to study other than Category A infectious diseases. Pandemic influenza did not become a concern of the U.S. government until early 2004, so that is where most of the money is now going. But too little has been done to provide a more adequate infrastructure. There are only two BSL-4 facilities in the United States. More are needed. There is also a need for better training and better communication. Public and congressional awareness of the threat of bioterrorism has provided a means for better support for more broadly based support for the U.S. public health system.

**SPARLING** was impressed with **HENDERSON**'s explanation, and hoped that NIH would, in fact, follow his advice and extend its generous support for research on potential pandemic pathogens more broadly.

## G. Plenary Session IV: *Implementation of Effective Policies*

The fourth and final plenary session of the seminar was chaired by **WU GUANLING**, Nanjing Medical University.

Prepared presentations were given by **DUK HYOUNG LEE**, Korea Center for Disease Control and Prevention; and **MARGARET HAMBURG**, NTI Global Health and Security Initiative.

**CHEN XIANYI**, Chinese Ministry of Health, **BO YOUL CHOI**, Hanyang University, and **DAVID R. CHALLONER**, U.S. Institute of Medicine, served as discussants/panelists.

The first part of **LEE's** presentation entitled, *Implementation of Effective Policies on Emerging Infectious Disease*, highlighted recent efforts by international organizations such as the World Health Organization (WHO) and the Food and Agricultural Organization (FAO), to mobilize and improve communication among relevant national organizations for effectively and efficiently controlling the public health threat of international concern including threat of emerging infectious diseases, with a focus on avian influenza (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/-PresentationIV-Lee.ppt). Thanks to the pandemic influenza issue, global cooperation and preparedness at national levels on avian and pandemic influenza are being enhanced and this will provide a template for global cooperation to address all types of public health emergencies. The International Partnership on Avian and Pandemic Influenza (IPAPI), advocated by the United Nations and U.S. President Bush in September 2005, is committed to protecting human and animal health as well as mitigating the global socioeconomic and security consequences of any influenza pandemic.

**LEE** then turned to the situation in Korea. Organizational and functional schemes for responding to public health threats of international concern were reshaped due to the global SARS outbreak. Thanks to SARS, the need for having technically advanced and leading national organization was highlighted. One result was creation of the Korea Center for Diseases Control and Prevention (KCDC) in January 2004. In recent years, seasonal influenza immunization has grown significantly. This year's supply of the vaccine amounts to about 17 million doses, covering one third of the population. Longer term measures being dealt with include resource allocation, dedication of domestic

resources (human and financial), improvements in public awareness, and development of economic and trade contingency plans.

**HAMBURG** began her presentation entitled, *We Must Act: Addressing the Challenge of Microbial Threats to Health*, by suggesting that the greatest twin challenges faced with respect to emerging infectious diseases will be to ensure that we can actually translate knowledge into action, and that we can avoid the age-old trap of complacency that has repeatedly undermined efforts to prevent and contain infectious disease. The best defense against any infectious disease outbreak is a robust and global system for public health−both its science and its practice. She devoted considerable attention to the threat of bioterrorism on the grounds that it raises a set of research issues and concerns of particular sensitivity for R & D policies and the responsible stewardship of science.

She went on to note that many of the actions that need to be taken had been discussed during the course of the seminar. Various speakers had referred to the issues of research needs and priorities, and the enormous importance of adequate, appropriate and sustained investments in a realistic, well-coordinated and far-reaching research agenda addressing basic research, new diagnostics, drug and vaccine development, and applied public health and behavioral research.

In planning for an effective response to an influenza pandemic, an array of legal concerns still looms. For example, there is still confusion about basic issues such as the declaration of an emergency. In any disaster, how the needs of the public are handled from the very beginning is critical to the overall response. For a biological event, this may be even more crucial. Correspondingly, the needs and concerns of response personnel, including health care workers, must also be addressed. Additionally, the media are key to efforts to communicate important information to protect health and control disease, as well as to reduce the potential for panic in a crisis. The prevention and control of infectious diseases are fundamental to individual, national, and global security. Failure to recognize−and act on−this essential truth will surely lead to disaster. The magnitude and urgency of the problem demand renewed concern and commitment.

**CHEN**, who serves as Director-General of the Office of Health Emergency Response (OHER) within China's Ministry of Health, began his commentary by highlighting the roles and responsibilities of OHER (his presentation is available at http://law.gmu.edu/-nctl/stpp/pubs/PanelIVChen.ppt). These are to: 1) organize/coordinate public health emergency management according to law; 2) draft public health emergency related laws and regulations; 3) draft public health emergency management related policies, guidelines, and measures; 4) set up and improve public health emergency surveillance and early warning systems, as well as emergency planning and drills; 5) organize emergency preparedness training for public health and medical professionals; 6) provide

technical assistance for local public health emergency planning and management, including rescue and treatment; 7) coordinate/organize public health components of work in disaster, bioterrorism, toxic and radiological emergencies; and 8) organize emergency medical rescue and treatment in emergencies involving deaths/casualties. He next considered how to build the capacity to implement emerging infectious diseases prevention and control strategies in terms of these roles and responsibilities. Strengthened training and enhanced R&D, as well as strengthened international cooperation and global action, are essential elements in such capacity building.

**CHEN** went on to describe how the experience and lessons learned from SARS are contributing to the early detection, rapid response and preparedness for other emerging diseases, for example, the control of avian influenza. Experts from the Ministries of Health and Agriculture are now required to travel together to sites of suspected outbreaks of infectious diseases and to conduct their investigations and undertake actions to manage epidemics at the same time. China's epidemic surveillance, disease reporting, early diagnosis, and early reporting systems are being enhanced, as are capabilities for early isolation and early treatment. Information exchange and public health education programs have been strengthened in order to raise the population's self protection awareness and abilities. In this regard, providing timely information to the public about confirmed cases of infectious diseases is essential.

**CHOI** based his commentary entitled, *Strengthening the National Communicable Diseases Control Systems for Local and Global Health, in Korea*, on his experience as a member of a committee charged, in 2005, with drawing up Korea's Millennium report (his presentation is available at http://law.gmu.edu/nctl/stpp/pubs/PanelIV-Choi_000.ppt). The public health components of that report, referred to as Millennium Goal 6, focus on three diseases: HIV/AIDS, malaria, and tuberculosis. He began by reviewing the achievement and future tasks to control each of these diseases which, while not urgent, endemic diseases, carry enormous burdens. Informal information exists that North Korea continues to experience a high incidence of tuberculosis. South Korea would be eager to share its many years of experience in dealing with this disease.

Experts and professionals from the Korea Center for Disease Control, as well as from universities and research institutes, have collaborated to establish goals for a communicable diseases control program as a part of the Korean Health People 2010 initiative. Goals pertinent to four categories of disease have been developed: 1) food and water borne diseases, 2) vaccine preventable diseases, 3) HIV/AIDS and tuberculosis, and 4) emerging infectious diseases. In the course of developing these goals, future research topics for each field were identified, including basic, epidemiological and

operational research. Additionally, evaluative research to assess the effectiveness of control programs and services should be conducted.

Since the early 1990s, Korea has expended considerable effort to develop a national communicable diseases program. However in **CHOI**'s opinion, the country requires more sustained efforts to strengthen that system. Its activities in that regard will be the basis for actively participating in international programs to improve global health.

**CHALLONER** focused his comments on mechanisms for cooperation involving both government and non-government organizations and institutions in the United States, which have been effective in exchanging information, issuing reports, and making recommendations regarding issues associated with public health, particularly emerging and re-emerging infectious diseases. As discussed in more detail by **FRED SPARLING** in his keynote address, the Institute of Medicine, a component of the National Academies complex, continues to assemble panels of experts from a range of relevant disciplines to prepare and issue such reports. Non-government organizations such as the National Academies in the United States, because of their neutrality, can play useful advisory and convening functions, and are able to catalyze cross-disciplinary conversations. **SPARLING** had also spoken of the activities of various Forums on Microbial threats starting in 1996. Activities of this sort can and are being extended to the international level. One example is the Disease Control Priorities Project, consisting of five international partners including the Institute of Medicine, which met most recently in Beijing in April 2005 hosted by the Chinese Academy of Sciences and Chinese Academy of Engineering.

**GERALD KEUSCH** opened the discussion period by asking why it is so difficult to implement an action agenda. He referred specifically to post-9/11 problems with implementing an effective homeland security system, as well as the U.S. government's woeful response to the damage resulting from Hurricane Katrina. Why don't the usual mechanisms seem to work? We must do something different with respect to emerging infectious diseases. But what?

**HAMBURG** asserted that Katrina demonstrated that rhetoric is certainly not enough. But perhaps the U.S. government really is taking the threat of an influenza pandemic more seriously. President Bush certainly does not want a bioKatrina on his hands!

**TOM (J. THOMAS) RATCHFORD** asked if WHO could be reorganized so that it could become a more effective international body. **OK PARK** noted that WHO cannot take any actions that its member states don't want it to take; it has no independent legal authority. However, member governments have now agreed on an emerging infectious diseases

program which gives WHO considerable authority to coordinate international cooperation.

**D.A. HENDERSON** explained that WHO was responsible for the coordination of a global reporting system for smallpox but not all countries always and fully participated. Some countries denied they had cases even when reliable sources reported otherwise. The new international health regulations will facilitate reporting but WHO has no legal authority to enforce reporting and is generally hesitant to expose countries that do not report epidemics. On the other hand, the system worked reasonably well with SARS, in no small part because much of the communication was between scientists. A problem with WHO is that meetings of the World Health Assembly, for example, are dominated by political rather than health leaders and the discussions often consist of representatives reading pre-meeting approved formal statements.

**PARK** emphasized that another problem with WHO is that national governments which pledge funds for international cooperation almost invariably spend most of those funds on themselves.

**KEUSCH** suggested that perhaps an approach to resolving such problems with WHO would be for leaders from the middle tier countries to assume leadership from the rich countries who think they are doing well and that everything is fine.

**WEN YU-MEI** noted that often national ministries themselves do not talk to each other. Prior to the SARS epidemic, officials from the Chinese Ministries of Health and Agriculture rarely communicated. Now the central government has adopted a policy requiring that teams from the Ministry of Health must accompany teams from the Ministry of Agriculture to the sites of avian influenza outbreaks.

**RUTH BERKELMAN** suggested that the data sharing problem extends to the non-government scientific community, whose members are often reluctant to share results prior to publication. Eliminating or at least reducing this considerable lag-time could lead to a more effective system for identifying and controlling emerging infectious diseases.