

ACUTE RESPIRATORY INFECTIONS PANELS

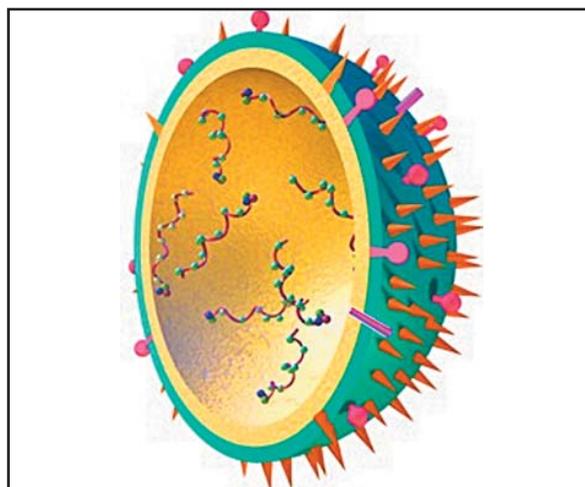
[Established 1996]

In the early 1990s, diarrheal diseases and acute respiratory infections were the leading causes of death in many developing countries. The U.S.–Japan Program had already established a panel to focus on cholera and other diarrhea-causing enteric pathogens, but by the mid-1990s, it had yet to address the problem of acute respiratory infections (ARI). As a prelude to creating a new panel on ARI, the USJCMSP held two ARI workshops, the first in 1993 and the second in 1994. After extensive discussion, the Joint Committee decided it was necessary to create new Japanese and U.S. panels on ARI. The financial situation in Japan made it difficult to expand the number of panels, but the problem was solved with the amalgamation of the Leprosy and Tuberculosis Panels in 1996. The Japanese and U.S. ARI Panels officially came into being the same year, an important and timely addition to the U.S. Japan Program. Topics of concern to the ARI Panels have also been addressed by the International Conferences on Emerging and Re-emerging Infectious Diseases in the Pacific Rim, sponsored annually since 1995 by the USJCMSP. The USJCMSP ARI Panels created in 1996 have already made significant contributions to the understanding of emerging viruses that cause acute infections in the human respiratory tract.

In March 1997, the ARI Panels held their first joint meeting in Nagasaki, Japan. Panel members discussed how they could best address the major ARI problems in Southeast Asia, and developed operational guidelines for the Panels. They established two working group subcommittees, each of which creates its own research agenda.¹

One ARI subcommittee focuses on influenza, particularly on human influenza surveillance and the use of inactivated vaccines. Most of the Panel's activities, especially in the earlier years, focused on the pathogenesis of influenza viruses, including avian influenza virus.

The second ARI subcommittee, which is focused on bacterial infections, emphasizes a range



Influenza virus

of research areas that include: comparing the use of antimicrobial drugs in Japan and the United States to identify patterns of drug resistance and develop intervention strategies; investigating the impact on ARIs that can be prevented with vaccination, e.g., *Haemophilus influenzae* B and pneumococci; and collaborating on studies to analyze non-typeable *H. influenzae*. Although the bacterial component of the ARI Joint Panel has had difficulty finding identity and focus within the Panel's activities, it has now emerged as the primary watchdog of drug resistance within the USJCMSP, a crucial activity that should be fostered.

“Since I joined the Japanese Delegation, I have become interested in infectious diseases,” Dr. Hiroo Imura said in an interview in August 2004. Dr. Imura, now a consultant to the Japanese Science and Technology Agency, is an endocrinologist by training. He served as a member of the USJCMSP Japanese Delegation from 1991 to 2002. Dr. Imura linked environmental changes and shifts in wild animal populations to the increase of ARIs in human populations. “Viruses occur in wild animals, and those viruses may be transmitted to humans,” he said. “SARS was most likely prevalent in wild civets

before it infected humans, and now avian flu is increasing in birds and in humans.”

Indeed, the 2002 emergence in Guandong Province, China, of Severe Acute Respiratory Syndrome (SARS) was the first major infectious disease to appear in the 21st century. The disease came to worldwide attention in February 2003, after a man who had traveled in Southeast Asia died in a Hanoi hospital of severe respiratory distress, following a high fever, dry cough, and muscle aches. By March 2003, the World Health Organization (WHO) had deployed Global Outbreak Alert and Response Network field teams to Vietnam and Hong Kong, where SARS cases and deaths were occurring, particularly among health care workers who came into contact with SARS patients. As of December 31, 2003, 8,096 probable cases of SARS and 1,706 SARS deaths had been reported to the WHO.² The disease has been considered contained since July 2003, and no further person-to-person transmission has been reported.³ In June 2004, U.S. scientists and their colleagues reported the development of a candidate SARS vaccine that protected animals from experimental challenge with the SARS coronavirus.⁴

Scientists affiliated with the USJCMSP played important roles in identifying and describing SARS and the coronavirus that causes the disease. They made use of two research sites—one in Hong Kong and the other in Sapporo, Japan—that had been established as part of the U.S.–Japan Cooperative Program on Animal Influenza. The Hong Kong research site was provided with emergency funds when the SARS outbreak occurred in Hong Kong. Scientists of the U.S.–Japan Program described the

Hong Kong SARS outbreak, the first and most complete description of SARS. In addition, they isolated and characterized the causative coronavirus and provided proof that it was the cause of SARS.

“The USJCMSP acute respiratory infections program has connections with the surveillance system in Southeast Asia and what we call syndromic investigations,” said Dr. Adel Mahmoud in a June 2004 interview. Dr. Mahmoud, who is currently president of Merck Vaccines at Merck & Co. in New Jersey, became a member of the U.S. Delegation in 1994 and has served as its Chair since 2001. “SARS started in the Far East in the fall of 2002, and by the next spring we had the virus and its sequence—so we’re doing something right!”

Another accomplishment of the ARI Panels has been the joint educational activities that have taken place under the jurisdiction of the committee. In addition to annual exchanges of scientific information, there have been exchanges of scientists and research fellows to U.S. laboratories and, recently, a joint training course in Japan for Asian scientists on the methods for study of animal influenza. Both U.S. and Japanese scientists conduct these educational programs.

The following is a list of important science advances in the field of acute respiratory infections to which USJCMSP scientists have contributed. The list is adapted from information supplied by Dr. Keizo Matsumoto (Japanese ARI Panel Chair from 1997–2000), and Dr. Robert Couch (U.S. ARI Panel Chair from 1997–2000).

Acute Respiratory Infections Panels

[Established 1996]

[*Science Advances: 1996 – 2000*]

- Described the molecular basis of influenza virus pathogenesis. At both the Shanghai and Yokohama meetings, Dr. Yoshihiro Kawaoka described the differential incorporation of the eight viral RNA segments of influenza virus. This process represents one of the most important fundamental developments in the molecular biology of influenza virus since the identification of the hemagglutinin and neuraminidase genes.
- Developed and implemented a public health policy in Japan for annual immunization of elderly adults with inactivated influenza virus vaccines. The highlight of the eight years of operation of the ARI Joint Panel was the manner in which it influenced Japanese policy on influenza immunization directly and indirectly. The Joint Press Conference in Kyoto in 1999 was a hallmark event and one of the most notable examples of how USJCMSP Panel's activities could materialize into national health policy. Inactivated influenza virus vaccines have been available in the U.S. for over 50 years. These subunit vaccines are generally less reactogenic than whole virus vaccines. The efficacy of such vaccines in preventing morbidity in healthy adults has been repeatedly demonstrated in control trials.

However, the situation in Japan was different. In the past, Japanese health policy for inactivated influenza vaccines was to vaccinate all school children in an effort to prevent epidemics of influenza. But the epidemics continued, and so the policy was withdrawn in 1994 by the Ministry of Health and Welfare. In response, the Japanese and U.S. ARI Panels combined to develop a plan to restore confidence in inactivated vaccines among public health officials in Japan, and provide inactivated vaccines to persons at high risk of severe complications from influenza. Subsequently, the Ministry of Health and Welfare of Japan established a policy of recommending inactivated influenza virus vaccines for elderly adults in Japan and provided financial support for implementation of this policy. Thus, the ARI Joint Panel can assume some of the credit for the recent report that the influenza virus vaccination rate is increasing in older (65+ years) Japanese in recent years.

- Established the U.S.–Japan Cooperative Program on Animal Influenza, which made important contributions toward understanding animal influenza viruses that can be transmitted to humans. As a component of developing this ARI program, the NIH funded a laboratory for animal influenza research in Hong Kong to be directed by Dr. Robert Webster. The Japanese equivalent of the laboratory and facility for animal influenza is directed by Dr. Hiroshi Kida in Sapporo, Japan. These two scientists have worked closely on numerous animal influenza problems in the past. The Hong Kong laboratory, as an Asian site, also cooperates with the WHO laboratory in Tokyo, which is directed by Dr. Masato Tashiro, an ARI Panel member, as well as with other WHO activities on animal influenza in the area. This research program was proposed by the ARI panel and accepted by the joint committee as a “Program of Excellence” in research. For this program, the following major accomplishments can be identified:
 - The description of the virus ecology and influenza A subtypes in domestic and migratory birds in Asia and North America. This was the original basis for establishing the cooperative program; both U.S. and Japanese scientists have a major interest in the area. Information about avian viruses in domestic and migratory birds is used to identify viruses that could cause human pandemic influenza. Understanding the biology of bird influenza viruses and how they present a risk to man is the major role of this effort. The effort is continuing in both laboratories.
 - The identification and characterization of the outbreak of influenza A/H5N1 (chicken influenza) in Hong Kong, China, and an assessment of the pandemic threat. In 1997, an outbreak of 18 human cases of influenza with six deaths attributable to infection with the A/H5N1 virus occurred in Hong Kong. Scientists of the U.S.–Japan Program played an integral role in identifying these avian influenza viruses, describing their behavior in the markets in Hong Kong, and providing information that was used for the culling of millions of chickens in the Hong Kong area. This is considered to be a major reason why this virus did not proceed to cause a human pandemic in 1997.
- Participation in assessing the recent recurrence of influenza A/H5N1 in poultry populations throughout Asia, and the risk for human pandemic influenza. This concern comes from the recent widespread occurrence of highly pathogenic influenza A/H5N1 among poultry throughout Asia. Forty-four human cases with a very high frequency of deaths from this infection have occurred in Vietnam and Thailand. Scientists of the ARI Panels have traveled throughout Asia, and have studied numerous poultry outbreaks and causative viruses. They have served as advisors to area public health authorities and to the WHO in Asia and in Geneva in the assessment and management of this pandemic threat to humans. Thus, ARI Panel scientists have been instrumental in providing information and guidance to the authorities on this subject.
- Demonstrated the pathogenesis of avian flu after its transmission to humans. Through its surveillance efforts, the ARI Panels demonstrated that direct passage of avian influenza virus from birds to humans leads to much greater pathogenesis than does the passage of influenza virus from pigs to humans. The epidemiology and consequences of this have been explored, including examinations of clinical symptoms in the context of the influenza-associated Reye’s syndrome, hemorrhagic shock, and encephalopathy and acute necrotizing encephalopathy in Japanese children during the 1999 epidemic and followup years.
- Made progress in testing new anti-influenza drugs and monitoring the consequences of their use. U.S. scientists have tested the efficacy of the newer neuraminidase inhibitors, zanamivir and oseltamivir. Japanese scientists are monitoring the extent of amantadine resistance in sentinel surveillance sites.
- Created a Cooperative Program for Surveillance of Human Influenza in China, Influenza Reference Laboratories in the U.S. and in Japan. This was a program that the ARI Panels developed and were pursuing. Panel members interacted with Chinese scientists and public health authorities in developing the surveillance activities. As the program developed, it became clear that it would be better accepted and facilitated in China as a WHO program rather than as a U.S.–Japan program. For this reason, the ARI Panels stepped back from an active role but continued to monitor the success of the effort. So, the role of the ARI Panels could best be described as facilitating development of a surveillance program of human influenza in China. The information gleaned from this surveillance program

guides vaccine development and expectations for influenza occurrences throughout the world.

- Identified a new encephalopathy syndrome (other than Reye's syndrome), which results in a high death rate in children in Japan. Japanese scientists on the ARI panel noted the unusual occurrence of an encephalopathy in association with influenza in very young children during a major influenza epidemic. Japanese and U.S. scientists associated with the USJCMSP ARI Panels collaborated to establish a system for evaluating this new encephalopathy syndrome, developing different types of studies to understand its cause, and proposing remedies. The status of this research is being monitored primarily by the Japanese ARI Panel, while both Japanese and U.S. scientists provide scientific input.
- Made important advances in understanding viral pathogenesis and viral chemotherapy, which include:
 - An improved understanding of measles, which is still one of the most important causes of mortality and morbidity of children in many developing countries. Some disturbing antigenic changes were observed in sub-Saharan Africa, although the current vaccine is still effective. Work continues on identification of the cellular receptors of measles virus, CD46 for laboratory strains and SLAM (signaling lymphocyte activating molecule) for clinical isolates. An animal model for measles virus was developed, involving the transfer of human peripheral blood mononuclear cells to SCID mice which then allowed virus replication and lymphocyte depletion. Infection with measles virus induces a transient immunosuppression, sometimes resulting in fatal opportunistic infections. It was shown in one study that this is due to profound lymphopenia arising from apoptosis.
 - A demonstration that the Sendai virus P gene gives rise to two accessory proteins, V and C, as well as to the phosphoprotein P, essential for viral RNA synthesis. The C proteins are non-essential gene products but greatly contribute to full replication and *in vivo* multiplication and pathogenesis. The V proteins are essential for the coping of Sendai virus and pathogenesis.
 - Important findings about the genetics of V and P proteins of parainfluenza type of virus, their functions, and also the mechanism of paramyxovirus-induced cell fusion.
- Assumed a key leadership role in tracking and studying rampant, serious drug resistance to a host of respiratory bacterial pathogens in diverse geographical regions. The Joint ARI Panel, particularly the Japanese Panel in recent years, has assumed responsibility for these studies. For instance, in one study in Vietnam, the order of drug resistance in isolates of *S. pneumoniae* and *H. influenzae* from children with diverse ARI, was usually greater than 50 percent to drugs such as ampicillin.

As in the United States, B-lactamase-positive *H. influenzae* is becoming a problem in Asia (8.5 percent in Japan, 64.7 percent in South Korea, and 17.1 percent in Hong Kong, according to one survey). USJCMSP scientists conducted another important comparative study of the etiology of community-acquired pneumonia (CAP) and drug resistance patterns in Bangladesh, Thailand, Uganda, and Japan, and demonstrated that most cases were due to *S. pneumoniae* and *H. influenzae*, and most isolates from all sources were penicillin-resistant.

- Addressed the etiology of respiratory infections in infants and children in the Pacific Rim by analyzing cultures from washed sputum and examining inflammatory cytology. Infections with *S. pneumoniae*, followed by *H. influenzae*, are generally the major causes of pneumonia. In one Japanese study, the ratio of *H. influenzae* type B to non-typeable was 4:1. However, in other respiratory infections such as chronic bronchitis, non-typeable *H. influenzae* was the leading pathogen, followed by *S. pneumoniae* and *M. catarrhalis*. The fact that 30 percent of bacterial exacerbation is due to *M. catarrhalis* is of particular interest, and there is a push to develop a vaccine. The outer membrane protein, CD, seems to be a good candidate.

[Science Advances: 2000 – 2004]

- Described a newly emerging virus, human metapneumovirus (HMPV), which causes lower respiratory tract disease in infants and children. At the 7th Joint Panel meeting in Yokohama (January 8-10, 2003), Dr. James Crowe described HMPV and its role in lower respiratory tract disease. There is also presumptive evidence for this condition in children, in Japan.
- Further characterized avian H5N1 influenza viruses in discussions at the 7th International Conference on Emerging Infectious Diseases in the Pacific Rim in Shanghai, China (October 31–November 1, 2002), and the 7th Joint ARI Panel meeting in Yokohama. In Hong Kong in 2001 and 2002, the H5N1 influenza virus emerged in poultry markets and aquatic birds in parks, and multiple different genotypes co-circulated on each occasion. Many strategies have been developed to control the emergence of highly pathogenic H5N1 viruses in Hong Kong poultry markets. Key phylogenetic analyses of H9N2 influenza viruses in mainland China conducted by Dr. Hiroshi Kida show genetic uniformity and indicate that genetic reassortment hardly takes place in mainland China but is much more likely in the poultry markets of Hong Kong. Both of these meetings featured interesting presentations on the applications of geographic information systems (GIS) to the study of the epidemiology of influenza virus infections in Japanese municipalities.
- Determined that adherence and invasion are also crucial to the pathogenesis of non-typeable *H. influenzae*. Dr. M. Apicella developed an *H. influenzae* lipo-oligosaccharide (LOS)-coated polystyrene bead assay to examine the structural basis of

adherence, and reported that a particular subset of phosphorylcholine (Cho-P) and lipo-oligosaccharide (LOS) glycoforms could mediate NTHi adherence to and invasion of airway cells through interaction with the platelet activating factor (PAF) receptor. Both *H. influenza* and *S. pneumonia* have Cho-P on their surfaces, a key virulence determinant. The genetic basis of Cho-P expression and molecular mechanism controlling its phase variation in *H. influenza* are being defined.

- Used the definition of the various *Streptococcus* genomes and its exceptional plasticity, to address Group A *Streptococcus* and *Streptococcus pneumonia* at recent ARI Panel meetings. For instance, Dr. Michael Wessels reported that the interaction

of the hyaluronic capsular polysaccharide with CD44 results in rearrangement of the cytoskeleton, disruption of tight junctions, and enhanced bacterial penetration leading to infections such as pharyngitis and soft tissue infections. In the case of pneumococcal adhesion to epithelial cells, the interaction is enhanced by anti-PnPS IgA1, which, on cleavage, enhances binding of phosphorylcholine and the PAF receptor.

- Helped determine the reasons for the severe virulence of the 1918 influenza virus by generating influenza viruses that contain the genes for viral haemagglutinin and neuraminidase from the 1918 pandemic virus.⁵

Footnotes — Acute Respiratory Infections Panels

¹ 35 Years of Progress. U.S.–Japan Cooperative Medical Science Program: Seventh Five-Year Report, 1996–2000. p. 25.

² World Health Organization. Communicable Disease Surveillance & Response. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. http://www.who.int/csr/sars/country/table2004_04_21/en.

³ Centers for Disease Control and Prevention. Severe Acute Respiratory Syndrome (SARS) Surveillance and Reporting. <http://www.cdc.gov/ncidod/sars/reporting.htm>.

⁴ See - Bukreyev A, Lamirande EW, Buchholz UJ, Vogel LN, Elkins WR, St Claire M, Murphy BR, Subbarao K, and Collins PL. Mucosal immunisation of African green monkeys (*Cercopithecus aethiops*) with an attenuated parainfluenza virus expressing the SARS coronavirus spike protein for the prevention of SARS. *The Lancet* 2004;363:2122-7; and Buchholz UJ, Bukreyev A, Yang L, Lamirande EW, Murphy BR, Subbarao K, Collins PL. Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity. *Proc. Natl. Acad. Sci. USA*. 2004 June 29;101:9804-9.

⁵ Kobasa D, Takada A, Shinya K, Hatta M, Halfmann P, Theriault S, Suzuki H, Nishimura H, Mitamura K, Sugaya N, Usui T, Murata T, Maeda Y, Watanabe S, Suresh M, Suzuki T, Suzuki Y, Feldmann H, and Kawaoka Y. Enhanced virulence of influenza A viruses with the haemagglutinin of the 1918 pandemic virus. *Nature* 2004;431:703–7.