The H5N1 Bird Flu Research Controversy

Adrianus D. Boon, Ph.D.

Bird flu or highly pathogenic avian H5N1 influenza virus has been circulating in South East Asia since the late 1990’s and has spread to Europe, The Middle East and parts of Africa. In addition to the millions of infected poultry, the World Health Organization has identified approximately 600 H5N1 infected human cases. The fatality rate for H5N1 virus is 50%, which is an order of magnitude higher than the 1918 Spanish Influenza virus which killed between 20-30 million people worldwide. Because the exact number of human H5N1 cases is unknown, it has been difficult to accurately estimate mortality rates. The lack of sensitive assays and the presence of cross-reactive antibodies in serum have made it difficult to identify subclinical cases. Regardless, H5N1 virus is extremely pathogenic following infection due to the unique genetic makeup of the virus and lack of preexisting immunity in the population.

Despite almost 10 years of continued circulation and occasional transmission of H5N1 virus to humans, the virus has not adapted to facilitate efficient human-to-human transmission. It was therefore speculated that this virus may not have the capacity to adapt to the human host. Two research teams, one lead by Dr. Yoshihiro Kawaoka at the University of Wisconsin-Madison and the other by Dr. Ron Fouchier at Erasmus Medical Center in The Netherlands, decided to test this hypothesis and attempted to create an airborne transmissible H5N1 influenza virus. Their findings were published in the scientific journals Nature and Science and have sparked a strong debate among scientists, government and in society. At the forefront of the discussion was the potential for Dual-Use; a scientific research finding which may be misused to pose a biologic threat to public health and/or national security. Initially, the National Science Advisory Board for Biosecurity (NSABB), an independent committee created to oversee Dual-Use research, advised against publication of the research. However, after discussions between scientists, government and NSABB, both manuscripts were approved for publication.

The key observation is that H5N1 influenza viruses can become airborne transmissible. As few as four amino acid substitutions in the hemagglutinin attachment protein are sufficient for airborne transmission between ferrets; the gold standard animal model...
Mitsuo Kitahara, M.D.
Tokyo, Japan

My infectious diseases training at Washington University was conducted by Drs. Medoff, G.S. Kobayashi, C. Harford, L. Gelb and J. Marr from 1973 to 1975. After leaving Washington University in 1975, I joined the Division of Hematology/Oncology of the University of Utah as a clinical fellow, later assistant professor. At that time Dr. Maxwell Wintrobe was an active hematologist and distinguished professor. My research interest in Utah was neutrophil function with myeloperoxidase deficiency supported by a NIH Grant. My career was interrupted by my father’s illness and I left the U.S. in November, 1979.

I accepted the position of Head of Section of Infectious Diseases, Hematology and Oncology at a hospital in Tokyo which was one of the major affiliated hospitals of Keio University School of Medicine (my alma mater). Dr. Medoff and Dr. Kobayashi gave us lectures of methicillin-resistant Staphylococcus aureus and treatment of fungal infection, respectively at this hospital. I was the head of a hospital in Tokyo from 2002 to 2007, and then I was invited as the Chief Operating Officer of the Hospital Management of Keio University Hospital from 2008 to 2010. I am now working as a company physician of an agricultural and fishery bank.

My involvement with infectious diseases in Japan include coeditor of a Japanese medical journal for 24 years and four medical textbooks, and giving lectures to medical students of Keio University and residents of hospitals.

Dr. Fraser heads Department of Medicine

Victoria J. Fraser, M.D. has been named Head of the Department of Medicine at Washington University School of Medicine in St. Louis. The new appointment became effective Sept. 1, 2012.

With more than 400 faculty members, Internal Medicine is the largest of the School of Medicine’s departments. It receives more grant funding than any other research enterprise at the school and is the largest clinical service at Barnes-Jewish Hospital.

Fraser, the former J. William Campbell Professor of Medicine and Co-Director of the the Infectious Diseases Division, has been interim head of the department since August 2010 when she was appointed to replace Kenneth S. Polonsky, MD, now Dean of the Division of Biological Sciences at the Pritzker School of Medicine and Executive Vice President for Medical Affairs at the University of Chicago.

Larry J. Shapiro, MD, Executive Vice Chancellor for Medical Affairs and Dean of the School of Medicine, announced Dr. Fraser’s permanent appointment.

H5N1 Bird Flu continued from page 1

for influenza virus transmission studies. Several substitutions were identified near the receptor binding site of the protein. One of these mutations is known to change the sialic acid receptor preference to the more human like receptor. Both studies also found that the removal of a glycosylation site on the hemagglutinin protein was required for transmission. This is particularly important because H5N1 viruses containing this mutation are frequently found in Egypt. In theory, these H5N1 viruses require only three additional substitutions to become airborne transmissible. The 4th mutation in Dr. Kawaoka’s study was important for protein stability revealing a novel mechanism important for transmission.

Overall, these studies clearly indicate that H5N1 virus is capable of adapting to the human respiratory tract. While many argued that these studies should not have been done and certainly not be published, they have provided us with important information. Foremost, these studies show that current antiviral therapeutics and stockpiled H5N1 vaccines are effective against these airborne transmission viruses. This information is very important for health care providers as well as governments stockpiling pandemic vaccines and antiviral agents. This information will also guide surveillance efforts and enable scientists worldwide to identify H5N1 viruses containing one or more of the published or similar substitutions associated with transmission. Finally, it reemphasized the continued need for surveillance and basic science research related to H5N1 influenza virus. To support the important work on influenza virus and highly pathogenic H5N1 influenza virus, Washington University School of Medicine has build a secured high containment facility (ABSL3+). Our research goals are to study the host response to H5N1 virus and find cures to minimize disease after infection. At the same time we will identify host polymorphisms associated with severe H5N1 disease. The host genes containing these polymorphisms reveal important influenza biology and provide support for the rational design of novel antiviral compounds.

Victoria J. Fraser, M.D.
President of Adolphus Busch Professor of Medicine
Awards & Announcements

RECENT RESEARCH AWARDS

<table>
<thead>
<tr>
<th>PRINCIPAL INVESTIGATOR</th>
<th>AWARD</th>
<th>PROJECT TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steve Lawrence, M.D., MSc</td>
<td>Pfizer</td>
<td>ASPIRE Award in Adult Vaccine Research Effect of medical comorbidities on pneumococcal Disease burden in older adults: a hospital-based nested case-control study</td>
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<td>Jonas Marschall, M.D., MSCI</td>
<td>Scholar on Washington University’s Building Interdisciplinary Research Careers in Women’s Health (BIRCWH) K12 Award</td>
<td>Understanding clinical, microbial, and host immunity differences between patients with E. coli symptomatic urinary tract infection versus Asymptomatic bacteriuria.</td>
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<tr>
<td>Melisaa Viray, M.D.</td>
<td>KM1</td>
<td>Comparative effectiveness of reimplantation of cardiac devices after infection.</td>
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Special Recognition

Carlos Santos, M.D. has been named director of the Infectious Disease Clinic at Washington University School of Medicine

Congratulations...

Nigar Kirmani, M.D., was selected to receive the 2012-14 Carol B. and Jerome T. Loeb Teaching Fellowships at Washington University School of Medicine. The fellowship program was established in 2004 by a gift from Loeb to advance clinical education and to honor local physicians committed to clinical excellence. Strengthened by a gift from the Barnes-Jewish Hospital Foundation, the program allows the fellows to take time from their regular duties to teach clinical medicine to students and residents. The two-year fellowship began July 1 and continues through June 30, 2014.

To enhance the training of students, residents and fellows, Dr. Kirmani, Professor of Medicine will develop new physician-education programs in infection prevention and hospital epidemiology and patient safety. She plans to develop interactive, web-based training modules that will allow trainees to access information when needed. The modules will include a pretest, a case study and a post-test.

Kirmani has been course master for the infectious diseases course taken by second-year medical students since 2000. She also is program director of the infectious diseases fellowship program, an attending physician at Barnes-Jewish Hospital, is medical director of the Barnes-Jewish Hospital Home IV Therapy service and treats outpatients in the infectious diseases clinic.
Welcome to our new staff

Anna Shanks previously worked in the Metabolism Division as the Purchasing Accountant for over a year. Prior to joining Washington University she worked as an accountant for the Farnsworth Group, Inc, an engineering firm in Webster Groves. She was with Farnsworth for five years. Anna has a Bachelors Degree in Accounting from Missouri Baptist University and is currently working toward a Masters Degree in Business from Webster University. She is the Purchasing Accountant for Infectious Diseases.

Anna can be reached at (314) 362-2125 or by email ashanks@dom.wustl.edu.
Hani Khair, M.D.
**Next Steps:** I will be joining the Dallas ID Associates, a private infectious diseases group that has 9 ID specialists serving the Dallas-Fort Worth (DFW) metropolitan area. I will be closer to my family in the DFW area.

**Highlights of fellowship:**
During my two years of fellowship at Washington University, I had the opportunity to learn from experts in the field, such as Dr. Medoff. I also enjoyed my research experience under the supervision and mentorship of Dr. Marschall who has been very helpful and supportive to me. I hope to stay in touch with all the friends I worked with here.

Makhawadee “Joy” Pongruangporn, M.D.
**Next steps:** I will be joining the BMT-Gold service at Barnes-Jewish Hospital/Washington University School of Medicine for the next three years and will also be working at the Infectious Diseases clinic at Washington University.

**Highlight of fellowship:**
These past two years have given me some wonderful memories. I have always enjoyed working with Dr. Medoff, my first clinic attending. We would walk together to the micro, radiology and pathology laboratories while he would provide personal consultation on my most interesting patients. He imparted so much knowledge and in a fun way. I would like to thank Dr. Warren, my mentor, for his patience, as I learned statistics from the beginning. I also would like to thank Dr. Kirmani and Dr. Fraser who gave me the opportunity to join this excellent fellowship training and for all the advice for my career plan.

In addition to my work as a fellow, I became a mother of my first baby. I felt an abundance of support from everyone during my pregnancy (Dr. Kirmani usually drove me home after our rounds together because she did not want me to have a heat stroke during last summer’s high temperatures). I really appreciate the wonderful teamwork of the infectious diseases team, and most importantly, my co-fellows: Sara Cross, George Kyei, Melissa Viray and Hani Khair. We are a big family and get along so well even with a terribly busy service. Thank you for giving me these two wonderful years.

Stephen Liang, M.D.
**Next steps:** I am staying on at Washington University School of Medicine as an Instructor in Infectious Diseases and Emergency Medicine. My clinical time will be split between the inpatient infectious diseases consult services and the emergency department. I will also continue as a KM1 Comparative Effectiveness Research scholar focusing on infectious diseases outcomes after open fractures. I hope to develop an academic niche in emergency and trauma-related infections.

**Highlights of fellowship:** I would like to acknowledge the outstanding mentorship I have received over the years from Drs. Fraser, Kirmani, Olsen, Warren, McDonald, and many, many other faculty, clinicians, and staff. The Division has really helped me build a solid foundation for a hybrid academic career in both infectious diseases and emergency medicine.

I have been fortunate to have had ample opportunities to write, teach, pursue clinical research, and obtain graduate-level coursework throughout my fellowship. It has been a distinct privilege to care for patients alongside so many physician educators in the Division who truly exemplify the humanity of medicine. It’s been a great ride.