Summary:
Advisory Committee on Blood Safety and Availability
Department of Health and Human Services
28th Meeting, January 5-6, 2006

The meeting was called to order by Dr. Jerry Holmberg at 9:05 AM. Emphasizing the importance of the Committee in advising the Secretary, DHHS, he suggested that members be mindful of the Committee's history. It was established in response to an Institute of Medicine report on the introduction of HIV into the blood supply and how the safety and availability of blood and blood products could be ensured. He announced that the Committee would reconvene at 8:00 AM the next morning for annual ethics training; the public will be admitted and the meeting proper started at 9:00 AM. He noted that with new members the Committee has a cross section of academic people.

Dr. Holmberg then introduced Dr. Art Bracey as the chairperson; he was appointed to the Committee in FY '05 to serve through '07. He graduated from Georgetown University School of Medicine in 1976, trained in internal medicine, anatomic pathology and transfusion medicine and is now Medical Director of the Transfusion Service at St. Luke's Episcopal Hospital and associate professor of Pathology at the University of Texas Medical School in Houston. New Committee members are: Dr. Gregg Bloche, a physician, lawyer and Co-Director of the Georgetown-Johns Hopkins Joint Degree Program in Law and Public Health, who is a widely published leader in medical ethics; Dr. Glenn Ramsey, Medical Director of the Blood Bank in Children's Memorial Hospital and Associate Professor of Pathology, Northwestern University in Chicago; Mr. David Matyas, a lawyer and Adjunct professor of law at the American University's Washington School of Law who specializes in legal and regulatory matters arising under Medicare, Medicaid and other third party payment programs; Mrs. Linda Thomas, widow of sickle cell victim Mr. Mark Thomas who died before he could begin his appointment to the Committee and represents the Sickle Cell Association of Austin; Dr. Judy Angelbeck (Pall Medical) who has been reappointed for an additional year; Ms. Julie Birkhofer, Executive Director, North American Plasma Protein Therapeutic Association; Dr. William Duffell, Director of Government Affairs and Quality Systems for Gambro BCT; Mr. John McGuire, Executive Director, American Red Cross Biomedical Services (not present); Dr. Jerry Sandler, Medical Director of the Transfusion Service at Georgetown University Hospital and representing the American Hospital Association; and Glenn Pierce, MD, PhD, nominated by the National Hemophilia Foundation. The roll was called (Dr. Klein was absent).

Dr. Holmberg then reviewed the Committee activities over the past year. Bacterial contamination of blood components, especially platelets, was extensively discussed. The Committee-recommended surveillance of the results of routine bacteriological testing has not been formalized. The Committee recommended principles to guide appropriate reimbursement for plasma-derived products and their recombinant analogues: reimbursement should be sufficient to ensure an adequate supply; individual products within classes should be recognized as therapeutically unique; reimbursement should be equivalent in different care settings; lifelong costs of treatment should be addressed in

any pricing structure, including the effect of co-pays. There have been no tangible results to report, although messages have been provided to CMS. The Medicare Modernization Act (MMA) imposes constraints on what can be done and the issues are not yet solved. The biggest issue with solving the reimbursement problems for IGIV has been understanding the complexity of the problem. There doesn't seem yet to be enough information to justify the declaration of a public health emergency as part of the solution. Manufacturers have set up a 1-800 phone lines, as has Medicare, to assist patients and physicians in obtaining needed supplies. An IG evaluation report is being readied for Congress. In September 2005, a strategic plan was put together; the Department continues to work on this via working groups to incorporate the Committee's proposals.

Dr. Christine Beato was scheduled to brief the Committee further on these matters but she couldn't come so her report was given by Dr. Holmberg later in the meeting. Her title has changed from Acting Assistant Secretary for Health to Principal Deputy Assistant Secretary for Health with the swearing in yesterday of Dr. Agwunobi as Assistant Secretary for Health. Dr. Holmberg introduced Dr. Celia Whitten, Director of the Office of Cell, Gene and Tissue Therapy at CBER. This office is charged with implementing the tissue program for safety of human tissues. Representatives from HRSA were also invited to the meeting.

Dr. Sayers asked if some of the recommendations made by the Committee might "atrophy" of they are not reviewed to determine their status and obstacles to their implementation. Dr. Bracey suggested that a tracking mechanism be established to facilitate follow up of previous recommendations. Ms. Lipton asked about the status of the recommendations for a strategic plan and the possibilities for further public involvement. In addition to various working committees from the involved agencies, there is the intention to include various people, e.g., special government employees, such as this Committee, in the creation of the strategic plan.

Dr. Holmberg announced that the primary focus of this meeting was to be the potential for pandemic influenza and its likely effects on the blood and blood product community and on those who transplant hematopoietic stem and progenitor cells. How should DHHS deal with these potential problems? Some of the issues include immunization of blood center staff and of regular repeat donors, monitoring and managing supplies during an outbreak, establishing donor policies, resolving false positive donor screening tests from immunization or infection, and handling communication to various publics. Dr Bracey, Chairman, then introduced the first speaker, May Chu, PhD, Technical Officer, Emerging and Dangerous Pathogens Section for the Department of Communicable Disease Surveillance and Response at the World Health Organization, Geneva (on loan from the US CDC).

Dr. Chu began by summarizing the structure of WHO. Under the Director General, there are 12 different clusters, one of which includes Communicable Diseases and the Alert and Response Operations. Blood banking is in a different cluster, Health Technical and Pharmaceutical, but they hope they have good links and communication. The WHO Assembly is the "Board of Directors" and consists of ministers of health of the 192

member countries. Mr. Mike Leavitt, Secretary of DHHS, represents the US. WHO is an entity that has no teeth and does everything by voluntary subscription and guidelines. The regulations are the only things that have legal status and those currently in place date from 1999, when only plague, cholera and yellow fever were notifiable. The previous version (1969) would not have permitted the identification of SARS, pandemic flu or many other diseases, because the specificity of the test at the time. The most recent version (2005) of the regulations won't have full effect for 5 years, with voluntary compliance beginning in 2007. These new International Health Regulations require each member state to designate a "focal point" as the legal entrée into the country to study outbreaks, but this part is not yet operational. Expert panels and review panels will be identified, as well as time periods for problems. In addition to asking member states to invite WHO in when potential outbreaks are identified, member states may request intervention if they are concerned about the international spread of disease. All of this requires very strong national public health systems and capacity. Dr. Chu reminded the Committee that annual flu outbreaks cause about half a million deaths in developed countries alone; it is likely the number is much greater in developing countries but adequate surveillance this is not available. An influenza pandemic would affect medical services and essential disease control functions and also other public sectors causing great political and social disruption. Although we now have avian flu, not pandemic influenza, it has the possibility of becoming adapted to a pandemic. The current fatality rate of H5N1 (avian flu) is high (around 54 %) and it is a disseminated disease causing multiple failure. Most of the fatalities have been in previously healthy individuals, children and young adults. It has not circulated widely in humans so that there is little cohort immunity.

Dr. Chu explained that WHO has a daily morning intelligence and verification meeting; when needed, a network of WHO regional and country offices provides consultation and input as does the Global Outbreak and Response Network (GOARN: 120 institutions around the world, including 12 in the US). WHO is an administrative secretariat without laboratories or other facilities. "Collaborating Centers" help with specific diseases. For influenza, WHO collaborating centers are in Melbourne, Tokyo, London and Atlanta. Many countries participate in a National Influenza Center network, but distribution is spotty(e.g., one center in China, hardly any in sub-Saharan Africa, but a number throughout Europe, Russia, Australia and the US). Avian flu was reported in Turkey just prior to this meeting and there are teams mobilized to to there.

Dr. Sayers asked if there were likely individuals who were infected but recovered and were not reported. Dr. Chu stated this has not been detected, but serological surveillance has been inadequate to be sure. Dr. Bloche wondered if the death rate might be different with treatment under "first world" medical standards. Is it also possible that the disease might become attenuated in severity once it is able to be transmitted person to person. To answer the second question, it is difficult to predict the disease behavior. For the first question, better treatment is likely to provide better results, but the degree of improvement would be difficult to predict. Dr. Epstein asked about the feasibility of providing immunization before there is a pandemic to reduce population susceptibility. The question is under discussion at WHO and NIAID (NIH). Current plans involve

immunization around outbreaks to try to contain the disease. Dr. Bracey asked if sufficient resources were available to cope with this likely problem. Dr. Chu replied that they could always use more. Dr. Kuehnert asked about the coordination of world-wide surveillance and the standardization of reporting. DHHS has funded the development of an event management system to help filter and analyze the information coming in to WHO. Intercluster communication (infection and blood) is largely informal at present. Dr. Pierce asked about susceptibility factors. These are under study. Dr. Angelbeck asked what triggers would identify a pandemic. Any efficient transmission within those with a common exposure or simultaneous geographically diversified reports would suggest a beginning pandemic. What are the immediate elements of the WHO containment plan? Suspicious cases need to be confirmed by a WHO lab. The country's minister of health is asked to invite WHO, whereupon a team would be activated including epidemiologists, clinicians, and other field people would be dispatched to investigate along with the country's public health staff. Dr. Bracey asked about control of avian spread. How do nations respond? SARS sensitized most countries to the potential for problems, so that compliance with control measures is currently good.

After a short recess, Anna Likos, MD (Epidemiology Section, Influenza Branch, CDC) was introduced to discuss: "Pandemic Surveillance at the Grass Roots Level: Transmission and Clinical Detection." She explained the term, influenza, refers both to the virus and the disease. The illness is contagious and poses a global threat as well as an annual public health problem. After an incubation period of one to five days, it affects primarily the respiratory tract and, in addition to its own severity, leads to complications such as bacterial pneumonia, myositis, myocarditis, encephalopathy and encephalitis. Systemic symptoms (e.g., fever, myalgia) are thought to result from cytokines and lymphokines. In some instances, virus has been isolated in tissues, including muscles, myocardium and cerebrospinal fluid. The virus presumably gets to those tissues via the blood stream, although virus has rarely been isolated from the blood and current dogma is that there is no viremia associated with flu. The cause is a single stranded negative sense RNA virus covered by a protein and lipid coat. On the surface is a hemoglutinin that is involved in entry into cells and neuramidase which is involved in exit of viral progeny from the cell. There are 16 different types of hemaglutinin ("H") and nine different subtypes of neuramidase ("N") in influenza A. The full descriptive name of one kind of influenza A, H3N2, is "A/Beijing/32/92(H3N2." This is translated into type A influenza, with surface proteins H3N2 and the32nd strain isolated in Beijing in the year 1992. The various types A are of most concern because it affects many kinds of animals including birds (tends to be species-specific) and humans of all ages. It causes epidemics and pandemics. Type B affects only humans, generally causes only epidemics and primarily infects children. Influenza viruses are transmitted the coughing, sneezing, talking and hand contact. They can persist and remain infectious for up to 48 hours on stainless steel surfaces. The best prevention tactics are good cough hygiene and frequent handwashing.

Influenza is a serious illness that produces an estimated 36,000 deaths and more than 200,000 hospitalizations annually. At greatest risk are persons 65 and older with chronic diseases, especially lung and heart disease as well as individual with diabetes, those who are pregnant or who live in nursing homes. So far, no human-to-human transmission of

avian flu (H5N1) has been proven. All cases have had close contact with birds, usually sick birds. In some instances, incubation period was up to eight or ten days. Historically, the 1918 pandemic (Spanish flu) was H1; this was replaced in 1957 with H2, which in turn gave way to H3 in 1968. H1 reappeared briefly in 1977 as "Russian flu." The virus causing flu was first isolated 15 years after the 1918 pandemic. Hemaglutinin testing started in 1941. It wasn't until recently that rapid laboratory flu tests became available along with PCR-based techniques to speed testing and identifying of the viruses.

In the discussion, Dr. Bracey asked if spiked blood samples had been studied for virus. The question was deferred for a later speaker. Dr. Epstein asked about the magnitude of the effort to detect viremia in case contacts. Dr. Likos was not aware that blood from contacts has been tested. Dr. Wong asked for clarification of person to person transmission in a Vietnam case. The case, reported in the NEJM, is a bit muddy with regard to such transmission. Dead birds could have been the source. In no other instances has person to person transmission been proven. Dr. Holmberg asked how good the data were to support that conclusion. Dr. Likos referred to question to Dr. Chu who noted that the investigative teams in China and the Far East included people from WHO and the studies were quite good. Dr. Holmberg also asked how the trigger signifying a pandemic was defined. Dr. Chu responded that finding really efficient human-to-human transmission is the key. Dr. Ramsey asked about the use of prophylaxis. Dr. Likos commented that some regard Tamiflu to be more effective in prevention than it is as therapy. Dr. Sandler asked about asymptomatic blood donors as disese transmitters. Currently, the information about asymptomatic viremic individuals is very limited. Dr. Sandler then asked if blood processing and storage might render units non-infectious, as is true about units with syphilis spirochetes in them. Dr. Likos did not know the answer. Dr. Bloche asked if the severity and mortality of flu would be the same in countries with modern medical practices. Also, he also asked of the virus should begin to circulate widely is there the likelihood that the pathogenicity would decrease. Some of the hospitals in Vietnam had excellent staff and facilities, but it is entirely impossible to predict what the situation here would be with a pandemic. Dr. Wong asked about clinical recognition of flu at ports of entry into the US and what is being done to train physicians at hospitals who might see patients with flu who escaped detection at entry. Dr. Bresee (CDC) noted that case definitions had been developed for travelers and more quarantine stations have been opened. This and increased training has reduced the likelihood of cases entering the country undetected.

The next speaker, Jesse Goodman, MD, MPH (Director, CBER, FDA) discussed "Vaccine Preparation and Process in an Influenza Pandemic." He explained that the FDA has an internal task force to deal with broad pandemic issues, e.g., antivirals, diagnostics, food supply, veterinary medicine. The FDA also participates in the cross-agency group for HHS and other agencies formulating plans for the US Government as a whole, including the White House. There are product development teams, which include industry participants, to develop and increase availability of various measures (e.g., flu vaccines and antivirals). This approach has resulted in small pox vaccine preparedness for the nation. These and other measures are resource intensive and additional resources have been made available for these purposes. There is some danger that if the H5N1

threat is not realized, the government will relax and the necessary systems won't be in place for the next threat in 5-10 years. It is important to realize that vaccines may not only prevent disease but, more importantly, their use may ameliorate illness and reduce fatalities. Recent flu vaccine shortages and increased public demand have stimulated commercial interests to invest in producing annually adjusted vaccines. Progress has been stimulated by the concept that antibody levels against hemagglutinin are a surrogate for protection, allowing evidence of efficacy to be obtained about one new vaccine within a month or two of preparation. Global coordination is essential, probably starting with regulatory convergence of science as a step toward regulatory harmonization. In general, vaccine development and production use technologies developed more than 50 years ago. Work is in progress to modernize techniques and shorten the time to bring a new vaccine to availability and use. Preliminary data suggest that relatively large doses of H5N1 antigens are necessary to generate sufficient antibodies for protection. Unless the requirements can be reduced by such approaches as the use of adjuvants, this will be a big problem in making enough vaccine to cover the needs. Advanced vaccination to increase population immunity and reduce the hazards of a pandemic may be desirable, but could increase the number of adverse effects (e.g., Guillain-Barre syndrome after swine flu vaccination in 1976).

Blood bank issues include concern about the use of a live attenuated virus vaccine (e.g., FluMist) and a period of asymptomatic viremia with the disease. The latter, however, is not known to be an issue with H5N1 (or other) flu viruses.

In the discussion, Ms Lipton asked about the public's view about new vaccines: was it shifting away from the fears that surfaced a few years ago. In response, Dr. Goodman noted that CDC and the National Vaccine Program Office monitored this and is attempting to explain and minimize, if possible, the public's concerns. For example, Thimerosal used to be in all routinely administered childhood vaccines; It is now absent from all vaccines except a very small number of flu. One problem is that people don't recognize the value of the vaccine because the diseases such as measles and polio have virtually disappeared. Ms. Birkhofer asked for further discussion of expedited reviews. They are a balance between rapid approvals and careful protection for the public. The procedure is resource intensive and, as mentioned above, additional resources have been made available. Dr. Bloche commented about risk communication to balance "complete safety" with the likelihood that side effects of large scale vaccination will arise. The example of the swine flu-Gullain Barre fiasco of 25-30 years ago was raised. Dr. Goodman noted that there is a serious problem of communication with the public and that the Department was concerned and attempting to approach it proactively. Dr. Epstein asked for comments on the questions addressed to the Committee concerning the preparedness of the blood system and addressing the scientific uncertainties surrounding the risks. Dr. Goodman believed that the AABB Disaster Preparedness Task Force was an important part of the procedure and mentioned particularly the need for surge capacity in the medical care systems as a whole.

The next speaker was Benjamin Schwartz, MD, Deputy Director, National Vaccine Program Office, Office of the Secretary, Office of Public Health and Science, DHHS. He

discussed the HHS Pandemic Plan (available on the Internet), with emphasis on vaccine and antiviral targeting. This plan is part of a National Plan being developed at the White House level. In December, 2005, a tabletop-exercise took place with the participation of all Executive Branch Secretaries. The National Strategic Plan and each of the departmental plans are works in progress. These plans are based on a series of assumptions. Although each of the 3 pandemics that occurred in the 20th century were different, there are enough similarities to support some of the planning. Virus changes, improved medical care, availability of antiviral drugs, increased complexities of global supply chains with increased effect of infrastructure operations all contribute to the complexities of planning. The illness rate during the first wave of the pandemic is estimated to be about 30%, regardless of the virus virulence which (governs illness severity in the wave transmission will occur by contact with respiratory secretions. Children will play a large role in transmission. The average period between infection and illness will be about 2 days, with virus shedding and some risk of transmission during the last half day. About 2/3 of those infected will be symptomatic and likely to transmit, while the other third will be asymptomatic, although still at-risk for transmission. Containing the pandemic by detecting and quarantining those who are symptomatic won't work. It is assumed that the work force will have about 40% absenteeism, including those who are ill, those caring for ill family members and those too worried to go to work. Closing schools and "snow days" when people are encouraged to stay home may have an effect. Peak absenteeism will occur within a couple of weeks of the outbreak peak. There will be some variation between communities, industries and work sites. The final set of assumptions suggest that the disease will hit travel hubs first with multiple sites at once and affecting the entire country within 1-2 months. The disease waves are most likely to occur in the fall, winter and possibly the spring. The duration of outbreaks is likely to be about 6 weeks and each one may be followed by a secondary peak soon after.

The HHS Pandemic Plan is centered around doctrine and guiding principles. The doctrine is to have sufficient vaccine available for the entire population within 6 months: New techniques are being developed with Federal support, but bringing them on line will take at least 5 years. An NIH trial of a H5N1 vaccine suggests that 2 doses of 90 micrograms each will be necessary for protection. That would protect about 1.7 million people per month of vaccine production at current rates. Antigen-sparing strategies (e.g., intradermal injection, use of adjuvants) won't have a major effect. In July 2005, the Advisory Committee on Immunization Practices and the National Vaccine Advisory Committee issued recommendations for prioritizing the use of vaccines and anti-viral drugs. For vaccine, four different tiers have been established: 1) essential health care workers and personnel at vaccine and antiviral manufacturing facilities, those at the highest risk of severe influenza disease, household contacts of those who can't be protected with active immunization and key governmental leaders and pandemic responders; 2) other high risk people and critical infrastructure groups; 3) health decision makers and mortuary personnel; and 4) healthy people not in any of the other groups. DHHS Secretary Leavit put it another way: target vaccine to preserve national security, to preserve constitutional government and preserve critical infrastructures. He suggested about 5% each to preserve constitutional government and support federal health care

providers (e.g., VA, Indian Health Service, Bureau of Prisons) with the rest allocated pro rata to the states. Blood center personnel were included as a priority group (critical infrastructure). There was no discussion about platelet or stem cell donors. The doctrine for antiviral drugs is to stockpile enough for 25% of the population, using them to help contain the initial outbreak, delay its spread and use it for treatment vs prophylsxis and for state decision-making and targeting. One suggested allocation shema includes 5% to contain an initial outbreak, 5% to slow disease spread, 5% to preserve constitutional government, 5% for federal health care providers and the remaining 80% for the states.

In the discussion, Ms. Birkhofer suggested there be more discussion about children as a vulnerable population and workers in the fractionation industry (collection, manufacture) be included among the priority groups. The plight of children has been discussed, especially as major instruments of disease spread, but quantitative data on what is needed have been lacking. For platelet and plasma donors and their collection centers, Dr. Schwartz suggested communication directly with Secretary Leavitt and Assistant Secretary Agwonobi and becoming directly involved at the state level. Dr. Roseff asked if there was monitoring to discourage private stockpiling counter to public resources. It was noted that one antiviral manufacturer stopped shipping to foil such stockpiling. At the instigation of Chairman Bracey, Dr. Schwartz reiterated that the blood community was considered part of the critical infrastructure. Dr. Katz suggested that the Committee make a strong statement about the importance of blood centers as infrastructure, noting that in his state it had been an uphill battle with the state health department. Dr. Sayers asked about the US planning vs that in Canada. Canada and the rest of the developed world are approaching their planning in much the same way. Dr. Wong suggested using Amantadine for regular flu, saving Tamiflu for possible pandemics and Relenza for Z-strains. In reply, Amantadine and Rimantadine are in the same drug class and are best given for prophylaxis because of the rapid development of resistant virus. How best to use the drugs is still under discussion. CDR Libby asked about live vs killed vaccines. FluMist is a licensed live attenuated vaccine; all of the others currently available or planned are killed. Dr. Angelbeck suggested that the shortages of vaccine and antivirals left only containment as a viable strategy. In reply, there are too many ifs involved in most containment strategies. Probably all strategies will need to be used together in so far as possible. Following a question from Dr. Holmberg regarding handwashing it was agreed that this was effective on preventing vival spread. Dr. Bloche asked if there was political will to move vaccine and Tamiflu to where they are needed. WHO is also accumulating a stock pile for world-wide purposes and the US will commit 5% of our stockpile if needed. This should be sufficient if the strategy works.

Dr. Goodman agreed that 5 years for a new vaccine was reasonable, but FDA is trying to speed this along as much as possible. There are a lot of unknowns about the efficacy of both vaccines and antivirals in a pandemic. With antivirals, the most that can be expected is to shorten and ameliorate the disease, rather than knock it out like penicillin hit pneumonia.

Mr. Marc Wolfson (Public Affairs Officer, Office of Public Health Emergency Preparedness) discussed Risk Communication in the setting of an influenza pandemic, a

situation that is immune to political boundaries. He stated that the US Government is working with WHO on international communication strategies. One of the major differences between today and the Spanish flu outbreak of 1918 is the 24 hour news cycle, which includes continuous TV News stations and the internet. For example, when a young boy died of H5N1 flu in Turkey, the information was available in Washington within hours of its confirmation. It is important to inform the public without inflaming them, providing truthful information to support informed decisions needed to protect themselves and their loved ones. WHO has set up a series of phases dealing with pandemics: Phases one and two have no new strains and there isn't much of a threat; phase three is a pandemic alert with human infections with a new sub-type but no human-to-human transmission (most believe that is in our current state). Phase four is human-to-human transmission in a localized area. Phase five those localized areas begin to grow (experts believe that a viable strategy is to try to keep the disease localized, without spread). There is an overwhelming need for subject matter experts to be interviewed in the media. If officials (e.g., HHS, CDC, NIH) don't provide them, the media will find their own and their quality may be uncertain. There may be trade-offs in sharing stockpiled vaccines and managing expectations of the public and special audiences (e.g., health care workers at various levels). An important point is that we have not found the virus in the US yet, but we are working closely with WHO and other international partners to try to contain the potential pandemic.

One tool that is under development and has been used by others is a series of "message maps." These are prepared, preferably in anticipation of problems, by a team of communications folks and subject matter experts. A recent example is Mayor Giuliani's approach after the Trade Center attack. After the first attack in 1993 and shortly after Major Giuliani took office, a team was instructed to plan for the contingency that they will be attacked again. One exchange followed an early media query about how many fatalities were expected from the attack. The mayor responded that it was more then any of is could bear but New Yorkers are a strong lot. We will learn from this experience and move on. We will get through this (this message was sketched out five years before the attack occurred). From experience, one looks for three short phrases that convey three key messages in up to 30 words. "Sound bites" usually last about 9 seconds and the main message of a story is usually in the first 30 words of print. For flu, the first key message is for people to stay informed about prevention and control actions. Public Health officials will be sharing information (e.g., CDC hotline, special Web site, public pronouncements) on how people can cooperate with containment measures; how they can care for themselves and their loved ones and share their concerns with their health provider, their health department and other trusted sources. HHS has been working on message maps for hundreds of questions and building a large database for use as needed, including we by partners at the state and local levels. Within the Federal Government, HHS has the lead for health communication; Agriculture on issues of animal health; and Homeland Security for incident management and communications. For pandemic influenza, HHS (including CDC) will be "in charge," although it will affect all aspects of our society and will require important coordination at all levels of government. Mr. Wolfson expects a National Joint Information Center with many people form various departments working on public awareness and education activities. States and locals will

be tied in via the internet and conference calls. Non-governmental organizations, such as the American Red Cross, will also be involved.

In response to a question for Dr. Holmberg regarding the Family Preparedness brochure, Mr. Wolfson stated that it would be available electronically on the Web site. Dr. Bracey asked about validating sources of information. In reply, HHS wants to be first, be right and be credible. Anyone can search the Internet but some of the information there is incorrect. It will be a challenge to get Secretary Leavitt or Dr Gerberding in front of cameras before they're comfortable with the available information. It will be necessary to say such things as, "We don't know yet, but here's what we are doing to find out." Dr. Epstein asked about communication about risk and uncertainty. In response, there will be heavy reliance on experts as to what measures should be taken, e.g., close schools, stay home from work. Dr. Pierce asked about trigger points for various messages. One major trigger point is when human-to-human transmission is easily occurring. Dr. Bloche noted that being first and being right can be at odds. In reply, the public information specialists rarely wind-up on Meet the Press or Wolf Blitzer; instead it is Secretary Leavitt, Dr Gerberding or Rudy Giuliani. It is a challenge to prepare them for making these appearances and communicating. Although they are authority figures, they are also human beings and have limitations. Some, like Dr. Gerberding, respond in situations with limited knowledge that the Government wishes it had more information at this time, but it's trying to find out this and this etc. It's best to have the scientific person meeting the press; Mayor Giuliani usually had his experts with him and let the most qualified person give the answers. CDC has developed a short course called "Risk Communications by Leaders for Leaders." It is on their Web site. Dr. Sayers suggested asking some media leaders to take a major educational role, eschewing the sensational. Mr. Wolfson agreed and noted that Secretary Ridge did just this when he was forming the new Department of Homeland Security.

The next speaker was Dr. Indira Hewlett, Chief of the Laboratory of Molecular Virology, a Division of Emerging and Transfusion Transmitted Diseases in the Office of Blood Research and Review: "Pandemic Influenza - Identifying Gaps of Knowledge in Transfusion and Transplantation Medicine." Flu viruses often undergo mutations and reassortments to generate new strains; however, how the H5N1 will react is unknown, as is the likelihood that new strains will be transmitted between humans with increasing efficiency. Since 1997 through December 2005, there have been 142 human cases of bird flu (74 deaths), but all thus far have apparently come from birds to man, not from human-to-human. Should a pandemic develop, effects might be felt in decreased donor availability, increased demand for blood and organs and illnesses in staff. With most influenza A infections, the incubation period is 1-3 days after inoculation. Virus can be isolated from nasopharyngeal swabs during the first 3 days of illness, up to 8-9 days after onset. For H5N1, viremia has not been systematically investigated. Bird flu generates a greater increase in inflammatory cytokines than most other flus; hemophagocytic syndrome was found in 2 of 6 fatal cases studied. H5N1 incubation time may be as long as 17 days, longer than other flus. Viral RNA levels were higher in pharyngeal than in nasal respiratory tracts in H5N1 infection than with other influenzas A. The GI tract and the brain is more likely to be involved. There has been some discussion about addressing

some of these knowledge gaps by studies in cynomologus macaques but funding is not available for such studies.

In the discussion period, Dr. Roseff asked if we were working with investigators in SE Asia where the disease is more common. The FDA and the CDC are working with SE Asian investigators. It would be useful if firms able to develop sensitive assays for flu virus (e.g., PCR) could be brought into the loop in test development. Dr. Pierce asked about the major impediment for moving these studies forward and the answer, as usual, was funding. An interagency collaboration will be needed between NIH and the CDC and is being discussed. Dr. Ramsey pointed out that issues of product recalls and withdrawals should also be considered. Mr. Walsh asked about the availability of biodefense funds to support the needed studies. Biodefense seems to focus more on basic pathogenesis, including vaccines and antivirals, than on clinical issues.

Chairman Bracey then called for Open Public Comments. Ms. Gretchen Wyatt (PPTA) commended the Committee and CMS for changes to improve reimbursement for the administration of IGIV. She urged three actions for a more permanent fix: 1) establish a comprehensive permanent add-on payment to capture true acquisition and other costs associated with IGIV therapy; 2) establish unique codes for each brand of IGIV to establish better average sales prices and 3) clarify that IGIV is a biologic response modifier for the purposes of paying for its administration. Mr. Dave Cavenaugh (Committee of Ten Thouseand) commented that the rapid development and deployment of nucleic acid-based tests for West Nile Virus was extremely successful and streamlined which contrasts to the apparently lack of action about the potential effects of H5N1 flu on recipients of blood and blood products. Although not as successful, actions to protect blood from the CJD threat have been greater than for flu. With no more comments, the Committee took a 15 minute break.

Committee discussion was begun by Dr. Holmberg's summary of major points presented in the meeting throughout the day. These included: 1) the importance of the state governments and encouragement for the directions that they take in planning; 2) the need to include other groups (e.g., plasmapheresis, progenitor cells, hematopoietic stem cells, cord blood stem cells, bone marrow donors); 3) the position of the blood community in the critical infrastructure; 4) the availability of a brochure on family preparedness, which could be advocated for donors and staff members; 5) the importance of a coordinated message and the identification of media leaders, educating them (CDC's short course on risk communication); and 6) the identification of knowledge gaps and the research that should be done to fill these in. Dr. Bracey added the need for developing trigger points for communications, educating people on the best practices for avoiding germs (on-going, not just in the context of a pandemic) and clinical/surveillance analyses (e.g., viremia in asymptomatic individuals). Blood centers must be key players in crafting the messages to be disseminated. There may be a need to relax certain donor criteria not involving infectious risks but perhaps donation frequency. Dr. Epstein emphasized studying asymptomatic contacts for viremia (e.g., Dr. Busch' studies during annual outbreaks of flu). It will be important to "go where the money is," get blood samples as part of the investigations of cases now occurring in SE Asia. This would be more

important than studies in such models as cynomoloogus monkeys. The Committee is advisory to the Department, but presumably the Department has some ability to influence some of the research directions internationally. He also noted that the focus of the HHS plan puts a lot of effort in the hands of the states, which predicts that many disparities may occur as it will be an uphill battle to convince every state public health authority to treat the blood system as part of the critical infrastructure. The Committee could make a clear statement to this effect and spell out what that means. Ms. Birkofer added that short, concise PSAs could be developed that would reach a wide audience, using as a model the Office of National Drug Control Policy. Further, once vaccines become available, there should be adequate reimbursement to ensure that they be widely used, drawing on the experience with IGIV. Dr. Angelbeck noted that the sudden loss of plateletpheresis donors could be serious, especially as there is no way to substitute whole blood derived platelets quickly. Blood centers need to be cognizant of this in their planning Dr. Kuehnert emphasized the importance of identifying in advance the organizations and the point people that must be involved with various topics. It also seconded Dr. Epstein's suggestion that existing protocols studying H5N1 in SE Asia include looking for viremia, noting that there was a similar problem with SARS because the people doing the studies were not thinking about viremia as an endpoint. I is also important to ask cases about blood donation and transfusion, as part of the epidemiological study. Dr. Pierce questioned if animal models were really pertinent, since there was no human-adapted H5N1 virus. He noted that the animal models used for the study of variant CJD, a very difficult agent to work with, had less relevance to the human situation than would be desirable. Nevertheless, he felt that animal models should not be ignored. Dr. Epstein reiterated the need for viremia studies, even though most flu spread via the respiratory tract. In the absence of information, we may overreact by deferring donors needlessly and by withdrawing components that are safe. Dr. Bloche suggested that animal models might not have the credibility of good epidemiological work. Should a pandemic occur, professional and scientific leadership should take the lead on communication, not the political leadership, to try to avoid a credibility gap. Dr. Roseff asked if UK had a plan for dealing with blood shortages during a flu pandemic; Dr. Bianco emphasized separating the local from the national; much of the research must be funded and done nationally. He also expressed concern that local policies may not only differ from state to state, but also within a state (e.g., NY City may develop different policies from those in other parts of the state). That would put "chaos on top of chaos." Dr. Sayers said that if a test were to be developed for H5N1, it should be put in place in a manner to discourage "test seeking" behavior from "donors." He also predicted that there might arise pressure for directed donations (patient recruited and selected). A sudden demand for directed donations could incapacitate a blood program. Dr. Holmberg suggested that preparations for a pandemic could force the transfusion community to develop standards of practice for such things as the transfusion trigger (the government can't and should not try to dictate this). Dr. Sandler asked where the blood community fit into the bigger picture, e.g., is there a super-committee looking out for police, etc. Dr. Holmberg replied that there were a number of working groups within DHHS that were involved with various issues. Dr. Pierce asked about the availability of resources. Dr. Epstein noted that there was a supplemental appropriation in 2006 to address pandemic influenza, but that it hadn't been earmarked or broken down as yet.

Dr. Epstein summarized "three key messages and three short phrases:" 1) the blood system must be recognized as critical infrastructure; 2) Research to resolve critical questions must be funded and 3) there should be a national plan to address potentially massive blood shortages. Ms. Birkofer reported scanning a document provided to the Committee from the Homeland Security Council, the National Strategy for Pandemic Influenza and finding it very comprehensive and detailed. The Committee should plan their recommendations into this broader context.

The Committee adjourned at 4:25 PM, to reconvene the next day at 9:00 AM.

The second day of the Committee meeting opened at about 9:00 AM. Dr. Holmberg distributed a Committee roster, asked that members make corrections to their listing and called the roll. He then read remarks from Dr. Beato, Acting ASH, who was unable to make her planned appearance

Dr. Beato said that the Committee is valuable and one upon which the Department relies. On reviewing Committee actions, she noted that they began in the 1990s examining issues related to hepatitis C, tackled mad cow disease and the human variant, vCJD and made recommendations regarding leukoreduction. The Committee suggested the establishment of a blood monitoring system and a national blood reserve. She is vitally interested in the last two and plans to pursue them. Most recently, the Committee has addressed IVIG availability and reimbursement. The Department has worked with IVIG manufacturers, distributors, physicians and their patients to alleviate the situation. In addition to short term changes planned by CMS, the Department Inspector General is assessing reimbursement issues and beneficiaries' access to care. Dr. Beato hopes that these steps and other ongoing corrections in the marketplace will ensure that supply volatility stabilizes in the next year. They will continue to monitor the problems. The recommendations for a coordinated strategic plan to ensure blood safety and availability are excellent and support the Secretary's 500 day plan for the Department. Working groups are being formed that include not only blood interests, but also organ, tissue and cellular products. The Committee is an excellent forum for the exchange of information between the private sector, government and the American people. She looks forward to future high quality recommendations from the Committee.

In discussion, Dr. Epstein asked that the record reflect the Committee's appreciation of the steady support that Dr. Beato has given to the blood issues during her tenure as the acting ASH.

With regard to the IGIV situation, Dr. Bracey saw two potential issues: availability and access. Is there a system to monitor progress in these areas? Dr. Holmberg replied that monitoring is carried out is in various ways: His office tracks complaints that come in. CMS has a hotline; 1-800-Medicare; there have been recent improvements in how it handle calls. There is an active dialogue between the user community and CMS, bringing in regional contractors as needed. It is also looking at the 340B set-asides, administered by HRSA, but with very limited flow of IGIV. It's been very beneficial for the Office of

the Inspector General to assess the current situation. Many patients have no problem getting the product, but have a definite problem in obtaining IGIV at a price they want to pay. The Immune Deficiency Foundation has been particularly helpful in communications between the various parties involved. Dr. Epstein commented that many of the Committee's deliberations have centered around the economics of the blood system. The problems have been very difficult to address because there haven't been many comprehensive studies of the health economics related to blood products. He asked if it might be suitable for the Committee to addres the general problem of how market forces and market constraints affect our blood system, both at the level of safety and supply. He noted that Paul Haas left the Committee with his outgoing essay on this subject, which is very thought-provoking and warrants further consideration. His suggestion was supported by Drs. Bracey, Sandler and Sayers. Dr. Holmberg responded that he would take this into consideration.

Dr. Holmberg then read from an informal E-Mail as a preliminary greeting sent by Dr. John Agwunobi, who has just been confirmed by the Senate and sworn in to be the Assistant Secretary for Health (ASH). He is honored by the Presidential appointment and is committed to empower the OPHS to achieve excellence in providing for better health and safety for all. He thanked Dr. Beato for her service as Acting ASH and expects to continue to use her help as Principal Deputy Assistant Secretary. Ms. Diane Bembo will be his administrative assistant. Soon, he will meet with the office directors as well as visiting each of the OPHS offices to meet the staff.

Dr. Bracey then introduced the first speaker of the day, Dr. Louis Katz, who is the Executive Vice President for Medical Affairs at the Mississippi Valley Regional Blood Center and has been chair of the AABB Transfusion Transmitted Diseases Committee, a member of the FDA BPAC and currently chair of the AABB Task Force on Pandemic Preparations and Risk Communication. He speaks on behalf of that task force, which consists of representatives from the American Red Cross, America's Blood Centers, AABB and Blood Centers of America, liaisons from FDA, CDC and this Committee. It is staffed by AABB (Caryl Auslander, Kay Gregory and Theresa Wiegmann). The Task Force began by developing and outline of the issues by brainstorming and then identify a range of options to respond to those issues. Plasma, tissue and organs were not specifically addressed, but the planning processes for these areas will be qualitatively similar. The most appropriate role for the Task Force is to brief as a parent the Interorganizational Task Force on Domestic Disasters and Acts of Terrorism, who should be the focus of responses to any disaster. The paradigm of the rest of the system pulling together to respond to problems is probably not correct for pandemic planning, since the entire country is likely to be affected so that regional resource sharing is unlikely to be appropriate. The basic outline of responses after an event occurs is for the affected blood centers to communicate with their customers (primarily hospitals), assess needs, contact the AABB that will convene the Task Force to develop an assistance and communications plan in partnership with DHHS in the broadest sense. The Task Force has not addressed the issue of transfusion transmission of flu, but focused their efforts on effects on the donor base and on operations, both at blood collection facilities and at transfusion services, particularly with regard to life-saving products (mainly platelets).

For most products, there is likely a decrease in both supply and demand, with little effect on safety. Elective surgery needs will decline. Most hospitals that have surge plans have triggers that will cancel elective surgery and elective hospital admissions. Nevertheless, the need for platelets to support hematologic malignancy treatment, hematopoietic progenitor stem cell transplants, complex cardiovascular surgery, etc., will not decrease. Some plans assume that flu victims will need few blood products, but this is likely incorrect. Patients with acute respiratory failure, apart from trauma, malignancy and other conditions classically associated with blood use, actually require transfusion support quite frequently. Hence, assumptions that blood demand will decline must be carefully reconsidered. There are no models for the effect of pandemic flu on the blood supply or blood usage with modern medical care. Donors are likely to react with the rest of the population, as far as staying home, avoiding public places, etc. There is no substantial resistance to the concept of immunizing donors in blood centers. Using antivirals for donors will require that it become a priority at DHHS. Staff immunization, use of antivirals and application of special work rules (e.g., stay home) must also be considered. There is not enough information to predict the possibility of FDA promulgated deferrals, whether related to exposure or potential transmissibility. Getting people to use simple prevention procedures, such as washing hands or using masks appropriately is an extraordinarily difficult ongoing task. Many hospitals have had little experience with blood shortages and triage procedures that might be necessary; others have developed approaches for the best use of scarce blood supplies. Developing consensus guidelines for this process will take considerable effort. Communication management will be a problem. A nice message was developed about the blood supply during Katrina, but off hand comments of a national leader on national television bypassed all that messaging and many blood centers had long lines of donors showing up where no need existed. The Task Force is aware of similar planning going on in the EU, Australia and Canada; communication internationally can prevent some redundant discussion and planning. He concluded with a quotation from E.D. Kilbourne in the January 2006 issue of the journal, *Emerging Infectious Diseases*: "Yes, we can prepare, but with the realization that no amount of hand washing, hand wringing, public education, or gauze masks will do the trick. The keystone of influenza prevention is vaccination. It is unreasonable to believe that we can count on prophylaxis with antiviral agents to protect a large vulnerable population for more than a few days at a time, and that is not long enough."

Dr. Sayers opened the discussion with a question about strategies to encourage immunization of regular donors, but the Committee did not accept this plan. Medical staff had no problems with that, but the legal and insurance people did. Dr. Katz favors giving vaccine to everyone, but considers platelet donors to be the highest priority. Dr. Sandler questioned that flu spread was likely to be so rapid that resource sharing wouldn't work. He thought that the Committee should focus on the blood supply and that resource sharing was the keystone. He also expressed doubt that there was a hemorrhagic component of flu that would increase transfusion requirements. In response, the 1918 pandemic spread quite rapidly; transfusion was not available then, however, so we don't know. Modeling is critical. Ms. Lipton said that the Disaster Task Force has estimated that the country could cope with two major cities being down at once. She also noted that

transplants take an enormous amount of products, probably the biggest user in our country; these are not really elective. She agreed that moving blood around may not be the answer. Dr. Bianco pointed out that there was no air transportation in 1918 and the way people travel now, spread will be faster and resource sharing difficult. Dr. Bracey commented that a major problem after 9/11 was the unavailability of transport. One of the lessons of Katrina is that state support may not be sufficient and the Federal assistance would be helpful. Dr. Katz replied that Federal support is not a top priority because pandemic flu is substantially different from 9/11 types of disasters. Dr. Bracey queried about the role of quarantine, even the shut down of transport between regions.. Dr. Kuehnert thought that was a possibility, but there would be a gradation of societal disruptions from recommendations to something more mandatory. Those should be included in the models. Dr. Holmberg noted that hemorrhagic manifestations of flu may not be common, but asked about the use of blood by people on respirators. Dr. Katz could find no credible information about the use of red cell and platelet transfusion in Acute Respiratory Distress Syndrome, with estimates from 10 to 50 percent chance of some use. From his own experience, these figures are not far off, although it's not certain how many were "appropriate." Dr. Pierce asked what information there was to support that flu is unlikely in blood products, particularly sero-prevalence studies during flu season, etc. Dr. Katz noted that the data were weak, but he doesn't believe it to be a major issue. Dr. Sayers noted that resource sharing would be more viable if he could predict that his center would be protected in some way from the pandemic, an unlikely occurrence. If it began elsewhere in the world, there might be a short period to overcollect an bolster the local supply. Although that is an obvious solution, it would help only red cells and not platelets, which are almost certainly going to be a major problem. Dr. Bracey asked if someone from the blood industry or this Committee would be inserted within the HHS pandemic team. Dr. Ramsey suggested that messages be prepared in advance to seek additional donors, should it became necessary. Dr. Katz doubted that there would be a shortage of willing people. Dr. Bracey asked about monitoring stockpiles and inventories. Dr. Katz noted that the Red Cross has a single FDA license and a good handle on their inventory from day to day. ABC is less detailed and uses a voluntary "stoplight" code with daily reports from most of their centers; green is more than three days supply, red is one day or less and yellow is in between. It has tracked what they hear about blood shortages very nicely. HHS has a system in preparation. Dr. Holmberg reported that they would have a beta version ready soon; some sites are already reporting. It looks like it will be very effective and it includes hospitals as well as blood centers and will have the capability of looking at geographic locations for local or national trends. Dr. Kuehnert asked if donor vaccination rates were different from those in the general population and if there is a precedent for blood centers offering vaccination. Dr. Katz has made several spot checks in his platelet room and cound about 80 percent of the donors had received or planned to get the flu vaccine. Dr. Fitzpatrick reported that the ABC Board approved a draft proposal to consolidate their monitoring in a state of emergency between Blood Centers of America and ABC so that all centers would report to a single entity, with logistical control from a single inventory coordinator. Dr. Alter opined that the Task Force had underestimated the transportation problem. In the event of a 30 percent attack rate, this will interrupt the high dependency on transportation; everybody is shipping everything everywhere – blood for testing,

manufacturers of test kits, etc. Dr. Katz reiterated that much depended on the blood industry being designated as part of the critical infrastructure. Dr. Alter also pointed out that if blood banks controlled vaccination, that might provide a powerful incentive to getting blood donors but that policy would be questionable. Ms. Lipton noted that the American Hospital Association is on the Pandemic Task Force and hence aware of these issues. Ms. Bridget Elis from PPTA noted the importance of the plasma industry in all this and expressed doubt that the demand for protein products would decrease, but perhaps even increase. Dr. Bloche asked if principles and priorities were being developed for rationing of the blood supply, nationally or locally. In reply, the potential for needing triage at the hospital level is very real. AABB will ask transfusion services to have triage criteria in place. Dr. Bloche asked if it was correct that they would rely on local providers to make their own, perhaps quite different decisions. That gets to the core of how we do business in American health care delivery. The question about who could say who may receive and transfusion was asked. The discussion indicated that there might be a local authority that may or may not influence blood use. Probably so at the local hospital level. Probably so at the blood center level. The level of variation is likely to be huge. Dr. Bloche suggested that a measure of due process in principles is essential. Dr. Roseff commented that she was heartened to see how little blood is really needed when shortages are present. Dr. Ramsey asked if stockpiling of FFP had been considered and if using "outdated" platelets as better than "no platelets." FDA is looking at plateletpheresis guidance to see if changes might be appropriate during a pandemic (e.g., increase the allowable donation frequency).

The next presentation is Philip Norris, MD, Associate Investigator and Director of Immunology at Blood Systems Research Institute. He also is a visiting scientist with the Gladstone Institute of Virology and Immunology. He discussed Influenza Viremia in Blood Donors and Potential Transmission through Transfusions and Transplantation. He started by reviewing the characteristics of the flu virus, noting that its hemagglutinin protein is responsible for tropism (e.g., avian, swine or humans). Mutations in that gene can alter the host preference of the virus. Recombinations between viruses can occur in any of the species. In one study done in 1966, 15 volunteers were infected with flu by nasal challenge. Only one sample was positive, a nasal sample, on Rhesus monkey kidneys (relatively insensitive). Six of the subjects seroconverted and for four of these they were able to culture virus from blood one day after the challenge (chicken egg amniotic sac culture). By day two, only half were positive and by day three, a quarter of them were. There were no further cultures, so It is unknown how long viremia persists. The person that was viremic for three days was asymptomatic, despite seroconversion. Dr. Norris then described a study proposed to the REDS-II working group for expedited review and implementation to determine the prevalence of viremia. Part of the study is to measure the elative sensitivity of RNA and antigen assays in different blood components (the available antigen or RNA detection assays are approved only for use with nasal secretions, oral-pharyngeal swabs or other respiratory secretion). The manufacturers are working with them to adapt TMA or PCR assays for use with various blood components. Once the assays are validated, they will collaborate with Dr. David Kelvin (Toronto) to study blood components in a ferret model of influenza. Gen-Probe has provided data that TMA with suitable primers is both sensitive and specific for influenza A. The sensitivity

is down to 250 copies per ml. Virus is widely disseminated in infected ferrets and uniformly fatal. It is almost certainly in the blood, but that has not yet been studied. REDS has a sample repository, with some donor-recipient pairs, and some samples identified only by ZIP code. They planned to examine donor specimens over peak periods of flu activity in 2004 to search for asymptomatic viremia. They planned to study 1,000 subjects and were powered to detect around 2% viremia. Studying transmission will be more difficult, but they hope to collaborate with the Deputy Director of the National Blood Bank in Vietnam to establish and test repositories.

Dr. Sandler asked why it would be so difficult to get samples from recipients of blood from donors who were infected. It was stated that the flu virus does not stick around like HIV or hepatitis, so that one is left with checking for antibodies and trying to determine if it is seroconversion from blood or from community infection. Dr. Alter is doing a TRIP study on transfusion transmitted diseases. He is collecting multiple recipient samples, but his numbers are so small that it would be pure chance if he found a transmission. Dr. Norris commented that if flu is transmitted by blood transfusion, it has gone unrecognized. Flu is so common that connecting it to a transfusion would be difficult. Dr. Kuehnert emphasized the need to do recipient surveillance when studying for an adverse outcome. Dr. Epstein noted that following up on recipients from a donor who called in a post-donation illness could be another approach. He then asked Norris to compare a primate model with the ferret model for human disease. The primate model would likely be better. Dr. Katz asked about generalizing from one type of flu to others. Dr. Norris stated that there are differences, but there also are similarities.

After a break, Alfred DeMaria, MD (Massachusetts Department of Health) spoke on behalf of the Council of State and Territorial Epidemiolgists. There is surprisingly little collaboration between blood collecting agencies and local and state public health authorities in pandemic planning, something that needs to be addressed. Massachusetts (and most states) has been working on pandemic planning for the last 10 years, although work has intensified with all of the attention to avian flu in Asia. An important part of the plan is ensuring continuity of operations. The approach is that a pandemic is inevitable. Interestingly, slides prepared in 1980 on this subject seem just as current today. Influenza A is very different from SARS or smallpox in that its genetic drift changes it from year to year and it is transmitted in the community in two to four days, with its two day incubation period. Many people get sick very quickly and are very infectious, making quarantine not very effective as a control measure. Each pandemic has been a bit different from the others in age groups affected, overall mortality, etc. Although the current focus is on H5N1, a case can be made that another strain, e.g., H7N7, will be the pandemic strain. Avian influenza is a disease of birds that occasionally affects humans and may be easier to deal with than the public reaction to a case in the US with its 24/7 news coverage. One of the big issues will be the change in health care practices to focus on moving people in and out of the system. There is no surge capacity in the “just-in-time” system. Reducing elective surgery and medical admissions are unlikely to be helpful because of the rapidity of pandemic development. Another key element is the maintenance of this societal functions in the face of absenteeism, e.g., police, fire, patient care. Non-vaccine, non-antiviral approaches to

control are unlikely to work and vaccine production is likely to be inadequate for at least five years. Prioritizing vaccine is likely to be anticlimactic because the brunt of the disease will be felt before sufficient supplies will be available. Prevention with antiviral medication will have to be continuous; missing a couple of days in the face of exposure will allow infection. Attenuated disease will still likely be infectious. Frequent hand washing and covering one's mouth when coughing will reduce the transmission of respiratory illnesses and should be emphasized.

Chairman Bracey opened the discussion, commenting that Massachusetts may be in the vanguard of planning which seems to be more inconsistent in his home state of Texas. The group discussed how the public health infrastructure is important but very fragmented. In Massachusetts, there are 351 independent health jurisdictions, so that planning meetings tend to be very large. It is also important to include private industry. Blood banks will have to be proactive and insert themselves into the planning process. Dr. Sandler suggested that one message might be for those who are over the flu and ready to return to work to be blood donors. Dr. DeMaria commented that in the absence of sufficient vaccine, people will be immunized against flu by becoming infected. This may provide better protection than does vaccine.

Stephen Anderson, PhD (CBER, FDA) discussed blood supply modeling when stressed, using as an example the effect of a 21-day nationwide smallpox vaccination campaign. Although the total period of stress from this source would be relatively short about 45 days, there may be some lessons applicable to a flu pandemic. The effect of pandemic flu on the blood supply will be sustained and likely to be 6 to 18 months. Models should take into consideration not only effects on blood centers but also their support, the transportation system, infrastructure for reagents and the demand for blood and blood components. Smallpox vaccination uses a live virus (vaccinia) and produces a viremia and the potential for transmission by blood transfusion. The smallpox model assumes a minimum of 21 days for recovery from the vaccination during which individuals would be deferred from donating blood. The model is for a dynamic system of supply and demand with daily turnover. It includes susceptible individuals, vaccinated subjects and those who have recovered from the vaccination (SVR model). Collections, less what is being utilized leaves the blood available in the system. That amount is about 14 million units of blood annually (38,500 units per day) utilization about 30,500 per day. Other factors considered include 5% of the population donates each year, although about 60% of the general population are eligible to donate. A donor is allow to give blood once every 56 days and blood can be stored for only 42 days. These last two factors are nearly irrelevant for the smallpox vaccination scenario but will be important for the flu's 6-18 months. Once set up, the model can help forecast what effect various changes will have, e.g., a preparatory period of overcollection, an emergency policy to reduce transfusions by 50%, a change in the duration of the stress (extend the vaccination campaign), or combinations of factors. Planning should include what interventions that could be used if the supply is being overly compromised. The model is now being applied to the flu pandemic in which susceptibility is assumed to be universal. The model can be applied to regions, as well as to the country (world) as a whole. The presence or absence of viremia in pandemic flu would influence the parameters put in the model.

Dr. Epstein asked about the feasibility of applying the model to platelets. In discussion it was determined that it can be done. The turnover rate for platelets is 5 days, rather than the 42 days for red cells. There would be extreme shortages of platelets if specific platelet donors were not identified and provided protective measures (e.g., vaccination, anti-virals). Dr. Bracey reminded the Committee that plasma protein products should be included. Dr. Kuehnert asked about the relative effect on transfusion need of viral vs bacterial pneumonia. Dr. Anderson has begun to look at CMS' data on blood utilization. The use of mechanical ventilation is 15th in the procedures for blood utilization. As the model is applied to flu, authorization will try to plug in these data. Dr. Pierce asked about quantitating the fear of leaving home and its effect on attendance at donor centers. Surveys could be done but they may not mirror what actually happens. Dr. Ramsey asked if there were data from Asia to address the effect of a pandemic on society, especially the fear of going out. CBER has been reluctant to use that type of data because of cultural differences. Mr Walsh asked about SARS data from Toronto. There is no expert on SARS present. Ms. Jane Starkey (ABC) noted that there was probably no normal donation rate. In a pandemic, high schools will be closed, wiping out all student donors at once. The flu season is the high school donation season. Dr. Holmberg asked if Drs. Katz or Bianco had data on the number of donations from high school students during the school year. Dr. Katz said no, but guessed that from September through April it might average 10% to 15%. Dr. Zou (Red Cross) reported that a survey of New York City health care workers suggested that up to 50% of that group might be unable or unwilling to report to work in the presence of SARS.

Dr. Sayers noted that with the number of transfusions during flu season, it is surprising that no one has identified post transfusion flu if there were viremia. He asked Dr. Norris if there anything unusual about flu viruses that made them non-viable after blood storage. Dr. Norris replied that he didn't know, but stated that intuitively it should survive storage. Failure to identify post-transfusion flu may be because it has not been sought.

After a lunch break, Brian Custer, PhD (Epidemiology and Health Policy Research Section, Blood Systems Research Institute) discussed his Community Blood Supply Model and its Potential Use in an Influenza Pandemic. His model was developed to look at trade-offs between blood safety and sufficiency, incorporating cost factors as well. It is also being used to look at threats to the blood supply. Blood Centers of the Pacific year 2000 donor data were stratified by age, sex, first-time or repeat and plotted throughout the year. Mean age varies throughout the year, especially among those of school age. The year may be viewed as a whole or segment it (e.g., 2 month intervals). The model has 432 event probabilities. It is a supply model and does not address demand or utilization, nor does it include components or outdates. Applying it to pandemic flu, the model assumed that the community would be affected for six to eight weeks; loss would be 40% in 16-20 year olds and 20% in other age groups. Focusing on the January February time period, a normal year would yield about 17,000 16-24 year old donors; the model predicts a loss of 3,500-4,000 donations (22%). Dr. Custer is updating the model using Blood Systems data from14 blood centers. It is hoped that this will provide greater

generalizability. He is also testing the effect of collecting various numbers of double red cell units.

In the discussion, Dr, Sayers asked if the model would enable a prediction of how much the collection of double red cell units would have to be enhanced to make up for the losses and Dr. Custer indicated that it could. Dr. Bloche asked for more discussion of estimating the reduction in donors or donations. Specifically Dr. Bloche wanted to know about estimates of hunkering down responses or subjective responses to other factors Dr. Custer indicated that he had not thought through this question but thought that this omission resulted in the model's underestimating supply reduction. Dr. Epstein asked how much the age and time of year stratification improve the estimate. In reply, policies that broadly affect all individuals may not require that stratification; should policies affect smaller groups, the stratification is likely helpful. Dr. Bracey asked if the model could help determine who, among donors should be targeted for vaccinations. Discussion indicated that the model should be helpful.

Shimian Zou, PhD (Transmissible Disease Department, Holland Laboratories, ARC), spoke on Assessing the Potential Impact of Pandemic Influenza and other Emerging Threats on the Availability and Safety of the US Blood Supply. He presented a proposal to study this topic. He has begun crude calculations based on a model published by CDC (Martin Meltzer and others) in 1999. His current plans include the supply side; utilization data are sparse. He hopes to get information from the Healthcare Cost Utilization Program (HICUP, Agency for Health Care Research and Quality). He plans to base the model on data available in the Red Cross system and hopes to reflect the entire process from potential donor to recipient.

Dr. Epstein began the discussion by suggesting that there should be cooperation between the model builders to determine similarities and differences and see if a consensus model could be developed. He asked if we need a system-specific model or do the various systems (Red Cross, Blood Systems) all behave similarly. Dr. Zou agreed that the three modelers could learn from each other and should work together. Dr. Custer noted that the Blood Systems Research Institute (led by Mike Busch) is all about collaboration. Dr. Kuehnert suggested that Dr. Zou's plan to use blood utilization data from HICUP may be flawed because it represents such a limited sample of hospital use. might consider using hospital discharge data, which is free but harder to work with. In reply, HICUP represents about 20 hospitals. Dr. Sandler cautioned about the stratification into elective and non-elective use. Doctors and hospitals vary in their definitions and cooperation. There is a reluctance to close down operating rooms because of financial pressure. Patients and family (and doctors) don't understand the concept of reducing elective surgery when blood is short. There isn't much elasticity in the system. Dr. Ramsey agreed and gave additional examples. Dr. Bloche expressed concern for prioritizing based on the intensity of a doctor's advocacy on behalf of a patient or his family. Public awareness of seeming unfairness could be explosive.

After hearing no response to a request for further comments from the public, Dr Bracey moved the Committee into a general discussion. Dr. Sayers commented that the models

could be used to help manage occasional excess of blood supply. For example, when it was suddenly recognized that individuals with metastatic breast cancer were not good candidates for marrow transplantation, his center's demand for platelets dropped precipitously and they underestimated the magnitude of cut back of plateletpheresis that was needed. Ms Lipton thought that the concept of national guidelines for transfusion was near unworkable. Many organizations, including the AABB, have tried, but none have come up with generally accepted guidelines. Dr. Bloche commented about clinical practice variations and the absence of evidence for most of the clinical decisions that doctors make. Dr. Sandler noted that the main job is to get blood and make it available; when that fails, one moves to telling people how to cope with using what is there. Dr. Bloche noted the difficulty in developing guidelines for good medical practice. He suggested that the approach should be different: guidelines for bad (or desperate) medical practice at a time of regional or national crisis. Guidelines should limit the amount of discretion described by Dr. Sandler. It will be important to avoid treating hospitals differently, depending on their clientele (race, affluence, etc). Dr. Bianco emphasized the importance that blood be considered as a major issue in the planning process.

After a brief recess, the Committee considered draft recommendations. Dr. Bracey noted three key points: 1) the blood supply is part of the critical infrastructure; 2) the safety of the blood supply must be assessed, especially with regard to viremia; and 3) the blood industry or blood system must be adequately represented in the planning process.

The draft recommendation was based on the five points for the Committee to consider provided at the beginning of the meeting by the Executive Secretary. They are: 1) what strategies should be considered to prepare the blood system for the possible flu pandemic (e.g., immunization of staff and repeat donors, supply monitoring and management); 2) how can DHHS help resolve scientific uncertainties underlying the potential need for donor deferrals; 3) what new approaches to communication between public health, blood, organ and tissue communities would be helpful in enhancing preparedness; 4) what would be the most efficient interfaces with global and domestic surveillance data, communication between collection, transfusion, local and state public health, and between blood, organ and tissue communities; and 5) what surveillance methods are needed for blood and plasma recipients to detect transfusion associated transmission of pandemic influenza to frequently transfused subjects. After considerable discussion, the following recommendation was made:

Whereas,

a) Evidence suggests the possibility in the near term for a global pandemic of influenza A based on recent, highly virulent, human infections with an avian H5Nl virus,

b) The HHS plan for pandemic influenza recognizes the priority to preserve critical infrastructure in our society,

c) Ensuring the safety and availability of blood and blood products, including plasma products, is a critical public health need,

d) Although the scope and impact of the potential pandemic are uncertain, the availability of blood products is likely to be highly compromised during an influenza pandemic,

e) Data have suggested the possibility that influenza viruses may be present in the blood, organs and tissues of asymptomatic donors

f) Influenza surveillance data, which come from diverse sources, are limited in scope, timeliness and integration

g) Risk education and communication to the public, delivered by scientific and medical experts, are essential components of preparedness for pandemic influenza

h) Preparedness of the blood and plasma systems for pandemic influenza would contribute to the general disaster preparedness

The Committee recommends that the Secretary take immediate steps to:

1. Establish national recognition of the blood and plasma systems (collection, processing, distribution and use) as key elements of the critical infrastructure under the HHS plan, specifically including facility staff, and committed blood and plasma donors

2. Assure full funding of research to resolve critical scientific questions regarding the potential impact of pandemic influenza on blood, organ and tissue safety and availability:

> a. Foster collaborations with investigators in countries affected by the current H5Nl influenza outbreak to promote studies of possible viremia in asymptomatic persons, including recent case contacts
>
> b. Support studies ofH5Nl and other potential pandemic strains in suitable animal models, including non-human primates, to investigate viremia and organ l ocalization of infectivity in preclinical, clinical, and convalescent stages of disease; transfusion transmissibility of virus if present in blood; and impact of infection and/or drug treatment on the accuracy of donor screening tests
>
> c. Support studies of influenza viremia during annual outbreaks of non-pandemic strains, including studies on blood and plasma donors, and product recipients
>
> d. Support development and validation of quantitative models for blood availability and utilization in an influenza pandemic and the potential value of candidate interventions to prevent shortages

3. Provide targeted federal support to enhance global and domestic surveillance for seasonal and pandemic influenza,

4. Recognize the central role of the AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism in the development and implementation of a national strategy to address potentially massive blood and blood product shortages during a pandemic of influenza by

a. assuring blood and plasma systems' input into key federal policy making and communication

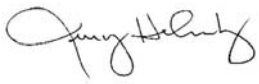
b. promoting communication and cooperation amongst state and local public health authorities and appropriate blood collection organizations, hospitals, medical professional organizations and patient advocacy organizations

5. Develop national principles under which state and local public health authorities and health care providers can prioritize allocation of and minimize disparities in blood and blood products' availability and use during critical shortages.

The Committee passed the resolution unanimously.

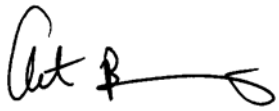
The Committee adjourned at 5:01 PM.

Submitted by:



Jerry A. Holmberg, Ph.D
Executive Secretary, Advisory Committee on Blood Safety and Availability

Certified by:



Arthur W. Bracey, M.D.
Chairman, Advisory Committee on Blood Safety and Availability

Summary prepared by: Paul R. McCurdy, M.D.