Organ and Tissue Safety Workshop 2007: 
*Advances and Challenges*
June 5-6, 2007
Reston, Virginia

Record of the Proceedings
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**List of Participants**

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ATTACHMENT 2

Acronyms Used In This Report

AATB — American Association of Tissue Banks
AERS — Adverse Event Reporting System
AFB — Acid-Fast Bacillus
BLA — Biologic License Application
BOOT — Blood, Organ and Other Tissues
BPD — Biological Product Deviation
BTS — Biomedical Tissue Services
CBER — Center for Biologics Evaluation and Research
CDC — Centers for Disease Control and Prevention
cGMPs — Current Good Manufacturing Practices
CNS — Central Nervous System
CTO — Cells, Tissues and Organs
DDTs — Donor-Transmitted Tumors
DHQP — Division of Healthcare Quality Promotion
DHS — Department of Homeland Security
DRS — Donor Referral Services
DRTs — Donor-Related Tumors
DTAG — Disease Transmission Advisory Group
EBAA — Eye Bank Association of America
EIAs — Enzyme Immunoassays
EIDs — Emerging Infectious Diseases
ELISA — Enzyme-Linked Immunosorbent Assay
EUSTITE — European Union Standards and Training in the Inspection of Tissues Establishment
FDA — Food and Drug Administration
HBV — Hepatitis B Virus
HCOs — Healthcare Organizations
HCT/Ps — Human Cells, Tissues, and Cellular and Tissue-Based Products
HCV — Hepatitis C Virus
HHS — U.S. Department of Health and Human Services
HIPAA — Health Insurance Portability and Accountability Act
HLA — Human Leukocyte Antigen
HRSA — Health Resources and Services Administration
ID-NAAT — Individual Donation NAAT
IgG — Immunoglobulin G
IgM — Immunoglobulin M
IOM — Institute of Medicine
LABS — Laboratories at Bonfils
LCMV — Lymphocytic Choriomeningitis Virus
MAB — Medical Advisory Board
MedSun — Medical Product Safety Network
MPS — Massively Parallel Sequencing
MRSA — Methicillin-Resistant *Staphylococcus aureus*
NAAT — Nucleic Acid Amplification Testing
OARS — Online Adverse Reaction Registry System
OPOs — Organ Procurement Organizations
OTPN — Organ Procurement and Transplantation Network
OTS — Organ and Tissue Safety
PCR — Polymerase Chain Reaction
PSC — Patient Safety Committee
PTLD — Post-Transplant Lymphoproliferative Disease
RCC — Renal Cell Carcinoma
RIPA — Radioimmune Precipitation Assay
SHOT — Serious Hazards of Transfusion
SOPs — Standard Operating Procedures
SRTR — Scientific Registry of Transplant Recipients
TACO — Transfusion-Associated Circulatory Overload
TMA — Transcription-Mediated Amplification
TRALI — Transfusion-Related Acute Lung Injury
TTDs — Transplant-Transmitted Diseases
TTSN — Transplantation Transmission Sentinel Network
UNOS — United Network for Organ Sharing
VRE — Vancomycin-Resistant Enterococcus
WHO — World Health Organization
WNV — West Nile Virus
ORGAN AND TISSUE SAFETY WORKSHOP 2007: 
ADVANCES AND CHALLENGES
June 5-6, 2007
Reston, Virginia

DRAFT Report of the Workshop

The “Organ and Tissue Safety Workshop 2007: Advances and Challenges” was convened with experts and other major stakeholders involved in the procurement, distribution, investigation and regulation of human organs and tissues in the United States. The workshop was held on June 5-6, 2007 at the Hyatt Regency Hotel in Reston, Virginia.

The overarching purpose of the workshop was for the participants to describe current activities, lessons learned and experiences in the organ and tissue transplant safety field and also to provide input on the future direction of TTSN. The workshop also served as a follow-up to the federally-sponsored meeting in June 2005 on “Preventing Organ and Tissue Allograft-Transmitted Infection: Priorities for Public Health Intervention.”

OPENING SESSION

Dr. Jay Fishman, of Massachusetts General Hospital and the Harvard Medical School, welcomed the participants to the workshop. He acknowledged the following groups for providing organizational assistance and financial resources to convene the workshop and support the TTSN project: the American Academy of Orthopedic Surgeons, American Society of Transplantation, American Society of Transplant Surgeons, Chiron Foundation/Novartis, Centers for Disease Control and Prevention (CDC), and United Network for Organ Sharing (UNOS).

BACKGROUND AND INTRODUCTION

Advances and Challenges of the Transplantation Field

Dr. Fishman presented background information to assist the participants in providing input and expert guidance. In April 2007, a previously unknown virus was reported in the media to have caused the deaths of three organ transplant patients in Australia. All three patients received organs from the same donor. An analysis of the organs found evidence of a virus related to lymphocytic choriomeningitis virus (LCMV).
LCMV is a rodent virus that occasionally infects individuals and also has been linked with disease in organ transplant patients. LCMV was discovered after the deaths of three women 44, 63, and 64 years of age who received the liver and kidneys of an organ donor 57 years of age who died of a brain hemorrhage in December 2006 shortly after returning to Australia from an extended stay in Europe.

A report to the media by the acting Chief Health Officer in Victoria, Australia initially caused confusion because the public was informed that the virus did not pose a risk to the community as a whole and was not believed to be an infectious disease. However, the following conclusions by Australian health officials were accurate. The transplant program was credited with saving many hundreds of lives each year. Although the case was characterized as a "one-off" event, the introduction of tests for the new virus would be discussed. One must keep in mind that the more tests that are performed, the more increase the delay in transplanting the organ. For a terminally ill patient who is waiting for an organ, transplantation should not be delayed to undertake tests that might not be properly validated or perform tests to identify an extremely rare event.

Organ or tissue transplantation also has played a role in the following events: (1) three LCMV outbreaks resulting in nine deaths; (2) two rabies virus outbreaks resulting in five deaths; (3) a West Nile virus (WNV) outbreak resulting in four infections, one death, three encephalitis cases and two cases with permanent neurological damage; (4) three transmissions of Chagas disease over ~4 years; and (5) two deaths from herpes simplex virus. Transplant recipients act as sentinels for new outbreaks, emerging infections and bioterrorism. Most notably, the Eastern Equine encephalitis, Japanese encephalitis, Dengue, Chikungunya and avian influenza viruses have the potential to be transmitted by tissues or organs.

Dr. Fishman asked the participants to consider a number of key challenges while providing input and expert guidance. New pathogens can be detected using molecular and immunologic techniques, but the sensitivity of these technologies may not be adequate for routine screening at this time. Infection is amplified in immunocompromised hosts. The risk of infection in organ transplant recipients is greater than in the general population. Infections might be overlooked in non-organ transplant allograft recipients, such as recipients of tissue grafts, eye grafts and corneas. Coordination of information among CDC, public health authorities, clinical centers and patients is rapidly needed.

Increased resources for outbreak investigations are a critical need as well. For example, reference laboratories should be available for access. The use of pathogen discovery technology with transplant recipients should be increased. Specimens from all donors should be archived for future investigations. Cost-effectiveness analyses and formal technology assessments should be performed to facilitate evidence-based decision-making regarding the implementation of new screening tests. Reporting and communication of specific infections and new clinical syndromes should be mandated to enhance allograft safety.

Dr. Fishman reviewed the background for this Workshop. Parallel efforts have been initiated to enhance the safety of organs and tissues procured in the United States. These activities
include the development of the TTSN Internet-based tracking system for organs and tissues; creation of the UNOS Disease Transmission Advisory Group to facilitate and monitor reports of donor-derived transmission; and revisions to policies governing the reporting of disease transmission with organs.

Dr. Fishman concluded his presentation by summarizing five key objectives that were established for the TTSN Workshop. One, the epidemiology of transmission of infection and malignancy with allografts would be reviewed. Two, technological advances that could be applied to enhance the safety of allograft transplantation would be examined. Three, approaches to optimize tracking of tissues and data collection would be considered to facilitate timely investigation of transmission events and appropriate interventions of benefit to graft recipients. Four, TTSN’s current status and future direction would be evaluated. Five, a forum to discuss interventions on safety issues would be provided for all stakeholders. A summary of the workshop would be prepared for publication.

**Review of the 2005 CDC/FDA/HRSA Transplantation Safety Workshop**

Dr. Matthew Kuehnert, of the CDC Office of Blood, Organ and Other Tissue Safety, described several events that led to federal agencies cosponsoring the transplant safety Workshop in 2005. In the mid-1990s, the Institute of Medicine (IOM) issued a report on *Microbial Threats to Health in the United States*. The IOM report prompted CDC to develop a program to prevent emerging infectious diseases (EIDs), address blood safety and form a Blood Safety Workgroup.

IOM’s follow-up report on *Microbial Threats to Health: Emergence, Detection and Response* addressed issues related to blood, organ and other tissue safety due to advances in healthcare technologies. The IOM report also recommended improvement of domestic and global infectious disease surveillance. CDC’s initial step in responding to IOM’s recommendation was to review the agency’s existing activities.

In looking at gaps in safety, it is important to consider regulatory structure. The Health Resources and Services Administration (HRSA) is a federal agency with regulatory oversight for organs, but not tissues. The Food and Drug Administration (FDA) is a federal agency with regulatory authority for blood and tissues, but not organs with the exception of diagnostic test approval. CDC is a federal agency with no regulatory authority for blood, organ and other tissue safety. Non-governmental organizations accredit institutions and produce standards. The Joint Commission is a non-profit organization that develops guidelines for hospitals.

CDC determined that blood, tissues and organs are similar to vaccines, drugs and devices in that they also provide opportunities and challenges for public health, regulation and response and emphasize the need for patient safety initiatives. These findings prompted CDC to expand its Blood Safety Workgroup in May 2004 to the newly reorganized Blood, Organ and Other Tissues (BOOT) Workgroup. The workgroup was charged with coordinating CDC’s activities, such as providing updates on investigations of transmission; identifying current and planned...
projects, determining gaps and priorities for intervention; harmonizing activities with other federal efforts; and collaborating with external partners to develop a BOOT safety agenda.

CDC acknowledged the need to convene a workshop with external partners to develop partnerships with organ and tissue procurement organizations, tissue banks and processors, front-line clinicians, oversight agencies and public health authorities. CDC, HRSA and FDA co-sponsored the “Preventing Organ and Tissue Allograft-Transmitted Infection: Priorities for Public Health Intervention” workshop in June 2005 in Atlanta, Georgia with ~75 participants representing >30 external partners. Federal and external partners served on a planning committee to identify essential partnerships; determine gaps in detection, data collection and communication; and identify priority focus areas for intervention.

The planning committee identified four critical points for intervention in preventing organ and tissue transplant-transmitted diseases (TTDs) and priority focus areas during each event. Donor information should be communicated during the donor evaluation and recovery period. Systems tracing and notification should be performing during the processing period. Hospital tracking should be performed during the distribution and use period. Adverse events in recipients should be recognized during TTDs.

To assist the participants in providing input to the federal agencies, presentations were made on BOOT safety and availability, CDC’s Futures Initiative and patient safety activities, the epidemiology of TTDs, current criteria for donor screening and disease reporting, tissue donor requirements, testing requirements for human cell and tissue donors, tissue standards in the healthcare setting, tissue bank system approaches, and recent transmission case studies of rabies and LCMV.

The participants were divided into breakout groups to discuss the following challenges and potential interventions for the four priority focus areas. (1) What are the needs and challenges for a communication network of organ and tissue procurement organizations, including appropriate diagnostic algorithms? (2) What are the challenges to allowing efficient tracing of allografts, including detection control points? (3) What are the largest issues in assigning and coordinating responsibility for tissues in healthcare settings? (4) What data elements are essential for investigations of adverse events? What methods can be used to encourage routine data collection for this purpose?

The participants agreed that readily identifiable gaps in transplant safety exist and made recommendations on interventions with an emphasis on short-term solutions. The participants also identified and agreed on the five most important interventions: (1) unique donor ID linking organs and tissues; (2) a notification algorithm for trace-back and trace-forward tracking; (3) clear mechanisms for adverse event reporting by healthcare facilities; (4) a better communication network within and between the organ and tissue community; and (5) stronger dissemination of information on these events to a broad array of clinicians, health professionals and patients.
Following the 2005 workshop, CDC issued the “Sentinel Network for Detecting Emerging Infections Among Allograft Donors and Recipients” program announcement. The successful applicant would be asked to develop a new network to detect and prevent disease transmission through improved communication among the tissue community. UNOS was awarded the cooperative agreement and developed TTSN in collaboration with several partner organizations. The TTSN development, illustrated by a task pyramid, is designed with five major components: donor identification, tracking, adverse recognition, data feedback and education.

Dr. Kuehnert announced that TTSN and other patient safety projects have a strong emphasis in CDC’s Futures Initiative. CDC drafted an objective under its “Healthy Healthcare” goal to improve surveillance of adverse events associated with the use of biologic products, vaccines, drugs or devices.

CDC proposed several measures and actions to achieve this objective. A pilot study of transfusion adverse event reporting will be completed in 2008 and expanded to 100% of the blood supply by 2011. The biovigilance component of HHS’s blood safety strategic plan will be developed with other federal agencies, including collaboration between HHS and AABB on the creation of the Biovigilance Network. The completion of TTSN by 2008 should result in tracking and adverse event reporting for 100% of all organs and tissues transplanted in the United States by 2011. At that time, the goals is that adverse events should be reduced by 50% through timely identification of infections in tissues from a common donor and prevention of additional implantation of infected tissue.

The TTSN Workshop participants made three key suggestions that should be considered to refine TTSN.

- Post-transplant screening should be performed due to the importance of this activity in patient follow-up. A system should be designed to capture these events through healthcare visits or death records.
- The TTSN task pyramid should be redesigned with two “educational” components in both the high and low ends of the pyramid.
- A root cause analysis approach should be incorporated into TTSN to determine the source of problems in processing of tissues and acceptance of tissues by donors. Reports of outcomes from these issues should then be distributed in a confidential manner.

### EPIDEMIOLOGY OF ORGAN AND TISSUE ALLOGRAFT-ASSOCIATED TRANSMISSION

#### Defining the Magnitude of TTDs

Dr. Arjun Srinivasan, of the CDC Division of Healthcare Quality Promotion (DHQP), recognized the importance of investigating reports of possible TTDs when knowledge is obtained about these infections. However, a systematic approach has not been developed to date to locate...
possible cases and track investigations. A systematic surveillance system would need to be developed to truly define the magnitude of TTDs and monitor these infections.

The system could be designed to meet several needs. The effectiveness of current and new measures to prevent transmission would be tracked. Discussions and research on the types of diseases that should be targeted for new screening measures would assist in understanding and characterizing TTDs. Enhanced knowledge of the types of transplants that pose certain levels of risk might guide prevention efforts.

Many safety approaches are currently being taken to minimize the risk of transmission from donors to recipients, such as a review of donor histories and records, laboratory testing of donors, and processing of tissues to eliminate pathogens. However, the frequency of transmission from donors to recipients is unknown at this time because surveillance systems have not been developed to define actual incidence. The published literature most likely represents an underestimate with reports of only ~40 cases of TTDs from 1998-2006.

In addition to underestimates, infections were not recognized in donors for nearly all cases because some patients were asymptomatic and other patients had non-specific symptoms, such as rabies or group A streptococcus. Moreover, recent cases involved tissues that most likely were contaminated during processing. Reports of both organ and tissue-associated cases in the past few years raises questions of whether infections have become more common or if capacity has improved to locate and diagnose cases.

On the one hand, severity of illness among all patients is rising as advances are made in health care. Immune suppressive medications are becoming more common and potent. Current organ and tissue transplant recipients might be more susceptible to infections than in the past. On the other hand, several factors have improved capacity to detect unexpected cases, such as heightened awareness among clinicians and improved diagnostic tests.

TTDs are rare, but outcomes from these infections have been severe. Organ transmitted diseases are associated with a mortality rate of ~75% while tissue transmission has resulted in one death, several hospitalizations, and surgery and prolonged courses of antimicrobials to treat infections in all patients. The current consensus is that published reports of TTDs are an underestimate of the true occurrence. The magnitude of underestimation is unknown at this time because several challenges have not been addressed to date.

The numerator of the number of existing cases divided by the number of transplants has not been clearly defined. The number of unreported cases is unknown because infections were not diagnosed or considered to be transplant-related. In some diagnosed cases, clinicians had no knowledge of proper authorities that should receive reports.

In terms of diagnostic challenges, laboratories implement a fairly straightforward process to diagnose bacterial infections. However, rare viral infections are more difficult to diagnose and highly specialized laboratories have made most of the organ transmission diagnoses. Clinicians have recognized transplant-transmitted infections in reported cases due to coincidence,
because the pathogen was unusual in many tissue transmissions, or when multiple organ transplant patients had similar clinical syndromes.

TTDs caused by common pathogens might be overlooked because organ transplant recipients are hospitalized at different facilities and a linkage is never made. Inadequate communication has also played a role. For tissues, a decentralized communication network has increased the difficulty of reporting, but most clinicians have knowledge of the need to contact the tissue bank, FDA, CDC or a health department. For organs, however, the communication network is fairly well established. Most transplant centers have formed ongoing relationships with and will report any issues to organ procurement organizations (OPOs).

In addition to defining the numerator, several barriers also have been identified in characterizing the denominator. Although the number of organs that are transplanted each year is well known, tissues are more difficult to determine. For example, “distributed” and “implanted” tissues are different. The number of implanted tissues should be identified to quantify the magnitude. Due to the poor return of implant cards, distributed tissues might provide the only reliable estimates.

Other challenges in defining the magnitude include different risks of infection for specific transplants. The risk of infection in organ transplants is not the same, particularly with immune suppression of the host. Some tissue allografts are not processed. Tissues that are disinfected should not necessarily be considered sterilized. To define the incidence and magnitude, an approach of calculating the combined transmission rate for all organs and tissues should be considered. Although organ and tissue transmission should be analyzed individually, this strategy would increase the difficulty in defining the magnitude because each type of organ and tissue transplant must be classified as to the risk of transmission.

Malignancy presents an additional challenge in defining the magnitude of transmission due to the minimal number of cases presented and published on transmission of malignancy from donors to recipients. Moreover, efforts to determine the incidence of cancer transmissions pose more barriers because of difficulty in identifying cases. Recognition of malignancy transmission might occur much longer after the transplant if the patient is not under the care of the transplant team and donor tissues are not available for testing. Because malignancy is expected to occur in recipients, transplant-related infections are difficult to determine. “Typing” studies are not as widely used as those in microbiologic pathogens to identify similarities in malignancies.

Several questions should be addressed to advance efforts to define the incidence and magnitude of transmission because these infections are still rare events even if current estimates are underestimated by as much as ten-fold. First, would the development and implementation of a comprehensive surveillance system be worth the investment? Second, what entities would be responsible for paying for a surveillance system? Third, would some current activities and efforts need to be terminated to develop and implement the surveillance system?

In support of a new transplantation transmission surveillance system, the usefulness of this effort would not be known until implementation. However, previous investigations have led to
improvements in patient safety, and one could ensure better progress with a comprehensive and systematic approach. Several actions would need to be taken to implement a new transplantation surveillance system.

1. Clinicians would need to be educated on specific events to report and about proper authorities that should receive their reports. Because most transmission cases have no initial diagnosis, simple and useful clinical syndromes and diagnoses that should be reported as a possible transplant-transmitted infection should be developed.

During the 2005 Workshop, the participants identified several “reporting triggers” for surgeons and clinicians who transplant tissues, such as a patient hospitalized for infection within 30 days of surgery, removal of a graft for possible infection, or recovery of an unusual organism. Development of “reporting triggers” for organs will be much more difficult due to the vast complexity of clinical syndromes.

2. In addition to educating clinicians, a mechanism also would need to be developed to investigate reports of potential TTI investigations. This protocol would need to be consistent with definitions of “TTIs” and “non-TTIs.” Recovery of the same pathogen from the donor and recipient, molecular testing, and identification of the same unusual pathogen in both the donor and recipient are relatively easy to perform. However, efforts to address common pathogens if isolates are not available are much more difficult.

3. Tissue denominators will be needed to improve tracking of tissue implantation and strengthen compliance with the return of implant cards.

4. A “culture of safety” should be strongly promoted to minimize fears of reprisal or punishment when providers report possible TTIs. Changes should be made to shift the focus from “assigning blame” to “improving the system.”

The TTSN Workshop participants made two key suggestions that should be considered in the development of a systematic surveillance system to define the magnitude of OTIs and TTIs.

- A gap analysis should be performed to identify existing activities to track OTIs and TTIs. For example, a team could be deployed to OPOs and tissue banks to evaluate current surveillance systems of adverse event reports and investigations. This systematic approach would eliminate the need to develop a new OTI and TTI surveillance system from the beginning.
- A research program should be developed and launched in the future to assist in defining the scope and magnitude of transmitted infections. For example, a panel of “X” number of tests could be performed on each organ and tissue recipient to identify possible infection and determine whether infection was transmitted.
Dr. David Blossom, of CDC/DHQI, explained that of ~1,020,000 organ and tissue transplants each year, the published literature contains reports of only ~40 cases of both organ and tissue transmitted infections from 1998-2006. These data suggest that transmissions are rare events. From 1985-2006, organ transplants have been associated with transmission of HIV, hepatitis C virus (HCV), Chagas disease, WNV, LCMV and rabies in the United States.

In a case involving LCMV, the liver, lungs and two kidneys from a donor who died following a stroke were transplanted into four recipients in April 2005 in Rhode Island. The recipients developed various symptoms within three weeks after transplantation. The three recipients who died all had autopsies that showed hepatocellular necrosis. Because routine testing did not reveal a cause, tissue and blood samples from the donor and recipients were sent to CDC. The diagnosis of LCMV was made by various laboratory tests, including immunohistochemical staining, reverse transcriptase-polymerase chain reaction (PCR), viral culture, and enzyme-linked immunosorbent assay (ELISA). Sequencing of the virus genome confirmed the LCMV diagnosis.

Source investigations were performed at the coordinating OPO and the hospitals involved in organ recovery and transplantation. An environmental assessment and interviews with family members of the donor revealed that a pet hamster had been recently acquired. The investigation showed that the hamster primarily was cared for by another family member who had specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to LCMV. The donor's tissue showed no evidence of LCMV. The pet hamster was found to be positive for LCMV by a variety of laboratory tests. The LCMV strain in the hamster was the same as the strain in the recipients.

In a case involving WNV, the liver, one lung and two kidneys from a donor who died following a traumatic head injury were transplanted into four recipients in August 2005. The liver and lung recipients developed symptoms on post-operative days 13 and 17, respectively, but one kidney recipient was asymptomatic and the other kidney recipient was not infected.

Serum and plasma collected from the donor were positive for WNV IgM and IgG enzyme immunoassays, but were negative for WNV RNA by PCR. Immunohistochemical analyses of other tissues from the donor were negative for WNV antigens. The source investigation revealed that all blood products to the donor and organ recipients were negative for WNV RNA. Investigators subsequently learned that the donor had lived near a park with WNV-positive mosquito pools and spent time outdoors prior to organ donation.

Two hospitals in Los Angeles County, California reported cases in February 2006 involving acute Chagas disease in two heart transplant recipients. The first recipient infection occurred in a patient 64 years of age who received a heart transplant for idiopathic cardiomyopathy and was readmitted to the hospital two months post-transplantation for anorexia, fever and diarrhea. Blood smear, blood cultures and endomyocardial biopsy were positive for Trypanosoma cruzi trypomastigotes.
The source investigation suggested recent infection because the heart recipient had no identifiable risk factors for *T. cruzi* infection, was seronegative for *T. cruzi* antibodies, and positive for *T. cruzi* DNA by PCR. The trace-back showed that all blood products transfused to the heart donor and recipients were negative, but blood from the organ donor tested seropositive for *T. cruzi* antibodies. The organ donor was born in the United States, but had traveled to a *T. cruzi*-endemic area of Mexico.

The second recipient infection of Chagas disease in 2006 occurred in a patient 73 years of age with ischemic cardiomyopathy who received a heart transplant. The patient was admitted to the hospital with fever, fatigue and abdominal rash; had no identifiable risk factors for *T. cruzi* infection; and was seronegative, but PCR-positive for *T. cruzi*. Blood smear and blood cultures were positive for *T. cruzi*, but serial endomyocardial biopsies did not reveal trypanosomes. The organ donor was born in El Salvador and tested positive for *T. cruzi* antibodies on serum collected at the time of death.

Similar to organ transplants, tissue transplants also have been associated with transmission of various infections in the United States since 2005, including *Candida albicans*, *Clostridium sordellii*, HCV, Group A Streptococcus, Clostridial endophthalmitis and *Chryseobacterium meningosepticum*. In a case involving *C. meningosepticum*, a patient underwent elective anterior cruciate ligament repair with a patellar tendon allograft in August 2006 and developed knee swelling and fevers on post-operative day 4. On post-operative day 10, a fluid analysis showed a significant white blood cell count of 275,225 cells with 92% neutrophils.

The initial gram stain showed no bacteria, but gram-negative rods were seen 24 hours later. Antimicrobial susceptibility testing showed multidrug-resistant *C. meningosepticum*. The patient retained the allograft and was successfully treated with two operative debridements of the wound. Clinicians reported the case to state public health officials and the tissue bank due to the unusual nature of the organism. The tissue bank initiated an investigation, reviewed microbiology records where the tissue had been processed, and noticed an increase in tissue rejection rates for sterility failures. The tissue bank took a cautious approach and recalled all tissues processed at this facility in October 2006.

A tissue bank was notified of a case involving *C. meningosepticum* in December 2006 in which a patient had undergone posterior cruciate ligament repair with allograft implantation. The patient had a more indolent course with many weeks of pain and swelling. The evaluation was complicated due to gouty arthritis and other underlying medical conditions. The report was triggered by the patient informing the surgeon of the October 2006 *C. meningosepticum* case, which had been publicized by the media.

In addition to infections, tissue transplants also have been associated with recovery agency “scandals.” In September 2005, a tissue processor notified FDA of concerns regarding the accuracy of donor eligibility for human cadaveric tissues received from Biomedical Tissue Services (BTS) in New Jersey. The investigation of BTS revealed the following information. BTS sent tissues to five tissue processors. Tissues were recovered from funeral homes in
several states from 2002-2005. BTS falsified death certificates and next-of-kin identities. BTS had not properly screened donors. The risk of transmission of infectious agents was considered to be low because all BTS tissues had been processed using standard disinfection methods.

CDC gathered information from processors and distributors to assist in determining the actual risk to recipients. FDA issued a class I recall of BTS tissues in October 2005 and ordered BTS to cease manufacturing and retain all products in January 2006. From 2002-2005, >25,000 BTS tissue products were distributed to all 50 states and international countries. FDA and CDC recommended that recipients of BTS tissues be offered testing for HIV, hepatitis B virus (HBV), HCV and syphilis. By June 2006, at least 3,000 recipients had received testing. CDC’s follow-up information suggested 34 patients had a confirmatory test that was positive for one or more of these pathogens. However, none of the cases was definitively attributed to an implanted tissue.

Barriers to the BTS investigation included limited ability to follow-up, due to difficulty in locating patients, instructions by attorneys of patients not to share follow-up testing information, and an underestimate of potential cases. Moreover, efforts to attribute infections to a transplanted tissue were difficult because the donor is required to be tested for infection. A definitive conclusion could not be reached on whether the donor was the source of the implanted tissue.

Another recovery agency “scandal” involved Donor Referral Services (DRS) in North Carolina. FDA ordered DRS to cease manufacturing and retain all products in August 2006. FDA also issued a public health notification because DRS had not met FDA requirements for donor eligibility. CDC was asked to assist in the DRS investigation following the identification of a donor who was infected with HCV at the time of tissue recovery. CDC helped to identify six recipients of the donor in four states. Although DRS admitted to falsifying results of donor blood tests, the risk of transmission is considered to be low because all tissues recovered by DRS underwent processing steps. No known transmissions have been reported to date.

Dr. Blossom reiterated that OTIs and TTIs appear to be rare events based on recent reports and suspected transmission of infection. However, these cases result in complex investigations that require coordination between several agencies and institutions. The recent cases also emphasize the need for better reporting of unusual circumstances in the future to identify other transplant-transmitted infections that have been overlooked in the past.

The Workshop participants made several suggestions to strengthen current capacity to report, track and monitor suspected OTIs and TTIs.

- Efforts should be made to address existing concerns regarding the sub-optimal quality of laboratory tests that are currently used to confirm the epidemiology of suspected transmissions.
- An approach of universal testing of donors should be considered. For example, testing is not required in the United States for Chagas disease.
- Caution should be taken in specifying a testing system because OPOs use donors for both organs and tissues, with different risks applying to recipients.
depending on tissue type. For example, processing of tissues would not necessarily protect an organ recipient and vice versa.

- A solid national initiative should be developed and launched to improve data exchange. For example, after a tissue processor identifies a problem and takes corrective actions, this information should be shared with other tissue processors that might encounter the same issue. Problems and resolutions that should be widely shared with tissue processors include power outages, water sources and increased rates of contaminated tissues. Moreover, agencies and institutions that investigate transplant-transmitted infections should ensure that the outcomes of these events are widely available in the published literature or some other venue.

- A temporary quarantine rather than a recall should be issued unless suspected transmissions are confirmed.

- Efforts should be made to increase reporting of transplant-transmitted infections and clearly distinguish between the root causes of these events, such as those related to processing, donors or surgical techniques.

- The organ and tissue communities should thoroughly review and apply lessons learned from the eye community. This group has a long and solid history in addressing potential transplant-transmitted infections through an accreditation process and other well-established procedures. For example, Eye Bank Association of America (EBAA) inspectors analyze adverse events for each transplanted tissue and document follow-up information in writing on the patient’s condition. EBAA inspectors also identify other tissue recipients who might be at risk in each case involving an adverse event. EBAA reports these findings to the proper entities.

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**ADVERSE EVENT REPORTING SYSTEMS AND REQUIREMENTS: TISSUES**

**FDA Adverse Event Reporting System**

Dr. Melissa Greenwald, of the FDA Division of Human Tissues, explained that FDA has regulatory authority for human cells, tissues, and cellular and tissue-based products (HCT/Ps). HCT/Ps contain or consist of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient. HCT/Ps include a wide range of products, but the following products are excluded: organs; whole blood and blood components; milk, collagen, cell factors, and other secreted or extracted products; ancillary products used to manufacture HCT/Ps; minimally-manipulated bone marrow; cells, tissues and organs derived from non-human animals; *in vitro* diagnostic products; and blood vessels recovered with organs.

For HCT/Ps, FDA defines an “adverse reaction” as a noxious and unintended response to any HCT/P for which a reasonable possibility exists that the HCT/P caused the response. FDA requires manufacturers to investigate adverse reactions involving communicable diseases related to HCT/Ps that the manufacturer has made available for distribution. Manufacturers are
required to report these adverse events with the following outcomes to FDA: fatal or life-threatening events; events resulting in permanent impairment of a function or permanent damage to a body structure; or events necessitating hospitalization or other medical or surgical intervention. However, manufacturers are not required to investigate any adverse reaction not involving a communicable disease, such as a product defect.

Adverse events that are required to be reported to FDA include bacterial infections in recipients; an allograft failure believed by the surgeon to be secondary to an infection; and viral seroconversion of a recipient with a suspected or known relationship to the allograft. Manufacturers must report required adverse events to FDA within 15 days after receiving information. Manufacturers are given an additional 15 days to submit follow-up information on the initial adverse event report. Adverse events that are not required to be reported to FDA include incorrect package labeling, mechanical failure of an allograft, an allergic reaction or product damage.

Manufacturers report required adverse events on FDA’s MedWatch form by either mail or facsimile. Hospitals, recipients, end-users and other voluntary reporters also can submit information to FDA on the electronic MedWatch form. FDA does not forward consumer reports directly to manufacturers. The FDA web site contains explicit guidance on completing a MedWatch form.

FDA’s Tissue Safety Team reviews and evaluates MedWatch reports to identify marketed HCT/Ps, conduct follow-up on infectious adverse reactions, and obtain additional information from manufacturers and clinicians as needed. Several offices in the FDA Center for Biologics Evaluation and Research (CBER) are involved in addressing all aspects of tissue safety, including data collection, compliance and communication.

Additional data FDA collects on MedWatch reports include the specific name and type of product implanted, symptoms and risk factors of the recipient, time frame of the symptoms, medical and surgical interventions undertaken, and extraordinary aspects of the surgery that might impact the recipient’s risk for infection. FDA also gathers information on special handling and preparation of the allograft prior to implantation, morbidity of the recipient, any devices implanted along with the tissue, culture results, and findings from hospital infection control investigations if applicable. FDA also asks the surgeon or clinician to give a general impression of whether the adverse reaction was related to the allograft. Data FDA collects from manufacturers include findings of the investigation performed by the processor, date of recovery of the donor’s tissue, medical records of the donor, deviations in processing, pre-/post-processing culture results, and any complaints related to the donor.

To strengthen adverse event reporting capacity, FDA is piloting the first stimulated surveillance program for transplant adverse events involving cells and tissues. Of 350 hospitals participating in the Medical Product Safety Network (MedSun), 35 are piloting the tissue and cell program. MedSun provides assistance to manufacturers for FDA reporting and also to hospitals for Joint Commission compliance by forwarding reports to source facilities. The objectives of the MedSun pilot project are to describe the frequency and types of adverse events following
HCT/P transplants; identify potential causes or “near-misses” associated with adverse events; and improve the safety of HCT/Ps. FDA received the first MedSun report on cells and tissues in October 2005, but the contents of these reports are classified. Although 15 MedSun reports involved infections, causality is not typically confirmed.

FDA initiated mandatory reporting beginning in May 2005. From January 2006-February 2007, 207 reports were submitted to FDA, with most of the reports focusing on tissue rather than cellular products. Bone, eye, skin and soft tissue represented the most common tissue reports. Manufacturers submit the largest number of adverse event reports to FDA, but clinicians, recipients and MedSun participants also provide information directly to FDA.

FDA acknowledges several challenges to its adverse reaction surveillance system, including limitations of a passive safety surveillance approach; difficulties in distinguishing between allograft-attributable infections and common post-operative wound infections; submission of reports to FDA for non-infectious adverse events; and difficulty with extremely labor-intensive follow-up activities.

Overall, FDA’s reporting requirements have practical implications. HCT/P establishments need to be made aware of potential adverse reactions to launch an investigation and submit a report to FDA if applicable. Voluntary reports from clinicians are reviewed in the same manner as mandatory reports from HCT/P establishments. Reports to HCT/P establishments do not need to be delayed until an infection is proven because tissue distribution could be placed on hold during an investigation.

Tissue Bank Adverse Event Reporting

Mr. Scott Brubaker, of the American Association of Tissue Banks (AATB), reported that state requirements for adverse event reporting in tissue banking widely vary. New York State has unique regulations that cover activities of both tissue banks and transplant centers. Other state regulations for tissue banking are not entirely clear. Canada’s proposed cell, tissue and organ regulations are scheduled to be finalized and published in either June or July 2007. Several tissue banks follow reporting schemes that combine tissues with other products and medical devices.

AATB has been publishing standards since 1984. AATB’s first or subsequent editions of its standards have included requirements for accredited medical facilities that store and issue tissue and tissue distribution intermediaries to maintain an adverse reaction file, develop recall procedures, and report adverse events to tissue banks. The 8th edition of AATB’s standards required accredited tissue banks to establish recipient follow-up collection protocols.

Key language in AATB’s standards is highlighted as follows. The working definition of “adverse outcomes” is consistent with definitions established by FDA and other groups. The working definition of “error” is a departure that might cause infectious disease transmission. ATBs must
retain a medical director with explicit responsibilities for adverse outcomes and investigations. The medical director must review adverse event policies and procedures on an annual basis. The medical director or designated licensed physician must review all adverse event reports and participate in a determination of the impact and resolution of the adverse outcome.

Accredited banks must develop and maintain adverse event policies and procedures and submit reports that are approved by the medical director. They must maintain a quality assurance program with responsibility for investigating adverse events and preparing summary reports documenting all resolutions of investigations of accidents, errors, complaints and adverse outcomes. They must retain the summary reports for a period of ten years. Banks must report contrary events, such as confirmed adverse events that are related to contamination or disease transmission. They are given flexibility to address some adverse outcome reporting in a complaint system.

AATB’s standards also contain specific language for tissue dispensing facilities and tissue distribution intermediaries to report adverse events. However, AATB acknowledges the need to update this language to provide tissue dispensing facilities and tissue distribution intermediaries with more explicit guidance on the time frame involved in adverse event reporting. AATB also requires each package insert to contain a warning for adverse outcomes to be promptly reported to the tissue supplier. Recalls of transplanted tissues must be handled as a potential adverse outcome investigation.

Banks are required to take several actions to report adverse events. Suspected allograft-transmitted infections (ATIs) are entered into a database. The ATB’s regulatory affairs or quality assurance program and the medical director review the initial report. Searches are performed to track adverse events and identify other complaints involving the same donor. Actions are taken to assure quarantine of any returned grafts and undistributed or unreleased inventory. The reporting individual is contacted to verify receipt of the complaint and confirm that an investigation is underway.

The donor chart is reviewed, including pre-/in-processing data, post-processing culture results, records of reagent equipment and materials, and environmental test results. The specific product involved in the adverse event is identified. The medical director reviews the internal donor record, including the medical history, clinical course, cause of death, autopsy, cultures, laboratory test results, and trauma or physical assessment that might affect contamination. For the recipient, the medical director reviews current clinical course, laboratory test results, cultures, operative reports, graft cultures taken at implantation if applicable, and viral testing history. The medical director communicates with the recipient’s physician or reporting individual.

Appropriate entities or agencies are immediately contacted, including the recovery agency, other contract processing agencies, FDA, CDC, AATB, appropriate state and county health departments, and international organizations if applicable. The quality assurance program takes corrective or preventive actions by reviewing the impact of the adverse event report during
in-processing methods. An adverse event report is submitted to FDA on the MedWatch form within 15 days if a determination is made of a possible ATI.

AATB acknowledges that the adverse event reporting process can be improved. For example, specific time frames for each step in the process should be included. Clinicians and reporting persons should respond to requests for information or assistance by ATBs during an investigation in a timely manner.

AATB and tissue banks, coordinated through a TTSN workgroup, are conducting a number of activities to enhance the adverse event reporting process of tissue banks and strengthen a potential TTSN system.

- Presentations are being made at meetings to inform tissue banks of experiences with “proven” adverse events.
- A guidance document on Identifying, Reporting and Investigating Recipient Adverse Reactions is being developed and will be targeted to end-users.
- The definition for “excluded” adverse events is being refined to provide more explicit guidance on making a determination when an allograft is not a probable cause of infection.
- Definitions for “probable” and “proven” adverse events are being refined and are expected to be completed in the near future.
- Definitions for “indeterminate” and “recognition” of adverse events with tissues only are being developed. “Confirmed” infectious disease test results are included in the “recognition” definition.
- Clinical guidance to qualify a “possible” ATI is being refined.
- Guidance is being developed on bacterial and fungal infections and parasitic and viral infections (but fresh skin is exempted from these guidelines).
- Specific examples are given for signs of inflammation or infection.
- Explicit guidance is provided to clarify that reporting of colds, influenza and other common community-acquired diseases is not required.
- A time frame of six months rather than one year is outlined for starting follow-up.
- An evidence base is provided for investigating past tissue transmissions.
- Additional guidance is provided on positive cultures or gram-stains from the operative site, previous ATI reports in the literature, patient readmission, and cultures of unexpected organisms from the wound drainage or site.
- The TTSN system is being designed with a pull-down menu of signs, symptoms and laboratory findings to guide input by end-users.

Mr. Brubaker announced that AATB administered a survey in 2005 to obtain feedback from ATBs on implant cards. The survey respondents reflected ~95% of all tissues processed in the United States. AATB standards require ATBs to conduct recipient follow-up to data collection protocols. To comply with this standard, institutions record data on implant cards or a similar reporting form and send the information to ATBs by mail or facsimile. ATBs enter data from the implant cards into a database.
Key findings of the survey are summarized as follows. For each allograft distributed, 100% of ATBs provide opportunities for institutions to complete and return implant cards. Of all survey respondents, ~50% of ATBs have a program to follow-up and encourage non-compliant institutions to complete and submit implant cards and ~66% of ATBs have a compliance rate >50%. End-users that had experienced large recalls found value in completing and returning implant cards. Dental offices, oral surgery facilities and day surgery centers were the top three non-compliant institutions by type. This finding emphasized the need to educate providers with innovative strategies because dental offices and oral surgery facilities are not often accredited by The Joint Commission.

Patient identifiers were most frequently withheld from implant cards compared to other types of information. Illegible handwriting and incomplete or inaccurate information on implant cards were the top two concerns expressed by ATBs. The TTSN system is being designed to resolve these issues. Some ATBs expressed concern about the burden placed on tissue banks to close gaps in the adverse event reporting process, particularly since compliance is uncontrollable and no federal requirement has been established to date. Some ATBs noted that information supplied on implant cards has limited practical application and is not adequate for use during a recall or safety alert. Hospitals that use their own forms rather than tissue bank-issued implant cards has complicated the reporting process.

Eye Banking Adverse Event Reporting System

Ms. Patricia Dahl, of EBAA, explained that the uses of ocular tissue include full or partial thickness grafts for penetrating, epithelial, endothelial or lamellar keratoplasty; sclera grafts for hydroxyapatite; and scientific studies to provide data to scientists who use ocular tissue. Corneas are unique from tissues due to several factors. The timeline for eye recovery is typically 12 hours. The cornea is preserved in Optisol GS or Eusol and is transplanted within five to seven days. However, tissue can be stored for emergency use for up to 28 days. The recipient is known before distribution. Unused tissue is returned on the same day. Sclera is typically preserved in ethyl alcohol, but could be frozen or stored at the transplant facility because refrigeration is not a requirement.

EBAA implemented its Medical Advisory Board (MAB) in January 1991 in response to the 1990 requirement for all eye banks to seek three- to 12-month follow-up of all patient outcomes. The eye bank adverse reaction reporting system was redesigned in 2005 to allow for online submission of reports. The MAB Medical Review Subcommittee reviews reporting results on a biannual basis. Eye banks have found that providing institutions with a self-addressed/stamped envelope to complete and return the follow-up form has increased the return rate to >85%. However, residents are the most non-compliant group due to the transient nature of physicians at this point in their careers.

Data collected from 1991-2005 showed that primary graft failures (PGFs), endophthalmitis, keratitis, cornea dystrophy/degeneration, and sclera graft rejection were the typical adverse
reactions. PGF cases have decreased over the past few years and mated (i.e., in both eyes) cases were not nearly as frequent. The spike in endophthalmitis cases in 1997 was due to a series of unexplained events attributed to a single technician at one eye bank. The significant reduction in these cases since 1997 was a result of standardized use in eye banks of a 5% ophthalmic povidone-iodine solution prior to recovery of the eye or cornea. The frequency of mated endophthalmitis cases was much lower. Adverse reactions involving sclera have not been reported for the most part with the exception of a fungal infection in the 1997-1999 time frame.

Eye banks ask surgeons a number of general questions during follow-up to an investigation of adverse reactions, such as pre-/post-operative diagnoses, date of surgery, and date of adverse reaction. Follow-up questions after ocular infection focus on cultures with sensitivities, donor rim, preservation media and the recipient. Follow-up questions after PGFs focus on whether the graft cleared post-operatively, the duration of clarity, and a potential association to the pre-operative diagnosis or surgical manipulation.

Follow-up questions to technicians focus on the donor chart review, interviews with the primary care physician, the recovery site, sink location, instrument placement, condition of the instrument, and deviations from standard operating procedures (SOPs). The roles and responsibilities of the medical director are to review all reports of adverse reactions and make a determination on whether the event was donor-related. The medical director would recommend corrective actions and report findings to the local MAB, EBAA, and state and federal authorities.

Ms. Dahl presented a live demonstration of EBAA’s new Online Adverse Reaction Registry System (OARS). Persons who submit reports on OARS must provide information on the adverse reaction, surgery, microbiology results, tissue mate status, donor, and method of transporting the tissue from the source eye bank. OARS is also designed with a text box for the user to submit additional comments.

**Hospital Adverse Event Reporting System**

Mr. Klaus Nether, of the Joint Commission, described the Joint Commission’s standards for tissue tracking and adverse event reporting. The Joint Commission is the nation’s oldest and largest accrediting body and accredits 95% of all U.S. hospitals. The Joint Commission accredits and evaluates >15,000 healthcare organizations (HCOs) and programs in the United States and also assesses compliance with standards during an onsite accreditation process. The mission of the Joint Commission is to continuously improve the safety and quality of care provided to the public through the provision of health care accreditation and related services that support performance improvements in HCOs.

Prior to July 2005, the Joint Commission only surveyed tissue standards in HCOs with Joint Commission-accredited laboratories. Since that time, tissue standards have become applicable for hospitals and ambulatory settings, including critical access hospitals and office-based
surgery programs. After FDA’s Good Tissue Practices went into effect in May 2005, tissue establishments have been required to track tissues through the consignee or final disposition and investigate and report adverse reactions.

The Joint Commission revised its tissue standards in July 2005 due to several factors. HCOs were exempt from FDA’s Good Tissue Practices. The Joint Commission’s standards at that time did not explicitly address the role of HCOs in the FDA requirement. Concerns were raised in the field about the lack of laboratory oversight of tissue programs. Events occurred in 2005 that raised national concern regarding the safety of transplantation, including traceability and adverse event investigation and reporting. Unfilled gaps existed between HCOs and the tissue industry. The Joint Commission’s revised standards do not apply to solid organs.

The Joint Commission’s revised tissue standards and performance elements address four major areas. One, the HCO must assign responsibility for overseeing the tissue program throughout the organization. The HCO must establish a coordinated effort to provide standardized procedures, systems, practices and processes for acquiring, receiving, storing and issuing tissues. The HCO can implement a centralized or decentralized process in which one or multiple departments have responsibility for the tissue program.

Two, the HCO must develop procedures to standardize systems and processes for tissue handling. For ordering tissue, the HCO must verify that the source facility is registered with FDA and licensed by the state if required. For receiving tissue, the HCO must log in all tissues regardless of whether implantation or transplantation will occur. The integrity of the tissue packaging must be verified as well. For storing tissue, the HCO must record temperatures once per day, continuously monitor refrigerators and freezers, and maintain a backup storage plan with functional alarms.

Three, the HCO must maintain records to ensure bi-directional traceability of the tissue. Implant cards must be returned to the source facility. The HCO must sustain capacity to trace the chain of events related to the transplanted or implanted tissue for both investigational and reporting purposes. The HCO’s records must track and clearly identify materials used to prepare and process tissue; staff involved in accepting, preparing and issuing tissue; dates and times of these events; and the clinical record of the recipient, including the tissue used and its unique identifier. The HCO must maintain these records for at least ten years.

Four, the HCO must develop systems to investigate and report adverse events. Prompt investigation of each event will facilitate response and treatment to recipients impacted by the affected tissue. Effective communication of an adverse event directly related to tissue use is critical to patient safety and will assist in preventing the spread of infection from an infected donor.

The HCO’s bi-directional investigation process must be designed to address the following issues: (1) actions taken when the source facility notifies the HCO that a tissue is suspected of carrying an infectious disease; (2) actions taken to identify and inform the recipient; (3) actions taken when the patient, via the physician, nurse or infection control practitioner, informs the
HCO of the potential for the tissue to cause an infection or other adverse event; (4) actions taken to report this information to the source facility; (5) actions taken to sequester unused tissue with possible infection; and (6) actions taken to identify and notify recipients who received infected tissue.

The current state of tissue transplantation is driven by well-documented cases of infections and other adverse events in recipients that have resulted in national attention. The potential for infections and other adverse outcomes in recipients is a significant quality and safety concern. However, coordination and communication of adverse events are still problematic, particularly in light of high non-compliance rates. Moreover, the numbers of transplantations are increasing.

Mr. Nether described the Joint Commission’s next steps to further advance hospital reporting of adverse events. Efforts on the Standards Improvement Initiative will be continued to address issues related to language, clarity, applicability and logical flow. Some of these standards were posted on the Joint Commission web site for public comment. A diverse expert panel representing both the organ and tissue communities will be convened to review and revise the current tissue standards as needed by the end of 2007 and explore the possibility of adding solid organs. The revised tissue standards will be distributed to the field for input and also posted on the Joint Commission web site for public comment in the spring or summer of 2008.

The TTSN Workshop participants made several suggestions to refine adverse event reporting systems and requirements for tissues.

- Communication of adverse events at federal and organizational levels should be improved, particularly among FDA, CDC and Joint Commission.
- Regulatory authorities and accrediting bodies should provide institutions with clear guidance on conducting follow-up of a potentially infected tissue when the report is made 60-90 days post-transplant and no further information is available.
- Guidance on adverse event reporting should place more emphasis on assisting surgeons and clinicians in notifying the patient about the possibility of an infected allograft without causing undue alarm. The Joint Commission should charge its new expert panel with addressing this issue.
- TTSN should be designed to address unique aspects of adverse event reporting of eye tissue.

In response to the participants’ suggestions, Mr. Brubaker confirmed that TTSN is being designed to fill current gaps and improve the overall adverse event reporting process. For example, the definitions and guidelines will provide explicit advice on actions institutions should take before contacting the tissue source facility or FDA. Moreover, enforcement of tissue standards by the Joint Commission and other accrediting bodies with oversight of dental offices, surgical centers and other facilities also will play a significant role in enhancing adverse event reporting capacity.
Dr. Elizabeth Ortiz-Rios, of HRSA’s Division of Transplantation, described exclusion criteria and tracking and reporting requirements of the Organ Procurement and Transplantation Network (OPTN). After Congress passed the National Organ Transplant Act in 1984. The Task Force on Organ Transplantation was formed to address the lack of uniform standards. OPTN and the Scientific Registry of Transplant Recipients (SRTR) were established. OPTN is a unified transplant network that is privately managed and operated by UNOS, the contractor for HRSA.

CDC defines “public health surveillance” as the ongoing and systematic collection, analysis, interpretation and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and improve health. The following goals of OPTN are consistent with this definition. All potentially affected recipients will be rapidly identified to assess risks and health and initiate interventions. All donor materials that have not yet been transplanted will be removed from inventory.

An investigation of the incident will be facilitated. Measures will be identified to prevent or respond to similar events in the future. Preparations will be made to respond to concerns raised by the public regarding the safety of organ donation and transplantation. Organ donation for transplantation will be increased. Organ sharing will be improved. Equity in organ allocation in the United States will be enhanced.

HHS passed the OPTN Final Rule in 2000 with an overarching objective to make allocation policies more strongly based on objective and measurable medical criteria. The Final Rule assigns responsibility to (1) HRSA for regulatory oversight, (2) OPTN for policy formation and compliance, and (3) SRTR for statistical analyses. The OPTN/UNOS Board of Directors and committees develop and submit OPTN policies to the HHS Secretary for approval.

Dr. Ortiz-Rios described a number of resources that have been developed to support OPTN. UNet is a secure online database for collection, storage, analysis and publication of all OPTN data regarding the patient waiting list, organ matching and transplants. UNet serves as a secure means of communication among OPTN members and a mechanism for dissemination of information to all transplant programs and OPOs. All transplant programs, OPOs and histocompatibility laboratories use UNet. DonorNet was recently developed in collaboration with the transplant community to improve the organ allocation process. DonorNet is an open and flexible system that provides a potential source of donor data and benefits OPOs, transplant centers and waiting patients.

The Board of Directors approved the OPTN/UNOS Policy 4.0 in November 2004 to focus on infectious disease transmissions that are believed to be of donor origin. The policy contains three key components. A list of diseases and medical conditions that must be communicated to the transplant center if known to be present in the donor was created. Requirements were established for prompt reporting of cases of potential transmission of diseases or medical
conditions of donor origin detected by the transplant center or OPO. Requirements were established for reporting potential or confirmed infectious diseases or malignancies in the recipient.

The policy also outlines specific responsibilities for transplant centers, OPOs and OPTN. With the exception of HIV infection, organs may be used at the discretion of the transplant program with informed consent of the recipient. When a transplant center is informed that an organ recipient at the program is confirmed positive for or has died from a transmittable disease of possible donor origin, the program must notify the procuring OPO within one working day.

The OPO must communicate test results and diagnoses to any transplant center or tissue bank that received organs or tissues from the donor. The OPO must manage the investigation and determine whether the donor was diagnosed with potentially transmissible disease. The OPO must notify and submit a final report to OPTN within 45 days.

OPTN must assist the procuring OPO in identifying transplant programs and recipients who received an organ from the donor. The OPTN must monitor the notification process and request that any additional diagnostic test results are forwarded to the OPO and OPTN. OPTN must forward a copy of the final report to HRSA.

The Disease Transmission Advisory Group (DTAG) is a subcommittee of the OPTN/UNOS Operations Committee that was formed to review current disease transmission reporting policies, develop disease reporting forms, review case reports through the secure Share Point site, and recommend revisions to Policy 4.0. HRSA and CDC serve on DTAG as ex-officio members.

Most OPTN data are collected on data collection forms. The four donor forms include the deceased donor registration form, living donor registration form, living donor follow-up form, and donor histocompatibility form. The five pre-/post-transplant forms for the recipient include the transplant candidate registration form, transplant recipient registration form, transplant recipient follow-up form, post-transplant malignancy form, and recipient histocompatibility form.

Specific data elements are collected on infectious diseases on both the deceased donor and living donor registration forms and also from the recipient at transplant and follow-up to determine seroconversion. Policy 4.0 requires certain diseases and medical conditions to be reported. However, the policy is currently being revised to include additional infectious diseases and more explicit descriptions. The expanded and stronger policy is expected to clarify guidance to transplant centers and OPOs and facilitate an increase in reporting.

The OPTN has a number of limitations. Most notably, no data are collected about serious viral, bacterial, fungal and parasitic infections. Donor-related malignancy data are limited compared to recipient immunosuppressive malignancy data. Data collected on the recipient related to malignancy includes the diagnosis date, immunosuppression, tumor type, treatment and outcome.
Dr. Marlon Levy, of Baylor All Saints Medical Center and Chair of the UNOS Operations Committee (UOC), described activities that OPTN/UNOS conducted following the 2005 BOSS Workshop. The UOC formed and charged DTAG as follows: (1) examine all aspects of patient safety in the context of disease transmission (2) evaluate and make recommendations on quality management; (3) specifically focus on organ donor-related disease transmission; (4) analyze the role of technology in achieving OPTN/UNOS goals; and (5) ensure that all OPTN policies are operational and reflect current practices of transplant centers, human leukocyte antigen (HLA) laboratories and OPOs.

DTAG expanded its initial focus on infectious diseases to include malignancy. The DTAG membership represents infectious disease, pathology and malignancy specialists; transplant surgeons and coordinators; OPO executive directors; and federal agencies. DTAG fulfills its charge with the following process. OPOs or transplant centers enter reported cases of adverse reactions into the UNOS Patient Safety System. The patient safety specialist is notified by e-mail of each new case. UNOS notifies the donor OPO and all recipient centers of the potential disease transmission. Tissue and eye banks also are notified when appropriate.

Electronic notification of new adverse event cases includes information on both potential and known transmitted diseases, the method of detection, and method of discovery by donor or recipient testing post-transplant. All reported cases are confidentially peer reviewed using the secure and password-protected Share Point site. DTAG provides feedback and guidance to UNOS on the system and these topics.

Ms. Joyce Hager, of UNOS, provided additional details about DTAG’s operation and process. UNOS posts donor records on the secure Share Point site when DTAG receives electronic notification of a new adverse event case. This approach allows DTAG to review details on the donor and make initial determinations on whether the adverse reaction potentially could be donor-related transmission. This strategy also provides DTAG with background information to formulate questions and obtain more clinical information from recipient centers.

Recipient data primarily include status reports and are less comprehensive than donor data. DTAG receives the most amount of information from centers that have experienced disease transmission events in the past and about recipients with significant morbidity and mortality. The willingness of recipient centers to share information with DTAG also depends on other factors, such as the type of disease, clinical status of other recipients, and organizational perspective on patient confidentiality or the Health Insurance Portability and Accountability Act (HIPAA). OPTN/UNOS policy asks transplant centers to provide copies of laboratory, pathology and imaging reports if confirmatory testing was performed on the recipient. However, DTAG does not provide clinical or medical guidance to recipient centers.
Ms. Hager outlined DTAG’s key challenges. DTAG is relatively new and has not been institutionalized. Gaps in education regarding potential or confirmed transmission incidence have not been filled to date. Institutions have a significant amount of uncertainty related to reporting in terms of specific data elements, an appropriate time frame, and the optimum reporting method. The incidence of reporting adverse event cases has increased since UNOS implemented its online Patient Safety System in March 2006. Guidance has not yet been developed to assist institutions in clearly distinguishing between post-transplant complications unassociated with the donor and actual disease transmission.

A passive and voluntary surveillance system is associated with bias, underreporting, variability in reporting standards, and difficulties in interpreting data. Historical information and experiences are minimal to guide and inform the current reporting process. Clinical recipient data are limited. Adverse reaction cases are infrequently reported. Transmission is often not confirmed, particularly in cases involving infection. DTAG has no authority to require OPOs and recipient centers to perform confirmatory testing. A true database has not been established to maintain data on donors, recipients, outcomes, and the clinical course of transmitted diseases. However, UNOS is collaborating with CDC to develop data elements and methods for analysis to ensure that the new database is a valuable resource to the transplant community.

The Workshop participants made two key suggestions to refine adverse event reporting systems and requirements for organs.

- Consensus-based definitions should be developed to provide the transplant community with guidance on “reporting triggers” for organs. DTAG should convene a panel of experts to identify specific clinical syndromes and other criteria to support this effort.
- Consideration should be given to revising the OPTN/UNOS policy to require organ donor screening with nucleic acid amplification testing (NAAT). This approach would play a critical role in minimizing adverse events because organs have a strong potential to transmit numerous infectious diseases. However, NAAT screening should not be viewed as an approach to replace clinical vigilance for recognition of transmission.

**ADVERSE EVENT REPORTING SYSTEMS AND REQUIREMENTS: BLOOD**

**FDA’s Safety Surveillance System for Blood and Blood Products**

Dr. Robert Wise, of FDA/CBER, explained that blood safety assurance and surveillance cover the protection of blood, blood components, blood products, donors and recipients. Multiple safety domains and reporting systems are interconnected and overlap, including donor and recipient deaths, product failures, device malfunctions, adverse events in product recipients, and medical errors.
Five major actions are taken to ensure the safety of blood. One, suitable donors are selected through donor education; extensive risk factor screens, some targeted for diseases such as malaria and variant Creutzfeldt-Jakob Disease; and a limited physical examination. Two, deferral registries are used to identify unsuitable donors. Three, infectious disease testing is performed. Four, blood is quarantined pending test results and a determination of donor suitability. Five, errors, accidents and adverse reactions are monitored, investigated and resolved through corrective actions. Current good manufacturing practices (cGMPs) apply to all five levels of blood safety, including staff training and certification, SOPs, use of approved methods, pathogen reduction for plasma derivatives, and bacterial contamination monitoring.

Donor safety is assured with a confidential interview, health status evaluations, rapid access to emergency care, and notification with medical referrals upon deferral for abnormal findings, including infectious disease test results.

Recipients are protected with four key activities. One, safe blood, including its components and products, are assured through the five blood safety levels and cGMPs. Two, human errors are reduced through automated processes, such as bar codes at this time and radio frequency ID tags in the future. Three, blood and its components are grouped, typed and cross-matched for compatibility with the recipient. Four, other safety systems are implemented, including recipient, sample and unit identifiers, hospital practice standards, event investigation and reporting, and corrective actions.

Blood safety reporting is characterized by three major levels. For “mandatory” reporting, manufacturers are required to report fatalities of donors and product recipients; product failures through biological product deviation (BPD) and medical reports. However, manufacturers of blood and blood components are currently exempted from the requirement to report other adverse events. For “voluntary” or “spontaneous” reporting, patients, family members, physicians, pharmacists and any other source can submit information to FDA’s Adverse Event Reporting System (AERS)/MedWatch. For “medical error” reporting, information is submitted to the hospital system rather than to FDA.

Blood fatality surveillance applies to both transfusions and donations. The blood collecting or transfusing facility that performed the typing and cross-match must notify the CBER Office of Compliance and Biologics Quality when a blood donor or recipient dies from a complication of donation or transfusion. Causality must be identified before reporting becomes mandatory. Based on data collected in 2006, the top four leading fatality categories were transfusion-related acute lung injury (TRALI) with a rate of 36.8%; the ABO blood group and other hemolytic transfusion reactions with a rate of 12.7%; volume overload with a rate of 8.4%; and bacterial contaminations with a rate of 7.4%.

Bacterial contamination is rarely implicated in deaths, but is frequently reported as a product deviation. Bacterial contamination is a special concern for platelets due to the requirement for room temperature storage and utilization before reliable culture becomes available. Potential sources of bacterial contamination include donor bacteremia that is asymptomatic or occurs
after a medical procedure; inadequate skin disinfection; skin coring from a needle; and contaminated apheresis solution water baths, pack exteriors or failed sterile connections.

BPD reporting has two major objectives. An early warning system is provided to identify potential problems prior to scheduled inspections that typically occur every two years. This system also serves as an indicator of potentially immediate problems, the need for a product or lot recall, or prompt directed inspection by FDA agents. Surveillance is provided to facilitate training of investigators and industry; give guidance to investigators before and during inspections; and assist in the development of guidance documents and policies for industry.

BPD reporting is required for licensed manufacturers of blood and blood components, including source plasma; unlicensed and registered blood establishments with no interstate commerce; and transfusion services. Data elements for BPD reporting include any event associated with the manufacture of licensed or unlicensed blood or blood components that (1) deviates from cGMP, regulations, standards or specifications with a potential impact on safety, purity or potency; or (2) is unexpected or unforeseeable and might affect safety, purity or potency; and (3) involves a distributed biological product.

Donor suitability and quality control and distribution accounted for 76.1% and 10.8%, respectively, of 38,188 BPD reports in 2006. Labeling, testing, collection, component preparation, and miscellaneous issues accounted for the remainder of BPD reports in 2006 with a range of 5.8%-1.7%.

Manufacturers are required to report a medical device-related death, serious injury or malfunction within 30 days of the event. These devices include viral marker test kits, blood bank reagents and other in vitro diagnostics; other devices, such as apheresis collection devices, hematology analyzers for donor testing, and bacterial detection systems to test blood and components; and incorrect results given by blood bank programs due to an inadequate design or validation of computer software.

AERS/MedWatch serves as FDA’s adverse event monitoring and reporting system. AERS/MedWatch maintains mandatory reports from manufacturers and voluntary reports from any source. Reports can be submitted to AERS/MedWatch electronically or by telephone, facsimile or mail. Non-fatal adverse events from blood and blood components are not required to be reported. However, blood collection and transfusion facilities are currently required to conduct investigations and maintain reports of all adverse events associated with either the collection or transfusion of blood or blood components. The reports are reviewed at least every two years during FDA establishment inspections. These facilities are not required to submit reports to AERS/MedWatch.

FDA published its “Safety Reporting Requirements for Human Drug and Biological Products Proposed Rule” in the Federal Register in March 2003 to change the existing reporting requirements for serious non-fatal adverse events from blood and blood components. Under the proposed rule, facilities performing compatibility testing for adverse events related to transfusion and collecting facilities of adverse events related to the blood collection procedure.
would be obligated to report. The facilities also would be required to submit a written report to CBER within 45 calendar days of the event. FDA is still reviewing comments that were submitted on the proposed rule.

Dr. Wise summarized both the strengths and limitations of blood surveillance systems. The advantages include capacity for any individual to report, confidentiality for reporters and patients, a non-punitive approach to avoid disincentives to reporting, an open-ended process to facilitate detection of unanticipated problems, a national scope, and capabilities for rapid recognition of issues and appropriate responses to assess tentative signals, control verified problems and learn from experiences.

The disadvantages include fragmented reporting systems, incomplete spontaneous reports, no control groups, minimal denominators, a casual or coincidental relationship between the adverse event and product, and a passive and voluntary surveillance system with under-reporting, biases and confounding factors.

Dr. Wise reiterated that blood safety depends on multiple and overlapping systems at every stage from assessing donors to identifying recipients. Important limitations include the fragmentation of blood surveillance systems and incompleteness of event ascertainment, particularly for voluntary reporting systems. Strengthened reporting requirements for serious adverse events may improve blood safety surveillance in the future.

### Hemovigilance Efforts of AABB

Dr. Michael Strong, of AABB, explained that AABB was established in 1947 and has a current membership of 11,200 institutional, individual and international members representing 50 states and 80 countries. AABB’s operating structure includes ~60 committees, subcommittees, program units, task forces and workgroups.

Several countries are actively involved in the European Hemovigilance Network, showing the advantages in monitoring outcomes globally. Data collected from Denmark in 2006 showed that transfusion of incorrect blood components accounted for 54% of adverse events from blood. Data collected from Norway in 2006 showed that the top five contributors to transfusion of incorrect blood components were analysis of the wrong blood sample, use of a wrong blood bag, prescribing routines, misinterpretation of blood grouping, and incorrect patient identification.

Québec’s hemovigilance system shows that monitoring, implementation of interventions and corrective actions could significantly improve outcomes for ABO-incompatible transfusions and acute or delayed hemolytic reactions. The United Kingdom’s “Serious Hazards of Transfusion” (SHOT) system collected data that showed mortality from transfusion-associated circulatory overload (TACO), major morbidity, serious hazards and acute hemolysis were the top four recipient outcomes in blood transfusions. SHOT data also showed that TRALI deaths
significantly decreased after the United Kingdom instituted a policy in 2003-2004 requiring male-only plasma. As a result of these findings, AABB published a bulletin in 2007 recommending that blood programs develop policies and procedures to reduce the risk of TRALI.

One of the other key features of the European Hemovigilance Network is the capacity for individual reporting systems to identify and broadcast problems to various countries. Corrective actions are then be incorporated into the Network and shared. This approach facilitates analyses of issues and identification of rare events.

AABB acknowledged the tremendous value of European surveillance systems in improving practice and decided to take a leadership role in creating a biovigilance system in the United States as part of its 2007 strategic plan. AABB will establish and house a data collection program in its national office to collect, analyze and report data that are relevant to transfusion medicine, cellular and related biological therapies. AABB expanded the initial concept of the system from hemovigilance of blood components and plasma derivatives to include biovigilance of blood components, plasma derivatives, cell therapies, and tissue and organ transplantation. The system will be designed to address both indications and outcomes.

AABB’s first step in developing the U.S. biovigilance system was to review existing data collection efforts. AABB has a federal contract to conduct the National Blood Survey. This initiative addresses blood collection and usage based on retrospective summary data of reactions. The 2005 Nationwide Blood Collection and Utilization Survey Report was recently published with an annual surgical volume, whole blood and red blood cell outdates by group and type, and cellular therapy collections. Individual blood centers have a decentralized process to collect data on TRALI, bacterial contamination of platelets, and donor incidence and safety. HHS’s Blood Availability and Safety Information System collects data from blood centers and hospitals on blood collection, production, inventory, use and shortages.

FDA’s BPD System provides an early warning system and surveillance. However, BPD reports are not particularly useful for process improvement due to the time delay between initial data entry and review of the reports by blood centers. TRALI, non-ABO hemolytic reactions, bacterial contamination, ABO hemolytic transfusion reactions, and transfusions not ruled out were the top five transfusion recipient fatalities reported to FDA in 2004-2006.

In response to the WNV epidemic that began in 1999, AABB established a WNV Biovigilance Network. All blood and tissue testing laboratories that regularly report to AABB’s central system report confirmed-positive and pending interpretation-positive test results to the network. The findings are plotted on maps of the United States and Canada. In 2006, 30 of 41 reporting laboratories had WNV cases. The mean reporting time was 11 days. AABB asked the laboratories to report reactive cases within 24 hours if possible to minimize overlap among collecting agencies, ensure that WNV cases are not overlooked, and improve surveillance with a more rapid response time. AABB also established a Chagas Disease component to our Biovigilance Network after screening with a licensed test was initiated in the United States in February 2007. The reporting system maintains data on repeat reactive and confirmed donations.
The AABB Biovigilance Network was created and is structured with a task force, steering committee and workgroup representing a large and diverse group of federal agencies, the transfusion medicine and tissue communities, and other stakeholders in both the United States and international countries. The various groups are charged with identifying the goals and objectives of the Network; giving moral support and encouragement for participation; determining funding mechanisms; providing direction and review; and sharing lessons learned and experiences.

The AABB Network is considering three potential options to contribute to the overall U.S. biovigilance system. Creation of an entirely new *de novo* system would provide the Network with complete control, but confidentiality and costs would be important considerations in this approach. Replication of systems developed by the Canadian Public Health Agency or other countries would build on experiences and lessons learned, but would require mechanisms to address legal and translation issues. Adaptation of CDC’s National Healthcare Safety Network would provide existing expertise and continuity in the United States. Regardless of the approach taken to develop the U.S. biovigilance system, the Network has agreed to undertake this effort in a public-private partnership.

The AABB Network has established a timeline and criteria for piloting and implementing a hemovigilance system from 2007-2010. The four major components of the pilot will include hemovigilance of transfusion services, hemovigilance of donor services, and vigilance of tissues and organs through a connection to TTSN. For the hemovigilance recipient component, adverse events and incidents with sufficient detail to improve practice will be emphasized. TRALI, TACO, severe allergic reactions, acute hemolysis and delayed hemolysis will be tracked as adverse events in the pilot. Wrong blood in-tube, special processing errors, computer warnings, and testing and transcription errors will be tracked as incident types in the pilot.

The hemovigilance pilot will be conducted throughout the United States with 10-20 institutions representing large and small transfusion services, hospital blood banks and centralized transfusion services. Beta testing will be performed to provide feedback to institutions participating in the pilot. The pilot is expected to be completed in ~12 months to allow for building, testing and implementing the hemovigilance system. The pilot will be expanded in the future to capture all adverse events with a wide scope of incidents, indications and outcomes.

Dr. Strong announced that preliminary activities are underway to support future efforts following the pilot of the hemovigilance system. A shift will be made to advance toward donor activities as the next component for development. As organs and tissues are incorporated, the efforts will encompass biovigilance. The system will be designed to generate reports. Overall, the Network acknowledges the critical need to engage the tissue and organ communities in the biovigilance system in the future.

The Workshop participants made several suggestions to improve adverse event reporting systems and requirements for blood.
• The Network should initiate efforts at this time to identify resources to develop, implement and sustain the biovigilance system over time. Funding will be a critical need for this initiative due to the fragmented healthcare system in the United States. The Centers for Medicare and Medicaid Services should be extensively engaged in these discussions.

• The Network should design the biovigilance system to facilitate easy reporting, minimize the burden on end-users, and rapidly obtain information. This approach could play a critical role throughout the United States in shifting the direction to electronic health records.

• The Network should review the new regulation established by the Department of Homeland Security (DHS) on the protection of the critical infrastructure and information. DHS’s experiences and lessons learned in creating firewalls and other security measures for this regulation could inform the development of the biovigilance system.

• The Network should provide leadership in developing common traceability standards.

OVERVIEW OF THE TTSN COMPONENTS

Review of TTSN Parts A and B

Mr. Kevin Myer, of LifeNet, provided an overview of the system design and practical issues of TTSN. TTSN was developed after CDC awarded the “Sentinel Network for Detecting Emerging Infections Among Allograft Donors and Recipients” cooperative agreement to UNOS in 2005. Federal language requires TTSN to be designed to develop and maintain a national sentinel network of organizations that recover, process and distribute tissues from organ and tissue donors. TTSN also must be designed to improve the safety of organ and tissue transplantation and identify EIDs in organ and tissue transplant recipients. To meet these requirements, the TTSN Advisory Group was established with representatives from major organ and tissue procurement organizations and federal agencies.

The advisory group is charged with performing three primary tasks. A secure web-based electronic communication forum will be developed that will serve all groups involved in allograft transplantation. Dissemination of information to clinicians, health professionals and patients will be improved. A notification algorithm will be developed for trace-back and trace-forward allograft tracking to optimize collaboration between the clinical community and public health authorities.

TTSN’s capabilities are summarized as follows. Capacity will be provided for traceability of allografts to end recipients by replacing paper implant cards with electronic methods. Capacity will be provided to allow banks and end-users to generate reports detailing graft utilization. Tissue and eye banks will be provided with knowledge of the number of donors recovered.
nationwide. An end-user-driven mechanism will be provided for communication of adverse events. A standardized mechanism will be provided for communication of potential or confirmed donor-related disease transmission among OPOs, tissue and eye banks. Inconsistencies in communication will be addressed to improve patient safety.

TTSN will not be designed to (1) replace existing tissue bank donor IDs; (2) replace existing adverse event reporting mechanisms; (3) require retroactive entry of donors; or (4) serve as an inventory system for hospitals or tissue banks. At this time, TTSN is only being designed to track tissues that are actually implanted. The TTSN web-based application has been divided into five stages of development: Part A-“Donor ID Registration;” Part B-“Graft Implant Registration;” Part C-“Adverse Event Registration;” Part D-“Regulatory and Public Health Notification;” and Part E-“Community Education.”

Part A of TTSN will be designed to generate a unique TTSN identifier using the recovering agency’s donor ID number and demographic data from each organ, tissue and eye donor. Each tissue processor or distributor will add donor IDs to the system. Part B of TTSN will be designed to track the final disposition of any allograft using the allograft identifier, type of allograft, surgeon, implanting institution, confidential recipient identifiers, and procedure type and date.

The web-based applications for Parts A and B of TTSN are highlighted as follows. On the “system login” page, the user will be able to create a user account; access links to organ, tissue or eye national associations or sites; and read descriptions on the TTSN background and purpose. On the “donor search” page, the user will be able to search for an existing TTSN donor record using the TTSN ID, UNOS donor ID, institution and donor ID, or name of the donor along with the date of birth, date of death or date of recovery. The donor search results will allow the user to view a list of donors meeting the search criteria, link to the “edit donor” page, perform a new search, and add a new donor to TTSN.

On the “register institution donor identifiers” page, users will be required to add their institutions’ names and donor IDs. The user also will have the option to enter the types of tissue recovered and print the record. The donor information will be able to be edited if the user entered the original donor identifiers to generate a TTSN ID. On the “graft implantation event” page, the user will search for the TTSN donor record using the TTSN ID or graft packaging institution and graft ID. Graft implantation search results will allow the user to view a list of donors meeting the search criteria, link to the “register graft implant event” page, perform a new search, and register and add a graft implant without a TTSN donor record. On the “graft implant registration” page, the user will be required to enter all data fields and save the record. The user will have the option to print the record.

Review of TTSN Part C
Dr. Kuehnert provided an overview of the tracking and adverse event surveillance, reporting, analysis and communication specifications of TTSN. Part C of TTSN will be designed to provide a simple trace-back and trace-forward notification system for adverse events using recipient and allograft identifiers, implanting institution, contact information, and the nature of the event, including a documented infection or syndrome. This portion of TTSN will be searchable by clinical personnel.

Three broad categories of clinical recognition criteria have been established to date to assist clinicians in identifying possible ATIs. Clinical findings would include signs, symptoms or the physical examination, such as fever, lymphadenopathy, or inflammation indicated by pain or discharge around the operative site. Laboratory test results would include seroconversion, evidence of an unusual or unexpected infectious agent, or culture from a sterile site, such as a wound or blood. “Other” notable findings would include sepsis, hepatitis or encephalitis.

DTAG’s reporting criteria have been thoroughly reviewed in an effort to provide specific direction on data elements that should be reported for TTSN Part C. Three major categories have been identified at this point: (1) visualization or culture of infectious agent with treatment, graft removal for organs, or re-hospitalization after transplant; (2) clinical events without organism identification, such as encephalitis, sepsis or recipient death; and (3) seroconversion within six months of the transplant or other evidence of recent infection post-transplantation even if asymptomatic.

Actions will be taken in Part C of TTSN at five levels. An end-user will enter the adverse event into TTSN. The notice will be sent to the allograft supplier or other entity with responsibility for reporting to FDA or OPTN. The responsible entity will launch an investigation to determine the relationship between the allograft and infection. Investigation results and determinations will be made available regarding the status of the allograft. Apart from TTSN, a report would be submitted to regulatory agencies as appropriate.

Several efforts will be made in the ongoing development of Part C of TTSN. The strength of an association between the allograft and transmission of infection will be determined by defining “possible,” “probable,” “confirmed,” “excluded” and “indeterminate.” Recognition criteria will be refined for clinicians due to possible variation by organ and tissue type. Algorithms will be developed to be input into TTSN. Requirements for time sensitivity will be defined. Levels of threshold will be established to generate alerts. Levels of sensitivity and specificity will be tested using OPTN and published data.

Dr. Kuehnert asked the workshop participants to provide input on several key issues, such as the extent of data entry on clinical events, “flagging” thresholds, feedback of data to users, access to immediate interpretation of data, and communication in TTSN among and between the organ, tissue and eye transplant communities. Overall, strong efforts will be made to design Part C of TTSN to streamline existing systems to appropriately disseminate information as rapidly as possible. Part C of TTSN also will be designed to interface with regulators.
Mr. Brubaker provided an overview of plans for the notification components of TTSN. Part D will expand TTSN to include notification to appropriate public health and regulatory agencies. This approach will allow CDC or FDA to assist with investigations if necessary. The notification algorithm has not yet been developed, but TTSN will be prioritized to coordinate with current reporting processes rather than replace existing adverse reaction reporting systems. Although the potential is high to have duplicate notification methods, TTSN will offer a number of advantages to enhance existing systems.

Overall activities will be tracked to determine the incidence of reports and confirmed transmissions. Mechanisms for user confidentiality and limited access will be built into TTSN. TTSN will provide the first opportunity for immediate and widespread notification of graft quarantine. Because multiple banks will provide tissue from the same donor, flags, alerts or notices will be incorporated into TTSN for users to learn whether a graft has been quarantined. TTSN also will serve as a replacement system for implant card management. The major disadvantage of TTSN will be reliance on user compliance, but the other parts of TTSN will be extensively used to strengthen user input and adherence.

Strong efforts will be made to coordinate TTSN with existing processes, including tissue and eye banks, FDA's MedSun project and MedWatch Form 3500, state health authorities and OPOs. Ideally, a link will be made between TTSN and UNet if the UNOS organ donor ID is used. Efforts also will be made to design Part D for a system administrator and eye and tissue banks to manage TTSN. This approach will allow data entry by the other users of the TTSN system if the end-user is not compliant with reporting information.

Other plans for Part D include immediate notification to banks of adverse reactions entered into TTSN. The banks will rapidly launch an investigation and submit reports to FDA within 15 days of receipt of the TTSN report when a reasonable possibility exists that the unintended or noxious response was related to the tissue or ocular tissue. Part D of TTSN will be designed to emphasize notification and communication among OPOs, eye and tissue banks, and state and federal regulatory authorities. Input will be extensively solicited from tissue banks to guide the development of TTSN flags, language and notifications.

Several efforts will be made in the ongoing development of Part D of TTSN. A decision will be made on notification algorithms to determine triggers for an investigation and appropriate recipients and a time frame for notification. Mechanisms will be developed to allow editing of original donor and graft alerts in TTSN to determine threshold levels and use definitions as an investigation progresses.

Mr. Brubaker asked the workshop participants to provide input on several key issues. Strategies are needed to increase education, promote awareness and strengthen compliance with the definitions. The success of TTSN will depend on recognition of a possible organ- or tissue-caused adverse reaction and appropriate and timely reporting. All definitions need to be
finalized due to the impact on the notification algorithm and decision-making. Expected time frames for decisions need to be finalized as well due to the critical importance to patient safety. Overall, Part D of TTSN will be designed to improve recognition compared with previous sentinel events. For example, lack of communication contributed to delays of five and two years, respectively, for initial recognition of HIV and HCV transmissions in tissue recipients.

**Review of TTSN Part E**

Dr. Michael Joyce, of the Cleveland Clinic, provided an overview of plans for the clinician and recipient communication/education components of TTSN. Part E will be designed to achieve the following objectives. Important information will be disseminated to users in a timely manner, such as risks for infection from emerging outbreaks, improved screening criteria, and the development of new assays. Media such as local newspapers, published literature, and alerts by FDA, UNOS and AATB continue to serve as common methods for the transplant community to receive information. However, information from these sources has not been timely or completely scientific to date.

Several options are being considered for TTSN to address these issues. A TTSN web page and e-mail server might be developed to disseminate information to the transplant community on emerging transmissible diseases and new assays in a timely manner. However, problems with these options include the need for constant supervision to update the web page, a committee to validate information and resources. Subscription services, online tutorials and online meetings to review current problems could be offered to pay for the TTSN web page.

Another communication/education issue is the need to provide additional services to recipients. A web page and transplant recipient chat rooms could be incorporated into the TTSN web site to specifically communicate information on organ- or tissue-specific issues to the layperson. Overall, Part E of TTSN needs to be expanded to change the paradigm in handling organs and tissues to improve safety. A real-time investment in safety should be made to provide education on the need for rapid notification. Advances that have been made to improve safety in organ and tissue transplantation should be widely publicized.

A number of approaches are being considered in the development of Part E of TTSN. “Guidelines for Managing Tissue Allografts in Hospitals” and the *Managing Tissues in the Hospital Handbook* should be broadly communicated as educational resources for institutions to meet Joint Commission criteria. Requests for Congressional support should be made. Personnel in hospital, surgical centers and offices should be educated on using TTSN. Strong efforts should be made to obtain endorsement of TTSN from these groups. Consideration should be given to replicating centralized systems in blood banks because this approach is easier than a decentralized system. Training would be needed only for specific staff rather than all personnel.
A dual model similar to device reporting should be created for adverse event reporting. OPOs and tissue or eye banks should serve as “level 1” in this system. Reporting of device failures and other problems is becoming centralized in major hospital systems. This approach allows for the physician to call a telephone number and then obtain and review information. Trained hospital staff members who are supported by a committee and general counsel would report the issue. Adverse event reports should be submitted to the manufacturer and MedSun with FDA oversight. This packaged strategy would incorporate education at the outset.

The current process of reporting adverse events to FDA for tissues is problematic due to slower reporting of deviations and errors by the tissue bank to FDA. The death of a graft recipient in 2001 from a *Clostridium* infection illustrated the problems in the timeliness of recognizing and reporting adverse events. Several options can be implemented to address these issues. A system should be designed that mirrors a dual system similar to device reporting. The system should be developed to be more centralized in a hospital setting. The current process includes reporting to UNOS, OPOs and tissue banks and then to FDA, but lower-level incidents or concerns also should be reported to TTSN to ensure accumulation to a threshold causes a temporary quarantine until a determination is made.

Recalls are a major problem at this time due to the lack of timeliness for hospitals to locate, remove and return infected grafts. As a result, the tissue is inadvertently used. Real-time notification would resolve this problem by allowing users to log into TTSN and obtain information either the previous day or the day of transplantation on whether the tissue is useable. Real-time temporary recall would include the following warning on the TTSN screen: “Do not use this tissue.” This strategy would help to change the current practice of confirming the usability of tissue after the patient is on the operating table. This approach also might emphasize the need for hospital systems to maintain backup tissue when the TTSN screen shows a temporary quarantine of the tissue.

To address concerns with sterility, Part E of TTSN should be designed to broadly communicate common definitions. Most notably, FDA and banks should validate standard definitions before “sterile” is placed on a package. Some package labeling is confusing in terms of sterility. For example, orthopedic surgeons might not have knowledge that the “R” on the label means the tissue is irradiated. Package labels do not clearly show whether the tissue was NAAT tested. Education should be provided to surgeons to clarify that “irradiated” tissue does not necessarily mean “sterile.” Examples of irradiated tissue that transferred bacteria have been published in the literature. Dr. Joyce emphasized that the major tasks in the future development of Part E of TTSN are to provide more education and communication.

The TTSN Workshop participants made a number of suggestions that should be considered in ongoing efforts to refine the TTSN components.

- Efforts should be made to simplify and reach agreement on the TTSN definitions. For example, the likelihood that a graft caused an infection could be defined as “<50% for possible” and “>50% for probable.”
• Professional associations should be extensively engaged in efforts to communicate to and educate physicians in the following areas. The physician should determine whether the tissue or organ was from an accredited bank. The physician should inform patients that human tissue will be transplanted. The physician should be aware of the need to obtain additional information on potentially infected tissues due to false-positives and other problems with clinical tests.

• Imputability scores incorporated into European hemovigilance systems should be reviewed as a model in standardizing the TTSN definitions.

• Part E of TTSN should be designed to provide education on both TTSN specifically and public health in general, particularly the detection of EIDs. Literature searches and reviews of journal articles have been the traditional methods for physicians to learn about EIDs that can be transmitted through transplantation. However, listservs and other more sensitive and timely tools are now available.

• Part E of TTSN should contain only critical or essential information to inform clinical decision-making.

• Caution should be taken in incorporating chat rooms and listservs into TTSN because these forums might result in users receiving information that is not relevant to allografts.

• Legal counsel should be extensively involved in the development of each of the five TTSN components. This approach would provide a legal basis if the definitions or other parts of TTSN are legally challenged in the future.

• Protocols should be developed for situations when multiple tissue or organ banks need to access TTSN at the same time.

• Procedures should be established to encourage use of tissue after TTSN lifts a temporary quarantine. This process will be extremely important because a physician might refuse to use tissue from the same donor in the future solely on the basis of the TTSN temporary quarantine.

• Flags should be incorporated into TTSN to advise surgeons on the appropriate time to notify recipients who previously received tissue with known infection. For example, a TTSN alert could instruct the surgeon to contact the tissue source facility or tissue bank to obtain more information.

• TTSN should be designed to advise surgeons to obtain information from FDA reviews to guide clinical decision-making and communications with patients regarding allografts.

• Consideration should be given to expanding TTSN to include different languages other than English. This design would allow international users to enter data into TTSN.

• Consideration should be given to broadening TTSN to send alerts to surgeons through their pagers and cell phones. An active notification system would advise physicians to immediately review information on suspected transmission of an allograft.

• The coordinator system in the bone marrow and solid organ transplant community should be reviewed as a model in the further development of Part E
of TTSN. Coordinators have been found to play a critical role in facilitating communications.

- Part E of TTSN should not be limited to communication/education to physicians. All persons who handle tissues should be educated on the risk of transmission, including staff members who regularly communicate with vendors and register tissues, circulating nurses who hand tissues to surgeons during surgery, and personnel who obtain consent forms from patients.
- TTSN should be designed to provide leadership in standardizing product labels. This strategy would allow users to quickly identify information on the label.
- Caution should be taken in initially designing TTSN as an active notification system in which alerts would be sent to pagers and cell phones of physicians on suspected transmission of allografts. Instead, TTSN should be implemented with a tiered approach over time to avoid the potential for a “gridlock” in the availability of tissue. For example, specific goals and directions should be identified for TTSN at two, five and ten years.
- TTSN should be designed as a centralized system in which a blood bank or centralized bank would serve as a clearinghouse for information and provide institutions with linkages to web sites, notifications and other data.

The panel of presenters made several remarks in response to specific questions and comments by the workshop participants on the TTSN components.

- UNOS is a HIPAA-compliant organization and will design TTSN as a secure and password-protected system to address HIPAA issues. For example, users will not have access to identifiers for other centers.
- Efforts are underway to minimize the burden on end-users of entering data into TTSN. For example, discussions have been held on the possibility of only including ~5 fields with drop-down menus. However, UNOS would not have authority to designate end-users to enter data into TTSN. Instead, institutions would assign responsibility to specific staff members for TTSN data entry, such as a surgeon, coordinator or nurse.
- Other communication and educational resources will be developed and made available in addition to TTSN web-based applications. For example, brochures will be distributed to provide guidance to end-users on specific data elements to enter into TTSN. These materials will also clearly outline the expectations of using TTSN.
- TTSN is being designed with an instant notification component because multiple organ recipients have received grafts from the same donor in the past. However, TTSN is not being designed to allow a surgeon to refuse all tissues from one donor because a single patient had an infection.
Dr. Angela Caliendo, of the Emory University School of Medicine, explained that three distinct steps are involved in NAAT: extracting nucleic acid from the clinical specimen, performing amplification of the target, and detecting amplification. The sensitivity, specificity and reproducibility of these assays are solid. The “limit of detection” of an assay is defined as the concentration of nucleic acid that can be detected in 95% of replicates. However, lower concentrations are detected less frequently.

Nucleic acid extraction is extremely labor-intensive. Automation of this process would be helpful to laboratories. Real-time methods are less labor-intensive and are preferred over conventional amplification methods. The time to results is an issue that must be considered from a technological perspective due to “STAT” testing for organs versus “batch” testing for tissues.

FDA-cleared assays are required for testing of tissue, but not for organs. Multiplex assays need secondary testing and add four to six more hours to the testing process. Laboratory operational issues include adaptation of existing blood screening assays, the STAT nature of organ testing, testing on evenings and nights to accommodate the schedules of donors, and efforts to maintain the competence of technologists and operation of instruments.

The following assays are currently available and have been cleared by FDA. Chiron’s PROCLEIX® assay is a transcription-mediated amplification (TMA) technology that is primarily manual. The assay is widely used in the blood screening industry. PROCLEIX® has an HIV/HCV combination test that detects both viruses. However, secondary testing is required because the assay does not distinguish between the two viruses. The HIV assay was designed to detect Groups M, N and O and the HCV assay was designed to detect all hepatitis C genotypes.

The multiplex PROCLEIX® ULTRIO assay detects HIV, HBV and HCV, but secondary testing would be required because the assay does not make a distinction among the three viruses. The assay is FDA-cleared for HIV and HCV, but not for HBV. The TIGRIS system is an automated “walk-away” and high throughput system. The system initially was used for laboratories with a large volume of chlamydia and gonorrhea testing. The TIGRIS system is designed to run hundreds of tests in large batches through the entire TMA assay, including extraction, amplification and detection.

The Roche AmpliScreen system is on a Cobas platform with individual assays for HIV, HBV and HCV that are all FDA-approved. The disadvantage of this system is the requirement to run three different assays for each patient. The Roche real-time AmpliPrep-TaqMan system allows for completely automated extraction. The multiplex assay detects HIV-1, HIV-2, Group O, HBV and HCV. Secondary testing with the Cobas system would be required to make a distinction among the viruses. Roche has submitted this assay to FDA for approval.

FDA approved GenProbe’s APTIMA HIV-1 and APTIMA HCV assays. The tests are designed for diagnostics, but not for blood screening. The HIV-1 assay was approved to detect acute
infection of Groups M and O and the HCV assay was approved to detect RNA in antibody-positive patients. The tests are solid and extremely reliable, but also are manual, labor-intensive and require at least six hours to run.

FDA has not approved any assays for HTLV. No commercial assays are available for HTLV at this time. HTLV testing is offered at select referral laboratories, but limited data are available on the performance of these assays. The assays are extremely difficult to validate due to the small number of HTLV cases in the United States. The assays cannot be completed within the necessary time frame due to the need to send results to referral laboratories.

The sensitivity and specificity of NAAT for blood screening are >99%. The analytical sensitivity of NAAT ranges from 5-50 copies/mL depending on the analyte and assay. From a clinical perspective, the addition of NAAT has reduced the window period from 22 to 11 days in HIV screening and from 70 to 10 days in HCV screening. A decision analysis was published in 2007 to determine whether high-risk donors of intravenous drug users, men who have sex with men, commercial sex workers and inmates should be used in renal transplantation. The analysis was performed with and without NAAT for HIV and HCV to determine the incidence of infection and a reduction in the window period with NAAT. An error rate for clinical laboratories was included in the analysis.

An analysis of the transplant policy over 20 years with NAAT showed that patients had higher survival rates, a greater number of quality-adjusted life years, more transplants and a lower cost of care. Viral infections were lower in the “transplant” group compared to the “discard” group. The discard group spent more time on dialysis and had higher HCV incidence. Without NAAT, the transplant group had better outcomes than the discard group and more viral infections were seen, particularly in HCV patients. Based on these findings, a recommendation was made to consider transplantation for NAAT-negative and CDC high risk donor-classified kidneys. This practice was estimated to be beneficial from both societal and individual patient perspectives.

For blood screening, NAAT uses sensitive and specific assays that are designed for high volume throughput with a turnaround time of 24 hours. NAAT for blood is available in batch testing at regional laboratories. For organ screening, NAAT use requires sensitive and specific assays with a rapid turnaround time of four to six hours. The specific virus needs to be known in some situations. Local laboratories can perform low-volume and individualized testing. For tissue donor screening, NAAT uses sensitive and specific assays with a turnaround time of 24 hours for eyes and days for tissue. Local or regional laboratories perform a moderate volume of batch testing.

Testing methods that are effective for blood screening and tissue might not be effective for organ and eye donors. To address this issue, Emory University has been conducting a study over the past two years to bring NAAT testing to all organ donors. The molecular laboratory performed daily and evening testing, while the HLA laboratory performed night and weekend testing. Emory tests ~270 renal donors per year with three to eight of these donors being high-risk each month. Emory selected the AmpliScreen HIV and HCV testing platform with 96 tests
Reagents could only be used eight times, but this number is expected to increase to ten. Four controls were run for negative, positive, and independent HCV and HIV.

HCV and HIV testing required three Cobas instruments, but a fourth instrument will be needed with the addition of HBV testing in the future. Emory found that the reliability of the instrument increased with frequency of use. The cost per test was ~$410 for each virus. Emory modified the assay for automated extraction with the QIAGEN instrument. The modified assay was a tremendous improvement for technologists, maintenance of proficiency and quality of results. The hands-on time was only one hour and the time to results was 4 to 4.5 hours. Emory needed time to become proficient with testing and recognized that this approach could not be used with tissue donors. Emory shifted to high-risk donor testing only after the HLA laboratory staff was unable to maintain pace with the volume on the night shift. The current volume is three to eight tests per months and the cost per test is higher. Emory plans to move all testing into the immunology laboratory in the fall of 2007.

Several options are available for other laboratories to replicate Emory’s experience. The volume of testing could be increased to decrease cost. All donors rather than high-risk donors only could be tested. The laboratory could become a regional laboratory. Testing could be performed for apheresis centers, infertility clinics, eye banks and tissue donors. Non-STAT testing could be performed and ran with STAT testing for organ donors.

Laboratories would need to consider several factors in applying findings from Emory’s research. Eye banks need 24-hour turnaround time. An FDA-cleared assay must be used with tissue. A significant amount of funding will be needed to purchase and maintain instruments, hire new staff for nights, evenings and weekends, and support expensive testing.

An ideal test would be low-volume, appropriate for STAT turnaround time with random access, cost-effective, and simple to perform. The ideal test also would require minimal hands-on time, generate results in a few hours, and serve as a self-contained system with onboard controls. The Xpert EV assay was designed as a moderately complete diagnostic test to detect enterovirus RNA in cerebrospinal fluid. The system includes an instrument, computer and disposable fluidic cartridges.

The Xpert EV assay performs sample preparation and real-time PCR with amplification and detection in 2.5 hours. The assay includes onboard sample preparation control and a probe check control step to ensure the integrity of reagents. The Xpert system includes sensitive and specific assays that are FDA-cleared for Methicillin-resistant Staphylococcus aureus (MRSA), Guillain-Barré Syndrome and enterovirus. The assays require minimal hands-on time, include onboard controls and provide random access. The system can accommodate separate tests for each analyte or multiplex testing.

Dr. Caliendo emphasized that from both clinical and laboratory perspectives, NAAT for organ and tissue donors is clinically indicated. The logistics of testing are extremely challenging for hospital-based laboratories. A better assay design is needed for organs that require STAT testing and rapid turnaround time.
Molecular Testing for WNV

Dr. Atul Humar, of the University of Toronto, explained that only 1% of persons who are bitten by an infected mosquito will develop severe disease. However, infection is amplified in organ transplant recipients due to the high incidence of central nervous system (CNS) disease of 40% and an extremely high fatality rate. In 2002 and 2005, two organ donors acquired WNV through a blood product and an infected mosquito, respectively, and collectively transmitted the pathogen to eight recipients.

Several lessons were learned from WNV NAAT screening of the blood supply from 2003-2006. During this time period, ~1,820 viremic donors were identified and ~2,639 infectious blood components were removed from the donation process. Only ~67% of NAAT-positive donors were found to be IgM-negative or likely infectious. Individual donor testing in epidemic areas increased the yield by 32%. Only 5%-10% of these donors were believed to be infectious. The short duration and low levels of viremia were problematic for WNV NAAT screening.

A number of unique issues must be addressed with organ donor screening. Molecular tests are sensitive to inhibition by blood components and degradation of donor samples that might rapidly occur after cessation of heartbeat or respiration. Molecular tests require speed and availability 24 hours per day/7 days per week for blood and tissue to be stored to await results. However, organs cannot be stored, so that most available tests require a minimum of four to six hours to perform. This requirement does not allow much time for retesting of weak or otherwise questionably positive samples.

Because of these limitations, the usefulness of a mini-pool format in the organ donor/OPO setting would be doubtful, so that individual donor testing would be required. False-positive tests result in loss of organs and recipient deaths. False-positive tests also are problematic for both NAAT and IgM testing. IgM testing might exclude potentially healthy donors or donors with past exposure with no active disease. The potential exists for non-viremic donors who are PCR-negative or NAAT-negative, but IgM positive to transmit infection.

Several assays are available at this time for molecular testing of WNV. Chiron’s Gen-Probe-PROCLEIX® WNV assay is FDA-approved for tissue donors. The sensitivity of this assay is ~5 copies/mL. Each assay requires between 3.5 to 5 hours to perform depending on the platform used. Other assays use various methods and platforms, including the Roche TaqScreen WNV test, the Bayer Target capture PCR, the NGI supplemental qualitative WNV assay, and the Artus WNV real-time PCR kit.

A study was published in 2006 with testing results of 15 low-level WNV viremia samples. The sensitivity of assays with a 50% level of detection ranged from 1.5-29 copies/mL. The sensitivity of assays with a 90% level of detection ranged from 6.4-125 copies/mL. The clinical sensitivity of the assays widely ranged from 3%-97% depending on whether the sample was
IgM- or IgG-positive. Most samples tested accurately against negative controls, exhibiting good specificity.

Although infrequent, false-positive results in WNV tests have become problematic. To address this issue, a medical decision analysis model was developed and published in 2004 with a number of assumptions: a screening test sensitivity rate of 99.5%, a specificity rate of 95%, and a case fatality rate of 25%. UNOS survival probabilities and transplant rates also were incorporated into the model. The findings showed that inclusion of WNV NAAT could potentially result in the loss of 452.4 total life years: 113.8 life years for the heart, 272.6 life years for the liver, and 66 life years for the kidney. Most positive tests were found to be false-positive. The study concluded that screening resulted in a net loss of life that might be justifiable for kidney donors where WNV prevalence was high and if the specificity of the test was higher than the assumptions of the model.

The University of Alberta tested the model with WNV NAAT in organ and tissue donors in 2003-2005. Alberta has a population of ~3.2 million persons and supports large and multi-organ hematopoietic stem cell transplant programs and tissue banks. WNV screening was seasonal from June 1 to October 31. From 2003-2005, 284 community WNV cases were reported with four asymptomatic blood donors. Seroprevalence IgG was 0.31% in the population, but as high as 4.6% in the southeastern part of the province.

The public health laboratory delivered both screening and confirmation for WNV NAAT within the specified turnaround time. Staff members who were skilled in molecular testing provided testing 24 hours/day and 7 days/week. Targeted turnaround times ranged from six hours to one week depending on the type of donor, including local and distant multiple organ donors, living kidney and liver donors, cornea donors, other tissue types, and bone marrow recipients and donors.

In the sample test methodology, the sensitivity of the assay was enhanced by extraction from 1 ml volume of plasma or serum into 50 µl eluate. WNV external controls were utilized to validate the assay runs. Internal control reactions were utilized to identify potential false-negative results due to extraction failure or inhibitory effects. Samples requiring a rapid turnaround time of ≤24 hours were first tested with the Artus WNV real-time PCR kit. Samples with longer turnaround requirements were batch tested with the nucleic acid sequence-based amplification assay.

WNV donor testing included in the analysis was from the May-December season over the three-year period from 2003-2005. Of 1,401 donors, 1,563 total specimens were tested from 99 multi-organ donors, 269 hematopoietic stem cell donors, 154 living-related organ donors, and 881 tissue donors. Over this time period, no positive donors were confirmed, no false-positive tests were generated, and no organs were lost. The estimated cost of $109,000 in Canadian dollars per season was found to be quite reasonable.

During the analysis, valid results could not be obtained from 18 donors within the required turnaround time. Samples that had an internal control failure in both NAATs were most likely from post-cardiac deaths of donors with visible hemolysis in the blood. This problem was most
often seen in tissue donors. Insufficient quantity or internal control failures prevented definitive reporting of results in 11 tissue donors.

The Alberta screening program reached the following conclusions in the analysis. A direct benefit of WNV screening to transplant recipients could not be demonstrated. No viremic donors were detected. NAAT for WNV can be implemented to provide timely and extremely specific results. WNV NAAT donor screening can be implemented without compromising the availability of scarce organ donors. A WNV NAAT screening program requires committed laboratory support and expertise.

A number of factors should be considered to guide decisions on whether to screen organ or tissue donors with WNV NAAT. High or low prevalence of WNV in the local population should be reviewed to determine whether the positive predictive value of the screening test would be useful. Evidence has been generated to demonstrate that WNV can be transmitted by organ donation. Transmission has been found to result in significant morbidity and mortality. A reliable and logistically applicable test is available for screening, but the test is difficult to perform. The cost-effectiveness of the screening test has not been validated and does not meet healthcare standards for technology implementation at this time.

Dr. Humar reiterated that no test will prevent transmission of infection 100% of the time. “Ideal” technologies have not been developed to date for individual donor testing of WNV in a timely round-the-clock manner. However, the development of these technologies is possible with sufficient commitment. Data gaps at this time include transmission from IgM-positive and non-viremic donors. IgM testing might detect these donors, but increase the risk of false-positive results. Testing should be considered in the context of screening for other pathogens.

### Bacteremic and Fungemic Donor and Resistant Pathogens

Dr. Fishman described several examples of bacteremic and fungemic donor and resistant pathogens from solid organ transplantation. Newer pathogens in transplantation have emerged over the past 10-15 years, including bacteria, fungi, viruses and parasites. These pathogens have resulted in a number of adverse outcomes. Patients who resume travel, employment, hobbies and other activities will be exposed to a variety of newer pathogens. Nosocomial flora have shifted due to antimicrobial resistance and prolonged hospitalizations for sicker patients.

Routine prophylaxis is increasingly used with a variety of drugs. Most organ, tissue and eye donors have been hospitalized for some period of time prior to donation and might become colonized with nosocomial flora. Immune suppression has been intensified in the transplant population with better agents that have resulted in less rejection and more infection. T-cell immune deficiency and survival with immune suppression are prolonged. Diagnostic assays have been improved with patients surviving for longer periods of time. Advances have been made in the development of new technologies, such as ventricular-assisted devices and stem cells that are stored for periods of time. Expanded criteria for organ donors might result in more
infectious transmission. Geographic backgrounds of donors and recipients have broadened over time.

Types of donor infection present at the time of organ procurement include bacterial, fungal, parasitic, viral, and prion. Tuberculosis continues to be transmitted. In donor-derived infection from bacteria, line infection, sepsis, pneumonia, peritonitis and meningitis contribute to bacteremia at the time of procurement. Transmission was rare in the past when prophylactic antimicrobials adequately treated most organisms, but this outcome has now changed due to the emergence of antimicrobial-resistant organisms, such as pseudomonas, salmonella, MRSA and vancomycin-resistant Enterococcus (VRE). The risk is greatest with hematomas at the anastamotic site (e.g., vascular, tracheal, ureteric, gastrointestinal or biliary).

In donor-derived infection from fungi, Candida is often nosocomially acquired in donors and also is associated with intravenous lines, peritonitis and bowel perforation, or antimicrobial selection in the donor or recipient. Aspergillus is fairly uncommon, but colonization is common in lung transplant recipients. Histoplasma, Coccidiodoideas and other endemic fungi are frequently seen in organ donors from certain geographic areas. Ubiquitous fungi include Cryptococcus in procured organs.

Donor-derived parasites include late and latent infection from Toxoplasma gondii in the heart and lungs and active infections from blood or organs, such as Chagas disease, malaria and babesia. Strongyloides stercoralis, Leishmania donovani and Trypanosoma brucei have not yet been described in the literature, but most likely are donor-derived parasites. Intestinal and liver flukes and Echinococcus also have not been described in the literature to date and are not T-cell dependent. Transmission of prions is unknown, but is possibly a greater concern in xenotransplantation.

Donor-derived viruses include herpesviruses, HTLV I and II, HIV, WNV, rabies, LCMV and respiratory viruses. However, a decision must be made on the number of viruses to include in a multiplex panel due to the tremendous expense of testing. The magnitude of screening at this time includes ~28,000 tests per year for solid organs, 1-2 million tests per year for tissues and eyes, and ~4 million tests per year for blood products. Screening is also performed for hematopoietic transplants. Federal governments mandate and regulate screening practices in the United States and Canada, requiring that each assay used for screening be approved for a specific use, such as for cadaveric organ and tissue donors, or for living blood donors.

In current donor screening, blood cultures are extremely useful to detect acute infections. Serologies are generally useful for assessment of post-organ transplant infection, but might overlook acute infections. PCR and antigen tests are highly useful, but are not adapted to the speed needed or may not screen for the array of potential infections.

In two cases involving kidney donors, kidneys were procured in another location and sent to New England as six-antigen matched and shared kidneys. Donor 1 had a Candida urinary tract infection that was treated with fluconazole for one week. The routine transplant followed native nephrectomy for polycystic renal disease. Perioperative prophylaxis was administered with
cefazolin. Post-transplant prophylaxis was administered with trimethoprim-sulfamethoxazole, valgancyclovir and clotrimazole. The patient was discharged with serum creatinine of 1.5 on day 4 following the transplantation.

Donor 1 contacted the hospital to report shaking chills, fever and wound drainage. The CT scan showed fluid collection and the wound drainage revealed white cells and yeast forms. Telephone calls were placed to the New England OPO, local OPO and procurement hospital. These communications confirmed that organisms from the donor had non-albicans yeast. Subsequent information revealed the donor had *Candida krusei* that was resistant to fluconazole and intermediate susceptibility to micafungin. The condition of the donor improved after treatment with liposomal amphotericin. The kidney function was retained.

Donor 2 had pneumonia that was treated with levofloxacin prior to donation. The routine transplant followed a native nephrectomy for diabetic nephropathy. Perioperative prophylaxis was treated with cefazolin. Post-transplant prophylaxis was administered with trimethoprim-sulfamethoxazole, valgancyclovir and clotrimazole. Telephone calls and facsimiles from the organ bank revealed that the donor was bacteremic with VRE *faecium* at the time of procurement and had been treated with levofloxacin for pneumonia. Fluid collection around the kidney graft revealed pus and VRE. The donor was discharged with linezolid and serum creatinine of 1.4 on day 6 following transplantation.

Dr. Fishman noted several lessons learned from the two cases. Neither of the cases was reported to OPTN/UNOS despite current reporting regulations. Important microbiologic data on bacterial, fungal, viral and other infections are routinely missed in graft donors. Even when recognized, communication is too slow at this point. This gap has implications for patient care and emphasizes the need to assess current technology for tissue donation. This approach should be taken to determine whether sterilization methods eradicate newer pathogens. Routine screening is extremely useful, but might be inadequate for existing needs. To preserve the quality and safety of organ screening, evidence-based improvements are needed for routine donor screening to demonstrate benefits to patients.

### Chagas Testing for Cadaveric Organ Screening

Dr. Louis Kirchhoff, of the University of Iowa, explained that *T. cruzi* parasites are in the feces of insects. Routes of transmission to mammals include contamination of the bite site, abrasions and mucosa surfaces. Acute Chagas disease can result in fever, malaise, anorexia, edema and rash and also myocarditis and meningoencephalitis in rare cases.

Chagas disease is a zoonosis. *T. cruzi* infection is life-long, but 10%-30% of persons with chronic *T. cruzi* infection will never have clinical manifestations attributable to the disease. The burden of *T. cruzi* includes infection to 10-12 million Latin Americans and 20,000 deaths per year. *T. cruzi* morbidity and mortality are primarily due to cardiac problems. Of 13 million persons in the United States from non-Caribbean endemic countries, ~100,000 are infected with
*T. cruzi*. The population of 8-9 million Mexicans who live in the United States represents 8% of Mexico’s total population. During the 1990s, the daily net emigration of Mexicans to the United States was 961 persons.

A study was conducted to determine the prevalence of *T. cruzi* infection among blood donors in Mexico. The Abbott Chagas ELISA assay or the Meridian Chagas IgG ELISA was used to screen 7,296 blood donors in five blood banks in two Mexican cities. The radioimmune precipitation assay (RIPA) was used for confirmatory testing. The study revealed 55 RIPA-positive donors. The rate of 1 in every 126 RIPA-positive donors was uniform throughout the five Mexican blood banks. Of nine recipients with contaminated blood, four were RIPA-positive by either platelet or whole blood transfusions. The study served as the first specific demonstration of transmission of *T. cruzi* by transfusion in Mexico.

Of seven cases of transfusion transmission of *T. cruzi* reported in the United States, all were in immunosuppressed patients. In the United States, five described cases of transplant transmission of *T. cruzi* were from three donors. No instances of transmission of *T. cruzi* via tissue transplants have been reported to date. Drugs are toxic and low cure rates include >95% in congenital cases, ~70% in acute disease, and <10% in chronic cases. A role for giving drugs to recipients of *T. cruzi*-infected organs post-transplant to prevent transmission has not been defined.

A number of problems have been identified in efforts to assess risk for Chagas disease. *T. cruzi*-infected persons are rarely aware of their parasitosis. Questions are notorious for producing poor data. Persons at geographic risk for Chagas disease present particular challenges, particularly language barriers. An approach of asking questions would miss autochthonous cases and congenital transmission. To address these issues, consideration should be given to adopting the blood industry model of serologic screening.

*T. cruzi* infection can be diagnosed by two methods. For serologic assays, titers are not related to clinical status or infectivity. In Latin America, >30 tests are commercially available with varying quality and different levels of sensitivity and specificity. The Hemagen and Wiener ELISA assays have been 510(k) cleared. CDC performs the immunofluorescence and recombinant Weiner assays. For the highly-automated Abbott PRISM Chagas assay, clinical trials will be launched and a biologic license application (BLA) will be submitted in the near future. Abbott will include both living donor and cadaveric claims in its BLA for the PRISM assay.

The Ortho *T. cruzi* ELISA Test System was approved in December 2006. In January 2007, the American Red Cross and Blood Systems, Inc. initiated screening of ~65% of the U.S. blood supply with the Ortho test. Current data suggest that the RIPA assay will confirm 23% of 1,300-1,500 repeat reactive results with the Ortho test. The Ortho test currently includes a living donor claim and is expected to be expanded in the second quarter of 2008 to include a cadaveric claim.
For supplemental tests, xenodiagnosis is only 50% sensitive. Hemoculture is only 50%-70% sensitive and requires a specialized homemade medium and weeks to perform. Hemoculture is not commercially available at this time. PCR has not fulfilled previous expectations of a sensitive assay due to sampling problems. The RIPA assay is not FDA-licensed as a supplemental test, but is currently being used to test all Ortho repeat reactive results of blood donors. The Abbott Chagas immunoblot assay uses the same four hybrid recombinant antigens as the PRISM assay, but a different format is used. Abbott is developing the immunoblot and PRISM assays in parallel and plans to submit both assays in the same BLA.

In serologic studies that were conducted in 2006 on a second \textit{T. cruzi} heart transplant case, the immunofluorescence assay at CDC was negative; the RIPA assay was positive at the American Red Cross; and the recombinant ELISA was positive at the University of Iowa laboratory. However, the Ortho ELISA, Abbott Prism Chagas and immunoblot assays, and recombinant Wiener ELISA were not used in the serologic studies. “Washout” due to organ donor transfusion might have been an important issue because no specimen pooling is allowed in serologic testing of \textit{T. cruzi}. The studies revealed that the heart donor received blood products prior to the receipt of samples.

Dr. Kirchhoff summarized several important issues in testing organ and tissue donors for Chagas disease. Testing before transplantation could be logistically difficult due to the relatively small number of laboratories that perform testing. Testing before transplantation might create a “two-tiered” system. An approach of giving specimens to blood donor centers should be prioritized over localized testing. A system is needed for tracking data to develop evidence-based perspectives on transmission rates, the usefulness of drugs and outcomes.

### Specific Screening Issues for Cadaveric Specimens

Dr. Steven Geier, of Laboratories at Bonfils (LABS), described several factors that emphasize the need for effective confirmatory steps in screening tests to reduce the loss of donors and enhance transplant safety. False-positive tests needlessly lose donors, while false-negative tests can cause great harm. Screening tests for deceased eye and tissue donors need to be improved to reduce the loss of these donors and enhance the safety of transplants. Multiple steps in high complexity tests require extremely accurate performance. Screening tests are optimized for blood donors, but not for deceased donor testing.

The sensitivity of screening tests is solid in detecting infected donors, but specificity is problematic due to reactions with non-infected donors. Blood and live donor samples are not equivalent to deceased donor samples. Screening tests have low numbers of initial reactive results, but the false-positive reactive rate is high. Laboratories must adhere to testing procedures in the product insert, but the result might not be accurate. Opportunity got confirmatory steps are limited.
Repeat reactive results for antibody enzyme immunoassays (EIAs) are not always effective in detecting false-positive results. Possible false-negative results are not always flagged. Only a small number of NAATs were designed with confirmatory steps. Automation for deceased donor testing is limited to high-volume blood testing and does not include eye, tissue or organ donor testing. Non-testable samples are problematic, particularly heavily hemolyzed samples from deceased donors that cannot be tested on some PCR platforms. Product inserts sometimes contain limited sample types, shipping and testing windows. A live donor is only deferred when a test is false-positive in most cases. However, organ donors might be lost and tissue and eye donors are lost forever.

One false-positive or non-testable sample in a panel of eight to ten tests will lose a deceased donor. Up to 50 transplantable tissue grafts can be made from one donor in general and also can result in live-saving or enhancing transplants. One organ donor can gift one to seven life-saving organs. False-positive results are better than false-negative results. However, false-positive results lose life-saving and enhancing donors; delay or lose life-saving organ transplants; deny donors and families their wish to help others; raise unnecessary anxiety in surviving family members, transplant recipients, public health departments and CDC; are expensive for tissue and eye banks; and will result in the loss of additional donors as more tests are required unless current screening tests are improved.

Several technical issues and problems related to samples can result in the loss of donors as a result of false-positive results, including cross-reactive antibodies, rheumatoid factors, human anti-mouse antibodies, bacterial contamination, fibrin from incomplete clotting, cryoprecipitate, grossly hemolyzed samples, cross-contamination from positive controls or samples, malfunction of ELISA washers, water baths and other equipment, inappropriate addition or incubation of reagents, and poor test kit lots. The false-positive rate of 0.3% is not acceptable if all tests have the same high rate (as the rates are cumulative). A panel of ten tests will result in the loss of 750 donors per 25,000 donors, ~37,500 fewer tissue allografts available for transplant, and the possible loss of ~2,600 organs.

A study was published in 2006 on the loss of donors with HTLV antibody testing from 2002-2003. Of 1,408 organ donors tested, 1.6% had repeat reactive results and 29% had false repeat reactive results with Western blot. The loss of 0.45% organs was equivalent to ~21 life-saving organs and 320 tissue transplants. When these results were multiplied by ten infectious disease tests, ~210 organs and ~3,200 tissues per 1,408 donors were lost.

False-negative donors can cause great harm to transplant recipients. Samples are not typically retested or rerun in duplicate to catch testing errors and obtain knowledge on the occurrence of false-negative results. All screening tests are not required to detect possible false-negative results or have a positive control added to each sample before plating.

Several technical issues and problems related to samples can result in unsafe transplants as a result of false-negative results, including low antigen, antibody or viral load levels, rheumatoid factors, shipping and handling problems, bacterial contamination, degraded samples, grossly hemolyzed samples, inappropriate addition or incubation of reagents, neutralization of detection
conjugate or antibodies, malfunction of ELISA washers, water baths and other equipment, and poor test kit lots.

A study was conducted to determine whether antibody EIAs would flag a sample addition failure. The study emphasized the need for all tests to have appropriate ranges that are effective in catching potentially false-negative results. Screening test validation studies of product inserts also showed that false-positive results were problematic in losing donors. The study showed that repeat reactive tests of product inserts were not always effective in catching false-positive results.

The initial reactive rate of both antibody tests and NAAT was low and ranged from 0.2%-6.7%. The study emphasized the importance of incorporating a duplicate repeat confirmatory step because this approach caught 13%-71% of technical errors made in laboratories. An analysis of the specificity of product inserts on blood donors also emphasized the need for screening tests to have effective confirmatory steps to reduce false-positive results.

NAAT for deceased donors needs confirmatory steps to stop the loss of donors as well. Pooled testing is performed in mini-pools of ~16 donors. Each donor is retested if a reactive pool exists. Live donors can be deferred and tested at a later time. The PROCLEIX® HIV/HCV test has a confirmatory step for any donor. A reactive initial test is repeated with separate HIV and HCV discriminatory tests. The HIV/HCV duplex test can be repeated if both discriminatory tests are non-reactive.

An analysis was performed on possible sources of false-positive and false-negative results in a NAAT protocol. The study showed that amplification and carryover from a positive control template played a significant role in false-positive and false-negative results. LABS confirmed the need for a confirmatory step in testing during its studies with 12,900 mini-pools of WNV live donors in 2005; 4,710 non-pooled deceased donors from September 2004-June 2006; and 12,523 non-pooled HIV/HCV NAAT deceased donors from February-September 2006. Based on these findings, CBER’s current position on confirmatory steps in NAAT is unclear.

Dr. Geier summarized several actions that can be taken to improve clinical tests. Technical errors that can cause false-positive and false-negative results should be identified. Testing procedures should be improved to minimize technical errors. All sample and reagent addition steps should be documented. Testing accuracy and continuous improvement should be emphasized rather than plating speed. Confirmed reactive rates and possible false-negative indicators should be tracked initially and repeatedly.

All tests should be required to have the following components: (1) effective confirmatory steps and reagent addition checking steps to minimize false-positive and false-negative results; (2) ranges for all controls for positive and negative results; and (3) technologists to invalidate samples or runs if specific technical, operator or instrument difficulties are observed and documented. Recurring meetings should be held with test manufacturers, laboratories, and tissue and eye banks.
Manufacturers should be provided with samples that need to be validated and necessary testing parameters. Tests for deceased donors should be optimized. Consent should be obtained from donors to conduct research. An FDA Tissue and Eye Products Advisory Committee should be established because FDA’s existing committees do not have adequate representation from eye and tissue experts. The potential for highly processed deceased donor products to pose any infectious disease risk should be evaluated.

Test manufacturers, clinical laboratories, donor organizations and banks should collaborate in improving screening tests; resolving existing problems; providing effective confirmatory steps or tests that can reduce false-positive and false-negative results; and validating flexible sample types, shipping and testing windows. Input should be solicited from clients when new tests are planned. Wishes of donors and their families to help other persons with life-saving and enhancing transplants should be honored. The needless loss of organ, tissue and eye donors should be reduced. The safety of transplants should be improved. The lives of more transplant patients should be saved and enhanced.

**Infectious Disease Assays for the Future**

Dr. Andrew Heaton, of Chiron, began with six cases of HBV transmission from tissues and organs reported in the United States and Canada from 2000-2003. Litigation of these cases emphasized the need to never underestimate the cost of a live damaged recipient. In terms of regulatory authorities and priorities, FDA released eligibility determination for donors of human cells, tissues and products in February 2007. The European Union issued technical requirements for human tissues and cells. Australia and Health Canada have issued similar regulations for tissues and organs.

The early infection phase of HIV was recently analyzed with the original test, approved HIV test, new combination assays, and p24 assays. The study showed that NAAT dramatically reduced the risk and window period. A study on the viral load in early hepatitis C infection demonstrated the importance of NAAT sensitivity. Individual donation NAAT (ID-NAAT) or mini-pool NAAT was found to reduce window periods from 21 to 6 or 3.4 days for HIV; from 58 to 5 days for HCV; and from 44 to 38 or 18 days for HBV. The study demonstrated that ID-NAAT makes a dramatic difference in terms of safety.

Automated TMA is a single platform with positive sample ID throughout the process. A single thermal cycle and light emission analysis are used. The time to first result is 3.5 hours. TMA is a single tube assay that include magnetic bead capture and internal controls throughout the extraction phase. TMA is much more resistant than PCR to hemoglobin inhibition and performs well with contaminated samples. TMA amplifies several target regions of nucleic acids. Most amplicon is RNA and is simpler to decontaminate. The hybridization protection assay inactivates unbound probe and reduces the likelihood of contamination in the laboratory. TMA is the most sensitive HCV and HIV assay.
A clinical trial is being conducted in the United States on the PROCLEIX® HBV ULTRIO assay. Several studies have been performed in Belgium, Italy and South Africa to determine whether the reproducibility rate of the ULTRIO assay is false-positive or true-positive. The assay reduced initial reactive rates in all countries. A study was conducted in Namur and Belgium on Zeptometrix seroconversion panels and showed that pools diluted the assay and reduced the window period. The more sensitive and rapid TIGRIS assay is now available and allows results to be generated in less than 24 hours.

Published data were summarized focusing on the yield of specific assays for HIV-1, HCV, HBV and WNV. The study showed dramatic differences in pickup rates between HBV and the other viruses. A study was conducted in Spain, Poland and Italy on HBV NAAT yield to compare ID and mini-pooled NAAT. The study showed a yield of ~5 times higher with ID-NAAT due to the slow three-day doubling time of HBV. A study was conducted that showed a core positive patient would be ten times more likely to be NAAT-positive and the organ of the patient would be ten times more likely to have HBV.

Transfusion studies have shown a load effect of transfusion transmission between HBV and HIV. HBV was found to be extremely infectious, while HIV was found to be much less infectious. The study also showed an antibody effect. The front-end yield was found to be highly infectious and the tail-end yield with numerous antibodies was found to be less infectious. Poisson distribution is problematic in terms of defining risk due to the need to consider rare events and viral loads. ID-NAAT has nearly eliminated the HIV risk, but risks for HBV and HCV are still significant.

Capacity was recently added to the ULTRIO HIV and HCV assay to test for human progenitor cells in dilution. A dilution option for the assay will be pursued by the end of 2007. Sample availability has been expanded because the quality of tissue and organ samples is weaker than the quality of whole blood donors.

The globalization of blood banking also has implications for future infectious disease assays. The European Union parvo plasma standard for whole blood products is now applicable to the United States and most likely will evolve to include the tissue industry. The spread of WNV to South America has significantly increased requests for WNV testing. Three outbreaks of Dengue fever have occurred in Honduras, Puerto Rico, Latin America and Asia. Three organizations have requested the development of a Dengue test.

Dr. Heaton described several issues that need customer input and stronger partnerships between industry and users to enhance infectious disease assays in the future. Customers should clearly define sample types that need to be validated by industry. Customers and industry should convene in a forum to discuss the ongoing development of upcoming assays. The organ, tissue and blood communities should collectively explore strategies to harmonize regulatory needs to ensure consistency of testing, ease the burden of industry and minimize litigation in the future.
Opportunities should be identified for industry to provide support to customers for confirmatory, follow-up and reference testing. For example, industry has a strong interest in linking new tests to identify potential rejection and early infection. Novartis Pharma has access to a range of antiviral therapeutics that can be combined with tests for the prediction or treatment of rejection, prediction of infection, and potentially treatment of infection. This approach might facilitate the use and decrease the loss of low viral load organs due to a positive NAAT result.

Challenges and Limitations of Infectious Disease Assays for the Future

Mr. John Saldanha, of Roche Molecular Systems, emphasized that the safety of tissues and organs depends on the sensitivity and specificity of the test and the turnaround time to obtain results, particularly with organ donation. For the sensitivity of tests, donor questionnaires have not been found to be useful. Serological tests remove most positive donations. NAAT removes window period donations by ~30-32 days for HCV, ~21 days for HBV, and ~14 days for HIV-1.

A tradeoff exists between sensitivity and specificity with NAAT. Most notably, an increase in sensitivity results in a decrease in specificity with current assays. ID testing is more likely than pool testing to result in false-positive results. Capacity to resolve false-positive reactive results with tissue and organ donors is uncertain at this time. False-positive reactive results are due to the very high sensitivity of tests. Inhibitors cause invalid results that are more likely with samples from cadaveric donors due to hemolysis, breakdown of fluids within the body, nucleic acid degradation, and contamination with bacteria. These outcomes can be overcome in most cases by a simple step to dilute inhibitors prior to testing.

The sensitivity of the assay can be increased by manually lowering the fluorescent threshold, but this approach will increase the risk of a false-positive result. Another problem related to sensitivity of the assay is that consistently detecting extremely low levels of viremia is nearly impossible. The turnaround time for testing results is critical for organ donation, but shortening of the turnaround time is challenging due to the loss of sensitivity.

Roche’s current assays include the FDA-approved Cobas AmpliScreen HCV, HBV and HIV-1 tests. These tests allow for single extraction of nucleic acids, but three different NAATs are needed to analyze the three viruses. Roche has submitted its license to FDA for the next generation of assays, but has not received approval to date. The s201 test is an automated multiplex test for HCV, HBV, HIV-1 Groups M and O, and HIV-2. Roche’s future tests include a multidye solution for simultaneous detection and identification.

Roche’s next generation blood screening tests include the Cobas s201 platform to run the Cobas TaqScreen multiplex and WNV tests. The basic configuration of the s201 system includes up to four pooling systems, up to four AL workstations, and up to five DM workstations. The Cobas s201 blood screening system is automated for NAAT blood screening. The modular system accommodates various throughput requirements and supports multiple pool sizes, single donation testing, and simultaneous pooling for multiple assays. The available pool sizes are one and six samples per pool. Completely new software improves ease in using the test.
reporting results, controlling the system and auditing. The system is enabled for future menu expansion.

The Cobas TaqScreen multiplex assay detects HIV-1 Group M and its subtypes, HIV-1 Group O, HIV-2, HBV and its genotypes, and HCV and its genotypes. All viral targets are detected in channel 1, internal controls are detected in channel 2, and one negative control and five positive controls are included. The current Cobas TaqScreen multiplex assay is a two-channel system with real-time PCR chemistries that utilize different reporter days for targets and internal controls along with a single quencher.

Roche is currently developing version 2.0 of the Cobas TaqScreen multiplex assay. The multi-channel system will include separate channels for various target groups and internal controls. The system will allow for simultaneous identification of the target in a multiplex assay and also will have capacity to turn off a target that is not desired for testing. Roche has conducted a multiplex feasibility study and completed the development of the four-dye system.

Mr. Saldanha reiterated that the key challenges to organ and tissue donor testing include the loss of organs as a result of false reactive results from NAAT screening. This outcome raises the question of whether NAAT should be mandated. However, additional safety of organs and tissues can be obtained by NAAT screening due to window period donations. Current NAATs have a tradeoff between sensitivity and specificity. False reactive results actually might be very low reactive samples in Poisson distribution or true false non-reactive samples. Despite enhanced sensitivity compared to serological tests, NAAT will never capacity to detect all reactive samples.

Overall, NAAT is useful in providing physicians with additional information and striking a balance between the loss of organs due to possible false reactive results, the need of the recipient, and the medical perspective. NAAT has increased the safety of organs and tissues, but the limitations and challenges of this technology also must be recognized. Efforts should be made at this time to develop more specific assays rather than focusing on increasing the sensitivity of NAAT.

The TTSN Workshop participants made several suggestions that should be considered to enhance the ongoing and future development of diagnostic and screening technologies.

- OPOs should be strongly encouraged to routinely provide tissue banks with culture results and information on organ recipients on a timely basis.
- Infectious disease specialists should provide guidance to organ banks on handling recipients who become infected with WNV after transplantation.
- A proactive approach should be taken in promoting prevention. For example, the incidence of CNS is very high in the immunocompromised population due to therapies that are only supportive.
- Efforts should be made to improve significant problems in diagnostic and screening technologies. Most notably, no confirmatory steps are available in NAAT to detect WNV and other pathogens at this time.
• The nature, sensitivity and other parameters of assays should be clearly communicated for each test that is performed. This approach will assist in ensuring that appropriate investigations are conducted.
• UNOS should explore the possibility of requiring FDA-licensed screening tests for testing of organ donors.
• Communication between the blood and organ communities should be improved to ensure that institutions are notified of WNV or other pathogens in a community or region. This approach will facilitate requests for enhanced testing and decrease the number of false-positive results.
• Efforts should be made to develop new tests that are practical for the organ donation community and hospital-based laboratories. For example, new assays being developed by Chiron and Roche are too large, automated and expensive for these settings.
• The needs of the particular organ, eye or tissue donor should be extensively considered and discussed in the development of any new tests.
• New research studies should be initiated to demonstrate the speed by which hemodilution would be replenished and lose detectability of the sample.

In response to one of the suggestions, Ms. Hager announced that OPTN/UNOS Policy 4.0 would be issued for public comment in mid-June 2007 to obtain feedback on current gaps in the policy related to donor testing and disease reporting.

**INTERNATIONAL ALLOGRAFT COORDINATION**

Dr. Luc Noel, of the World Health Organization (WHO), reported that several objectives have been established for global vigilance and surveillance of cells, tissues and organs (CTO). The individual safety of the recipient and live donor will be enhanced. Appropriate corrective and preventive measures will be taken. Early detection of potentially recurrent risk will be followed. Global vigilance and surveillance will be optimized through advocacy, the commitment of health professionals and authorities, harmonization tools and organizational models. Communication will be ensured through a global network of collaborating centers. Biovigilance is viewed as a desirable capacity in the regulations.

A number of principles have been identified to guide global vigilance and surveillance of CTO. The actual donor or recipient is the common denominator in all health products of human origin. The safety of these products is a global issue due to the circulation of transmissible pathogens, donors and recipients, and products. The International Health Regulations were adopted in 2005 and will be enforced on June 15, 2007 to provide a legal framework for actions to prevent the international spread of disease. The regulations include several procedures for event management and requirements related to national disease surveillance and response systems.

Shared safety risks of human cell and tissue products include altered functional properties, transmission of a pathogen or disease by the donor, microbial contamination during the process, incompatibility, physiological interaction, and toxic risk of the process. The World Health Assembly adopted the “Human Organ and Tissue Transplantation Resolution” in 2004.
and charged member states as follows. Effective national oversight of procurement, processing and transplantation of human CTO will be implemented. Accountability of human material for transplantation and its traceability will be assured.

To support the resolution, WHO held global consultations in 29 countries with clinicians, practitioners and regulators. Reports from each country, professional organizations and regulators would be developed and distributed. The first global consultation on regulatory requirements for human cells and tissues for transplantation was held in Ottawa in December 2004. Conclusions reached by participants in the first consultation are outlined below.

Vigilance and surveillance should be incorporated at an early stage due to human origin, risk of transmissible agencies, susceptibility to microbial contamination, and minimal experience in clinical trials of processing methods or clinical use. Vigilance and surveillance should not be limited to adverse event reporting. Active and comprehensive surveillance should be included as well. Opportunities should be available for strong collaboration between clinicians, operators, regulators and policymakers in both the United States and international countries.

The second global consultation was held in Geneva in June 2006 to focus on global harmonization through graduated standards. The participants acknowledged that many countries are in the process of developing systems for vigilance and surveillance. The participants also recognized the pioneering value of WHO’s participation in the European Union Standards and Training in the Inspection of Tissues Establishment (EUSTITE) Project and regulatory approaches and systems for vigilance and surveillance.

Conclusions reached by participants in the second consultation are summarized as follows. A global aspect should be incorporated into vigilance efforts to ensure that risks and events are communicated and appropriate actions are taken. The WHO Global Knowledge Base on Transplantation should evolve to serve as a global source of information on risk. The development of tools for intercommunication between national and regional programs should be required.

The European Commission issued a directive in 2004 to establish standards for the quality and safety of donations, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. The preamble of the directive emphasized the desirability to develop worldwide standards on tissue and cell therapy due to intensive global exchange. Articles 5-7 of the directive address supervision of human tissue and cell procurement; accreditation, designation, authorization or licensing of tissue establishments and tissue or cell preparation processes; and inspection and control measures.

Article 8 of the directive addresses traceability of all tissues and cells from the donor to the recipient and vice versa; implementation of a donor identification system; and assignment of a unique code to each donation and its associated products. Article 11 of the directive addresses vigilance surveillance to assure the availability of a system to report, investigate, register and transmit information and also to clarify reporting requirements for all persons or establishments using human tissues and cells regulated by the directive.
In further support of vigilance for human tissues and cells, the directive contains specific definitions for "serious adverse events" and "serious adverse reactions." The directive also clearly outlines the process for the exchange of information among tissue establishments, organizations responsible for human application, the European Commission, competent authorities and procurement organizations.

The EUSTITE Project is co-funding €2.5 million and includes 12 partners throughout the world. The time frame of the project is December 2006-November 2009 and was established to address inspections of tissue establishments, adverse events and reporting of reactions. WHO is the main partner in the development of a model for reporting and investigating adverse events and reactions. The first EUSTITE meeting was held in Madrid in March 2007 with partners from the United States and Canada. The second EUSTITE meeting will be held in Rome in July 2007 with WHO global representation from all regions.

Similar to TTSN, global efforts are underway to develop tools for harmonized guidance and technology. The tools are being designed with a clinical description, grading severity, assessment of imputability, and evaluation of critical elements at each stage. The tools will include triggers to identify and report serious adverse events or reactions, a list of known cross-cutting and product-specific trigger situations, and guidance in the following areas: principle awareness of possible unknown risks; generic situations; and examples of situations to strike a balance between standardization, simplicity, spontaneity and the clinician's primary report.

The tools also address management and system components, such as simple solutions; encouragement of reporting with incentives and linkages to clinical staff; structured networks at national, global and European levels; focal points for responsible organizations and persons; linkages to other vigilance systems for blood, devices and drugs; utilization of the Internet with e-mail and web sites; and rapid alerts and feedback.

International coordinated efforts also are focusing on coding systems. Participants at the second global consultation in 2006 on regulatory requirements for human cells and tissues for transplantation recognized the indisputable need for globally standardized labeling, coding and description of tissues. The participants reached the following conclusions. Opportunities should be available for harmonized collaborations before individual countries or regions develop disparate systems. WHO should play a leading role in this effort. During the consultation, a commitment was made to one global coding system for cellular therapy products by relevant scientific and professional societies at the global level.

Two regions of the world have an identified need for a coding system for human cell and tissue products. As an initial step in addressing this issue, the “Second Global Consultation on Critical Issues in Transplantation Toward a Common Global Attitude to Transplantation” was held in March 2007 in Geneva. A number of key points were made during the consultation. Quality and safety are key issues of human CTO transplantation because risks are real. Surveillance should be implemented based on codification, traceability and capacity to maintain
confidentiality. A strong recommendation was made for WHO to lead global traceability efforts by producing an international shared coding system for CTO.

The outcomes of the 2007 consultation led to the following resolution that will be proposed to the WHO Executive Board in January 2008. Creation of a global network of collaborating centers on vigilance and surveillance for CTO transplantation should be encouraged. WHO should facilitate adoption of a common global basis for a CTO transplantation coding system.

In preparation of taking action on the resolution, WHO drafted two new guiding principles for transplantation with the following language. Quality of care, safety and efficacy of procedures are mandatory for both donors and recipients. Long-term outcomes of CTO donation and transplantation should be assessed for both donors and recipients to document the benefit and harm to recipients and living donors.

The level of safety, efficacy and quality of human CTO for transplantation as health products of an exceptional nature should be maintained and optimized on an ongoing basis. This approach will require implementation of quality systems, including traceability and vigilance with adverse event and reaction reporting. The organization, execution and clinical results of donation and transplantation activities should be transparent and open to scrutiny, while assuring that the anonymity of donors and recipients is always protected.

The TTSN Workshop participants made several suggestions that should be considered to strengthen global vigilance and surveillance of CTO and enhance coordination between the United States and international countries.

• Logistical issues to safely transfer CTO into the United States should be addressed. For example, CDC has encountered problems in transferring bone marrow and hematopoietic stem cells from Europe to the United States due to inconsistent packaging and labeling that confuse customs officers. This issue has prompted CDC’s quarantine medical officers to rescue products. Other federal agencies also have encountered problems in attempting to pass airport security measures with bone marrow. The Transportation Security Administration now requires originals rather than copies of official authorizations to bring bone marrow into the United States. WHO and other international organizations should provide assistance to the United States in approving CDC’s request. CDC has asked bone marrow registries that transplant stem cells from other countries to standardize labeling and inform U.S. Customs and Border Control of the need to distribute a directive to all 5,000 customs agents in all 473 U.S. ports of entry. This approach would ensure that no products are lost.

• Stronger efforts should be made to ensure that all member states establish and adhere to guidelines on the transfer of organs and tissues from other countries to the United States. This process would assure the viability of CTO.

• Global vigilance and surveillance systems should be developed with feedback mechanisms when products are transferred from the United States to other countries and additional testing is performed outside of the United States.
• A clearly defined checklist should be developed with specific tasks to facilitate easy entry of tissue and organs into the United States. The checklist also should outline the roles and responsibilities of CDC, DHS or UNOS in this effort.

EFFORTS TO ADDRESS LESS COMMON DONOR-DERIVED TRANSMISSIONS

The Need for Diagnostic and Epidemiologic Algorithms Based on Lessons Learned from Recent Investigations

Dr. Kuehnert described several challenges in diagnostic and epidemiologic algorithms. The absence of specimens for testing might hinder diagnosis. The disposition of tissues depends on the interpretation of recipient adverse events. Clinical management decisions rely on available donor information. To address these challenges, resources must be balanced due to differences in safety measures and availability of blood, organs and tissues.

With the exception of HIV, organs from donors with a positive screening test or confirmed medical condition that might be transmitted may be transplanted at the discretion of the transplanting program with the informed consent of the recipient. All other suspected or confirmed transmissible conditions may be transplanted at the discretion of the transplant center. However, OPTN policy was recently modified with an extensive list of conditions in which communication between the OPO and transplant regarding the disease must occur.

New reporting rules also were issued in 2005 regarding tissues. FDA’s Good Tissue Practices require HCT/P manufacturers to report certain adverse reactions involving a communicable disease. The Joint Commission’s tissue issuance and storage standards require hospitals or other organizations that store or issue tissue to develop and maintain procedures to investigate adverse events involving recipients and also to promptly report cases of post-transplant infections or adverse events to the source facility.

Despite these reporting rules, challenges still exist in diagnostic and epidemiologic algorithms. Over eight days in a rabies case, a hospital contacted a health department about a patient with suspected encephalitis. CDC was contacted to “rule out” suspected rabies. The case also was referred to CDC’s Unexplained Illness and Deaths Program. Further investigation revealed that the patient was also an organ donor. The OPO and UNOS were notified about the suspicion of encephalitis and possibly rabies. The three recipients were rapidly tracked and reportedly had no problems according to information given to the CDC.

On days 23-28, CDC contacted the transplant center to follow-up and update the status of the recipients. The transplant centers upon this inquiry reported the deaths of two of the three recipients. UNOS was notified of these deaths. During this time, surgeons were unaware of links to the potentially infected donor. Autopsies were not performed on any of the recipients. Specimens and medical records of the deceased recipients were not immediately available.
CDC was unable to establish a transmissible disease link, but ruled out rabies in the donor based on antibodies.

CDC’s five investigations from 2002-2005 revealed >20 recipients with viral encephalitis-related illnesses with the majority of these cases being fatal. Nearly all donors had a presumed non-infectious cause of death, but some donors had evidence of encephalitis at the time or in retrospect. The risk of using donors with encephalitis is unknown and remains a controversial issue.

In CDC’s investigation of a WNV case, a kidney recipient developed neurologic symptoms three weeks post-transplant and died. The autopsy confirmed WNV meningoencephalitis. The donor sample was located, but an autopsy was not performed. The donor sample was PCR-negative and IgM-positive specifically for WNV. Follow-up performed by the hospital showed that other organ transplant recipients were IgM-negative, but PCR had not been performed at that time. Musculoskeletal tissues, heart valves and skin were procured from the donor and quarantined, but none of the tissues were used.

CDC communicated its finding of “evidence of possible WNV transmission” to the surgeon six months post-transplant. The hospital was not convinced of CDC’s finding that the recipient event was transplant-related. The tissue bank medical director contacted CDC nine months post-transplant to ask whether the tissue could be used. However, the tissue bank was unaware of the donor results, recipient autopsy or results. Agreement was reached on the significant possibility of transmission. The tissue was discarded after a review of results and FDA was notified about all aspects of the case.

WNV can be transmitted to organ recipients despite negative PCR results and the presence of IgM antibody in the donor. Results of recipient autopsies and further donor testing might not be readily available to OPOs and tissue banks. Protocols have not been established to address situations in which public health authorities, OPOs, tissue banks and hospitals disagree on the interpretation of test results.

In CDC’s investigation of a TB case, a child eight months of age developed a persistent fever following a liver transplant. An abscess was drained and found to be acid-fast bacillus (AFB) positive. The child had a questionable risk factor for TB based on close contacts who were purified protein derivative-positive, but had no evidence of active TB. Other patients who received two kidneys and the other half of the liver from the same donor were tracked and reportedly had no problems. These findings raised questions regarding the epidemiology of the donor, whether TB was transplant-transmitted, or if the other recipients should be placed on prophylaxis versus treatment.

The CT scan of the donor revealed “patchy” opacities in the right middle and left upper lobes. Contusions were likely associated with trauma from the donor’s motor vehicle accident. Bronchoalveolar lavage was negative. Organ or tissue donation was not contraindicated. The condition of the child who received the split liver was poor. The child had pulmonary nodular lesions and was placed on four drugs for TB treatment. The adult who received the remainder...
of the liver was asymptomatic and was not placed on TB medications. Both kidney recipients were asymptomatic, but one was placed on isoniazid for prophylaxis and the other was placed on a three-drug TB regimen.

Based on a re-review of the CT scan, the donor was found to have cavitary lesions. Bronchoalveolar lavage was performed for bacterial culture rather than for AFB smear. The donor might have been a foreign visitor from an Asian country. TB in the donor was considered to be likely following an investigation by state and local health departments. The investigation emphasized the need to consider foreign-born persons to be at risk for TB and recognize that active disease might be asymptomatic. TB might be disseminated, controlled and then reactivated with immunosuppression. Management of recipients might depend on information that can be obtained from donor results.

CDC learned several lessons from these investigations. Information on suspected transmission is not well known or communicated in all cases. Confusion exists on roles and responsibilities. Standard detection and surveillance tools are critical to investigations. Certain data are essential for a thorough investigation. The lack of adequate laboratory specimens in doors and recipients presents a tremendous challenge. Autopsies in both donors and recipients are a critical need.

A number of groups can provide assistance in investigations, including OPOs, transplant centers, UNOS, HRSA, FDA, and state and local health departments. CDC also can provide specialized assistance from its Blood, Organ and Other Tissue Safety Office that serves as a coordinator and link to UNOS; the Infectious Diseases Pathology Activity; the Unexplained Deaths Project; and pathogen-specific laboratories, such as those focusing on arboviruses, rabies and herpesviruses.

Overall, roles and responsibilities should be clearly defined. Algorithms for trace-back should be developed. Contingencies should be created for suspected transmission cases, such as suspected infected donors and adverse recipient outcome clusters. Thresholds should be established for investigations to trigger a public health response and network notification. For example, an investigation-triggered response to evaluate transmission should prospectively outline anticipated needs for notification, samples, syndromic surveillance and record review. This type of response should be initiated by clinicians who request assistance in the diagnosis of a donor or recipient.

A routine response to evaluate transmission should include an autopsy and collection of pre-/post-procurement serum and cell samples from donors. Real-time follow-up of transplant outcomes should be performed for recipients. These efforts should be made in a stepwise process. Structured information should be shared between OPTN/UNOS and partners first. Transplant clinicians should have access to available data to improve communication. Investigation forms and notification algorithms should be improved. Health departments should be educated. In an initial step to enhance education, transplantation issues will be discussed during the annual meeting of the Council of State and Territorial Epidemiologists in June 2007.
Dr. Kuehnert reiterated the critical needs in diagnostic and epidemiology algorithms. Procedures for investigations are poorly defined. Algorithms should be feasible and involve more rigorous specimen collection and recipient follow-up. This approach should not adversely impact availability. A workgroup should be formed to discuss implementation of these options. Education should be provided on diagnostic capabilities of CDC and other partners.

The Emerging Role of Pathology in Identification of Transplant-Associated Infections

Dr. Sherif Zaki, of the CDC Infectious Diseases Pathology Branch, explained that the 1992 IOM report outlined several factors in the emergence of infectious diseases in the context of transplantation, including human demographics and behavior, technology and industry, economic development and land use, international travel and commerce, microbial adaptation and change, and breakdown of public health measures. Moreover, a case that showed an association between prairie dogs and human cases of monkeypox was published in the literature in 2003.

Infectious disease pathology plays a critical role in public health. Pathologists are among the first healthcare workers to encounter infectious disease outbreaks and also are in an excellent position to discover EIDs. Pathologists extensively engage in collaborative research projects with epidemiologists, clinicians, veterinarians and microbiologists to elucidate infectious diseases. Autopsy is increasingly being viewed as an effective surveillance tool. Several examples of recent EIDs were diagnosed through autopsies. Pathologic specimens can serve as sentinel indicators of emerging pathogens.

The syndromic approach to diagnosing EIDs includes a histopathologic pattern to determine the source of disease from hemorrhagic fever, pneumonia, pulmonary hemorrhage, encephalitis or rash. The multidisciplinary laboratory approach includes basic and contemporary techniques, such as culture, serology, immunohistochemistry and molecular testing. Recent investigations of organ and tissue allograft-associated infections have focused on WNV, LCMV and rabies. These investigations have highlighted transmission-related issues and identified a number of challenges and opportunities for improved prevention and control.

A WNV cluster in August 2002 showed that all four transplant recipients had unexplained fever and three had a change in mental status. The four patients received a liver, heart and two kidneys organs from the same donor. The Georgia Department of Health contacted CDC due to unexplained encephalitis in three recipients from the same donor. The kidney recipient died with IgM-negative WNV and an autopsy was performed. The case emphasized the need for immunohistochemistry, interpretation of seronegative results and autopsy.

The liver was transplanted into a patient 40 years of age with alcoholic cirrhosis. The patient developed fever, elevated hepatic transaminases and leukopenia one week post-transplant. Liver biopsies showed cetrilobular necrosis and changes that were consistent with mild
rejection. Results from herpes, adenovirus and cytomegalovirus tests were all negative. The patient died on post-operative day 18 and an autopsy was performed. The two remaining organ recipients died as well.

The male donor was 51 years of age and was declared brain dead after being admitted to the hospital with a large right subdural hematoma. Results from all screening tests were negative. Serology, PCR and immunohistochemistry did not show evidence of WNV in the donor.

The Wisconsin Department of Health contacted CDC in December 2003 regarding the deaths of multiple organ recipients from a common donor at a single medical center. The OPO was contacted and all stored tissues were quarantined. Selected biopsy and autopsy tissues were sent to CDC for evaluation, revealing LCMV. The investigation demonstrated the value of tissue culture in identifying the agent.

In May 2005, CDC received a report of severe illness in four patients who had received solid organ transplants from a common donor. The medical history of the donor was remarkable only for hypertension and CNS herniation. Results of all tests performed on the donor were negative and the organs were recovered and donated. However, additional tests were positive for LCMV. One of the patients in this cluster recovered.

CDC’s investigation revealed that the donor’s daughter had a pet hamster that was sick. The donor did not have direct contact with the hamster, but did clean the cage. Animals maintained in the facility were found to have high rates of infection based on immunohistochemistry of the organs of these animals. The investigation demonstrated that reviewing the history of the donor is a better approach to determine possible exposure because current laboratory tests are not effective in screening for LCMV. However, massively parallel sequencing (MPS) is a new technology that is 100 times faster than Sanger sequencing. MPS produces sequences for 25 million bases in four hours. MPS was used in the cluster of three patients in Australia who received LCMV following organ transplantation from the same donor.

In June 2004, CDC was contacted by a pathologist in Texas regarding the deaths of three patients who received a liver and two kidneys from a common donor. Tests were highly suggestive of rabies. The donor had previously presented to two different hospitals with hyperventilation, anxiety, nausea and vomiting. The donor was 20 years of age, agitated, confused and delirious. The donor was intubated in the emergency room, had a urine drug screen that was positive for cocaine, and suffered a heart attack.

The donor’s organs were collected following death from a subarachnoid hemorrhage. The investigation revealed that the donor had informed friends of a previous bat bite. Residents in the same apartment complex indicated a bat infestation problem. The donor’s serum was positive for anti-rabies antibodies. A sequence analysis showed the same strain in all three recipients. A rabies variant from the Mexican free-tailed bat was confirmed as the common source.
Findings from an autopsy review of another death from encephalitis showed consistency with viral encephalomyelitis and suspected WNV. The deceased patient had received a liver transplant from a different donor. The pathologist sent the specimens to CDC for evaluation. CDC’s analysis revealed another case of rabies, but a number of questions could not be initially answered in terms of whether rabies was naturally occurring, transplant-transmitted or healthcare-associated and if the recipient and a second donor were infected.

Dr. Zaki summarized several lessons from CDC’s epidemiologic investigations. Unexpected exotic and zoonotic infectious agents might be transmitted through blood transfusion and organ transplantation. Traditional and contemporary diagnostics are important in epidemiologic investigations, including culture, serology, immunohistochemistry, histopathology and molecular testing. Several recent clusters of transplant-transmitted EIDs emphasize the need to improve awareness and education of clinicians and pathologists, such as the second LCMV cluster, the “LCMV-like” transplant cluster in Australia in 2007, and the second cluster of transplant-transmission of rabies in Germany in 2005.

A thorough clinical history and evaluation of donors are critical to epidemiologic investigations, particularly to determine animal and pet exposures. The development of post-transplant surveillance should be strengthened with unique tissue donor IDs, better banking of donor tissues, enhanced screening strategies and cluster identification.

Donor-Related Malignancies in the UNOS Transplant Tumor Registry

Dr. Myron Kauffman, of UNOS, reported that UNOS began collecting data on transplant-related tumors in 1994. A summary of cases of donor-related tumors (DRTs) in 47 recipients in 1975 showed that 17 recipients developed donor cancer; six of eight recipients died from donor cancer; and two recipients immunologically rejected their cancer after immunosuppressive drugs were stopped. One of these recipients was successfully re-transplanted several years later. An active malignancy was detected in the donor. After the transplanted kidneys were removed from the surviving recipients, immunosuppression ceased and the patients were returned to hemodialysis. The study provided the first evidence of immunologic rejection of cancer.

UNOS defines DRTs in two ways. “Transmitted” tumors are cancer cells that are mechanically transferred with the organ either in the blood or the actual organ. These types of DRTs are most common. “Derived” tumors include the development of de novo cancer in donor cells. These types of DRTs are typically lymphoid and hematogenous.

UNOS conducted a study from April 1994-December 2004 with a cohort of 61,024 living kidney and liver donors, 65,930 deceased donors, and 202,233 cadaveric organ recipients. For DRTs, 25 of 65,930 deceased donors had DRTs for a DRT rate of 0.04%. Of 202,233 deceased donor transplants, 37 had DRTs for a transplant-related rate of 0.018%. Of 58,257 living kidney donors, four tumors developed for a living donor rate of 0.006%.
For donor-transmitted tumors (DTTs), 19 of 65,930 deceased donors had DTTs for a DTT rate of 0.03%. Of 202,233 deceased donor transplants, 31 transmitted tumors for a transplant transmission rate of 0.015%. Post-transplant lymphoproliferative disease (PTLD) that developed in lymph node tissues accompanying the organs was the cause of donor-derived tumors. However, many of the patients survived because PTLD is treatable. Of 88 liver, kidney, lung, heart and kidney/pancreas transplants that were at risk, the tumor transmission rate ranged from 30%-100%. Tumor transmission rates for the liver and lung were found to be significant.

Of 202,233 deceased donor recipients, 23 donor-related deaths occurred for a death rate of 0.01%. The death rate was 0.012% in 18 transmitted tumor deaths. These data demonstrated that mortality from a transmitted tumor is extremely rare. Over the ten-year period of the study, 58,747 patients on the wait list did not receive an organ and died. Of the patients who died, 28,587 did not receive a life-saving organ of the liver, heart or lung. During this same time period, 12,620 patients developed de novo post-transplant malignancies.

The UNOS Patient Safety Committee (PSC) was established in 2006 for OPOs or transplant centers to report any confirmed, suspected, or potential transmissible disease or malignancy to UNOS. UNOS would then notify all recipient centers, tissue banks and OPTN. In 2006, 8,015 deceased donors, 25 donor-related infections, and 24 donor-related malignancies were reported to PSC. Of the donor-related infections, 13 were viral from WNV, HCV, HBV, HTLV or Epstein-Barr virus; five were bacterial from mycobacteria, listeria, acinetobacter, pseudomonas or syphilis, three were fungal from cryptococcus; and four were parasitic from toxoplasma and schistosomes.

Of the malignancies reported to PSC, ten were from incidental renal cell carcinoma (RCC); two were from incidental thyroid; one was from glioblastoma multiforme; one was from leukemia of a living-related donor; and ten were from tumor transmissions of lung, undifferentiated and ovarian cancers, lymphoma, Kaposi cell carcinoma, and neuroendocrine carcinoma. Incidental RCC is not a rare event. The mean age of patients who developed incidental RCC following transplantation was 53 years with a range of 29-68 years. The tumor size ranged from 0.1-3.0 cm. Intracranial hemorrhage was the cause of death in four patients. The transplanted organs included two hearts, seven livers, 12 kidneys and one pancreas.

A study was conducted on 70 incidental RCC cases with a tumor size <2.5 cm. No evidence of recurrence was seen post-transplant. The study showed an extremely low incidence of transmissibility of small RCCs, but more data are needed to confirm whether organs with these small tumors can be safely transplanted. A study was conducted on 141 localized RCC cases with a tumor size <2.5 cm. The recurrence rate was 1.4% at five to ten years post-transplant. The same study showed that in 165 cases, the recurrence rate was 5.5% at five to ten years post-transplant with a tumor size 2.5-4.0 cm.
PSC’s last follow-up showed that tumor transmissions involved ten donors, 30 recipients, 14 transmissions and seven deaths. Causes of deaths included three adenocarcinomas of the lung, two melanomas, one ovarian tumor and one small cell.

Dr. Kauffman reiterated that small RCCs are frequent, but the potential for transmission of these tumors is low. The possibility exists to excise RCC and transplant kidneys. Deceased donor kidneys should be carefully examined. A history of melanoma is a contraindication to organ recovery. Non-traumatic and non-hypertensive intracranial hemorrhage should be considered as tumor metastasis until proven otherwise.

The TTSN Workshop participants made three key suggestions that should be considered in future investigations of less common donor-derived transmissions.

- Surveillance should be increased or specifically targeted to patients who receive organs from substance abusers, incarcerated persons and other high-risk donors to determine transmission of infectious diseases.
- Actions should be taken at this time to strengthen epidemiologic investigations of less common donor-derived transmissions. For example, the fundamental components of properly taking a donor history should be clarified and reinforced. Electronic medical records should be widely implemented to link seemingly unconnected events in multiple medical institutions that are actually related.
- An information sheet should be developed to assist physicians in counseling recipients on potential risks, particularly for tissues and organs from high-risk donors.

OPEN DISCUSSION

The workshop was opened for all of the speakers to clarify any aspect of their respective presentations and answer questions posed by the participants. The open discussion session also provided an opportunity for the participants to make additional comments or pose more questions to the speakers.

During this session, the TTSN Workshop participants identified the following issues that should be considered in the ongoing development of TTSN.

- Improved reporting of transplant-related adverse events to FDA.
- Responsibility of end-users to enter and correct data in TTSN.
- Irradiation and biomechanical effects from bone grafts and tendon transplants.
- Sterility in package labeling.
- Future research to support the possibility of upgrading culture media to include fungus.
- Efforts to change behaviors of clinicians in notifying tissue banks earlier in the reporting process.
• Modification of FDA’s current reporting requirement in which FDA would notify all entities involved in the adverse event because FDA serves as the repository of this information.

• Inclusion of two screens on the TTSN web site for end-users to input two different entries, such as two implants from two different tissue banks.

• Development of rules, procedures and confidentiality policies to make the TTSN data set available to physicians, researchers and public health authorities.

• Clear guidance on roles and responsibilities of conducting academic and applied research with TTSN data.

• Clear guidance on CDC’s ownership and decision-making authority regarding the release of TTSN data.

• Clear guidance on responsibilities of paying for the long-term maintenance and sustainability of TTSN data at the end of the UNOS three-year cooperative agreement.

• Establishment of collaborative efforts to facilitate international exchange of organs and tissues, such as the development of a uniform coding system encompassing blood, tissues, organs, corneas and eye products.

• Agreement on uniform implementation of International Society of Blood Transfusion standards rather than the use of different donor numbers.

• Development of a uniform template to assist surgeons in outlining the risks, benefits and options for transplantation of blood, organs and tissues.

• Development of an online module to assist physicians and nurses in complying with HIPAA when requesting informed consent for tissues and organs.

• Enhancement of patient education by providing patients with access to information on informed consent issues for organs and tissues.

• Wide distribution of best practices in obtaining informed consent for tissues and organs, such as tape recording all conversations between the surgeon and patient.

• Clarification on the risk of xenografts versus allografts and the potential need for a different type of informed consent for xenografts.

• The need for extra screening of donors with an unexplained or untreated mental status, such as performing an “emergency” autopsy and examination of the brain on the same day organs are procured.

• Revisions to existing donor questionnaires to include new questions on bat bites, “cave walking,” and exposure to hamsters or mice.

• Development of a biological model to test recipients in a timely fashion rather than adding other serological tests for WNV and other pathogens.

• Broad implementation of clinician behavior modification activities to increase utilization of TTSN, such as a centralized approach in which only a few staff members would be required to enter data in a prospective manner before tissues are released.

• Efforts to promote dissemination of real-time information, such as mandatory recalls from FDA and voluntary recalls from tissue banks to retrieve tissues from the system.
NEXT STEPS

Dr. Kuehnert described a number of actions that would be taken to support the ongoing development of TTSN. The Advisory Group would continue to develop TTSN with extensive input from partners. The remaining TTSN funds would be used to convene an “implementation workshop” in 2008 and pilot TTSN in a few institutions prior to national implementation. Part E of TTSN, “Community Education,” would be extensively incorporated into the development phase. Discussions would continue on releasing a new cooperative agreement for the implementation of TTSN because the UNOS cooperative agreement is limited to development of the system.

Dr. Kuehnert pointed out that several participants emphasized the need to conduct three major activities beyond TTSN. First, surveys of current screening and other testing practices in transplantation should be widely administered. Second, a workshop should be convened to specifically focus on testing challenges and opportunities in transplantation. Although the TTSN cooperative agreement does not have sufficient funds to support a testing workshop, this activity would be prioritized and thoroughly discussed by CDC and its partners.

Third, a governmental committee should be established to provide a forum for discussing organ and tissue safety issues. The Blood Safety and Availability Advisory Group is considering the possibility of serving in this capacity. However, a non-governmental forum also should be available for external stakeholders to discuss specific issues that are not directly related to public health, such as industry concerns regarding testing, studies with animal models and outcome research.

CLOSING SESSION

Drs. Kuehnert and Fishman thanked the presenters, participants and planning committee for their respective contributions in the TTSN Workshop. They also acknowledged UNOS’s outstanding efforts and activities in the development of the overall TTSN project. Dr. Kuehnert particularly noted that input provided during the workshop would be extremely valuable to CDC and its partners.