Infections and Screening: Solid Organ Donors

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April 23, 2007: New virus caused transplant deaths in Australia

- “WASHINGTON (Reuters) - A previously unknown virus has killed three organ transplant patients in Australia….
- The three patients all received organs [liver, two kidneys] from the same donor….They analyzed the organs and found little pieces of a virus related to lymphocytic choreomeningitis virus or LCMV, a rodent virus that occasionally infects people and that has also been linked with disease in organ transplant patients.”

Background

- The virus was discovered after the deaths of three women, aged 63, 64 and 44. They had received the liver and kidneys of a 57-year-old organ donor who died of a brain hemorrhage in December 2006 shortly after returning to Australia from an extended stay in Europe.

Confusion

- UPI: “Victoria’s acting Chief Health Officer…told the Australian Broadcasting Company that the virus does not pose a risk to the community as a whole as **it was not believed to be an infectious disease**.”

Conclusions

- "The transplant program saves many hundreds of lives every year. This is a one-off event.“
- The introduction of tests for the new virus [will] be discussed….
- **The more tests that are done the longer the delay (in) … transplanting the organ. If someone is terminally ill waiting for an organ, you don't want to delay that procedure to undertake tests that may not be properly validated yet or tests that are to look for an extremely rare event."**

Not a unique event! (but uncommon)

- Lymphocytic choriomeningitis (LCMV, hamsters and rodents) → 3 outbreaks (2 in USA) with 9 deaths
- Rabies virus (bat bite) → 2 known outbreaks with 5 deaths in USA
- West Nile virus (mosquitoes and birds) → now less common but 2002-2003 outbreak with 4 infections 1 death, 3 encephalitis, 2 with some permanent neurological damage
- Chagas' Disease (Trypanosoma cruzi) 2 transmissions over ~4 years
- Herpes simplex virus – not rare (2 died in Boston despite knowing the pathogen)

OK, then let's screening every donor for everything!!
--or not??

What are we screening?

- Solid organs: ~28,000 transplanted from ~8000 deceased donors each year
- Solid Organ Waiting list candidates: 96,374 as of May 4, 2007
  - Kidney - 71,506
  - Liver - 16,890
  - Pancreas - 1704
  - Kidney / Pancreas - 2347
  - Heart - 2800
  - Lung - 2760
  - Heart / Lung - 124
  - Intestine – 227
- All will receive immune suppression to prevent immunologic graft rejection

6600 Americans die each year waiting for an organ

- Organs must be used in 4-24 hours after procurement →Testing/screening must be available 24/7
- CANNOT waste organs for FALSE + ASSAYS and cannot discard “possibly” infected organs; people die when organs are not available – each + test must be confirmed
- Testing is different than for blood products – no “batch” testing, approved assays not available for many organisms for organ donor testing

Detecting Pathogens in Organ Donors

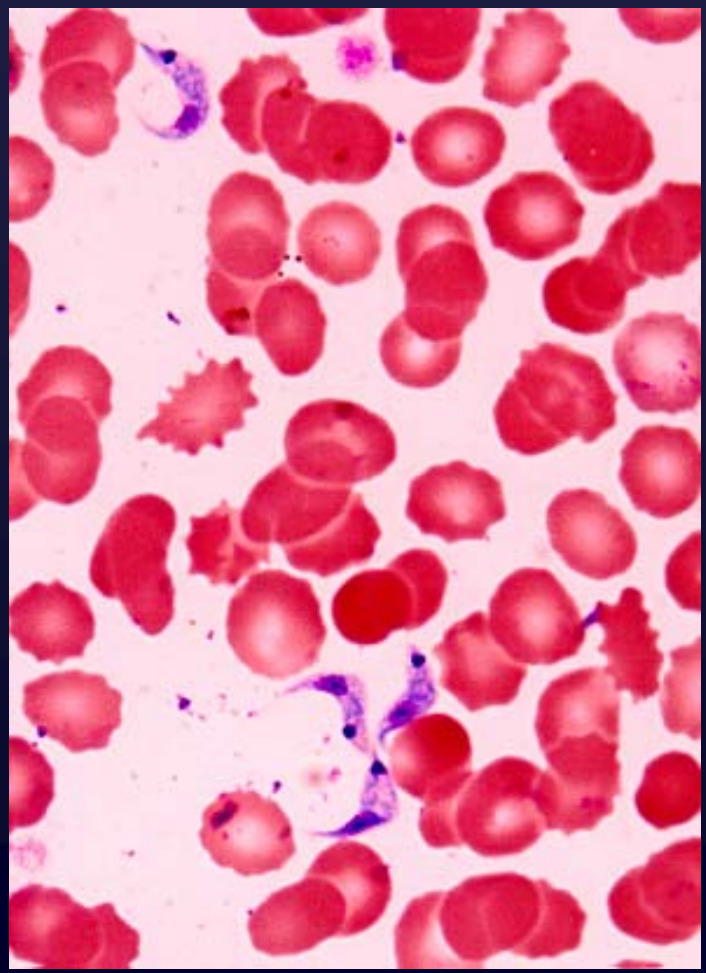
- Immune suppression – infection is at least four to five times (possibly more) more likely in the transplant recipient than in normal individuals (e.g., infected by transfusions)
- Improved diagnostic assays (molecular) – do they work?
- Broader social and geographic backgrounds of donors & recipients

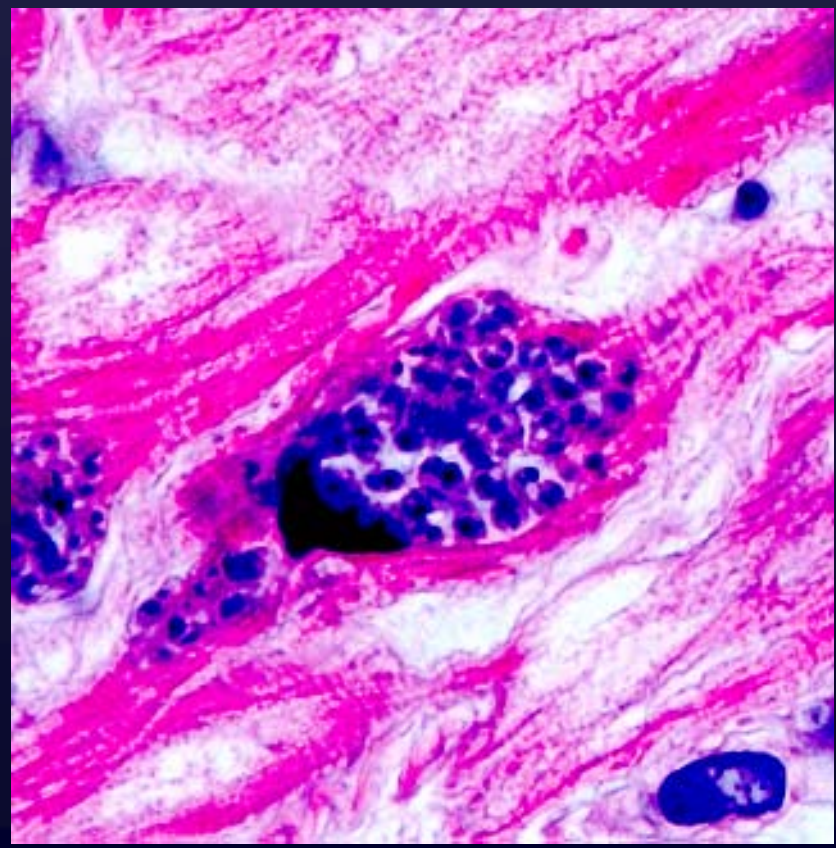
Wilck M, Fishman JA. The Challenges of Infection in Transplantation: Donor-derived infections. Current Opinion in Organ Transplantation 10:301-306, 2005.

Types of Infection Transmitted with Solid Organ Transplantation

- Bacterial infection: bacteremia or infection of tissues
- Fungus: fungemia or colonization
- Parasites: latent infection or acute infection
- Viruses: latent infection and viremia
- Prions: infection

Donor-derived Chagas' Disease after Cardiac Transplantation





Courtesy of B. Kubak

Transmission Events Reported to UNOS/OPTN/DTAG

Pathogen	Clinically Significant?
Histoplasma	Yes
Cryptococcus	Yes, No
Candida species	Yes
VRE, MRSA	Yes
Toxoplasma (3)	Yes
T. cruzi	Yes
LCMV	Yes
CMV	Yes
Listeria	not transmitted (donor culture)
Influenza A	No
Tuberculosis (2)	Yes, No
West Nile Virus	False + assay
HIV	False + assay (x2)

What does screening for SOT mean?

- Social History (to exclude high-risk behaviors)
- Blood and urine cultures (results available after implantation)
- Serologies: syphilis, HIV, CMV, EBV, HSV, VZV, HBV (SAg, anti-HBs), (Toxoplasma)
- Review of microbiology data

Note: Screening of deceased organ donors must be preformed on a 24/7 basis, usually within 6-8 hours of death to allow the organs to be used.

Consider two aspects of screening

- **Detection – how well does it work?**
  - Availability of approved assays (esp. new tests)
  - Sensitivity - need to exclude risk
  - Specificity – donor shortage vs. false + assay
  - Timeliness – organ use in 4-24 hours
  - Cost (assays and personnel)
- ***Communication (pre- & post-transplant)***
  - Speed - physicians determine risk/benefit
  - Accuracy of information
  - Data to correct people for timely intervention (Public Health + care providers) post-Tx

How To Approach Screening?

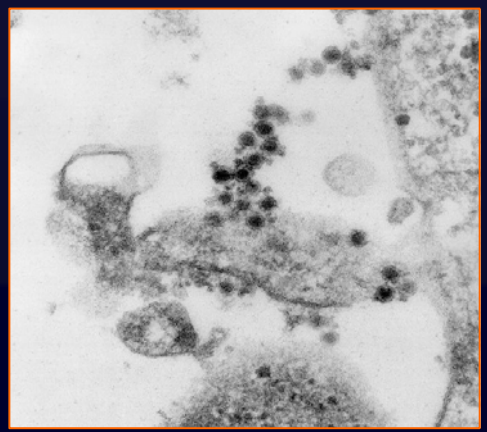
- Consider assays in terms of both sensitivity and timing of “conversion” to positive test
  - Serologies – may be negative in acute infection (up to weeks in normal host)
  - Antigen tests (HBsAg, respiratory viruses) – not available for all organisms
  - NAT: Nucleic Acid-Amplification Testing – highly sensitive, false + assays common, not available for all pathogens, costly, specialized labs

Imperfections of NAT

- Recent cases of West Nile Virus (NY/PA) blood testing on donor was negative by PCR (degraded samples) while tissues were positive in recipients
- Recent cases of LCMV (US, Australia) – virus never detected in donor blood or tissues – even with improved, specific molecular assays – amplified in recipients
- Recent cases of rabies (US and Europe): No history of bat bite until after the recipients had become ill
- Which are the “correct” assays?

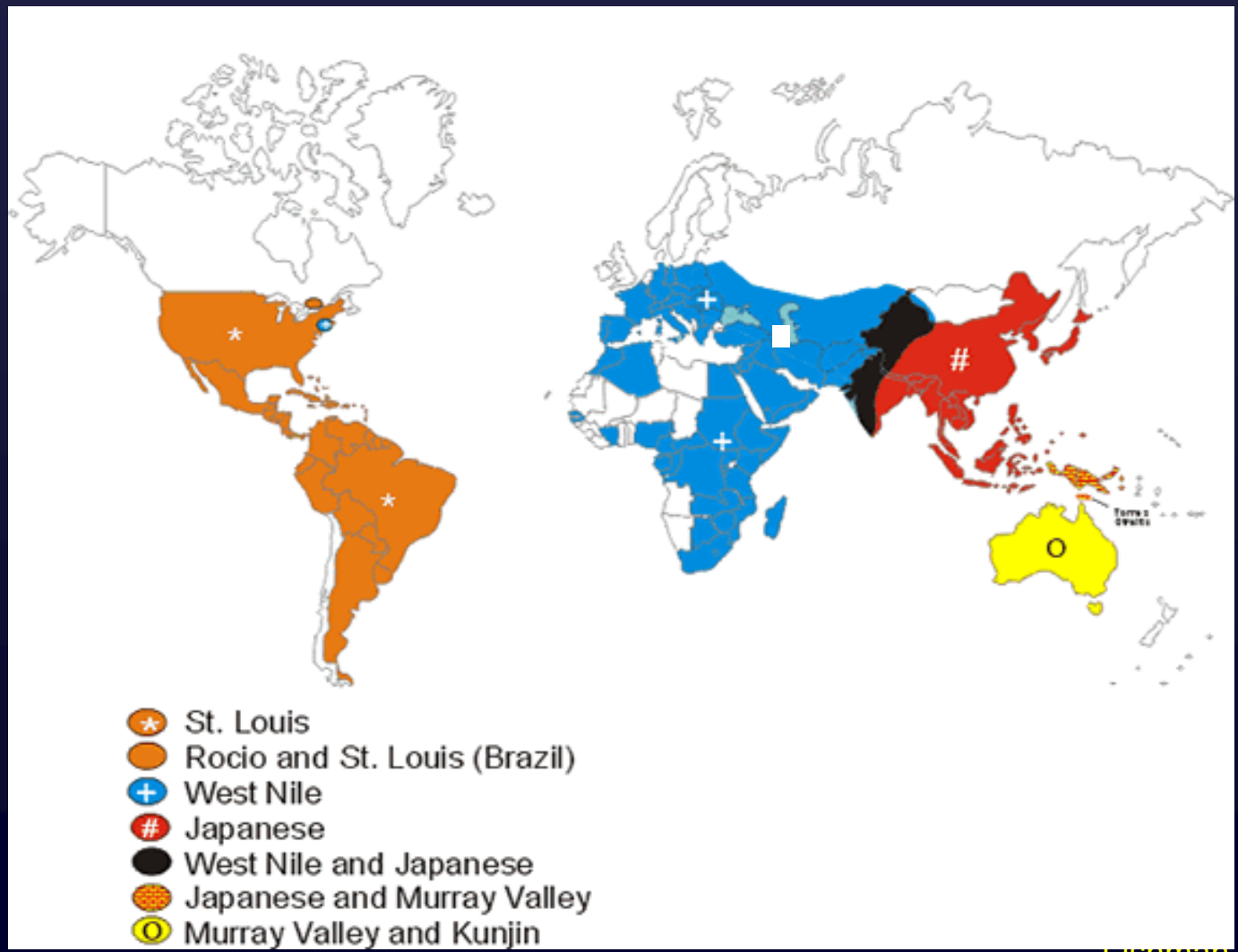
An Example: West Nile Virus

- Flavivirus (family of Japanese viral encephalitis arboviruses) first isolated in Uganda in 1937 - Neurotropic
- Transmitted by mosquitoes (Culex spp) & Carried by migratory birds → local birds, marsh and Culex (house) mosquitoes
- Causes encephalitis – brain infection



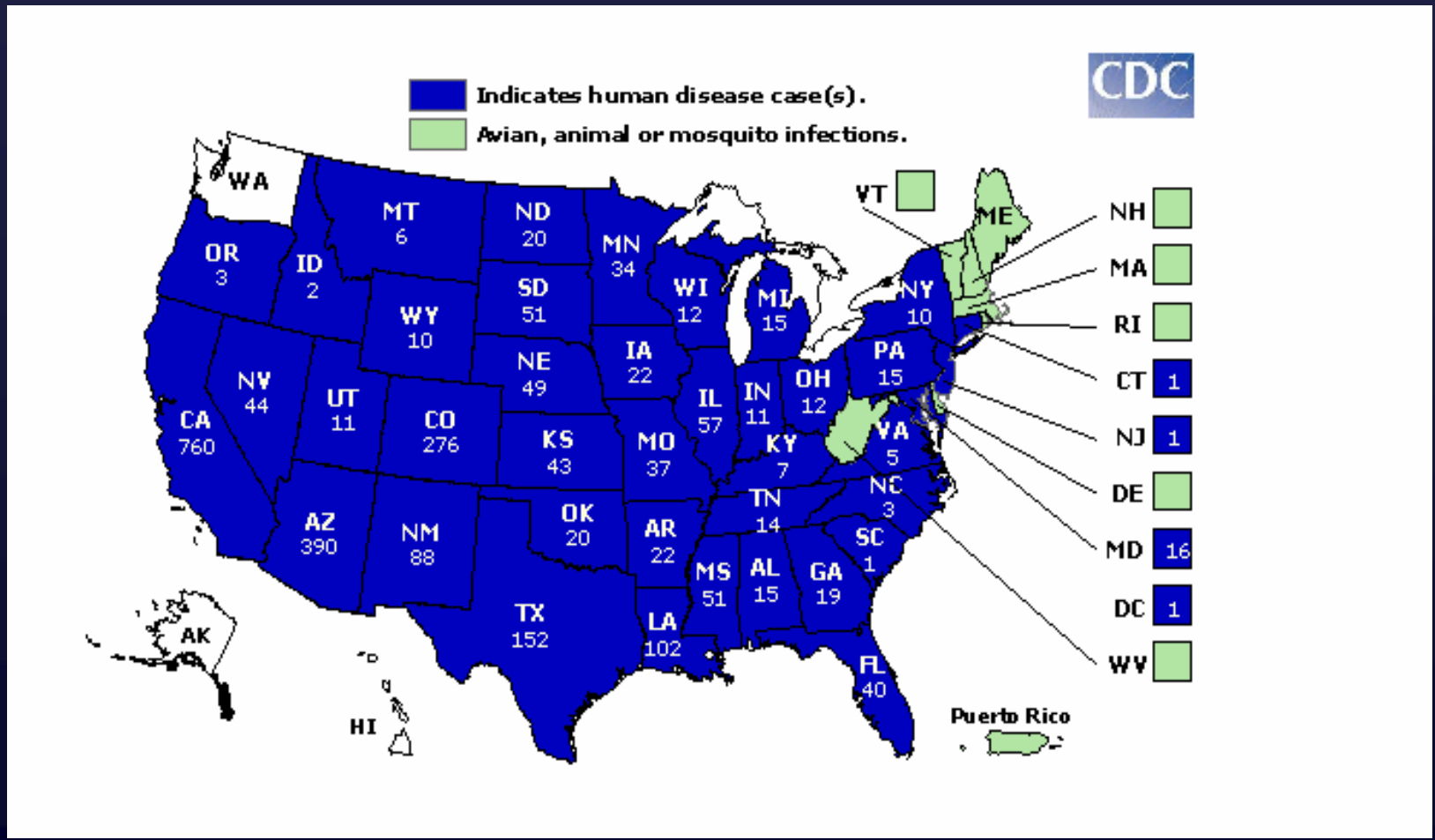
West Nile virus isolated from brain tissue from a crow found in New York City

The Geographic Distribution of Japanese Encephalitis Serocomplex of the Family *Flaviviridae*



Distribution of West Nile Virus as of October 1999

West Nile Virus 2004



West Nile Virus in Recipients of Organ Transplantation and Blood Transfusion

- 2002 - Four organs from a single organ donor were transplanted into four persons. WNV brain infection was confirmed in three recipients (one died, 2 with some permanent injury) and WNV fever in one recipient.
- Rate of infection has dropped nationally – is WNV testing still worth performing?
- Need ability to shift testing paradigm based on epidemiology, patient characteristics

What's Coming?
Where might donor screening go?

- Eastern Equine Encephalitis
- Japanese Encephalitis
- Dengue, Chikungunya virus
- Avian Influenza
- Others?
- **Transplant recipients as sentinels for new outbreaks, emerging infections, bioterrorism**

Goals for Screening/Safety

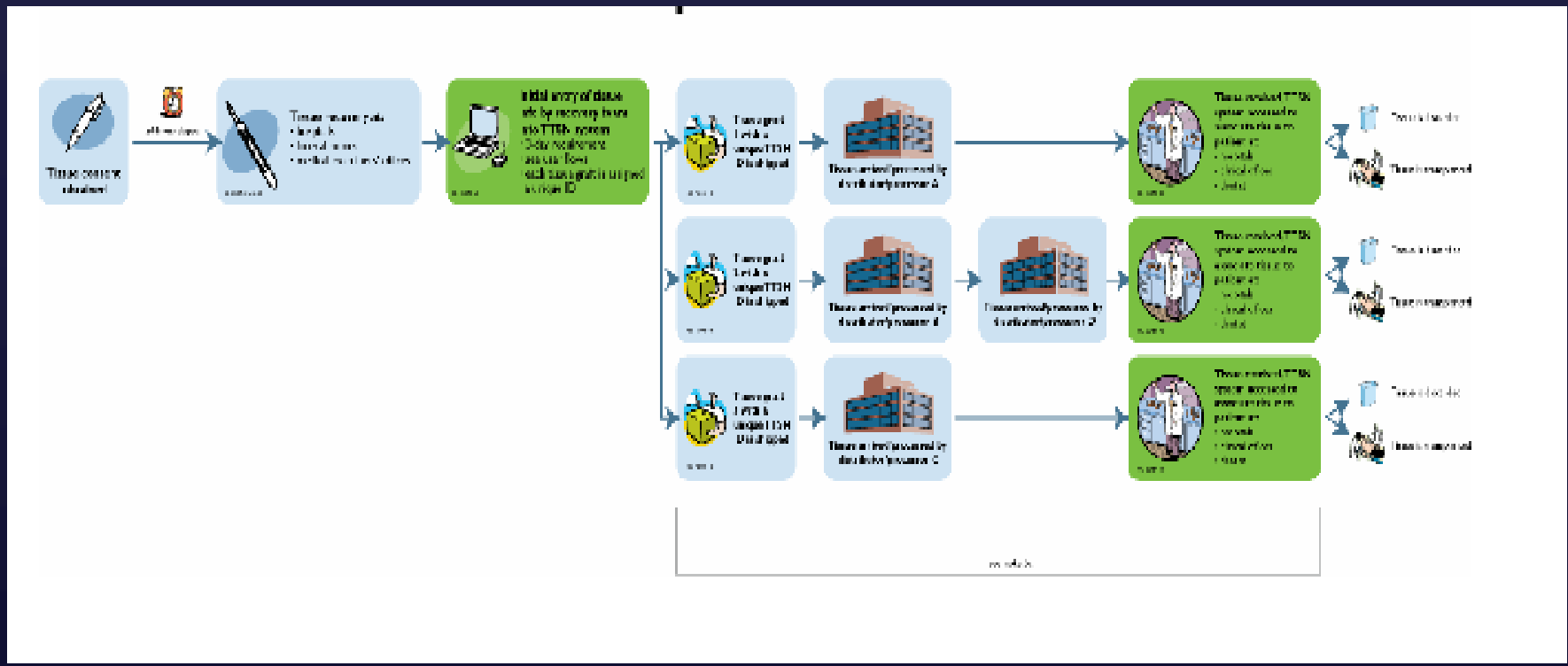
- Rapid assays of high sensitivity for organs (**NO TEST** will prevent transmission of infection 100% of the time) – How do we select needed tests?
- Rapid communication of data from organs/tissues/eyes via central repository
- Tracking system for each donor for epidemiologic tracing - public health investigation

Communication: Initials

- **DTAG: Disease Transmission Advisory Group** - subcommittee of UNOS' Operations Committee to review reports of Donor-Derived infection and malignancy (Policy 4.0: **REPORTING OF POTENTIAL DONOR-DERIVED RECIPIENT DISEASES OR MEDICAL CONDITIONS)**

- **TTSN: Transplant Transmission Sentinel Network** - a web-based reporting system under development by contract from CDC to UNOS track infections in tissue/organ/eye transplantation

Tracking/Communication



Donor-derived infection

REPORTING

Clinical Syndrome in Recipient

The Transplantation Transmission Sentinel Network (TTSN)

A. Development of a system that generates unique tissue identifiers (numbers, bar codes or similar) that can track any tissue or organ from donor to recipient.
   - There are currently many systems for eye and tissue tracking (internal to the various procurement groups)
   - Organs are regulated by HRSA while FDA regulates tissues and some procurement organizations require JCAHO certification.

B. A system to track the final disposition of the tissue including nature of the allograft, surgeon, site/institution, tissue bank, recipient identifiers

TTSN – Coming

C. Notification system for adverse events. Simple system that allows clinical personnel to input patient and tissue identifier number, clinical institution, date, contact information, and the nature of the event - documented infection, syndrome (hepatitis, gangrene, sepsis etc) and find out status of other recipeitns. Secure, web-based.

D. Notification of appropriate authorities: CDC, FDA (MedWatch), OPTN, local public health authorities -- automatically if appropriate This would allow CDC or FDA (via their tissue surveillance teams or TST) to start investigation.

E. Education - epidemiologic etc. information

ttsn

TRANSPLANTATION TRANSMISSION SENTINEL NETWORK

ADMIN | LOGIN

Welcome to the TTSN Web site

Please login to get started

SECURE LOGIN

Username

Password

Login

This section is password-protected for secure data entry by authorized users. Contact your site administrator for information on becoming an authorized user of this system or click the following link to create a new account.

About TTSN

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ttsn TRANSPLANTATION TRANSMISSION SENTINEL NETWORK

ADMIN | LOGOUT

DONOR SEARCH | GRAFT IMPLANT | ADVERSE EVENTS

3 ways to search

This is where the system explanation or instructions will be displayed for the user...

1 Search by ID:

TTSN ID: _____ or UNOS Donor ID: _____ Search

2 Search by Institution:

Institution: * AAUNOSCORP Donor ID: * _____ Search

3 Search by Donor Info:

Last Name: * _____ First Name: * _____

Date of Birth: _____ Date of Death: _____ Recovery Date: _____ Search

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Problems

- TTSN not yet completed
- No agreement on appropriate screening paradigm
- No mandated compliance with reporting
- No implementation (i.e., funding) plan for TTSN nationally
- Screening of solid organ donors cannot be folded into a paradigm developed for blood or tissue screening as the issues, while closely related, are distinct.

What are the lessons?

- New pathogens can be detected using molecular and immunological techniques – sensitivity not yet adequate for routine screening
- Infection is amplified in transplant recipients with immune suppression – risk is greater than in general population
- Need rapid coordination of information (CDC, Public Health Authorities, clinical centers, patients)

Lessons

- Need resources for outbreak investigations
- Reference labs available for access
- Increased use of “pathogen discovery technology” with transplant recipients
- Mandate reporting of specified infections and new clinical syndromes
- Archiving of specimens from all donors for future investigations
- Perform cost-effectiveness analysis and formal technology assessments → evidence-based decisions regarding implementation of new screening tests