Donor-Derived Infections in Transplantation

What Are We Missing?

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Conflicts: Consultant for Primera, Inc.

You get a 3AM Phone Call…

- 42 year old deceased donor thought to have had cardiac arrest
- Had URI (upper respiratory infection) in week prior to death. No antiviral therapy.
- H1N1-2009 influenza (“swine flu”) swab pending
- Do you want to use the organs?

Sensitivity of QuickVue Influenza A+B Test (Rapid Antigen) Compared to RT-PCR

	Sensitivity	Specificity
Novel H1N1	20/39 (51%)	99%
Seasonal H1N1	12/19 (63%)	99%
Seasonal H3N2	6/19 (31%)	99%

Faix et al. NEJM 2009;361:728-29

What are the key questions?

- How often do clinically significant infections result from transmission of donor-derived pathogens?
- Which pathogens?
- How good are the current “approaches” to screening of organ donors?
- How can these be improved?
  - Bigger list? (more pathogens)
  - Better assays? (molecular vs. serologic)
  - Better communication of positive results? (TTSN, DTAG)
  - More flexibility?
    - New pathogens (outbreaks)
    - Regional variability (endemic pathogens)
    - Donor epidemiologic history (travel, immigration)

How often do clinically significant infections result from transmission of donor-derived pathogens? Which pathogens do we care about?

- The types and significance of infection in transplant recipients is dependent on the type/intensity of immunosuppression, underlying immune deficits, the presence or absence of pre-existing immunity.
- The “importance” is a reflection of the morbidity and mortality associated with the disease and the availability (toxicity) of therapy – in transplant recipients

How often do clinically significant infections result from transmission of donor-derived pathogens?
Which pathogens do we care about?

- Answer: We do not know how often transmission occurs, with or without clinical signs.
- In general, infection due to viruses and parasites may be of greater concern than those due to bacteria or fungi due to **the greater incidence of symptomatic infection, limited microbiologic testing and the relative absence of effective or non-toxic therapies.**

Uncommon but not unique events!

- **Lymphocytic choriomeningitis** (LCMV, hamsters and rodents) → 4 outbreaks (3 in USA, 1 arenavirus in Australia) with 9 deaths
- **Rabies virus** (bat bite) → 2 known outbreaks with 5 deaths in USA, Germany
- **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) multiple transmissions
- **HIV** – now rare but 2 recent outbreaks (US and Italy)

Common Features

- Donor dying of possibly unrelated acute neurologic event (CVA, hemorrhage) – or undiagnosed meningoencephalitis
- Donor with unknown epidemiologic history (pet hamster, bat exposure, homelessness)
- Uncommon virus (organism) with increased virulence in immunocompromised hosts and/or unavailable testing
- Urgency for transplantation?
- Use of induction therapy for transplantation; “improved” immunosuppression?

Why new pathogens?

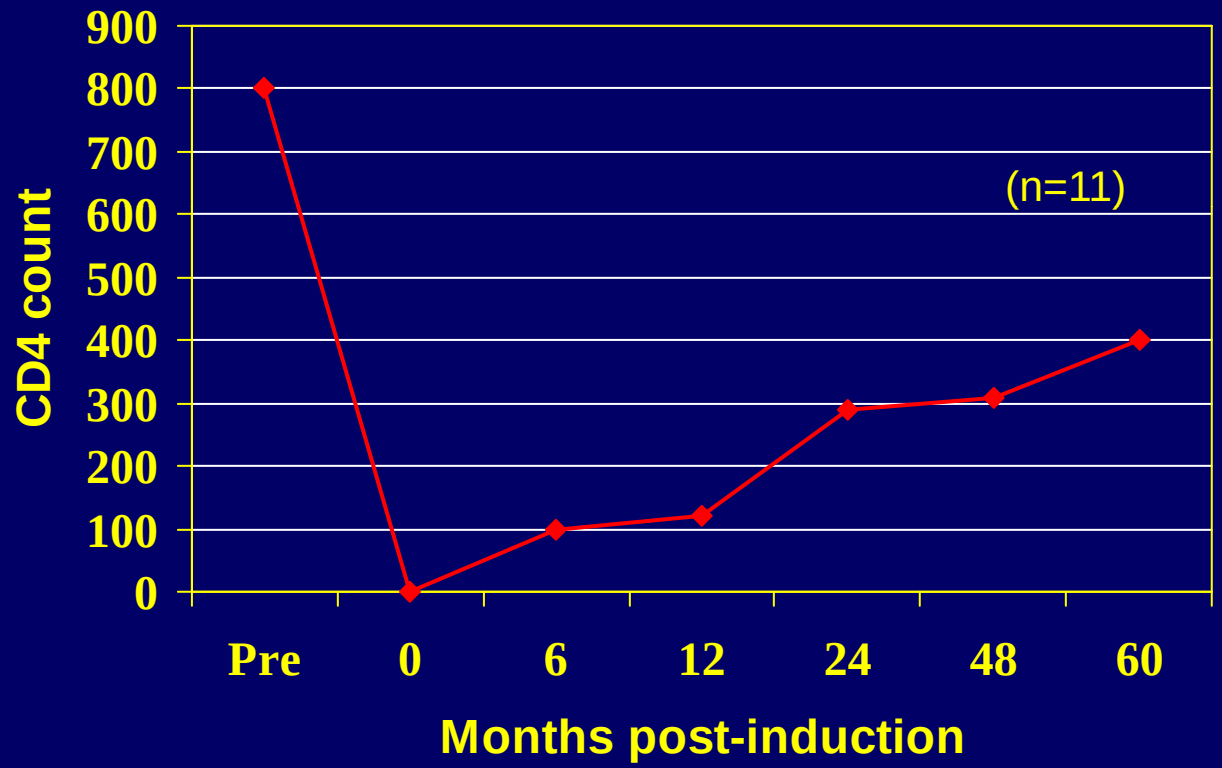
- Prolonged survival (travel, employment)
- Shifts in nosocomial flora (antimicrobial resistance), prolonged hospitalizations
- Intensified Immune suppression
- Improved diagnostic assays (molecular)
- Organ Shortage? (Expanded criteria donors?)
- Broader geographic backgrounds of donors & recipients

Detecting Pathogens in Organ Donors: The Challenges

- Immune suppression – infection is at least four to five times (possibly more) more likely in the transplant recipient than in normal individuals (i.e., sentinels for infection)
- Broader social and geographic/travel backgrounds of donors & recipients
- Need improved diagnostic assays (molecular) with sensitivity greater than for normal hosts

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

Anti-Thymocyte Globulins and CD4+ T-cell Depletion



- *CD4/CD8 ratio remains persistently inverted*

Muller et al, Transplantation 1997

Types of Infection Transmitted with Allograft Transplantation

- Bacterial infection: bacteremia or infection of tissues - resistance
- Fungus: fungemia or colonization - resistance
- Parasites: latent or acute infections - epidemiology
- Viruses: latent infection and viremia – diagnostic assays
- Prions: infection – not yet?

Donor-Derived Infection: Bacteria

- Bacteremia at the time of procurement due to (e.g.): Line infection, Sepsis, Pneumonia, Peritonitis, Meningitis
  - Rare transmission notably when prophylactic antimicrobials “cover” organisms
  - **Increasingly, antimicrobial-resistant organisms– Pseudomonas, Salmonella, MRSA, VRE**
  - Risk greatest at anastamotic site (vascular, tracheal, ureteric, GI, biliary) or hematomas (“Sticky organisms”)
- Tuberculosis: notably in endemic regions

Donor-Derived Infection: Fungi

- *Candida* – often nosocomial in donor (lines) or peritonitis (bowel) – antimicrobial selection in donor or recipient
- *Aspergillus* – fungemia uncommon but colonization common (lungs, sinuses)
- Endemic – *Histoplasma, Coccidoides*
  - Note: organ sharing may obscure endemic history
- Ubiquitous – *Cryptococcus* (pulmonary nodule)

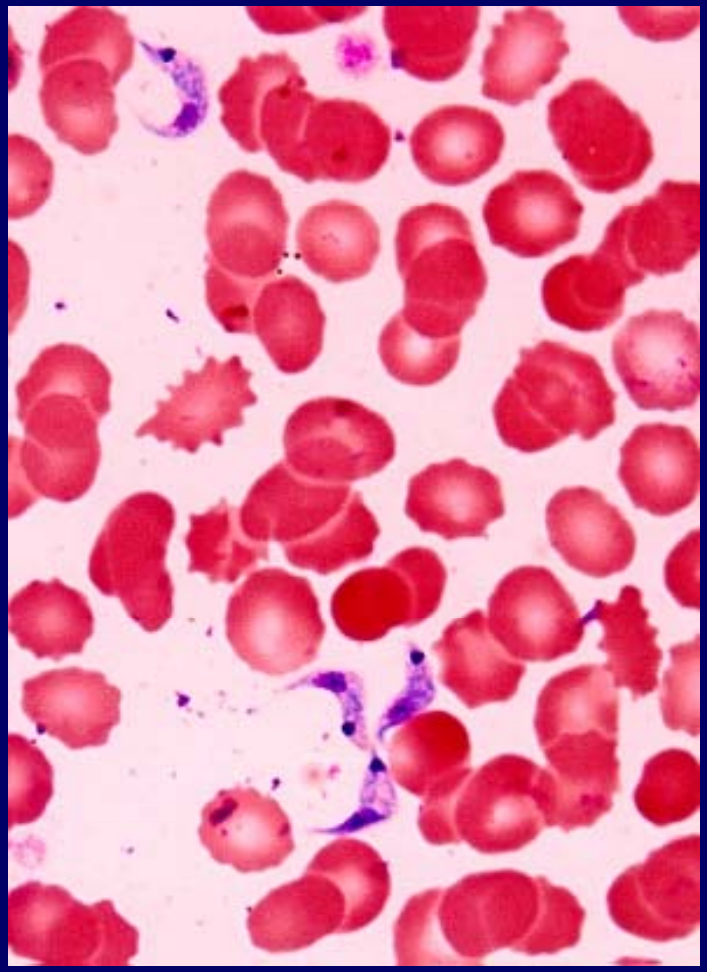
Donor-Derived Infection: Candida

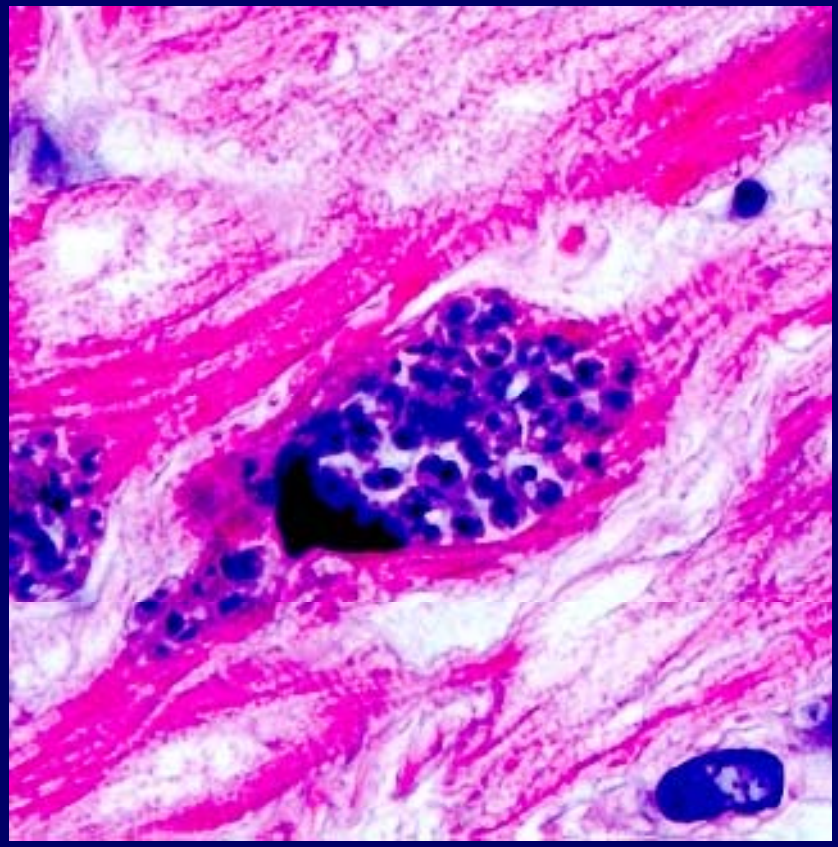
- 59 yo man and 47 yo woman received uneventful deceased donor renal transplants from same donor from outside the region
  - Thymoglobulin induction
  - Tacrolimus, MMF, prednisone taper
- Notified day 3 that donor had urinary yeast infection with *Candida* species
- Patients placed on fluconazole prophylaxis
- Male returned one week after transplant with fever and perinephric fluid collection = *Candida glabrata* (resistant to fluconazole, S micafungin). Other recipient with similar abscess (asymptomatic). Both surgically drained, responded well to therapy.

Donor-derived Parasites

- Late, latent infection
  - ***Toxoplasma gondii*** (hearts, lungs)
- Active infections (blood or organ)
  - **Chagas' Disease** (*Trypanosoma cruzi*)
  - Malaria – not accelerated in transplantation
  - Babesia – hemolysis
- Not yet described in recipients, but likely
  - *Strongyloides stercoralis*
  - *Leishmania donovani*
  - *T. brucei* – African sleeping sickness
- Not yet described & not T-cell dependent:
  - Intestinal/Liver flukes-*Opisthorcis/Clonorchis*
  - *Echinococcus*

Donor-derived Chagas' Disease after Cardiac Transplantation





Courtesy of B. Kubak

Donor-Derived Viruses

- Herpesviruses – CMV, EBV, HHV6, HSV, VZV
- HTLV I and II
- HIV
- West Nile Virus – mosquitoes and birds
- Rabies – bat bite
- LCMV – hamsters and rodents
- Respiratory Viruses: influenza (swine, avian), adenovirus, SARS coronavirus, metapneumovirus?
- Risks of Xenotransplantation – Porcine Endogenous Retrovirus, others?

Current Donor Screening

- **Social History** (to exclude “high-risk behaviors” for HIV only) - accuracy?
- **Blood, urine cultures** – useful for acute infections (results available after implantation)
- **Serologies** – generally useful for risk of post-organ transplant infection, but not acute infections syphilis, HIV, CMV, EBV, HSV, VZV, HBV, HCV, (Toxoplasma)
- **PCR & Antigen Tests** – useful (e.g., P24, viral load) but not (currently) adapted to speed needed or the array of potential infections

There is a marked organ shortage

- Organs must be used in 4-24 hours after procurement →Testing/screening must be available 24/7/365 (who pays?)
- **CANNOT waste organs due to FALSE + ASSAYS or "possibly" infected organs**
- Need to close the "window period" (i.e., pre-conversion) of serologic testing AND have the flexibility to provide assays for new pathogens (e.g., West Nile)

Transmission Events Reported to UNOS/OPTN/DTAG

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

Screening vs Diagnostic tests

- Clinical trials to support **donor screening** tests perform testing in a “pre-screened”, low-prevalence population (emphasis on sensitivity). Result: more false positives than false negative results.
- Clinical trials to support **diagnostic** tests generally perform testing in a symptomatic population with suspicion of having a particular disease before the test is performed (more emphasis on specificity)
- Performance of a diagnostic test in a low-prevalence population is generally not known

The Need for New Platforms for Diagnostic Assays

- Consider limitations of currently available assays. This may include both sensitivity and timing of "conversion" (window period) 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, but highly useful
  - NAT: Nucleic Acid-Amplification Testing – highly sensitive, false + assays common, not available for all pathogens, costly equipment, specialized labs
  - New Assays: Large diagnostic companies may not be interested in creative development for the limited transplant market

Imperfections of NAT

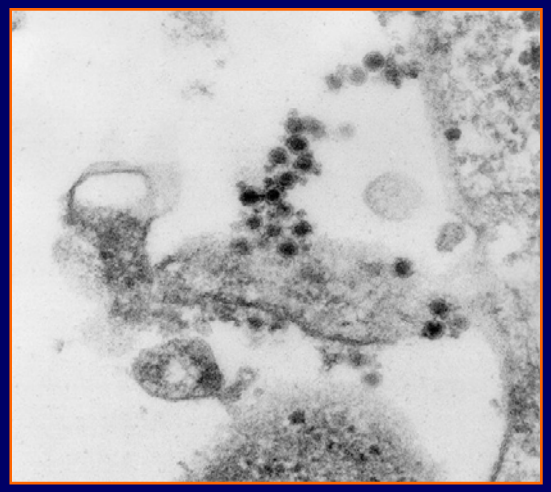
- Cases of West Nile Virus (NY/PA) blood testing on donor was negative by PCR (degraded samples) while tissues were positive in recipients
- LCMV (US, Australia) – virus never detected in donor blood or tissues – even with improved, specific molecular assays – amplified in recipients. Assays for each cluster not useful for general population.

Practical Aspects in Making Lists of Assays for Screening: Complex Matrix of Risk-Benefit

- Epidemiology – changing patterns
- Diagnostic tools (assays) - availability
- Likelihood of infection (virulence) after exposure in transplant recipients
- Disease morbidity/mortality
- Available therapies - toxicity
- Cost, expertise

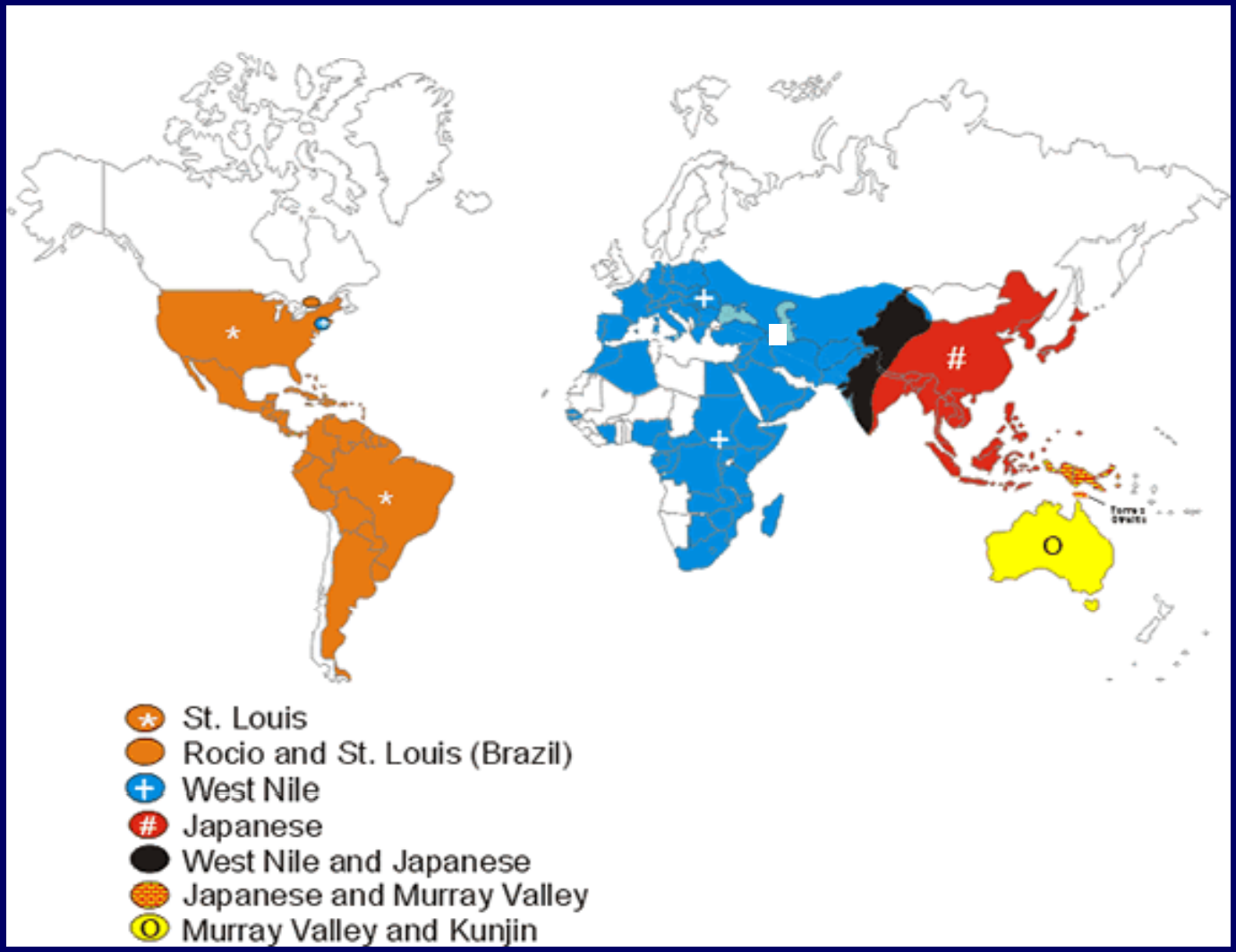
Flexibility: Changing Epidemiology
West Nile Virus

- Neurotropic Flavivirus (family of Japanese viral encephalitis arboviruses)
- Transmitted by mosquitoes (Culex spp) & Carried by migratory birds → local birds, marsh and Culex (house) mosquitoes
- Causes encephalitis – <u>rate ⇑ in transplant</u>



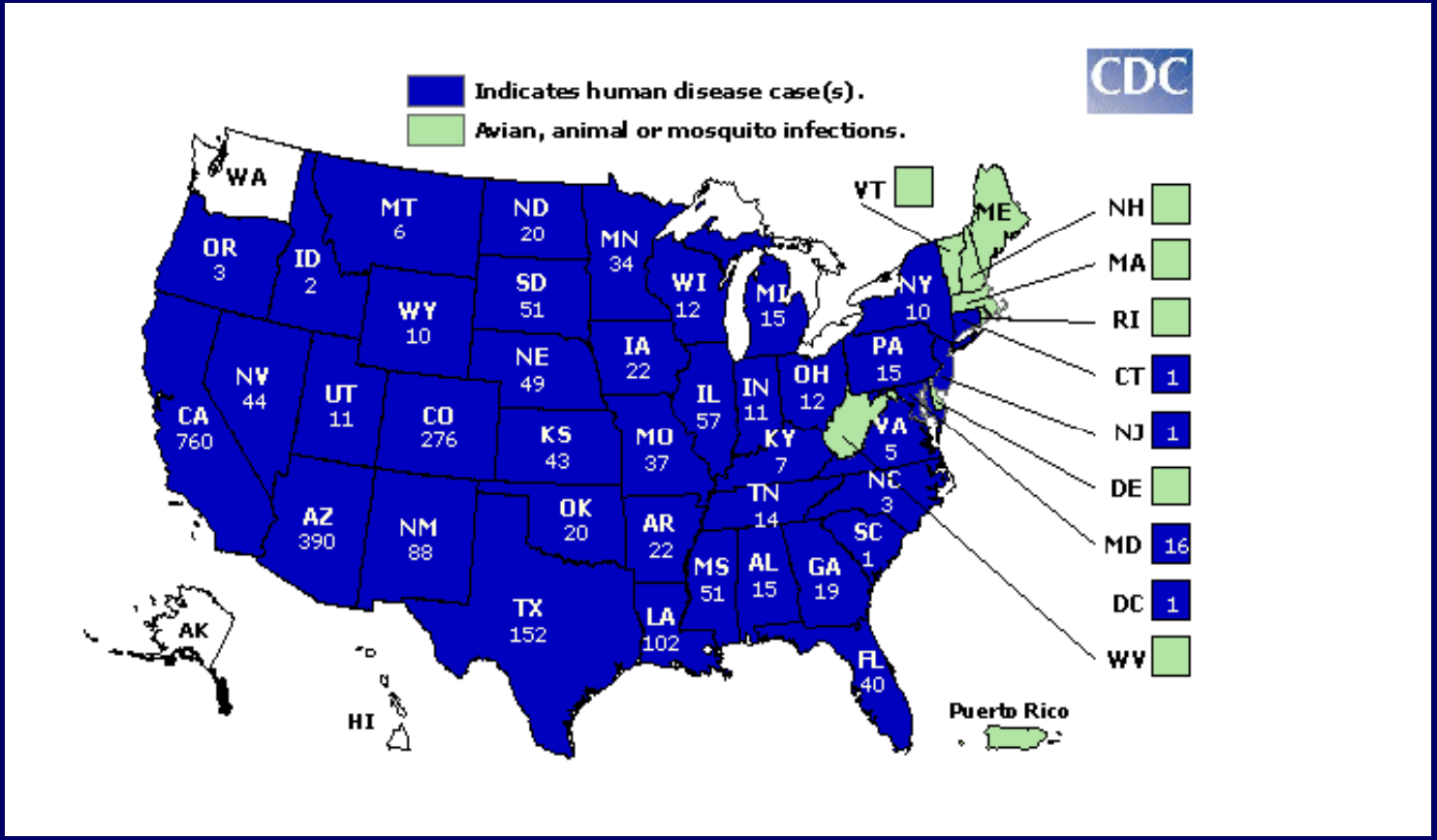
West Nile virus isolated from brain tissue from a crow found in New York City

The Geographic Distribution of Japanese Encephalitis Serocomplex of the Family *Flaviviridae:* *The need for flexibility in assay deployment*



Distribution of West Nile Virus as of October 1999

West Nile Virus 2004



- Rate of infection has dropped nationally – is WNV testing still worth performing?
- Need ability to shift testing paradigm based on epidemiology, patient characteristics

Testing for Strongyloides?

- Relatively non-toxic therapy (ivermectin) at modest cost
- Active disease is quite severe
- Tests are slow (serology) but the risk/benefit is quite good.
- Therefore: Testing is performed but generally treat empirically while awaiting results.

Chagas

- Relatively toxic therapies: nifurtimox and benznidazole. In the USA, these are not FDA approved & are available for treatment only from CDC under investigational protocols (no cost).
- Disease is quite severe and may not be curable (need long term therapy/prophylaxis/immunity)
- Tests are becoming available for blood, but not for organs, sensitivity is an issue. In endemic regions three tests are used for each donor/recipient
- The main risk (from donors) is after cardiac transplantation.
- In some areas (e.g., Miami or Providence or Los Angeles) blood positivity may approach 15%. In others it is ~absent.

LCMV

- Epidemiology may not be helpful – common pathogen of normal hosts
- Tests are slow (CDC-PCR, high throughput sequencing); **virus may not be detectable in donors with available assays**
- Therapy uncertain: benefit of ribavirin?
- Disease may be fatal in transplant recipient
- Therefore: Testing desirable, but not available yet.

Donors from (e.g.) Brazil?

- **Paraccoccidioides**
- **Chagas' Disease** (Trypanosoma cruzi)
- **Hepatitis A, B, C**
- **Typhoid, Yellow fever, Dengue**
- **Schistosomiasis, leishmaniasis**
- **Malaria, Filariasis**
- **Rabies**
- **HHV-8 (KSHV)**

HHV-8 Transmission

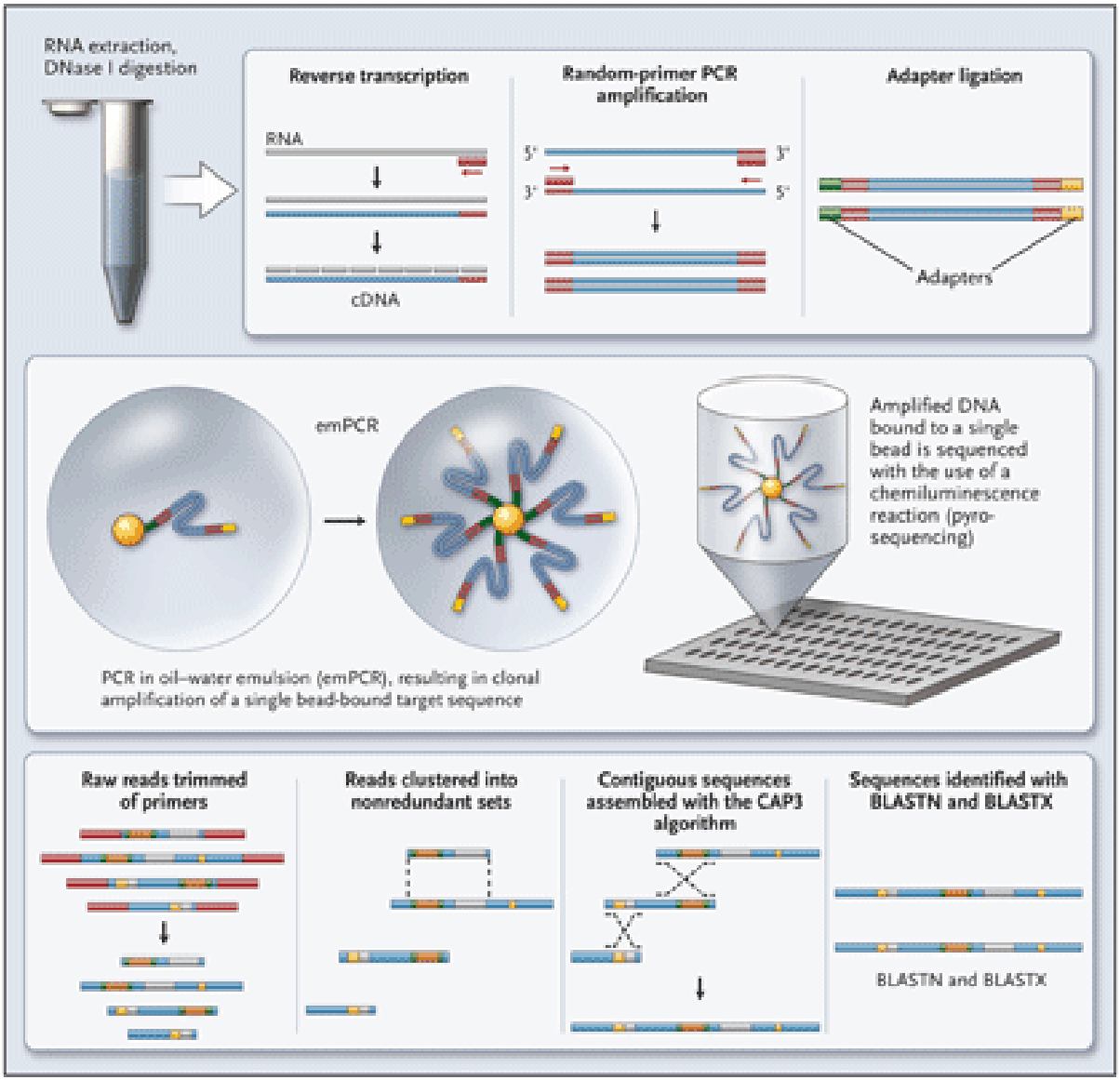
- Increasing in Europe (Italy), endemic regions
- French Study: 2001 to 2006 (3 years of inclusion and 3 year of follow up) in renal transplantation. The prevalence of HHV8+ donors and recipients was 1.08% and 3.24%
- D+/R-
  - 1 of 64 developed severe clinical HHV-8 infection with cytopenia, fever and hemophagocytosis
  - Two patients developed KS with low HHV-8 viremia
  - **Seroconversion to positive HHV-8 status was documented in 24.8% of D+/R- over three years.**

What's Coming?
Where might donor screening go?

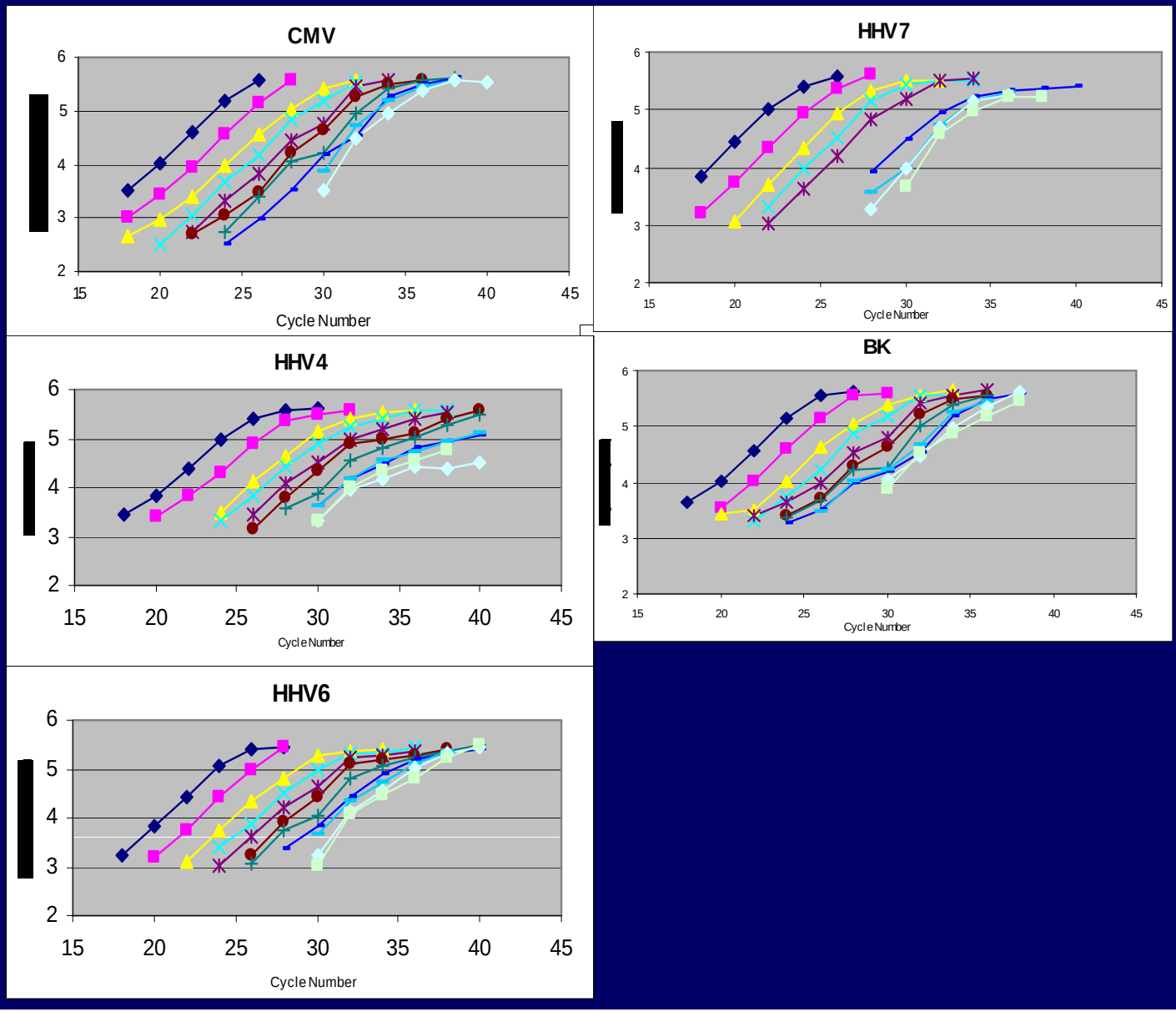
- Eastern Equine Encephalitis
- Japanese Encephalitis
- Dengue, Chikungunya virus (e.g., in Italy)
- Avian Influenza, Swine Influenza
- Others?
- **Transplant recipients as sentinels for new outbreaks, emerging infections, bioterrorism**

High-Throughput Sequencing Method

G. Palacios et al, NEJM 358: 991

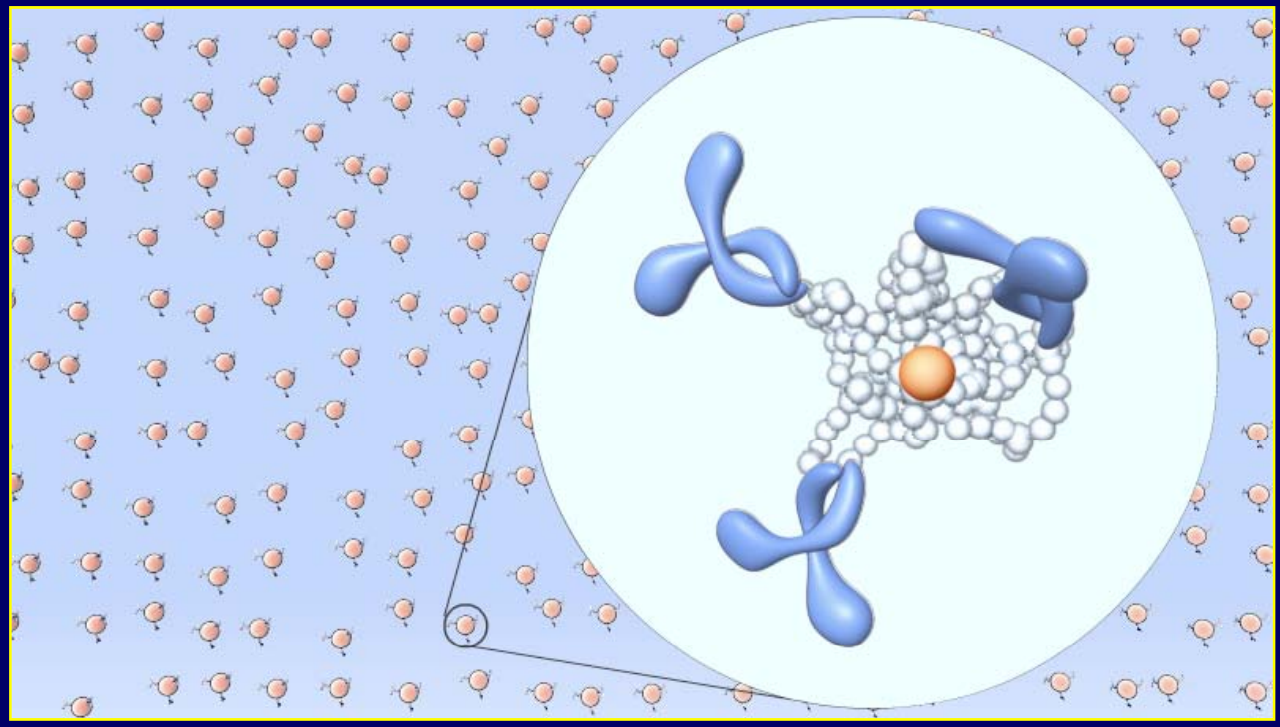


Primera ViraQuant Assay:
Quantitative Detection of Multiple Viral Targets



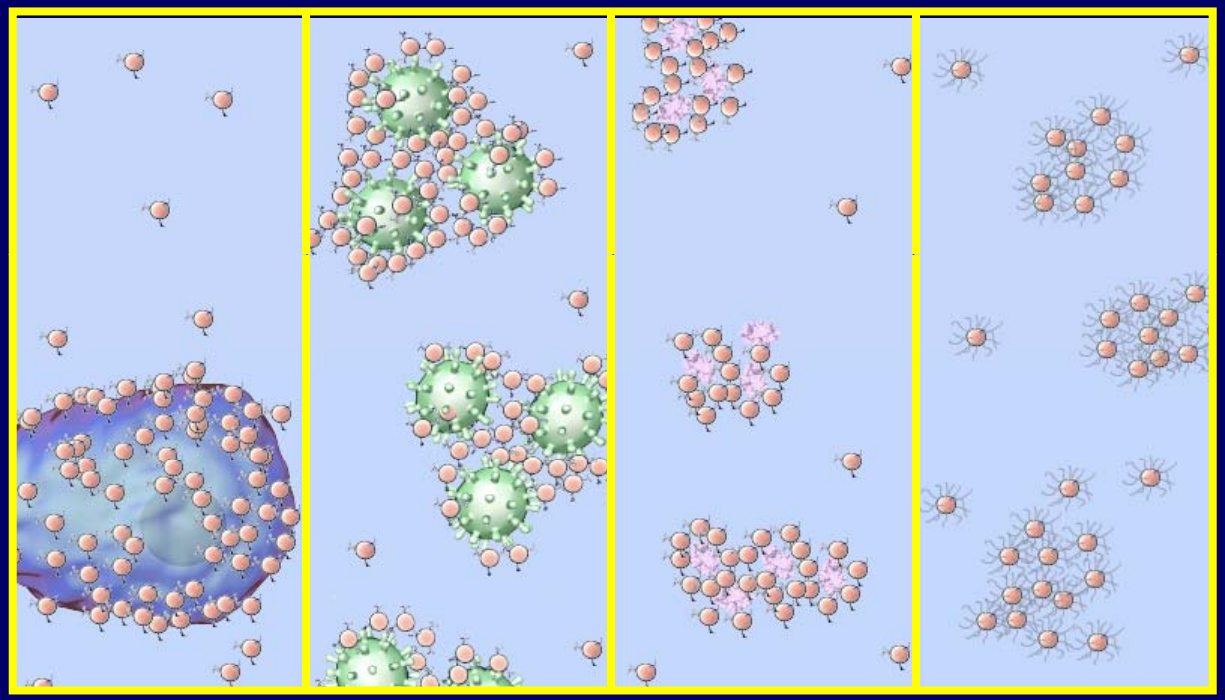
T_2: Technology-Nanoparticles

Nanoparticles are composed of an iron oxide metal core covered with dextran polymer. These are in turn functionalized with a detection moiety (in this case, an antibody recognizing a virus).

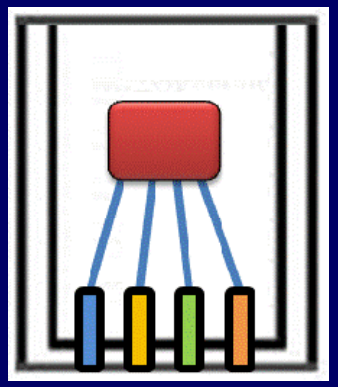


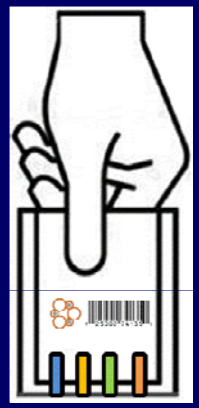
Courtesy of T_2 Biosystems

Multiplexed Detection



Multiplexing inside cartridge

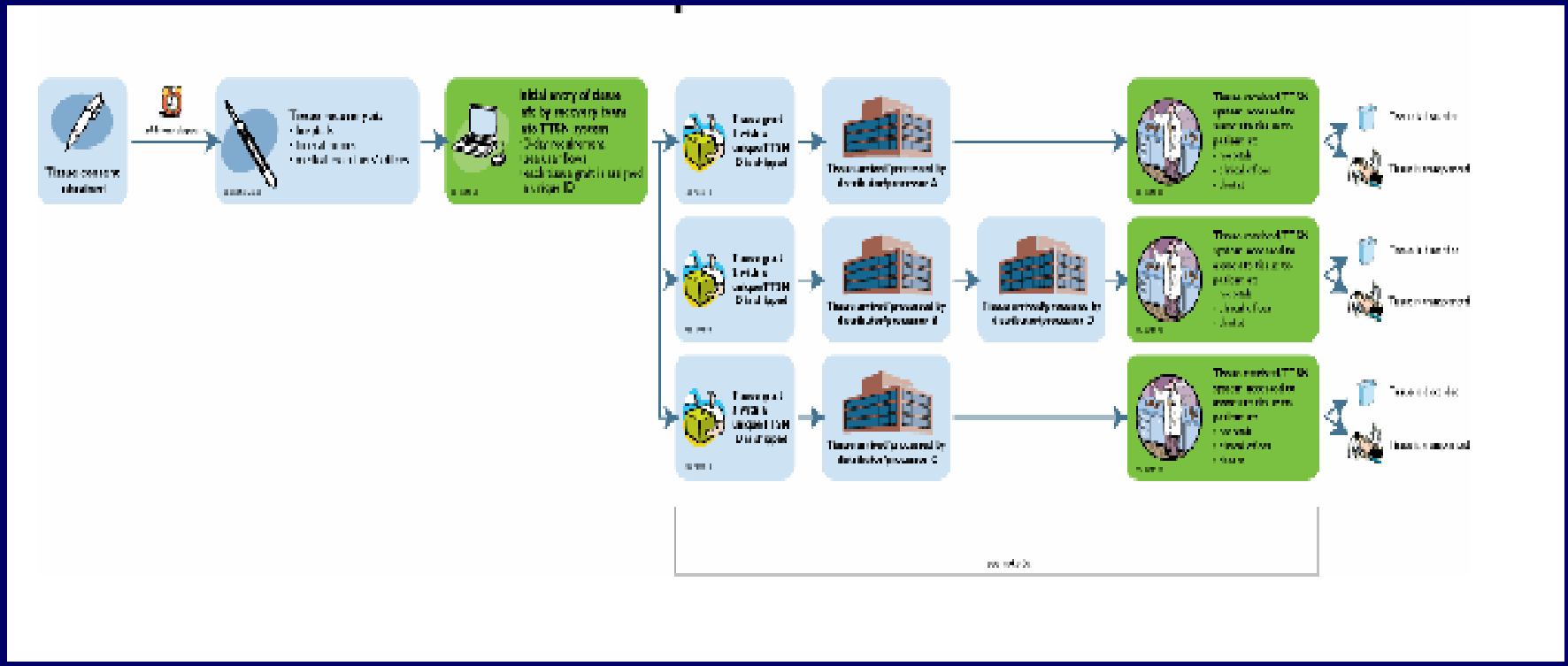




Communication: Initials

- **DTAC: Disease Transmission Advisory Committee** – reviews reports and recommend policy for 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
- Under development

Tracking/Communication



Donor-derived infection

REPORTING

Clinical Syndrome in Recipient

Considerations

- What frequency of disease in the community or donor pool justifies routine donor screening? 1%? 5%? 10%?
- Why are bloods and tissues tested more rigorously than organs? Should the FDA regulate and certify all testing?
- Do we want to test based on country of origin? Known risk factors (e.g., what does someone infected with HIV look like?)?
- How to best diagnose latent TB (systemic)? Strongyloidiasis (GI)? Histoplasmosis (Lung)? Toxoplasmosis (CNS)? Chagas' (blood)?
- What needs to be communicated from the OPO to clinical centers? And how?

What are the lessons?

- New pathogens can be detected using molecular and immunological techniques – sensitivity/specificity/availability not yet adequate for routine screening
  - Need new assay platforms
  - Need assays designed for donor screening
- Development of list for testing must include consideration of the nature and severity of the disease and implications for therapy

- Need rapid coordination of information (CDC, Public Health Authorities, clinical centers, patients)
- Need transparency of reporting to achieve safety for our patients.

H1N1 Guidelines

- H1N1 is pandemic (incubation 2-7 days)
  - How many are asymptomatic?
  - How many are viremic? (estimate: “many”)
- Potential donors who have “flu-like illness” (fever, sore throat) ≤ 2 weeks of death → deferred from lung or bowel donation.
- Donors treated with antiviral agents (48 hours? 5 days?) with an effective agent (oseltamavir or zanamivir) are probably OK for other organs.
- Recipients need treatment with antivirals.

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I would be happy to answer any questions.

If I can help:
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