Donor-derived infectious disease risk through solid organ transplantation and surveillance in the United States
Quebec Biovigilance Committee Public Forum on Vigilance for human-derived products

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Sridhar V. Basavaraju, M.D.

Centers for Disease Control and Prevention

National Center for Emerging and Zoonotic Infectious Diseases

Division of Healthcare Quality Promotion

Office of Blood, Organ, and Other Tissue Safety

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

Objectives

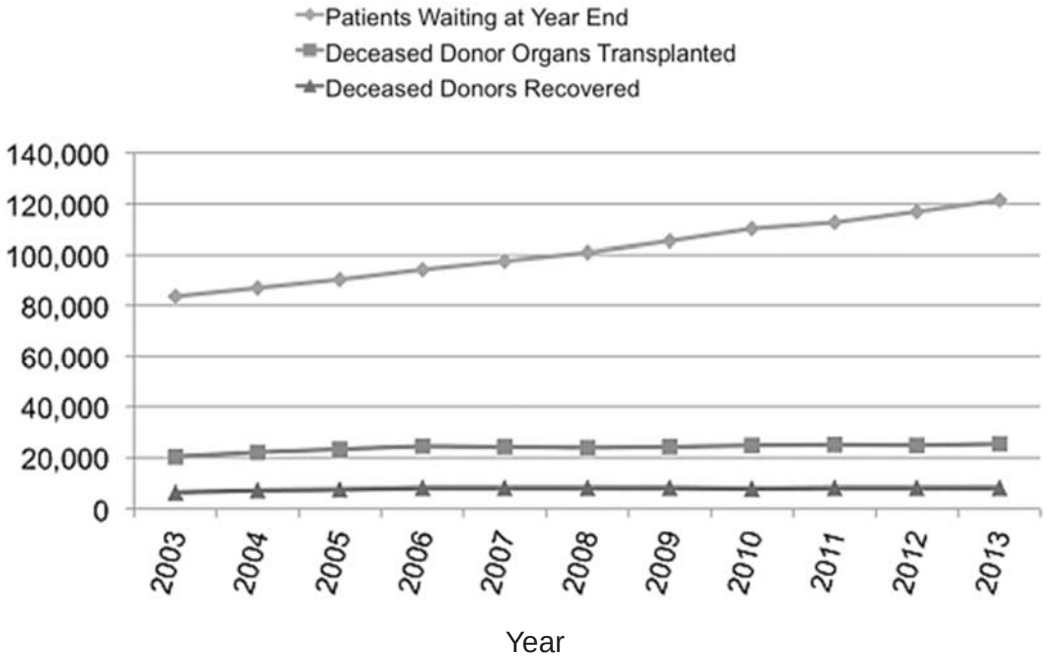
- **Background and setting the context**
- **Description of current efforts in U.S. to identify cases of donor-derived disease transmission**
- **Quantifying donor-derived disease infection risk**

BACKGROUND

The current state of transplantation in the U.S.: technological advances and challenges

- *30,000 solid organs transplanted annually*
- *“Composite” allografts are now possible*
  - *entire face, hand, or foot*
  - *nerve, vessel complexes*

Organ Transplant Supply and Demand



http://optn.transplant.hrsa.gov

Balancing Resources

Differences between blood and organs

SAFETY

AVAILABILITY

For blood, the emphasis is on safety, and availability is less of a concern.
For organs, the emphasis is on availability, and safety is less of a concern.

Organ Safety in the U.S.: Who's in charge?

- Food & Drug Administration (FDA) –Regulatory authority for blood and tissues, not organs (except for test approval)
- Health Resources & Services Administration (HRSA) –Regulatory oversight for organs
  - Oversight through contract with United Network for Organ Sharing (UNOS), which operates the Organ Procurement and Transplantation Network (OPTN)
  - Transplant centers and Organ Procurement Organizations (OPO) must be part of OPTN
  - Potential donor-derived disease transmissions, including infections and malignancies, to be reported to OPTN

Ad Hoc Disease Transmission Advisory Committee (DTAC)

- **Part of OPTN patient safety program**
- **Examine and classify potential donor-derived transmission through transplantation of infection or malignancy**
- **Educate transplant community**
- **Help change policy and improve processes**
- **Membership includes CDC, FDA, transplant centers, transplant infectious disease, lab testing, organ procurement organizations**

What role does CDC play?

- **Public Health Service (PHS) agency with primary responsibility for surveillance and detection of public health risks**
  - **not a regulator**
  - **not authorized to investigate events on own, but only by assisting local and state authorities**
  - **Creates recommendations in concert with other PHS agencies (we cannot enforce them)**
- **Through an agreement with HRSA, has representation on DTAC and investigates possible infectious disease transmission of nationally notifiable diseases or other infections of public health importance**
  - **Nationally Notifiable disease in donor or recipient**
  - **Multiple ill recipients**
  - **Encephalitis in donor or recipient(s)**
  - **Unknown syndrome**
- **Goal is it determine whether infection was donor-derived**
  - **~ 50 case investigations annually are referred to CDC**

SURVEILLANCE FOR DONOR-DERIVED DISEASE TRANSMISSION IN THE UNITED STATES

Major goals of public health surveillance systems

- **Measure the burden of a disease**
  - Incidence
  - Prevalence
- **Monitor trends in the burden of a disease**
  - Detect outbreaks
  - Identify epidemics
- **Guide immediate action for cases of public health importance**
- **Other**
  - Evaluate public policy
  - Detect changes in public health practice
  - Prioritize allocation of resources

MMWR recommendations and report. Updates guidelines for evaluating public health surveillance systems, 2001

Public Health Surveillance Systems cont'd

- **Types of reporting**
  - Active
  - Passive
- **Data components to facilitate incidence and prevalence estimation**
  - Complete reporting of numerator data (e.g. case reporting)
    - Standardized case definition
  - Complete report or reliable estimate of denominator data
    - Population in a geographic area where surveillance is conducted
    - Total blood components transfused (if estimating incidence of transfusion reactions)
    - Total organs transplanted (if estimating incidence, prevalence of donor-derived disease transmission events)

Reporting of donor-derived disease transmission events in the United States: Surveillance?

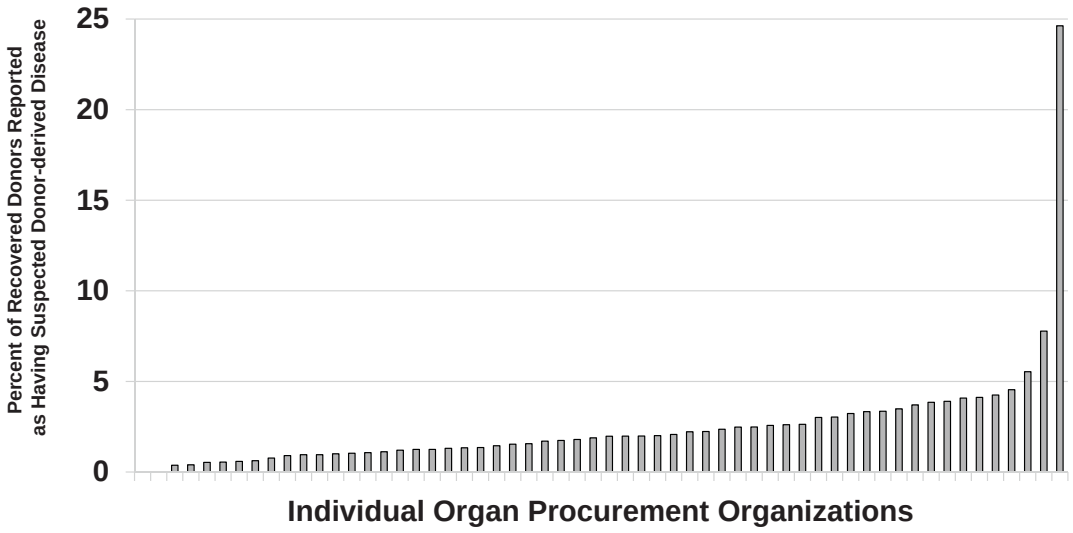
- **Passive reporting by facilities to OPTN/UNOS (referred to DTAC for review)**
  - Transplant centers
  - Organ procurement organizations
- **Numerator reporting**
  - No standardized criteria for what is reported
    - Any infectious disease or malignancy suspected to be transmitted to an organ recipient from the organ donor (at discretion of clinical team or OPO)
    - May include recipient illness or in some cases, if donor is suspected to have a disease (at time of organ recovery or retrospectively)
  - Goal is to determine whether disease is donor-derived
- **Denominator data**
  - Not routinely reported
- **More of a case reporting system than surveillance**

DTAC Classification Algorithm

Disease reporting by transplant centers and OPOs

- **Variable by center**
  - Bronchoscopy, blood, urine culture reported though organisms may be routinely encountered, treated by standard antimicrobial prophylaxis, and not associated with significant morbidity/mortality
- **Donor infection may be unrecognized**
  - Some diseases are rare and infrequently encountered
  - Some donors have no evidence of infectious cause of death
- **Difficulty in linking donor and recipient infections**
  - Onus on transplant centers/OPO to suspect donor-derived disease
  - Some infections difficult to recognize and diagnose in recipient
  - Geographic distance
  - Timeliness of information

Variability of Reporting Suspected Donor-derived Diseases by Organ Procurement Organizations



OPTN/UNOS DTAC-Cases reported through 2013.

Pathogens of special interest- reportable for suspected or confirmed donor or recipient illness

Amebic encephalitis
Anaplasma or Ehrlichiosis
Anthrax
Babesiosis
Brucellosis
California Serogroup Virus Diseases
Chagas
Chikungunya Virus Disease
Coccidioidomycosis/Valley Fever ** Specifically identified by autopsy, biopsy, or cultures. Exclude serology only
Crimean-Congo Hemorrhagic Fever virus
Dengue virus infections
Eastern Equine Encephalitis Virus Disease
Ebola virus
Enterovirus D68
Hantavirus
Hepatitis A
Hepatitis C (acute, past or present)
HIV Infection
Influenza-associated pediatric mortality

Lassa virus
LCMV
Leptospirosis
Listeriosis
Lujo virus
Lyme disease
Malaria
Marburg virus
Measles/Rubeola
Microsporidia
MERS co-V
Mumps
New World Arenaviruses
Pandemic Influenza strains
Plague
Poliomyelitis, paralytic
Poliovirus infection, nonparalytic
Powassan Virus Disease
Q fever (acute, chronic)
Rabies, animal or human
Rubella/ German Measles
Severe Acute Respiratory Syndrome (SARS)-Associated Coronavirus Disease
• Smallpox/Variola

Spotted Fever Rickettsiosis (
St. Louis Encephalitis Virus Disease
Strongyloides
Tuberculosis (TB)
Tularemia
Varicella / Chickenpox
Viral Hemorrhagic Fever
West Nile Virus Disease
Western Equine Encephalitis Virus Disease
Yellow fever
Zika virus

OPTN/UNOS Disease transmission advisory committee

Cumulative Estimated Incidence of Disease Transmission: PDDTE Reported Through 2013 Involving Donors Recovered 2008-2012

	Deceased Donors N (%)	Living Donors N (%)	Total N (%)
Donors recovered	40,223	31,278	71,501
Donors with PDDTE	763 (1.9%)	24 (0.08%)	787 (1.1%)
Donors with proven/probable PDDTE	141 (0.4%)	5 (0.02%)	146 (0.2%)
Total recipient transplants performed	110,402	31,277	141,679
Recipients with proven/probable disease	177 (0.16%)	4 (0.01%)	181 (0.13%)
Recipient deaths due to proven/probable disease	39 (0.04%)	1 (0.003%)	40 (0.03%)

33,407 individuals died between 2008-2012 while on the wait list

PDDTE: Potential donor-disease transmission events

UNOS/OPTN Ad hoc disease transmission advisory committee

Suspected Donor-derived disease reports to the DTAC: 2005-2011

Disease	Number of Donor Reports	Number of Recipients with Confirmed Transmission	Number of DDD-Attributable Recipient Deaths
Virus[a]	166	48	16
Bacteria[b]	118	34	9
Fungus[c]	75	31	10
Mycobacteria[d]	53	10	3
Parasite[e]	35	22	7
Total Infections	**447**	**145**	**45**

In 2013: 31/284 (11%) cases reviewed by CDC

[a] **Adenovirus, HBV, HCV, HEV, HIV, HTLV, herpes simplex, influenza, LCMV, Parainfluenza (PIV)-3, Parvovirus B19, rabies, West Nile virus**

[b] ***Acinetobacter,*** **Brucella** ***Enterococcus*** **(including VRE),** ***Ehrlichia*** **spp,** ***E. coli*****, Gram Positive Bacteria,** ***Klebsiella*****, Legionella, Listeria, Lyme Disease, Nocardia,** ***Pseudomonas*****, Rocky Mountain Spotted Fever,** ***Serratia ,*** ***S. aureus*** **(MRSA), Streptococcus spp, Syphilis,** ***Veillonella*****; bacterial meningitis and bacterial emboli**

[c] ***Aspergillus*** **spp,** ***Candida*** **spp,** ***Coccidioides imitis*****,** ***Cryptococcus neoformans*****,** ***Histoplasma capsulatum*****, zygomyces**

[d] **Tuberculosis, non-TB mycobacteria**

[e] **Babesia,** ***Balmuthia mandrillaris*****, Chagas (***Trypanosoma cruzi***),** ***Naegleria fowleri,miasis, Strongyloides***

DTAC: Disease Transmission Advisory Committee DDD: Donor-derived disease
Data includes cases classified as possible, probable or proven from 2005-2007 as published in AJT, and all reviewed cases from 2008-2011.

DONOR-DERIVED INFECTIOUS DISEASE TRANSMISSION RISK

Donor-Derived Infection Transmission

- **Suspected in 1-2% of solid organ transplantations**
  - Allograft failure
  - Death
- **Confirmed in <1% (0.2%) of transplantations**
- **Suspected and confirmed pathogens can include viruses, bacteria, parasites, fungi**
- **Published U.S. guidelines for infection transmission risk reduction focused on HIV, HBV, HCV -2013**
  - Specific informed consent required if donor has risk factors (e.g., injection drug use [IDU])
  - Organ donor NAT screening for HCV, HIV

Quantifying the risk of infectious disease transmission through organ transplantation: CDC efforts

- **Special challenges**
  - No active surveillance system (as just described)
  - Very rare events (<1% of transplants)
  - Diverse group of pathogens
  - No screening tests (for some pathogens)
- **Pathogens of focus**
  - Viral bloodborne pathogens: HIV and hepatitis C in particular
  - Infectious encephalitis-causing agents: Rabies, West Nile Virus, Lymphocytic Choriomeningitis Virus (LCMV) and *Balamuthia mandrillaris*
    - *Very high morbidity/mortality among recipients*
- **Techniques to estimate risk**
  - Mathematical modeling
  - Clinical decision aid tools

Methods: Determine Per-Act Transmission Risk for HIV and HCV

- PubMed search terms for HIV: HIV, HIV infection, human immunodeficiency virus, AIDS and disease transmission, per-contact, per-act
  - Resulting in > 7000 abstracts and four cohort studies were selected and original datasets were obtained.
    - MSM seroconversion study- California, Colorado and Illinois (1998); IVDU cohort-Thailand (2002); Serodiscordant couple study- Uganda (2005); Female sex worker cohort-Kenya (2008)
- PubMed search terms for HCV: HCV, HCV infection, per-contact, and needle sharing
  - Resulting in > 2000 abstracts and one described per-act HCV transmission risk -- quantified for IVDU
    - Per-Event Probability of Hepatitis C Infection during Sharing of Injecting Equipment (2014)

Methods: Determine HIV/HCV NAT Screening Assay Characteristics

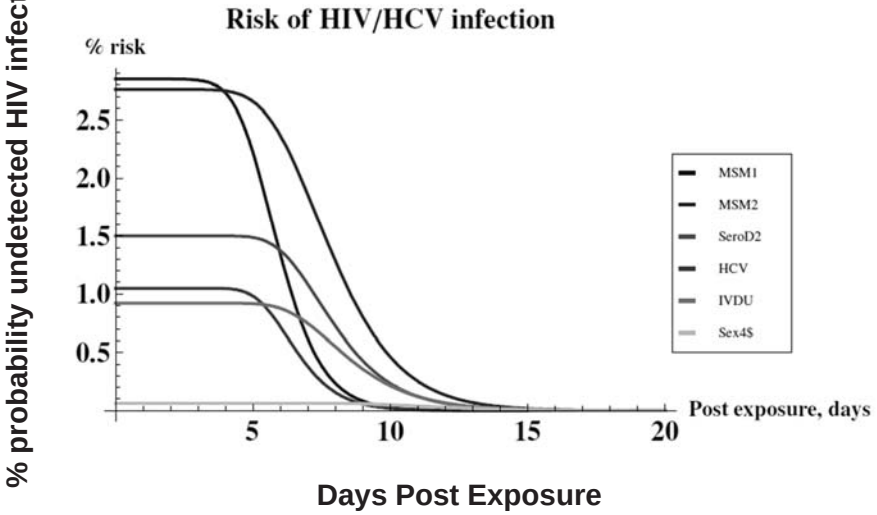
- PubMed Search terms: HIV screening, HCV screening, NAT assay, mathematical models
- Variables for selection
  - Window period of detection
  - Sensitivity
  - Specificity
  - Lower limit of detection

Methods: Monte Carlo Simulation

- Estimation of the upper end probability of undetected HIV or HCV infection by day following each increased risk exposure
  - Single exposure
  - Per-act transmission risk at the reported 95% CI
  - Negative NAT
- Risk computation based on
  - Log-normal distribution per act viral inoculum
  - Log-normal distributed NAT detection threshold
  - Normally distributed viral exponential growth rate
  - Mean initial viral inoculum assumed to be proportional to per act infection risk
  - Several studies supported these assumptions
- Viral growth simulated 1000x per behavior
- Resulting simulation results closely fit a 4 parameter Johnson S_U distribution

Results

Probability of undetected HIV and HCV infection despite negative nucleic acid testing by increased risk behavior



"A model to estimate the probability of HIV and HCV infection despite negative nucleic acid testing among increased risk organ donors", Pallavi Annambhotla[#], Brian Gurbaxani[#], Matthew Kuehnert, Sridhar Basavaraju (under review, *Transplant Infectious Diseases*)

Results

Percent risk probability of HIV and HCV infection undetected by pre-donation NAT screening, expressed by percentage by days since exposure for different increased risk activities

	Days Since Exposure (%)						
Risk Behavior	1	5	10	28	91	182	365
HCV IDU	1.05	0.98	0.02	1.05×10^{-9}	0	0	0
HIV IDU	0.92	0.92	0.21	5.13×10^{-6}	9.19×10^{-16}	0	0
MSM1	2.85	2.22	0.03	2.79×10^{-9}	0	0	0
MSM2	2.76	2.66	0.46	4.72×10^{-6}	0	0	0
Sex with CSW	0.06	0.06	0.05	3.56×10^{-5}	1.26×10^{-11}	1.68×10^{-16}	0
Sero-discordant couple	1.50	1.49	0.23	3.02×10^{-6}	6.66×10^{-16}	0	0

Based on the resulting time to NAT threshold crossing after fitting a Johnson S_U distribution

Notable Organ Transplant-Transmitted Infections Investigated by Public Health Authorities: United States, 1985-2014

- **HIV, 1985**
- **Hepatitis C (HCV), 2000**
- **Chagas Disease, 2001**
- **West Nile Virus (WNV), 2002**
- **Lymphocytic Choriomeningitis Virus (LCMV), 2003**
- **Rabies, 2004**
- **LCMV, 2005**
- **WNV, 2005**
- **Chagas, 2006**
- **HIV/HCV, 2007**
- **Tuberculosis (TB), 2007**
- **LCMV, 2008**
- **Babesiosis, 2008**
- **WNV, 2008**
- **Zygomycosis, Coccidiodomycosis, TB, 2009**
- ***Balamuthia mandrillaris*, HIV in a living donor, 2010**
- **WNV, HCV (organ and tissue), 2011**
- **Microsporidium, TB 2012**
- **Rabies, LCMV, MRSA, 2013**
- **Microsporidiosis, 2014**

Approximately 1% of transplants result in suspected, unexpected disease transmission; 0.2% are confirmed

Unusual Transplant-transmitted Infectious Encephalitis Clusters

Clusters in the United States, Reported to CDC, 2002-2014			
Infectious Agent	Total donors and clusters	Total Recipients	Total Deaths
West Nile virus	6	16	4
LCMV	4	13	10
Rabies	2	8	5*
Balamuthia mandrillaris	2	7	3**
Microsporidia	1	3	1**
Total	15	47	23

* Three recipients received rabies post-exposure prophylaxis and survived.
** remaining recipients received prophylatic treatment and survived.
Emerg Infect Dis 2014.

LCMV: Lymphocytic choriomeningitis virus
Basavaraju SV, et al.

Common Themes in Unusual Transplant-transmitted Infection Clusters

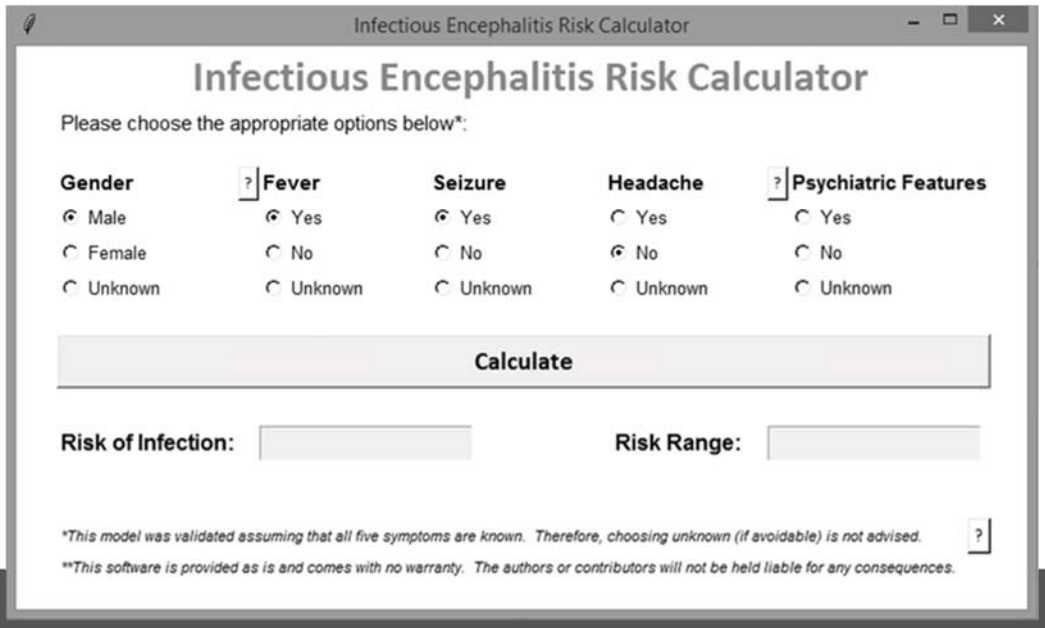
- **Donor infection is unrecognized**
  - Diseases are rare and infrequently encountered
  - Some donors have no evidence of infectious cause of death
  - Other donors diagnosed with meningoencephalitis of unknown cause, but have evidence of infectious etiology including abnormal lumbar puncture
- **Disease risk factors are not known (e.g., microsporidia)**
- **Donor risks and exposures are not clearly identified**
  - Next of kin complete the donor history questionnaire, but they may be unaware of exposures or certain behaviors

What is CDC working on?
Development of Risk Stratification Model Identifying Donors with Infectious Encephalitis

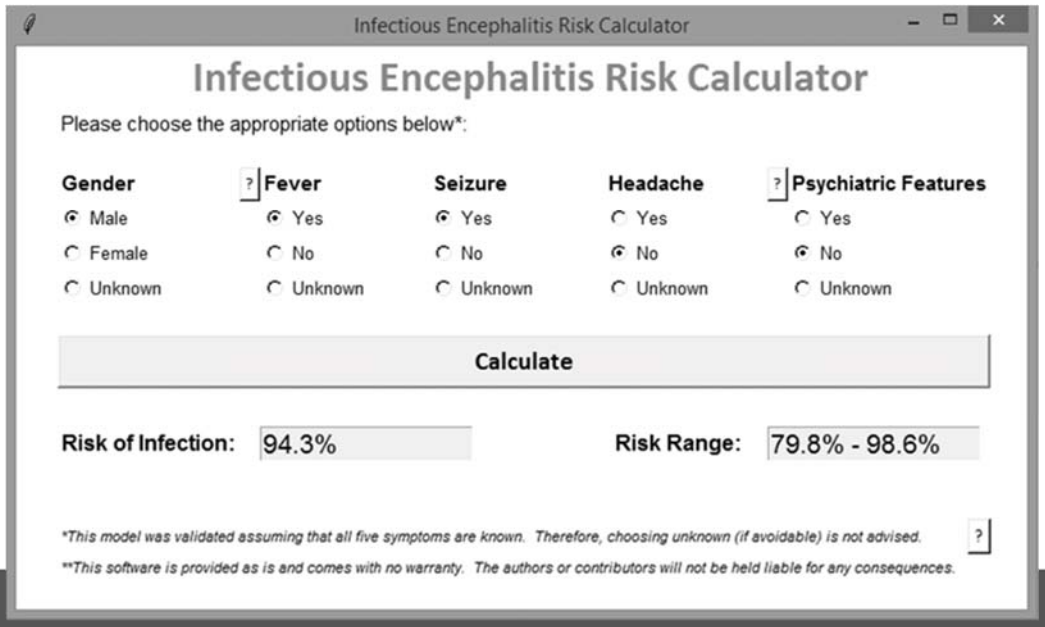
1. **Clinical tool to identify donors with infectious encephalitis**
   - Must distinguish infectious from non-infectious encephalitis
   - Use available clinical data including
     - Fever and other symptoms
     - Cerebrospinal fluid analysis
     - Imaging results (e.g., CT, MRI and x-rays)
   - Incorporate donor history questionnaire

2. **Properly allocate organs from donors with infectious encephalitis**
   - Maximize survival benefit for recipients

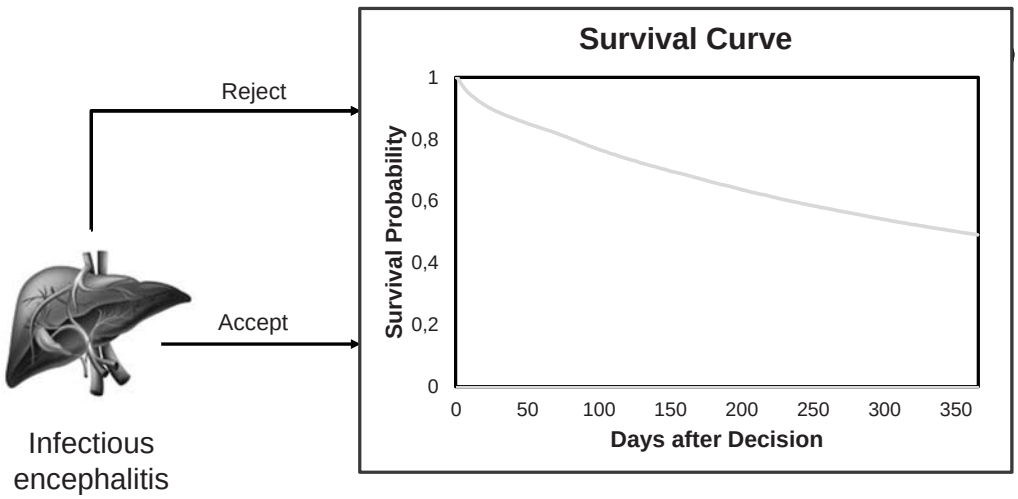
Infectious Encephalitis Risk Calculator



Infectious Encephalitis Risk Calculator

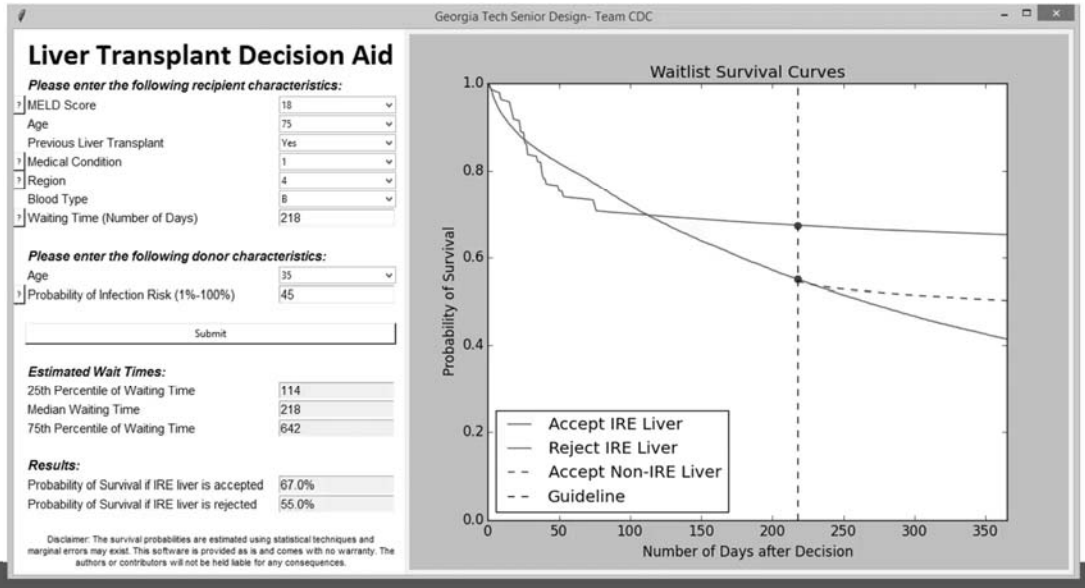


Who could benefit most from a liver from these donors?



Infectious encephalitis risk liver available for transplant

Encephalitis donor Liver Transplant Decision Aid



Conclusions

- Donor-derived disease transmission risk is low; main consideration for patients on wait list is organ availability
- U.S. has a case reporting, but not surveillance, system for suspected donor-derived disease transmission
- Active surveillance would allow for more timely detection and accurate estimates of incidence/prevalence
- Mathematical modeling can augment surveillance efforts to estimate infectious disease risk among organ donors to better inform clinical decision making

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- **HRSA: Melissa Greenwald, James Bowman**
- **CDC: Matthew Kuehnert, Pallavi Annambhotla, Brian Gurbaxani**

Thank you

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion

ADDITIONAL SLIDES

Case reports of infectious and non-infectious encephalitis

Case data (370 records):
Infectious encephalitis caused by four viruses:
- West Nile Virus
- Rabies
- Balamuthia Mandrillaris
- Lymphocytic Choriomeningitis

Control data (96 records):
Non-infectious encephalitis causes:
- Autoimmune
- Bickerstaff
- Optic Neuritis
- 12 more causes

Limitations:
Small sample size
Missing data fields
Unknown true population ratio of case to control

Variable selection to determine infection risk

Method	Gender (98%)	Fever (93%)	CSF Protein (72%)	Seizure (71%)	Headache (71%)	Psychiatric (95%)	Abnormal MRI (62%)	Altered Mental State (87%)	CSF WBC (75%)
CART	x	x	x	x	x				
Sequential		x		x	x	x			
Binary	x	x	x	x	x	x	x		
Forward	x	x		x	x	x			
Backward		x		x	x	x	x		
Best Subset	x	x	x	x	x	x	x	x	

Infectious encephalitis identification