



# Monitoring the occurrence of adverse events associated with use of medical products of human origin in the United States

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ICCBBA Global Forum on MPHO

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# Declaration of conflict of interest

- Nothing to declare

# Outline

- What is surveillance?
- CDC activities and challenges related to monitoring adverse events in
  - Blood
  - Organ
  - Tissue

**What is surveillance?**

# 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

# 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)

# Regulation of MPHO

# Regulation of MPHO

- Food and Drug Administration has regulatory authority over blood and blood products, tissues, and cellular therapies
  - Licensing and approval of MPHO donor/donation infectious disease screening test
- Health Resources and Services Administration has oversight over solid organ transplantation
  - Organ Procurement and Transplantation Network
  - All Organ Procurement Organizations and Transplant Centers are members
- Hospital oversight by accrediting organizations and state governments

**Blood**

# Blood transfused in United States - 2017

- RBC: 10,575,000 units
- Platelets: 1,936,000 units
- Plasma: 2,318,000 units
- Cryoprecipitate: 1,068,000 units

# Blood surveillance - National Healthcare Safety Network Hemovigilance Module

- ~300 hospitals enrolled
- Includes reports of
  - transfusions-transmitted infections and other adverse events
  - total number of transfusions
- Standard definitions required
- Training
- Reports reviewed by CDC at least monthly

# National Healthcare Safety Network Hemovigilance

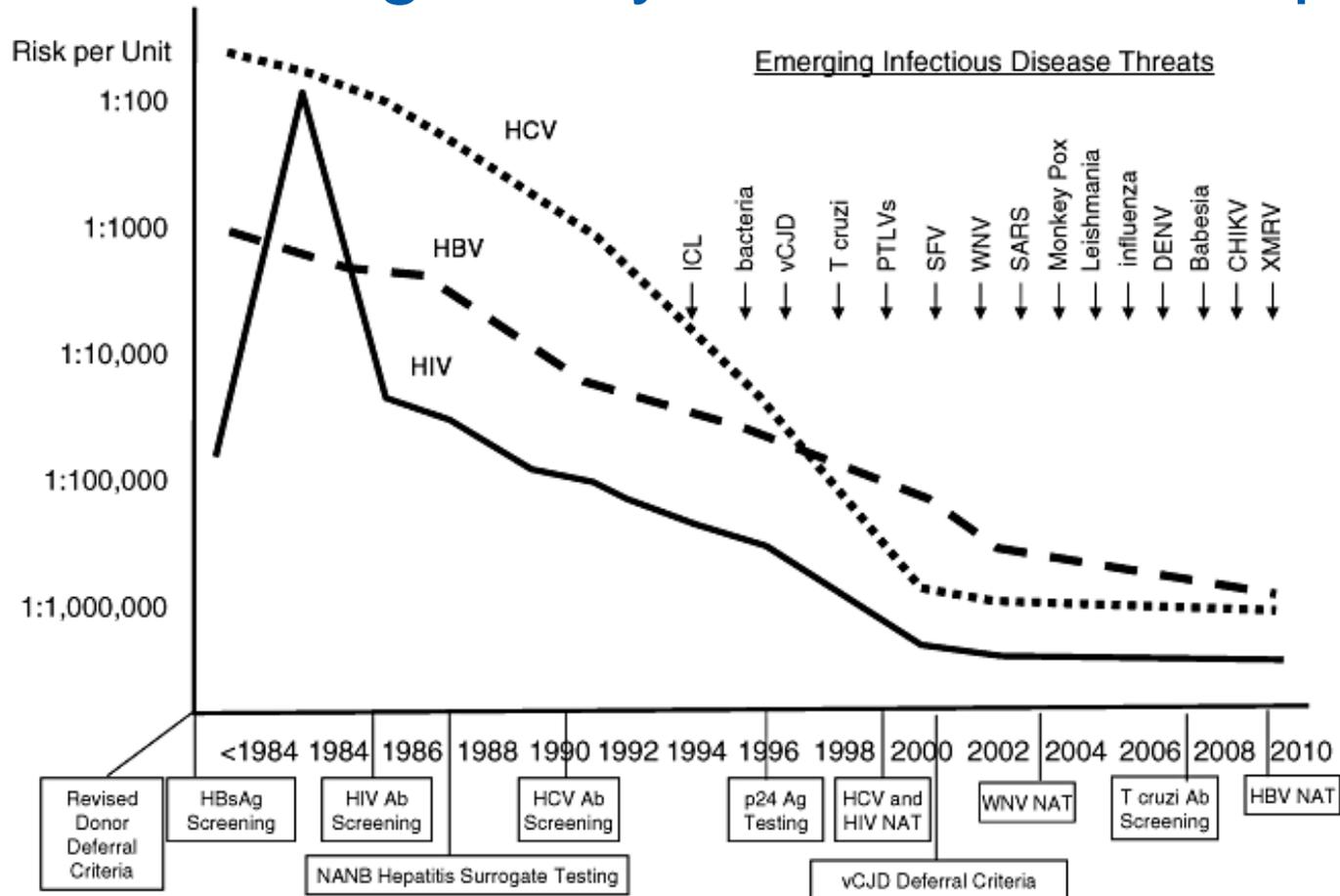
## Module data – 2010-2016

- 54 transfusion-transmitted infections
  - 4 deaths, 5 life-threatening
- 1 viral infection (HCV)
- 16 parasitic infections (all *Babesia* spp.)
- 37 bacterial infections
- Rates:
  - Total 0.68 TTI per 100,000 transfused components
  - Bacterial contamination of apheresis PLT (1.95 per 100,000) > whole blood-derived PLT (0.86 per 100,000)

# Is the Hemovigilance Module surveillance?

- Passive reporting by transfusion facilities to Hemovigilance Module
- Numerator reporting
  - Standardized definitions of adverse events reported
- Denominator reporting
  - Regularly reporting of number of transfusions by product type
- Data regularly analyzed
- Yes, it is a surveillance system

# Increasing safety of U.S. blood supply



Adapted from TRANSFUSION 2006;46:1624-1640

# Case study: Zika virus outbreak in Puerto Rico

- First locally-acquired case in Puerto Rico in December 2015
- From April 3 – August 12, 2016, estimated 469,321 persons in Puerto Rico (12.9% of population) were infected\*
- Concern for safety of US (including Puerto Rico) blood supply



The screenshot shows the top portion of the Wall Street Journal website. At the top right, there are links for "Subscribe Now" and "SPECIAL OFFER: JOIN N". The main header features the "THE WALL STREET JOURNAL" logo in a large, serif font. Below the logo is a navigation menu with links for "Home", "World", "U.S.", "Politics", "Economy", "Business", "Tech", "Markets", "Opinion", "Arts", "Life", and "Real Estate". A horizontal carousel of news items is displayed below the navigation menu, each with a small image and a headline. The first item shows a man in a suit with the headline "Merkel Condemns Russian Strikes in Syria". The second item shows a rocket launch with the headline "North Korea Rocket Launch Could Boost Kim Domestically". The third item shows a group of people with the headline "Protests Escalate Against Greek Plans for Migrant Camps".

WORLD | LATIN AMERICA

## Brazil Identifies Two Cases of Zika Transmitted by Blood Transfusions

Provincial health authorities say two people found to have been infected with mosquito-borne virus when they got transfusions in early 2015

By REED JOHNSON and LUCIANA MAGALHAES

Updated Feb. 3, 2016 11:45 p.m. ET

SÃO PAULO—Health officials in Brazil reported two cases of the Zika virus being transmitted through blood transfusions, the latest challenge in the global battle

\*Chevalier et al. Use of blood donor screening data to estimate Zika virus incidence, Puerto Rico, April–August, 2016. *Emerg Infect Dis.* 2017 May 15; 23(5).

# CDC Zika blood safety activities

- Hemovigilance module modified to collect data on transfusion-transmitted Zika
  - Trainings given to participating hospitals
- Rapid assessment of blood collection and utilization in Puerto Rico
- CDC supports FDA blood donation screening requirements by providing epidemiologic insight into Zika risk in US states



# Challenges in hemovigilance

- No robust national hemovigilance system
  - <10% of acute hospitals report to Hemovigilance Module
- Patchwork system of various adverse reaction reporting
  - FDA only requires reporting of transfusion-related deaths and product deviations
  - Blood centers request facility reports but are not aggregated nationally
- No mandate to report to CDC
- State reporting requirements vary

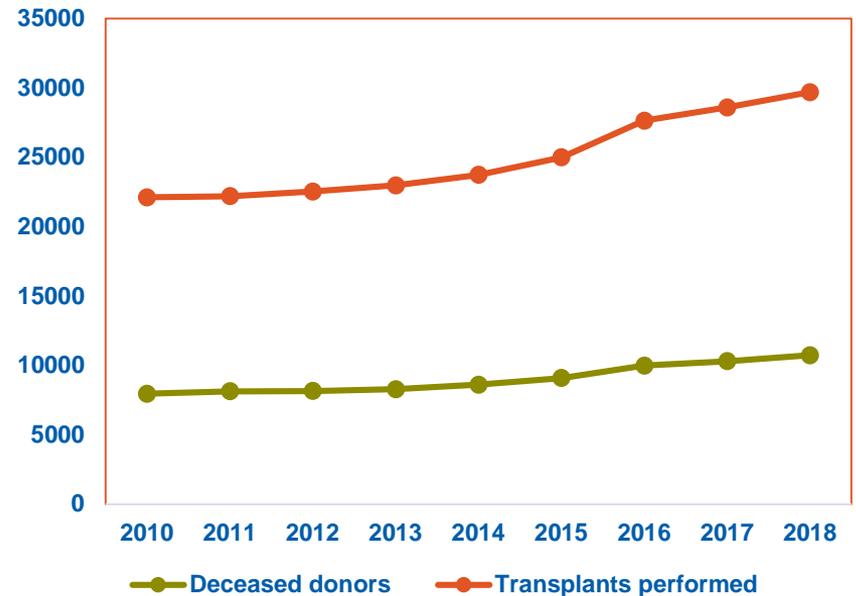


**Solid organs**

# Organ supply in United States

- Number of deceased donors and transplants increasing
- Waiting list also increasing
  - >110,000 on waiting list
- 6,000 on waiting list died during 2018

Number of deceased donors and transplants performed — United States, 2010–2018



# National Organ Transplant Act

- Passed in 1984
- Established Organ Procurement and Transplantation Network (OPTN)
  - Directs organ allocation
  - Links all organizations involved in donation and transplantation
  - Establishes transplant policies
- Established Organ Procurement Organizations (OPO)
  - Evaluate donor and recovers organs
  - Coordinate matching organs to recipient

# Monitoring of solid organ donor-derived disease transmission events in the United States

- OPO's and transplant centers must report suspected donor-derived disease transmission events to the OPTN.
- OPTN is then tasked with determining whether that event was derived from the donor
  - Performed by disease transmission advisory committee
- Results of organ donor-derived investigations
  - Education to transplant community
  - Policy changes
    - After rabies and LCMV investigations, animal contact questions added to donor questionnaire
    - After toxoplasmosis transmission resulting in severe morbidity in recipients beyond heart, universal toxoplasmosis screening implemented

# Role of CDC

- CDC not regulatory agency
- As member of disease transmission advisory committee, investigates potential infectious disease transmissions
  - Nationally notifiable diseases in donor or recipient
  - Multiple ill recipients
  - Encephalitis in donor or recipient(s)
  - Unknown syndrome
- ~ 50 case investigations annually are referred to CDC

# Notable Organ Transplant-Transmitted Infections Investigated by Public Health Authorities: United States, 1985-2017

- 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, Coccidiomycosis, 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
- HAV, TB, 2015
- Tularemia, 2017
- EEEV, 2017

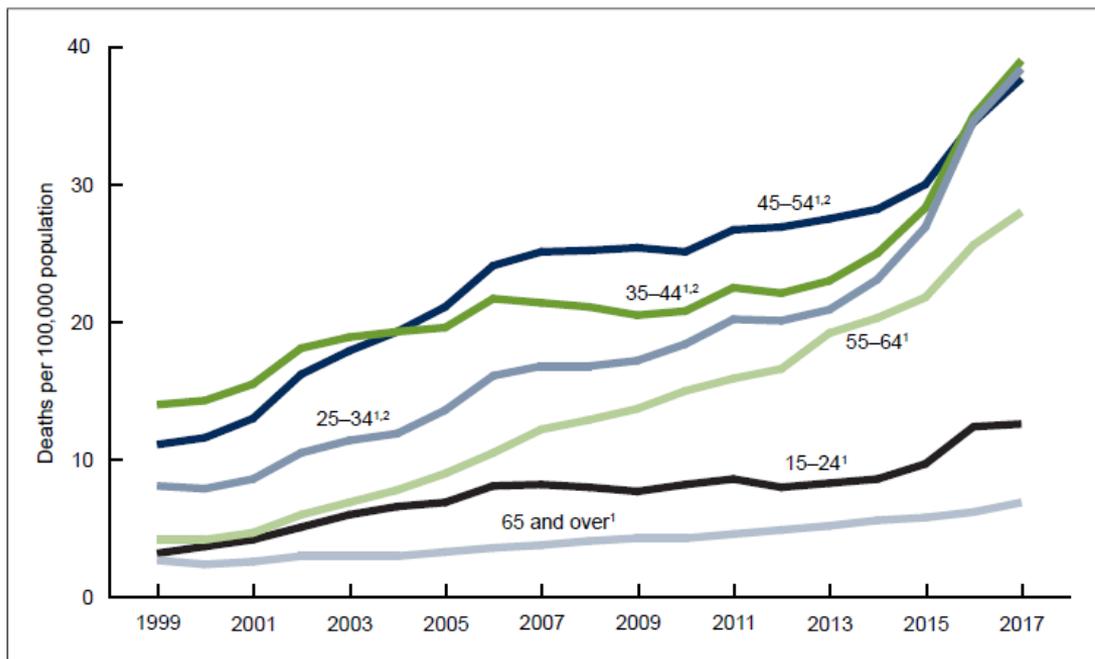
# DTAC reports 2005–2017

Disease type	Donors	Recipient potentially involved	Recipients with proven or probable transmission	Recipient deaths attributed to donor -derived disease
Malignancy	577	1342	164	43
Viruses	463	1463	216	27
Bacteria	467	1524	230	21
Fungi	299	1043	179	26
Mycobacteria	136	468	35	7
Parasites	118	385	103	17
Other disease	121	402	68	3
<b>Total</b>	<b>1980</b>	<b>5688</b>	<b>908</b>	<b>135</b>

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

# Fatal overdose by age group, United States, 1999-2017

<https://www.cdc.gov/nchs/data/databriefs/db329-h.pdf>



<sup>1</sup>Significant increasing trend from 1999 through 2017 with different rates of change over time,  $p < 0.005$ .

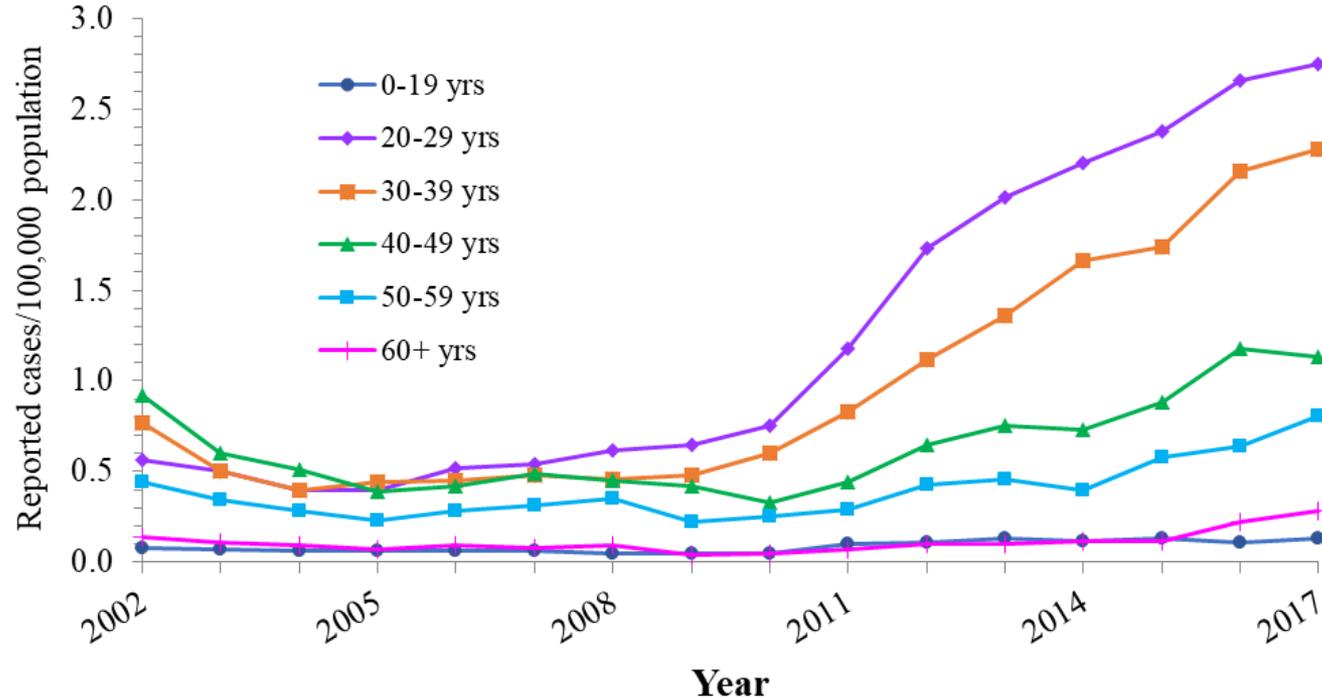
<sup>2</sup>2017 rates were significantly higher for age groups 25-34, 35-44, and 45-54 than for age groups 15-24, 55-64, and 65 and over,  $p < 0.05$ . The rate for age group 35-44 was significantly higher than the rate for age group 45-54 and statistically the same as the rate for age group 25-34.

NOTES: Deaths are classified using the *International Classification of Diseases, 10th Revision*. Drug-poisoning (overdose) deaths are identified using underlying cause-of-death codes X40-X44, X80-X84, X85, and Y10-Y14. Access data table for Figure 2 at:

[https://www.cdc.gov/nchs/data/databriefs/db329\\_tables-508.pdf#2](https://www.cdc.gov/nchs/data/databriefs/db329_tables-508.pdf#2).

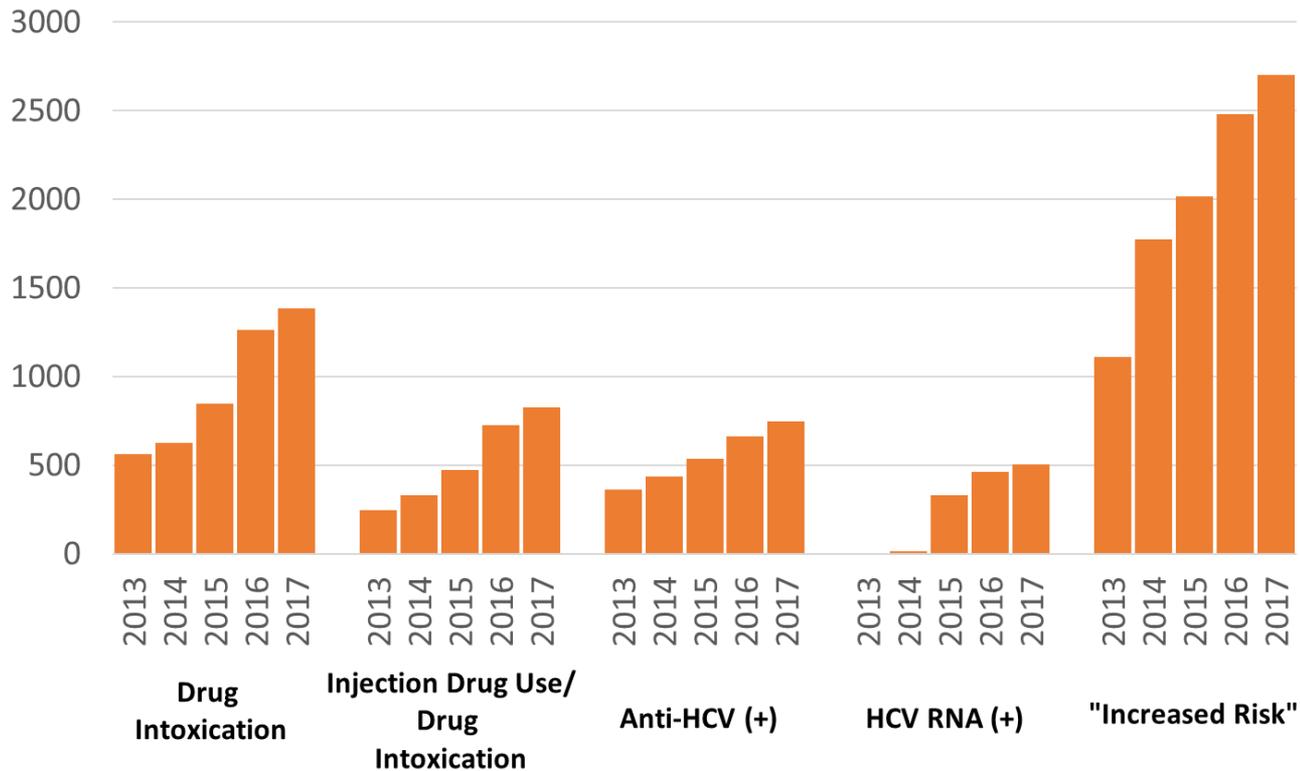
SOURCE: NCHS, National Vital Statistics System, Mortality.

# Rates of reported acute hepatitis C, by age group — United States, 2002–2017



Source: CDC, National Notifiable Diseases Surveillance System.

## Risk Characteristics of Deceased Organ Donors, United States, 2013-2017



Source: Abara, et al. MMWR, 2019; 68(3);61–66

# Is current system of reporting solid organ donor-derived disease surveillance?

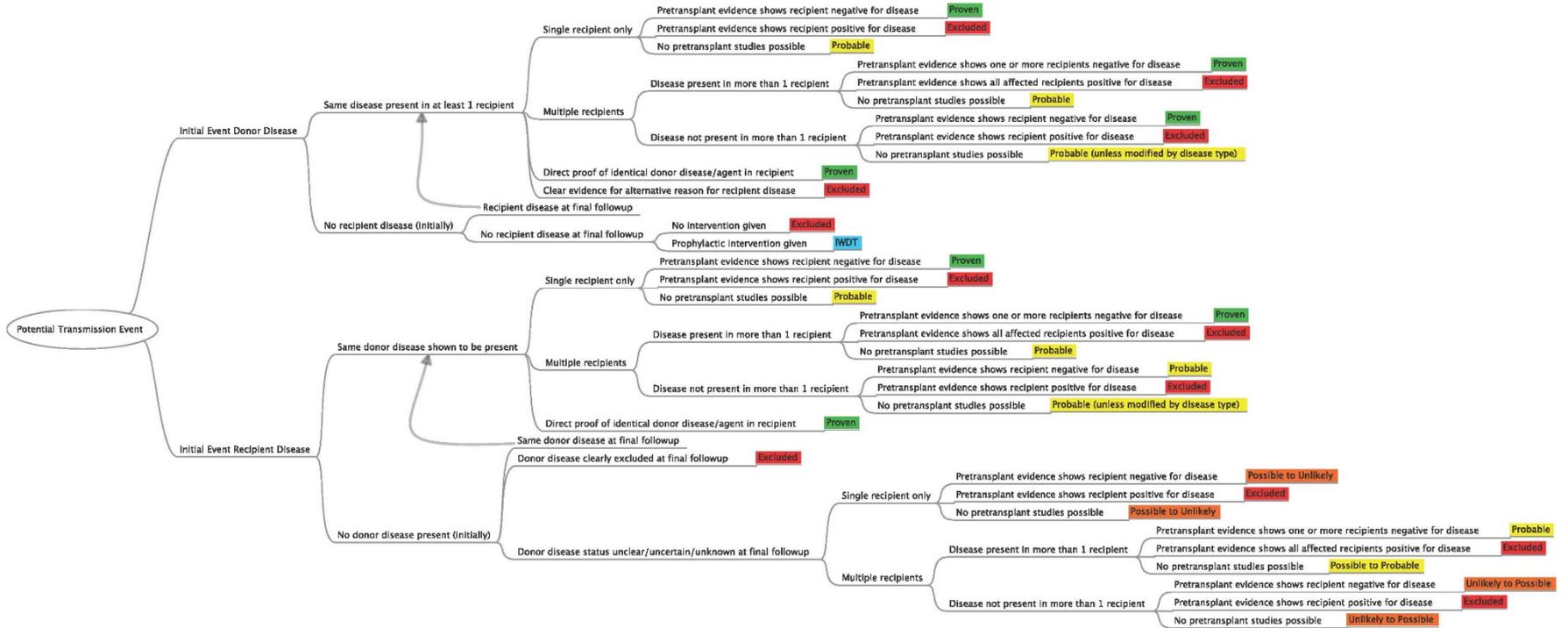
- Passive reporting by facilities to OPTN (referred to DTAC for review)
  - Transplant centers
  - Organ procurement organizations
- Numerator reporting
  - No standardized criteria for what is reported
    - Any infectious disease or malignancy suspected to be transmitted to an organ recipient from 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
- Case reporting system and not surveillance

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

- Acute Flaccid Myelitis
- Amebic encephalitis
- Anaplasma or Ehrlichiosis
- Anthrax
- Arboviral Infections
- Babesiosis / *Babesia microti*
- Brucellosis / *Brucella* species
- California Serogroup Virus Diseases
- Chagas / *Trypanosoma cruzi* (*T. cruzi*)
- Chikungunya Virus Disease
- Coccidioidomycosis (*Coccidioides* species) /Valley Fever
- Enterovirus D68, A71
- Fungi/Mold (if growing from sterile site o e.g. blood culture excluding *Candida* species)
- Hantavirus
- Hepatitis A
- Hepatitis B (active only) \*
- Hepatitis C (acute, past or present)2
- Histoplasmosis
- HIV Infection
- Influenza-associated pediatric mortality
- Lymphocytic choriomeningitis virus (LCMV)
- Leptospirosis / Leptospira Fever, Crimean-Congo Hemorrhagic Fever
- Listeriosis / *Listeria monocytogenes*
- Lyme disease / *Borrelia* species
- Malaria / *Plasmodium*species
- Measles / Rubeola
- Microsporidia
- Middle East Respiratory Virus(MERS)
- Mumps
- New WorldArenavirus
- Pandemic Influenza strains
- Plague / *Yersinia pestis*
- Poliomyelitis, paralytic
- Poliovirus infection,nonparalytic
- Q fever / *Coxiella burnetii*
- Rabies, animal or human
- Rubella / German Measles
- Severe Acute Respiratory Syndrome (SARS)- Associated Coronavirus Disease
- Smallpox/Variola
- Spotted Fever Rickettsiosis
- Strongyloides
- Tuberculosis (TB)
- Tularemia / *Francisella tularensis*
- Varicella / Chickenpox
- Viral Hemorrhagic Fevers • West Nile Virus Disease
- Zika virus

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- **Zika virus**



**Tissue**

# Tissue transplantation in the United States

- National Tissue Recovery through Utilization Report – voluntary survey sponsored by U.S. government to all tissue banks
  - Performed in 2007, 2012, 2015
- 3,294,066 grafts distributed in 2015
- Over half of U.S. tissue banks distribute tissues internationally
  - Most common countries distributed to are U.K, Canada, and South Korea

## Reports of Suspected Transmission of Disease or Graft Failure Following Transplantation in 2015

Causes of disease or graft failure	Number of reports
Bacterial	147
Other infection	78
Viral	6
Malignancy	5
Fungal	3
Graft failure only	117
Total	356

# Is there a surveillance system for tissues?

- Numerator reporting
  - Notification of adverse events is voluntary
- Denominator reporting
  - No ongoing collection of number of procured or transplanted tissues
- No surveillance system in place

# Challenges in tissue surveillance

- Lack of standard coding and nomenclature
- Notification of adverse events is voluntary
  - Tissue banks required to track to level of transplant facility
  - Transplant facilities asked to fill “implant card” with date/type of procedure and healthcare provider/recipient information
  - >50% of tissue banks receive <50% of implant cards
- In many healthcare facilities, tissue management decentralized

# Case study: HCV transmitted from deceased donor

- 2 kidney recipients diagnosed with post-transplant HCV infection
- Laboratory error led to misreading positive HCV NAT as negative
- 44 tissue allografts procured from donor
- From time CDC notified
  - Mean time to locate and notify physician who transplanted graft: 13 days
  - Mean time to notify and test tissue recipient: 29 days

# Case study: amniotic tissue product

- 4 patients developed surgical site infections at a single hospital
  - All had received amnion tissue allograft from common donor
  - 2 patients and unopened vial had WGS-linked *Mycoplasma hominis*
- 30 product vials produced and shipped to 7 states
  - Implant cards not always helpful
    - No fields for date information filled or adverse event
    - Some implant cards inaccurate
  - 5 vials unable to confirm if transplanted because of lack of proper documentation

# Opportunities to improve monitoring of MPHO safety

- Blood
  - Improve participation in Hemovigilance Module
- Organs
  - Establish standardized criteria for what needs to be reported
  - Perform ongoing analysis and report data to detect trends
- Tissues
  - Adopt common nomenclature and coding for tissue specific to donor
  - Establish tissue traceability requirements
  - Consider surveillance system for adverse events

For more information, contact CDC  
1-800-CDC-INFO (232-4636)  
TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



# Disease reporting by transplant centers and OPOs

- Variable by center
  - Bronchoscopy, blood, urine culture reported
  - Certain organisms frequent, treated by standard antimicrobial prophylaxis, and no associated with significant morbidity/mortality
- Donor infection might 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
  - Suspecting donor-derived disease responsibility of transplant centers/OPO
  - Some infections difficult to recognize and diagnose in recipient
  - Geographic distance
  - Timeliness of information