

13th Annual Canadian Blood Services International Symposium

Blood-Borne Pathogens: Defend, Detect, and Destroy

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CURRENT PERSPECTIVES ON TRANSFUSION-TRANSMITTED INFECTIOUS DISEASES: EMERGING PATHOGENS WORLDWIDE

Roger Y. Dodd PhD
Canadian Blood Services
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Conflict of Interest Disclosures

Roger Y Dodd

- I have had, in the past 5 years, financial interest, arrangement or affiliation with the following organizations that could be perceived as a direct or indirect conflict of interest in the content of this presentation:
 - Consultant: Quotient/Mosaiq, Roche
 - Speaker's honorarium: Cerus, Grifols



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Reports that say that something hasn't happened are always interesting to me, because as we know, there are known knowns; there are things we know that we know. There are known unknowns; that is to say, there are things that we now know we don't know. But there are also unknown unknowns – there are things we do not know we don't know.

—Former [United States Secretary of Defense](#), [Donald Rumsfeld](#)

Outline

- What are emerging infections and why do they occur?
- Why do some emerging infections impact blood safety?
- How is the impact managed?
- Some current examples
- Summary and comments

Emerging Infectious Diseases

“...those whose incidence in humans has increased within the past two decades or threatens to increase in the near future. Emergence may be due to the spread of a new agent, to the recognition of an infection that has been present in the population but has gone undetected, or to the realization that an established disease has an infectious origin. Emergence may also be used to describe the reappearance (or reemergence) of a known infection after a decline in incidence.”
(IOM)

Emerging infections

- Numerous emerging infections
- All classes of agent
- 60-70% are zoonoses
- Most, if not all transmission routes
- Acute and chronic
- Many derive from human activities
- Transportation has a critical role
- Emergence is unpredictable
- Essentially no features are common to all

Why do infections emerge?

- **New agent**
 - vCJD
- **Species jump, possibly with mutation**
 - HIV, SARS
- **Environmental change (eg global warming)**
 - Dengue, malaria, babesia
- **Failure of control – resistance and mutations**
 - HBV mutants, malaria, drug resistance
- **Population movements – migration, travel**
 - T. cruzi, chikungunya
- **Transport of agents, reservoirs, vectors**
 - WNV, monkeypox
- **Behavioral change among humans, including conflict**
 - HIV, leishmania
- **Agriculture, urbanization**
- **In most cases (including those mentioned) there are multiple factors**



<http://openflights.org>

Hot spots: do they help?

- There are areas where emergence is considered to be more likely (hot spots)
 - China (crowds, pigs, ducks – influenza)
 - China (Live food markets, exotic animals – SARS)
 - Africa (Bush meat – HIV)
 - Developing world urbanization, crowds, poor sanitation etc.(HEV)
- Surveillance may be helpful, but not foolproof
- Many EIDS in these conditions respiratory or enteric

Local, global, or both?

- Some infections may be constrained regionally by their epidemiologic characteristics and environment – e.g. Babesia
- Some may expand slowly as a result of population movements, but be constrained in their new environment e.g. Chagas disease
- Infections that spread directly between humans are likely to gain worldwide distribution at differing rates; e.g, HIV, influenza, SARS
- Some may emerge explosively in new areas with appropriate conditions e.g. WNV, dengue, chikungunya
 - Vectors, environment, susceptible population

Can EIDs be predicted?

- Emergence itself is not predictable, other than in general terms
 - “Classic” model not necessarily relevant
- Some events may be more likely
 - Arbovirus outbreaks in the face of travel plus vectors
- Once recognized, impact of an EID on blood safety may be estimated

Potential warning signals

- Outbreak of disease
- Blood-borne nature or potential
- Sentinel populations
 - Chronically transfused
 - Transplant
- But, has any TTI made its first appearance in transfused patients?
 - HIV – 2%, WNV 23 of 3-400,000 infections

Requirements for transfusion-transmitted disease

- Asymptomatic blood-borne phase
 - Chronic and/or acute
- Survival of agent in donated blood
- Infectious by IV route
- Susceptibility of recipients
- Recognized disease in recipients
- Level of concern dependent on
 - Severity, incidence and/or prevalence, rate of emergence

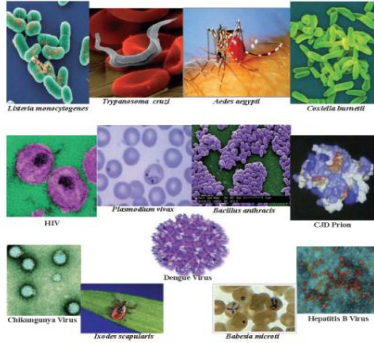
Risk of TTI

- Risk is the chance that a blood recipient will be transfused with an infectious blood unit
 - A direct function of the proportion of donations that are infectious and the number of units received
 - May be impacted by survival of agent in blood and the susceptibility of the recipient

Risk evaluation

- Agent known to be transmissible by transfusion
- Agent has appropriate properties
- Agent similar to known agent
- Agent causes dread disease
- Experimental studies
- Epidemiologic properties
- RBDM

TRANSFUSION



Emerging Infectious Disease Agents and their Potential Threat to Transfusion Safety



August 2009;49:1S-29S

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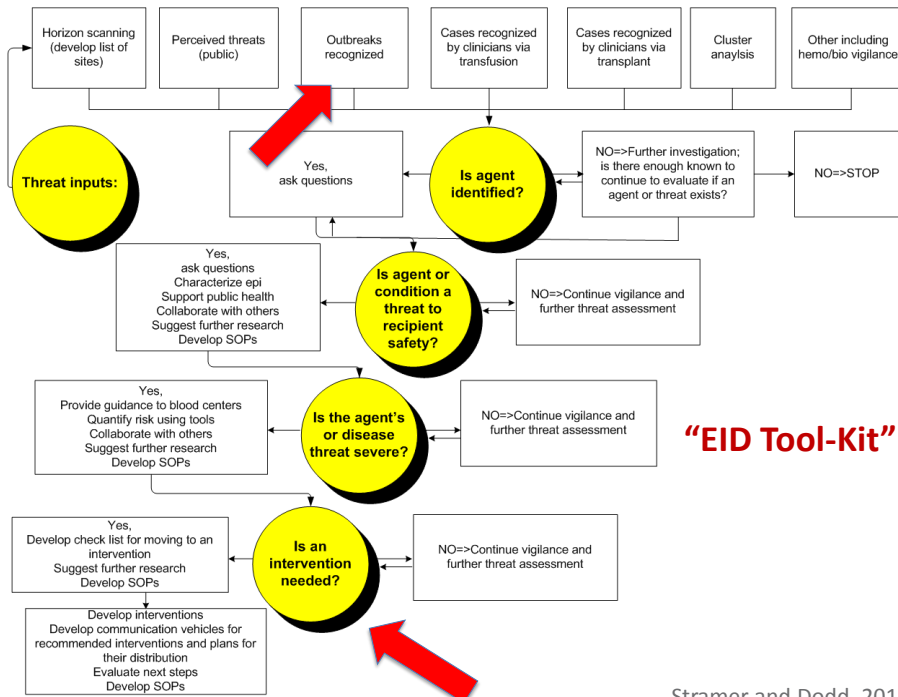
- List and prioritize EIDs lacking a current effective intervention & posing a potential threat to transfusion safety
- 68 agents identified and Fact Sheets developed
- New Fact Sheets added; others updated

Highest Priority Agents:

Dengue viruses

Babesia

vCJD

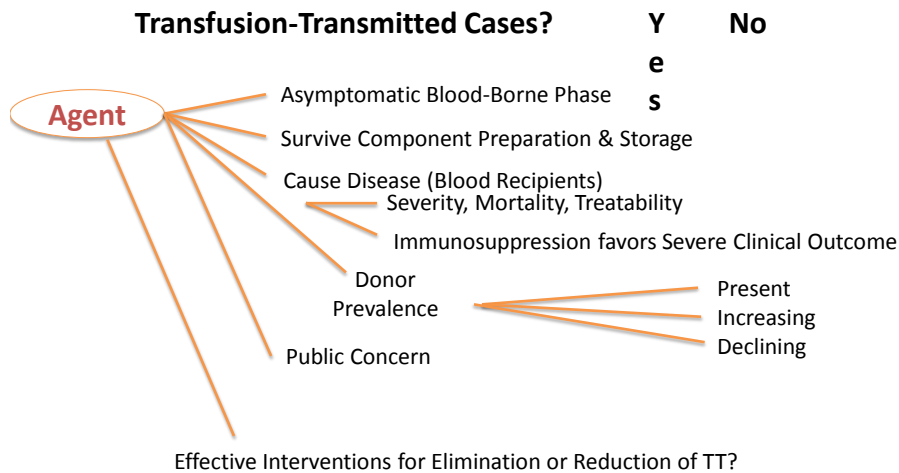


"EID Tool-Kit"

Stramer and Dodd, 2013

Key questions to assess risk of transfusion transmissibility of an infectious agent

Dodd 2012: Practical Transfusion Medicine



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Current concerns?

- Tropical arboviruses
 - WNV, dengue, chikungunya, Zika
- Respiratory infections
 - Influenza, SARS, MERS-CoV
- Tick-borne infections
 - Babesia, SFTSV, Heartland, Bourbon
- Prions
 - vCJD, CWD
 - Other protein-folding diseases – Alzheimers, etc (?)
- Zoonoses
 - HEV, Q fever, Nipah, Hendra,
- Retroviruses
 - Overreaction likely (XMRV)

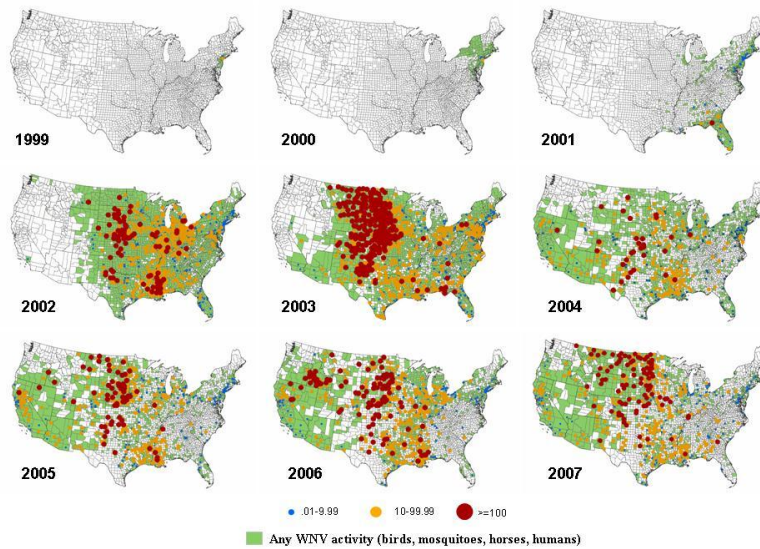
West Nile fever

- Agent: Flavivirus (RNA), transmitted by culicine mosquitoes
- S Europe, Africa, Middle East to India, arrived US 1999, endemic in essentially all of the continental US by 2004
- EID status: Explosive imported outbreak in Americas, but generally stable elsewhere
 - Up to 400,000 individuals infected in 2002, 2003 in US
- Species issues: Infects many vertebrates, birds as amplifying hosts, not naturally transmitted between humans
- Risk status: TTI occurs as a result of high incidence of acute viremia, controlled via NAT in US

What happened in the US?

- Unexposed population, human and avian
- US strain virulent to corvids
- Mosquito feeding preference shifts to humans in summer due to the dispersal of breeding birds
- Irrigation patterns, standing water (abandoned swimming pools), tires, etc.
- Most severe outbreaks associates with heat, drought, however
- Movement into Caribbean, Central and S Americas
 - Human disease, however, is infrequent
- Why aren't there overlapping WNV and dengue – chikungunya epidemics?

WNV Neuroinvasive Disease Incidence, by County, United States, 1999-2007



CDC, courtesy Lyle Petersen

WNV

- 23 cases of TTI reported in 2002
- MP-NAT implemented in 2003
- 13 subsequent cases
 - Donors not detected by pooled NAT
- ID-NAT implemented in areas/times of high incidence

WNV in the US:

Example of a rapidly emerging agent and a successful intervention

Year/No.	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
WNND (16,196)	2946	2866	1148	1309	1495	1227	689	386	629	486	2873
WNV (+) donors (3725)	N/A	714	224	417	437 *	481	218	161	182	139	752
Trans- fusion cases^ (36)	23	6	1	0	2	0	2	0	1 ***	0	1

*2003-2005 reported by CDC ArboNet; 2006-2010 reported by the AABB WNV site

^ All transfusion transmission cases were identified from May-Oct

*** 1 WNV NAT-untested granulocyte

Dodd, Foster, Stramer, Transfus Med Rev. 2015 doi: 10.1016/j.tmr.2015.03.001.

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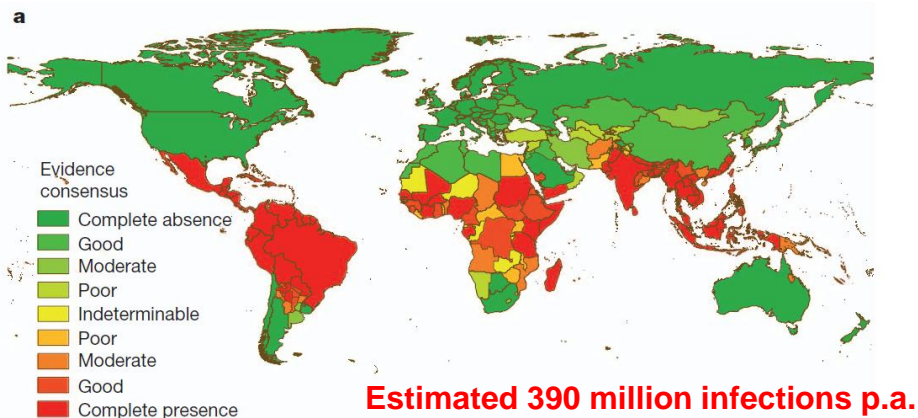
WNV: What did we learn?

- Imported infections unpredictable and may be overwhelming
- Acute infections transmissible by transfusion
- NAT offers rapid route to testing (if appropriate)
- Pooled testing may have inadequate sensitivity
- Epidemic continues to be unpredictable

Dengue viruses

- Mosquito-borne (*Aedes*) flavivirus ; 4 closely related “types”
- Most important arbovirus
- Rapidly expanding global footprint; >2.5 billion people (~1/3 world's population) live in areas of risk; endemic in >100 countries
 - Asia/Latin America – leading cause of hospitalization in children
- Humans are the amplifying host
- No vaccine or specific treatment; vector control is the only effective intervention
- Immunity to a given type is lifelong but cross reactivity between types is short lived and increases risk for severe dengue
- **50-80% asymptomatic**
- **7 clusters of transfusion transmission reported**
 - **Hong Kong, Singapore (2), Puerto Rico (2), Brazil (2)**
- **Kidney, BM transplant, need-stick and lab infections**
- **No FDA-licensed test**
- **Testing under IND in Puerto Rico; yield comparable to WNV**

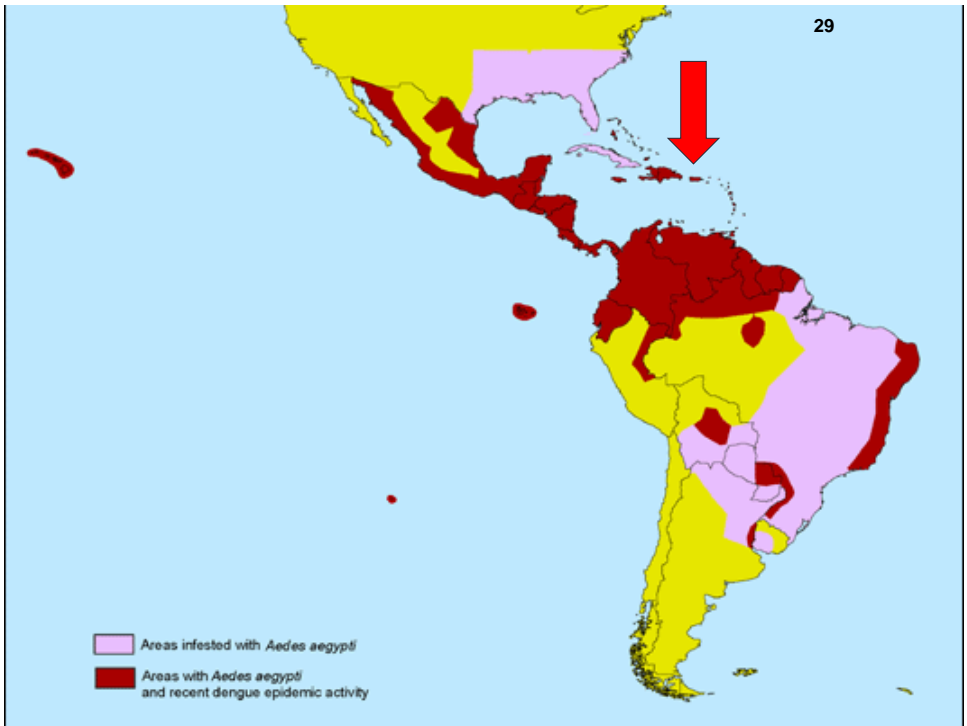
Global Evidence Consensus: Burden of Dengue 2010; complete absence (green); complete presence (red)



The global distribution and burden of dengue

Samir Bhatt¹, Peter W. Gething¹, Oliver J. Brady^{1,2}, Jane P. Messina¹, Andrew W. Farlow¹, Catherine L. Moyes¹, John M. Drake^{1,3}, John S. Brownstein⁴, Anne G. Hoen⁵, Osman Sankoh^{6,7,8}, Monica F. Myers¹, Dylan B. George⁹, Thomas Jaenisch¹⁰, G. R. William Wint^{1,11}, Cameron P. Simmons^{12,13}, Thomas W. Scott^{9,14}, Jeremy J. Farrar^{12,13,15} & Simon I. Hay¹⁻⁹

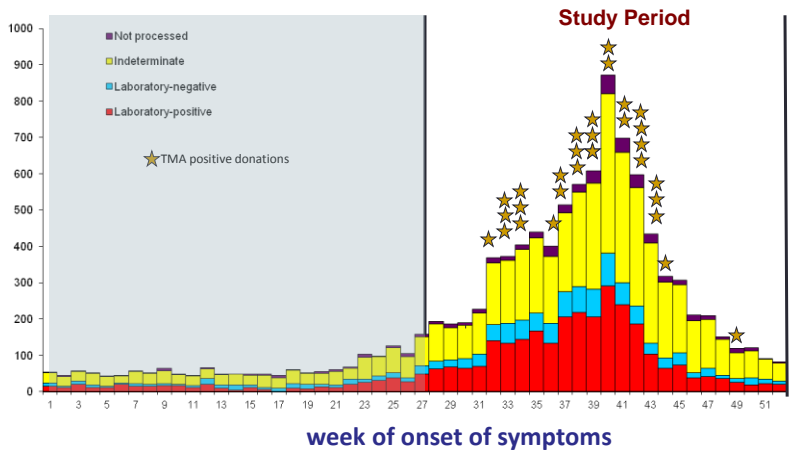
Nature. 2013 Apr 25;496(7446):504-7



2007 Puerto Rico Donation Retrospective Study

Stramer et al. *Transfusion* 2012;52:1657

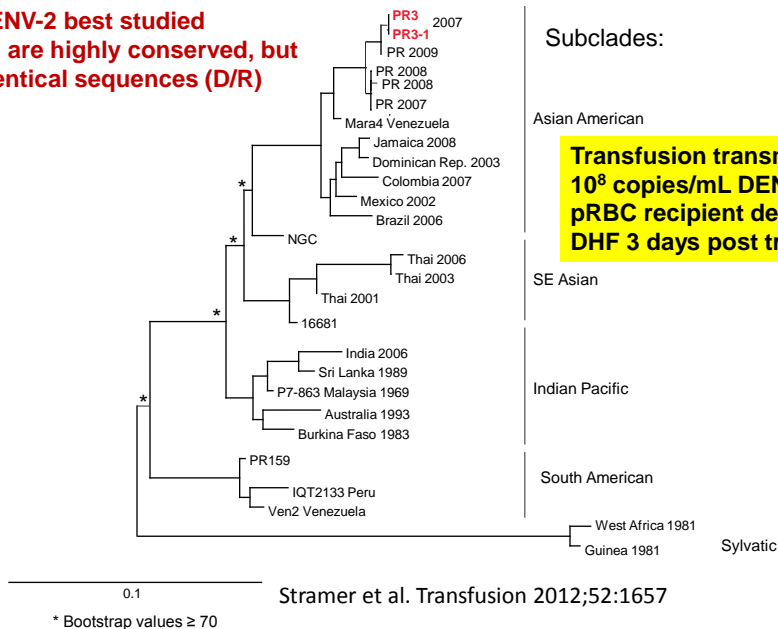
- 29 of 15,325 TMA (+) 1:529; 12 PCR (+) 10^5 - 10^9 copies/mL, DENV-1, 2, 3
- 12 infected mosquito cultures, 6 IgM (+)



TMA = Transcription Mediated Amplification

Maximum Likelihood Sequence Analysis of DENV-2 Env (1482 nucleotides)

**DENV-2 best studied
All are highly conserved, but
identical sequences (D/R)**



Subclades:

Asian American

**Transfusion transmission
 10^8 copies/mL DENV-2
pRBC recipient developed
DHF 3 days post transfusion**

SE Asian

Indian Pacific

South American

Sylvatic

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Dengue Blood Donation Screening under IND in Puerto Rico (2010-2013)

	No. Donations Tested; N=323,498	No. Reactive; N=386	No. (%) Confirmed Positive; N=173 [^]	Rate of Confirmed Positives	No. False Positive; N=213	Rate of False Positives
NS1 Ag 2010-2012	181,232	117	10 (9)	1:18,123	107	1:1,693
Prospective TMA 2012-2013	88,817	171	155 (91) ⁺	1:573 ^{**} (0.17%)	16	1:5,551

[^] 8 additional positives from retrospective testing (NS1 Ag neg/TMA pos)

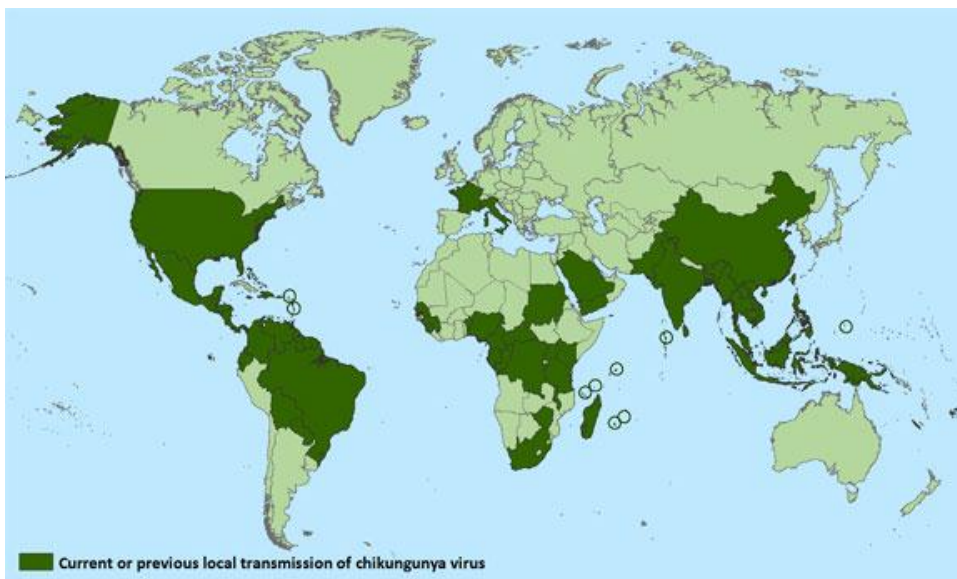
⁺ 20 (13%) NS1 Ag positive at index

^{**} Specificity = 99.98% (95% CI = 99.97-99.99%)

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Chikungunya

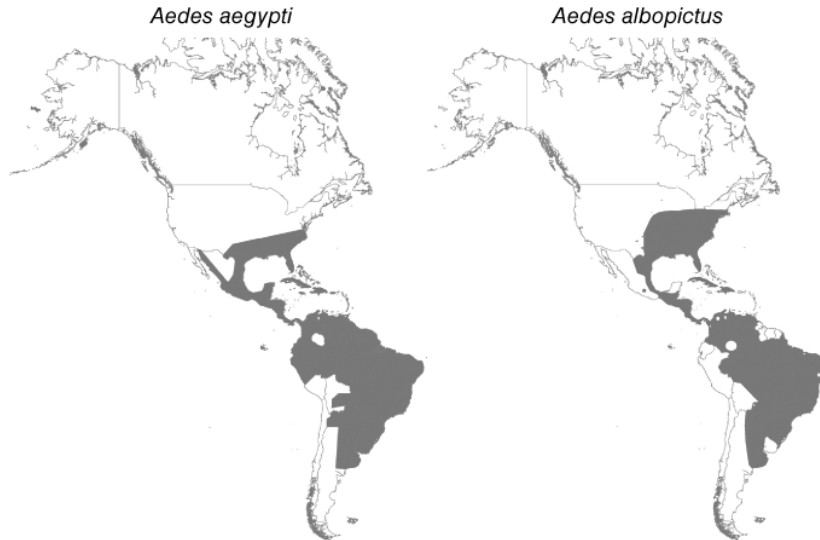
- Toga virus (alphavirus group)
- Mosquito-borne (*Aedes aegypti* & *albopictus*)
- Human-mosquito-human cycle
- Co-exists with DENV
- Has caused massive, explosive outbreaks
- Most recently appeared in Caribbean
- No TTI as yet



March 10, 2015

<http://www.cdc.gov/chikungunya/geo/index.html>

Chikungunya Fever (CHIKV)



Transfusion 2014;54:1911-1915

<http://onlinelibrary.wiley.com/doi/10.1111/trf.12790/full#trf12790-fig-0001>

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Chikungunya Fever – Americas Week 31, 2015



Asiatic genotype
(E2-I211T)

36 http://new.paho.org/hq/images/stories/AD/HSD/IR/Viral_Diseases/Chikungunya/CHIKV-Data-Caribe-2015-EW-31.jpg

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Approaches to Chikungunya

- Stop collection of rbc, plasma
- Deferral for contact/exposure/symptoms
- Active (or passive) post-donation information (PDI)
- NAT for viral RNA
- Pathogen reduction/inactivation
- In non-endemic areas, travel deferrals

- ARC in Puerto Rico
 - Import products from mainland
 - Provide pathogen-reduced apheresis platelets
 - Investigational study, even though product now licensed in US
 - Monitor for evidence of transmission

MERS CoV

- Middle East Respiratory Syndrome Corona Virus
- Apparent origin Middle East
- Zoonosis – Camels, bats?
- Infection transmitted to HCW, family
- Travel cases
- Outbreaks S Korea, China
- Relatively slow expansion
- No evidence of transfusion transmission

SFTSV

- Severe Fever with Thrombocytopenia Syndrome Virus
- Bunyavirus (Phlebovirus)
- Tick-borne
- Central China, but similar virus reported from US (Heartland)
- Also reported from Japan
- Reasonable to assume it is transfusion transmissible, but no reports of such transmission
- Low prevalence, slow expansion

Q Fever

- Causative agent, *Coxiella burnetii* (a small bacterium)
- Transmission routes include airborne
- One report of transfusion transmission
- Recent major outbreak in Netherlands, attributable to intensive goat farming
- Agent identified in donor circulation
- Suggestive, but not definitive evidence to transfusion transmission
- Localized PCR testing
- Outbreak controlled through veterinary public health

HEV

- Hepatitis E virus
- Small, non-enveloped RNA, hepevirus
- Global distribution, 4 genotypes
 - 1, 2 transmitted human-human, feca-orally, massive outbreaks
 - 3, 4, zoonoses transmitted to humans through ingestion
- Good evidence of occasional transfusion-transmission at least by genotype 3
- May cause serious/chronic infection in immunosuppressed
- High seroprevalence (5-30%), but low apparent incidence
- ARC data: 7.7% seroprevalence, 1:9000 RNA positive
- To test or not?

vCJD and other prions

- “New” prion – BSE transmitted to humans via diet
- Intensive farming practices
- Early concern about TTI
- Preventive measures (presumed) implemented
 - Leukoreduction
 - Reduced blood use (esp pediatric)
 - UK stops fractionation
 - Deferrals for residence history
- TTI recognized, 3 clinical, one infection
- Continuing concern, but lessening
- Alert for CWD

Commentary

- Agents, diseases emerge globally but unpredictably
- Many are readily transported globally
- Some EIDS threaten blood safety
- Horizon scanning is important
- Many factors must be considered in the context of blood safety
- Decision-making is complex
- Testing has been effective, but other interventions msy be necessary
- Pathogen reduction/inactivation will likely become increasingly important