

Transfusion transmissible pathogens relevant to the region

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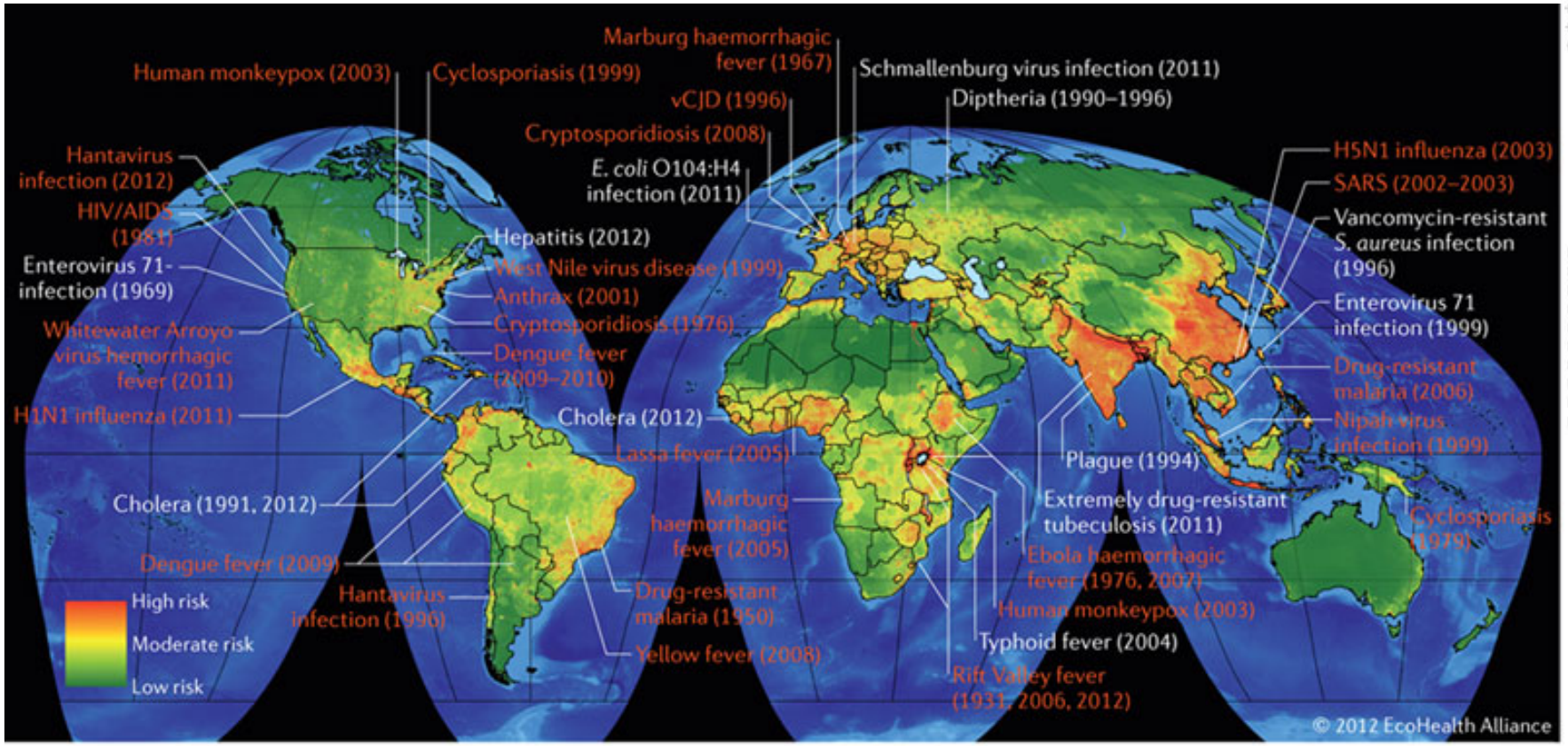
Overview



- Infectious diseases of relevance to region
  - Impact on transfusion safety

- Examples
  - Zika virus
  - Chikungunya virus
  - Hepatitis E virus

Hot spots: infectious disease outbreaks



Nature Reviews | Microbiology

Image: Lipkin WL., Nature Reviews Microbiology 11, 133-141 (2013)

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When do they pose a threat to blood safety?



DIRECT: blood-borne

1. Are present in the donor population at significant levels
2. Demonstrate transfusion transmissibility or high likelihood
3. Lead to a clinically significant infection in blood recipients

INDIRECT: others

- Impact on donor attendance → impact sufficiency



The list is long and growing!

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Zika virus (ZIKV)

- Flavivirus (related to DENV, YFV, JEV, WNV)
  - Icosahedral, enveloped virus
  - Nonsegmented, (+)ssRNA genome
- Two lineages: African & Asian
- Described in non-human primates in Africa in 1947 [1]
- Human infection first described in 1954 [2], but first isolated in Nigeria in 1968 [3]
- Human infection reported in other countries in Africa and Asia[4]
  - Uganda, Tanzania, Egypt, Sierra Leone, Gabon
  - India, Malaysia, the Philippines, Thailand, Vietnam and Indonesia

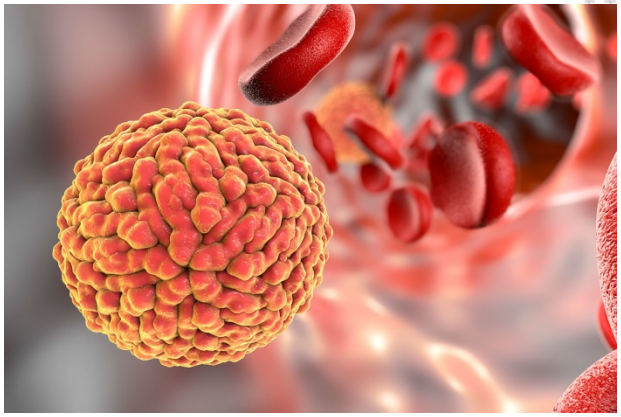


Image: Kateryna Kon/Science Photo Library

1. Dick, GW, et al., Trans R Soc Trop Med Hyg;46: 509-20 (1952); 2. Macnamara, FN. Trans R Soc Trop Med Hyg.;48(2):139-45 (1954); 3. Moore, DL,. Et al Ann Trop Med Parasitol 1975;69:49–64 (1975); 4. .Hayes, E. B. et al., EID 1**5**, 1347-1350 (2009).

Spread outside Africa/Asia

- 1st outbreak outside Africa and Asia on the island of Yap in early 2007 [1]
- Outbreaks have rapidly spread across the pacific
  - French Polynesia, the Cook Islands, Easter Island, New Caledonia[2-6]
- Spread to the America's[7]
  - Mid-2015: Brazil
  - End-2015: Puerto Rico
  - Spreading rapidly → transmission in 31 countries[8]
- Virus spreading in the Americas is most closely related to the Asian strain[9,10]
  - 89% identical to African genotypes

1. Hayes, E. B., EID 15, 1347-1350 (2009); 2. Musso, D., et al. CMI 20, O595-596 (2014); 3. Ioos, S. *et al.* MMI44, 302-307 (2014); 4. Cao-Lormeau, V. M. *et al.* EID 20, 1085-1086 (2014); 5. Dupont-Rouzeyrol, M. *et al.* EID 21, 381-382(2015); 6. Roth, A. *et al. Euro surveillance* 19 (2014); 7. Yakob, L., et al Lancet Glob Health 4(3): e148-9 (2016); 8. http://www.who.int/emergencies/zika-virus/situation-report/4-march-2016/en/; 9. Antoine, E et al., Lancet 387: 227–8. 775124 (2016); 10. Lanciotti, RS, et al., EID. *doi:10.3201/eid2205.160065*. *(*2016)

Current situation

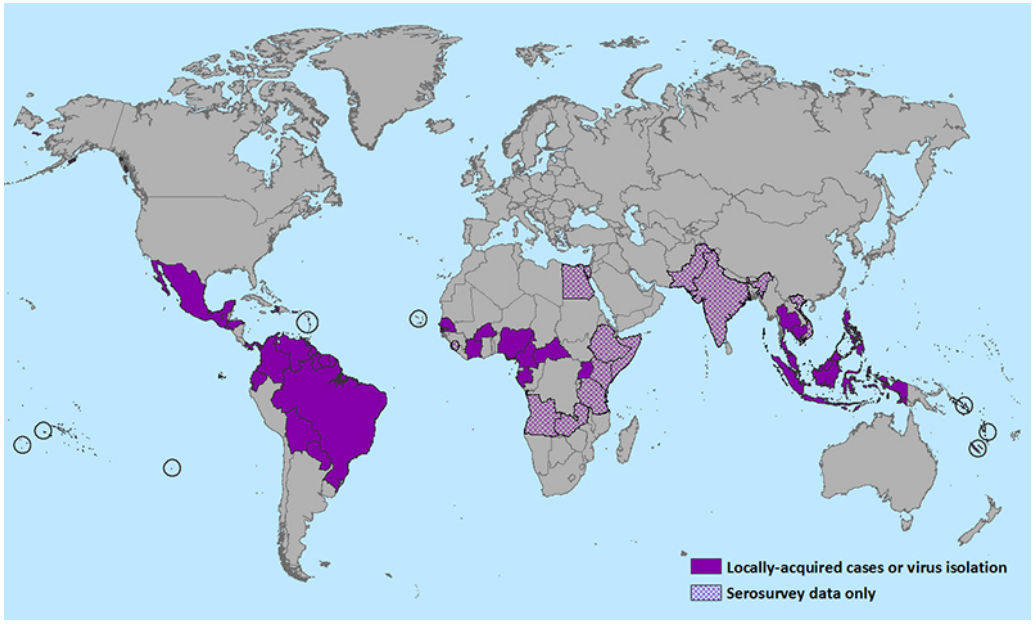


Image: http://gizmodo.com/zika-virus-outbreak-prompts-cdc-to-expand-travel-adviso-1754572559

- 52 countries/territories reported autochthonous transmission or indication of transmission (01/01/07 – 03/03/16)[1]
  - 41 countries/territories since 1 January 2015
- Lao People's Democratic Republic → latest to report autochthonous transmission[1]
- Estimated 1.5 million cases[2]

1. http://www.who.int/emergencies/zika-virus/situation-report/4-march-2016/en/; 2. World Health Organization – Zika situation report (12 February 2016) http://www.who.int/emergencies/zika-virus/situation-report/who-zika-situation-report-12-02-2016.pdf

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Symptoms

- Incubation period not clear → likely a few days
- Symptoms similar to other arbovirus infections, such as DENV[(reviewed in1)]
  - Fever, skin rashes, muscle and joint pain, malaise, headache, **conjunctivitis**
  - Usually mild and last for 2-7 days
- Asymptomatic infection possible: ~80% infected persons [2,3]
- No direct fatalities proven
- Treatment
  - Disease usually mild → no specific treatment
  - Unwell → rest, fluids, painkillers if needed
- Currently no vaccine available



Image: http://dominicanewsonline.com/news/homepage/news/health/the-zika-virus-a-regional-perspective/

1. Hayes, E. B. EID 15, 1347-1350 (2009); 2, CDC. Zika virus: 2016. http://www.cdc.gov/zika/index.html. 3. Duffy MR, et al., N Engl J Med;360:2536–43 (2009);

Possible complication: microcephaly

- Increase in microcephaly reported in late-2015 in Recife, Brazil
  - At 30 January 2016: 4783 cases of microcephaly and/or CNS malformation, reported[1]
  - At 12 February 2016: 17 had confirmation of ZIKV infection, all from Northeast Region[1]

- Birth data review from 2013-14 outbreak in French Polynesia → congenital abnormalities of the CNS in children born during outbreak well above average[1]

- ZIKV RNA detected in:
  - Amniotic fluid of 2 pregnant women whose fetuses had microcephaly → indicating that the virus can cross the placenta[2]
  - Brain tissue from 2 newborns with microcephaly who died [3]
  - Placenta and other tissue of two miscarriages [3]

- WHO February 2016: Causal link between the Zika virus and microcephaly was "strongly suspected but not yet scientifically proven"[4]

1. http://www.who.int/emergencies/zika-virus/situation-report/who-zika-situation-report-12-02-2016.pdf; 2. Schuler-Faccini L, et al., MMWR 65 (3): 59–62 (2016).; 3. Martines, RB., ,et alk, MMWR Ritter, Jana (65 (6): 159–160 (2016);
4. http://apps.who.int/iris/bitstream/10665/204348/1/zikasitrep_5Feb2016_eng.pdf?ua=1

Other possible complications

Guillain-Barré syndrome (GBS)

- French Polynesia (2013-14 outbreak)
  - 42 people with GBS → 98% had neutralising antibodies against Zika virus[1]
- Americas (current outbreak)
  - Brazil, Colombia, El Salvador, Suriname and Venezuela reported an increase of GBS[2]

Other

- French Polynesia outbreak (2013-14 outbreak)
  - Encephalitis, meningoencephalitis, paraesthesia, facial paralysis or myelitis[3]
  - Central nervous system malformations in foetuses and infants[4]
  - Leukopenia and moderate thrombocytopenia in returned travelers[5]

Image: Petersen, L.,Vox Sang .2010

1. Cao-Lormeau, VM, et al., doi.org/10.1016/s0140-6736(16)00562-6 (2016); 2. http://www.who.int/emergencies/zika-virus/situation-report/who-zika-situation-report-12-02-2016.pdf; 3. Faye, OF, et al., PLoS NTD 8 (1): e2636. (2014); 4. Enfissi, A., etl al., Lancet 387 (10015): 227–8 (2016); 5. http://ecdc.europa.eu/en/publications/Publications/Zika-virus-French-Polynesia-rapid-risk-assessment.pdf

Transmission

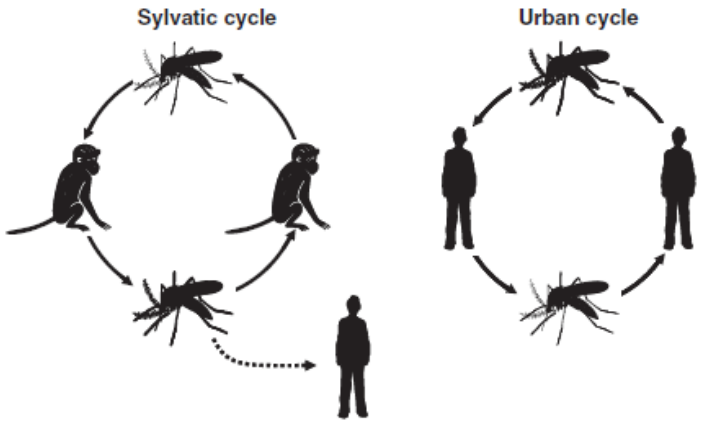


Image: Petersen, L.,Vox Sang .2010

- Vertebrate host primarily monkeys
  - Enzootic cycle
  - Before 2007: occasional transmission to humans
- Mosquito vector, genus *Aedes* (daytime biters)
  - Primarily transmitted by female *A. aegypti* [1]
  - Transmission by *A. Albopictus* reported[2]
  - Extent of the vectors is still unknown (isolated from other *Aedes* species[3], *Anopheles* and *Culex*)[4]
- Extrinsic incubation period of about 10 days[3]

1. http://www.cdc.gov/dengue/resources/30Jan2012/aegyptifactsheet.pdf; 2. Grard, G et al., PLOS NTD :e2681 (2014); 3. Hayes, E ., EID 15 (9): 1347–50 (2009); 4. Constância, FJ., Lancet ID doi:10.1016/S1473-3099(16)00073-6 (2016);

Other routes of transmission

- **Sexual transmission**
  - At least 8 reported cases[1]
  - Additional cases are under investigation[1]
  - Virus found in semen for at least two weeks (up to 10) after Zika infection[2,3]
  - ? whether women can transmit



- **Transfusion transmission**
  - Asymptomatic infections occur, therefore possible
  - 2 credible cases reported from Brazil[4]

- Intra-uterine transmission, intrapartum transmission, laboratory exposure[5]

1. Hills, SL., et al. MMWR 65; released 26 Febuary (2016); 2. Oster, AM., et al., MMWR 65; released 5 February (2016); 3. Musso D., et al., EID;21:359–61 (2015); 4. ABCNewsletter #7; released 26 February (2016); 5. http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-withmicrocephaly-rapid-risk-assessment.pdf

Risk management: fresh components



- Dependent on region
  - Endemicity
  - Maturity of blood operator

Options:

1. Accept risk
2. Donor management : education/deferral
3. Donation testing: ZIKV NAT[1]
4. Pathogen inactivation: one system effective[2]

Activities in the Asia Pacific:

- French Polynesia: ZIKV NAT, pathogen inactivation
- Australia & New Zealand: Travel restrictions

1. Musso D, et atl. Euro Surveill;19 (2014); 2. Aubry, M., Transfusion,;56(1):33-40 (2016)

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Risk management: plasma-derived products

- Manufacturing processes include validated & effective inactivation/removal steps → enveloped viruses (Flaviviridae)[1]

  (Bovine Viral Diarrhea Virus (BVDV; HCV model) , YFV, WNV, DENV)

  - **Inactivation:** Solvent–Detergent treatment, pasteurization, low pH treatment and Dry-Heat treatment
  - **Removal:** Nanofiltration (filters of 15-20 nm or 35 nm pore sizes)
  - Purification steps also contribute to virus reduction.

- Manufacturing processes include 2/3 reduction steps for enveloped viruses[1]

- Since implementation of these inactivation/removal steps → no report of transmission of an enveloped virus[1]

Zika virus does not represent a risk of transmission through plasma-derived products[1]



1. http://www.ipfa.nl/nieuws/ipfa-position-paper-zika-virus

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Chikungunya virus (CHIKV)



- Alphavirus
  - (+)ssRNA virus
  - Enveloped
- Transmitted by mosquitoes[1]
  - *Ae. aegypi* and *Ae. Albopictus*
- Sylvatic zoonotic cycle
  - Humans major source
  - Natural host (Africa) wild primates, other small mammals (bats)
- Symptoms[2]
  - High fever, severe myalgia, arthralgia, headaches, skin rash, photophobia
  - Name derived from the Makonde root verb - “that which bends up”
  - Asymptomatic infection possible → 72%-97% develop symptoms[3]

1. Van den Hurk A.F. et al., VBZD 10 489-95 (2010); 2. Rezza G., et al., Lancet 370 1840-6 (2007); 3. Nakkhara P., et al. Trans R Soc Trop Med Hyg 107(12):789-96 (2013); 4. Thiberville SD, et al., Antiviral Research 99 (3): 345–370 (2013)

Global CHIKV re-emergence

- First recorded epidemic in Tanzania (1952)
  - Endemic to Africa
- Spread
  - India, South-East Asia, Western Pacific
- Large outbreaks becoming more frequent
  - Indian Ocean Islands[1]
  - PNG, New Caledonia[2]
  - Historically non-endemic areas (i.e. Italy[3])
  - Introduced to Caribbean countries and territories in late 2013[4]
  - Spread across Caribbean islands and Latin America → local transmission in 45 countries/territories with >1.7 million suspected cases[4]

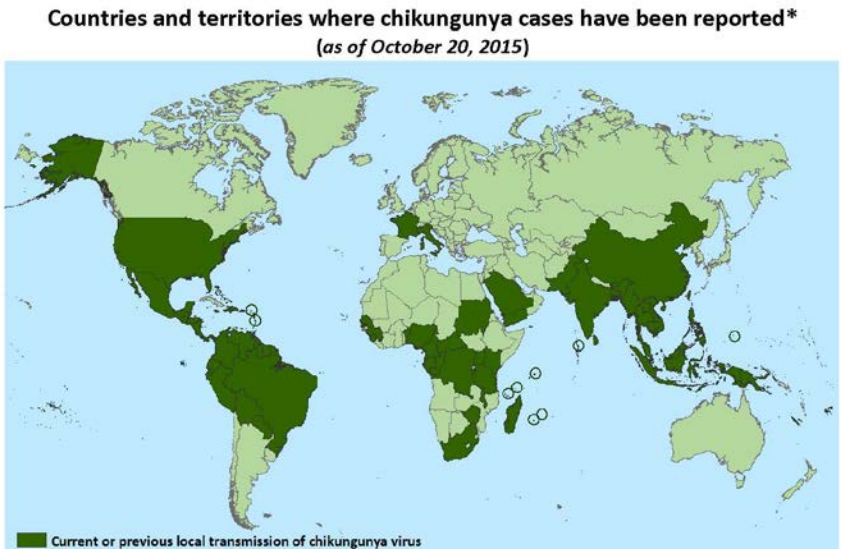


Image courtesy of the CDC

1. Sourisseau M., et al. PLoS Pathogen 3 e89 (2007); 2. Dupont-Rouzeyrol, M., et al., VBZD 12 1036-41 (2012); 3. Rezza G., et al., Lancet 370 1840-6 (2007). 4. http://www.cdc.gov/chikungunya/geo/index.html; 5. http://www.cdc.gov/chikungunya/geo/index.html

CHIKV and blood safety

- No reported cases of CHIKV transfusion transmission
  - Theoretically possible
    - Asymptomatic infection possible[1]
    - High levels of viraemia[2]



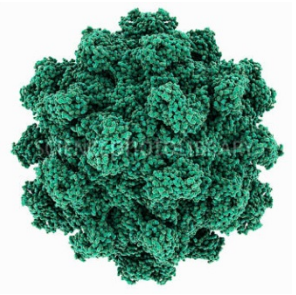
- La Reunion (2005)[3]
  - Suspension of local blood donation
    - Importation of RBCs
    - Implementation of pathogen inactivation for platelets
- Saint Martin (2014)[4]
  - CHIKV NAT implemented
- Not likely to represent a risk of transmission through plasma-derived products

1. Nakkhara P., et al. Trans R Soc Trop Med Hyg 107(12):789-96 (2013); 2. Sourisseau M., et al. PLoS Pathogen 3 e89 (2007); 3. Rasongles P., et al. Transfusion 49 1083-91 (2009); 4. Gallian P, et al. Blood 123 3679-81 (2014).

ZIKV & CHIKV: comparison

	ZIKV	CHIKV
Genome	(+)ssRNA	(+)ssRNA
Genus	Flavivirus	Alphavirus
Vector	*Aedes* (*A. aegypti*, other?)	*A. Aegypi, A. Albopictus*
Symptoms	Dengue-like + conjunctivitis	Dengue-like + more severe joint pain
Complications	Neurological	-
Asymptomatic rate	High	Lower
TTI?	Brazil	Theoretical risk only
Risk management: fresh components	Accept, donor deferral, NAT, pathogen inactivation	Accept, donor deferral, NAT, pathogen inactivation
Risk management: plasma-derived	Not likely to represent a risk	Not likely to represent a risk

Hepatitis E Virus (HEV)



- **Morphology:** Icosahedral, 27-34 nm, non-enveloped virus[1]
- **Genome:** ssRNA, three ORFs



- **Genotypes:** 1-4 (24 subgenotypes)
- **Case fatality rate:** 0.2-4% (epidemics)[1]
- **Clinical features:** Epigastric pain, diarrhoea, jaundice, hepatomegaly
- Asymptomatic infection possible

1. Kamar N., et al., Lancet 379, 2477-2488 (2012).

Modes of transmission



Drinking contaminated water



Transfusion-transmission



Consumption of uncooked infected meat



Congenital





Contact with infected animals



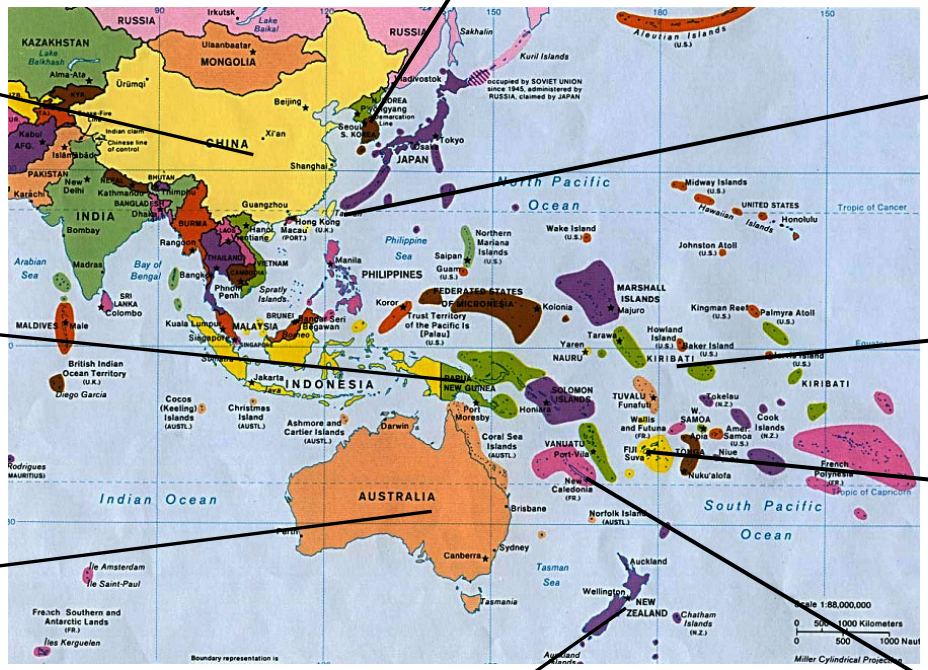
Organ transplantation

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HEV prevalence: Asia Pacific

Republic of Korea
6% (general pop^{n})[7]

China
33%[5]



China
33%[5]

Taiwan
30% (swine farmers)
12% (health workers)[6]

PNG
15 % (general pop^{n})[4]

Kiribati
9% (general pop^{n})[4]

Fiji
2% (general pop^{n})[4]

Australia
6% (blood donors)[1]

New Caledonia
2% (military)[3]

New Zealand
4% (blood donors)[2]

1. Shrestha, A,C., et al., Emerging Infectious Diseases DOI: 10.3201/eid2011.140412 . 2. Dalton H.R., et al. J Gastroenterol Hepatol; 22: 1236-40 (2007). 3. Bendall, R., et al. J Med Virol; 82:799-805 (2010). 4. Halliday, J.S., Emerging Infectious Diseases; 20: 6 1057 – 8 (2014). 5. Guo QS., et al., J Clin Microbiol 48(1), 317-318 (2010); 6. Lee JT, et al., PLoSOne 26;8(6)e67180 (2013). 7. Yoon Y, et al., BMC Infect Dis 14:517 (2014)

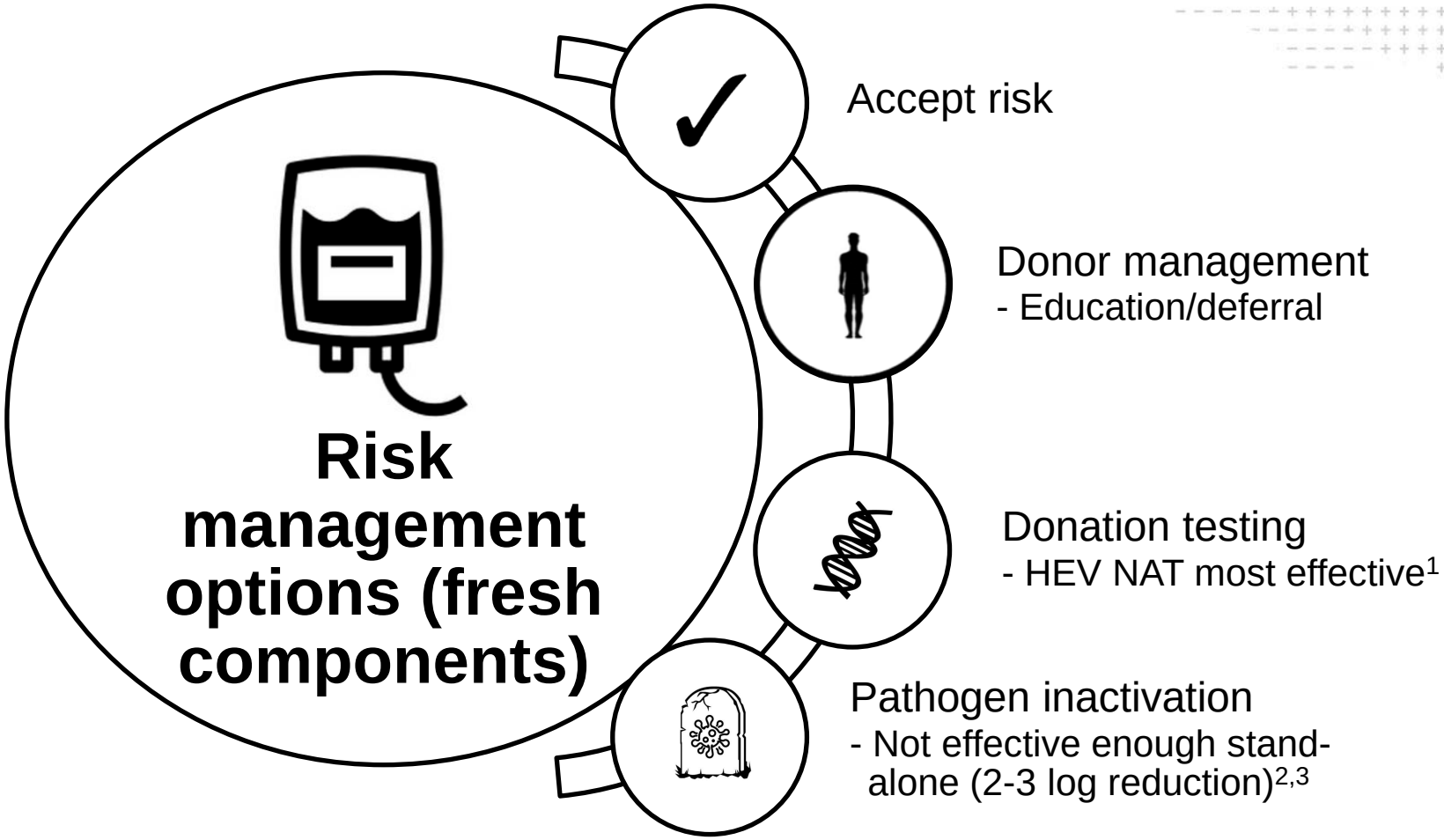
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HEV and blood safety

- HEV RNA detected in blood donors from China, UK, Germany, Japan, the Netherlands, Scotland[1]
- Documented HEV transfusion transmission in UK, France, Japan, Saudi Arabia, and Germany[1-6]
  - Including in Intercept treated plasma[7]
- Chronic HEV cases reported in immunocompromised patients[1]



1. Kamar N., et al., Lancet 379, 2477-2488 (2012); 2. Colson P., et al., Emerging Infectious Diseases 13, 648-649 (2007); 3. Boxall E., et al., Transfusion Medicine 16, 79-83 (2006); 4. Matsubayashi K., et al., Transfusion 44, 934-940 (2004); 5. Khuroo MS., et al., J Gastroenterol Hepatol 19(7), 778-84 (2004); 6. Huzly et al., Eurosurveillance 19(21) (2014); 7. Hauser, et al., Blood 128, 796 (2014).



Activities in the Asia Pacific:

- Hokkaido, Japan: HEV NAT
- Australia: Overseas-acquired HEV managed through travel restrictions

1. Juhl D et al. Transfusion. 2014;54: p. 49-56; 2. Hauser L et al. Blood. 2014;123: p. 796-797; 3. Owada T et al. Transfusion. 2014.

Management: plasma-derived products

- Substantial HEV reduction during processes commonly used in the manufacturing of plasma products[1]
  - FVIII: reduction of 3.9 log (immunoaffinity chromatography) & > 3.9 log (20-nm nanofiltration)
  - Immunoglobulin: reduction of > 3.5 log (cold ethanol fractionation) (below LOD)
  - Human albumin: reduction of > 3.1 log (heat treatment) (below LOD) & 4.0 log (35-nm nanofiltration)

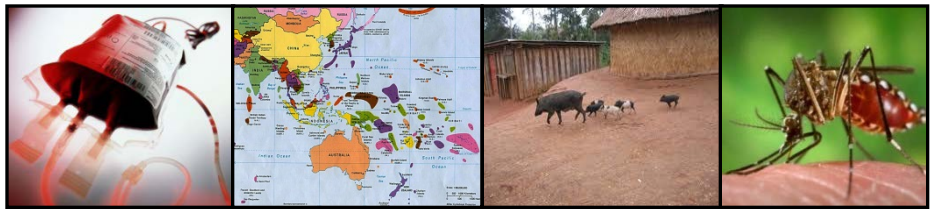


1. Farcet MR, et al., Transfusion 56(2): 383-91 (2016)

Conclusions

- Infectious diseases pose an on-going threat to safe blood transfusions
  - Risk different for fresh components versus plasma-derived products
  - Risk management decision must be based on local risk assessment, epidemiology, ‘risk-appetite’ and circumstances

- Zika, chikungunya, hepatitis E viruses → current potential threats
  - Various management approaches for fresh blood components (accept risk, donor education/deferral, NAT, pathogen inactivation)
  - Risk of transmission through plasma-derived products likely to be low, but additional studies are needed



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