

How to respond to emerging transfusion-transmissible infections (TTIs)

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Australian governments fund the Australian Red Cross Blood Service for the provision of blood, blood products and services to the Australian community

Presentation outline

- What are emerging transfusion-transmissible infections (TTIs) and are they taking over the planet?
- Preventing emerging TTIs
 - Societal context: TTIs and the online digital age
 - International context: collaboration, surveillance, containment
- Emerging TTIs and blood safety: strategies to reduce transfusion-transmission risk
 - Patient and donor management
 - Risk mitigation strategies
- Conclusions

What do we mean by emerging transfusion-transmissible infections?

- **Emerging** infectious diseases (EIDs): “those whose incidence in humans has increased within the past 2 decades or threatens to increase in the near future”¹
- When are EIDs **transfusion-transmissible**?^{1,2}
 - able to establish infection in humans and spread within populations
 - infection includes an asymptomatic blood phase
 - able to survive during blood processing and storage
 - transmissible by the intravenous route, and
 - associated with a clinically apparent disease in at least a proportion of recipients.
- **Transfusion-transmissible** defines the context as blood safety

1. Stramer S et al. Transfusion 2009; Suppl 2:1S-29S
2. Stramer S et al. ISBT Sci Ser 2014; 9:30-36

Have we entered the era of EIDs?

- Some 21st century headlines:
 - severe acute respiratory syndrome corona virus (SARS-CoV) in China in 2002-3
 - re-emergence of avian influenza virus H5N1 (A(H5N1))
 - chikungunya virus (CHIKV) on La Reunion island in 2005-07 followed by the Western Pacific region in 2012 and the Americas in 2013
 - Middle East respiratory syndrome corona virus (MERS-CoV) in 2012 in the Middle East
 - influenza A virus H7N9 (A(H7N9)) in 2013 in China
 - Zika virus (ZIKV) on Yap Is in 2007, the Western Pacific region in 2014 and the Americas in 2015
 - Ebola virus (EBOV) in West Africa 2014-15
 - Yellow fever virus (YFV) in Angola/Democratic Republic of the Congo/Uganda in 2015

And the list goes on.....

Table 2. Type and number of disease outbreaks meeting the selection criteria in a study assessing global capacity for emerging infectious disease detection, 1996–2014*

Disease	No. outbreaks, N = 347
Anthrax	1
Avian influenza (H9N2)	1
Chikungunya	4
Cholera	93
Dengue	13
Diphtheria	1
Dysentery	1
Enterovirus D68	1
H5 influenza	39
H7 influenza	3
Hand, foot, and mouth disease	4
Hemorrhagic fevers (Crimean-Congo, Ebola, Marburg, undiagnosed)	29
Hantavirus	2
Henipavirus	4
Hepatitis E	2
Japanese encephalitis	3
Lassa fever	2
Legionellosis	4
Leptospirosis	3
Louseborne typhus	1
Lujovirus	1
MERS	2
Malaria	3
Measles	3
Meningitis	24
Monkeypox	1
Nonavian influenza A	4
O'nyong-Nyong fever	1
Plague	10
Poliomyelitis	24
Relapsing fever	1
Rift Valley fever	6
SARS	3
Shigellosis	4
<i>Streptococcus suis</i>	1
Tularemia	2
Typhoid fever	4
West Nile virus	3
Yellow fever	39

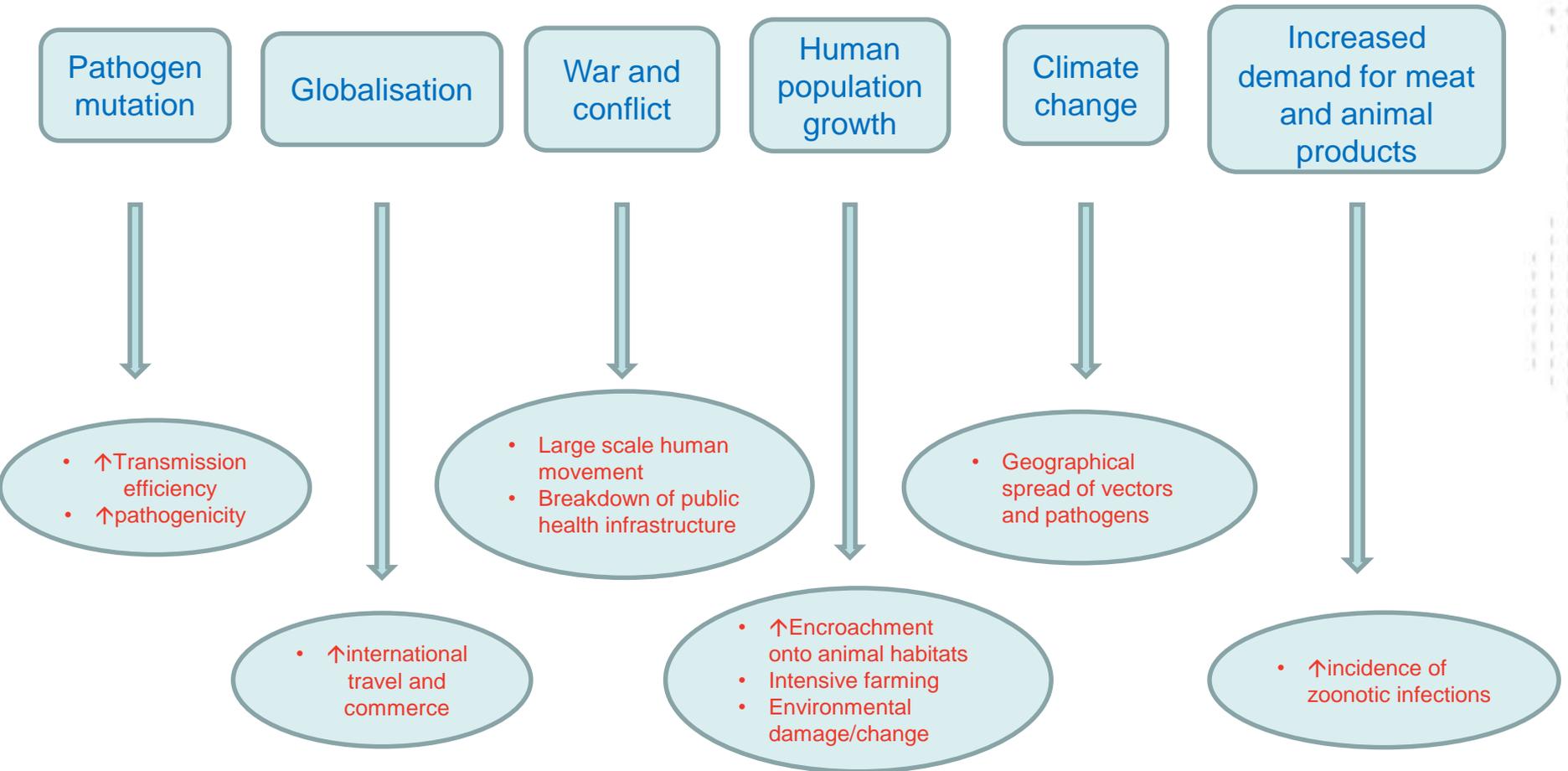
*MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

347 outbreaks/40 pathogens¹

Based on WHO Disease Outbreak News (1996-2014)

- Excluded ongoing/endemic/seasonal/foodborne diseases
- Known start date

....why we can expect more



How should we respond to emerging TTIs?



Emerging TTIs: the societal context

- Age of internet and social media^{1,2,3}
 - Common source of information (including medical)
 - Much of the information is unreliable
 - But can play an important role in control of, and data gathering for, emerging TTIs
- How non-experts perceive risk^{4,5}
 - Influenced by events that are widely publicised, dramatised and image-laden
 - Higher risk perception is associated with lower human development index and lower educational levels
- The need to maintain public confidence in the safety of the blood supply which impacts both willingness to give and receive blood^{4,5}
- Cooperation and confidence of the general population is essential

1. Venkatraman A et al. *Travel Med Infect Dis* 2016; 14:421-422

2. Al-Surimi K et al. *Adv Exp Med Biol*. 2016 Dec 22. doi: 10.1007/5584_2016_132.

3. McGough SF et al. *PLoS Negl Trop Dis* 2017; 11(1): e0005295. doi:10.1371/journal.pntd.0005295

4. Merz E-M et al. *Vox Sang* 2016; 10:258-65

5. Ngo LT et al. *Trans Med Revs* 2013; 27:119-127

A case study: Hendra virus risk mitigation

- HeV causes periodic fatal infections in horses and humans in eastern Australia. Natural host is the fruit bat.
- Factors affecting uptake of risk mitigation strategies by horse owners in Australia¹:
 - Belief that strategies would be effective – *education*
 - Practicality of implementing strategies – *provision of feasible risk mitigation strategies*
 - Perception of risk e.g. heightened by nearby infection – *communicating the meaning of risk levels to non-experts*
 - Support of veterinarians and government assistance – *evidence-based, confidence in experts and authorities*

1 Manyweathers J et al. Risk Mitigation of Emerging Zoonoses: Hendra Virus and Non-Vaccinating Horse Owners. *Transbound Emerg Dis.* 2017 Jan 4. doi: 10.1111/tbed.12588. [Epub ahead of print]

Emerging TTIs: international context

Responding to TTIs requires international **collaboration**:

- Governments at all levels
- Health Departments
- National and international health bodies
- Blood centres
- Regulators
- Experts including epidemiologists, modellers, infectious disease experts
- Cooperation of the general public and stake holders
-even plasma fractionators

Preventing infection with emerging TTIs: *surveillance* - eternal vigilance

- Rapid turn around information: daily to weekly outbreak monitoring
 - ProMED, WHO, ECDC, CDC, government health departments, international collaborative groups that share EID information including the Alliance of Blood Operators (ABO), Asia Pacific Blood Network (APBN), the Pacific Public Health Surveillance Network and the European Blood Alliance (EBA).
- Information that may take weeks, months or longer to collate and publish: longer term trend monitoring
 - These include Emerging Infectious Diseases (CDC), Eurosurveillance (ECDC), Morbidity and Mortality Weekly – MMWR (CDC) and the Weekly Epidemiological Record - WER (WHO); peer-reviewed scientific literature



Dengue, chikungunya and Zika viruses: 10 years of surveillance¹

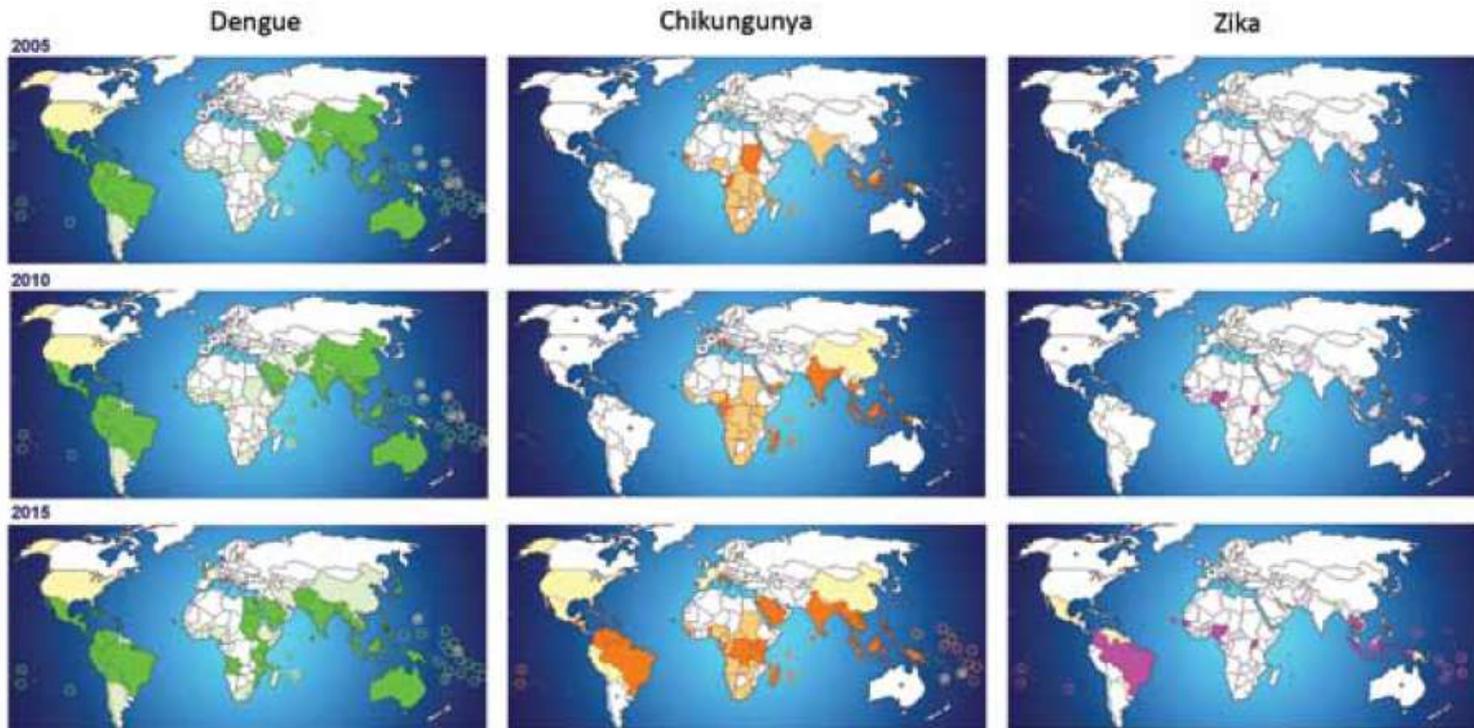


Figure. Areas affected by dengue, chikungunya, and Zika viruses, worldwide, 2005, 2010, and 2015, illustrating the evolution of the geographic distribution of these viruses over the past decade (1–5,7). Light shading/circles indicate countries with endemic transmission; dark shading/circles indicate countries with outbreaks recorded during the previous 5 years; dots indicate imported cases in countries without autochthonous transmission; stars indicate countries with reported autochthonous transmission.

Preventing infection with emerging TTIs: *containment*

A number of emerging TTIs are vector-borne (e.g. *Aedes aegypti*) RNA viruses of zoonotic origin¹⁻⁵. Prevention and containment strategies include:

- Environmental management: reducing vector larval habitats
- Chemical control: larvicides, pesticides
- Biological control
 - genetically modified vectors
 - *Wolbachia*-infected vectors
- Reducing human contact
 - Nets and screens
 - CDC gravid ovitraps
 - Don't play Pokemon!
- Vaccine development
- Widely available rapid testing⁶



1 WHO: http://www.who.int/denguecontrol/control_strategies/en/

2 CDC: <http://johnwhock.com/products/mosquito-sandfly-traps/cdc-gravid-trap/>

3 Barrera R et al. Am J Trop Med Hyg. 2014 Dec 3; 91(6): 1269–1276

4 Mohanty I et al J Vector Borne Dis 53, September 2016, pp. 199–207

5 Oidtman RJ PLoS Curr. 2016 Nov 15;8.

6. Dhillon RS et al BMJ 2017; 356

Pokémon Go and Exposure to Mosquito-Borne Diseases: How Not to Catch 'Em All

November 15, 2016 · Discussion

Citation

Oidtman RJ, Christofferson RC, ten Bosch QA, Espana G, Kraemer MUG, Tatem A, Barker CM, Perkins TA. Pokémon Go and Exposure to Mosquito-Borne Diseases: How Not to Catch 'Em All. PLOS Currents Outbreaks. 2016 Nov 15 . Edition 1. doi: [10.1371/currents.outbreaks.2d885b05c7e06a9f72e4656d56b043cd](https://doi.org/10.1371/currents.outbreaks.2d885b05c7e06a9f72e4656d56b043cd). Tweet



Preventing infection with emerging TTIs: predictive epidemiological modelling

Epidemiological modelling:

- can help predict the timing, extent and location of EID outbreaks, particularly as there is often a need to act when empirical data is limited and pathogens are not well characterised
- therefore is subject to uncertainty
- can inform decisions regarding risk mitigation strategies

Case study: modelling RRV notification rate

- Cutcher et al performed modelling to predict changes in Ross River virus (RRV) notifications rates in Australia¹
 - Rainfall and vapour pressure (air temperature and pressure) were the key variables for predicting RRV notifications.
 - The modelling also predicted that increasing sea surface temperature and sea levels would increase human RRV notifications.
 - Subsequently:
 - "With the large number of Australians now travelling, it would not be unreasonable to expect one or more tourists to carry RRV overseas to seed a new epidemic. With the right conditions, this could take off globally in exactly the same way that Zika did."^{2,3}

1 Cutcher Z et al. Epidemiol Infect 2016; doi:10.1017/S0950268816002594

2 Lau C et al. New evidence for the endemic circulation of Ross River virus in the Pacific Islands and the potential for emergence. Int J Infect Dis 2017

3 News Medical Life Sciences. 23 February, 2017. <http://www.news-medical.net/news/20170223/Australias-Ross-River-Virus-could-be-next-global-epidemic-study-suggests.aspx>

Emerging TTIs: reducing the transfusion-transmission risk

Risk assessment:

- Is it transfusion-transmissible?
- Does it cause disease in recipients?
- What is the incidence?
- Can the transfusion-transmission risk be reliably estimated by modelling?
- Are risk mitigation strategies proportionate and cost efficient?



TTIs and blood safety: reducing the transfusion-transmission risk

“...*the safest transfusion is the one that is not given.*”¹

- Patient blood management: reducing the need for transfusion^{2,3}
 - Optimise erythropoiesis pre-operatively
 - Reduce perioperative blood loss
 - Restrictive transfusion practices
 - Reducing inappropriate transfusions/educational interventions
 - Technological advances in blood management⁴
- Donor management
 - Deferral of donors with infection or contact with infected individuals
 - Geographical deferral (non-endemic/non-outbreak countries) of donors returning from endemic/outbreak countries – typically covers **multiple** EIDs as tropical areas often have co-circulating EIDs.
 - Donor education and self-deferral
 - Post-donation information – notification of post-donation symptoms
- Restricting use of donations during outbreaks in non-endemic countries or quarantine of donations (notification of post-donation symptoms)



1 Katz L & Rossmann SN. Arch Lab Pathol Med 2017 Jan;141(1):85-92

2 Goodnough LT et al. Anesth Analg 2017

3 Abelow A et al. Vox Sang 2017

4 AABB SmartBrief, 13 January 2017

January 13, 2017

AABB SmartBrief



News for the transfusion medicine and cellular therapy community

SIGN UP · FORWARD

TOP STORY

Technology changes reduce blood transfusions at Calif. hospital

University of California at Los Angeles Health reported reducing red blood cell transfusions by almost 20% when it transitioned blood administration processes to all-electronic bar code scanning. The switch from the systems' previous hybrid electronic-paper format involved an eight-month bar coding project and an eight-month embedded clinical decision support project. The results of the change will be presented at a meeting of the Healthcare Information and Management Systems Society.

[Healthcare IT News](#) (1/11)



Case study: FDA deferral recommendations for Zika virus

- 4 weeks deferral after:
 - resolution of symptoms for donors with a history of Zika virus infection
 - resolution of symptoms for donors who report symptoms suggestive of ZIKV within 2 weeks of departure from an area with active transmission of ZIKV.
 - last sexual contact with a man who has been diagnosed with ZIKV or who traveled to or resided in an area with active transmission of ZIKV in the 3 months prior to that instance of sexual contact.
 - leaving outbreak area
- For donors who test positive after screening: 120 days after positive test or resolution of symptoms, whichever is the longer

TTIs and blood safety: reducing the transfusion-transmission risk

- Modelling the transfusion-transmission risk
 - Biggerstaff-Petersen and EUFRAFT models
 - Risk estimates can inform risk mitigation strategies
 - Modelling is necessarily subject to uncertainty
- Donor screening
 - Screening tests available for limited number of EID pathogens including West Nile virus, *T. cruzi*, hepatitis A virus, human parvovirus B19, *Plasmodium* spp., Zika virus (investigational).
 - Cost and cost-effectiveness
- Pathogen reduction technology (PRT)
 - Commercially available systems
 - In use in a number of countries
 - Cost-effectiveness dependant on risk level
 - No system for RBCs
 - Limitations: may not be effective against bacterial spores or high viral loads

Transfusion-transmission risk modelling for TTIs: applications

Applications of the Biggerstaff-Peterson model

Pathogen	Country (date of outbreak)	Reference
Chikungunya virus (CHIKV)	La Reunion Island (2005-2007)	Brouard et al, 2008
Dengue virus	Australia (2004)	Seed et al, 2009
Dengue virus	Australia (2008-2009)	Faddy et al, 2013
Chikungunya virus	Italy (2007)	Liumbruno et al, 2008; Oei et al, 2013
Hepatitis A virus (HAV)	Latvia (2008)	Perevoscikovs et al, 2010
Chikungunya virus	Thailand (2009)	Appassakij, et al, 2014
Ross River virus (RRV)	Australia (2004)	Shang et al, 2012
Ross River virus (RRV)	Australia (2013-14)	Seed et al, 2016

Applications of the EUFRAT model

Pathogen	Country (date of outbreak)	Reference
Chikungunya virus (CHIKV)	Italy (2007)	Oei et al, 2013
Dengue virus (DENV)	Dutch donors returning from Suriname and Dutch Caribbean (2011-11)	Oei et al, 2016
Chikungunya virus (CHIKV)	Italy (2007)	Mapako et al, 2016
Coxiella burnetti (Q fever)	Netherlands (2007-09)	Mapako et al, 2016
Ross River virus (RRV)	Australia (2013-14)	Seed et al, 2016

Case study: blood donor screening and detectable ZIKV viraemic rates

Country	Period of screening	Number of donors	Prevalence of ZIKV RNA	Reference
French Polynesia	Nov 2013 – Dec 2014	1,501	42/1,505 (2.8%)	Musso D et al, 2013
Puerto Rico	April – June, 2016	12,707	68/12,777 (0.5%)	Kuehert MJ et al, 2016
Martinique	Jan – June, 2016	4,129	76/4,129 (1.84%)	Gallian P et al, 2016
US	May – October, 2016	358,786	14/358,786 (0.004%)	Galel SA et al, 2017

Conclusions

- We can expect more emerging TTI outbreaks
- An adequate response requires *international collaboration*
- *More research* (and therefore commitment of resources) is required to understand TTI pathogens, their epidemiology and outbreak potential
- Blood centres need to engage in intensive *ongoing surveillance, risk assessments and employ risk mitigation strategies* which take into account sufficiency of supply, cost-effectiveness and feasibility.
- We need to be mindful that TTI outbreaks will continue to predominately occur in low income developing countries that will require resource assistance to effectively respond to emerging TTIs.

Thank you!