Evaluación del riesgo de nuevas infecciones emergentes

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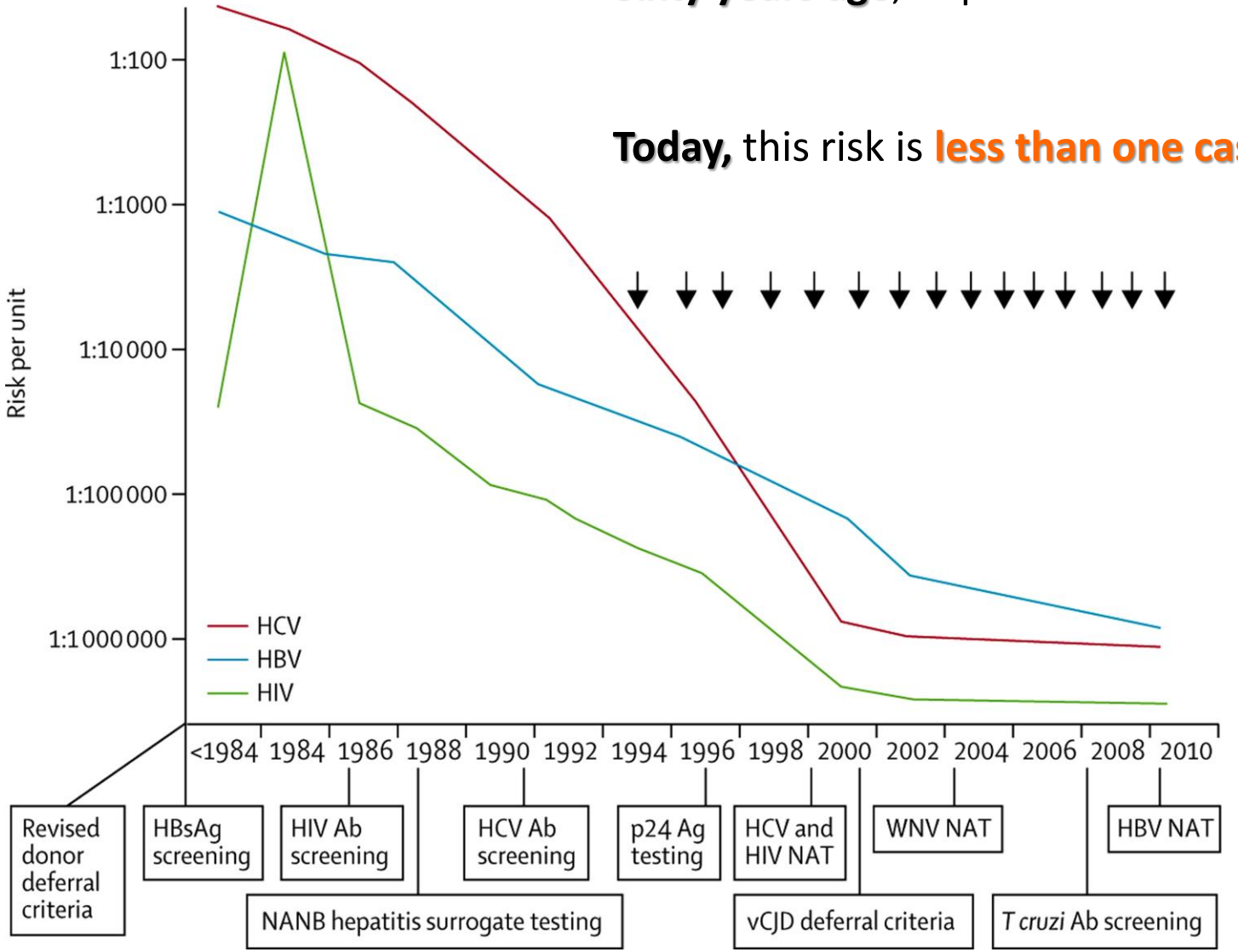
Sixty years ago, hepatitis was a common outcome of blood transfusion!

Today, this risk is **less than one case per million transfusions**.

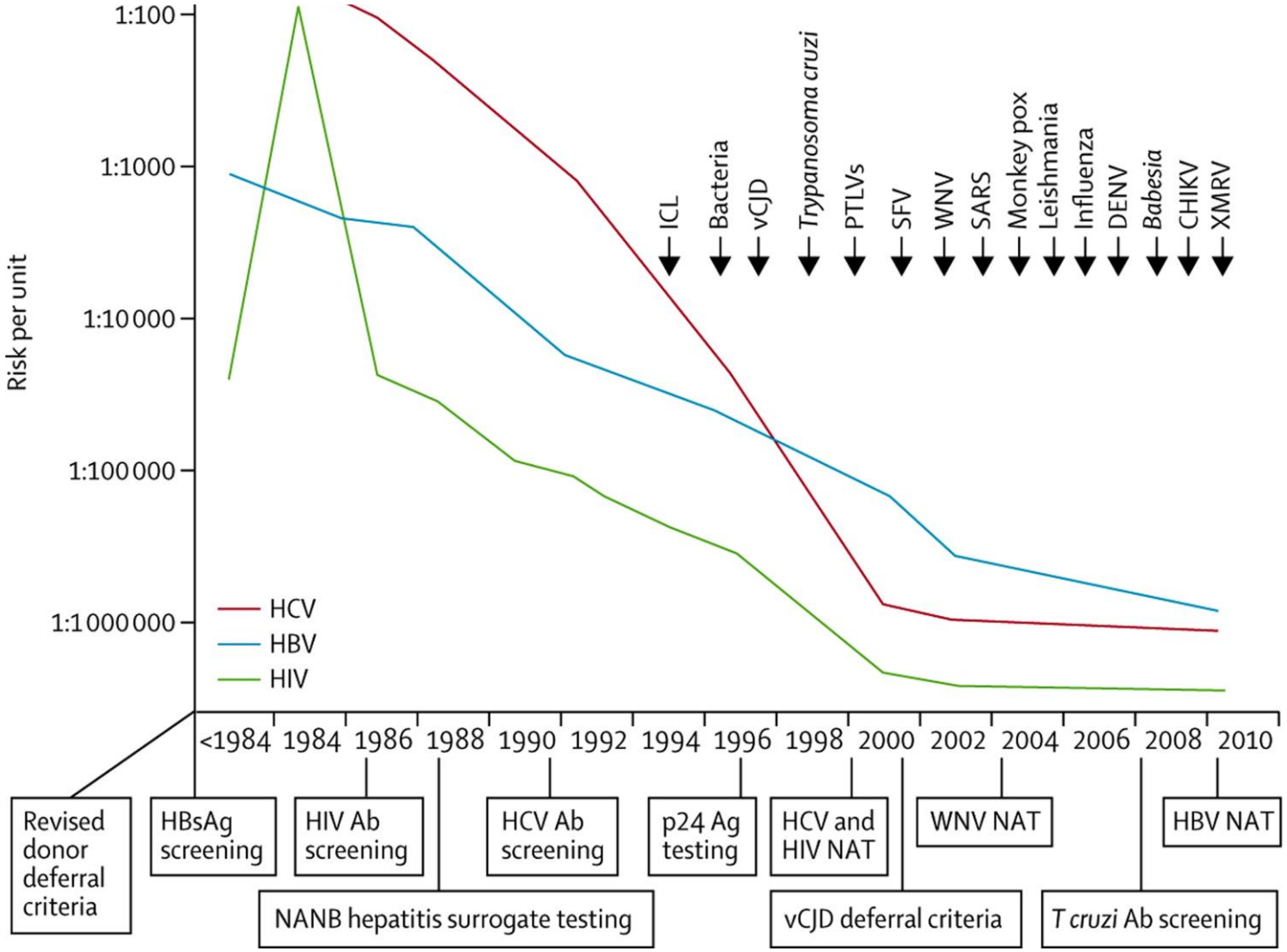


This is the result of continuous efforts to reduce or eliminate the risk through:

- **rigorous donor selection criteria**,
- **more sensitive laboratory testing**,
- and most recently, the introduction of **pathogen inactivation**,
- along with extraordinary advances in molecular biology.

The Lancet 2013 3811791-1792DOI: (10.1016/S0140-6736(13)60673-X)

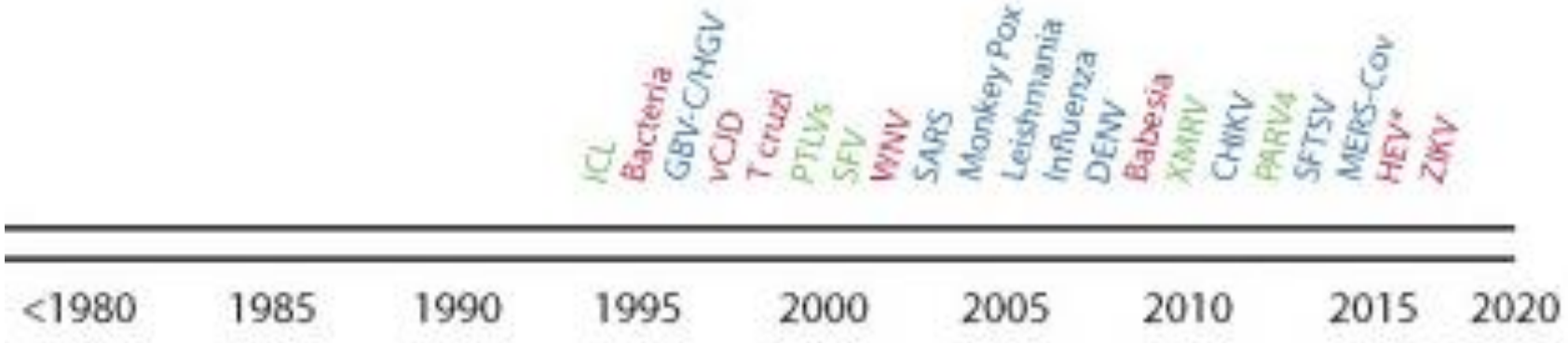
In the last 20 - 30 years, the frequency of EID outbreaks has increased:



and experts predict that

this will continue…

The Lancet 2013 3811791-1792DOI: (10.1016/S0140-6736(13)60673-X)



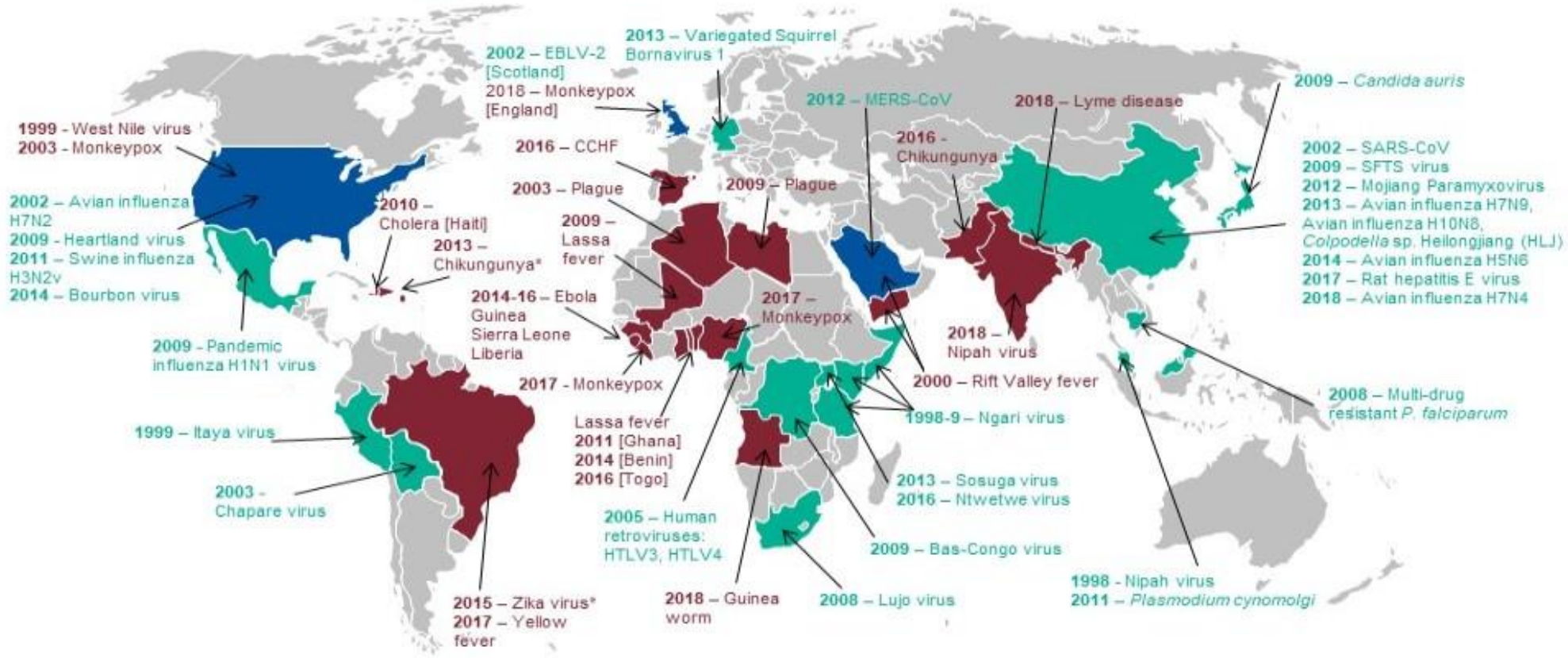
Over this period, for each new emergent agent, the risk to transfusion safety has been analyzed and addressed.

- But, in many cases, the time between recognition and resolution of the risk was a matter of years.

Nowadays, this time has been significantly decreased, largely due to advances in science and molecular biology, providing:

1. the **agent of a novel disease can now be identified in hours**;
2. and **high throughput tests for DNA / RNA can be designed and implemented in months**.

Global map of significant and new emerging infections in humans: spread to new areas since 1998



*Incursion followed by regional spread

Is the agent present and transfusion-transmissible?

EID TRANSFUSION-TRANSMISSIBLE CRITERIA:

1. Able to establish **infection in humans** and spread within populations;
2. Presence of the **agent in blood** during the **donor's asymptomatic phase**;
3. The **agent's survival / persistence** in blood during processing and **storage**;
4. Transmissible by the intravenous route;
5. The agent must be **recognized as responsible** for a clinically apparent disease in at least a proportional of recipients.

Transfusion Medicine Reviews 2017; 31: 154-164
Transfusion 2009; 49(Suppl. 2): 1S-29S
ISBT Sci Ser 2014; 9: 30-36
BMJ 2014; 348: g1499

Timeline of new and emerging infections since 1998

Prairie dog— monkeypox reservoir in 2003 outbreak in USA

Rift Valley fever [Saudi Arabia and Yemen]

Monkeypox [USA]

Chaparevirus

Plague [Algeria]

Ngari virus

Nipah virus

Camel – MERS reservoir

Lujo virus [southern Africa]

Multi-drug resistant *P falciparum* [SE Asia]

MERS-CoV

Mojiang Paramyxovirus

Cholera [Haiti]

Aedes albopictus – vector for chikungunya

CCHF [Spain]

Chikungunya [Pakistan]

Lassa fever [Togo]

Ntwetwe virus

Ebola [West Africa]

Avian influenza H5N6

Lassa fever [Benin]

Bourbon virus

Emergence of a female Guinea worm from a sufferer's lower leg

Guinea worm [Angola]

Lyme disease

Avian influenza H7N4

Monkeypox [Liberia, UK]

Nipah virus

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

Pteropus poliocephalus— suspected Nipah virus reservoir

EBLV-2 [Scotland]

SARS-CoV

Avian influenza H7N2

Human retroviruses, HTLV3, HTLV4

Candida auris

Heartland virus

Bas-Congo virus

Lassa fever [Mali]

Pandemic influenza 2009 H1N1 virus

Huaiyangashan virus – SFTS virus

Plague [Libya]

Lassa fever [Ghana]

Plasmodium cynomolgi

Swine influenza H3N2v

Avian influenza H7N9 virus

Sosuga virus

Avian influenza H10N8 virus

Chikungunya [Caribbean]

Variegated Squirrel Bornavirus 1

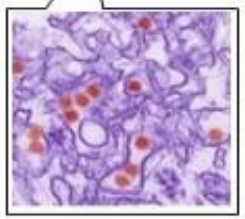
Colpodella sp. Heilongjiang (HLJ)

Monkeypox [Nigeria]

Yellow fever [Brazil]

Rat hepatitisE virus

Zika virus [Americas]



Zika virus

West Nile virus [USA]

Itaya virus

Oriental rat flea, *Xenopsylla cheopis*, a known plague vector

Prevost's squirrel – VSB 1 reservoir
Image by: Matthias Buehler

Images taken from the CDC Public Health Image Library: https://phil.cdc.gov

Viremia; TT; receptor disease

Viremia; TT

Viremia

Dengue

Hepatitis E virus

Japanese encephalitis

Babesia

Plasmodium

- More recently, the **COVID-19 pandemic** illustrated the alarming speed with which an infection can spread.
  - There was little time to prepare and there were considerable difficulties in managing the blood supply,
  - even though **the agent has not been shown to be transmissible by transfusion**, even considering that viral RNA can be identified in blood.

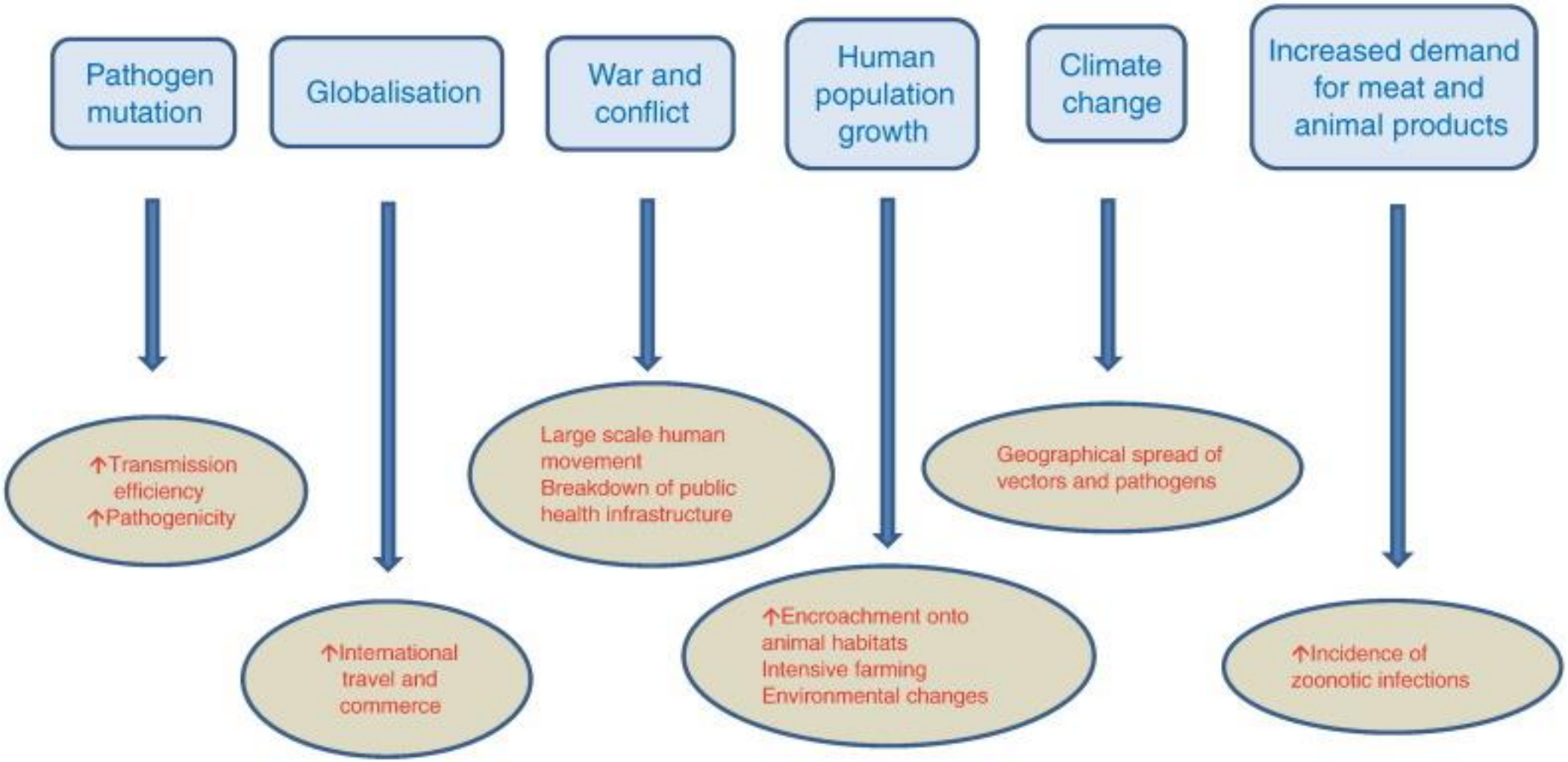
- Currently, there is a **widespread outbreak of monkeypox**, classified as a public health emergency by the WHO, on July 23, 2022.
  - By early August 2022, the disease was present in 82 countries with over 30,000 confirmed cases.
  - **The agent is potentially transfusion transmissible since viral DNA can be recovered from blood** and spread throughout the body undoubtedly occurs via the blood route.
  - **And the Blood Establishments are considering the necessity and nature of interventions**.

R.Y. Dodd and S.L. Stramer, How do we forecast tomorrow's transfusion: Infectious safety?, Transfusion clinique et biologique, https://doi.org/10.1016/j.tracli.2022.08.143

WHY WE CAN EXPECT MORE EID OUTBREAKS

- globalization and environmental change;
- demographic drivers;
- changes in the patterns of human behavior, social organization, urbanization, agriculture & animal husbandry;
- public health system drivers.

Once an agent has crossed the species barrier to humans, subsequent transmission may be enhanced by a number of factors, predominately related to human activity:



https://doi.org/10.1016%2Fj.tmrv.2017.05.002
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7126009

Although new emerging and re-emerging infections may not be truly predictable,

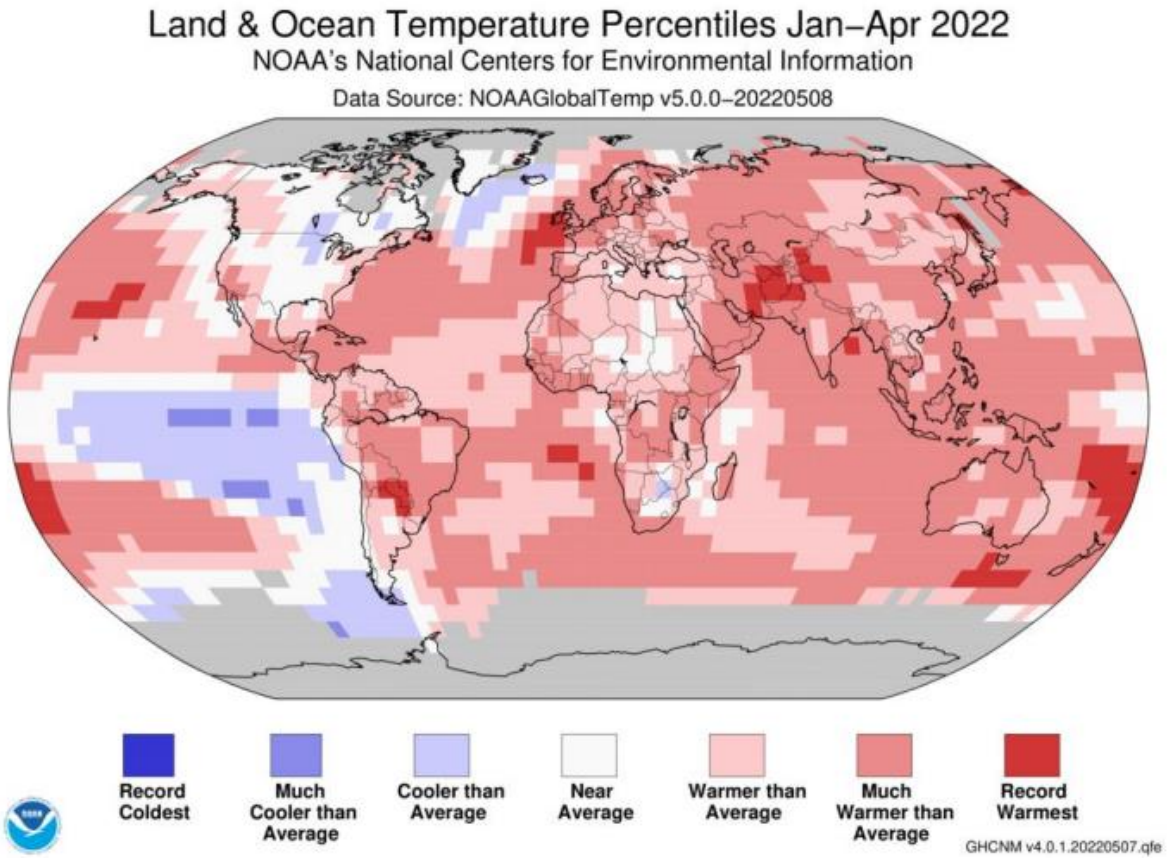
there may be circumstances that can suggest a need to prepare for adverse impacts on blood safety.

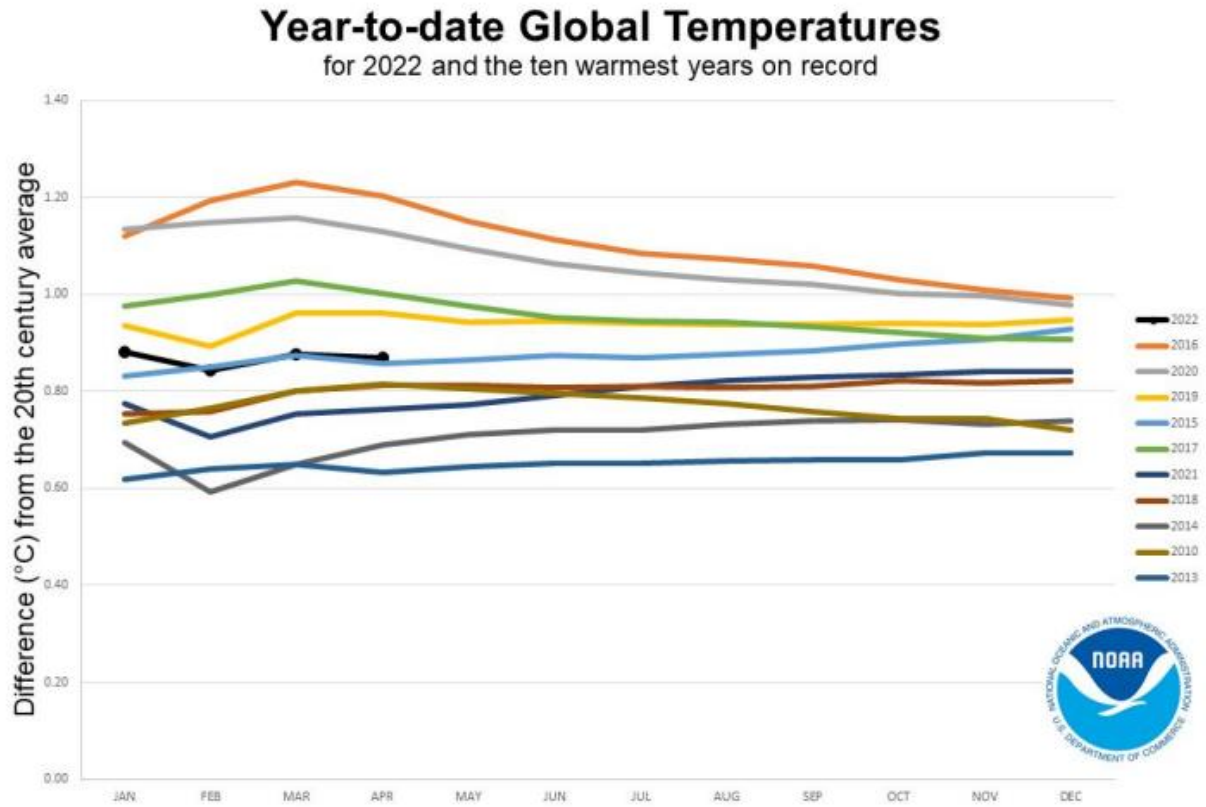
- Perhaps most promising are efforts to **assess the impact of climate change on vector-borne infections**, generally focused on the **likely expansion of areas with specific vectors for known agents**,
  - as is the case for *Aedes spp*. mosquitoes and selected flaviviruses,
  - and *Anopheles spp*. mosquitoes and the malaria parasite.

However, such approaches do not necessarily define when, of if there will be an outbreak, but do suggest a need for enhanced surveillance.

R.Y. Dodd and S.L. Stramer, How do we forecast tomorrow's transfusion: Infectious safety?, Transfusion clinique et biologique, https://doi.org/10.1016/j.tracli.2022.08.143

The global temperature record dates back to 1880 (143 years)



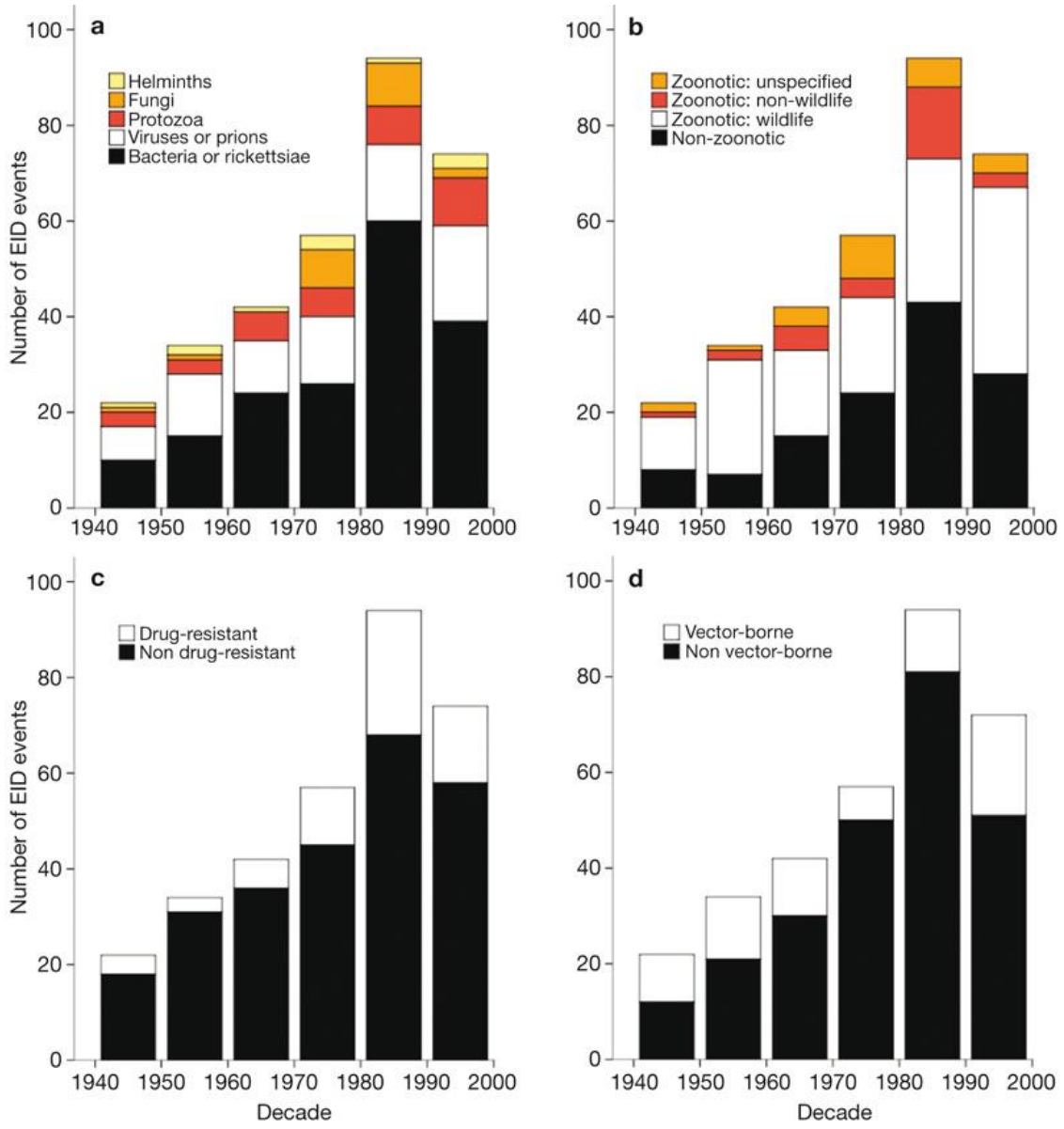


- **Global Land & Ocean:** +0.87°C / +1.57°F, the fifth-highest for Jan-Apr period on record.

https://www.ncei.noaa.gov/access/monitoring/monthly-report/briefings/20220519.pdf

Climate change – possible mechanism of acting on zoonotic and vector borne diseases (60-70% of the EID)

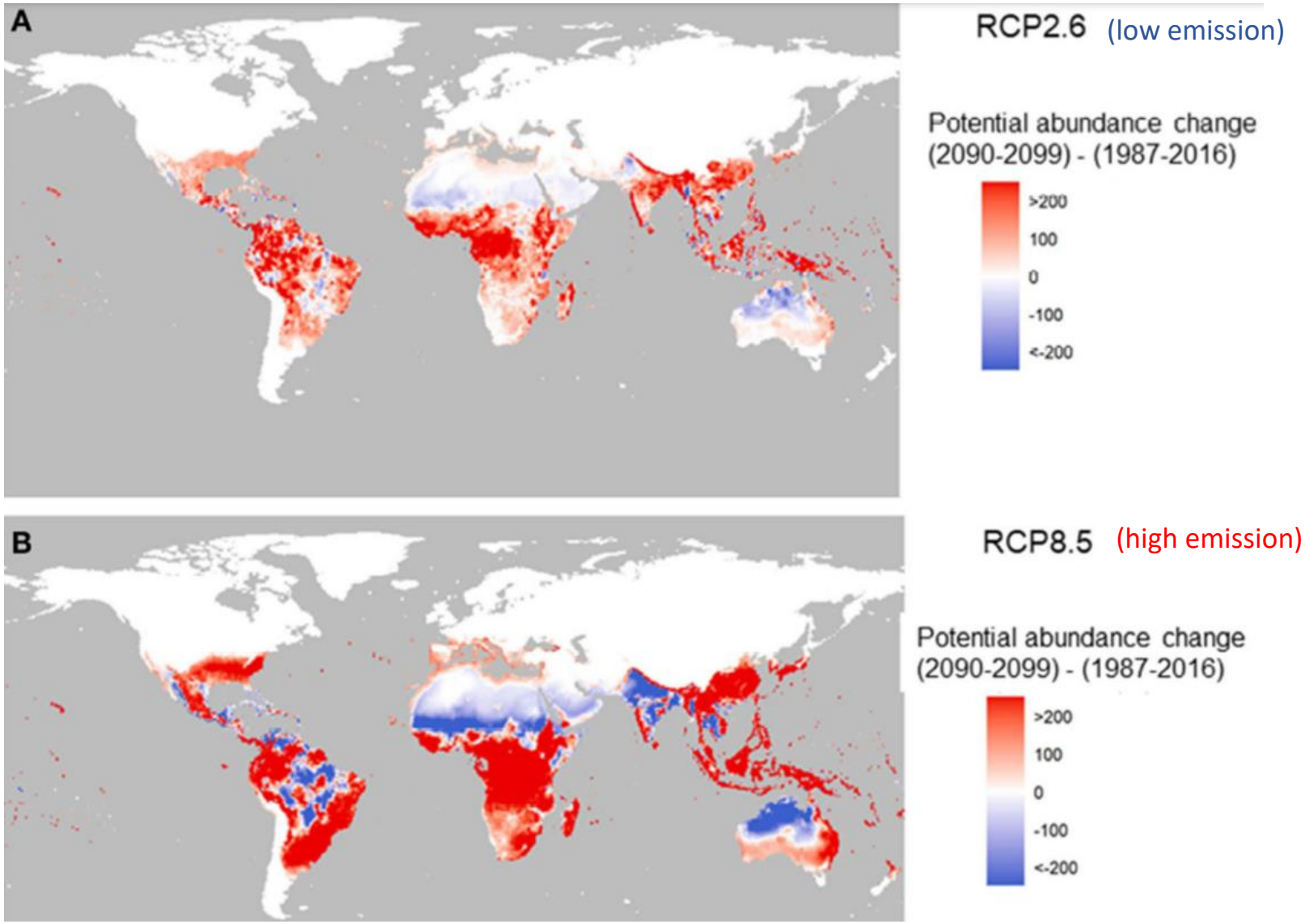
- Changes in the **prevalence of pathogen** in the host or vector population
- Changes in the **pathogen load:**
  - changes in the rates of pathogen reproduction, replication, or development in hosts or vectors
- **Increased contacts of infected animal hosts and vectors with humans** or with other hosts and vectors



Mills JN et al. Environ Health Perspect 118:1507–1514 (2010)

Jones KE et al. Global trends in emerging infectious diseases. Nature 451, 990-993, 2008.

Change in the potential abundance of A. aegypti (per larval site) over the twenty-first century (2090–2099 relative to 1987–2016). The two panels correspond to two carbon emission scenarios: RCP2.6 (a) and RCP8.5 (b).

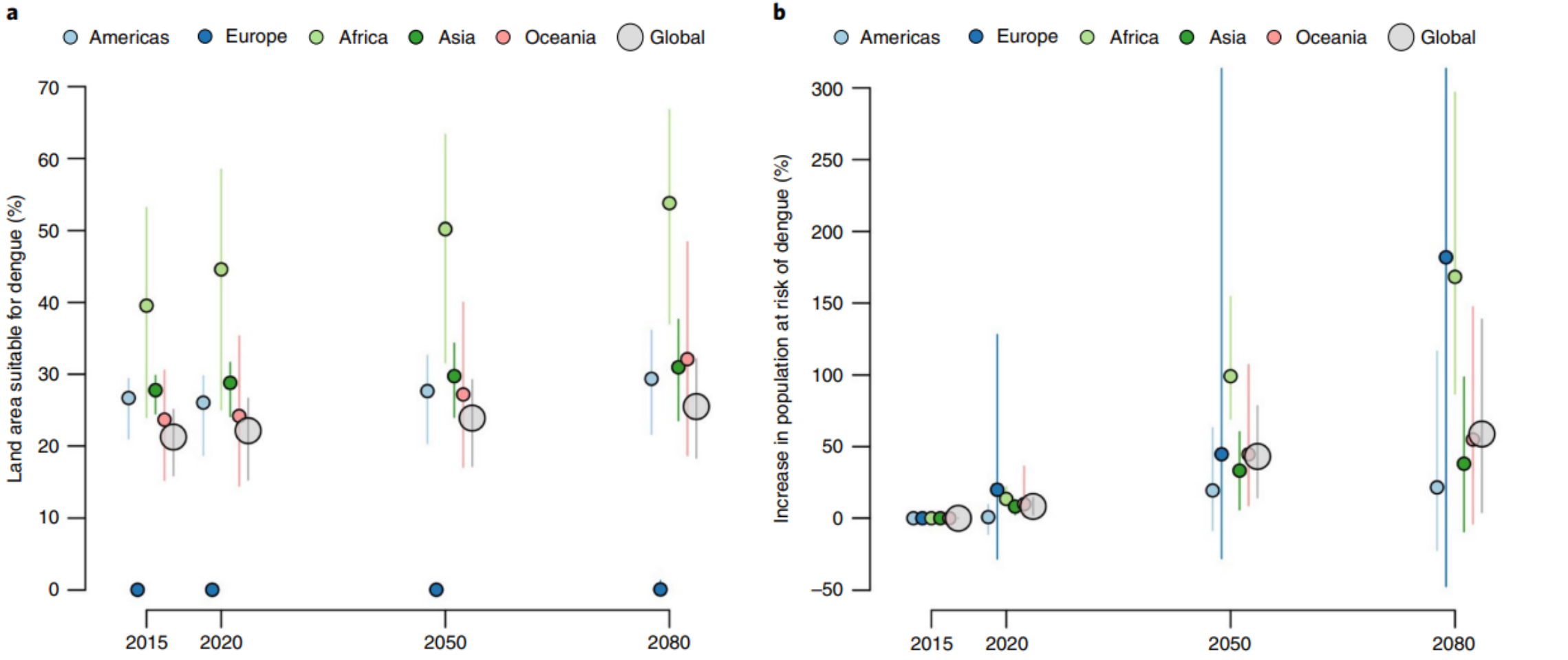


Nature Microbiology | VOL 4 | SEPTEMBER 2019 | 1508–1515. https:// doi.org/10.1007/s40121-022-00647-3

Projected changes in the risk of dengue occurrence.

There are predicted changes in the land area (a) and population (b) at risk of dengue in the future.

Mean and 95% credible intervals are shown for each ensemble.



https:// doi.org/10.1007/s40121-022-00647-3.

In this scenario, with the explosive

outbreaks of arboviruses,

a **high rate of asymptomatic** subjects

and with a **short-term viremia…**

It's important to :

I. Discuss the **epidemiological surveillance strategies** to **identify emerging infectious diseases** that might threaten blood safety worldwide;

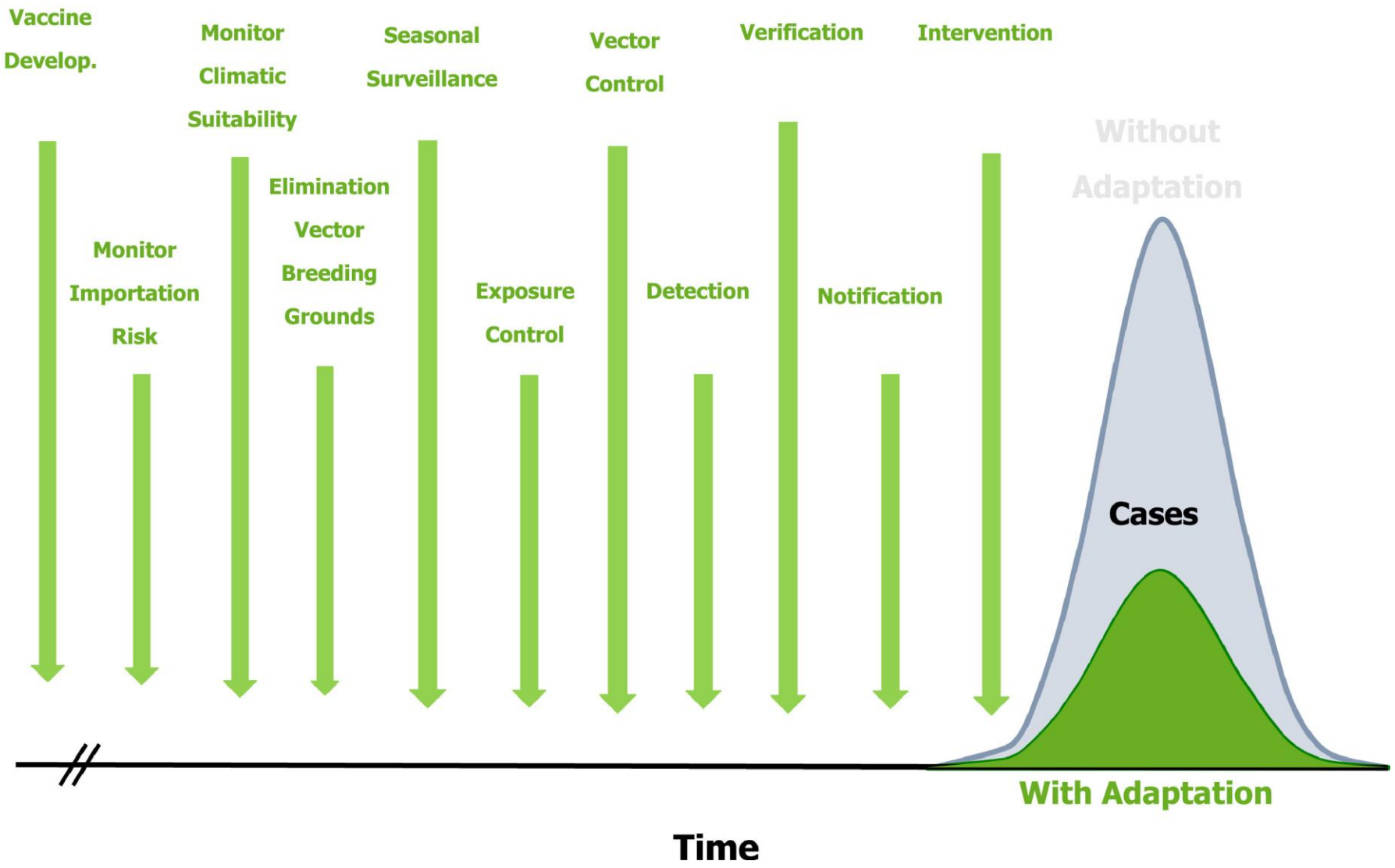
- There have been suggestions that blood donations should be **routinely tested for selected agents**, but this seems impractical and there is not yet an effective way to choose the target agents.

II. Describe **mitigation strategies** based on mathematical modelling to **ensure blood safety;**

- **Broad blood donor screening may not be sufficiently timely** to prevent the early spread of a transfusion-transmissible agent.

Climate change adaptation options for vector-borne diseases in Europe. Note: Time scale is relative.

Source: Adapted from: Semenza JC. Cascading risks of waterborne diseases from climate change. *Nature Immunol* 2020;**21(5):**484-487.



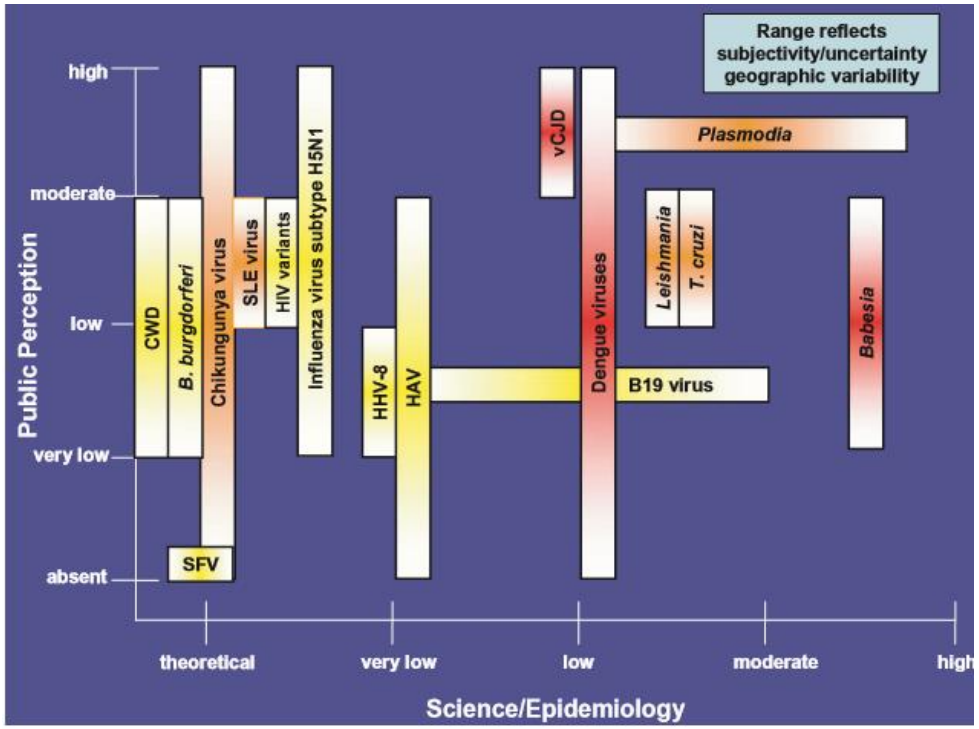
Predicting the emergence of a novel human pathogen is inherently challenging.

There is no established proactive approach to projecting the impact of EIDs on blood safety and availability.

- The AABB has generated some tools, including a listing of agents potentially transmissible by transfusion, but this process is based upon voluntary, unsystematic activities.

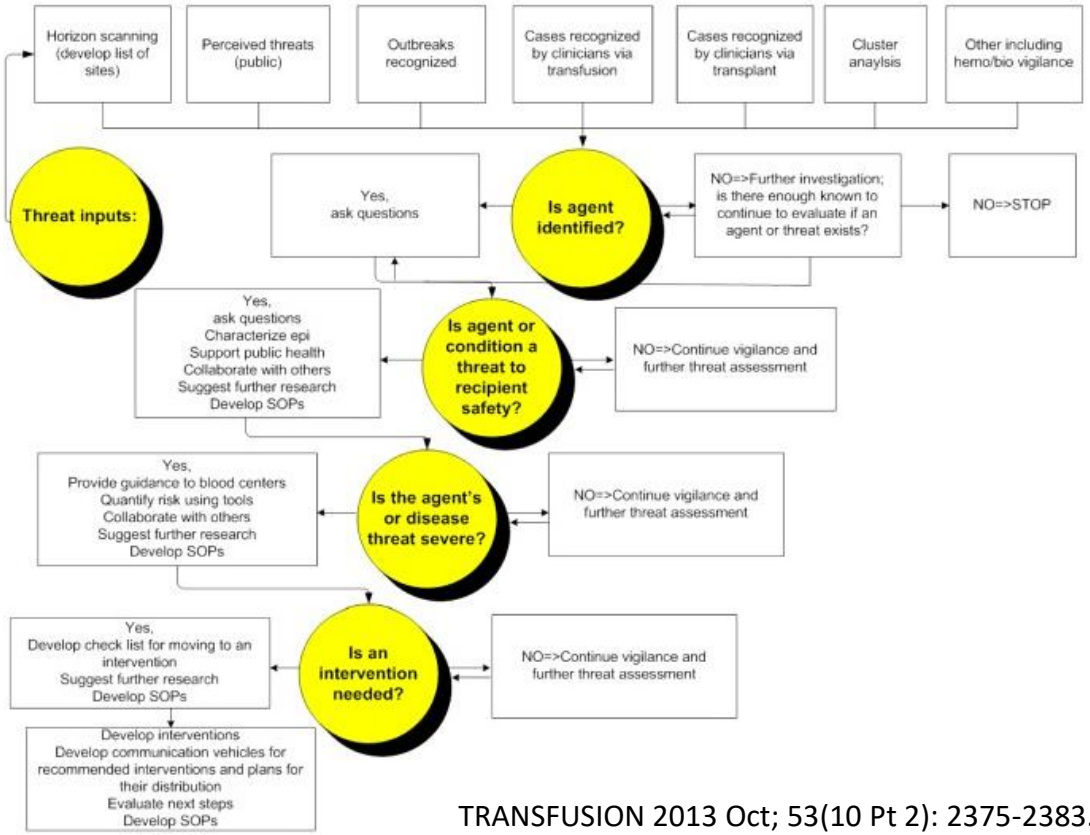
ORIGINAL ARTICLE

Emerging infectious disease agents and their potential threat to transfusion safety



doi: 10.1111/j.1537-2995.2009.02279.x TRANSFUSION 2009;49:1S-29S.

Outline of AABB EID subgroup's toolkit including the framework for recognition, assessment, and management of EID agents for risk of transfusion-associated transmission and disease



TRANSFUSION 2013 Oct; 53(10 Pt 2): 2375-2383.

To ensure the early identification of a new EID with risk for TT

Patterns of key characteristics of transfusion-transmissible EID agents.

Are there consistent patterns to potential TT-EIDs?

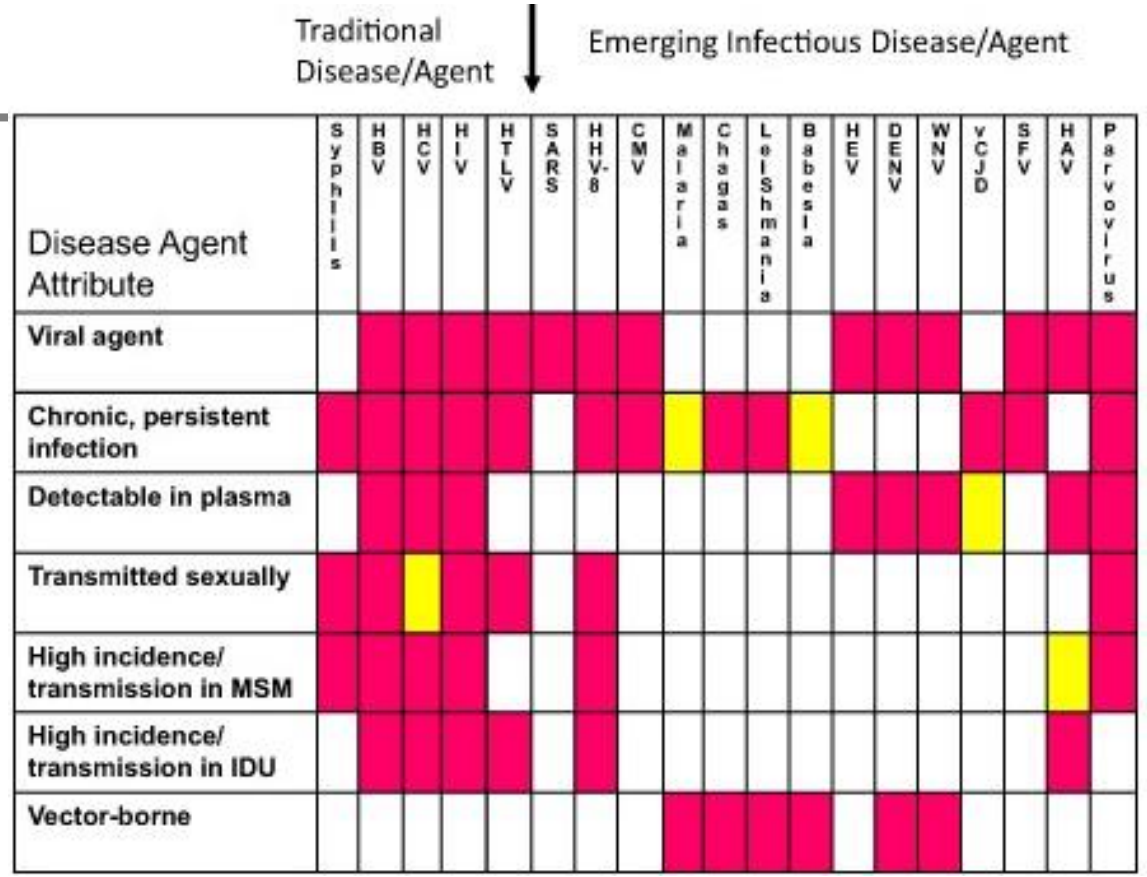
Traditional Disease/Agent ↓ Emerging Infectious Disease/Agent

Disease Agent Attribute	Syphilis	HBV	HCV	HIV	HTLV	SARS	HHV-8	CMV	Malaria	Chagas	Leishmania	Babesia	HEV	DENV	WNV	vCJD	SFV	HAV	Parvovirus
Viral agent		■	■	■	■	■	■	■					■	■	■		■	■	■
Chronic, persistent infection	■	■	■	■	■		■	■	■	■	■	■				■	■		■
Detectable in plasma		■	■	■									■	■	■	■		■	■
Transmitted sexually	■		■	■	■		■												■
High incidence/ transmission in MSM	■	■	■	■			■											■	■
High incidence/ transmission in IDU		■	■	■	■		■											■	
Vector-borne									■	■	■	■		■	■				

Transfusion. 2013 Oct; 53(10 Pt 2): 2375–2383.

The Major Transfusion-Relevant Viruses and EID Agents: What are the Differences?

- While the **major transfusion-relevant viruses** are transmitted human-to-human **without vectors or host reservoirs** and have an endemic **worldwide distribution**,
- a number of **EID agents** known to be transfusion-transmissible, including DENV, WNV, Plasmodium spp. and T. cruzi, are primarily **vector-borne** and have a defined **geographical distribution**.



The Major Transfusion-Relevant Viruses and EID Agents: What are the Differences?

- While the major transfusion-relevant viruses are transmitted human-to-human without vectors or host reservoirs and have an endemic worldwide distribution,
- Due to the focus on the major transfusion-relevant viruses in the 1980s and 1990s, sensitive and specific assays for **universal donor screening** have been developed and implemented in most countries, and
- **TT risks can be estimated by risk models.**

- a number of EID agents known to be transfusion-transmissible, including DENV, WNV, Plasmodium spp. and T. cruzi, are primarily vector-borne and have a defined geographical distribution.
- In contrast, donor screening is not possible for most EID agents as suitable assays have only been **developed and approved for a limited number of agents** (WNV, T. cruzi, HAV, human parvovirus B19, DENV and Plasmodium spp).
- Even when a suitable assay is available for an EID agent, **universal donor screening is not always implemented** as it may not be mandated or not feasible due to inadequate resources.

Transfusion-Transmission Risk Modeling

- Estimating TT risk is well established using models based on **two key parameters**:
  - the **incidence of infection** in the donor population (which is known due to universal donor screening) and
  - the **infectious window period** (the period during which an acutely infected donor may be infectious but not detectable by the screening assay).

- However, modeling based on **incident window period methodology is not applicable to EID agents** for which **donor screening has not been implemented** as the **incidence of infection in the donor population is not known** and an assay window period is not applicable.

- Therefore, **alternative risk models** have been developed which included estimating the EID incidence in the blood donor population based on the **observable (i.e. reported) incidence in the general population**.

The Biggerstaff-Petersen Model:

To estimate the risk of collecting an infectious donation from an asymptomatically infected donor during the period of observation

$$Average\ risk = \frac{D_{asym}}{T} * R * I_p$$

D_{asym} is the mean duration of asymptomatic viraemia,

T is the period of observation,

R is the ratio of total infections/reported cases and

I_p is the population incidence of reported (ie, symptomatic) infections

In 1999, the BP model used the reported incidence of **WNV neurologic disease** → to derive an **estimate of the incidence of asymptomatic infection in the general population** which was used → to **estimate the proportion of donors who were asymptomatic and viraemic** → which in turn was interpreted as the **TT risk**.

The European Up-Front Risk Assessment Tool (EUFRAT): The Risk of Transmitting Infection

- The first step estimates the **risk of a donor being infectious at the time of donation** which is assumed to be proportional to the prevalence of infection in the general population.
- The second step estimates the **number of donations derived from infectious donors** and incorporates the prevalence of infection in the donor population (from step 1), the mean donation frequency and the probability that an infected donor will be interdicted by a predonation assessment procedure.
- The third step estimates the number of infected donations released for processing into blood components and **infected end products** based on pathogen removal or inactivation due to the blood processing procedures and, if implemented, the effectiveness of donor screening and pathogen reduction technology.
- The final step is an estimate of the **risk of recipients becoming infected** following transfusion which will depend on the **TT efficiency of the agent** and the proportion of **recipients who are immune** to the agent.

Applications of the Biggerstaff-Petersen model for estimating transfusion-transmission risk

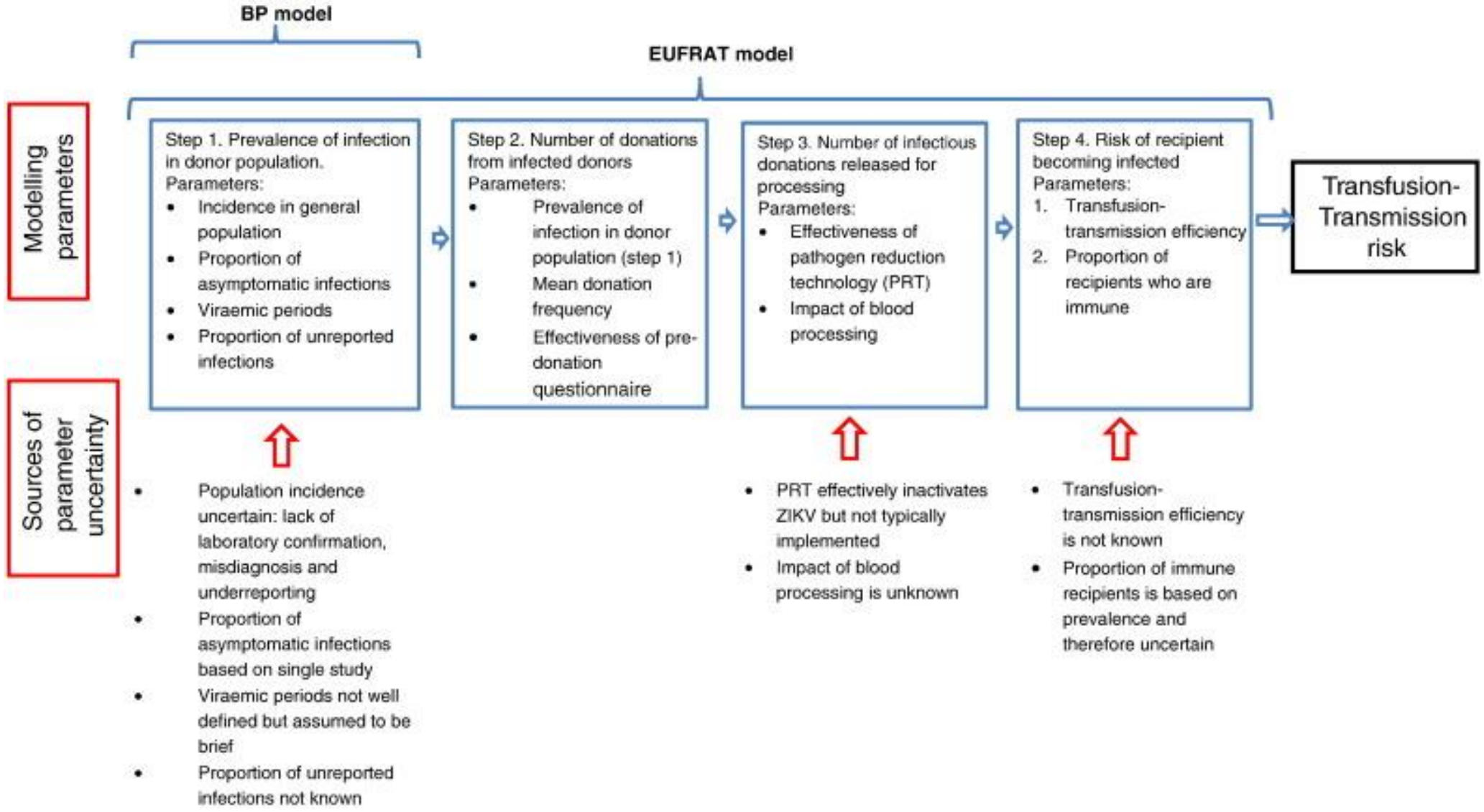
Pathogen	Country (date of outbreak)	Formula/resampling[1]
Chikungunya virus (CHIKV)	La Reunion Island (2005–2007)	Formula
Dengue virus (DENV)	Australia (2004)	Formula
Dengue virus (DENV)	Australia (2008–2009)	Formula
Chikungunya virus (CHIKV)	Italy (2007)	Resampling
Hepatitis A virus (HAV)	Latvia (2008)	Formula
Chikungunya virus (CHIKV)	Thailand (2009)	Formula
Ross River virus (RRV)	Australia (2004)	Formula
Ross River virus (RRV)	Australia (2013–14)	Formula

1. Refer to text for details.

Applications of the EUFRAT model

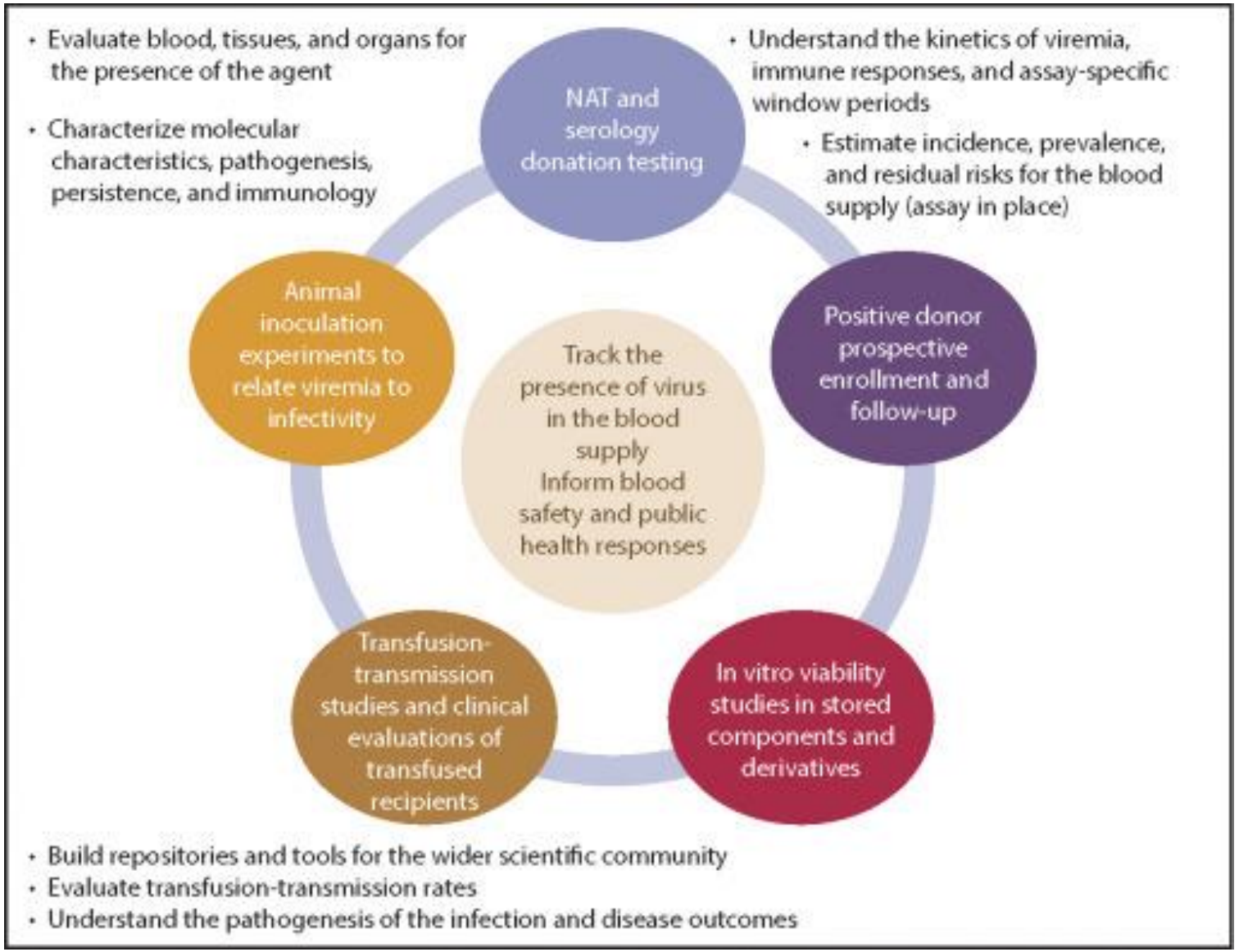
Pathogen	Country (date of outbreak)
Chikungunya virus (CHIKV)	Italy (2007)
Dengue virus (DENV)	Dutch donors returning form Suriname and Dutch Caribbean (2011–11)
Chikungunya virus (CHIKV), *Coxiella burnetti* (Q fever)	Italy (2007), Netherlands (2007–09)
Coxiella burnetti (Q fever)	Netherlands (2007–09)
Ross River virus (RRV)	Australia (2013–14)

ZIKV risk modeling parameters and sources of uncertainty



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7126009/

Modeling the TT risk of EID agents can be an important part of decisions regarding when risk mitigation strategies should be implemented and which strategies are the most appropriate.



Conclusion

- If the expert consensus is correct then **EID outbreaks will continue to occur** during the course of the 21st century and pose an ongoing challenge for maintaining the safety of the blood supply.

- So that **health authorities are able to anticipate and respond quickly to EID outbreaks and potential threats to blood safety**, intense ongoing surveillance, epidemiological modeling and risk assessments are essential.

Testing is central to the response to EIDs…

- **Proactive detection of EID agents** is necessary to understand their potential threat to blood safety before substantial numbers of recipients are exposed.

- Further, there is a need to integrate new tests into current algorithms with a view to reduce redundancy in donor screening (**multiplexed technologies and rapid high-volume sequencing**).

Additionally, pathogen reduction !

- A reasonable expectation is that pathogen reduction will continue for platelets and plasma and expand to red cells and/or whole blood, so that the availability of pathogen-reduced blood and blood components will be the norm and will greatly simplify the currently overly complex processes of donor qualification and testing.

"Obviously, while infectious agents will continue to emerge, we do not know what future transfusion needs will be required, and we do not even know how stable the blood supply will be.

Nevertheless, our current understanding of blood safety is good by experience with many diverse disease agents; we appear to be well-equipped to maintain and continue to improve the current levels of safety in cost-effective and efficient ways."

R.Y. Dodd and S.L. Stramer, How do we forecast tomorrow's transfusion: Infectious safety?, Transfusion clinique et biologique, https://doi.org/10.1016/j.tracli.2022.08.143

Data Analytics can be key to **propose associations** that could held make better health care decisions or **identify and predict patterns and trends** that were previously unknown and inform **future studies and interventions**.

Gracias por la atención!

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