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Emerging Infectious Diseases and Blood Safety: Modeling the Transfusion-Transmission Risk

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ABSTRACT

While the transfusion-transmission (TT) risk associated with the major transfusion-relevant viruses such as HIV is now very low, during the last 20 years there has been a growing awareness of the threat to blood safety from emerging infectious diseases, a number of which are known to be, or are potentially, transfusion transmissible. Two published models for estimating the transfusion-transmission risk from EIDs, referred to as the Biggerstaff-Petersen model and the European Upfront Risk Assessment Tool (EUFRAT), respectively, have been applied to several EIDs in outbreak situations. We describe and compare the methodological principles of both models, highlighting their similarities and differences. We also discuss the appropriateness of comparing results from the two models. Quantitating the TT risk of EIDs can inform decisions about risk mitigation strategies and their cost-effectiveness. Finally, we present a qualitative risk assessment for Zika virus (ZIKV), an EID agent that has caused several outbreaks since 2007. In the latest and largest ever outbreak, several probable cases of transfusion-transmission ZIKV have been reported, indicating that it is transfusion-transmissible and therefore a risk to blood safety. We discuss why quantitative modeling the TT risk of ZIKV is currently problematic.

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Blood supplies internationally are as safe as they have ever been [1]. In most developed countries, the transfusion–transmission (TT) residual risks (RRs) for the major transfusion-relevant viruses, hepatitis B virus (HBV), human immunodeficiency virus types 1 and 2 (HIV-1/2)

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and hepatitis C virus (HCV) have been reduced to very low probabilities [2,3]. This has been achieved by a combination of community education, non-remunerated voluntary blood donations, pre-donation donor questionnaires designed to elicit risk behaviors, universal donor screening, pathogen inactivation procedures incorporated into the production of plasma-derived products and the availability of pathogen reduction technologies for fresh blood components [2,4-7]. Additionally, most countries perform serological screening for *Treponema pallidum* (syphilis) [8], while a number also screen for antibodies to human T-cell lymphotropic virus types 1 and 2 (anti-HTLV-1/2) [9,10] and bacterial contamination of platelet components [11].

However, over the last 20 years there has been an increasing awareness of the threat to blood safety from emerging infectious disease (EID) agents [12-21]. In this review we provide an overview of how EID agents can be defined, when they represent a potential risk to blood safety and how they differ from the classical transfusion-relevant agents. We then describe and compare the methodological principles and limitations of two models that have been developed and applied to estimate the TT risk of EID agents. Finally, we use Zika virus (ZIKV) as a contemporary case study for assessing the risk of an EID agent to blood safety.

Defining Emerging Infectious Diseases – and Why We Can Expect More Outbreaks

A widely accepted definition of EIDs are "those whose incidence in humans has increased within the past 2 decades or threatens to increase in the near future" [17,22]. This is, perhaps necessarily, an imprecise definition which does not specify the level of past or 'threatened' incidence increase and does not differentiate true increases in incidence from apparent increases due to greater awareness. Additionally, it does not take into account geographical variation whereby an EID agent may be emerging in one region but established in another [23], and the period of 2 decades is somewhat arbitrary. Therefore, in the absence of a precise and universally applicable definition, "emerging" could be applied to infectious diseases on a regional basis taking into account local epidemiology.

Causative agents of EIDs include new or previously undetected agents, as well as known agents that are re-emerging following a period of low incidence or those for which a disease association has not been previously recognized [17,24,25]. An important class of novel EIDs in humans are zoonotic infections [17,24,26-29], driven in part by the increased human demand for meat and animal products [28]. 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 (Fig. 1).

While EIDs are not a new phenomenon, the frequency of reported outbreaks has increased in the last 20 years and experts predict that this will continue [17,18,21,26,28-30]. To emphasize this point, the list of 21st century outbreaks already includes, in addition to ongoing outbreaks of West Nile virus (WNV) [31,32], severe acute respiratory syndrome corona virus (SARS-CoV) in China in 2002–3 [33,34], the re-emergence of avian influenza virus H5N1 (A(H5N1) [35], chikungunya virus (CHIKV) on La Reunion island in 2005–07 followed by the Western Pacific region in 2012 and the Americas in 2013 [36-39], influenza A virus H1N1 ((A(H1N1)) [40], Middle East respiratory syndrome corona virus (MERS-CoV) in 2012 in the Middle East [41], influenza A virus H7N9 (A(H7N9)) in 2013 in China [42], ZIKV on Yap Is in 2007, the Western Pacific region in 2014 and the Americas in 2015–16 [43] and Ebola virus (EBOV) in West Africa in 2014–15 [44].

From a blood safety perspective, a number of EID agents are known to be, or are potentially, transfusion-transmissible based on the following criteria [17,20,28]:

- 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
- associated with a clinically apparent disease in at least a proportion of recipients.

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

EID agents are typically less well characterized than the major transfusion-relevant viruses noted above, either because they are newly identified or have been known for some time but not considered

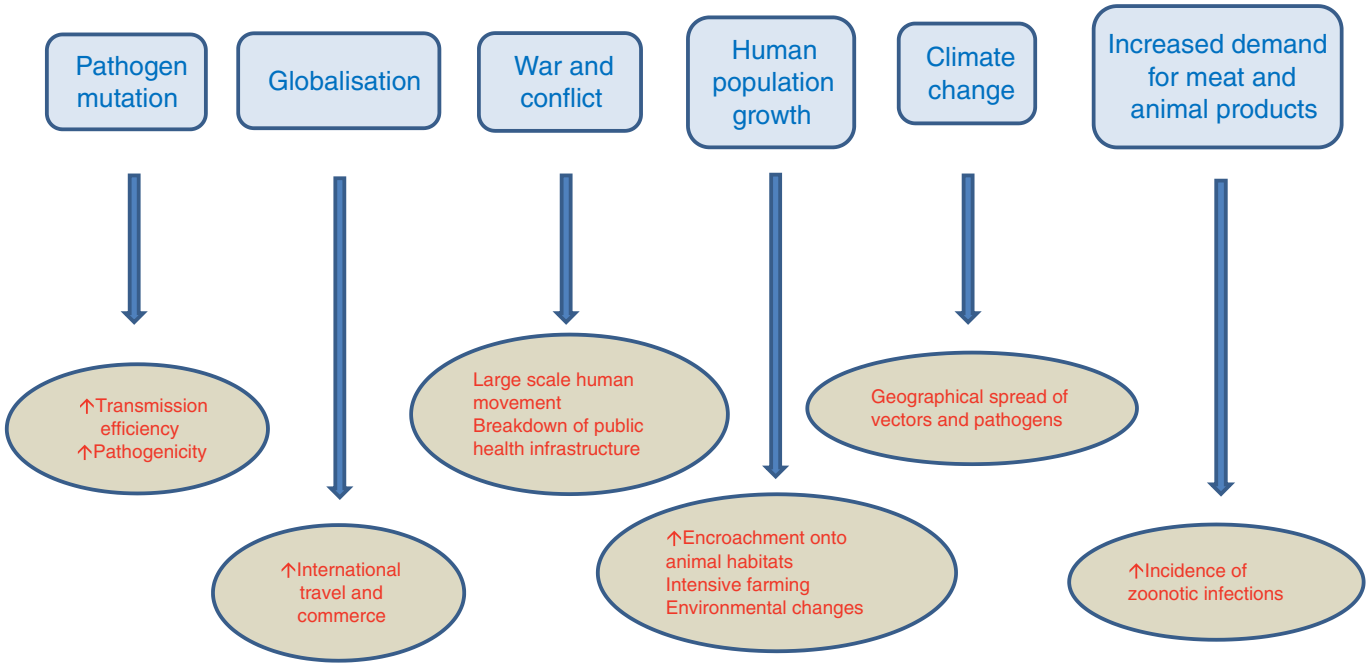

Fig. 1. Why we can expect more EID outbreaks.

a research priority. Therefore EID outbreaks are typically difficult to predict and risk assessments often have a high degree of uncertainty. 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 dengue virus (DENV), West Nile virus (WNV), *Plasmodium* spp. and *Trypanosoma cruzi*, are primarily vector-borne and have a defined geographical distribution [19]. 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 [45-49]. 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, including WNV [23,50,51], *T. cruzi* [52], hepatitis A virus (HAV), human parvovirus B19 (primate erythroparvovirus 1) [53-55], DENV [56,57] and *Plasmodium* spp. [58]. Moreover, 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 considered a proportionate response to the perceived level of risk, or not feasible due to inadequate resources.

Emerging Infectious Disease Agents and Transfusion-Transmission Risk Modeling

Estimating the TT risk of pathogens can be an important part of overall risk assessments. While risk estimates necessarily include a measure of uncertainty, they nonetheless provide an indication of the risk level which in turn can be used to inform decisions about the implementation of risk mitigation strategies.

For the classical transfusion-relevant viruses for which universal screening has been implemented, 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) [59-67]. 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: The Risk of Asymptomatic Infection in Blood Donors

The first published model for estimating the TT risk of an EID agent was developed by Biggerstaff and Petersen [68,69] (BP model) in response to WNV outbreaks in the US, first reported in Queens, New York city in 1999 [23,70]. WNV is a mosquito-borne flavivirus and TT has been well documented. [23,70-80]. Prior to the implementation of donor screening for WNV in 2003 [23], Biggerstaff and Petersen retrospectively estimated the TT risk of WNV during the outbreak in Queens in 1999 [68] and, subsequently, other regions of the US [69].

The BP model used the reported incidence of WNV neurologic disease (WNND) to derive an estimate of the incidence of asymptomatic infection in the general population which in turn was used to estimate the proportion of donors who were asymptomatic and viraemic. Based on a number of assumptions (Table 1), the estimated proportion of asymptomatic viraemic donors was equated to the *risk of an infected donation entering the blood supply, which in turn was interpreted as the TT risk*. Development of the BP model included both a statistical resampling method (Monte Carlo simulation) for estimating the proportion of the population who were asymptomatically viraemic at any *point in time*, and a formula for estimating the average proportion of asymptomatic viraemic donors *over a specified time period*. More recently, Shang et al. have developed a "hybrid" approach to the BP model, combining the statistical resampling and formula methodologies [81].

Description of the Biggerstaff-Petersen Model

To perform statistical resampling, the required input variables based on the local outbreak data were the:

- number of reported cases of WNND (meningoencephalitis) for the period of observation
- dates of symptom onset for each reported case, and
- population of the outbreak area.

In addition, a number of variables derived from published historical data were also required:

- time course of WNV viraemia
- ratio of WNND cases to total number of WNV infections, and
- ratio of asymptomatic/symptomatic infections.

Based on the symptom onset dates for the reported WNND cases, the statistical resampling simulated the number of symptomatic viraemic cases at time t based on the range of possible viraemic periods prior and subsequent to symptom onset. Further, based on the size of the general population, the ratio of total WNV infections/reported WNND cases and the assumption that infected donors who develop symptoms are only at risk of donating prior to symptom onset, the model derived a risk curve that represented the estimated proportion of asymptomatic cases in the population which was equated to the TT risk of WNV.

The authors also developed a methodologically simpler formula to estimate the average WNV TT risk for a specified time period which provided comparable estimates and has subsequently been applied in a number of published studies (Table 2).

The BP formula can be conceptually expressed as

$$\textit{Average risk} = \frac{D_{asym}}{T} * \mathrm{R} * \mathrm{I}_p$$

Where D_{asym} is the mean duration of asymptomatic viraemia, taking into account that the asymptomatic viraemic period in the proportion of cases that do not develop clinical symptoms is the entire viraemic period, and for the proportion that develop clinical symptoms it is only the pre-symptomatic viraemic period, 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.

As the first term represents the risk of each infected donor presenting to donate while asymptomatic and viraemic, and the product of the second and third terms represents the incidence of all infections (those that develop symptoms and those that remain asymptomatic), the above formula can be expressed as

$$\textit{Average risk} = Pr\left(\begin{array}{c}\textit{collecting viraemic donation}\\ \textit{from each asympomatitically infected donor}\end{array}\right) * (\textit{incidence of infection})$$

Therefore, the BP formula for average risk is an estimate of *the risk of collecting an infectious donation from an asymptomatically infected donor during the period of observation.*

Applications of the Biggerstaff-Petersen Model

Since its original application to WNV outbreaks in the US, the BP model has been used to estimate the TT risk of DENV in Australia during outbreaks in 2004 and 2008 to 2009 [57,82], CHIKV on La Reunion island in 2005–07 [83], Thailand in 2009 [84] and Italy in 2007 [85], hepatitis A virus (HAV) in Latvia in 2008 [86] and Ross River virus (RRV) in Australia in 2013–14 [87,88] (Table 3). In most of these studies the BP formula for average risk for a defined time period was used rather

Table 1
Assumptions and limitations of the Biggerstaff-Petersen and EUFRAT models

	Assumptions common to both models	Additional assumptions for the BP model	Additional assumptions for EUFRAT
Assumptions related to reported case numbers	• *Reported* incident infections represent all symptomatic infections	• Symptom onset dates for reported (symptomatic) cases are similar to asymptomatic infections	
Assumptions related to blood donor	characteristics	• Donation frequency is constant throughout the period of observation • All donors have the same risk of infection, which is constant, during the period of observation • Asymptomatic infection does not affect the donation behavior of donors • Likelihood of detection of infectious donors by the pre-donation questionnaire is constant throughout the infectious period	• Donors have the same risk of infection as the general population. • Blood components from viraemic blood donors transmit infection with 100% efficiency • Donors with symptomatic infections would either not present to donate or would be excluded from donating
Assumptions related to infection	• Historically estimated asymptomatic/symptomatic infection ratio and viraemic periods are applicable to the study population and remain constant during period of observation • Relative timing and duration of viraemia is independent of symptom onset time • Duration of viraemia is the same for both symptomatic and asymptomatic cases		• Risk from traveling donors is based on the duration of visit to outbreak/endemic area and time from departure to donating. • Traveling donors have the same risk of infection as local inhabitants in outbreak/endemic area. • The proportion of donors that develop chronic infections is constant during period of observation.
Limitations	• Input parameters required for both models are often not well defined and contribute to the inherent uncertainty of the models.	• To perform the statistical resampling in the BP model, the dates of symptom onset for reported incident cases are required. • The BP model does not take into account the reduction in TT risk related to efficiency of transmission by transfusion, pathogen reduction/inactivation due to blood processing and storage, and recipient immunity.	• A number of parameters in the EUFRAT model, including the difference in risk of infection between donors and the general population, the proportion of symptomatic cases in the general population that do not seek health care or are misdiagnosed, the TT efficiency of infected end products and the level of immunity in the general population, are typically unknown for EID agents.

than the statistical resampling approach. Presumably this is due, at least in part, to the former being computationally simpler and not requiring the exact dates of symptom onset for reported cases. These studies show that the BP model can be applied to a range of EID agents and demonstrate that regular risk modeling across regions can provide an indicator of changing risk levels over time and geographically, thereby informing decisions regarding the implementation of risk mitigation strategies.

The EUFRAT: The Risk of Transmitting Infection

The European Centre for Disease Prevention and Control (ECDC) has also developed a model for estimating the TT risk of EID agents, referred to as the European Up-Front Risk Assessment Tool (EUFRAT)) [89,90]. The EUFRAT has a web-based interface, the stated aims of which are to assess and quantify the TT risk of an EID during an ongoing outbreak.

Table 2
Applications of the Biggerstaff-Petersen model for estimating transfusion-transmission risk

Pathogen	Country (date of outbreak)	Formula/resampling[1]	Comments	Reference
Chikungunya virus (CHIKV)	La Reunion Island (2005–2007)	Formula	• Proportion of asymptomatic infections based on local seroprevalence data • Estimate of symptomatic cases accounts for cases who did not consult a GP • Risk estimates did not take into account uncertainty of key parameters • Estimates of CHIKV viraemic periods based on DENV • Incidence based on clinical definition which may be an overestimate due to misdiagnosis of cases not due to CHIKV	[83]
Dengue virus (DENV)	Australia (2004)	Formula	• risk modeling used to monitor changes in risk over time	[82]
Dengue virus (DENV)	Australia (2008–2009)	Formula	• Mean donation frequency used to estimate number of infectious donations • Estimated proportion of asymptomatic infections based on the seroprevalence data in outbreak area • Assumed donors who became symptomatic within a few days after donating would notify the blood service and donation would be discarded	[57]
Chikungunya virus (CHIKV)	Italy (2007)	Resampling	• Risk contribution for donors in the 2-day presymptomatic period was regarded as negligible and therefore excluded from modeling	[85]
Hepatitis A virus (HAV)	Latvia (2008)	Formula	• Model incorporated seroprevalence (immunity level) in general Latvian population who were assumed to be immune • Modeling restricted to individuals >18 years (blood donor eligibility) • Accounted for ALT testing of donors and deferral if levels are high (>90 IU/L) • Did not take into account exclusion of donors who have a history of contact with HAV-infected individuals	[86]
Chikungunya virus (CHIKV)	Thailand (2009)	Formula	• Modeled risk estimate of asymptomatic viraemic donors was higher than indicated by donor screening	[84]
Ross River virus (RRV)	Australia (2004)	Formula	• Duration of RRV viraemia in humans based on mouse model	[87]
Ross River virus (RRV)	Australia (2013–14)	Formula	• Demonstrated changing risk levels geographically and over time • Duration of RRV viraemia in humans based on mouse model	[88]

1. Refer to text for details.

Table 3
Applications of the EUFRAT model

Pathogen	Country (date of outbreak)	Comments	Reference
Chikungunya virus (CHIKV)	Italy (2007)	Applied both Biggerstaff-Petersen and EUFRAT models and calculations were performed: • using both weekly and average cumulative notified cases • using fixed input data and variable distribution values; estimated risk of asymptomatic viraemic infection in donors was very similar by both methods	[89]
Dengue virus (DENV)	Dutch donors returning form Suriname and Dutch Caribbean (2011–11)	Estimated the risk of traveling donors: • becoming infected while in outbreak area • transmitting infection to recipients upon return	[91]
Chikungunya virus (CHIKV), *Coxiella burnetti* (Q fever)	Italy (2007), Netherlands (2007–09)	Extension of EUFRAT. Modeled risk of infection: • prior to time of observation • potential risk subsequent to time of observation.	[92]
Coxiella burnetti (Q fever)	Netherlands (2007–09)	• Risk modeling for an infection with acute and chronic phases • Compared probability of donor being infected as estimated by EUFRAT and Biggerstaff-Petersen models.	[93]
Ross River virus (RRV)	Australia (2013–14)	• Applied both EUFRAT and Biggerstaff-Petersen models • Demonstrated temporal and geographical variations in risk.	[88]

In this section we describe the conceptual basis of the EUFRAT and its reported applications, and then provide a comparative analysis with the BP model.

Conceptual Basis of the EUFRAT

The EUFRAT considers the risk of transmitting an EID agent to a recipient as a series of risks that begin with the risk of blood donors becoming infected. Depending upon how the input variables are grouped, methodologically the EUFRAT can be divided into a logical sequence of four [90] or five [89] steps, each with an associated risk. In our description of the EUFRAT we will consider it as a 4-step process as outlined in the EUFRAT User Manual [90].

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. This risk is a function of the length of the infectious period and includes correction factors for the difference between the risk of donors becoming infected compared to the general population (if known) and the proportion of undetected cases. For donors who have returned from an outbreak area, the risk of infection will be proportional to the infection incidence in the outbreak area and the duration of the visit, while the risk of an infected donor remaining infectious until the time of donation will be inversely proportional to the duration of the period from leaving the outbreak area to time of donating.

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. Additionally, the EUFRAT has the option for defining input parameters as either fixed values or a distribution of values. The latter allows for parameter uncertainty by using Monte-Carlo simulation which determines the value of a parameter by repeat random sampling from a triangular distribution defined by a plausible range entered by the user [89,90].

Applications of EUFRAT

EUFRAT has been used in a number of reported studies to estimate the TT risk for CHIKV, DENV, *Coxiella burnetii* and RRV (Table 2). In the original description of the EUFRAT, the investigators retrospectively applied it to the 2001 CHIKV outbreak in the Emilia-Romagna region in the north-east of Italy [89]. The results demonstrated how the final estimated risk of transmitting infection to recipients can be substantially less than the estimated risk of asymptomatic infection in blood donors. For example, based on an estimated weekly donor prevalence of 1.07 CHIKV cases per 100 000 (95% CI, 0.38-2.03) donors at the outbreak peak, the actual risk of severe infection in recipients was estimated as 0.0001 per 100 000 donations. While TT risk is typically expressed as the risk of transmitting infection regardless of clinical outcome, this was not specifically reported by the authors.

The EUFRAT has also been used in a non-outbreak area to estimate the TT risk associated with donors returning from an outbreak area [91] and has been extended to retrospectively estimate the TT risk during an outbreak period AND the subsequent (future) risk associated with donors who potentially remain infectious for some time following the end of the outbreak [92].

BP and EUFRAT Models: From Population Incidence to Donor Incidence

Both the BP and EUFRAT models are based on a number of assumptions which are summarized in Table 1. In particular, a number of these assumptions are required to estimate the EID incidence in the eligible donor population based on the incidence in the general population, which is an important part of both models. Firstly, the diagnosis and reporting of symptomatic infections in the general population represents all symptomatic cases. Secondly, published historic data estimating the ratio of asymptomatic/symptomatic infections is applicable to the study population. This ratio is important as it allows the total incidence (symptomatic and asymptomatic) in the general population to be estimated from the incidence of reported symptomatic infections. Thirdly, individuals with symptomatic infections would either not present to donate or would be excluded from donating. In the BP model this assumption is the basis for determining the period for which an infected

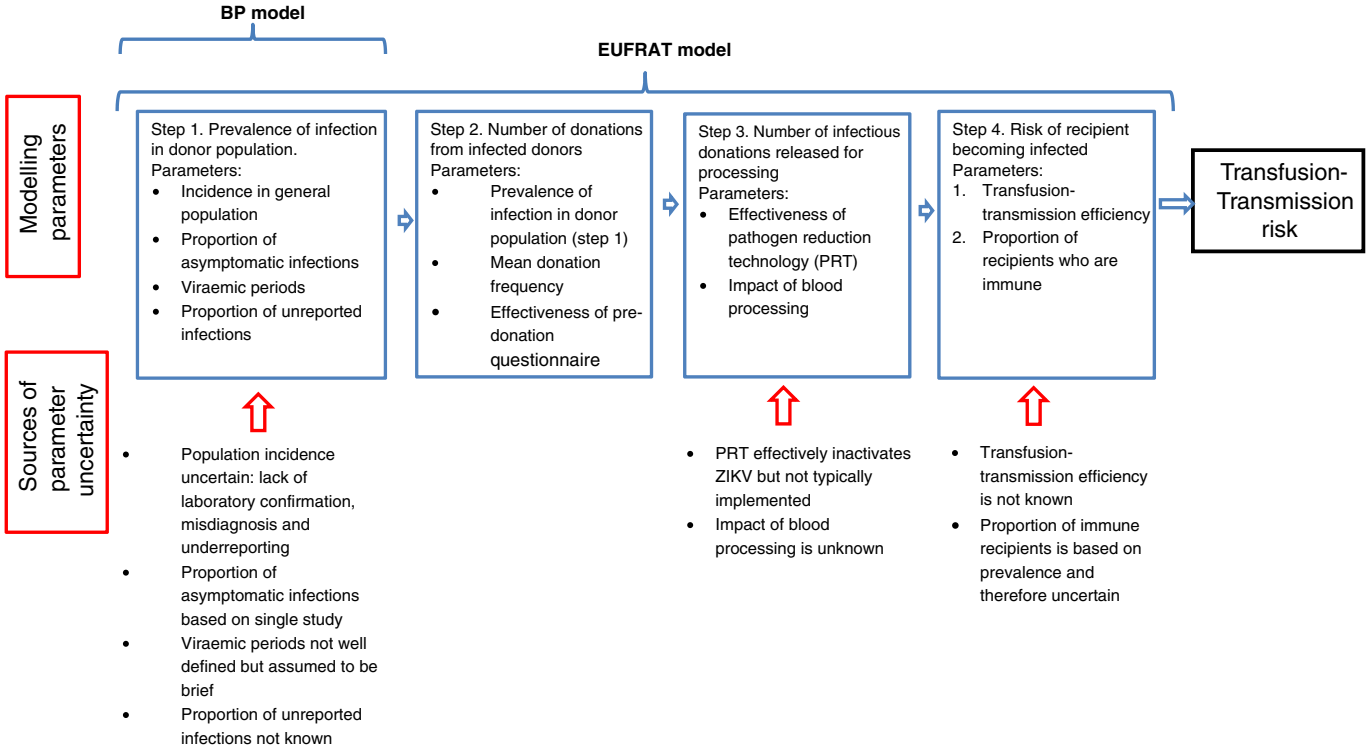

Fig. 2. ZIKV risk modeling parameters and sources of uncertainty.

donor is at-risk of presenting to donate – the entire viraemic period for donors who remain asymptomatic and the pre-symptomatic period for those who do develop symptoms**.** Fourthly, blood donors have the same risk of infection as the general population and therefore the incidence of infection in the blood donor population is the same as that in the general population.

Biggerstaff-Petersen and EUFRAT Models: Is It Valid to Compare Outcomes?

In this section we discuss the validity of comparing outcomes from the BP and EUFRAT models, noting three important methodological differences between the two models [68,69,89,90].

1. Additional risk components of EUFRAT

As already noted, both the BP and EUFRAT models estimate the risk of asymptomatic infection in donors; however, the EUFRAT incorporates additional risk components: the risk of collecting an infectious donation (steps 1 and 2), blood product-related risks (step 3), and recipient-related risks (step 4).

2. EUFRAT excludes the risk from asymptomatic donors who subsequently develop symptoms

The BP model and steps 1 and 2 of the EUFRAT are methodologically most similar when the assumptions discussed below can be made. It is worth noting that these assumptions are often applicable to EID outbreaks.

Assuming that donors have the same risk of infection as the general population and the period of infectiousness (D) is less than the period of observation (T), step 1 of the EUFRAT can be expressed as

$$P_d = \left(\frac{I_p}{NT(1-\rho)}\right)D$$

Where P_d is the prevalence of infectious donors, I_p is the number of reported infections in the population, N is the size of the population and ρ is the proportion of undetected infections.

If it is also assumed that the *reporting system is 100% effective*, ie, all symptomatic cases are reported, ρ is effectively the proportion of asymptomatic infections, $(1-\rho)$ is the proportion of detected (i.e. symptomatic) donors and $1/(1-\rho)$ is the ratio of total infections/symptomatic infections. Further, Ip/N is the incidence of reported (symptomatic) cases and D/T is the proportion of the observation period that each donor is infectious (i.e. at risk of giving an infectious donation). Therefore, the above equation can then be expressed as

$$P_d = \left(\frac{Ip}{N}\right)^{*}(1/(1-\rho))^{*}\left(\frac{D}{T}\right)$$

If it is further assumed that *infection does not include a chronic phase and that donor testing has not been implemented*, then the prevalence of asymptomatically infected donors (P_a), who would therefore not be interdicted, is

$$Pa = (P_d)^{*}(\rho)$$

For applications based on the above assumptions, the EUFRAT estimate of "prevalence of infectious donors after screening and/or testing" is in fact an estimate of the prevalence of asymptomatic infectious donors who remain asymptomatic for the course of the infection. Therefore, the EUFRAT model excludes the risk associated with asymptomatic donors who subsequently develop symptoms (ie, the pre-symptomatic infectious period). This represents a second difference between the BP and EUFRAT models as the BP model incorporates the risk associated with the pre-symptomatic infectious period. As a consequence, the EUFRAT model could potentially underestimate the risk of asymptomatic infections in donors – the higher the proportion of asymptomatic infections that subsequently develop symptoms, the greater the underestimation.

3. Differences in parameter distributions

A third difference between the BP and EUFRAT models relates to the distributions of the input parameters which may potentially contribute to output differences. As noted, the BP model uses Monte Carlo simulation based on assumed distributions for the pre-symptomatic viraemic period and the duration of the entire viraemic period. The EUFRAT also uses Monte Carlo simulation and defines a triangular distribution for input parameters whereby uncertainty in incidence and prevalence estimates is accounted for by sampling from a beta distribution. This would be expected to affect the uncertainty estimates but have a lesser impact on the mean or median estimate of risk.

Due to these methodological differences, it would be expected that even when using the same data set, there would be differences between the risk estimates derived from the two models, although these differences will be minimized when the assumptions noted above can be made. Direct comparison of TT risk estimates from the BP model and EUFRAT have been reported for three EID outbreaks, either by different investigators in separate studies or by the same investigators as part of a single study. Using the same data set and input parameters, both models have been applied to the 2007 CHIKV outbreak in Italy [85,89] and the Q fever outbreak in the Netherlands in 2007–2009 [93] with very similar risk estimates for each outbreak. A third study comparing the EUFRAT and the BP model was performed for RRV in Australia, also using the same data set and input parameters for both models [88]. Unlike the 2 previous examples, the RRV modeling showed what appeared to be a substantial difference between the risk estimates of the EUFRAT and BP models. For example, the EUFRAT estimate for risk of (asymptomatic) infection in donors (ie, the risk of collecting a viraemic donation) in the state of Western Australia for the 12-month period June 2013 to May 2014 was 1 in 33, 481 (95% CI, 11 415-109 695) compared to the BP model estimate of the risk of collecting a viraemic donation of 1 in 58 657 (uncertainty range, 17 320-232 208). This difference in the risk estimate may be due to methodological differences between the models noted above. The BP modeling was performed using most plausible (with lower and upper) point estimates for viraemic periods and asymptomatic/symptomatic infection ratio while the EUFRAT model estimates were based on assumed distributions for these parameters. Additionally, unlike the BP model, EUFRAT does not take into account the pre-symptomatic viraemic period for the proportion of infections that develop clinical symptoms. However, it should be noted that the most plausible estimate of the BP model was within the 95% CI for the EUFRAT estimate indicating the risk estimates were not significantly different.

Zika Virus: A Blood Safety Perspective

Zika Virus as a Global Public Health Concern

ZIKV is the latest EID agent to be recognized as a potential global health threat [43,94], driven by the unprecedented and ongoing outbreak in the Americas and evidence that ZIKV is a causative agent of a number of neurological disorders, including microcephaly in newborns [95,96]. In February 2016, these concerns culminated in the WHO declaring that the ZIKV outbreak in Brazil constituted a Public Health Emergency of International Concern [97].

ZIKV is a mosquito-borne flavivirus, first isolated in 1947 from a Rhesus monkey in the Zika forest in Uganda and first isolated from a human in Nigeria in 1954 [43,98,99]. Until the ZIKV outbreak on Yap Island in 2007, no major outbreaks had been reported [43,100]. However, a number of ZIKV outbreaks since 2007 have dramatically demonstrated the outbreak potential of the virus. The first reported outbreak occurred on Yap Island in 2007 with an estimated 5000 cases [43,101-103], followed by an outbreak in French Polynesia in May 2013 with an estimated 30 000 cases by May 2014 and subsequent spread to the Western Pacific region during 2014–15 [43,99,103-113]. In early 2015 a ZIKV outbreak was reported in the Americas which remains ongoing and has become the largest ever reported outbreak. As at 14 November 2016, there were 46 countries (excluding the US mainland) in the Americas that had reported active ZIKV transmission [106]. By 2 March, 2017 a total of 548 690 suspected and 205 013 confirmed ZIKV cases had been reported by the Pan American Health Organization in the Americas [114] and 221 cases of locally acquired ZIKV had been reported on the US mainland [115]. In these recent outbreaks outside of Africa, transmission is believed to be primarily a human-mosquito-human cycle with *A. aegypti* as the primary mosquito vector [116]. However, non-vector-borne modes of transmission have been reported: sexual [117-133] including male to male [134] and female to male [135], perinatal and intrauterine [136-144], breast feeding [136,144,145] and blood transfusion [43,146-149].

Why ZIKV Represents a Potential Threat to Blood Safety

The ongoing outbreak of ZIKV in the Americas has raised concerns about the potential risk to blood safety [147,150-155]. Firstly, as noted above, ZIKV has demonstrated an ability to establish infection in humans and spread within human populations. Secondly, an estimated 80% of ZIKV infections do not develop symptoms and symptomatic infection includes a pre-symptomatic viraemic period [102,105,156-160], although the viraemic period appears to be typically brief with relatively low levels of virus [102,105,161,162]. In addition, ZIKV RNA has been detected in asymptomatic blood donors during outbreaks in French Polynesian (2013–14) [105,163], Puerto Rico (April 3–June 11, 2016) [164], Martinique (January to June 2016) [165] and the continental US (May to October, 2016) [166]. Thirdly, there is a general consensus that ZIKV is the causative agent of severe neurological disorders [43,167-171] including microcephaly in newborns [95,96,172-175] and Guillain-Barré syndrome (GBS) in the wider population [109,176-179]. Fourthly, there is evidence that ZIKV is transfusion-transmissible as at least four probable TT cases have now been reported, all from Brazil during the current outbreak. [148,149,155,180,181] Therefore, there is now sufficient evidence that ZIKV is a transfusion-transmissible EID agent, similar to the phylogenetically related DENV [56,182-190] and WNV [72-75,77,191,192].

However, accurately modeling the TT risk of ZIKV is currently problematic, due to the uncertainty associated with the required input parameters, and to our knowledge ZIKV TT risk modeling has not been published to date. In Fig. 2 we have summarized the basis for this parameter uncertainty. Nonetheless, in response to the growing evidence that ZIKV represents a threat to blood safety, a number of jurisdictions have implemented risk mitigation strategies as a precautionary or preemptive approach, even though this risk has not been estimated by formal modeling. For example, following the US Food and Drug Administration's (FDA) approval of the use of two investigational blood donor screening assays for ZIKV nucleic acid testing (NAT) under an investigational new drug application (IND) [193,194], it subsequently issued a guidance for industry recommending the implementation of either universal screening of all donations in the US for ZIKV by individual donation (ID)-NAT or pathogen reduction technology for platelets and plasma [195]. It has been noted that this guidance was issued without a formal risk assessment and without stakeholder consultation [152].

Although the ZIKV outbreak in the Americas is now declining, the virus will remain endemic in many countries where it had not previously been reported and future epidemic outbreaks cannot be excluded. Therefore, further research is required to improve our understanding of ZIKV epidemiology and virology which in turn will provide the basis for reliable TT risk modeling.

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 those with responsibility 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. Modeling the TT risk of EID agents can be an important part of risk assessments, informing decisions regarding when risk mitigation strategies should be implemented and which strategies are the most appropriate. In this review we have described the methodological principles of two published models for estimating the TT risk of EID agents. An understanding of the methodology that underpins these models will assist investigators in applying them to specific EID outbreaks and interpreting the uncertainty associated with risk estimates.

Conflict of interest

All authors declare, "conflicts of interest: none."

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Erratum

Erratum to "Emerging Infectious Diseases and Blood Safety: Modeling the Transfusion-Transmission Risk" (*Transfusion Medicine Reviews* 31/3 [2017] 154-164)

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(See Tables 1–3.)

The publisher regrets that there are some errors in the format of the tables used in the final version of this article. The publisher includes reformatted versions of the tables below.

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Table 1
Assumptions and limitations of the Biggerstaff-Petersen and EUFRAT models

	Assumptions common to both models	Additional assumptions for the BP model	Additional assumptions for EUFRAT
Assumptions related to reported case numbers	• *Reported* incident infections represent all symptomatic infections.	• Symptom onset dates for reported (symptomatic) cases are similar to asymptomatic infections.	
Assumptions related to blood donor characteristics	• Donation frequency is constant throughout the period of observation • All donors have the same risk of infection, which is constant, during the period of observation. • Asymptomatic infection does not affect the donation behavior of donors. • Likelihood of detection of infectious donors by the predonation questionnaire is constant throughout the infectious period.	• Donors have the same risk of infection as the general population. • Blood components from viremic blood donors transmit infection with 100% efficiency. • Donors with symptomatic infections either would not present to donate or would be excluded from donating.	
Assumptions related to infection	• Historically estimated asymptomatic/symptomatic infection ratio and viremic periods are applicable to the study population and remain constant during period of observation. • Relative timing and duration of viremia are independent of symptom onset time. • Duration of viremia is the same for both symptomatic and asymptomatic cases.		• Risk from traveling donors is based on the duration of visit to outbreak/endemic area and time from departure to donating. • Traveling donors have the same risk of infection as local inhabitants in outbreak/endemic area. • The proportion of donors that develop chronic infections is constant during period of observation.
Limitations	• Input parameters required for both models are often not well defined and contribute to the inherent uncertainty of the models.	• To perform the statistical resampling in the BP model, the dates of symptom onset for reported incident cases are required. • The BP model does not take into account the reduction in TT risk related to efficiency of transmission by transfusion, pathogen reduction/inactivation due to blood processing and storage, and recipient immunity.	• A number of parameters in the EUFRAT model, including the difference in risk of infection between donors and the general population, the proportion of symptomatic cases in the general population that do not seek health care or are misdiagnosed, and the TT efficiency of infected end products and the level of immunity in the general population, are typically unknown for EID agents.

Table 2
Applications of the Biggerstaff-Petersen model for estimating transfusion-transmission risk

Pathogen	Country (date of outbreak)	Formula/resampling[a]	Comments	Reference
Chikungunya virus (CHIKV)	La Reunion Island (2005-2007)	Formula	• Proportion of asymptomatic infections based on local seroprevalence data • Estimate of symptomatic cases accounts for cases who did not consult a GP. • Risk estimates did not take into account uncertainty of key parameters. • Estimates of CHIKV viremic periods based on DENV • Incidence based on clinical definition which may be an overestimate due to misdiagnosis of cases not due to CHIKV	[83]
Dengue virus (DENV)	Australia (2004)	Formula	• Risk modeling used to monitor changes in risk over time	[82]
Dengue virus (DENV)	Australia (2008-2009)	Formula	• Mean donation frequency used to estimate number of infectious donations • Estimated proportion of asymptomatic infections based on the seroprevalence data in outbreak area • Assumed donors who became symptomatic within a few days after donating would notify the blood service, and donation would be discarded	[57]
Chikungunya virus (CHIKV)	Italy (2007)	Resampling	• Risk contribution for donors in the 2-d presymptomatic period was regarded as negligible and therefore excluded from modeling	[85]
Hepatitis A virus (HAV)	Latvia (2008)	Formula	• Model incorporated seroprevalence (immunity level) in general Latvian population • Modeling restricted to individuals over 18 y (blood donor eligibility) • Accounted for ALT testing of donors and deferral if levels are high (>90 IU/L) • Did not take into account exclusion of donors who have a history of contact with HAV-infected individuals	[86]
Chikungunya virus (CHIKV)	Thailand (2009)	Formula	• Modeled risk estimate of asymptomatic viremic donors was higher than indicated by donor screening.	[84]
Ross River virus (RRV)	Australia (2004)	Formula	• Duration of RRV viremia in humans based on mouse model	[87]
Ross River virus (RRV)	Australia (2013-14)	Formula	• Demonstrated changing risk levels geographically and over time • Duration of RRV viremia in humans based on mouse model	[88]

[a] Refer to text for details.

Table 3
Applications of the EUFRAT model

Pathogen	Country (date of outbreak)	Comments	Reference
Chikungunya virus (CHIKV)	Italy (2007)	Applied both Biggerstaff-Petersen and EUFRAT models and calculations were performed: • Using both weekly and average cumulative notified cases • Using fixed input data and variable distribution values; estimated risk of asymptomatic viremic infection in donors was very similar by both methods.	[89]
Dengue virus (DENV)	Dutch donors returning form Suriname and Dutch Caribbean (2011-11)	Estimated the risk of traveling donors: • Becoming infected while in outbreak area • Transmitting infection to recipients upon return	[91]
Chikungunya virus (CHIKV), *Coxiella burnetti* (Q fever)	Italy (2007), Netherlands (2007-09)	Extension of EUFRAT. Modeled risk of infection: • Prior to time of observation • Potential risk subsequent to time of observation	[92]
C burnetti (Q fever)	Netherlands (2007-09)	• Risk modeling for an infection with acute and chronic phases • Compared probability of donor being infected as estimated by EUFRAT and Biggerstaff-Petersen models	[93]
Ross River virus (RRV)	Australia (2013-14)	• Applied both EUFRAT and Biggerstaff-Petersen models • Demonstrated temporal and geographical variations in risk.	[88]