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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.

Contents

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

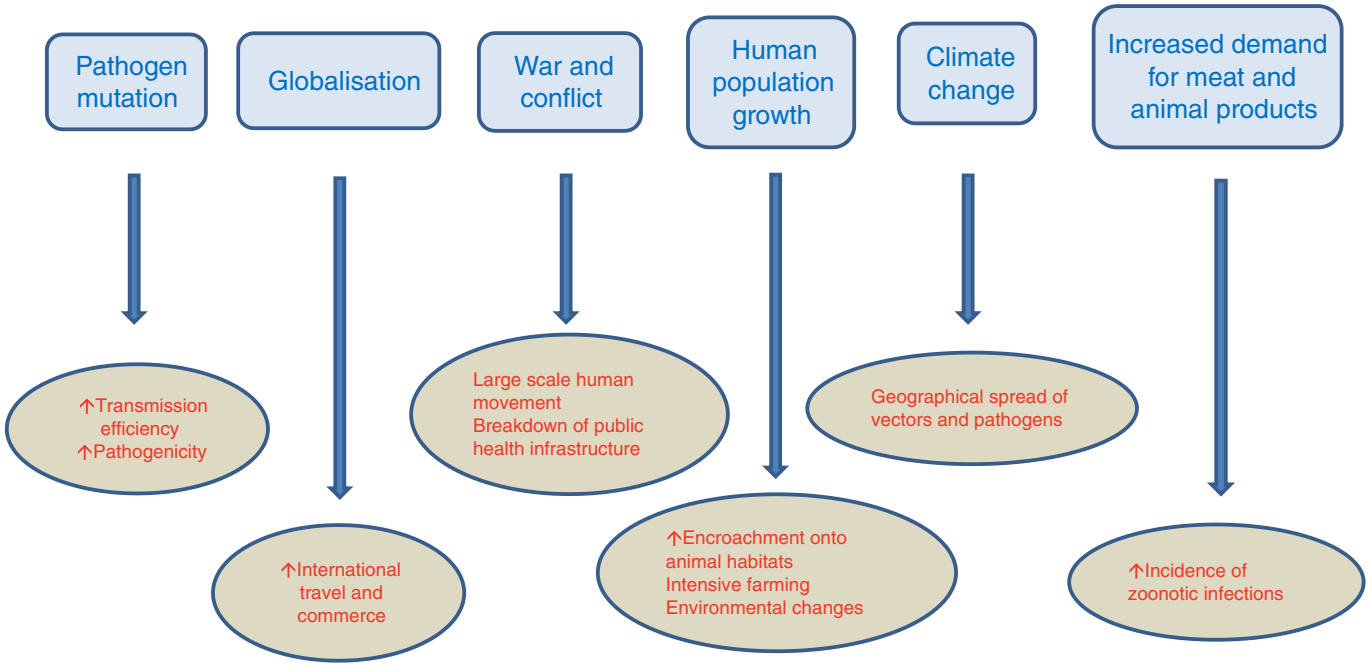

Fig. 1. Why we can expect more EID outbreaks.