ISBT Science Series
An affiliated publication to Vox Sanguinis

ISBT Science Series (2014) **9**, 30–36

STATE OF THE ART 1B-H3-01

Current perspectives in transfusion-transmitted infectious diseases: emerging and re-emerging infections

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Background In August 2009, a group from the AABB (Stramer et al., Transfusion 2009;99:1S–29S, Emerging Infectious Disease Agents and their Potential Threat to Transfusion Safety; http://www.aabb.org/resources/bct/eid/Pages/default.aspx) published a Supplement to Transfusion that reviewed emerging infectious disease (EID) agents that pose a real or theoretical threat to transfusion safety, but for which an existing effective intervention is lacking. The necessary attributes for transfusion transmission were outlined including: presence of the agent in blood during the donor's asymptomatic phase, the agent's survival/persistence in blood during processing/storage, and lastly that the agent must be recognized as responsible for a clinically apparent outcome in at least a proportion of recipients who become infected. Without these attributes, agents are not considered as a transfusion-transmission threat and were excluded. Sixty-eight such agents were identified with enough evidence/likelihood of transfusion transmission (e.g., blood phase) and potential for clinical disease to warrant further consideration. In the Supplement, Fact Sheets (FS) were published providing information on: agent classification; disease agent's importance; clinical syndromes/diseases caused; transmission modes (including vectors/reservoirs); likelihood of transfusion transmission, and if proven to be transfusion-transmitted, information on known cases; the feasibility/predicted success of interventions for donor screening (questioning) and tests available for diagnostics/ adapted for donor screening; and finally, the efficacy, if known, of inactivation methods for plasma-derived products. The Supplement included a separate section on pathogen reduction using published data. Agents were prioritized relative to their scientific/epidemiologic threat and their perceived threat to the community including concerns expressed by the regulators of blood. Agents given the highest priority due to a known transfusion-transmission threat and severe/fatal disease in recipients were the vCJD prion, dengue viruses and the obligate red-cell parasite that causes babesiosis (*B. microti* and related *Babesia*). Although the focus of the Supplement was towards the United States and Canada, many of the agents (and the process) are applicable worldwide.

Next steps Since the publication of the Supplement, six new FSs (yellow fever viruses-including vaccine breakthrough infections, miscellaneous arboviruses, XMRV, human parvoviruses/bocaviruses other than B19, and most recently the Middle East respiratory syndrome coronavirus, MERS-CoV) were added and 14 existing FSs updated (Anaplasma, Babesia, Bartonella, Erhlichia, chronic wasting

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disease-CWD, human prions other than vCJD, vCJD, *Coxiella burnetii*-the agent of Q fever, dengue viruses, HAV, HEV, Japanese encephalitis-JE complex, tick-borne encephalitis viruses-TBEV, and human parvovirus B19). Also, tables were released outlining pathogen reduction clinical trials/results (published) and availability/commercial routine use of such technologies by country. Of necessity, the list of EID agents is not, and can never be, complete due to the nature of emergence. We recognized that a system of assessing the risk/threat of EIDs for their potential impact on blood safety and availability must include processes for monitoring, identifying, evaluating, estimating severity, assessing risk and developing interventions. Thus, a 'toolkit' containing the necessary 'tools' from EID monitoring (horizon scanning) to validation/effectiveness evaluations of interventions is being developed. The goal is, to develop a systematic approach to risk assessment and intervention development for the impact of emerging infectious upon blood safety intended to educate and provide advise about risks/interventions in a timely/accurate fashion.

Conclusions The process and final product (toolkit) including methods to monitor EID agent emergence, identification/recognition of a transfusion-transmission threat, methods for quantitative risk assessments, and the appropriate management of such threats should be considered for implementation by all blood systems.

Key words: blood donation testing, epidemiology, transfusion, transmissible infections

Introduction

The recognition of newly described infectious disease agents will continue to place demands on the collectors of blood worldwide to ensure safety. Approaches are needed to ensure that mechanisms are in place to allow surveillance, threat assessments, triggers for action, and as needed, intervention development, implementation and assessment of efficacy. Agents of concern are diverse in nature and emergence is unpredictable. Some examples of agents internationally recognized as potential or existing threats to blood safety include the newly described Middle East respiratory syndrome coronavirus (MERS-CoV), dengue viruses, chikungunya virus and hepatitis E virus (HEV).

Defining emerging infectious disease (EID) agents and their risk to transfusion safety

In August 2009, a group from the AABB in the United States [1] published a supplement to transfusion that reviewed the definition and background of EID agents that pose a real or theoretical threat to transfusion safety, but for which, an existing effective intervention is lacking. The definition includes recognition of a new agent, a previously undetected agent or that a disease has an infectious origin and lastly, the re-emergence of a known infection after a decline in incidence. One estimate of the rate of emergence from 1940 to 2004 includes 5·3 new viruses discovered every year, of which 60–70% have an animal origin but can infect humans in cases where exposure by one of several routes occurs; the predicted rate of such emergence will continue well beyond the year 2020 [2–4]. Human exposure can occur by a number of overlapping conditions, many of which humans have clearly precipitated in 'forcing' a new agent by mutation, species jump, failure of prior control measures, population growth and movement, transportation, behavioural changes (sanitary, dietary and war) and intensive farming practices to name a few. In addition to most EID agents having a zoonotic origin, they represent a diverse group of agents, infect by multiple transmission routes, may result in acute or chronic infections, derive from human activity, but most importantly, their emergence is unpredictable. The necessary attributes for transfusion transmission include the following: presence of the agent in blood during an asymptomatic phase in the donor, the agent's survival/persistence in blood during processing/storage and lastly that the agent must be recognized as responsible for a clinically apparent outcome in at least a proportion of recipients who become infected [1, 2]. The response with respect to blood safety approaches to EID agents has varied related to the severity of the agent, its incidence and prevalence and rate of emergence.

Originally, the AABB group identified 68 EID agents of concern to blood safety; each agent had enough evidence/likelihood of transfusion transmission (e.g. blood phase) and potential for clinical disease to warrant further consideration. In the Supplement [1], fact sheets were published providing information on the following: agent classification; background on the disease agent's

importance; the clinical syndromes/diseases caused; transmission modes (including vectors/reservoirs); likelihood of transfusion transmission, and if proven to be transfusion transmitted, information on known cases; the feasibility and predicted success of interventions that could be used for donor screening (questioning) and tests available for diagnostics or that could be adapted for donation screening; and finally, the efficacy, if known, of inactivation methods for plasma-derived products. The Supplement also included a separate section on pathogen reduction technologies for all blood components using published data. Agents were prioritized relative to their scientific/epidemiologic threat as well as their perceived threat to the community including concerns expressed by the regulators of blood. Agents given the highest priority due to a known transfusion-transmission threat, and severe/fatal disease in recipients were the vCJD prion, dengue viruses and the obligate red-cell parasite that causes babesiosis (*B. microti* and related *Babesia*). Although the focus of the supplement was the United States and Canada, many of the agents (and the process) are applicable worldwide. Other experts have prioritized agents differently depending on their local needs with priority given to West Nile virus, dengue viruses, *Leishmania*, chikungunya virus, the agents of malaria and Lyme disease, and tick-borne encephalitis virus [5]; of note, several of these agents, including the agent of Lyme disease, have never been documented to be transfusion-transmitted.

Next steps

Since the publication of the Supplement, six new Fact Sheets were released:

(1) yellow fever viruses including vaccine breakthrough infections,
(2) miscellaneous arboviruses,
(3) XMRV including a comprehensive table of published literature,
(4) human parvoviruses other than B19, and bocaviruses,
(5) measles due to localized US outbreaks,
(6) MERS-CoV.

Also, 14 existing Fact Sheets were updated:

(1) human prions other than vCJD,
(2) the chronic wasting disease prion,
(3) the vCJD prion,
(4) bartonella,
(5) *Coxiella burnetii* the agent of Q fever, which resulted in a massive outbreak in the Netherlands from 2007 to 2010 precipitated by high-intensity goat farming,
(6) HEV due to increasing reports of RNA-positive blood donors in Japan and Europe; of note, in the Netherlands, increasing numbers precipitated by high-intensity pig farming,
(7) Japanese encephalitis (JE) complex,
(8) tick-borne encephalitis viruses (TBEV),
(9) dengue viruses with three transfusion-transmission clusters, one each reported in Hong Kong, Singapore and Puerto Rico,
(10) human parvovirus B19,
(11) hepatitis A virus (HAV) due to a large multi-state outbreak in the US,
(12) *Anaplasma phagocytophilum* with eight transfusion transmissions reported in the US,
(13) *Erhlichia* including the first report of transfusion transmission in the US,
(14) *B. microti* with data reported for research testing interventions in the US.

In addition, tables were released outlining pathogen reduction clinical trials and their published results, and the availability and commercial routine use of such technologies by country for platelets, plasma, red cells and whole blood.

Of necessity, the list of EID agents is not, and can never be, complete due to the nature of emergence. We recognized that a system of assessing the risk and threat of EIDs for their potential impact on blood safety and availability must include a process for monitoring, identifying, evaluating, estimating disease severity, assessing risk and development of interventions. Thus, the AABB EID group is now developing a 'toolkit' containing the necessary 'tools' starting with links to EID monitoring sites (horizon scanning), risk assessment tools, a flow diagram to follow as one proceeds to determine whether intervention development and implementation are required, and methods to validate and assess the efficacy of any introduced intervention [2]. The goal is 'to develop a systematic approach to risk assessment and intervention development for the impact of emerging infections upon blood safety intended to educate and advise blood systems in a timely and accurate fashion'. When developed, this toolkit may be adapted to the needs of ISBT members.

The lessons learned from the AABB exercise are that each country or region of the world needs to decide their own priority list of infectious agents that may represent a threat to transfused recipients, as well as processes for surveillance and action should any of those agents pose an immediate safety threat. Countries, especially those in the developing world where EID agents have originated in the past such as China, sub-Saharan Africa, tropical Central and South America, may also choose to establish an epidemiologic/molecular surveillance laboratory or collaborations with any such existing laboratories to enable rapid agent identification and disease characterization.

Specific agents of recent concern

Some examples of agents internationally recognized as potential or existing threats to blood safety include MERS-CoV, dengue viruses, chikungunya virus and HEV; each will be briefly reviewed.

MERS-CoV

The MERS-CoV agent is a betacoronavirus first described in September 2012 from a patient in Saudi Arabia [6]. It is related to the severe acute respiratory syndrome coronavirus (SARS) that from 2002 to 2003 resulted in over 8000 infections in 17 countries (including Macau and Hong Kong) with a 10% fatality rate [7]. In the case of SARS, bats were confirmed as the natural reservoir although the introduction of the agent to humans was likely through contact with animals (masked palm civets) held in southern Chinese markets where the disease was first recognized in Nov 2002 [8, 9]. Middle East respiratory syndrome coronavirus also likely represents a zoonotic agent that infected humans via viral adaptions or a species jump through an intermediate host. Bats are suspected as the ultimate reservoir with camel infection as the most likely link to human infection, but these theories at present are unproven. The majority of cases are associated with severe disease of the lower respiratory tract resulting in pneumonia and multi-organ failure; the most susceptible to clinical disease and death are those with pre-existing co-morbidities [10]. Other chronic conditions have been reported in 96% of clinical cases including diabetes, hypertension, heart disease and kidney disease. It is unclear whether persons with these specific conditions are disproportionately infected or have more severe disease. To 30 November 2013, as reported by the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO), ten countries have reported 160 clinical cases with 68 deaths. All cases and transmissions have been associated with the Arabian Peninsula where the vast majority of cases and deaths have occurred; travel of infected patients with limited person-to-person transmission are responsible for cases reported elsewhere. Although it appears that there is limited person-to-person transmission, clusters of cases have been described. A cluster of 21 human cases occurred associated with four hospitals in Eastern Saudi Arabia that was ultimately sourced to one community-acquired case [11]. Updated MERS-CoV rapid risk assessments are routinely published by the European Centres for Disease Control (ECDC). Regarding actions with respect to blood safety, careful surveillance is required as risk involving MERS-CoV is rapidly evolving at present. To date, only one study has reported testing blood donors including 110 in Saudi Arabia; all were nonreactive for MERS-CoV neutralizing antibodies [12]. There is no evidence of transfusion transmission.

Dengue viruses

Dengue viruses include four genetically related viruses (65% genetic homology between the four) classified as 'arboviruses' (arthropod-borne viruses). All arboviruses involve replication through an arthropod host (usually a mosquito or tick) have a worldwide distribution and are responsible for huge periodic epidemics. Dengue viruses are in the family *Flaviviridae* along with related viruses: West Nile virus, yellow fever virus and over 65 other related viruses. Arboviruses also include hundreds of agents, of which many are human pathogens in other viral families (*Bunyaviridae* and *Togaviridae* including the alphavirus, chikungunya described below). Dengue viruses are the most important of all of these agents due to the number of human infections, clinical disease, associated deaths and ongoing expansion worldwide. It is estimated by the WHO that greater than 100 countries are endemic in the tropics and subtropics with over 2·5 billion people at risk. It is impossible to know the number of clinical cases that actually occur each year, but one estimate of the global burden of dengue during the 2010 worldwide pandemic was 390 million infections across four continents of which 96 million were symptomatic including 500 000 cases of severe dengue [13]. In Asia and Latin America, dengue is the leading cause of hospitalization in children. Since there is no effective vaccine or specific treatment, vector control is the only intervention. The dengue cycle involves humans and mosquitoes (primarily *A. aegypti*), but sylvatic cycles also occur and are recently being investigated associated with preliminary reports of a new dengue virus type (DENV-5). Immunity to a given viral type is considered lifelong, but due to incomplete antibody neutralization between types, secondary infection with a different type can lead to more severe disease referred to 'severe dengue' including haemorrhagic fever and/or shock. The majority of clinical cases are classified as 'fever' defined by WHO as fever plus two other symptoms most commonly including chills, painful eyes, body aches (that can be severe, 'break-bone fever'), rash, easily bruised or other evidence of haemorrhagic conditions. Three transfusion-transmission clusters have been reported [1]; the first in Hong Kong, another in Singapore (where two clinical cases and one antibody seroconversion were documented) and lastly a case of transfusion-transmitted haemorrhagic fever in Puerto Rico [14]. Infected individuals may donate blood since it has been estimated that 53–87% of dengue-infections are

asymptomatic, and even individuals who develop symptoms will have a 1–2 day asymptomatic period. Puerto Rico, an island in the Caribbean and a US territory, experiences annual outbreaks. Research blood donation screening in Puerto Rico has documented the rate of dengue RNA in blood donors during the outbreak years of 2005, 2007, 2010, 2011 and 2012 at between 0·03% and 0·31%. The estimated number of viremic donations and the risk of dengue transfusion transmission have been modelled by the CDC. The resulting model output and the observed number of RNA-positive donors from blood donation screening show the same trend [15]. Although routine screening by the American Red Cross occurs in Puerto Rico, the clinical efficacy of the intervention is unknown since the number of transfusion transmissions documented has been few. It is unclear why the number of transfusion transmissions is not higher in endemic areas considering the magnitude of dengue outbreaks and high viral loads associated with infected donors. Possible theories include an absence of effective hemovigilance in many of the countries impacted by dengue, inability to differentiate mosquito versus transfusion transmission, protection of secondary infection due to heterologous antibodies present in the transfused unit, immunosuppression in many recipients and possibly different clinical outcomes dependent on the route of infection (i.e. mosquito versus transfusion) [16].

Chikungunya virus

Another flavivirus, chikungunya virus, is endemic in many of the same tropical areas as dengue and frequently presents with similar symptoms and during the same epidemic periods but with more severe body aches, especially joint pains and crippling arthritis than that of dengue. The name 'chikungunya' refers to the inability to straighten up due to intense pain ('that which bends up' in the Makone language) [1]. An explosive outbreak occurred on Reunion Island and the islands of the southwest Indian Ocean off east Africa from late 2005 through the beginning of 2007 [17]. During this outbreak, over 300 000 clinical cases on Reunion island were documented effecting over 40% of the population with 75% of those infected exhibiting symptoms with another 1·3 million cases during the same outbreak in India. The increased severity and extent of the 2005–2007 outbreak was believed to be due to a mutation affecting the viral envelope protein allowing replication in an alternate mosquito vector, *A. albopictus* [18]. This resulted in increased viral loads and greater virulence as compared to replication in its primary mosquito vector, *A. egypti*. Transfusion-transmitted risk modelling estimated a risk of up to 1500 per 100 000 donations [17]; however, transfusion transmission was never documented. What is notable in the islands of this French colony is the number of interventions put into place to prevent theoretic transfusion transmission. These included the suspension of blood collections in areas where risk was estimated to be higher than the risk from hepatitis B virus transfusion transmission, the implementation for platelets of pathogen inactivation and chikungunya virus RNA nucleic acid testing, and for continental France, the deferral of those who lived or travelled to an endemic area [19]. Subsequently, an outbreak in Northern Italy occurred in 2007 involving approximately 250 cases; the viral introduction was believed to have been a clinical case in an individual returning from India, and consequently, spread locally via *A. albopictus* [20]. The data from this outbreak were used to validate a risk assessment tool developed to provide quantitative transmission estimates of EID risks through blood transfusion. The output of the model based on the outbreak peak estimated a prevalence of 1·07 per 10 000 donors, leading to 0·04 infectious donations, 0·13 infectious blood components and a severe outcome in 0·0001 recipients, based on an assumed 0·1% of infected individuals who develop severe disease [21]. Subsequently, a case-control study during a chikungunya outbreak in Thailand in 2009 investigated the development of symptoms and viremia. Of 134 laboratory-confirmed positives, 9% (n = 12) were asymptomatic controls who were RNA positive or seroconverted having a median viral load of $3{\cdot}4 \times 10^3$ pfu/ml (range: $8{\cdot}4 \times 10^1 - 2{\cdot}9 \times 10^5$ pfu/ml) versus 91% (n = 122) classified as symptomatic cases with viremia for 8 or fewer days and RNA positivity for 17 or fewer days. Symptomatic individuals had a median viral load of $5{\cdot}6 \times 10^5$ pfu/ml (range: $1{\cdot}3 \times 10^1 - 2{\cdot}9 \times 10^8$ pfu/ml; P = 0·22 vs. controls) [22].

HEV

Hepatitis E virus is a single-stranded, RNA-containing, small, non-enveloped virus in the genus *Hepesvirus*. There is one serotype but four genotypes with differing geographic distribution, epidemiology and clinical features. Hepatitis E virus is globally the most common cause of acute hepatitis with an estimated 20 million incident infections per year, over 3 million acute cases and 700 000 deaths per year [1, 2]. Genotypes 1 and 2 are most commonly associated with large, explosive waterborne outbreaks along with some foodborne outbreaks similar to HAV. Genotypes 1 and 2 also are associated with an overall higher rate of acute disease and for an unknown reason with increased severity in pregnant women (20% mortality especially in the third trimester). In contrast, genotypes 3 and 4 occur in humans but commonly in swine and several other animals. Thus, infections with

genotypes 3 and 4 have occurred from transmissions through food, most notably via raw or undercooked pork products containing liver and/or blood [1, 2]. Generally, less virulent than either genotype 1 or 2, genotype 3 or 4 infection results in severe disease in immunosuppressed individuals, most notably solid organ transplant (SOT) recipients leading to chronic infection (>60%), and to cirrhosis and severe liver disease in 14% of those who become chronically infected [23]. Of 1200 SOT recipients investigated for HEV RNA in the Netherlands, 1% were positive; of those, 11 of 12 HEV-RNA-positive patients developed cirrhosis [24].

Antibody prevalence in blood donors varies greatly (<1% to >50%) depending on geographic location and the test used but is reproducibly seen to increase with age unrelated to a cohort effect but more likely the result of increasing prevalence over time [25–27]. RNA from genotype 3 can be recovered from Dutch blood donors at rates of as high as 1:3000 with sequences closely related to patients and pigs in the area [25]. In the same study, IgG antibody prevalence was 27%, and 3·5% for IgM, with increasing prevalence with age. Intensive pig farming in the Netherlands, as an example, may be amplifying the virus, which is then spread via contaminated meat and contaminated water used for irrigation. Even higher IgG seroprevalence rates of 52·5% have been documented in Southwest France [26], linked to the consumption of locally produced pork products containing undercooked pork. In another study, 1939 blood donors in the US had a prevalence of IgG of 18·8% (95% CI: 17·0–20·5%) and 0·4% for IgM, but no donor had circulating RNA [27]. Of the 1939 donors, 916 were collected in 2006 (vs. the remainder in 2012 in which prevalence was 16·0%; $P < 0{\cdot}01$ vs. 2006); prevalence ranged from 3·4% in those between 18 and 35 years old to 42·2% in those > 65 years old. As part of this study, a donor-recipient-linked repository was tested, in which two suspect cases of HEV transfusion transmission were investigated but neither could be confirmed. In one case, passive antibody (and RNA) was transfused, but the patient died prior to determining the infectivity of the transfused HEV RNA from the only RNA-positive donor in the study. The other case was one where the level of IgG pre-transfusion was just below the assay cut-off, and post-transfusion was just above the assay cutoff. Since further antibody evolution did not indicate recent seroconversion, the recipient was likely infected prior to transfusion. Since 1979, at least 10 transfusion transmissions have been documented worldwide including cases in Japan, the UK, France, Saudi Arabia, Taiwan and India. Because HEV is non-enveloped, it is very resistant to inactivation; thus, some solvent–detergent plasma manufacturers screen plasma donors and/or pools to reduce the HEV RNA concentration (i.e. OctaPlas in the US); commercial tests are being developed to screen plasma for HEV RNA.

Conclusions

Each blood system must consider preparing for the unknown including triggers for action (or not and why) and the development of interventions with respect to the safety of blood from EID agents. The examples reviewed represent a wide variety of agents with diverse characteristics, epidemiology, transmission routes and very different risks leading to differing considerations for the introduction of an intervention. The tool-kit development process and final product including methods to monitor EID agent emergence, identify and recognize a transfusion-transmission threat, quantify risk, and appropriately reduce the associated risk to transfusion recipients should be considered for implementation by all blood systems.

Disclosure

The author declares no conflict of interests.

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