Chapter 10
The Emergence of Zoonotic Pathogens as Agents of Concern in Transfusion Medicine

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Our Historic Challenges: The Reactive Paradigm

Among the "classic" transfusion-transmitted infections (TTIs), person-to-person transmission was the important route of donor infection, and we *reacted* to incontrovertible evidence of a clinical burden in transfusion recipients. These included syphilis, malaria, hepatitis B, hepatitis C, and HIV (originally a nonhuman primate zoonosis). Over time, epidemiologic and other scientific data about risk were examined with the aim of developing (roughly sequentially) overlapping mitigation strategies that included (1) the virtual elimination of paid blood donors in the United States, (2) donor risk education to promote self-deferral, (3) explicit deferral criteria to be applied at the time of the donor interview, and (4) laboratory testing to reduce donation of infectious blood by donors who might have limited understanding of and/or were reluctant to recognize or admit their "behavioral" risks. The morbid impacts of these historical agents on many thousands of recipients make the disadvantages of reactive approaches obvious—one need not look further than the thousands of transmissions of HIV and non-A and non-B hepatitis (i.e., before the description of HCV) [1]. In part resulting from shortcomings enumerated in the Institute of Medicine report, the US blood community has explored more precautionary and proactive applications of these approaches to the assessment and mitigation of infectious risks in recent decades.

Surrogate testing using donor testing for alanine aminotransferase and antibody to the hepatitis B core antigen was an early initiative in this direction before the identification of hepatitis C virus and the availability of specific assays [2–4]. Testing for human T-lymphotropic retrovirus types I/II (HTLVs) in the United States was another early effort at a more proactive approach to donor screening [5, 6]. Infection with HTLV-I was known to cause acute T-cell leukemia and

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myelopathy, albeit with low disease penetrance, and infection was present in healthy individuals who would otherwise qualify as donors. Transfusion transmission was documented, but the attendant disease burden was poorly characterized. In the wake of events caused by another retrovirus (HIV), antibody testing was required in the United States in 1988. Controversy about its impact and cost-effectiveness persists [7].

During the last 30 years, additional nonspecific measures have been deployed in furtherance of transfusion safety. These include stringent process controls: in the United States, "current good manufacturing practices" (cGMP) from the Code of Federal Regulations [8] prevent distribution for transfusion of blood from unacceptable donors and donations that manages to enter the supply chain. Development and deployment of ever more complex information systems cleared by the Food and Drug Administration as medical devices (blood establishment computer systems) have been required to support these kinds of quality systems. Finally, with a litany of real and purported adverse outcomes attendant on transfusion (infectious but also serious non-infectious hazards), the clinical cascades that ultimately expose a patient to transfusion are under scrutiny under the rubric of "patient blood management."

All these approaches contribute to the impressive safety of transfusion from *recognized* infections in the developed world [9]. Pathogen reduction processes for labile blood components are proactive solutions but remain aspirational, as they are not yet available for all components, and will not be potent against all agents. Further, consensus on the health economic justification for pathogen reduction is absent when viewed from a societal perspective.

Emerging Zoonotic Agents: Toward a more Proactive Approach

Overlaying our history with these classic pathogens is "new" pathogen emergence and discovery. Identification of new agents is accelerating. The number of viral species recognized to infect human is predicted to rise from less than 10 in 1900 to more than 200 by 2020, with the large majority of the increase since 1960 (Fig. 10.1) [10]. The reasons are diverse and beyond the scope of this chapter, but a shrinking globe puts pathogens from the sub-Saharan rain forest within 24 h of a blood center in the Northern Plains. Urbanization, especially when combined with poverty and overcrowding, and human changes of and encroachment into diverse ecologic niches change host, pathogen, and vector relationships. Alterations of climate and animal husbandry also affect reservoir, pathogen, and vector distributions. New discovery systems like next-generation sequencing and metagenomics identify *potential* pathogens in the environment, wildlife reservoirs, and humans (our microbiome), well before disease associations are even considered. Social media via the Internet brings us nearly instantaneous news and speculation about new diseases and
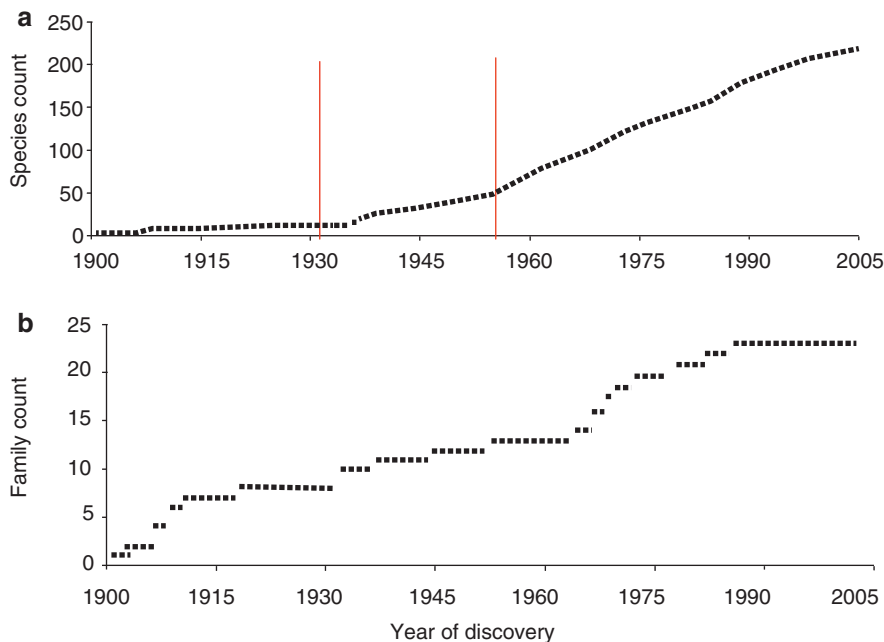
Fig. 10.1 New viruses infecting humans. Discovery curves for human viruses. (**a**) Virus discovery curve by species. Cumulative number of species reported to infect humans. Statistically significant upward breakpoints are shown (vertical lines). (**b**) Virus discovery curve by family. Cumulative number of families containing species reported to infect humans [10]. (Data source: Woolhouse et al. [89])

outbreaks from anywhere in the world. How do we integrate, or decide not to, the potential threats into our blood safety regime? Our difficult task in the transfusion medicine community is choosing a proactive framework within which to approach emerging infections despite initially incomplete information about their impacts on transfusion safety.

WNV, the severe acute respiratory syndrome coronavirus (SARS-CoV), *Trypanosoma cruzi*, Zika, and *Babesia microti* are recent demonstrations that zoonotic infections, as they emerge (or emerge in our consciousness), become targets for intervention. There are many other zoonotic and/or arthropod-borne agents for which we have not implemented mitigation measures (beyond the requirement that donors are well when they give) but about which we need to think. They include, but are by no means restricted to, dengue, chikungunya, MERS-CoV, Nipah, Hendra, the severe fever with thrombocytopenia syndrome virus (SFTSV), Bourbon and Powassan viruses, Mayoro virus, the tick-borne agents (*Erlichia sp.*, *Anaplasma phagocytophilum*) and *Leishmania*. These agents persist in arthropods and/or nonhuman vertebrate reservoirs with spillover into human populations either by contact or vector transmission. Tick-borne infections are not further considered herein.

Zoonotic infections, excluding HIV, have certainly had less clinical impact in transfusion medicine than the classic sexually and parenterally transmitted agents, but, especially under epidemic scenarios, several are presently prominent in conversations about if and when to intervene for blood safety. In this context, we have taken to speculating on the need for interventions for pathogens for which transfusion transmission, when the asymptomatic presence of an agent is biologically plausible, is theoretical. This is indeed proactive, in contrast to our historical approach, but risks a response (and consumption of scarce resources) where none is appropriate. In the best light, this is "precautionism."

In a perfect world, we will answer four questions about a putative transfusion-transmitted agent before recipients are infected to prospectively inform consideration, development, and deployment of mitigation strategies [11].

1. Is the agent present in the blood of otherwise qualified donors?
2. Is the agent parenterally transmissible (by blood, organ/tissue transplantation), or is such transmission biologically plausible?
3. Will the agent survive in contemporary blood components to be transmitted?
4. Does the agent, if transmitted, pose a material clinical risk after transfusion—Does it cause significant illness among susceptible transfusion recipients?

Unfortunately, with current surveillance and pathogen discovery techniques in an increasingly interconnected world, the answers to these questions are not available or are incomplete when decision-making must be started—that is, initial responses are necessarily considered in a precautionary context. The question of a "correct" process by which we ought to select agents to examine for risk before reports of transfusion transmission come to light is unanswered [12]. Several historical examples are provided that describe how we have actually approached some of these pathogens.

Historical Zoonoses (Excluding HIV)

Variant Creutzfeldt-Jakob Disease (vCJD)

vCJD is a zoonotic transmissible spongiform encephalopathy (TSE) that spreads from bovines to humans, mainly in the United Kingdom. Precautionary deferrals were required before the recognition of transfusion transmission based largely on the occurrence of TSEs (sporadic CJD, Kuru et al.) in humans, the presence of the vCJD prion in the reticuloendothelial system of apparently food-borne human cases, and a precedent of parenteral transmission of the prion that causes classic or sporadic CJD [13]. These deferrals aim to prevent an adverse outcome that has proven to be very rare, even in the United Kingdom epicenter of the bovine spongiform encephalopathy epidemic [14]. The cost has been the ongoing loss of many thousands of donors for residence in and travel to (and transfusion in some) the countries with risk. In addition to difficult donor counseling sessions, the estimates of donor loss ranged as high as 5% in the United States [15, 16]. We will likely maintain them until concerns about theoretical subsequent waves of the vCJD epidemic, largely related to incubation periods associated with polymorphisms in the human prion protein gene, are adjudicated [17, 18].

West Nile Virus (WNV)

Mitigation strategies for the mosquito-borne avian pathogen WNV were implemented after the recognition of a single transmission of the virus from a blood donor to an organ donor and forward to the organ recipients [19]. An emergency response ramped up over several weeks in 2002, using an incomplete understanding of the level of risk being addressed based on clinical information from the cases and modeling data that had been produced before observation of those transmissions [20, 21]. Twenty-three blood recipient infections were documented (retrospectively) during that first season [22]. These were in the context of 4156 WNV cases reported to CDC [23]. Within less than 1 year after the first case report, minipool nucleic acid tests were developed and implemented across the US blood supply. In subsequent seasons, strategies to trigger individual donation testing with increased sensitivity evolved and, despite persistent endemic activity in the United States, transfusion transmission WNV has been essentially eliminated [24].

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)

SARS-CoV is an enveloped RNA viral respiratory pathogen of zoonotic origin causing significant mortality. First identified in Asia during 2003, it spread from Asia to North America with sporadic travel-associated cases and subsequent extensive localized healthcare-associated (nosocomial) transmission. SARS was met with an FDA guidance for immediate implementation requiring the interrogation of US blood donors about a history of SARS, potential exposure to cases, and travel to or residence in areas during the 14 days before presentation to donate. Temporary deferral was required if "risk" was present. This was based on the theoretical possibility of asymptomatic viremia and isolation of the virus from tissues outside the respiratory tract, presumably as a result of blood-borne spread. These interventions occurred absent any clinical evidence of parenteral or transfusion risk [25]. SARS-CoV RNA was subsequently found in patient plasma as early as day 2 after onset of symptoms [26, 27], but there are still no data on infectious viremia in the incubation period or among asymptomatic contacts of cases on which to judge the plausibility of parenteral transmission. The requirement for donor screening was allowed to lapse 90 days after CDC lifted the last travel alerts and SARS has not reemerged.

Ebola Virus

Ebola, recognized in 1976, spreads from an animal reservoir to humans unpredictably. The massive West African Ebola outbreak in 2014–2016 resulted in promulgation of FDA guidance to prevent transfusion transmission of a pathogen not recognized to be transmitted by this route. That response was predicated on the

observation that the virus is present in blood and body fluids, direct contact with which is associated with a highly morbid infection [28].

Zika Virus

Zika virus, a nonhuman primate virus that has spilled over into human populations causing a pandemic, is covered elsewhere, but its example bears repetition here. Its nucleic acid is present in the blood of asymptomatic individuals (including donors), US donors have frequent travel to affected areas outside the mainland United States, the major vector is present in areas of the mainland United States, and sexual transmission is a documented, if poorly quantitated, route of infection [29, 30]. Driven by the recognition of severe clinical outcomes among infants infected in utero (and neurologic morbidity in a proportion of infected adults), investigational individual-donation nucleic acid screening for Zika virus was implemented emergently in the United States in 2016. This was absent evidence of clinically significant morbidity associated with receipt of blood from viremic donors. At this writing, there have been three apparent transfusion transmissions of the virus published, all in Brazil, with none causing recognizable morbidity [31, 32]. CDC investigators have estimated the cost for the emergency implementation of Zika screening in US collection facilities at $137,000,000 annually [33].

"Newer" Zoonoses

As interesting as the examples above, where interventions have been required or widely implemented voluntarily, is a list (by no means exhaustive) of potential pathogens for which we have not acted. The examples chosen are epidemic pathogens (somewhere) and exemplify the difficulties faced when trying to assess the risks of transfusion-transmitted infection, with particular reference to the four questions.

Dengue and Chikungunya Viruses

Aedes mosquitos transmit both dengue, a *Flavivirus*, and chikungunya, an *Alphavirus*. They cause explosive epidemics, primarily in tropical and subtropical regions of the developing world, and manifest asymptomatic viremia; vector-borne infections are associated with morbidity and, in the case of dengue, mortality. The large global areas affected by dengue and chikungunya overlap those with endemic malaria, and temporary malaria deferral for travel to these areas surely provides partial protection of the blood supply in unaffected areas. However, the use of

malaria deferral is clearly an incomplete approach [34], failing to address risks associated with malaria-free areas and from autochthonous transmission in the United States or other non-endemic countries where competent vectors are established (e.g., as has been seen sporadically with dengue in the United States [35]).

Dengue, while not strictly zoonotic, has a sylvan nonhuman primate-mosquito cycle in addition to the urban human-mosquito cycle responsible for human epidemics. Our response to dengue risk, or lack thereof, is informative of considerations used to address emerging pathogens. It is the most common human arboviral infection in the world (recent estimates suggest that more than 390,000,000 million infections occur annually) [36]. Human infections can range from asymptomatic to a lethal hemorrhagic fever. It is increasing in incidence worldwide, and transfusion transmission has been documented (albeit infrequently) [37–39]. Accordingly, dengue was labeled a priority agent in an AABB Transfusion-Transmitted Disease Committee exercise [11]. However, to date, no interventions are being seriously considered in the United States, beyond the requirement that donors be well when they are bled and what is contributed by malaria deferrals. For donors with risk for dengue from travel or outbreaks, who can be identified prior to donation, management strategies that temporarily restrict their donations or use (currently investigational) donor screening tests have been considered or used with variable costs and impacts on the availability of donors [40–43]. Recent data, using nucleic acid amplification tests, suggest that the clinical burden after transfusion transmission may be quite modest and not require action [44]. In this study from Brazil, 16 susceptible transfusion recipients of blood from dengue RNA-positive donors were clinically indistinguishable from susceptible controls who did not. Five exposed recipients experienced probable dengue transmissions, and one was a possible infection. Surveillance for the clinical sequelae of transfusion transmission is clearly a priority as the blood community considers the relevance of this virus.

Chikungunya originated in Africa where, historically, it circulated in a sylvan cycle among forest-dwelling *Aedes* mosquitos and nonhuman primates, with occasional human spillover. Human infection is generally symptomatic but was thought to be benign. However, during the recent pandemic, the occurrence of severe joint pain persisting for many weeks and months was recognized [45]. A mutation in the viral envelope protein allowed its adaptation to and high-level replication in the cosmopolitan vector *Aedes albopictus* [46]. Subsequently, the virus emerged from Africa as a pandemic that spread across the Indian Ocean, Asia, and the Pacific starting in 2005, reaching the Americas (St. Martin in the Caribbean) in late 2013 [38, 47]. The explosive (attack rate >30%) 2005–2006 epidemic on Reunion Island in the Indian Ocean was met with suspension of the collection of red blood cells and plasma on the island, their importation from Metropolitan France, and the emergent introduction of pathogen reduction for platelets collected from local at-risk donors [48]. The virus can be transmitted by IV inoculation of monkeys [49]. Modeling exercises suggest a substantial risk of transmission by blood [50, 51]. Donor testing in the Caribbean using nucleic acid tests during 2014–2015 identified 0.19–0.54% of tested donors to be "RNA-emic" [52, 53]. The positive units were discarded if prospectively tested or de-linked, so recipient outcomes are not available.

Internationally, and during its spread in the Americas where more than 2,000,000 cases have been reported to the Pan American Health Organization from 2014 to mid-September 2017 [54], transfusion transmission has been neither recognized nor alleged. No transfusion medicine interventions are planned in the United States beyond continued surveillance. Limited local transmission in South Florida provoked a scaled response depending on the case load, monitoring in conjunction with local public health, addition of travel deferrals for potential exposures in epidemics ex-US, proactive donation quarantine in zip codes with autochthonous cases and callback to assure the donor remained well before components could be distributed for transfusion, and zip code-based staged cessation of collections for local cases beyond a predetermined threshold number [55].

The absence of recognized or alleged transfusion-associated morbidity from these two viruses may be a result of several things. It may be nearly impossible to recognize such events against a background of epidemic vector-borne transmission, especially when transfused cohorts might have risk from both sources. In non-epidemic locations, the diagnosis may never be considered by clinicians unfamiliar with a potential for parenteral transmission. The infections can be clinically nonspecific, patients ill enough to require transfusion may have multiple sources of fever, and (in the experience of this infectious diseases clinician) febrile patients are generally not asked for a recent transfusion history, i.e., clinical surveillance is passive and limited. Finally, there are important pathogenic differences between mosquito transmission and parenteral transmission that relate to the effects of arthropod mediators injected with virus and the innate immune or inflammatory responses associated with vector transmission [56].

The pathogen reduction techniques being developed for labile components are likely effective against both viruses [57]. Likewise, multiple steps in the manufacture of plasma derivatives should make their risk de minimis. These include wet heat, dry heat, lyophilization, solvent-detergent treatment, and nanofiltration. The purification steps used to manufacture plasma-derived medicinal products including cold ethanol or chemical precipitation and chromatographic steps should further mitigate risk.

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

In contrast to SARS-CoV, no interventions have been required in response to MERS-CoV. This enveloped RNA betacoronavirus emerged as a human pathogen in 2012 [58] and has been reported subsequently from 27 countries. The infection is endemic on the Arabian Peninsula where the large majority of cases have occurred or originated. Cases are occasionally exported elsewhere [59]. MERS-CoV causes respiratory infection including pneumonia and respiratory failure with an incubation period of days but up to 2 weeks. Gastrointestinal signs and symptoms may also occur. Treatment is supportive, and effective prophylactic measures have not been described.

Symptomatic MERS-CoV infection is associated with a high-mortality ($\approx$35%) respiratory illness in humans, but asymptomatic infections (relevant to concerns about transfusion) have been recognized during aggressive laboratory investigation of contacts of cases, and infection is certainly considerably less lethal than the mortality reported for recognized disease [60]. From emergence to September 2017, 2081 laboratory-confirmed cases have been reported (82% from the Kingdom of Saudi Arabia). 21.5% have had no or mild symptoms. 46.8% had severe disease or died [61]. Two imported infections have been recognized in the United States, both in 2014, affecting healthcare workers exposed in Saudi Arabia. The potential for more extensive transmission outside the endemic area is exemplified by the large 2015 outbreak of healthcare-associated infection in South Korea (185 linked cases) where the index patient was a traveler to the Middle East [62]. The ultimate reservoir is not established, but the agent is likely to have evolved in bats and then was transmitted to camels [63, 64]. Direct contact with dromedary camels and consumption of raw camel milk have been suspected epidemiologically to be routes of primary infection and MERS-CoV transmission to humans [65]. Secondary cases are predominantly in healthcare settings in the absence of or with nonadherence to standard infection prevention and control strategies.

Transfusion transmission of MERS-CoV is neither reported nor suspected to date, and there is no such precedent with other coronaviruses. The occurrence of asymptomatic infection is obviously problematic, however [58]. Evidence for viremia is rarely sought but, where evaluated to date, has been confined to severely ill patients. The index patient in a family cluster in Tunisia in 2013 had viral sequences amplified by PCR from serum after more than a week of illness [66]. Another patient, with fatal infection, had sequences detected 4 weeks after onset of the illness, but was not apparently tested earlier [67]. In neither case was infectious virus sought. One hundred ten Saudi blood donors were seronegative for neutralizing antibodies [68], but there are no systematic studies looking for asymptomatic RNA-emia or viremia in higher-risk cohorts such as contacts of cases. The most recent formal WHO MERS-CoV risk assessment includes no mention of a risk from transfusion-transmitted infection [69], nor does the European CDC rapid risk assessment of communicable diseases risk associated with the 2017 Hajj [70]. Given the low number of cases outside of the Middle East, and the apparent requirement for close contact with ill patients for person-to-person transmission to occur (esp. to healthcare workers), it does not appear that specific travel or risk deferrals are appropriate. Continuous monitoring (i.e., systematic "horizon scanning") for changes in the epidemiology and clinical pathology of MERS to be alert to changes that would suggest some risk of parenteral spread and transfusion risk seems an appropriate response.

In 2013, the AABB TTD emerging infections working group rejected the use of specific screening questions and referenced the FDA guidance on SARS for donors who spontaneously provide a history of exposure or illness [71]. Were a donor to provide such information during screening, the deferral criteria used for SARS (14 days from the last exposure and 28 days from completion of treatment and resolution of illness) seem rational, if wholly empirical.

Riboflavin and ultraviolet light and amotosalen with ultraviolet light have been reported to inactivate >4 and >5 logs of MERS-CoV in plasma [72, 73]. Data on platelets, RBC, and whole blood are not available. The manufacturing steps used for plasma derivatives should render such medicines safe.

Nipah and Hendra Viruses

Nipah, Hendra (and the apparently nonpathogenic Cedar virus), are *Henipaviruses* are from the *Paramyxovirinae* family. They are currently confined to South Asia and Australia (Fig. 10.2) [74]. Nipah is an emerging bat zoonosis, which spills over into humans to cause human infections ranging from inapparent to lethal encephalitis. It is an enveloped RNA virus sharing 70–90% amino acid homology across regions of the genome with Hendra virus. Nipah emerged in Malaysia in 1998–1999 where bats infected swine and the swine infected humans. During that outbreak of encephalitis and respiratory illness, there were approximately 300 human cases and more
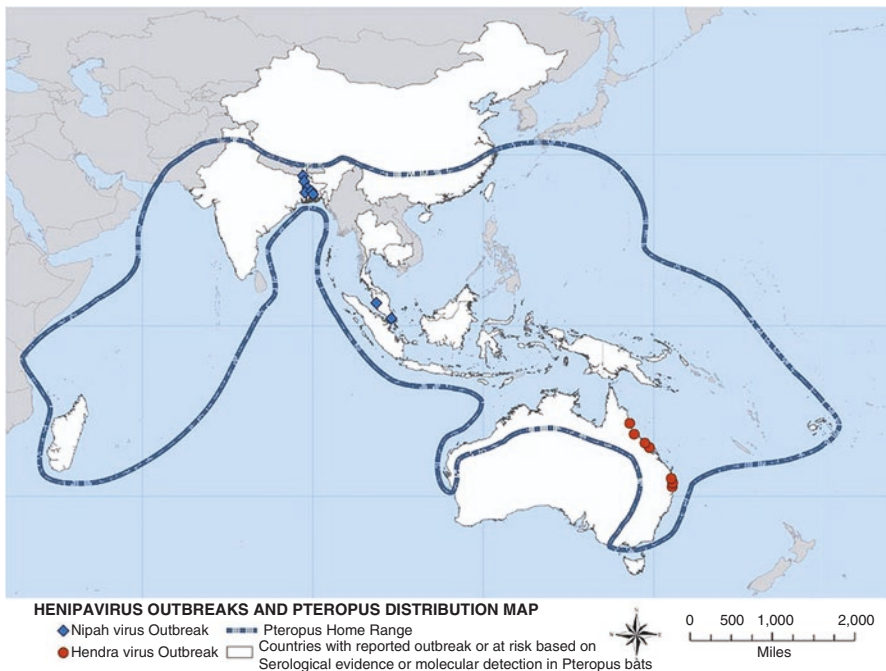

Fig. 10.2 Geographic distributions of Nipah (blue diamonds) and Hendra infections (red circles), with home range of *Pteropus* bats (blue line). (Source: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High-Consequence Pathogens and Pathology (DHCPP), Viral Special Pathogens Branch (VSPB). https://www.cdc.gov/vhf/nipah/outbreaks/distribution-map.html. Accessed 4 Oct 2017)

than 100 deaths [75, 76]. The clinical spectrum seems variable across geographically separate outbreaks. Treatment is supportive, but the antiviral ribavirin has been used in uncontrolled circumstances with some success. No effective prophylaxis (medication, immunoglobulin, or vaccine) has been reported. The human incubation period has ranged from 4 days to 2 months (90% ≤14 days), and there is, again, some variation according to the location of the outbreak. Direct contact with the respiratory secretions of infected swine that generally have a mild illness (apparently infected by consumption of mangoes contaminated with bat urine) was the source of the index outbreak. Bats of the genus *Pteropus* ("flying foxes") appear to be the natural reservoir and can infect a variety of mammalian secondary hosts (i.e., felines, canines, swine, and equines). An outbreak in Bangladesh was associated with the consumption of date palm sap, again contaminated by infected bats. Direct contact with infected bats may also result in transmission. Human-to-human transmissions, including family and healthcare associated, are documented. There is indirect evidence (i.e., lacking virus isolation or nucleic acid tests) of reactivation of latent, chronic infection resulting in recurrent CNS disease and death [77–79]. Despite recurrent outbreaks, especially in Bangladesh and India, there have been no allegations of transfusion transmission, and little attention has been paid to implications for blood safety.

Hendra virus is closely related to Nipah at the sequence level. Recognized human Hendra virus infection is much rarer than Nipah, with seven cases and four deaths recognized since the first equine outbreak in Australia in 1994 [80]. Horses are infected after contact with infected urine from *Pteropus* bats. A total of 53 outbreaks of equine respiratory illness involving more than 70 horses have all been confined to the northeast coast of Australia [81]. There is no evidence of the infection before its 1994 emergence after serological studies on a number of vertebrate and invertebrate repository samples. It causes a spectrum of human illness from nonspecific fever to flu-like syndromes to fatal encephalitis, generally as a consequence of spillover from equine infections. Treatment is supportive. No effective prophylaxis is available. The incubation period is from 5 to 21 days from exposure. Transmission to humans occurs mainly after direct contact during the care of sick horses or at the time of their autopsies. In early studies, recipient horses were infected intravenously using homogenates of the spleen and lung from two of the index horses. Postmortem lung, liver, kidney, and spleen from a human decedent were infectious in tissue culture [70]. In one case of CNS infection, the patient recovered but had recurrent neurological illness over a year later and died. There are no reports alleging transfusion transmission.

There is a small amount of evidence for an acute, low-level viremia for Nipah virus, and one might expect the same for Hendra. Pathologic studies demonstrate that respiratory and vascular endothelial cells are important targets for both Nipah and Hendra. How they spread from the portal of entry, likely the respiratory epithelium, is not fully characterized. In later stages of clinical infection, pulmonary endothelium is infected, and small vessel vasculitis ensues. They are believed to enter the bloodstream at that point and disseminate as free and cell-associated virus [82, 83] and gain entry to the central nervous system. At least one mouse model has dis-

counted the requirement for viremia for development of encephalitis with Hendra [84]. Direct evidence of human viremia has not been provided for either virus. Whether an asymptomatic infected individual sustains a potentially infectious viremia has not been addressed. Blood donor studies have not been published.

Donor screening, whether by health history or in vitro assays, has not been proposed for either of these viruses. Donor questions to understand exposure risk can be developed and implemented at need, in the event of outbreaks that might affect blood donors. High-throughput assays are not available, although diagnostic assays might be repurposed for this indication if the need arose.

Donor deferral strategies for a history of exposure or infection will, necessarily, be empiric. For a history of exposure, they would be some multiple of the maximum credible incubation period (e.g., perhaps 6 weeks for Hendra and 6 months for Nipah). Since some proportion of infections are asymptomatic, donor reentry with a negative diagnostic serology might be considered. A history of infection is more problematic, given the apparent persistence of some Nipah infections and a single case report of relapsing Hendra in the CNS. A lifetime deferral is defensible for both viruses after clinical infection.

In an outbreak context (potentially including travel to areas experience significant activity) or when a donor is diagnosed with one of these viral infections, it seems reasonable for a blood collection organization to have (generic) procedures to guide a recall of co-components of donations from exposed or ill donors from within some reasonable interval before donation. These would reflect their incubation periods and the best data on the presence and duration of putative viremia. It would be prudent to perform a lookback to recipients of blood transfused before such a recall was undertaken, for the purposes of assessing their likelihood of having been infected. Likewise, an allegation of transfusion transmission should be carefully evaluated and the need to evaluate donors assessed.

Appropriate studies of pathogen reduction for labile blood products have not been published for either Nipah or Hendra, but similar viruses (i.e., enveloped RNA viruses) are effectively inactivated by the processes being advanced for approval in the United States. Likewise, one would expect that one or more of the specific viral inactivation, removal and purification steps in commercial plasma fractionation processes, would eliminate risk from derivatives.

Looking Forward

The foregoing depict a very *ad hoc* process for recognizing and responding to emerging infectious threats to transfusion safety, whether zoonotic, arthropod-borne, or others. Given the unpredictability attending the emergence of a specific pathogen, this is perhaps inevitable. That said, that new pathogens will emerge is axiomatic. The task for infectious diseases and epidemiology experts in the blood community is to be sensitive to this inevitability and to spend real effort anticipating which agents of many candidates pose material threats that bear forethought and

planning. To that end, the emerging infections subgroup at AABB has engaged in developing a toolkit to guide that process (Fig. 10.3). The most critical activity is "horizon scanning" that daily surveils a spectrum of online and print resources to identify new and emerging human pathogens. These include media reports, professional meetings, organizational and peer-reviewed publications, open source and subscription websites (e.g., ProMED [85], CDC.gov, WHO.int, PAHO.org, and many others), and personal networks. Perhaps difficult element for horizon scanning is effective hemovigilance. This requires of clinicians the routine elicitation of a transfusion history as they establish a differential diagnosis in patients with apparent infections, so that they can ask themselves the four questions we have proposed as critical for imputing blood as a "vector."

Criteria for more detailed review include the *de novo* identification or expansion of the range of a pathogen, especially its involvement in an outbreak; reports of transmission by organ and tissue transplantation; infection following parenteral inoculation via needle stick and laboratory accidents; an association with injection drug use or sexual activity; a close relationship to a recognized TTI; and actual allegations of transfusion transmission.
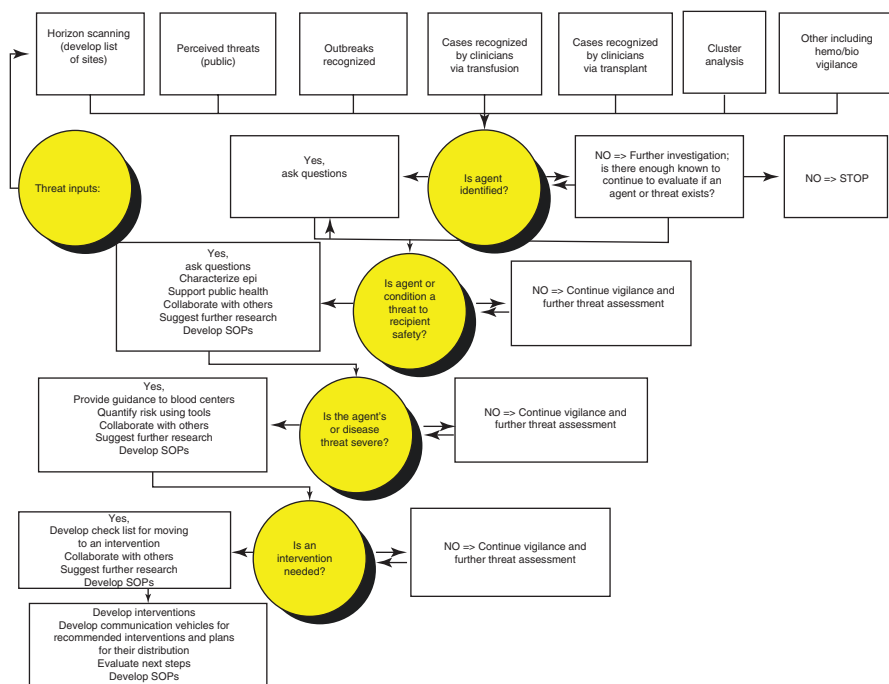

Fig. 10.3 Outline of AABB emerging infectious diseases subgroup's toolkit including the framework for recognition, assessment, and management of EID agents for risk of transfusion-associated transmission and disease. SOP standard operating procedure [24]. (Used with permission from: Stramer SL and Dodd RY for the AABB Transfusion-Transmitted Diseases Subgroup [90])

The role and effectiveness of advanced molecular techniques (e.g., pathogen discover via metagenomics or next-generation sequencing and other non-culture-based techniques) to study clinically infected patients for diagnostic indications and populations (including blood donors) to elucidate the human microbiome and explore new disease associations are not yet clear. False alarms will occur when members of the "normal human flora" are discovered. TT virus (an anellovirus) was discovered using representational difference analysis for the amplification of nucleic acids in patients with posttransfusion non-A, B, and C hepatitis [86], causing its brief consideration as a target for interventions in transfusion medicine, but any association of the ubiquitous virus with either transfusion pathology or other illness was eventually refuted. More recently, next-generation sequencing was applied to sera from 204 US patients with acute liver failure of unknown etiology and failed to identify unexpected pathogens [87].

With the suspicion that a new infection threatens blood transfusion recipients, a risk must be quantified, initially using provisional clinical and epidemiological descriptions that will be refined over time. Online risk modeling tools to accomplish these analyses are being developed for transfusion medicine [88], with the critical, if obvious, caveat that the precision of their output is wholly dependent on input parameters. These are necessarily least precise in the earliest stages of emergence when initial preparedness decisions must be made generally and specifically with regard to transfusion safety. There are critical data needed to inform any quantitative assessment of the importance of a potential pathogen. A "routine" search for and reports of the presence of the infectious agent (or the imperfect surrogates, nucleic acids, and antigens) in the blood of asymptomatic individuals at risk would be a valuable standard operating procedure during epidemiologic investigations of emerging infections; this does not often occur early and before the blood community must respond to a potential threat. Likewise, prospective determination of pathogen survival through contemporary component production, processing, and storage should be a research priority.

When we conclude that material risk may be present, interventions must be considered and prioritized. They will range from information and education to donor queries and deferrals. For example, would it not be rational in the temperate world to consider a blanket travel deferral of several weeks for donors visiting tropical and subtropical venues where acute arthropod-borne and zoonotic agents are common? Donor testing and determining the role of pathogen reduction techniques are more aggressive responses to greater perceived risk. These considerations are all, necessarily, cyclic, iterative processes. The pivotal role of risk-based decision-making from a societal perspective is covered elsewhere in this book.

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