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The Need for Continuing Vigilance: Addressing the Threat for Transmission of Blood-Borne Infectious Disease

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As international travel and human encroachment into previously isolated areas have increased, so too has the potential for the emergence of new infectious diseases. Populations likely to be susceptible to new infectious diseases have also increased in size. The past three decades have seen outbreaks of diseases caused by parvoviruses, Nipah virus, circoviruses, and prions. Infectious pathogens such as these are formidable opponents; they can adapt to new hosts or cause variant diseases within new hosts. Many are also resistant to current inactivation techniques. In order to prevent or contain outbreaks, pathogens that emerge must be identified quickly and efficiently; research and ongoing global surveillance are therefore of primary importance. To effectively protect the blood supply and blood-based therapies, this research should include investigations into improved techniques for detection, screening, and viral inactivation, as well as into ways to reduce patient exposure to infectious pathogens via therapeutic agents. The proactive devotion of appropriate resources to infectious disease containment and prevention prior to an epidemic should be perceived as both essential public health policy and cost effective.

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In the wake of the significant strides in vaccines and antibiotics that followed World War II, most of the public health community believed that infectious diseases could be effectively controlled. By the 1990s, however, as new infectious pathogens emerged, public health experts could no longer believe that the threat of infectious diseases had receded.¹ In fact, the potential for the emergence of new infectious diseases was increasing, a result of commonplace and extensive international travel and steady human encroachment into previously isolated areas.

Infectious diseases are categorized as “emerging” based on either their documented increased incidence in humans over the past two decades or on evidence of their potential to increase in the near future.¹ Such evidence would include reports of a pathogen’s demonstrated ability to increase its host range by jumping species to infect new populations. Emerging infectious pathogens in recent decades have included human immunodeficiency virus (HIV), avian/variant influenza, severe acute respi-

ratory syndrome (SARS) virus, West Nile virus, dengue fever, monkeypox, parvovirus, Nipah virus, Ebola virus, and variant Creutzfeldt-Jakob disease (vCJD). Not all infectious diseases are a threat to the blood supply, because the clinical presentation associated with many infectious diseases is severe enough that infected patients are not likely to be blood donors. For example, the Ebola virus is blood-borne, but infected persons are not likely to donate blood because they become ill very quickly. However, other infectious diseases, such as HIV and vCJD, have long latent infectious periods during which persons can donate blood with no knowledge that they are infected. These latter types of infectious diseases as well as others with mild clinical sequelae have the potential to infect the blood supply through donation and be transmitted to the hemophilia community and other persons through blood products (Figure 1).

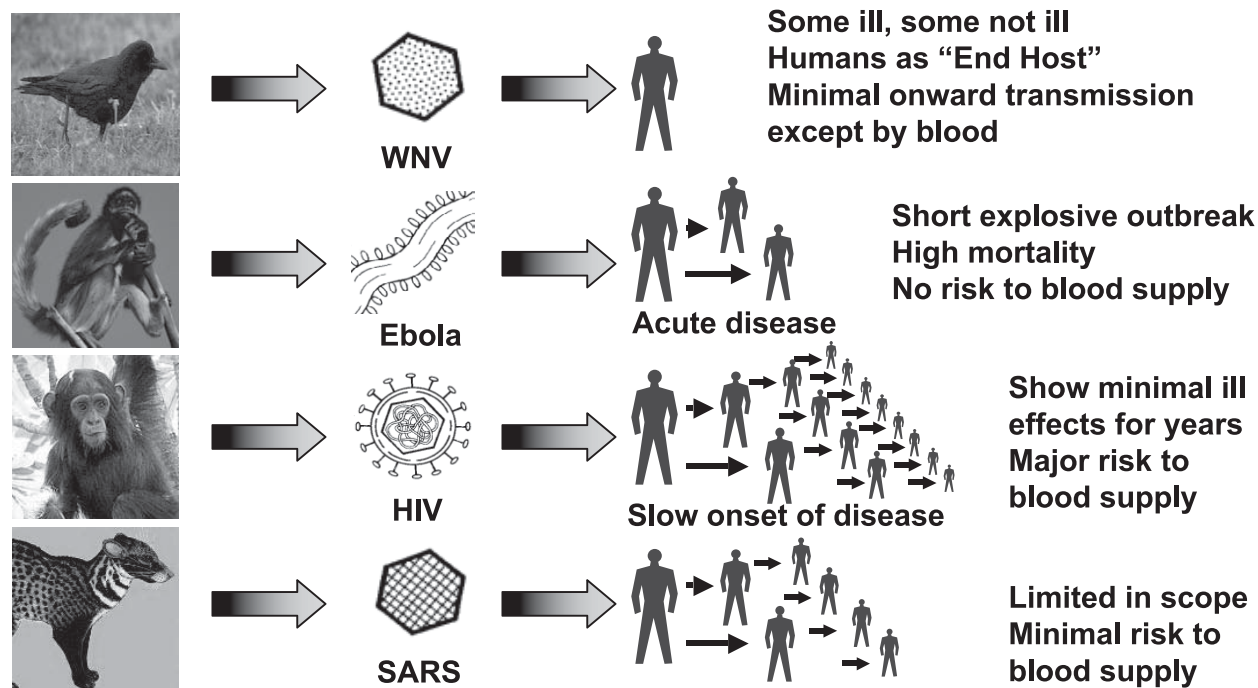
There are multiple arguments to support a belief in the inevitability of the emergence of additional infectious diseases, principally reflecting the following five factors:

- Adaptability of viruses allows for viral mutations that enable defensive or aggressive adaptation to new environments, promoting development of drug resistance or achievement of cross-species transmission²
- Human encroachment into previously unexplored habitats increases exposure to new agents²

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Patterns in New Zoonotic Infections



HIV=human immunodeficiency virus, SARS=severe acute respiratory syndrome, WNV=West Nile virus

Figure 1 Infectious diseases have different potential impact on the blood supply. Figure courtesy of Dr David Onions.

- Increases in the numbers of susceptible hosts (eg, elderly, HIV-infected, or chemotherapy patients) offer greater opportunities for infectious pathogen disease transmission²
- Advances in pathogen screening technologies have resulted in increased sensitivity and, as a result, better detection of novel (or previously unrecognized) pathogens
- Currently unknown biological factors that may become evident in the future (referred to as the “X-factor”).

Specific Pathogen Threats

Parvoviruses

Parvoviruses are non-lipid-enveloped, single-stranded DNA viruses that prefer to infect and lyse rapidly dividing cells, and are a continuous viral threat.³ Currently, parvovirus B19 (PVB19) is the only known pathogenic parvovirus in humans,⁴ in whom it is capable of causing several diseases. PVB19 typically causes a self-limiting febrile illness, *erythema infectiosum*, also called slapped cheek syndrome or Fifth disease.⁵ However, in patients with immunosuppression or hematologic disorders, PVB19 can cause aplastic crises.⁵

Parvoviruses are potential threats to human health and safety because they can alter their host-specific proteins and effect cross-species transmission. Feline parvovirus (FPLV), for example, which causes feline panleukopenia disease (ie, feline distemper), altered its host specificity, and in the mid to late 1970s there was an outbreak of a new disease in dogs with symptoms similar to feline distemper, including a high mortality rate.^{3,6,7} The most widely accepted hypothesis is that mutations in FPLV (or a closely related virus infecting mink or foxes) caused the emergence of a new virus, canine parvovirus (CPV-2)³; essentially, FPLV jumped species. There was no natural resistance to CPV-2 in dogs and the result was a rapid global epidemic³ stopped within a year only by the development of a new vaccine for dogs and the use of the previously available cat vaccine.⁷

The ability of parvoviruses or related viruses to mutate and cross to humans is particularly alarming because they are difficult to eliminate. Parvovirus and other non-lipid-enveloped viruses are highly resistant to the multiple viral inactivation protocols used in blood product processing, eg, pasteurization, heat treatment, and solvent/detergent techniques, that are effective against lipid-enveloped viruses.^{8,9} Parvovirus contamination has been extensively documented in animal products such as tryp-

sin, used in the preparation of recombinant factors and serum.¹⁰ PVB19 can also be transmitted from asymptomatic blood donors and there are numerous reports of transmission through transfusion of virus-inactivated or purified clotting factor concentrates. Many of these cases have serious clinical consequences.^{11–14} PVB19 DNA has been found in virally attenuated plasma-derived clotting factors VIII (FVIII) and IX (FIX) and in first-generation recombinant FVIII (rFVIII) therapies.^{11,15,16} Contaminated human albumin used as a stabilizer was the most likely source for PVB19 DNA in these clotting factor therapies.¹⁶ PVB19 has also infected a patient who received a contaminated intravenous immune globulin infusion.⁵ Purification techniques, involving polymerase chain reaction (PCR) screening and removal of infected blood, reduce the presence of parvovirus in blood products but do not eliminate it entirely.^{8,17} As of yet, there have been no reports of the development of parvovirus disease subsequent to transfusion with any recombinant preparation, but the possibility has not been eliminated. Until more effective elimination techniques can be developed, there will always be the concern that animal- or human-derived products could serve as a source of transmission.

Nipah, Zoonoses

Malaysia, between September 1998 and June 1999, suffered a sudden outbreak of encephalitis, with more than 50% of those affected exhibiting reduced consciousness and brain stem dysfunction.^{2,18} Authorities determined that the epicenter of the outbreak was a Nipah river village in which all 27 of the initial cases had had contact with pigs infected with a respiratory disease. The disease spread throughout Malaysia as farmers sold their pigs across the country. The resultant epidemic caused 265 cases of acute encephalitis and 105 deaths, a mortality of approximately 40%.¹⁸ The new virus, identified as belonging to the Paramyxovirus family (measles and mumps),¹⁹ was named Nipah for the village of origin.¹⁸

Evidence suggests that the viral reservoir for Nipah is the fruit bat in whose urine Nipah has been isolated. It is conjectured that bats feeding on fruit in an orchard adjacent to a piggery in Nipah urinated and defecated onto the fruit; the pigs then ate the fruit and contracted the virus. The close proximity of the pigs in the piggery fostered pig-to-pig transmission.¹⁸ The Nipah virus was transmitted to humans primarily through direct contact with infected pigs or contaminated pig tissue.² Pigs also transferred the Nipah virus to cats, dogs, and horses.¹⁸ There have been epidemics of Nipah in Bangladesh in 2001, 2003, and 2004²⁰; although the source of the virus was unclear, Nipah-positive bats were found.²¹ The evolution of the Nipah virus emphasizes the real threat of cross-species transmission.

Circoviruses, Viral Plasticity

Circoviruses are non-lipid-enveloped, single-stranded circular DNA viruses that can be pathogenic within animal hosts and could become pathogenic within humans.^{22,23} Circoviruses have extraordinarily small genomes (3,750 to 3,900 bases) and are some of the smallest viruses known. The circovirus family includes porcine circovirus (PCV), chicken

anemia virus (CAV), and TT virus (TTV), which affects humans, although at this time TTV's ability to cause disease is unclear. Blood-borne TTV displays substantial genetic diversity and it is unknown whether genetic variability could lead to an increased potential to cause disease. Detection rates for TTV DNA in humans are very high and TTV infection may be universal²³; in fact, some individuals are infected with multiple genotypes of TTV. Although the potential repercussions of such infection are unknown,²⁴ TTV can be transmitted both by blood and by fecal–oral routes and there is debate about mother–infant transmission.^{22,23,25} TTV is a particular concern because circoviruses demonstrate a high degree of plasticity, and animal circoviruses can cause severe disease in their respective hosts. In addition, circoviruses, which are non-lipid-enveloped and have small genomes, are very resistant to standard inactivation methods, including irradiation.

Prions

Prions are insoluble cellular protein particles that lack nucleic acid and, therefore, do not depend on genes or other factors for transmission of their traits. In humans, the prion protein gene (*PRNP*) on chromosome 20 usually encodes for a normal prion protein. In some instances, a post-translational conformational change occurs that creates an abnormal and transmissible particle, PrP^{Sc}, termed a prion.²⁶ Believed to be responsible in humans for at least five clinical diseases (Kuru, Gerstmann-Straussler-Scheinker disease, fatal familial insomnia, Creutzfeldt-Jakob disease [CJD], and variant CJD [vCJD]), prions are also present in other species. In animals prions cause scrapie, bovine spongiform encephalopathy (BSE or “mad cow” disease), chronic wasting disease, or feline encephalopathy.²⁷ While prion diseases can develop spontaneously, they are more likely to be transmitted by dietary or blood-borne contamination²⁶; vCJD may be transmitted through consumption of contaminated meat or blood transfusion, while classical CJD has been transmitted by contaminated human pituitary hormones, dura matter grafts, corneal grafts, and surgical instruments.²⁸ Given the characteristics of prions and their transmission, vCJD-associated prions present an alarming and real concern for all patients reliant on blood products, including patients with hemophilia.

As of December 2005, there have been 159 cases of vCJD reported worldwide.²⁹ Although a majority of the cases have occurred in the United Kingdom, vCJD has also been identified in France, Ireland, Italy, the United States, and Canada.^{26,30} Patients with vCJD initially present with psychiatric symptoms such as depression, withdrawal, anxiety, cognitive impairment, and persistent painful sensory symptoms²⁶; eventually the symptoms progress to dementia and death. The median age at death is 28 years old, indicating that vCJD most frequently occurs in young people.^{26–30}

Susceptibility to vCJD, clinical symptoms of the disease, and the time to appearance of symptoms are determined by a polymorphism at codon 129 of the *PRNP*. Individuals who are heterozygous at codon 129 may be infected but still in the incubation period and, as a case report (detailed later) dem-

onstrates, vCJD can be transmitted while the patient is in the incubation period.³¹ Therefore, though the incidence of vCJD has been decreasing worldwide since 2000,³⁰ latent infection may still be present, and the threat for transmission remains.

Blood transfusions are possibly responsible for two known cases of vCJD.^{28,31} In one case, a 62-year-old patient received a transfusion of red cells during surgery in 1996. One unit of the transfused blood was donated by a 24-year-old, who developed symptoms of vCJD 3 years and 4 months after the blood donation and died in 2000. In 2002, 6.5 years after the transfusion, the recipient manifested clinical symptoms of vCJD and died 13 months later.²⁸ In the second case, an elderly patient received a transfusion of red blood cells in 1999. The blood donor developed symptoms of vCJD 18 months after the donation and died in 2001; vCJD was confirmed at autopsy. The recipient patient died 5 years after the transfusion, but showed no evidence of a neurologic disease. Nonetheless, postmortem, the patient was shown to be positive for vCJD.³¹

In response to the vCJD threat, the United Kingdom announced that patients with hemophilia and other congenital bleeding disorders were at risk for vCJD,³² an announcement that has had notable financial and psychological impact, since patients with hemophilia and other congenital bleeding disorders who might be infected with vCJD are now considered capable of transmitting it to others. Therefore, the United Kingdom has implemented a new standard of care that includes disposal of those instruments used on patients with hemophilia that cannot be easily disinfected (eg, endoscopes, some dental equipment).³² This new standard of care is very costly, and some dentists are refusing to treat patients with hemophilia.

Other countries are also being forced to confront the spread of prion diseases. In October 2004, the French health ministry announced that a blood donor, who is still alive, had developed vCJD, and within a month French authorities announced discovery of blood donations by another individual later diagnosed with vCJD. The Belgian Red Cross used French-sourced plasma (from one infected donor) to produce factor VIII and IX in 1995 and 2002.³³ Although as of yet there have been no reports of vCJD transmission in any person with hemophilia,³³ it is clear that continued vigilance is necessary.

Vigilance Is Expensive

Interventions to improve blood safety can be expensive. By comparing the cost of an intervention to the benefit given, the quality-adjusted-life year (QALY) can be calculated. To improve blood safety, the HIV antibody testing was developed and introduced in the mid 1980s. With 16 million transfusions each year in the United States, and an estimated prevalence of HIV of one in 10,000 blood donors, the cost per QALY for this intervention is calculated at \$3,600.³⁴ By contrast, the cost per QALY for p24 antigen testing for HIV is estimated at \$2.3 million and for HIV NAT at \$2.0 million. This difference in cost-effectiveness reflects the decreasing

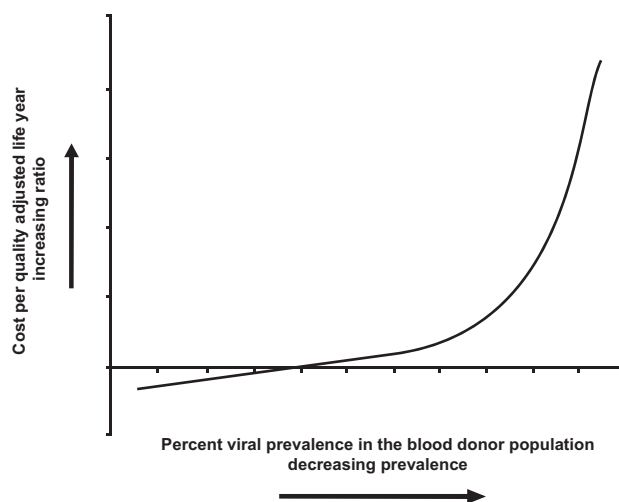


Figure 2 Hypothetical relationship between cost-effectiveness and viral prevalence. As the prevalence of blood donor disease decreases, the costs of blood screening increases because there is little health benefit for the general population. Conversely, when disease prevalence is high, blood screening is cost effective because it prevents spread of disease. Reprinted from Custer et al,³⁵ © 2004, with permission from Elsevier.

prevalence of HIV in the blood donor population.³⁵ However, new defensive interventions could be very cost effective if (and when) a new blood-borne pathogen enters the blood supply (Figure 2).³⁵ The costs of pathogen screening techniques must be considered in relation to the potential future costs for disease treatments in those who become infected. The medical costs associated with treatment of viral infections can be substantial: the costs involved in treating a patient with hemophilia co-infected with HIV are nearly 1.5 times greater than costs for those without co-infection.³⁶

Cost-effectiveness and cost-utility analyses are important for developing resource allocation decisions and many resources are used to ensure that transfusions of donated blood carry nearly “zero risk.”³⁵ Economic evaluations of techniques for ensuring blood safety show that interventions may not be cost effective, but these conclusions have limited impact on developing blood policy decisions; society appears to accept that the value of protecting a nation’s blood supply from pathogen infection could transcend standard cost considerations. In addition, lessons appear to have been absorbed from the HIV epidemic, in which economics-based decisions could not control, and in fact inadvertently contributed to, the spread of the epidemic. Finally, policymakers fear litigation if their decisions with respect to infectious disease control are later shown to be irresponsible.³⁷

Continued vigilance may present a major financial burden, but is currently considered to be worthwhile in the face of the continuous emergence of new pathogens potentially transmissible through blood and blood products. It is important that this attitude be reinforced in the years to come, when the incidence of emerging pathogens is unlikely to diminish while the costs of pathogen control are likely to increase.

Addressing the Threat

Vigilance requires the establishment of a public health infrastructure that can operate appropriately in response to a crisis. This will need to include improved surveillance, constantly reviewed and updated to respond to emerging diseases. Since emerging pathogens occur worldwide, effective surveillance must be global.² Currently the Centers for Disease Control and Prevention collaborates with the World Health Organization on surveillance and reporting of emerging infectious disease.

To ensure that emerging pathogens are identified quickly and efficiently, research into new technology is of primary importance. To be effective in protecting the blood supply and blood products these techniques should include improvement in detection, blood screening, and viral inactivation processes, as well as reducing exposure of patients to animal proteins capable of transmitting infectious pathogens.

Conclusion

Currently available hemophilia therapies have varying levels of exposure and vulnerability to contamination by blood-borne pathogens, reflecting the degree to which they incorporate components of human- or animal-derived plasma or albumin. Wherever possible, levels of vulnerability should be reduced, and those therapies with the least exposure to human- or animal-derived proteins, and therefore the lowest levels of vulnerability, should be made widely available.

Continued vigilance over the nation's—and the world's—blood supply is critical as long as infectious disease is a possibility, which is to say, far into the foreseeable future. Infectious pathogens are formidable opponents; they have the ability to change their genetic blueprint to adapt to new hosts or to cause variant diseases within new hosts. Globalization is increasing risks for pathogen emergence, and populations likely to be susceptible to new infectious diseases are growing in size. To proactively devote appropriate resources to infectious disease containment and prevention prior to an epidemic should be perceived as both essential public health policy and cost-effective.

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