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Emerging pathogens and their implications for the blood supply and transfusion transmitted infections

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Summary

The threat of infection by conventional transfusion-transmitted agents has been essentially eliminated from the blood supply in developed countries, thus focusing attention on the potential risk from emerging infections. Over recent years, actions have been taken to manage a number of such risks to blood safety. These illustrate the inherent variability of the agents concerned and of the measures needed to define and control the risk.

Keywords: blood transfusion, safety, emerging infections.

Emerging infections are simply defined as 'those whose incidence has increased within the past two decades or threatens to increase in the near future'. The term emergence is, however used to cover a number of situations that go beyond an increased presence of an existing or new pathogen. It is also used to cover the recognition of an agent known to be present but previously undetected (such as hepatitis C virus, HCV), or to the recognition that an established disease has an infectious origin (as was the case for *H. pylori* and gastric ulcers). Emergence (or reemergence) may also be used to describe an increase in a disease that had previously declined or had been controlled. Perhaps unexpectedly, completely novel infections are quite rare and, even cases like human immunodeficiency virus (HIV), variant Creutzfeldt Jakob disease (CJD) or severe acute respiratory syndrome (SARS), can often be traced back to a previously existing infection in animals, although often with some sort of mutation fitting it to its new host. In fact, the majority of emerging infections in humans (60% or more) are defined as zoonoses.

Emergence is not confined to any particular group or classification of pathogens or transmission routes. In some cases, aspects of emergence may be predictable, as is the case for the impacts of climate change on, for example, mosquito-borne disease. Other situations are not at all predictable, as was the case for SARS, or for West Nile virus (WNV) in North America. Overall, however, it is essentially impossible to predict the timing or dynamics of emergence.

Many factors may contribute to the emergence of pathogens and often a number of such factors operate in concert (Weiss & McMichael, 2004; Morens *et al*, 2008). Perhaps the most dramatic form of emergence is the finding of a previously unknown pathogen causing human disease. This may reflect a new agent that arose by mutation or reassortment, or transfer of an animal pathogen to humans, possibly with an accompanying mutation. Examples are HIV, variant CJD, SARS, and some influenza virus strains. Mutations or other heritable change may also occur in known human pathogens and may impact their pathogenicity or transmission mechanisms. A clear example is the emergence of drug-resistant strains (for example of bacteria or malaria) or vaccine escape mutants (for example with hepatitis B virus, HBV). Another interesting instance was the development of a mutation in the chikungunya virus resulting in its ability to use *Aedes albopictus* as the preferred vector rather than *Ae. aegypti* (Tsetsarkin *et al*, 2007). In this context, changes in vector control or behaviour may have profound effects, as has been the case with malaria and dengue. Vector behaviour is particularly affected by environmental and climate change. Human behaviours contribute extensively to the emergence of infections: conflict, sexual behaviour and urbanization are major contributors (Weiss & McMichael, 2004). Population movements, whether at the individual or mass level, contribute extensively to the introduction of pathogens into new environments; two clear examples are SARS, which spread rapidly on a global basis, while the introduction of *T. cruzi* into North America and Spain has been a more gradual process. The speed and convenience of modern travel increase opportunities for movement of disease agents by infected humans and also other hosts or vectors – the probable cause of introduction of WNV into North America (Petersen & Hayes, 2004).

Risks of emerging infections to blood safety

In order to offer risk to blood safety, there must be an asymptomatic period during which an emerging agent is present in the blood. Early experience with viral hepatitis

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and retroviruses suggested that this period would be prolonged, but it is now clear that acute infections may also be transmitted, as exemplified by WNV and dengue virus. Clearly, in addition to this requirement, in order to be of concern, the involved agent must be transmissible by the intravenous route and it must cause symptomatic disease in some or all recipients. In this context, it is known that there are a number of viruses, including hepatitis G virus/GB virus type C (HGV/GBVC), SEN virus (SENV) and torque teno virus (TTV), that are clearly transmissible by transfusion but that have not been associated with any diseases. Given the rapid progress in viral detection methods, it is very likely that many other such 'orphan' viruses will be identified (Bernardin *et al*, 2010).

Recognizing the threat

Experience suggests that it is very unlikely that the earliest manifestation of an emerging infection will be disease in blood recipients, although it is of interest to note that at least one novel virus was first recognized in transplant patients (Palacios *et al*, 2008). Thus, while those who care for transfusion recipients are encouraged to be alert for unexpected outcomes in their patients, managing transfusion safety is usually a function of blood collection organizations and public health and regulatory agencies. As a new or emerging infection is recognized, steps should be taken to assess whether or not it meets the conditions for transfusion transmissibility, as outlined above. Electronic media facilitate horizon scanning for disease outbreaks; it is a simple matter to obtain current information from national and supranational health agencies and from aggregation sources such as ProMed-mail (http://www.promedmail.org/) and Healthmap (http://www.healthmap.org/en/). In addition, professional societies may provide such services for their members or the general public. One such example is AABB, a US-based membership association for those involved in transfusion medicine and cellular therapies. AABB has published a set of fact sheets about emerging infections that may impact blood safety and also maintains and updates this information on its website (Stramer *et al*, 2009).

How to assess the risk of transfusion transmission

A key issue is to define the risk of a potentially transmissible agent to transfusion safety. Many factors need to be considered, including the anticipated frequency of recipient infection and disease, the likely evolution of the size of the outbreak, the severity of the resultant disease, the extent to which it is treatable and the public, professional and political concern around the disease. The impact of these measures will be discussed in the context of the examples below. However, it is evident that risk differs significantly among agents and that the response also differs greatly. In the case of SARS, the severity of the disease and the rapidity with which it spread globally was of enormous concern and the World Health Organization provided guidance relating to blood safety in the absence of any evidence or perception that the disease might be transfusion transmissible. Although the reaction was less rapid, measures were also taken to ameliorate transfusion transmission of variant CJD, based only upon concern about the potential for transmissibility by transfusion – a concern that was subsequently validated. In both of these cases, disease severity and public concern drove priorities and action. In contrast, WNV was first seen in the U.S.A. in 1999 and the risk to transfusion safety was recognized quantitated and, indeed, demonstrated in 2002; an intervention was in place in 2003 (Biggerstaff & Petersen, 2002; Pealer *et al*, 2003; Stramer *et al*, 2005). The outbreak garnered considerable public attention, exhibited rapid geographic spread and also resulted in severe disease, albeit in a small proportion of those infected. Even with this relatively prolonged time, the response was largely considered to be creditable.

Interventions

An intervention to prevent or ameliorate transmission of an emerging infection by transfusion may be necessary. Such an intervention should ideally be evidence-based and should be justifiable in the context of public health and risk-benefit or cost-benefit ratio. In some countries, a strong version of the precautionary principle may be invoked, often overriding these issues in pursuit of absolute safety. Focused interventions are usually based upon questions and/or tests. Questions typically relate to the donor's medical, social, behavioural, residence or travel history in an attempt to exclude those judged to be at high risk of the infection. Depending upon the nature of the infection, a donor giving a positive response may be temporarily or permanently deferred. While this approach may be implemented rapidly, it is usually neither sensitive nor specific. However, questioning is often the first measure to be taken. Unfortunately, questions are not often discarded once a test is in place. Testing donations for evidence of infection or potential infectivity is used when a validated test is available. Ideally, the test would identify only those donors or donations that are infectious, but this is not usually possible. Historically, those transfusion-transmitted infections that result from a chronic carrier state in the donor could be identified by tests for antibodies to the infectious agent (except in the unique case of HBV, where carriers usually have a copious excess of circulating viral antigen – HBsAg). However, this approach does not detect early infection when the agent may circulate prior to the appearance of detectable antibody. In these cases, the addition of a direct test for the agent (usually a test for nucleic acid) improves safety. On the other hand, interventions for acute infections (such as WNV) require only a direct test for the agent – in this case, for viral RNA (Stramer *et al*, 2005).

Pathogen reduction

It is anticipated that widespread availability of pathogen reduction technology will be the eventual solution to the threat of transfusion transmission of emerging infections. Currently, a number of photochemical methods are available for the treatment of platelet concentrates and plasma for transfusion. These methods are based upon amotosalen, (a synthetic psoralen), or riboflavin. Additionally, methylene blue and direct ultraviolet irradiation have been used for plasma, as has a solvent-detergent process. A different approach involving a so-called frangible anchor-linker-effector compound has been developed for red cell concentrates but has not yet entered the market and there are also some efforts to apply some of these technologies to whole blood. To date, there has been variable adoption of these methods for platelets and plasma and published experience has been favourable (Stramer *et al*, 2009). It is unclear, however, whether the methods have adequate capacity to inactivate very high titres of some agents and optimal safety may require that the methods be used in conjunction with testing such as NAT for at least some agents. (For a brief review, see Stramer *et al*, 2009).

Relevance of emerging infections to haematology

Emerging infectious diseases clearly have an impact on the practice of haematology. Firstly, infectious agents may result in clinical outcomes that are primarily in the realm of this discipline. Examples are the human B19 parvovirus (B19V), which selectively infects erythrocyte progenitor cells, leading to red cell aplasia, aplastic crisis or even generalized pancytopenia in patients with immune compromise or with diseases that result in increased erythropoiesis (Young & Brown, 2004). Some viruses, including the haemorrhagic fever viruses and dengue virus may cause bleeding disorders, capillary leakage or platelet deficiencies (Halstead, 2007). Also, parasites such as *Babesia* and *Plasmodium* spp. can lead to haemolytic disorders (White *et al*, 1998). Secondly, there are parasitic diseases that may be detected during examination of blood films; this may be the first indication of a transfusion transmission of, for example, *Babesia, Plasmodium* or *Trypanosoma cruzi*. Finally, some infections may require treatment to correct bleeding or other symptoms, as is the case for dengue and viral haemorrhagic fevers.

A major concern for haematologists is the safety of plasma-derived therapeutics, vividly illustrated by the extensive transmission of HIV and HCV by Factor VIII concentrates manufactured prior to the introduction of effective pathogen reduction technologies. Fortunately, such procedures are safe and effective and there have been no transmissions of these (or many other) viruses since the introduction of these methods. Current inactivation methods are most effective on enveloped viruses and it is true that some risk had been seen from the non-enveloped hepatitis A virus (HAV) and B19 viruses, but testing of plasma for further manufacture is now in place for both of these agents (Burnouf, 2007). In the context of emerging infections, there will continue to be some concern about an agent that may occur at high titre, particularly if it is non-enveloped. The case of hepatitis E virus (HEV) (discussed below) is of interest in this context. There are continuing efforts to validate the safety of these products as new threats are identified. A special case is that of variant CJD, but it seems likely, on the basis of specific studies and experience, that the fractionation process itself may well reduce the titre of this pathogen to levels below an infectious dose (Burdick *et al*, 2006). There is also the promise of affinity methods to further reduce this risk (Gregori *et al*, 2006). Additionally, of course, the availability of products developed through recombinant technology eliminates any infection risk.

Examples. Many of the points made above may be illustrated by consideration of specific examples. While it is not possible to be exhaustive, the agents described below may all be considered to fit the definition of emerging and all have been considered to be a potential or actual threat to blood safety. Specific interventions have been considered, evaluated or implemented for each of them. For want of a better system, they are presented alphabetically.

Babesia

Babesia spp. are intraerythrocytic protozoan parasites and the causative agent of babesiosis; a variety of species may be found throughout the world. With respect to human disease and transfusion transmission, however, *B. microti*, which is endemic in the northeastern and Midwestern United States, is of greatest concern. Human cases of infection with this agent are increasing in both incidence and geographic range, in part because of increased exurban lifestyles (Leiby, 2011). *Babesia* spp. are transmitted by ticks and primarily affect mammals, with humans as an accidental host. Babesiosis has symptoms similar to those of malaria, with more severe disease in the elderly and those patients without a functioning spleen (Vannier & Krause, 2012). Transfusion-transmitted babesiosis may be confused with malaria, as the characteristic 'Maltese cross' appearance of the parasite in red cells is quite infrequent. A recent report detailed 162 transfusion-transmitted cases in the US since 1979; 159 of these cases were due to *B. microti* and 3 to *B. duncani* (Herwaldt *et al*, 2011). Few cases have been reported from any other countries. The disease is generally treatable, but nevertheless, transfusion-transmitted cases have a significant fatality rate. At the time of writing, there has been no effective intervention available, as donor questioning regarding tick bite or clinical disease is insensitive and licenced donation tests are not available. Infection may be diagnosed by inspection of blood films and by the more sensitive serological and nucleic acid tests. The

latter two tests are undergoing limited, geographically selective evaluations in the US (Young *et al*, 2012).

Chagas disease

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi*, which is endemic through large portions of continental Latin America, and to some extent, the southern United States (Cantey *et al*, 2012). It infects a wide range of mammals and is transmitted via reduviid bugs. Its status as an emerging infection is questionable, as extensive and largely successful measures have been taken to control human infections in Latin America. However, infection is essentially life-long and the agent is moving into non-endemic areas (particularly the United States and Spain) through large-scale population movements. Indeed, it has recently (and inappropriately) been compared to the acquired immunodeficiency syndrome (AIDS). While acute infection is accompanied only by mild disease (if at all), the chronic effects of infection may be severe or life-threatening as a result of impairment of cardiac or gastrointestinal function. The parasite may be found free in the blood and, as a consequence, may be transmitted by transfusion. While the South American literature suggested in the past that transfusion transmission of *T. cruzi* was frequent, this has not been the case in the US and Canada: indeed, until recently, only seven transmissions were documented (Benjamin *et al*, 2012). Nevertheless, studies showed that an appreciable proportion of blood donors were seropositive (about 1 in 30 000 nationwide, but 1 in 7000 to 1 in 9000 in areas with high migrant populations). Nevertheless, it has been shown that, in the United States, a selective testing strategy in which each donor is tested only once, is safe and effective. Elsewhere outside Latin America, only those donors considered to be at risk, by virtue of birth and/or maternal origins in endemic countries, are subject to testing (Benjamin *et al*, 2012).

Chikungunya

Chikungunya virus (CHIKV) is an arbovirus belonging to the *Alphavirus* genus. It is transmitted by *Aedes* spp. mosquitoes either via a sylvatic cycle involving primates, or by a direct human-mosquito-human cycle. The virus is endemic to Africa, India, Southeast Asia and the Phillippines, where it is known to cause severe disease, typically manifesting as headache, fever, severe joint pain, and rash. Recently, it has been notable for causing explosive outbreaks, particularly in islands in the Indian Ocean (Charrel *et al*, 2007). It appears that such outbreaks may, in part, be attributable to a point mutation that favours *Ae. albopictus* as a vector, rather than *Ae. aegypti* (Tsetsarkin *et al*, 2007). This, along with travel by infected subjects, has contributed to smaller outbreaks elsewhere; in Italy, for example (Liumbruno *et al*, 2008). While there have been no documented cases of transfusion transmission of CHIKV, this possibility is a matter of concern by analogy to WNV and dengue (see below). French authorities implemented significant precautionary measures during an outbreak in la Réunion (an overseas department of France), by halting the local collection of red cell concentrates, and implementing NAT and pathogen reduction for locally produced platelet concentrates (Brouard *et al*, 2008; Rasonglès *et al*, 2009). Measures other than pathogen reduction were discontinued once the outbreak was over.

Dengue

Dengue is caused by four arboviruses (DENV 1–4) belonging to the *Flavivirus* genus. It is transmitted primarily by *Ae. aegypti* mosquitoes, but *Ae. albopictus* is also a competent vector. While there is a sylvatic cycle involving primates, a human-mosquito-human cycle is most common and of greatest concern. Dengue is endemic throughout the tropics and some 40% of the global population is at risk of infection. DENV infection results in a wide range of outcomes, from asymptomatic infection to a fatal shock syndrome. Dengue disease is now broadly categorized as the milder dengue fever or as severe disease. Infection with a given type of DENV will result in long-term, type-specific immunity, but only brief immunity to other types. In fact, it appears that preexisting immunity to a single viral type exacerbates the outcome of infection with any other DENV type. As with WNV, there is a brief presymptomatic (or asymptomatic) period of viraemia prior to the appearance of detectable antibodies. Viraemia may reach high levels (up to 10^8–10^9 genome copies per ml) and it is now clear that, during this phase, transmission of the virus by transfusion is possible (Stramer *et al*, 2012). To date, there have been three well-documented clusters of such transmission, in Hong Kong, Singapore and Puerto Rico (Chuang *et al*, 2008; Tambyah *et al*, 2008; Stramer *et al*, 2012). There are also a number of publications demonstrating the presence of viral RNA and/or viraemia among asymptomatic blood donors in affected areas. Limited investigational testing of blood donors for potential infectivity using NAT or viral antigen testing has been implemented, notably in Puerto Rico. It should be recognized that transfusion transmission would represent only a minute fraction of cases of dengue and implementation of donor testing may not represent good public health in highly endemic areas. However in locations, such as northern Queensland, Australia, it is usual to stop collecting fresh blood components during a dengue outbreak and thus, the use of a donor test could better help to maintain the blood supply.

Hepatitis E virus

HEV is a small, non-enveloped RNA virus belonging to the *Hepeviridae* family. Three genotypes have been associated with human disease, although type 3 is considered to be a zoonosis primarily affecting pigs. The distribution of these genotypes varies geographically, with type 3 being found predominantly in the West. This genotype seems to be associated

with mild disease or asymptomatic infection, except in those who are immunocompromised. The virus is primarily spread enterically by the faecal-oral or waterborne routes but has also been associated with the consumption of undercooked pork products. The resultant disease is typically a relatively mild, acute hepatitis although the impact may be much more severe among pregnant women. Studies suggest a relatively high seroprevalence of 10% or more in many countries and it is now apparent that there is a viraemic phase. There have been a number of reports of transfusion-transmission of HEV, including at least one from England (Boxall *et al*, 2006). A number of cases have been reported from parts of Japan, and NAT for HEV RNA has been implemented as a trial in some areas in order to reduce the risk (Sakata *et al*, 2008).

Despite the rarity of transfusion transmission in the West, HEV is attracting increasing attention in the context of blood safety, with particular reference to pooled plasma and derivatives, as the virus is not susceptible to inactivation by solvent-detergent processes. It is possible that there will be some movement towards the introduction of NAT for at least some blood-derived products.

Q fever

Q fever is caused by the small Gram-negative bacterium, *Coxiella burnettii*, which primarily infects domesticated animals. It is transmitted primarily by inhalation although it may also be present in milk. Among domestic animals, transmission by ticks is common. On the basis of serological surveys, the agent is widespread, but human disease is infrequent (Raoult *et al*, 2005). Bacteraemia has been described and there has been one reported case of transfusion transmission. Recently, however, there has been a large outbreak of several thousand cases of human disease in the Netherlands (van der Hoek *et al*, 2010). The cause was airborne exposure to the agent, which was being shed by intensively farmed goats: the majority of human cases were clustered around affected goat farms. Concern about the possibility of transfusion transmission led Dutch transfusion authorities to evaluate the situation by seeking evidence (by NAT) of asymptomatic bacteraemia among blood donors; a small number of instances were identified. There was also suggestive (but not definitive) evidence that transfusion transmission may have occurred (Hogema *et al*, 2012). As a result, donations collected in affected areas were subjected to NAT, but veterinary public health measures essentially eliminated the underlying disease among farmed goats, terminating the human outbreak.

SARS

SARS, or severe acute respiratory syndrome, emerged explosively in China and rapidly spread essentially globally, with more than eight thousand human cases occurring within the year of its origin (Peiris & Yuen, 2004). The disease is caused by a novel coronavirus, thought to have been introduced into the human population through the sale of live exotic animals for food. The severity of the disease and the rapidity of its spread resulted in great concern, including a theoretical concern about the possibility of transmission by transfusion, even though this is highly unlikely for respiratory infections. In the absence of any other available measure, presenting donors were deferred for a history of contact with any case, or travel from any area known to be affected. Possibly as a result of effective public health measures, the outbreak was not sustained and has not recurred.

Variant CJD

Variant CJD is a novel human transmissible spongiform encephalopathy transmitted by the consumption of tissues from cattle affected by bovine spongiform encephalopathy (BSE) (Head & Ironside, 2012). The latter is a disease of cattle that resulted from feeding the animals with meat and bone meal. Variant CJD differs from classic CJD in a number of ways, including the nature of symptoms and its occurrence at an early age (Spencer *et al*, 2002). Both CJD and variant CJD are uniformly fatal. Relatively early studies on variant CJD indicated that the infectious agent associated with lymphoid tissue to a greater extent than the agent of classic CJD, raising concern about the possibility that the agent was transfusion-transmissible. This concern led to the implementation of a number of different precautionary measures. In the United Kingdom (UK), universal leucoreduction was implemented; plasma for fractionation and for transfusion of patients born after January 1996 was imported from a low-risk country and there were generalized efforts to reduce blood usage. In addition, individuals who had received blood transfusions in the UK since January 1980 were permanently deferred: this policy was subsequently extended to transfusions anywhere in the world. In other countries, such as the US, policies were implemented to defer donors with a history of travel or residence in the UK and parts of Europe during the BSE epidemic. Several years later, the first cases of transfusion-transmitted variant CJD were reported from the UK: there have now been three such cases linked to donors who themselves developed variant CJD after donation and a fourth case in which the variant CJD prion was found at autopsy in a recipient of a donor with a similar history (Hewitt *et al*, 2006). It is of some interest that, in each of these cases, the implicated blood components had not been leucoreduced. A similar case of apparent transmission of the variant CJD prion has been attributed to receipt of Factor VIII concentrates (UK Health Protection Agency, 2009). It is not really possible to assess whether or not the current interventions have been effective or successful and it is fortunate that the incidence of new cases of variant CJD appears to be declining to negligible levels. Nevertheless, there is still interest in further interventions. Some progress

has been made in developing affinity filters capable of reducing the titre of prions in red cell concentrates and plasma components (Gregori *et al*, 2006), but the cost benefit ratio of these approaches appears to be unfavourable. At the time of writing, no test for asymptomatic infection with prions is available, although a great deal of effort has been put into attempts to develop such a test. It is clear, however, that the implementation of such a test would neither be simple, nor without ethical concerns.

West Nile virus

WNV was first recognized in Uganda in 1937. It is a flavivirus, in the Japanese encephalitis group that is transmitted by mosquitoes. The amplifying hosts are birds, and humans are accidental end-hosts. Until 1999, the virus was endemic in parts of Africa, the Middle East and southern Europe, where it causes occasional, geographically restricted outbreaks of human disease. However, the first case of WNV disease in the Americas was reported from New York City in 1999 (Petersen & Hayes, 2004). Thereafter, the virus and resultant disease spread rapidly, and affected essentially the entire continental United States and parts of Canada by 2002, resulting in as many as 400 000 infections within that year. It was recognized that, even though the infection was acute, there was a definite period of asymptomatic viraemia, defining the possibility of transmission by transfusion and indeed, 28 such cases were reported in 2002 (Biggerstaff & Petersen, 2002; Pealer *et al*, 2003). This resulted in the rapid, nationwide implementation of NAT for WNV RNA among all blood donations, as of July 2003 (Stramer *et al*, 2005). It was found that testing in pools was not sufficiently sensitive to detect all infectious donations and measures were added to implement individual donation testing in times and places of high incidence of infection. It appears that this intervention has been successful, as some 1232 RNA-positive donations have been detected between 2003 and 2010 from the Red Cross, which collects about 40% of the US blood supply. Only 11 breakthrough infections have been reported, none of which were attributable to the Red Cross, plus one that occurred as a result of administration of a granulocyte concentrate prior to the availability of the (positive) test result (Meny *et al*, 2011). In other countries, such as Italy, there have been small outbreaks of WNV disease, leading to temporary cessation of blood collection or to the implementation of testing. More substantial outbreaks occurred in Greece in 2010 (262 cases) and 2011 (101 cases). In addition, there are now policies in many European countries to defer and/or test presenting blood donors who have recently travelled in WNV-affected areas. It might be argued that the response to the WNV outbreak in the United States represented an optimal model, inasmuch as blood collectors, public health agencies, regulators and industry worked in concert to implement an effective intervention once the threat had been recognized. However, some might argue that a four-year period between first appearance of the disease and launching a blood safety measure is unacceptably long.

XMRV

The xenotropic murine leukaemia virus-related virus (XMRV) offers an instructive and cautionary case study, albeit one that is not entirely unique (Voisset *et al*, 2008). The virus was first described in 2006 in association with some cases of human prostate cancer (Urisman *et al*, 2006), but the observations were not readily replicated. It was not until a report in 2009, suggesting an association between XMRV and chronic fatigue syndrome (CFS) (Lombardi *et al*, 2009), that the virus received substantial attention, including concern that it might be transmissible by blood transfusion. Some blood organizations emphasized that individuals with a diagnosis of CFS should not give blood. Although the CFS observations were not repeatable, another study did report mouse leukaemia viruses also in association with CFS and in a substantial proportion of the normal population (Lo *et al*, 2010). This second paper led to further confusion, but also turned out not to be reproducible. Ultimately, both XMRV and the murine leukaemia viruses (MLVs) were shown to have been laboratory contaminants and both of the key papers were eventually retracted (Alberts, 2011; Lo *et al*, 2012). XMRV itself was shown to be an artefact attributable to recombination of two separate MLV fragments attendant on the passage of tumour cell lines in nude mice (Paprotka *et al*, 2011). However, a great deal of public pressure and concern arose from the purported relationship of these gamma retroviruses to CFS and their possible transmissibility by transfusion. A specific workgroup was funded to evaluate this possibility and the group ultimately showed, through careful blinded evaluations of different laboratories, that neither the viruses nor their corresponding antibodies could be reliably detected (Simmons *et al*, 2011). Further, it was separately shown that XMRV could not be detected in a large population of blood donors, making the issue of transmissibility moot (Dodd *et al*, 2012). A number of factors led to what was, in retrospect, an overreaction to this situation. First, there is a specific concern about the threat offered by retroviruses, in part reflecting lessons learnt from the HIV crisis, but also because retroviruses are unstable and may become pathogenic as a result of mutations, particularly in the context of species-jump. Second, the newly recognized virus was (mistakenly) associated with a dreaded, and currently unexplained disease. Third, a number of affected patients and their advocates believed that XMRV was the causative agent of CFS and generated considerable public concern. In particular, there was an attempt to draw attention to CFS by suggesting that there were parallels between XMRV and HIV and that blood safety was at risk, despite the absence of epidemiological similarities between the two viruses. The situation took two years, and a good deal of scientific effort, to resolve. As pointed out by Lipkin (2012), it is relatively simple to establish a relationship between an agent and a

disease, even by accident, but it is very difficult to de-identify the relationship.

Risk summary

The residual risk offered by the conventional transfusion-transmissible agents has been estimated on the basis of the incidence/window period model and estimates are available for many countries. It is not so easy to establish meaningful estimates for most of the examples discussed above because they are dependent upon a number of parameters that are poorly characterized and vary very much between and within countries. The risks of collecting a viraemic blood donation have been calculated for specific outbreaks of CHIKV, DENV and WNV, and the methods used could be used in other outbreaks where the incidence is known. In the absence of a known outbreak, however, the risk is not present or must be regarded as negligible. Somewhat analogous is the case of Babesia, where prevalence and incidence vary geographically. In areas of high prevalence, the risk may be on the order of one infection per thousand red cell concentrates, but elsewhere, may be absent or negligible. Experience with Chagas disease in North America has suggested that the risk of infection, even from seropositive donors, is very low and there are questions as to the value of the testing programme itself. Other infections mentioned here, such as SARS, Q fever and XMRV, do not now appear to offer any meaningful risk, although both SARS and Q fever could reemerge. Finally, the difficulties of defining the overall risk of transfusion transmission of variant CJD are well known; a somewhat disconcerting situation.

Lessons learnt and the future

The examples above reflect recent experience with emerging infections and blood safety. Two issues are clear: first, that emerging infections are unpredictable and do not conform to any particular pattern. Second, when such an infection threatens blood safety, there is no set response. Experientially, each circumstance is essentially unique and has been managed in a different fashion. This raises the question of whether there is, or should be, a formally defined, consistent set of actions to be taken each time a new threat emerges. While a number of worthy attempts have been made to do this, none has given a clear path forward. A glance at a recent compendium of selected known agents that may be transfusion transmissible illustrates the inherent variability of the threat and the potential interventions (Stramer *et al*, 2009). At the same time, the public and political response to the disease itself may override objective considerations. The impact of a possible intervention upon the adequacy of the blood supply must also be considered. Finally, public health and financial priorities may certainly impact the ability to implement safety improvements. Those responsible for the safety of the blood supply are uneasy with the increasing burden of testing and point out that this incremental approach to the maintenance of safety is neither sustainable nor economically realistic. Many hope for a generic solution to the problem in the form of an effective and accessible pathogen reduction technology for all blood components, but it is unclear whether such an approach can stand alone, or whether it can only supplement other interventions.

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