An affiliated publication to Vox Sanguinis
ISBT Science Series

ISBT Science Series (2009) **4**, 188–191

ORIGINAL PAPER AC04

Emerging infections in Asia and its possible global effects

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Introduction

Management of risks associated with the possibility of transfusion transmission of viral infections is an ongoing concern for blood services across the globe. The environment in which decisions are made is influenced heavily by the legacy of Human Immunodeficiency Virus (HIV) transmission in the 1980s and hepatitis C (HCV) in the 1990s. A precautionary approach is taken in a situation of ongoing review of past actions. Such reviews are often critical of delayed and inadequate responses by national blood services.

Considerable efforts have been devoted to improving systems for assuring the safety of donated blood for known viral risks. It is noteworthy that, at least in developed countries, the acknowledged major blood borne viruses shared a common epidemiology enabling the application of donor exclusion criteria based on sexual behaviour and other lifestyle risks. This along with the application of increasingly sensitive serological testing methods and in many countries the introduction of molecular based testing has significantly improved the overall safety of donated blood. Indeed by the end of the 20th Century the residual risk of transmission of viruses such as HIV and hepatitis B and C had become very small indeed with reported risks of less than 1 in 2 or more million for major viruses commonly quoted.

The emphasis in the initial decade of the 21st Century has been very different indeed. Concerns now increasingly relate to the emergence of new viruses or the re-emergence of known viruses in different geographic areas. This change in the pattern of risk has occurred in an environment where blood services appetite for risk continues to reduce and also in an era in which the capability of new technologies continues at a rapid pace. A potential concern then arises where the availability of technology itself drives the agenda rather than a careful consideration of the risks posed by an individual agent.

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General considerations

Drivers to the emergence of new or changing viruses

A number of factors contribute both to the emergence of new threats to the safety and security of the blood supply and the ability of these agents to rapidly establish themselves across the globe. These include the impacts of globalization of commerce, increased travel and migration and of climate change [1]. These issues impact significantly in Asia where in addition the effects of rapid population growth, increasing urbanization, high population densities and changes in the use of land (deforestation and use of agricultural chemicals), will also play an important role.

Impact of emerging agents on blood services

Infectious agents can impact on the blood supply in a number of ways. The primary focus of concern usually relates to the potential for transfusion transmitted infection. New infections can also impact on blood services in other ways. This includes a reduction in the available donor pool. This can arise either due to the infection itself, i.e. potential donors are too ill to donate, or as a consequence of the application of new donor exclusion criteria aimed at reducing the risk of disease transmission. In this context, careful management of the balance between safety and supply becomes very important. Finally, emerging threats can impact on the blood supply because of increased demand for blood components to treat patients. Some infections will impact in a number of ways.

Tools available to manage emerging threats

Blood services can utilize a number of mechanisms to address emerging threats. These will often need to be applied at a time when only limited information is available relating to the extent of the threat. Mechanisms include donor exclusion criteria which will often be the primary response to a new threat. These will often be based on geographic considerations and where known should be consistent with known incubation periods for the agents. Testing might also play an important role. For new infections there

will inevitably be a delay before suitable assays are available but the application of nucleic acid-based testing will potentially shorten this. There is also increasing interest in the use of pathogen reduction systems in the management of emerging threats. These technologies will potentially 'disinfect' blood components in the same way as specific viral inactivation procedures have revolutionized the safety of fractionated plasma products. Care will however be needed to ensure that these novel technologies do not introduce new risks or impact adversely on the clinical efficacy of the component itself.

Developing a framework for decision making

Individual blood services should have mechanisms in place to support horizon scanning for emerging threats and also effective systems for timely decision-making. Considerable information is easily accessible through the AABB, US Centre for Disease Control and the websites of major international blood services.

Specific challenges

Arthropod borne viruses (Arboviruses)

These viruses are an important area of current concern. The risk associated with an arbovirus will be determined by a number of factors including the availability of the vector species, the presence of the normal animal hosts and ultimately whether the virus is capable of infecting humans.

The North American response to the West Nile Virus (WNV) is a good example for study. WNV was initially identified in New York City in 1999. The virus quickly established itself and subsequently epidemics have occurred in each year since 2002. This demonstrates the risk these agents can present and also the speed with which blood services working closely with industry can respond [2].

WNV is a flavivirus (RNA enveloped virus) that is spread by infected mosquitoes, Culex species being the most important. Birds are the normal hosts but horses and humans can become infected. WNV was initially described in Uganda in 1937 and has since been reported in a number of countries including those in western and South East Asia, particularly India. Epidemics similar to those that occurred in North America are however uncommon in other geographical areas.

The incubation period for WNV has been reported as being up to 2 weeks. Many cases are asymptomatic. In others, a severe illness including meningitis and encephalitis does however occur and can be fatal. WNV is readily transmitted by transfusion [2]. Nucleic acid testing is used to prevent this in North America. Virus levels are relatively low and hence single donation testing will be more effective than the use of mini-pools. Countries outside of North America predominantly use travel based donor deferrals to minimize the risk of transmission. The Council of Europe Guide recommends a 4 week deferral following return from North America during the mosquito season [3].

The WNV events in North America have raised awareness of the risk associated with other arboviruses. In Asia, current concerns include Dengue and Chikungunya viruses.

Dengue is a flavivirus that is endemic in many parts of Asia, South America and Africa [4]. It is spread by infected Aedes mosquitoes and human to mosquito to human transmission has been demonstrated, i.e. no non human host is needed to maintain the virus. Dengue is now the most frequent arbovirus infection in the world. Symptoms range from mild fever with headache and muscle joint pain to the more serious dengue haemorrhagic fever. Four serotypes of the virus have been reported. Immunity appears to be restricted to each individual serotype. There are currently few reports of transfusion transmitted dengue, these include case reports from Hong Kong in 2002 [5] and Singapore in 2009 [6]. Detection of cases attributable to transfusion will however be problematic in endemic countries during periods when large numbers of cases are occurring in the community. Nucleic acid based tests are currently in development, initial results indicate that during epidemics the virus is detectable in donated blood at rates between 0.04–0.3% [7]. A recent study in Singapore concluded that 'further studies are needed to establish the magnitude of the threat that dengue poses to blood safety in countries where it is endemic' [8].

Chikungunya virus is an alpha virus that is spread by Aedes and Albopictus mosquito species [9]. Similar to dengue this agent can be readily spread via a human-mosquito-human cycle with no requirement for a separate non human vector. Cases of transfusion transmission have not been reported. Mathematical modelling based on sentinel surveillance data, duration of viraemia and the frequency of asymptomatic infection during an epidemic in Reunion Island in 2005-07 however suggests that this might occur [10].

Given the North American experience of WNV, the lack of significant evidence of transfusion transmission of Dengue and Chikungunya is intriguing. A number of possible explanations have been proposed to explain this [9].

Many other arboviruses exist some of which share features with those of WNV, dengue and chikungunya [10]. This is currently a particular concern to authorities in Australia.

Vector borne protozoal infections including malaria

Transmission of malaria by transfusion is well-documented [11]. Systems to prevent malaria transmission based on

either donor exclusion (travel history) or malaria antibody testing are commonly used in non endemic areas/countries. Prevention of transfusion transmission is more problematic in endemic areas. Various strategies have been adopted to reduce but not eliminate the risk. This includes malaria antigen testing and examination of blood films.

Many Asian countries have devoted efforts to eradicate the disease particularly in large urban areas. Considerable success has been achieved. The combined impact of climate change, urbanization and poor sanitation associated with poverty will potentially lead to a re-emergence of the infection. Blood services will need to closely monitor local epidemiology and public health initiatives to ensure that threats are identified early and managed appropriately.

SARS, Influenza viruses and pandemics

The outbreak of Severe Acute Respiratory Syndrome (SARS) in Hong Kong and Canada in 2003 is an excellent example of the impact of a novel agent on blood services. SARS is believed to have emerged in China and then spread rapidly mainly via air travel of infected people. SARS is caused by a coronavirus that was spread by close contact. It was a new human infection believed to have arisen by cross species transmission from infected animals (zoonosis). The virus was detectable in the blood of symptomatic patients. It is unclear as to whether viraemia might occur in asymptomatic cases. Donor deferrals were implemented widely to prevent possible transfusion transmission. These were predominantly travel based in countries with no affected cases and symptom/contact related in those countries with significant numbers of reported cases.

The SARS epidemic has heavily influenced blood services responses to the threat of pandemic influenza. Initial concern focussed on the H5N1 strain of influenza, an avian influenza strain. Epidemics became apparent in poultry populations in many Asian countries during 2004/05. Infected birds appeared capable of infecting humans although infrequently. Occasional clusters of human to human transmission have also been reported. Infections were often serious with significant mortality evident in hospitalised patients [12]. Virus was detectable in the blood of symptomatic patients. The World Health Organisation (WHO) advised national authorities to develop plans to manage a possible pandemic of H5N1.

During June 2009, the WHO has notified pandemic influenza to a new strain of influenza now called novel influenza A H1N1 09. This strain appears to have developed in pigs in Mexico and subsequently passed to humans. The infection spread rapidly across the globe, the number of cases in individual countries has been linked closely to air travel patterns with Mexico [13]. By the end of June 2009, over 70 000 cases had been confirmed worldwide. The infection appears to be relatively mild although over 200 deaths have already been reported.

There have been no documented cases of influenza transmission by transfusion. During a pandemic it will be difficult to identify confidently any such cases. The primary concern for blood services will be the availability of donors. This will in part reflect the direct impact of the pandemic but also potentially a reluctance of healthy donors to donate because of concerns around cross-infection in the donor environment. Pandemic planning within blood services will need to address both of these issues. Pandemic influenza will also impact blood services in other ways. Staff sickness and restrictions on movement will potentially impact adversely on business continuity. Demand for blood products will also be affected. The blood service response to novel influenza H1N1 09 has been inconsistent. Some national blood services initially implemented travel-based donor deferrals. The utility of these quickly became uncertain as the infection spread. Other blood services have emphasized the importance of donors continuing to donate making decisions on donor eligibility only on the absence of influenza type symptoms.

Hepatitis E virus

Hepatitis E virus (HEV) is a non-enveloped RNA virus that is normally spread by the faeco-oral route. Outbreaks are often associated with contaminated water supplies. Transfusion transmission of HEV has been reported in the Hokkaido region of Japan [14]. This was linked to eating poorly cooked pork meat and offal. Sporadic cases of HEV also occur in non-endemic areas. HEV RNA has also been reported in a German plasma donor prior to the onset of an elevated alanine aminotransferase [15]. These sporadic cases are often linked to contact with pigs or pork.

Studies undertaken by the Japanese Red Cross have shown that up to 20% of donors with an elevated ALT, above 500 IU/l will have HEV RNA detectable in their blood [16]. The JRC has developed a NAT-based assay to detect infected donations. Potentially this could be used to screen donations selectively in areas where infection is known to be a problem or potentially all donations.

Hepatitis B virus – occult infections and mutants

Hepatitis B infection (HBV) is endemic in many Asian countries. High prevalence rates inevitably lead to situations where occult HBV will develop. Interest in this area has increased significantly following the availability of nucleic acid based tests capable of detecting low levels of HBV DNA. This is an example of technology leading to an emergence of interest in an area and enabling blood services to intervene to address long standing issues.

Occult HBV infection is defined 'as the presence of HBV DNA in blood or tissues without detectable hepatitis B surface antigen (HBsAg), with or without antibodies to hepatitis B core antigen (anti-HBc) or hepatitis B surface antigen (anti-HBs), outwith the preseroconversion window period' [17]. Many cases are not associated with clinical disease. There is however considerable clinical data to indicate that occult HBV infection can be associated with chronic hepatitis and cirrhosis. Hepatitis B infection can be transmitted by transfusion of blood collected from healthy donors with occult HBV infection. This may reflect 'tail end' carriage of normal HBV infection or might occur due to the presence of mutant forms of the virus that are not easily detected by standard HBsAg assays. Occult HBV infection thus raises a number of questions for blood services in Asia. This extends beyond the question as to whether costly HBV DNA testing should be implemented to include a requirement for careful evaluation of HBsAg assays to ensure both high sensitivity and also to maximize the detection of common mutant forms that exist in the local community.

Concluding comments

Continued vigilance is necessary to ensure that emerging infectious threats are identified and managed in a timely manner. Decisions will often need to be made during a period when only limited scientific and clinical data is available. Specific challenges can be identified for Asia. It is already the most populous continent. Many countries are developing at a rapid pace. This will present new challenges for local blood services. Increasingly however these local issues will take on a more global dimension and no blood service anywhere in the world can afford to be complacent that infections emerging in one part of the world will not quickly present a threat to the security of their blood supply.

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