Current risk for transfusion transmitted infections

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Purpose of review

Blood safety is a topic of continuing concern, and much effort is expended on measures to decrease the risk for transmission of infectious agents via transfusion. At the same time, emerging infections may threaten this safety. A periodic review of risk is therefore appropriate.

Recent findings

The risk for major transfusion transmissible infections continues to decline as a result of continually strengthening interventions and because of more general improvements in public health. More attention is being paid to emerging infections, and recently donor testing has been implemented for West Nile virus and *Trypanosoma cruzi.* Within the period covered by this review, the transmission of variant Creutzfeldt–Jakob disease by transfusion has been confirmed. Our understanding of other agents is improving.

Summary

The estimated risk for transfusion transmitted hepatitis viruses and retroviruses is now vanishingly small, but clinicians should be alert to the possibility of infection with emerging infectious agents, because preventive measures may not be available in all cases.

Keywords

emerging infections, risk, transfusion-transmitted infections

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Abbreviations

CJD	Creutzfeldt–Jakob disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HTLV	human T-lymphotropic retrovirus
WNV	West Nile virus

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Introduction

This review addresses changes in risks for transfusion transmitted infections that have occurred or have been documented since the beginning of 2005. There are now well defined approaches to estimating the residual risk for infection with viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, and human T-lymphotropic retrovirus (HTLV), and current numerical estimates are presented, along with some newer approaches to their estimation [1•]. Continuing attention is being paid to emerging infections [2•], and some definitive studies have been conducted in variant Creutzfeldt–Jakob disease (CJD), human herpesvirus (HHV)-8, West Nile virus (WNV), and sepsis resulting from bacterial contamination; these are all discussed. In addition, new tests for HBV DNA and for antibodies to *Trypanosoma cruzi* (the agent of Chagas disease) have been licensed and partially implemented. Finally, a number of new risks have appeared and are briefly discussed, including hepatitis E, chikungunya, and dengue viruses. An emerging concern for the blood supply is the impact of pandemic influenza, although the major threat is likely to be the adequacy of the blood supply rather than infection risk.

Residual risk for conventional transfusion transmissible agents

In the developed world, there continues to be a downward trend in risk for infections with HBV, HCV, HIV, and HTLV [3,4]. Although there continue to be improvements in test technology, there also appears to be an underlying decline in the prevalence and incidence of these infections in the donor population and, in many cases, in the overall population.

Estimates of residual risk have traditionally been made using the incidence/window period model, but this approach, although generally successful, has two major shortcomings: the need for an accurate definition of the length of the infectious window period, and the difficulty in estimating the incidence of new infection among first time donors. Busch *et al.* [5] used doubling time estimates to arrive at a window period definition and combined this with estimation of incidence using less sensitive serologic tests or nucleic acid testing to establish a new strategy for estimating risk. Using these approaches, they estimated the residual risk for HIV to be 1 in 2.3 million donations, and that for HCV to be 1 in 1.8 million donations; these estimates are somewhat lower than those reported by Dodd *et al.* in 2002 [3]. In addition to direct estimates of risk, it appears that the residual risk for HTLV-I/II

infection (previously estimated at 1 in several millions) is also very low, based on the potential yield of lookback [6•]. In another report, Busch [1•] compared different methods of estimating risk and found them all to be broadly similar. Studies from the UK [7] and Australia [8] have shown even lower levels of residual risk. An alternate approach based on the extent to which testing is incomplete has been reported for South America [9], and may be applied in developing countries. A study of risk, based on segmentation of the donor population, has also been reported for South Africa [10•].

The situation for HBV is not quite as clear because the tools for defining incidence rates generally require additional assumptions that are not well validated; it is also thought that more attention needs to be given to testing [11]. Additional information about infectious risk from HBV is emerging from carefully conducted lookback studies in Japan, which show that infectivity may be associated with low DNA levels early in infection but is less likely in later stages of infection [12••]. Lookback for HBV is not currently performed in the USA and this may contribute, at least in part, to the low frequencies of observed cases of post-transfusion hepatitis B. It does, however, appear that only a few of those cases that are reported truly reflect transmission by transfusion, as noted in an editorial by Stramer [13], quoting work from the US Centers for Disease Control and Prevention. Over the past 2 years, one multiplex test for the detection of HBV DNA (along with HIV and HCV RNA) in donor blood has been licensed, and another multiplex assay is available, although its claims for HBV detection have not yet been accepted by the US Food and Drug Administration. The use of nucleic acid testing for HBV DNA is somewhat controversial, because the sensitivity of available tests, when they are used on pools, is very similar to that of advanced tests for hepatitis B surface antigen [13]. Nevertheless, routine use of HBV nucleic acid testing does appear to generate a yield of around 1 detection per 350 000 serology-negative donations; this figure is compatible to at least some estimates of residual risk for HBV [14]. Finally, there is some increasing concern about so-called occult HBV infection, in which DNA can be detected in chronically infected individuals in the absence of detectable levels of hepatitis B surface antigen [15,16,17•].

Variant Creutzfeldt–Jakob disease

One of the concerns surrounding variant CJD was that it might be transmissible by transfusion. This was based on the close association of the variant CJD prion with lymphoid tissue, on its differences from classic CJD, and on animal model studies that demonstrated such transmission. Now, the risk has been clearly confirmed by the recognition of four cases of transmission of variant CJD infection in England [18••,19–23]. Three of these cases have been reported and one has been reported by the health ministry. In all cases the infection was transmitted from an individual who developed variant CJD some 17–42 months after donation. One donor transmitted twice. In three cases variant CJD developed in the recipient some 6–8 years after the transfusion, and in the fourth case the recipient died from a different cause but was found to have the variant CJD prion in the spleen and one cervical lymph node. Interestingly, this case was heterozygous (methionine–valine) at codon 129 of the prion protein gene, whereas all other clinical cases have been homozygous (methionine–methionine). These cases have been interpreted as indicating at least a 4 in 66 and potentially a 4 in 17 risk for transmission of the variant CJD prion from presymptomatic cases.

It is not known how many people may be at risk for transmitting the prion, but some estimates have been made from studies of the frequency of variant CJD prions in excised tonsils and appendices in England, with three positives found among 12 674 samples examined [24,25•]. This suggests that there may be as many as 237 silently infected individuals per million in the UK. In contrast, there continues to be no evidence of transmission of classic CJD by transfusion. Recent lookback reports from the UK and the USA have shown no CJD among a total of 314 recipients of blood from 36 donors who subsequently developed CJD [18••,26,27]. There is a statistically significant difference between the variant CJD and CJD observations ($P < 0.001$).

A potential approach to reducing the infectious prion content of red cell concentrates has been reported by two groups. Affinity methods are used to remove prions directly via a filtration process [28,29•]. The two methods have proceeded to the point of 'CE' marking in Europe, but the extent (if any) of their future use has not yet been determined. The methods have been shown to reduce the infectivity of exogenous infectious prions from brain tissue, spiked into red cells, by about 4 $\log_{10}$, and in one case reduction in endogenous infectivity from the blood of infected hamsters has been shown. The levels of infectivity are low, and therefore it has not been possible to show removal beyond about 1.2 $\log_{10}$ [29•].

Human herpesvirus-8

HHV-8 is another agent that has attracted some concern regarding blood safety. This virus is the causative agent of Kaposi's sarcoma and possibly of some other malignancies. Until recently, there had been presumptive evidence suggesting that the virus might be transmissible by transfusion. In 2005, Dollard *et al.* [30] reported a study that suggested that there had been two HHV-8 seroconversions in a cohort of 284 highly transfused cardiac surgery patients, for a risk of 0.082% per unit transfused. It was not possible, however, to link these apparent

infections to specific seropositive donors, and neither was the frequency of infection found to be significantly different from that in a nontransfused population. Subsequently, Hladik *et al.* [31••] reported on a study conducted in Uganda that clearly demonstrated significantly increased risk (amounting to about 2.8% per seropositive unit) of acquisition of HHV-8 infection among seronegative recipients of seropositive units.

Taken together, these studies clearly demonstrate that transfusion transmission of this virus can occur. The appropriate response to these findings is not clear, however, because the true frequency of transmission of HHV-8 is undefined, the consequences of such transmission are not apparent, and there is as yet no clearly appropriate test [32,33•]. Furthermore, the studies discussed here did not involve the use of leukoreduced blood, which might carry significantly lower transmission risk.

Bacterial contamination in platelets

Driven by voluntary standards, blood collectors in the USA have followed the lead of a number of other countries and have implemented methods to detect bacteria in platelet components. Although a variety of methods are used for whole blood derived platelets, most apheresis platelets are subjected to culture, most frequently using automated instruments originally designed for routine blood culture. These methods have provided a means of assessing the frequency of those levels of contamination that are detectable by culture 24 h after collection of the platelets. Overall, confirmed positive (i.e. repeatable) cultures are found in about 1 in 5000 platelet collections [34••,35]. Evaluation of the frequency of septic outcomes among platelet recipients, however, has shown that culture has not eliminated this problem, although it appears to have been reduced by about a half, to two fatal cases per million. An additional finding of this study was that double-arm apheresis procedures were disproportionately associated with implicated platelets, and further investigation revealed that such procedures involved a sample collection pouch on the return arm [34••]. At the same time, Canadian and Dutch studies clearly demonstrated the value of diversion pouches in reducing sepsis associated with skin bacteria by more than 50% [36,37•].

Trypanosoma cruzi

In late 2006, an enzyme immunoassay for the detection of antibodies to *T. cruzi* was licensed for screening blood donations. At the time of writing there had been no comprehensive published report on the results of using the test. Data have been reported, however, by the US Centers for Disease Control and Prevention [38•], at a Food and Drug Administration Blood Products Advisory Committee meeting [39], and on a web-site maintained by the AABB (formerly known as the American Association of Blood Banks) [40]. As a result of several months of testing about 65% of the US blood supply, it has been shown that 1 in approximately 25 000–30 000 donors has confirmed positive results. The majority of infected donors have been identified in Florida and California, but some have also been detected in 24 other states. Even so, there are still only seven documented cases of transfusion transmission of the parasite in the USA and Canada, with the most recent case occurring in Rhode Island [41].

This low number is something of a puzzle, because the testing data imply that, until recently, several hundred seropositive components were transfused each year. Lookback studies have not demonstrated infections either, at least until now, with one exception [42]. A recent study from Mexico [43•], however, clearly demonstrated four infections among nine recipients of seropositive whole blood or platelet concentrates. Whole blood is rarely used in the USA, and few lookbacks have involved platelets. Enhanced attention, brought about by the availability and use of the screening test, will probably lead to the detection of more transmissions and a better assessment of risk in the USA. It is also of interest to note that there have been a number of transmissions of *T. cruzi* by organ transplantation [44,45].

West Nile virus and other viruses

The appearance, evolution, and management of the WNV epidemic in the USA have been remarkable. Recognition of the transmissibility of this virus by transfusion came in 2002, with a total of 23 reported cases, but two different donor screening tests for WNV RNA were developed and implemented before the onset of the 2003 season [46]. Within the first 2 years of testing, 540 viremic donations had been identified and withheld from use in the Red Cross system. Although this test is usually conducted on small pools of samples, a process of conversion to single donor testing, triggered by the appearance of a given number or frequency of infected donors in a given area, had been very effective in reducing the number of transmissions to very low levels. Indeed, no cases were reported in 2004 and 2005, although a single donor did infect two patients in 2006 [47]. These latter cases could perhaps have been prevented by earlier adoption of single donation testing by the involved blood collection organization.

Experience with WNV has increased concern about other similar viruses and their threat to transfusion safety. In particular, there has been focus on dengue virus, with a number of ongoing studies evaluating the frequency of viremic donations in areas endemic for the virus [48] (Stramer SL, personal communication, 2007). To date, however, the findings have been presented only in abstract form. It is nevertheless clear that such viremic

donations may be found at meaningful frequencies in selected areas. There has also been a large outbreak of chikungunya virus infection, particularly in the Indian Ocean area [49•]. Although no cases of transfusion transmission of this virus have been reported, significant precautions, including import of blood from the (European) mainland, testing, and viral inactivation, have been introduced in the French overseas Department of Reunion. A number of imported cases among travelers have been identified in the USA [50].

The possibility of an influenza pandemic has attracted significant attention, in large part as a result of the number of fatal human infections with the highly pathogenic H5N1 avian influenza virus. Although this virus is not readily transmitted from person to person, a number of such transmissions have occurred. Furthermore, there is some evidence of a viremic phase among symptomatically infected persons. This has raised concern about blood safety in the event of a pandemic, although it is unclear whether such viremia would also occur if the virus developed the characteristics necessary for the development of a such a pandemic. Even if the virus is not transmissible by blood, a pandemic approaching the scale of the 1918 outbreak would have a profound impact on blood availability, although its impact on usage is not so clear [51•].

Finally, hepatitis E virus, which is another virus that causes only acute infections, has been shown to be transmissible by transfusion in three widely separated instances in Japan, England, and France [52–54].

Malaria and babesiosis

Malaria currently offers little risk to blood recipients in the USA, with fewer than one case of transfusion transmitted malaria per year recently reported [55]. Even with increasing travel, the trend continues downward. The principal intervention is questioning donors about their recent travel to or residence in areas endemic for malaria. This approach results in the deferral of many donors, however (more than 100 000 per year in the USA); many of them never return to give blood. In addition, the required questioning is complex and subject to error. In some countries, although questioning is conducted, those donors with a positive history are subjected to serologic testing for plasmodial infection and, if nonreactive, they are returned to the donor pool [56,57]. Although this approach is an improvement, it may be preferable to eliminate questioning altogether by implementing a suitable test. At the current time, however, a test that would satisfy the requirements of the Food and Drug Administration is not yet available in the USA.

Babesia parasites are similar in many ways to malaria, but they are usually transmitted by ticks. *Babesia microti*, which is endemic in some north-eastern coastal areas and in the upper Midwest of the USA, is quite frequently transmitted by transfusion, with more than 50 recorded cases. The actual risk for transmission has been shown to be in the order of 1 case per 1000 units in parts of Connecticut. Despite this, no routine test is available and other interventions have limited efficacy [58••]

Conclusion

It is clear that the risk for the familiar transfusion transmitted infections is declining, both in the developed and the developing world. This is due in large part to a continuing focus on improvements in donor selection and testing, along with a commitment to quality systems. In addition, in the developed world at least, the frequency of these infections continues to decline in the population at large, thanks to enhanced public health and educational measures. The emergence of new or mutant strains of these agents offers a potential threat to this progress, however, particularly in circumstances in which such strains evade detection by standard test methods.

Increased attention is being given to emerging infections, some of which are actually or potentially transmissible by transfusion. Most of these emerging infections are zoonoses and they almost all challenge previous expectations that new transfusion threats would have epidemiologic patterns similar to those of hepatitis B and HIV. In some cases, such as WNV, there has been a remarkably rapid response, with implementation of donor screening tests within a short time. In contrast, tests for *T. cruzi* have been developed and implemented over a much longer time frame. Other infections, even those of longstanding, such as babesiosis, have received little attention, and no test or effective intervention is available.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 707).

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