



**American
Red Cross**

PLUS

AN EDUCATIONAL RESOURCE PUBLISHED BY AMERICAN RED CROSS BLOOD SERVICES | SUMMER 2010



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Researchers Examine XMRV in Blood Cells of Chronic Fatigue Syndrome Patients

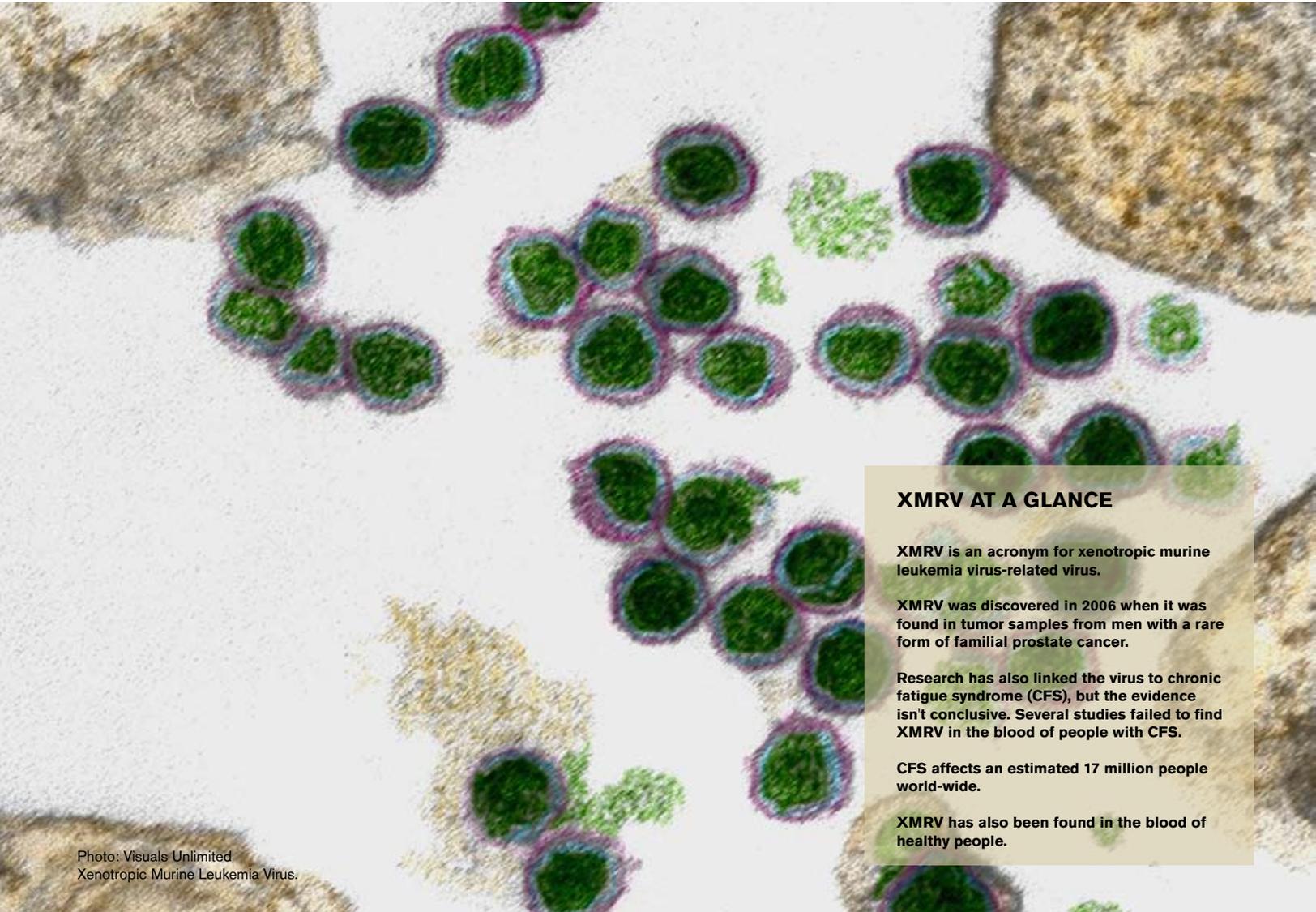


Photo: Visuals Unlimited
Xenotropic Murine Leukemia Virus.

XMRV AT A GLANCE

XMRV is an acronym for xenotropic murine leukemia virus-related virus.

XMRV was discovered in 2006 when it was found in tumor samples from men with a rare form of familial prostate cancer.

Research has also linked the virus to chronic fatigue syndrome (CFS), but the evidence isn't conclusive. Several studies failed to find XMRV in the blood of people with CFS.

CFS affects an estimated 17 million people world-wide.

XMRV has also been found in the blood of healthy people.

There is little consensus in the medical community on whether chronic fatigue syndrome (CFS) is a distinct disease.

As its name implies, the condition is characterized by debilitating fatigue persisting for many years, and it affects as much as 17 million people, which equates to about 1% of the world's population.

Although chronic inflammation is often found in these patients, no infectious or toxic agent has been clearly implicated in this syndrome, which is diagnosed largely by excluding other conditions that cause similar symptoms.

Researchers have detected xenotropic murine leukemia virus-related virus (XMRV) in about two-thirds of patients diagnosed

with CFS. Cell culture experiments revealed that patient-derived XMRV is infectious and that both cell-associated and cell-free transmission of the virus are possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines after their exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients. These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS.

Both laboratory and epidemiological studies are needed to determine whether this virus has a causative role, not only in this syndrome, but perhaps in others as well.

Lombardi VC, Ruscetti FW, Das Gupta J, Pfof MA, Hagen KS, Peterson DL, Ruscetti SK, Bagni RK, Petrow-Sadowski C, Gold B, Dean M, Silverman RH, Mikovits JA. Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome. *Science*. 2009. 326:585-589.

What is XMRV?

XMRV is a newly identified human retrovirus that is similar to a mouse retrovirus that scientists have known about for years. XMRV refers to xenotropic murine leukemia virus-related virus. It was first identified in samples of human prostate cancer tissue. Some additional studies have suggested that a high percentage of persons with chronic fatigue syndrome (CFS) may be infected with XMRV, but this result needs to be confirmed by other groups of scientists.

The frequency of XMRV infection in healthy persons and the potential role of this virus in causing diseases such as prostate cancer and CFS are unknown at this time. If it is determined that XMRV may have a role in causing disease and illness, prevention recommendations can be made.

How is XMRV transmitted? Are certain individuals more likely to be infected with the XMRV virus?

The manner in which XMRV is transmitted is unknown. It is unclear whether certain individuals are more likely to be infected with XMRV. Studies of XMRV have been under way for only a short time, and therefore, these and similar questions have not been answered.

If researchers find that XMRV is found in a majority of patients who have CFS, does this mean that CFS may be contagious?

One study that has been conducted on CFS and close contacts suggests that there is no evidence that CFS is contagious or spread person to person. Occurrence of CFS is not more common in family members of patients with CFS, and none of the features typical of contagious disease have been associated with CFS. These features include seasonal or regional occurrence, travel history, occupation, exposure to animals, injection drug use, and sexual behavior.

Since a recent study reported finding XMRV in healthy persons, can XMRV be transmitted through blood transfusion or organ/tissue transplantation?

This possibility will be studied carefully. At present, we do not know whether XMRV can be transmitted through blood transfusion. Since XMRV is thought to infect many types of human cells, including some blood cell types, the safety of blood could be a concern if XMRV infection is confirmed to cause human disease.

What is being done to evaluate the risk of transmission of XMRV through blood transfusion or organ transplantation?

Several studies are under way to evaluate the risk of XMRV transmission through blood transfusion. The Department of Health and Human Services (HHS) is conducting studies to determine the prevalence of XMRV in the blood donor population. In addition, HHS scientists are working with scientists in industry and academia to determine if XMRV can be transmitted by blood transfusion. If a link between XMRV and transfusion is established, action will be taken to reduce the risk.

Additionally, a Public Health Service (PHS) working group plans to coordinate testing of specimens to assess transfusion-transmissibility of XMRV. If an agent is found to be transmissible by blood, studies must begin quickly to evaluate if the agent causes disease in transfusion recipients.

If researchers have a test for XMRV, why can't it be used for diagnosis and screening of blood donors?

At present, although it is theoretically plausible that XMRV can be transmitted through blood transfusion, no such transmission has been identified, and there is no known evidence of XMRV infection or XMRV-related illness in transfusion recipients. Therefore, there is currently no requirement for testing of the blood supply for the presence of XMRV.

HHS scientists are working with scientists in industry and academia to determine if XMRV can be transmitted by blood transfusion. If a link between XMRV and transfusion is established, action will be taken to reduce the risk. Such a risk, if it exists, could be decreased by developing and using blood donor screening assays or other measures. The use of a donor screening assay by blood establishments would require U.S. Food and Drug Administration (FDA) approval of the test.

There are many steps between what is currently known about XMRV and the release of an FDA-approved test, if such a test were warranted. The test components and procedures must be standardized, and the test performance assessed in research studies before licensure (approval) by the FDA. However, if the risk is demonstrated, these steps could be taken more quickly, as occurred for screening approval of West Nile virus.

Is it possible to determine whether XMRV can be transmitted via blood transfusion, without waiting for it to occur in a patient?

Yes. There are several steps necessary to evaluate if a new infectious agent presents a threat to transfusion recipients. HHS scientists are taking these steps by working with scientists in industry and academia to determine if XMRV can be transmitted by blood transfusion.

The first step is to determine whether the agent is present in the blood supply by looking at the fraction of blood donors who have the infectious agent in their blood. Next, it is also important to determine the risks of the blood components themselves to spread infection, since preparation and storage may impact these risks (e.g., filtering out white blood cells or refrigerating a blood unit may decrease the risk of an infectious agent).

If the agent is found to be in the blood supply, the second step is to evaluate whether it is transmitted by transfusion. To do this, investigators can use animal studies, case report investigations, and the evaluation of biological specimens that have been collected and stored in repositories for this purpose.

For more information, please see www.cdc.gov/ncidod/dhqp/bp_xmrv_qa.html

-CDC

Researchers Detect No H1N1 in Blood Donated Before Onset of Flu

Researchers from the Japanese Red Cross Society Blood Service could find no evidence of the pandemic H1N1 2009 virus in plasma and red blood cell (RBC) samples taken from 96 blood donors who had symptoms of the flu within seven days after donating. Although no cases of transfusion-transmitted influenza have been published, evidence exists of brief viremia before onset of symptoms. The Tokyo-based team attempted to identify the viral genome in the donated blood products by using nucleic acid amplification technology (NAT).

From June to November 2009, blood samples were collected from plasma and RBC products that had been processed from donations; post-donation information indicated diagnosis of H1N1 infection soon after donation. Of the 96 donors, 20 were diagnosed with the H1N1 virus within one day after donation; another 20 were diagnosed with it within two days post-donation. Viral (RNA) was extracted from plasma samples and RBC fractions. RNA samples were subjected to real-time reverse transcription-PCR of hemagglutinin and matrix genes of influenza A using PRISM 7900. The RT-PCR of HA was specific for pandemic H1N1 virus, whereas the RT-PCR of M was designed to detect both pandemic and seasonal influenza viruses.

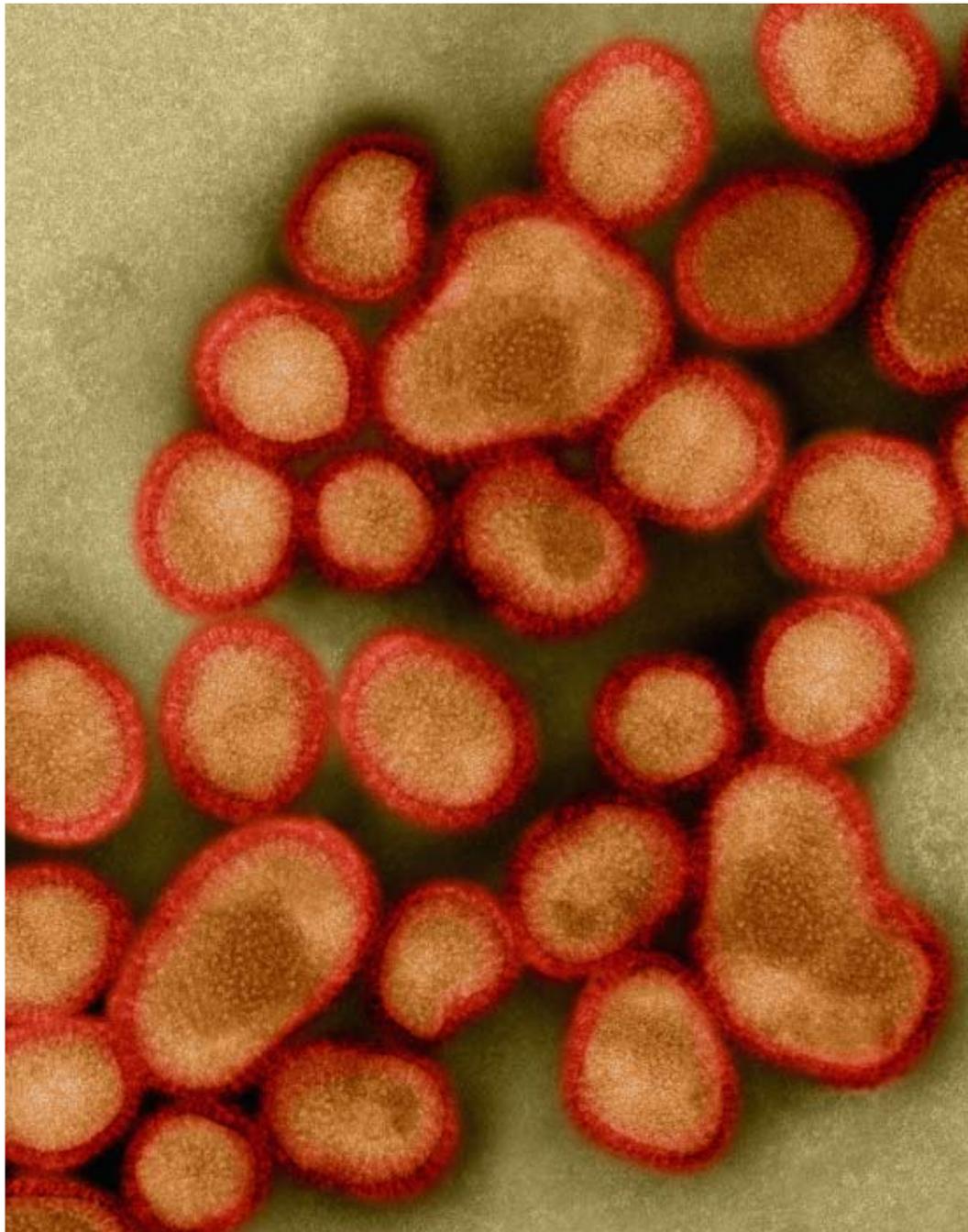
The sensitivity of the NAT system was checked by spiking experiments. Viral particles of virus donated by the National Institute of Infectious Diseases were spiked into plasma and RBC samples from healthy volunteers. Viral RNA was detected in the plasma samples spiked with viral particles corresponding to 300 genome equivalents per milliliter (mL) and in the packed RBC samples spiked with viral particles corresponding to 3,000 genome equivalents/mL.

The results, published in the journal *Emerging Infectious Diseases*, showed that H1N1 was not found in any samples tested, though it was consistently detected in the external control.

"These results suggest that the viremia with pandemic (H1N1) 2009 virus, if any, is very low and can be missed by current NAT or that the viremic period is too brief to identify viremia," the

authors conclude. "Although the risk for transmission of pandemic influenza by transfusion seems to be low, further investigation is needed to elucidate this risk."

Matsumoto C, et al. Risk for transmission of pandemic (H1N1) 2009 virus by blood transfusion [letter]. *Emerg Infect Dis.* 2010 [Ahead of print.]



Negative stain electron micrograph of the Swine Influenza Virus. TEM X29,800
Photo: Visuals Unlimited

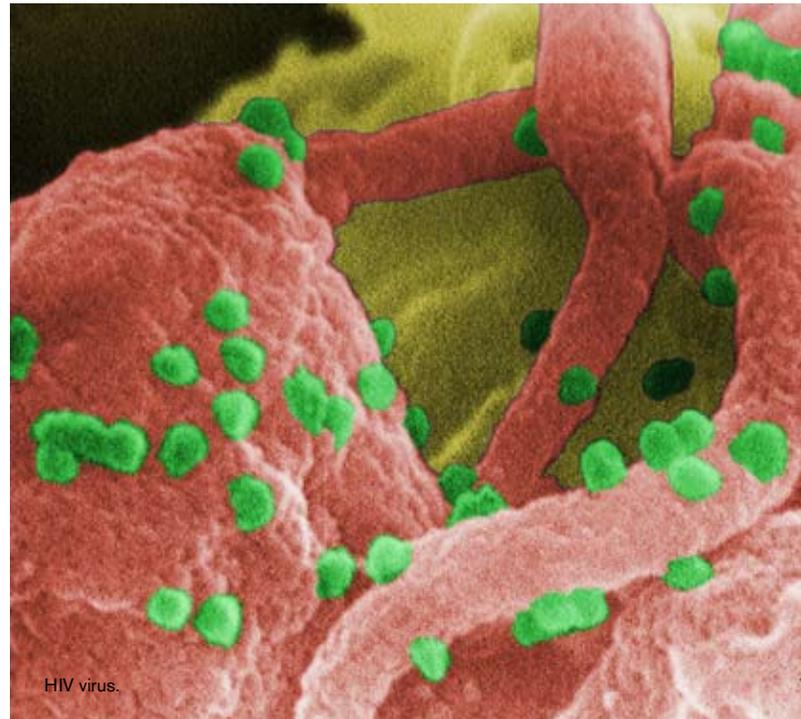
Study Looks At HIV and HCV Infections Among US Blood Donors Since the Introduction of Nucleic Acid Testing

Nucleic acid testing (NAT) for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) was introduced for blood donation screening in the United States in 1999. An American Red Cross Biomedical Services study analyzes temporal trends of these two infections since NAT introduction.

Donation data from 1999 to 2008 were analyzed; each donation was tested for antibodies and viral RNA for HIV and HCV. Incidence for first-time (FT) donors was derived by multiplying that among repeat (RP) donors by the ratio of NAT yield rates between FT and RP donors. Incidence for all donors was the weighted mean based on percentage of FT and RP donors. Residual risk (RR) was determined using the window-period model.

During the 10-year period approximately 66 million donations were screened with 32 HIV (1:2 million) and 244 HCV (1:270,000) NAT yield donations identified. HCV prevalence among FT donors decreased by 53% for 2008 compared to 1999. HIV and HCV incidence among RP donors increased in 2007 through 2008 compared to 2005 through 2006. During 2007 through 2008, HIV incidence was 3.1 per 105 person-years (py), with an RR estimate of 0.68 per 106 (1:1,467,000) donations; HCV incidence was 5.1 per 105 py, with an RR estimate of 0.87 per 106 (1:1,149,000). The increase in HIV incidence was primarily among 16- to 19-year-old, male African American donors and that in HCV was primarily among Caucasian donors of 50 or more years. Donors from the Southern United States had higher incidence rates.

The study concluded HCV prevalence decreased significantly since NAT introduction. The increase in HIV and HCV incidence in 2007 through 2008 warrants continued monitoring and investigation.



Zou S, Dorsey KA, Notari EP, Foster GA, Krysztof DE, Musavi F, Dodd RY, Stramer SL. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion*. 2010. [Ahead of print].

Study Compares Two Robotic Platforms to Screen Plateletpheresis Donors for HLA Antibodies as Part of a TRALI Mitigation Strategy

Efforts to minimize white blood cell alloantibodies, responsible for transfusion-related acute lung injury (TRALI) in components with high-volume single-donor plasma include consideration of plateletpheresis donor screening for human leukocyte antigen (HLA) antibodies. High-throughput screening platforms make this feasible for large blood centers. Important questions include: Which platforms should be used? Which donor subgroups should be screened? What are the characteristics of detected antibodies? What is the operational impact of deferring reactive donors?

American Red Cross Biomedical Services scientists screened 2,462 plateletpheresis donor sera for HLA antibodies on automated instruments using HLA Class I and II enzyme-linked immunosorbent assays (ELISA) or a mixed Class I/II Luminex flow analyzer. Screen-reactive samples were further tested by manual Luminex single-antigen assay to determine antibody specificity, estimated corresponding antigen frequency, and signal strength.

Alloexposed females had the highest reactivity rate on both platforms (21.0%), with much lower rates for nonexposed individuals or transfused males (1.4%-5.4%). Increasing parity and more recent pregnancy increased their likelihood of screen reactivity. Deferring screen-reactive parous females would result in at least a 4.8% plateletpheresis donor base decrement. Supplemental testing showed higher rates of nonspecific or natural antibodies in ELISA screen-reactive alloexposed females (2.5%) than Luminex (0%). Both assays were more likely to identify antibodies directed against a larger number of HLA antigens and/or of presumed higher titer in alloexposed donors.

The researchers concluded that a strategy screening only parous female donors is reasonable. Both automated HLA antibody detection platforms are easy to use and preferentially identify alloexposed individuals with antibodies of presumed higher titer directed against more recipient HLA antigens.

Vassallo RR, Hsu S, Einaron M, Barone J, Brodsky J, Moroff G. A comparison of two robotic platforms to screen plateletpheresis donors for HLA antibodies as part of a transfusion-related acute lung injury mitigation strategy. *Transfusion*. 2010. [Ahead of print].

Study Reviews Deceased Recipients of vCJD-Implicated Blood Transfusions

To date, four instances of probable transfusion-transmission of variant Creutzfeldt-Jakob disease (vCJD) infection have been described, and surviving recipients of vCJD-implicated blood components have been informed that they may be at risk of vCJD. Nearly two-thirds of all recipients of vCJD-implicated blood components are deceased, and many died before the vCJD risk was known.

The primary aim of this study was to determine retrospectively whether there was evidence that any of the other deceased recipients of vCJD-implicated blood components had any clinical signs or symptoms suggestive of vCJD in life. In addition, pathological material from recipients, stored at the time of surgery or autopsy, was sought to allow testing for evidence of vCJD infection. Another purpose of the study was to obtain information on invasive healthcare procedures undertaken on recipients following the transfusion to identify the potential for onward transmission of infection.

A review of medical case notes of deceased recipients of vCJD-implicated blood components was carried out, and relevant information was extracted. In cases undergoing post-mortem, details of the findings were obtained. The medical case notes of 33 (83%) deceased recipients of vCJD-implicated blood components, not already known to be infected with vCJD, were reviewed. The median age of recipients was 68 years (interquartile range 57-79 years). Almost half (16) were male. The median time from transfusion to death was 175 days (interquartile range 43-701 days). Most (66%) recipients died in hospital. None of the recipients had documented evidence of clinical signs or symptoms suggestive of vCJD. Only two recipients, both of whom died within a year of transfusion, underwent autopsy examination. Neither brain nor peripheral lymphoreticular tissue was available from either recipient, and pathological material was unavailable from any of the other deceased recipients. Almost half of all recipients underwent at least one invasive healthcare procedure post-transfusion.

A retrospective review of the medical case notes of the deceased recipients of vCJD-implicated blood components found no evidence that any further cases expressed clinical signs or symptoms suggestive of vCJD during life, but only four of the recipients survived for more than 5 years post-transfusion.

Gillies M, Chohan G, Llewelyn CA, MacKenzie J, Ward HJ, Hewitt PE, Will RG. A retrospective case note review of deceased recipients of vCJD-implicated blood transfusions. *Vox Sang.* 2009. ;97:211-8



CREUTZFELDT-JAKOB DISEASE (CLASSICAL AND VARIANT FORMS) AT A GLANCE

* Classical Creutzfeldt-Jakob disease (CJD) affects about one person in every one million people per year worldwide.

* In the United States, there are about 200 cases per year.

* Classical CJD usually appears in later life and runs a rapid course. Typically, onset of symptoms occurs about age 60, and about 90 percent of patients die within 1 year.

There are three major categories of CJD:

* In sporadic CJD, the disease appears even though the person has no known risk factors for the disease. This is by far the most common type of CJD and accounts for at least 85 percent of cases.

* In hereditary CJD, the person has a family history of the disease and/or tests positive for a genetic mutation associated with CJD. About 5 to 10 percent of cases of CJD in the United States are hereditary.

* In acquired CJD, the disease is transmitted by exposure to brain or nervous system tissue, usually through certain medical procedures. There is no evidence that CJD is contagious through casual contact with a CJD patient. Since CJD was first described in 1920, fewer than 1 percent of cases have been acquired CJD.

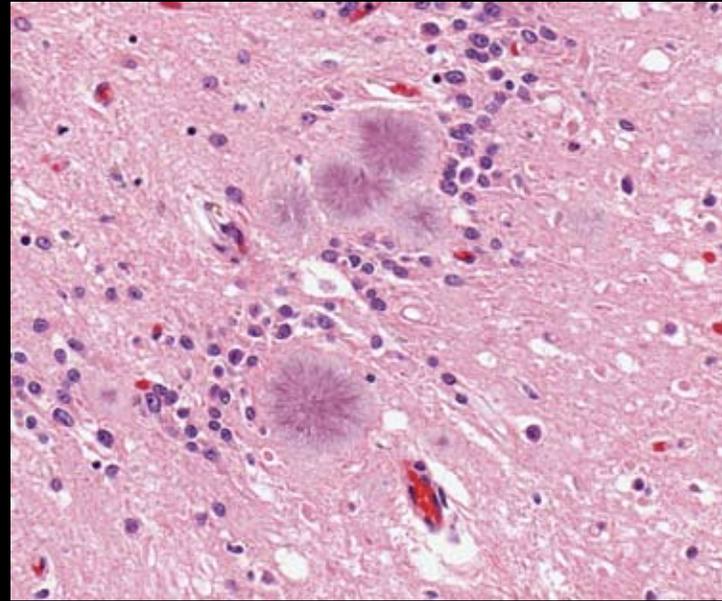
* Variant Creutzfeldt-Jakob disease, or vCJD, is a very rare, fatal disease that can infect a person for many years before making them sick by destroying brain cells.

* Eating beef and beef products contaminated with the infectious agent of bovine spongiform encephalopathy (BSE) is the main cause of vCJD.

* Most cases of vCJD have occurred in the United Kingdom (UK).

* As of April 2007, there have been 202 individuals with vCJD reported worldwide, 165 of them in the UK, 3 in the US.

Case Report: Variant Creutzfeldt-Jakob Disease in a Transfusion Recipient: Coincidence or Cause?



Through the United Kingdom Transfusion Medicine Epidemiology Review (TMER) the fate of blood donations from individuals who develop vCJD is traced and recipients of labile components are identified. The details of recipients are cross-checked with the register of vCJD cases held at the National CJD Surveillance Unit (NCJDSU) to identify any linkage between donors and recipients. In the reverse study, when individuals with vCJD are found to have a history of blood transfusion the donors of the transfused blood components are traced and their details cross-checked with the vCJD register to identify any missed or unrecognized linkage between donors and recipients. A case of vCJD has been identified with a history of blood transfusion in infancy. The donors who provided the components transfused cannot be identified, but a blood donor known to have donated blood to another individual who subsequently developed vCJD could have been a donor to the index case. The at-risk donor is alive 20 years after the relevant donation and continued to donate for some years, until identified as at risk, with 27 other blood components issued for use in patients, none of whom are known to have developed vCJD. Circumstantial evidence has raised the possibility that the case in this report represents a further instance of transfusion transmission of vCJD. However, detailed investigation indicates that the pattern of events may have occurred by chance and disease in this individual may have been caused by transmission of bovine spongiform encephalopathy infection, as is the presumed cause in other primary cases of vCJD.

Chohan G, Llewelyn C, Mackenzie J, Cousens S, Kennedy A, Will R, Hewitt P. Variant Creutzfeldt-Jakob disease in a transfusion recipient: coincidence or cause? *Transfusion*. 2010. [Ahead of print].

Study Examines Transfusion Premedication to Prevent Acute Transfusion Reactions

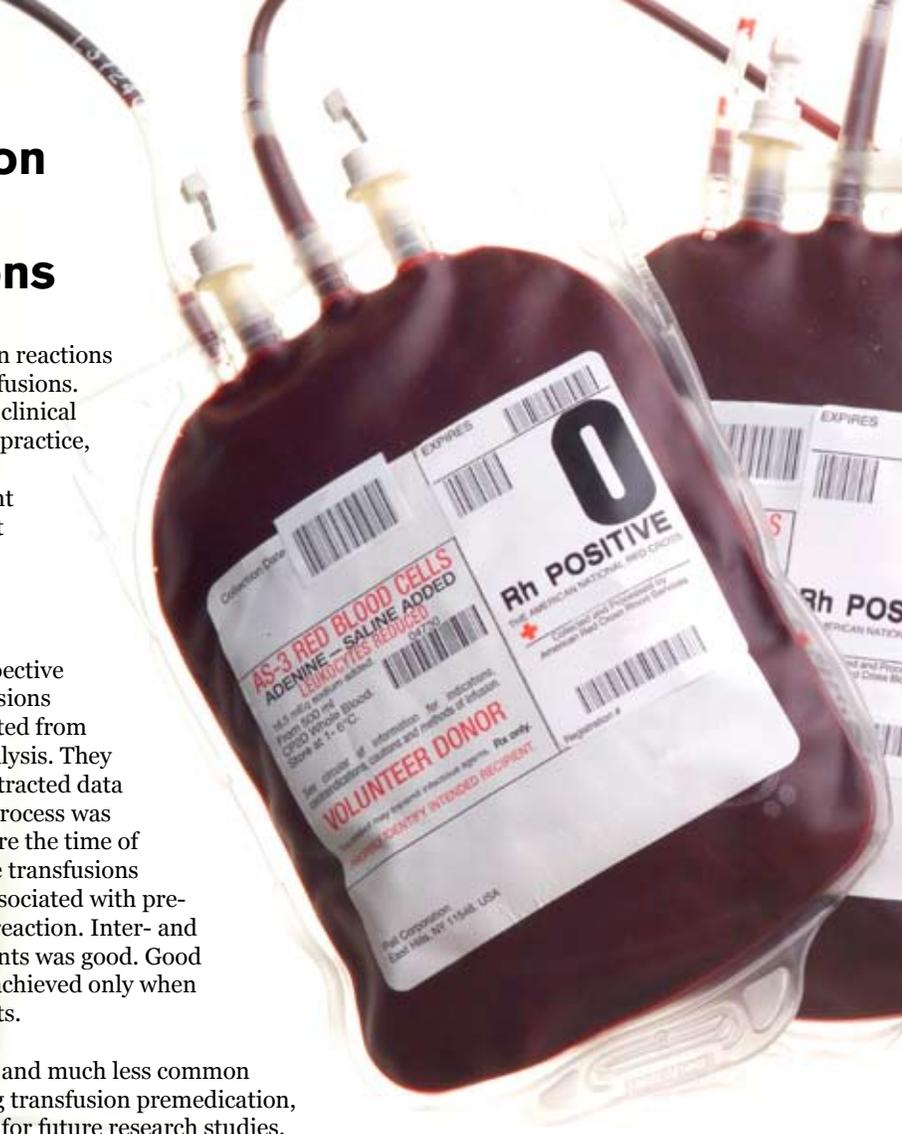
The use of premedication to prevent acute transfusion reactions has been estimated to occur in 50% to 80% of transfusions.

While this practice has some biologic rationale, few clinical studies have been performed to assess the efficacy of this practice, and the methodologic quality of these studies is variable. The primary objective of this study was to describe current practices regarding transfusion premedication to prevent febrile nonhemolytic transfusion reactions, mild allergic transfusion reactions, and transfusion-associated circulatory overload.

Canadian researchers conducted an observational retrospective chart review of a stratified random sample of 324 transfusions that took place over a 6-month period. Data were abstracted from medical records and then scanned into a database for analysis. They calculated inter- and intraobserver agreement on key abstracted data to estimate assessment error. A two-phase adjudication process was used to determine whether or not medications given before the time of each transfusion were intended as premedications. Of the transfusions sampled, 1.6% (95% confidence interval, 0.4-3.9) were associated with pre-transfusion medications to prevent an acute transfusion reaction. Inter- and intraobserver reliability in the abstraction of key data points was good. Good agreement in adjudicator classification of outcomes was achieved only when adjudicators were provided with patient source documents.

The researchers found premedication use was infrequent and much less common than previously reported. Improved methods of capturing transfusion premedication, which likely require prospective assessments, are needed for future research studies.

Fry JL, Arnold DM, Clase CM, Crowther MA, Holbrook AM, Traore AN, Warkentin TE, Heddle NM. Transfusion premedication to prevent acute transfusion reactions: a retrospective observational study to assess current practices. *Transfusion*. 2010. [Ahead of print].



Study Assesses Allergic Transfusion Reactions from Blood Components Donated by IgA-deficient Donors with and without anti-IgA

IgA deficiency is common (1/500) and up to 40% of affected individuals will develop anti-IgA. A few studies suggested that passive transfusion of anti-IgA was not associated with an increased risk of allergic reactions. This study was designed to assess the safety of transfusing blood components containing anti-IgA.

IgA-deficient blood donors with and without anti-IgA were identified from Héma-Québec's (HQ) computerized database. IgA deficiency was confirmed by an ELISA method and the presence of anti-IgA by a passive hemagglutination assay. Blood donations from IgA-deficient donors issued to hospitals between March 1999 and December 2004 were retrieved. Medical charts of recipients were reviewed for the occurrence of a suspected transfusion reaction. Presence and nature of transfusion reactions were assessed blindly by an adjudicating committee.

A total of 323 IgA-deficient blood products were issued by HQ to 55 hospitals. Of these, 48 agreed to participate [315 blood products (97.5%)]. A total of 272 products were transfused: 174 contained anti-IgA, and 98 did not. Only two minor allergic reactions occurred in each group. Incidence of allergic reactions was 1.15% in the anti-IgA group and 2.04% in the group without anti-IgA ($P = 0.91$). There was no anaphylactic reaction in either group.

This study indicates that the proportion of allergic reactions does not appear to be greater in recipients of blood components containing anti-IgA compared to recipients of non-anti-IgA-containing components. The researchers concluded that allowing donations from IgA-deficient donors with anti-IgA may therefore be contemplated.

Robitaille N, Delage G, Long A, Thibault L, Robillard P. Allergic transfusion reactions from blood components donated by IgA-deficient donors with and without anti-IgA: a comparative retrospective study. *Vox Sang* 2010. [Ahead of print]



Six Strategies to Further Reduce Allogeneic Blood Transfusion-Related Mortality

After reviewing the relative frequency of the causes of allogeneic blood transfusion-related mortality in the United States today, researchers presented 6 possible strategies for further reducing such transfusion-related mortality:

1. Avoidance of unnecessary transfusions through the use of evidence-based transfusion guidelines, to reduce potentially fatal (infectious as well as noninfectious) transfusion complications;
2. Reduction in the risk of transfusion-related acute lung injury in recipients of platelet transfusions through the use of single-donor platelets collected from male donors, female donors without a history of pregnancy, or female donors who have been shown not to have white blood cell (WBC) antibodies;
3. Prevention of hemolytic transfusion reactions through the augmentation of patient identification procedures by the addition of information technologies, as well as through the prevention of additional red blood cell alloantibody formation in patients who are likely to need multiple transfusions in the future;
4. Avoidance of pooled blood products (such as pooled whole blood-derived platelets) to reduce the risk of transmission of emerging transfusion-transmitted infections (TTIs) and the residual risk from known TTIs (especially transfusion-associated sepsis [TAS]);
5. WBC reduction of cellular blood components administered in cardiac surgery to prevent the poorly understood increased mortality seen in cardiac surgery patients in association with the receipt of non-WBC-reduced (compared with WBC-reduced) transfusion; and
6. Pathogen reduction of platelet and plasma components to prevent the transfusion transmission of most emerging, potentially fatal TTIs and the residual risk of known TTIs (especially TAS).

Researchers Attempt to Predict and Manage Bleeding in Cardiac Surgery

Excessive bleeding after cardiac surgery can result in increased morbidity and mortality related to transfusion- and hypoperfusion-related injuries to critical organ systems.

The objective of this study was to review mechanisms that result in bleeding after cardiac surgery as well as current and emerging interventions to reduce bleeding and transfusion. The researchers discovered that point-of-care (POC) tests of hemostatic function can facilitate the optimal management of excessive bleeding and reduce transfusion by facilitating administration of specific pharmacologic or transfusion-based therapy and by allowing physicians to better differentiate between microvascular bleeding and surgical bleeding. Emerging interventions like recombinant FVIIa have the potential to reduce bleeding and transfusion-related sequelae and may be life-saving; however, randomized, controlled trials are needed to confirm safety before they can be used as either first-line therapies for bleeding or bleeding prophylaxis.

The researchers concluded that careful investigation of the role of new interventions is essential as the ability to reduce use of blood products, to decrease operative time and/or re-exploration rates has important implications for overall patient safety and health care costs.

Panel Offers Evidence-Based Practice Guidelines for Plasma Transfusion

There is little systematically derived evidence-based guidance to inform plasma transfusion decisions. To address this issue, the AABB commissioned the development of clinical practice guidelines to help direct appropriate transfusion of plasma. A systematic review (SR) and meta-analysis of randomized and observational studies was performed to quantify known benefits and harms of plasma transfusion in common clinical scenarios. A multidisciplinary guidelines panel then used the SR and the GRADE methodology to develop evidence-based plasma transfusion guidelines as well as identify areas for future investigation.

Based on evidence ranging primarily from moderate to very low in quality, the panel developed the following guidelines:

- 1) The panel suggested that plasma be transfused to patients requiring massive transfusion. However,
- 2) the panel could not recommend for or against transfusion of plasma at a plasma : red blood cell ratio of 1:3 or more during massive transfusion,

3) nor could the panel recommend for or against transfusion of plasma to patients undergoing surgery in the absence of massive transfusion.

4) The panel suggested that plasma be transfused in patients with warfarin therapy–related intracranial hemorrhage,

5) but could not recommend for or against transfusion of plasma to reverse warfarin anticoagulation in patients without intracranial hemorrhage.

6) The panel suggested against plasma transfusion for other selected groups of patients.

The panel systematically developed evidence-based guidance to inform plasma transfusion decisions in common clinical scenarios. Data from additional randomized studies will be required to establish more comprehensive and definitive guidelines for plasma transfusion.

Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A, Fung M, Hamilton M, Hess JR, Luban N, Perkins JG, Sachais BS, Shander A, Silverman T, Snyder E, Tormey C, Waters J, Djulbegovic B. Evidence-based practice guidelines for plasma transfusion. *Transfusion*. 2010. [Ahead of print]

Study Focuses On Transfusion Medicine Knowledge in Postgraduate Year One Residents

Transfusion medicine is an important, complex subspecialty of pathology. Although fellowship training exists in transfusion medicine, the majority of transfusion decisions are made by clinicians without formal training.

Madigan Army Medical Center researchers conducted a study evaluating 116 recently graduated medical students entering 10 residency programs at a single medical center over 2 years using a standardized patient encounter to determine baseline knowledge. Transfusion medicine knowledge was assessed during the encounter by obtaining verbal consent for red blood cell transfusion, answering patient questions, and completing a written quiz. Final performance was scored using a peer-reviewed data collection sheet.

Scores ranged from 24.0% to 67.1%. Postgraduate Year 1 (PGY-1) residents graduating from allopathic medical schools had higher scores than those from osteopathic schools (mean, 41.3% vs. 37.5%; $p = 0.036$). There was no significant difference between PGY-1 residents entering primary care versus surgical specialties (38.2% and 41.6%; $p = 0.10$). Although not significant, PGY-1 residents with previous transfusion medicine education demonstrated a trend toward better performance than those without prior education (47.0% vs. 43.0%; $p = 0.057$). A total of 17.2% of PGY-1's could define transfusion-related acute lung injury, 6.0% knew the transfusion transmission rate of human immunodeficiency virus, 5.2% knew the transfusion transmission rate of hepatitis C virus, and 0% knew the indication for blood product irradiation.

Researchers noted marked knowledge deficits in transfusion medicine. They concluded that if the results of this study could be reproduced at other training institutions, medical schools may be willing to donate more resources into transfusion medicine education.

O'Brien KL, Champeaux AL, Sundell ZE, Short MW, Roth BJ. Transfusion medicine knowledge in Postgraduate Year 1 residents. *Transfusion*. 2010. [Ahead of print]



Is There a Relationship Between Blood Groups and Disease?

The relative contribution of founder effects and natural selection to the observed distribution of human blood groups has been debated since blood group frequencies were shown to differ between populations almost a century ago.

Recent advances in our understanding of the migration patterns of early man from Africa to populate the rest of the world obtained using Y chromosome and mitochondrial DNA markers do much to inform this debate. There are clear examples of protection against infectious diseases from inheritance of polymorphisms in genes encoding and regulating the expression of ABH and Lewis antigens in bodily secretions particularly in respect of *Helicobacter pylori*, Norovirus and Cholera infections.

However, available evidence suggests surviving malaria is the most significant selective force affecting the expression of blood groups. Red cells lacking or having altered forms of blood group-active molecules are commonly found in regions of the world where malaria is endemic, notably the Fy(a-b-) phenotype and the S-s- phenotype in Africa and the Ge negative and SAO phenotypes in South East Asia. Founder effects provide a more convincing explanation for the distribution of the D negative phenotype and the occurrence of Hemolytic Disease of the Fetus and Newborn in Europe and Central Asia.

Anstee DJ. The relationship between blood groups and disease. *Blood*. 2010. [Ahead of print]



When and Why Is Blood Crossmatched?

A United Kingdom National Health Service study was undertaken to provide data relating to the timing of laboratory crossmatch procedures, and the source of requests for out of hours crossmatch, to support interpretation of error reports originating in the transfusion laboratory, received by the Serious Hazards of Transfusion (SHOT) hemovigilance program.

Data on the timing, origin and urgency of all crossmatch requests were collected in 34 hospitals in northern England over a 7-day period in 2008. Additional data on clinical urgency were collected on crossmatches that were performed out of hours.

Data were obtained on 2423 crossmatches, including 610 (25.2%) performed outside core hours. 30.3% of out of hours crossmatch requests were for transfusions that were set up outside 4 h of completion of the crossmatch.

2008 SHOT data showed that 29/39 (74%) of laboratory errors resulting in 'wrong blood' occurred out of hours while the audit

showed that only 25% of crossmatch requests were made in that time period, suggesting that crossmatching performed outside core hours carries increased risks. The reason for increased risk of error needs further research, but 25 laboratories had only one member of staff working out of hours, often combining blood transfusion, hematology and coagulation work. A total of 25% of out of hours requests were not clinically urgent.

The study recommended that hospitals should develop policies to define indications for out of hours transfusion testing, empower laboratory staff to challenge inappropriate requests, and ensure that staffing and expertise is appropriate for the workload at all times.

Tingate HN, Davies T, Elshaw RJ, Jane G, Lyon M, Norfolk DR, Plews DE, Troy CB, Watson D. When and why is blood crossmatched? *Vox Sang*. 2010. [Ahead of print]

Studies Question Duration of Red Blood Cell Storage and Its Impact on Transfused Patients

Disquieting reports of increased complication and death rates after transfusions of red blood cells (RBCs) stored for more than 14 days prompted researchers to perform an observational retrospective cohort study of mortality in relation to storage time.

A study funded by the National Heart, Lung, and Blood Institute of the U.S. National Institutes of Health utilized data on all recipients of at least one RBC transfusion in Sweden and Denmark between 1995 and 2002, as recorded in the Scandinavian Donations and Transfusions (SCANDAT) database. Relative risks of death in relation to storage time were estimated using Cox regression, adjusted for several possible confounding factors.

After various exclusions, 404,959 transfusion episodes remained for analysis. The 7-day risk of death was similar in all exposure groups, but a tendency for a higher risk emerged among recipients of blood stored for 30 to 42 days (hazard ratio, 1.05; 95% confidence interval [CI], 0.97-1.12), compared to recipients of blood stored for 10 to 19 days. With 2-year follow-up, this excess remained at the same level (hazard ratio, 1.05; 95% CI, 1.02-1.08). No dose-response pattern was revealed and no differential effect was seen when the analyses were restricted to recipients of leukoreduced units only.

Although a small excess mortality was noted in recipients of the oldest RBCs, the risk pattern was more consistent with weak confounding than with an effect of the momentary exposure to stored RBCs. It seems, thus, that any excess mortality conferred by older RBCs in the combined Swedish and Danish transfusion recipient population is likely less than 5%, which is considerably smaller than in the hitherto largest investigation.

In another study, a meta-analysis examined whether the available data support an adequate suspicion that transfusion of old red blood cells (RBCs) is associated with increased mortality, organ failure, infection, prolonged mechanical ventilation, and prolonged stay in the hospital or the intensive care unit. Such suspicion is required for intentionally exposing patients enrolled in randomized controlled trials (RCTs) to the known or probable—but rare—risks of old RBCs, to document (and prevent) purported common adverse effects of old RBCs.

Remember These Websites

Immunohematology Journal
redcross.org/immunohematology
Reimbursement
redcrossblood.org/reimbursement

PLUS
Summer 2010, Volume Four, Issue Three



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Observational studies presenting adjusted results were eligible for analysis if the adequacy of the adjustment for confounding factors could be assessed. Three RCTs and 24 observational studies were retrieved. Medically and statistically homogeneous studies were integrated by fixed-effects methods. Otherwise homogeneous studies conducted in different clinical settings were integrated by random-effects methods.

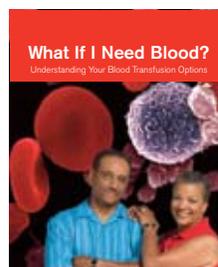
Based on “as-treated” analysis, transfusion of old RBCs was associated with a significant reduction in mortality (summary odds ratio, 0.38; 95% confidence interval, 0.14-0.99; $p < 0.05$) across two small RCTs. Integration of adjusted findings on the same outcome, from observational studies conducted in the same setting, produced summary results that were either negative (in six analyses) or impossible to evaluate owing to uncontrolled confounding by the number of transfused RBCs (in two analyses).

In this study, the researchers concluded that the available data do not support an adequate suspicion that old RBCs may be associated with common adverse morbidity and/or mortality outcomes, so as to justify exposing experimental subjects to the other known or probable—but rare—risks of old RBCs.

Edgren G, Kamper-Jørgensen M, Eloranta S, Rostgaard K, Custer B, Ullum H, Murphy EL, Busch MP, Reilly M, Melbye M, Hjalgrim H, Nyrén O. Duration of red blood cell storage and survival of transfused patients. *Transfusion* 2010. [Ahead of print]

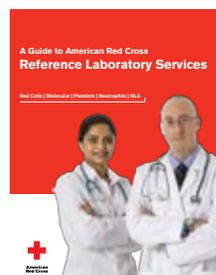
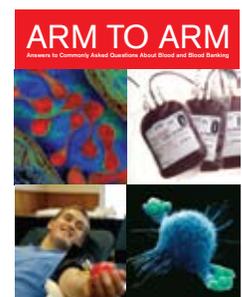
Vamvakas EC. Meta-analysis of clinical studies of the purported deleterious effects of “old” (versus “fresh”) red blood cells: are we at equipoise? *Transfusion*. 2010. 50: 600-610

Resources



What If I Need Blood?, a brochure which answers commonly asked questions and explains the transfusion options for patients, is available through your American Red Cross representative.

Arm to Arm is a comprehensive guide which answers commonly asked questions about blood and blood banking.



A Guide to American Red Cross Reference Laboratory Services is a guide describing the many services offered by the American Red Cross Immunohematology Reference Laboratories.