American Red Cross

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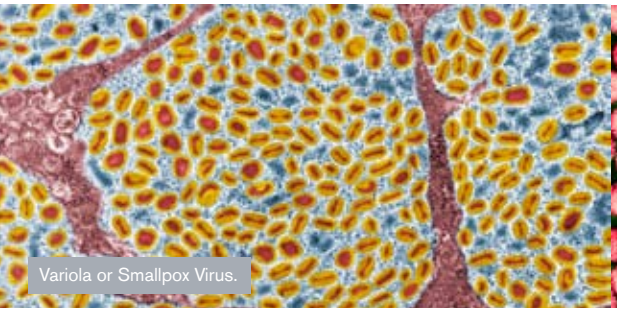
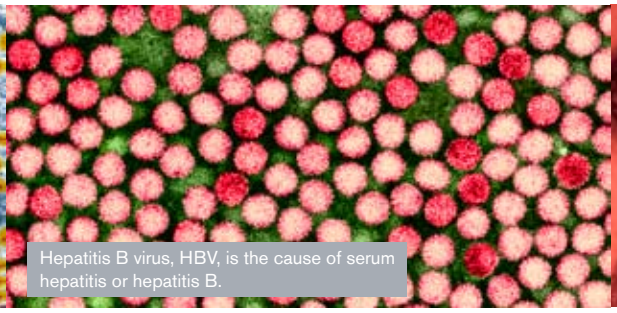
Emerging Infectious Disease Agents and Their Potential Threat to T


Variola or Smallpox Virus.


Hepatitis B virus, HBV, is the cause of serum hepatitis or hepatitis B.


Borrelia burgdorferi, the bateria that causes Lyme disease.

In a supplement to the journal *Transfusion*, American Red Cross Biomedical Services scientists and members of the AABB's Transfusion Transmitted Diseases Committee reviewed numerous sources in order to identify 68 infectious agents with an actual or potential risk of transfusion transmission now or in the future in the United States or Canada. Emerging infections were defined as those whose incidence in humans has increased within the past two decades or threatens to increase in the near future.

In this study, transfusion medicine experts assigned a priority risk level to each agent under three different categories:

· scientific/epidemiologic evidence regarding blood safety,
· public perception and/or regulatory concern regarding blood safety,
· and public concern regarding the disease agent.

Categories of agents deemed to be of high or moderate priority are indicated by color: red, orange, yellow, and white as indicated below.

Red. Agents with low to high scientific/epidemiologic evidence of risk regarding blood safety with the potential for severe clinical outcomes. This priority also may be influenced by the committee's estimate of the risk of emergence of these agents in the US and Canada as well as public and/or regulatory concern.

- Human variant Creutzfeldt-Jakob disease (vCJD)
- Dengue viruses (DENV)
- Babesia species

Orange. Agents with sufficient scientific/epidemiologic evidence of risk in regard to blood safety that might support their elevation to a higher priority in the future.

- Chikungunya virus (CHIKV)
- St Louis encephalitis virus (SLEV)
- Leishmania species
- Plasmodium species
- Trypanosoma cruzi

Yellow. Agents with absent to low scientific/epidemiologic evidence of risk regarding blood safety for which there is public and/or regulatory concern.

- Chronic wasting disease (CWD)
- Human herpesvirus 8 (HHV-8)
- HIV variants
- Human parvovirus B19 (B19V)
- Influenza A virus, subtype H5N1
- Simian foamy virus (SFV)
- Borrelia burgdorferi
- Hepatitis A virus (HAV)

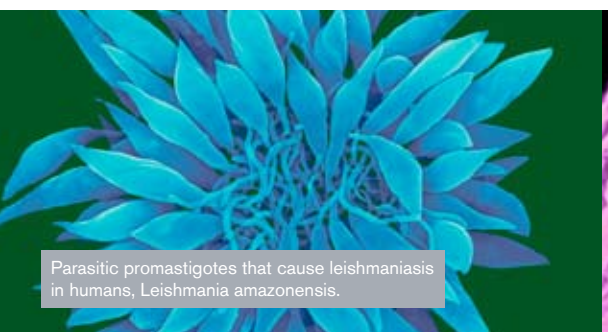
White. Agents that were evaluated but no higher priority appears warranted at this time. This category represents a watch list, subject to modification as circumstances change.

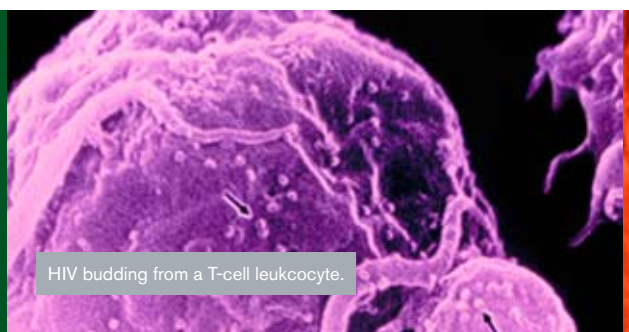
In addition to the previously categorized agents, several agents on the watch list (i.e., white category agents) merit further discussion, either because of recently changing information or because of concerns about the potential use of the agent in a bioterrorist attack. Some of these latter agents are discussed in more detail in the section on bioterrorism.

- Hepatitis E virus (HEV)
- Anaplasma phagocytophilum

Category A. Agents of Bioterrorism: Blood Safety Implications and Actions in the Event of an Attack

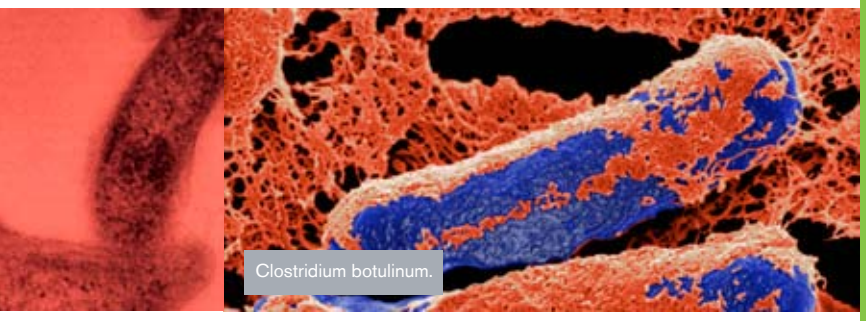
- Anthrax
- Botulism
- Plague
- Smallpox
- Tularemia
- Viral hemorrhagic fevers


Parasitic promastigotes that cause leishmaniasis in humans, Leishmania amazonensis.


HIV budding from a T-cell leukocyte.


Ring stage of the Protozoan parasite that causes Malaria (Plasmodium falciparum).

Transfusion Safety


Clostridium botulinum.

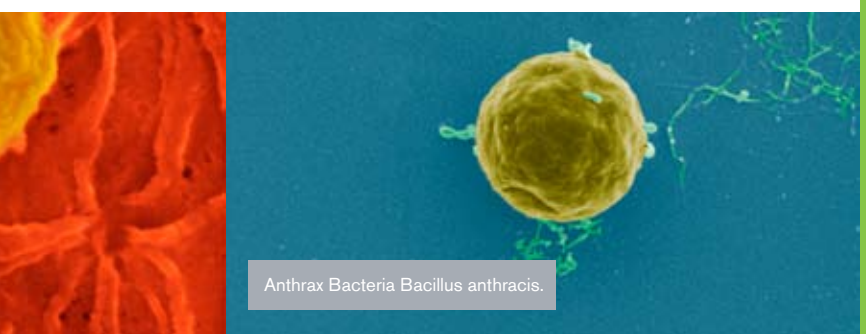
"West Nile virus and the H1N1 influenza virus are two relatively new infectious agents making headlines today, but many more emerging infectious diseases could greatly affect our population," said Susan L. Stramer, PhD, American Red Cross Biomedical Services Executive Scientific Director. "Vigilance and preparation are essential, and the August *Transfusion* supplement is designed to focus attention on these emerging infectious disease agents, thereby creating dialogue among blood establishments, regulatory authorities, public health agencies, the medical community and industry — all of whom will need to proactively work together to develop implementation intervention plans."

The supplement contains a set of 68 fact sheets, each of which references systematic information about a single agent. The fact sheets include background information about each agent, along with a variety of assessments such as the clinical features of the agent and those characteristics specifically related to transfusion transmission. The fact sheets do not represent compliance requirements, but instead serve as a starting point for developing policies.

Also included are a narrative introducing the concept of emergence, a description of how agents were assessed and prioritized, a section describing agents potentially involved in bioterrorism and a section describing what is known about pathogen reduction methods — the most proactive approach against such agents. Tables summarize the agents by agent category, priority, those documented to be transfusion transmitted, and those in which an arthropod vector is the usual mode of transmission.

Consensus opinions about prudent approaches (such as donor deferral periods) are included wherever possible based on facts that are currently inferred or known. Additionally, the agents are ranked according to the consensus opinion about their anticipated impact upon blood safety using scientific data and data related to the public perception of the agent.

Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR, Dodd RY. Emerging infectious disease agents and their potential threat to transfusion safety. *Transfusion*. 2009 49 Suppl 2:1S-29S.


Anthrax Bacteria Bacillus anthracis.

Blood Experts Report on Blood Banking in Afghanistan

As a result of more than 20 years of war in Afghanistan, its blood supply system has been damaged. Transfusion medicine experts from the American Red Cross, the University of Minnesota, the Afghanistan National Blood Safety and Transfusion Service, and the University of Louisville School of Medicine assessed Afghanistan's blood supply system to determine the type and extent of assistance needed to increase blood availability and safety.

The scientists found that since there was no donor recruitment organization in the nation, most blood was obtained by the family replacement system. They also found that there was an inadequate supply of stored blood, which led to use of blood before screening test results for transfusion-transmitted disease were complete. Whole blood was provided but blood components were not produced. Blood was tested intermittently for human immunodeficiency virus Types 1 and 2, hepatitis B surface antigen, hepatitis C virus, and syphilis using agglutination-based screening methods.

The researchers reported that although a dedicated staff is in place to strengthen the blood supply system in Afghanistan, it will be important to address infrastructure and facilities, organization, standard operating methods, supplies and equipment, training, quality assurance, and transfusion medicine education. This work was supported in part by a grant from the National Heart, Lung, and Blood Institute; the American Red Cross; and the University of Minnesota Institute for Engineering in Medicine.

Ayyoubi MT, Konstenius T, McCullough JC, Eastlund T, Clay M, Bowman R, Rahmani AM, Riley W, McCullough J. Status of blood banking and the blood supply in Afghanistan. *Transfusion*. 2009. Ahead of print.

Focus on TRALI

TRALI Risk Reduction: Donor and Component Management Strategies

Transfusion-related acute lung injury (TRALI) occurs in approximately 1 in 5,000 transfusions and may cause considerably more morbidity and mortality that is not recognized in clinical practice. Based on the current understanding of the etiology of TRALI, blood centers have implemented or are evaluating various donor and component management strategies in an effort to mitigate the risk of TRALI. Many cases of TRALI are likely caused by antibodies to leukocyte antigens (HLA or HNA) in blood components. Approximately 10 to 20% of female blood donors with a history of pregnancy and 1 to 5% of male blood donors harbor these antibodies. Alternatively, TRALI may be mediated by other bioactive lipids or substances that accumulate during storage and cause a reaction when transfused to susceptible patients. The complex interplay among various donor-, component-, and patient-related factors underlying TRALI guarantees that effective prevention will not be a single or simple intervention, but rather will require a multifaceted approach. Perhaps, the most important risk reduction strategy is the effort to ensure appropriate use of blood products. Blood collection agencies, however, have more proximate control over donor selection and component management than transfusion practice. AABB has provided some guidance on deferring donors implicated in TRALI and minimizing the preparation of high plasma volume components from donors who have anti-leukocyte antibodies or are at increased risk of leukocyte alloimmunization. Blood centers have taken various approaches to mitigate the risk of TRALI, and the possible benefits and the inherent limitations of the current strategies are being reviewed.

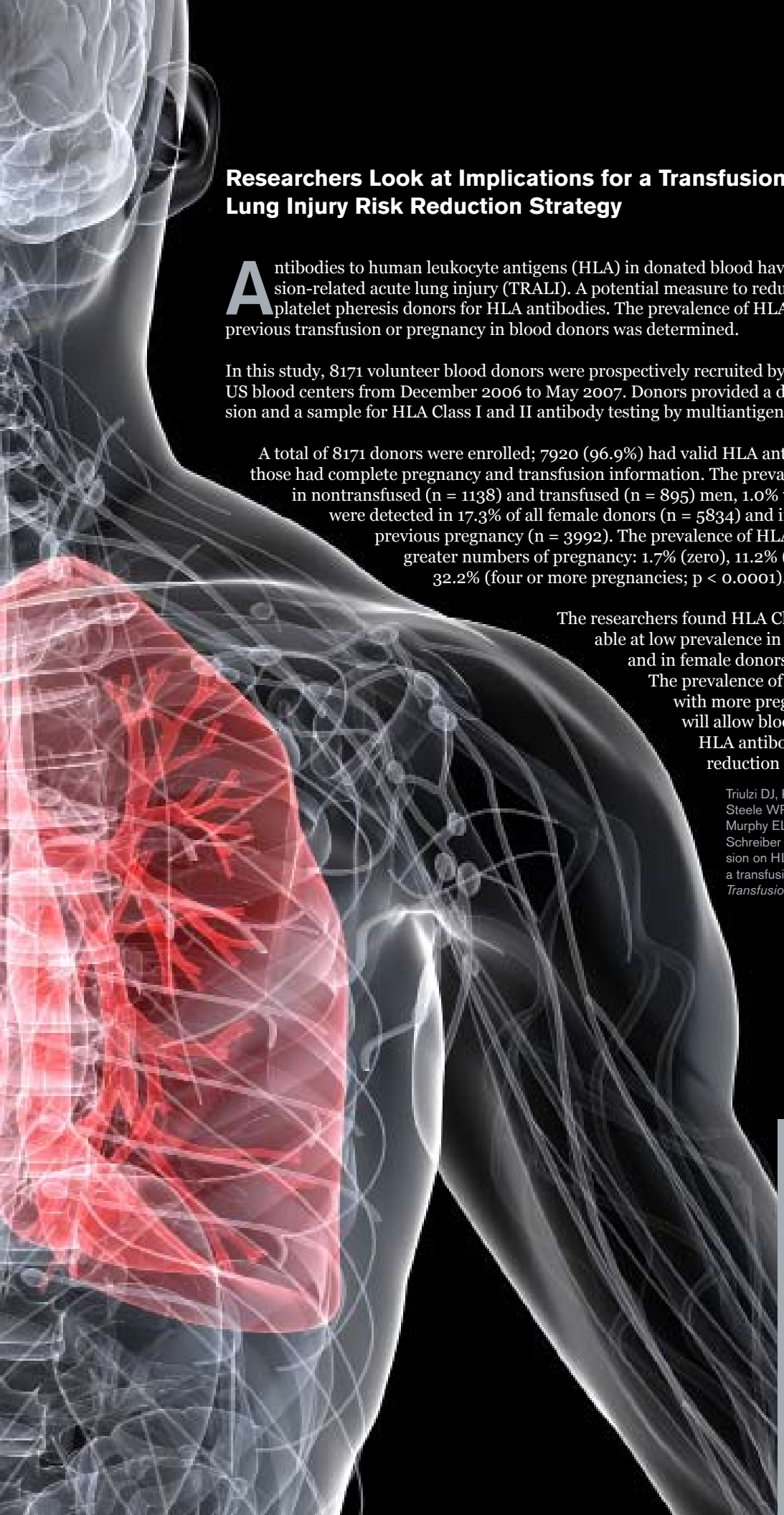
Eder AF, Benjamin RJ. TRALI risk reduction: donor and component management strategies. *J Clin Apher.* 2009. 24:122-9.

Neotrophils And Their FC γ Receptors Are Essential In A Mouse Model Of Transfusion-Related Acute Lung Injury

To explore the pathogenesis of TRALI, University of California, San Francisco researchers developed an in vivo mouse model based on the passive transfusion of an MHC class I (MHC I) mAb (H2Kd) to mice with the cognate antigen.

Transfusion of the MHC I mAb to BALB/c mice produced acute lung injury with increased excess lung water, increased lung vascular and lung epithelial permeability to protein, and decreased alveolar fluid clearance. There was 50% mortality at a 2-hour time point after Ab administration. Pulmonary histology and immunohistochemistry revealed prominent neutrophil sequestration in the lung microvasculature that occurred concomitantly with acute peripheral blood neutropenia, all within 2 hours of administration of the mAb. Depletion of neutrophils by injection of anti-granulocyte mAb Gr-1 protected mice from lung injury following MHC I mAb challenge. FcR γ–/– mice were resistant to MHC I mAb–induced lung injury, while adoptive transfer of wild-type neutrophils into the FcR γ–/– animals restored lung injury following MHC I mAb challenge. The researchers concluded that in a clinically relevant in vivo mouse model of TRALI using an MHC I mAb, the mechanism of lung injury was dependent on neutrophilis and their Fc γ receptors.

Looney MR, Su X, Van Ziffle JA, Lowell CA, Matthay MA. Neutrophils and their Fcγ receptors are essential in a mouse model of transfusion-related acute lung injury. *J. Clin. Invest* 2009. 116: 1615-1623.



Researchers Look at Implications for a Transfusion-Related Acute Lung Injury Risk Reduction Strategy

Antibodies to human leukocyte antigens (HLA) in donated blood have been implicated as a cause of transfusion-related acute lung injury (TRALI). A potential measure to reduce the risk of TRALI includes screening platelet pheresis donors for HLA antibodies. The prevalence of HLA antibodies and their relationship to previous transfusion or pregnancy in blood donors was determined.

In this study, 8171 volunteer blood donors were prospectively recruited by the American Red Cross and five other US blood centers from December 2006 to May 2007. Donors provided a detailed history of pregnancy and transfusion and a sample for HLA Class I and II antibody testing by multiantigen bead flow analysis.

A total of 8171 donors were enrolled; 7920 (96.9%) had valid HLA antibody test results and 7841 (99%) of those had complete pregnancy and transfusion information. The prevalence of any HLA antibody was similar in nontransfused (n = 1138) and transfused (n = 895) men, 1.0% versus 1.7% (p = 0.16). HLA antibodies were detected in 17.3% of all female donors (n = 5834) and in 24.4% of those with a history of previous pregnancy (n = 3992). The prevalence of HLA antibodies increased in women with greater numbers of pregnancy: 1.7% (zero), 11.2% (one), 22.5% (two), 27.5% (three), and 32.2% (four or more pregnancies; $p < 0.0001$).

The researchers found HLA Class I and Class II antibodies are detectable at low prevalence in male donors regardless of transfusion and in female donors without known immunizing events. The prevalence of HLA antibodies increases significantly with more pregnancies. They contend that these data will allow blood centers to estimate the impact of HLA antibody testing as a potential TRALI risk reduction measure.

Triulzi DJ, Kleinman S, Kakaiya RM, Busch MP, Norris PJ, Steele WR, Glynn SA, Hillyer CD, Carey P, Gottschall JL, Murphy EL, Rios JA, Ness PM,. Wright DJ, Carrick D, and Schreiber GB. The effect of previous pregnancy and transfusion on HLA alloimmunization in blood donors: implications for a transfusion-related acute lung injury risk reduction strategy. *Transfusion*. 2009. 49:1825-1835.

DEFINING TRALI

1951 Clinical symptoms now known as TRALI are first reported.

1985 TRALI is recognized as a distinct clinical entity.

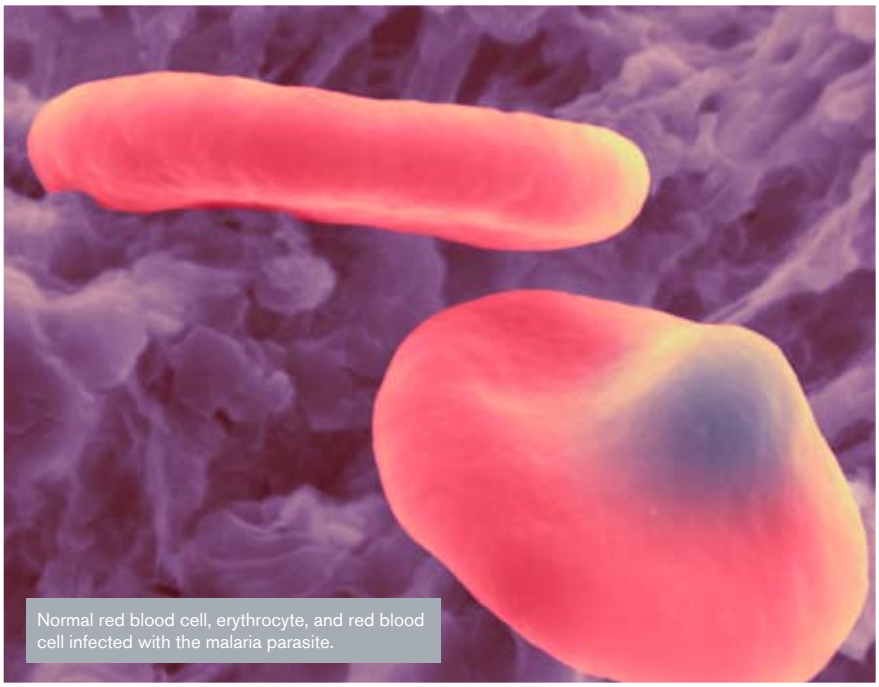
2004/2005 Definitions of TRALI developed by Canadian Consensus Conference Panel and the National Heart, Lung, and Blood Instituite Working Group published.

Red Cross Scientists Examine the Malaria Risk for Donors Deferred for Travel to Mexico

Every year >45,000 potential American Red Cross (ARC) donors are lost because of deferral for possible exposure to *Plasmodium spp.*, the agent of malaria. Among these donors, ~91% are deferred for travel to malaria endemic regions. However, relatively few U.S. travelers visit endemic areas of Sub-Saharan Africa, the source of most U.S. cases of transfusion-transmitted malaria (TTM). Particularly problematic are the large number of U.S. donors deferred for travel to Mexico, a country thought to be low risk for malaria.

To better understand transmission risk, ARC scientists tested donors deferred for travel to Mexico for evidence of past or present infection with *Plasmodium spp*. and compared the results to the known distribution of malaria in Mexico.

Malaria travel deferred donors, identified in a single ARC collection region during 2006-2009, were invited to enroll in the study. Approximately one-third of randomly selected travel deferred donors who enrolled provided two tubes of EDTA blood and completed a malaria exposure questionnaire. Blood samples were tested for *Plasmodium spp*. antibodies by EIA, as per the manufacturer's instructions. Samples found repeat reactive (RR) were considered positive and tested by real-time PCR for parasite DNA. Questionnaires were analyzed for country of deferral, travel history and past episodes of malaria. Malaria endemic areas were defined based on information available from the WHO.



Normal red blood cell, erythrocyte, and red blood cell infected with the malaria parasite.

Among the 2,809 travel deferred donors tested, 29 (1.03%) were RR. 1426 (51%) were deferred for travel to Central America/Caribbean, 673 (24%) for Mexico, 459 (16%) for Asia/ Western Pacific, 129 (5%) for Africa, and 122 (4%) for South America. Only 1 of 673 (0. 15%) donors deferred for travel to Mexico was found to be RR, but this donor reported being infected in Turkey during 1976. PCR testing was negative. Four of 673 (0.59%) deferred donors traveled to the high risk states of Chiapas or Oaxaca, 3 of 673 (0.45%) traveled to Chihuahua (moderate risk), and 2 (0.30%) traveled to Jalisco or Sonora (low risk). The vast majority of donors (n = 583, 87%) traveled to areas with little or no risk for malaria (i.e. resorts in Quintana Roo). The remaining 12% (n = 81) did not provide states visited.

The researchers found that based on the serological data, donors deferred for travel to Mexico are not a primary risk for transmission of malaria to U.S. blood recipients. Only 1% of donors traveling to Mexico visited low to high risk malarias areas; most donors deferred for travel to Mexico are not visiting areas where the risk of acquiring malaria is of concern. In either case, these donors had no evidence of infection with *Plasmodium spp*. acquired in Mexico. They concluded that implementing changes in deferral criteria for travelers to Mexico should be considered in light of the extremely low risk of malaria associated with these donors.

Another American Red Cross Biomedical Services study compared the impact of existing deferral requirements to the risk that a presenting donor with malaria travel history harbors malaria parasites under current and hypothetical alternate regulations.

Deferred donors from six blood centers were sampled to estimate a national cohort of donors deferred annually for malaria travel to different geographic regions. Risk for malaria infection after travel to each region and distribution of incubation periods for each malaria species were estimated for U.S. travelers. Region-specific travel risks were used to estimate the risk that a presenting blood donor with malaria travel might asymptomatically harbor malaria parasites at different intervals after return to the United States.

Travel to Africa presents risk for malaria infection greater than 1000 times that of travel to malaria-endemic parts of Mexico, yet Mexico accounts for more than 10 times as many deferred donors. Shortening the deferral period from 12 to 3 months for travelers to Mexico increases the risk of collecting a contaminated unit by only 1 unit per 57 years (sensitivity analysis, 1 every 29-114 years), an annual gain of more than 56,000 donations.

This study provides the first systematic appraisal of the U.S.requirements for donor qualification regarding travel to malarial areas. Consideration should be given to relaxing the guidelines for travel to very-low-risk areas such as Mexico.

Nguyen M, Goff T, Gibble JW, Leiby DA. Defining the malaria risk for donors deferred for travel to Mexico. Abstract P2-020A. *Transfusion*. 2009. 49 (Supp): 1A.

Spencer B, Steele W, Custer B, Kleinman S, Cable R, Wilkinson S, Wright D. Risk for malaria in United States donors deferred for travel to malaria-endemic areas. *Transfusion*. 2009. 49:2335-45.

BPAC Advises FDA to Drop Deferral for Travel to Quintana Roo

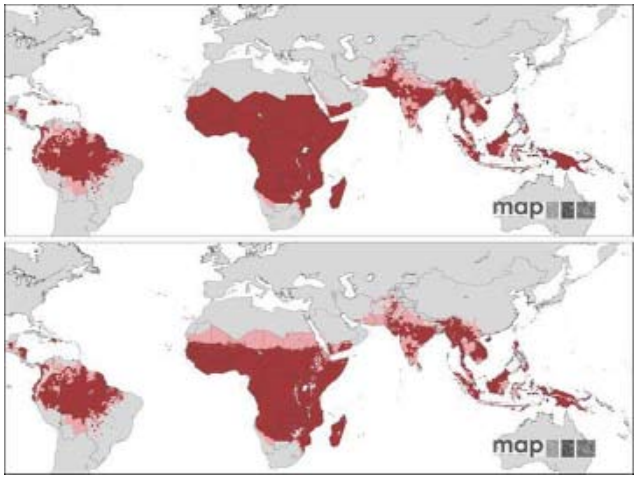
In November 2009, the Food and Drug Administration's Blood Products Advisory Committee (BPAC) voted 17-1 to allow people who have traveled to the Mexican state of Quintana Roo to donate blood. Quintana Roo is the sole destination of 85 percent of American tourists who visit Mexico. Many are visiting the popular resorts, Cancun and Cozumel.

Sanjai Kumar, PhD, chief of the Malaria Research Program at the FDA, advised BPAC that cases of malaria from mosquitoes are rare in the United States, with only about 1,500 diagnosed each year. Most were acquired when Americans visited countries where malaria is endemic.

While malaria can be spread through blood transfusions, there is no licensed test. The only way to protect the blood supply is to defer donors who have had malaria or been exposed to it recently by living in or traveling to areas where the disease is endemic.

People who have traveled to an endemic area are deferred from donating blood or blood products for one year after they leave that area. Those who have had malaria or who have lived in endemic countries cannot donate for three years. Between 1 percent and 3 percent of potential donors are deferred each year because they have traveled to or lived in malaria endemic areas. Kumar estimated that those deferrals cause the loss of more than 150,000 donors per year.

Bryan Spencer, MPH, of the American Red Cross presented the results of the REDS-II study, in which blood centers in New England, Cincinnati, Pittsburgh, and Milwaukee analyzed data on donors that had been deferred for travel to Mexico. The study found such deferrals have increased 50 percent in the past 10 years. Eliminating the deferral would increase the number of units of donated blood by as many as 92,000 a year.



P. falciparum Malaria Risk Defined by Annual Parasite Incidence (top), Temperature, and Aridity (bottom). (Credit: Guerra CA, Gikandi PW, Tatem AJ, Noor AM, Smith DL, et al. 2008 The Limits and Intensity of Plasmodium falciparum Transmission: Implications for Malaria Control and Elimination Worldwide. PLoS Med 5(2): e38. doi:10.1371/journal.pmed.0050038). Maps created by the Malaria Atlas Project are available at www.map.ox.ac.uk

The CDC provides an interactive malaria risk map that can be found at www.cdc.gov/malaria/risk_map.

An e-mail service which provides notification about malaria outbreaks and other information is also available through the CDC.

Transfusion-transmitted malaria (TTM) has been rare in the United States, with only 97 cases from 1963 to 2009.

The average annual number of cases has dropped steadily, with only four cases since 2000. All four of these TTM cases have been traced to donors who were former residents of countries where malaria is endemic. Of the approximately 34 million U.S. residents who travel each year to countries with high levels of malaria, 18 million go to Mexico.

Red Cross to Begin HIV-1 Group O Testing

The American Red Cross National Testing Laboratories (NTL) will add the fourth and final assay to the Abbott PRISM platform by February 1, 2010. The Abbott PRISM is a fully automated testing platform that currently is used in the NTLs for serologic viral donor screening for HBsAg, anti-HBc, and anti-HTLV-I/II.

HIV is a highly variable virus that mutates readily. Viral strains are classified into types, groups, and subtypes.

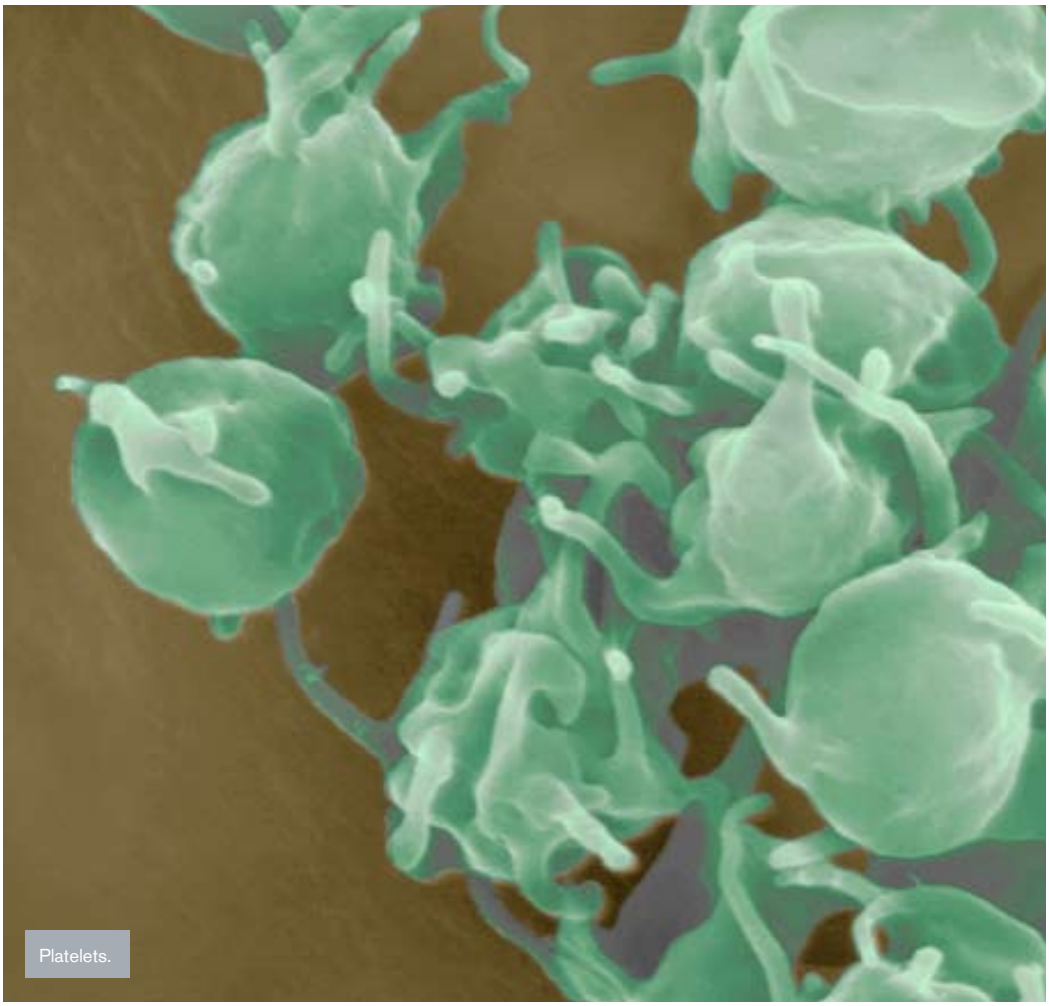
HIV-1 is the most common and pathogenic form of HIV and accounting for the vast majority of all infections. HIV-2 is not widely seen outside Africa. The American Red Cross tests for antibodies to HIV-1 and HIV-2 in a combination screening assay. Further testing is performed on all repeat reactive donations to distinguish between HIV-1 and HIV-2 antibodies.

HIV-1 is classified into four groups: Group M (major), Group O (outlier) and two newer Groups, N and P. Within Group M there are several subtypes (minor types). The first case of HIV-1 Group O infection in the U.S. was reported in 1996 in a woman recently returned after living in Central Africa for several years. Since that time, HIV test manufacturers have modified their tests to contain specific Group O antigens; all newly licensed tests must demonstrate ability to detect antibodies to HIV-1 Group O in addition to Group M.

In 1996, the FDA published "Interim Recommendations for Deferral of Donors at Increased Risk for HIV-1 Group O Infections". This recommendation introduced the inclusion of predonation questions related to HIV-1 Group O risk. These questions were used to determine whether donors have traveled to or were born, resided, received a blood transfusion or medical treatment in eight specific West and Central African countries where HIV Group O was known to be present. If a donor's response was affirmative, they were indefinitely deferred. In September 2009, FDA revised the earlier recommendation and included several more countries to the list used to screen donors for HIV Group O risk, bringing the total number to fourteen. Annually, the Red Cross defers almost 1,500 donors per year for this reason.

The Abbott PRISM assay, which received FDA licensure in September 2009, and will be implemented in the NTLs in February 2010, is specifically labeled as being sensitive for detection of antibodies to HIV-1 Group O.

Researchers Find Platelets May Have Potential Antifungal Effects



Platelets.

Zygomycosis is increasingly recognized in immunocompromised hosts.

German and Austrian scientists investigated whether platelets become activated after contact with Zygomycetes and adhere to conidial and hyphal structures using immunofluorescence. The platelets' influence on fungal viability was evaluated by assessing hyphal elongation and hyphal damage. Platelets became activated and strongly adhered to conidia and hyphae of Zygomycetes. Platelets induced time dependent damage to hyphae and significantly reduced hyphal elongation.

The researchers found that platelets possess antifungal capacities against Zygomycetes based on granule dependent mechanisms and significantly reduce fungal growth and spread, both of which are of major importance in evolving invasive disease.

Perkhofer S, Kainzner B, Kehrel BE, Dierich MP, Nussbaumer W, Lass-Flör Cl. Potential Antifungal Effects of Human Platelets against Zygomycetes In Vitro. *Jour Infect Dis.* 2009. 200:1176-1179.

Study Analyzes in Vitro Properties of Leukoreduced Whole Blood-derived Pooled Platelets after a 24-hour Interruption of Agitation

Continuous agitation during platelet concentrate (PC) storage is frequently interrupted during shipping. Studies have evaluated the effects of interrupted agitation in apheresis and single whole blood-derived PCs, but not PC pools. This study evaluated in vitro properties of pooled whole blood-derived platelets (PLTs) after a 24-hour interruption of agitation.

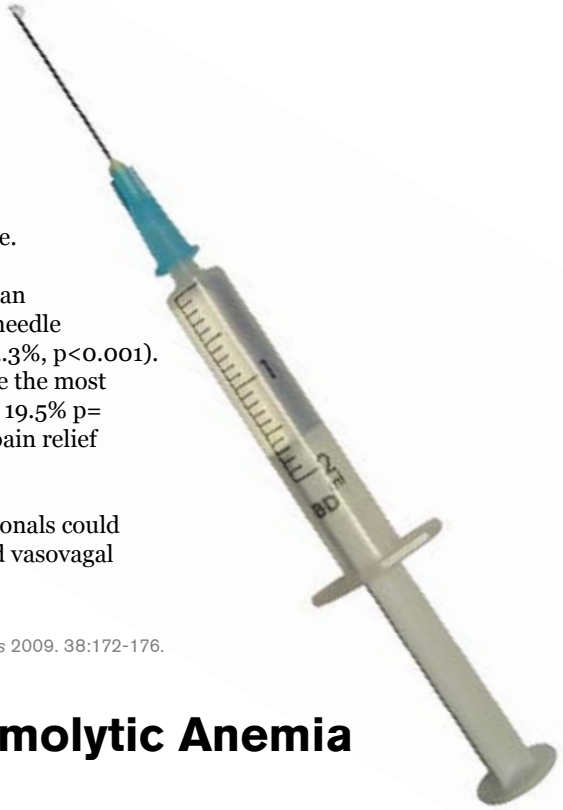
Eleven ABO-identical leukoreduced whole blood-derived PCs (Leukotrap RC-PL, Pall), pooled in a transfer container, were equally divided into each of two CLX-HP containers (Acrodose PL, Pall). One pool (test) was held in a shipping container unagitated for 24 hours between Day 2 and Day 3, while the other (control) was continuously agitated.

Ten pairs underwent in vitro assays after 5 and 7 days' storage. Pools contained a mean (±SD) of 5.0 × 10ell ± 0.4 × 10ell PLTs. Interrupting agitation for 24 hours reduced test pool pH versus control after 5 days' storage (6.77 ± 0.15 vs. 6.98 ± 0.06, p = 0.0005). Test and control pH differences were greater after 7 days' storage (6.17 ± 0.29 vs. 6.65 ± 0.14, p < 0.0001); 5 of 10 test pool pHs were less than 6.2 (vs. 0 of 10 controls). Other test pool key in vitro variables were reduced compared with controls after 5 days' storage, with greater differences after 7 days.

After 5 days' storage, pooled leukoreduced whole blood-derived-PCs in CLX-HP containers adequately maintained pH and other key in vitro variables after a 24-hour interruption of agitation. After 7 days' storage, 5 of 10 pools did not maintain a pH value of 6.2 or greater while matched continuously agitated units did.

Vassallo RR, Wagner SJ, Einarson M, Nixon J, Ziegler D, Moroff G. Maintenance of in vitro properties of leukoreduced whole blood-derived pooled platelets after a 24-hour interruption of agitation *Transfusion*. 2009. 49: 2131-2135.

Study Examines the Effect of the Fear of Needles on Medical Practice and Blood Donation



The extent to which a fear of needles influences health decisions remains largely unexplored. This study investigated the prevalence of fear of needles in southeast Queensland, Australia.

The study focused on 177 participants who responded to a questionnaire on their fear of needles, symptoms associated with needles, and its influence on their use of medical care.

22% of participants reported a fear of needles. Affected participants were more likely than participants with no fear to report vasovagal symptoms, have had a previous traumatic needle experience (46.2 vs. 16.4%, p<0.001) and avoid procedures involving needles (20.5 vs. 2.3%, p<0.001). Of those who avoid medical treatment involving needles, donating blood was found to be the most avoided procedure (76.9 vs. 16.4% p=<0.00001) when compared with flu shots (64.1 vs. 19.5% p= <0.00001), tetanus (30.8 vs. 7.0% p= 0.0004), blood test (10.3 vs. 2.3% p= 0.047), or pain relief (25.6 vs. 6.3% p= 0.003).

Fear of needles is common and is associated with health care avoidance. Health professionals could better identify and manage patients who have a fear of needles by recognizing associated vasovagal symptoms and past traumatic experiences.

Wright S, Yelland M, Heathcote K, Ng SK. Fear of needles - nature and prevalence in general practice. *Aust Fam Phys* 2009. 38:172-176.

Scientists See First Case Of Immune Hemolytic Anemia Due to an Antibody to Cimetidine

Cimetidine is a histamine H_2-receptor antagonist that inhibits gastric acid secretion. Five patients have been reported to develop hemolytic anemia (HA) while receiving cimetidine, but drug-dependent antibodies were not demonstrated in any (2 were tested and 3 were not tested for the presence of drug-dependent antibody). Two of the 5 patients were rechallenged with cimetidine and did not have a recurrence of hemolysis. Thus, it was not proven that cimetidine was the cause of HA in these patients.

In this case report, a 63-year-old woman with metastatic breast cancer received cimetidine, benadryl & decadron with her chemotherapy regimen of carboplatin & taxol. Signs of HA were noted after receipt of cimetidine (300 mg) on August 13 and September 5. In August, the patient's hemoglobin (Hb)/ hematocrit (Hct) dropped to 5.6 g/dL/ 16.2%; lactate dehydrogenase (LDH) & total bilirubin (TBili) peaked at 1424 IU/dL and 3.0 mg/dL respectively. The patient was transfused two units of red blood cells (RBCs) and started on steroids. In September, the patient had severe back pain 30 minutes after receiving cimetidine (carboplatin & taxol were not given). The Hb/Hct dropped from 10.4 g/dL/30.0% to 7.4 g/dL/20.2% and the LDH & TBili peaked at 1893 IU/L & 3.4 mg/dL respectively; spherocytes were noted. The patient was transfused RBCs and fresh frozen plasma and given IVIg. Samples were sent for serological workup at the time of the September episode. The direct antiglobulin test was positive (IgG 0, C3 3+) and an antibody to cimetidine was detected in her serum by testing both cimetidine-treated RBCs and untreated/ enzyme-treated RBCs in the presence of cimetidine (Table). The anti-cimetidine was shown to have IgM and IgG components after treatment of the serum with dithiothreitol. An eluate from the patients' RBCs was nonreactive. On a technical note, drug-treated RBCs needed to be prepared at room temperature (at 37C there was significant hemolysis) and needed to be tested on the day they were prepared (results were negative with cimetidine-treated RBCs that had been stored overnight at 4C).

This is the first case of drug-induced immune HA due to cimetidine where an antibody to cimetidine was demonstrated in the patient's serum. The HA occurred on two separate occasions. The researchers concluded that if cimetidine-treated RBCs are tested, they should be freshly prepared.

Arndt PA, Garratty G, Brasfield FM, Vemuri SL, Asuncion DG. Immune hemolytic anemia due to cimetidine—the first example of anti-cimetidine. (Abstract S79-030K). *Transfusion*. 2009. 49 (Supp):33A.

Test	Patient's serum/plasma	Pool of normal sera/plasma
Cimetidine-treated RBCs 37C (titer) AGT (titer)	4+ agglut (128) 4+ (64)	0 0
Untreated RBCs ± PBS	0	0
Untreated RBCs + cimetidine 37C (titer) AGT (Titer)	1+lysis; 4+ agglut (128) 4+(64)	0 0
Ficin-treated RBCs + PBS	0	0
Ficin-treated RBCs + cimetidine 37C AGT	4+lysis; No RBCs No RBCs	0 0

agglut = agglutination, PBS = phosphate buffered saline, AGT = antiglobulin test

CDC Researchers Estimate Chagas' Disease Incidence in the United States

Chagas disease causes the highest burden of any parasitic disease in the Western hemisphere. Vector-borne transmission occurs only in the Americas , where an estimated 8 million people are currently infected with *Trypanosoma cruzi (T.cruzi)*.

By applying published seroprevalence figures to immigrant populations, CDC researchers estimated that 300,167 individuals with *T. cruzi* infection live in the United States, with 30,000-45,000 cardiomyopathy cases and 63-315 congenital infections annually.

The study found that most *T. cruzi* infected individuals are immigrants from endemic areas of Latin America. Historically, transmission was concentrated in rural Latin America, but successful vector-control programs have greatly decreased transmission in areas where the disease was formerly endemic, whereas migration has brought infected individuals to cities in Latin America, as well as to the United States, Europe, and Japan.

The researchers found that there have been at least 11 triatomine species involving enzootic *T. cruzi* transmission with hosts such as raccoons, opossums, and domestic dogs, but the scientists found that the vast majority of *T. cruzi*-infected individuals are immigrants from Latin American endemic areas. Only 7 autochthonous vector-borne cases of infection (4 in Texas and 1 each in California, Tennessee, and Louisiana) have been reported in the United States since 1955.

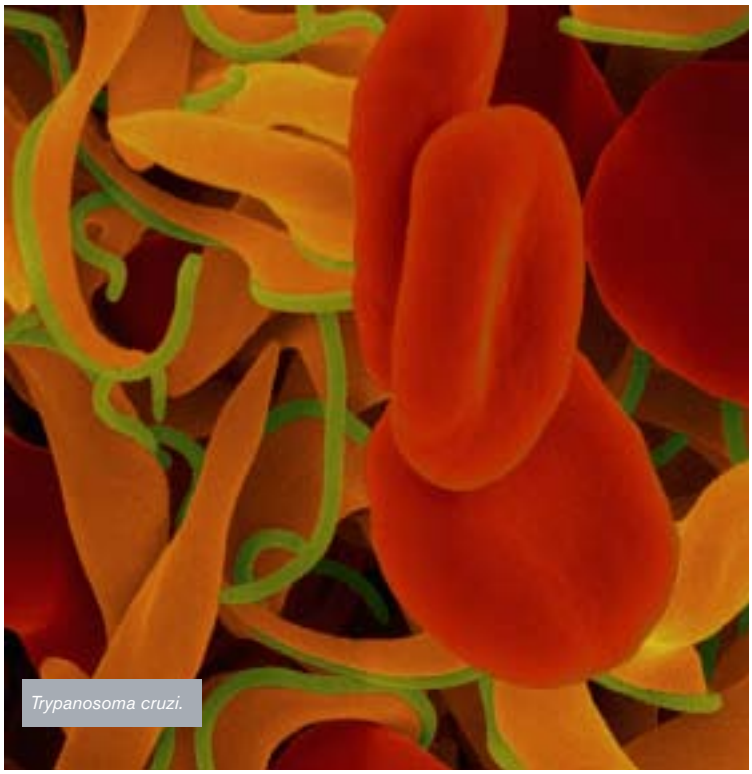
The researchers estimated the number of infections by determining the immigrant population of endemic areas of Latin America using data from the Pew Hispanic Center for authorized immigrants and the Department of Homeland Security for unauthorized immigrants. Using *T. cruzi* seroprevalence statistics from the Pan American Health Organization (PAHO), they determined the estimated number of U.S. immigrants with *T. cruzi* infection.

The researchers acknowledged that estimating of the number of *T. cruzi*-infected individuals in the United States is challenging, because the underlying data are sparse. Previous calculations have relied on a "patchwork" of *T. cruzi* prevalence estimates, derived from blood donor screening data and surveys from Latin America applied to the immigrant population.

In 2006, the PAHO published updated country-specific estimates of the prevalence and burden of *T. cruzi* infection, representing the first attempt since 1990 to produce integrated estimates that are based on the best currently available national data.

Widespread U.S. blood donation screening for *T. cruzi* began in January 2007. The US Food and Drug Administration-approved Ortho's *T. cruzi* enzyme-linked immuno sorbent assay (ELISA) test system is based on parasite lysate antigen. It is currently used as the screening assay for blood donor testing. ELISA-repeat reactive units are confirmed using the radioimmune precipitation assay (RIPA).

Bern C, Montgomery SP. An Estimate of the Burden of Chagas Disease in the United States. *Clin Infect Dis* 2009.49:52-4.



Trypanosoma cruzi.

Calculated Prevalence of *T. cruzi* Infections in Latin American Born Persons Living in the United States in 2005

Country of origin	Immigrant population living in the United States	*T. cruzi* prevalence in country of origin, %	Estimated no. of immigrants with *T. cruzi* infection in the United States
Mexico	16,963,851	1.03	174,388
El Salvador	1,458,014	3.37	49,164
Guatemala	1,014,669	1.98	20,313
Honduras	567,002	3.05	17,311
Argentina	223,931	4.13	9246
Ecuador	345,204	1.74	6003
Colombia	554,821	0.96	5304
Brazil	501,036	1.02	5106
Bolivia	61,453	6.75	4149
Nicaragua	223,931	1.14	2553
Peru	371,980	0.69	2552
Venezuela	151,350	1.16	1754
Chile	92,761	0.99	914
Costa Rica	95,761	0.53	509
Paraguay	16,707	2.54	425
Uruguay	51,737	0.66	339
Belize	42,130	0.74	312
Panama	107,601	0.01	6
Total	22,843,939	1.31	300,167

Researchers Analyze Anti-Ceftriaxone in Drug-Induced Immune Hemolytic Anemia Patients

Ceftriaxone (a cephalosporin) is currently one of the most commonly encountered drugs causing drug-induced immune hemolytic anemia (DIIHA). Over the past 22 years, American Red Cross scientists have tested samples from 62 patients suspected of having DIIHA due to ceftriaxone (trade name: Rocephin®).

Direct antiglobulin tests (DATs) were performed using anti-IgG, -C3, -IgM, and -IgA. Sera were tested in the presence of ceftriaxone ± the addition of fresh normal serum as a source of complement (C), against untreated (UT) and enzyme-treated (ET) red blood cells (RBCs), i.e., "immune complex" method. Drug-treated RBCs were tested in 13 cases. Polyspecific antihuman globulin was used for indirect antiglobulin tests (IATs).

Antibodies to ceftriaxone were detected in 21 patients; 15/21 (71 %) were children (≤ 14 years old) and 6/21 (29%) were adults. Twelve patients had received ceftriaxone previously (others were unknown). Six children had reactions ≤1 hour after receiving the drug. Hemoglobin dropped to <5 g/dL in 13 patients; three were 1 g/dL. Sixteen patients had intravascular hemolysis; fatalities occurred in 8/21 (38%): 6 children and 2 adults. The researchers performed DATs in 16 cases; 16/16 (100%) reacted with anti-C3 and 9/16 (56%) with anti-IgG; 4/15 (27%) reacted with anti-IgM and 1/15 (7%) with anti-IgA. Drug-treated RBCs were either non-reactive or equal in reactivity to UT RBCs. When testing UT RBCs in the presence of ceftriaxone, 1/16 (6%) showed hemolysis, 14/17 (82%) showed direct agglutination after the 37 C incubation, and 12/17 (71%) reacted by IAT (9 with little or no agglutination carry-over). When testing ET RBCs in the presence of ceftriaxone, 12/19 (63%) showed hemolysis (total hemolysis in one case), 20/20 (100%) showed agglutination after the 37C incubation, and 17/19 (89%) reacted by IAT (9 with little or no agglutination carryover). Hemolysis was sometimes only seen when fresh C was added to the test system. Thirteen patients (62%) appeared to have circulating drug and/or drug immune complexes present in their samples; two sera reacted with UT RBCs + phosphate buffered saline (PBS) (IAT only) and all 13 sera reacted with ET RBCs + PBS (1 IAT only, 2 agglutination + IAT, 10 agglutination only). Two of the 13 cases had sera samples from 1 or 6 days later available; reactivity + PBS was no longer present. Four sera were treated with sulfhydryl reagents; in all cases the agglutinin was shown to be IgM.

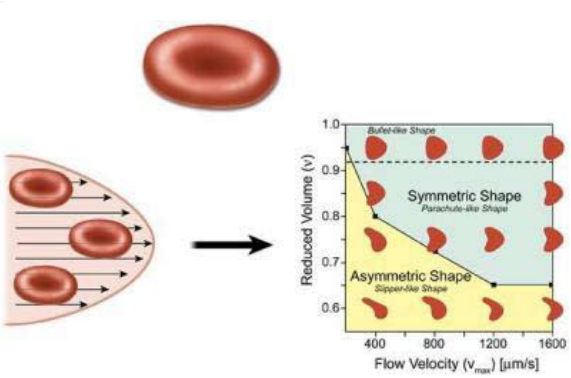
Please see next page.

Why Do Red Blood Cells Have Asymmetric Shapes Even in a Symmetric Flow?

Red blood cells (RBCs), normally take the shape of circular cushions with a dimple on either side. But they can sometimes deform into an asymmetrical slipper shape. A team of physicists have used simulations to explore how fluid flow might be responsible for this deformation, as well as how the deformation in turn affects blood flow. The insights could help understand the mechanisms involved in arterial disease and other blood flow-related ailments. Their research is reported in Physical Review Letters.

When a RBC flows through an artery, one face usually balloons out like a parachute, but sometimes the cell can deform to resemble a slipper. To find out why, Badr Kaoui at the Université Joseph Fourier in Grenoble, France and his colleagues modeled the cells as two-dimensional fluid-filled sacks flowing in a liquid. They found that when the cells weren't sufficiently plump, the symmetric parachute collapsed into a slipper. They also found that this morphing helped the sacks catch up with the rest of the fluid, suggesting that the slipper shape achieves more efficient blood flow.

Little is known about how the shape of red blood cells could change how they transport oxygen or how they interact with chemicals in the body. More generally, understanding circulation is important to pathology of illnesses like coronary heart disease. The ailment, which develops when plaque obstructs blood flow in an artery, is the leading cause of death in the United States. Kaoui and his colleagues' research takes the first steps toward understanding the consequences of RBC shape and behavior on overall blood flow.



The motion and shape of red blood cells depends on the flow environment. **(Top)** The shape of a red blood cell at rest is symmetric, with both sides of the membrane concave. **(Bottom left)** The velocity profile of the fluid that carries the cells through a blood vessel is assumed to have a symmetric parabolic shape. **(Bottom right)** The simulated shapes of the cells as a function of the surrounding flow velocity and their reduced area. Under some conditions, the cells tend to form asymmetric shapes.

Understanding why red blood cells RBCs move with an asymmetric shape (slipperlike shape) in small blood vessels is a long-standing puzzle in blood circulatory research. By considering a vesicle (a model system for RBCs), the researchers discovered that the slipper shape results from a loss in stability of the symmetric shape. It is shown that the adoption of a slipper shape causes a significant decrease in the velocity difference between the cell and the imposed flow, thus providing higher flow efficiency for RBCs. Higher membrane rigidity leads to a dramatic change in the slipper morphology, thus offering a potential diagnostic tool for cell pathologies.

Kaoui B, Biros G, Misbah C. Why Do Red Blood Cells Have Asymmetric Shapes Even in a Symmetric Flow? *Phys. Rev. Lett.* 2009. 103:188101.

Study Finds Use of Cell-Free Hemoglobin-Based "Blood Substitutes" Results in Increased Risk of Myocardial Infarction and Death

Hemoglobin-based blood substitutes (HBBSs) are infusible oxygen-carrying liquids that have long shelf lives, have no need for refrigeration or cross-matching, and are ideal for treating hemorrhagic shock in remote settings. Some trials of HBBSs during the last decade have reported increased risks without clinical benefit.

In this study, scientists assessed the safety of HBBSs in surgical, stroke, and trauma patients by reviewing PubMed, EMBASE, and Cochrane Library searches for articles using *hemoglobin* and *blood substitutes* from 1980 through March 25, 2008, as well as reviews of Food and Drug Administration (FDA) advisory committee meeting materials, and Internet searches for company press releases.

Researchers analyzed randomized controlled trials including patients aged 19 years and older receiving HBBSs therapeutically. The database searches yielded 70 trials of which 13 met these criteria; in addition, data from 2 other trials were reported in 2 press releases, and additional data were included in 1 relevant FDA review. They then extracted data on death and myocardial infarction (MI) as outcome variables. They identified 16 trials involving 5 different products and 3,711 patients in varied patient populations. They concluded that a test for heterogeneity of the results of these trials was not significant for either mortality or MI (for both, I2 = 0%, P .60). Data were combined using a fixed-effects model.

Overall, they found there was a statistically significant increase in the risk of death (164 deaths in the HBBS-treated groups and 123 deaths in the control groups; relative risk [RR], 1.30; 95% confidence interval [CI], 1.05-1.61) and risk of MI (59 MIs in the HBBS-treated groups and 16 MIs in the control groups; RR, 2.71; 95% CI, 1.67-4.40) with these HBBSs. Subgroup analysis of these trials indicated the increased risk was not restricted to a particular HBBS or clinical indication.

Based on the available data, the study found that the use of HBBSs is associated with a significantly increased risk of death and MI.

Natanson C, Kern SJ, Lurie P, MD, Banks SM, Wolfe SM. Cell-Free Hemoglobin-Based Blood Substitutes and Risk of Myocardial Infarction and Death. *JAMA*. 2008. 299.

Researchers Analyze Anti-Ceftriaxone in Drug-Induced Immune Hemolytic Anemia Patients, continued

Most cases of DIIHA due to ceftriaxone are found in children and a high percentage of them are fatal. Anti-ceftriaxone appears to be predominantly an IgM complement-binding antibody capable of causing in vivo and in vitro hemolysis. This study is, by far, the largest series of DIIHA due to anti-ceftriaxone reported.

Arndt PA, Leger RM, Garratty G. Serologic characteristics of anti-ceftriaxone in a large series of patients with drug-induced immune hemolytic anemia (Abstract S78-030K) *Transfusion*. 2009. 49(Supp): 33A.

Remember These Websites

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American Red Cross

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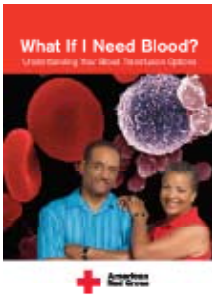

"*What If I Need Blood*?", a brochure which answers commonly asked questions and explains the transfusion options for patients, is available through your American Red Cross representative.

The second edition of "*Practice Guidelines for Blood Transfusion: A Compilation of Peer-Reviewed Literature*", is available through your American Red Cross Blood Services representative. This pocket guide is a concise transfusion medicine resource, providing guidelines for some of the more commonly encountered clinical situations.

"*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.