Title

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Journal

Transfusion Medicine Reviews, 26(4)

ISSN

0887-7963

Authors

Kleinman, Steven
King, Melissa R
Busch, Michael P
et al.

Publication Date

2012-10-01

DOI

10.1016/j.tmrv.2012.04.004

Peer reviewed

The National Heart, Lung, and Blood Institute Retrovirus Epidemiology Donor Studies (Retrovirus Epidemiology Donor Study and Retrovirus Epidemiology Donor Study-II): Twenty Years of Research to Advance Blood Product Safety and Availability

Steven Kleinman, Melissa R. King, Michael P. Busch, Edward L. Murphy, and Simone A. Glynn, for The National Heart Lung Blood Institute Retrovirus Epidemiology Donor Study and Retrovirus Epidemiology Donor Study-II

The Retrovirus Epidemiology Donor Study (REDS), conducted from 1989 to 2001, and the REDS-II, conducted from 2004 to 2012, were National Heart, Lung, and Blood Institute–funded, multicenter programs focused on improving blood safety and availability in the United States. The REDS-II also included international study sites in Brazil and China. The 3 major research domains of REDS/REDS-II have been infectious disease risk evaluation, blood donation availability, and blood donor characterization. Both programs have made significant contributions to transfusion medicine research methodology by the use of mathematical modeling, large-scale donor surveys, innovative methods of repository sample storage, and establishing an infrastructure that responded to potential emerging blood safety threats such as xenotropic murine leukemia virus–related virus. Blood safety studies have included protocols evaluating epidemiologic and/or laboratory aspects of human immunodeficiency virus, human T-lymphotropic virus 1/2, hepatitis C virus, hepatitis B virus, West Nile virus, cytomegalovirus, human herpesvirus 8, parvovirus B19, malaria, Creutzfeldt-Jakob disease, influenza, and *Trypanosoma cruzi* infections. Other analyses have characterized blood donor demographics, motivations to donate, factors influencing donor return, behavioral risk factors, donors' perception of the blood donation screening process, and aspects of donor deferral. In REDS-II, 2 large-scale blood donor protocols examined iron deficiency in donors and the prevalence of leukocyte antibodies. This review describes the major study results from over 150 peer-reviewed articles published by these 2 REDS programs. In 2011, a new 7-year program, the Recipient Epidemiology and Donor Evaluation Study-III, was launched. The Recipient Epidemiology and Donor Evaluation Study-III expands beyond donor-based research to include studies of blood transfusion recipients in the hospital setting and adds a third country, South Africa, to the international program.

THE NATIONAL HEART, Lung, and Blood Institute (NHLBI) has a more than 40-year history of promoting multicenter studies to improve blood safety. In 1989, the NHLBI began funding the Retrovirus Epidemiology Donor Study (REDS). The REDS was initiated in response to concerns about the impact of human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV) infection on recipient safety in the United States [1]. Although the original mission of this program was to initiate and facilitate investigations of human retroviruses in volunteer blood donors, the goals of the program were soon broadened to include many other critical questions concerning blood safety and availability. The REDS program spanned a total of 13 years, from 1989 through 2001.

Based on the significant contributions of REDS, a new study—the REDS-II—was begun in 2004 and has completed most of its work, although some additional projects will extend until the end of 2012. Both of these research programs have focused on studies of US blood donors with the aim of improving blood product safety and

From the Department of Pathology, University of British Columbia, Victoria, British Columbia, Canada; Westat, Health Studies, Rockville, MD; Blood Systems Research Institute, San Francisco, CA; Laboratory Medicine, University of California San Francisco, San Francisco, CA; Laboratory Medicine and Epidemiology/Biostatistics, University of California San Francisco, San Francisco, CA; Blood Systems Research Institute, San Francisco, CA, and Transfusion Medicine and Cellular Therapeutics Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.

Conflict of interest statement: Each of the authors declares that he/she has no conflicts of interest regarding any of the work presented in this publication.

Contract support: The Retrovirus Epidemiology Donor Study was supported by the National Heart, Lung, and Blood Institute contracts N01-HB-97077 (superseded by N01-HB-47114), -97078, -97079, -97080, -97081, and -97082. The Retrovirus Epidemiology Donor Study-II was supported by the National Heart, Lung, and Blood Institute contracts N01-HB-47168, -47172, -47175, and -57181.

Address correspondence to Steven Kleinman, MD, 1281 Rockcrest Avenue, Victoria, British Columbia, Canada V9A 4W4.

E-mail: skleinman@shaw.ca

0887-7963/$ - see front matter

doi:10.1016/j.tmrv.2012.04.004

availability. In addition, REDS-II added an international component that has focused on similar aims in 2 countries (China and Brazil) characterized by ongoing concerns about HIV transmission through blood transfusion. Most recently, in 2011, the NHLBI began funding a 7-year program, the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). The REDS-III expands the donor-based research focus of the original 2 REDS programs to include studies of blood transfusion recipients in the hospital setting and expands the international program by supporting transfusion medicine and blood banking research in South Africa as well as in Brazil and China.

This review will describe the major results and contributions of the epidemiologic and laboratory studies conducted in the REDS and REDS-II programs. As will be described, protocols were conducted that not only built upon methodological advances implemented in the early years of the program but also addressed changing research needs and emerging priorities, illustrating the flexibility of the REDS and REDS-II programs. The research areas encompassed in the REDS programs have been and continue to be hypothesis generating, leading to the development of new basic and translational research projects with implications well beyond blood banking and transfusion medicine.

PARTICIPATING INSTITUTIONS

The REDS and REDS-II each was structured around a central coordinating center, a central laboratory, and multiple participating blood centers as described in Online Appendix A. In each program, donations collected by the participating blood centers comprised approximately 8% of total US collections. An international component, conducted in China and Brazil, respectively, was added to the REDS-II program in 2006 and was organized with a similar infrastructure (Online Appendix B).

THE DOMESTIC RESEARCH PROGRAM—MAJOR FINDINGS

The REDS and REDS-II have made substantial contributions in 3 major research areas in transfusion medicine/blood banking in the United States, namely, infectious disease risk evaluation, blood donation availability, and blood donor characterization. The largest body of research conducted by the REDS and REDS-II was related to transfusion-transmitted infectious disease risks and included (*a*) assessing the prevalence and incidence, residual risks, and test yield rates of known transfusion-transmitted agents (HIV, HTLV, hepatitis C virus [HCV], and hepatitis B virus [HBV]) and evaluating demographic influences on the occurrence of these infections; (*b*) evaluating the performance of existing, new, and proposed donor screening and confirmatory assays; (*c*) providing a rapid response capability for suspected new transfusion-transmitted agents; (*d*) evaluating risk of other possible transfusion-transmitted agents; (*e*) evaluating the donor screening process and the behavioral and demographic characteristics of donor infectious disease risk; (*f*) projecting the impact of changing donor acceptance/deferral criteria on selected infectious disease risks; and (*g*) defining the natural history of HTLV infections in donors. In the area of blood donation availability, REDS and REDS-II efforts concentrated on (*a*) determining donor demographic characteristics and the factors influencing donation return, (*b*) evaluating the characteristics of deferred donors and the impact of temporary deferral on donation patterns, and (*c*) understanding the factors that may lead donors to delay reporting information that would otherwise have led to their deferral at the time of a previous donation (postdonation information [PDI]). Finally, REDS-II extended the scope of research conducted in the original REDS program by executing specific studies to gain a better understanding of the impact of blood donation on donor iron status and of the factors influencing the development of iron deficiency in blood donors as well as studies to evaluate the prevalence of leukocyte antibodies in alloexposed blood donors and the potential association of high-volume plasma components containing these alloantibodies with transfusion-related acute lung injury (TRALI) in recipients. Table 1 provides a broad overview of the studies conducted in the United States.

Infectious Disease Research

A major focus of the initial REDS program was related to studies of blood safety and to the laboratory and behavioral screening of blood donors. These are described in detail below.

Assessing the Prevalence and Incidence, Residual Risks, and Test Yield Rates of Known Transfusion-Transmitted Agents (HIV, HTLV, HCV, and HBV) and Evaluating Demographic Influences on the Occurrence of These Infections. An early contribution of REDS was the development of the

Table 1. The REDS and REDS-II Study Portfolios Highlights—United States

Major research area	Major subject matter investigated
Blood safety	Prevalence and incidence, residual risks, and test yield rates of known transfusion-transmitted agents (HIV, HTLV, HCV, and HBV) and their relationship to donor demographics
	Performance characteristics of existing, new, and proposed donor screening and confirmatory assays
	Rapid evaluation of suspected new transfusion-transmitted agents
	Risk of other possible transfusion-transmitted agents
	Behavioral and demographic characteristics of donor infectious disease risk
	UDR
	Effectiveness of the donor screening process
	Impact of changing acceptance/deferral criteria on selected infectious disease risks
	The natural history of HTLV infections in donors
Blood availability	Donor demographic characteristics
	Motivations for and deterrents to blood donation
	Factors influencing donor return
	Characteristics of deferred donors and the impact of temporary deferral on donation patterns
	Donors reporting PDI
Special donor studies	Iron deficiency in blood donors
	Prevalence of leukocyte antibodies in alloexposed blood donors

incidence-window period mathematical model—which was also independently developed by Centers for Disease Control and Prevention (CDC) and American Red Cross (ARC) investigators—to estimate the residual risk of agents (HIV, HTLV, HCV, and HBV) for which blood screening was performed [2-4]. After initial publication of this model with infectious risk estimates in the mid 1990s, REDS made further refinements to the model, which included methods to model HBV incidence from hepatitis B surface antigen (HBsAg) incidence and modeling of HIV incidence using either a less sensitive detuned antibody assay or a new strategy of analyzing minipool (MP) nucleic acid testing (NAT) yield rates [5,6]. Related to these modeling efforts, trends in incidence and prevalence of transfusion-transmissible viral infections in the donor population were reported, and various demographic characteristics of infected donors were studied [7-10]. One important finding was that prevalence of a viral infection (eg, HIV, HCV, HBV, or HTLV) in the overall donor population did not consistently reflect its corresponding incidence [11]. Because of this work, the incidence-window period (sometimes with minor modifications) has been used by multiple international investigators to model residual risk in their jurisdictions [12].

Using these same models and testing performed on plasma donor seroconversion panels, REDS investigators refined window period estimates for HIV, HCV, and HBV and projected the yield of enhanced viral detection assays (eg, MP and individual donation [ID] NAT) in targeting window-phase units for these viruses [6,13]. These studies allowed for a better understanding of the window period and eclipse phase of infections and resulted in the discovery of intermittent viremia (also called *blip viremia*) in early (pre–ramp-up) HIV and HCV infection before exponential viral replication [14-16]. Further studies have shown that plasma units with HCV blip viremia did not transmit infection in a chimp model of HCV infection [17].

Evaluating the Performance of Existing, New, and Proposed Donor Screening and Confirmatory Assays. As tests for new infectious agents are considered or implemented in blood donor screening, it is important that the performance characteristics of these assays and related testing algorithms are established. Within REDS, this issue was also important to ensure that viral marker data used in epidemiological analyses were accurate and to guide the conduct of studies related to donor counseling and recipient lookback. Significant findings related to this subject matter area are presented in Table 2 [18-39].

Providing a Rapid Response Capability for Suspected New Transfusion-Transmitted Agents. The REDS infrastructure allowed researchers to evaluate a new agent quickly for its prevalence in the

Table 2. Major Infectious Disease Testing Studies

Topic	Findings	References
NAT	Calculated HIV and HCV NAT yield data and made estimates of residual risk. Demonstrated comparable performance of 2 major manufacturers' NAT assay platforms in standard pool sizes.	[18,19]
HIV serology	Determined frequency of false-positive HIV-1 Western blots Developed and evaluated an operational algorithm for resolution of HIV status of donors/persons with possible false-positive HIV Western blot patterns Found that HIV-1 p24 antigen indeterminate donors were not infected with HIV-1 Found that some p24 antigen–positive neutralization results were false positive Showed that HIV antibody indeterminate test results in blood donors were rarely, if ever, associated with HIV infection Showed very limited value of anti-HBc as a surrogate for detecting window period HIV infections	[20-24]
HTLV serology	Evaluated accuracy of supplementary serological testing Classified positive donors as infected with either HTLV-1 or HTLV-2 Evaluated performance of algorithms to confirm HTLV infection Reported high rates of indeterminate and false-positive reactivity by HTLV viral lysate and recombinant antigen (p21e)-spiked Western blots Demonstrated that indeterminate HTLV confirmatory results (eg, reactivity to the HTLV p24 protein) were not due to infection with primate T-lymphotropic viruses	[25-27]
HCV serology	Demonstrated virtual absence of residual benefit of ALT screening for prevention of HBV and HCV transmission after introduction of second-generation HCV antibody screening. Showed only marginal incremental yield of window phase infections by HCV EIA 3.0 relative to HCV EIA 2.0 Showed that the RIBA version 3.0 needed to be used in conjunction with EIA 3.0 for accurate donor-counseling purposes	[28-31]
HBV serology	Evaluated the utility of anti-HBc testing in detecting units that could transmit HBV infection Determined HBV viral loads in HBsAg-positive donations Established methodology for estimating the reduction of transfusion-transmitted HBV infection with HBV NAT testing Documented that some HBsAg EIA reactive, neutralization-confirmed test results were false positive and developed an algorithm to evaluate such results	[32-35]
General serology	Established that donor screening assays had a low rate of false-negative test results Established that the rate of false-positive donor screening tests increased when switching test kit manufacturers and varied depending on reagent lot	[36-38]
MS	Determined that the clade/genotype/subtype distribution of HIV, HCV, and HBV isolates from US blood donors in 2006 to 2009 was similar to that seen in high-risk US populations In donors with incident vs prevalent infections, determined the frequency of antiviral drug resistance mutations in HIV and HBV isolates and the rate of HBV vaccine and immune escape mutations	[39]

Abbreviations: RIBA, recombinant immunoblot assay; HBc, hepatitis B core; EIA, enzyme immunoassay.

US donor population, risk factors, transfusion-transmission potential, and clinical relevance to the blood recipient population [40]. Both REDS and REDS-II designed research protocols to evaluate threats to transfusion safety that were unknown and unanticipated at the time the REDS programs were established. Studies on the following agents/syndromes have been conducted: idiopathic CD4 T-cell lymphocytopenia in 1992, West Nile virus (WNV) in 2002 to 2004, influenza viruses in 2008, and xenotropic murine leukemia virus related virus (XMRV) in 2009 to 2011.

Idiopathic CD4 T-cell lymphocytopenia was identified as a potential threat to blood safety when it was hypothesized that this condition of low CD4 T-cell counts was caused by a yet undiscovered retrovirus that induced an immunodeficiency syndrome similar to HIV. The REDS rapidly responded to this potential threat by conducting a study to evaluate several rapid CD4 screening methods and determined that none of these methods were suitable for blood donor screening [41]. Fortunately, further studies by multiple research groups established that there

was no association between diminished CD4 cell counts and a new retrovirus.

In the early 1990s, HCV transmission was documented with a specific manufacturer's intravenous immunoglobulin preparation, raising concern that other immunoglobulin products such as Rh immunoglobulin preparations might also have been at risk for transmitting HCV. The REDS examined the rates of anti-HCV positivity in female Rh-negative donors and found that these donors were no more likely to be HCV-positive than Rh-positive female donors [42].

The REDS played a major role in evaluating several aspects of WNV infection. First, in collaboration with America's Blood Centers (ABC), REDS evaluated a voluntary market withdrawal of fresh frozen plasma collected during the 2002 WNV season and established that this withdrawal averted a small number of WNV transfusion-transmissions [43]. A second study evaluated the performance of WNV NAT assays after their introduction in July 2003, just 10 months after the first transfusion-associated WNV infections were detected in the United States. The REDS group developed a protocol to monitor national WNV NAT yield and compiled the first year of WNV screening data from ABC blood centers [44]. This study established definitions and criteria for the interpretation of results and calculated sensitivity, specificity, and positive and negative predictive values for MP and ID WNV NAT screening. This study, when combined with follow-up studies of WNV-infected donors performed by others, allowed for characterization of the dynamics of acute WNV infection and the kinetics of NAT and antibody detection and also established the relative yield of MP NAT vs ID NAT [45]. This, in turn, led to the nationwide implementation of targeted ID NAT testing of individual blood donations. Third, in collaboration with CDC, ARC, and Blood Systems Research Institute (BSRI), REDS synthesized blood donor NAT yield rates and cumulative seroincidence data with national WNV clinical data to estimate the proportion of WNV infections that progress to serious neurologic disease [46].

Spurred on by concerns initially prompted by the avian flu outbreak (H5N1) and, subsequently, by the H1N1 epidemic, the REDS-II Central Laboratory evaluated the performance of several nucleic acid detection systems for detection of influenza virus in plasma and/or whole blood [47,48]. After this assay evaluation, 3 assays were used to test for the presence of influenza virus in blood donor samples from donors with increased influenza risk. These included REDS Allogeneic Donor and Recipient Repository (RADAR) repository donation samples (see below) that had been collected during a seasonal flu epidemic as well as samples obtained from contemporary Blood Systems Inc and ARC donors who reported postdonation febrile and/or respiratory illnesses. This study found no evidence of influenza viremia in 1482 donor "at-risk" specimens, establishing that it is extremely unlikely for seasonal influenza virus to pose a significant transfusion-transmission risk [48].

With the reported association of XMRV and chronic fatigue syndrome in October 2009, concerns were raised that XMRV might be a transfusion-transmitted pathogen that could cause significant clinical disease. As a response, the NHLBI quickly convened a Blood XMRV Scientific Research Working Group composed of experts in retrovirology, blood banking and infectious diseases, and chronic fatigue syndrome. The Scientific Research Working Group embarked upon a 3-phase project partially funded under the REDS-II contract and coordinated by the REDS-II Central Laboratory. The final conclusion from these studies was that current XMRV/polytropic murine leukemia virus (P-MLV) assays are not able to reproducibly detect XMRV/murine leukemia viruses (MLV) in patients who had been previously reported as infected with these viruses and, consequently, that blood donor screening for XMRV/MLV is not warranted [49,50]. These results were consistent with negative results from many other studies and with the finding that XMRV is a laboratory contaminant that originated by recombination of 2 endogenous MLV proviruses during tumor passaging of prostate cancer tissue in mice to generate prostate cancer cell lines [51,52].

Another major resource for studying emerging pathogens is the use of frozen repositories of donor, recipient, or linked donor-recipient samples [1,53]. Three major repositories were established in REDS.

- The General Serum Repository, completed in 1994, consists of serum specimens from more than 500 000 blood donors at the 5 REDS blood centers.
- The General Leukocyte and Plasma Repository (GLPR), completed in 1995, consists of whole blood (including leukocytes suitable for

human and pathogen DNA diagnostics) and plasma specimens from more than 147 000 blood donors at the 5 REDS blood centers.

- The RADAR, collected from 2000 to 2003, is a linked donor-recipient repository with donor specimens collected at 7 participating blood centers and recipient specimens collected by 8 participating hospitals that received the designated donor units [54]. In addition to the 5 REDS participating cities, 2 additional blood center hospital sites were established in Tampa, FL (Florida Blood Services), and Pittsburgh, PA (Institute for Transfusion Medicine), through CDC collaboration and funding. The repository contains whole blood and plasma aliquots from 3575 recipients (these were collected pretransfusion and 6- to 12-month posttransfusion, mostly from cardiovascular surgery patients) that are linked to 13 201 donation samples. In addition, there is a supplemental repository of over 99 000 donation specimens not linked to recipients.

Samples from these repositories have been used for several REDS and REDS-II studies of potential transfusion-transmitted agents (cytomegalovirus [CMV], parvovirus B19 [B19V], and human herpesvirus 8 [HHV-8]; see below). In addition, because ethical and consent issues about repository storage have been reevaluated over the past decade, REDS-II evaluated the willingness of donors to participate in repository-based research and found that, overall, 87% of donors would agree to have their blood specimens stored for future research in a long-term repository if they were asked; this percentage was lower in African American donors (78%) than in white (88%) or Hispanic and Asian donors (about 85%) [55].

Currently, the General Serum Repository, GLPR, and RADAR repositories are housed in the NHLBI Biorepository and are accessible through the NHLBI BioLINCC Program. This program makes repository samples and their associated data accessible to the scientific community upon review of meritorious requests. Details are available at https://biolincc.nhlbi.nih.gov/home/.

Evaluating Risk of Other Possible Transfusion-Transmitted Agents. The REDS and REDS-II have performed studies related to 3 other possible/actual transfusion-transmitted agents: CMV, HHV-8, and B19V.

Cytomegalovirus. Because of widely differing blood donor CMV DNA prevalence reported from different laboratories, REDS conducted a blinded multicenter evaluation of 7 CMV DNA polymerase chain reaction (PCR) assays in 5 independent laboratories using an analytic and clinical sample set assembled at the REDS Central Laboratory [56]. There was marked variation in the sensitivity, specificity, and reproducibility of the assays with only 3 of the 7 judged to have sufficient sensitivity and specificity for potential use in donor screening algorithms. Based on these results, 2 assays were selected for use in a subsequent blood donor prevalence study that tested 1000 paired plasma and whole blood samples obtained from the REDS GLPR. Only 2 of 416 CMV-seropositive samples had reproducibly detectable CMV DNA, whereas all CMV seronegative samples were DNA negative. This study established that CMV PCR assays, when compared with CMV serology, did not increase the detection of potentially infectious blood components [57].

Human Herpesvirus 8. Because of the lack of a criterion standard assay or algorithm for HHV-8 antibody, REDS investigators conducted a study of HHV-8 antibody detection in 6 laboratories with expertise in this area [58]. In this study, replicate panels of 1000 blood donor plasma specimens obtained from the REDS GLPR and 41 samples from patients with Kaposi sarcoma were tested for HHV-8 antibody. After performing a latent class analysis on the results from these laboratories, the prevalence of HHV-8 antibodies in US blood donors was estimated to be 3.3%. Additional HHV-8 PCR testing of samples from antibody positive donors failed to detect any HHV-8 DNA positive donor, establishing that HHV-8 DNA is either not present or present infrequently in asymptomatic donors with positive HHV-8 serology.

Parvovirus B19. The REDS-II investigators accessed specimens from the RADAR repository to determine the prevalence of B19V in donor and recipient populations and to evaluate the possible transmission from potentially infectious blood donors to their recipients. The REDS Central Laboratory adapted a commercial TaqMan real-time PCR assay targeting the VP1 region of the genome to provide very high sensitivity (50% limit of detection [LOD] of 1.6 IU/mL) for B19 detection

and to quantitate B19V DNA. Using this assay, 0.88% of donors were found to be viremic, most with very low DNA levels [59]. This assay was then applied to linked donor and recipient samples to establish that B19 viremic donors with DNA levels less than 10^6 copies per mL did not transmit B19V infection to 24 susceptible (B19V seronegative) recipients. Based on this sample size, the 95% upper confidence interval (CI) for transmission was 11.7%, thus establishing that either transmission from components with less than 10^6 IU/mL does not occur or, if it does, it is an uncommon event, leading to the conclusion that routine screening of blood donations with a sensitive B19V DNA nucleic acid assay is not warranted [60]. A further study performed PCR testing on paired whole blood and plasma samples from 104 donations from 43 donors in the RADAR repository to assess whether B19V DNA concentrations were higher in whole blood because of the known ability of B19V to infect red blood cell (RBC) progenitors. The relative B19V DNA concentration varied by the stage of infection, with a 30-fold higher B19V DNA concentration in whole blood relative to plasma when immunoglobin M was present (ie, relatively recent infection) but with approximately equal concentrations in the 2 sample types when immunoglobin M was absent (ie, remote infection) [61].

Evaluating the Donor Screening Process and the Behavioral and Demographic Characteristics of Donor Infectious Disease Risk. Numerous REDS data analyses and publications have been directed toward assessing behavioral characteristics of donor infectious disease risk, particularly for transfusion-transmitted viral infections (TTVIs). These assessments included establishing demographic correlates for positive infectious disease tests and observing them over time, surveying donors for behavioral risk factors, evaluating donors' knowledge about HIV testing and transfusion-transmission risk, and modeling how changes in donor eligibility/deferral criteria could impact upon infectious disease risk and upon donor availability. These analyses have been important for influencing Food and Drug Administration (FDA) policy as well as for their broader public health implications.

Hepatitis C virus and HTLV. The REDS determined the prevalence and demographic characteristics of HCV and HTLV infection in US blood donors and found interesting parallels between HCV and HTLV-II infection, likely due to the shared mode of transmission by injection drug use (IDU). From March 1992 through December 1993, HCV seroprevalence was markedly age dependent: 0.5 per 1000 in donors younger than 20 years, 6.9 per 1000 in donors aged 30 to 39 years, and lower in older age groups [62]. In 1997, REDS performed a case control study using an anonymous questionnaire targeted to 2316 HCV-seropositive blood donors and an equal number of seronegative donors matched on age, sex, race/ethnicity, blood center, and first-time vs repeat-donor status. Independent HCV risk factors identified included IDU, sex with an IDU, blood transfusion in non-IDU, having been in jail for more than 3 days, religious scarification, having been stuck or cut with a bloody object, pierced ears or body parts, and immunoglobulin injection [63].

Further work on HCV infection was conducted immediately after HCV NAT implementation in 1999 through December 2001 [64]. In first-time recombinant immunoblot assay–positive donors, 402 (19.1%) of 2105 tested negative for HCV RNA by NAT (presumptive resolved infections). There were significant differences in the frequency of RNA negativity by alanine aminotransferase (ALT) levels and by race and/or ethnicity. The ALT levels were more likely to be elevated in RNA-positive first-time donors ($P < .0001$). Viremia was less likely to resolve in Asian (8.2%) and black non-Hispanic (14.4%) donors. Subsequently discovered genetic factors underlie these differences in HCV RNA clearance in black relative to white non-Hispanic donors [65].

Among 959 281 first-time donors in a large cross-sectional prevalence study conducted in REDS-II (2006-2007), HCV antibody prevalence was lower than in 1992 to 1993 and peaked in older age groups; this was attributed to both culling of seropositive donors and a birth cohort effect [66]. New associations were identified between anti-HCV prevalence and gravidity and obesity. RNA-negative status was associated inversely with black race and education and positively with body mass index.

For HTLV, antibodies to HTLV-I and HTLV-II were measured in 1.7 million REDS donors during 1991 to 1995; 156 (9.1 per 100 000) were HTLV-I seropositive and 384 (22.3 per 100 000) were HTLV-II seropositive [67]. In contrast to monotonously increasing age-specific HTLV-I seroprevalence, HTLV-II prevalence rose until the age of 40

Table 3. The REDS Donor Surveys

Year	Major aims	No. of donors surveyed	n (%) of donors responding	Publication reference number
1993	Undetected behavioral UDRs; HIV test-seeking behavior	50 162	34 726 (69%)	[69,118]
1995	Blood donation incentives	12 000	8091 (67%)	[73]
1997	Response to notification of reactive infectious disease screening or confirmatory test results	4141	1728 (42%)	[76]
1998	Undetected behavioral risks, safety of incentives, HIV test-seeking behavior, motivations to donate, attitudes about screening process	92 581	52 650 (57%)	[70-72,78-80,119]
2003	Motivations and barriers to donation in current donors Motivations and barriers to donation in lapsed donors	34 494	12 064 (35%)	[114-117]

to 49 years and declined thereafter, suggesting a birth cohort effect similar to that seen for HCV [68]. Risk factor interviews showed that low educational attainment, accidental needlesticks or cuts, prior blood transfusion, 7 or more sex partners, and a sex partner from an HTLV-I endemic area were significantly associated with both HTLV-I and HTLV-II. Injection drug use or having sex with an IDU partner were significant risks for HTLV-II but not for HTLV-I [67].

Survey Research. To better evaluate the donor screening process as well as the donor notification process and the determinants of blood donor return (see below), REDS pioneered the use of large-scale, multicenter, anonymous, mail-in surveys as a methodology for generating data from blood donors and conducted 6 such surveys (see Table 3). The main objectives of donor surveys were to estimate the prevalence of unreported TTVI deferrable risk factors (UDRs), determine the motivations/reasons for donating in individuals with risk factors, estimate the prevalence of HIV test-seeking behavior among donors, assess the impact of donor incentives on TTVI risk, and to evaluate the value of multiple steps in the donor screening process including donor educational materials, the confidential unit exclusion (CUE) option, and attitudes toward computer-assisted donor screening [69-80].

a. Unreported Deferrable Risks. The 2 most comprehensive donor surveys were conducted approximately 5 years apart in 1993 and 1998. A major finding of the 1993 survey was that 2% of donors acknowledged a behavioral risk that was unreported at the time of their donation (ie, a UDR) [69]. Unreported deferrable risk was higher in men, first-time donors, and donors with reactive infectious disease screening test results. Donating to receive HIV test results was reported by 6% of respondents with 3.2% doing so within the prior 12 months. This behavior was higher among donors with self-reported male-to-male sex (MSM); 14% of MSM donors reported donating at some time in their life to receive an HIV test, with 7% having done so in the previous year. Similarly, UDR rates of 21% (ever) and 10% (last year) were reported by men who had contact with a sex worker. In addition, the survey found that the value of CUE as a self-deferral mechanism was limited given that most donors with UDR did not use the CUE option and that most donors who used CUE did not report a risk.

The 1998 donor survey was conducted at the 5 REDS centers as well as at 3 additional blood centers. Although the UDR rate was similar to that in the 1993 survey, it was slightly higher (3%) because of an expanded definition of UDR [70]. Leading categories of UDR were MSM, receiving money or drugs for sex, IDU, and sex with an IDU in the past 12 months. Human immunodeficiency virus test-seeking behavior was decreased compared with the 1993 survey; however, of concern was that test seekers were more likely than non–test seekers to report a UDR. Furthermore, in the 1998 survey, both UDR and HIV test-seeking behavior were higher in younger aged (<25 years) donors [71]. Data for the 569 donors reporting MSM activity were analyzed relative to whether the donor had a reactive anti-HBc or syphilis screening test result. Compared with non-MSM donors, the prevalence of a reactive screening test result was higher among donors who reported MSM activity within the preceding 5 years but was not increased for donors whose last MSM activity was more remote than 5 years [72].

b. Effect of Incentives on Risks. A smaller donor survey conducted in 1995 provided insight on the issue of incentive use by blood centers for recruiting and retaining blood donors [73]. At the time, young and long-term donors were the donor groups who seemed to potentially be most

influenced by an incentive of limited value. Furthermore, it was concluded that the offering of more valuable cash or cash-equivalent incentives could potentially have a negative impact on blood safety, given that donors who were motivated by cash were 60% more likely to have a UDR than those not motivated by this incentive. However, offering blood credits and items of limited value appeared to be safe and effective strategies for retaining donors.

The 1998 donor survey further examined the issue of incentives by comparing the impact of incentives in apheresis vs repeat community blood donors, first-time vs repeat donors giving at different donation frequencies, and donors who gave at different donation sites [74]. Related to the incentives issue, the survey found that 0.8% of donations were from donors who were also patients with hemochromatosis; these donors had UDR rates similar to the larger donor population supporting the safety of transfusing such units [75].

c. Assessing Donor Notification and Counseling. An anonymous mail survey was conducted of 4141 donors notified with 1 or more of 15 abnormal infectious disease screening and confirmatory test results [76]. The survey, which had a 42% response rate, documented that most donors correctly understood their deferral status. However, about a quarter of donors did not, and confusion and emotional distress were reported by 81% and 75% of notified donors, respectively.

The REDS also measured psychologic distress associated with notification of HTLV infection in 464 HTLV-I– and HTLV-II–positive donors [77]. General well-being scores for donors who had tested seropositive for HTLV-I and HTLV-II indicated significantly more psychologic distress than in seronegative donors ($P < .0005$) or in a large national sample ($P < .05$). Variables that predicted higher general well-being scores were negative HTLV status, older age, higher income, better health, fewer sick days, and fewer work limitations because of health problems.

Projecting the Impact of Changing the Acceptance/Deferral Criteria on Selected Infectious Disease Risks. The REDS explored how changes to donor screening procedures or donor eligibility criteria for selected infectious disease risks might impact blood safety and availability. The first such analysis established that the CUE procedure had low sensitivity and specificity for detecting donors with positive infectious disease markers and, therefore, was likely to have similar poor performance characteristics for detecting donors in the window period of HIV infection [81]. The REDS modeled whether the increased detection of HIV-infected donors expected after the implementation of the HIV p24 antigen test would be offset by the potential for additional infectious HIV p24 antigen–negative donors to donate based on their desire to obtain this test result (ie, the magnet effect) [82]. Another analysis was related to the possible strategy of deferring older age donors (>age 50 or 60 years) because of an increased frequency of Creutzfeldt-Jakob disease, which, at the time, was considered to be a theoretical transfusion-transmission risk. Replacement of donors older than 50 years with younger donors was estimated to increase the risk of transmitting HIV, HCV, and HBV infection, whereas no such increase was projected for deferral of donors older than age 60 years [83]. When concern arose over the transfusion-transmission of variant Creutzfeldt-Jakob disease, REDS analyzed the effect that a lifetime deferral of donors with a history of transfusion would have on blood safety and found that transfused and nontransfused donors had a similar viral incidence and comparable rates of UDR [84]. The 1998 donor survey assessed projected deferrals that would occur if donors were asked questions about whether they had ever eaten mammalian or bovine brain and found that this would result in a substantial rate of deferral, especially among certain demographic subgroups of donors [85]. Because of the very low risk of transfusion-transmitted malaria in the United States and the large impact of malaria-related travel deferral on blood availability, REDS-II constructed mathematical models to evaluate the impact of potential changes to deferral criteria for deferral to various international locations. It was determined that shortening the deferral period for travel to Mexico from the current 12-month requirement to 3 months would result in 1 additional case of transfusion-transmitted malaria per 57 years at an annual gain of more than 56 000 donations [86]. In a subsequent, more detailed analysis of travel solely to Mexico, it was found that more than 70% of Mexican travel deferrals were for visits to Quintana Roo, an area of very low malaria transmission. It was estimated that eliminating the travel deferral for all areas of Mexico except the state of Oaxaca might result in the recovery of

Table 4. Major Scientific Accomplishments of the REDS HTLV Cohort Study

HTLV research questions	Findings	References
HAM	Novel finding that HAM is associated with HTLV-II infection in addition to HTLV-I, albeit with lower penetrance and somewhat milder presentation.	[88-90]
Bronchopulmonary infection	Higher incidence of bronchitis and pneumonia among HTLV-II subjects, but pulmonary function is not impaired, and both T-cell (delayed hypersensitivity skin testing) and B-cell (antibody production in response to pneumococcal vaccination) functions are intact.	[91-96]
HTLV PVL	Mean PVL was 1905 copies per 10^6 PBMCs for HTLV-I and 398 copies per 10^6 PBMCs for HTLV-II and varied by HTLV-II subtype, route of infection, and sex. Both HTLV-I and HTLV-II PVL vary widely between individuals but are stable at the same "setpoint" in each individual over a median of 10.4 years of follow-up.	[97-99]
Sexual transmission	HTLV-I and HTLV-II incidence of 0.6 per 100 person-years (95% CI, 0.2-1.6) within serodiscordant heterosexual couples. Transmission is associated with higher PVLs in the infecting partner; no difference in transmission between HTLV-I and HTLV-II nor between male-to-female vs female-to-male directions.	[100,101]
Hematology outcomes	HTLV-II infected subjects have long-term increases in adjusted lymphocyte counts (+ 7%), mean corpuscular volume, and adjusted platelet counts. Sex, race, smoking, and alcohol consumption all had significant effects on blood counts.	[102-104]
APH-2	APH-2 mRNA was detected in PBMC from 4 of 15 HTLV-II–infected blood donors and could explain the lymphocytosis frequently observed in patients with HTLV-II.	[105]
HTLV-II molecular epidemiology	HTLV-II subtype a0 was independently associated with age older than 30 years and with black race/ethnicity. The HTLV-II RFLP subtypes b4 and b5 were significantly more common among American Indian and other race/ethnicity and at the Oklahoma City Blood Center.	[106,107]

Abbreviations: HAM, HTLV-associated myelopathy; PVL, proviral load; PBMCs, peripheral blood mononuclear cells; APH-2, antisense protein of HTLV-II; mRNA, messenger RNA; RFLP, restriction fragment length polymorphism.

almost 65 000 blood donors annually at a risk for approximately 1 malarial transmission every 20 years [87].

Defining the Natural History of HTLV Infections in Donors: The HTLV Cohort Study. A multicenter, prospective cohort study of HTLV-I– and HTLV-II–infected blood donors was initiated in 1990 as one of the first REDS protocols. This natural history study has become a benchmark study of HTLV health outcomes worldwide. The REDS cohort of HTLV-infected and non–HTLV-infected blood donors was enrolled in 1990 to 1992 and was then followed with a health questionnaire, physical examination, and blood testing for an additional 7 visits approximately every 2 years through 2009. In 1998 to 1999, the study transitioned from the REDS research contract to an independent R01 funding mechanism from NHLBI and was renamed the HTLV Outcomes Study.

Major scientific accomplishments of the HTLV cohort study are presented in Table 4 [88-107].

Blood Donation Availability Research

The REDS and REDS-II strove to better understand the determinants of blood donation availability by evaluating donor demographics as well as return behavior and deferral patterns using the REDS and REDS-II donation databases as well as the REDS-II donor deferral database that compiled information during the span of these research programs. In addition, motivations and barriers to donation were assessed through the 1998 donor survey and 2 additional donor surveys conducted in 2003.

Determining Donor Demographic Characteristics and the Factors Influencing Donation Return. The REDS has performed multiple studies describing individuals who donate and assessing donation patterns and rates of donor return and blood availability determinants including what motivates and deters people from donating blood [108-124]. The goal of these studies was to provide blood centers with information to evaluate the effectiveness of ongoing donor recruitment and retention strategies and identify where additional efforts were warranted to improve blood availability. These studies were conducted using the backbones of these programs, the centralized donation and deferral databases. These longitudinal databases were built using blood center operational data with a few REDS/REDS-II program-specific additions. As described in Table 5, database

Table 5. Donation/Donor Database elements in REDS/REDS-II

Identification information
Donor identification number (encrypted) *
Blood identification number
Standard donation variables
Blood center
Donation type
Donation site
Date of donation
Date of previous donation, if any
First time to blood center
Date of birth
Sex
Zip code of residence
Specially collected variables
Race/ethnicity
Educational level
Country of birth
Transfusion history
Pregnancy history †
CUE status ‡
Laboratory results
Blood type
All donor screening and confirmatory infectious disease test results §
Deferral status and reason for deferral †
Quantitative fingerstick hemoglobin level and hematocrit ‖

* Allows linkage of all donations from a given donor.
† Collected only in REDS-II.
‡ Collected in the early years before discontinuation.
§ Updated as new assays were added (eg, HIV NAT, HCV NAT, WNV NAT, *T cruzi* antibody) during the 20 year interval.
‖ Collected only in the later years of REDS-II.

elements comprised screening and confirmatory test results, reasons for deferral, and donor demographics, including age, sex, race/ethnicity, educational status, country of birth, transfusion history, pregnancy history, and previous blood donation history. As an example of the type of analysis conducted using these data, REDS published ABO and Rh D phenotype frequencies of different racial/ethnic groups in the United States using one of the largest donor databases compiled to date [125].

The REDS/REDS-II donation databases of approximately 1 million donations per year made possible continuous monitoring of the demographic profiles of the donor population. Thus, as the demographic profile of the US population shifted over approximately 20 years, the databases provided a mechanism to analyze the demographics of the donor base [108,109] as well as the return patterns for specific types of donors. Multiple analyses during the course of the REDS programs assessed the time to return or the interdonation intervals between donations [110-119]. For example, a study to evaluate whether repeat blood donors who develop antibodies to HIV or other viral infections change their donation pattern in some way because of seroconversion was conducted [110]. This necessitated the development of a new statistical adjustment to account for length-biased sampling [111]. In addition, REDS evaluated probability of return and trends for repeat donation among specific types of blood donors and even assessed the impact of the September 11 disaster on the blood supply and safety as well as whether first-time disaster donors returned subsequent to the crisis period [112].

In an effort to help improve donor recruitment and retention programs, 2 large donor surveys were conducted in 2003, one in lapsed donors and the second in donors who had donated within the prior 12 months [118-121]. The surveys focused on examining factors that influenced the decision to donate and the decision to return as well as barriers and obstacles to blood donation. Over 90% of respondents were motivated by either a desire or a perceived duty to help others. Between 13% and 18% of donors in each demographic group reported that at least 1 of several incentives such as a gift, a ticket to a performance, time off work, or a reward was important or very important in their decision to donate, but over 50% did not find any of the incentives important at all in their decision to donate. Health incentives such as cholesterol screening appeared to appeal to many donors. Conclusions drawn from these surveys were the need for recruitment and retention programs to build upon people's sense of social responsibility and that the types of appeals and incentives needed for minority donors were possibly different than those needed for white donors. It was also found that inaccessibility to donation opportunities was a major barrier for blood donation and that more mobile drives were needed along with an increase in hours of operation to retain donors.

Because information from these surveys could be linked to donation information compiled in the core donation database, REDS was able to evaluate if particular motivational and/or deterrent factors were associated with donor return. Altruism, empathy, and social responsibility were not significant predictors of actual return within 12 months. However, prior donation frequency, intention to return, donation experience, and having a convenient

location to donate appeared to significantly predict donor return.

Evaluating the Characteristics of Deferred Donors and the Impact of Temporary Deferral on Donation Patterns. With the advent of REDS-II, compilation of routine blood center donor deferral records into a centralized database was initiated with the goal of studying the impact of donor deferrals on blood availability. Specific studies included evaluating the risk for malaria among US donors deferred for travel to malaria-endemic areas (described in a previous section), [86,87] examining the factors associated with low hemoglobin level deferral [126], and analyzing donor return patterns after temporary deferral or after an adverse reaction [127-130].

The study that examined the demographic characteristics of donors most likely to be deferred for a low hemoglobin level, the largest donor deferral category, evaluated return and deferral patterns of 715 000 whole blood donors over a 2-year period [126]. Women were found to be 11 times more likely to be deferred for low hemoglobin level than men, and among these deferred women, older African American women were 2 to 2 1/2 times as likely as white women to be deferred for this reason. In men, increasing age was associated with higher odds of deferral.

An analysis of donors who experienced adverse reactions showed that donors with major reactions had longer return times and that, regardless of donation history, any type of adverse reaction significantly reduced the odds of return. Temporarily deferred donors identified between 2006 and 2008 were passively followed up over a 3-year period. Of the 3.9 million donor presentations, 13% resulted in deferral. Low hematocrit (59% of the deferrals), blood pressure or pulse (5%), feeling unwell (5%), malaria travel (4%), "could not wait or had second thoughts" (3%), and tattoos or piercing and related exposures (2%) represented the most common reasons for deferral. Donors who were temporarily deferred for an extended period (up to a year) had the lowest rate of donor return. However, factors such as age and first-time/repeat-donor status were still the major determinants of donor return among those donors who did return. Thus, repeat and older donors were still more likely to return than first-time and younger donors, respectively, regardless of the reason for their predonation temporary deferral.

An additional cross-sectional analysis examined the correlates of systemic vasovagal reactions in 591 177 whole blood donors donating in 2006 and 2007 at the 2 ARC REDS-II blood centers [130]. The results indicated that donors who were younger, first time, or with a low estimated blood volume were more likely to have a prefaint or systemic vasovagal reaction, indicating that high school– and college-age donors are potentially at greater risk for these reactions.

Understanding the Factors That May Lead Donors to Delay Reporting Information That Would Otherwise Have Led to Their Deferral at the Time of a Previous Donation (Post PDI). One of the most frequent reasons for donor suitability–related biologic product deviation reports filed with the FDA is the situation in which a health history that would have deferred the donor from donation is discovered sometime after the donation has been made; this is classified as a PDI report. Most often, PDI reports are due to the donor failing to disclose preexisting information that is subsequently disclosed at a future donation; it may also be due to a donor developing symptoms of illness shortly after the donation and reporting this to the blood collection agency. Given the burden that PDI places on staff at blood centers, REDS-II conducted studies aimed at understanding the reasons for PDI and the characteristics of donors who report PDI. Comparing appropriately deferred donors and PDI donors within the same broad deferral categories (travel, medical, blood disease or exposure, and high-risk sexual and high-risk nonsexual behaviors), it was found that PDI donors were more likely to be older, more educated, and male [131]. In a separate qualitative study, telephone interviews were conducted with appropriately deferred donors, PDI donors, and accepted donors just after their donation attempt or successful donation, respectively. Based on the interviews, it was theorized that donors may need assistance from the blood center staff on remembering dates for deferrable activities or, in some cases, in understanding specific items on the health history questionnaire. Overall, it did not appear that PDI was caused by donors attempting to be deceptive on the day of donation [132].

Blood Donor Characterization for Iron Deficiency and Alloimmunization

The REDS-II conducted 2 large-scale studies, each enrolling large numbers of blood donors, to

address 2 major areas of concern in transfusion medicine: (1) the development of iron deficiency in blood donors and (2) the presence of leukocyte (primarily human leukocyte antigen [HLA]) antibodies in blood donors and their potential relationship to TRALI in transfusion recipients.

The REDS-II Donor Iron Status Evaluation Study. The REDS-II Donor Iron Status Evaluation (RISE) Study was an in-depth evaluation of iron status in a contemporary US blood donor population. It was designed to evaluate the effects of blood donation intensity on iron status and hemoglobin levels, assess factors that could modify that relationship, and provide data to help formulate optimal whole blood donation frequency.

The RISE Study was a 24-month longitudinal study conducted between 2007 and 2009 of iron status in 2 cohorts [133]. A total of 2425 whole blood or double RBC donors were enrolled, which included 888 first-time or reactivated donors (eg, who had either never given blood before or had not given a donation in the 2 years before enrollment; FT/RA), in whom baseline iron and hemoglobin level status were assessed without the influence of previous donations, and 1537 frequent donors, consisting of men who had given the equivalent of 3 or more and women who had given 2 or more RBC units in the last year. Only individuals who successfully donated whole blood or double RBC units and were not deferred at their enrollment visit and who agreed to donate frequently in the following 24 months were included in the study.

The RISE is the largest study of donor iron status that has been conducted. It is also somewhat unique in that it provided assessments at baseline and after 15 to 24 months of follow-up so that the cumulative effect of additional frequent blood donations could be assessed [134,135]. Data collection included a baseline and follow-up questionnaire as well as hemoglobin level (fingerstick and venous) and iron measurements (ferritin and serum transferrin receptor) on all baseline and final visit specimens and on a selected subset of interim visit specimens. Donors were genotyped for a transferrin polymorphism (G277S) and 2 hemochromatosis (HFE status) polymorphisms (C282Y and H63D) using novel allele-specific high-throughput PCR assays developed by the REDS-II Central Laboratory.

Iron depletion was defined at 2 levels: iron-deficient erythropoiesis (IDE) (log [soluble transferrin receptor/ferritin $\geq$2.07]) and absent iron stores (AISs) (ferritin <12 ng/mL). Data on previous blood donation history, smoking history, diet, use of vitamins and supplements, and reproductive history (female donors) were collected through a self-administered questionnaire. Blood donation frequency before and after enrollment, height, weight, country of birth, race and/or ethnicity, and highest educational level were compiled from blood center records. Models to predict hemoglobin level deferral, AIS, and IDE were developed and included the impact of a large number of factors such as donation intensity, interval since last donation, dietary habits, iron supplementation, HFE status, and demographics.

The most important finding in RISE was that a large proportion of both female and male blood donors have iron depletion. At enrollment, FT/RA female donors had IDE and AIS rates of 22% and 6%, respectively, whereas frequent female donors had rates of 66% for IDE and 27% for AIS. Even frequent male donors had high rates of iron depletion; 49% had IDE, and 16% had AIS [133]. At the conclusion of the longitudinal follow-up, even larger percentages of donors showed evidence of iron depletion [134]. Rates of IDE and AIS in returning first time (FT) female donors (who averaged 2.2 donations annually during the study) were 51% and 20%, respectively, and the corresponding rates in returning FT male donors were 20% and 8%, respectively. In the frequent donor cohort, these rates were 62% and 27% in women and 47% and 18% in men. Strong associations between higher prior donation intensity and a shorter time since last donation and iron depletion were observed. In addition, sex, weight, age, and the use of self-administered iron supplements were found to be important independent predictors of AIS and/or IDE. Transferrin and HFE genotypes did not show marked associations with iron status [136].

The RISE also modeled the factors associated with failure to meet hemoglobin level eligibility requirements and determined how accurately fingerstick hemoglobin level measurement reflected venous hemoglobin level, particularly at the deferral cutoff of 12.5 g/dL. Hemoglobin level deferral was associated with time since last RBC donation, black race, female sex, and younger age in women. Fingerstick hemoglobin level overestimated venous hemoglobin level in the lower part of the acceptable blood donation hemoglobin

level range. This overestimate was accentuated in women and in iron-deficient donors such that 40% of female donors with AIS and a fingerstick hemoglobin level of 12.5 g/dL had a venous hemoglobin level below this donor eligibility threshold value [137].

The RISE data led to the conclusion that reducing the frequency of blood donation and/or lengthening the interdonation interval is likely to reduce the prevalence of iron deficiency among blood donors. This might also be accomplished by implementing routine iron supplementation, at least for selected groups of donors whose demographics and/or prior donation history put them at risk for iron depletion.

The Leukocyte Antibody Prevalence Study I and II. In late 2006, the American Association of Blood Banks recommended that blood collection centers implement a TRALI risk mitigation strategy over the next several years. One recommendation was that high plasma volume components be prepared from donors who had a low likelihood of being alloimmunized to leukocyte antigens. This gave rise to consideration of testing selected populations of platelet apheresis donors (eg, previously pregnant women) for HLA antibodies and then redirecting HLA antibody–positive donors away from these high plasma volume donations. The REDS-II investigators launched the Leukocyte Antibody Prevalence Study (LAPS) I to obtain scientific data relevant to this proposed intervention [138]. This study was designed to measure the prevalence of HLA and neutrophil antibodies in blood donors with or without a history of pregnancy or blood transfusion and to develop a repository of blood samples from these donors.

Over a 6-month period from December 2006 through May 2007, approximately 7900 whole blood and apheresis donors were enrolled in the study [139]. Donors completed a questionnaire related to pregnancy and transfusion history. Blood specimens were screened for HLA classes I and II antibodies using a state-of-the-art flow cytometry technique (eg, the Luminex platform with multiantigen One Lambda [Canoga Park, CA] reagents) previously used in organ transplantation programs. After validating the accuracy of tests performed after a freeze-thaw cycle, testing was conducted on plasma specimens. Cutoff values for positive screening results were determined by calculating the mean plus 3 SDs (3 SD cutoff) of the natural log-transformed distribution of assay values (expressed as the normalized background [NBG] ratio) in the enrolled cohort of 1138 nontransfused male blood donors; assay cutoffs were thereby set at NBG values of greater than 10.8 for class I and greater than 6.9 for class II. Conversion factors were calculated for relating plasma specimen results to those obtained on serum specimens [140]. Further testing to determine the specificity of HLA antibodies (classes A, B, C, DR, DQ, and DP) was performed using the One Lambda single-antigen bead assays; the assay cutoffs for a positive result were set at a median fluorescence intensity of greater than 2500 for class I and greater than 1500 for class II [141].

Major scientific findings of LAPS-1 and some of their policy implications are presented in Table 6 [139,141-146].

The LAPS-II was a retrospective cohort study using lookback methodology. It was conducted at 5 of the LAPS-I centers with the primary outcome being the combined incidence of TRALI and possible TRALI in study recipients (who had received at least 1 HLA antibody–positive high plasma volume component from a LAPS-I tested donor) vs control recipients (selected based on having received at least 1 HLA antibody–negative high plasma volume component from a LAPS-I tested donor) [147]. Components donated at the time of enrollment or within 2 years before the index donation were traced to participating hospitals (42 hospitals in total), and a staged recipient record review was conducted. Final recipient diagnosis was based on case review by a blinded expert panel of pulmonary and critical care physicians.

Recipients of 2596 plasma-rich blood components (transfusable plasma and plateletpheresis) were evaluated. Half of these components were collected from anti–HLA-positive donors (study arm) and half from anti–HLA-negative donors (control arm) matched by sex, parity, and blood center. The TRALI incidence was 0.59% (7 cases) in recipients of anti–HLA-positive components vs 0.16% (2 cases) in control arm recipients for an odds ratio of 3.6 (95% CI, 0.7-17.4; $P = .10$). Based on this trend of an increased incidence of TRALI in the study arm along with recent surveillance data from other sources, the conclusion was that the data were consistent with the

Table 6. Major Scientific Accomplishments of the LAPS-I

Research/policy questions	Findings	References
Relationship of donor HLA antibody prevalence to pregnancy history	HLA antibodies detected in 17.3% of all female donors and in 24.4% of those with a pregnancy history. Prevalence increased with no. of pregnancies: 1.7% (0), 11.2% (1), 22.5% (2), 27.5% (3), and 32.2% (≥4, $P < .0001$). Analysis of single-antigen bead testing data confirmed these results.	[139,141]
Relationship of donor HLA antibody to sex and transfusion history	HLA antibodies were detectable at low prevalence (1.0%-1.7%) in male donors regardless of transfusion history ($P = .16$). A similar prevalence (1.7%) was found in never-pregnant female donors; concluded that HLA antibody testing of transfused male donors or never-pregnant female donors was not warranted as a TRALI risk mitigation strategy.	[139,142]
Determining the effect of assay cutoff on product availability	Screening all previously pregnant apheresis donors using a 3 SD assay cutoff would result in loss of 5.8% of apheresis platelet donations. Screening only those women with >4 pregnancies using a >5 SD assay cutoff would result in a donor loss of 0.9% while identifying 31% of all LAPS donations that were reactive using the 3 SD strategy.	[143,144]
Correlation of assay values with antibody titer and breadth of specificity	Established that, among donors with NBG values above the LAPS-defined cutoff, the highest values were associated with an increased breadth of HLA antibody specificities and were correlated with an increased probability of a cognate antigen match in potential recipients. A serial titration/dilution substudy on 96 HLA antibody–positive samples established that anti–HLA-positive specimens with higher NBG values had higher antibody titers.	[144]
Comparison of different HLA antibody assays	Compared with ELISA-based assays, flow cytometry and multiplex bead based–assays (Luminex) classified a larger proportion of samples as HLA Ab–positive. In this substudy of 525 donors, assay agreement was higher in ever-pregnant women than in men and never-pregnant women.	[145]
HNA antibody prevalence	HNA antibody prevalence was 0.7% (95% CI, 0.3%-1.3%) with antibodies detected in female and nontransfused male donors. Of 5 HNA antibodies in women, 4 showed a definable HNA specificity, whereas the HNA antibodies detected in 3 male donors were nonspecific; concluded that HNA antibody screening would not greatly reduce TRALI risk.	[146]

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HNA, human neutrophil antigen.

likelihood that TRALI risk is decreased by selecting high-volume plasma components for transfusion from donors at low risk for having HLA antibodies.

THE INTERNATIONAL RESEARCH PROGRAM—MAJOR STUDIES AND FINDINGS

Research efforts in the REDS-II international programs in Brazil and China have focused on the primary goal of identifying the scope of HIV/acquired immunodeficiency syndrome transfusion-transmission in these countries as well as other known transfusion-transmitted agents (eg, HBV and HCV) and novel or emerging agents of potential public health concern (eg, dengue virus and *Trypanosoma cruzi*). These international programs provide the opportunity to acquire data on new or emerging infectious disease threats that are difficult to study in the United States because of their current rarity, although they may pose a future threat to the US blood supply. Another goal of the international programs is to improve the scientific and analytical skills of professionals responsible for blood safety in these countries, thereby helping them make evidence-based decisions concerning blood safety and other public health policies. As in the domestic REDS/REDS-II programs, a core objective of the REDS-II international programs was construction of comprehensive research databases of donor demographic, donation, and infectious disease marker testing data that allow for longitudinal studies of the compiled donor data from participating centers. In addition, specific study protocols were conducted in each country. Table 7 provides a broad overview of research areas in the international portfolio.

Brazil

A comprehensive donor and donation database for allogenic donors including data for 1 378 348 donations from January 2007 through March 2011 enabled numerous analyses that have led to a series of publications including (1) the first comprehensive report of donor demographics and donation profiles for different geographic locations in Brazil [148]; (2) an analysis of demographic characteristics and

Table 7. The REDS-II International Portfolio of Studies

	Brazil	China
Studies related to blood safety		
HIV MS	x	x
HIV serologic donor screening	x	
HIV risk factor case-control study	x	x
HCV and HBV prevalence and incidence	x	
HCV and HBV risk factor case-control study		x
HBV serologic donor screening		x
HBV MS		x
Syphilis serologic donor screening		x
HTLV prevalence and incidence	x	
T cruzi serologic donor screening	x	
T cruzi (Chagas disease) natural history	x	
Donor screening procedures including CUE, donor education materials, and sexual behavior deferral criteria and HIV test seeking	x	
Infectious disease marker prevalence in deferred donors	x	
Studies related to blood availability and donor issues		
Donor demographics and donation profiles	x	x
Response to a natural disaster		x
Donor return behavior	x	x
Donor motivation and knowledge of donation procedures	x	x
Differences between community and replacement donors	x	

prevalence of serologic markers of donors who used CUE to assess the effectiveness of this policy [149]; (3) a review of Chagas serologic test results, classification of reactivity patterns, and prevalence and incidence of *T cruzi* infection in the 3 REDS-II Brazil centers [150]; (4) an analysis of HIV test data, including performance of parallel screening of Brazilian blood donors with 2 HIV immunoassays, with broader implications for sequential immunoassay testing algorithms in other countries as well as prevalence and incidence of HIV infection and residual risk in Brazil [151,152]; (5) associations between number of sexual partners among eligible blood donors and prevalence of infectious markers [153]; and (6) analyses of test seeking by blood donors and the impact of on-site donor education materials to reduce test seeking and rates of infected donation in the Sao Paolo REDS-II blood center [154,155]. In addition, the REDS-II center in Sao Paolo was able to access hospital data to characterize survival rates among recipients, the first analysis of transfused patient survival in Latin America [156].

Four major prospective studies were launched for REDS-II Brazil; study aims and methods are described below.

The Natural History of Disease and Laboratory Findings in T Cruzi Antibody Positive Donors Study. The specific aims of this project were to (1) characterize the natural history of clinical Chagas disease in *T cruzi*–seropositive blood donors, (2) determine the persistence of *T cruzi* antibody reactivity over time, and (3) determine the rate of "serosilent" *T cruzi* infection in seronegative populations from endemic regions. *T cruzi*–exposed donors were identified from seropositive donor registries established at Sao Paulo and at Hemominas (in a historically highly endemic region of Montes Claros, Minas Gerais) in the mid 1990s to 2002. Using these registries, 511 *T cruzi*–seropositive donors and 504 matched seronegative control donors were enrolled. Donors were interviewed for risk factors and symptoms, examined by experienced cardiologists who performed rigorous electrocardiographic and echocardiographic studies, and sampled for serologic, parasitemia, and genetic studies. A substudy was performed to identify biomarkers through genomic and proteomic analyses that could be prognostic for progression of cardiac disease or used in disease monitoring. For the purpose of comparison, 106 additional Chagas cardiomyopathy clinical patients were enrolled and underwent the same clinical, diagnostic, and laboratory workups as other study participants. Results of these studies were processed through the US REDS-II coordinating center, including blinded reading of electrocardiographic and echocardiographic findings. A panel of 3 Brazilian cardiologists with extensive experience with Chagas disease then adjudicated cases under code to classify them for presence and severity of Chagas and non-Chagas cardiomyopathy.

The HIV Case-Control and Molecular Surveillance Study. For this study, 343 HIV-infected donors and 901 matched seronegative control donors were enrolled to determine the risk factors associated with HIV infection among blood donors and to evaluate HIV subtypes and drug resistance profiles among HIV-positive donors according to their HIV infection status (recent vs long standing), year of donation, site of collection, and risk behaviors. An audio computer-assisted self-interview on a touch-screen desktop computer was used to elicit risk factor and other research information from study participants. Molecular genotype and resistance testing was performed in Brazil on samples from the HIV-infected donors

using protocols that were similar to the REDS-II domestic molecular surveillance (MS) project.

Additional Donor Studies. One study involved a survey of donor motivation and knowledge of donation procedures in a representative sample of 7635 donors with the purpose of examining associations between donor motivation and successful donation vs deferral outcomes as well as donor return patterns. A second study assessed disease marker prevalence in 4013 deferred donors by collection of a blood sample at the time of deferral. These results were analyzed relative to motivations for attempting to donate, whether additional HIV risk factors were present, and the safety impact of several higher risk sexual exposure category deferrals: multiple sexual partners, MSM, exchanging money or drugs for sex, and sex with a partner who has HIV.

China

Three calendar years (2008-2010) of donation and deferral data from 5 participating blood centers were collected and compiled for REDS-II China. The database includes information on 833 828 donations. Because confirmatory testing for reactive infectious disease screening test results was not performed as part of standard blood center operating procedures, this additional testing was performed as part of the REDS-II research program. Manuscripts generated using these data include (1) demographic characterization of Chinese blood donors [157]; (2) the impact of the May 12, 2008, earthquake on blood donations [158,159]; (3) donor return patterns [160]; and (4) syphilis prevalence in donors during a time when the country was experiencing a syphilis epidemic [161].

Four major prospective studies were launched for REDS-II China.

Evaluating Current and New HBV Screening and Confirmatory Assay Strategies in a High-Prevalence Setting. This study evaluated the residual risk of HBV transmission under the current laboratory screening protocol of HBsAg and ALT testing. A total of 5521 donations qualified by routine screening and 5034 deferred donations because of elevated ALT alone were collected for this study. Samples were tested for HBV DNA by ID NAT, and reactive samples were further tested by additional HBV serologic assays and alternative NAT. The study found that ALT donor screening had no added value over standard HBsAg screening for detecting HBV infections. The HBV NAT yield rate was 1 in 1104 in qualified donations, with most of these yield cases occurring in donors with occult HBV infection, which has a low rate of transfusion-transmission. It was estimated that nationwide implementation of ID NAT for HBV would detect 9964 viremic donations that are currently being transfused among the 11 million donations collected annually in China [162].

Evaluation of Risk Factors Associated With HIV Infection in Chinese Blood Donors. A pilot case-control study was conducted to understand the risk factors associated with HIV infection in blood donors. Between March 2010 and March 2011, 77 HIV-positive (cases) and 77 HIV-negative (controls) donors completed a survey about potential HIV risk factors including IDU, heterosexual transmission, family history, transfusion history, history of previous whole blood or plasma donation, MSM, medical injections, acupuncture, tattoos, and other potential routes of exposure.

Evaluation of Risk Factors Associated With HCV and HBV Infection in Chinese Blood Donors. A large multicenter, case-control study was conducted to understand the risk factors associated with HBV and HCV infection in blood donors. Although the major modes of HBV and HCV transmission in China (eg, IDU, maternal-child transmission, family history, MSM, and heterosexual transmission) have been well documented, their relative importance in blood donors was unknown. The study enrolled 364 HBV cases, 174 HCV cases, and 627 controls.

The MS Study. The MS program was conducted to (1) determine the frequency of distinct viral lineages for HIV- and HBV-positive donations, (2) determine the frequency of antiviral drug resistance mutations among the HIV positive donations, and (3) analyze any variation of viral genotypes or drug-resistance mutations by region and by donor characteristics such as age, sex, or ethnicity. All testings were performed at the Chinese Ministry of Health's Institute of Blood Transfusion (IBT). The IBT attempted molecular characterization of samples confirmed as HIV or HBV serologically reactive from all 5 centers. Of the 172 HIV-confirmed positive samples, 113 (66%) were successfully amplified and yielded a diverse subtype distribution that was reflective of the several circulating recombinant forms seen in Chinese high-risk populations [163].

THE REDS-III

The REDS and REDS-II were focused on donor research issues but, in the later years, conducted a few studies involving transfusion recipients (B19V transfusion-transmission study using the RADAR repository; LAPS-II). To focus additional research on transfusion recipients while maintaining the capability to respond to new threats and to continue donor-related research, a successor program, the REDS-III, was established in 2011. Similar to REDS-II, REDS-III includes a domestic and an international component and will conduct studies in blood donors to improve blood safety and availability in the United States and in countries seriously affected by the acquired immunodeficiency syndrome epidemic. In addition to Brazil and China, which participated in REDS-II, REDS-III includes a third international site in South Africa, which is a partnership between the South African National Blood Service and US investigators at University of California San Francisco/BSRI. In the REDS-III domestic program, a new emphasis has been placed on research involving transfusion recipients. Thus, the REDS-III research portfolio is expected to include studies that examine blood component use and evaluate clinical outcomes as a function of transfusion strategies and alternative blood management practices.

ACKNOWLEDGMENTS

The authors thank the many additional investigators, scientists, study coordinators, laboratory technologists, statisticians, data analysts, and data managers whose contributions were vital to the success of these programs. Principal investigators and coprincipal investigators are listed in Online Appendix C.

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ONLINE APPENDIX A. THE REDS DOMESTIC PROGRAMS: PARTICIPATING INSTITUTIONS

REDS

Coordinating Center: Westat; Rockville, MD
Central Laboratory: SRA Laboratories, Rockville, MD (1989-1993)
BSRI, San Francisco, CA (1994-2001)
Blood centers: ARC Greater Chesapeake and Potomac Region, Baltimore, MD, and Washington DC
ARC Southeastern Michigan Region, Detroit, MI
ARC Southern California Region, Los Angeles, CA
Blood Centers of the Pacific, San Francisco, CA
Oklahoma Blood Institute, Oklahoma City, OK

REDS-II

Coordinating Center: Westat, Rockville, MD
Central Laboratory: Blood Systems Research Institute (BSRI), San Francisco, CA
Blood Centers: ARC New England Region, Dedham, MA
ARC Southern Region, Douglasville, GA
Blood Center of Wisconsin, Milwaukee, WI
Blood Centers of the Pacific, San Francisco, CA
Hoxworth Blood Center/University of Cincinnati Academic Health Center, Cincinnati, OH
Institute for Transfusion Medicine, Pittsburgh, PA

The REDS and REDS-II collaborating institutions for targeted projects:
ARC
ABC
Blood Systems Inc
CDC
FDA
Test kit manufacturers

ONLINE APPENDIX B. REDS INTERNATIONAL PROGRAM: PARTICIPATING INSTITUTIONS

Coordinating Center: Westat, Rockville, MD
Central Laboratory: BSRI, San Francisco, CA
US Principal Investigator for Brazil site: BSRI, San Francisco, CA
US Principal Investigator for China site: Johns Hopkins University, Baltimore, MD
Brazil Blood Centers: Fundação Pró- Sangue/Hemocentro São Paulo; São Paulo
Fundação Hemominas, Minas Gerais, Brazil
Fundação Hemope; Pernambuco, Brazil
China Blood Centers: Yunnan Kunming Blood Center, Kunming, Yunnan
Urumqi Blood Center, Urumqi, Xinjiang
Luoyang Blood Center, Luoyang, Henan
Mianyang Blood Center, Mianyang, Sichuan
Liuzhou Blood Center, Liuzhou, Guangxi
China Operations Center: IBT, Chengdu, Sichuan
China Data Coordinating Center: FEI, Hanover, Maryland and Xian, China

ONLINE APPENDIX C. THE FOLLOWING PERSONS HAD PRIMARY RESPONSIBILITY AT VARIOUS TIMES FOR THE REDS (1989-2001):

Blood centers

ARC Blood Services, Chesapeake and Potomac Region, Baltimore, MD, and Washington DC
AE Williams and CC Nass
ARC Blood Services, SouthEast Michigan Region, MI
HE Ownby, DA Waxman, M Higgins, and J Campbell
ARC Blood Services, Southern California Region, CA
S Kleinman, G Garratty, and S Hutching
Blood Centers of the Pacific, University of California San Francisco, BSRI, San Francisco, CA
EL Murphy and MP Busch
Oklahoma Blood Institute
RO Gilcher and JW Smith

Coordinating Center: Westat, Inc

GB Schreiber, R Thompson, SA Glynn, and MR King

NHLBI, NIH

GJ Nemo and C Hollingsworth

Central Laboratory

BSRI
MP Busch
Steering Committee Chair
TF Zuck
The REDS-II (2004-2012) has been the responsibility of the following persons:

Blood Centers

ARC Blood Services, New England Region
R Cable, J Rios, and R Benjamin
ARC Blood Services, Southern Region/Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA
C. Hillyer and J.D. Roback
Hoxworth Blood Center, University of Cincinnati Academic Health Center, Cincinnati, OH
RA Sacher, SL Wilkinson, and PM Carey
Blood Centers of the Pacific, University of California San Francisco, BSRI
EL Murphy, B Custer, and N Hirschler
The Institute for Transfusion Medicine
D Triulzi, R Kakaiya, and J Kiss
Blood Center of Wisconsin
J Gottschall and A Mast

International programs

Brazil
MP Busch, E Sabino, B Custer, and AB Carneiro-Proietti
China
H Shan, J Wang, and PM Ness

Coordinating Center: Westat, Inc

GB Schreiber, J Schulman, and MR King

NHLBI, NIH

GJ Nemo and SA Glynn

Central Laboratory: BSRI

MP Busch and P Norris

Steering Committee Chair

RY Dodd