Published in final edited form as:
Transfus Med Rev. 2012 October ; 26(4): 281–304.e2. doi:10.1016/j.tmrv.2012.04.004.

The NHLBI Retrovirus Epidemiology Donor Studies (REDS and REDS-II): Twenty years of research to advance blood product safety and availability

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Abstract

The Retrovirus Epidemiology Donor Study (REDS), conducted from 1989–2001, and the Retrovirus Epidemiology Donor Study-II (REDS-II), conducted from 2004–2012, were National Heart Lung and Blood Institute (NHLBI) funded multicenter programs focused on improving blood safety and availability in the United States. REDS-II also included international study sites in Brazil and China. The three 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 XMRV. Blood safety studies have included protocols evaluating epidemiologic and/or laboratory aspects of HIV, HTLV I/II, HCV, HBV, WNV, CMV, HHV-8, B19V, malaria, CJD, influenza, and T. 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, two 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

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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

peer-reviewed articles published by these two REDS programs. In 2011, a new seven year program, the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III), was launched. REDS-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.

Keywords

blood safety; transfusion-transmitted infections; blood availability; blood donors

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). REDS was initiated in response to concerns about the impact of HIV and Human T-lymphotropic Virus (HTLV) infection on recipient safety in the US.[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 Retrovirus Epidemiology Donor Study-II (REDS-II) - was begun in 2004 and has completed the large majority of its work, although some additional projects will extend until the end of 2012. Both of these research programs have focused on studies of U.S. blood donors with the aim of improving blood product safety and availability. In addition, REDS-II added an international component which has focused on similar aims in two countries (China and Brazil) characterized by ongoing concerns about HIV transmission through blood transfusion. Most recently, in 2011, the NHLBI began funding a seven year program, the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). REDS-III expands the donor-based research focus of the original two 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 the fields of blood banking and transfusion medicine.

PARTICIPATING INSTITUTIONS

REDS and REDS-II each was structured around a Central Coordinating Center, a Central Laboratory, and multiple participating blood centers as described in on-line appendix 1. 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. (On-line appendix 2)

THE DOMESTIC RESEARCH PROGRAM– MAJOR FINDINGS

REDS and REDS-II have made substantial contributions in three major research areas in transfusion medicine/blood banking in the US, namely, infectious disease risk evaluation, blood donation availability, and blood donor characterization. The largest body of research conducted by 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, HCV and 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 (post donation information). 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 allo-exposed blood donors and the potential association of high-volume plasma components containing these allo-antibodies with transfusion-related acute lung injury (TRALI) in recipients. Table 1 provides a broad overview of the studies conducted in the US.

I. 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 incidence-window period mathematical model -which was also independently developed by CDC and 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 HBsAg incidence and modeling of HIV incidence using either a less sensitive detuned antibody assay or a new strategy of analyzing minipool (MP) 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 (e. g. HIV, HCV, HBV, HTLV) in the overall donor population did not consistently reflect its corresponding incidence. [11] As a result 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 (e.g.; MP and 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 prior to 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 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 (ICL) in 1992, West Nile Virus (WNV) in 2002–2004, influenza viruses in 2008, and Xenotropic Murine Leukemia Virus Related Virus (XMRV) in 2009–2011.

ICL 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. 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 of transmitting HCV. 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]

REDS played a major role in evaluating several aspects of WNV infection. Firstly, in collaboration with ABC, REDS evaluated a voluntary market withdrawal of FFP 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 US. 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 individual donation (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 versus ID NAT. [45] This, in turn, led to the nationwide implementation of targeted ID NAT testing of individual blood donors. Thirdly, in collaboration with CDC, ARC, and 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 neurological 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] Following this assay evaluation, three assays were used to test for the presence of influenza virus in blood donor samples from donors with increased influenza risk. These included RADAR repository donation samples (see below) that had been collected during a seasonal flu epidemic as well as samples obtained from contemporary BSI and ARC donors who reported post-donation 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 (CFS) 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 (SRWG), comprised of experts in retrovirology, blood banking and infectious diseases, and chronic fatigue syndrome. The SRWG embarked upon a three-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/P-MLV assays are not able to reproducibly detect XMRV/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 two 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 (GSR), completed in 1994, consists of serum specimens from more than 500,000 blood donors at the five 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 five REDS blood centers.
- The REDS Allogeneic Donor and Recipient Repository (RADAR), collected from 2000–2003, 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 five REDS participating cities, two additional blood center-hospital sites were established in Tampa, FL (Florida Blood Services) and Pittsburgh, PA (ITXM) through CDC collaboration and funding. The repository contains whole blood and plasma

aliquots from 3,575 recipients (these were collected pre and 6–12 month post-transfusion, mostly from cardiovascular surgery patients) which 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 (CMV, parvovirus B19, HHV-8; see below). In addition, as 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 GSR, 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—REDS and REDS-II have performed studies related to three other possible/actual transfusion-transmitted agents: cytomegalovirus (CMV), human herpes virus 8 (HHV-8), and parvovirus B19 (B19V).

CMV: Due to widely differing blood donor CMV DNA prevalence reported from different laboratories, REDS conducted a blinded multi-center evaluation of seven CMV DNA PCR assays in five 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 three of the seven judged to have sufficient sensitivity and specificity for potential use in donor screening algorithms. Based on these results, two assays were selected for use in a subsequent blood donor prevalence study which 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 to CMV serology, did not increase the detection of potentially infectious blood components. [57]

HHV-8: Due to the lack of a gold standard assay or algorithm for HHV-8 antibody, REDS investigators conducted a study of HHV-8 antibody detection in six 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 Kaposi's Sarcoma patients 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 is present infrequently in asymptomatic donors with positive HHV-8 serology.

B19V: 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% 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 $<10^6$ copies/mL did not transmit B19V infection to 24 susceptible (B19V seronegative) recipients. Based on this sample size, the 95% upper CI for transmission was 11.7%, thus establishing either that transmission from components with $<10^6$ 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 due to the known ability of B19V to infect red blood cell 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 IgM was present (i.e. relatively recent infection) but with approximately equal concentrations in the two sample types when IgM was absent (i.e. 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 (TTVI). 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 FDA policy as well as for their broader public health implications.

HCV and HTLV: 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 2,316 HCV-seropositive blood donors and an equal number of seronegative donors matched on age, sex, race/ethnicity, blood center, and first-time versus repeat-donor status. Independent HCV risk factors identified included IDU, sex with an IDU, blood transfusion in non-IDU, having been in jail 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 RIBA-positive donors, 402 of 2,105 (19.1%) tested negative for HCV RNA by NAT (presumptive resolved infections). There were significant differences in the frequency of RNA negativity by ALT levels and by race and/or ethnicity. ALT levels were more likely to be elevated in RNA-positive, first-time donors ($p < 0.0001$). 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 1992–1993 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 -II were measured in 1.7 million REDS donors during 1991–1995: 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 age 40–49 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 -II. IDU 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 six such surveys (see Table 3). The main objectives of donor surveys were to estimate the prevalence of unreported TTVI deferrable risk factors (UDR), 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 two 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 (i.e., a UDR). [69] UDR was higher in males, 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 males who had contact with a sex worker. Additionally, the survey found that the value of CUE as a self-deferral mechanism was limited given that the majority of donors with UDR did not use the CUE option and most donors who used CUE did not report a risk.

The 1998 donor survey was conducted at the five REDS centers as well as at three additional blood centers. Although the UDR rate was similar to that in the 1993 survey, it was slightly higher (3%) due to 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. HIV test seeking behavior was decreased compared to 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 to 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 that seemed to potentially be most influenced by an incentive of limited value. Further 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 versus repeat community blood donors, first time versus 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 one or more of 15 abnormal infectious disease screening and confirmatory test results. [76] The survey, which had a 42% response rate, documented that the majority of 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.

REDS also measured psychological distress associated with notification of HTLV infection in 464 HTLV-I and –II positive donors. [77] General well-being scores for donors who had tested seropositive for HTLV-I and HTLV-II indicated significantly more psychological distress than in seronegative donors ($p < 0.0005$) or in a large national sample ($p < 0.05$). 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 due to health problems.

Projecting the impact of changing the acceptance/deferral criteria on selected infectious disease risks—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] 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 (i.e., the magnet effect). [82] Another analysis was related to the possible strategy of deferring older age donors (>age 50 or 60) due to an increased frequency of Creutzfeldt-Jacob disease, which at the time was considered to be a theoretical transfusion-transmission risk. Replacement of donors over age 50 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 over age 60. [83] When concern arose over the transfusion- transmission of variant Creutzfeldt-Jacob disease (vCJD), 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 non-transfused 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] Due to the very low risk of transfusion-transmitted malaria in the US 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 one 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 almost 65,000 blood donors annually at a risk of approximately one 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 –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 1990–1992 and then followed with a health questionnaire, physical examination and blood testing for an additional seven visits approximately every two years through 2009. In 1998–1999, the study transitioned from the REDS research contract to an independent R01 funding mechanism from NHLBI and was renamed the HTLV Outcomes Study (HOST).

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

II. Blood Donation Availability Research

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. Additionally, motivations and barriers to donation were assessed through the 1998 donor survey and two additional donor surveys conducted in 2003.

Determining donor demographic characteristics and the factors influencing donation return—REDS has performed multiple studies describing individuals who donate; 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 elements comprised screening and confirmatory test results, reasons for deferral, and donor demographics, including age, gender, 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 US using one of the largest donor databases compiled to date. [125]

The REDS/REDS-II donation databases of approximately one 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] Additionally, REDS evaluated probability of return and trends for repeat donation among specific types of blood donors, and even assessed the impact of the September 11th 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, two 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, 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 13–18% of donors in each demographic group reported that at least one 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 Caucasian 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 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, the largest donor deferral category, evaluated return and deferral patterns of 715,000 whole blood donors over a two-year period. [126] Women were found to be eleven times more likely to be deferred for low hemoglobin than men, and among these deferred women, older, African American females were two to two and a half 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 over a three 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 pre-donation temporary deferral.

An additional cross sectional analysis examined the correlates of systemic vasovagal (SV) reactions in 591,177 whole blood donors donating in 2006 and 2007 at the two American Red Cross 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 pre-faint or SV 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 donation information or PDI)—One of the most frequent reasons for donor suitability-related biological 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 post donation information (PDI) report. Most often, PDI reports are due to the donor failing to disclose preexisting information which is subsequently disclosed at a future donation; it may also be due to a donor developing symptoms of illness shortly following 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 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]

III. Blood Donor Characterization for Iron Deficiency and Alloimmunization

REDS-II conducted two large scale studies, each enrolling large numbers of blood donors, to address two major areas of concern in transfusion medicine, 1) the development of iron deficiency in blood donors and 2) the presence of leukocyte (primarily HLA) antibodies in blood donors and their potential relationship to TRALI in transfusion recipients.

The REDS-II Donor Iron Status Evaluation (RISE) Study—The REDS-II Donor Iron Status Evaluation Study (RISE) 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.

RISE was a 24-month longitudinal study conducted between 2007 and 2009 of iron status in two cohorts.[133] A total of 2,425 whole blood or double red blood cell donors were enrolled which included 888 first time or reactivated donors (e.g., who had either never given blood before or had not given a donation in the 2 years prior to enrollment; FT/RA) in whom baseline iron and hemoglobin status were assessed without the influence of previous donations, and 1,537 frequent donors, consisting of men who had given the equivalent of ≥ 3 and women who had given ≥ 2 red cell 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.

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 – 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 (fingerstick and venous) and iron measurements (ferritin and serum transferrin receptor [sTfR]) 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 two 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 two levels: Iron Deficient Erythropoiesis (IDE) [log (soluble transferrin receptor/ferritin ≥ 2.07)] and Absent Iron Stores (AIS) (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 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 FT female donors (who averaged 2.2 donations annually during the study) were 51% and 20% and the corresponding rates in returning FT male donors were 20% and 8%. In the frequent donor cohort, these rates were 62% and 27% in females and 47% and 18% in males. Strong associations between higher prior donation intensity and a shorter time since last donation and iron depletion were observed. In addition, gender, 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]

RISE also modeled the factors associated with failure to meet hemoglobin eligibility requirements and determined how accurately fingerstick hemoglobin measurement reflected venous hemoglobin, particularly at the deferral cutoff of 12.5 g/dL. Hemoglobin deferral

was associated with time since last red cell donation, black race, female gender and younger age in women. Fingerstick hemoglobin overestimated venous hemoglobin in the lower part of the acceptable blood donation hemoglobin range. This overestimate was accentuated in females and in iron deficient donors such that 40% of female donors with AIS and a fingerstick hemoglobin of 12.5 g/dL had a venous hemoglobin 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 (LAPS I and II)—In late 2006, the AABB 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 (e.g., previously pregnant females) for HLA antibodies and then redirecting HLA antibody positive donors away from these high-plasma-volume donations. REDS-II investigators launched the Leukocyte Antibody Prevalence Study (LAPS-I) in order 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 six month period from December 2006 through May 2007, approximately 7,900 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 Class I and Class II antibodies using a state of the art flow cytometry technique (e.g. the Luminex platform with multi-antigen One Lambda reagents) previously used in organ transplantation programs. After validating the accuracy of tests performed following a freeze-thaw cycle, testing was conducted on plasma specimens. Cutoff values for positive screening results were determined by calculating the mean plus three standard deviations (3SD cutoff) of the natural log-transformed distribution of assay values (expressed as the normalized background ratio- NBG) in the enrolled cohort of 1138 non-transfused 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 (Class 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]

LAPS-II was a retrospective cohort study using lookback methodology. It was conducted at five 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 one HLA antibody-positive high-plasma-volume component from a LAPS-I tested donor) versus control recipients (selected based on having received at least one 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 2,596 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. TRALI incidence was 0.59% (seven cases) in recipients of anti-HLA–positive components versus 0.16% (two cases) in control arm recipients for an odds ratio of 3.6 (95% confidence interval, 0.7–17.4; $p = 0.10$). 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 likelihood that TRALI risk is decreased by selecting high-volume plasma components for transfusion from donors at low risk of 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/AIDS transfusion-transmission in these countries, as well as other known transfusion-transmitted agents (e.g., HBV and HCV), and novel or emerging agents of potential public health concern (e.g., 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 U.S because of their current rarity, even though they may pose a future threat to the U.S. 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.

I. Brazil

A comprehensive donor and donation database for allogeneic 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 prevalence of serologic markers of donors who used CUE in order 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 three REDS-II Brazil centers; [150] 4) an analysis of HIV test data, including performance of parallel screening of Brazilian blood donors with two 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 (FPS) 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 electrocardiogram (EKG) and echocardiography (ECG) studies, and sampled for serological, 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 employed in disease monitoring. For the purpose of comparison, 106 additional Chagas cardiomyopathy clinical patients were enrolled and underwent the same clinical, diagnostic, and laboratory work ups as other study participants. Results of these studies were processed through the US REDS-II coordinating center, including blinded reading of EKG and ECG findings. A panel of three 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 versus long-standing), year of donation, site of collection, and risk behaviors. An audio computer-assisted self-interview (ACASI) 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 project.

Additional donor studies—One study involved a survey of donor motivation and knowledge of donation procedures in a representative sample of 7,635 donors with the purpose of examining associations between donor motivation and successful donation versus deferral outcomes as well as donor return patterns. A second study assessed disease marker prevalence in 4,013 deferred donors by collection of a blood sample at the time of deferral. These retuls 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, male to male sex, exchanging money or drugs for sex, and sex with a partner who has HIV.

II. China

Three calendar years (2008–2010) of donation and deferral data from five participating blood centers were collected and compiled for REDS-II China. The database includes information on 833,828 donations. Since 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;[158] 2) the impact of the May 12, 2008 earthquake on blood donations;[159,160] 3) donor return patterns;[161] and 4) syphilis prevalence in donors during a time when the country was experiencing a syphilis epidemic.[162]

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 5,034 deferred donations due to 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 1,104 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 9,964 viremic donations that are currently being transfused among the 11 million donations collected annually in China.[163]

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, male to male sex, 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, multi-center, case-control study was conducted to understand the risk factors associated with HBV and HCV infection in blood donors. While the major modes of HBV and HCV transmission in China (e.g., IDU, maternal-child transmission, family history, male to male sex, 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 molecular surveillance study—The Molecular Surveillance (MS) program was conducted to: 1) determine the frequency of distinct viral lineages for HIV and HBV positive donations; 2) determine the frequency of anti-viral 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, gender, or ethnicity. All testing was performed at the Chinese Ministry of Health's Institute of Blood Transfusion (IBT). IBT attempted molecular characterization of samples confirmed as HIV or HBV serologically reactive from all five 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. [164]

THE RECIPIENT EPIDEMIOLOGY DONOR STUDY-III (REDS-III)

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). In order 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 Recipient Epidemiology Donor Study-III (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 U.S. and in countries seriously affected by the AIDS 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 UCSF/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 utilization, and evaluate clinical outcomes as a function of transfusion strategies and alternative blood management practices.

Acknowledgments

Contract support

REDS was supported by NHLBI contracts N01-HB-97077 (superseded by N01-HB-47114), -97078, -97079, -97080, -97081, and -97082.

REDS-II was supported by NHLBI contracts N01-HB-47168, -47172, -47175 and -57181.

The authors would like to 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 co-principal investigators are listed in on-line appendix 3.

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Table 1

REDS and REDS-II Study Portfolios Highlights – US

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 Unreported deferrable 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 post donation information
Special Donor Studies	Iron deficiency in blood donors Prevalence of leukocyte antibodies in alloexposed blood donors

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 two major manufacturer's 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 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 (e.g., 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 following 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 recombinant immunoblot assay version 3.0 (RIBA 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
Molecular surveillance	Determined that the clade/genotype/subtype distribution of HIV, HCV, and HBV isolates from US blood donors in 2006–2009 was similar to that seen in high-risk US populations. In donors with incident versus prevalent infections, determined the frequency of anti-viral drug resistance mutations in HIV and HBV isolates and the rate of HBV vaccine and immune escape mutations.	39

Table 3

REDS Donor Surveys

Year	Major Aims	Number of donors surveyed	Number (%)of donors responding	Publication reference number
1993	Undetected behavioral deferrable risks (UDR); HIV test seeking behavior	50,162	34,726 (69%)	69, 118
1995	Blood donation incentives	12,000	8,091 (67%)	73
1997	Response to notification of reactive infectious disease screening or confirmatory test results	4,141	1,728 (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

Table 4

Major scientific accomplishments of the REDS Human T-Lymphotropic Virus (HTLV) cohort study.

HTLV Research Questions	Findings	References
HTLV associated myelopathy (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
Broncho-pulmonary 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) function is intact.	91–96
HTLV proviral load (PVL)	Mean proviral load was 1,905 copies/10^6 PBMCs for HTLV-I and 398 copies/10^6 PBMCs for HTLV-II, and varied by HTLV-II subtype, route of infection and sex. Both HTLV-I and –II proviral load 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 –II incidence of 0.6 per 100 person- years (95% CI, 0.2–1.6) within serodiscordant heterosexual couples. Transmission associated with higher proviral loads in the infecting partner; no difference in transmission between HTLV-I and HTLV-II, nor between male-to-female versus female-to-male directions.	100,101
Hematology outcomes	HTLV-II infected subjects have chronic 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 (antisense protein of HTLV-II)	APH-2 mRNA was detected in PBMC from 4 of 15 HTLV-II-infected blood donors, and could explain the lymphocytosis frequently observed in HTLV-II patients.	105
HTLV-II molecular epidemiology	HTLV-II subtype a0 was independently associated with age over 30 years and with Black race/ethnicity. 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

Table 5

Donation/Donor Database elements in REDS/REDS-II

Identification (ID) information
Donor ID (encrypted)[a]
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 [b]
Confidential Unit Exclusion (CUE) status [c]
Laboratory Results
Blood type
All donor screening and confirmatory infectious disease test results [d]
Deferral Status and reason for deferral [b]
Quantitative fingerstick hemoglobin and hematocrit [e]

Table footnotes

[a] Allows linkage of all donations from a given donor

[b] Collected only in REDS-II

[c] Collected in the early years prior to discontinuation

[d] Updated as new assays were added (e.g., HIV NAT, HCV NAT, WNV NAT, T cruzi antibody) during the 20 year interval

[e] Collected only in the later years of REDS-II

Table 6

Major scientific accomplishments of the Leukocyte Antibody Prevalence Study (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 number of pregnancies: 1.7% (zero), 11.2% (one), 22.5% (two), 27.5% (three), and 32.2% (four or more; $p < 0.0001$). Analysis of single antigen bead testing data confirmed these results.	139, 141
Relationship of donor HLA antibody to gender and transfusion history	HLA antibodies were detectable at low prevalence (1.0 – 1.7%) in male donors regardless of transfusion history ($p = 0.16$). A similar prevalence (1.7%) was found in never pregnant female donors. Concluded that HLA antibody 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 >5SD assay cutoff would result in a donor loss of 0.9% while identifying 31% of all LAPS donations that were reactive using the 3SD 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]	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 females than in males and never pregnant females.	145
HNA antibody prevalence	HNA antibody prevalence was 0.7% (95% CI, 0.3 – 1.3%) with antibodies detected in female and non- transfused male donors. Four of five HNA antibodies in females showed a definable HNA specificity whereas the HNA antibodies detected in three male donors were non- specific. Concluded that HNA antibody screening would not greatly reduce TRALI risk.	146

Table 7

REDS-II International Portfolio of Studies

Studies related to Blood Safety		
	Brazil	**China**
HIV molecular surveillance	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 molecular surveillance		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	