

I. INTRODUCTION

Health outcomes research methods can provide important insights into blood supply safety and the implications of transfusion interventions. Careful collection and analysis of data using methods that allow for the comparison of the risk, benefit and cost profiles of interventions contributes to better informed decision making. By using evidence-based methods, the health outcomes research group at BSRI contributes constructive information to blood centers, regulators and the larger healthcare system.

Research activity in 2008 has been concentrated in four areas; first, protocol development and implementation plans for the Retrovirus Epidemiology Donor Study (REDS-II) Brazil HIV case control study, second, *Trypanosoma cruzi* (*T. cruzi*) after the advent of screening at Blood Systems, third, international cost-effectiveness analyses of blood safety screening, and fourth, economic evaluation of riboflavin light treatment pathogen reduction technology (PRT) for blood components. Other notable activities include additional REDS-II domestic and Brazil studies and teaching the Training in Clinical Research course offered in South Africa and Brazil.

Major research areas:

Observational and analytic epidemiology studies
Health outcomes (modeling and cost effectiveness studies)

Major BSRI collaborations:

Epidemiology studies, policy analysis, REDS-II, Edward Murphy, Mike Busch

Major BSI collaborations:

Medical Affairs, Hany Kamel, Peter Tomasulo

1. Donor adverse reactions analyses
2. Donor symptom and risk factor studies
3. *T. cruzi* testing and Chagas disease symptoms

Major non-BSRI collaborations:

1. REDS-II domestic – Donor deferral analyses, malaria risk and deferral in the USA, Susan Wilkinson, Bryan Spencer, Karen Schlumpf, Alan Mast, Steve Kleinman
2. REDS-II international Brazil – Infectious markers in deferred donors, HIV risk factors, *T. cruzi*/Chagas disease follow-up studies, Ester Sabino, Anna-Barbara Proietti, Thelma Goncalez, George Schreiber
3. ISBT TTID WP – International Society of Blood Transfusion, Transfusion-transmitted infectious disease working party, blood safety and cost utility analyses, Cees van der Poel, Rene van Hulst, Gijs Hubben, and Mart Janssen, John-Pierre Allain
4. Risk factors in virus positive donors in the USA, Susan Stramer, ARC, Debbie Kessler, NYBC

II. PROGRAM SUMMARY and PROGRESS REPORT - 2008

OBSERVATIONAL DONOR STUDIES

Retrospective Studies

1. Predictors of adverse reactions in donors

Using BSI's data warehouse coupled with UBS adverse reaction report forms, an analysis of the predictors of moderate and severe adverse reactions in whole blood donors was conducted. An example of the difference in adverse reaction rates according to age and gender is provided in the Figure below. This figure for the gender and age is interesting because it suggest that not only do young women have higher adverse reactions rates but that elderly women appear to have an increasing rate of adverse

reactions. Predictors of reactions were: age, gender, race, blood volume, blood pressure, pulse and body mass index. Compared to donors without reactions, the strongest predictor of a reaction was a donor's blood volume <3500 mL (Odds Ratio (OR) 2.9, 95% Confidence Interval (CI) 2.57 – 3.23). Age and first time status were also associated with a significantly higher risk of reaction with 17-18 years olds (OR 2.8, 95% CI 2.59 – 2.98) and 19-24 year olds (OR 2.39, 95% CI 2.23 – 2.56) at higher risk compared to 25-65 year olds, and first time donors at higher risk compared to repeat donors (OR 2.2 95% CI 2.07 – 2.33). A more comprehensive database was assembled by Medical Affairs covering all adverse event data from 2007. Additional analyses and manuscripts are underway to further investigate the predictors of offsite/delayed adverse reactions because these reactions may have a greater potential to lead to serious injury. Future manuscripts will also use similar methods to assess adverse reactions in automated procedures.

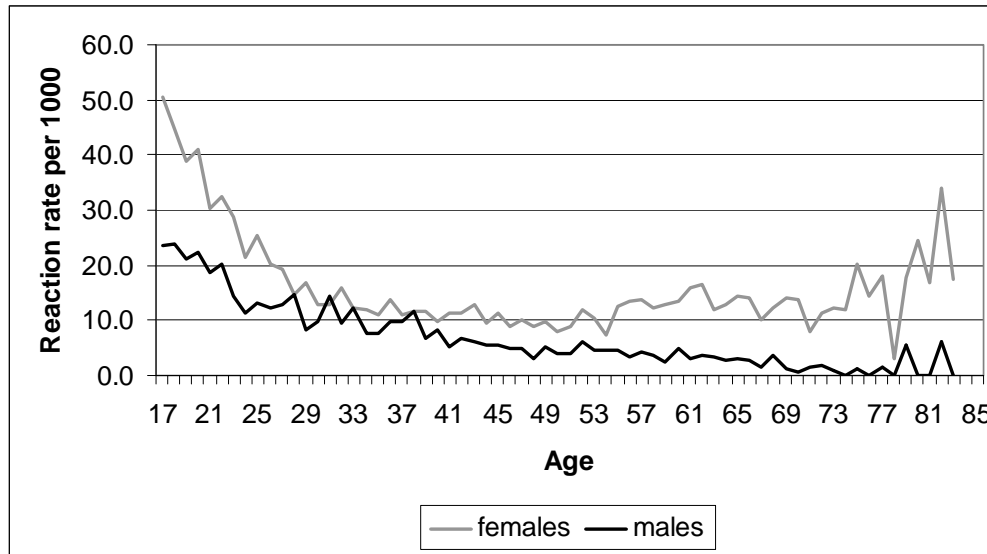


Figure. Adverse reaction rates in United Blood Services whole blood donors according to age and gender.

Prospective studies

1. Donors with WNV infection

The analysis of 4 years of donor reported symptoms in 423 donors who tested initially reactive for WNV including possible risk factors is now complete. Two hundred ninety three of these donors were confirmed to have WNV infection (CP) whereas 130 were negative in confirmatory testing providing a case-control type dataset for analysis. Skin rash before and after donation was significantly higher for CP donors (OR = 3.0, 95%CI 1.2–7.9 and OR = 5.2, 95%CI 1.8–14.9, respectively). Fever, eye pain, body aches and muscle weakness after donation were more common in CP donors. Body aches after donation resulted in the largest odds ratio (OR = 5.5, 95%CI 2.3–13.2). Donors with 3 or more symptoms were more likely to have WNV infection (OR = 2.5, 95%CI 1.9–5.1). Demographic characteristics, pre-donation symptoms, and serology on the index RNA positive donation did not predict post-donation symptom severity. The number rather than type of symptoms reported before donation is associated with confirmed WNV infection and is able to predict infection status better than individual symptoms or symptom combinations. However, the overall predictive value of symptoms is not high.

2. *Trypanosoma cruzi* infection in blood donors: transfusion safety, donor health and policy implications

Chagas disease is caused by the parasite *Trypanosoma cruzi*, which infects up to 10 million people in Latin America causing approximately 50,000 deaths annually. Immigration from and travel to rural areas of Latin America are potential risk factors for acquisition of *T. cruzi* infection and could lead to the risk of transmission by donated blood.

Donors who test repeat reactive using the *T. cruzi* ELISA were likely infected in endemic areas many years earlier and later moved to the U.S, but this has not been clearly documented. It is also possible that the U.S. has areas of endemic infection. The performance characteristics of the ELISA are being evaluated using additional testing for *T. cruzi* by radioimmunoprecipitation (RIPA). Donors who test repeat reactive by ELISA are interviewed using a standard risk factor and symptoms questionnaire. A recall study is underway in which additional blood samples are drawn and tested by ELISA, RIPA and PCR. Those donors who are confirmed *T. cruzi* positive using RIPA or PCR will be invited to enroll in a clinical assessment study to determine current clinical signs and symptoms and whether these findings are related to persistent parasitemia based on quantitative PCR. Additionally, an overarching question for blood supply safety is whether expected risk factors are predictors of infection and what combination of donor questioning, screening of specific blood components (such as platelets), and donation testing can maintain transfusion safety, while conserving resources for other safety initiatives. A decision analysis of strategies for donor questioning and screening to determine both the effectiveness and cost-effectiveness of specific interventions will bring all of the evidence from the currently ongoing studies together in a formal policy analysis. The addition of donor country of birth, shown in the table below, to the BSI health history form allows the organization to provide important information on the risk of infection based donor birth country or region.

Table. *T. cruzi* prevalence in Blood Systems donors according to country of birth based on data from the first year of testing (through February 2008).

Country	All Allogeneic Donors Number (%) N=457,486	<i>T. cruzi</i> RIPA+ Number (%) N=31	<i>T. cruzi</i> RIPA+ Prevalence by Birth Country or Region
USA	322,026 (70.4)	6 (20.7)	1:53,671
Mexico	9,355 (2.0)	7 (24.2)	1:1,136
Central or South America	1,179 (0.3)	10 (37.9)	1:118
All other countries	7,756 (1.7)	2 (6.9)	1:3,878
Missing/Unknown	117,170 (25.6)	6 (10.3)	1:19,528

The estimated cost-effectiveness of universal ongoing screening approaches \$2.0 million per quality-adjusted life year. While this appears to be on par with other blood safety interventions such as HIV/HCV NAT it must be kept in mind that the *T. cruzi* ELISA is the only screening intervention in place whereas for HIV and HCV, NAT was added to previously adopted antibody screening for each virus. In addition, based on lookback studies of blood recipients so far there has been no confirmed evidence of previous transfusion-transmission caused by repeat donors with *T. cruzi* who were identified after the advent *T. cruzi* screening.

3. Risk factors for disease marker positive donations in the USA.

This study is a major new initiative and collaboration. In this study we will ask blood donors at Blood Systems blood centers (United Blood Services and Blood Centers of the Pacific) to complete a risk factor questionnaire following notification of their confirmed positive test(s) for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and/or human T-cell lymphotropic virus (HTLV). The collection of risk factor information will be invaluable for understanding how donors become infected with transfusion-transmissible viruses. In addition, it could help to improve the pre-donation screening process by identifying problem areas. This is also consistent with current efforts underway to develop a basic nationwide donor-based hemovigilance system. The three largest U.S. blood centers, the American Red Cross (ARC), New York Blood Center (NYBC) and BSI have agreed to conduct this study in order to obtain a nation-wide understanding of risk factors for donating virus positive blood. Study enrollment is planned to begin early in 2009.

HEALTH OUTCOMES (Modeling and Cost Effectiveness Studies)

1. Economic Analysis of Mirasol Pathogen Reduction Technology (PRT)

The economics of pathogen reduction technologies (PRT) pose complex questions for the healthcare system. Evidence indicating the potential for PRT to substantially decrease the risk of both infectious and non-infectious transfusion threats is mounting but incorporating multiple lines of evidence into analyses that can be used to assess costs and benefits requires new modeling approaches. Previous research on PRT has not included comprehensive evaluation of the potential benefit of preventing several non-infectious threats. While PRT may have broad-ranging capability to reduce transfusion-threats, from an economic perspective the technology is very expensive (assumed treatment cost of ~\$100 per unit). We are currently working on a project funded by CaridianBCT. The grant provides funding to; 1) Develop an analysis model that combines both infectious and non-infectious threats in a manner that is sufficiently flexible so that country-specific data can be entered to assess the cost-effectiveness profile of Mirasol PRT in different settings, 2) Provide support to users of the model to help develop appropriate country-specific data and associated economic dossiers, 3) Conduct and publish formal economic evaluation of Mirasol PRT compared to current transfusion-safety practice.

2. Global risk assessment and cost utility of blood safety interventions – development of a web-based application and multi-country analysis framework

The purpose of this research project is to demonstrate the applicability of a common cost utility analysis evaluation method and web-interface in a large set of countries with diverse levels of development. This will permit the first direct comparison of the cost-effectiveness of HIV, HBV, and HCV screening in up to 7 countries. It will also provide important information that will support the submission of a larger research proposal to international funding agencies for a multi-year project with long term milestones related to economic evaluation of the range of interventions intended to increase either the safety or availability of blood in different settings. The health outcomes model for each virus has been re-designed using the experience gained from developing a preliminary model (see www.bloodsafety.info) to meet current standards and also allow future modular extensions, such as genotype differences. We will also enhance the web-interface so that analyses may be conducted more easily and can be compared more transparently.

REDS-II STUDIES

REDS-II international Brazil

The first large protocol study to launch consists of recalling up to 500 *T. cruzi* positive blood donors and similar controls who may have donated up to 10 years ago to assess current infection and disease status, including a formal clinical work-up of current evidence of Chagas or other heart disease as assessed by ECG and electrocardiogram. This study is being conducted in a small city in Minas Gerais state highly endemic for *T. cruzi* and in Sao Paulo city. We began enrolling subjects in August 2008, with an enrollment now over 100. The other large protocol study has been delayed pending USA Office of Management and Budget approval (OMB) and is not expected to begin until early 2009. This study is a case control study of HIV risk factors in blood donors including molecular surveillance of HIV infection. Risk factors will be assessed using an audio-computer assisted self-interview. This study will include the blood center in Rio de Janeiro in addition to the 3 principal REDS Brazil centers (Minas Gerais, Pernambuco, and Sao Paulo).

The protocols for two additional studies are being developed at this time. The first study will be a pilot study to assess blood utilization at the largest hospital in Sao Paulo according to medical indication and patient characteristics including survival at discharge and at one year post-transfusion. This protocol is now pending IRB approval in Brazil and IRB submission in the US. The second study is an assessment of infectious disease markers in donors who are deferred at the time of presenting to donate. The research question in this study is to determine the predictive value of pre-donation deferral for several deferrals related to potential infectious exposures. This study will also assess motivations for donating in donor who are deferred.

REDS II Domestic

1. Deferral working group

Deferred donor study

Comparison of temporary blood donor deferrals between blood centers has not been previously detailed. Deferral rates might vary due to the intake process (vital signs or health history first) and differences in eligibility assessment procedures. We compared the frequencies of 4 temporary deferrals (low hematocrit/hemoglobin, feeling unwell/high temperature, blood pressure or pulse, and weight too low or high) likely to be identified during the mini-medical assessment were compared. The analysis was restricted to white female to focus on the role of center eligibility assessment procedures. Stratified deferral proportions are reported according to first time or repeat status, female gender, and white race. The results show an unexpected and significantly high level of variability across centers (Table). Low hematocrit/hemoglobin deferral ranged from 498 to 1899 per 10,000 presenting first time white females, a nearly 4-fold difference between centers. One center had a nearly 10 times higher proportion of weight-based deferrals whether first time or repeat than the other centers. The root causes of variability need further investigation, but the data indicate that generalizing results obtained from deferral studies conducted by one blood center should be undertaken with caution.

Frequency of deferral per 10,000 prospective donor presentations in white female first time and repeat blood donors.

<i>Deferral Category</i>	<i>Center 1</i>	<i>Center 2</i>	<i>Center 3</i>	<i>Center 4</i>	<i>Center 5</i>	<i>Center 6*</i>	<i>P-value from homogeneity test</i>
<i>First Time White Female Donors</i>							
Low hematocrit/hemoglobin	498	906	1346	1899	560	1223	<0.0001
Unwell/ Colds/ Temperature	73	353	91	158	249		<0.0001
Blood pressure/ pulse	75	112	124	74	128		<0.0001
Weight too low or too high	8	65	22	26	300		<0.0001
<i>Repeat White Female Donors</i>							
Low hematocrit/hemoglobin	962	1410	1337	1708	1079	1490	<0.0001
Unwell/ Colds/ Temperature	59	156	39	62	87		<0.0001
Blood pressure/ pulse	53	58	47	29	51		<0.0001
Weight too low or too high	3	8	2	2	33		<0.0001

* Center 6 was only included in the low hematocrit analysis because it grouped several temporary deferrals into a single category that could not be separated.

Malaria risk and deferral

Deferral for travel to malaria-endemic areas excludes a large number of presenting blood donors in the United States. Almost no analysis has been performed that compares the impact of the existing deferral guidelines to the likelihood that a presenting donor with malaria travel history might be harboring malaria parasites. Travel destination was recorded from a representative sample of presenting blood donors deferred for malaria travel from six blood centers. An equivalent risk of malaria infection based on the risk of acquiring malaria as observed in all U.S. residents with similar travel history was imputed for blood donors under current and hypothetically altered guidelines. Travel to Africa represents a risk for acquiring malaria infection three orders of magnitude greater than that for the areas of lowest malaria transmission. These latter areas, especially Mexico, account for the great majority of donors deferred for malaria travel.

A three-month deferral period applied to Mexico might yield > 56,000 donations per year with additional marginal risk of one parasitemic donor every 57 years. The current malaria deferral guidelines have the greatest impact on blood availability where the risk of collecting malaria-infected blood is the lowest.

III. GRANTS, CONTRACTS, AND AWARDS

Current

Source/Contract #	PI	Period
1) N01-HB47174 Co-Investigator Retrovirus Epidemiology Donor Study-II (REDS-II) Epidemiological studies of transfusion safety and blood supply. Six blood centers participate in a network which will conduct epidemiology and clinical laboratory studies involving issues such as transfusion-associated infections, donor leukocyte antibody prevalence, iron balance in donors and donor risk factor surveys.	E. Murphy	09/01/04-08/31/10
2) HHSN268200417175C Co-Investigator Retrovirus Epidemiology Donor Study-II (REDS-II) International Component Conduct epidemiology and clinical laboratory studies involving issues blood donor and transfusion recipient safety in Brazil and China. The focus is on measuring and reducing the number HIV, HBV, and HCV blood donations. Additional infectious agent research specific to each country will be conducted.	M. Busch	09/01/05-08/31/10
3) Ortho Clinical Diagnostis Trypanosoma cruzi infection in blood donors: transfusion safety, donor health and policy implications.	B. Custer	05/01/07 – 04/31/09
4) CaridianBCT Health economic evaluation of Mirasol pathogen reduction technology.	B. Custer	09/01/07 – 12/31/08
5) ISBT TTID-WP Global risk assessment and cost utility of blood safety interventions – development of a web-based application and multi-country analysis framework	B. Custer	06/01/08 – 05/31/09

Past

1) National Blood Foundation Retrospective cohort analysis of temporarily deferred donors designed to estimate the impact of deferral on future blood donations. Deferred donor return behavior was compared to that of eligible donors over the same time period.	B. Custer	7/1/05-06/30/06
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OTHER SIGNIFICANT ACTIVITIES

Training in Clinical Research (TICR)

In addition to co-teaching the TICR course in Johannesburg, South Africa in October 2007 with Ed Murphy and Willi McFarland (UCSF and San Francisco Department of Health). This year I was a co-instructor for the course in Belo Horizonte, Brazil and in Durban South Africa. The training course in Brazil was funded in part by BSI and by a grant obtained by Anna Barbara Proetti. The South Africa course was funded by Chiron/Novartis. In 2008 over 20 trainees took this course, with more participating in the same course given in Paris for francophone Africa. This export version of the TICR course, which Ed Murphy condensed from an 8-10 week course provides an intensive exposure to the process of developing and writing a research protocol and consists of morning lectures and afternoon independent study by and mentorship of trainees in an 8-day period.

Reviewer for professional publications:

Ad hoc referee for Transfusion, Vox Sanguinis, Transfusion Medicine, Vaccine, Medical Decision Making, Management Research News, Journal of Infection, Cancer Research

2008 Manuscripts

1. Guiltinan AM, Kaidarova Z, Custer B, Orland J, Strollo A, Cyrus S, Busch MP, Murphy EL. Increased All-Cause, Liver, and Cardiac Mortality among Hepatitis C Virus-seropositive Blood Donors. *Am J Epidemiol*. 2008 Mar 15;167(6):743-50.
2. Wiltbank T, Giordano G, Kamel H, Tomasulo P, Custer B. Faint and pre-faint reactions in whole blood donors: An analysis of pre-donation measurements and their predictive value. *Transfusion*. 2008 Sep;48(9):1799-808.
3. Su L, Kamel H, Custer B, Vanderpool S, Harpool D, Busch M, Tomasulo P. Bacterial detection in apheresis platelets: Blood Systems experience with a two-bottle and one-bottle culture system. *Transfusion*. 2008 Sep;48(9):1842-52.
4. Custer B, Hoch JS. Cost effectiveness analysis: What it really means for transfusion medicine decision-making. *Transfusion Medicine Reviews*. 2009 Jan;23(1):1-12..
5. Custer B, Kamel H, Kiely NE, Murphy EL, Busch MP. Associations between WNV infection and symptoms reported by blood donors identified through nucleic acid test screening. *Transfusion* (In Press).

Book Chapters

1. The cost and cost effectiveness of allogeneic blood and autologous blood. Alternatives to Blood Transfusion in *Transfusion Medicine*. Publication in 2009

2008 Oral Abstracts and Posters

1. Custer B, Kamel HT, Tomasulo PA, Murphy EL, Busch MP. 10-Month Experience Screening USA Blood Donors for *Trypanosoma cruzi*: Yield, Risk Factors, and Cost Effectiveness. XXXth International Congress of the International Society of Blood Transfusion (ISBT), Macao SAR, People's Republic of China, June 8-11, 2008.
2. Rice MS, Custer B, Hindes DA, Hirschler N, Nguyen KA, Busch MP, Murphy EL. Genetic Research in the Blood Bank: Acceptability to Donors. XXXth International Congress of the International Society of Blood Transfusion (ISBT), Macao SAR, People's Republic of China, June 8-11, 2008.
3. Kamel H, Custer B, Wiltbank T, Tomasulo P, Bravo M. Delayed Reactions After Whole Blood and Automated Blood Collections. American Association of Blood Banks, 61st Annual Meeting. Montréal, QUE, Canada, Oct 3-8, 2008.
4. Custer B, Schlumpf K, Kakaiya R, Cable R, Wilkinson S, for NHLBI Retrovirus Epidemiology Donor Study-II. Large Variation in Donor Deferral for Low Hemoglobin and Other Temporary Medical Deferrals at 6 Different Blood Centers. American Association of Blood Banks, 61st Annual Meeting. Montréal, QUE, Canada, Oct 3-8, 2008.
5. Kiely N, Custer B, Kamel H, Bravo M, Kon M, Thorn J. Recruitment Yield and Study Participation from Donors Eligible for Research Studies. American Association of Blood Banks, 61st Annual Meeting. Montréal, QUE, Canada, Oct 3-8, 2008.
6. Sabino EC, Carneiro-Proietti AB, Leao SC, Proietti F, Gonçalez TT, Mendrone A, Ferreira JE, Custer B, Schreiber GB, for the International Retrovirus Epidemiology Donor Study-II. Prevalence of Transfusion Transmitted Infections in Brazilian Blood Donors as Determined by a Dual EIA Strategy. Association of Blood Banks, 61st Annual Meeting. Montréal, QUE, Canada, Oct 3-8, 2008.
7. Lee T-H, Sabino E, Montalvo L, Wen L, Chafets D, Custer B, Busch MP, for the Retrovirus Epidemiology Donor Study-II (REDS-II). Quantitative Real-Time PCR Assay for *Trypanosoma cruzi*. American Association of Blood Banks, 61st Annual Meeting. Montréal, QUE, Canada, Oct 3-8, 2008.
8. Custer B, Kamel H, Tomasulo P, Busch M. Should We Screen Blood Donors in the USA for *Trypanosoma cruzi*? Society for Medical Decision Making, Philadelphia PA, Oct 19-22, 2008.

2008 Invited Presentations

1. US Department of Health and Human Services, Advisory Committee on Blood Safety and Availability, Washington DC, Economic Issues of Pathogen Inactivation.
2. America's Blood Centers Annual Meeting, SMT Forum, New York NY
3. Public Health Agency of Canada, International Expert Advisory on Risk Modeling, Ottawa, Canada
4. WHO/Global Collaboration on Blood Safety 9th Meeting, International Cost Utility Analyses in Blood Safety, Geneva Switzerland

Workshops and Educational Sessions

1. AABB 2008, US blood donor pool workshop; Organizer, Jeffrey McCullough
2. AABB 2008, Risk assessment and cost effectiveness of blood safety measures, Organizer; Brian Custer