Donor Testing and Risk: Current Prevalence, Incidence, and Residual Risk of Transfusion-Transmissible Agents in US Allogeneic Donations

Shimian Zou, Susan L. Stramer, and Roger Y. Dodd

Over the past 20 years, there has been a major increase in the safety of the blood supply, as demonstrated by declining rates of posttransfusion infection and reductions in estimated residual risk for such infections. Reliable estimates of residual risk have been possible within the American Red Cross system because of the availability of a large amount of reliable and consistent data on donations and infectious disease testing results. Among allogeneic blood donations, the prevalence rates of infection markers for hepatitis C virus (HCV) and hepatitis B virus have decreased over time, although rates for markers of human immunodeficiency virus (HIV) and human T-cell lymphotropic virus did not. The incidence (/100 000 person-years) of HIV and HCV among repeat donors showed apparent increases from 1.55 and 1.89 in 2000 through 2001 to 2.16 and 2.98 in 2007 through 2008. These observed fluctuations confirm the need for continuous monitoring and evaluation. The residual risk of HIV, HCV, and human T-cell lymphotropic virus among all allogeneic donations is currently below 1 per 1 million donations, and that of hepatitis B surface antigen is close to 1 per 300 000 donations.

THE BLOOD SUPPLY in the United States and many other countries has become safer than ever, thanks to continuing improvements in donor selection and testing, along with broad improvements in public health. However, it has become increasingly challenging to develop statistically meaningful measures of blood safety as a result of the small numbers of positive test results. As the largest supplier in the United States, the American Red Cross (ARC) collects over 6 million donations from over 4 million donors annually, accounting for 42% of the country's supply. Furthermore, all 36 regions of the ARC system, located across the country, follow the same procedures for donor selection, blood collection, and donation testing. A research database has been established that is regularly updated at the ARCNET Data Center of the ARC Holland Laboratory containing data for all donations since 1995; the database includes donation history, donor attributes, and donation testing data extracted from the regulated central database but also verification of specific categories of confirmatory testing results [1]. As a result of standardized practices across the ARC system and the efforts to ensure quality data, the ARCNET database is a valuable resource for measuring the frequencies of transfusion-transmissible agents for which testing has been performed. This review summarizes our recently published results along with unpublished data from our ongoing surveillance efforts. We also include information on the demographic composition of our donor population, including its changing age structure.

DEMOGRAPHY OF DONOR POPULATIONS

In 2008, a total of 3 830 094 volunteer blood donors successfully made 6 638 877 blood donations to ARC Blood Services, with whole blood and apheresis components accounting for approximately 89% and 11% of the collections, respectively. Females accounted for approximately half (50.1%) of the successful donors, although they contributed slightly fewer (48.6%) of the successful donations. Repeat donors accounted for 74% of all donors and 81.9% of total donations. Female donors aged 16 to 24 years, 25 to 49 years, and 50 years or older, respectively, made an average of 1.56, 1.73, and 2.16 donations, and males of the same age groups gave 1.60, 1.98, and 2.51 donations during the year. Donors aged 16 to 24 years accounted for 29.1% of all donors and 21.7% of all donations. The proportion of donations by repeat donors 50 years or older has increased over the past several years, accounting for 37.4% in 2008, whereas the proportion from repeat donors of 25 to 49 years decreased to 32.9% in 2008 (Table 1). Part of the shift could be a reflection of the aging of baby

From the American Red Cross Holland Laboratory, Rockville, MD; and Scientific Support Office, American Red Cross Biomedical Services, Gaithersburg, MD.

Address reprint requests to Shimian Zou, PhD, National Heart, Lung and Blood Institute, National Institutes of Health, Rockledge II, 6701 Rockledge Dr, Bethesda, MD 20892.

E-mail: shimian.zou@nih.gov

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Table 1. Changing Age Composition (%) of Donors and Donations

		First-time donors			Repeat donors		
	Year	16-24 y	25-49 y	50+ y	16-24 y	25-49 y	50+ y
Donors	1996	12.2	11.0	2.3	12.4	44.7	17.4
	1999	13.9	13.3	3.4	11.2	38.7	19.5
	2002	13.7	10.5	3.1	11.7	37.8	23.2
	2005	13.9	8.8	3.0	13.0	34.8	26.5
	2008	14.8	8.1	3.1	14.3	31.3	28.4
Donations	1996	8.5	8.1	1.8	10.5	49.2	22.0
	1999	9.5	9.7	2.6	9.2	43.2	25.8
	2002	9.3	7.5	2.3	9.5	41.3	30.1
	2005	9.5	6.2	2.3	10.5	37.1	34.4
	2008	10.1	5.7	2.3	11.6	32.9	37.4

boomers [2]. The results in Table 1 also illustrate recent efforts within ARC Blood Services in recruitment and retention of new donors in the youngest age grouping [2-4]. Nevertheless, the results still indicate the need for improved recruitment and retention in the middle-aged groups. It is expected that the new procedures that have been implemented most recently for high school blood drives (boys who are shorter than 5 ft and girls who are shorter than 5 ft 6 in must weigh more than 110 lb, depending on their height; see Ref. [5]) will likely reduce the number of reactions among young donors. Thus, further changes in the overall age composition of our donor population would be predicted as return donation by the newly recruited young donors is enhanced. Such demographic changes need to be taken into account when prevalence and incidence data for different periods are compared because infectious disease (ID) marker rates differ by sex and age.

INFECTIOUS DISEASE MARKER PREVALENCE AMONG BLOOD DONATIONS

Prevalence reflects the number of confirmed-positive donations as determined for a given transfusion-transmissible agent over the total number of donations tested. Prevalence among first-time donations reflects the rate of an infection among the population of eligible individuals who have never undergone blood donation testing; comparison with prevalence rates for the overall population defines the impact of donor self-deferral and donor-eligibility selection. Prevalence among repeat donations reflects the additional impact of donation testing and deferral of test-reactive donors; marker reactivity among repeat donors reflects changes in those donors since their prior donation.

Testing algorithms in use during 2008 for antibodies to human immunodeficiency virus (anti-HIV), hepatitis C virus (anti-HCV) and human T-cell lymphotropic virus (anti-HTLV), HIV and HCV RNA by nucleic acid testing (NAT), hepatitis B surface antigen (HBsAg), *Treponema pallidum* (syphilis), West Nile virus (WNV), and *Trypansoma cruzi* (Chagas) are available in previous publications [1,6-14]. Table 2 shows the prevalence of major transfusion-transmissible agents among allogeneic whole blood and apheresis donations to the ARC in 2008.

Prevalence rates for almost all markers among first-time donations were consistently higher than those among repeat donations. Donations from male donors (first time or repeat) tended to have higher prevalence rates than those from female donors for HIV and to a lesser degree for HBsAg, although this was not necessarily the case for other agents. For HTLV, donations from female donors had higher prevalence rates than those from male donors. Rates for WNV did not differ between first-time and repeat donations because WNV RNA is present only acutely, but donations from males had higher prevalence rates than those from females (Table 2).

Compared with data in 2001 [1], the prevalence of HCV among first-time donors decreased significantly; the prevalence of HIV remained stable. However, the prevalence of HIV among first-time, female donors did show a significant decrease between 1999 and 2008 [11]. The prevalence of HBsAg also showed a significant reduction over this period, likely because of vaccination against HBV infection among young donors [9]. The prevalence of HTLV among first-time donors was essentially unchanged in 2008 compared with 2001, at approximately 0.01% or 10 per 100 000

Table 2. Prevalence of Markers* of Transfusion-Transmissible Infections Among Allogeneic Donations (Whole Blood and Apheresis) to the ARC in 2008

		First-time donations			Repeat donations			All donations			Ratio of prevalence first-time vs repeat
Donor sex	Marker	No. of positive donations	Positive rate (%)	1 positive per no. of donations	No. of positive donations	Positive rate (%)	1 positive per no. of donations	No. of positive donations	Positive rate (%)	1 positive per no. of donations	
Male	HIV	84	0.0147	6825	59	0.0020	50 161	143	0.0040	24 705	7.3
	HCV	1149	0.2004	499	127	0.0043	23 303	1276	0.0361	2769	46.7
	HBsAg	320	0.0558	1791	15	0.0005	197 298	335	0.0095	10 546	110.1
	HTLV	42	0.0073	13 649	2	0.0001	1 479 745	44	0.0012	80 290	108.4
	T pallidum	643	0.1122	892	181	0.0061	16 351	824	0.0233	4287	18.3
	T cruzi	29	0.0051	19 768	16	0.0005	184 969	45	0.0013	78 506	9.4
	WNV‡	9	0.0028	35 618	53	0.0031	32 503	62	0.0030	32 955	0.9
Female	HIV	30	0.0048	20 961	12	0.0005	206 437	42	0.0014	73 954	9.8
	HCV	815	0.1296	772	124	0.0050	19 978	939	0.0302	3308	25.9
	HBsAg	176	0.0280	3573	5	0.0002	495 443	181	0.0058	17 160	138.7
	HTLV	118	0.0188	5329	26	0.0010	95 278	144	0.0046	21 570	17.9
	T pallidum	561	0.0892	1121	122	0.0049	20 305	683	0.0220	4548	18.1
	T cruzi	30	0.0048	20 961	8	0.0003	309 656	38	0.0012	81 739	14.8
	WNV‡	5	0.0014	71 801	22	0.0015	66 542	27	0.0015	67 516	0.9
All	HIV†	114	0.0095	10 545	71	0.0013	76 574	185	0.0028	35 886	7.3
	HCV†	1964	0.1634	612	251	0.0046	21 660	2215	0.0334	2997	35.4
	HBsAg	496	0.0413	2424	20	0.0004	271 835	516	0.0078	12 866	112.2
	HTLV	160	0.0133	7513	28	0.0005	194 168	188	0.0028	35 313	25.8
	T pallidum	1204	0.1002	998	303	0.0056	17 943	1507	0.0227	4405	18.0
	T cruzi	59	0.0049	20 375	24	0.0004	226 531	83	0.0013	79 986	11.1
	WNV‡	14	0.0021	48 541	75	0.0024	42 488	89	0.0023	43 440	0.9
Ratio of male vs female	HIV		3.07			4.12			2.99		
	HCV		1.55			0.86			1.19		
	HBsAg		1.99			2.51			1.63		
	HTLV		0.39			0.06			0.27		
	T pallidum		1.26			1.24			1.06		
	T cruzi		1.06			1.67			1.04		
	WNV‡		2.02			2.05			2.05		

* For HIV and HCV, both confirmed antibody positivity, and positive viral RNA testing results are included [11]. Donations that were HBsAg confirmed positive but hepatitis B core antigen (anti-HBc) nonreactive were verified by HBV DNA testing; all donations are also tested for antibodies to anti-HBc, but there are no confirmatory tests available for the marker [9]; universal testing for HBV DNA by NAT was not implemented until June 2009. For HTLV, chemiluminescent immunoassay (Abbott PRISM, Abbott Diagnostics, Abbott Park, Ill) replaced enzyme immunoassay (bioMérieux, Durham, NC) as one of the screening methods in April 2008 [8]. We are also testing selected donations for cytomegalovirus antibodies, but the testing is not universal [15]. Consequently, data for anti-HBc and cytomegalovirus are not included in the table.

† Prevalence rates among first-time donations were reported previously [11].

‡ Testing for WNV is performed year-round, but the infection has been seasonal in the United States; as a result, the data shown refer to testing results from the WNV infection season, June 1 through December 31.

donations, although there were fluctuations during the period [8].

INCIDENCE AND WINDOW-PERIOD RISK AMONG REPEAT DONORS

The incidence of transfusion-transmissible agents among blood donors is the number of observed new infections over the total number of person-years observed (properly termed *incidence density*). In the past, incidence was determined by evaluation of data from repeat donors only, but now, methods have been developed to estimate incidence for first-time donors.

Table 3 presents incidence density data observed among repeat allogeneic blood donors to ARC in 2007 to 2008 along with residual risk estimates based on the observed incidence and reported infectious window periods for these markers. Detailed descriptions on the methods have been previously described [1,9-12]. Repeat donors included in the analysis were those who donated a unit within the targeted period of 2007 to 2008 (index donation) with at least 1 nonreactive donation up to 730 days (2 years) before the index donation. A *converter* is defined as a donor who donated a confirmed-positive blood unit (including viral RNA for HIV and HCV) during the period of 2007 to 2008 with at least 1 nonreactive donation up to 730 days before the confirmed-positive donation. For HBsAg, the incidence estimates were then adjusted upward by a factor of 2.38 to take into account the transient nature of the marker [9,16]. Residual risk associated with infectious window period was derived through the window-period model by multiplying the incidence estimate with the corresponding infectious window period [17-19].

As it can be seen from Table 3, male repeat donors had higher incidence rates of HIV markers, HBsAg, and *T pallidum* antibody than female repeat donors, although the reverse was true for anti-HTLV. Combined, residual risks caused by donations during the window period for HIV, HCV, and HTLV among donations from repeat allogeneic donors were in the range of 1:2 to 3 million and that for HBV, based on confirmed and verified (DNA-positive) HBsAg testing results, was 1:366 000 among repeat donors. No window-period data are available for *T pallidum* antibody to permit the estimation of residual risk estimates. In fact, there does not appear to be any current risk of transfusion-transmitted syphilis [10,23-25]. In general, comparable data have been reported from Canada [26]. At the moment, meaningful models with which to define residual risk for WNV do not exist. A total of 23 transfusion-transmitted WNV cases were reported in 2002 in the United States before WNV

Table 3. Incidence and Window-Period Residual Risk of Transfusion-Transmissible Infections Among Repeat Allogeneic Blood Donors to the ARC, 2007-2008*

	Male donors		Female donors		All donors		
Marker	No. of incident cases	Incidence rate (per 100 000 person-years)	No. of incident cases	Incidence rate (per 100 000 person-years)	No. of incident cases	Incidence rate (per 100 000 person-years)	Ratio of incidence male vs female
HIV	71	3.19	21	1.03	92	2.16	3.1
HCV	61	2.74	66	3.23	127	2.98	0.9
HBsAg	29	3.10	18	2.09	47	2.62	1.5
HTLV	1	0.04	8	0.39	9	0.21	0.1
T pallidum	216	9.72	108	5.28	324	7.59	1.8

Residual risk† (frequency of infectious window period donations)

	Male donations		Female donations		All donations		
	/100 000 donations	1 per no. of donations	/100 000 donations	1 per no. of donations	/100 000 donations	1 per no. of donations (d)	Infectious window
HIV	0.080	1 256 035	0.026	3 905 846	0.054	1 860 883	9.1
HCV	0.056	1 797 786	0.065	1 528 270	0.060	1 657 722	7.4
HBsAg	0.323	309 412	0.218	458 499	0.273	366 509	38.0
HTLV	0.006	15 911 917	0.055	1 829 357	0.029	3 394 086	51.0

* For details, refer to Zou et al, 2010, on HIV and HCV [11]; Zou et al [9], 2009, and Korelitz et al [16], 1997, on HBsAg (note different timeframe); and Stramer et al [8] on HTLV.

† Incidence rate times infectious window period (in years): 9.1 days for HIV, 7.4 days for HCV, 38 days for HBsAg, and 51 days for HTLV [1,9,11,17-22].

NAT, but after the implementation of testing, only 11 cases have been reported from 2003 through 2010, suggesting the efficacy of testing [27,28]. Furthermore, none of the 11 WNV transfusion-transmitted cases came from the ARC, which is probably attributable to the use of effective triggering policies by the ARC for the conversion from minipool NAT to individual donation NAT.

The incidence (/100 000 person-years) of HIV and HCV among repeat donors showed apparent increases from 1.55 and 1.89 in 2000 through 2001 to 2.16 and 2.98 in 2007 through 2008 [1,11]. The increase in HIV may be associated with increased representation of certain donor groups, such as young African American donors, whereas the increase in HCV may be associated with increased transmission among white donors of 50 years or older. The latter trend was consistent with a recent report that increased use of non–hospital health care facilities may contribute to HCV infection in the United States [29]. It is also of interest to note that, in some European countries, endoscopy is regarded as a risk factor for HCV infection and there has been recent concern about such risk in a number of well-publicized clusters in the United States [30-32]. Given that endoscopy is recommended for those aged 50 years or older, this is a possible contributor to the increased incidence of HCV [11]. The observed fluctuations over the period underline the need for continuous monitoring and evaluation [11,33].

OVERALL INCIDENCE AND WINDOW-PERIOD RISK ESTIMATES

A single-sample method for estimation of incidence among first-time donors allows incidence and residual risk to be estimated for all donations. A "detuned" or less sensitive assay was developed for HIV infection, although no such assays have yet been widely used for other infections. Implementation of NAT for viral RNA (HIV RNA and HCV RNA) and thus the availability of 2 tests indicative of different stages of an infection (anti-HIV and HIV RNA or anti-HCV and HCV RNA) made it possible to identify recent infections through testing of a single blood sample. As a result, measuring "NAT yield" donations, namely, antibody-negative but viral RNA–positive donations, and comparing such "NAT yield" rates between first-time and repeat donations have allowed the estimation of incidence among first-time donors. The ratio of NAT-yield rates between first-time donations and repeat donations reflects difference in incidence between the 2 donor groups [1]. Furthermore, NAT-yield data and the NAT-yield window period (the period between viral RNA becoming detectable and viral antibody becoming detectable) were used to directly estimate incidence among all donations. The NAT-yield window period multiplied by the number of donations approximates at-risk person-time observed [20]. Similarly, an approach based on the "HBsAg yield period," that is, the time during which HBsAg is present but antibodies to hepatitis B core are absent, was used to derive incidence ratio between first-time donors and repeat donors and to directly estimate incidence among all donations [9]. There have also been reports on incidence estimation methods based on prevalence data among first-time donors [34]. For this review, however, we have used only incidence data estimated as described above and in our previous publications. Residual risk associated with the infectious window period for all allogeneic donations was derived from the weighted sum of residual risk for first-time and repeat donations [11].

Table 4 shows incidence and window-period risk estimates for the 4 viral markers among first-time allogeneic donors as well as weighted overall estimates among all donors. The ratios of incidence between first-time donors and repeat donors for HIV, HCV, and HBsAg were as described in our recent reports [9,11]. For HTLV, a value of 2.5 was assumed, as was done in our tissue risk assessment [35]. The number of HIV NAT-yield cases among female donations was too small to give a stable NAT-yield rate, so sex-specific incidence was not estimated. For all allogeneic, whole blood, and apheresis blood donations, the window-period risk of HIV, HCV, and HTLV is currently below 1 per 1 million donations, and that of HBV is close to 1 per 300 000 donations. As with estimates among repeat donations, data reported from Canada between 2001 and 2005 showed generally similar overall residual risk levels for HIV, HCV, HBV, and HTLV [26].

Testing failures or errors and errors in quarantine release may also cause infectious or potentially infectious units to be released for transfusion. Based on data presented in Table 4 and Table 2, the total number of collections in the United States

Table 4. Incidence and Window-Period Residual Risk of Transfusion-Transmissible Infections Among All Allogeneic Blood Donors to the ARC, 2007-2008 *

Marker	Incidence (/10^5 person-years)			Residual risk[§] (/10^5 donations)			Residual risk[§] (1/no. donations)		
	Repeat donors	First-time donors[†]	All donors[‡]	Repeat donations	First-time donations	All donations[‖]	Repeat donations	First-time donations	All donations[‖]
HIV	2.16	5.41	3.11	0.054	0.135	0.068	1 860 883	741 388	1 466 671
HCV	2.98	10.38	5.14	0.060	0.211	0.087	1 657 722	474 992	1 148 628
HBsAg	2.62	6.34	3.71	0.273	0.660	0.342	366 509	151 450	292 561
HTLV	0.21	0.53	0.30	0.029	0.074	0.037	3 394 086	1 357 634	2 678 836

* For details, refer to Zou et al [11], 2010, on HIV and HCV; and Zou et al [9], 2009, on HBsAg (note different timeframe).

† Incidence among first-time donors estimated by multiplying incidence among repeat donors with the incidence ratio of the 2 donor groups: 2.51 for HIV, 3.49 for HCV, 2.42 for HBsAg, and 2.5 for HTLV.

‡ Weighted sum of incidence among repeat donors and incidence among first-time donors by proportions of the 2 donor groups: 29.2% first time and 70.8% repeat.

§ Incidence rate times infectious window period (in years): 9.1 days for HIV, 7.4 days for HCV, 38 days for HBsAg, and 51 days for HTLV.

‖ Weighted sum of residual risk among repeat donations and that among first-time donations by proportions of the 2 types of donations: 17.8% first time and 82.2% repeat.

[36] as well as estimates of false-negative test errors and quarantine release errors [37], it is estimated that 10.2 potentially infectious donations may enter the US blood supply annually, of which window-period donations account for greater than 99.5% (unpublished). These estimates are very similar to those reviewed earlier [38] and again show that window-period infections account for the overwhelming proportion of the estimated residual risk. Although the estimates for false-negative test results and quarantine release errors together are less than 0.5% of the total when combined, the likelihood of false-negative test results, considering redundant testing systems for most markers, or quarantine release errors in sophisticated blood centers appears to be an overestimate.

REFLECTIONS

Estimated Residual Risks Versus Observed Transfusion Transmissions

Estimated residual risks do not necessarily reflect the actual number of transfusion transmissions to recipients. In fact, only the original observations on HIV window-period risk were based on transfusion-transmitted infections [17]. Residual risk estimates have been continuously updated based on measures of test sensitivity. However, the window periods used in this review are based on viral doubling periods and assumed infectious doses. Other factors contribute to the lack of reported transfusion transmissions [9,21,39]. First, detectable viral loads measured in donations within the window period may not represent infectious virions or may be below the infectious dose; window-period estimates assume equal infectivity during the entire window period. Second, infectivity may be reduced during component processing, storage, and delivery. Third, an abortive infection may result from transfusion transmission. Fourth, recipient immunity may block an infection. Fifth, a proportion of transfusion-transmitted infections could be asymptomatic and, therefore, are not identified. Finally, there are many other reasons that contribute to underreporting, including recipient deaths and failure or inability to recognize or appropriately diagnose infections. It should also be noted that almost all recent posttransfusion HIV infections have been identified through lookback, a mechanism that is not possible if the implicated donor does not return for a further donation [40,41]. Data are lacking on many of these aspects, which has prevented quantitative description of risks associated with each of these factors. Of note, tracing recipients from known HIV seroconverting donors (ie, lookback) with the ARC from 1999 to 2008 has confirmed HIV transmission to 2 recipients. In contrast, no reported HIV infections could be substantiated as transfusion transmitted from recipients reporting possible or suspect HIV transfusion transmissions over this period; most of these reported cases were attributable to prior HIV infection in the recipient [42,43]. Interestingly, both of the implicated units identified by lookback from HIV seroconverting donors were processed into 1 plasma component and 1 red cell component; both

plasma components but neither of the red cell units resulted in infection, leading to the conclusion that the current levels of test sensitivity are approaching the infectious dose. Similar cases of differential transmission of HIV have been reported in other countries [44].

Current Determinants of Residual Risks of the Blood Supply

Residual risks of the blood supply essentially depend on the incidence rates of transfusion-transmissible infections among donors and on the characteristics of the tests used. The significant decline in prevalence of anti-HCV in our donor population since 1995 has been much more rapid than that seen in the general population, indicating the effectiveness of the donor selection process [45-47]. However, the rate of decline of donor prevalence has slowed in recent years, suggesting that donor selection measures may have reached their limits. Similarly, the anti-HIV prevalence among our donor population, which is much lower than that of anti-HCV, has not changed much over the same period [11,48,49].

However, incidence drives the overall residual risk, given the sensitive and redundant assays currently used for donation screening. Incidence among both first-time and repeat donors should reflect the transmission force of an infection in the general population as modified by the effectiveness of donor selection processes. The recent increase in HIV and HCV incidence among our donor population, when there was no change in our donor selection process, suggests that transmission forces in the general population have become the principle determinants of changes in residual risk of the blood supply. Indeed, our recent study showed that the observed increase in HIV and HCV incidence could be associated with increased HIV transmission among certain young, male groups and increased health care–associated HCV transmission among those of 50 years or older. After differences in donor sex and age composition were accounted for through regression analysis, the increases in HIV and HCV incidence remained statistically significant [11]. The decrease in HBV residual risk, on the other hand, may be attributable to increasing representation of vaccinees in the donor population. Among donors tested for antibodies against HBV in July 2008, more than 65% of those who were 29 years or younger had anti-HBs antibodies; significant decreases in HBV incidence were observed in the same groups from 1997 through 1999 to 2006 through 2008 [9]. Thus, the observed changes in residual risks during recent years do indicate that changes in the general population have become the principal determinants for variations in the safety of the blood supply.

Other factors may influence residual risk, including donations by those who have had a history of exposure but present for donation anyway as a result of (for example) peer pressure, failure to remember an exposure risk, or even test seeking. Earlier studies in the United States showed that 2% to 3% of allogeneic, repeat whole blood, and plateletpheresis donors had unreported deferrable risks and 1% to 2% donated because they wanted the results of test(s) such as that for HIV [50]. Among a group of HCV RNA–positive but anti-HCV–negative donors, 29.2% had recent injection drug use, which, if reported at the time of donation, should have resulted in deferral of their donations [51]. A study of confidential unit exclusion also showed that donors who chose the option had higher seroconversion rates than those who did not, suggesting unreported deferrable risk histories, although the option had very limited value in reducing the residual risk [52]. A more recent study in Canada examined Canadian Blood Services Donor Health Assessment Questionnaire records between 1990 and 2004 and tracked changes in them. The results showed that face-to-face interviewing during predonation screening for high-risk behaviors had no effect on HIV or HCV rates in first-time donations [53]. In summary, unreported deferrable risks, especially those among seroconverting or NAT-yield (RNA/DNA-positive but serology-negative) cases, likely continue to impact the safety of the blood supply, and the current donor selection process has not been effective in completely eliminating such risks. A large study including most of the US donor population will examine reported risk factors among test-positive donors and thus may reveal additional behavioral factors impacting further improvements in blood safety.

Where Do We Go From Here?

The past 3 decades have witnessed the success of blood safety measures that have driven the residual risks of HIV, HCV, and HTLV well below 1:1 million donations. With the introduction of NAT

for HBV and continual improvements in sensitivity, it is expected that the HBV residual risk should also decrease. The current state of blood safety is caused by donor selection and donation testing; however, this process has resulted in donor loss and has high associated costs [54,55]. For emerging blood-borne disease agents [56], we will undoubtedly use similar strategies for the foreseeable future in selective testing modes prioritizing risk reduction as appropriate (eg, by targeting geography, season, donor group, or component(s) associated with transmission). In the United States, the agents for which interventions are needed include dengue viruses [57] and the *Babesia* parasite [58]. The intervention with the greatest impact for such agents is testing; donor-screening questions have already been shown to be ineffective for *Babesia* [59]. It is possible that a 2-week deferral period may be applied to travelers to dengue-epidemic areas, but this will not be effective if there is autochthonous risk. Similarly, questioning of donors for symptoms or disease would be of little value as demonstrated by our current donor health history question for babesiosis or Chagas disease and as observed from our experience with asking a headache with fever question for WNV [60,61].

Despite ongoing progress in blood safety, it is clear that there is room for improvement. What can be done to achieve such improvement without adding further financial and operational burdens? Can the process of donor qualification be simplified? Can we better educate those at risk so that they do not present for donation? Are there ways to further enhance the proportion of low-risk individuals within the donor population? Research needs to continue to determine effective approaches for continuing protection of the blood supply from ID risks. Reduction and even elimination of ID agents have been achieved by the use of pathogen-reduction/inactivation methods. Such methods have been in place for decades for plasma for further manufacture with a virtual elimination of reported cases of HIV, HCV, and HBV, and such methods have been in place in Europe for platelets [56]. However, further research, licensing, and funding mechanisms are needed before its adoption in the United States.

Another approach to risk reduction includes renewed efforts in prevention at the community level. Approaches may include public education about risk behaviors and other possible transmission routes as well as enhanced identification of infected individuals. Given increasing number of people living with HIV in the United States each year and continuing transmission, HIV incidence is expected to remain stable or even increase among the population and thus among blood donors in the foreseeable future. The Centers for Disease Control and Prevention has proposed 4 key strategies to reduce HIV transmission: (1) making HIV testing a routine part of medical care; (2) implementing new models for diagnosing HIV infections outside medical settings; (3) preventing new infections by working with HIV-infected persons and their partners, as well as others at high risk for HIV infection; and (4) further decreasing mother-to-child HIV transmission [62]. The first 3 of the 4 strategies should help reduce HIV transmission among people who are potential blood donors. The more widely available HIV testing might also lead to a reduction in blood donation among test seekers and further reduce the risks of transfusion-transmissible infections among blood donors. As recommended by an expert panel to Centers for Disease Control and Prevention [63], more research may be able to identify new approaches to addressing the current challenges in prevention and intervention.

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