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THE RISK OF TRANSFUSION-TRANSMITTED VIRAL INFECTIONS

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Abstract *Background.* Accurate estimates of the risk of transfusion-transmitted infectious disease are essential for monitoring the safety of the blood supply and evaluating the potential effect of new screening tests. We estimated the risk of transmitting the human immunodeficiency virus (HIV), the human T-cell lymphotropic virus (HTLV), the hepatitis C virus (HCV), and the hepatitis B virus (HBV) from screened blood units donated during the window period following a recent, undetected infection.

Methods. Using data on 586,507 persons who each donated blood more than once between 1991 and 1993 at five blood centers (for a total of 2,318,356 allogeneic blood donations), we calculated the incidence rates of seroconversion among those whose donations passed all the screening tests used. We adjusted these rates for the estimated duration of the infectious window period for each virus. We then estimated the further reductions in risk that would result from the use of new and more sensitive viral-antigen or nucleic acid screening tests.

Results. Among donors whose units passed all screening tests, the risks of giving blood during an infectious window period were estimated as follows: for HIV, 1 in 493,000 (95 percent confidence interval, 202,000 to 2,778,000); for HTLV, 1 in 641,000 (256,000 to 2,000,000); for HCV, 1 in 103,000 (28,000 to 288,000); and for HBV, 1 in 63,000 (31,000 to 147,000). HBV and HCV accounted for 88 percent of the aggregate risk of 1 in 34,000. New screening tests that shorten the window periods for the four viruses should reduce the risks by 27 to 72 percent.

Conclusions. The risk of transmitting HIV, HTLV, HCV, or HBV infection by the transfusion of screened blood is very small, and new screening tests will reduce the risk even further. (N Engl J Med 1996;334:1685-90.)
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T HE discovery in the mid-1980s that the acquired immunodeficiency syndrome (AIDS) could be transmitted by transfusion heightened public concern about blood safety. Over the past decade, efforts have been made to quantify the risks of transfusion-transmitted infectious disease accurately.[1-3] Although numerous calculations of the risk of human immunodeficiency virus (HIV) infection have been made, there are fewer reliable estimates of infection rates for the other major agents transmissible by transfusion. Accurate estimates of the risks of transfusion-transmitted viral infections are needed in order to monitor the safety of the blood supply and evaluate the yield and cost effectiveness of new techniques of screening and alternatives to allogeneic transfusion.

The most direct way of estimating the risk associated with transfusion is to study the rate of infection prospectively in transfusion recipients.[4-7] The current very low risk of transfusion-transmitted infectious disease makes such studies impractical, however, because an exceedingly large number of recipients is required for the risk to be measured accurately. Alternatively, the rate of infection in samples of donated blood that test negative on routine screening can be determined by further testing with extremely sensitive assays of viral antigens or nucleic acid.[8-11] Such studies are prohibitively expensive, however, and may detect only a subgroup of infectious units, given the imperfect sensitivity of direct assays for virus. Techniques other than the direct monitoring of residual risk are therefore needed to quantitate risk and evaluate proposed risk-reduction procedures.

The greatest threat to the safety of the blood supply is the donation of blood by seronegative donors during the infectious window period when the donors are undergoing seroconversion. Such people represent new, or incident, infections. Estimating rates of seroconversion, or incidence, requires the ability to track large numbers of donors at multiple centers. When rates of seroconversion are combined with estimates of the probability that blood was donated during the donor's window period, the residual risks of transmitting infectious disease can be calculated.

We present incidence rates of seroconversion among

blood donors for each of four major blood-borne viruses — HIV, the human T-cell lymphotropic virus (HTLV), the hepatitis C virus (HCV), and the hepatitis B virus (HBV) — during the three years 1991 through 1993. We calculated these rates among people who donated blood more than once and whose units passed all screening tests. Residual risks were then derived from current estimates of the length of the window period for each agent. We calculated the potential effect of improved methods of testing on risk reduction with the same model.

METHODS

The Retrovirus Epidemiology Donor Study is a multidisciplinary research program designed to monitor the safety of the nation's blood supply through epidemiologic studies of the incidence of retroviruses and other infectious agents among volunteer blood donors.[12-14] The study is conducted at five blood centers in different parts of the United States: the Irwin Memorial Blood Centers in San Francisco; the Oklahoma Blood Institute in Oklahoma City; and American Red Cross Blood Services in the Greater Chesapeake and Potomac (Baltimore), Southeastern Michigan (Detroit), and Southern California (Los Angeles) regions. Westat, Inc., in Rockville, Maryland, is the medical coordinating center.

The analysis reported here is based on files from the study centers containing information on donors, results of serologic screening, and confirmatory test results. It includes all allogeneic-blood donations, of either whole blood or components obtained through apheresis, from people who made at least two donations from January 1, 1991, through December 31, 1993. The study protocol was approved by the institutional review board at each center.

All the donations were tested for infectious disease as required by the Food and Drug Administration. The seven tests included screening and confirmatory tests for antibodies to HIV type 1 and (after March 1992) HIV types 1 and 2, HTLV type I (this test also identifies blood infected with HTLV-II), and HCV. Tests for exposure to HBV included assays for hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc). The donations were also tested for syphilis and elevated levels of alanine aminotransferase. The data on HCV were limited to the donations screened by second-generation enzyme immunoassays (EIA 2.0), which began to be used in the various centers in March and April 1992.

For each virus, crude incidence rates were calculated as the number of seroconverting donors divided by the total number of person-years at risk. A seroconverting donor was defined as a donor who, during the study period, initially made a nonreactive donation and subsequently made a donation that was confirmed to be positive. The total number of person-years used as the denominator was calculated by totaling the intervals between donations for all donors. In the case of seroconverting donors, an adjustment was made by assuming that seroconversion occurred at the midpoint between the last seronegative donation and the seropositive donation. The results of screening and confirmatory tests were reviewed in all cases of seroconversion to exclude possible false positive results or indeterminate test interpretations.[15-18] This process included a review of data on the donations made before and after seroconversion, as well as of available information on the follow-up of the donor.

Adjusted incidence rates of seroconversion were calculated for donors whose previous seronegative donations met all the screening requirements for transfusion. Intervals were included in this calculation only if the first donation in the interval was usable — i.e., if it was nonreactive on all seven standard serologic screening tests and was not excluded by the process of confidential unit exclusion. For each agent, seroconversion was thus defined as a change from nonreactivity on all seven assays to confirmed seropositivity for the agent on the second donation in the interval.

Incidence rates of seroconversion for HBsAg were further adjusted to account for variable patterns of antigenemia after primary infection. The adjustment assumed that 70 percent of HBV-infected donors have transient antigenemia, 25 percent have a primary antibody response but no detectable antigenemia, and 5 percent become long-

term carriers.[19] All the long-term carriers, none of the donors with primary antibody responses, and some of the donors with transient antigenemia are identified with the HBsAg test. By dividing the estimated duration of transient antigenemia (63 days)[19,20] by the observed median interval between donations for the 33 persons in the study who seroconverted to positivity for HBsAg (119 days), we calculated that 53 percent of donors with transient antigenemia would be identified by the HBsAg test. The overall probability of detecting an incident HBV infection with the HBsAg test was estimated as 0.70 × 53 percent (for donors with transient antigenemia) + 0.25 × 0 percent (for those with primary antibody responses) + 0.05 × 100 percent (for long-term carriers), or 42 percent. Because only 42 percent of donors seroconverting for HBV are likely to be identified with the HBsAg test, the observed incidence rate of HBsAg was multiplied by 1/0.42, or 2.38. This approach was used partly because of the nonspecificity of the anti-HBc test, which renders it useless in quantitating the incidence of HBV.[21]

The adjusted rates of seroconversion were used to calculate the residual risk of transfusion-associated transmission for each virus and to project the yield of new screening tests for HBV, HCV, and HIV. The adjusted incidences of seroconversion were multiplied by the reported window periods before seroconversion,[20,22-25] expressed in fractions of a year. The product is the probability that a seroconverting donor gave an infectious unit of blood during the window period that was not detected as seropositive by the screening tests currently used and therefore could have been given in transfusion. Likewise, the adjusted incidences were multiplied by the estimated reductions in the length of the window periods achieved with additional proposed tests[3,22,26] to project the yield of the new tests (the number of infected units detected per 12 million units screened annually in the United States).

RESULTS

During the three-year study period, 586,507 people who donated blood more than once made a total of 2,318,356 allogeneic donations. The crude incidence rates of HIV, HCV, and HBsAg seropositivity were similar and were each approximately four times higher than the crude incidence rate of HTLV (Table 1). After we adjusted the incidence rate of HBsAg to derive the total incidence of HBV, the estimated rate of HBV infection exceeded each of the other rates by a factor of two or more.

The adjusted incidence rates of seroconversion are also shown in Table 1. Although 33 donors seroconverted to HIV positivity, for 6 the last donation made before the one in which HIV antibodies were detected could not be used, either because it tested positive for another marker (elevated alanine aminotransferase levels and HBsAg in 1 donation each, and anti-HBc in 2) or because of confidential unit exclusion (2 donations). This resulted in a 16 percent reduction in the incidence of HIV seroconversion, from 4.01 to 3.37 per 100,000 person-years. The incidence of HCV was also reduced, since units from 2 of the 16 incident donors could not be used because of elevated alanine aminotransferase levels.

The adjusted incidence rate of seroconversion, expressed in person-years, is an estimate of the probability that a donor who gave a usable donation was infected within a one-year period thereafter. The relevant risk to the blood supply, however, is the risk that the donor was already infected (that is, was in the infectious window period) at the time of the seronegative donation. In Table 2, the adjusted incidence rate for each virus is multiplied by the length of the window period

Table 1. Crude and Adjusted Incidence Rates of Seroconversion Associated with Each of Four Major Blood-Borne Viruses.

VIRUS*	CRUDE RATE			ADJUSTED RATE		
	NO. OF SEROCON-VERSIONS	NO. OF PERSON-YR	INCIDENCE RATE PER 100,000 PERSON-YR	NO. OF SEROCON-VERSIONS	NO. OF PERSON-YR	INCIDENCE RATE PER 100,000 PERSON-YR (95% CI)†
HIV	33	822,494	4.01	27	801,571	3.37 (2.22–4.76)
HTLV	9	822,417	1.09	9	801,572	1.12 (0.51–1.98)
HCV‡	16	330,924	4.84	14	324,356	4.32 (2.35–6.87)
HBV						
HBsAg	33	822,426	4.01	33	801,553	4.12 (2.83–5.64)
Total HBV§	—	—	9.54	—	—	9.80 (6.74–13.42)

*Markers for each virus were assayed as described in the Methods section.

†Among donors whose prior donations were usable. CI denotes confidence interval.

‡Data are limited to donations screened by the second-generation enzyme immunoassay, the use of which began in March and April 1992.

§Data were adjusted for transient antigenemia by multiplying the incidence rate of HBsAg seroconversion and the 95 percent confidence interval by 2.38, on the assumption that 42 percent of HBV infections are detected by the assay for HBsAg.

for that virus, expressed as a fraction of a year, to estimate the residual risk to the blood supply. The risks of a donation infectious for HIV or HTLV entering the blood supply are on the order of 2 per million donations. For HCV, the risk is approximately five times greater, and for HBV it is approximately eight times greater.

Similarly, we combined the adjusted incidence rates of seroconversion with estimates of window-period reductions for potential screening tests, to project their yield and the effect of their implementation on the estimates of residual risk (Table 3). This calculation showed that viral-antigen and nucleic acid testing for HIV would be expected to detect from 7 to 12 HIV-infected but seronegative donations per 12 million screened units. The estimated yield of nucleic acid tests for HCV and HBV was 84 and 81 infected donations, respectively, per 12 million screened units.

DISCUSSION

Because all seropositive donated units are discarded and pose no risk to the blood supply, estimates of the prevalence of infectious disease are not adequate for assessing the residual risk of transfusion-transmitted disease. Accurate assessments of risk must account for infectious donations made in the window period between the initial infection and detectable seroconversion. Our data show that the adjusted incidence rates of HIV, HTLV, HCV, and HBV seroconversion are small among persons who donated blood more than once in the study period, with a combined incidence estimated at 18.61 per 100,000 person-years. The seroconversion rates among these donors were highest for HBV (9.80 per 100,000), followed by HCV (4.32 per 100,000), HIV (3.37 per 100,000), and HTLV (1.12 per 100,000). These rates are lower than those in the general population,[27,28] a finding that confirms the effectiveness of donor-education and history-taking procedures. For HBV, unlike the other viruses, seroconversion cannot be measured precisely. The methods of screening that are used (tests for HBsAg and anti-HBc) have limitations in the estimation of incidence.

Our calculations apply a correction factor of 2.38 to the observed rate of HBsAg seroconversion, a factor derived from the observed intervals between donations and the known duration of positivity for HBsAg. It is noteworthy that HBV accounted for almost 53 percent of all seroconversions among donors who gave blood more than once. This finding reflects the endemic nature of HBV infection and is consistent with our knowledge that the primary cause of acute hepatitis is HBV.[29] We estimated the rate of HBV seroconversion among blood donors to be about 1/10 the estimated rate in the population.[30]

The estimates of residual risk reported in this study represent the probability that a unit is infectious but was donated in the antibody-negative window period before seroconversion. We calculate that the risk of viral exposure ranges from 1.56 (for HTLV) to 15.83 (for HBV) per million donations, with an overall risk of 29.12 per million units for the four viruses combined. The probability that a transfusion recipient would be infected would be slightly lower for HIV, HCV, and HBV, given the reported 90 percent rates of viral transmission from transfused products seropositive for these agents,[5,31] and significantly lower for HTLV, given its transmission rate of 30 percent.[32]

For HIV, the estimated residual risk of approximately 1 in 493,000 (95 percent confidence interval, 202,000 to 2,778,000) among persons giving multiple donations is significantly lower than the estimates reported in the late 1980s and early 1990s[1,2,6,9,33] and is consistent with

Table 2. Residual Risks to the Blood Supply Associated with Window-Period Donations by Seroconverting Donors.

VIRUS*	LENGTH OF WINDOW PERIOD (DAYS)		RESIDUAL RISK (PER MILLION DONATIONS)	
	ESTIMATE	RANGE	ESTIMATE†	RANGE‡
HIV	22§	6–38	2.03	0.36–4.95
HTLV	51¶	36–72	1.56	0.50–3.90
HCV	82‖	54–192	9.70	3.47–36.11
HBV				
HBsAg	59**	37–87	6.65	2.87–13.43
Total HBV††	—	—	15.83	6.82–31.97

*Markers for each virus were assayed as described in the Methods section.

†Calculated by multiplying the adjusted incidence rate of seroconversion (Table 1) by the length of the window period.

‡The lower and upper bounds of the range were calculated by multiplying the lower and upper limits of the window-period range by the lower and upper limits of the 95 percent confidence interval for the adjusted incidence rate, respectively.

§Data were obtained from Busch et al.[22]

¶Data were obtained from Manns et al.[23]

‖Data were obtained from Busch et al.[24] and Lelie et al.[25]

**Data were obtained from Mimms et al.[20]

††Data were adjusted for transient antigenemia by multiplying the estimated residual risk of HBsAg seroconversion and the range by 2.38, on the assumption that 42 percent of HBV infections are detected by the assay for HBsAg.

Table 3. Projected Yield of Additional Tests for HIV, HCV, and HBV.

Virus and Test	Estimated Reduction in Window Period (days)	Residual Risk with Additional Tests		Projected Yield (Infected Units Detected per 12 Million Units)
		Projected (per million donations)*	Percent Reduction	
HIV				
p24 antigen assay	6†	1.48	27.3	7
DNA PCR	6†	1.48	27.3	7
RNA PCR	11†	1.01	50.0	12
HCV				
RNA PCR	59‡	2.72	72.0	84
HBV				
DNA PCR	25§	9.12	42.4	81

*Calculated by multiplying the adjusted incidence rate of seroconversion (Table 1) by the revised window period (the window-period estimate shown in Table 2 minus the estimated reduction in the window period).

†As compared with the value obtained when the combination assay for HIV-1 and HIV-2 was used, as reported by Busch et al.[22]

‡As compared with the value obtained by the third-generation enzyme immunoassay for HCV, as reported by Alter.[3]

§As compared with the value obtained by the assay for HBsAg, as reported by Jagodzinski et al.[26]

the estimate of 1 in 450,000 to 1 in 660,000 recently reported by Lackritz et al.[34] This low residual risk is attributable both to the low incidence rate among donors and to the dramatically improved sensitivity of the HIV-antibody screening tests used by blood banks.[22] The highest transfusion-associated risks are due to HBV and HCV, which, with their higher incidence rates and longer window periods, accounted for 88 percent of the residual risk of viral transmission in our study. Although the risk of exposure to hepatitis virus is much higher than that of exposure to HIV, the adverse outcomes of HIV disease are much worse. Although it is estimated that up to 90 percent of HCV infections become chronic, long-term follow-up studies indicate that clinical liver disease develops in only 10 to 20 percent of those infected during a period of approximately 20 years after transfusion.[1,3,35-37] The health consequences of transfusion-acquired HBV infection have not been well studied, but are probably of limited consequence, since the majority of such infections in adults are transient and asymptomatic.[1,33]

Our analyses indicate that introducing new techniques of screening would substantially reduce the residual risk of transmitting infectious disease by transfusion. Most attention has been given to the further reduction in the risk of HIV infection achieved by shortening the window period. New tests will have limited effect, however, because the risk of HIV transmission is already very small. On the basis of the estimated reduction in the length of the window period, implementing either p24 antigen testing or DNA polymerase-chain-reaction (PCR) assays would identify 7 infectious donations among the 12 million units collected annually. The reduction in the residual risk of HIV infection could exceed 50 percent if RNA PCR assays were used, because that technique could result in the detection of 12 additional infectious units annually. The risks of HCV and HBV infection can be expected to be reduced

by 72 and 42 percent, respectively, if the results of initial studies of the performance of nucleic acid screening assays for these agents are confirmed.

The incidence rates and residual risks derived in our study have several limitations. First, we could not estimate the incidence of seroconversion among one-time blood donors. One adjustment frequently used in estimates of HIV incidence assumes that the infection rate among such donors is 1.8 times that among donors who give blood more than once. This adjustment factor is based on the relative prevalence of seropositivity for HIV antibody among first-time donors as compared with multiple-time donors when the HIV-antibody test was implemented in 1985.[38] The current relevance of this adjustment factor is uncertain, however, and no adjustment factors of this type are available for the other viruses. Therefore, we chose not to adjust our analysis for first-time donors. We believe that such adjustment would not alter our results significantly, because first-time donors accounted for only 20 percent of the donations in this study.

Second, it is important to consider the sources of the estimates of the window period that we used in calculating residual risk and the precision of those estimates. In the case of HIV, we used an estimate derived from data on the infectivity of transfused blood components from donors who later tested positive for HIV antibody.[22,39] In the cases of HBV,[20] HCV,[24,25] and HTLV-I and HTLV-II,[23] however, we used data from well-documented cases of transfusion-transmitted infection and considered the infectious window period to be the time from the transfusion of an infected unit to seroconversion, as detected by routine donor-screening assays. Estimates of reductions in the length of the window period associated with direct virus-detection assays are based on laboratory studies in which contemporary PCR assays (and in the case of HIV, tests for p24 antigen) were performed on serial specimens obtained before seroconversion from seroconverting plasma donors or subjects enrolled in cohort studies.[3,22,26] Because the availability of appropriate specimens from the time of seroconversion is relatively limited, each such estimate has a relatively wide confidence interval. Refining the estimates is clearly a priority.

Third, our risk estimates for HTLV and HCV are based on incident infections in donors and do not reflect the possible contribution of chronic infections that do not produce detectable seropositivity. With regard to HTLV infection, one study estimated that up to 22 percent of HTLV-II–infected donors are missed by current HTLV-I–based screening tests.[40] There may be a similar situation with HCV infection. Data from a 1992 investigation by the Centers for Disease Control and Prevention (CDC) indicated that up to 10 percent of persons with community-acquired HCV infection were not identified by the HCV-antibody assays used in screening blood donors.[28] These data have not been confirmed by others, however. Because this 10 percent rate of undetected HCV infection has been used in previous models of the risk of transfusion-transmitted

HCV infection, it is not surprising that our risk estimate, based solely on donors with window-period infections, is substantially lower than the rates of 1 in 3300 to 1 in 5000 previously reported.[10]

Finally, since our risk estimates are based on data from a limited number of blood centers, we do not know whether they reflect national averages. The centers participating in our study do, however, account for about 1.1 million donations annually, or about 9 percent of all donations collected nationwide. These centers are located in large metropolitan areas where the prevalence and incidence of infectious disease may be higher than the average. However, our estimate of the crude incidence of HIV among donors of multiple blood donations is similar to the estimate of 3.4 per 100,000 person-years recently reported by the CDC in their study of 19 American Red Cross blood centers.[34] Thus, wider generalizability from our data appears warranted.

Our program provides a mechanism with which to monitor needed data on blood-safety issues and respond rapidly. As additional tests and changes in donor-screening practices are instituted to safeguard the blood supply further, seroconversion rates and estimates of residual risk will continue to be calculated. Although new techniques of testing will bring us closer to the goal of zero risk, it is unlikely that any test or combination of tests will be 100 percent effective in detecting window-period infections. It is also important to recognize that new, direct viral-detection tests will supplement existing screening assays rather than replace them. Because levels of virus decline after seroconversion, a small percentage of antibody-positive donors will test negative for viral antigens and nucleic acids yet still be infectious. Therefore, the yield and cost effectiveness of new, direct assays for virus will be low,[41] and decisions about their implementation will be difficult, given the many demands on health care resources.

APPENDIX

The members of the Retrovirus Epidemiology Donor Study Steering Committee are as follows: *American Red Cross Blood Services* — A.E. Williams and C.C. Nass (Greater Chesapeake and Potomac Region), H.E. Ownby and D. Waxman (Southeastern Michigan Region), and S.H. Kleinman and S. Hutching (Southern California Region); *Irwin Memorial Blood Centers* — E.L. Murphy and M.P. Busch; *Oklahoma Blood Institute* — R.O. Gilcher and J.W. Smith; *Westat, Inc.* — G.B. Schreiber and R.A. Thomson; *National Heart, Lung, and Blood Institute* — G.J. Nemo; *Steering Committee Chairman* — T.F. Zuck.

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