Special Communication

Strategies for Screening Blood for Human Immunodeficiency Virus Antibody

Use of a Decision Support System

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A decision analytic model was used to examine alternative strategies to screen donated blood for human immunodeficiency virus (HIV) using data from the literature and from 1987 blood-screening programs in areas with high and low prevalence of HIV. Sensitivity analyses incorporated uncertainties about HIV infection and test performance. Current screening strategies are estimated to allow 20.5 infected units per million donated units to be transfused at a cost of $16 850 per HIV-positive unit detected in high-prevalence areas and 4.7 infected units per million donated units to be transfused at a cost of $32 275 per HIV-positive unit detected in low prevalence areas, with nine false-positive notifications of uninfected patients per million units screened and 14.9 discarded, noninfected units per HIV-positive unit in low-prevalence areas. Testing donated blood for HIV can be improved by individualizing screening strategies for areas with different prevalences of HIV. Efforts to further reduce transfusion-associated HIV should focus on improved test performance in early stages of infection, reduction of unnecessary transfusions, donor recruitment in lower-risk groups, and public health measures to reduce HIV infection among the general population.

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THE PREVALENCE of human immunodeficiency virus (HIV) in blood donors and its transmission via blood and blood products require that blood donors be screened for HIV or markers of HIV infection.[1,2] The development of an optimal, efficient screening program is a function of (1) the biology, epidemiology, natural history, and manifestations of HIV infection; (2) the performance characteristics (sensitivity and specificity) of diagnostic tests; and (3) the effectiveness of registries and counseling programs in removing people who test positive for HIV and of educational programs in removing high-risk people from the donor population.[3] Knowledge of many of these factors is limited, resulting in imprecise estimates of the effectiveness of current testing programs.

Decision support systems are especially useful for making complex decisions when information is uncertain. They assist in structuring problems, organizing data, identifying key decision points, and exploring the benefits and costs of alternative strategies and assumptions when the size and complexity of the variables make simple heuristics cumbersome and inefficient. The advantages of such models include flexibility, accuracy, speed, and ease of use. When these systems are applied to rapidly changing areas such as HIV testing, flexibility is perhaps the greatest advantage. Decision support models can incorporate new data as they become available, assess the impact of data of varying degrees of certainty, and examine different populations and subpopulations.

We developed a decision support system to evaluate the effectiveness and efficiency of alternative strategies used to screen blood donors for HIV infection under a variety of epidemiologic conditions. We examined the number of units of HIV-infected blood products transfused, the number of noninfected units of donated blood discarded, and the costs incurred.

METHODS

In the decision support model (Fig 1), a random sample of the population of potential blood donors enters the blood donor pool for a given time period (a donor cycle). Each unit of donated blood is tested for HIV using one of several available diagnostic tests, after which it may be released for transfusion, retested, or discarded. Donors of discarded units may be informed of the test results and may be placed on a registry. The chance of donors testing positive for HIV rejoining the blood donor pool depends on the effectiveness of the discard option chosen.

Model Components

Populations.—The blood donor pool consists of individuals with no recognized risk factors for HIV infection (general low-risk population) and of people with particular risk factors for HIV infection: homosexual or bisexual behavior, prior receipt of transfusions, intravenous drug abuse, and sexual contact with high-risk persons.[4,5] These subpopulations continue to contribute most of the detected HIV-infected units, despite efforts to encourage self-deferral.[6-8]

Diagnostic Tests.—The model allows for up to six diagnostic tests for HIV, chosen from a registry of 15 test options, to be performed on a single unit of blood. Each test has a particular initial sensitivity, initial specificity, and a

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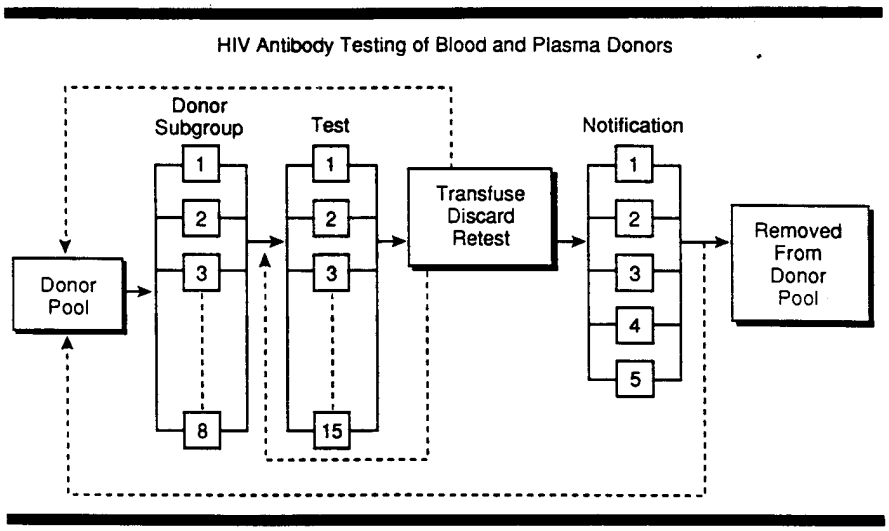

Fig 1.—The decision support model. Potential blood donors from up to eight donor subgroups (A1 through A8) donate a unit of blood. Each unit is tested for human immunodeficiency virus (HIV), using up to six of 15 available diagnostic tests (B1 through B15). After a unit of donated blood is tested, the unit may be released for transfusion, retested, or discarded. When a unit is discarded, one of several notification and registry schemes (C1 through C15) may be used. The chance of the donor's rejoining the blood donor pool depends on the effectiveness of the discard option chosen.

sensitivity and a specificity conditional on prior testing results. The sensitivity of a diagnostic test for HIV varies according to the stage of infection.[9-12] Early in the course of HIV infection, seroconversion is variable and incomplete (state 1). In the later stages of infection, seroconversion routinely is present (state 2). In the model, the sensitivity of a test in a given disease state is applied to the portion of the population in that disease state during a specific donation cycle. The specificity of a test is applied to all nondiseased individuals who receive the test.

Blood Use Options.—After a unit of blood is tested, the unit may be either retested, released for transfusion, or discarded. Retesting may be performed with any of the available tests in any sequence, including repetition of a test.

Registry Options.—If donors of discarded blood are neither informed of the test result nor discouraged from redonating, the chances of their redonating are those of the average donor (approximately 75% to 80%).[6] Alternatively, the blood bank may notify and counsel donors and place them on a local registry, the current practice of much of the blood-banking community.

Model Updating.—The model updates the population for the next donor cycle using a Markov process.[12] First, the original population is adjusted for those members who are effectively excluded from the blood donor pool. Then, using a transition matrix, the population is redistributed among the health states during the subsequent time period. Either the same or another testing sequence may be chosen in the updated population in the subsequent donor cycle.

Model Inputs

Epidemiology.—Since data regarding HIV infection and donation characteristics are most reliable for the aggregate blood supply, we used 1987 data obtained from screening blood donors. The distribution of HIV in the donor population was calculated from the testing experiences of a blood bank with a high prevalence of HIV infection (2.9 per 10 000 donors) and a blood-banking system with a low overall prevalence of HIV infection (1.6 per 10 000).

The donor population in disease state 2 is equivalent to HIV prevalence. The population in state 1 was estimated from the number of previously screened, seronegative donors who became seropositive in 1987, adjusted for imperfect Western blot (WB) sensitivity.[14,15] The donor population without virus was obtained by taking the annual donor pool for each blood system and subtracting the calculated number of infected individuals (state 1 and state 2). The probability of donation was calculated by multiplying the donor pool by the average number of donations per donor per year and distributing this number of "donor units" evenly over six 2-month periods.[16]

Diagnostic Tests.—The performance characteristics of the various diagnostic tests and assays were obtained from the literature, abstracts presented at recent scientific meetings, and unpublished data obtained from manufacturers, state referral laboratories, and blood bank systems. The sensitivity of the WB was estimated at 0.96.[17,18] derived from studies where WB was compared with viral culture. Either WB or culture positivity was considered to indicate HIV infection.[19-21] When compared with a sensitive monoclonal assay and subsequent WB testing, the sensitivity of an initial WB was 0.97.[22] The estimates of WB sensitivity were derived from, and thus only apply to, populations already screened by enzyme immunoassay (EIA). In the base case, the specificity of the WB was set at 0.994, consistent with current practice for highly suggestive blot patterns and with results using very sensitive culture, monoclonal antibody, and polymerase chain-reaction techniques in WB-positive individuals in large screening programs.[22-27]

The base rate and range of EIA sensitivity used in these analyses were obtained from studies that retested a sample of initially nonreactive EIA specimens with a WB assay and/or viral culture,[9,19,28-31] adjusting for the imperfect sensitivity of WB and culture. We estimated EIA sensitivity to be 0.94 to 0.99, with a base estimate of 0.98.[32-34] Specificity of the initial EIA was derived from blood-donor screening results and calculated as the number of initially reactive units less the adjusted WB-positive rate in the donor population, divided by the total number of units screened. Initial specificity was calculated to be 0.994 to 0.996 for 1987 screening data.[15,35]

An EIA may falsely classify an uninfected unit of blood as reactive for several reasons, often because cellular products and proteins of similar structure in the blood cross-react with the EIA.[36,37] Enzyme immunoassays from different cell lines (H-9, CEM-F) exhibit greater independence than those from the same cell line.[36,38] The conditional specificity of the EIA (the probability that an uninfected unit will be classified as uninfected, given an initial reactive EIA) was calculated by identifying the test performance characteristic that would generate the number of false-positive units (ie, EIA repeatedly reactive, adjusted WB-negative) observed in the American Red Cross system for 1987.[15] For second-generation EIAs presently in use, the conditional specificities for repetition of the same EIA range from 0.49 to 0.70.[35,39]

Transfusion recipients exhibit prolific viral replication within 3 to 6 weeks of infection. High levels of identifiable antibodies are observed at approximately 6 weeks. Sequential testing of recipients of HIV-infected blood products suggests that the mean window period (ie, the time frame during which

Table 1.—Central Assumptions and Alternative Values for the Analysis of Donated Blood for Human Immunodeficiency Virus (HIV)

	Donation Period	
	2 mo Central Assumption	4 mo Sensitivity Analysis
Epidemiology		
High prevalence/ 10 000 donors	2.9	
Low prevalence/ 10 000 donors	1.6	
High incidence of HIV infection/100 000 donors	5.3	12.0
Low incidence of HIV/ 100 000 donors	3.0	1.0
Infectivity posttransfusion	0.90	0.999
Test characteristics		
Enzyme immunoassay(EIA)		
Sensitivity		
Initial	0.980	0.940-0.995
Positive 2nd time	0.990	0.990-0.995
Negative 2nd time	0.600	0.200-0.980
Window	0.600	0.110-0.830
Window, negative	0.200	0.050-0.500
Specificity		
Initial	0.995	0.960-0.996
Positive 2nd time	0.870	0.490-0.995
Negative 2nd time	0.987	0.987-0.995
Given EIA-positive	0.992	0.800
Western blot		
Sensitivity	0.960	
Sensitivity (window)	0.600	0.900
Specificity	0.994	0.95-1.00
Cost, $		
EIA	4.12	3.50-10
EIA uncorrelated assay for test	4.53	3.85-11
Western blot (discard)	37	15-50
Processing blood (transfuse)	65	
Processing blood (discard)	55	
Informing donor	12.50	30
Registry performance		
Registry failure/1000 HIV-positive donors	3.3	1.0-6.0

individuals infected with HIV do not produce antibodies and are thus not identifiable by current screening tests that detect antibody to HIV)[11,12,40] is 6 to 12 weeks[12,17,18,41-43] but ranges in some people from 7 to more than 42 months.[11,12,17,40] Our base assumptions used data from the National Institutes of Health Multicenter AIDS Cohort Study. The sensitivities of the EIAs compared with those of WB in the first 6 months following infection were calculated by adjusting the reported sensitivities by the proportion of recently infected donors who were WB-positive at 8 weeks to derive a predicted 2-month EIA sensitivity[9,41] (consistent with models suggesting that 95% of individuals seroconvert within 6 months of HIV infection).[44] A more pessimistic estimate of EIA sensitivity, reflecting recent evidence of reduced EIA sensitivity in an extended window period, was calculated by adjusting the number of WB-positive donors by the proportion of all polymerase chain-reaction–positive and HIV-infected donors detected by current EIAs.[11] The population in the window period was calculated by inflating the number of seropositive, previously seronegative donors by the proportion of such individuals demonstrating prolonged viral latency.[11]

Cost.—Cost estimates for tests included the 1988 costs of testing reagents, test kits, labor, and information processing. Western blot costs included in-house labor and materials. The retail price and the actual price paid for the Biotech$ WB kit also were used. Cost estimates reflect the substantial price discounts for test kits and reagents available to large purchasers.[45] The cost of maintaining two different EIA systems was estimated to be 10% greater than the cost of using a single assay (T. Levschevsky, MBA, University of Maryland, oral communication, May 1989).

Effectiveness of Notification Policies.—The effectiveness of donor-notification policies on subsequent donor behavior was estimated from data in two high-risk areas.[14,46] Notification costs were developed from the perspective of the blood bank, as obtained from the staff of several regional blood banks. The costs of identifying and counseling individuals were included but not the costs of follow-up medical care resulting from a positive test result.

Model Outputs

Modifications in criteria for discarding a donated unit of blood, retesting units nonreactive by initial EIA, and using confirmatory test and various other test combinations were examined. A series of sensitivity analyses was performed for key variables (Table 1).

The model calculates seven outputs for each testing strategy: the number of infected units entering the blood supply during a time period; the number of noninfected units discarded; the number of noninfected donors falsely notified of infection; the cost per donated unit for the screening program; a wasted-unit index (the number of noninfected units discarded because of false-positive results divided by the number of infected units discarded—a lower wasted-unit index value reflects superior test strategy performance); and the incremental cost and incremental number of wasted units

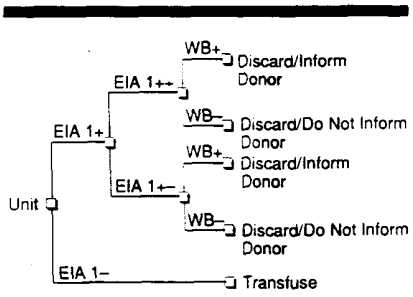

Fig 2.—Strategy 1 (base case): All units are tested with an enzyme immunoassay (EIA). Units testing negative by EIA are transfused. Units testing positive by EIA are retested twice with the same EIA. If both of these subsequent EIAs test negative, the unit is transfused. If either of these subsequent EIAs tests positive, the unit is discarded and a Western blot (WB) is performed. Donors with positive WB results are informed of the results and placed on a registry.

(the additional cost and the additional number of wasted units, respectively) resulting from the testing strategy compared with the strategy presently used by most US blood banks (strategy 1, Fig 2).

In calculating the number of cases of infection transmitted, we assumed that 90% of individuals transfused with an infected unit develop HIV infection.[28,47,48] Each unit of donated blood was assumed to be converted to 1.6 U of blood components, of which 30% were heat treated (heat treatment was assumed to reduce infectivity by 99%). Each component derived from a unit of donated blood was assumed to be transfused to different individuals (White et al,[49] Centers for Disease Control,[50] Transfusion Safety Study,[51] and Paul Cummings, PhD, American Red Cross, oral communication, May 1988).

RESULTS

We examined the impact of seven alternative strategies for screening blood for HIV in donor populations (Table 2). The strategies differ from each other as to whether (1) units nonreactive on initial EIA are transfused or are retested with the same or a different EIA, (2) EIA-positive units are discarded or are retested with the same or different EIAs and are either used or discarded based on the results of the subsequent testing, and (3) donors with positive test results are informed of the result and placed on a registry.

Factors Influencing Model Output

The results of the analyses are sensitive to donor-population HIV prevalence and incidence. The risk of receiving a unit of HIV-infected blood products varies approximately fourfold to eightfold; the rate of discarding noninfected donor units per infected unit

Table 2.—Strategies for Screening Donated Blood for Human Immunodeficiency Virus (HIV)

Strategy 1: All units are tested with an EIA*: EIA-negative units are transfused; EIA-positive units are retested twice with the same EIA. If both of these subsequent EIAs are negative, the unit is transfused. If either of these subsequent EIAs is positive, the unit is discarded and a WB† is performed. Donors with WB-positive results are informed of the results and placed on a registry.

Strategy 2: All units are tested with an EIA: EIA-negative units are transfused; EIA-positive units are tested with a WB. WB-negative units are retested with an EIA from a different cell line. All units positive by the first EIA are discarded, but only donors who test positive by WB or negative by WB but positive by the second EIA are informed of the test results.

Strategy 3: All units are tested with an EIA: All units are retested with the same EIA, regardless of the result of the first EIA. Units negative by both EIAs are transfused. If either EIA is positive, the same EIA is performed a third time. Units negative by two of the three EIAs are transfused. Units positive by two EIAs are discarded and tested with a WB. WB-positive donors are informed of the test results.

Strategy 4: All units are tested with an EIA: EIA-negative units are transfused; EIA-positive units are retested with an EIA from a different cell line. If this second EIA is negative, the unit is retested again with the second EIA. Units negative by two EIAs are transfused. Units with two positive EIAs are discarded and tested with a WB. Donors with WB-positive results are informed of the results and placed on a registry.

Strategy 4B: All units are tested with an EIA: EIA-negative units are transfused; EIA-positive units are retested with an EIA from a different cell line. If this second EIA is negative, the unit is retested again with the first EIA. Units negative by two EIAs are transfused. Units with two positive EIAs are discarded and tested with a WB. Donors with WB-positive results are informed of the results and placed on a registry.

Strategy 5: All units are tested with EIAs from two different cell lines. Units negative by both EIAs are transfused. All units testing positive by either EIA are discarded and tested with a WB. Donors with WB-positive results are informed of the results and placed on a registry.

Strategy 6: All units are tested with EIAs from two different cell lines. Units negative by both EIAs are transfused. Units positive on only one EIA are retested with the EIA that was positive and tested with a WB. WB-positive units are discarded and the donor is informed of the test results. Units positive by two EIAs but negative by a WB are discarded, but the donor is not informed of the results. Units positive by only one EIA and WB-negative are transfused.

*EIA indicates enzyme immunoassay.
†WB indicates Western blot.

Table 3.—Results of Alternative Strategies for Screening Donated Blood for Human Immunodeficiency Virus (HIV) Infection (Base Case Central Assumptions)

	Risk/M*		Discard/M		WUI				$/HIV Detected		MC/MU	
Strategy†	High	Low	High	Low	High	Low	FP Pts/M	$/Unit	High	Low	High	Low
1	20.5	4.7	1924	1925	7.6	14.9	9.2	4.27	16 850	32 275	...	...
2	17.7	4.6	1769	1768	6.9	13.8	9.1	4.17	16 120	31 495	...	...
3	11.2	2.9	2009	2011	8.0	15.4	10.1	8.20	31 368	61 148	0.45	2.18
4A	20.5	4.7	1152	1155	4.5	8.9	6.9	4.13	16 456	32 216	...	...
4B	20.8	4.8	41	49	0.1	0.4	0.3	4.17	16 712	31 543	...	...
5	2.4	0.3	15 917	15 922	58.7	119.7	0.4	8.52	32 670	62	0.25	0.97
6	3.4	0.7	113	115	0.5	0.9	0.4	8.19	31 456	60 070	0.25	0.97

*High risk refers to HIV prevalence among donors of 2.9 per 10 000. Low risk refers to HIV prevalence among donors of 1.6 per 10 000.
†M indicates per million units donated; WUI, Wasted-unit index; FP Pts/M, patients testing false positive (per million units donated); and MC/MU, incremental cost per additional infected unit detected.

detected varies approximately twofold to threefold; and the incremental cost of screening per additional infected unit detected varies threefold to fourfold between high- and low-prevalence areas, depending on the testing strategy examined (Table 3). In contrast, prevalence has little impact on the total number of noninfected units discarded.

The risk of transfusion-mediated HIV infection is sensitive to even the narrow range of test sensitivities examined in this model, varying approximately fourfold as test sensitivity varies from 0.96 to 0.98. As prevalence and incidence increase, the impact of reduced EIA sensitivity is increased.

The rate of transfusion of HIV-infected units is highly dependent on EIA sensitivity in the window period, varying fourfold across the range of window-period sensitivities examined. Donors in the window period account for approximately 45% and 73% of the infected units transfused in the low- and high-prevalence areas, respectively.

The number of noninfected units discarded and the costs of screening are extremely sensitive to small changes in test specificity. Increasing initial test specificity from 0.988 to 0.995 reduces the wasted units in the low-prevalence area by 1120 U per million units donated.

Comparison of Alternative Screening Strategies

A comparison of alternative screening strategies (Table 3) reveals that strategy 2 (WB testing of all specimens with a single reactive EIA and retesting WB-negative units with a second EIA) results in a slightly lower transfusion risk of HIV-infected units, less discarding of noninfected units, and lower costs than the strategy currently used by most blood banks (strategy 1, Fig 2).

Retesting all units with the same EIA, regardless of the result of the first EIA (strategy 3), reduces the risk of transfusion-related HIV transmission by 40%. However, the incremental cost per additional HIV-infected unit detected is almost $6 million.

Strategy 4 is similar to strategy 1, except that units initially positive by EIA are retested by an EIA derived from a different cell line than the initial assay. This strategy results in a similar rate of transfusion-related HIV transmission as the standard strategy, at a somewhat lower average cost per unit tested. The number of discarded noninfected units is significantly decreased, the result of the higher test-retest conditional specificity that results from repetitive testing with an assay derived from a different cell line from that of the initial EIA. When the two different EIAs produce discordant results, the unit is retested with a third EIA. Retesting with the EIA that was negative (strategy 4A) results in a 2% increase in the rate of transfusion of HIV-infected units and a 25-fold decrease in the discard rate of noninfected units compared with retesting with the EIA that was positive (strategy 4B, Fig 3).

Extremely low rates of transfusion-related HIV transmission can be achieved using strategies that require testing each donated unit with two EIAs from different cell lines. Strategy 5 discards all units testing positive by either EIA. Strategy 6 retests discordant units with the EIA that was negative and discards all units with two positive EIAs. However, the low transmission rates are accompanied by a more than sevenfold increase in the discard rate of noninfected units (strategy 5, Fig 4) and by marginal costs per additional HIV-infected unit detected of $970 000 (strategies 5 and 6) in the low-prevalence population and of $250 000 in the high-prevalence population.

The extreme range of estimates of EIA sensitivity in the window period (stage 1) results in a more than 100-fold variation in risk estimates for the low-prevalence population representative of the general blood-banking donor pool. However, the relative effectiveness and efficiency of the alternative strategies are not altered (Table 4).

COMMENT

Strategies for screening donated blood should be modified for local differences in disease prevalence and incidence. Within reasonable bounds of test sensitivity and specificity, more-extensive screening strategies become more cost-effective as the incidence of disease

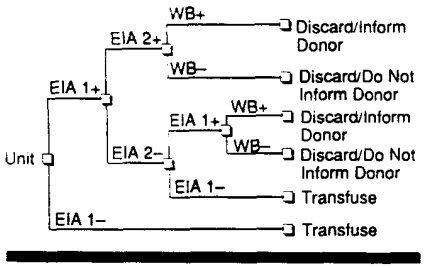

Fig 3.—Strategy 4B: All units are tested with an enzyme immunoassay (EIA). Units testing negative of EIA are transfused. Units testing positive by EIA are retested with an EIA from a different cell line. If this second EIA is negative, the unit is retested again with the first EIA. Units negative by two EIAs are transfused. Units with two positive EIAs are discarded and tested with a Western blot (WB). Donors with positive WB results are informed of the results and placed on a registry.

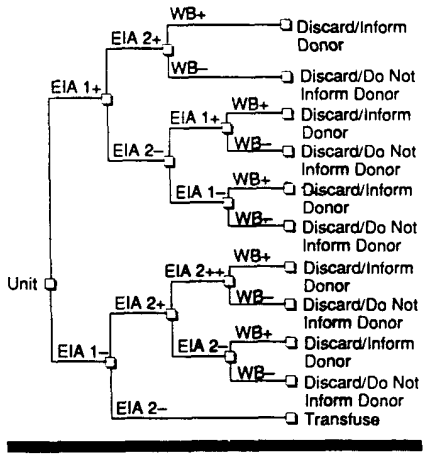

Fig 4.—Strategy 5: All units are tested with enzyme immunoassays (EIA)s from two different cell lines. Units negative by both EIAs are transfused. All units testing positive by either EIA are discarded and tested with a Western blot (WB). Donors with positive WB results are informed of the results and placed on a registry.

increases.

Alternative strategies differ on the number of HIV units transfused, the number of noninfected units discarded, and the amount of money spent on testing and counseling. The cost and effectiveness of alternative testing strategies depend on the tests used and the assumptions made about the natural history and epidemiology of HIV infection.

Improving test sensitivity in patients in whom anti-HIV antibodies are present will have only limited impact on blood system–screening strategies. The estimates of initial EIA sensitivity of 0.98 and of window sensitivity of 0.60 yield an estimated risk of 0.0027% for contracting HIV-1 infection from transfusion, which is consistent with the observed risk of 0.003% reported in Baltimore for 1986.[52] The base estimates of our model suggest a lower 1988 risk of 0.0016%, or one per 69 500 U, the result

Table 4.—Comparison of Results of Alternative Strategies for Screening Donated Blood for Human Immunodeficiency Virus (HIV) Infection

	Risk/M		WUI		MC/MU	
Strategy†	Pessimistic	Optimistic	Pessimistic	Optimistic	Pessimistic	Optimistic
1	166.2	1.12	12.6	14.60	. . .	. . .
2	165.6	1.09	11.6	13.06	. . .	. . .
3	162.9	0.69	12.9	15.12	1.19	7.8
4A	165.6	1.42	7.6	8.70	. . .	. . .
4B	165.7	1.15	0.32	0.37	. . .	. . .
5	133.7	0.04	86.3	119.40	0.13	3.9
6	149.1	0.13	0.68	0.86	0.23	3.9

*Alternative assumptions regarding the window period in a low-prevalence area (HIV prevalence among donors of 1.6 per 10 000) are used. In the optimistic scenario the mean window period is estimated to be 6 months and enzyme immunoassay sensitivity in the window period is estimated to be 0.60. In the pessimistic scenario, the mean window period is estimated to be 36 months and enzyme immunoassay sensitivity in the window period is estimated to be 0.17.

†M indicates per million units donated; WUI, Wasted-unit index; and MC/MU, incremental cost per additional infected unit detected.

of continued test improvement, compatible with the reported absence of any observed seroconversions in Baltimore among more than 20 000 studied transfusion recipients in 1987 and 1988.

Variation in test performance relating to quality control and technical skill is unlikely to be a major factor in blood-bank screening,[53] which is conducted by highly trained and skilled technicians in high-volume laboratories with rigorous quality control.

More troublesome is the reduced sensitivity of current antibody tests used to screen for HIV in a yet undetermined proportion of individuals in early stages of infection. Improved sensitivity in the early stages of infection will significantly reduce the risk of infected units being transfused. The impact will be greater the longer the window period. Reports of prolonged window periods in a substantial proportion of HIV-infected patients underscore the importance of developing improved screening tests to detect HIV infection in the early stages of infection when anti-HIV antibody production is low or nonexistent.

Slight improvements in the already high EIA test specificity will substantially reduce the amount of wasted blood, since more than 99.98% of the 12 million units annually donated are not infected. Reducing the probability of a retest false-positive result given an initial false-positive result will substantially improve the specificity of the current testing sequence. This may be accomplished either by making technical improvements in the tests themselves or by combining EIAs derived from different cell lines.[38]

Recent empiric studies of HIV-test-sequence specificities that report 0 to 7.5 false-positive notifications per million low-risk persons screened are consistent with our base estimates of test specificity.[24,26] In contrast, a study using a simple joint false-positive rate for two tests estimated 49 false-positive notifications per million.[54] These comparisons underscore the importance of considering conditional test performance when evaluating a testing sequence.

The strategies that most dramatically reduce risk are highly dependent on the probability that an infected unit nonreactive by EIA will be reactive when the EIA is repeated. Data on such conditional performance are lacking. The only study that presents data to calculate conditional EIA sensitivity suggests that the conditional sensitivity of a positive EIA when repeated may be as low as 0.97, given initial sensitivity of 0.985.[55]

Presenting test results using continuous data, rather than considering results only as reactive or nonreactive, permits adjustment of test characteristics to best accommodate local needs.[56] Units that are highly reactive are less likely to be false positives than those that are marginally reactive. An EIA result is more specific if the unit is highly reactive.[9,19,56,57] Earlier use of confirmatory tests in patients with strongly reactive EIA results improves test sequence sensitivity and specificity at reduced cost. The net result is equivalent to a technical improvement in EIA specificity, yet can be achieved by using current information more effectively. Similarly, WB results should report band patterns for all cases, rather than only for indeterminant specimens, to allow comparison and selection of alternative criteria with different sensitivities and specificities.[34,58]

Our analyses assumed that a program of confidential self-exclusion of blood donors with high-risk behaviors, mandated for blood banks since December 1986, was in place. Thus, the results represent the incremental impact of screening programs over and above the benefits and costs of confidential self-exclusion. Recent data from major urban blood banks indicate that as much as 0.6% to 0.8% of units self-

excluded by donors is WB-positive (Marleine Harper, MPH, Baltimore American Red Cross, oral communication, May 1989; Celso Bianco, MD, New York Blood Center, oral communication, May 1989), in contrast to prior estimates of 1.6% to 2%.[29,46,59] The changing distribution of risk factors among blood donors, in particular the reduced contribution of blood by gay and bisexual men,[7,8] may be responsible for the smaller proportion of HIV-infected cases detected among confidential self-excluded donors compared to previous reports (Barbara Hosein, MD, New York Blood Center, oral communication, May 1989). The importance of removing individuals engaged in high-risk activities from the effective donor pool is increased by the poor sensitivity of screening tests during the earliest stages of HIV infection.[9,11,12,40]

The sensitivity analyses identified a number of crucial data points that need improved information. Variations in the incidence of HIV infection may alter risk estimates threefold.[60,61] With most of the blood donor pool representing previously screened donors, incidence, rather than prevalence, of HIV infection is now critical. The risk of HIV transmission varies 100-fold, depending on estimates of the proportion of infected persons in the window period (a function of the incidence of infection and of viral replication and antibody production patterns in infected persons). Previous studies on incidence have relied on serologic tests with poor window-period sensitivity compared with assays such as the polymerase chain reaction. Data from populations that are repeatedly screened for HIV, such as blood donors or military recruits, will provide better information of disease incidence. Repetitive testing of higher-risk blood donor populations with a range of diagnostic tests (eg, EIA, WB, culture polymerase chain reaction, and antigen assays) may clarify many of the important issues surrounding the window period in blood donors.

Other analyses of the risk of HIV exposure from blood transfusion have suggested both more optimistic and pessimistic pictures.[47,62,63] The more optimistic analyses examined a narrow range of EIA sensitivity (worst case, 0.98), limited the window period to 4 weeks (after which no further effect on test sensitivity was assumed), and applied only a single EIA.[47] The more pessimistic scenario used an incidence of 12 per 100 000 and considered all prior donors who seroconverted as incident cases, regardless of whether their prior donation had been screened.[63] When incident donors were defined as those donors who were seronegative on prior screening who subsequently were found to be seropositive, the incidence rate was three per 100 000. (Roger Dodd, PhD, American Red Cross, oral communication, May 1989). Using this revised incidence rate, the risk of transfusing an infected unit from the 1986-1987 blood donor population decreases to 7.1 per million units, or 126 infected units per year, compared with the estimate of 460 previously reported.[63]

This is similar to our baseline analysis, which suggests that approximately 86 HIV-infected units were among the 18 million units of blood and blood components transfused in 1987. The risk of secondary transmission and the impact on the public health is even smaller, since as many as 35% to 60% of transfusion recipients die of their underlying disease within 6 months of receiving transfusions.[64]

This analysis used blood bank system HIV prevalence data from 1987. The adjusted overall prevalence of HIV among blood donors was stable during 1988 (Carla Perkins, MPH, California Health Service, Office of AIDS, oral communication, April 1989) as a result of repetitive screening of a largely stable group of donors and incremental improvements in test performance.[65] Thus, the principles of test use and the relative efficiency of different strategies are still applicable.

The most effective and least costly strategies to reduce HIV infection transmitted by transfusion of blood and blood products involve decreasing the use of homologous blood transfusions.[66] Increased use of autologous blood for individuals with elective surgery and the capacity to donate blood that is then stored short-term for future use involves small administrative cost and no risk. Minimal-exposure transmission reduces exposure of transfusion recipients to a single donor who supplies all anticipated blood products.[67] Intraoperative blood salvage techniques also reduce the need for transfusions. Safest and least expensive is the elimination of unnecessary blood transfusions altogether. Such low-technology options should be given more emphasis, even as other more costly alternatives are evaluated and pursued.

Improved test combinations using principles of test evaluation and performance can reduce the amount of noninfected discarded blood. Areas with a high incidence of HIV can substantially decrease the risk of HIV exposure from blood products with more extensive screening. This analysis identified several strategies for screening donated blood for HIV that reduce risk of transfusion of HIV-infected units at lower or reasonable cost. Improvements in test performance (particularly improvements in window-period sensitivity and in test sequence specificity) will make several of these strategies more attractive. Test sequences should be developed based on the degree of EIA reactivity, rather than on a dichotomous (reactive/nonreactive) result.[56,68] Blood-screening strategies should be tailored to the local epidemiology of HIV infection. When retesting specimens with EIAs is indicated in low-prevalence areas, the retesting should use an assay from a different cell line than that from which the initial assay was derived. The strategies identified as optimal by these analyses, however, must be verified in settings with adequate power for proper evaluation. Finally, improved use of data developed in current screening programs can clarify many of the uncertainties required to optimally protect the blood supply from HIV, thus improving screening effectiveness and efficiency and the safety of the blood system.

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