Lookback on donors who are repeatedly reactive on first-generation hepatitis C virus assays: justification and rational implementation

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BACKGROUND: The purpose of this study was to explore strategies to minimize the number of unwarranted consignee notifications resulting from hepatitis C virus (HCV) first-generation (single-antigen) enzyme immunoassay (EIA 1.0) targeted lookback.

STUDY DESIGN AND METHOD: The four blood centers participating in this study contributed data on 3753 HCV EIA 1.0-repeatably reactive (RR) donations. The analysis focused on 1) statistical evaluation of HCV EIA 1.0 signal-to-cutoff (S/CO) ratios versus HCV second-generation recombinant immunoblot assay (RIBA 2.0) interpretation from all participating blood centers and 2) RNA testing using transcription-mediated amplification on all HCV EIA 1.0 RR/RIBA 2.0-positive or -indeterminate specimens and a subset of RIBA 2.0-negative donations for which specimens were available.

RESULTS: Analysis of HCV EIA 1.0 S/CO ratios versus RIBA 2.0 indicated that 1180 (89%) of 1326 RIBA 2.0-positive specimens had an S/CO ratio >2.5, while 146 (11%) had a ratio ≤2.5. In contrast, of 2253 RIBA 2.0-negative specimens, 299 (13%) had an S/CO ratio >2.5, while 1954 (87%) had a ratio ≤2.5. Of 248 HCV EIA 1.0-RR/RIBA 2.0-positive samples with stored specimens available for additional testing, 198 (80%) were HCV RNA positive; 15 (7.5%) of these specimens had an S/CO ratio ≤2.5, while 183 (92%) had a ratio >2.5. HCV RNA was detected in only 2 (1.5%) of 137 HCV EIA 1.0-RR/RIBA 2.0-negative specimens: 1 of these 2 specimens had an S/CO >2.5, while the other had an S/CO ≤2.5.

CONCLUSION: A highly significant (<0.0001) correlation was found between the S/CO ratio on HCV EIA 1.0- and RIBA 2.0-positive or -negative results. An S/CO ratio >2.5 yielded an 89- percent sensitivity for RIBA 2.0-positive specimens, and donations with an S/CO ratio >2.5 had a 75-percent probability of being RIBA 2.0 positive. A policy recommendation to use the S/CO ratio to triage lookback would prevent unwarranted notification of 87 percent of recipients of blood from RIBA 2.0-negative donors and would result in a failure to notify only 5 to 10 percent of recipients potentially exposed to infectious units.

After a year of debate,[1] the recently constituted Advisory Committee on Blood Safety and Availability (ACBSA) recommended in August 1997 that the Public Health Service initiate hepatitis C virus (HCV) lookback using a combination of targeted and general lookback strategies based on reactivity in multiantigen enzyme immunoassay (EIA) HCV testing.[2] The companion general lookback campaign recommended HCV testing of all recipients transfused before the introduction of multiantigen assays (i.e., before March 1992), as well as of other at-risk populations. This policy was subsequently

ABBREVIATIONS: ACBSA = Advisory Committee on Blood Safety and Availability; BCA = Blood Center A, Blood Centers of the Pacific; BCB = Blood Center B, Community Blood Center of Greater Kansas City; BCC = Blood Center C, Southeastern Michigan Region, American Red Cross; BCD = Blood Center D, Greater Chesapeake and Potomac Region, American Red Cross; DHHS = Department of Health and Human Services; EIA(s) = enzyme immunoassay(s); FDA = Food and Drug Administration; HCV = hepatitis C virus; RIBA 2.0 = second-generation recombinant immunoblot assay (HCV supplemental test); RIBA 3.0 = third-generation RIBA; RR = repeatably reactive; S/CO = signal-to-cut-off.

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Supported in part by contracts from the National Heart, Lung, and Blood Institute to the Retrovirus Epidemiology Donor Study (NO1-HB-47114) and Gen-Probe (NHLBI-HB-67130).

Received for publication April 16, 1999; revision received September 3, 1999, and accepted September 9, 1999.

TRANSFUSION 2000;40:15-24.

endorsed by the secretary of the Department of Health and Human Services (DHHS) with implementation requirements and supporting documents developed by the Food and Drug Administration (FDA),[3] the Centers for Disease Control and Prevention,[4] and the Interagency Task Force on HCV Lookback.[5]

The issue of whether targeted lookback should also be triggered for donors identified as reactive by single-antigen EIAs (HCV EIA 1.0), implemented in March 1990, was extensively debated by ACBSA. Major arguments for triggering HCV lookback from HCV EIA 1.0-repeatably reactive (RR) donations were

1) recognition that HCV EIA 1.0 identified a high proportion of the infected donors giving blood after initiation of HCV screening;

2) concern over the effectiveness of general HCV lookback; and

3) the ethical principle that patients have the right to know of a specific infectious exposure, even though the probability that the donors were infected may have been as low as 25 percent.[6-8]

The major arguments against HCV lookback from HCV EIA 1.0-RR donations include the relatively poor sensitivity of these tests, with approximately 20 percent of infected donors not identified, versus nearly 100-percent identification of HCV-infected donors by multiantigen assays (second-generation HCV EIA [HCV EIA 2.0] and third-generation HCV EIA [HCV EIA 3.0]).[9-11] Lack of sensitivity of HCV EIA 1.0 meant that recipients of HCV EIA 1.0-negative units were at significant risk (approx. 1/1000 units) and therefore must be included in the general lookback notification campaign. Concern was raised that triggering lookback for donors identified as reactive by HCV EIA 1.0 would give a false impression that non-notified recipients transfused during this period were not at risk.

Another major argument on this topic is the specificity of HCV EIA 1.0 is relatively poor, with only 30 to 50 percent of HCV EIA 1.0-RR donors tested by the subsequently licensed HCV second-generation recombinant immunoblot assay (RIBA 2.0) confirmed as HCV positive.[12,13] This specificity issue is problematic, given the absence of supplemental data or retained specimens for a high proportion of HCV EIA 1.0-RR donations. Supplemental assays only became available through the reference laboratory at Chiron (Emeryville, CA) by the end of the first year of HCV EIA 1.0 screening, and a licensed supplemental test was not available until June 27, 1993, after multiantigen HCV EIAs were licensed. There was concern that triggering lookback for HCV EIA 1.0-reactive but nonconfirmed donations would result in unwarranted notifications, which would alarm several hundred thousand recipients and their families.

Subsequent to the initial recommendations, there was strenuous criticism of the limited scope of the original targeted lookback policy and the delayed response by the Public Health Service to implement HCV notification and prevention guidelines that included general HCV lookback recommendations. In September 1998, the DHHS Congressional Oversight Committee issued a report instructing the secretary of DHHS to reexamine HCV lookback policies and urging the extension of targeted lookback to include donors identified by HCV EIA 1.0.[14]

After extensive debate on November 24, 1998, the majority of ACBSA members concluded that the patient's right to know of exposure to prior donations from donors identified by HCV EIA 1.0 outweighed any limitations in HCV EIA 1.0 performance. Therefore, the advisory committee voted to recommend that the lookback policy be extended to include HCV EIA 1.0-RR donors. However, the committee also recommended that this policy not be implemented until the FDA and the blood industry had explored strategies to minimize the number of unwarranted notifications (i.e., false-positive results) without markedly affecting the objective of notifying most transfusion recipients of blood from truly infected donors.

To address these issues, the following analyses were performed. Data were reviewed from two blood centers for which data on RIBA 2.0 were available from the onset of HCV EIA 1.0 screening, to determine the temporal trend in the yield of infected donations triggering lookback from HCV EIA 1.0-RR/RIBA 2.0-positive donors over the 2 years of HCV EIA 1.0 screening. Also investigated was the probability that HCV EIA 1.0-RR/RIBA 2.0-indeterminate donors were infected, and further testing of these samples by HCV third-generation RIBA (RIBA 3.0) and HCV RNA amplification methods was performed. Finally, we analyzed the relationship of the average signal-to-cutoff (S/CO) ratio of HCV EIA 1.0-RR donations relative to RIBA 2.0 and HCV RNA results. The results of this analysis offer a reasonable strategy for triaging HCV EIA 1.0=RR donations lacking RIBA 2.0 results into those that should trigger lookback (i.e., those with high S/CO ratio) and those that should not trigger lookback (i.e., those with low S/CO ratio).

MATERIALS AND METHODS

Temporal trends of HCV EIA 1.0-RR/HCV RIBA 2.0-positive donations

Two databases were created that represent RIBA 2.0-positive (Chiron) donations from Blood Centers of the Pacific (Blood Center A, BCA) and Community Blood Center of Greater Kansas City (Blood Center B, BCB). Both databases included all HCV EIA 1.0-RR/RIBA 2.0-positive repeat donors—that is, those who would trigger HCV targeted lookback. The database from BCA contains 144 HCV EIA 1.0-RR/RIBA 2.0-positive repeat donors, listed by donation date, for the period from 04/14/90 to 01/29/92. The cutoff of 01/29/92 was chosen to control for inventory testing af-

ter licensing and implementation of HCV EIA 2.0 on 03/14/92 at BCA. An analogous database was created for 63 HCV EIA 1.0-RR/RIBA 2.0-positive repeat donors at BCB for the period 05/04/90 to 03/13/92.

HCV EIA 1.0 S/CO ratio vs. RIBA 2.0 and HCV RNA results

A database and repository of HCV-RR allogeneic donations had been compiled since the licensing and implementation of HCV screening at BCA. This database contained detailed HCV EIA 1.0 and RIBA 2.0 results for 353 HCV EIA 1.0-RR donors who donated between 05/2/90 and 01/30/92. This data set was expanded both geographically and numerically by creating two additional databases, one representing 933 RR donations made at BCB from 05/04/90 through 03/13/92 and a second representing 2467 HCV EIA 1.0-RR donations made between 05/01/91 and 03/01/92 at two American Red Cross regions: Southeastern Michigan (Blood Center C, BCC)(n = 952) and Greater Chesapeake and Potomac (Blood Center D, BCD) (n = 1515). The combined databases included 3753 HCV-RR donations from four distinct geographic regions of the United States. We examined the relationship between HCV EIA 1.0 reactivity (average S/CO ratio) and RIBA 2.0 results by using statistical software (StatView, SAS Institute Inc, Cary, NC). We also examined the relationship between HCV EIA 1.0 reactivity and HCV RNA results for 385 specimens for which HCV RNA data were obtained.

RIBA 3.0 analysis of RIBA 2.0-indeterminate donations

RIBA 3.0 (Chiron) was performed on 32 (94%) of 34 HCV EIA 1.0-RR/RIBA 2.0-indeterminate specimens from BCA and all 37 HCV EIA 1.0-RR/RIBA 2.0-indeterminate specimens from BCB (residual serum was not available for untested specimens). HCV EIA 1.0-screened aliquots were not available for any donations from the American Red Cross regions, and therefore no further testing could be performed on RIBA 2.0-indeterminate donations.

HCV RNA testing

HCV RNA testing employing transcription-mediated amplification[15,16] (TMA, Gen-Probe, San Diego, CA) was performed on stored aliquots from the two participating blood centers with stored aliquots (i.e., BCA and BCB). All available HCV EIA 1.0-RR/RIBA 2.0-negative, -indeterminate, and -positive repository specimens identified at BCA were submitted for HCV RNA testing. Because of concerns about possible cross-contamination during the aliquoting process at BCB, only RIBA 2.0-positive and -indeterminate/RIBA-3.0-positive donations were submitted for HCV RNA analysis.

RESULTS

Temporal trend of HCV EIA 1.0-triggered lookback

We first examined the temporal trend of HCV EIA 1.0-RR/RIBA 2.0-positive donations from repeat donors at the two participating blood centers with access to RIBA 2.0 results from the outset of HCV EIA 1.0 screening. As seen in Fig. 1, 52 percent (BCA and BCB) of the total number of confirmed-positive donors identified by HCV EIA 1.0 screening were identified within the first 6 months of the date of implementation of HCV EIA 1.0 screening; 69 percent (BCA) and 83 percent (BCB) were identified during the first 12 months after implementation of HCV EIA 1.0 screening. Thus, approximately 80 percent of infected donors detected by HCV EIA 1.0 were identified before the availability of RIBA 2.0 at Chiron's reference laboratory.

Table 1 shows the impact at BCB of progressive HCV EIA 1.0 screening on the number of hospital notifications associated with prior donations by these RIBA 2.0-positive donors. A decline in triggered notifications parallels the decline in confirmed-positive donors over time. Forty-eight percent (120/250) of the components triggering consignee notification were generated during the first 6 months of HCV EIA 1.0 screening, and 72 percent (181/250) were generated during the first year of screening.

Evaluation of lookback on HCV EIA 1.0-RR/RIBA 2.0-indeterminate donations

RIBA 3.0 and TMA results for 69 HCV EIA 1.0-RR/RIBA 2.0-indeterminate donors are summarized in Table 2. The 32 RIBA 2.0-indeterminate specimens from BCA included 2 (6%) with reactivity to 5-1-1, 21 (66%) with reactivity to c100-3, 3 (9%) with reactivity to c33c, 6 (19%) with reactivity to c22-3, and 2 with dual reactivity to 5-1-1 and c100-3. In RIBA 3.0, 24 (75%) of the 32 specimens with single-band reactivity in RIBA 2.0 were negative, while 4 (12.5%) remained indeterminate and 4 (12.5%) tested positive. Three (75%) of the four RIBA 2.0-indeterminate specimens that tested RIBA 3.0-positive reacted with the c22-3 antigen band in RIBA 2.0 (3 to 4+ reactivity), and one (25%) reacted with the c33c recombinant antigen (1+ reactivity). HCV RNA was not detected in any of the four RIBA 2.0-indeterminate/RIBA 3.0-positive specimens from BCA.

The 37 RIBA 2.0-indeterminate specimens from BCB included 1 (3%) with reactivity to 5-1-1, 23 (62%) with reactivity to c100-3, 5 (13%) with reactivity to c33c, 7 (19%) with reactivity to c22-3, and 1 (3%) with reactivity to human superoxide dismutase. By RIBA 3.0, 28 (76%) of these specimens tested negative; 2 (5%) remained indeterminate and 7 (19%) tested positive. The RIBA 3.0-positive specimens included 4 (57%) with reactivity to c22-3 and 3 (43%) with reactivity to the c33c by RIBA 2.0. Four (57%) of the seven RIBA 2.0-indeterminate/RIBA 3.0-positive specimens were from repeat donors who would trigger HCV lookback, and

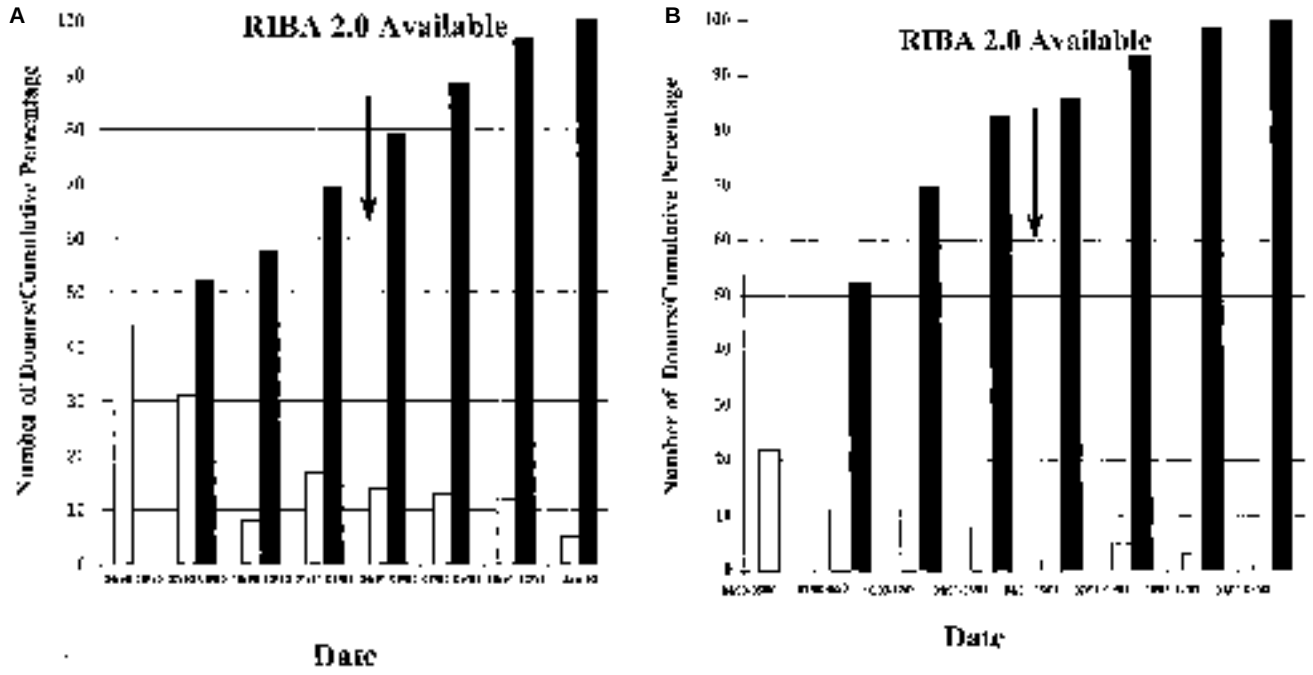


Fig. 1. Identification of HCV EIA 1.0-RR/RIBA 2.0-positive repeat blood donors after implementation of HCV EIA 1.0 screening. A) The number of HCV EIA 1.0-RR donors ( ) during the initial 22 months at BCA and the corresponding cumulative percentage ( ) from BCA. B) The number of HCV EIA 1.0-RR/RIBA 2.0-positive donors ( ) during the initial 24 months at BCB and the cumulative percentage from BCB ( ).

TABLE 1. Number of donors and components triggering lookback from HCV EIA 1.0-RR/RIBA 2.0-positive donors during 24 months after implementation of HCV EIA 1.0 screening at BCB

Donation Date	Number of HCV EIA1.0-RR/ RIBA 2.0-positive donors	Number of components*	Percentage	Cumulative percentage
04/90-06/90	22	85	34.00	
07/90-09/90	11	35	14.00	48.00
10/90-12/90	11	42	16.80	64.80
01/91-03/91	8	19	7.60	72.40
04/91-06/91	2	11	4.40	76.80
07/91-09/91	5	47	18.80	95.60
10/91-12/91	3	9	3.60	99.20
01/92-03/92	1	2	0.80	100.00
Total	63	250		

* The testing period was from 05/90 through 03/92, while the HCV targeted lookback period was from 01/88 through 03/92.

these specimens were further tested for HCV RNA. All four were HCV RNA negative.

Use of HCV EIA 1.0 reactivity ratio to predict RIBA 2.0 and HCV RNA status and to triage lookback

Given that RIBA 2.0 results are not available for most blood centers for the critical first year of HCV EIA 1.0 screening, when 70 to 80 percent of HCV EIA 1.0-RR/RIBA 2.0-positive donations occurred (Fig. 1), we sought to identify an alternative strategy to sort HCV EIA 1.0-RR donations into those with high or low probability of HCV infection. Figure 2 shows graphs of HCV EIA 1.0 S/CO ratios for RIBA 2.0-positive, -indeterminate, and -negative donations at four large blood centers. The results from all four centers were similar and show a significant correlation of HCV EIA 1.0 S/CO ratio and RIBA 2.0 results. Statistical analysis of the median S/CO ratio by blood center for RIBA 2.0-negative versus -positive specimens was identical and significant for all centers by using the Mann-Whitney U test at a significance level of 0.05 ($p < 0.0001$).

The S/CO ratio data and RIBA 2.0 results from all four blood centers were combined into one database (Fig. 3). This database included 3753 HCV EIA 1.0-RR donations, of which 1326 (35%) tested RIBA 2.0-positive, 174 (5%) tested

RIBA 2.0-indeterminate, and 2253 (60%) tested RIBA 2.0-negative. Percentile analysis of this database indicated that 90 percent of RIBA 2.0-positive specimens had an S/CO ratio >2.26, while 90 percent of RIBA 2.0-negative specimens had an S/CO ratio <2.76. The small proportion (174/3753, 4.6%) of donations with indeterminate HCV RIBA 2.0 results had an intermediate S/CO ratio distribution.

On the basis of the strong correlation between the HCV EIA 1.0 S/CO ratio and RIBA 2.0 results, we examined the predictive value of a fixed HCV EIA 1.0 S/CO of 2.5 vis-a-vis RIBA 2.0 results and the implication of using such a level for triggering lookback. As summarized in Table 3, of 3753 HCV EIA 1.0-RR donations in the combined database, 2177 (58%) had an S/CO ratio ≤2.5, while 1576 (42%) had an S/CO ratio >2.5. Of 1326 RIBA 2.0-positive donations in the data set, 1180 (89%) had an S/CO ratio >2.5 (i.e., sensitivity of S/CO >2.5 = 89%). On the other hand, of 2253 RIBA 2.0-negative donations, only 299 (13%) had an S/CO ratio >2.5 (i.e., specificity = 87%). Analysis of the data from a different perspective found that 1180 (75%) of 1576 specimens with an S/CO ratio >2.5 were RIBA 2.0 positive (positive predictive value = 75%), while only 146 (6.7%) of 2177 donations with S/CO ratios ≤2.5 were RIBA 2.0-positive (negative predictive value = 93.3%).

TABLE 2. RIBA 3.0 and TMA results for HCV EIA 1.0-RR/RIBA 2.0-indeterminate donors identified during the 22 and 24 months after implementation of HCV EIA 1.0 screening at two blood centers

Blood centers	Number of donors	Number (%) of RIBA 3.0 results			TMA results for RIBA 3.0-positive specimens
		Positive	Indeterminate	Negative	Positive/Tested
BCA	32	4 (12.5%)	4 (12.5%)	24 (75%)	0/4
BCB	37	7 (19%)	2 (5%)	28 (76%)	0/4
Total	69	11 (16%)	6 (9%)	52 (75%)	0/8

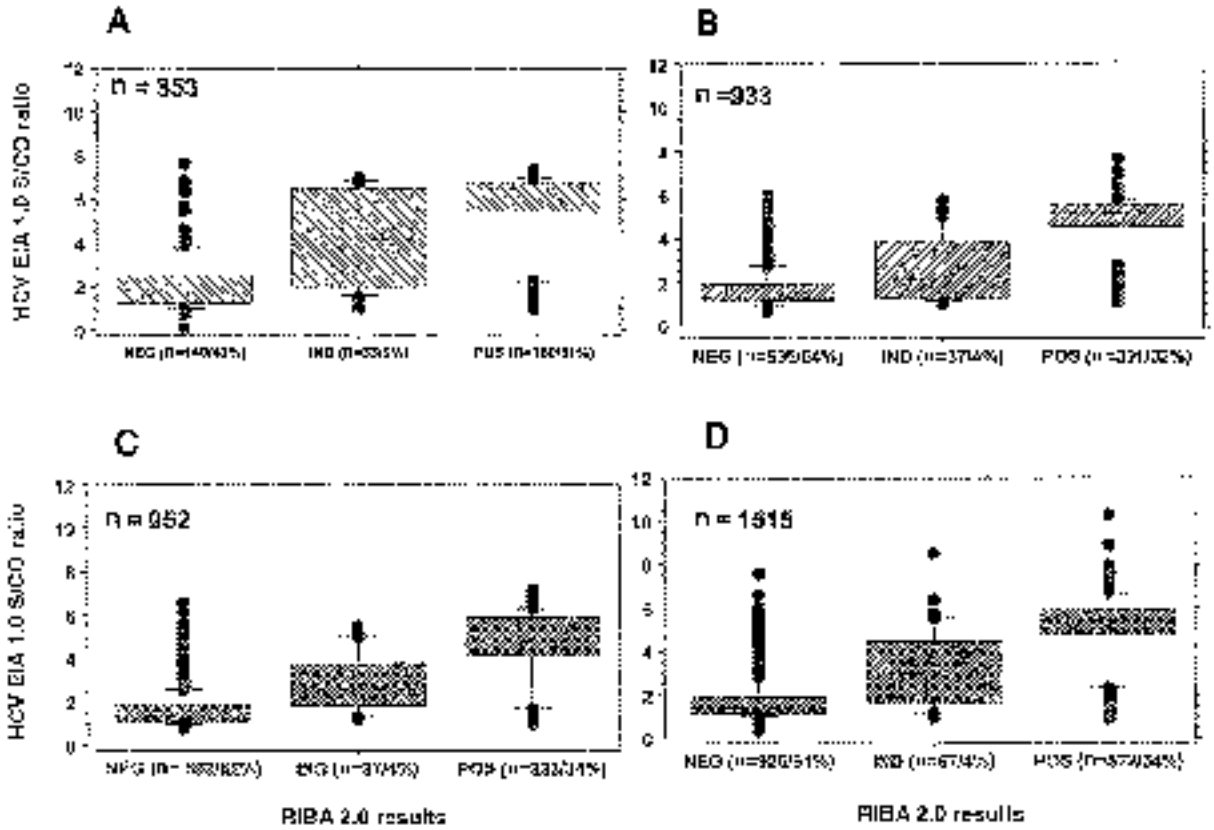


Fig. 2. Evaluation of RIBA 2.0 results versus S/CO ratio in HCV EIA 1.0-RR donations from four participating blood centers (A=BCA; B=BCB; C=BCC; D=BCD). Statistical analysis of the median S/CO ratio by blood center for RIBA 2.0-negative (NEG) versus -positive (POS) specimens was identical and significant ($p<0.0001$) for all centers. Each box plot is composed of five horizontal lines that display the 10th, 25th, 50th, 75th, and 90th percentiles of a variable, with the filled box representing the 25th through the 75th percentiles. Values above the 90th percentile and below the 10th percentile are plotted as points. IND = RIBA 2.0 indeterminate.

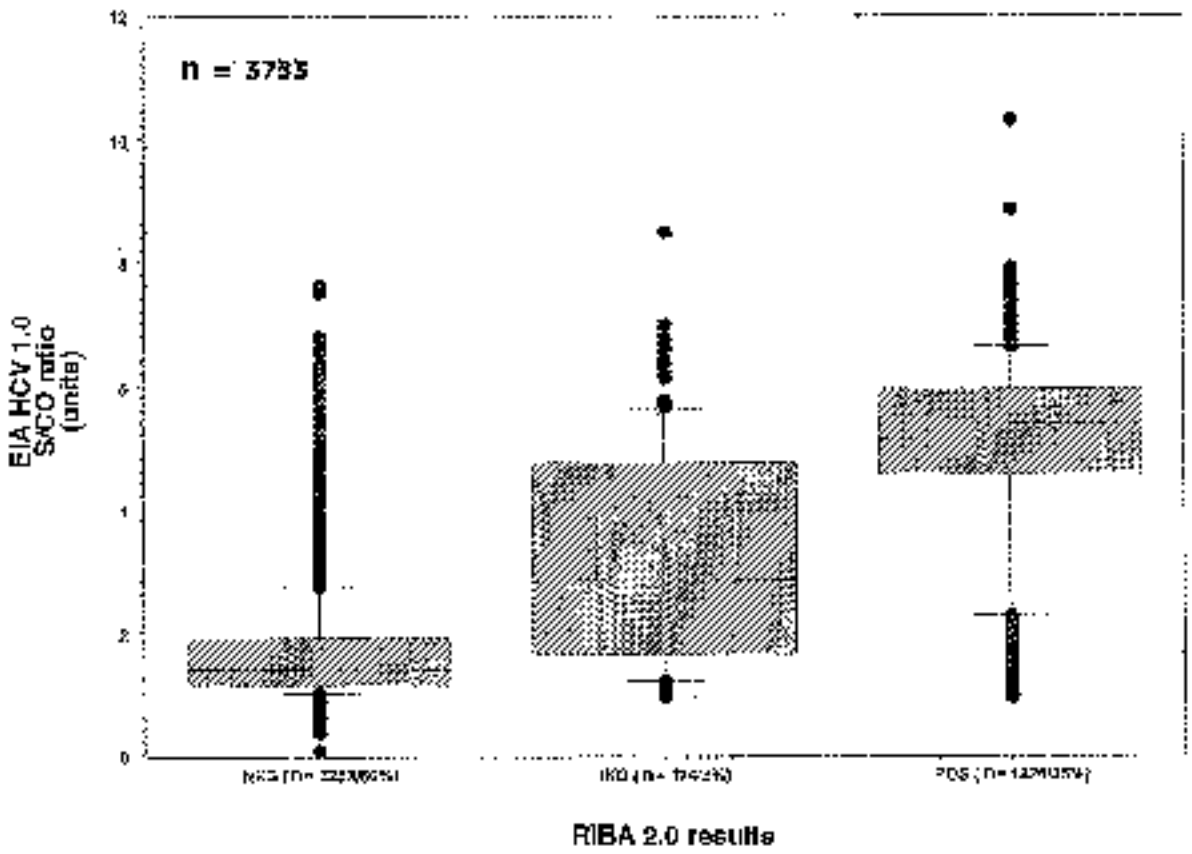


Fig. 3. Summary RIBA 2.0 results versus S/CO ratio in HCV EIA 1.0-RR donations for all four participating blood centers. Statistical analysis showed that 90 percent of RIBA 2.0-positive (POS) specimens had an S/CO ratio >2.26, while 90 percent of RIBA 2.0-negatives (NEG) specimens had an S/CO ratio <2.76. Each box plot is composed of five horizontal lines that display the 10th, 25th, 50th, 75th, and 90th percentiles of a variable, with the filled box representing the 25th through the 75th percentiles. Values above the 90th percentile and below the 10th percentile are plotted as points. IND = RIBA 2.0 indeterminate.

TMA results of RIBA 2.0-positive and -negative specimens

To investigate whether RIBA 2.0-positive donations with a low S/CO ratio (≤2.5) had a rate of viremia similar to that in those with a high S/CO ratio (>2.5), we tested without knowledge of their RIBA 2.0 results a total of 248 RIBA 2.0-positive specimens. HCV RNA was detected in 198 (80%) of these confirmed-positive (HCV EIA 1.0-RR/RIBA 2.0-positive) samples. Table 4 shows that the rate of HCV RNA positivity among samples with an HCV EIA 1.0 S/CO ratio >2.5 was significantly greater (84%) than that among RIBA 2.0-positive samples with an HCV EIA 1.0 S/CO ratio ≤2.5 (48%) ($p<0.001$ by chi-square analysis). Overall, 183 (92%) of the HCV RNA-positive/RIBA 2.0-positive specimens had an S/CO ratio >2.5, whereas only 15 (7.5%) had an S/CO ratio ≤2.5.

In addition to the RIBA 2.0-positive specimens, 137 RIBA 2.0-negative specimens were submitted without knowledge of their RIBA 2.0 results for HCV RNA testing. HCV RNA was not detected in 135 (98%) of the RIBA 2.0-negative specimens. One RIBA 2.0-negative/HCV RNA-positive specimen had an HCV EIA 1.0 S/CO ratio of 2.9 and therefore would trigger HCV lookback if a policy requiring lookback on samples with S/CO ratios >2.5 was adopted. The second RIBA 2.0-negative/HCV RNA-positive specimen had borderline reactivity for HCV RNA (i.e., 2 out of 3 replicates reacted at the provisional TMA cutoff). The S/CO ratio for this specimen was 1.9, and hence this donation would not trigger lookback according to the proposed S/CO ratio algorithm. Repeat TMA testing of these latter two specimens yielded results consistent with the initial TMA testing.

TABLE 3. Relationship between S/CO ratio of HCV EIA 1.0 and RIBA 2.0 results for 3753 HCV EIA 1.0-RR donations identified at four blood centers

		RIBA 2.0		
HCV EIA 1.0 S/CO ratio	Number (%)	Positive	Indeterminate	Negative
≤2.5	2177 (58%)	146 (11%)	77 (44%)	1954 (87%)
>2.5	1576 (42%)	1180 (89%)	97 (56%)	299 (13%)
Total	3753	1326	174	2253

TABLE 4. Relationship between HCV EIA 1.0 S/CO ratio and HCV RNA status for 248 HCV EIA 1.0 RR, RIBA 2.0-positive donations

HCV EIA 1.0 S/CO ratio	Number	Number (%) HCV RNA-positive
≤2.5	31	15 (48%)
>2.5	217	183* (84%)
Total	248	198 (80%)

* Single HCV RNA-positive/RIBA 2.0-negative specimen was excluded from this analysis.

TABLE 5. Sensitivity and specificity of S/CO ratio triage strategy by various levels

	Sensitivity		Specificity
S/CO ratio	RIBA 2.0 results	TMA results	RIBA 2.0 results
>1.5	1261/1326 = 95%	193/199* = 97%	961/2253 (43%) = 57%
>2.0	1212/1326 = 91%	189/199 = 95%	495/2253 (22%) = 78%
>2.5	1180/1326 = 89%	184/199 = 92%	299/2253 (13%) = 87%

* The single HCV RNA-positive/RIBA 2.0-negative sample was included in this analysis.

Effect of alternative HCV EIA 1.0 S/CO ratio on targeted lookback

We explored alternative HCV EIA 1.0 S/CO ratios of 1.5 and 2.0 to evaluate the trade-off of enhanced sensitivity and reduced specificity associated with lower cutoffs (Table 5). For example, lowering the S/CO ratio to 2.0 would increase detection of RIBA 2.0- and HCV RNA-positive units by 2 percent (from 89% sensitivity to 91%) and 3 percent (92% to 95% sensitivity), respectively. However, this would be at the cost of an additional 9 percent "false-positive" notifications (from 13% specificity to 22%). The impact of an S/CO ratio of 1.5 would be a small further increase in sensitivity (4% and 2% for RIBA 2.0- and HCV RNA-positive units, respectively) with an additional 21-percent (from 22% to 43%) increase in "false-positive" notifications.

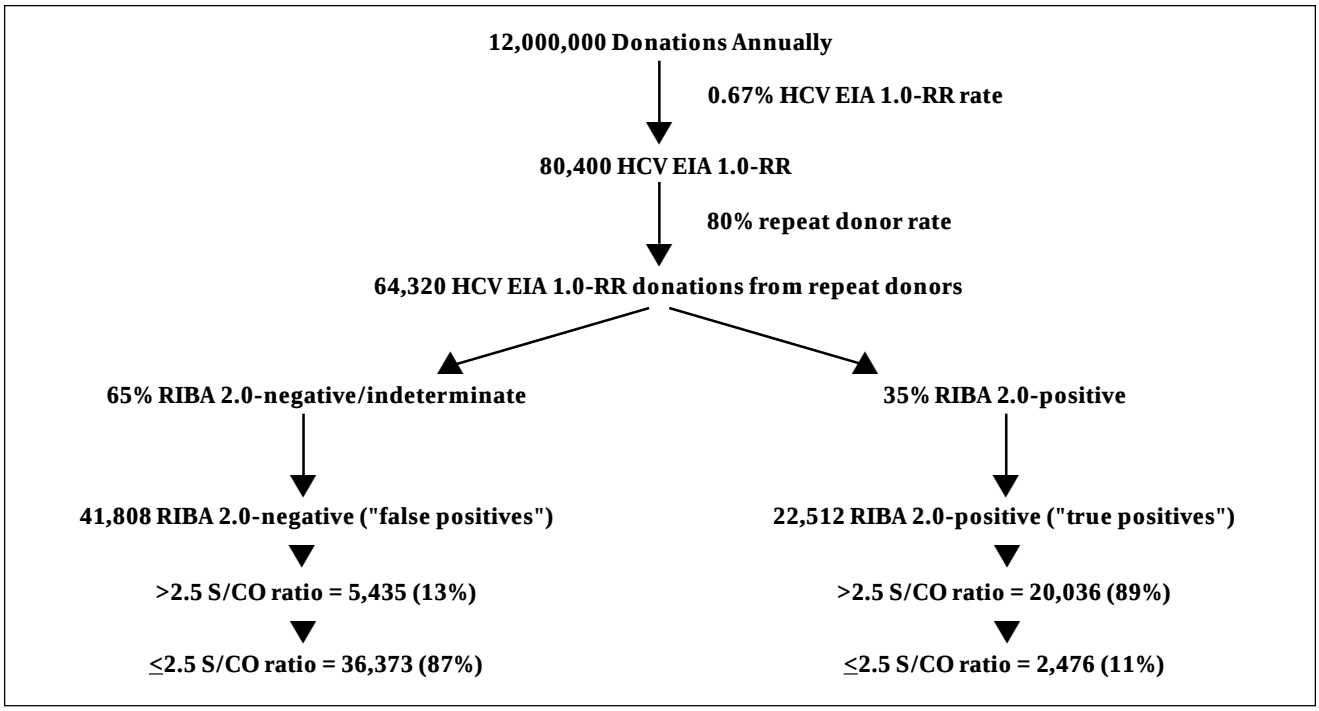
Impact on targeted lookback and consignee notification

The impact on targeted lookback of using an S/CO ratio of >2.5 for HCV EIA 1.0-RR specimens during the first year of screening is projected in Fig. 4. The analysis assumed an HCV EIA 1.0-RR rate of 0.67 percent, the receipt of 80 percent of all donations annually from repeat donors (Schreiber G, written communication, June 1999), and the RIBA 2.0 distribution rate observed in the present study (Fig. 2). In the absence of an HCV EIA 1.0 S/CO ratio sorting strategy, 64,320 HCV EIA 1.0-RR donations would trigger lookback investigations. By utilization of the proposed >2.5 ratio, 20,036 of 22,512 "true-positive" donors would trigger lookback, while 36,373 "false-positive" lookbacks would be avoided (Fig. 4A). By applying the lookback experience from BCB (Table 2), we estimate that 255,350 HCV EIA 1.0-RR components were distributed. Using the HCV EIA 1.0 S/CO triage approach, 79,541 (89%) of the 89,372 components derived from "true-positives" and 21,577 (13%) of the 165,978 components originating from "false-positives" would result in consignee notification (Fig. 4). In contrast, lookback would not occur for 144,401 components from "false-positive" donors and for 9,831 from "true-positive" donors.

DISCUSSION

Given the decision to perform a targeted lookback for HCV EIA 1.0-RR donations, a number of issues arise with respect to how to optimize policies and procedures to maximize notification of exposed prior recipients and minimize notifications of nonexposed recipients. One proposed option was to limit lookback to prior donations by donors whose HCV EIA 1.0-RR donation was subjected to RIBA 2.0 testing. Unfortunately, however, RIBA 2.0 results are widely available only for donations that tested reactive during the second year of HCV EIA 1.0 screening. Our analysis of the identification of HCV EIA 1.0-RR/RIBA 2.0-positive donors over time indicates that approximately 76 percent of RIBA 2.0-confirmed-positive donations by repeat donors were detected during the first year of HCV EIA 1.0 screening. The progressive reduction in the yield of infected repeat donors identified over time probably reflects a classic culling effect, whereby regular donors who were HCV infected were identified by HCV EIA 1.0 as reactive and were deferred from subsequent donation. This means that an HCV EIA 1.0 lookback program that is triggered only for donations detected as RIBA 2.0-positive subsequent to widespread access to RIBA 2.0 in mid-1991 would fail to identify approximately 80 percent of exposed prior recipients. Consequently, we conclude that an HCV EIA 1.0 lookback program that is limited to donations for which RIBA 2.0 data are available is not tenable.

A second issue relates to whether lookback should be triggered for donations that tested RIBA 2.0-indeterminate as well as those that tested RIBA 2.0-negative. The current FDA guidance document recommends lookback for HCV EIA 2.0-RR /RIBA 2.0-indeterminate donations unless these



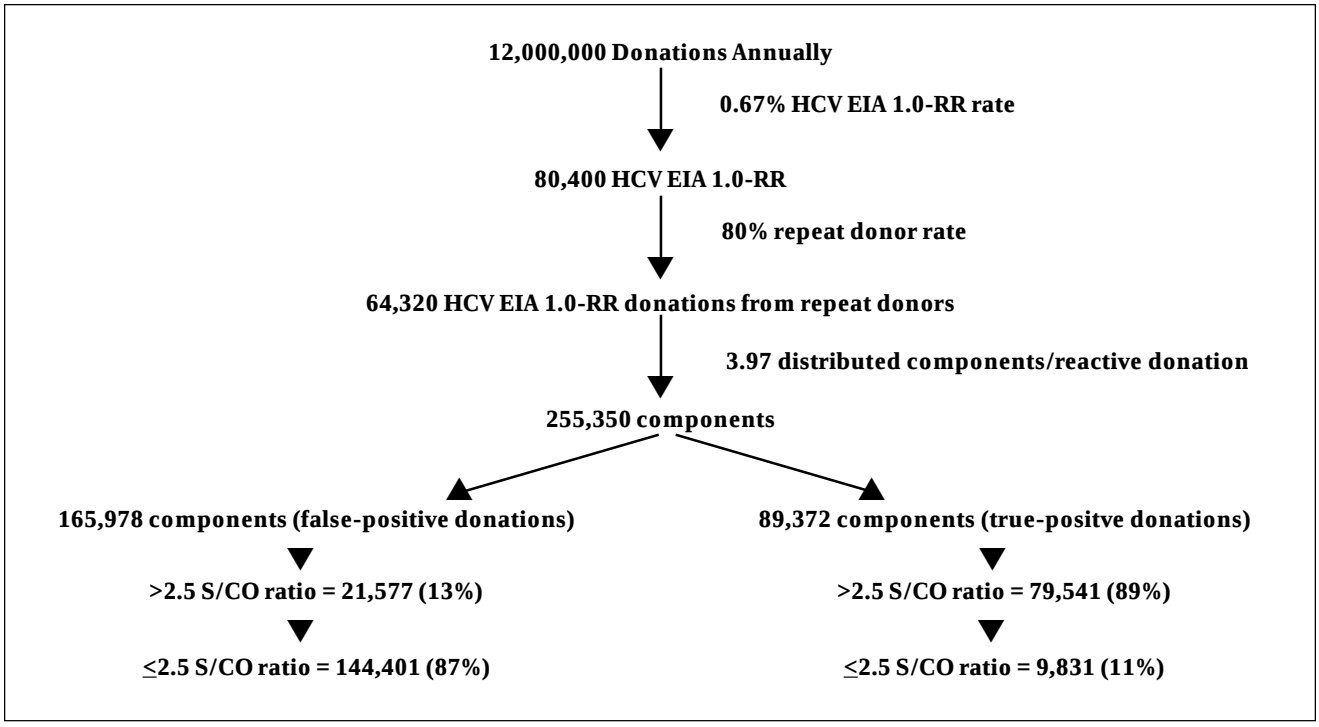


Fig. 4. Impact of a 2.5 S/CO ratio on HCV EIA 1.0-targeted lookback. A) The number of "false-positive" donations versus the number of "true-positive" donations using 12 million donations annually, an HCV EIA 1.0-RR rate of 0.67 percent, 80 percent of all donations from repeat donors, and the frequency of RIBA 2.0 interpretations from this study (RIBA 2.0-negative, 60%; RIBA 2.0-indeterminate, 5%; RIBA 2.0-positive, 35%). For the purposes of this calculation, the RIBA 2.0-indeterminate results were assigned the specificity of RIBA 2.0-negative specimens. B) The number of components that would derive from "false-positive" versus "true-positive" donors was estimated by use of the rate of 3.97 components per donor observed at BCB.

specimens or donors are further tested and determined to be nonreactive by the subsequently licensed HCV EIA 3.0 or either negative or indeterminate by RIBA 3.0. Given the increased antigen representation and enhanced sensitivity of RIBA 2.0 relative to HCV EIA 1.0, we suspected that few if any HCV EIA 1.0-RR /RIBA 2.0-indeterminate donations would prove to be from actively infected donors. To evaluate this, we further studied 69 such donations by RIBA 3.0 and TMA for HCV RNA. Although approximately 15 percent of HCV EIA 1.0-RR/RIBA 2.0-indeterminate donations tested positive by RIBA 3.0, all of these specimens tested negative for HCV RNA (80% of HCV EIA 1.0-RR/RIBA 2.0-positive donations tested in parallel without knowledge of the test results were HCV RNA positive). On the basis of these data, we recommend against initiating lookback on HCV EIA 1.0-RR/RIBA 2.0-indeterminate donations.

The third issue addressed in this study is whether the level of reactivity of the HCV EIA 1.0 could be used to determine whether lookback is justified in cases where RIBA 2.0 data are not available. We found a highly significant correlation between HCV EIA 1.0 reactivity, expressed as S/CO ratio, and RIBA 2.0 results. On the basis of the distribution of HCV EIA 1.0 reactivity among RIBA 2.0-negative versus -positive donations, we selected an S/CO ratio of 2.5 to examine the consequences of triaging donations according to S/CO ratio for lookback. Donations with reactivity >2.5 had a 75-percent probability of testing RIBA 2.0-positive, and over 90 percent of the RIBA 2.0-positive donations with high S/CO (>2.5) ratios that were evaluated tested HCV RNA-positive. Limiting lookback to such highly reactive units would prevent triggering inappropriate notifications for 87 percent of HCV EIA 1.0-RR/RIBA 2.0-negative donations. The downside of such a policy is that a small but potentially significant proportion of RIBA 2.0-positive donations with relatively low HCV EIA 1.0 reactivity (S/CO ratio $\leq$2.5) would not trigger recipient notification. In our study, approximately 11 percent of RIBA 2.0-positive donations had S/CO ratios $\leq$2.5. Although the rate of viremia among these RIBA 2.0-positive donations with a low S/CO ratio was lower than that seen among those with a high (48% vs. 84%), this approach would nevertheless result in the failure to notify a small proportion of recipients exposed to HCV-viremic transfusions. Moreover, donors who tested RIBA 2.0-positive but had low S/CO ratios and negative HCV RNA results may represent cases of cleared HCV infection with evolving seroreversion.[17] Hence, it is possible that a higher proportion of these donors were viremic at the time of their earlier unscreened donations than were documented here by TMA analysis of their HCV EIA 1.0-RR donation.

Despite these limitations, we believe that a policy recommendation to use the S/CO ratio to determine the appropriateness of lookback for HCV EIA 1.0-RR donations for which RIBA 2.0 data are not available is warranted. Such an approach would avoid false notifications of 87 percent of RIBA 2.0-negative and 50 percent of RIBA 2.0-indeterminate donors, groups that provide 60 and 5 percent, respectively, of HCV EIA 1.0-RR donations (Fig. 3). Concern over the fact that approximately 11 percent of RIBA 2.0-positive and 7.5 percent of HCV RNA-positive donations would not trigger targeted lookback if this policy is implemented is tempered by the recognition that all targeted lookback strategies have substantial limitations, and, consequently, general lookback will be operating in parallel.

On January 28, 1999, having reviewed this data, the DHHS ACBSA voted that targeted lookback should be initiated on HCV EIA 1.0-RR donations unless one of three conditions was met: a supplemental assay was performed and did not indicate significant risk of infection; no supplemental test was performed, but the S/CO ratio on the HCV EIA 1.0-RR donor was <2.5; or follow-up testing was negative. On the basis of our projections, implementation of this policy will reduce by 60 percent the number of consignee notifications required, yet result in triggered notification of approximately 90 percent of truly exposed recipients. This recommendation represents a rational public health policy that balances the obligation to notify exposed recipients of their risk while minimizing the burden of over 100,000 unwarranted lookback investigations, notifications, and their consequences.

ACKNOWLEDGMENTS

The authors acknowledge Nelly Gefter for her precision and persistence in creating the database of HCV EIA 1.0 and RIBA 2.0 results from 3753 donors, as well as Eberhard Fiebig, MD, and Dale Hirschkorn for their continued support with StatView.

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