

Screening Blood Donations for Hepatitis C in Central Africa:

Analysis of a Risk- and Cost-based Decision Tree

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Four screening strategies (no testing, HC Abbott, HC Pasteur, and a combined test) for the detection of hepatitis C virus (HCV) antibody in donated blood were considered in a formal decision tree. Decision criteria included residual risk of infection and overall monetary cost. Tree parameters were determined using data from the Central African Republic. The prevalences observed among blood donors for HIV infection, hepatitis B, syphilis, and hepatitis C varied between 6% and 15%. The current residual risk of transfusion-transmitted infections is very high (8.4%). Screening for HCV would bring that risk down to about 3% with either the HC Pasteur, the HC Abbott, or the combined test. Even though baseline analysis gives preference to the HC Abbott test (the combined test coming out last), Monte Carlo sensitivity and uncertainty analyses showed that Abbott's and Pasteur's tests are interchangeable, on the basis of either risk or cost considerations. *Key words:* Africa; blood donation; blood transfusion; decision tree analysis; hepatitis B virus; hepatitis C virus; human immunodeficiency virus; Monte Carlo; syphilis. (**Med Decis Making 1999;19:296–306**)

In industrialized countries, prevention of transfusion-transmitted hepatitis C has been considerably improved by systematic screening of all donated blood for hepatitis C virus (HCV) antibodies. In many African countries, large investments have been made to increase access to blood screening, especially for human immunodeficiency virus (HIV) infection, infection with hepatitis B virus (HBV), and syphilis (Sy). Yet few of these countries screen for infection with hepatitis C virus (HCV). Several reasons can be advanced to propose HCV screening: hepatitis C has major health consequences¹ and its prevalence is high in sub-Saharan countries.^{2–5} Furthermore, transfusions are a medical necessity and, in principle, no infectious disease should be transmitted this way. However, the decision to institute a screening program for HCV depends not only on the prevalence of hepatitis C or its health consequences, but also, for example, on the sensitivity and specific-

ity of the available screening tests, and on their costs.

Strategies for HCV screening that are used in industrialized countries to improve the safety of blood supplies may not be directly applicable in developing countries, where the economic situations, laboratory technology, and prevalences of infections are different. For example, in developing countries, blood collection is often costly and difficult to organize; therefore, screening assays must not only be sensitive, to discard infectious blood donations, but also particularly specific, to avoid discarding too many falsely positive donations. Current HCV screening assays have made possible gains in the sensitivity and specificity of detection of anti-HCV antibodies.⁶ However, their use with sera originating from Africa remains largely unknown. African sera are generally considered frequently to give rise to unspecific reactivities (false positivity) by immunoenzymatic assays,⁷ including those for HCV infection.⁸

It is therefore necessary to conduct specific decision analyses to determine the optimal testing strategy for HCV (including the option of no testing) for developing countries. Such an analysis is presented here for the case of the Central African Republic. Four screening strategies for detection of HCV antibody in blood donations were considered in a formal decision tree.^{9–12} Two decision criteria were studied: a health-based one (the residual risks of infection after screening for HIV, HBV, *Treponema*

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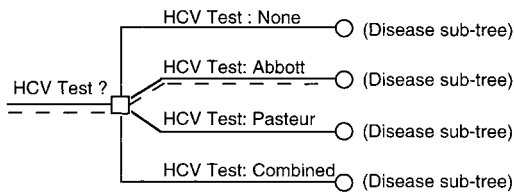


FIGURE 1. Structure of the decision tree. A choice is to be made between four blood screening strategies (see text). For example (dotted line), the decision can be made to screen donated blood for hepatitis C virus (HCV) with the HC Abbott Test. A “disease subtree” (figure 2) is grafted at the end of each decision branch.

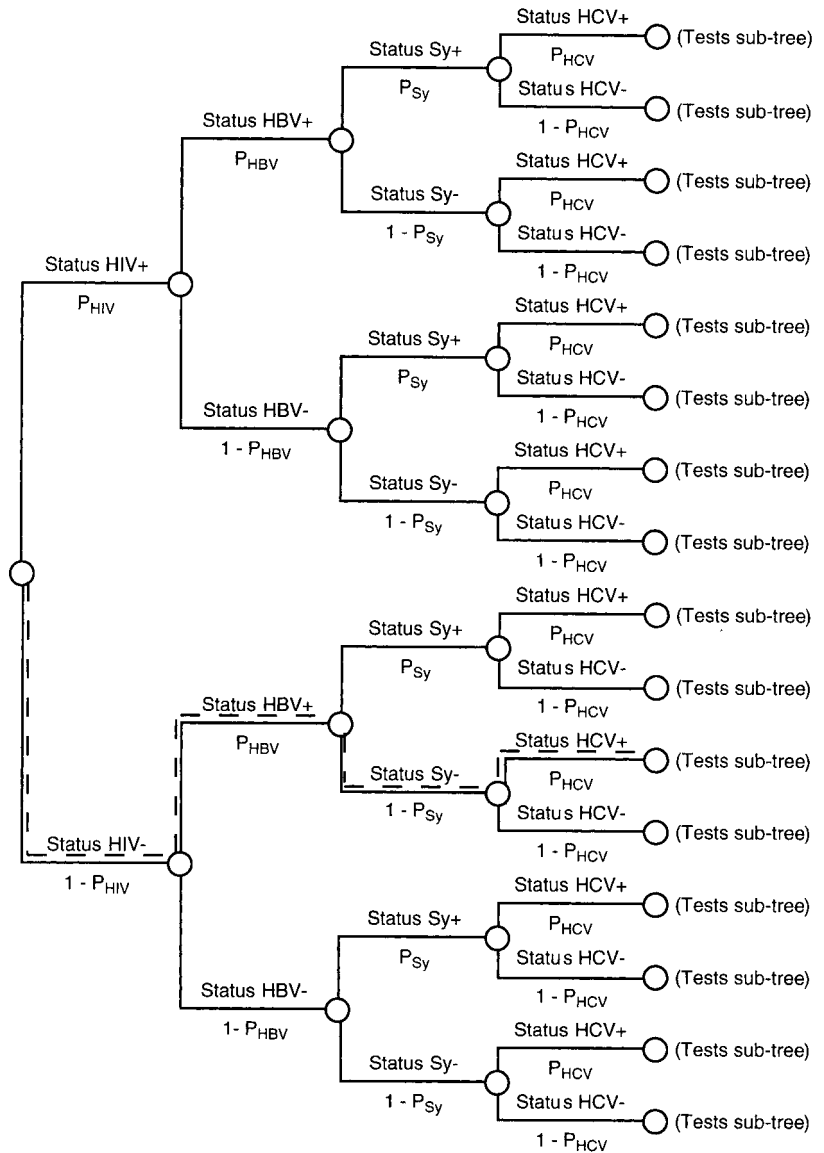


FIGURE 2 (right). Disease subtree. Such a tree is grafted at the end of each decision branch in figure 1. Chance nodes (circles) determine the infectious status (positive or negative) of a given blood donation for HIV, hepatitis B virus, *Treponema pallidum*, or hepatitis C virus (HCV), with corresponding probabilities P_{HIV} , P_{HBV} , P_{Sy} , and P_{HCV} . For example, a simulated blood donation can be negative for HIV, positive for HBV, negative for syphilis (*Treponema pallidum*), and positive for HCV (dotted line). A “tests subtree” (figure 3) is grafted on each terminal chance node.

pallidum, the spirochete that causes syphilis, and HCV) and an economic one (the costs associated with the screening strategies).

The decision tree parameters were determined using data from the Centre National de Transfusion Sanguine (CNTS) of Bangui, Central African Republic. In addition to obtaining average estimates of decision criteria, we performed sensitivity and uncertainty analyses of the results via Monte Carlo simulations.

Methods

TESTING STRATEGY DEFINITIONS

Three blood tests are already routinely performed in Bangui: an HIV second-generation enzyme immunoassay (Genelavia mixt®, Sanofi-Diagnostics Pasteur, Marnes-la-Coquette, France), an HBV enzyme immunoassay (Monolisa® HBs, Sanofi-Diagnostics Pasteur), and a non-*Treponema* flocculation

test for syphilis (Card-test BioMérieux®, BioMérieux, Marcy l’Etoile, France). Two HCV third-generation ELISAs, using different sets of antigens, were evaluated: Abbott HCV EIA 3.0® test (Abbott, Chicago, Illinois), and Monolisa® anti-VHC/Pasteur (Sanofi-Diagnostics Pasteur, Paris, France). Consequently, four blood screening strategies were evaluated:

- Tests for HIV, HBV, and *Treponema pallidum*, and no HCV test
- Tests for HIV, HBV, and *T. pallidum*, and HCV with HC Abbott Test
- Tests for HIV, HBV, *T. pallidum*, and HCV with the HC Pasteur Test
- Tests for HIV, HBV, *T. pallidum*, and HCV with both Abbott and Pasteur HCV tests performed in parallel (HC combined test); this test battery has better specificity than either test alone. (The combined test was deemed positive when both

Table 1 • Correlation Matrix between Infectiousness Status for HIV Infection, Hepatitis B, Syphilis, and Hepatitis C among 99 Blood Donors in Bangui

| Infectiousness Status | HIV+ | HBV+ | Syphilis+ | HCV+ |
|-----------------------|-------|-------|-----------|------|
| HIV+ | 1 | | | |
| HBV+ | 0.14 | 1 | | |
| Syphilis+ | 0.02 | 0.00 | 1 | |
| HCV+ | -0.02 | -0.90 | -0.08 | 1 |

Abbott and Pasteur tests were positive, and negative otherwise.)

DECISION TREE

The decision tree describes the sequence of decisions and uncertain events associated with the process of screening donated blood (figure 1). For our study, the only decision node represents the choice among the four screening strategies and has four main branches.

A “disease subtree” (figure 2) is grafted at the end of each of the main four branches. This subtree determines all possible infectious statuses of a given blood unit for HIV, HBV, *T. pallidum*, or HCV. Blood donations are assumed to be either infectious (status positive) or non-infectious (status negative) with respect to each infection. The probability P_i that a blood donation is infectious for an infection i is equal to the prevalence of i among blood donors. Infectiousness prevalences for HIV, HBV, *T. pallidum*, and HCV have been determined using reference tests on a panel of blood samples from the CNTS of Bangui (see parameter values section, below).

The probabilities P_i were assumed independent from each other: the probability that a donation is infectious for a given disease is the same regardless of its status with regard to other infections. This assumption seemed reasonable given the lack of correlation observed between infectious agents in the blood samples tested for determination of the infectiousness prevalences (table 1). In the presence of strong correlations between disease status, the order of the diseases in the tree would be still be arbitrary (there is no “natural” order for disease), but the values of the P_i would differ from branch to branch.

A “tests subtree” (figure 3) is grafted at each terminal chance node of the disease subtree (for the three test branches of the main tree). This subtree describes all possible outcomes of the array of blood screening tests implemented. Screening test results are assumed to be either positive or negative with regard to each infectious agent. The probability that a screening test result is positive for a given infection i is:

$$\begin{cases} \text{Sensitivity, if blood donation is infectious} \\ 1\text{-specificity, if blood donation is not infectious} \end{cases} \quad (1)$$

The probability that a screening test result is negative is:

$$\begin{cases} 1\text{-Sensitivity, if blood donation is infectious} \\ \text{Specificity, if blood donation is not infectious} \end{cases} \quad (2)$$

Here, also, we have assumed that the above probabilities are independent: the probability that a blood donation is positive for a given test is the same whatever may come of the other tests (the tests are performed in parallel). The order of the tests is arbitrary, and only their global result matters. These test results are used, together with the infectiousness status given by the disease subtree, to determine a final blood donation status.

Several simple outcomes of the decision tree can be defined and computed, such as the probability that a blood donation will be false positive (FP) for a given infection (i.e., having negative status with a positive test result). Similarly, the probabilities of its being true positive (TP) (i.e., positive status with a positive test result), false negative (FN) (i.e., positive status with a negative test result), and true negative (TN) (i.e., negative status with a negative test result) can be computed. More complex outcomes can also be defined. Because we are interested in transmitting no infection at all, we considered the infectious statuses and the test results for the four infectious agents as a whole. We therefore defined as “total false negative” (TFN) a blood donation infectious for at least one of the four infections (for example, status +/–/+–) and with all negative test results (tests –/–/–/–). Similar definitions can be given for total true positive (TTP), “total true negative” (TTN), and “total false positive” (TFP). A TTP result indicates a blood donation infectious for at least one of the four infectious agents (for example, status +/+ /+–) with at least one positive test result (for example, tests +/–/+– or –/–/–/+). Notice that infectiousness and test results do not need to match pairwise. A TTN result indicates a blood donation that is not infectious (status –/–/–/–), with all negative test results (tests –/–/–/–). A TFP result indicates a non-infectious blood donation (status –/–/–/–) with at least one positive test result (for example, tests +/+ /+–).

To make the description of the tree clearer, we invite the reader to follow step by step a branch from the tree root to one of its terminal nodes in figures 1, 2, and 3 (in the figures, a dotted line indicates the path followed though the decision tree). Suppose we decide to screen blood for HCV using

the HC Abbott test (figure 1). We next have to consider the possible infectious status of a simulated blood donor (figure 2). According to our example, this donor is negative for HIV infection, positive for HBV infection, negative for syphilis, and positive for HCV infection. The probability of this status at the end of the relevant branch of the disease subtree is the product:

$$P_{s_{-+++}} = (1 - P_{HIV})P_{HBV}(1 - P_{Sy})P_{HCV}$$

Screening tests for HIV, HBV, *T. pallidum*, and HCV (Abbott test) are applied to the blood donation (figure 3). The results of the tests happen to be positive for HIV, negative for HBV, negative for *T. pallidum*, and positive for HCV. Given the infectious status of our donor, it is easy, using equations 1 and 2 to determine the probability of this combination of test results:

$$P_{t_{-+++}} = P_{t_{HIV}}(1 - P_{t_{HBV}})(1 - P_{t_{Sy}})P_{t_{HCV}} \\ = (1 - Sp_{HIV})(1 - Se_{HBV})Sp_{Sy}Se_{HCVAbbott}$$

In terms of simple outcomes, the blood donation considered is a false positive for HIV, a false negative for HBV, a true negative for *T. pallidum*, and a true positive for HCV. In terms of complex outcomes, the blood donation is considered to be a TTP because it is infectious for HCV and has at least one positive test result. The probability, P_{branch_j} , associated with these outcomes at the end of the branch (figure 3) is the product of $P_{s_{-+++}}$ by $P_{t_{-+++}}$:

$$P_{branch_j} = (1 - P_{HIV})(1 - Sp_{HIV})P_{HBV}(1 - Se_{HBV}) \\ \cdot (1 - P_{Sy})Sp_{Sy}P_{HCV}Se_{HCVAbbott}$$

DECISION CRITERIA

Residual risk of infection. The residual risk of blood-transmitted infection was defined as the probability that a blood donation delivered by the CNTS of Bangui actually infects a recipient with at least one of the four infections studied (HIV infection, HB, syphilis, and HC). The following assumes that donations testing positive for at least one infection are discarded (which is the case in Bangui).

We use the following notation for the mathematical expectation over the tree of a variable X :

$$E(X) = \prod_{j=1}^{j=2^8} (P_{branch_j} X_j)$$

where P_{branch_j} is the probability associated with terminal branch j of the tree ($j = 1, 2 \dots 2^8$), and X_j the outcome value at the terminal branch j .

In order to calculate the residual risk, we need to

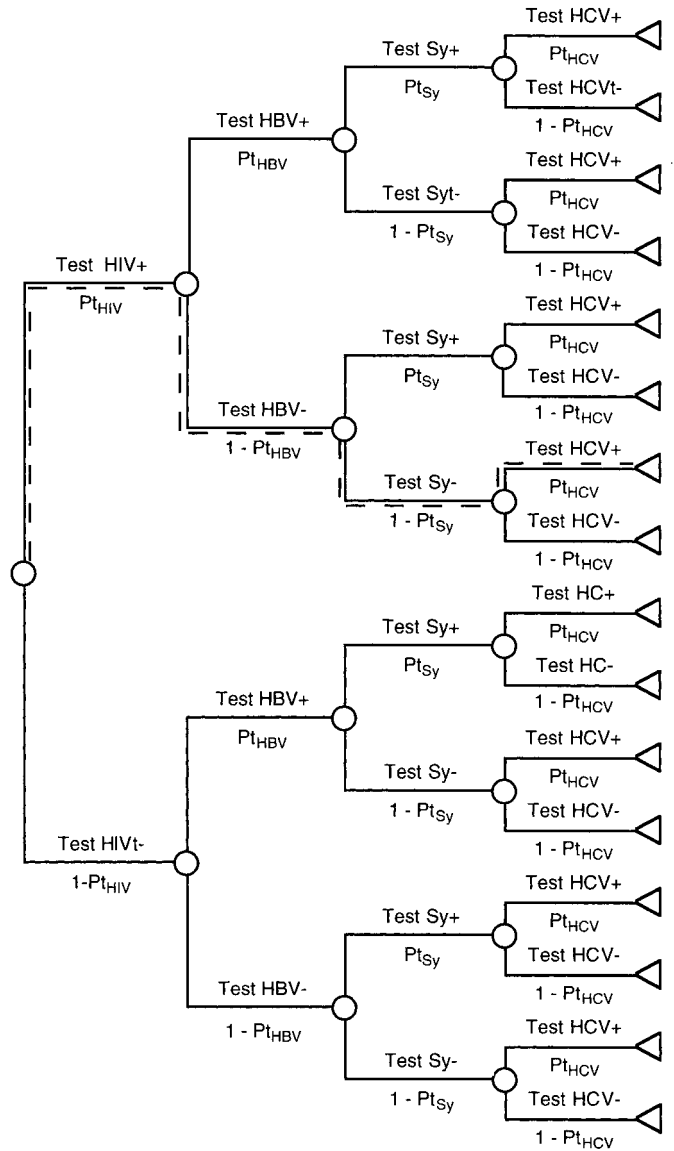


FIGURE 3. "Tests subtree." Such a tree is grafted at the end of each branch of the "disease subtree" (figure 2), for the three test branches of the main tree. Chance nodes determine the blood screening tests results (positive or negative) for each infection (HIV, HB, syphilis, and HC). The probabilities (P_t) that a screening test result is positive for infection i is equal to the test's sensitivity if the blood donation is infectious and equal to $1 -$ specificity otherwise. The dotted line is a possible path in the tree.

determine the probability that the recipient of a blood donation would be infected by one of the four agents studied through transfusion of a blood donation considered to be non-infectious (all screening tests negative).

Let us define the probability that Pd_i ($i = HIV, HBV, Sy, HCV$) will infect a blood recipient with infection i . Pd_i is equal to the probability, P_{Transf_i} , of actually transmitting infection i during transfusion if the blood donation is infectious for i (case of a false-negative blood donation) times I_{FN_i} . I_{FN_i} is an indicator variable equal to 1 if the blood donation is a

“false negative” for i and equal to 0 otherwise. P_{Trans_i} is lower than 1 because transfusion of infected blood does not always result in contamination. Pd_i is zero if the blood donation is not infectious for i .

Therefore, the probability of infecting a recipient with at least one of the four agents Pd_{total} (total = HIV \cup HBV \cup Sy \cup HCV) is, according to elementary probability calculus:

$$\begin{aligned} Pd_{\text{total}} &= Pd_{\text{HIV}} + Pd_{\text{HBV}} + Pd_{\text{Sy}} + Pd_{\text{HCV}} - Pd_{\text{HIV}}Pd_{\text{HBV}} \\ &- Pd_{\text{HIV}}Pd_{\text{Sy}} - Pd_{\text{HIV}}Pd_{\text{HCV}} - Pd_{\text{HBV}}Pd_{\text{Sy}} \\ &- Pd_{\text{HBV}}Pd_{\text{HCV}} - Pd_{\text{Sy}}Pd_{\text{HCV}} \\ &+ Pd_{\text{HIV}}Pd_{\text{HBV}}Pd_{\text{Sy}} + Pd_{\text{HIV}}Pd_{\text{HBV}}Pd_{\text{HCV}} \\ &+ Pd_{\text{HIV}}Pd_{\text{Sy}}Pd_{\text{HCV}} + Pd_{\text{HBV}}Pd_{\text{Sy}}Pd_{\text{HCV}} \\ &- Pd_{\text{HIV}}Pd_{\text{HBV}}Pd_{\text{Sy}}Pd_{\text{HCV}} \end{aligned}$$

The probabilities Pd_i and Pd_{total} are defined for each terminal branch of the tree. Overall, the probability that a blood recipient will be infected with one of the four agents is the mathematical expectation of Pd_{total} over the tree, i.e., $E(Pd_{\text{total}})$.

The risk needs to be normalized by the fraction of blood donations kept after screening. Assume that the arbitrary decision is taken to halve the number of donations delivered. For a given number of blood donations in input this would automatically result in a halving of the risk of infection (at the limit discarding all donations would result in zero risk). However, in reality, the output of the CNTS is variable, and its input (recruited donations) is adjusted to match demand. If a new screening strategy discards many donations, input will automatically be increased in proportion of the fraction of donations kept (e.g., a threefold, increase if a third of the donations are kept). To take this effect into account, it is necessary to normalize by the fraction kept, which is equal to the fraction of blood donations with negative test results. This fraction is therefore the sum of $E(I_{\text{TTN}})$ and $E(I_{\text{TFN}})$. (I_{TTN}) is an indicator variable equal to 1 if the blood donation is a “total true negative,” and to 0 otherwise. Similarly, I_{TFN} is an indicator variable equal to 1 if a blood donation is a “total false negative,” and to 0 otherwise.

Thus, the residual risk was defined as:

$$R = \frac{E(Pd_{\text{total}})}{E(I_{\text{TTN}}) + E(I_{\text{TFN}})} \quad (3)$$

Costs of screening strategies. In addition to residual risk, the annual financial cost per blood donation associated with HCV screening strategies (cost_{HCV}) was estimated. This total cost is function of the cost (Cf) to collect a blood donation, which includes operations and investment costs, of the cost

(Ct) of test kits for HIV, HBV, *T. pallidum*, and eventually HCV, and of Ci , the mathematical expectation over the tree of the cost to contaminate with at least one of the infectious agents studied a recipient free of that infection. We define Pdh_i ($i = \text{HIV, HBV, } T. \text{ pallidum, HCV}$) as the probability of infecting with agent i a blood recipient not yet infected by i . Pdh_i is equal to the product of the probability Pd_i (see previous section) by the fraction of healthy population for i , $(1 - P_i)$, P_i being the infectiousness prevalence of i . The probability (Pdh_{total}) of contamination of a recipient HIV-free by HIV, or of a recipient HCV-free by HCV, etc., is:

$$\begin{aligned} Pdh_{\text{total}} &= Pdh_{\text{HIV}} + Pdh_{\text{HBV}} + Pdh_{\text{Sy}} \\ &+ Pdh_{\text{HCV}} - Pdh_{\text{HIV}}Pdh_{\text{HBV}} \\ &- Pdh_{\text{HIV}}Pdh_{\text{Sy}} - Pdh_{\text{HIV}}Pdh_{\text{HCV}} \\ &- Pdh_{\text{HBV}}Pdh_{\text{Sy}} - Pdh_{\text{HBV}}Pdh_{\text{HCV}} - Pdh_{\text{Sy}}Pdh_{\text{HCV}} \\ &+ Pdh_{\text{HIV}}Pdh_{\text{HBV}}Pdh_{\text{Sy}} + Pdh_{\text{HIV}}Pdh_{\text{HBV}}Pdh_{\text{HCV}} \\ &+ Pdh_{\text{HIV}}Pdh_{\text{Sy}}Pdh_{\text{HCV}} + Pdh_{\text{HBV}}Pdh_{\text{Sy}}Pdh_{\text{HCV}} \\ &- Pdh_{\text{HIV}}Pdh_{\text{HBV}}Pdh_{\text{Sy}}Pdh_{\text{HCV}} \end{aligned}$$

Then C_i is:

$$C_i = \text{cost}_{\text{inf}} \times E(Pdh_{\text{total}}) \quad (4)$$

where cost_{inf} is the cost of subsequent medical care incurred by transfusing infectious blood into a recipient: cost of hospitalization, post-hospitalization or long-term care, or death.

Finally, for the above reason, cost_{HCV} was normalized by dividing the numerator by the fraction of blood donations kept after screening (i.e., the sum of $E(I_{\text{TTN}})$ and $E(I_{\text{TFN}})$). Therefore, cost_{HCV} is given by:

$$\text{Cost}_{\text{HCV}} = \frac{C_f + C_i + C_j}{E(I_{\text{TTN}}) + E(I_{\text{TFN}})} \quad (5)$$

PARAMETER VALUES

Parameter values were determined from original data when available, and otherwise from the literature.

The prevalences of infectiousness of HIV, HBV, *T. pallidum*, and HCV were determined using reference tests of a panel of randomized blood samples ($n = 99$) from the CNTS of Bangui. True infectiousness of a blood donation was defined as: seropositivity in two ELISA or Western blot assays or a confirmed p24-antigen positivity for HIV; confirmed exposure to HB surface antigen for HBV; both VDRL and TPHA tests being positive for syphilis; and HCV PCR positivity for HCV. All assays used to determine blood

infectiousness except ELISA for HIV were performed or confirmed at the virology laboratory of the Hôpital Broussais (Paris). In Bangui, two ELISA tests were applied to confirm HIV infectiousness according to revised WHO recommendations.¹³ We used the results of these two tests to determine HIV infectiousness. Sera that yielded discrepant results were tested with a Western blot assay at the virology laboratory of the Hôpital Broussais (Paris), and in this instance the outcome of the Western blot determined the definitive result.

Specificities and sensitivities of the screening tests used at the CNTS of Bangui for HIV, HBV, and *T. pallidum* were determined by applying the screening tests to the same blood samples as the reference tests (described above). Specificities and sensitivities of the screening tests for HCV were determined similarly at the virology laboratory of the Hôpital Broussais (Paris). Given the definition of the HC combined test, its sensitivity is equal to the product of the HC Abbott and Pasteur test sensitivities. Its specificity is given by the formula:

$$Sp_{HCV\text{combined}} = Sp_{HCV\text{Pasteur}} + Sp_{HCV\text{Abbott}}(1 - Sp_{HCV\text{Pasteur}})$$

A Bayesian approach was used to estimate the prevalences of infectiousness of HIV, HBV, *T. pallidum*, and HCV, as well as test sensitivities and specificities. According to Bayes' rule, the posterior distribution is the product of the prior distribution assigned to the individual parameter times the likelihood of the data (screening and reference test results for the 99 blood samples).^{14,15} Prevalences, sensitivities, and specificities were assumed to be independent a priori, and each probability was assigned a standard (i.e., reference) beta (0.5,0.5) prior distribution.¹⁶ The total number of infectious blood donations among collected blood, the total number of positive screening tests among those that were infectious, and the total number of negative screening tests among those that were not infectious, were assumed, as usual, to be distributed binomially. The resulting posterior distributions are beta with parameters $1/2 + k$ and $1/2 + n - k$, k being the number of successes out of n blood donations.¹⁴ The resulting quantiles of the posterior distributions for prevalences, sensitivities, and specificities are given in table 2.

The probabilities of contamination of a recipient by an infectious donation, P_{Transp} were estimated from the literature data at 95% on average (and distributed uniformly between 0.9 and 1.0) for HIV, HCV, and HBV^{17,18} and at 10% (distributed uniformly between 0.0 and 0.5) for *T. pallidum*.¹⁹ For syphilis, posttransfusal risk is lower because the blood donations are maintained at 4°C for a few days.¹⁹

The cost associated with screening strategies,

Table 2 • Baseline (Median) Values and Posterior 2.5 and 97.5 Percentiles for Prevalences, Test Sensitivities, and Test Specificities for HIV Infection, Hepatitis B, Syphilis, and Hepatitis C, obtained in the Centre National de Transfusion Sanguine of Bangui

| Parameter | Baseline Value | 2.5–97.5 Percentiles* |
|----------------------------|----------------|-----------------------|
| Infectiousness prevalences | | |
| P_{HIV} | 0.15 | 0.091–0.23 |
| P_{HBV} | 0.11 | 0.060–0.18 |
| P_{Sy} | 0.092 | 0.046–0.16 |
| P_{HCV} | 0.062 | 0.026–0.12 |
| Sensitivities | | |
| Se_{HIV} | 0.92 | 0.73–0.99 |
| Se_{HBV} | 0.98 | 0.80–1.0 |
| Se_{Sy} | 0.024 | 0.0–0.24 |
| $Se_{\text{HCV Abbott}}$ | 0.96 | 0.67–1.0 |
| $Se_{\text{HCV Pasteur}}$ | 0.96 | 0.67–1.0 |
| $Se_{\text{HCV combined}}$ | 0.93 | 0.55–1.0 |
| Specificities | | |
| Sp_{HIV} | 0.88 | 0.80–0.94 |
| Sp_{HBV} | 0.91 | 0.84–0.96 |
| Sp_{Sy} | 0.95 | 0.90–0.99 |
| $Sp_{\text{HCV Abbott}}$ | 0.86 | 0.78–0.92 |
| $Sp_{\text{HCV Pasteur}}$ | 0.85 | 0.77–0.91 |
| $Sp_{\text{HCV combined}}$ | 0.98 | 0.96–0.99 |

*This defines a 95% confidence interval.

$cost_{\text{HCV}}$, depends in large part on the cost of subsequent medical care incurred by transfusing infectious blood to a recipient ($cost_{\text{inf}}$). This cost is not easily identified. For this reason, it was analyzed only via sensitivity analysis and was sampled in our analyses from a log-uniform distribution with bounds 10 and 10^8 FF. The cost of collecting one blood donation, C_f , was estimated to be 158 FF (French francs), based upon data from Bangui.²⁰ The costs of the test kits, C_t were estimated to be 1.00 FF, 4.00 FF, 1.30 FF, 29.70 FF, and 29.55 FF for the HIV, HBV, *T. pallidum*, HC Abbott, and HC Pasteur kits, respectively. The sum of the HC Abbott and HC Pasteur test costs was used for the combined test. For the tests currently used in Bangui, the costs are those actually incurred by the CNTS; the costs of the HCV tests were based on price quotations from Abbott and Pasteur laboratories.

BASELINE ANALYSIS

The residual risks and the costs of screening strategies were computed at the decision node for four choices (i.e., no screening for HCV, screening for HCV with the Abbott assay, screening for HCV with the Pasteur assay, and screening for HCV with the combined Abbott and Pasteur assays. The software program MCSim, version 3.55^{21,22} was used.

Table 3 • Tree-computed Mathematical Expectations of Several Outcomes for Four Hepatitis C Screening Strategies*

| Outcome | Without HCV Test† | With HCV Pasteur Test† | With HCV Abbott Test† | With HCV Combined Test† |
|---------------------------------|-------------------|------------------------|-----------------------|-------------------------|
| Fraction total true positive | 0.30 | 0.35 | 0.35 | 0.34 |
| Fraction total false positive | 0.11 | 0.19 | 0.18 | 0.13 |
| Fraction total true negative | 0.49 | 0.41 | 0.42 | 0.47 |
| Fraction total false negative | 0.10 | 0.05 | 0.05 | 0.06 |
| Fraction of donations discarded | 0.41 | 0.54 | 0.53 | 0.47 |

*Screening tests for HIV infection, hepatitis B, and syphilis are always performed.

†In addition to HIV, HBV, and syphilis screening tests.

SENSITIVITY ANALYSIS

Sensitivity analyses of the residual risks and the costs of the screening strategies, with respect to parameter values, were performed to check the robustness of the conclusions of the baseline analysis. In one-way sensitivity analyses, the value of only one parameter was varied, all other parameters retaining their median values. In two-way sensitivity analyses, values of two parameters were varied. Parameters' values were randomly sampled from uniform distributions (or log-uniform for $cost_{inf}$) over their variation intervals according to the Monte Carlo method.^{23,24} One hundred numerical values were sampled for one-way sensitivity analyses and 1,000 for two-way sensitivity analyses.

UNCERTAINTY ANALYSIS

We also performed a multivariate uncertainty analysis by Monte Carlo simulations in which all parameters were sampled. The Monte Carlo simulations allowed us to estimate the distributions of the

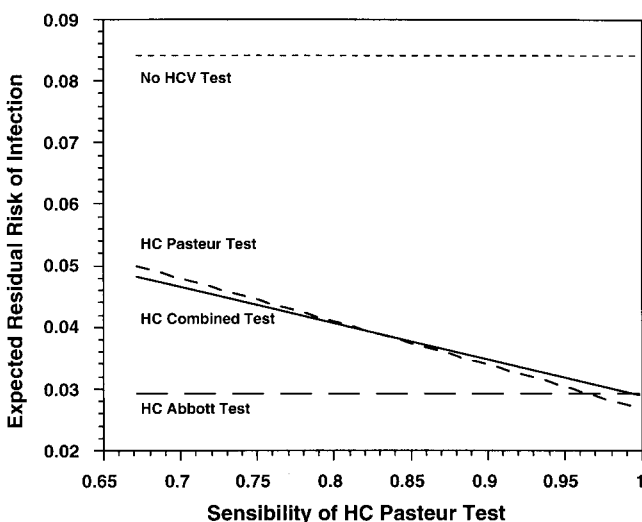


FIGURE 4. Influence of the HC Pasteur test sensitivity on the mathematical expectations of residual risk of infection by HIV, hepatitis B virus, *Treponema pallidum*, and hepatitis C virus for a blood donation delivered by the Centre National de Transfusion Sanguine of Bangui, Central African Republic.

residual risks or costs of screening strategies taking into account the uncertainty in all parameters. At each iteration, for each parameter, a value was randomly sampled with respect to its own distribution (beta for all parameters except for $cost_{inf}$ and the probabilities of transmission, which were assigned log-uniform or uniform distributions). As explained above, beta distributions were used because the posterior distribution of a parameter (such as prevalence, sensitivity, and specificity) determined from binomially distributed data is a beta distribution.¹⁴ Ten thousand Monte Carlo runs were performed.

The software program MCSim, version 3.55,^{21,22} was also used to perform the sensitivity and uncertainty analysis.

Results

BASELINE DECISION ANALYSIS

Part of the results of the baseline decision analysis are summarized in table 3. Even when no HCV test is used, about 41% (30% total true positive, 11% total false positive) of all blood donations are discarded because of positive test results for either HIV, HBV, or *T. pallidum*. About 10% of the donations are infectious for either HIV, HBV, or *T. pallidum* but not discarded because they are total false negatives. When Pasteur, Abbott, or combined tests are used, 54%, 53%, or 47% of donations are discarded, respectively. These correspond to relative increases (over the no-testing option) of 28%, 27%, and 11%, respectively. Total false-negative rates are halved, compared with the no-testing option. Testing would therefore largely reduce the risk of infection, particularly for HCV. However, this has a cost above that of test kits, since more donations would be rightly or wrongly discarded.

The residual risk of infection is estimated to be 8.4%, with 95% confidence intervals (CI_{95}) of [4.5–15.7] for no HCV screening test, 2.93% (CI_{95} : [0.96–8.8]) for the Pasteur test, 2.92% (CI_{95} : [0.97–8.3]) for the Abbott test, and 3.1% (CI_{95} : [1.3–9.1]) for the combined test. These confidence intervals were obtained

from the uncertainty analysis. According to the residual risks, with all parameters at their median values, the HC Abbott test would be marginally favored, closely followed by the Pasteur test. This comes from the fact that the estimated specificity for the HC Abbott test was a little higher than that for the HC Pasteur assay. Even though the proportion of false negatives is a little higher with the HC Abbott test than with the HC Pasteur test, preference is given to the latter because of its lower rate of false-positive results. Because of its parallel operationalization, the combined test, although more specific, is the least sensitive, and leads to a higher residual risk.

SENSITIVITY ANALYSIS

Residual risks of infection. One-way and two-way sensitivity analyses of the decision tree for all parameters demonstrated that residual risk essentially varies with the sensitivities of the HC Abbott and Pasteur assays, and to a lesser extent with their specificities.

Figure 4 shows that when the HC Pasteur test sensitivity goes from 0.65 to 1, the residual risk decreases from 5% to 3% when this test is used. The HC Pasteur assay is favored only if its sensitivity exceeds 96.5%. Another cross point is observed at abscissa 0.81, where the HC Pasteur test becomes preferable to the combined test, but it does not correspond to a change in strategy. Similar results are obtained when the HC Abbott test sensitivity is varied (data not shown), the HC Pasteur assay being favored only if the HC Abbott test sensitivity is below 96.5%. In addition, the HC Pasteur assay is favored when its specificity is better than HC Abbott specificity (i.e., greater than 86%), and vice versa (data not shown).

Costs of screening for HCV. One-way sensitivity analysis of the annual cost of screening for HCV showed that this cost depends mostly on the cost of infecting a recipient ($cost_{inf}$, equation 7). Because that cost is difficult to determine precisely in Central African Republic, we chose to study the economic criterion only through sensitivity and uncertainty analyses.

To obtain figure 5, all parameter values, other than $cost_{inf}$, were set at their median values (given in table 2). If $cost_{inf}$ is less than approximately 2,400 FF, $cost_{HCV}$ is minimal when no screening test is performed. Between 2,400 FF and 8,500 FF, $cost_{HCV}$ is minimal when the combined test is used. Above 8,500 FF, the HC Abbott test is preferred. The HC Pasteur test is never considered the optimal strategy.

Two-way sensitivity analyses of the annual costs of HCV screening showed that only six parameters ($cost_{inf}$, sensitivities and specificities of the HCV Pas-

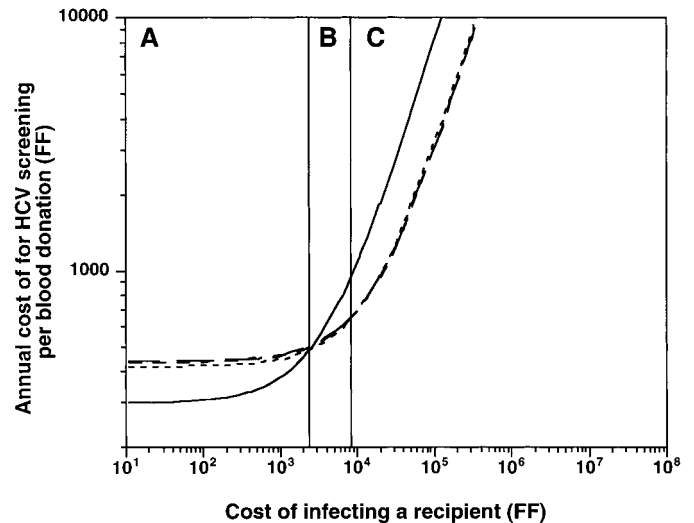


FIGURE 5. Influence of the costs of infecting a recipient on the mathematical expectations of the annual cost of screening one blood donation for hepatitis C virus (HCV), for various testing strategies. Strategies are: no HCV test (solid line), HC Abbott (long dashes), HC Pasteur Test (medium dashes), and combined test (short dashes). The strategies minimizing the total cost are "no HC test" in Area A, "HC combined test" in area B, and "HC Abbott test" in area C.

teur and Abbott tests, and HCV infectiousness prevalence) were able to influence the choice of testing strategy. For example, figure 6 shows the influence of Pasteur HCV specificity ($Sp_{HCV\text{Pasteur}}$) and $cost_{inf}$ on the choice of HCV screening strategy. If $cost_{inf}$ is less than approximately 2,400 FF, no screening test should be done. From 2,400 FF to 8,500 FF, the choice is somewhat complex: the best strategy is to screen with either the HC combined test or the HC Pasteur test, depending on $Sp_{HCV\text{Pasteur}}$. Above 8,500 FF, the best strategy also depends on $Sp_{HCV\text{Pasteur}}$, but the best choice is between the HC Abbott test and the HC Pasteur test.

The main conclusions of the two-way sensitivity results of $cost_{HCV}$, as a function of $cost_{inf}$ and either HC Pasteur or HC Abbott test specificities or sensitivities, can be summarized as follows: The best strategy is always not to perform any HC screening test if $cost_{inf}$ is less than 2,400 FF. Above 8,500 FF, the choice is between Abbott's or Pasteur's test, choosing the test with the better performances. From 2,400 to 8,500 FF, the choice is between the combined test and either Abbott's or Pasteur's, depending on the test performances.

The prevalence of HCV infectiousness can also influence the choice of strategy if $cost_{inf}$ is between 2,000 FF and 20,000 FF (figure 7). For example, for a $cost_{inf}$ of 2,000 FF, at low prevalence, the best strategy is not to perform an HCV screening test (in this case Abbott's, since all other parameters were set at their median values), while at high prevalence, the best strategy is to screen with the combined test.

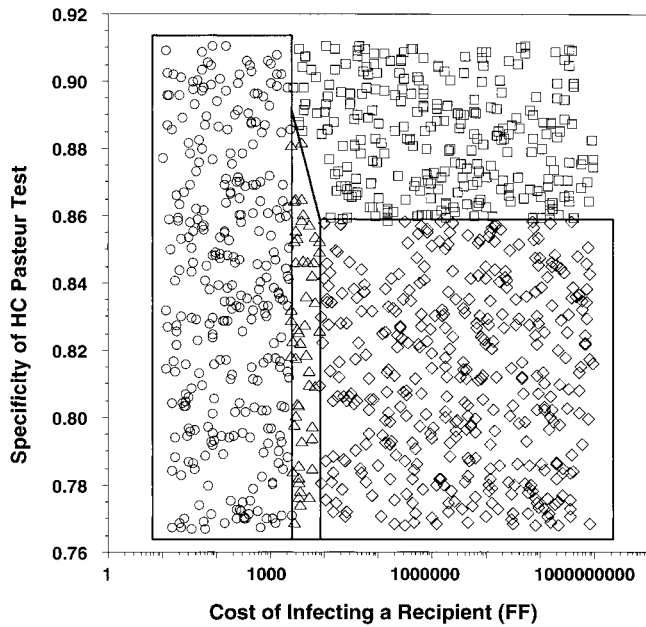


FIGURE 6. Influences of variations of the cost of infecting a recipient and of the HC Pasteur specificity test on the choice of screening strategy, with the annual cost per blood donation as decision criterion. Circles indicate that the best strategy choice is no HC test; squares correspond to HC Pasteur test, diamonds to the HC Abbott test, and triangles to the HC combined test.

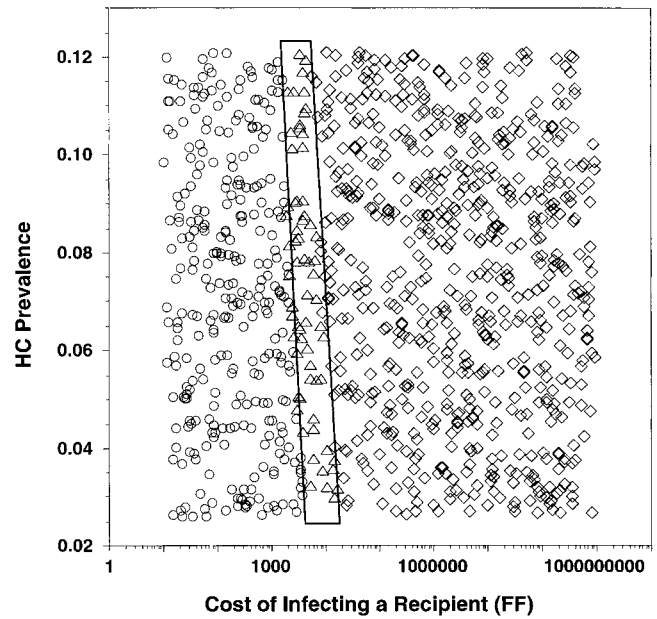


FIGURE 7. Influences of variations of the cost of infecting a recipient and of prevalence of hepatitis C (HC) infectiousness on the choice of screening strategy, with the annual cost per blood donation as decision criterion. Circles indicate that the best strategy choice is no HC test; diamonds correspond to the HC Abbott test, and triangles to the HC combined test.

UNCERTAINTY ANALYSIS

The Abbott and Pasteur tests for HCV have comparable sensitivities and specificities. As we demonstrate above, a change in strategy choice occurs each time the value of a parameter for a given test is close to the value of the same parameter for the other test. Because of the large uncertainty in these parameter values, results and decisions could be different from one study to another. That is why we analyzed the uncertainty affecting the decision criteria and estimated the probabilities of occurrence of the different strategies, given the uncertainties in the basic tree parameters (as specified in table 2 and the methods section). According to the residual-risk-

of-infection criterion, the probability to choose, as the best strategy, the HC Abbott or the HC Pasteur test was estimated to be 50.5% or 49.5%, respectively. This indicates that those two tests have about equal probabilities of being the best test. Uncertainty analysis results of the economic criterion are summarized in table 4. For example, if the cost of infecting a recipient is very high, about 10^7 to 10^8 FF, the HC Abbott test has a probability of 0.52 of being the best strategy. In summary: with $cost_{inf}$ under 1,000 FF, it is certain that no test should be performed. Between 1,000 and 10,000 FF, no test is still most likely to be the best option. Above 10,000 FF, either Abbott's or Pasteur's test could be chosen with equal probabilities of making an optimal decision.

Table 4 • Probabilities for Different Screening Strategies to be Optimal, with the Annual Cost of Screening One Blood Donation for Hepatitis C Virus as Decision Criterion

| Value of $Cost_{inf}^*$ | Without HCV Test† | With HCV Pasteur Test‡ | With HCV Abbott Test‡ | With HCV Combined Test‡ |
|-------------------------|-------------------|------------------------|-----------------------|-------------------------|
| 10–1,000 FF† | 1.0 | 0.0 | 0.0 | 0.0 |
| 1,000–10,000 FF | 0.39 | 0.19 | 0.22 | 0.20 |
| 10,000–100,000 FF | 0.0 | 0.45 | 0.47 | 0.08 |
| 100,000– 10^6 FF | 0.0 | 0.50 | 0.49 | 0.01 |
| 10^6 – 10^7 FF | 0.0 | 0.50 | 0.50 | 0.0 |
| 10^7 – 10^8 FF | 0.0 | 0.48 | 0.52 | 0.0 |

*Cost of infecting a donation recipient.

†In addition to HIV infection, hepatitis B, and syphilis screening tests.

‡French francs. The franc is equal to approximately U.S. 16¢.

Discussion

A technical point of this analysis concerns our choice of infectiousness measures. Optimal estimates of the residual risks of transfusion-transmitted infection should account for infectious donations made in the window period between the initial infection and detectable seroconversion. Because of technical limitations, this has been achieved in the present study only for HIV (through the use of p24-antigen detection) and for HCV (by TR-PCR). For HBV the reference assay used is close to optimal, but for the detection of syphilis the assay might be improved. In any case, the possible underestimation of infectiousness prevalences for HBV and *T. pallidum* should be very small and should not perceptibly affect our results.

We evaluated assays with an African blood panel in order to take into account African sera particularities and to get better estimates of the risks of blood-transmitted infections in Central African Republic. Usually reported assays' performances are not obtained with African blood panels. In addition, the dependence of the optimal decision choice on HCV prevalence (shown by sensitivity analysis) warrants, a posteriori, an analysis specific to the country or geographic area concerned. Our estimates of the tests' sensitivities and specificities are lower than the nominal values, showing the importance of using field conditions for test performance evaluation. Notice that the confidence intervals for the sensitivities are quite large. In order for the CI_{95} to span only 0.1, about 3,000 blood samples would have had to be analyzed. To estimate specificity with the same precision, about 230 samples would be needed. It was not possible to obtain very good precision with respect to sensitivity, because we had only 100 samples.

We used a rather large decision tree, and considered not only hepatitis C but also other infections already screened for in the current testing procedure. We included the other infections to estimate total transfusion risk and to estimate the incremental gain yielded by HCV screening. The tree was also built so as to be able eventually to take correlations into account. However, our data do not point to large correlations between the infectiousness statuses in our population.

There could be several ways to define outcomes for our decision tree. The estimates of residual risk reported here represent the probability that a blood donation delivered by the CNTS of Bangui infects a recipient with at least one of the four agents (i.e., HIV, HBV, *T. pallidum*, and HCV). Although, the resulting diseases differ in severity, we take the position that no infectious disease should be transmitted by blood transfusion and considered all infections jointly. The second outcome considered, the cost of

HCV screening, is closely related to residual risk (see equations 3–5). A major difference, aside from the introduction of monetary costs, is that residual risk is based on the probability of infecting a recipient with at least one of the four infectious agents studied, while the cost of screening is derived from the probability of infecting a blood recipient not yet infected. In our view, the risk estimate should be independent of the status (naive infected) of the transfusion receiver, since receiver status is not known in advance, and may even never be known. On the other hand, the cost of infecting a recipient does depend on the status of that recipient. We considered here that reinfecting a recipient with an already acquired infection brought no additional cost. This is obviously oversimplification of the reality. Our economic analysis is rather crude and could be improved in many ways with further research. Economic studies to better estimate the economic consequences of transfusion-transmitted infection of recipients would allow better evaluation of the cost of screening strategies. The use of the MCSim program, written in C, allowed us to quickly solve the tree and perform extensive Monte Carlo simulations (10,000 Monte Carlo runs of the tree take a few minutes on a Power PC Macintosh machine).

The prevalences of HIV infection, hepatitis B, syphilis, and hepatitis C observed among blood donors are very high (from 6% to 15%) in Central African Republic. These findings are similar to those of other investigators in the same area.^{2–5,25–28} As mentioned above, the results of the screening tests performed locally were somewhat disappointing. As a result, the proportion of blood donations discarded because of test results positive for HIV, HBV, or *T. pallidum* is considerable (about 41%) in the CNTS of Bangui. Despite that screening, the current residual risk of transfusion-transmitted infection is very high (8.4% with CI_{95} : 4.5–16%). The infectiousness prevalence of HCV is close to 6% among blood donors, and the transfusion risk for contamination with HCV is currently correspondingly high. Screening for HCV (in addition to HIV, HBV, and *T. pallidum*) could reduce the residual risk by about 60%, bringing it down to values close to 3% with either the HC Pasteur, the HC Abbott, or the combined test. This would be at the cost of discarding additional true-positive and false-positive donations.

Even though baseline analysis gives preference to the HC Abbott test (the combined test coming out last), sensitivity and uncertainty analyses showed that the Abbott and Pasteur tests are in fact interchangeable, on the basis of either risk or cost considerations. These tests minimize residual risk and thus the cost of screening strategies when infecting a healthy person is costly for society. If the prices of these two tests were different, it would be possible

to determine between them. The status of the combined test is interesting. This test was devised to have increased specificity compared with either the Abbott or Pasteur test. In a context of expensive blood collection (as in Bangui) an increase in specificity, leading to a lower rate of false-positive test results, would be an economic advantage. The use of the Abbott or the Pasteur test would be associated with an increase of about 27% in discarded blood donations, while the combined test would increase discards by only about 11%. However, the combined test has lower sensitivity than either single test, and it leads to a higher risk of infection; the test itself is also twice as costly. As a result, our cost analysis shows that the combined test is the best strategy only if the cost of infecting a recipient is between 2,400 FF and 8,500 FF.

Additional strategies for HCV screening, in particular tests based on different principles, could be evaluated in the future by extending our decision tree. For example, the so-called "rapid" tests developed in Japan appear to be efficient, cheap, and easy to perform.²⁹ Unfortunately, "rapid" test kits were not yet commercially available at the time of this study.

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