



Hold everything! Holding policies for protecting plasma supplies

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Abstract

In spite of advances in testing technologies for detecting infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), occasionally blood or plasma is collected that is potentially infectious, but is not detected as such by existing screening tests. We consider the effect of a holding policy for further reducing the number of potentially infectious units that are released for fractionation. The policy dictates a holding period during which all donated units are stored. If a donor tests positive for the infection in question at a subsequent donation, then all of that donor's units currently in storage are discarded. Otherwise, donated units are released at the end of the holding period. In the case of a single disease, we determine optimal holding periods as well as policies that are as effective as the best screening tests currently available. © 1999 Elsevier Science Inc. All rights reserved.

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1. Introduction

In spite of advances in testing technologies for detecting infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C

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virus (HCV), occasionally potentially infectious blood or plasma is collected but not detected by existing screening tests. Such false negative results occur primarily because of the delay between the onset of infectiousness and the ability of a screening test to detect the infection [1,2]. For example, the window period between the onset of HIV infectiousness and the ability of a recombinant HIV-1/2 combination enzyme-linked immunoassay (EIA) test to detect HIV antibodies is estimated to average 22 days [3–5]. As a result of this window period, blood or plasma donors infected within a few weeks prior to the date of donation may not test positive for HIV.

To reduce the likelihood of admitting infectious donations, many have argued for the implementation of more sensitive (and more expensive) screening tests. For example, the p24 antigen assay used to screen blood donations for HIV since 1996 has reduced the window period to about 16 days [3,5,6]. In the United States, the incremental cost of p24 screening has been estimated to equal nearly \$60 000 000 annually [7]. The estimated return on this investment in HIV prevention has been modest. For example, it was estimated that only eight transfusion-related cases of HIV were averted as a result of p24 screening, with a cost-effectiveness ratio of \$2 281 000 per quality adjusted life year compared to HIV antibody testing alone [7].

In the US, blood donation is a voluntary activity where donors receive no financial rewards. Blood donors are also unable to donate more frequently than once every two months on average to allow for the regeneration of red blood cells. By contrast, source plasma donors are typically paid between \$15 and \$20 per donation, and are able to donate as often as twice per week because during plasmapheresis, red blood cells are reinfused into plasma donors. It therefore might be expected that plasma donors have an incentive to hide known risk factors for infection, leading to a riskier donor pool. Indeed, disease incidence rates for paid plasma donors are much higher than for voluntary blood donors (e.g. HIV incidence among voluntary repeat blood donors has been estimated as 3.3/100 000/yr, while HIV incidence among paid plasma donors was estimated as 61.8/100 000/yr, almost a factor of 20 greater [5]). Given that source plasma donations are pooled via fractionation to create usable products such as Factor VIII (critical in the treatment of hemophilia) and albumin (for the treatment of burns, shock and trauma), infectious plasma donations could conceivably contaminate large pools of finished product, placing those dependent on plasma products at risk for various infections. In addition, the plasma obtained from paid donors in the United States is used to meet demands both in the US as well as in many foreign countries.

The source plasma industry has implemented viral clearance techniques such as heat treatment with the goal of inactivating any infectious virus that enters the supply [5,8]. Properly conducted, these methods can inactivate serious viruses (such as HIV, HBV and HCV) that have somehow entered the supply.

However, the Food and Drug Administration (FDA) has discovered numerous quality control lapses in the plasma industry's implementation of viral clearance techniques. Violations include failure to properly sterilize containers used for plasma processing, the use of invalidated software for evaluating plasma tests, and delays in reviewing reports of problems with distributed plasma. As a result, it is important to reduce the number of potentially infectious units released for viral clearance processing even though these processes theoretically remove all risk of disease transmission [5].

Indeed, plasma consumer advocates have expressed the desire that the 'input' to the plasma processing system should be as safe as donations that enter the whole blood supply. One approach might be to create an all-volunteer plasma donation system. Instead, the plasma industry has responded with a series of filters, such as accepting donations only from repeat donors (the whole blood system uses donations from first time donors), screening for infectious diseases, and a 60 day holding period on all donated units. Under a holding policy, all donated units are stored before being released for fractionation. If a donor tests positive for the infection in question at a subsequent donation, then all of that donor's units currently in storage are discarded. Otherwise, donated units are released at the end of the holding period [5]. The benefits of such a policy are that undetected but potentially infectious donations in storage will be discarded upon the detection of subsequent positive donations made by the same donor. However, uninfected units in storage will also be discarded (and hence wasted), while there is also a cost for freezing (or refrigerating) and storing donated units over time, as well as other costs involving assurance that the holding period has passed before a donation is released. Similar holding policies are not commonly used for blood donors due to the high cost of processing whole blood before and after freezing.

Note that under a holding policy, units are only discarded given confirmatory evidence of infection (e.g. a positive test for HIV). This is different from a *quarantine* policy. With quarantine, donated units are also held, but at the end of the holding period, the donor must make a subsequent donation that tests negative for all screened infections before the original donated unit is released for fractionation. Holding policies thus retain donated units unless proof of infection is obtained, while quarantine policies discard donated units unless such units are shown to be free of infection. Even though the risk of releasing an infectious donation for further processing must be greater for holding policies than for quarantine, it is also true that quarantine would require discarding many more donated units, most of which would be healthy (and hence wasted). For this reason, the plasma industry uses a holding policy as opposed to a quarantine.

In this paper, we focus on the impact of holding policies for reducing the number of potentially infectious units that are released for fractionation. Our analysis is rooted in a renewal process model of plasma donation in the

presence of a single infectious disease; this model is described in Section 2. Following this, we add a holding policy to the donation process, and determine the probability of interdicting undetected infectious donations, as well as the probability of interdicting (and hence wasting) uninfected units. In Section 4, we determine the expected total storage time of both infectious and uninfected donations. Section 5 formulates and solves the problem of selecting the optimal holding period according to the economic criterion of maximizing the difference between the benefits and costs of the policy. Useful approximations are developed that qualitatively explain the behavior of the optimal holding period as a function of the underlying model parameters. An alternative approach to selecting holding periods is explored in Section 6, where holding policies are devised that either deliver the same benefit or assume the same cost as more sensitive screening tests. The paper concludes with a summary of our results and some suggestions for further work.

2. A renewal process model of screened plasma donation

We assume that all donations are screened for the presence of infection, and only those donations that test negative are released for further processing. A new donor makes the second of two *qualifying donations* at time 0 (donations are only accepted from repeat donors; qualifying donations are used to establish donor eligibility via two consecutive negative screening tests [5]). In a disease-free world (or alternatively, if donations were not screened for infection), the new donor would continue to donate over a lifetime (or career) of (random) duration L as measured from the time of the second qualifying donation. In the absence of disease, all subsequent donations occur in accord with a renewal process with interdonation times independently and identically distributed as random variable T (independent of L) over the course of the donation career.

However, there is an infectious disease circulating in the population with a constant incidence rate (or hazard rate) λ . Consequently, the random variable H , which measures the time from the second qualifying donation until the onset of infectiousness, is exponentially distributed with mean $1/\lambda$ (independent of L and T).

To test for the presence of the infectious disease, all donations are screened. The (random) time from the onset of infectiousness until the infection becomes detectable, known as the *window period* and denoted by W , is assumed to be independent of the random variables H , L and T . A donation that tests positive ends a donation career (and the contaminated plasma is discarded).

Relying solely on a screening test with a window period of W fails to detect some potentially infectious donations. In particular, it is well known that the probability that a donation is potentially infectious (i.e. in the window period),

given that it has tested negative on the screening test, is very well approximated by [1,2]

$$\Pr \{\text{Infectious donation} \mid \text{Negative Screening Test}\} = \iota E(W) \quad (2.1)$$

(where $E(\cdot)$ denotes mathematical expectation).

3. Interdicting donated units under a τ -period hold

From Eq. (2.1), some number of undetected infectious donations can be expected to be released for fractionation. The success of any screening test at detecting infectious donations relies crucially on the duration of the associated window period. Reducing the duration of the window period both reduces the expected number of undetected infectious donations and increases the probability of detecting a positive donation over the course of a donation career. However, reducing window periods is not a simple matter. Different markers of infection (e.g. HIV antibody versus p24 antigen versus PCR for HIV RNA) admit different characteristic window periods, requiring the design (and optimization) of marker-specific screening tests, some of which are quite expensive to administer on a test per donation basis.

A policy alternative to the design of more sensitive (but more expensive) screening tests is a τ -period hold for all donated units. The policy is simple: *hold everything!* Focusing on a particular repeat donor, all donated units are stored for a *holding period* τ . If the donor in question tests positive at any time, then *all* of that donor's units currently in storage are discarded. Otherwise, donated units are released for further processing τ time units following their date of donation [5].

3.1. The probability of interdicting an undetected infectious unit

As a function of the holding time τ , what is the probability that an undetected infectious donation would be interdicted and hence averted from further processing? Let $I(\tau)$ denote the event that a randomly selected donation is interdicted under a τ -period hold, given that the donation is infectious but undetected by the screening test. For this event to occur, first note that the donation in question must have occurred during the window period (for if the donation occurred prior to the window period, it would not be infectious, while if the donation occurred after the expiration of the window period, it would have been detected by the screening test). Second, for a window period donation to be interdicted by a holding policy, the window period must expire, and then a subsequent donation (which would test positive since the window period will have expired) must occur. Both the expiration of the window period and the subsequent donation, however, must occur before the holding period runs out and before the donation career itself ends.

Since the window period donation took place at random relative to the time the donor became infectious, the window period sampled is *length biased* [9], implying that the remaining time in the window period will be distributed according to the equilibrium forward recurrence time of the window period [9]. That is, if W^* denotes the remaining duration of the window period, then the probability density function for W^* , $f_{W^*}(x)$, is given by [9]

$$f_{W^*}(x) = \frac{\Pr\{W > x\}}{E(W)} \text{ for } x \geq 0. \quad (3.1)$$

Once the window period expires, the time to the next donation will be distributed as the remaining time in the interdonation interval entered at time W^* following the window period donation. This corresponds to the forward recurrence time in an ordinary renewal process that has been operating for W^* time units [9]. However, since the mean interdonation time for paid plasma donors is short (5.3 days [5]) relative to the mean window period (22 days for HIV antibody [3–5]), this recurrence time will approach the remaining life in a randomly entered interdonation interval [9]. Intuitively, the window period expires at a point in time that is essentially random relative to the time of the most recent donation. Let T^* be the remaining time from the end of the window period until the next donation. Using the limiting result, the density of this random variable can be written as

$$f_{T^*}(x) = \frac{\Pr\{T > x\}}{E(T)} \text{ for } x \geq 0. \quad (3.2)$$

Finally, note that the window period donation took place at random relative to the end of the donation career. Measured from the time of the window period donation, then, the remaining life in the donation career L^* will also be an equilibrium forward recurrence time with density given by

$$f_{L^*}(x) = \frac{\Pr\{L > x\}}{E(L)} \text{ for } x \geq 0. \quad (3.3)$$

Combining the arguments above we have

$$\Pr\{I(\tau)\} = \Pr\{W^* + T^* \leq \min(\tau, L^*)\}. \quad (3.4)$$

We can evaluate this expression as

$$\Pr\{I(\tau)\} = \int_{x=0}^{\tau} \int_{y=0}^{\tau-x} f_{W^*}(x) f_{T^*}(y) \Pr\{L^* > x + y\} dy dx. \quad (3.5)$$

3.2. The probability of interdicting an uninfected unit

Determining the probability of interdicting (and hence wasting) an uninfected unit as a function of the holding time τ proceeds in similar fashion.

Define the event that a donated unit is interdicted, given that it is not infectious, as $U(\tau)$. What must happen for an uninfected donation to be interdicted? First, the donor in question must become infected. The time from the date of donation until this occurs is given by H^* , for the donation occurs at a random time relative to the future date of infection. Given our assumption of constant disease incidence, the random variable H^* will be exponentially distributed with mean $1/i$. Second, upon infection, the window period of duration W must elapse. Third, the donor must make a subsequent donation (which will test positive due to the completion of the window); this requires an additional T^* units of time (as the window period expires at a time that is essentially random relative to the interdonation interval). All of these events must transpire prior to the completion of the holding period, or to the completion of the donation career. Combining these arguments we have

$$\begin{aligned} \Pr\{U(\tau)\} &= \Pr\{H^* + W + T^* \leq \min(\tau, L^*)\} \\ &= \int_{x=0}^{\tau} \int_{y=0}^{\tau-x} \int_{z=0}^{\tau-x-y} f_{H^*}(x) f_w(y) f_{T^*}(z) \\ &\quad \times \Pr\{L^* > x + y + z\} \, dz \, dy \, dx. \end{aligned} \tag{3.6}$$

4. Storing donated units under a τ -period hold

Interdicting (and wasting) uninfected units is one drawback of using a τ -period holding policy. The accumulated storage of donated units over time presents another problem. On average, how long are donated units kept in storage?

4.1. Storing infectious units

Let $S_1(\tau)$ denote the length of time undetected and infectious donated units are stored. Note that

$$S_1(\tau) = \begin{cases} W^* + T^* & \text{if } W^* + T^* \leq \min(L^*, \tau), \\ \tau & \text{if } W^* + T^* > \min(L^*, \tau). \end{cases} \tag{4.1}$$

To justify this equation, note that if an infectious unit is not interdicted, then it will be held for the entire holding period of duration τ . If the donation is interdicted, such interdiction occurs at the first donation following the expiration of the window period, that is, $W^* + T^*$ time units following the donation itself. These observations jointly imply 4.1.

The expected storage time for infectious donations is thus given by

$$E = [S_I(\tau)] = (1 - \Pr\{I(\tau)\}) \times \tau + \int_{x=0}^{\tau} \int_{y=0}^{\tau-x} (x+y) f_{W^*}(x) f_{T^*}(y) \Pr\{L^* > x+y\} dy dx. \quad (4.2)$$

4.2. Storing uninfected units

The calculations for uninfected units are similar. First note that donated units that are not interdicted are held for the entire holding period of duration τ . Uninfected units are interdicted only if the donor becomes infected, and a subsequent infectious donation is detected before the holding period expires and before the completion of the remaining donation career. Interdicted units are detected at the first donation following the expiration of the window period, which occurs at $H^* + W + T^*$ time units following the uninfected donation eventually trapped. Together these observations imply that the storage time for uninfected units, $S_U(\tau)$, is given by

$$S_U(\tau) = \begin{cases} H^* + W + T^* & \text{if } H^* + W + T^* \leq \min(L^*, \tau), \\ \tau & \text{if } H^* + W + T^* > \min(L^*, \tau). \end{cases} \quad (4.3)$$

The expected storage time for uninfected units is thus given by

$$E[S_U(\tau)] = (1 - \Pr\{U(\tau)\}) \times \tau + \int_{x=0}^{\tau} \int_{y=0}^{\tau-x} \int_{z=0}^{\tau-x-y} (x+y+z) f_{H^*}(x) f_w(y) f_{T^*}(z) \times \Pr\{L^* > x+y+z\} dz dy dx \quad (4.4)$$

4.3. Expected total storage

For a random donation that has screened negative, the storage time $S(\tau)$ is given by

$$S(\tau) = \begin{cases} S_I(\tau) & \text{with probability } iE(W) \\ S_U(\tau) & \text{with probability } 1 - iE(W) \end{cases} \quad (4.5)$$

and thus the expected storage time per donation is given by

$$E[S(\tau)] = iE(W) \times E[S_I(\tau)] + (1 - iE(W)) \times E[S_U(\tau)]. \quad (4.6)$$

5. Finding the optimal holding period τ^*

Having derived expressions for the probability of interdicting an undetected infectious donation ($\Pr\{I(\tau)\}$), the probability of interdicting an uninfected donation ($\Pr\{U(\tau)\}$), and the expected storage time per donation ($E[S(\tau)]$), we now consider approaches for selecting appropriate holding periods τ to balance the costs and the benefits. Suppose that we assign a benefit b to each undetected infectious donation interdicted and hence averted, a cost c_w to each uninfected unit interdicted and hence wasted, and a cost c_s per donated unit held in storage per unit of time. Then the expected net benefit of a τ -period hold, denoted by $\beta(\tau)$, is given by

$$\beta(\tau) = b \times \iota E(W) \times \Pr\{I(\tau)\} - c_w \times (1 - \iota E(W)) \times \Pr\{U(\tau)\} - c_s E[S(\tau)]. \tag{5.1}$$

A plot of this function appears in Fig. 1 under the following epidemiological assumptions: the duration of a donation career L is exponentially distributed with a mean of 2 yr; donations occur in accord with a Poisson process with rate

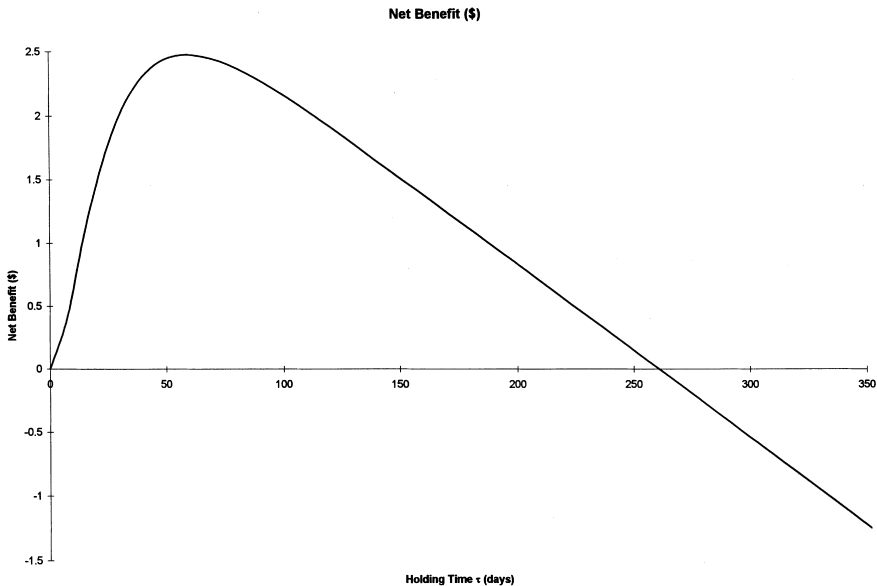


Fig. 1. Net benefit of holding policies up to one year in duration for assumptions representing paid plasma donors in the US: the duration of a donation career L is exponentially distributed with a mean of 2 yr; donations occur in accord with a Poisson process with rate 68.9 donations per year; the window period W is exponentially distributed with a mean of 22 days; and the incidence rate of HIV ι is 0.000618 infections per uninfected person per year. Also, $b = \$100\ 000$, $c_w = \$50$, and $c_s = \$5/\text{year}$.

68.9 donations per year (so T is exponentially distributed with mean 5.3 days); the window period W is exponentially distributed with a mean of 22 days; and the incidence rate of disease $\iota = 0.000618$ infections per uninfected person per year. These assumptions are roughly descriptive of HIV infection among US paid plasma donors [5]. In addition, Fig. 1 assumes that $b = \$100\,000$ (to be explained below), $c_w = \$50$ (the plasma industry pays donors roughly \$20 per donation [5], but sells recovered plasma to hospitals at an average of \$50 per unit [10]), and $c_s = \$5$ per year [10]. The optimal holding period τ^* is defined as the (nonnegative) value that maximizes the net benefit function $\beta(\tau)$, that is, τ^* is the solution to

$$\max_{\tau \geq 0} \beta(\tau). \quad (5.2)$$

For the example of Fig. 1, $\tau^* = 0.1629$ years or about 60 days, the holding period actually implemented by the US plasma industry [5]. The probability that a screened negative donation is actually infectious equals $\iota E(W) = 37$ per million. The holding policy serves to interdict 88.5% of these undetected infectious donations. The net benefit of this holding policy amounts to roughly \$2.50 per donation under the stated assumptions.

Note that under the assumptions that $c_w = \$50$ and $c_s = \$5/\text{year}$, this result reveals an *implicit valuation* by the plasma industry: preventing a potentially infectious donation from undergoing further processing is worth \$100,000. We are *not* suggesting that the plasma industry has actually chosen a holding period of 60 days based on such calculations. Rather, *if* the model above was used to select the holding period, *then* it must be that, given the other parameters considered, preventing a potentially infectious donation from entering fractionation is worth \$100,000.

A sensitivity analysis is presented in Fig. 2, which reports the optimal holding periods that result as a function of varying both the benefit per potentially infectious donation interdicted (b) and the storage cost per donated unit held per unit time (c_s), keeping the other parameter values assumed in Fig. 1 constant. The optimal holding times in this Fig. range from 20 days (when $b = \$50\,000$ and $c_s = \$15/\text{year}$; 47% of undetected infectious units are interdicted) to 113 days (when $b = \$250\,000$ million and $c_s = \$1/\text{year}$; 96% of undetected infectious units are interdicted).

5.1. Approximating the optimal holding period

Though there is no problem determining optimal holding periods numerically, it is difficult to see the dependence of the optimal holding period on the model parameters. However, it is possible to approximate the net benefit function $\beta(\tau)$ in a way that admits simpler expressions for τ^* . Doing so requires the following additional assumptions:

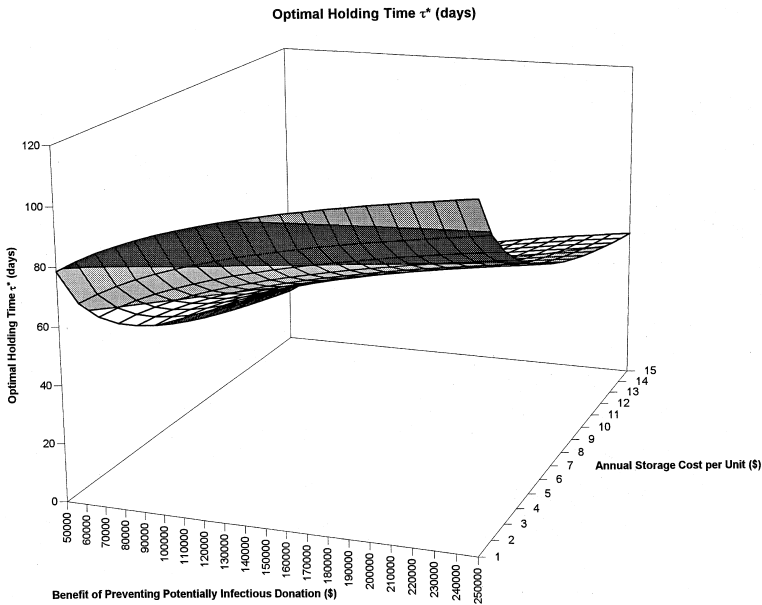


Fig. 2. Optimal holding periods τ^* as a function of the benefit per infectious donation averted (b) and the storage cost per donated unit per year (c_s) with the other model parameters fixed as in Fig. 1.

(i) The expected total cost of wasting uninfected units ($c_w(1 - iE(W)) \Pr\{U(\tau)\}$) is negligible relative to the expected total benefit of interdicting undetected infectious units ($biE(W) \Pr\{I(\tau)\}$). Though the number of uninfected units wasted will exceed the number of infectious units interdicted, the benefit of preventing a serious infection (such as HIV or HBV) is much greater than the cost of wasting a healthy unit.

(ii) The expected total storage time for all donations approximately equals the holding period τ , that is, $E[S(\tau)] \approx \tau$. The number of infectious units held is negligible relative to the number of uninfected units, while the overwhelming majority of uninfected units stored are held for τ periods.

(iii) The duration of a donation career (L) is sufficiently large relative to the holding period to enable the approximation $\min(L^*, \tau) \approx \tau$.

(iv) Interdonation intervals are small relative to the duration of the window period. This approximation reflects the situation with paid plasma donors where weekly donations are not uncommon [5].

To proceed, consider the expression for $\Pr\{I(\tau)\}$ shown in Eq. (3.4). Assumptions (i)–(iv) above combine to yield

$$\Pr\{I(\tau)\} \approx \Pr\{W^* \leq \tau\} \tag{5.3}$$

and consequently

$$\beta(\tau) \approx bI E(W) \Pr\{W^* \leq \tau\} - c_s \tau. \quad (5.4)$$

Differentiating the expression above with respect to τ and equating the result to zero (and recalling the density function for W^* from Eq. (3.1)) yields an approximate optimal holding period $\tilde{\tau}^*$ as the solution to

$$bI \Pr\{W > \tilde{\tau}^*\} = c_s. \quad (5.5)$$

If one assumes that the window period follows an exponential distribution (as we assumed in the example of Fig. 1), we obtain the explicit solution

$$\tilde{\tau}^* = E(W) \log \left(\frac{bI}{c_s} \right), \quad (5.6)$$

which suggests that the optimal holding period is a constant multiple of the mean window period. The holding period should clearly increase with increasing incidence rates and benefit valuations, and decline with increasing storage costs. For the example of Fig. 1, $\tilde{\tau}^* = 0.1515$ years or 55 days (in contrast to the ‘exact’ solution $\tau^* = 60$ days).

6. Holding period equivalents to sensitive screening tests

Selecting a holding period via maximizing net benefits requires the assignment of a dollar value to the prevention of an infectious donation. Of course, determining the numerical value of such a benefit measure can be controversial. A different approach is to consider holding periods that yield equivalent benefits to alternative policies for preventing infectious donations, and then compare the costs of the holding policies to the costs of the alternatives. If a holding policy can prevent the same expected number of infectious donations at a lower cost than some alternative approach, then the holding policy is the more efficient of the two. Alternatively, one can simply fix the budget, and compare the expected number of potentially infectious donations prevented by competing policies.

A great deal of emphasis in recent years has been placed on the development of more sensitive screening tests. By focusing on different markers of infection, different tests create different window periods during which false negative tests will result (and potentially infectious donations will be released for further processing). The shorter the window period, the more sensitive the screening test.

Consider the current screening test as the ‘old’ test with an average window period of $E(W_{\text{old}})$. Recall from Eq. (2.1) that the probability a screened negative donation is infectious is given by

$$\Pr\{\text{Infectious donation} \mid \text{Negative Screening Test}\} = \iota E(W_{\text{old}}). \quad (6.1)$$

Suppose that a new screening test is available that reduces the expected duration of the window period from $E(W_{\text{old}})$ to $E(W_{\text{new}})$, but at an additional cost over the old test of $\$k$ per donation screened. Denote the incremental reduction in the probability that an infectious donation goes undetected by R , and note that

$$E(R) = \iota[E(W_{\text{old}}) - E(W_{\text{new}})]. \quad (6.2)$$

To determine a holding policy that would yield the same prevention benefits requires finding that value $\tilde{\tau}$ that solves the equation

$$\iota E(W_{\text{old}}) \Pr\{I(\tilde{\tau})\} = E(R) \quad (6.3)$$

or equivalently

$$\Pr\{I(\tilde{\tau})\} = \frac{E(W_{\text{old}}) - E(W_{\text{new}})}{E(W_{\text{old}})}, \quad (6.4)$$

where $\Pr\{I(\tilde{\tau})\}$ is computed using W_{old} . Note that incremental to the cost of using the old screening test, the cost per donation will approximately equal $c_s \tilde{\tau}$ for the holding policy and k for the new screening test.

As an example, consider the case of HIV infection among paid US plasma donors. We retain the epidemiological parameters and distributional assumptions used in Fig. 1 [5]. The ‘old’ screening test used is the EIA antibody screen with a window period assumed exponentially distributed with a mean of 22 days. The ‘new’ screening test is the polymerase chain reaction (or PCR) test for HIV RNA. This test can reduce the window period to approximately 11 days [3,5,7]. We will assume that PCR costs an incremental $\$8$ per donation beyond antibody testing [7], which reflects either the use of a fully automated procedure, or perhaps mini-pools of size 150 units [10]. We recognize that using PCR to test individual donations would cost more, perhaps as much as $\$50$ per test [11]. Of course, this would only serve to make the holding policy more attractive by comparison.

Employing PCR can thus be expected to reduce the probability that a potentially infectious donation escapes detection by 50%. In this example, solving equation 6.4 yields the result $\tilde{\tau} = 21$ days. This holding policy also reduces the probability that an infectious donation escapes detection by 50%. However, the approximate expected cost per donation is only 29 cents, more than a factor of 25 reduction in cost.

Alternatively, suppose officials had already considered spending an incremental $\$8$ per donation for PCR screening. If this money were instead invested in a holding policy on top of regular ELISA testing, it would be possible to implement a 1.6 yr hold (as follows from noting that $E[S(\tau)] \approx \tau$, and then setting $c_s \tau = \$8$). Doing so would prevent 96.4% of the current number of potentially infectious donations, again rendering the holding policy more cost

effective than PCR screening in spite of the near factor of 10 increase in the inventory level of stored plasma that would result.

7. Summary and suggestions for further work

This paper has analyzed the performance of holding policies via a renewal process model of plasma donation. We have shown how to compute the probability that a holding policy will interdict a previously undetected but potentially infectious donation, the probability that a holding policy will interdict and waste an uninfected donation, and the expected storage time per donation. We then showed how optimal holding periods can be selected to maximize the difference between the benefits of preventing infectious donations and the costs of wasting uninfected units and storing donated units over time. We also showed how to select holding period equivalents to more sensitive screening tests by choosing holding periods to match either the benefits or the costs of the new screen. In the example we considered where parameters were chosen to correspond to the current state of the US plasma industry, the holding policy was more cost effective than PCR screening for detecting HIV infection among paid plasma donors.

While this paper has generated several analytical results, we only considered the impact of a holding policy in the context of a single infection. In practice, plasma donations are screened for several infections. The natural extension of the analysis would be to consider the impact of a holding policy on the *simultaneous* prevention of different infections (such as HIV, HBV and HCV). Determining the expected number of interdicted infectious donations of different types would be more challenging owing to correlations in the infection processes of different diseases, and the different window periods associated with infection-specific screening tests.

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