

Evaluating plasma holds in the presence of multiple infections

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To protect plasma supplies, donors are screened for infectious diseases. As an added measure of protection, donations are identified and stored for a period of time to allow future discard in the event that an identified donor subsequently tests positive for some screened disease. Previous models for evaluating such plasma holds have only addressed the case of a single infectious disease. This paper extends the analysis to the case of multiple infections. Given knowledge of the marginal incidence rates for those infections checked, upper and lower bounds for important quantities such as the probability of interdicting an infectious but undetected donation, the expected number of infections interdicted per donation, and the net economic benefits of the holding policy are developed. Several examples are developed, illustrating how the models can be used to evaluate the consequences of a plasma hold.

Keywords: Plasma donor screening; holding policy; renewal theory; coinfection; linear programming.

1. Introduction

Donations to blood and plasma supplies are routinely screened for infectious diseases to prevent subsequent infections in the recipients of blood or blood products. As an added precaution, the US plasma industry has instituted a holding policy. Plasma donations that screen negative for all infections checked are placed in storage for some period of time referred to as a holding period (60 days in the USA). If a donor tests positive for any of the diseases in question, then all prior donations from that donor currently in storage are discarded along with the newly identified donation. Donated units that last through the holding period without being discarded are released for further processing (GAO, 1998).

Kaplan & Satten (1999, henceforth KS) developed a model for evaluating plasma holds in the case of a single disease. The present paper extends the models of KS to the more realistic case where plasma donors are screened for several infections. Following a brief review of the single infection model, a stylized model where infections with different viruses are mutually exclusive (any donor can be infected with at most one infection) is introduced. This framework is used to develop a model of coincident infections, whereby donors can be infected with any combination of the diseases under consideration. Given marginal estimates of disease incidence rates and a particular holding period, it is possible to place upper and lower bounds on quantities such as the probability of interdicting

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an infectious donation, the expected number of infections averted per donation, and the expected net benefits associated with the holding policy. Several examples utilizing data from a study of the US plasma supply (GAO, 1998) are provided.

2. Review of the single infection model (Kaplan & Satten, 1999)

Consider a single infection circulating among plasma donors with constant incidence rate ι . A screening test is used to check donors for this infection. The test is assumed to be perfectly specific (that is, no false positive errors), but false negative results can arise as follows: associated with the test is a (random) window period denoted by W . The window period is the time that must pass from the onset of infectiousness with the disease until the test can detect the presence of infection. Recently infected donors will falsely test negative if the window period has not expired at the time of donation.

Plasma donors are assumed to donate in accord with a renewal process (Cox, 1962). The (random) time between successive donations for a given donor is denoted by T . Donors continue to provide plasma over a donation career with (random) duration L . The non-negative random variables W , T and L are assumed to be mutually independent across donors (and donations for W and T) with probability density functions given by $f_W(x)$, $f_T(x)$, and $f_L(x)$, respectively. Associated with these random variables are the *residual lifetimes* (or *forward recurrence times*) denoted by W^* , T^* and L^* . The residual window period W^* , for example, represents the remaining time until the end of a randomly entered window period, and has probability density

$$f_{W^*}(x) = \frac{\Pr\{W > x\}}{E(W)} \text{ for } x \geq 0 \quad (2.1)$$

where $E(W)$ denotes the expected duration of the window period; see KS for details.

All donations are screened, and only those donations that test negative are considered for further processing. An excellent approximation for the conditional probability that a donation that has tested negative is actually infectious is given by

$$\Pr\{\text{infectious donation} \mid \text{negative screening test}\} = \iota E(W) \quad (2.2)$$

as is well known (Lackritz *et al.*, 1995; Satten, 1997).

Suppose that a holding period of duration τ is employed to further protect the plasma supply. Let $I(\tau)$ define the conditional event that a donation is interdicted during the holding period, given that such a donation screened negative for disease and is infectious. KS argue that such an interdiction occurs with conditional probability

$$\Pr\{I(\tau)\} = \Pr\{W^* + T^* \leq \min(\tau, L^*)\}. \quad (2.3)$$

Given the assumptions, this quantity can be evaluated as

$$\Pr\{I(\tau)\} = \int_{x=0}^{\tau} \int_{y=0}^{\tau-x} f_{W^*}(x) f_{T^*}(y) \Pr\{L^* > x + y\} dy dx. \quad (2.4)$$

For example, if we let W , T , and L all follow exponential distributions with rates ω , δ , and θ respectively, then the residual lifetimes W^* , T^* , and L^* will follow respectively the

same exponential distributions, yielding

$$\begin{aligned} \Pr\{I(\tau)\} &= \int_{x=0}^{\tau} \int_{y=0}^{\tau-x} \omega e^{-\omega x} \delta e^{-\delta y} e^{-\theta(x+y)} dy dx \\ &= \frac{\omega}{\omega + \theta} \frac{\delta}{\delta + \theta} \frac{1}{\delta - \omega} \{ \delta(1 - e^{-(\omega+\theta)\tau}) - \omega(1 - e^{-(\delta+\theta)\tau}) \\ &\quad - \theta(e^{-(\omega+\theta)\tau} - e^{-(\delta+\theta)\tau}) \}. \end{aligned} \quad (2.5)$$

The joint probability that a donation that has screened negative is both infectious and interdicted is then given by

$$\Pr\{\text{infectious interdiction}\} = \iota E(W) \times \Pr\{I(\tau)\}. \quad (2.6)$$

A very good approximation to $\Pr\{I(\tau)\}$ results if the duration of the holding period is much less than the residual duration of a randomly entered donation career (in which case $\min(\tau, L^*) \approx \tau$), and the residual time to the end of a randomly interrupted interdiction interval is much less than the remaining duration of a randomly entered window period (in which case $W^* + T^* \approx W^*$). This leads to the simple (upper bound) approximation

$$\Pr\{I(\tau)\} \approx \Pr\{W^* \leq \tau\}. \quad (2.7)$$

For exponential window periods, this simplifies (2.5) to

$$\Pr\{I(\tau)\} \approx 1 - e^{-\omega\tau}, \quad (2.8)$$

which the reader can verify is the limit of (2.5) as $\theta \rightarrow 0$ and $\delta \rightarrow \infty$.

KS present several applications of this modelling framework to the US plasma supply where the goal is to prevent contamination with HIV infection, including the determination of ‘optimal’ holding periods from an economic point of view.

3. Multiple infections: the mutually exclusive model

This section presents a simplified model that will be modified to allow for co-circulating infections (and multiple infections of individual persons). Suppose that plasma donors are screened for n different infections. Suppose further that in the population of donors, only a proportion p_j are *susceptible* to the j th infection, and everyone is susceptible to exactly one of these infections (so no one can be infected with more than one), $\sum_{j=1}^n p_j = 1$. Associated with the j th infection is an incidence rate $\tilde{\iota}_j$ that applies per susceptible per unit time *in the population susceptible for j* .

Further assume that it is impossible to determine the p_j values (indeed, when faced with a given donor it is impossible to determine which subgroup they are in unless the donor tests positive for some screened disease). Consequently, it is not possible to estimate the individual disease incidence rates (the $\tilde{\iota}_j$ values). However, the number of infections of each type in the donor population at large can be observed over time, so what can be estimated are the rates

$$\iota_j = p_j \tilde{\iota}_j \quad (3.1)$$

which report the number of new infections with disease j per susceptible per unit time in the overall donor population.

How would donor screening augmented by a holding policy work in such a circumstance? A fraction p_j of the donors are from group j . All donors are screened for all n infections, but only those from group j would ever be infected with the j th infection. The probability that a random donation from a member of the j th group occurs during the window period for that infection given negative screening tests on all infections would therefore equal $\tilde{\iota}_j E(W_j)$ where W_j is the window period associated with the screening test for the j th disease, while the conditional probability that such a window period donation infectious with the j th disease would be interdicted by a τ period hold is just given by $\Pr\{I_j(\tau)\}$ (by (2.4) using W_j^* for the residual duration of the window period). On any donation, the probability of interdicting an infectious donation with disease j would then equal $p_j \times \tilde{\iota}_j E(W_j) \times \Pr\{I_j(\tau)\} = \iota_j E(W_j) \times \Pr\{I_j(\tau)\}$, and the overall probability of interdicting an infectious donation would be given by

$$\Pr\{\text{infectious interdiction}\} = \sum_{j=1}^n \iota_j E(W_j) \times \Pr\{I_j(\tau)\}. \quad (3.2)$$

Thus, under the assumption of mutually exclusive infections, the probability of interdicting an infectious donation is just the sum of the probabilities of interdicting infectious donations of each disease type as computed in the single infection model. Of course this oversimplifies matters, for coinfections with more than one disease can occur, and at potentially high rates relative to the marginal incidence rates for any disease. This complicates matters in a manner that could prove surprising. For example, for a given holding policy, it might be that the probability of interdicting *any* infection in the case of multiple diseases is actually lower than the probability of interdicting an infection with a specific disease in the corresponding single disease model. The next section presents a more realistic approach to this problem.

4. Multiple infections: the mutually exclusive coincidence model

A satisfactory representation of reality is to imagine combinations of different diseases as new diseases in and of themselves. Then one can use the mutually exclusive model above to see what happens. So, retain the idea that there are n different diseases, but now allow for all $2^n - 1$ combinations of coinfections (all donors are presumed susceptible to at least one infection). The device of splitting the population up into groups at risk for the different diseases can then be employed over all *combinations* of infections. Define C_k as the collection of infections present in the k th subset of coinfections, $k = 1, 2, \dots, 2^n - 1$. The notation $i \in C_k$ implies that disease i is a member of the collection C_k . A fraction p_k of the population is susceptible to the *simultaneous* infection of all diseases contained in C_k . Within C_k , individuals become (co)infected with incidence rate $\tilde{\iota}_k$, implying that in the overall population of donors, (co)infections with the diseases contained in C_k occur at rate $\iota_k = p_k \tilde{\iota}_k$, $k = 1, 2, \dots, 2^n - 1$. The marginal incidence rate for an individual *disease* i , now denoted by ρ_i , is then given by

$$\rho_i = \sum_{k|i \in C_k} p_k \tilde{\iota}_k = \sum_{k|i \in C_k} \iota_k \text{ for } i = 1, 2, \dots, n. \quad (4.1)$$

Typically, data are only available for the marginal incidence rates ρ_i .

In this model, note that coinfections, when they occur, occur simultaneously. Thus, for example, a drug injector might be infected with both HIV and HCV when injecting with a previously used needle, a situation not at all unreasonable when one considers the co-prevalence of these diseases among drug injectors. While it is certainly possible that a person could be infected with one infection at one point in time and another infection at a subsequent point in time, remember that the population of interest in this paper, plasma donors, is repeatedly screened for infectious diseases (once every 5.3 days on average in the USA according to GAO (1998)). The event that corresponds to a donor escaping detection having been infected with one disease, proceeding to become infected with a second disease, and further proceeding to escape detection when screened for all diseases would thus be extraordinarily rare.

Assume then that all coinfecting donors are infected with whatever diseases are involved simultaneously. An immediate implication is that for a donor who is a member of C_k , the screening tests administered will combine to yield an effective window period equal to the minimum of the window periods for the various diseases associated with C_k . More succinctly, define

$$W^{C_k} = \min_{i \in C_k} W_i \quad (4.2)$$

as the effective window period associated with C_k , $k = 1, 2, \dots, 2^n - 1$, where W_i denotes the duration of the window period associated with the screening test for the i th disease. The conditional probability that a donation that has tested negative for all screened diseases would, in fact, be infectious with the diseases that comprise the collection C_k then equals $\iota_k E(W^{C_k})$, while the probability of interdicting such an effective window period donation would be given by $\Pr\{I_k(\tau)\}$ (where W^{*C_k} is the appropriate residual duration of the window period discussed below). Barring specific information regarding the interaction of different screening tests, the window periods of the screening tests for the diseases involved will be assumed to be mutually independent. Doing so yields the simple results

$$\Pr\{W^{C_k} > x\} = \prod_{i \in C_k} \Pr\{W_i > x\} \quad (4.3)$$

and

$$E(W^{C_k}) = \int_{x=0}^{\infty} \prod_{i \in C_k} \Pr\{W_i > x\} dx, \quad (4.4)$$

from which the density of the residual window duration W^{*C_k} follows as

$$f_{W^{*C_k}}(x) = \frac{\Pr\{W^{C_k} > x\}}{E(W^{C_k})} \text{ for } x \geq 0. \quad (4.5)$$

With these assumptions, if one knew the population coincidence rates ι_k for all collections of infections C_k , $k = 1, 2, \dots, 2^n - 1$, it would be possible to deduce several quantities directly, including the following:

1. the probability that a donation that has screened negative is both infectious and interdicted, given by

$$\Pr\{\text{infectious interdiction}\} = \sum_{k=1}^{2^n-1} \iota_k E(W^{C_k}) \times \Pr\{I_k(\tau)\}, \quad (4.6)$$

2. the expected number of infections interdicted per donation that has screened negative, given by

$$E[\text{infections interdicted}] = \sum_{k=1}^{2^n-1} m_k \times \iota_k E(W^{C_k}) \times \Pr\{I_k(\tau)\} \quad (4.7)$$

where $m_k = |C_k|$ = the number of different infections contained in the collection C_k ,

3. the expected benefit of the holding policy (incremental to screening) per donation that has screened negative, given by

$$E[\text{benefit}] = \sum_{k=1}^{2^n-1} b_k \times \iota_k E(W^{C_k}) \times \Pr\{I_k(\tau)\} - c_s \tau \quad (4.8)$$

where b_k is the monetary benefit of preventing an infectious donation from collection C_k from release for further processing, and c_s is the storage cost per unit time for a unit of plasma.

Unfortunately, one is unlikely to have estimates of the coincidence rates ι_k . However, one is quite likely to have estimates of the marginal disease incidence rates (the ρ_i values), a fact that enables the construction of upper and lower bounds for the key quantities displayed above.

5. Linear programming bounds for the mutually exclusive coincidence model

For any holding period τ , upper and lower bounds can be constructed for any linear function of the coincidence rates ι_k in a manner that preserves consistency with the (assumed known) marginal disease incidence rates. All of the measures considered thus far are of this form. Let r_k denote the coefficient of ι_k in a particular performance measure (for example, $r_k = m_k \times E(W^{C_k}) \times \Pr\{I_k(\tau)\}$ for the expected number of infections interdicted). An upper bound for the performance measure in question can then be found by solving the following linear programme:

$$\max_{\iota_1, \iota_2, \dots, \iota_{2^n-1}} \sum_{k=1}^{2^n-1} r_k \iota_k \quad (5.1)$$

subject to the constraints

$$\sum_{k|i \in C_k} \iota_k = \rho_i \text{ for } i = 1, 2, \dots, n \quad (5.2)$$

and

$$\iota_k \geq 0 \text{ for } k = 1, 2, \dots, 2^n - 1, \quad (5.3)$$

while a lower bound can be found by minimizing $\sum_{k=1}^{2^n-1} r_k \iota_k$ subject to the same constraints. Note that both of these bounds are functions of τ , enabling one to choose a value of τ that appears advantageous given the bounds computed.

A small imperfection in the above proposal arises because the model focuses only on the disposition of donations that have *already* screened negative. In the case of multiple infections, allowing the coincidence rates to vary as suggested above will ever-so-slightly change the likelihood that a donation will test positive for some disease because of the multiple screening tests involved. However, in a repeatedly screened donor population, the prevalence of detectable infection for any (screened) disease among active donors is negligible, leaving the results above and below essentially unchanged.

There is one special case worth mentioning: for the objective of maximizing the probability of interdicting an infectious donation, no computations are required because the solution is provided by the mutually exclusive model with *no* coincidence terms. This is most easily seen via the approximation $\Pr\{I(\tau)\} \approx \Pr\{W^* \leq \tau\}$ (though the result is generally true). Using this approximation, note that

$$\begin{aligned} r_k &= E(W^{C_k}) \times \Pr\{I_k(\tau)\} \\ &\approx E(W^{C_k}) \times \Pr\{W^{*C_k} \leq \tau\} \\ &= \int_0^\tau \Pr\{W^{C_k} > x\} dx \\ &= E[\min(W^{C_k}, \tau)]. \end{aligned} \quad (5.4)$$

Let $C_{\{i\}}$ correspond to that collection consisting only of persons susceptible to disease i , and hence $W^{C_{\{i\}}} = W_i$, the window period for the screening test associated with the i th disease. Because $W^{C_k} = \min_{i \in C_k} W_i$, clearly $E[\min(W^{C_{\{i\}}}, \tau)] = E[\min(W_i, \tau)] \geq E[\min(W^{C_k}, \tau)]$ for all collections $k \mid i \in C_k$. In other words, $r_{\{i\}} \geq r_k$ for all $k \mid i \in C_k$. It is feasible to equate $\iota_{\{i\}}$ to the marginal incidence rate ρ_i ; doing so for each disease i thus yields the maximum probability of interdicting an infection via the holding policy (as $r_{\{i\}} \geq r_k$ for all $k \mid i \in C_k$).

6. Examples and discussion

As an application of these bounds, consider the case of paid plasma donors in the USA. It has been estimated that the incidence rates for HIV, HBV and HCV among plasma donors are given by 61.9, 245.5 and 63.5 per 100 000 per year respectively (GAO, 1998). Mean window periods for the screening tests associated with these infections equal 22, 59 and 82 days, respectively (GAO, 1998). The per donor plasma donation rate has been estimated to equal 68.9 donations per year. Assume further that the duration of a donation career is exponentially distributed with a mean of 2 years, and that the window periods and interdonation times are exponentially distributed and mutually independent. These assumptions enable the use of (2.5) to determine the conditional probability of interdicting a donation given that it is infectious and has screened negative for disease,

**Pr{Interdicting Infectious Donation}
Upper and Lower Bounds**

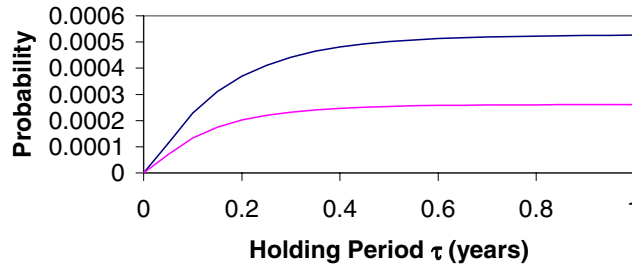


FIG. 1. Upper and lower bounds for Pr{interdicting infectious donation}.

and consequently the joint probability that a donation that has screened negative is both infectious and interdicted.

For holding periods τ lasting up to 1 year in duration, Fig. 1 reports upper and lower bounds for the probability that a donation that has screened negative for all diseases is both infectious and interdicted. As described in Section 5, the upper bound corresponds to the situation where HIV, HBV and HCV infections occur in mutually exclusive fashion. To appreciate the vertical scale, the maximal probability that a donation that has screened negative is infectious simply equals $\sum_{i=1}^3 \rho_i E(W_i) = (61.9 \times 22 + 245.5 \times 59 + 63.5 \times 82) \times 10^{-5} / 365.25 = 5.76 \times 10^{-4}$. A holding policy equal to 60 days in duration would thus prevent between 31.9 and 57.2% of this maximal level, for example.

One might expect that the probability of interdicting an infection via a holding period can only increase if the number of diseases screened increases. Perhaps surprisingly, this is not necessarily the case. Again consider a 60 day holding period, and suppose that donations were screened only for HBV. In this case, only the HBV incidence rate and window period would matter. The probability that a donation testing HBV negative is both infectious and interdicted would equal 2.3 in 10 000. Yet from Fig. 1, the probability that a donation is infectious and interdicted given that it has screened negative for HIV, HBV and HCV could fall anywhere between 1.84 and 3.295 in 10 000, indicating that fewer than (the solitary HBV screened) 2.3 in 10 000 donations could be interdicted. How can this be?

This apparent paradox is easily resolved when one realizes that the probability that a screened negative donation is infectious must decline as the number of diseases checked increases. This is a direct consequence of the fact that $W^{C_k} \leq W_i$ for all $k \mid i \in C_k$, for

$$\sum_{i=1}^n \sum_{k \mid i \in C_k} \iota_k E(W^{C_k}) \leq \sum_{i=1}^n \sum_{k \mid i \in C_k} \iota_k E(W_i) = \sum_{i=1}^n \rho_i E(W_i). \tag{6.1}$$

Thus, while the *conditional* probability of interdicting an infectious donation that has screened negative (i.e. $\Pr\{I(\tau)\}$) must grow as the number of infections checked increases (because replacing W_i by a shorter window W^{C_k} makes $\Pr\{I_k(\tau)\} \geq \Pr\{I_{\{i\}}(\tau)\}$), the joint probability that a screened negative donation is infectious and interdicted need not.

Of course, for any given disease, the probability that a donation that has screened

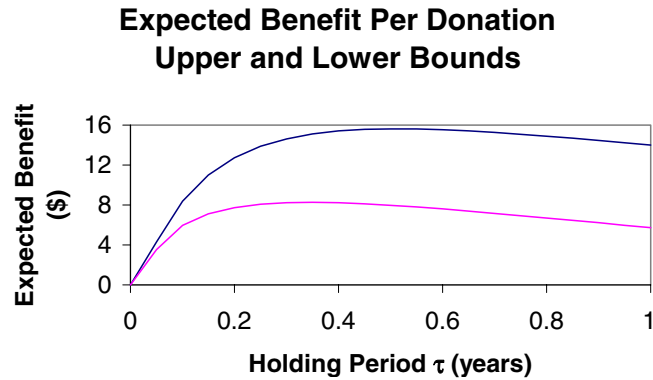


FIG. 2. Upper and lower bounds of expected benefit per donation.

negative is both infectious and escapes the holding period for further processing must also decline as the number of infections checked increases. This result follows from the fact that

$$\begin{aligned}
 & \sum_{k|i \in C_k} \iota_k E(W^{C_k})(1 - \Pr\{I_k(\tau)\}) \\
 & \leq \sum_{k|i \in C_k} \iota_k E(W_i)(1 - \Pr\{I_{\{i\}}(\tau)\}) \\
 & = \rho_i E(W_i)(1 - \Pr\{I_{\{i\}}(\tau)\}).
 \end{aligned} \tag{6.2}$$

Screening for multiple diseases does improve the safety of the plasma supply after all!

While longer holding periods increase the probability of interdicting infectious donations, as is the case with the single infection model, there are clear diminishing returns as the holding period is increased. This suggests that from an economic point of view, it is possible to ‘overhold’ in that the inventory costs of stored plasma might overwhelm the benefits of interdicting infectious donations. As an example, Fig. 2 reports upper and lower bounds on the net benefits of holding under the assumptions that interdicting HIV, HBV and HCV infections are worth \$100 000, \$25 000 and \$50 000, respectively, while the cost of storing plasma equals \$5 per unit per year. It is further assumed that the benefit of interdicting coinfectious donations is equal to the sum of the benefits for all infections present (so the benefit of interdicting an HBV/HCV coinfection would equal \$75 000, for example). The lower bound shows that a holding period of 0.35 years or about 4 months would guarantee a net benefit of at least \$8.25 per donation, while the upper bound shows that at most \$15.60 would be gained (at a holding period of 6 months). Any holding period between 4 and 6 months seems reasonable given the dollar valuations assumed.

Determining appropriate dollar valuations for interdicted infectious donations is a challenging problem in resource economics beyond the scope of this paper. However, maintaining the 4 : 1 : 2 ratios of benefits for interdicting HIV, HBV and HCV infections, respectively, it is possible to solve for the benefit valuations that render the observed holding policy of 60 days in the USA reasonable if not optimal. For example, setting

the benefit valuations equal to \$12 000, \$3000, and \$6000, respectively, yields an (upper bound) optimal holding period of 61 days with an optimal net benefit of \$0.66 per donation. The lower bound reports a net benefit of \$0.15 for these same parameters. This provides an interesting contrast to the finding in KS that the current 60 day holding period is optimal when interdicting HIV infections provides a \$100 000 benefit in the single disease model.

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