Clin. Lab. 2021;67:XXX-XXX

ORIGINAL ARTICLE

Mathematical Model to Assess Potential Reduced Specificity When Switching to New Screening Assays at Blood Donation Centers

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SUMMARY

Background: **Switching to new infectious disease blood donor screening assays can precipitate an initial decrease in specificity in an established donor population followed by an increase of specificity, referred to as a "cleaning effect". We developed a mathematical model to simulate this and to measure the stabilization of specificity.**
Methods: **A modified exponential distribution curve was created to show the impact of donation frequency on the cleaning of the donor pool. Other parameters (e.g., number of donations from repeat donors/donations per month, average and minimum times between donations, retention of regular repeat donors, ratio of false positives for regular repeat donors/first-time donors and specificity of newly introduced assays) were also used to simulate the rise and fall in number of additional false positives. The mathematical model created was compared with real-world data from a South African blood donation center.**
Results: **In the mathematical model, the degree and duration of the cleaning effect were influenced by certain parameters. A longer time interval between donations resulted in a higher number of deferred blood donations than a shorter time interval, if deferred after a 1st, 2nd or 3rd false positive result prior to a stable plateau of specificity. Real-world data on false positive, discarded donations from a South African blood donation center were consistent with numbers from the mathematical model.**
Conclusions: **The mathematical model can identify and describe any "cleaning effect" observed upon switching to a new infectious disease blood screening assay, allowing affected blood donation centers to prepare and adjust, while specificity is stabilized.**
(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2021.201122)

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Manuscript accepted January 30, 2021

KEY WORDS

infectious disease screening assays, HIV, HCV, HBV, mathematical model, cleaning effect, switch effect, false reactivity, first-time donor, regular repeat donor

INTRODUCTION

The establishment of systems to ensure that all donated blood is screened for transfusion-transmissible infections is a core component of every national blood program [1]. Screening for transfusion-transmissible infections excludes blood donations that could transmit infection from donors to recipients, thereby ensuring transfusion is as safe as possible.

The safety of donated blood has greatly improved since the 1980s, with the introduction of new blood donor screening tests for human immunodeficiency virus (HIV)-1/2, hepatitis C (HCV), and hepatitis B (HBV), as first-generation screening tests were replaced by assays of increasing sensitivity (second-generation, third-generation and fourth-generation) which resulted in the earlier detection of infected donors [2,3]. The minimum evaluated sensitivity and specificity levels of all assays used for blood screening should be as high as possible, and preferably no less than 99.5% [1]. Increasing sensitivity, however, can often be associated with decreased specificity if new assays lack well-balanced cutoffs separating negative and positive specimens [4], and the selection and presentation of antigens and antibodies needs to be optimized [2]. As a consequence, there has been an increased rate of false-positive (FP) test results, with several reports during the 1990s introducing concerns over the positive predictive value and the false-positive rates of some screening tests [2,5].

FP results have various possible causes, including the non-specific or cross-reactive binding of antibodies to antigens, increased immune reactivity, such as due to vaccination, acute illness or allergies [5-7], and the presence of non-specific polyreactive antibodies (predominantly immunoglobulin M) [7]. Two large studies in the United States also identified a correlation between FP results and various demographic subgroups [6,7]. In general, FPs are comparatively more frequent in first-time donors than in regular repeat donors [8].

An FP test result can have serious consequences for both the individual blood donor and the donor screening center [5,7,9,10]. For the donor it creates uncertainty and psychological stress, as well as potential costs for medical follow-up [2,5,7,9]. In turn, this can discourage potential future donors [5], thereby compromising the maintenance of adequate blood supplies. For the donor screening center, it causes increased workload with additional time required for retesting and confirmatory tests, which must follow a full re-entry testing algorithm [2]. Discarded blood donation products, along with their containment bags, adds to the significant associated cost burden [6], and every year a large number of eligible donors are lost because of FP screening test results [6, 7].

Blood screening centers usually rely on a regular repeat donor pool (~90% of total donors) which is complemented and renewed continuously by a smaller pool of first-time donors (~10%) [11]. Donors are managed as per World Health Organization (WHO) guidelines [1] and/or national transfusion guidelines, and are deferred after a reactive (positive) screening result, including FP reactivity, either permanently or for a specified period of time. The period for exclusion depends on the serological marker and can vary by country. The algorithm used can also vary; some blood screening centers defer donors immediately after one FP result, while some do so only after two or three FPs, and the duration of the deferral can differ from center to center. Blood donors who have repeated FP results are a continual problem for blood banks for reasons discussed, although multiple studies indicate that they are very rarely genuinely infected with the transmissible agent in question [2,6].

Through the process of donor management, a regular repeat donor pool is "cleaned" over time to differentiate donors with confirmed reactivity and FP reactivity, thus "increasing" the specificity of the screening test(s) used within the pool [12]. This effect is hereafter referred to as the "cleaning effect". Studies investigating the replacement of existing screening tests and/or platforms with newly introduced screening assays have illustrated the loss in donors, sometimes described as "switch effect" [2,13]. It has been observed, in head-to-head comparisons of different screening assays in regular repeat donors, that the specificity of newly introduced screening assays was inferior to those in long-term routine use due to the removal of confirmed positive and FP donors by the existing assays over time, thus "culling" the donor pool [2,13]. For newly introduced assays, the "culled" donor pool can be seen as a "juvenile" donor pool, similar to a first-time donor pool, with increased rates of FPs and donor deferrals. The pre-selection bias of a pre-screened donor pool can affect the perception of overall lower specificity of a newly introduced assay [13].

Blood donation centers have traditionally preferred to retain a chosen screening assay, but an increasing tendency to switch to a newer assay is being driven by the emergence of screening assays with improved sensitivity (and specificity) as well as a full automation. However, fear of a potential cleaning effect can act as a barrier to the adoption of these new assays, despite their benefits [13]. Centers may be apprehensive about switching to a new screening assay, or an assay from a new manufacturer, due to the unknown characteristics of the cleaning effect: its initial rate, the starting point and how long the process of cleaning will take [13]. During the process of cleaning, the temporary drop in specificity means an increase in FPs, which carries the negative consequences described above.

A scarcity of literature on the cleaning effect means that the issue is poorly understood, further complicating decision-making around adopting new assays. We have developed a mathematical model, with the aim of assisting decision-making. The model described in this report has been designed to quantify the cleaning effect and investigate the duration of any initial reduced specificity and number of additional FP donations that may have to be accounted for after the switch, until the donor pool is "cleaned" and specificity has improved and stabilized.

Real-world data (RWD) from a South African blood donation center that switched from existing assays in use for more than 20 years, to newly introduced screening assays or platforms in 2015, have been used to monitor the cleaning of the affected donor pool. The mathematical model and the RWD were compared and correlated in order to facilitate understanding and assist blood donation centers considering a change from an existing

screening assay to a different assay manufacturer or new screening tool.

MATERIALS AND METHODS

Mathematical modeling

To create a realistic and accurate mathematical model to reflect the cleaning effect after switching to a new blood screening assay requires detailed donor information (e.g., the donor management at the blood bank, the FP rate for the respective serological screening assay(s) and the time interval between donations). Some parameters are easily defined for a donor cohort, specifically the minimal time ($T_{\min}$) a donor has to wait before being allowed to donate again, and the number of times (K) an FP donor will be tested before being excluded completely. More difficult to estimate for each donor is the mean number of donations, the FP rate, and the average time between donations. Nevertheless, it is possible to derive a realistic estimate of the cleaning effect, based on a restricted set of parameter estimates with the following assumptions (Equation 1):

1) The donor cohort is stable. The number of donors, their donation rate A_{total} (i.e., the number of donations per unit of time) and the rate of donors entering or leaving the cohort is constant.
2) There are two groups of donors: regular repeat donors, who have donated at least once before and who contribute the fraction A_{rep} to the donation rate, and first-time donors, who have never donated before and make up A_{first} of the donation rate. Both rates are also assumed constant, where the total donation rate is $A_{\text{total}} = A_{\text{rep}} + A_{\text{first}}$.
3) The probability of a first-time donation being FP is p_{first}. For the mathematical model, this probability is taken as the maximum value stated within the package insert of the new test.
4) Donors donate periodically every T days, with a distribution characterized by a density $q(T)$ dependent on the average period length $\overline{T}$.

Equation 1

$$q(T) = \frac{A_{rep}}{\sigma} Texp\left(-\frac{T - T_{min}}{\sigma}\right) \quad if\ T > T_{min},$$
$$= 0 \quad if\ T \le T_{min},$$

where $\sigma = (\overline{T} - T_{\min})$.

5) The probability that a regular repeat donor, who has been true negative before, will show an FP result with the same test, is lower than for a first-time donor. If the screening test result from the donor's last donation was negative, the probability of an FP result is $p_{\text{rep}} \le p_{\text{first}}$. In a more refined treatment, one would expect this rate to depend on T, such that with increasing time since the last donation, the probability p_{rep} increases from 0 to larger values $\le p_{\text{first}}$. Furthermore, it is assumed that the probability of an FP result in a repeated test, after an initial FP result, is 1. This will yield a rather conservative estimate of the total number of FP results if $K > 1$.

However, the probabilities p_{first} and p_{rep} are so small, that the influence of donor loss due to FP results on the overall rate of donations can be discounted, given the much larger temporal donor fluctuations for other reasons. With the exponential dependence of specificity recovery on time, and the distributional form of the respective curve with period T, the model is quite flexible. For example, setting $\overline{T} = T_{\min}$, a donor population will be described where all members donate regularly at an equal period $T_{\min}$, while for values $\overline{T}$ larger than $T_{\min}$, broader distributions will be obtained (Figure 1).

To describe the "cleaning effect" following the "switch effect", the following parameters are needed:

1) Minimum time between donations $T_{\min}$
2) Average time between donations $\overline{T}$
3) Number of tests permitted until a donor is completely excluded from donation due to false reactivity K (K = 1, 2 or 3)
4) Number of regular repeat donors A_{rep}
5) Probability of a first-time donation being FP p_{first}
6) Probability of a regular repeat donation being FP p_{rep}
7) Specificity of the new assay

The switch from one assay to another may be accompanied by two conceptually distinct changes in the rate of FP donations. On one hand, the new test may differ from the previous test with respect to the FP rate for both new and regular repeat donors, and this difference may persist for a long time after switching. The relevant parameters for both tests are p_{first} and p_{rep}.

On the other hand, the switch may lead to an immediate increase in the FP rate, before slowly returning back to a stable value. If the FP equilibrium that prevails a long time after the assay switch is called R_{eq} and the excess rate is called $R_{\text{ex}}(t)$, then the total FP rate becomes: $R(t) = R_{\text{eq}} + R_{\text{ex}}(t)$ (Figure 2).

After switching, the rate of excess FP test results from donors with period T is:

$$R_T(t) = \Delta p \frac{q(T)}{T} \quad \text{for } 0 \le t \le KT,$$
$$= 0 \quad \text{for } t > KT,$$

i.e., the excess FP rate remains constant from immediately after the switch until $t = KT$; the time when the last donor has delivered his K^{th} FP result and gets excluded.

Here, $\Delta p = p_{\text{first}} - p_{\text{rep}}$.

Integration over T yields the total excess FP rate:

$$R_{\text{ex}}(t) = \int R_T(t)dT = \Delta p A_{\text{rep}} \ for\ t \le KT_{min},$$
$$= \Delta p A_{\text{rep}} \exp\left(-\frac{t - KT_{\min}}{K\sigma}\right) \quad for\ t > KT_{min}$$

This means that the excess FP rate remains constant; ΔpA_{rep} from $t = 0$ to $t = KT_{\mathrm{min}}$, and then drops exponentially with a time constant $K\sigma$.

In total the number of FPs observed will be:

$$N = K\Delta pA_{\mathrm{rep}}$$

The time taken for the excess FP rate to fall back to 5% of its final value is:

$$t_{0.05} \approx K(3\overline{T} - 2T_{\mathrm{min}}).$$

Finally, the equilibrium FP rate, which is reached after this time, is:

$$R_{\mathrm{eq}} = p_{\mathrm{first}}A_{\mathrm{first}} + Kp_{\mathrm{rep}}A_{\mathrm{rep}}.$$

Calculation of scenarios which could impact the cleaning effect

The mathematical model described above was used to calculate three scenarios to test the impact of key parameters on the cleaning effect (characterized by the number of FP results/rate of FP, and time for normal specificity to be restored). Common variable parameters were selected for these scenarios: duration of time between donations (scenario 1); assay specificity (scenario 2); and ratio of $p_{\mathrm{rep}}/p_{\mathrm{first}}$ (scenario 3). The following wider selection of parameters was included in each calculation, and scenarios 1 - 3 were created by changing the relevant parameter whilst keeping others constant. Reference values were selected for use in the model (displayed), as typical values, taken from European and South African blood donation centers:

- number of donations from repeat donors per month: 10,000
- assay specificity: 99.88%
- average time between donation: 8.8 months
- ratio of $p_{\mathrm{rep}}/p_{\mathrm{first}}$: 0.56
- minimum time between donation: 55 days

Real-world data (archived and recorded) from South Africa

The Western Cape Blood Service (WCBS) in Cape Town screens donations from around 155,000 donors every year, and the proportion of first-time donors is 11.8%. The demography of donors is shown in Table 1. From May 1996 to December 2015 the center adopted the Abbott PRISM screening assays HIV O Plus, Anti-HCV, and HBsAg (Abbott Laboratories, USA). In December 2015, the center switched to the automated screening assays Elecsys® HIV combi PT, Elecsys Anti-HCV II and Elecsys HBsAg II on the cobas e 601 analyzer (Roche Diagnostics International Ltd., Rotkreuz, Switzerland).

The monthly FP rate for the screening assays HIV combi PT, Anti-HCV II, and HBsAg II (cobas e 601 analyzer) between January 2016 and December 2019 was recorded. The number of donations from repeat donors per month, the average time between donations, and the minimum time between donations were also recorded.

RESULTS

Scenario 1: Variation in duration of time between donations

The average time between donations was fixed at either 8.8 months or 3.2 months, to represent the two alternatives used in different blood donation centers, and show the impact on the cleaning effect of a longer (8.8 months) and a shorter (3.2 months) time between donations.

Depending on the donor management, and whether regular repeat donors were deferred after the 1st, 2nd, or 3rd FP result, an average of 8.8 months between donations resulted in 46, 93, and 139 additional FP results within periods of 23 months, 45 months, and 68 months, respectively (Figure 3A). Fixing at 3.2 months between donations resulted in 17 additional FP results within 6 months, before the FP rate declined to $t_{0.05}$ (5% above the equilibrium rate R_{eq}), if the donors were deferred from the donor pool after the 1st FP result. To defer donors after either the 2nd or 3rd FP resulted in 34 additional FP results in 12 months and 51 FP results in 18 months, respectively, until the FP rate declined to $t_{0.05}$ (Figure 3B).

Scenario 2: Variation in assay specificity

Two assay specificities for standard serological blood donation screening assays (e.g., HIV, HCV, HBsAg) were selected, to reflect a switch to assays of either lower (99.88%) or higher (99.98%) specificity. Adopting the lower specificity value (99.88%) resulted in an additional 46 FPs in 23 months, 93 in 45 months and 139 in 68 months, if donors were deferred after the 1st, 2nd, or 3rd FP result, respectively (Figure 4A). However, adopting the higher specificity value (99.98%) resulted in a smaller number of additional FPs, with 8 additional FP results in 23 months, 16 in 45 months and 23 in 68 months, after the 1st, 2nd, or 3rd FP result, respectively (Figure 4B). The time taken for the excess of FP results to decline to $t_{0.05}$ for both levels of specificity remained identical.

Scenario 3: Variation in ratio of $\mathbf{p_{rep}/p_{first}}$

In the third scenario, the ratio $p_{\mathrm{rep}}/p_{\mathrm{first}}$, which is the probability of repeat donors having an FP result divided by the probability of first-time donors having an FP result, was varied. Figure 5A shows the impact on the cleaning effect with a ratio $p_{\mathrm{rep}}/p_{\mathrm{first}}$ of 0.56, and Figure 5B shows the impact on the cleaning effect of a ratio of 0. A ratio of 0.56 reflects an almost two-times greater probability of first-time donors having an FP than repeat donors. A ratio of 0 reflects only first-time donors having an FP result.

The ratio $p_{\mathrm{rep}}/p_{\mathrm{first}}$ had no influence on the time until the rate of excess FP results decreased to $t_{0.05}$, hence the duration of the "cleaning" of the donor pool. The number of additional FP results increases from 46 to 106 in 23 months if the donor is deferred from the do-

Table 1. Donor demographics.

Characteristic		Female	Male	Total
N (%)		38,768 (53.9)	33,105 (46.1)	71,873 (100.0)
Race, n (%)	Caucasian	22,298 (31.0)	20,040 (27.9)	42,338 (58.9)
	Black	2,630 (3.7)	1,797 (2.5)	4,427 (6.2)
	Asian/Indian	358 (0.5)	476 (0.7)	834 (1.2)
	Mixed race	13,482 (18.8)	10,792 (15.0)	24,274 (33.8)
Donor type, n (%)	First-time	4,850 (6.7)	3,614 (5.0)	8,464 (11.8)
	Repeat	33,918 (47.2)	29,491 (41.0)	63,409 (88.2)

Table 2. Calculation of the false-positive ratio between regular repeat donors and first-time donors ($p_{\mathrm{rep}}/p_{\mathrm{first}}$) at the Western Cape Blood Service, 2016 to 2019.

Category	Assay	Donor type	Quantity
Number of donations, n	All assays	Total *	362,000
		First-time	50,680
		Repeat	311,320
False positives, n	HIV	First-time	72
		Repeat	209
	HBsAg	First-time	14
		Repeat	59
	Anti-HCV	First-time	65
		Repeat	223
	Total	First-time	151
		Repeat	491
Probability of obtaining false positives, %	All assays	First-time	0.30
		Repeat	0.16
	Ratio of false positives †		0.53

*** Proportion of repeat vs. first-time donors = 86% vs. 14%.**
† Repeat donor/first-time donor.
Anti-HCV - anti-hepatitis C virus, HBsAg - hepatitis B surface antigen, HIV - human immunodeficiency virus.

Table 3. A comparison of the number of additional false-positive results when introducing new screening assays for HIV, HCV, and HBV using real-world data from Western Cape Blood Service versus calculations from the mathematical model.

Assay (specificity) *	Additional false-positive results, n	
	Mathematical model calculation	WCBS RWD
Elecsys HIV Combi PT (99.88%)	47	72
Elecsys HCV (99.85%)	63	36
Elecsys HBsAg II (99.98%)	8	9
TOTAL	118	117

*** Time until donor pool is "cleaned" to the equilibrium rate R_{eq} = 15.5 months.**
HBV - hepatitis B virus, HCV - hepatitis C virus, HIV - human immunodeficiency virus, RWD - real-world data, WCBS - Western Cape Blood Service.

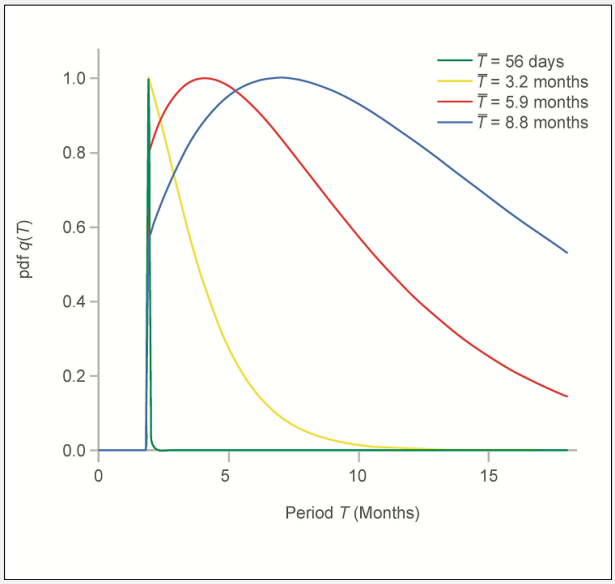

Figure 1. Plot of the probability density functions (pdf) $q(T)$ (Equation 1) of the periods T assuming different mean times ($\overline{T}$) of 56 days, 3.2 months, 5.9 months, and 8.8 months.

The minimum time between donations is 55 days.

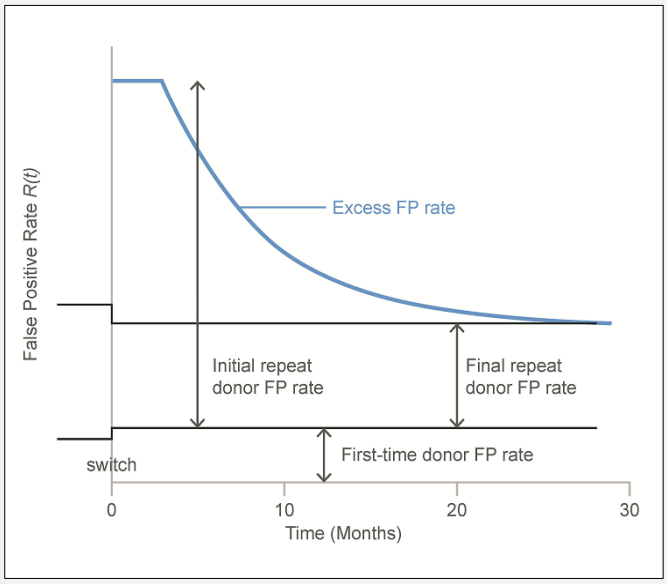

Figure 2. Composition of false positive rates $R(t) = R_{eq} + R_{ex}(t)$ and decline to the equilibrium rate R_{eq}.

Assay switch occurs at time point 0. In this example, the FP rate of first-time donors (bottom horizontal line) is a little higher following the switch. The top horizontal line is the FP rate of repeat donors. The graph illustrates how, while the first-time donor FP rate remains stable after initial elevation, the repeat donor FP rate increases dramatically after the switch (initial repeat donor FP rate). The top horizontal line is the final equilibrated repeat donor FP rate. FP, false positive.

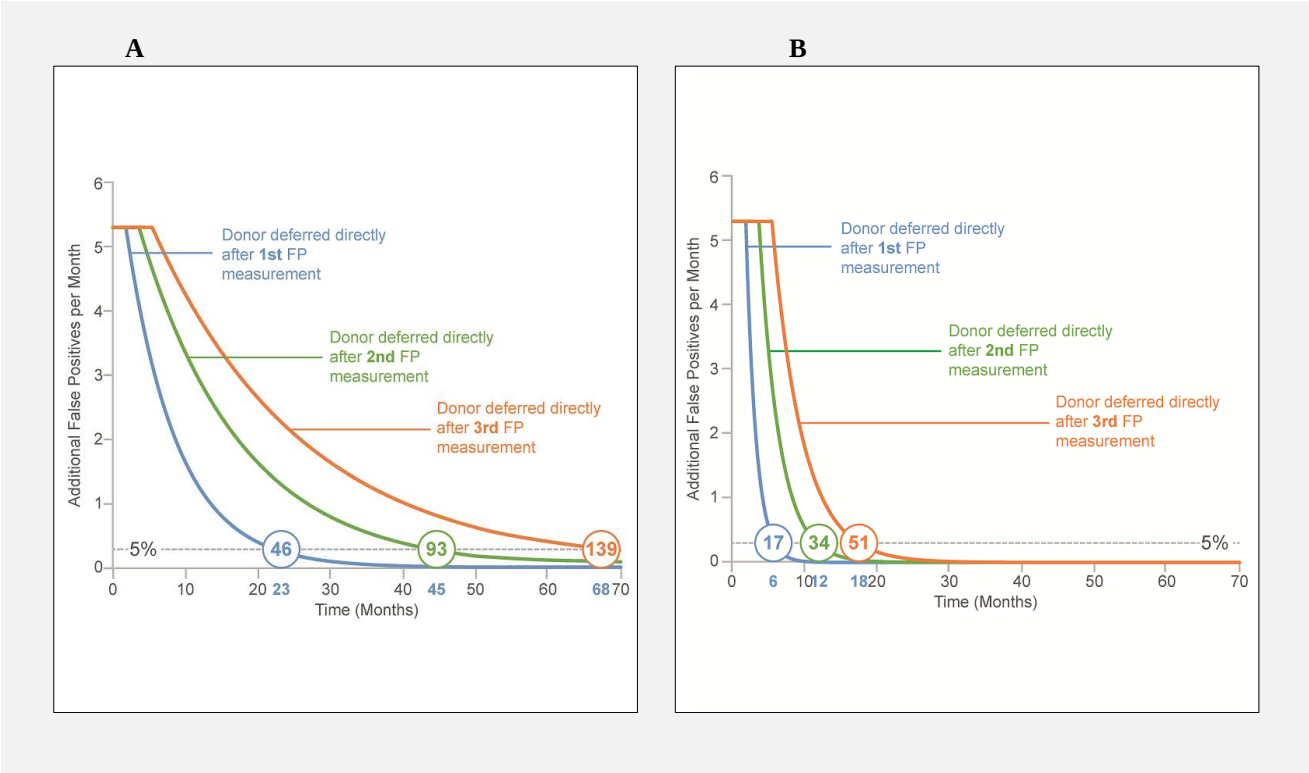

Figure 3. Scenario 1: Variation in duration of time between donations.

Decrease of additional FP results with an average time between donations of 8.8 months (3A) and 3.2 months (3B), when donors are deferred after 1st, 2nd, and 3rd FP result. All other parameters are identical (10,000 donations from repeat donors per month, assay specificity of 99.88%, ratio of p_{rep}/p_{first} of 0.56, minimum 55 days between two donations). Numbers in circles are the additional FP results until the donor pool is cleaned and specificity is stable. The highlighted timepoints (months) indicate when the FP rate has dropped to + 5% of the final specificity and is considered cleaned. FP, false positive.

nor pool after the 1st FP result, and we assume that all FP results come from first-time donors only. If the donor is deferred from the donor pool after the 2nd FP, the number increases from 93 to 211 additional FP results in 45 months; and from 139 to 316 additional FPs in 68 months, if the donor is deferred after the 3rd FP result.

Potential cleaning effect: Mathematical model versus real-world data

In addition to calculating the three theoretical scenarios to demonstrate the impact of different parameters on the cleaning effect, the mathematical model was used to simulate a potential cleaning effect at WCBS in Cape Town. The resulting data were then compared with RWD recorded at WCBS following the switch from the Abbott PRISM assay to the corresponding Roche Diagnostics Elecsys assay. To calculate the cleaning effect at WCBS, the number of repeat donors per month (10,000), the average time between donations (3.8 months), the minimum time between donations (55 days) and the assay specificity (99.88% for Elecsys HIV combi PT, 99.85% for Elecsys Anti-HCV II and 99.98% for Elecsys HBsAg II assay) of the new test introduced in the donor pool were inserted into the model. Calculations were performed for each of the three screening parameters described above. The standard WCBS practice of deferring blood donations after the 2nd FP result for each respective assay was also taken into account.

The ratio of p_{rep}/p_{first} was calculated for WCBS and is shown in Table 2. To cover a reasonable time span, data in records from the years 2016 - 2019 were included. The percentage of FP donor samples was calculated for first-time and repeat donors using the main screening assays HIV, HCV, and HBsAg. The percentage of FP results for all assays together on regular repeat donors was 0.16%, and for first-time donors it was 0.30%, resulting in a ratio of 0.53 (0.16%/0.30%). Hence, the probability of first-time donors having an FP result is almost twice as high as that of repeat donors.

When the data from the WCBS were inputted into the mathematical model, the result showed it would take an expected 15.5 months for the excess FP rate to decrease to $t_{0.05}$. The calculated number of additional FP results expected with the Elecsys HIV combi PT, Elecsys Anti-HCV and Elecsys HBsAg assays are shown in Table 3.

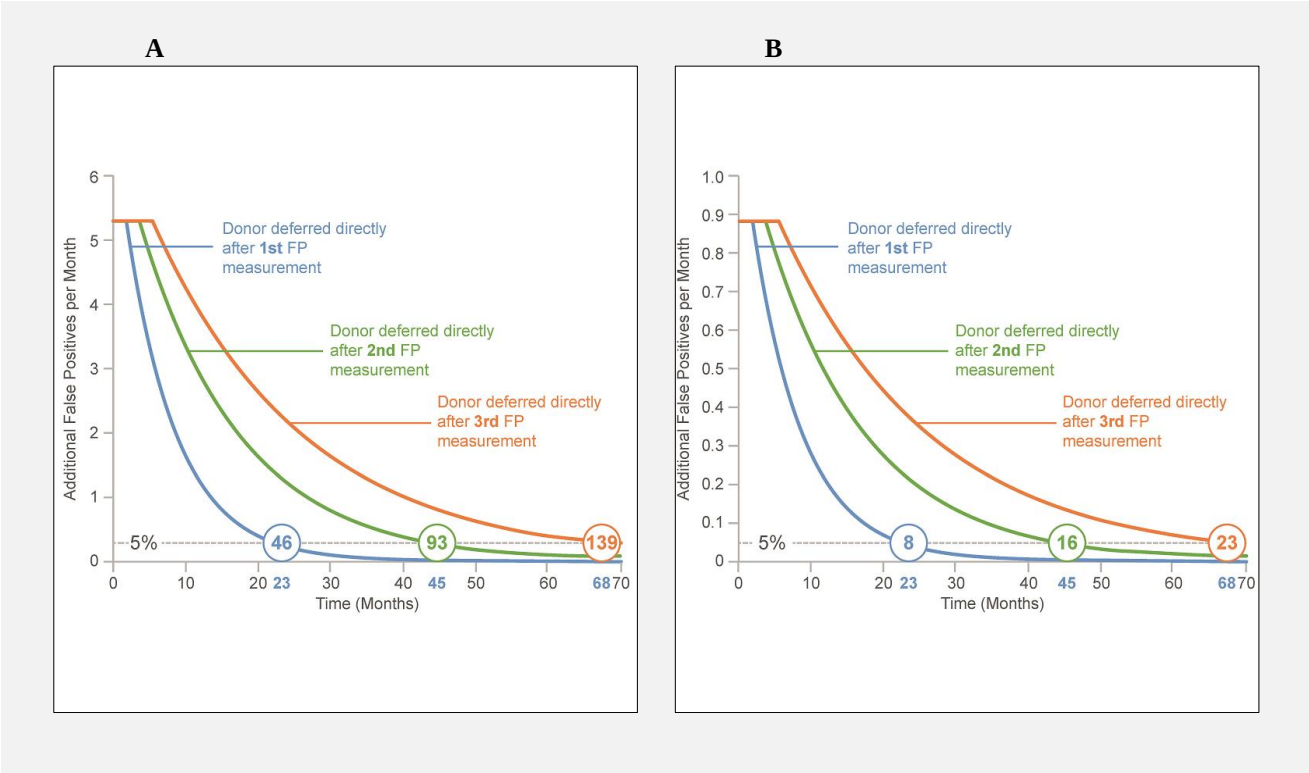

Figure 4. Scenario 2: Variation in assay specificity.

Decrease in additional FP results when using an assay of lower (99.88%) (4A) or higher (99.98%) (4B) specificity, if donors are deferred after 1st, 2nd, or 3rd FP result. All other parameters are identical (10,000 donations from repeat donors per month, average time between donations of 8.8 months, ratio of p_{rep}/p_{first} of 0.56, minimum 55 days between two donations). Numbers in circles are the additional FP results until the donor pool is cleaned and specificity is stable. The highlighted timepoints (months) indicate when the FP rate has dropped to + 5% of the final specificity and is considered cleaned. FP, false positive.

To compare the WCBS RWD and the data generated by the model, the number of FPs at the WCBS center for the HIV, HCV and HBsAg screening tests observed within the first 15.5 months after switching to a new assay were compared with those obtained during the subsequent 15.5 months. The differences are shown in Table 3, where they are compared to the calculated findings.

Results from the mathematical model showed that for the HIV screening assay, 47 additional FP results could be expected within the first 15.5 months post-switch, compared with the subsequent 15.5 months. The actual number demonstrated by the WCBS RWD was 72. For the HCV assay, 63 additional FP results were calculated, whereas 36 were observed at WCBS. Eight additional HBsAg positive results were calculated, and nine were observed at WCBS. The cumulative number of FP results recorded at the WCBS center for HIV, HCV and HBsAg was 117 when comparing the first 15.5 months post-switch with the subsequent 15.5 months. The corresponding value achieved with the mathematical simulation tool was 118.

DISCUSSION

The switch from one screening assay platform to another in a blood donation center is a very time- and cost-intensive investment, and must be planned carefully in advance. Aside from technical features, convenience, hands-on time, and training on a new screening system, there are administrative and ethical considerations [5-7, 10]. Of particular importance is the potential loss of both donors and donations, which is markedly associated with switches to new HIV, HCV, and HBsAg assays, and triggered by an increase in additional FP results followed by an exponential decline in a certain time period [2].

The use of a mathematical model to simulate the potential cleaning effect after a switch to a new blood screening assay has helped clarify the impact of varying relevant parameters on the decrease, then gradual recovery, of specificity following the switch.

The time interval between donations is a parameter with great impact on the cleaning effect, with the longer time interval of 8.8 months protracting the time required for the regular repeat donor pool to be “cleaned” to an equi-

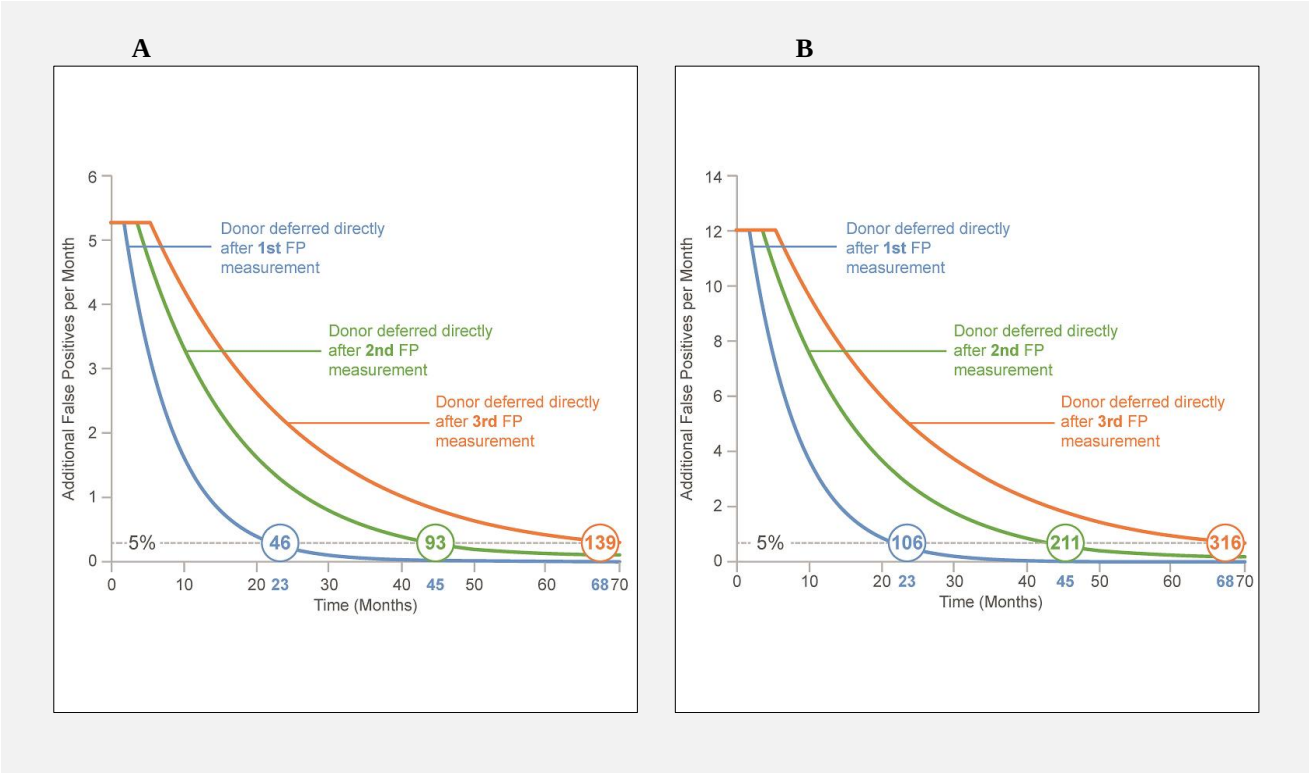

Figure 5. Scenario 3: Variation in ratio of p_{rep}/p_{first}.

Decrease in additional FP results with a ratio of p_{rep}/p_{first} of 0.56 (5A) and a ratio of 0, meaning that only first-time donors and no repeat donors get FP results (5B), if donors are deferred after 1st, 2nd, or 3rd FP result. All other parameters remain unchanged (10,000 donations from repeat donors per month, assay specificity of 99.88%, average time between donations of 8.8 months, minimum 55 days between two donations). FP, false positive.

librium specificity level. According to the model, the cleaning process could take 3 - 4 times longer when a longer (8.8 months) versus a shorter (3.2 months) time interval is selected (Figure 3A, 3B). This effect is enhanced by the larger number of additional FP results observed when the longer time interval between donations is observed; a 2.7 times greater number of additional FP results was generated for the longer time interval, compared with the shorter interval. The cleaning effect is also dependent on the deferral policy of the respective blood donation center (whether donors are deferred after a 1st, 2nd or 3rd FP result). Postponing deferral after the 1st FP result (blue line), until the 2nd (green line) or 3rd FP (orange line) delays the "cleaning" of the donor pool, and this effect can be observed in all three scenarios (Figures 3 - 5). These findings indicate that a shorter time interval between donations, coupled with a conservative deferral policy of donors being deferred after their first FP result, would expedite the cleaning effect and facilitate the restoration of acceptable specificity. Conversely, postponing the deferral of donors with FP results may be beneficial for donor retention [5]. A model was created based on the outcome of several different donor management strategies focusing on donor loss for different anti-human T-lymphotropic virus FP deferral policies. The modeling suggested that waiting until the 2nd or even 3rd FP result before deferring donors may assist donor retention. Hence, when considering donor management strategy following a switch to a new assay, blood donation centers may need to strike a balance between the desire to expedite recovery of specificity and encouraging donor retention.

When assay specificity was varied, the model showed that a higher specificity (i.e., 99.98%) was associated with a lower number of additional FP results than a lower specificity (i.e., 99.88%) (Figure 4A, 4B). This effect was independent of whether donors were deferred following a 1st, 2nd, or 3rd FP result, and the number of FP results was approximately 5 - 6 times smaller with a higher, rather than lower, specificity.

When the ratio of p_{rep}/p_{first} to be FP was reduced from 0.56 (probability of an FP result roughly twice as high for first-time than for repeat donors) to 0 (an FP result for first-time donors only), results from the model reflected a 2.3 - 2.7 times greater number of FPs (Figure 5A, 5B). It should be noted, however, that a ratio of $p_{rep}/p_{first} = 0$ is a purely theoretical assumption not

seen in practice, as FP results are not only observed in first-time donors.

Various other parameters not discussed here could potentially influence the cleaning effect and may be worthy of consideration by blood donation centers. These include the minimum time between donations being defined by regional/national regulations, and the proportion of number of regular repeat donors versus first-time donors. Furthermore, different parameters may have a combined impact (e.g., combining different assay specificities with different average times between donations) which could prolong or shorten the cleaning effect. The model we have developed can be individualized depending on the needs of each blood bank by using different key parameters as input variables. Thus, the model can effectively be utilized by different blood bank centers, irrespective of any variations in appropriate parameters. The information generated could alert the donation center to the possibility that a cleaning effect might occur upon switching to a new assay, and inform on the degree and duration of this effect. In addition, the information could facilitate the decision to switch to a new assay, or one from a new manufacturer, by alleviating potential concerns, and assist with planning any necessary adjustments to accommodate the impact on the center's business.

Depending on the number of additional FPs, and the presumed time period until stable specificity is restored, a blood donation center may plan ahead with a donor reinstatement program to retrieve blood donors who may have been previously banned from donation due to continuous FP results for the respective parameter(s) prior to the switch. It is probable that results identified as FPs by the former assay are correctly found negative with the new assay platform [14]. The re-entry of these previously banned donors to the donor population could help compensate for a potential loss of donors during the cleaning effect.

CONCLUSION

We have developed a mathematical model for use as a simulation tool to 'test' the cleaning effect that could occur when introducing a new blood screening assay to a blood donation center. Data generated by the model for additional FP results during a given time period before and after an assay switch corresponded well with recorded RWD. Our findings support the use of the model as a simulation tool to help blood donation centers anticipate any potential loss of donors/donations, and the time until a stable specificity level is reached, following switch to another infectious disease blood screening assay or assay manufacturer. Further studies are required to verify these data in other blood screening centers with different specific impact variables, and to establish if the same high level of congruence between simulation and recorded data is observed.

Acknowledgment:

COBAS, COBAS E, and ELECSYS are trademarks of Roche. All other product names and trademarks are the property of their respective owners. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Elizabeth Hilsley, BSc of Ashfield MedComms (Macclesfield, UK), an Ashfield Health company, and was funded by Roche Diagnostics International Ltd., (Rotkreuz, Switzerland).

Study Funding:

No funding to declare.

Declarations of Interest:

Florian Dufey and Florina Langen are employees of Roche Diagnostics GmbH. Charlotte Pistorius, Russell Cable and Walter Melchior declare no conflicts of interest.

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