

Optimale belasting van anti-RhD donors: selectie van optimale booster- en donatiefrequenties op basis van individuele donorkarakteristieken.

Eliau Griffioen
Supervisor: Mart Janssen

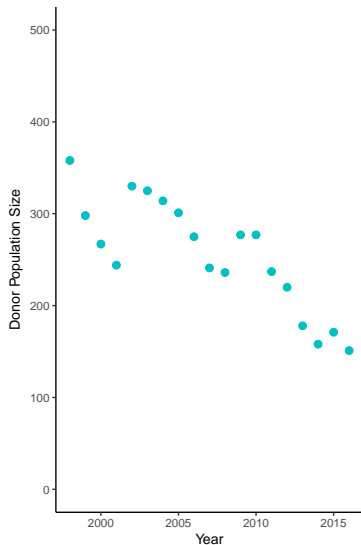
Transfusion & Technology Assessment, Sanquin Bloedvoorziening
Departement Methoden en Statistiek, Universiteit Utrecht

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Rhesusprik wordt toegediend om rhesusziekte te voorkomen

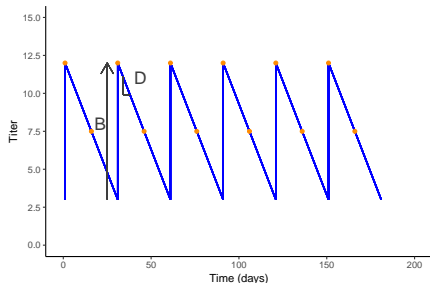
Donorpopulatie neemt af:

- Donors worden te oud
- Weinig nieuwe natuurlijk gemmuniseerde potentile donors door succes rhesusprik



Donorkarakteristieken bepalen opbrengst (titer) van donatie:

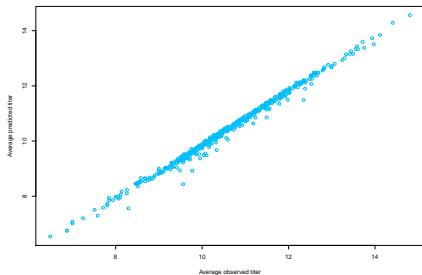
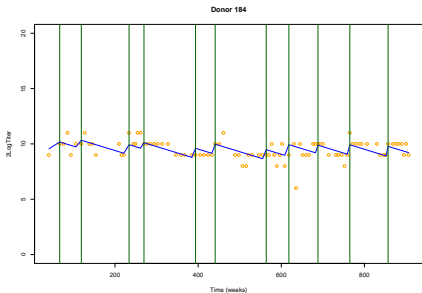
- Booster effect (B): toename na toediening van RhD-antigen aan donor
- Daalsnelheid (D): natuurlijke daling in titer over de tijd



Doel: op basis van individuele donorkarakteristieken optimale booster-en donatiefrequenties vinden

Drie unieke parameters geschat voor elke donor:

- Daalsnelheid (D): afname titer per 14 dagen
- Booster effect: toename in titer na booster event
($B = B_{abs} - c \cdot T_0$)
 - Absoluut booster effect (B_{abs}): toename in titer na booster bij $T_0 = 0$
 - Correctie coefficient (c): afname van booster effect als T_0 toeneemt



Donors worden verdeeld in vier groepen op basis van daalsnelheid en booster effect

Doel: zo min mogelijk inspanning voor de donors wat betreft boosters en donaties

Voorwaarden:

- Jaarlijkse vraag voor anti-RhD immunoglobulines
- Aantal boosters tussen 1 en 5 per jaar
- Aantal donaties tussen 1 en 26 per jaar

Optimaliseer booster- en donatiefrequentie voor elke groep donors

Minimaliseer doelfunctie: combinatie van

- 1 Gemiddeld aantal donaties
- 2 Gemiddeld aantal boosters
- 3 Verschil in groepen tussen donaties

Oplossing is booster- en donatiefrequentie voor elke groep donors

- Inspanning van gehele donor populatie minimaal
- Genoeg immunoglobulines voor Sanquin

Table: Geoptimaliseerde donatie- en boosterfrequenties, subset grenzen en gecorrigeerde subsetgroottes for strategieën met verschillende gewichten voor de penaltyfunctie

Gewicht Afwijking in donatie- frequentie (γ)	Aantal per jaar*								Grenzen		Subsetgroottes [†] (n)			
	HB-LD		HB-HD		LB-LD		LB-HD		Plateau	Daal- snelheid ($\cdot 10^{-2}$)	HB-LD	HB-HD	LB-LD	LB-HD
	Boosters	Donaties	Boosters	Donaties	Boosters	Donaties	Boosters	Donaties			HB-LD	HB-HD	LB-LD	LB-HD
0			1/3	1/3	1/3	1/3	1/3	1/3	13.5	-1.56	27	30	41	52
2	2/3	11 1/3	1/3	1/3	1/3	1/3	1/3	1/3	13.5	-1.49	25	33	39	54
3	1	7	1/3	2	1/3	2	1/3	2	13.5	-1.49	25	33	39	54
5	1	7	1/3	4	1/3	4	1/3	4	13.5	-1.49	25	33	39	54
8	1	7	1/3	5	1/3	5	1/3	5	13.5	-1.49	25	33	39	54
19	1	7	1/3	6	1/3	6	1/3	6	13.5	-1.48	24	33	39	54
100	1	7	1/3	7	1/3	7	1/3	7	13.5	-1.48	24	33	39	54

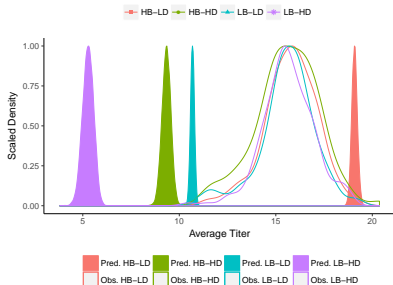
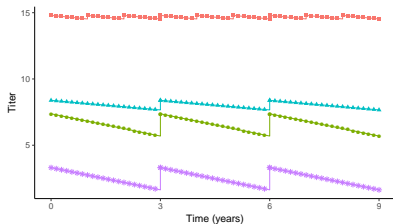
[†] Oorspronkelijke subsetgroottes waren 30, 27, 40, and 43 voor respectievelijke HB-LD, HB-HD, LB-LD, and LB-HD donors.

Huidige strategie Sanquin:

- Boosters als titer beneden bepaalde waarde is
- Titer verschilt amper tussen donors

Optimale strategieën laten zien:

- Sterke donors kunnen veel meer leveren dan ze nu doen
- Overige donors hoeven minder geboosterd te worden en te doneren



Op basis van data kunnen er met deze procedure geoptimaliseerde donatie- en boosterfrequenties bepaald worden

Een kleine groep donors goed benutten zorgt voor verlichting voor overige donors

Data-gedreven donor management is een oplossing voor de afname van anti-RhD donors

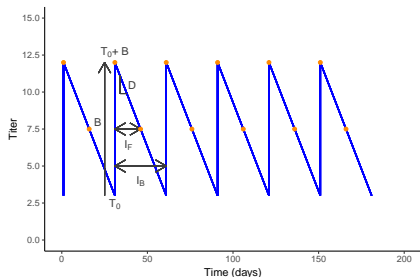
Strategieën alleen gevalideerd op historische data

Historische data van donorpopulatie komt niet overeen met huidige donorpopulatie

Volgende stap: behandel kleine groep donor volgens strategie en test of de uitkomsten zijn zoals verwacht

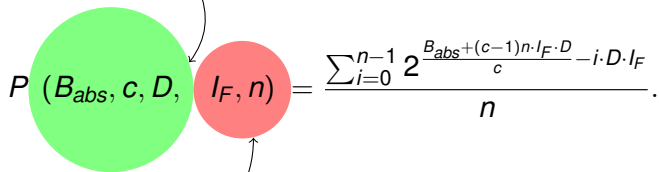
The titer (yield of donation) of a donor is described with several parameters

- Natural decline rate per day D
- Boostering effect B , modelled as $B = B_{abs} - c \cdot T_0$
 - B_{abs} : absolute boosting effect (B at $T_0 = 0$)
 - c : correction coefficient, corrects for inverse relation boosting effect and titer at boosting T_0
- Donation frequency f
- Boostering frequency b



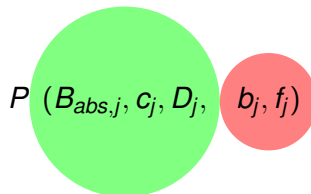
The average titer per donation per donor is formulated as

- Estimated with data


$$P(B_{abs}, c, D, I_F, n) = \frac{\sum_{i=0}^{n-1} 2^{\frac{B_{abs} + (c-1)n \cdot I_F \cdot D}{c} - i \cdot D \cdot I_F}}{n}.$$

- Selected in strategy

We derived a function to compute the three-year anti-RhD immunoglobulin production with individual strategy parameters b_j and f_j and individual donor characteristics $B_{abs,j}$, c_j and D_j .


$$P(B_{abs,j}, c_j, D_j, b_j, f_j) = \sum_{j=1}^J b_j \cdot \sum_{i=0}^{f_j/b_j - 1} 2^{\left(\frac{B_{abs,j} + (c_j - 1) \frac{1}{b_j} \cdot 1095 \cdot D_j}{c_j} - i \cdot D_j \cdot \frac{1095}{f_j} \right)}$$

Donor characteristics are estimated with longitudinal data of Sanquin; strategy parameters are determined in optimization steps

$$Titer_{i,t} = \beta_{0,i} + \beta_{1,i} Fortnights_{i,t} + \beta_{2,i} \sum_{k=1}^t Boost_{i,k} + \beta_{3,i} \sum_{k=1}^t Boost_{i,k} \cdot Titer_{i,k-1} + e_{i,t},$$

$$e_{i,t} \sim \mathcal{N}(0, \sigma^2), \quad t = 1, \dots, T_i, \quad \text{and } i = 1, \dots, N.$$

- D_j : decrease in titers per fortnight, represented with $\beta_{1,i}$
- $B_{abs,j}$: the increase in titer after a booster event at a titer at boosting of zero ($T_0 = 0$), represented with $\beta_{2,i}$
- c_j : the correction coefficient c corresponds to the decrease in boosting effect at an increase of titer at boosting with one and is represented with $\beta_{3,i}$

To find optimal strategies, we minimize a penalty function with constraints

$$\underset{b_j, f_j}{\text{minimize}} \quad \alpha \sum_{j=1}^4 \frac{n_j b_j}{15 n_{tot}} + \beta \sum_{j=1}^4 \frac{n_j f_j}{78 n_{tot}} + \gamma \sum_{j=1}^4 \frac{n_j (f_j - \bar{f})^2}{1482.25 n_{tot}}$$

$$\text{subject to} \quad 1 \leq b_j \leq 15, \quad j = 1, \dots, 4,$$

$$1 \leq f_j \leq 78, \quad j = 1, \dots, 4,$$

$$P(f_j, b_j, B_{abs,j}, c_j, D_j) \geq 13,500,000$$

Solutions are booster and donation frequencies for each subset of donors

For each strategy, the penalty function is minimized with constraints by varying the subset boundaries for the plateau (p_b) and decline rate (D_b)

$$\begin{aligned} & \underset{p_b, D_b}{\text{minimize}} && \alpha \sum_{j=1}^4 \frac{n_j(p_b, D_b) \cdot b_j}{15 \cdot n_{tot}} + \beta \sum_{j=1}^4 \frac{n_j(p_b, D_b) \cdot f_j}{78 \cdot n_{tot}} + \gamma \sum_{j=1}^4 \frac{n_j(p_b, D_b) \cdot (f_j - \bar{f})^2}{1482.25 \cdot n_{tot}} \\ & \text{subject to} && P[f_j, b_j, B_{abs,j}(p_b, D_b), c_j(p_b, D_b), D_j(p_b, D_b)] \geq 13,500,000 \\ & && n_j(p_b, D_b) \geq 20, j = 1, \dots, 4 \end{aligned}$$

Solutions are subset boundaries for each strategy

		Mean	Standard Error of Estimate	95-% Credibility Interval	Effective sample size (N_{eff})
Part 1*	$\mu_{\beta_0}^\dagger$	9.3	0.00047	9.1 , 9.5	60 000
	μ_D	-0.016	$2.2 \cdot 10^{-6}$	-0.017 , -0.015	60 000
	$\mu_{B_{abs}}$	2.2	0.0019	2.1 , 2.3	793
	μ_C	-0.16	0.00022	-0.17 , -0.15	548
	$\sigma_{\beta_0}^2$	5.9	0.0016	5.2 , 6.7	60 000
	σ_D^2	$8.9 \cdot 10^{-5}$	$2.7 \cdot 10^{-8}$	$7.6 \cdot 10^{-5}$, 0.0001	60 000
	$\sigma_{B_{abs}}^2$	0.21	$6.1 \cdot 10^{-5}$	0.18 , 0.24	60 000
	σ_C^2	$1.2 \cdot 10^{-5}$	$6.7 \cdot 10^{-9}$	$1 \cdot 10^{-5}$, $1.4 \cdot 10^{-5}$	25 281
Part 2*	μ_{β_0}	9.3	0.00045	9.1 , 9.5	60 000
	μ_D	-0.016	$2.2 \cdot 10^{-6}$	-0.017 , -0.015	60 000
	$\mu_{B_{abs}}$	2.3	0.0032	2.1 , 2.4	326
	μ_C	-0.17	0.00036	-0.18 , -0.16	228
	$\sigma_{\beta_0}^2$	6.1	0.0016	5.3 , 6.9	60 000
	σ_D^2	$9.1 \cdot 10^{-5}$	$2.8 \cdot 10^{-8}$	$7.9 \cdot 10^{-5}$, 0.00011	60 000
	$\sigma_{B_{abs}}^2$	0.23	$6.6 \cdot 10^{-5}$	0.2 , 0.26	60 000
	σ_C^2	$2.1 \cdot 10^{-6}$	$1.1 \cdot 10^{-9}$	$1.8 \cdot 10^{-6}$, $2.5 \cdot 10^{-6}$	27 719

Table: Optimized donation and boosting frequencies, subset boundaries, and corrected subset sizes for strategies with different weights of the terms in the penalty function

Weights Deviation in donation frequency (γ)	Annual Frequency*								Boundaries		Subset size [†] (n)				
	HB-LD		HB-HD		LB-LD		LB-HD		Plateau	Rate ($\cdot 10^{-2}$)	Decline	HB-LD	HB-HD	LB-LD	LB-HD
	Boosters	Donations	Boosters	Donations	Boosters	Donations	Boosters	Donations				HB-LD	HB-HD	LB-LD	LB-HD
0	$\frac{2}{3}$	11 $\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	13.5	-1.56	27	30	41	52
2	1	7	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	13.5	-1.49	25	33	39	54
3	1	7	$\frac{1}{3}$	2	$\frac{1}{3}$	2	$\frac{1}{3}$	2	13.5	-1.49	25	33	39	54	
5	1	7	$\frac{1}{3}$	4	$\frac{1}{3}$	4	$\frac{1}{3}$	4	13.5	-1.49	25	33	39	54	
8	1	7	$\frac{1}{3}$	5	$\frac{1}{3}$	5	$\frac{1}{3}$	5	13.5	-1.49	25	33	39	54	
19	1	7	$\frac{1}{3}$	6	$\frac{1}{3}$	6	$\frac{1}{3}$	6	13.5	-1.48	24	33	39	54	
100	1	7	$\frac{1}{3}$	7	$\frac{1}{3}$	7	$\frac{1}{3}$	7	13.5	-1.48	24	33	39	54	

[†] Original corrected donor subset sizes were 30, 27, 40, and 43 for HB-LD, HB-HD, LB-LD, and LB-HD respectively.

Table: Optimized donation and boosting frequencies, production, risk, and expected difference for strategies with different weights of the terms in the penalty function.

Weights Deviation in donation frequency (γ)	Annual Frequency*								Results [‡]			
	HB-LD		HB-HD		LB-LD		LB-HD		Production (10^7)	Risk (%)	Expected difference (10^5)	
	Boosters	Donations	Boosters	Donations	Boosters	Donations	Boosters	Donations				
0	$\frac{2}{3}$	$11\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	1.377	3.8	4.204
2	1	7	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	1.358	7.1	5.070
3	1	7	$\frac{1}{3}$	2	$\frac{1}{3}$	2	$\frac{1}{3}$	2	$\frac{1}{3}$	1.365	6.3	4.953
5	1	7	$\frac{1}{3}$	4	$\frac{1}{3}$	4	$\frac{1}{3}$	4	$\frac{1}{3}$	1.373	5.3	4.880
8	1	7	$\frac{1}{3}$	5	$\frac{1}{3}$	5	$\frac{1}{3}$	5	$\frac{1}{3}$	1.377	5.0	4.780
19	1	7	$\frac{1}{3}$	6	$\frac{1}{3}$	6	$\frac{1}{3}$	6	$\frac{1}{3}$	1.350	7.8	4.986
100	1	7	$\frac{1}{3}$	7	$\frac{1}{3}$	7	$\frac{1}{3}$	7	$\frac{1}{3}$	1.354	7.3	4.869

[‡] Production and expected difference are calculated in titer units.