Sanquin

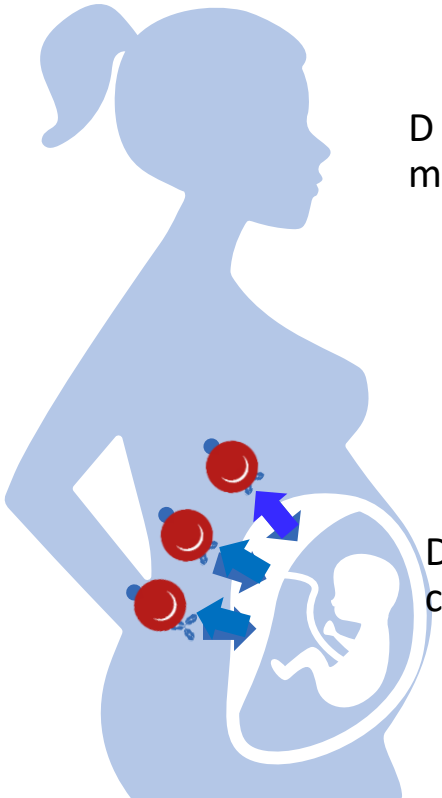
Can we have a common European Anti-D plasma programme?

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on behalf of the TS119 Anti D Working Group of CD-P-TS

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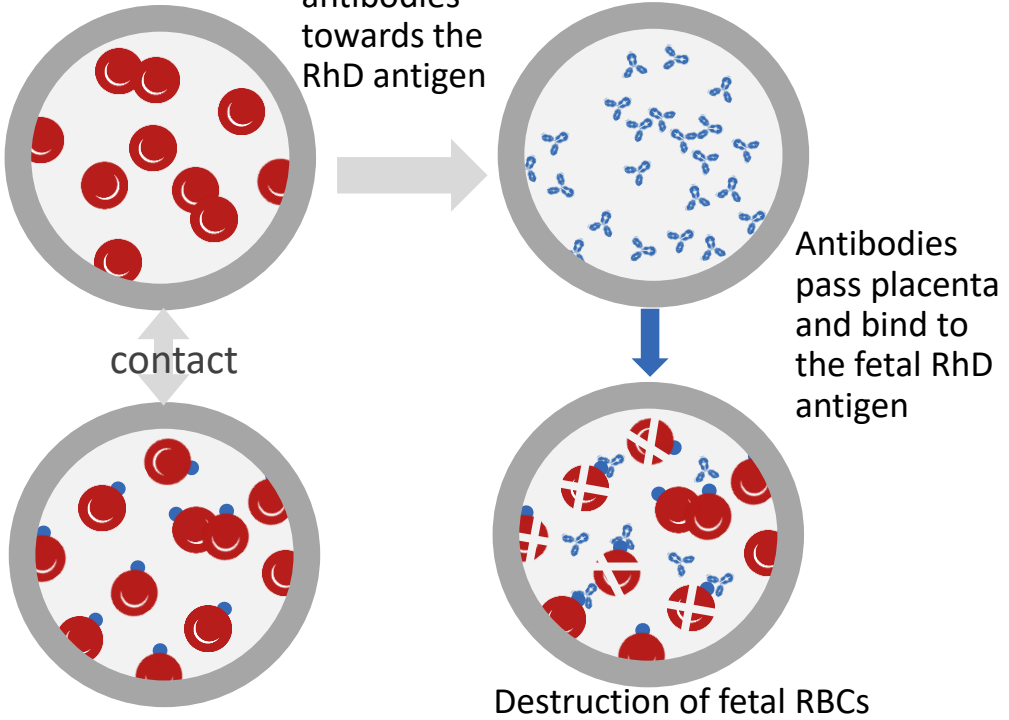
For Life.

Hemolytic disease of fetus newborn (HDFN)



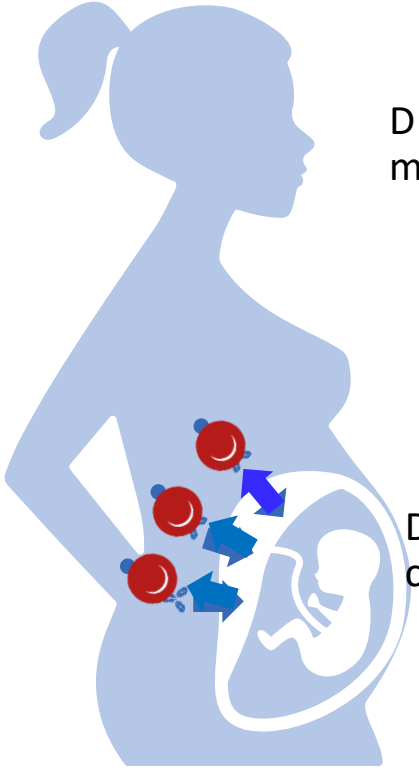
D neg mother

D pos child



Anti-D Ig prevents immunization

HDFN has become a rare disease



Before introduction of immunoprophylaxis

- 17 % of women at risk became immunized

After introduction of postnatal prophylaxis

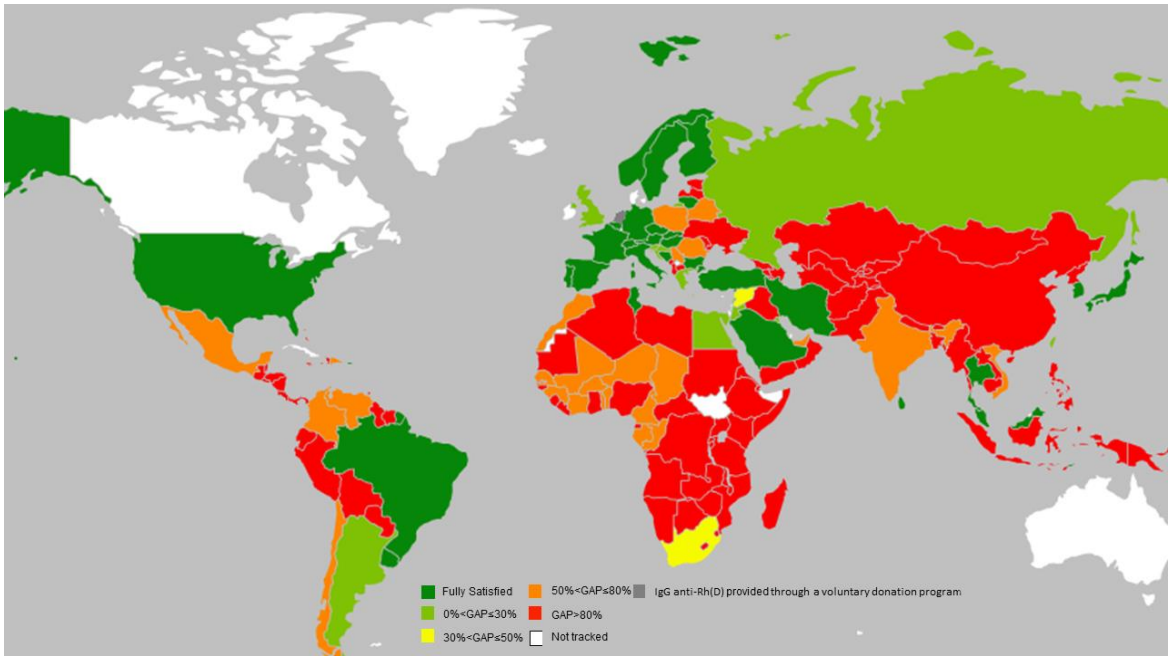
- 0.6% of women at risk became immunized

Combined antenatal and postnatal prophylaxis

- 0.3% of women at risk become immunized

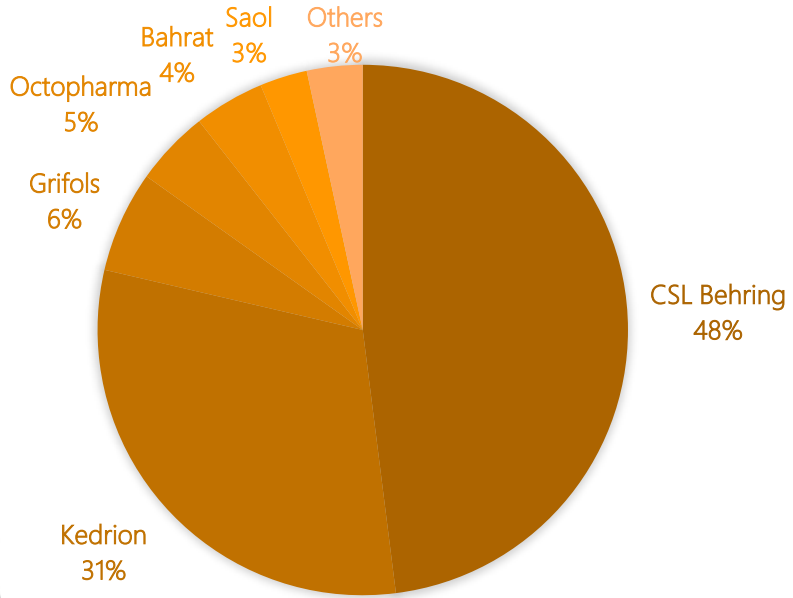
Anti-D immunoprophylaxis is prepared
from human plasma of hyperimmunized donors

Gap between demand and supply:
50% of the women do not get anti-D



Pegoraro V et al.
PLoS ONE 2020;15: e0235807

Total market of Rh immunoglobulin 4.4 x10^6 Units (2020)



All current anti-D IgG licensed in EU are national MA (no central MA)

Anti-D plasma donors

- IPFA 2023: no European member is collecting anti-D plasma
- PPTA survey 2020 : Entire EU supply for anti-D IgG is from US donors

- During COVID pandemics: 25% decrease in available anti-D plasma

- Inventory TS119 Working Group – Anti D Immunoglobulin (2023)
  - The Netherlands stopped anti-D program in 2020
  - Ukrain is collecting anti-D plasma at 4 sites
  - Poland is collecting and fractionating anti-D plasma but no active hyperimmunization program in place

Anti-D Ig from European donors?

- Donor recruitment and sustainability
- Plasma collection and fractionation
- EMA Regulations

Donors recruitment

Ethical considerations:

- Donors are at risk for hemolytic transfusion reactions in emergency situations(especially in Asia)

How many donors are needed? (4.10^6 births /year in EU)

Very much dependent on the efficiency of the program

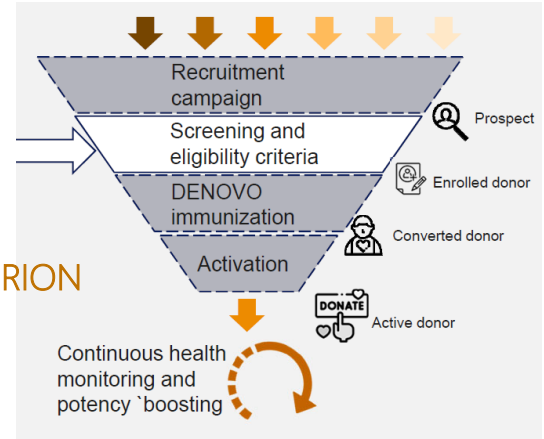
- The Netherlands (stopped collection program in 2020)
  For 170.000 births we would have needed 640 anti-D donors (5 donations/year)

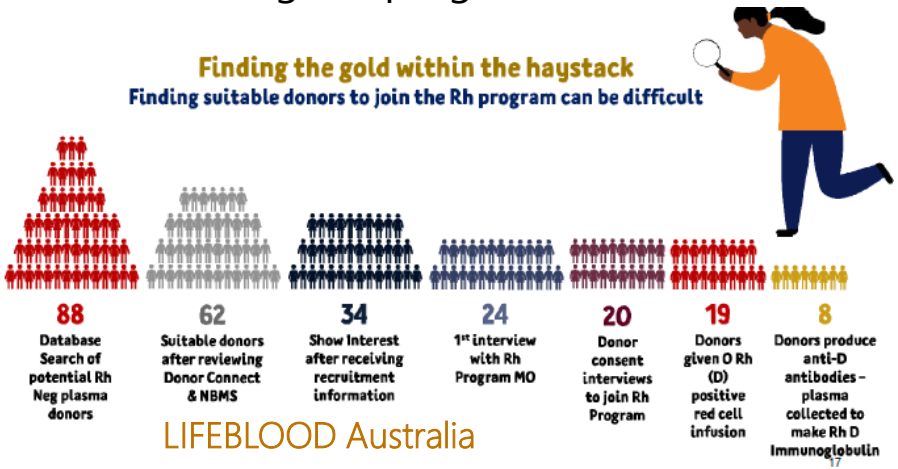
- Australia is self sufficient since 2006
  In 2020 315.000 births and 100 anti-D donors (4 donations/year, >45 IU /mL)

- Kedrion (>30% of world wide supply)
  3 de novo immunization sites, 5 collection sites (100 donations /year)

Which RhD negative donors are eligible?

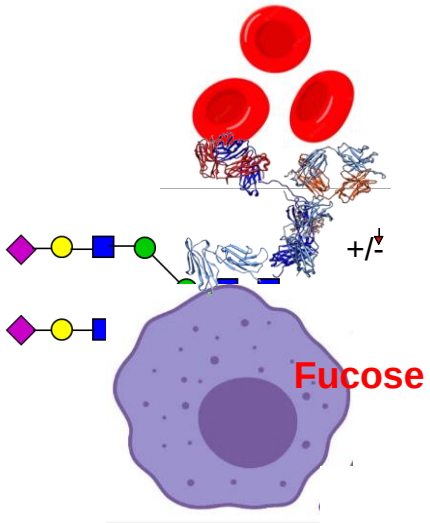
- Eligible as blood donor
- male or post-menopausal women
- Commitment to donate for long period (distance to centre)
- Reaching high anti-D titers (33-50% of donors entering the program!)

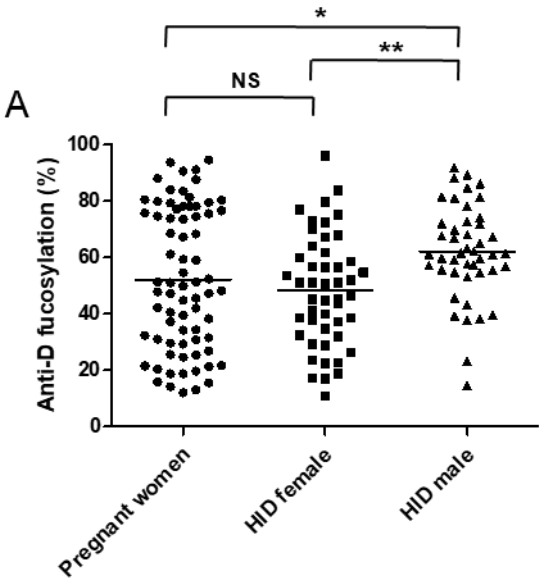


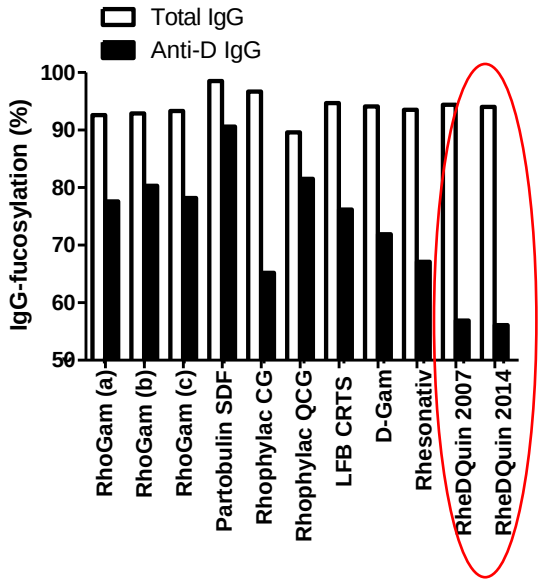


Naturally immunized or de novo donors?

Pregnancy induced anti-D IgG display **optimal** Fc-fucosylation profile







Kapur R et al. Transfusion. 2015;55:553-62

Facilitators and barriers for RhD-immunized women to become and remain anti-D donors

- Questionnaire to women (43-65 yrs) with anti-D antibodies
  - 93 of 134 women (**~ 70%)** would have considered **to become donors** if they had known about the possibility

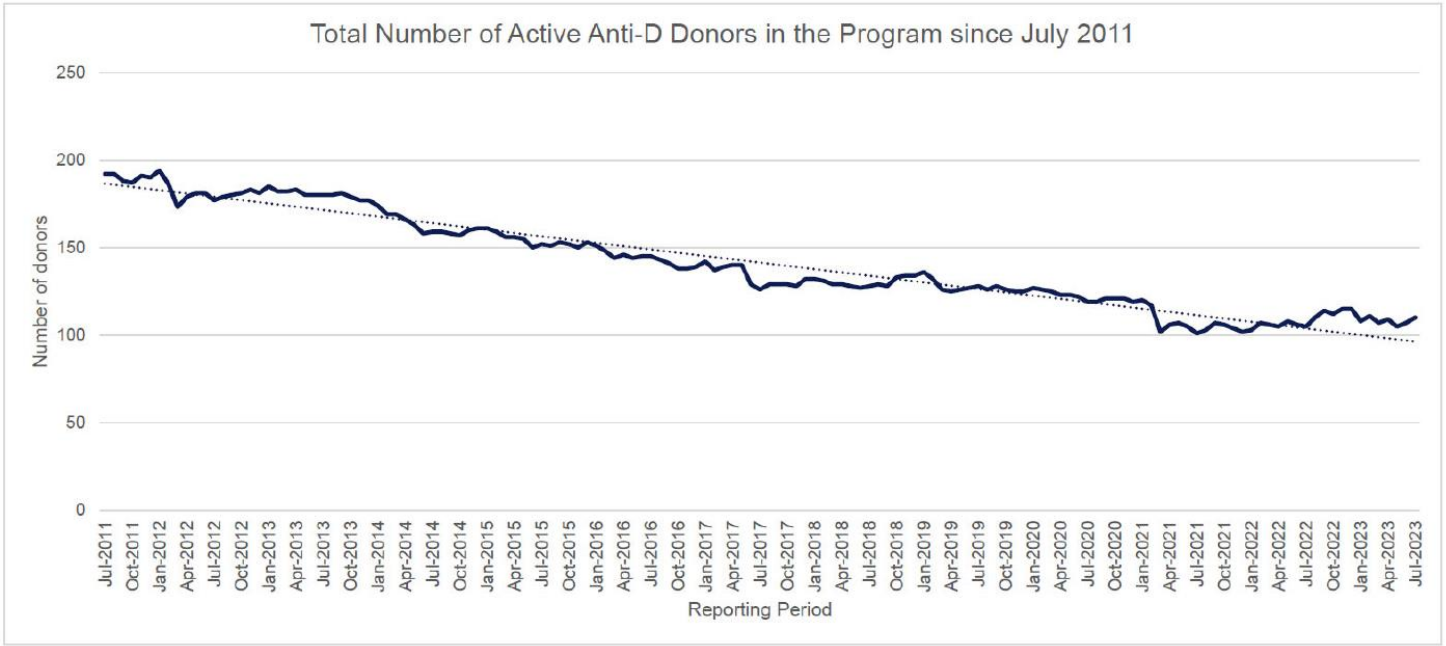
- Motivators of being anti-D donors (n=174)
  - Anti-D donors are needed
  - It does not cost me much trouble, and it helps others
  - I want to do something in return

- Negative factors of anti-D donorship (n=174)
  - Time (36%)
  - Travel time (21%)
  - No negative factor (50%)

Slootweg YM et al. Transfusion 2018;58:960-968

Sustainability?
Lifeblood-Australia

5.2. National summary of Rh Program active donors since July 2011



European plasma collection and fractionation
Hurdles to overcome

- Each EU Member State sets individual plasma and HI-IG donor requirements

➢ Anti-D donor provisions need to be adjusted per EU country
➢ Small volume batches : Administration, effort and resource-intensive for collectors and manufacturers (effort) compared to volume(s) (>1000 L /lot)

- NOTE: US HI-IG plasma is in regulatory terms ‘universally’ accepted in EU

➢ Would it be possible to pool plasma units collected in different European countries?
  - IPFA: In the case of anti-D, derogations to this state-of-the-art practice may be accepted at the level of fractionators

EMA regulations

Biological, pharmacodynamic and pharmacokinetic data

- *In vitro* potency assays addressing red cell destruction to assess product comparability
- The pharmacodynamic effect is established
- Single dose pharmacokinetics studies should be carried out in 15 Rh(D) negative subjects

EMA regulations
Clinical trial

• Effective prevention of Rh(D) isoimmunization in Rh(D) negative women who are pregnant with a Rh(D) positive fetus (including D, Dweak, Dpartial)

• At least 200 non-immunised patients and should include both ante-partum and post-partum administration

• Blood samples should be collected just before treatment and at 72 hours and 3-6 months after treatment with the anti-D immunoglobulin

Summarizing remarks and conclusions

- Worldwide shortage of anti-D : more anti-D donors are needed
- Recruitment of donors naturally immunized by pregnancy might be considered
- Europe is completely dependent on US plasma
- European anti-D plasma collection is needed, but to become cost-effective harmonization of European Hyperimmune IgG requirements is needed in order to make pooling of plasma possible

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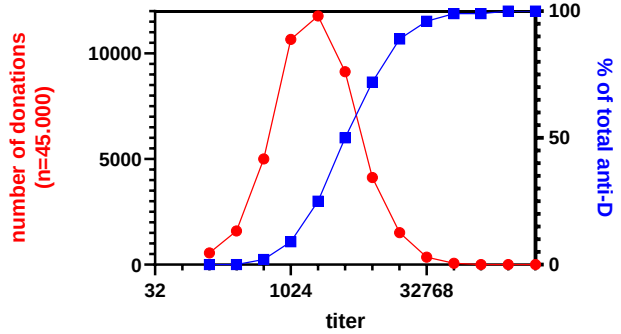
Prof. Morten Hanefeld Dziegiel (DK),

Dr Soner Yilmaz (TR)

Aleksandra Nowakowska (PL)

Potential improvements to increase yield

- Donation frequency has not been guided by titers!



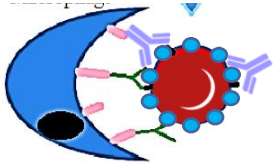
60% of donations
titers ≤ 2000
only 25% of total anti-D

  - ➢ More frequent plasmapheresis of only donors with highest titers will increase the yield and might even decrease the total number of fereses

- Optimization of hyperimmunization protocol (not evidence based)
- Better timing of plasmapheresis in relation to boost immunization
- Pre-selection of HLA-DRB1*15*01 positive donors?

Working mechanism of anti-D Ig?

1. Clearance of RBCs ?



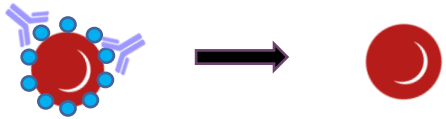
NOT THE ONLY mechanism : Moabs that clear are less effective than polyclonal IgG

2. Epitope masking?

NO (no sturation needed)



3. Antigen modulation?



POSSIBLY: In murine models of antibody mediated immune suppression antigen modulation is major mechanism