“D” times they are a-changin’… Using RhD-positive RBCs in massive bleeding

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Disclosures

- Grífols: Honoraria & SAB
- Macopharma: Scientific advisory board
- Octapharma: Scientific advisory board

- Terumo: Honoraria and travel reimbursement
- Haemonetics: Honoraria
- Cook Biotech: Scientific advisory board
- Verax Biomedical: Scientific advisory board
- Hemanext: Honoraria, scientific advisory board
- Aktivax: Scientific advisory board
- Cerus: Travel reimbursement

How to provide transfusions if you don't know the recipient's type

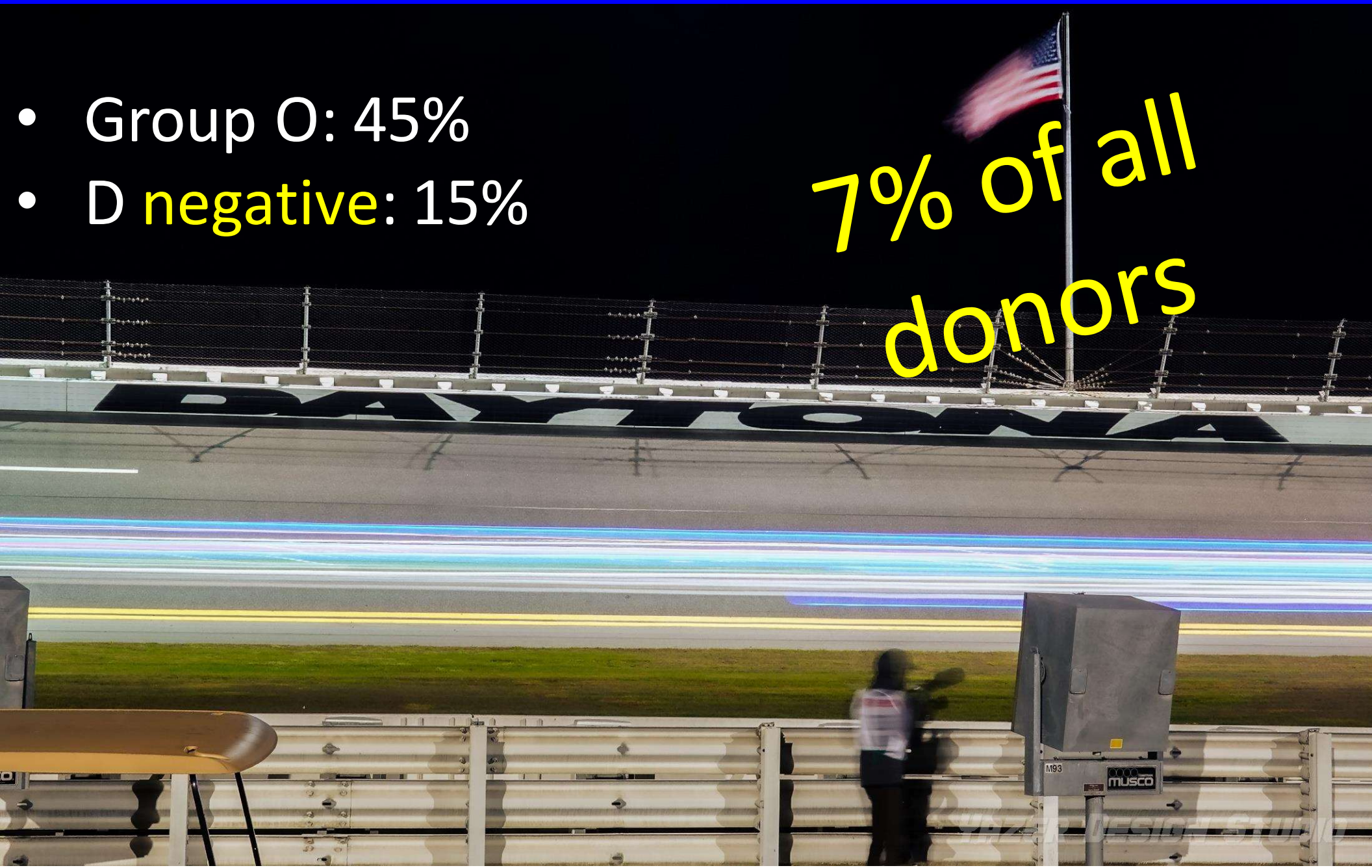
- Group O RBCs
  - Safe for all recipients of any ABO group
- There's a protein on most people's RBCs called RhD
- Very immunogenic
  - "Very" is a relative term
- D- recipients can make anti-D after D+ transfusion
- Ideally, we would give everyone D- RBCs until we know they are D+

Highmark Stadium

It's not easy to find RhD-negative RBC donors?

- Group O: 45%
- D negative: 15%

7% of all donors



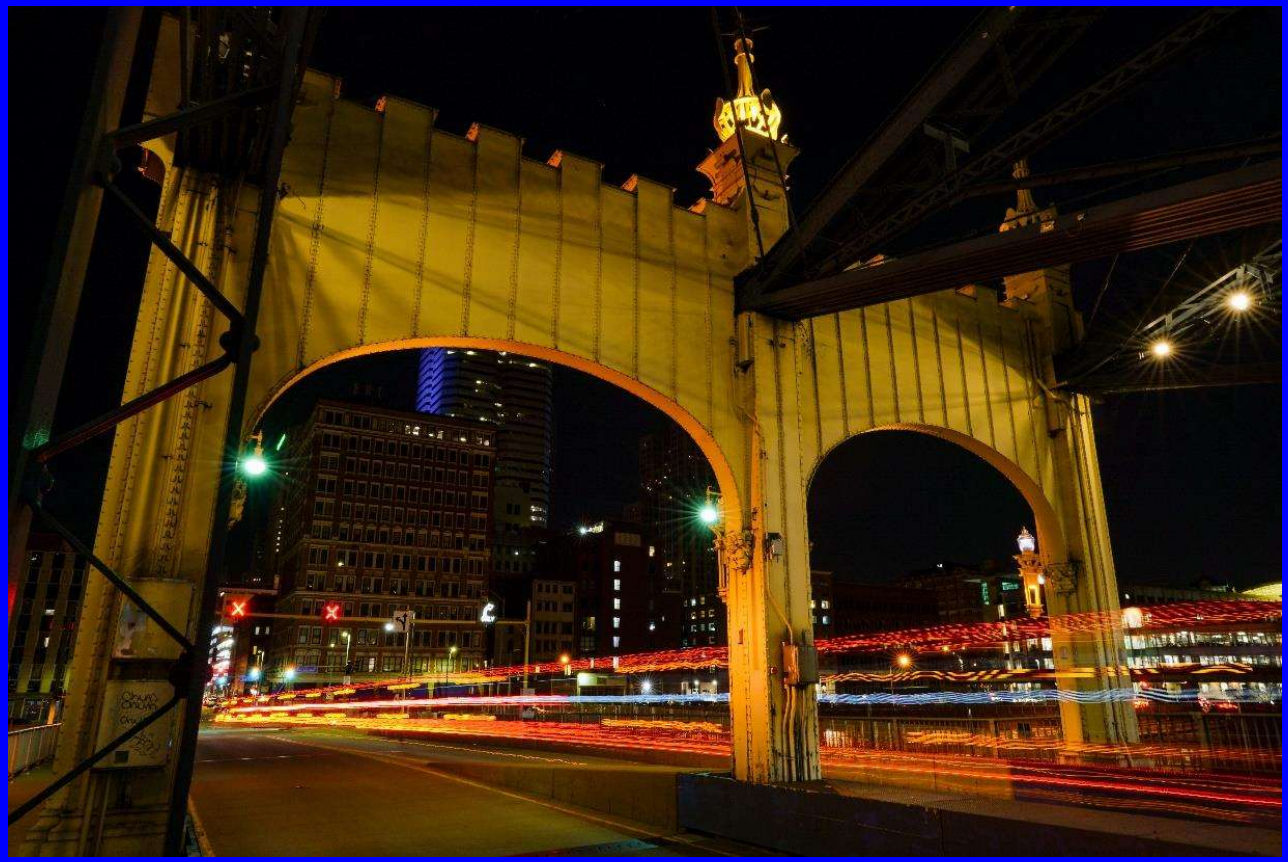
It's not easy to find RhD-negative LTOWB donors?

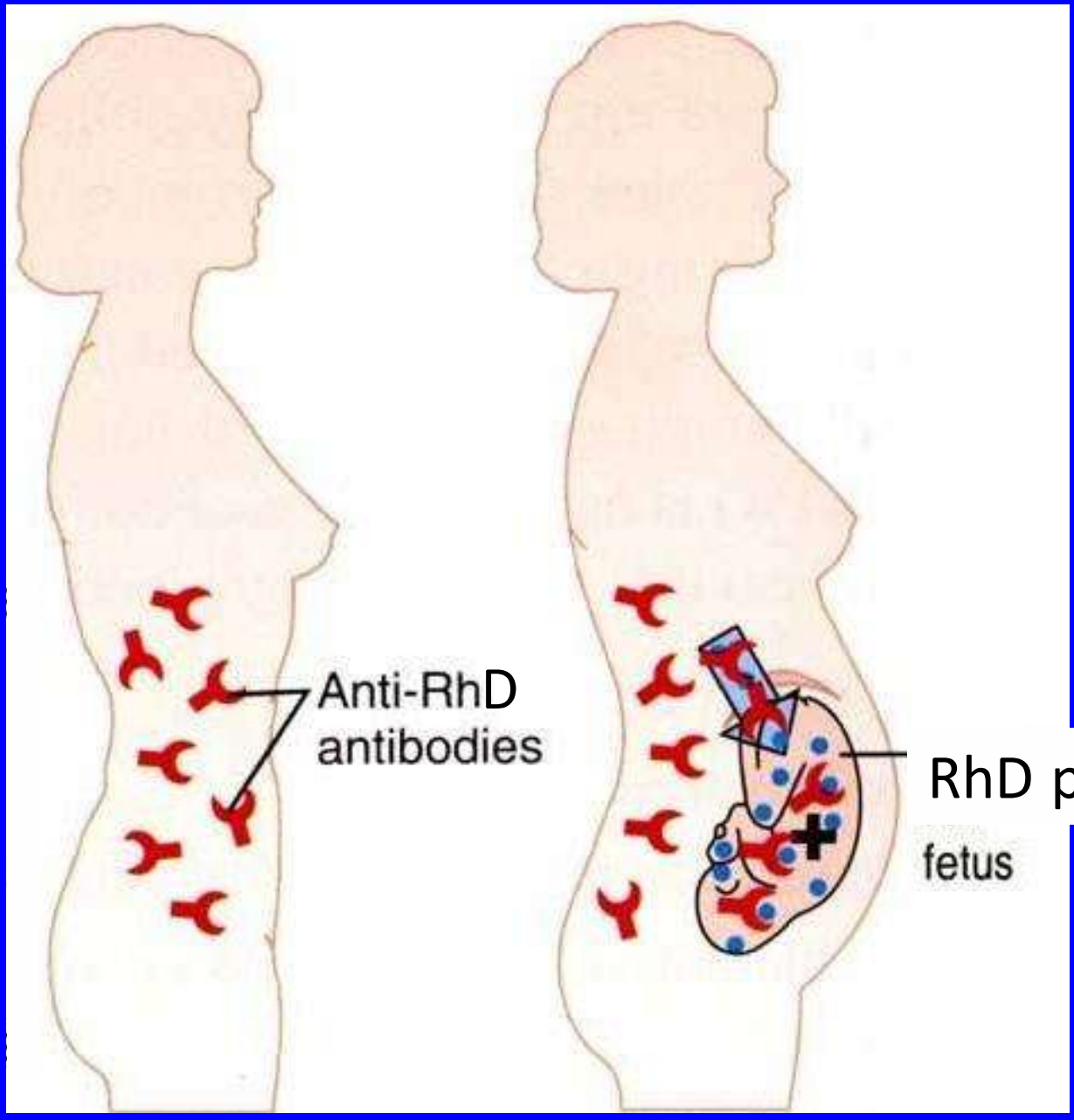
- Male donors: 50%
- Group O: 45%
- D negative: 15%
- Low titer (<100): 93%

3% of all donors

Consequences of D-alloimmunization

1. Immediate hemolytic reactions following D+ transfusion
2. Future delated hemolytic reactions
3. Hemolytic disease of the fetus and newborn (HDFN)

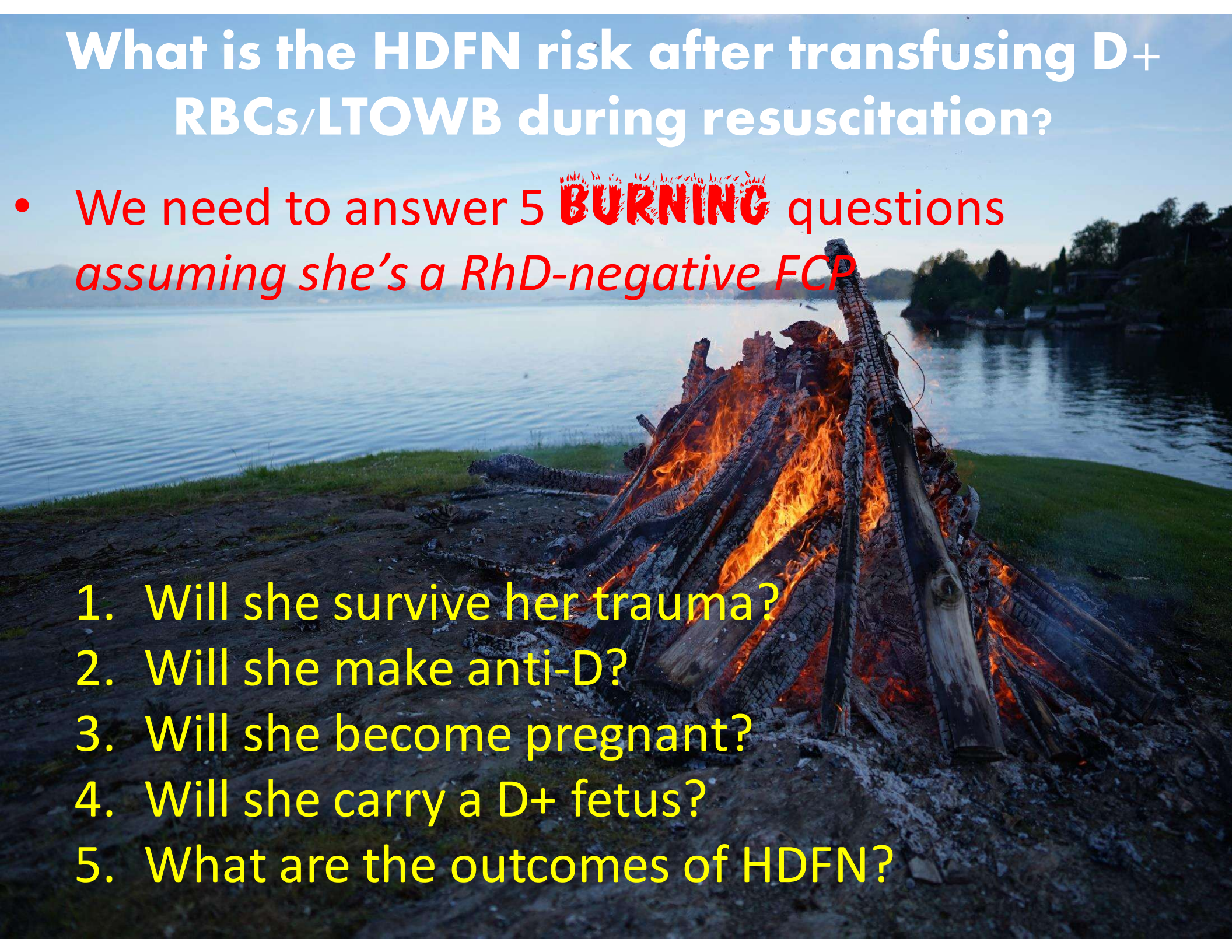




A potential problem for females of childbearing potential (FCP)

What is the HDFN risk after transfusing D+ RBCs/LTOWB during resuscitation?

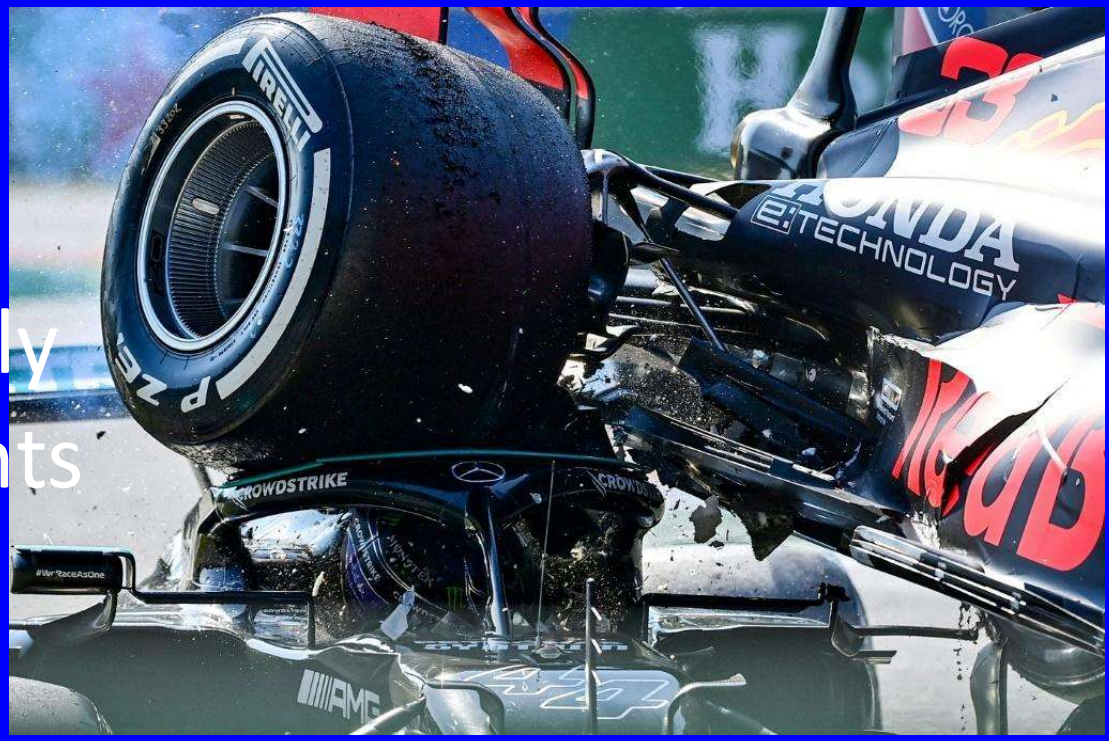
- We need to answer 5 **BURNING** questions
  assuming she's a RhD-negative FCP



1. Will she survive her trauma?
2. Will she make anti-D?
3. Will she become pregnant?
4. Will she carry a D+ fetus?
5. What are the outcomes of HDFN?

1. Will she survive her trauma?

- Most do, actually
- 30 Day mortality in PROPPR trial of severely bleeding trauma patients 164/676 = 24%
- 76% survival rate



	30 Days		
	No. (%)		
	1:1:1 Group (n = 335)	1:1:2 Group (n = 341)	Difference (95% CI), %[a]
Total No. of deaths	75	89	
Cause of death[b]			
Exsanguination	36 (10.7)	50 (14.7)	−3.9 (−9.1 to 1.2)

Holcomb JB et al. *JAMA* 2015;313:471

2. Will she make anti-D?

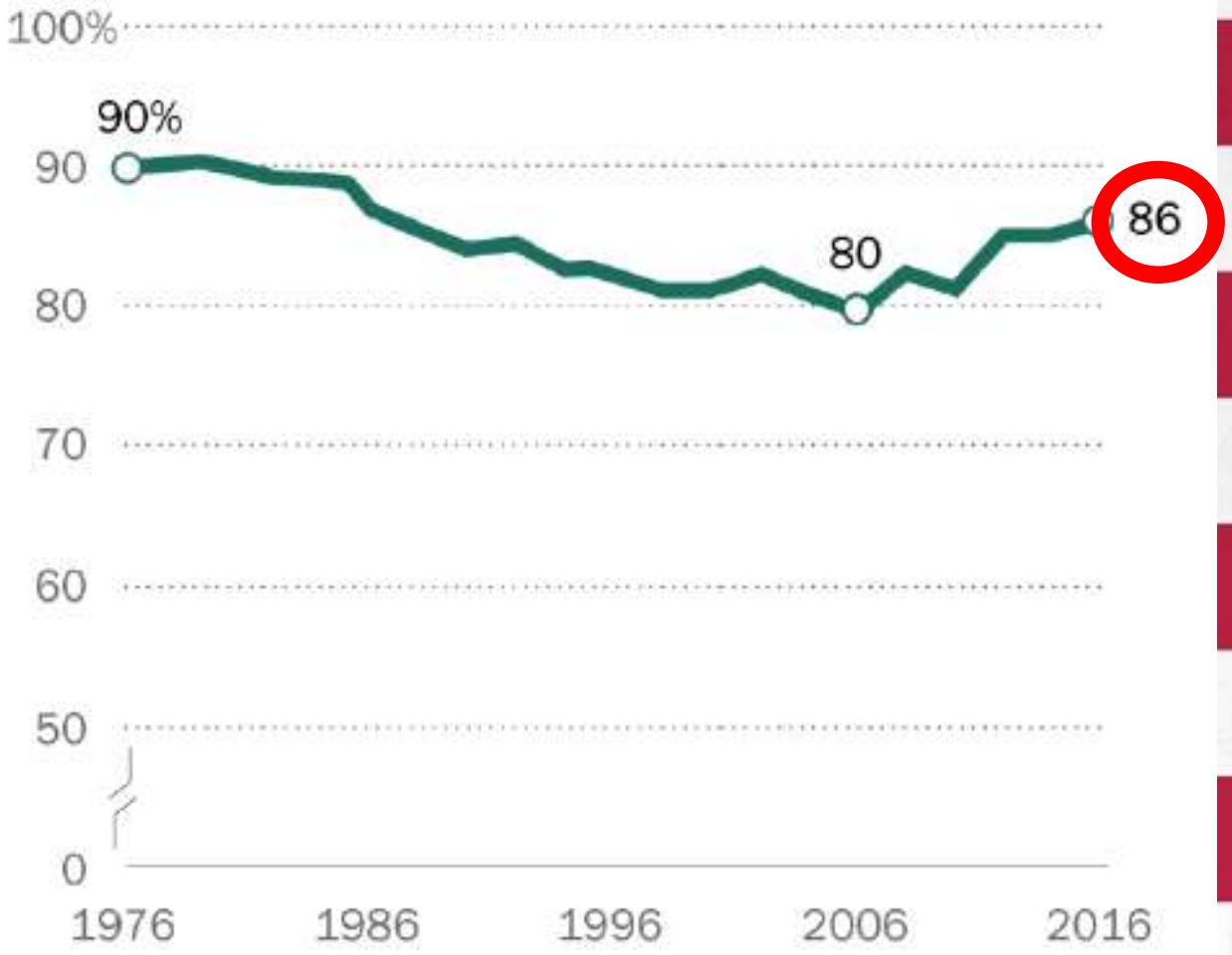
- 80% alloimmunization rate is correct
  - But it's amongst *healthy* volunteers!
  - Healthy people don't get transfused

Country[Reference]	Year	Nature of patients	Number of RhD-negative patients transfused with RhD-positive RBCs who met inclusion criteria	RhD-alloimmunization rate (%)
Germany[5]	2003	Surgery 75%, trauma 14%, DIC 5%, other 6%	78	20.5 (modeled estimate: 30.4)
USA[7]	2007	82% of RhD-positive units issued to ED, OR, ICU, or medicine ward	98	22
Spain[8]	2008	Surgery, hematological diseases, solid tumor, other	159	Overall: 21.4 Hematological malignancies: 41.6, non-hematological malignancies: 20.9. Solid tumors: 15.3
USA[10]	2014	Trauma (57.7), CV surgery (19.3), Other (11.6), Oncology (7.6), Transplant (3.8)	26	11.5
Germany[13]	2017	Hospitalized patients	110	20 (Modeled estimate: 26)~
USA[14]	2019	MTP activations for trauma	59	16.9

Yazer et al. *Hematology* 2021;26:321-327

3. Will she become pregnant?

% of American women ages 40-44 who have ever given birth



Pew research center, January 2018; available online

3. Will she become pregnant after trauma

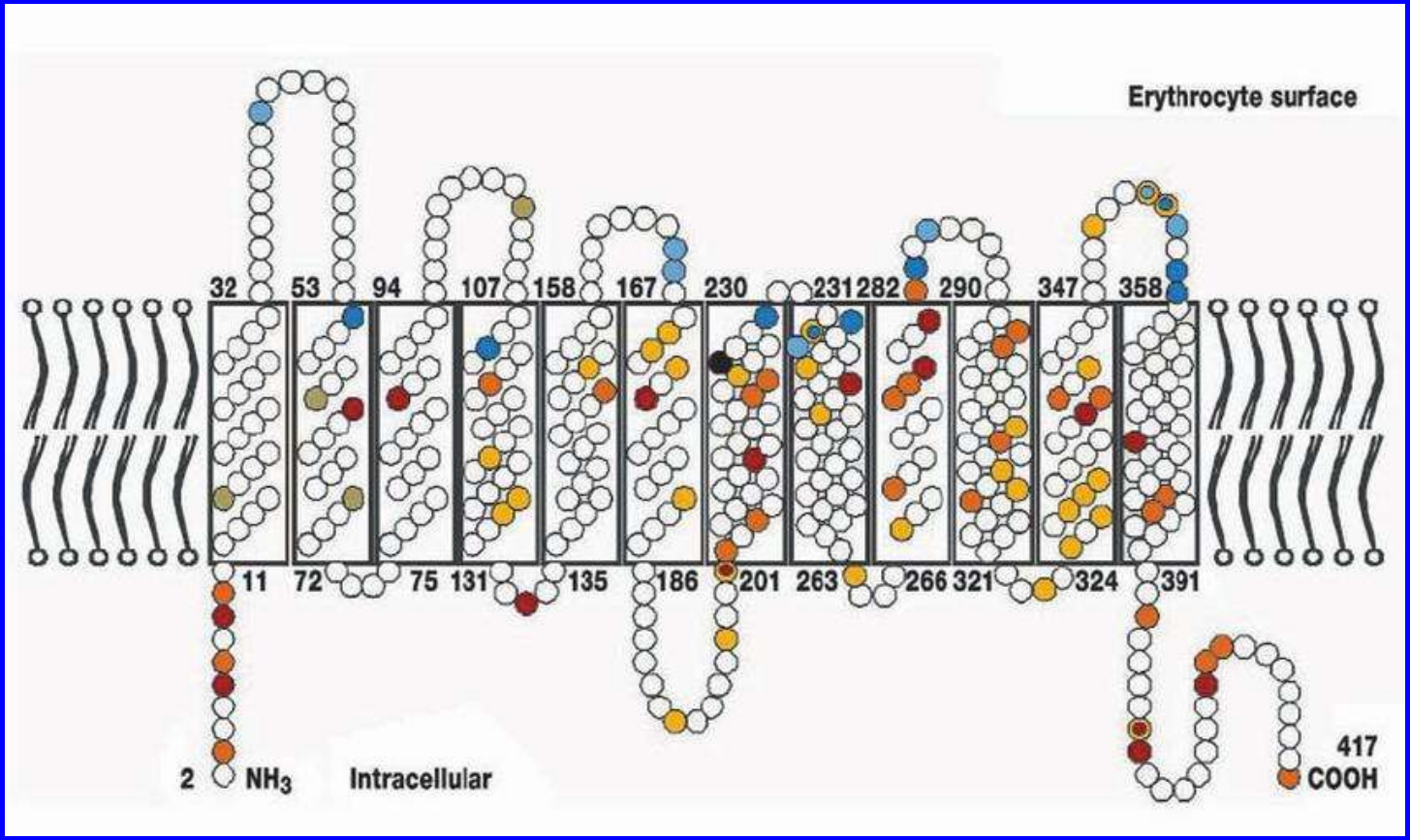
- Two Finnish data registries were analyzed from 1998-2018
- Five year follow up post injury to determine if they became pregnant
- Hazard ratios were calculated by comparing birth rate to similarly aged women with wrist fractures

Age	15–24 years	25–34 years	35–44 years
TBI group N=22,780			
Hazard ratio (CI)	1.09 (0.98–1.21)	0.92 (0.83–1.02)	0.99 (0.76–1.29)
Spine fracture group N=3627			
Hazard ratio (CI)	1.02 (0.88–1.17)	0.91 (0.78–1.06)	1.06 (0.74–1.51)
Pelvic fracture group N=1820			
Hazard ratio (CI)	0.91 (0.77–1.09)	0.79 (0.64–0.97)	0.67 (0.39–1.18)
Hip or thigh fracture group N=1769			
Hazard ratio (CI)	0.72 (0.58–0.88)	0.65 (0.52–0.82)	0.60 (0.35–1.01)

Vaajala M et al. *Reproductive Health* 2022;19:73

4. Will she carry a D+ fetus?

- 85% of Caucasian population is D+
- Higher in other populations
- Due to zygosity, “risk” of transmitting *RHD* gene from father is 60%



5. HDFN outcomes - historical

- In a word…
- HDFN was a terrible disease in 1980s
- Perinatal mortality from HDFN ~50%
- High morbidity amongst survivors
- Imperative to avoid maternal alloimmunization
- Luckily, that was then…

5. HDFN outcomes – now

- HDFN is a very treatable condition

Group	Total N = 645	1987-1992 N = 92	1993-1998 N = 127	1999-2004 N = 159	2005-2010 N = 152	2011-2016 N = 115
Overall survival*	598/641 (93)	73/9 (79)	115/127 (91)	157/159 (99)	146/152 (96)	107/11 (96)
Without hydrops	473/492 (96)	49/54 (91)	75/80 (94)	118/119 (99)	130/134 (97)	101/105 (96)
With mild hydrops	87/92 (95)	16/18 (89)	27/28 (96)	27/28 (96)	12/13 (92)	5/5 (100)
With severe hydrops	38/57 (67)	8/20 (40)	13/19 (68)	12/12 (100)	4/5 (80)	1/1 (100)

Zwiers C et al. *Prenat Diagn* 2018: 38:943

Risk of D alloimmunization, fetal death

Survive trauma

positive

X Fetal death

0.3%

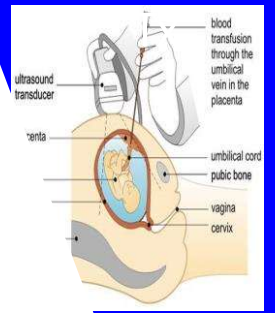
76% 86% 60% 4%

Risk of D alloimmunization, alt definition

Survive trauma

Anti itive

Fetal demise, IUT, exchange



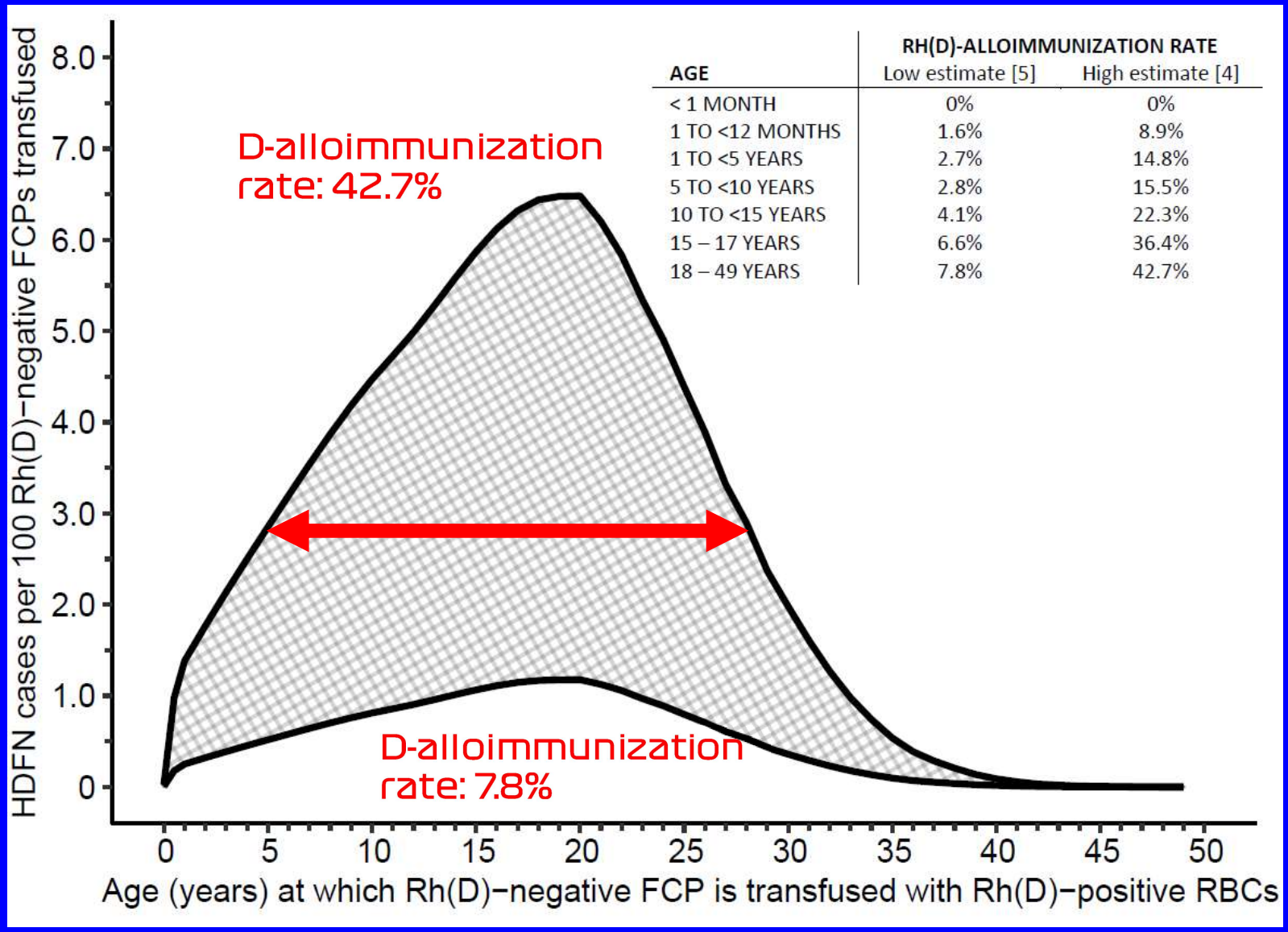
2%

76% 86% 60% 25%

Koelewijn JM et al. *Transfusion* 2008;48:1721

What about the children?

- Simulation of overall risk of HDFN
- FCP age, number of expected future pregnancies & FCP age, multiple partner rate, frequency of population RhD positivity



AGE	RH(D)-ALLOIMMUNIZATION RATE	
	Low estimate [5]	High estimate [4]
< 1 MONTH	0%	0%
1 TO <12 MONTHS	1.6%	8.9%
1 TO <5 YEARS	2.7%	14.8%
5 TO <10 YEARS	2.8%	15.5%
10 TO <15 YEARS	4.1%	22.3%
15 – 17 YEARS	6.6%	36.4%
18 – 49 YEARS	7.8%	42.7%

Seheult JN et al. *Vox Sang* 2022;117:291-292

My opinion


≤6% risk of HDFN
Prehospital transfusion saves lives!
JAMA | Original Investigation
Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan
Resuscitation with blood products in patients with trauma-related haemorrhagic shock receiving prehospital care (RePHILL): a multicentre, open-label, randomised, controlled, phase 3 trial
Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock
EFFECT OF PREHOSPITAL RED BLOOD CELL TRANSFUSION ON MORTALITY AND TIME OF DEATH IN CIVILIAN TRAUMA PATIENTS
Prehospital whole blood reduces early mortality in patients with hemorrhagic shock

How often will this be a problem?

- In Pittsburgh, 5 *injured* RhD- FCPs transfused with RhD+ RBCs per year
  - Risk of HDFN: 1.2 HDFN cases every 20 years
- In San Antonio, Texas, one *injured* RhD- FCP transfused with RhD+ LTOWB unit every 30 months
  - Would take 250 years to D-alloimmunize 3-30 FCPs

	All recipients	D-negative females of childbearing potential
Prehospital transfusions per year	5561	100
Years to one HTR major morbidity or death due to index D-positive transfusion	4.8 (1.4–61)	66 (18–910)
Years to one future HTR major morbidity or death	150 (35–3700)	1400 (310–37,000)
Years to one future anti-D HDFN death or disability	5.2 (2.2–21.6)	5.7 (2.6–22.5)
Years to any of three above harms	2.5 (1.0–7.5)	5.2 (2.5–17.3)

Cardigan et al. *Vox Sang* 2022;117:701-707

Perception of risk…Depends whom you ask

- 309 women >18 from the *general public* living in the St. Louis, Missouri area
- Assessed their acceptance of an urgent transfusion that could harm a future pregnancy at various risk reduction levels

Key Survey Question:

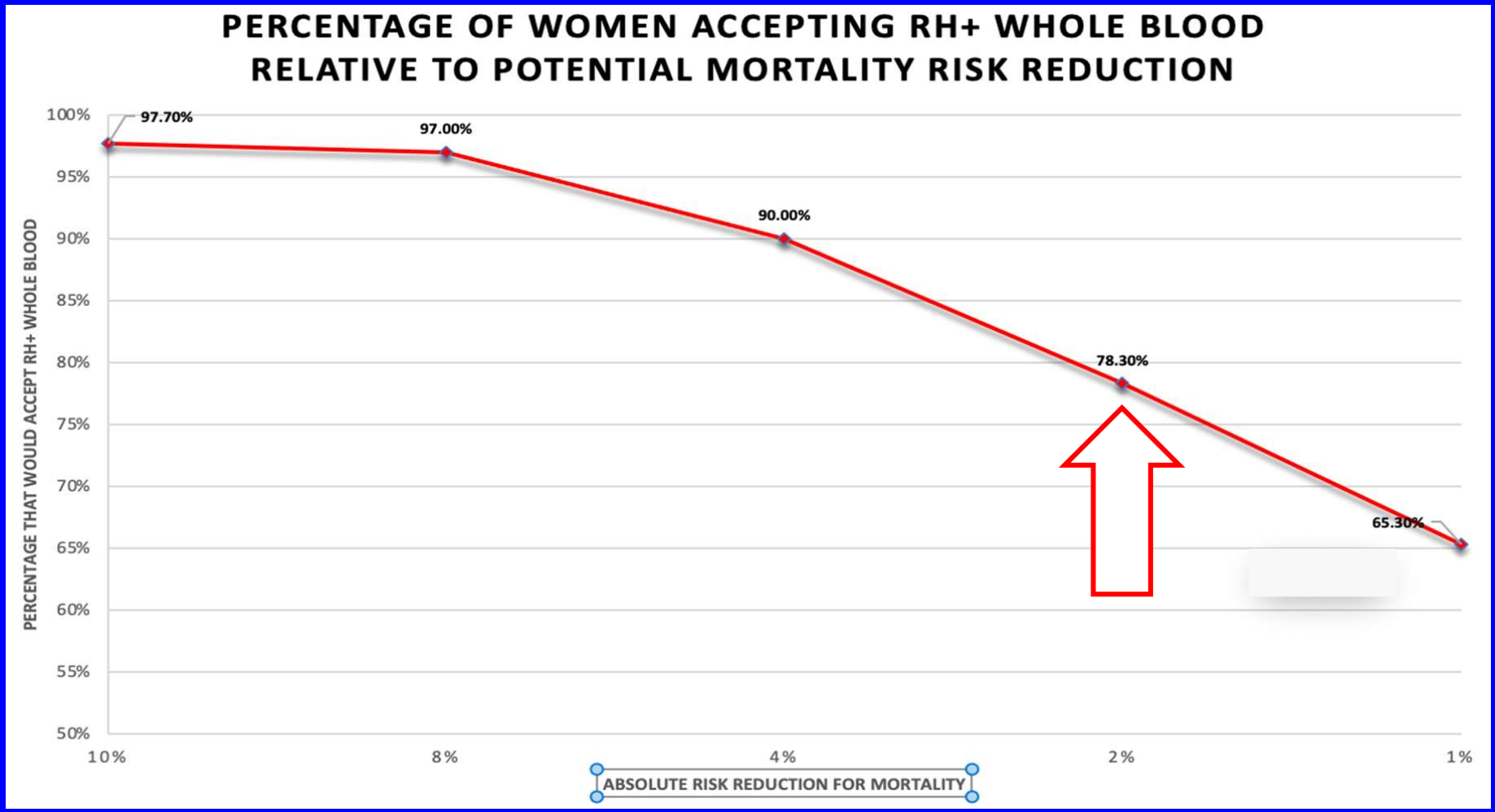
Research has shown that giving blood to a woman who is bleeding to death from trauma may reduce the rate of death by 20%. But if the blood is a different Blood Type than the Blood Type of the female patient there may be a 0.3% to 4.0% increased risk to current or future pregnancies that may include death or major disability to the baby.

Knowing this, if you suffered a traumatic injury and had a "X"% chance of bleeding to death, would you want to receive blood if receiving blood would lower your chance of death to "Y%" but increase the risk of complications with a future or current pregnancy by 0.3-4.0%? (See Table 2 for X & Y values)

Yu G et al. *Transfusion* 2022;62 Suppl 1:S211-S217

Perception of risk…Depends whom you ask

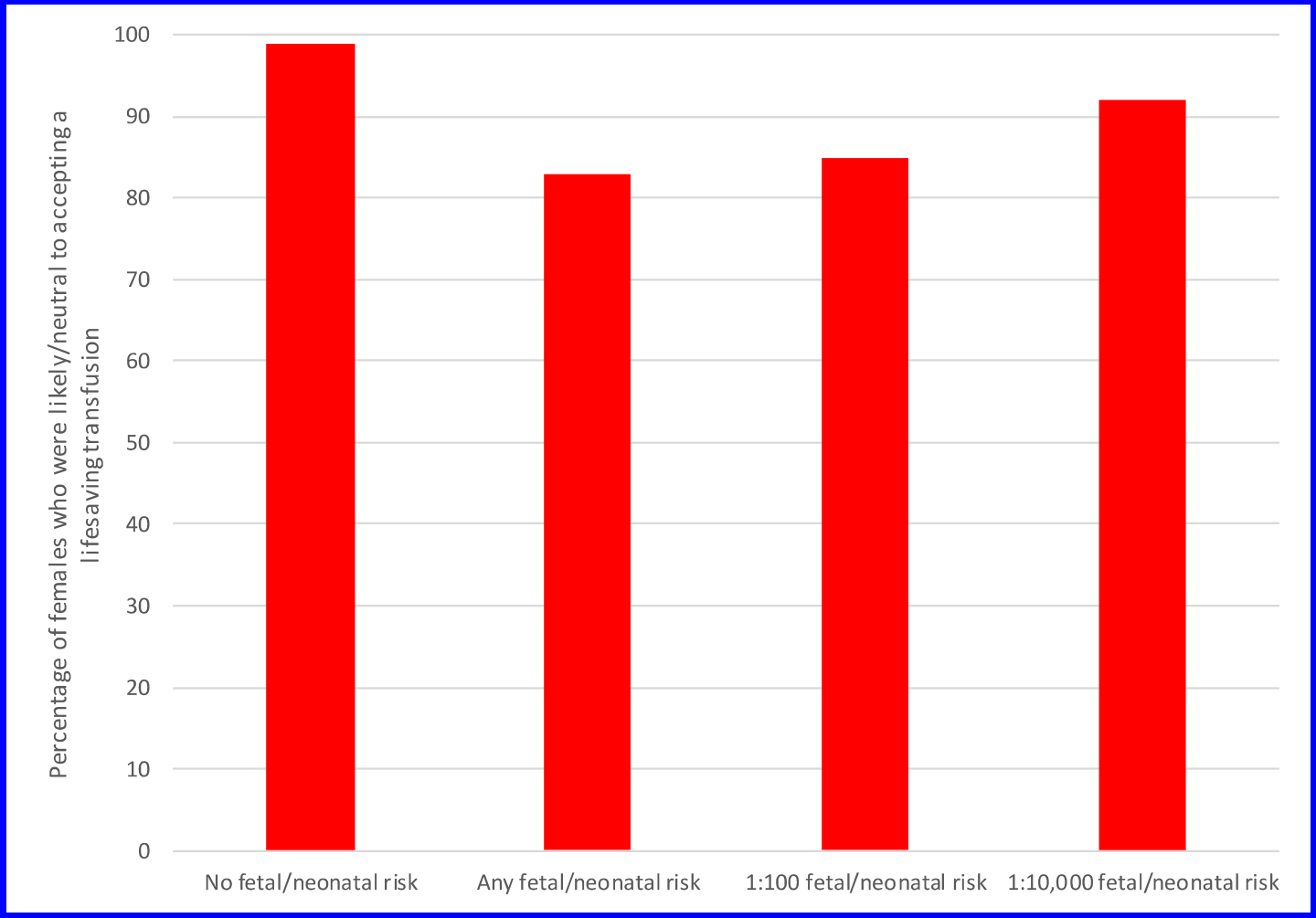
- Interesting inflection point below the uppermost bound of fetal harm risk



Yu G et al. *Transfusion* 2022;62 Suppl 1:S211-S217

Perception of risk…Depends whom you ask

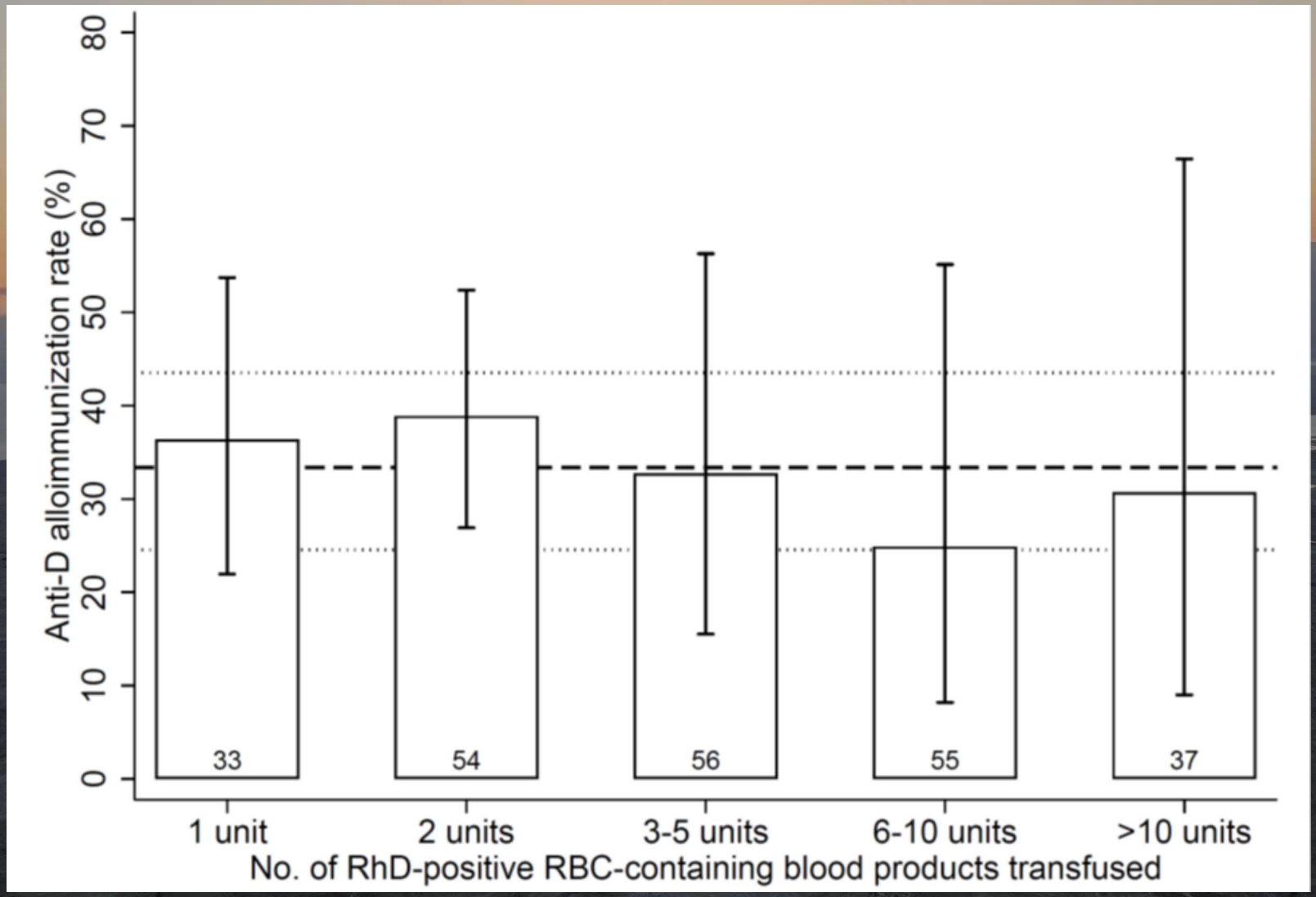
- Facebook-based study
- 2,049 fully completed surveys by females
  - 80% were FCP



Uhlich R et al. *submitted*

Seen one, you've seen them all

- Risk of RhD alloimmunization does not increase after multiple exposures in general hospitalized patients
- 77/235 patients (32.7%) alloimmunized



Yazer MH et al. *Transfusion* 2022;62 Suppl 1:S185-S192

In conclusion

- Use RhD-negative RBCs/LTOWB if you have them
- Do not hesitate to use RhD-positive RBCs/LTOWB if that is all that you have
- HDFN is a manageable disease
- Saving the mother or future mother's life is the most important thing we can do

Thank you!

Pittsburgh, Pennsylvania