Fetal and neonatal alloimmune thrombocytopenia

Treatment of platelet alloimmunization

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HEEL HOLLAND
BAKT

Part I

Clinical outcome in HPA-1a and HPA-5b alloimmunization

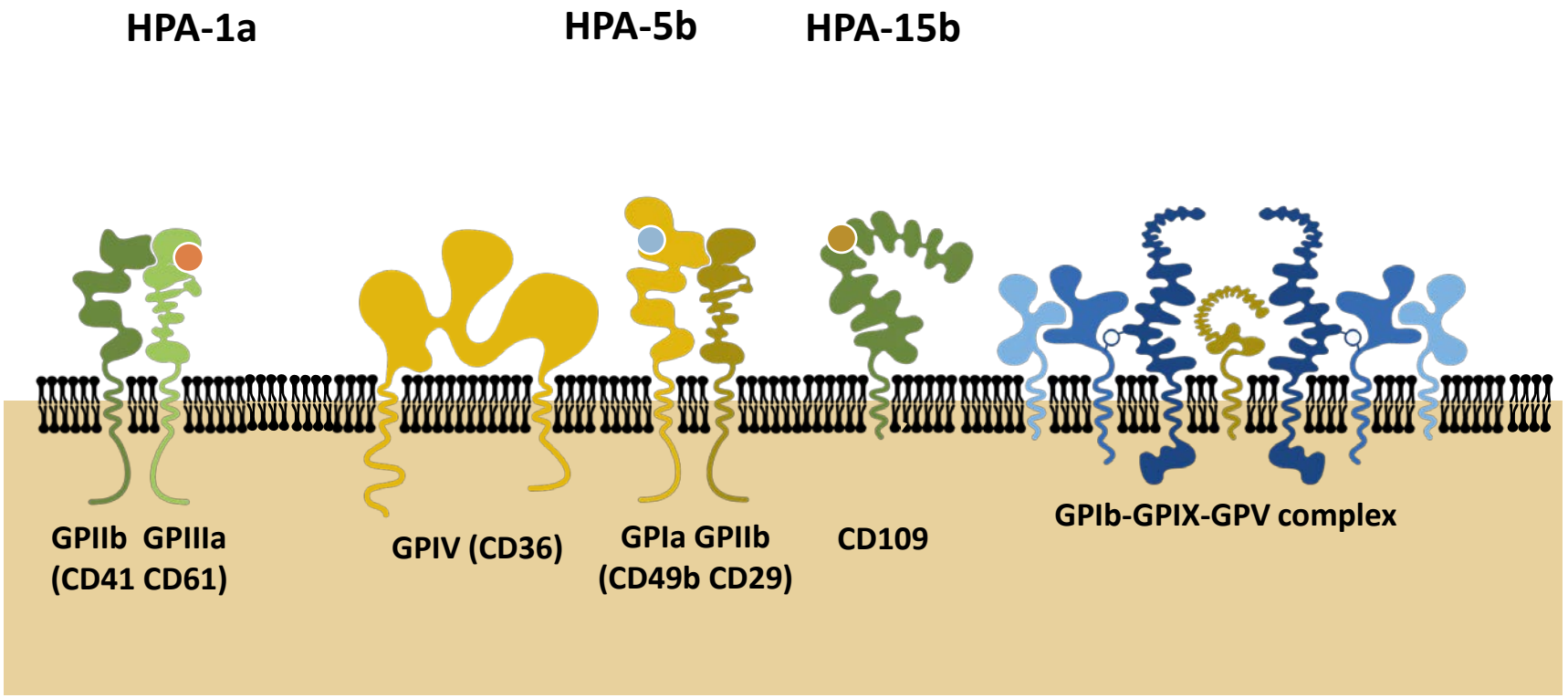
Part II

Antenatal treatment strategies in FNAIT

Part III

Postnatal treatment strategies in FNAIT

HPA specificity of antibodies most frequently involved in FNAIT



de Vos *et al.,* Transfusion and Apheresis Science, 2019

HPA specificity and clinical outcome

	Anti-HPA-1a	Anti-HPA-5b
Prevalence of antibodies in pregnant women[1,2]	0.2%	1.8%
Prevalence of antibodies in clinical FNAIT cases[3,4]	75-78%	9-15%

Compare clinical outcome between anti-HPA-1a and anti-HPA-5b associated FNAIT.

Is anti-HPA-5b associated with clinical FNAIT or an incidental finding?

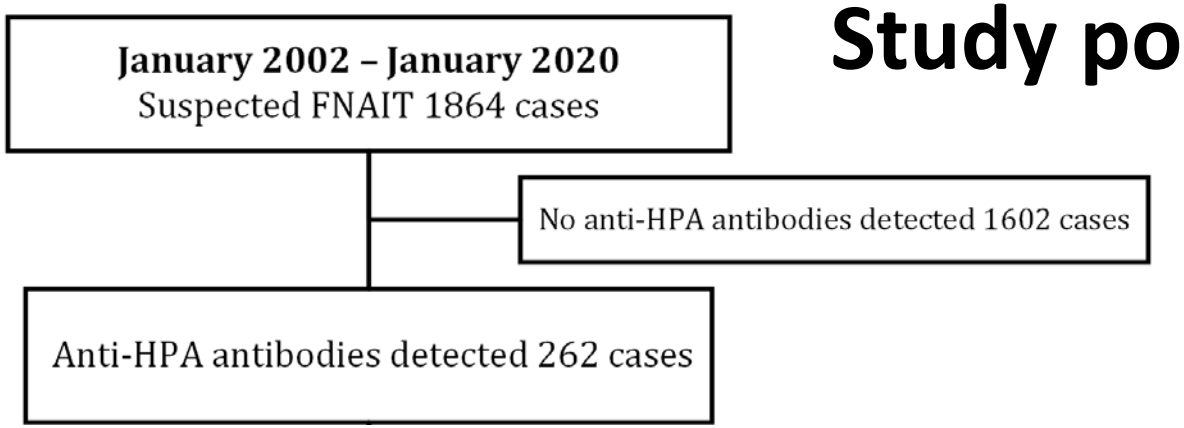
1. Kamphuis *et al.*, BJOG, 2010 ; 2. Panzer *et al.*, BJH, 1995;
3. Davoren *et al.*, Transfusion 2004; 4. Ghevaert *et al.*, Transfusion 2007.

In ~10% of the FNAIT cases, anti-HPA-5b is implicated

Should clinical management be adapted based on HPA specificity of the implicated antibody?

de Vos *et al.*, BJH, 2021

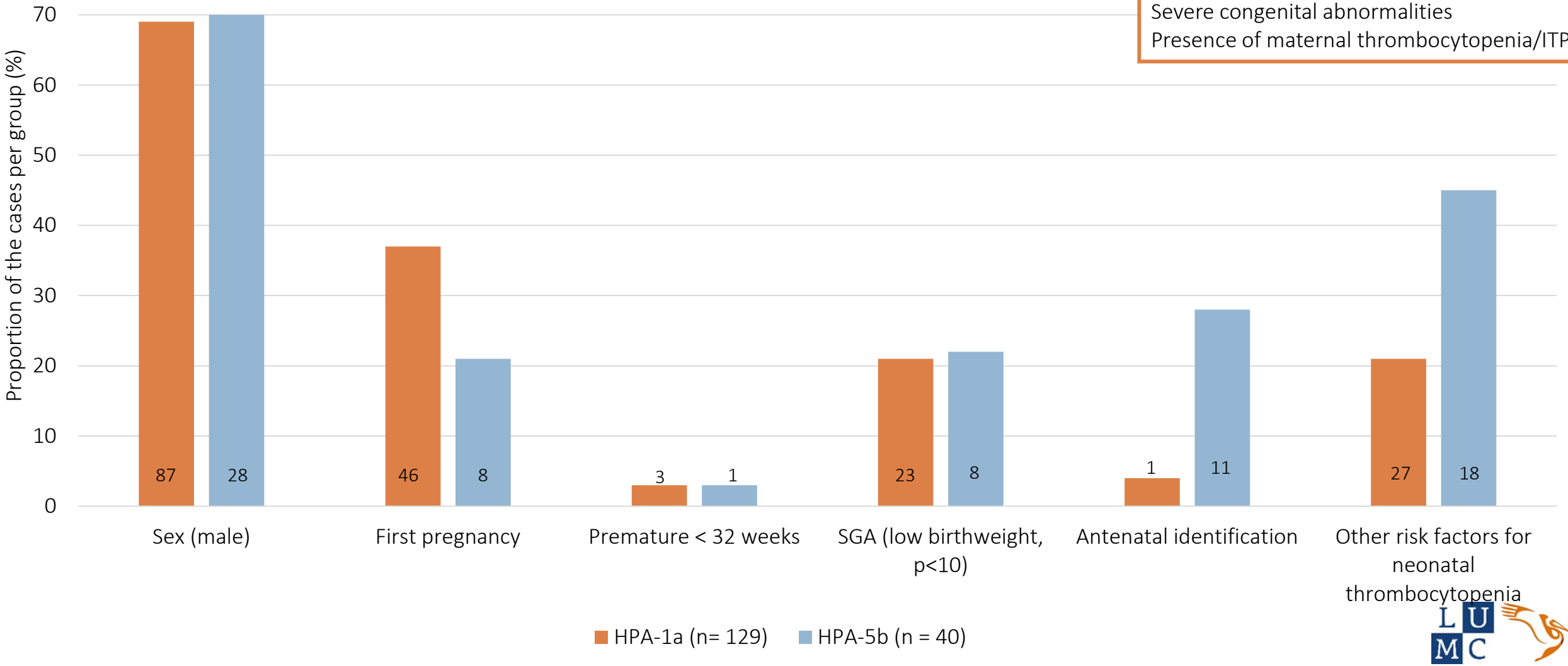
Study population



Primary outcome:
Prevalence of severe bleeding in newly detected FNAIT cases

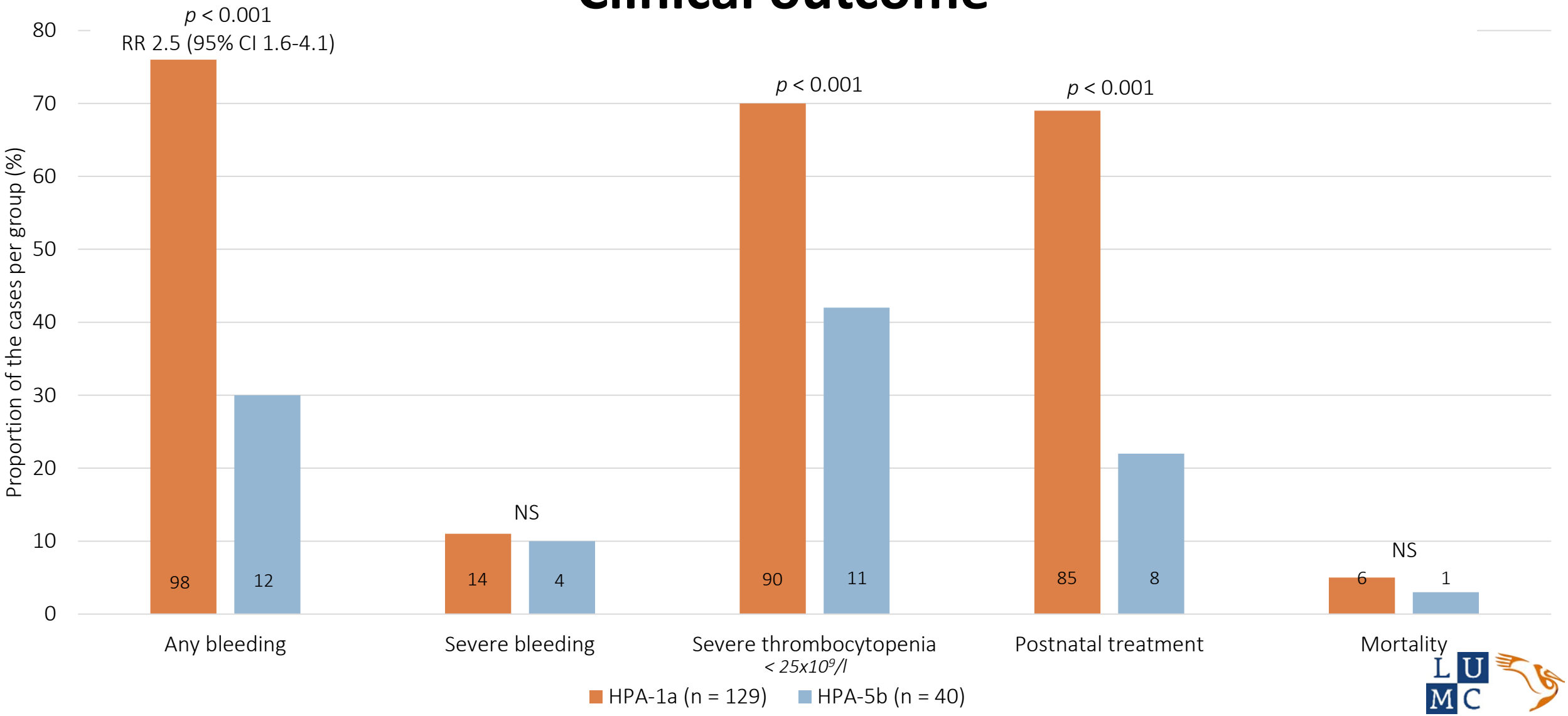
Clinical characteristics

Other risk factors:
Prematurity (<32 week' gestation)
Small for gestational age (birthweight <p10)
Neonatal sepsis
Perinatal asphyxia
Severe congenital abnormalities
Presence of maternal thrombocytopenia/ITP



de Vos *et al.*, BJH, 2021

Clinical outcome



All HPA-1a cases are compared to all HPA-5b cases, categorical variables (bleeding status, thrombocytopenia < 25x10^9/l, treatment status) were compared with Chi-square test, perinatal death was compared with by the Fisher's Exact Test, continuous variables (platelet counts) were compared by using Mann Whitney U-test.

Observed rate of HPA incompatibility in HPA-1a and HPA-5b immunised cases is higher than calculated rate

1864 cases of suspected FNAIT
(neonates with thrombocytopenia and/or bleeding)

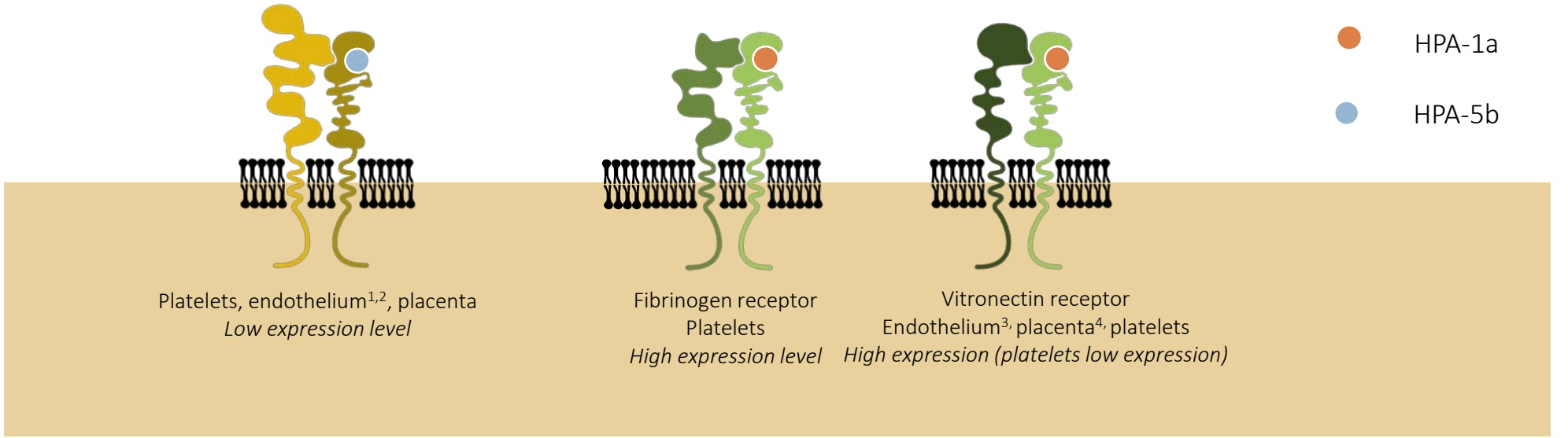
	161 cases (8.6%) anti-HPA-1a		60 cases (3.2%) anti-HPA-5b	
Multigravida women:	81 cases		48 cases	
HPA incompatible *HPA causal*	81 cases	*Expected: 70 cases*	38 cases	*Expected: 25 cases*
HPA compatible *HPA not causal*	0 cases	*Expected: 11 cases*	10 cases	*Expected: 23 cases*

Based on allele frequencies available from: https://www.ebi.ac.uk/ipd/hpa/freqs_1.html; Metcalfe 2021.

Discussion

Anti-HPA-5b cannot not be regarded as an incidental finding in FNAIT suspected cases.

Anti-HPA-5b mediated FNAIT is often, but not always, less severe compared to anti-HPA-1a mediated disease.



1. Leeksma *et al*. BJH, 1987 2. Pischel, *et al*. Journal of clinical investigation. 1988.
3. van Gils, *et al.* Molecular immunology, 2004. 4. Kumpel, *et al*., Transfusion, 2008

HIP STUDY

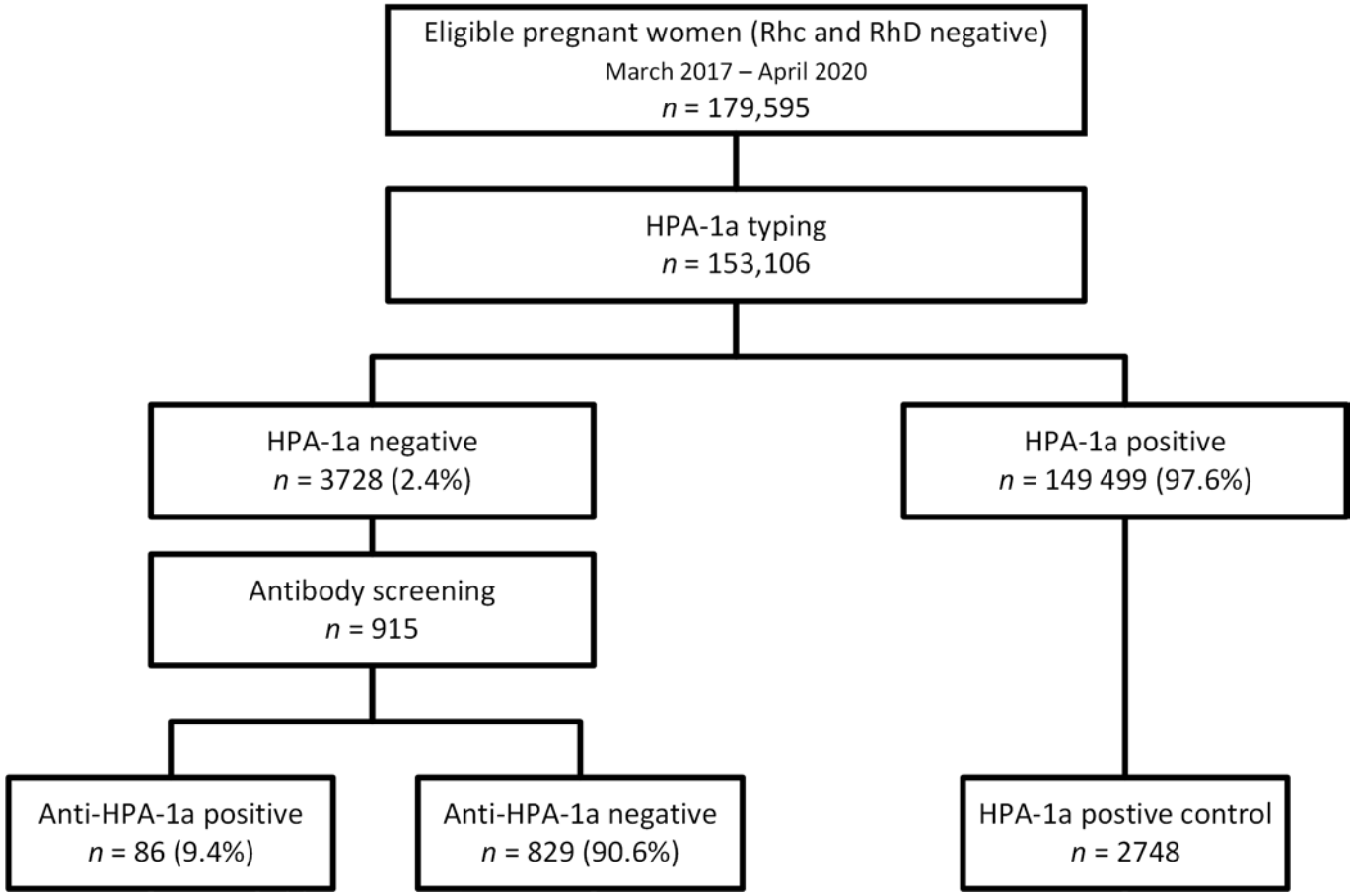
HPA-screening In Pregnancy

Prospective screening study
Natural history of anti-HPA-1a mediated FNAIT
Identify pregnancies at risk for severe outcome

Additional analysis:
Outcome of pregnancies complicated by anti-HPA-5b

Winkelhorst, de Vos *et al*., BMJ Open, 2020

Study population HIP study



Winkelhorst, de Vos *et al*., BMJ Open, 2020

In ~10% of the FNAIT cases, anti-HPA-5b is implicated

Should clinical management be adapted based on HPA specificity of the implicated antibody?

Anti-HPA-5b can rarely lead to severe bleeding.

Currently identification of pregnancies at risk for severe outcome is difficult.

de Vos *et al.,* BJH, 2021

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Clinical outcome in HPA-1a and HPA-5b alloimmunization

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Postnatal treatment strategies in FNAIT

Most intracranial hemorrhage in FNAIT occur during pregnancy

Which antenatal management strategy is recommended?

Treatment

INDEX PREGNANCY

Minimizing complications

Postnatal management

SECOND PREGNANCY

Prevention

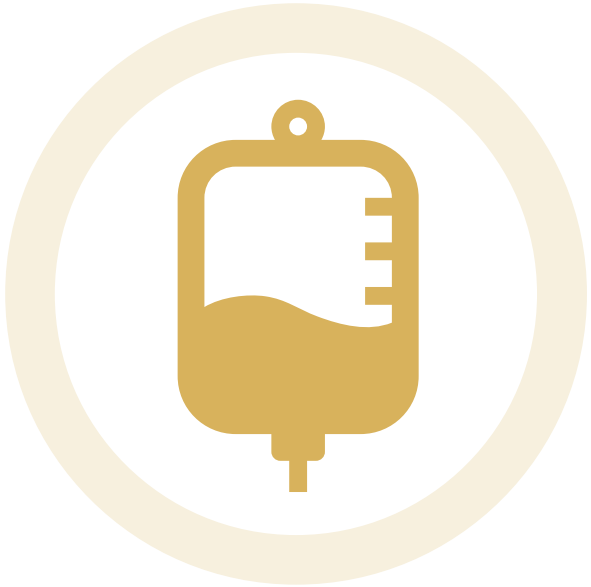
Antenatal treatment

Invasive: IBS, IUPT | Non-invasive

Antenatal treatment strategies

IVIG (to the mother)

98.7% effective in
preventing severe bleeding

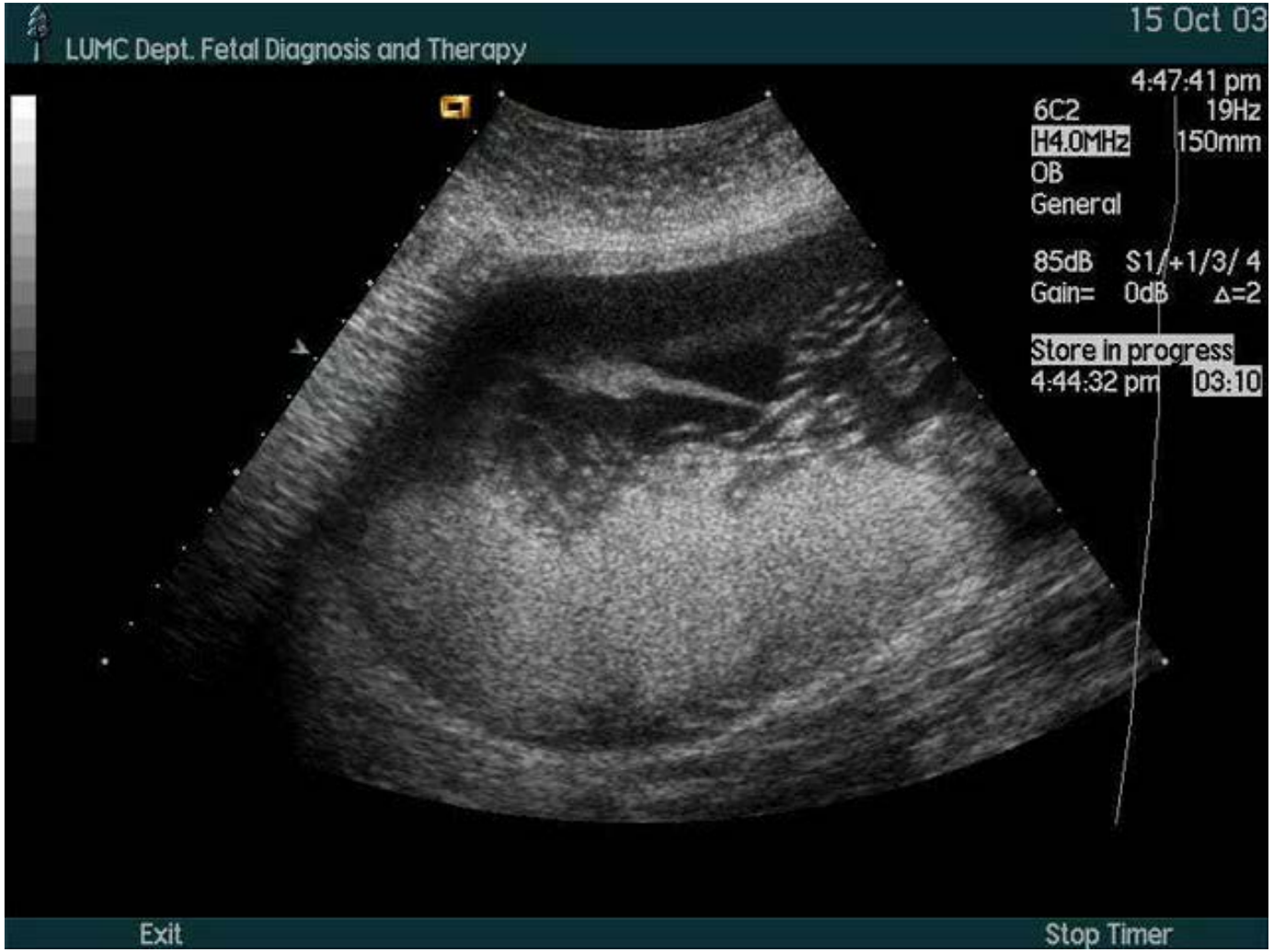


Intra-uterine platelet transfusion

associated with **high risk complications**
10% per pregnancy, 32% of complications perinatal death
53% of all perinatal deaths

Winkelhorst *et al.*, Blood, 2017

Complication (intrauterine bleeding)



Winkelhorst *et al.*, Blood, 2017

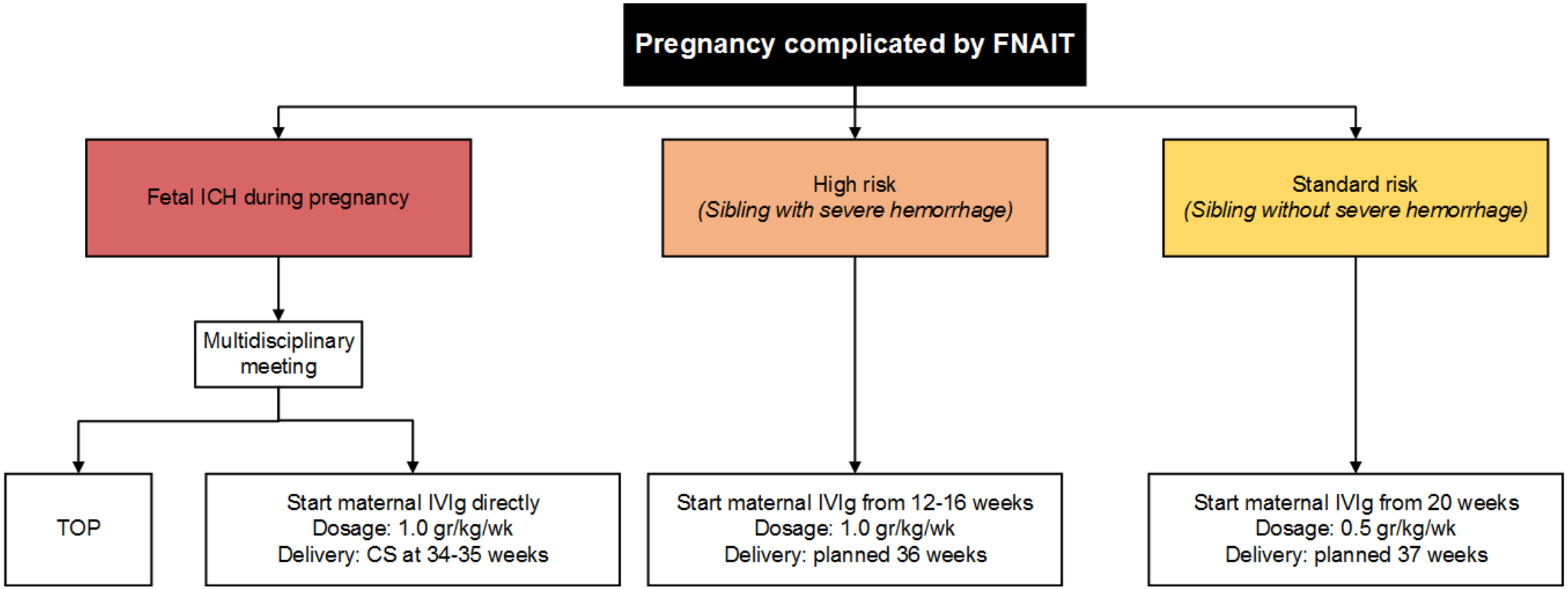
Most intracranial hemorrhage in FNAIT occur during pregnancy

Which antenatal management strategy is recommended?

Weekly administration of IVIg to the mother

Liebermann *et al.,* BJH, 2019
de Vos *et al.,* Transfusion and Apheresis Science, 2019

Antenatal treatment



de Vos *et al.*, Transfusion and Apheresis Science, 2019

What is the long-term neurodevelopmental outcome of children affected by FNAIT that were antenatally treated with IVIg?

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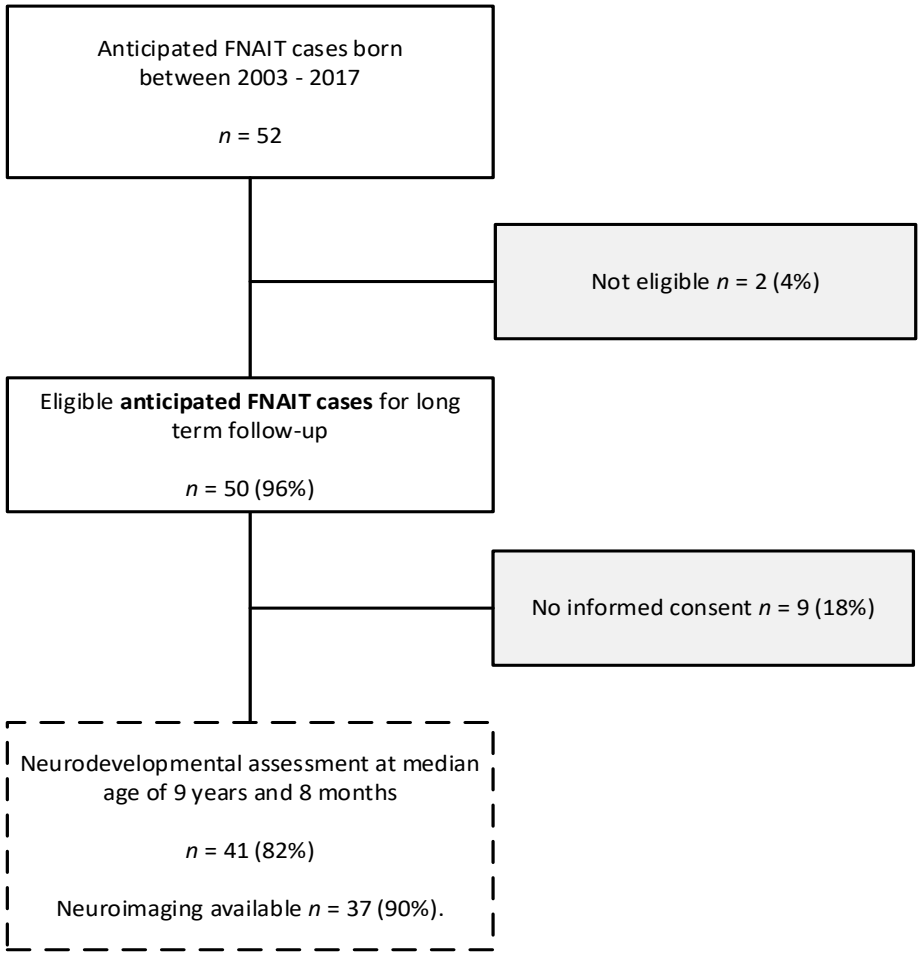
Neurodevelopmental outcome in children after antenatal IVIg treatment



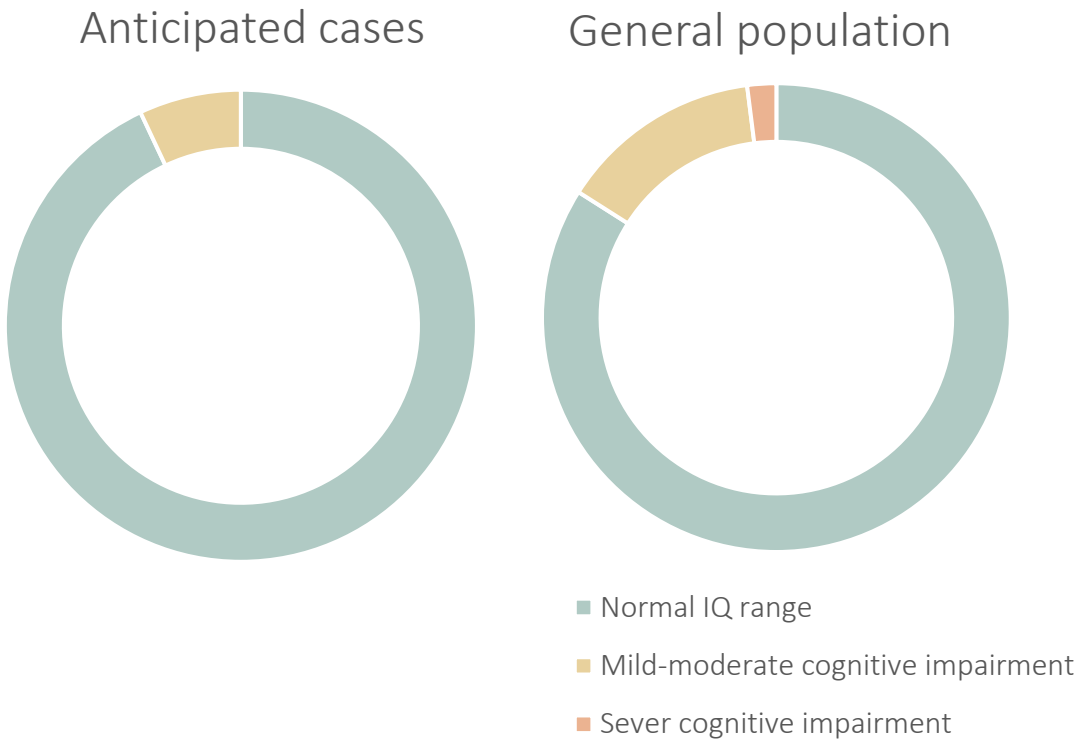
Characteristics

Variable	N = 41
Gestational age at delivery, weeks^{+days}, median (IQR)	37^{+5} (37^{+2} – 38^{+3})
Female sex, n (%)	21 (51)
Birthweight, gram, median (IQR)	3210 (2838 – 3427)
SGA (birthweight < 10^{th} percentile), n (%)	2 (5)
Intracranial hemorrhage, n/N (%)*	3/37 (8)
Minor	1/37 (3)
Severe: Parenchymal	2/37 (5)
Platelet count nadir × 10^9/L, median (IQR)	65 (20 – 161)
Maternal education level, n (%)	
Low	3 (7)
Intermediate	13 (32)
High	25 (61)

de Vos *et al.*, *submitted*, 2022

Neurodevelopmental outcome in children after antenatal IVIg treatment

Variable	N = 41
Full IQ scale, mean (SD)	104 (11)
Normal range (TIQ > 85), n (%)	38 (93)
Mild-moderate cognitive impairment (TIQ 85 – 70)	3 (7)
Severe cognitive impairment (TIQ < 70)	0
Minor Neurologic Dysfunction, n/N (%)	
Simple MND	4/40 (10)
Complex MND	0
Cerebral Palsy, *n* (%)	0
Bilateral deafness requiring hearing amplification, *n* (%)	0
Bilateral blindness, *n* (%)	0
Neurodevelopmental impairment (NDI), *n* (%)	
Normal	35 (85)
Mild-moderate NDI	6 (15)
Severe NDI	0



All cases with ICH had normal neurodevelopmental outcome.

No adverse outcome (severe NDI or perinatal death).

de Vos *et al., submitted*, 2022

What is the long-term neurodevelopmental outcome of children affected by FNAIT that were antenatally treated with IVIg?

Their neurodevelopmental outcome is comparable to the general population.

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de Vos *et al.*, *submitted*, 2022

Content

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Clinical outcome in HPA-1a and HPA-5b alloimmunization

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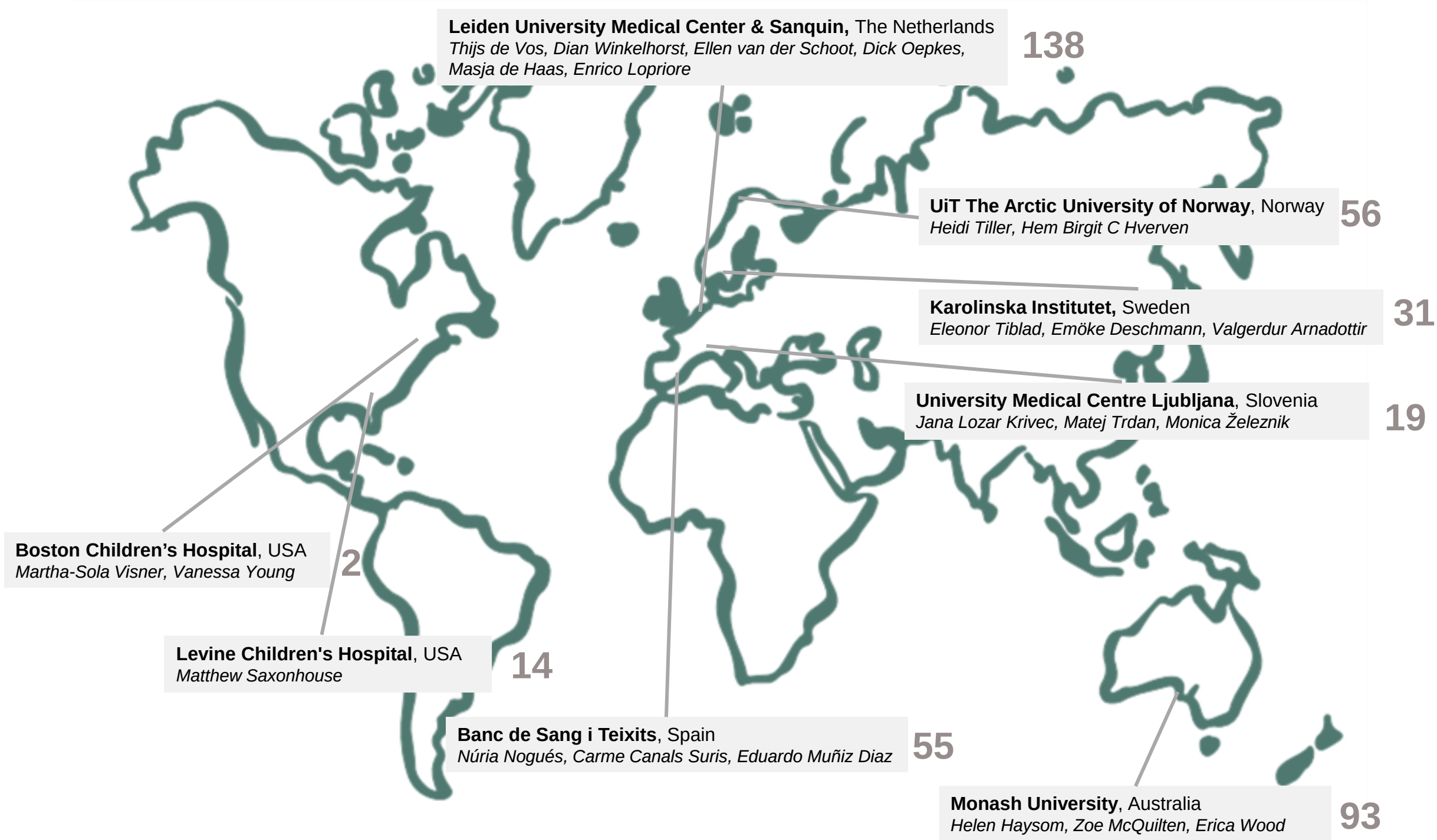
Postnatal treatment strategies in FNAIT

FNAIT registry 2020

- **Study design:** International multicenter observational study.

- **Study population:** All live born FNAIT cases with and without antenatal treatment that were born between 2010 and 2020.

- **Primary objective:** To describe the postnatal management and outcome of children with FNAIT in an international perspective.



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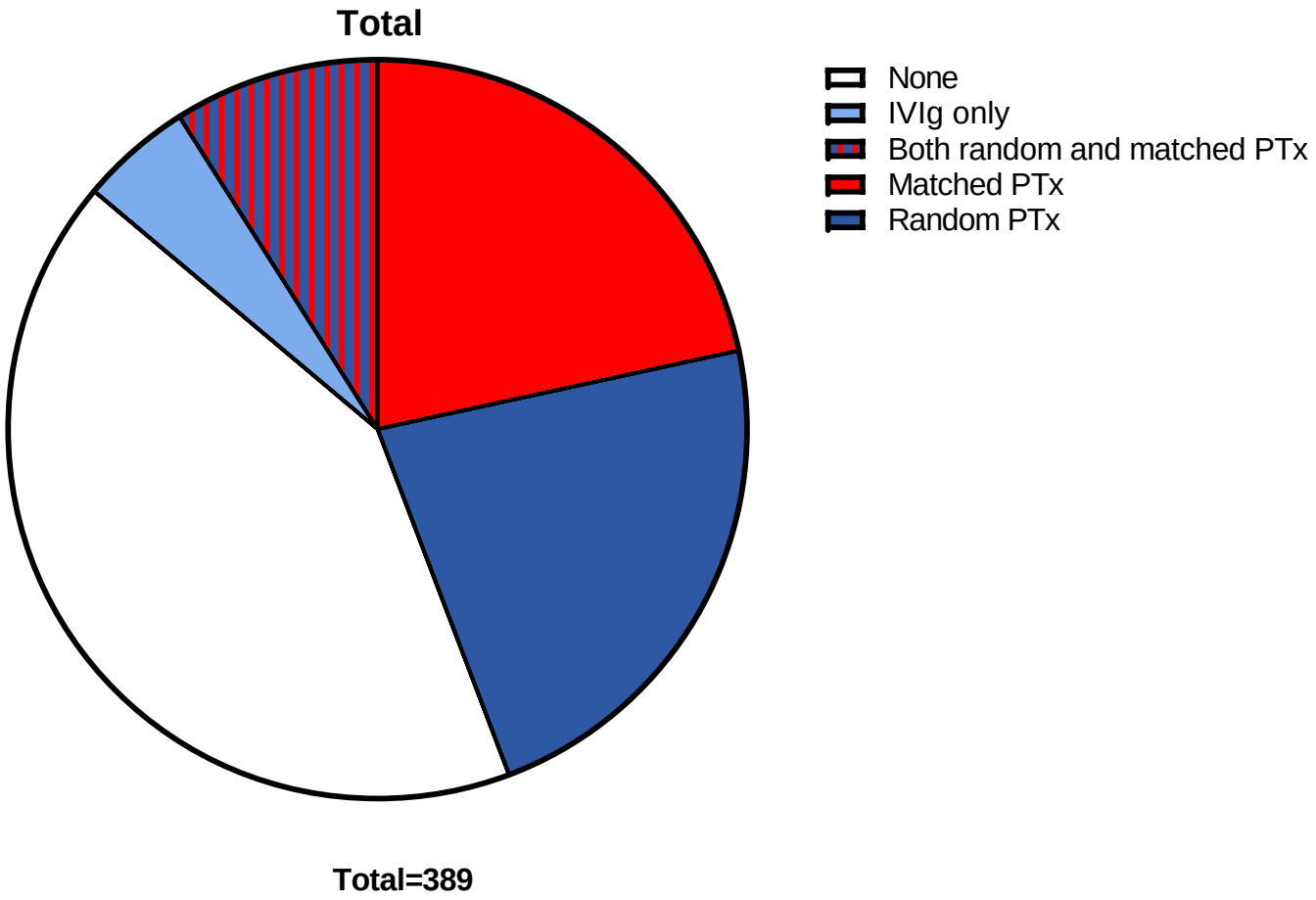
Clinical characteristics of liveborn neonates with FNAIT

Variable	Total (n = 408)
Antenatal diagnosis, *n* (%)†	138 (34)
Postnatal diagnosis, *n* (%)	270 (66)
Antenatal treatment (% of the 138 cases with antenatal FNAIT diagnosis)	107 (78)
First pregnancy, *n* (%)	85 (21)
Male sex, *n* (%)	261 (63)
Gestational age at birth (weeks) - median (IQR)	38 (37-40)
Birthweight (grams) - median (IQR)	3055 (2578-3430)
Small for gestational age (SGA), *n* (%)	81 (21)

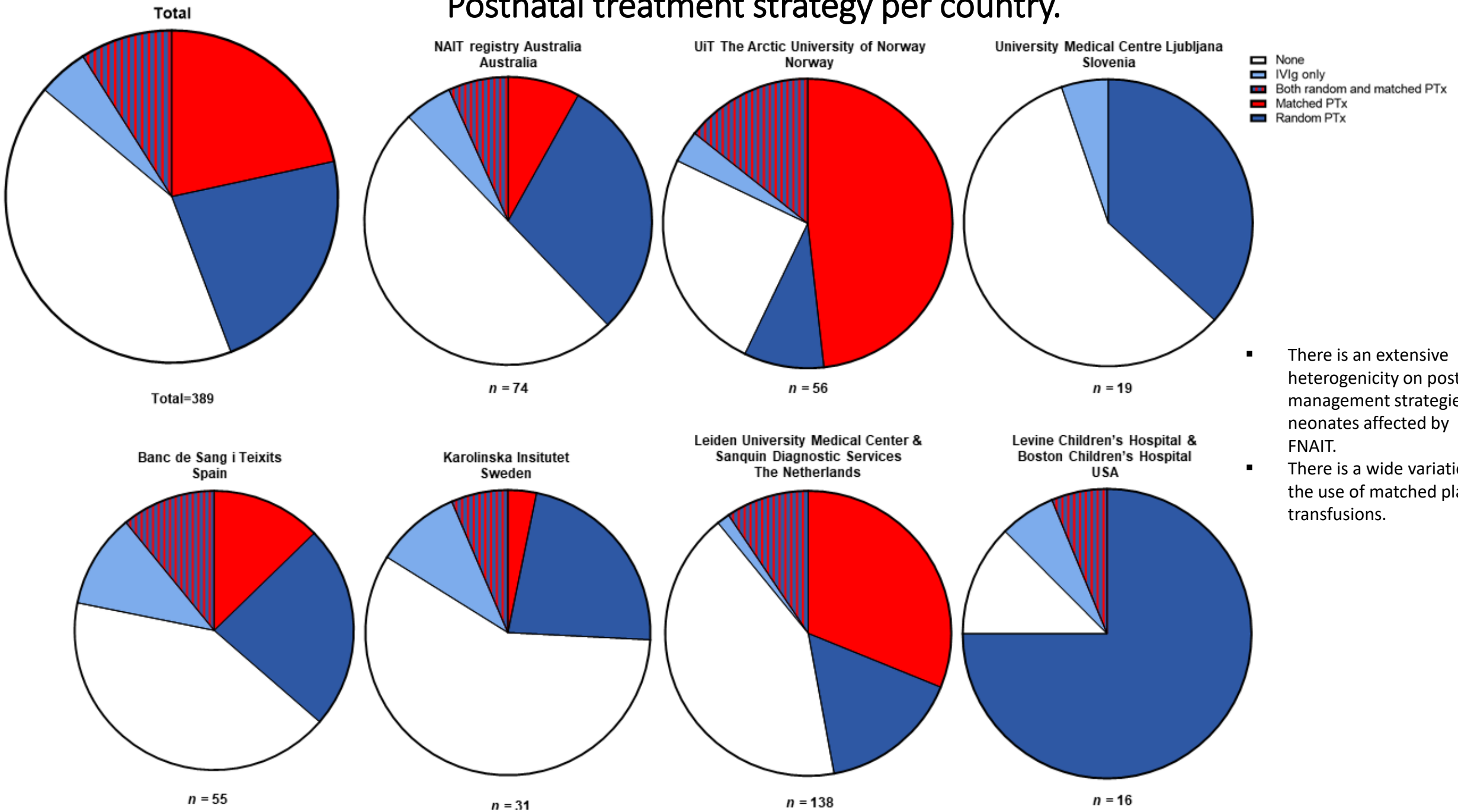
All statistics and percentages are calculated based on the valid numbers. i.e. excluded the missing.

† 122 FNAIT cases were diagnosed antenatally after a previously diagnosed FNAIT pregnancy, 16 cases were newly diagnosed in this current pregnancy.

Results

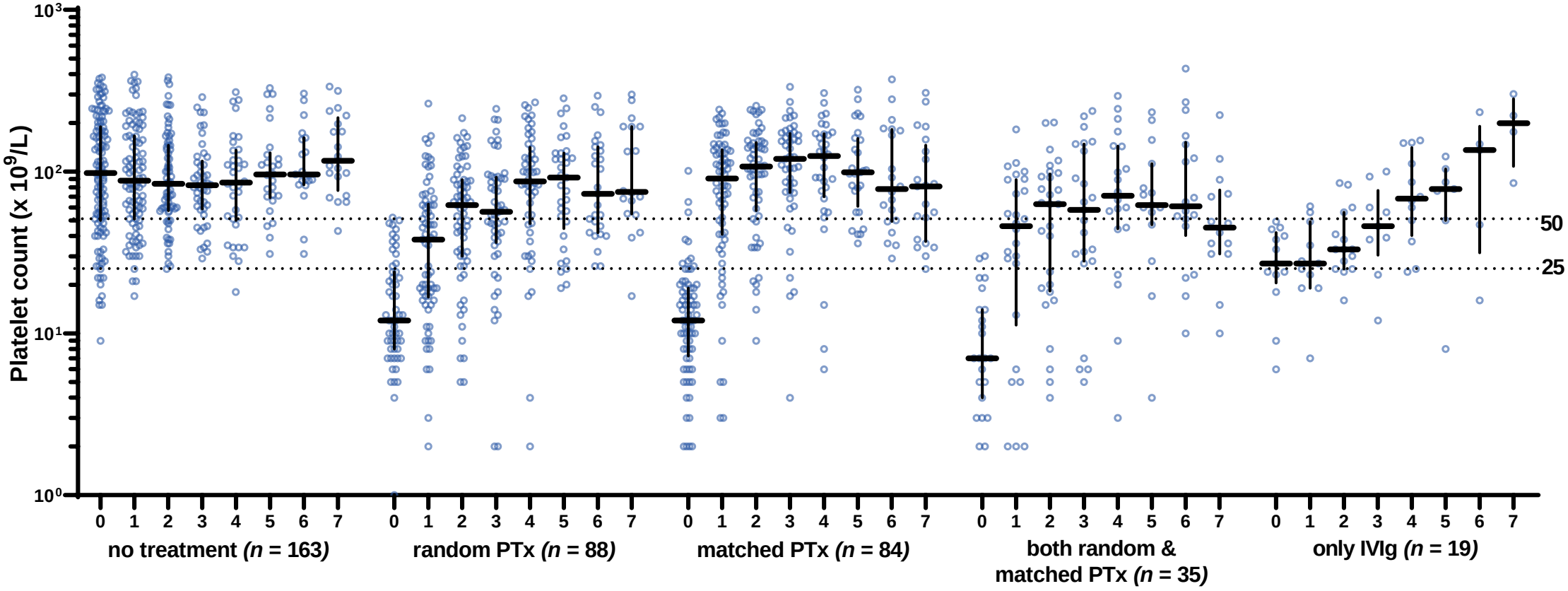

Total
None
IVIg only
Both random and matched PTx
Matched PTx
Random PTx
Total=389

Postnatal treatment strategy per country.



- There is an extensive heterogenicity on postnatal management strategies in neonates affected by FNAIT.
- There is a wide variation in the use of matched platelet transfusions.

Platelet count per treatment strategy



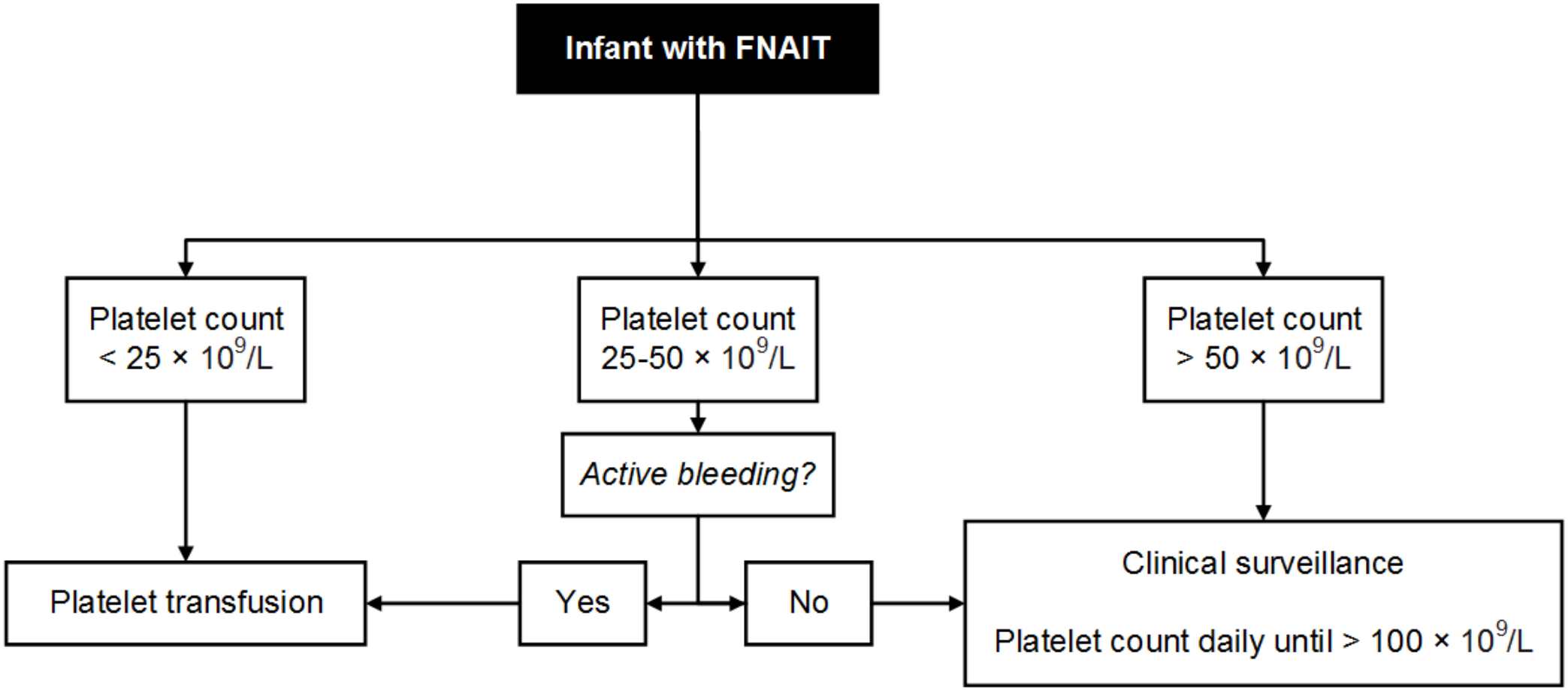
Which postnatal management strategy is recommended?

Liebermann *et al.,* BJH, 2019
de Vos *et al.,* Transfusion and Apheresis Science, 2019

Platelet count per treatment strategy

- Recommendations based on expert opinion and observational studies
- Occurrence of severe postnatal bleeding difficult to assess
- Preference for matched platelet products justified?
- IVIg treatment – not as first line treatment

Postnatal treatment strategy



HPA typed and matched are first choice if direct available.
Postnatal IVIg treatment not as first line treatment.

Winkelhorst *et al*, BJH 2018.
de Vos *et al.*, Transfusion and Apheresis Science, 2019

Future perspectives

- Observational prospective screening study: HIP study (HPA Screening in Pregnancy Study)
  - Natural course of HPA-1a immunization in pregnancy
  - Risk factors for severe neonatal outcome
- Long term neurodevelopmental outcome of index cases affected by FNAIT
- Cost-effectiveness analysis of platelet screening program in pregnancy

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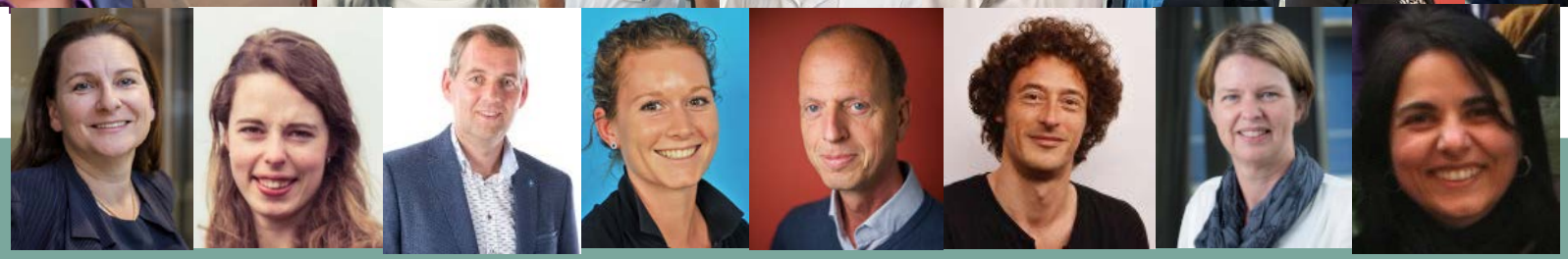

Questions?
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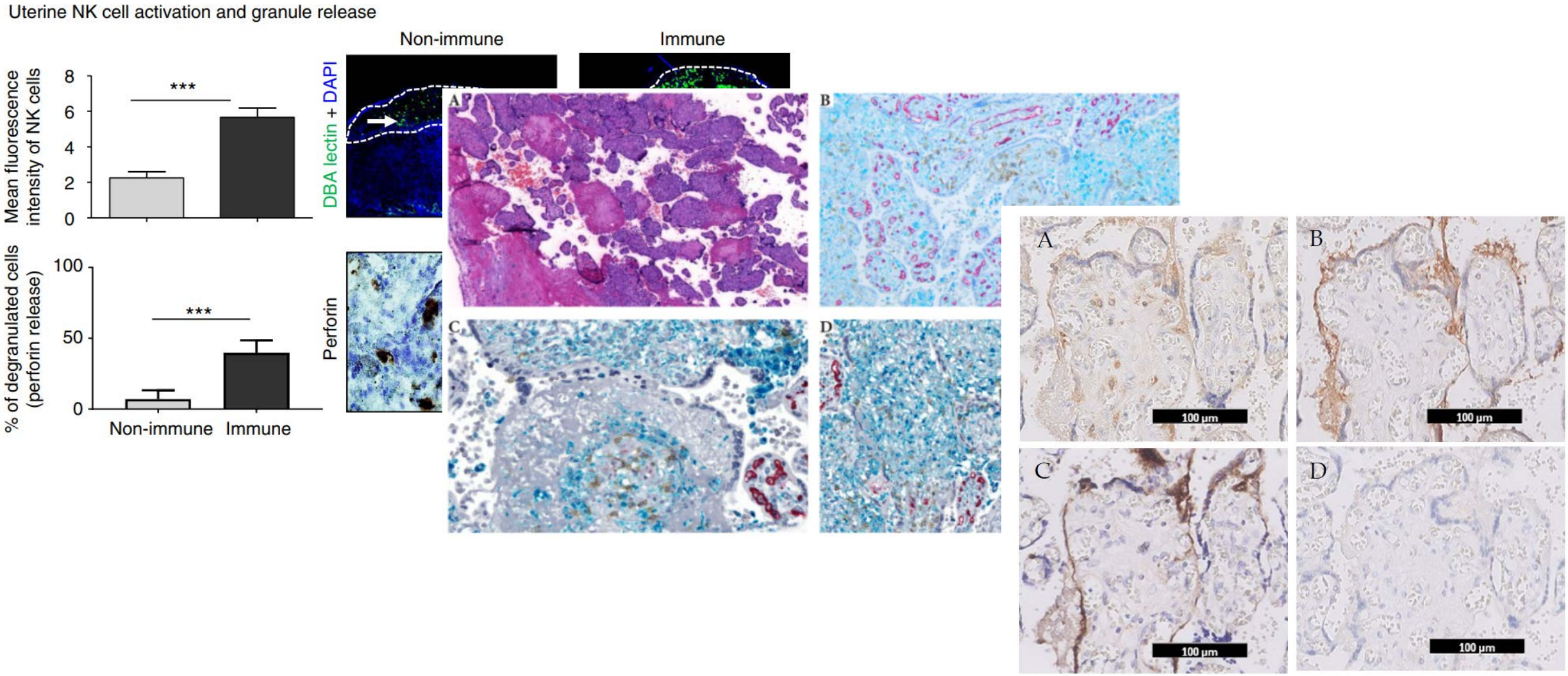
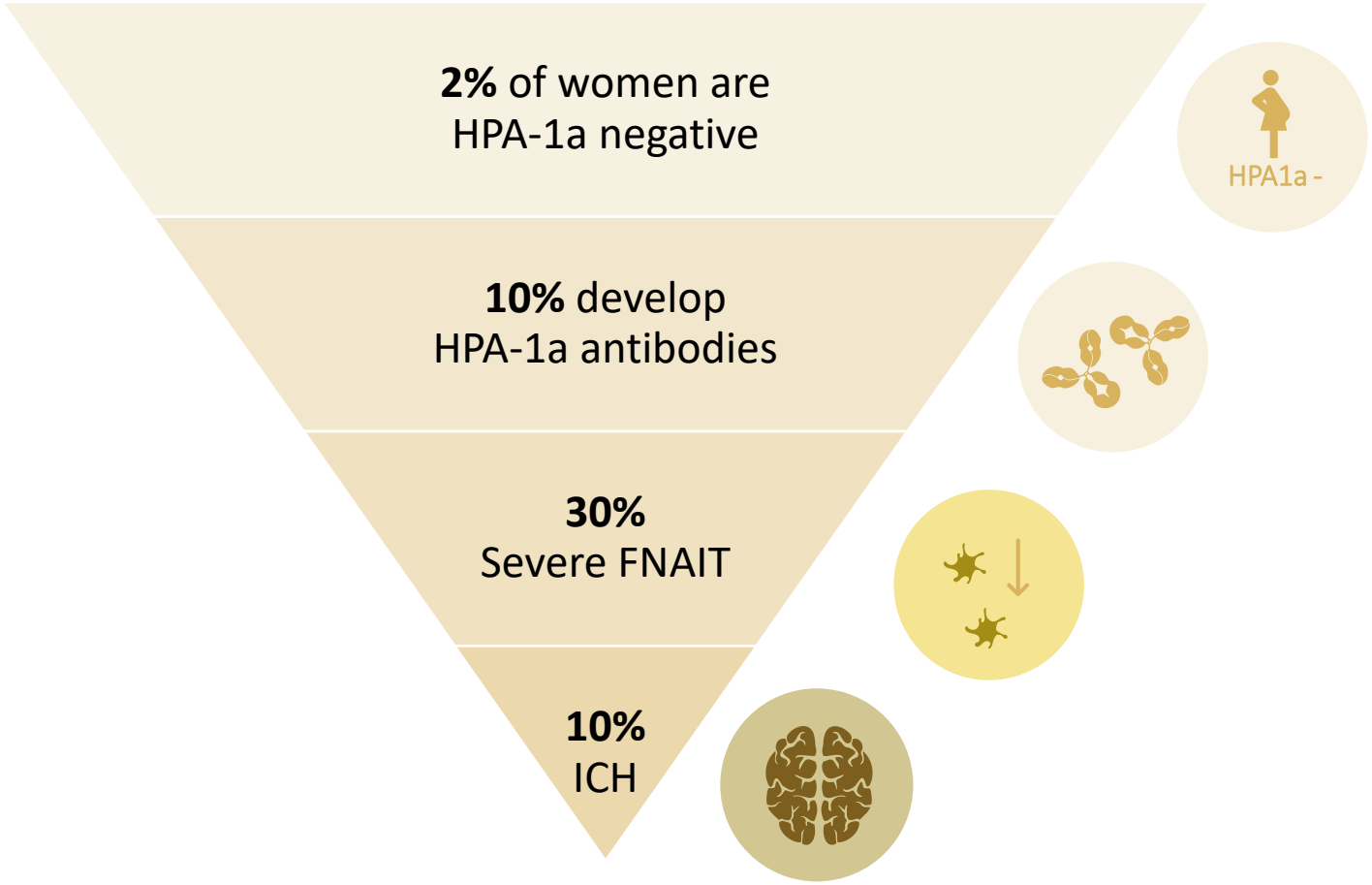
Cellular or antibody (complement) induced placental damage in HPA-1a mediated FNAIT?



1. Tiller, AOGS, 2011. 2. Yougbaré, Nat Commun., 2017
3. Hersoug Nedberg, Placenta, 2021, 4. de Vos, Int J Mol Sci., 2021

Incidence HPA-1a mediated FNAIT



de Vos *et al.,* Transfusion and Apheresis Science, 2019