PedNet Haemophilia Research Foundation

PedNet

Annual report 2020
PedNet cohort studies

Data export January 2021

On behalf of the PedNet study group

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Chairman of the management board

H. Marijke van den Berg, MD, PhD
Director of the PedNet Haemophilia Research Foundation

Contents

PedNet (the European Paediatric Network for Haemophilia Management) started in 1996 as a collaboration of 22 paediatricians in 16 European countries. PedNet was initiated to provide an infrastructure for clinical research on the management of children with haemophilia. Currently the PedNet study group consists of 33 haemophilia treatment centres in 19 countries.

The PedNet Registry started in 2003 and, in order to prevent selection bias, is set up as a birth cohort study. It collects real-life data from all newly diagnosed children treated in the participating centres. Data are collected through well-defined web-based E-CRF forms that contain details on all aspects of haemophilia from birth to adolescence and adulthood.
Patients with FVIII/IX levels up to 25%, born from January 1, 2000 are included in the PedNet Registry. Annual data exports are used for analysis of ongoing studies.

The PedNet Haemophilia Research Foundation was founded in December 2016 in The Netherlands and is the legal owner of the database and all its assets.

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Key numbers

In total

2409

patients included in registry

105 new patients included in 2020

1312

PUPS with severe haemophilia A

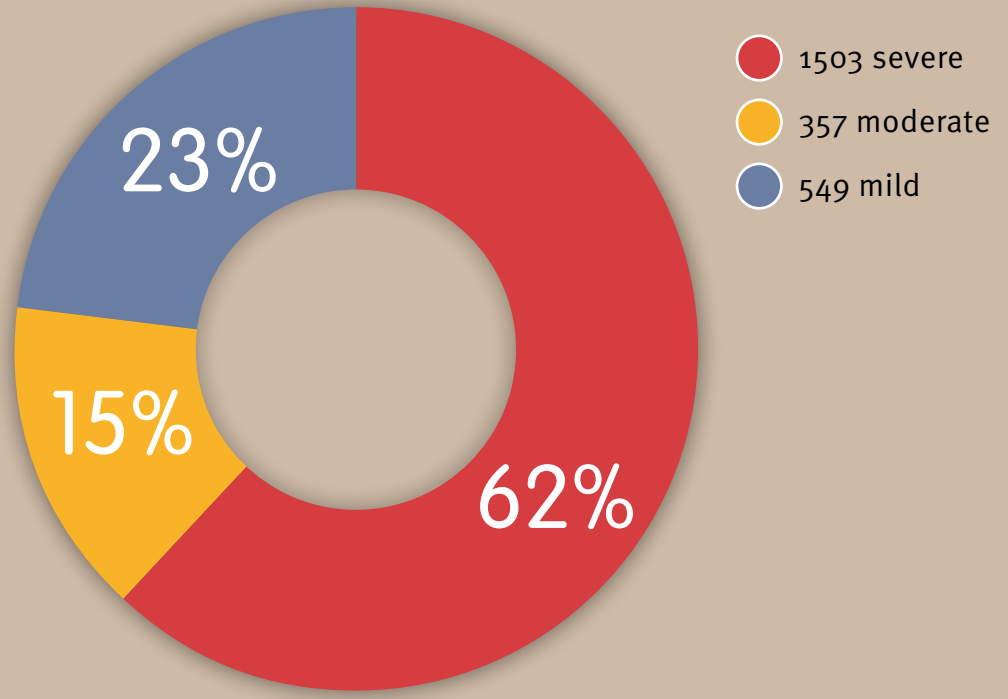
52 new severe haemophilia A PUPS in 2020

191

PUPs with severe haemophilia B

9 new severe haemophilia B PUPS in 2020

Included patients according to disease severity



33

participating centers in **19** countries

Gene mutations known in

86%

of all patients

Total number of follow up years

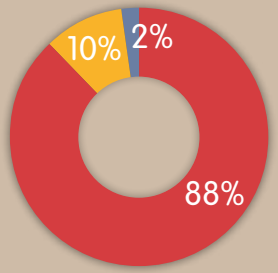
19,956

Data export January 2021

Key numbers

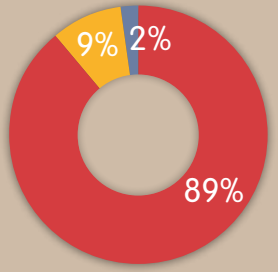
Prophylaxis

1445
Patients started prophylaxis
60% of 2409 included patients
Minimum of 2 consecutive months



- 1271 severe
- 150 moderate
- 24 mild

1119
Patients started prophylaxis
before (‹) ED50
46% of 2409 included patients
Minimum of 2 consecutive months



- 998 severe
- 105 moderate
- 16 mild

Inhibitors

441
Inhibitors diagnosed
between 2000-2020

A
394 severe haemophilia

B
16 severe haemophilia

3421
Follow up years for
inhibitor patients

A
3116 years for severe
haemophilia A
inhibitor patients

B
113 years for severe
haemophilia B
inhibitor patients

In total
20,356
inhibitor test results
are collected

14,145 tests of the 441 inhibitor patients
Median of 24 tests per inhibitor patient
(IQR 15-39.5)

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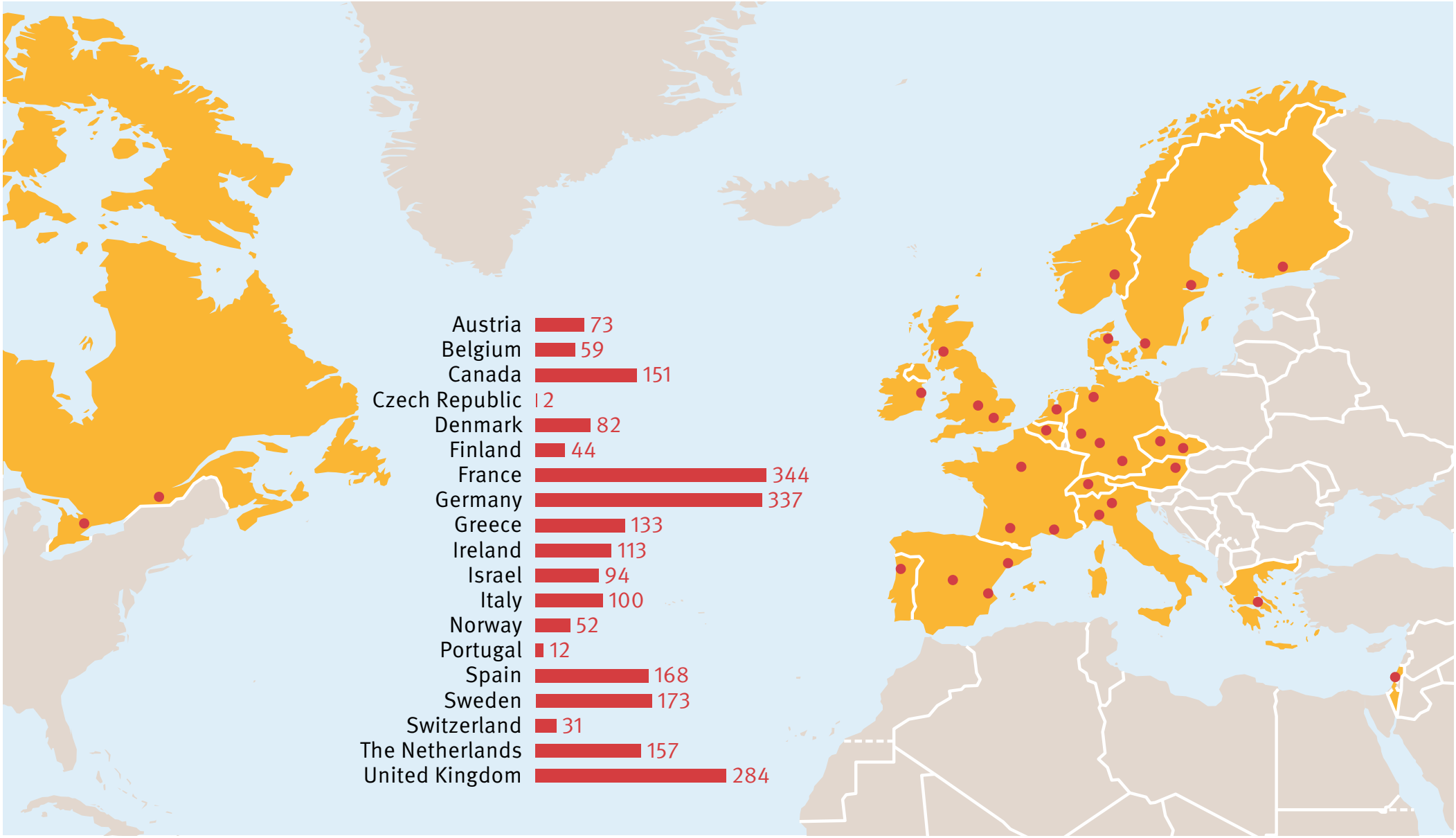
Participating countries and numbers of included patients



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Introduction

The PedNet study group (the European Paediatric Network for Haemophilia Management) is a collaboration of now 33 haemophilia treatment centres (HTCs) in 19 countries, including Canada (Toronto and Montreal) and Israel. The PedNet cohort studies include all patients with FVIII/IX levels up to 25%, born from January 1, 2000 onwards and diagnosed in one of the participating HTCs.
On 16 December 2016, the PedNet Haemophilia Research Foundation was founded in Amsterdam. The Foundation was instituted to incorporate the PedNet study group and to ascertain that it can continue to function in the future. More information can be found on our website: www.pednet.eu.
This report provides an overview of the status of the PedNet registry up to January 2021 and of the research activities performed by the PedNet study group in 2020. More information on all research activities can be found in the Research program 2021-2023.

Mission of the PedNet Haemophilia Research Foundation

The mission of the PedNet foundation is to improve the current and future care of children with haemophilia by collection of high-quality data from a large cohort of unselected previously untreated children with haemophilia A and B, thus enabling front-line research projects on inhibitor development, safety, efficacy and long-term outcome of replacement and non-replacement therapies.
The foundation is not-for-profit and publishes annual reports on activities and financial reports on www.pednet.eu.

PedNet Registry

In the PedNet Registry prospective data of well-defined clinical parameters are collected through a secured data capture system (Research Online).
For participating centres a minimum inclusion rate of 95% of all newly diagnosed patients is mandatory. PedNet has contracts with the participating centres and they are reimbursed for the new inclusions and follow-up reports.

Data of all included patients are regularly updated and they are checked for validity and completeness during the year. Yearly data exports are performed every January and used for new studies in that particular year.

Monitoring

Data collected in the PedNet registry are monitored to improve data quality. This is done by built-in checks on the e-CRF and regular data control on exports. Study coordinators employed by the foundation are in frequent contact with centres and perform regular visits. On-site monitoring is performed by an independent research organisation according to a predefined monitor plan. The PedNet centres agreed together that 100% of all baseline data and informed consent forms are checked with the medical files in the centres. For 10% of the patients, all exposure days and follow-up data are checked.

Current status

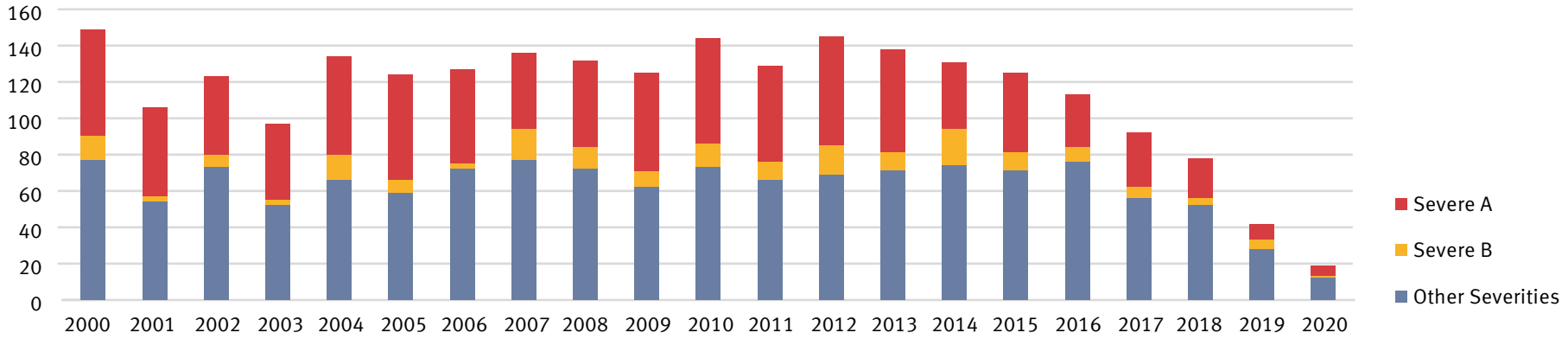
As of 1 January 2021, a total of **2409** previously untreated patients (PUPs) with haemophilia A or B are included in the study. Of these, **1312**, have severe haemophilia A (**52 more than last year**) and **191** have severe haemophilia B (9 more than last year) (see Appendix 1). **1333** (89%) of the severe haemophilia patients (A plus B) have reached 50 exposure days. Data on gene defects are available for **2071** (8%) patients included in the registry.

Bleeding during prophylaxis

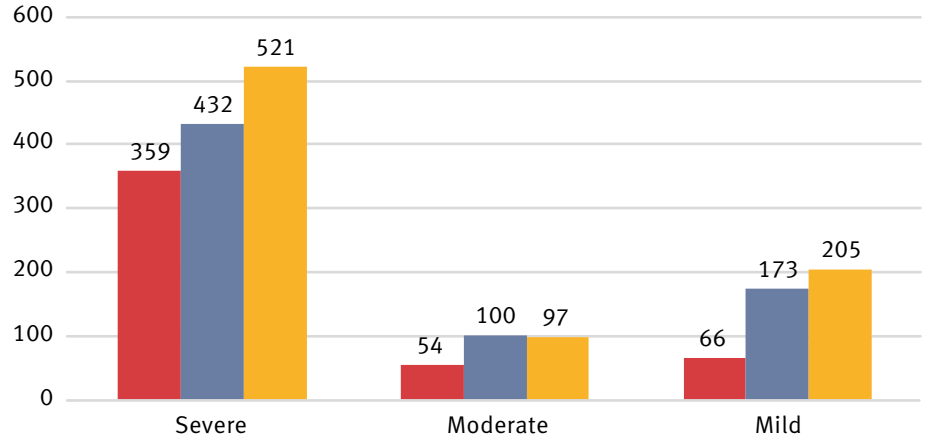
A total of **1445** patients started prophylactic treatment with a minimum duration of 2 months, **1271** severe, **150** moderate and **24** mild (A&B) patients. The study staff is working on a project to calculate the annual bleeding rate (ABR) in moderate and severe patients without inhibitor treated with prophylaxis for at least six months. Preliminary results were presented at the sponsor meeting and are planned to be published in the coming year. ABR will be calculated in 3 age groups; 0-5, 6-11 and 12-18 years.

Tables & Figures

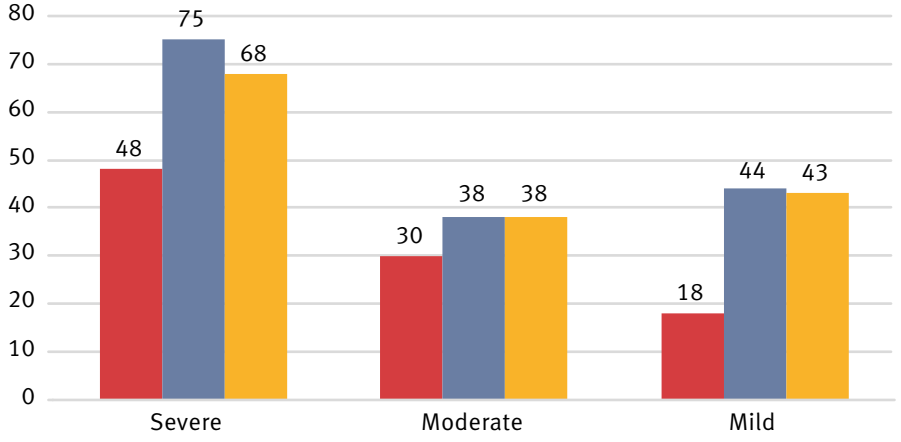
N Patients per birth year

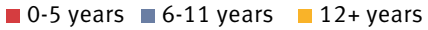


Current age haemophilia A



Current age haemophilia B





Data export January 2021

Tables & Figures

Haemophilia A

	Severe		Moderate	Mild	Total HA	
Baseline	1,312		251	444	2007	
Known gene mutations	1,194		198	339		86%
At least 50 EDs	1,172	89%	125	45	1,342	
Follow-up data	1,265		240	429	1,943	96%
Total FU years	11,133		2,084	3,633	16,850	
Lost to follow-up during first 50 EDs	34	3%	16	48	98	5%

Haemophilia B

	Severe		Moderate	Mild	Total HB	
Baseline	191		106	105	402	
Known gene mutations	170		89	81	340	85%
At least 50 EDs	161	84%	41	6	208	
Follow-up data	183		97	100	380	95%
Total FU years	1,583		749	774	3,106	
Lost to follow-up during first 50 EDs	8	4%	3	9	20	5%

Display of PedNet Numbers

	2016	2017	2018	2019	2020	2021
Baseline	1,531	1,733	1,972	2,142	2,304	2,409
Known gene mutations	1,260	1,449	1,691	1,834	1,958	2,071
At least 50 exposure days	950	1,094	1,235	1,382	1,483	1,550
Patients with follow-up data	1,413	1,615	1,858	2,029	2,203	2,314

Adverse events in 2020 in PedNet

		Inhibitor	No inhibitor	Total
Total events		4	13	17
Type of adverse event	Allergic reaction	0	2	2
	Thrombloembolic Event	0	0	0
	Local subcutaneous reaction	1	4	5
	Death	0	1	1
	Other	3	6	9

Details on inhibitor patients in PedNet

	All	Severe Haem A	Severe Haem B
N	441	394	16
Sum FU (yrs) after 1st positive sample	3,421	3,116	113
Median (yrs; IQR)	7 [3.4-11,4]	7.3 [3.6-11.8]	6.6 [2.9-10.5]

Inhibitor test results

20,356
Inhibitor tests for all patients

14,145
Inhibitor tests for N=441 inhibitor patients

A median of 24 (IQR 15-39.5)
tests per inhibitor patient

Data export January 2021

Activities of PedNet Working Groups

All planned research activities of the PedNet study group can be found in the Research Programme 2021-2023 https://pednet.eu/pednet-group/

Neonatal working group

PedNet participated in a study of the ICH study group on the long term follow up of children with severe HA who suffered from an intra cranial haemorrhage in the neonatal phase: *Long-term follow-up of neonatal intracranial haemorrhage in children with severe Haemophilia (Andersson NG et al, British Journal of Haematology, 2020, 190,e95-e125)*.

The intra cranial haemorrhage group is a collaboration of 32 centres in Europe, Israel, Turkey and the USA since 2011. Twenty eight of them also participate in the PedNet Registry and study group. The results of this study showed that neonates with severe haemophilia who did not receive immediate treatment within less than 24 h after the onset of symptoms and diagnosis of ICH were significantly more likely to develop neurological impairments or death (80%) than those receiving immediate treatment. These results confirm neonatal ICH as a major contributor to morbidity and mortality in children with severe haemophilia. Diagnosis of haemophilia and treatment should be as early as possible to prevent neurological impairment.

Genetic working group

After re-evaluation of all genetic reports in the PedNet database an extract on all novel variants was made. These 88 variants were not previously reported in the HGMD or CHAMPS, CHMBS and EAHAD hemophilia variant databases. The article: *Novel F8 and F9 gene variants from the PedNet hemophilia registry classified according to ACMG/AMP guidelines (Andersson et al., 2020)* was published in Human Mutation. The new variants will be published in the EAHAD data base.

New genetic reports are continuously reviewed according to the HGVS nomenclature and the pathogenicity according to ACMG/AMP guidelines. The group is working on an article that will describe inhibitor development in haemophilia A from a genetic point of view.

Working group on Inhibitors

Two new articles will be submitted in 2021: one on product type and inhibitor development and the other on early prophylaxis and inhibitor development.

More information can be found in the Research programme 2021-2023.

CVAD working group

The PedNet study group is collecting data on all CVADs implanted in the patients, both for inhibitor and non-inhibitor patients. The working group performed a study with the aim to evaluate if haemostasis coverage of maximum four days is as effective and safe as a longer period of haemostatic coverage. The analysis was performed in a group of 144 non-inhibitor SHA patients who received their first CVAD without a major bleed within 1 month before surgery. The group was divided in two groups; 34 children received ‹= 4 days haemostatic coverage, 110 received more than 4 days coverage. As the bleeding complications were rare in each group (one bleed related to the CVAD surgery in each group) the conclusion is that 4 days haemostatic coverage is as effective as coverage of =› 5 days. The results of this study: *Correction of hemostasis can be reduced to four days for CVAD implantation in severe haemophilia A patients; Data from the PedNet study group (Koskenvuo et al)* were accepted for publication in Haemophilia.

Haemophilia B working group

Last year PedNet published an inhibitor incidence of 10.2% in 154 PUPs with severe haemophilia B followed up to 500 Eds *(Male et al.,Hematologica 2020)*[9].

An article on patients with severe haemophilia B and an inhibitor and their response to ITI is almost ready for submission.

REMAIN study (Real-life MAnagement of INhibitors among PUPs with severe haemophilia A)

The PedNet study group collects follow up data of all (inhibitor and non-inhibitor) patients. This includes data on treatment regimens, immune tolerance induction (ITI), bleedings and surgeries. Recently data on long term outcome are collected too. Laboratory results are collected continuously for every patients that ever tested positive. The first article, titled: *Risk factors for the progression of low-titre to high-titre inhibitors in 260 children with severe haemophilia A and newly developed inhibitors (Mancuso et al.)*, described the cohort of inhibitor patients born between 1990-2009 and was published in 2017.

The second article analysed ITI treatment in the same cohort of SHA patients with a low titer inhibitor and was published last year. It was concluded that prophylaxis was equally effective than ITI in children with a low titre inhibitor. More information can be found in the article. *ITI Treatment is not First-Choice Treatment in Children with Hemophilia A and Low-Responding Inhibitors: Evidence from a PedNet Study (van den Berg et al, Thrombosis and Haemostasis, 2020)*.

Publications PedNet study group since 2019

1. Andersson NG, Chalmers EA, Kenet G, Ljung R, Mäkipernaa A, Chambost H, on behalf of the PedNet group. Mode of delivery in haemophilia: Vaginal delivery and cesarean section carry similar risk for intracranial hemorrhages and major bleeds. Haematologica Oct 2019, 104 (10) 2100-2106
2. van den Berg HM, Fischer K, Carcao M, Chambost H, Kenet G, Kurnik K, Königs C, Male C, Santagostino E, Ljung R. Timing of inhibitor development in >1000 previously untreated patients with severe hemophilia A. Blood 2019; 134 (3): 317-320.
3. Male C, Andersson NG, Rafowicz A, Liesner R, Kurnik K, Fischer K, Platokouki H, Santagostino E, Chambost H, Nolan B, Königs C, Kenet G, Ljung R, van den Berg HM. Inhibitor indicence in an unselected cohort of previously untreated patients with severe haemophilia B: A PedNet Study. Haematologica Jan 2020, haematol.2019.239160.
4. van den Berg HM, Mancuso ME, Königs C, D'Oiron R, Platokouki H, Mikkelsen TS, Motwani J, Nolan B, Santagostino E. ITI Treatment is not First-Choice Treatment in Children with Hemophilia A and Low-Responding Inhibitors: Evidence from a PedNet Study. Thrombosis and Haemostasis, 2020.
5. Jonker CJ, Oude Rengerink K, Hoes AW, Mol PGM, van den Berg HM. Inhibitor development in previously untreated patients with severe haemophilia: A comparison of included patients and outcomes between a clinical study and a registry-based study. Haemophilia, 2020.
6. Andersson NG, Wu R, Carcao M, Claeyssens-Donadel S, Kobelt R, Liesner R, Mäkipernaa A, Ranta S, Ljung R, the ICH study group. Long-term follow-up of neonatal intracranial haemorrhage in children with severe Haemophilia. British Journal of Haematology,2020.
7. Andersson NG, Labarque V, Letelier A, Mancuso ME, Bührlen M, Fischer K, Kartal-Kaess M, Koskenvuo M, Mikkelsen T, Ljung R, the PedNet study group. Novel F8 and F9 gene variants from the PedNet hemophilia registry classified according to ACMG/AMP guidelines. Human Mutation, 2020.

* For full publication list see www.pednet.eu/publications

Abstracts & Presentations

EAHAD 2019, Prague	Oral	Until what age should we worry about inhibitors? New data from the PedNet registry on 1038 PUPs with severe hemophilia A followed from the first until over 1000 exposure days
EAHAD 2020, the Hague	Poster	Time to negative inhibitor titre in severe haemophilia A patients with low titre inhibitors is similar regardless of ITI treatment: Data from PedNet cohort
ISTH 2020, Virtual	ePoster	Hemlibra treatment in pediatric Hemophilia A patients – real world data of safety and uptake in the PedNet cohorts

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Sponsor page

The PedNet foundation receives unrestricted funding from several pharmaceutical companies.

Current sponsors are:

- Bayer AG
- Biotest
- CSL Behring GmbH
- Novo Nordisk Health Care AG
- Pfizer SRL
- Swedish Orphan Biovitrium AB
- Takeda
- Hoffmann-La Roche

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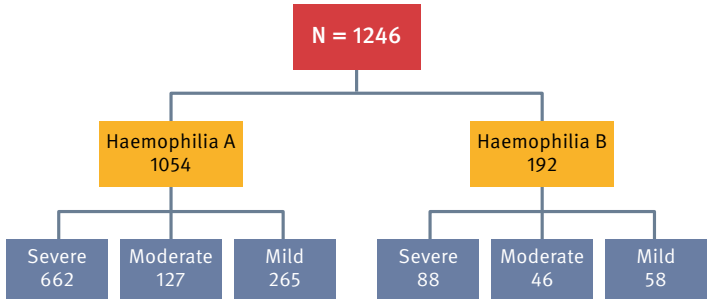
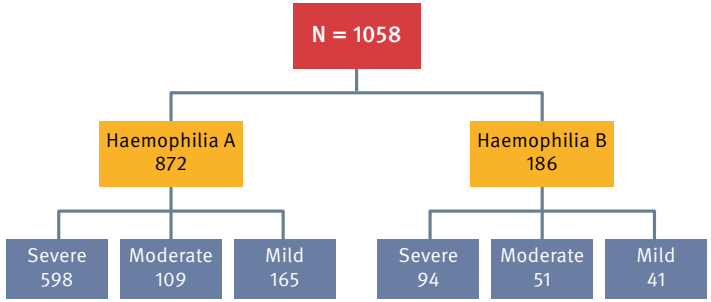
Appendix 1 Flowcharts January 2020

PedNet Birth Cohort 1 (2000 - 2009) - 31 centres

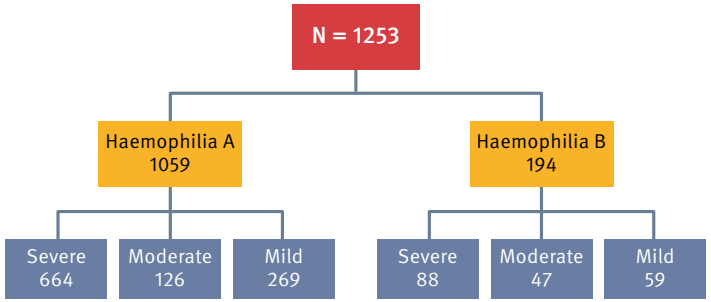


PedNet Birth Cohort 2 (2010 - 2019) - 31 centres

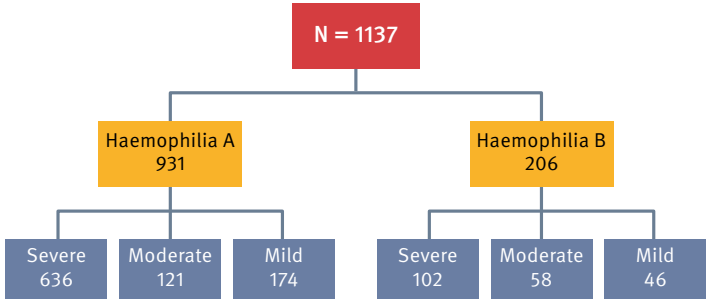


Appendix 2 Flowcharts January 2021

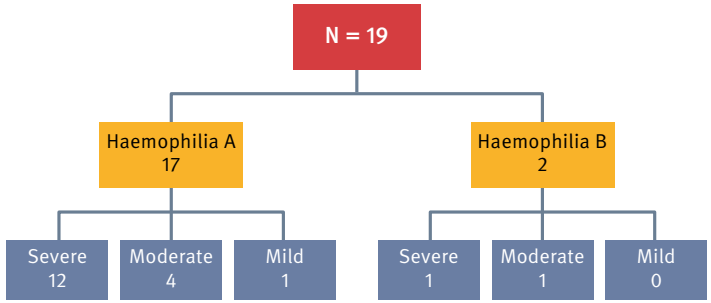
PedNet Birth Cohort 1 (2000 - 2009) - 31 centres



PedNet Birth Cohort 2 (2010 - 2019) - 31 centres



PedNet Birth Cohort 3 (2020 - 2029) - 33 centres



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