PedNet Haemophilia Research Foundation

PedNet

Annual report 2023
PedNet cohort studies

Data export January 2024

On behalf of the PedNet study group

Christoph Male, MD, MSc
Chairman of the management board

Gili Kenet, MD
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 32 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. It collects real-life data from all newly diagnosed children treated in the participating centres. Data are collected through well-defined 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.

In 2022 the first director of the foundation Marijke van den Berg retired. The position of director has been taken over by Gili Kenet. Christoph Male took over the position as chair of the board from Rolf Ljung, who remains board member.

Management Board

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Scientific Advisory Council:

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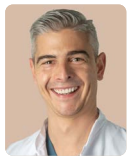

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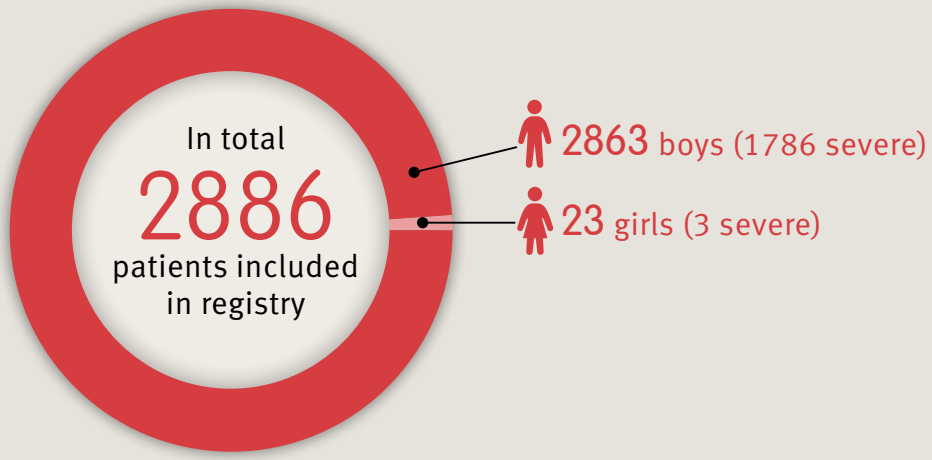
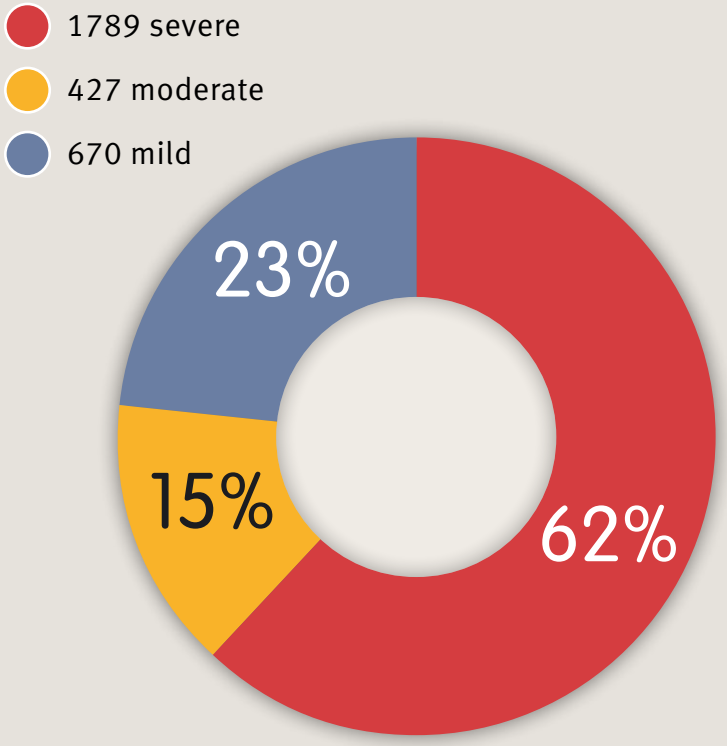
Key numbers



127 new patients included in 2023

Included patients according to disease severity



1557 PUPS with severe haemophilia A

66 new severe haemophilia A PUPS in 2023

232 PUPs with severe haemophilia B

13 new severe haemophilia B PUPS in 2023

32 participating centers in 19 countries

Detailed data on gene mutation available in 86% of all patients

Total number of follow up years 26,654

Data export January 2024

Key numbers

Follow up data

86%

severe haemophilia A patients reached 50 exposure days.
Lost to follow up during first 50EDs is 3%

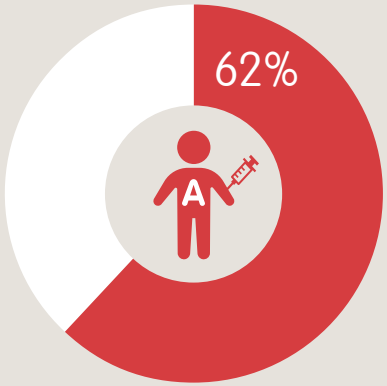
A

85%

severe haemophilia B patients reached 50 exposure days.
Lost to follow up during first 50EDs is 4%

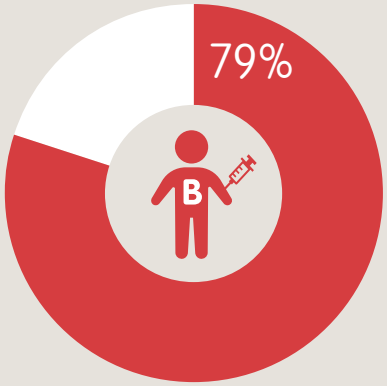
B

Start prophylaxis



965

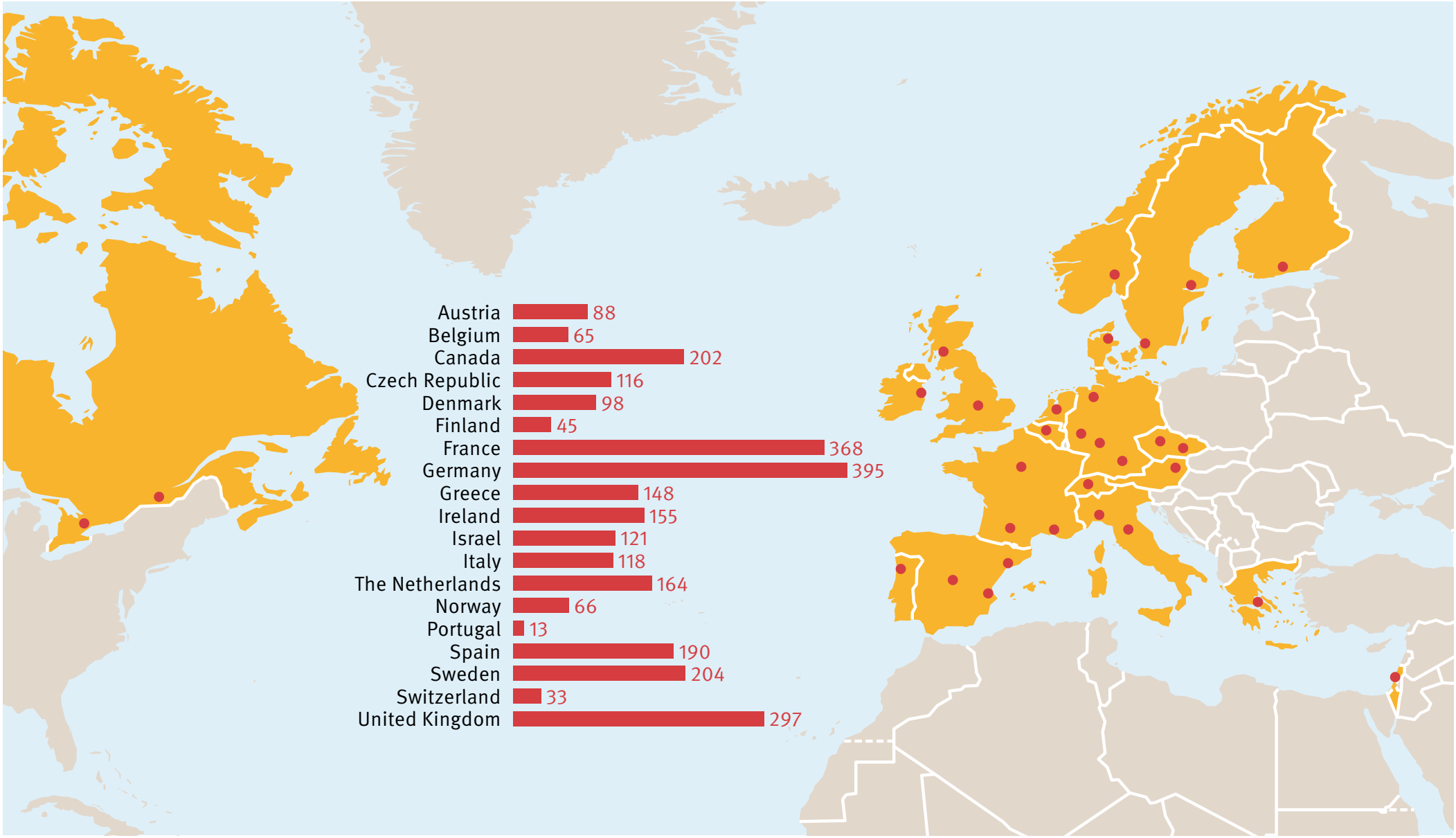
Severe haemophilia A patients started prophylaxis(CFC) before (‹) ED50.
Minimum of 2 consecutive months.
Median age at start in years is 1.2 (IQR 0.9–1.8)



183

Severe haemophilia B patients started prophylaxis (CFC) before (‹) ED50.
Minimum of 2 consecutive months.
Median age at start in years is 1.3 (IQR 0.9–2.0)

Participating countries and numbers of included patients



Data export January 2024

Introduction

The PedNet study group (the European Paediatric Network for Haemophilia Management) is a collaboration of now 32 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 2024 and of the research activities performed by the PedNet study group in 2023. More information on all research activities can be found in the Research programme 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 of replacement and non-replacement therapies and long-term outcome. The foundation is not-for-profit and publishes annual reports on activities and financial reports on www.pednet.eu.

PedNet Registry

The protocol of the PedNet Registry follows the EMA guideline on registry based studies (EMA/426390/2021). Well-defined clinical parameters are collected through a secured data capture system (Research Online and Castor).
For participating centres a minimum inclusion rate of 95% of all newly diagnosed patients is mandatory. PedNet has consortium agreements with the participating centres and they are compensated 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. Coordinators employed by the foundation are in frequent contact with centres and perform regular checks on the inclusion of new patients and follow up data entry. On-site monitoring of source data and informed consent is performed by an independent research organisation according to a predefined monitor plan. The PedNet centres agreed together that 100% of 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

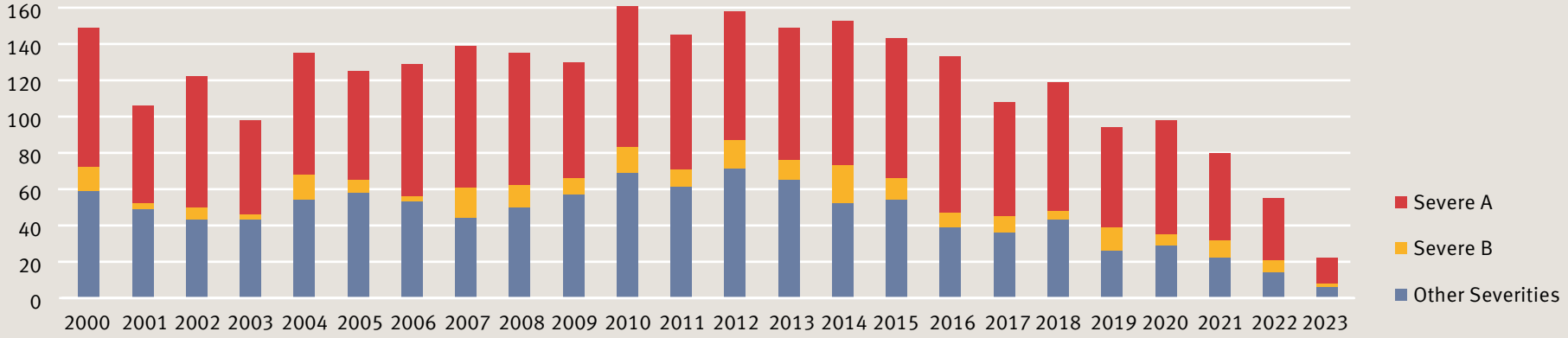
As of 1 January 2024, a total of **2886** previously untreated patients (PUPs) with haemophilia A or B are included in the registry. Of these, **1557** have severe haemophilia A (**66 more** than last year) and **232** have severe haemophilia B (**13 more** than last year) (see Appendix 1). **1540** (86%) of the severe haemophilia patients (A plus B) have reached 50 exposure days. Data on gene defects are available for **2479** (86%) patients included in the registry.

Start prophylaxis

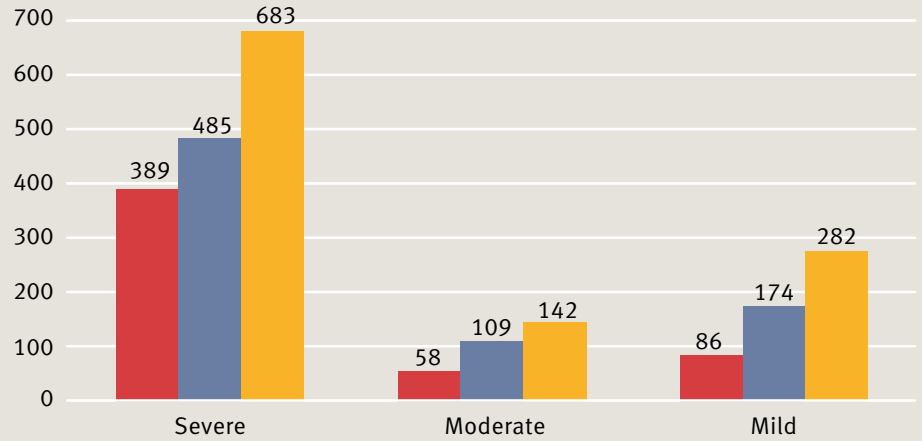
A total of **1316** patients started prophylactic treatment with clotting factor concentrate before ED50 and with a minimum duration of 2 months, **965** severe A and **183** severe B patients. The median age at start prophylaxis was 1.2 years for severe A and 1.3 for severe B patients.

Tables & Figures

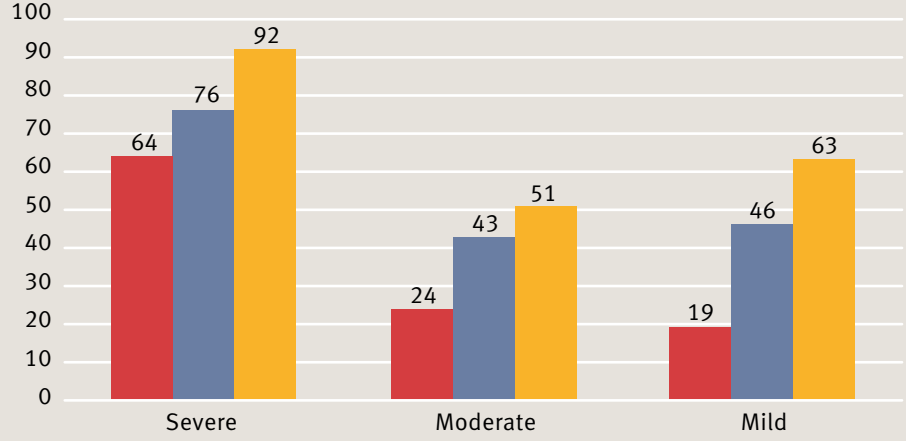
N Patients per birth year

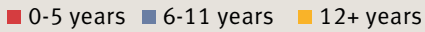


Current age haemophilia A



Current age haemophilia B





Tables & Figures

Haemophilia A

	Severe		Moderate	Mild	Total HA	
Baseline	1,557		309	542	2,408	
Girls	3		2	10	15	
Known gene mutations	1,418		247	408	2,073	86%
At least 50 EDs	1,343	86%	172	63	1,578	
Inhibitors	457		27	9	493	
Follow-up data	1,507		302	520	2,329	97%
Total FU years	14,775		2,817	4,895	22,487	
Lost to follow-up during first 50 EDs*	48	3%	38	192	278	12%

* excl. patients =›16 yrs

Haemophilia B

	Severe		Moderate	Mild	Total HB	
Baseline	232		118	128	478	
Girls	1		2	5	8	
Known gene mutations	206		100	100	406	85%
At least 50 EDs	197	85%	56	13	266	
Inhibitors	20		0	0	20	
Follow-up data	221		114	126	461	96%
Total FU years	2,053		1,022	1,092	4,167	
Lost to follow-up during first 50 EDs*	10	4%	25	42	77	16%

* excl. patients =›16 yrs

Display of PedNet Numbers

	2020	2021	2022	2023	2024
Baseline	2,304	2,409	2,576	2,759	2,886
Known gene mutations	1,958	2,071	2,219	2,373	2,479
At least 50 exposure days	1,483	1,550	1,653	1,737	1,844
Patients with follow-up data	2,203	2,314	2,472	2,633	2,790

Adverse events in 2022 & 2023*

		Inhibitor	No inhibitor	Total
Total events		5	3	8
Type of adverse event	Allergic reaction	0	0	0
	Thromboembolic event	1	1	2
	Thrombotic microangiopathy	0	0	0
	Neurological event (other than ICH)	0	0	0
	Local subcutaneous reaction	3	0	3
	Death	0	0	0
	Other	1	2	3

* reporting of AE may be delayed, as centres first report to National and local authorities

Activities of PedNet Working Groups

Research projects are been structured into working groups each with one chair, 5-8 members, and analytic and administrative support from the study staff in the Netherlands. All planned research activities of the PedNet study group can be found in the Research Programme 2021-2023 https://pednet.eu/pednet-group/. For full publication list see www.pednet.eu/publications

Genetic working group

New genetic reports are continuously reviewed according to the HGVS nomenclature and the pathogenicity according to ACMG/AMP guidelines. The group compared the spectrum of F8 and F9 variants in the PedNet data base with the spectrum of variants found in the "randomly reported" EAHAD and CHAMP/CHBMP databases. This comparison demonstrated a higher proportion of missense variants in severe HB in EAHAD (68%) compared to PedNet (48%) and CHBMP (46%). The F8 and F9 variants in the PedNet population based cohort offer a new frame of reference as an alternative to the established 'random-report" databases. The full article was accepted for publication by Research and Practice in Thrombosis and Haemostasis in 2022 and published in 2023.

The working group wrote a letter to the editor on Factor VIII genotype and the risk of developing high-responding and low-responding inhibitors in severe haemophilia A. This letter was accepted for publication by Haematologica (doi: 10.3324/haematol.2023.284095)

Follow Up of SHA patients with inhibitors

Previously REMAIN study (Real-life Management of Inhibitors among PUPs with severe haemophilia A)

After the first two publications in 2017 and 2020, the working group decided to update the study population with patients from cohort II (born 2010-2019) and follow up beyond 3 years after inhibitor development. Analyses for the next two manuscripts are performed on inhibitor patients born 2000-2019. The second manuscript will focus on the results of ITI in patients with high titre inhibitors. The first manuscript evaluates the bleeding rates of all inhibitor patients before and during ITI, until the first negative titre. This manuscript has been accepted for publication by Blood Advances (doi: 10.1182/Bloodadvances.202311442). The second manuscript is expected to be finalized in 2024.

Haemophilia B working group

In 2020 a paper on the inhibitor incidence in severe haemophilia B was published. Inhibitor incidence in an unselected cohort of previously untreated patients with severe haemophilia B: A PedNet Study *(Male et al., Hematologica 2020)*. A manuscript on patients with severe haemophilia B and an inhibitor and their response to ITI is underway.

Working group on Long-term outcome

Patients in PedNet are followed from diagnosis until adulthood. The collection of data on validated outcome tools started in 2018. In 2021 a pilot project was performed on data of 141 patients (100 without inhibitors, and 41 with current/past inhibitors) from five PedNet centres with the aim to explore the feasibility to answer several research questions on long-term outcome. The results showed that most adolescents had a favourable joint health, while patients with inhibitors showed a two-fold increased proportion with joint deterioration by Haemophilia Joint Health Score. Project results are described in the article: *Long-term joint outcomes in adolescents with moderate or severe haemophilia A (Schmidt et al)*, which has been published in Haemophilia in 2022.

The next project started in 2022: the comparison of treatment joint health status in Greek and Swedish children with severe haemophilia on prophylactic treatment was accepted for a poster presentation on EAHAD 2023 in Manchester, UK. The group is currently drafting a full article.

Working group on novel therapies

As many new concentrates and alternative therapies are currently entering the market for haemophilia, the PedNet study group sees the need to study both the safety and efficacy of these new therapies. The study group conducted a survey on the implementation of emicizumab in the PedNet centres. The results of the survey were accepted for publication in Haemophilia (doi: 10.1111/hae.14847) and was noted as the most accessed paper in Haemophilia in 2023.
Data on bleeding control after switching to emicizumab in 251 children was accepted for a poster presentation on EAHAD 2023. Manuscript submission is pending review.

Working group on bleeding

Bleeding in non-severe haemophilia

Novel therapies, including modified replacement therapy and gene therapy, provide opportunity to substantially increase baseline FVIII activity levels, or (partially) correct haemostasis. Information on bleeding phenotype in non-severe haemophilia provides the best possible information regarding optimum target for prophylactic treatment. The aim of this project is to assess bleeding according to baseline FVIII activity in children with non-severe haemophilia A (HA). Data on comparing non-severe haemophilia A and B was presented at the ISTH in July 2022. At the same congress, a poster focused on bleeding in non-severe haemophilia A was presented. A full manuscript is pending review.

Bleeding pattern in severe haemophilia A and B on prophylaxis

Few data exist on long-term follow-up of type and frequency of bleedings in children 0-18 years with severe haemophilia on primary prophylaxis with FVIII/FIX. The aim of this study is to compare bleeds in real-world data between different age groups in children with severe haemophilia A (SHA) or B (SHB) on primary prophylaxis. Data was presented at ISTH in July 2022. A full manuscript is in preparation.

Task force on rare bleeding disorders

The PedNet members agreed to expand the current registry by including children with other rare bleeding disorders. A survey was conducted among PedNet Centres to identify the best approach and gauge the number of children to include. A unique task force (consisting of PedNet members) is currently working on a procotol and preparing the e-CRF.

Publications PedNet study group 2023

1. Fischer K, Carcao M, Male C, Ranta S, Pergantou H, Kenet G, Kartal-Kaess M, Königs C, Carvalho M, Alvarez MT, Brakenhoff T, Chambost H, van den Berg HM. Different inhibitor incidence for individual factor VIII concentrates in 1076 PUPS with severe hemophilia A: data from the PedNet cohort. Supplemental material: https://pednet.eu/publications/2022_jth_fischer
   Letter: https://doi.org/10.1016/j.jtha.2022.11.020
2. Labarque V, Mancuso ME, Kartal-Kaess M, Ljung R, S. Mikkelsen T, G. Andersson N. F8/F9 variants in the population-based PedNet Registry cohort compared with locus-specific genetic databases of the European Association for Haemophilia and Allied Disorders and the Centers for Disease Control and Prevention Hemophilia A or Hemophilia B Mutation project.
   https://doi.org/10.1016/j.rpth.2023.100036
3. Ranta S, Motwani J, Blatny J, Bührlen M, Carcao M, Chambost H, Escuriola C, Fischer K, Kartal-Kaess M, de Kovel M, Kenet G, Male C, Nolan B, d'Oiron R, Olivieri M, Zapotocka E, G. Andersson N, Königs C. Dilemmas on emicizumab in children with haemophilia A: A survey of strategies from PedNet centres.
   https://onlinelibrary.wiley.com/doi/10.1111/hae.14847
4. G. Andersson N, Labarque V, Kartal-Kaess M, Pinto F, S. Mikkelsen T, Ljung R, PedNet Study Group. Factor VIII genotype and the risk of developing high-responding or low-responding inhibitors in severe hemophilia A: data from the PedNet Hemophilia Cohort of 1,202 children.
   https://doi.org/10.3324/haematol.2023.284095
5. Fischer K, Kenet G, Kurnik K, Carcao M, Oldenburg J, Stamm-Mikkelsen T, Cid Haro AR, Koskenvuo M, Blatny J, Königs C, PedNet Study Group. Determinants of bleeding before and during immune tolerance in 222 boys with severe hemophilia A and inhibitors >5 BU.
   https://www.sciencedirect.com/science/article/pii/S2473952923006249

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

Abstracts & Presentations

EAHAD 2023, Manchester	Poster	Bleeding control improves after switching to emicizumab: Real world experience from 251 children in the PedNet Registry
EAHAD 2023, Manchester	Poster	Treatment and Joint health status in children with Severe Haemophilia on prophylaxis: A comparison of Sweden and Greece based on the PedNet Registry
ISTH 2023, Montreal	Poster	Clinical characteristics, therapy and outcome of children with hemophilia B and inhibitors: A PedNet study
ISTH 2023, Montreal	Oral	Dilemmas on emicizumab in children with haemophilia A: A survey of strategies from PedNet centres
EAHAD 2024, Frankfurt	Poster	Characteristics of girls with haemophilia A or B included in the PedNet registry

Sponsor page

The PedNet foundation receives unrestricted funding from several pharmaceutical companies.

Current sponsors are:

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

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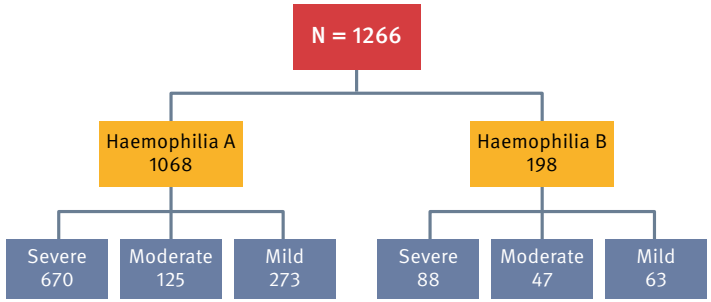
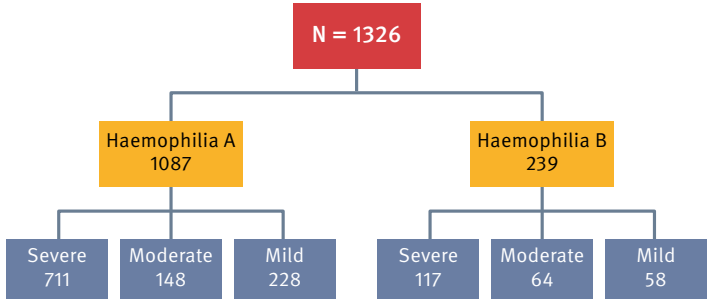
Participants PedNet Meeting Malmö, Sweden 2023

Appendix 1 Flowcharts January 2023

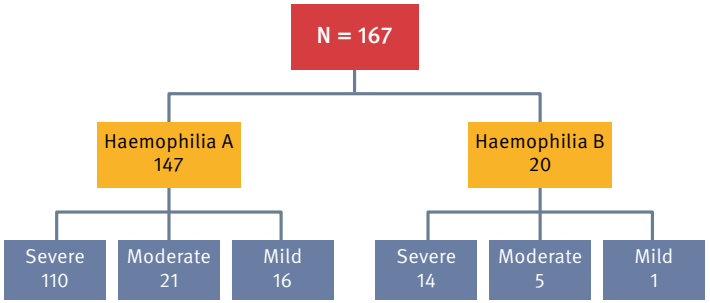
PedNet Birth Cohort 1 (2000 - 2009) - 31 centres



PedNet Birth Cohort 2 (2010 - 2019) - 33 centres

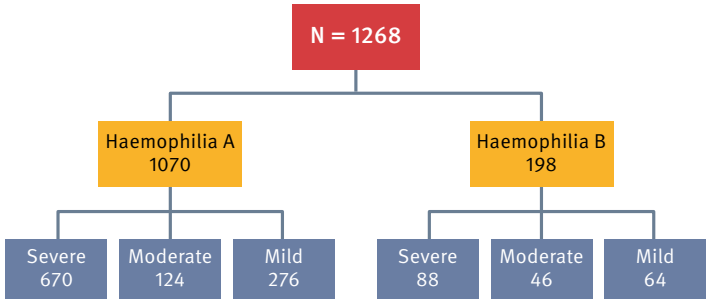


PedNet Birth Cohort 3 (2020 - 2029) - 33 centres

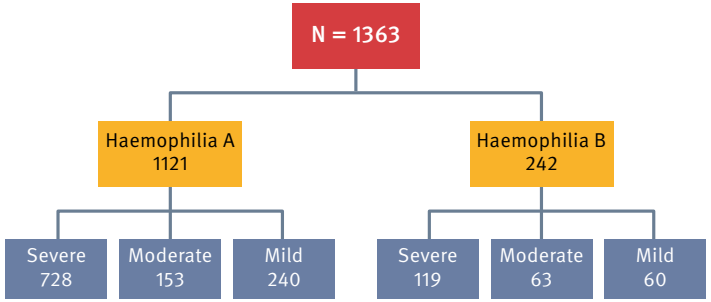


Appendix 2 Flowcharts January 2024

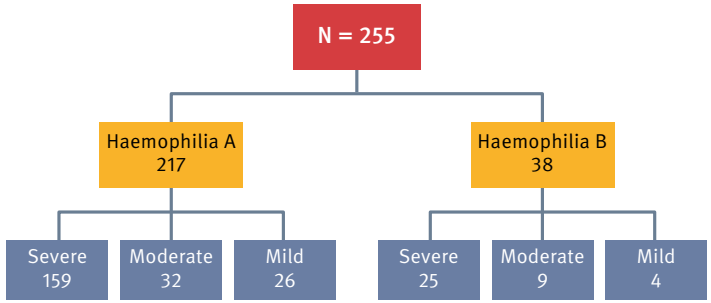
PedNet Birth Cohort 1 (2000 - 2009) - 31 centres



PedNet Birth Cohort 2 (2010 - 2019) - 33 centres



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



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