PedNet Haemophilia Research Foundation

PedNet

Annual report 2021
PedNet cohort studies

Data export January 2022

On behalf of the PedNet study group

Rolf Ljung, MD, PhD
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.

Management Board

Carmen Escuriola, MD
Hämophilie Zentrum Rhein Main GmbH
Mörfelden-Walldorf, GERMANY

Gili Kenet, MD
The National Hemophilia Center
Ministry of Health
Sheba Medical Center
Tel Hashomer, Ramat Gan, ISRAEL

Rolf Ljung, MD, PhD
Department of Clinical Sciences
Lund University, Lund
Department of Pediatrics and Malmö
Centre for Thrombosis and Haemostasis
Skåne University Hospital
Malmö, SWEDEN

Christoph Male, MD
Department of Paediatrics
Medical University of Vienna
Vienna, AUSTRIA

Roseline d'Oiron, MD
Centre de Référence pour le Traitement
des Maladies Hémorragiques (CRTH)
Hôpital Bicêtre
Kremlin Bicêtre AP-HP, FRANCE

Scientific Advisory Council

María Teresa Álvarez Román, MD, PhD
Unidad de Coagulopatías
Hospital Universitario La Paz
Madrid, SPAIN

Manuel Carcao, MD
Hospital for Sick Children
Toronto, Ontario, CANADA

Hervé Chambost, MD, PhD
CHU Timone
Marseille, FRANCE

Kathelijn Fischer, MD, PhD
Van Creveld Kliniek
University Medical Center Utrecht
Utrecht, THE NETHERLANDS

Nadine Gretenkort Andersson, MD, PhD
Department of Clinical Sciences
Lund University, Lund
Department of Pediatrics and Malmö Centre
for Thrombosis and Haemostasis
Skåne University Hospital
Malmö, SWEDEN

Chris Königs, MD, PhD
Clinical and Molecular Hemostasis,
Department of Pediatrics
University Hospital Frankfurt &
Goethe University
Frankfurt/Main, GERMANY

Jayashree Motwani, MD
Department of Haematology
Birmingham Children's Hospital NHS Trust
Birmingham, UNITED KINGDOM

Key numbers

In total
2576
patients included in registry

167 new patients included in 2021

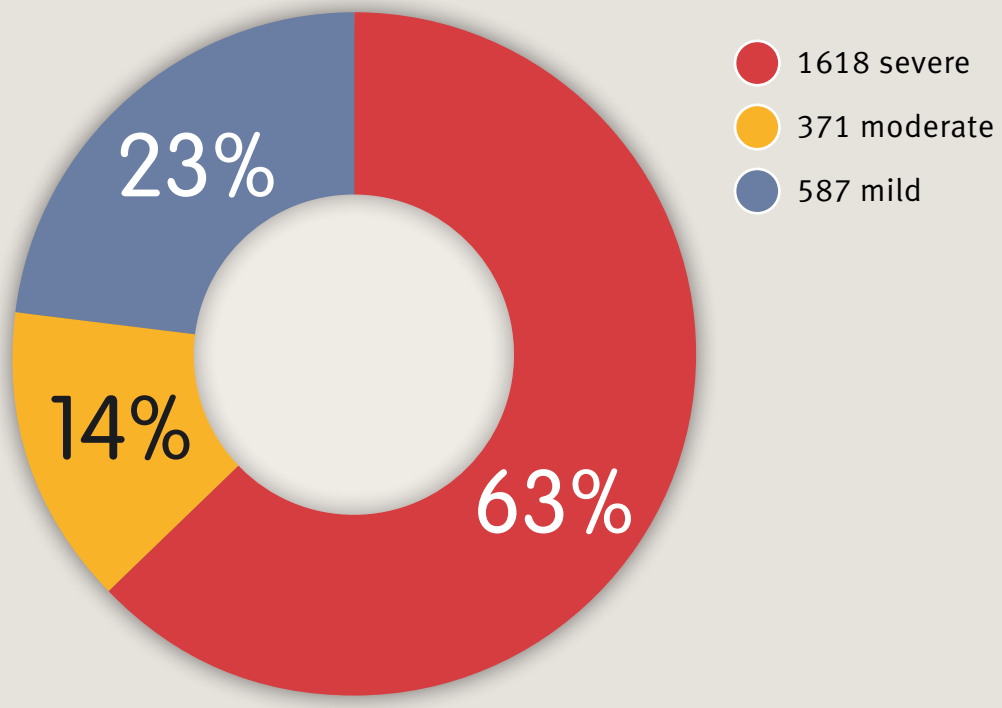
1411
PUPS with severe haemophilia A

99 new severe haemophilia A PUPS in 2021

207
PUPs with severe haemophilia B

16 new severe haemophilia B PUPS in 2021

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
22,098

Data export January 2022

Key numbers

Follow up data

88%

severe haemophilia A patients reached 50 exposure days.

Lost to follow up during first 50EDs is 2%

A

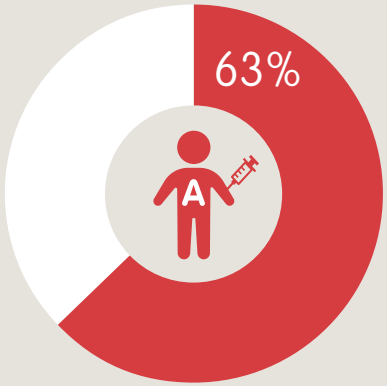
85%

severe haemophilia B patients reached 50 exposure days.

Lost to follow up during first 50EDs is 4%

B

Start Prophylaxis

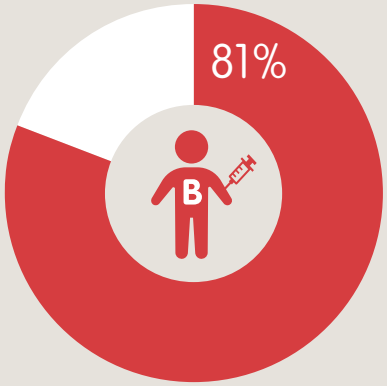


885

Severe haemophilia A patients started prophylaxis before (‹) ED50.

Minimum of 2 consecutive months.

Median age at start in years is 1.3 (IQR 0.9–1.8)



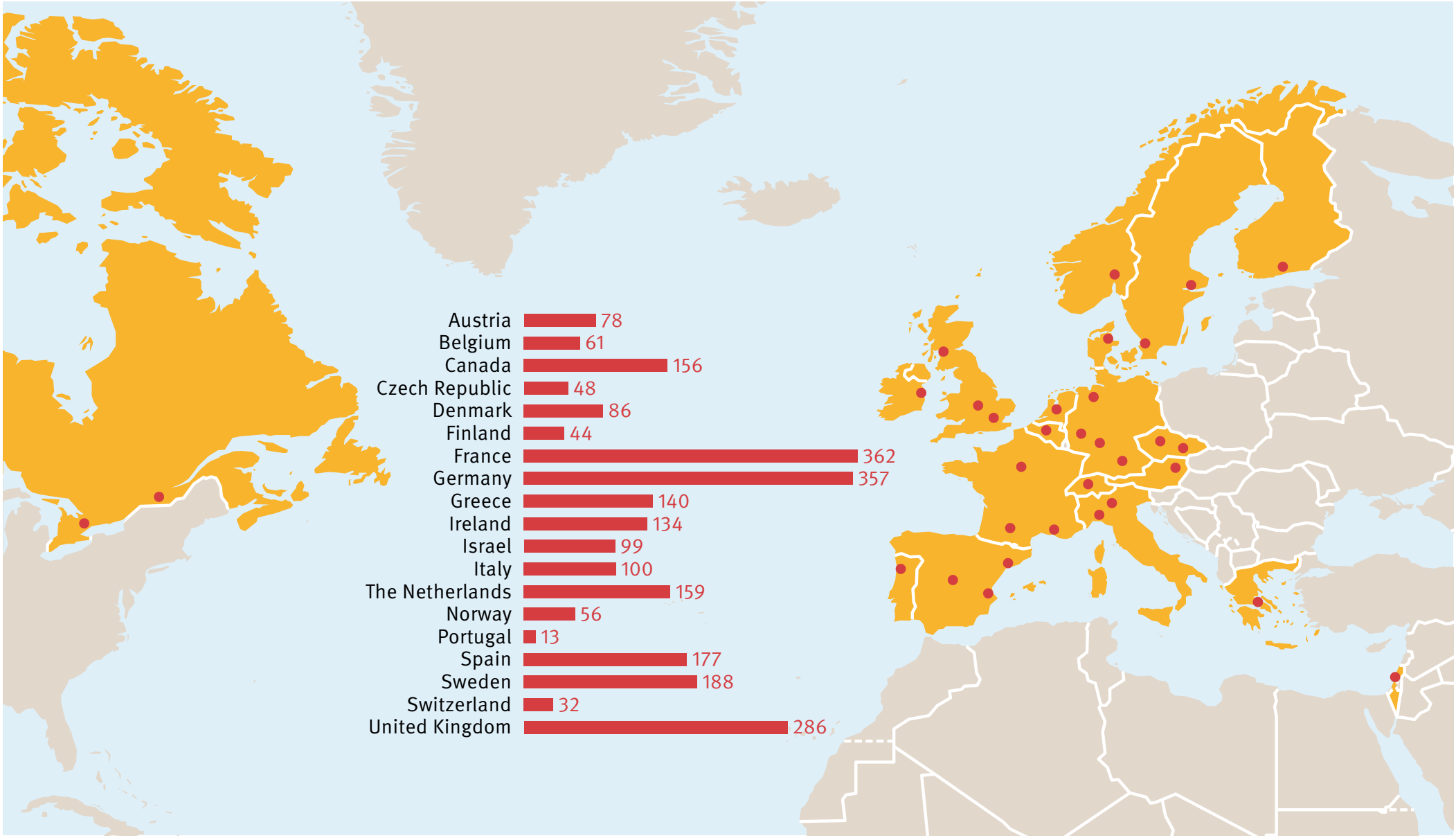
167

Severe haemophilia B patients started prophylaxis before (‹) ED50.

Minimum of 2 consecutive months.

Median age at start in years is 1.4 (IQR 1–2.2)

Participating countries and numbers of included patients



Data export January 2022

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 2022 and of the research activities performed by the PedNet study group in 2021. 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). 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 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 2022, a total of **2576** previously untreated patients (PUPs) with haemophilia A or B are included in the registry. Of these, **1411**, have severe haemophilia A (**99 more** than last year) and **207** have severe haemophilia B (**16 more** than last year) (see Appendix 1). **1413** (87%) of the severe haemophilia patients (A plus B) have reached 50 exposure days. Data on gene defects are available for **2219** (86%) patients included in the registry.

Start prophylaxis

A total of **1188** patients started prophylactic treatment with clotting factor concentrate before ED50 and with a minimum duration of 2 months, **885** severe A and **167** severe B patients. The median age at start prophylaxis was 1.3 years for severe A and 1.4 for severe B patients.

Key numbers

Inhibitors

470
Inhibitors diagnosed between 2000-2021

414 severe haemophilia

17 severe haemophilia

3923
Follow up years for inhibitor patients

3598 years for severe haemophilia A inhibitor patients. Median of 8.5 years per severe haemophilia A inhibitor patient (IQR 4.2–12.7)

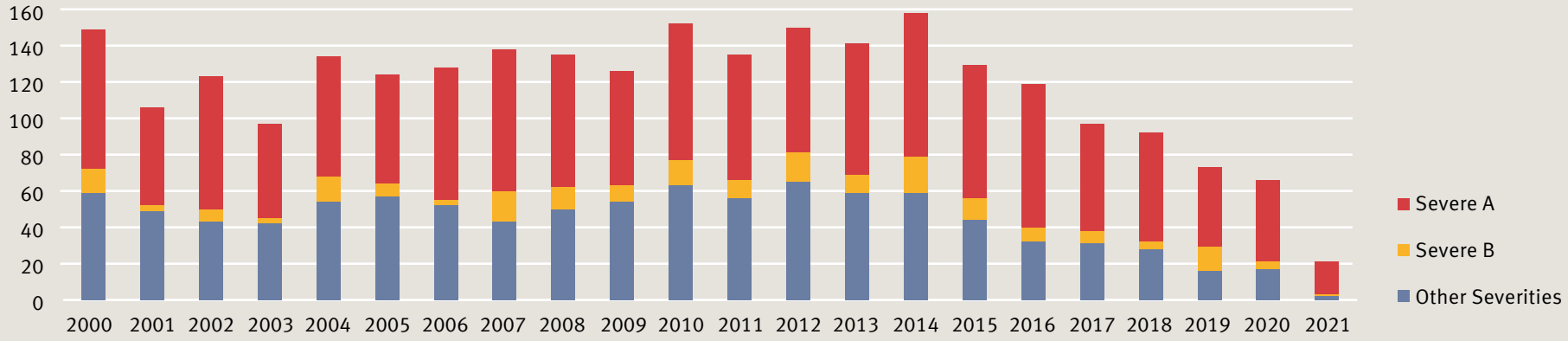
125 years for severe haemophilia B inhibitor patients. Median of 6.9 years per severe haemophilia B inhibitor patient (IQR 3–10.7)

In total
21,638
inhibitor test results are collected

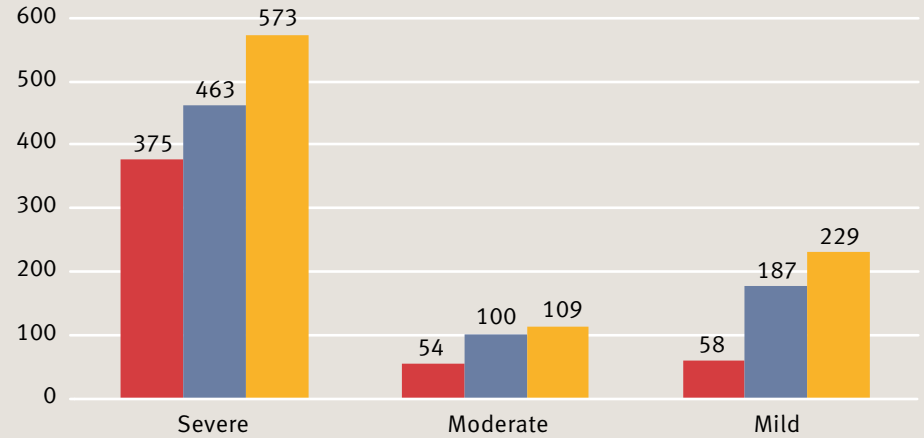
14,750 tests of the 470 inhibitor patients. Median of 23 tests per inhibitor patient (IQR 14–38.25)

Tables & Figures

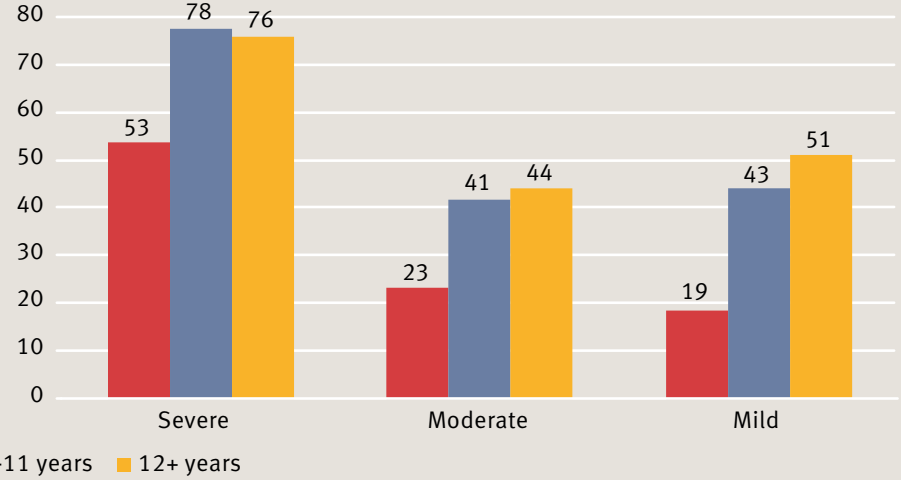
N Patients per birth year



Current age haemophilia A



Current age haemophilia B



Data export January 2022

Tables & Figures

Haemophilia A

	Severe		Moderate	Mild	Total HA	
Baseline	1,411		263	474	2,148	
Known gene mutations	1,278		213	368	1,859	87%
At least 50 EDs	1,237	88%	137	53	1,427	
Follow-up data	1,358		251	455	2,064	96%
Total FU years	12,425		2,258	4,026	18,709	
Lost to follow-up during first 50 EDs	35	2%	18	51	104	5%

Haemophilia B

	Severe		Moderate	Mild	Total HB	
Baseline	207		108	113	428	
Known gene mutations	182		91	87	360	84%
At least 50 EDs	176	85%	41	9	226	
Follow-up data	197		101	110	408	95%
Total FU years	1,737		800	852	3,389	
Lost to follow-up during first 50 EDs	9	4%	4	10	23	5%

Display of PedNet Numbers

	2017	2018	2019	2020	2021	2022
Baseline	1,733	1,972	2,142	2,304	2,409	2,576
Known gene mutations	1,449	1,691	1,834	1,958	2,071	2,219
At least 50 exposure days	1,094	1,235	1,382	1,483	1,550	1,653
Patients with follow-up data	1,615	1,858	2,029	2,203	2,314	2,472

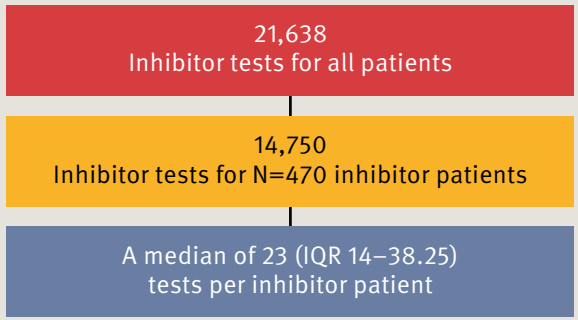
Adverse events in 2021

		Inhibitor	No inhibitor	Total
Total events		0	0	0
Type of adverse event	Allergic reaction	0	0	0
	Thromboembolic event	0	0	0
	Neurological event	0	0	0
	Local subcutaneous reaction	0	0	0
	Death	0	0	0
	Other	0	0	0

Details on inhibitor patients in PedNet

	All	Severe Haem A	Severe Haem B
N	470	419	17
Sum FU (yrs) after 1st positive sample	3,923	3,598	125
Median (yrs; IQR)	7.9 [4.1–12.5]	8.5 [4.2–12.7]	6.9 [3–10.7]

Inhibitor test results



Data export January 2022

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/

Genetic working group

New genetic reports are continuously reviewed according to the HGVS nomenclature and the pathogenicity according to ACMG/AMP guidelines. The group has prepared an article that describes the different genetic variants of F8/F9 in the PedNet Registry, which is now internally under review and prepares an article on genetic variant and inhibitor development.

Working group on Inhibitors

Two new articles will be submitted in 2022: 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.

Follow Up of SHA patients with Inhibitor

Previous 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. At the same time patients born 1990-1999 were excluded. Analyses for the next two articles are performed on inhibitor patients born 2000-2019. The first article will focus on the results of ITI in patients with high titre inhibitors. The second article evaluates the bleeding rate of all inhibitor patients before and during ITI, until the first negative titre. Results are under review and full articles are expected to be submitted in 2022.

Haemophilia B working group.

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

Working group on Long-term outcome

Patients in PedNet are followed from diagnosis until adulthood (18 years).
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 is currently under review for publication.

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. In 2020 and 2021 e-Posters evaluating safety of emicizumab treatment were published during the ISTH virtual meetings. A full article focussing on side effects and bleeding during treatment with emicizumab is expected for publication in 2022.

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). Two abstracts on this subject have been submitted to ISTH in July 2022. The first abstract is focused on bleeding in non-severe haemophilia A. The second abstract compares the bleeding tendencies of haemophilia A and B. A full manuscript is in preparation.

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. An abstract has been submitted to ISTH in July 2022. A full manuscript is in preparation.

Publications PedNet study group since 2020

1. 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.
2. 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. https://www.thieme-connect.de/products/ejournals/abstract/10.1055/s-0040-1713097
3. 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. https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14100
4. 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. https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.16740
5. 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. https://onlinelibrary.wiley.com/doi/10.1002/humu.24117
6. Koskenvuo M, Mäkipernaa A, Nolan B, Kobelt R, Ranta S. Correction of haemostasis can be reduced to four days for CVAD implantation in sever haemophilia A patients: Data from the PedNet study group https://onlinelibrary.wiley.com/doi/10.1111/hae.14231
7. Álvarez-Roman MT, Kurnik K, the PedNet study group. Care for children with haemophilia during COVID-19: Data of the PedNet study group https://onlinelibrary.wiley.com/doi/10.1111/hae.14231

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

Abstracts & Presentations

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
ISTH 2021, Virtual	Oral presentation	Long-term outcome in adolescents with moderate or severe hemophilia A: a PedNet study
ISTH 2021, Virtual	ePoster	Spectrum of F8/F9 gene mutations in the PedNet cohort
ISTH 2021, Virtual	ePoster	Emicizumab treatment in paediatric haemophilia A patients: ›1 year safety based on real-world data from the PedNet cohorts

Study staff

Marijke van den Berg
Director

Ella van Hardeveld
Study coordinator

Elsbeth de Boer-Verdonk
Senior data manager

Marloes de Kovel
Data manager

Marieke Blom-Smink
Research assistant

Sponsor page

The PedNet foundation receives unrestricted funding from several pharmaceutical companies.

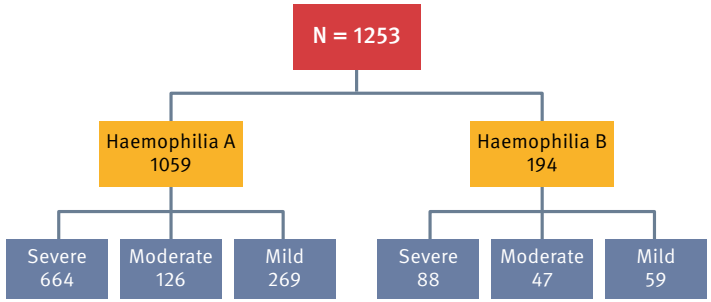
Current sponsors are:

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

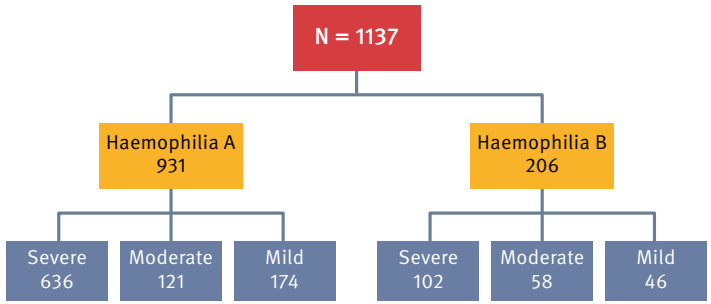
Correspondence
PedNet Haemophilia Research Foundation
Mollerusstraat 1
3743 BW Baarn
The Netherlands
info@pednet.eu

Appendix 1 Flowcharts January 2021

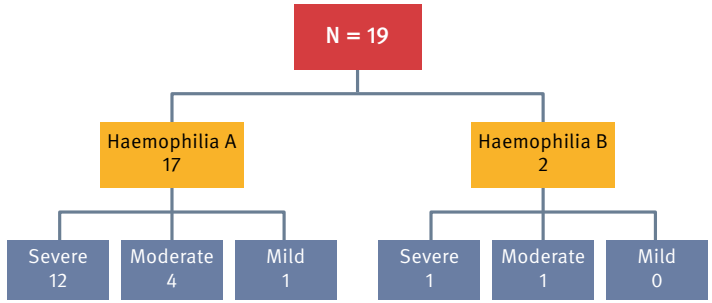
PedNet Birth Cohort 1 (2000 - 2009) - 31 centres



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

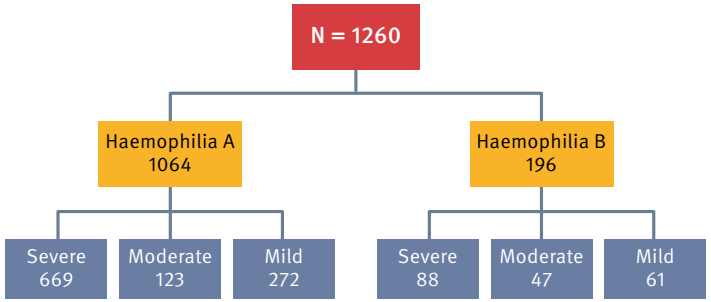


PedNet Birth Cohort 3 (2020 - 2029) - 33 centres

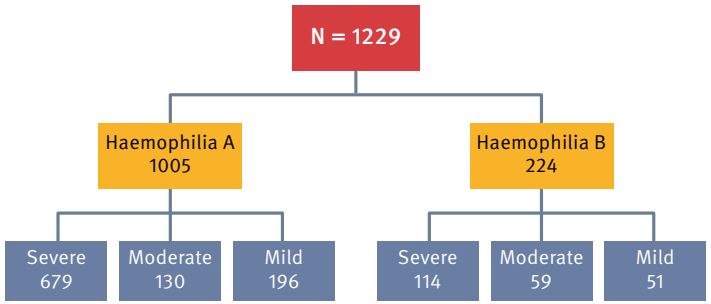


Appendix 2 Flowcharts January 2022

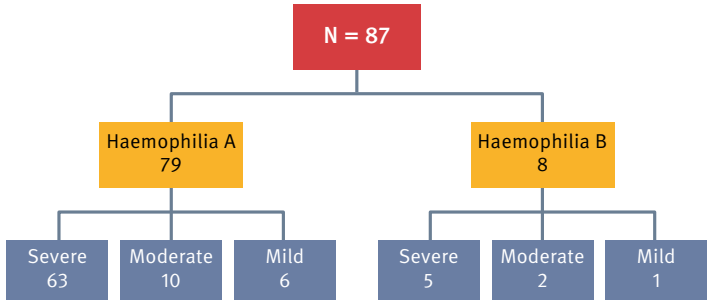
PedNet Birth Cohort 1 (2000 - 2009) - 31 centres



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



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



PedNet Haemophilia Research Foundation

PedNet

www.pednet.eu

info@pednet.eu