

PedNet

Annual report 2019 PedNet cohort studies

Data export January 2020

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



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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 31 haemophilia treatment centres in 18 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









Total number of follow up years 18,104



Included patients according to disease severity



Key numbers

Follow up data

90%

of the severe haemophilia A patients reached 50 Exposure Days Lost to follow up before 50 EDs is only **3%**

83%

of the severe haemophilia B patients reached 50 Exposure Days

Lost to follow up before 50 EDs is only 5%

Inhibitors

42/ Inhibitors diagnosed between 2000-2020



382 severe haemophilia

16 severe haemophilia

3097 Follow up years for inhibitor patients



2824 years for severe haemophilia A inhibitor patients TB

106 years for severe haemophilia B inhibitor patients

In total 19,200 inhibitor test results are collected

13,490 tests of the 427 inhibitor patients Median of **24** tests per inhibitor patient (IQR 15-38)



Contents 🔣 🕻 🌀 🔪 🎾

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 31 haemophilia treatment centres (HTCs) in 18 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: <u>www.pednet.eu</u>.

The objectives of the Foundation are to promote scientific research related to haemophilia and to stimulate international cooperation between centres specialised in the treatment of children with haemophilia. The foundation is not-for-profit and will publish an annual report on activities and a financial report. This report provides an overview of the status of the PedNet registry up to January 2020 and of the research activities performed by the PedNet study group in 2019. More information on all research activities can be found in the Research program 2018-2020.

General aim

The general aim of the PedNet study group and of the foundation is to improve clinical research on inhibitors, phenotype and long-term outcome of different treatment regimens.

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.

The first data export for analyses was performed in May 2011, 8 years after the start of the database in 2003. The data were used for the first satellite study of the PedNet registry, the RODIN study.

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 2020, a total of **2304** previously untreated patients (PUPs) with haemophilia A or B are included in the study. Of these, **1260**, have severe haemophilia A (**87 more than last year**) and **182** have severe haemophilia B (**9 more than last year**) (see Appendix 1). **1283** (89%) of the severe haemophilia patients (A plus B) have reached 50 exposure days. Data on gene defects are available for **1958** (85%) patients included in the study.

Tables & Figures





Current age haemophilia A

Data export January 2020

Tables & Figures

Haemophilia A

	Sever	e	Moderate	Mild	Total HA
Baseline	1,260		236	430	1,926
Known gene mutations	1,121		185	329	1,635 85%
At least 50 EDs	1,132	90%	118	45	1,295
Follow-up data	1,204		230	409	1,843 96%
Total FU years	10,062		1,908	3,340	15,310
Lost to follow-up during first 50 EDs	38	3%	16	45	99 5%

Display of PedNet Numbers

	2015	2016	2017	2018	2019	2020
Baseline	1,340	1,531	1,733	1,972	2,142	2,304
Known gene mutations	1,096	1,260	1,449	1,691	1,834	1,958
At least 50 exposure days	851	950	1,094	1,235	1,382	1,483
Patients with follow-up data	1,253	1,413	1,615	1,858	2,029	2,203

Details on inhibitor patients in PedNet

	All	Severe Haem A	Severe Haem B
Ν	427	382	16
Sum FU (yrs) after 1st positive sample	3,097	2,824	106
Median (yrs; IQR)	6.8 [3-10.8]	6.9	6.4 [2.9.10.3]
	[3-10.0]	[].1-11]	[2.9-10.5]

Haemophilia B

	Severe	Moderat	e Mild	Total HB
Baseline	182	97	99	378
Known gene mutations	163	83	77	323 85%
At least 50 EDs	151 8	33% 32	5	188
Follow-up data	173	91	96	360 95%
Total FU years	1,429	660	705	2,794
Lost to follow-up during first 50 EDs	95	5% 5	8	22 6%

Inhibitor test results



Activities of PedNet Working Groups

Neonatal working group

PedNet performed a study on the optimal mode of delivery for a pregnant haemophilia carrier. Results were published last year.

Mode of delivery in hemophilia: Vaginal delivery and Cesarean section carry similar risks for intracranial hemorrhages and major bleeds (Andersson et al., Hematologica 2019; 104 :2100-2106)

In short; A total of 926 neonates, 786 with severe and 140 with moderate haemophilia were included in this PedNet multicentre study. Vaginal delivery was performed in 68.3% (n=633) and Caesarean section in 31.6% (n=293). Twenty intracranial haemorrhages (2.2%) and forty-four other major bleeds (4.8%) occurred. Intracranial haemorrhages occurred in 2.4% of neonates following vaginal delivery compared to 1.7% after Caesarean section (P=ns); other major bleeds occurred in 4.2% born by vaginal delivery and in 5.8% after Caesarean section (P=ns). Further analysis of subgroups (n=813) identified vaginal delivery with instruments being a significant risk factor for both intracranial haemorrhages and major bleeds (RR 4.78-7.39, p<0.01); no other significant differences were found between vaginal delivery without instruments. In summary, vaginal delivery and Caesarean section carry similar risks of intracranial haemorrhages and major bleeds.

The Neonatal working group has a collaboration with dr Julie Tarrant (Queen's University, Kingston, Ontario, Canada) on the effect of mode of delivery on inhibitor development.

Genetic working group

During the last year all genetic reports in the PedNet database have been re-evaluated and updated to match new HGVS nomenclature and have uniform reporting in the database. An extract on all novel variants was made. These variants were not previously reported in the HGMD or CHAMPS, CHMBS and EAHAD hemophilia variant databases. The article on these new variants will soon be published in a scientific journal by the PedNet group. New genetic reports have been collected and re-evaluated during autumn and a new extract was drawn in January 2020 to facilitate new projects: spectrum of mutations in a large population-based cohort and haemophilia variants and inhibitors in haemophilia A from a genetic point of view.

Working group on Inhibitors

A letter on the timing of inhibitor development in severe haemophilia A, was published in the July issue of Blood.

Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A. (van den Berg et al, Blood 2019 Jul 18; 134(3):317-320)



Kaplan-Meier survival estimates

Few data exist on the inhibitor incidence after 50-75 EDs. Last year PedNet published the results on 1038 PUPs with severe haemophilia A that were followed until 1000 EDs. A total of N=934 (89.8%) were followed until 75 EDs and 514 (50%) until 1000 EDs. In total, 300 inhibitors developed: 78% within 20 and 99.3% within 75 EDs. These data confirmed the importance of collecting data after 20 EDs. After 75 EDs only 2 low titre inhibitors developed. For the non-inhibitor patients the median calendar age was calculated at different time-points. The median age (IQR) for non-inhibitor patients at ED 1 was 0.8 (0.4-1.1) years; at ED 75, it was 1.8 (1.4-2.6) years. The cumulative incidence of inhibitor development was 23.5% at 20EDs, 29.9% at 75 EDs and 30,2% at 1000 EDs.

Conclusion: In 1038 PUPS with severe haemophilia A followed until 1000 EDs, 298 out of 300 inhibitors developed within the first 75 EDs.

Patients with severe haemophilia A can be defined as PTP after 75 instead of 150 exposure days.

Currently this working group is writing a new article on product type and inhibitor development. The article will be circulated and submitted later this year.

CVAD working group

The PedNet study group is collecting data on all CVADs implanted in the patients, both for inhibitor and non-inhibitor patients. Procedures for the implantation of CVADs vary between centres. Our group reported that intensive treatment is a risk factor for antibody formation. This caused concern and many physicians avoid CVADs or try to postpone the time of insertion to minimise this risk. Since bleeding during implantation of CVADs is a risk, investigating the different periods of haemostatic correction during CVADs will give insight into whether a short period is as effective to control haemostasis as a longer period. The results of this study are submitted for publication.

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*, described the cohort of inhibitor patients born between 1990-2009 has been published (Mancuso et al., 2017).

More articles are currently prepared:

- 1. An article on the "Natural History of low titre inhibitors diagnosed between 1990-2009 in the PedNet study group and the effect of ITI has been submitted recently for publication.
- 2. Additional data have been collected for all patients with an inhibitor born after 1-1-2000 until 1-1-2020. It is too be expected that several papers on bleeding phenotype before and during immune tolerance induction therapy will be submitted.
- 3. Further article are to be expected on high titre inhibitors and response to different ITI regimens.

Haemophilia B working group.

PedNet published the inhibitor incidence in 154 PUPs with severe haemophilia B followed up to 500 EDs. PedNet reported an inhibitor incidence of 10.2% (Male et al., Hematologica). The data in an unselected group of patients followed until at least 500 EDs gives important insight into the development of inhibitor in patients that were frequently treated with prophylaxis.

A separate article on patients with severe haemophilia B and an inhibitor and their response to ITI will be reported later this year.

Publications PedNet study group since 2017

- 1. Khair K, Ranta S, Thomas A, Lindvall K; PedNet study group. The impact of clinical practice on the outcome of central venous access devices in children with haemophilia. Haemophilia 2017;23:276-81.
- 2. Mancuso ME, Fischer K, Santagostino E, Oldenburg J, Platokouki H, Königs C, Escuriola-Ettingshausen C, Rivard GE, Cid AR, Carcao M, Ljung R, Petrini P, Altisent C, Kenet, G, Liesner R, Kurnik K, Auerswald G, Chambost H, Mäkipernaa A, Molinari AC, Williams M, van den Berg HM. Risk factors for the progression from low- to high-titers in 260 children with severe haemophilia A and newly developed inhibitors. Thromb Haemost 2017;117:2274-82
- 3. Andersson NG, Auerswald G, Barnes C, Carcao M, Dunn AL, Fijnvandraat K, Hoffmann M, Kavakli K, Kenet G, Kobelt R, Kurnik K, Liesner R, Mäkipernaa A, Manco-Johnson MK, Mancuso ME, Molinari AC, Nolan B, Perez Garrido R, Petrini P, Platokouki HE, Shapiro AD, Wu R, Ljung R. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B – the impact of prophylactic treatment. Br J Haematol 2017;179:298-307.
- 4. 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
- Platokouki H, Fischer K, Gouw SC, Rafowicz A, Carcao M, Kenet G, Liesner R, Kurnik K, Rivard GE, van den Berg HM. Vaccinations are not associated with inhibitor development in boys with severe haemophilia A. Haemophilia 2018; 24:283-90.
- 6. Keipert C, Jonker CJ, van den Berg HM, Hilger, A. Clinical trials and registries in haemophilia: Opponents or collaborators? Comparison of PUP data derived from different data sources. Haemophilia 2018; 24:420-8.
- 7. van den Berg HM. A Cure for Hemophilia within Reach. N Engl J Med. 2017 Dec 28;377(26):2592-2593.
- 8. 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.

9. 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.

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

Abstracts & Presentations

EAHAD 2018, Madrid	Oral	Inhibitor incidence in PUPs with severe haemophilia B is higher than usually reported; data from the PedNet registry
EAHAD 2018, Madrid	Poster	Does blood group 0 influence inhibitor development? Data from the PedNet registry
WFH 2018, Glasgow	Oral	Inhibitor incidence in 1083 PUPs with severe haemophilia A treated with class Recombinant or with class Plasma-derived products is similar; Recent data from the PedNet study group
ASH 2018, San Diego	Poster	99.3% of Inhibitors in Severe Hemophilia a Develop before Exposure Day 75. Time to Change Definition of Previously Treated Patients; Data from 1038 Patients with Severe Hemophilia a of the Pednet Registry
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

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Sponsor page

The PedNet foundation receives unrestricted funding from several pharmaceutical companies.

Current sponsors are:

- Bayer AG
- 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 2019

PedNet Birth Cohort 1 (2000 - 2009) 31 centres



PedNet Birth Cohort 2 (2010 - 2019) 31 centres N = 911 Haemophilia A 751 Haemophilia B 160 Severe Moderate Mild 139 Severe Moderate Mild 33

Appendix 2 Flowcharts January 2020

PedNet Birth Cohort 1 (2000 - 2009) 31 centres











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