PedNet Haemophilia Research Foundation

PedNet

Newsletter parents & patients

Data export January 2020

On behalf of the PedNet study group

Rolf Ljung, MD, PhD
Chairman of the management board

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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 31 haemophilia treatment centres in 18 countries.

The PedNet Registry started in 2003 and is set up as a birth cohort study, in order to prevent selection bias. It collects real-life data from all newly diagnosed children treated in the participating centres.
Patients with FVIII/IX levels up to 25%, born from January 1st 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 PedNet Registry.

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Key numbers

In total
2304
patients included in registry

162 new patients included in 2019

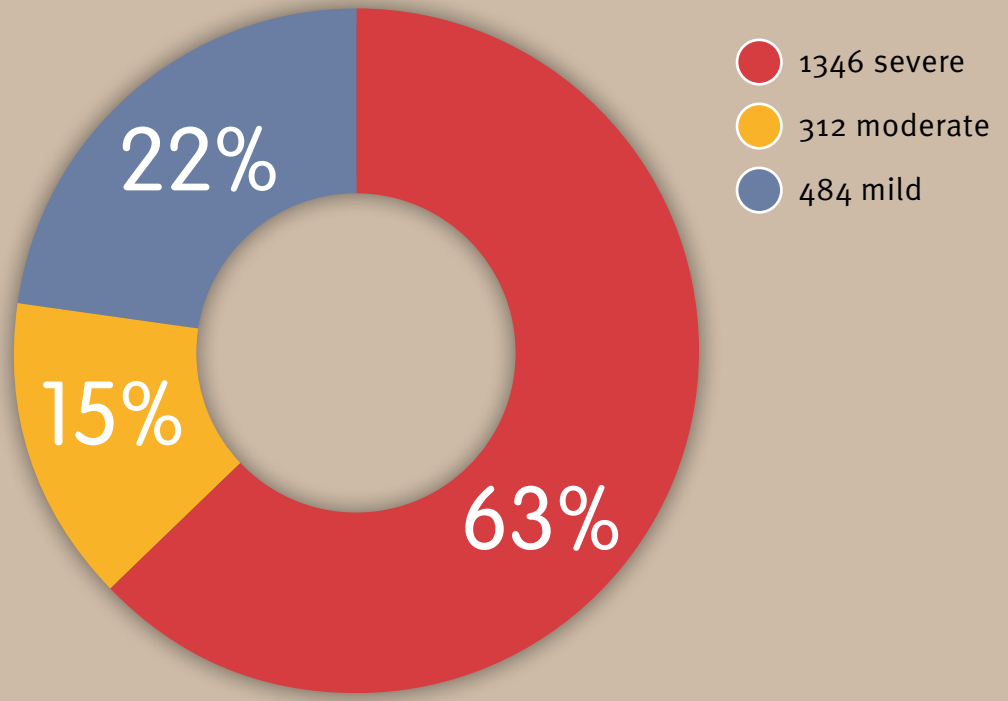
1260
patients with severe haemophilia A

87 new severe haemophilia A patients

182
patients with severe haemophilia B

9 new severe haemophilia B patients

Included patients according to disease severity



31
participating centers in **18** countries

Gene mutations known in
85%
of all patients

Total number of follow up years
18,104

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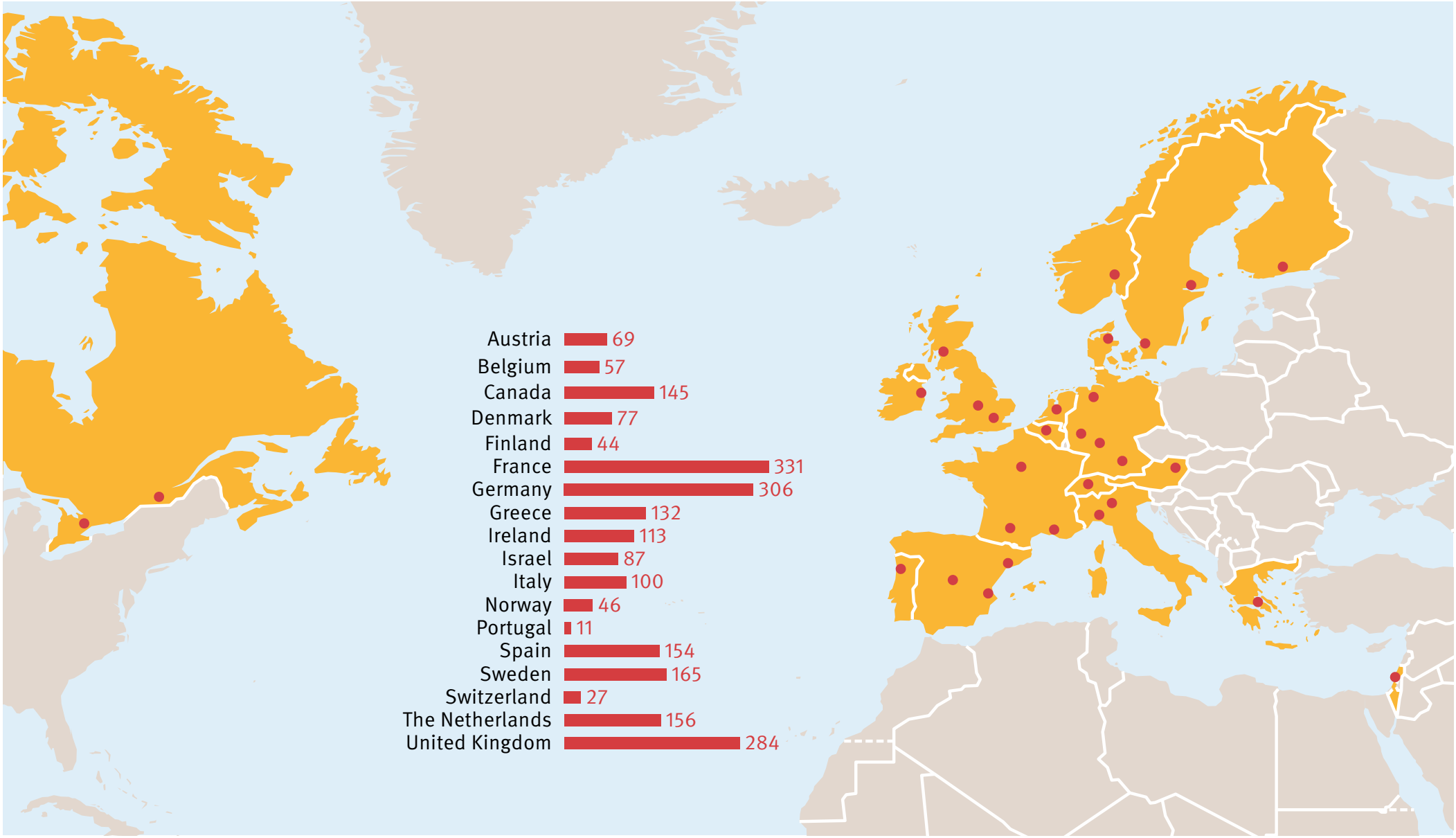
Participating countries and numbers of included patients



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Introduction

Your child is participating in one of the largest multicentre haemophilia registries, the PedNet Haemophilia Registry. PedNet is a collaboration of 31 haemophilia treatment centres (HTCs) in 18 countries. This collaboration started in 2003. The aim is to improve the knowledge on treatment and other relevant factors in children with haemophilia. Included in PedNet are patients diagnosed in the participating HTCs who are born from January 1st 2000 onwards and who have factor VIII or factor IX levels up to 25%. The privacy of the children is protected: the individual patient data are coded by the HTC and anonymously entered in the registry. The current inclusion rate in the participating HTCs is more than 95%, this means that almost all children with haemophilia who are treated in the participating centres are part of the PedNet Registry. The PedNet Registry has developed into an effective resource helping us to answer various research questions. More information can be found on our website www.pednet.eu

This newsletter 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. More information on all research activities can be found in the Research program 2018-2020.

PedNet Registry

In the PedNet Registry, patients are followed during their childhood and information from their medical files is collected using a secured data capture system (Research Online).

Data of all included patients are regularly updated and they are checked for validity and completeness throughout the year. The data quality is monitored in the centres by an independent clinical research associate (CRA) (also known as clinical monitor).

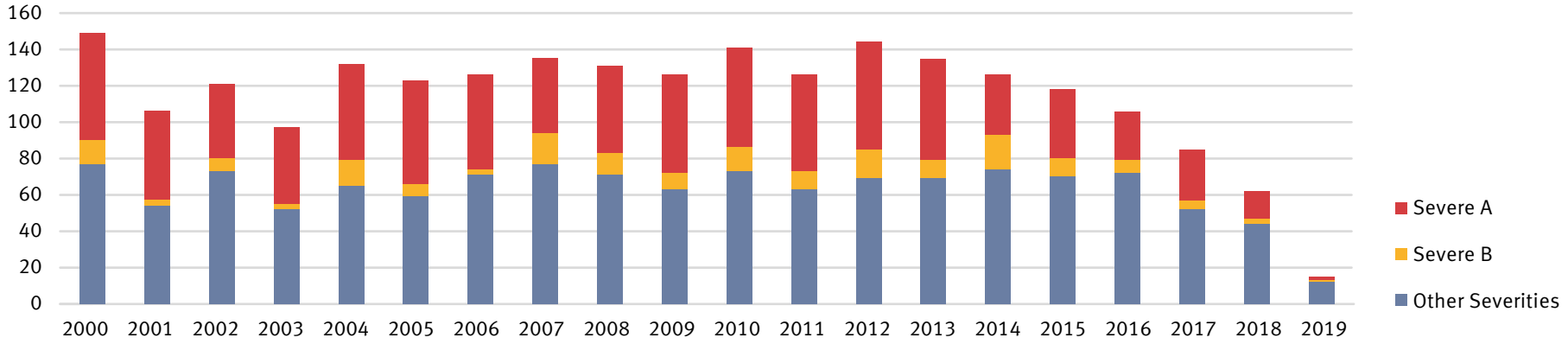
The first data export for research analyses was performed in May 2011, 8 years after the start of the database in 2003. The data were used for the first satellite study of the PedNet registry, the RODIN study.

Current status

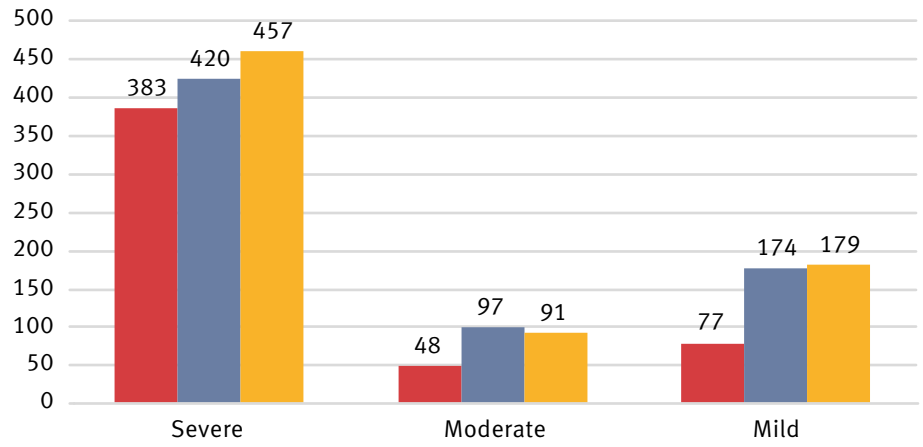
As of 1 January 2020, a total of **2304** previously untreated patients (PUPs) with haemophilia A or B are included in the study. Of these, **1260** have severe haemophilia A and **182** have severe haemophilia B (see Appendix 1).

Graphs

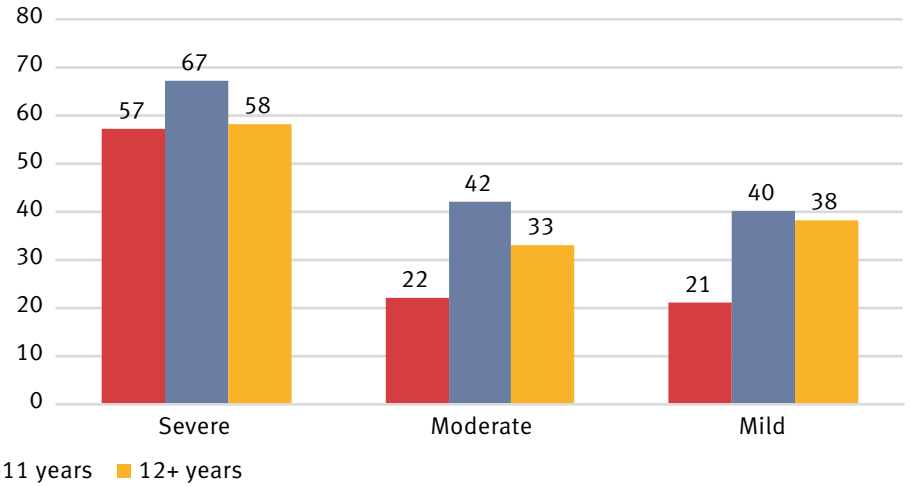
N Patients per birth year



Current age haemophilia A



Current age haemophilia B



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Activities of PedNet Working Groups

There are several working groups active within the PedNet group. These working groups focus on the following subjects: neonatal period, genetic profiles, inhibitors, central venous access devices (CVADs), severe haemophilia A patients, and haemophilia B patients. For example the inhibitor group is working on an article about inhibitor development in relation to treatment and product. Another example of a PedNet working group subject is CVADs. CVADs are placed in patients to make it easier to give medication and the PedNet working group is looking into the different procedures of CVAD placement, since not all centres use the same procedures.

The working groups frequently publish articles about their studies. The most recent notable articles include a study about baby delivery and studies about inhibitors.

Working group on follow up of inhibitor patients

Data on patients with an inhibitor are limited and the results are difficult to interpret for the paediatric age groups. In the past, treatment was limited and inhibitors were diagnosed at a later age. This had major limitations, mainly on how to interpret these results in children that develop an inhibitor in the 2000s. In the PedNet study group children are included from diagnosis and due to the early start of prophylaxis inhibitors are diagnosed very early. The inhibitor patients in PedNet are carefully followed and several publications are to be expected in the coming years. Below the results of the first publication are presented.

Title of article: **Risk Factors for the Progression from Low to High Titres in 260 Children with Severe Haemophilia A and Newly Developed Inhibitors**

Authors: **Maria Elisa Mancuso, Kathelijn Fischer, Elena Santagostino, Johannes Oldenburg, Helen Platokouki, Chris Königs C, Carmen Escuriola-Ettingshausen, George Rivard, Ana Cid, Manuel Carcao, Rolf Ljung, Pia Petrini, Carmen Altisent, Gili Kenet, Ri Liesner, Karin Kurnik, Günther Auerswald, Hervé Chambost, Anne Mäkipernaa, Claudio Molinari, Mike Williams, Marijke van den Berg**

In the frame of the PedNet registry a special attention is given to the subgroup of patients who develop inhibitors which represent the main complication of haemophilia therapy. A study was done looking at children with severe haemophilia A born between 1990 and 2009, who developed anti-FVIII inhibitors, in order to better understand the behaviour of those antibodies and their impact on the management of these children. Inhibitors can be present at low or high titers, being the latter those rendering more challenging patients' management. In the study we explored potential risk factors for the development of high-titer inhibitors. In the study 260 children had been included and we found that at diagnosis almost half of them had low-titer inhibitors, however during follow-up 50% progressed to high titers and only 25% maintained low titers. The progression to high-titer inhibitors was more frequent in children with family history of inhibitors, in those with severe mutations of FVIII gene and in those who received high-dose FVIII for immune tolerance induction, which is the only proven treatment strategy to attempt inhibitor eradication. These results suggest that in patients who develop low-titer FVIII inhibitors high-dose immune tolerance induction should be avoided as the initial treatment strategy in order to try to prevent the progression from low to high titers.

> "High dose ITI should be avoided as first treatment strategy in patients with low titer inhibitors"

Neonatal working group

The optimal way to deliver a baby when the mother is a carrier of haemophilia is up to debate. The key question is mainly if the way of delivery may impact the risk of serious bleeds. Studies on this subject has been done but vary in results. The comparison between these studies is very complicated since they do not include the same information (i.e. some include known family history or mild haemophilia and others do not). In the following publication, a lot of detailed information on the new-born babies with haemophilia is included to give a better insight into whether the mode of delivery has an impact on the risk of serious bleeds.

Title of article: **Mode of delivery in haemophilia: Vaginal delivery and cesarean section carry similar risk for intracranial hemorrhages and major bleeds**

Authors: Nadine Gretenkort Andersson, Elizabeth Chalmers, Gili Kenet, Rolf Ljung, Anne Mäkipernaa, Hervé Chambost

What is the optimal mode of delivery for a pregnant carrier of haemophilia? How high is the risk to experience serious bleedings at birth for the child with haemophilia? And is Caesarean section safer than giving birth vaginally? These were the main questions for our study on mode of delivery in haemophilia. To answer these questions, 926 new-born babies, 786 with severe and 140 with moderate haemophilia were included in this PedNet study. Most haemophilia babies were born by vaginal delivery (68.3%) and 31.6% by Caesarean section. A total of 20 bleeds in the brain (2.2%) and 44 other serious bleeds needing treatment (4.8%) occurred. The number of bleeds between vaginal delivery or Caesarean section was statistical not different. When looking more detailed into the subgroups of delivery – vaginal delivery with and without instruments, Caesarean section prior and during to labour, we could identify vaginal delivery with instruments (e.g. vacuum extraction or forceps) as a clear risk factor for both bleeds into the brain and other serious bleeds. The risk was around 5-7 times higher compared to the other ways of delivery, but instrumental vaginal delivery had only to be used in 7.3% in the whole group. When comparing a planned Caesarean section – which mostly is done prior to labour, but in some cases during labour – and vaginal delivery – which is mostly done without instruments, but sometimes with instruments or sometimes has to be switched to a Caesarean section in labour – no differences were found regarding risk of bleeds. We even compared babies with a known family history of haemophilia (roughly half of the cases) with those without a family history. The same pattern could be found, and no differences were seen between the groups. In conclusion, Caesarean section and vaginal delivery carry similar risks for bleeds at birth and Caesarean section is not a safer option in itself; so, there is no optimal mode of delivery. However, instrumental vaginal delivery should be avoided as far as possible. Serious bleeds at birth occur in around 6% of the haemophilia babies. For the final choice of mode of delivery, it is important to weigh in all considerations around mother and child, both haemophilia and non-haemophilia related.

> "Caesarean section and vaginal delivery are both safe options, but instrumental delivery should be avoided"

Working group on inhibitor development

Inhibitor development in children with haemophilia is currently the largest side effect of treatment with clotting factor VIII. One of the factors that made comparison between studies difficult was the study endpoint. In general it is thought that inhibitors occur mostly within the first 50 exposure days to factor VIII. In the following publication the PedNet study group investigated the risk for inhibitor development at different follow up times in more than 1000 children with severe haemophilia A. Details can be found in the publication below.

Title of article: **Timing of inhibitor development in >1000 previously untreated patients with severe hemophilia A**

Authors: **Marijke van den Berg, Kathelijn Fischer, Manuel Carcao, Hervé Chambost, Gili Kenet, Karin Kurnik, Chris Königs, Christoph Male, Elena Santagostino, Rolf Ljung**

The most serious complication of haemophilia A treatment, is the development of inhibitor antibodies (inhibitors) against factor VIII (FVIII) products. Inhibitors develop in 25% to 35% of previously untreated patients (PUPs) with severe haemophilia A. Most inhibitors develop during the first 50 exposure days to FVIII. Development of an inhibitor after 50 exposure days is rare. A definition designed to separate high-risk and low-risk category patients was established in the 1990s, after the outbreaks of two product-specific inhibitors. According to this definition, previously treated patients (low-risk for inhibitor development) are patients with at least 150 exposure days.

Haemophilia treatment has changed considerably over the last decades due to the development of many new therapies. Prophylaxis has become standard of care and is started at increasingly earlier ages and with higher dosing and frequencies. The aim of this study was to define the risk periods for inhibitor development until 1000 exposure days, and to refine the definition of previously treated patients (PTPs) and the age at which patients have reached this “near-zero” risk situation. 1038 severe haemophilia A patients included in the PedNet Registry were followed until inhibitor development, or until their last exposure day. Our study shows that children (on prophylaxis) reach near-zero risk plateau of inhibitor development at 75 exposure days. This is only 1.2 years after the first exposure to FVIII. The median age at 75 exposure days was 2.3 years. These results are applicable to children who receive early prophylaxis, as almost all of the patients in the PedNet registry were started on prophylaxis very early in life. In countries where this is not the case, the timing of inhibitor development could potentially be different. In conclusion, we have strong evidence from the largest prospective cohort study of PUPs that virtually all inhibitors develop by exposure day 75. Consequently, we propose that 75 exposure days should be the cut-off to distinguish PUPs from PTPs.

> “Inhibitors in children with severe haemophilia A hardly ever occur after exposure day 75”

Participants PedNet Meeting Leuven, Belgium September 2019

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. van den Berg HM. A Cure for Hemophilia within Reach. N Engl J Med. 2017 Dec 28;377(26):2592-2593.
5. 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. 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
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 se-vere 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

Sponsor page

The PedNet foundation receives unrestricted funding from several companies. This means, that there are no restrictions to the way the PedNet group analyses the data and publishes the results. The PedNet group is scientifically independent.

Current sponsors are:

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

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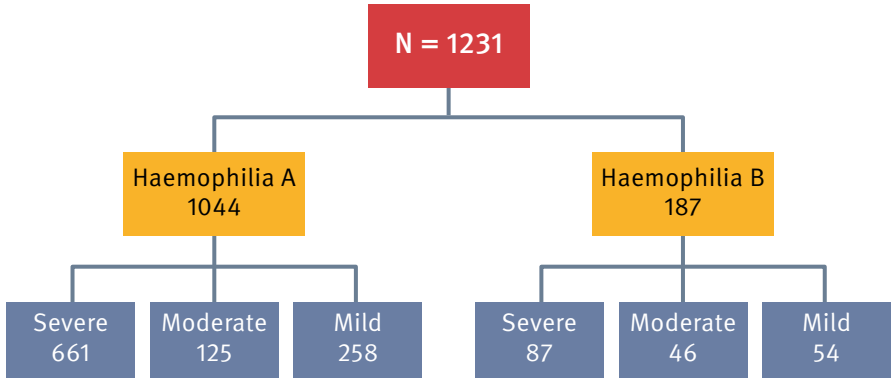
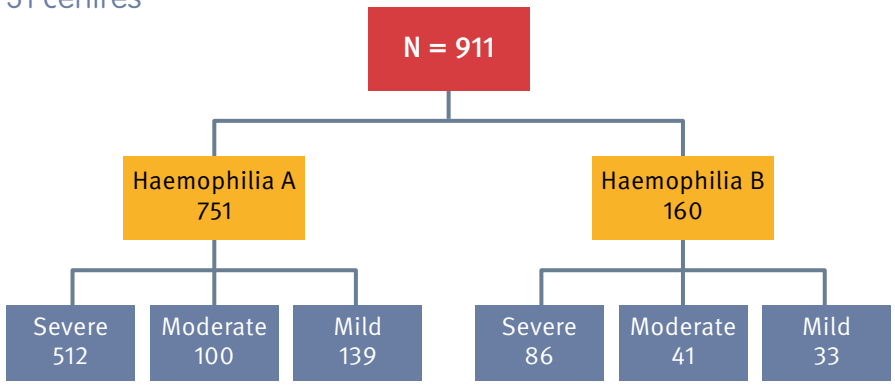
Appendix 1 Flowcharts January 2019

PedNet Birth Cohort 1 (2000 - 2009)
31 centres

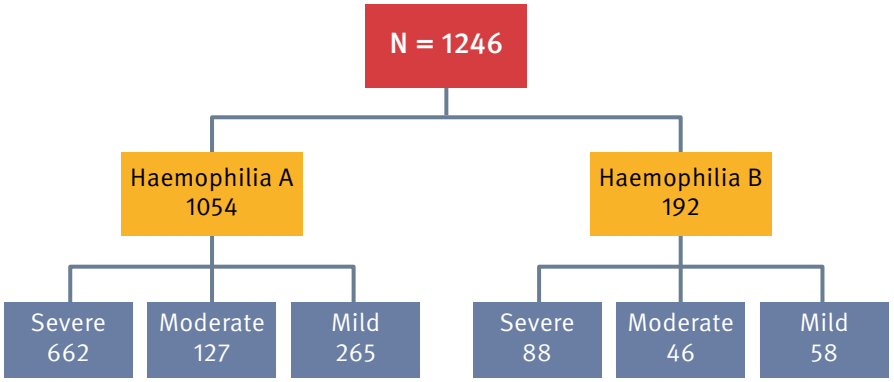


PedNet Birth Cohort 2 (2010 - 2019)
31 centres

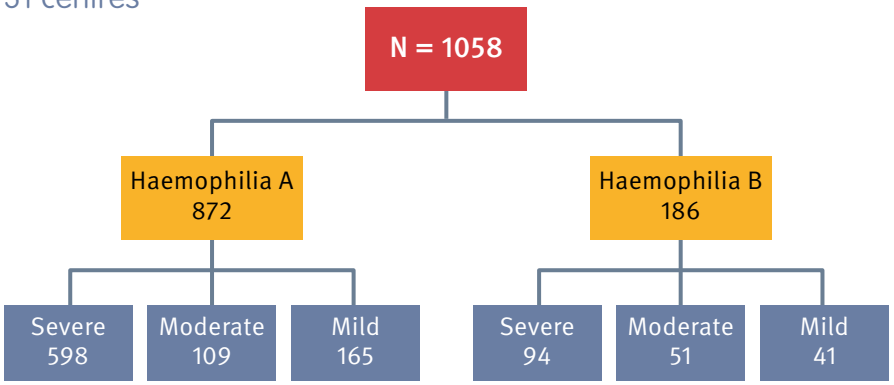


Appendix 2 Flowcharts January 2020

PedNet Birth Cohort 1 (2000 - 2009)
31 centres



PedNet Birth Cohort 2 (2010 - 2019)
31 centres



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