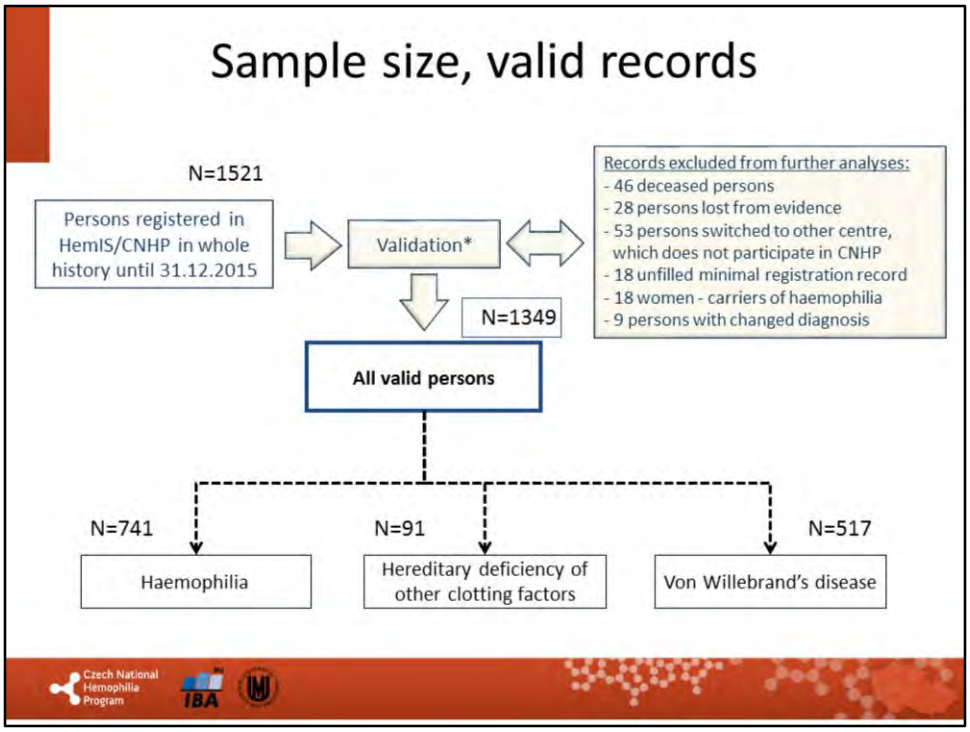
The status of care for persons with haemophilia and von Willebrand's disease registered within CNHP registry Annual Report 2015

Jan Blatný, Petra Ovesná
on behalf of
Centres contributing to common database
of the CNHP (Czech National Haemophilia Programme)

July 2016

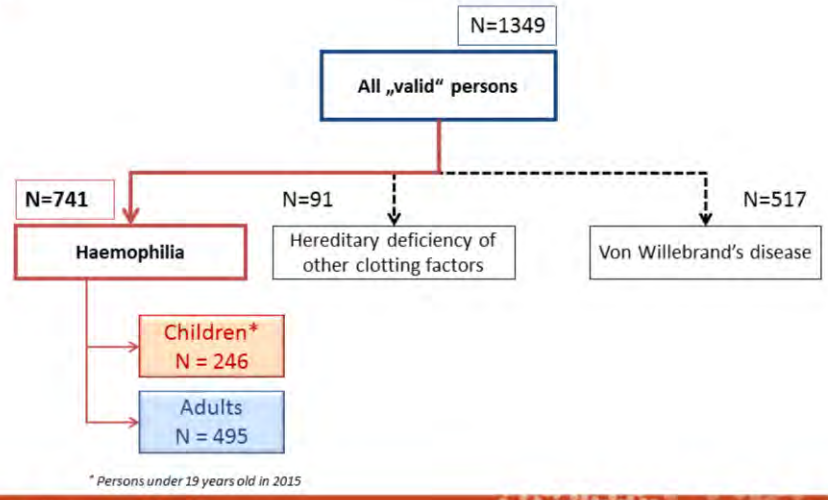


This slide describes the process of records' validation within the registry.

Part A

Persons with haemophilia (PWH)

Sample size



* Persons under 19 years old in 2015

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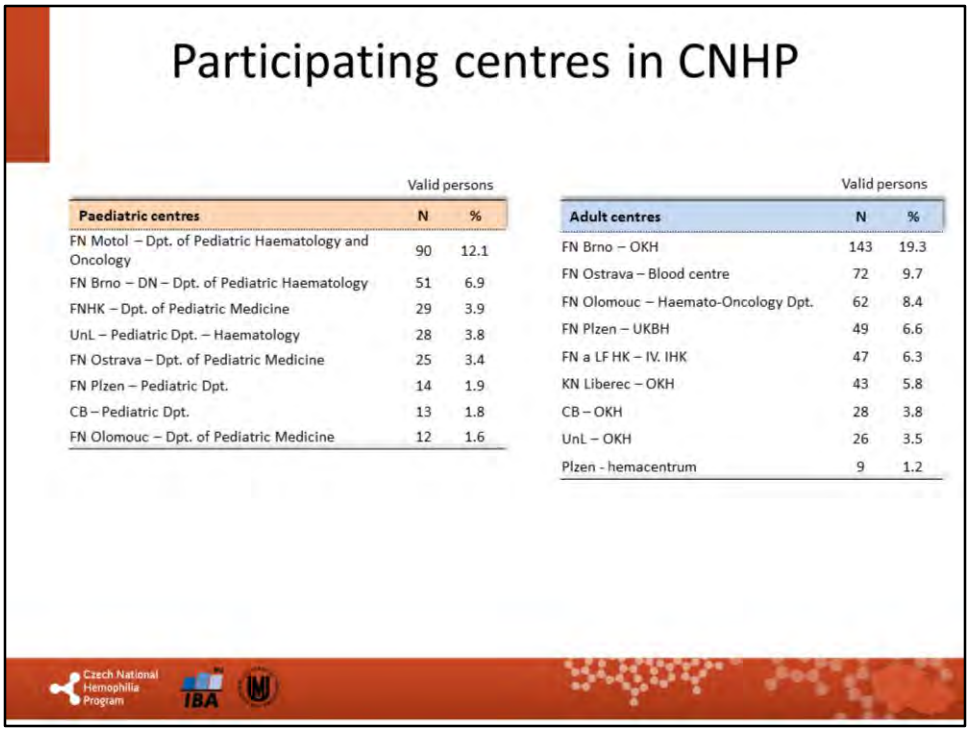
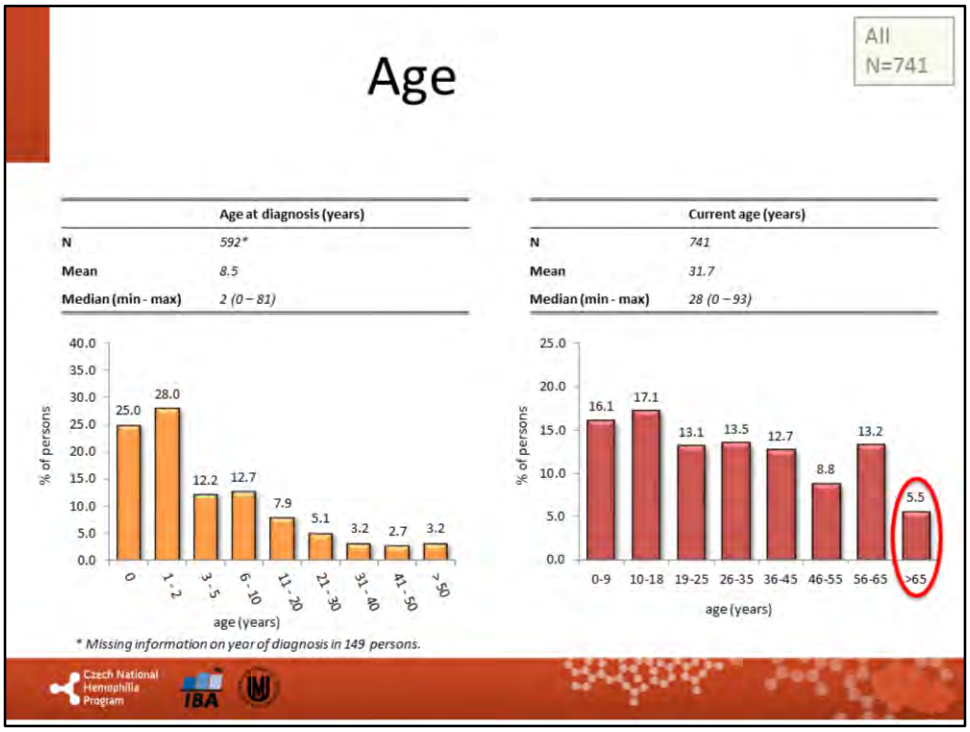


Centres contributing to the CNHP registry.

Part A.1

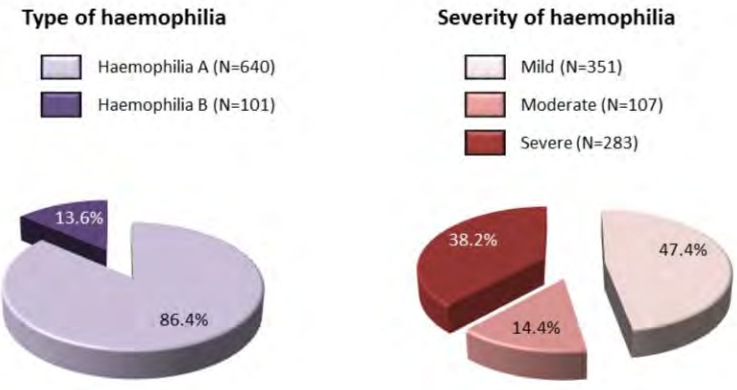
Demographic characteristics of persons with haemophilia



Though the percentage of PWHs over 65 years has not been increasing dramatically over last several years, dealing with elderly people with haemophilia will be the challenge for treaters.

Type and severity of haemophilia I

All
N=741



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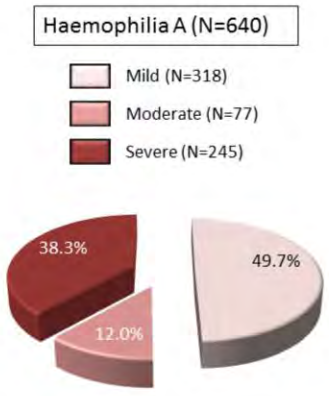
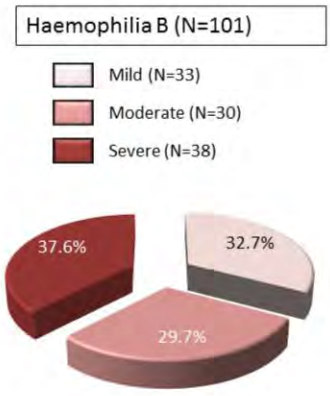
Type and severity of haemophilia II

All
N=741





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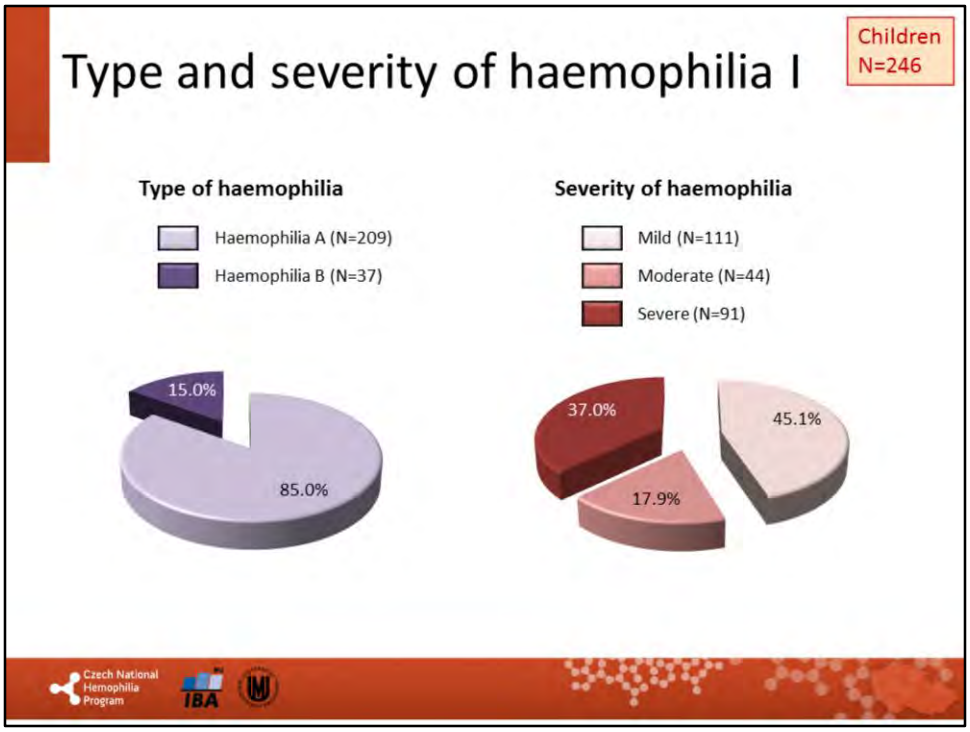
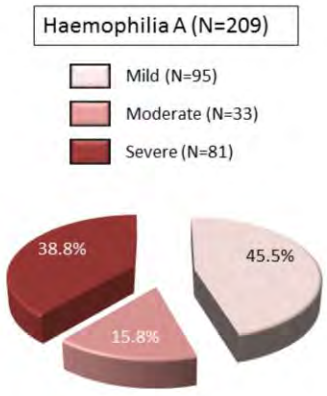
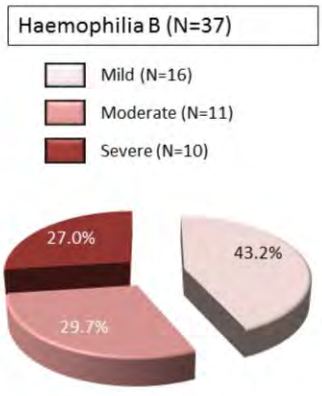


10 new children with severe haemophilia registered in 2015.

Type and severity of haemophilia II

Children
N=246





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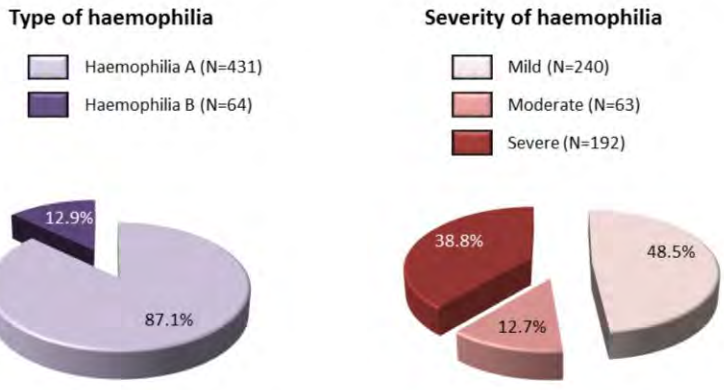
Type and severity of haemophilia I

Adults
N=495



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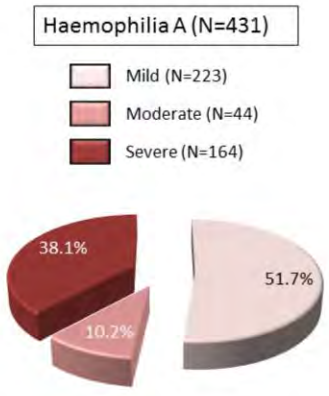
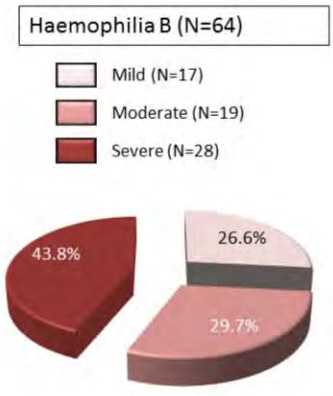
Type and severity of haemophilia II

Adults
N=495





Czech National Hemophilia Program

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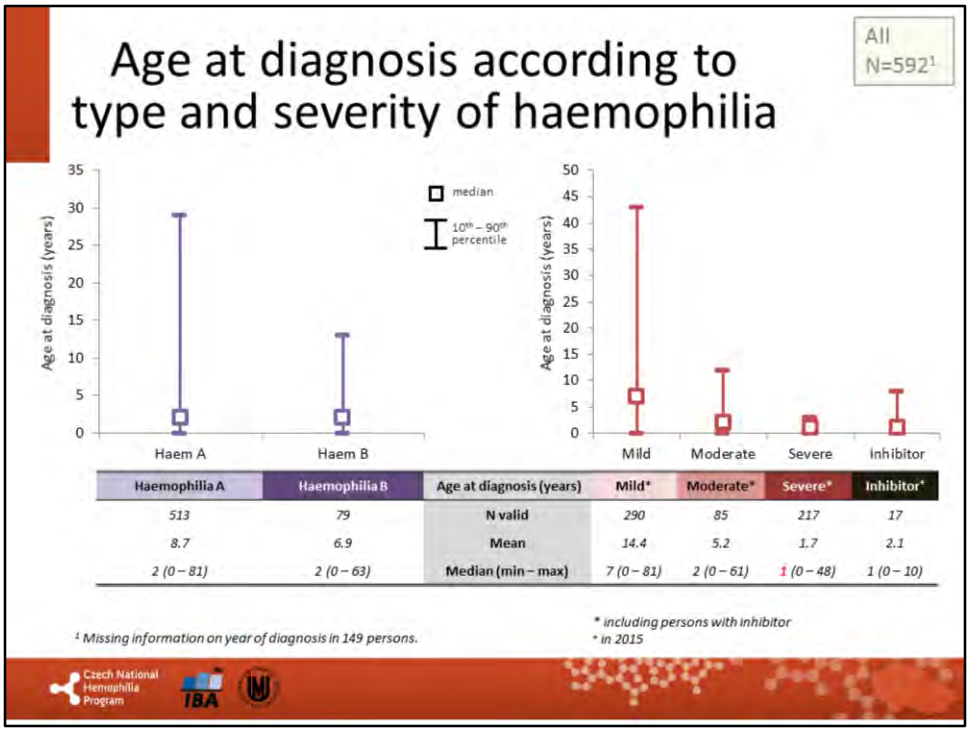
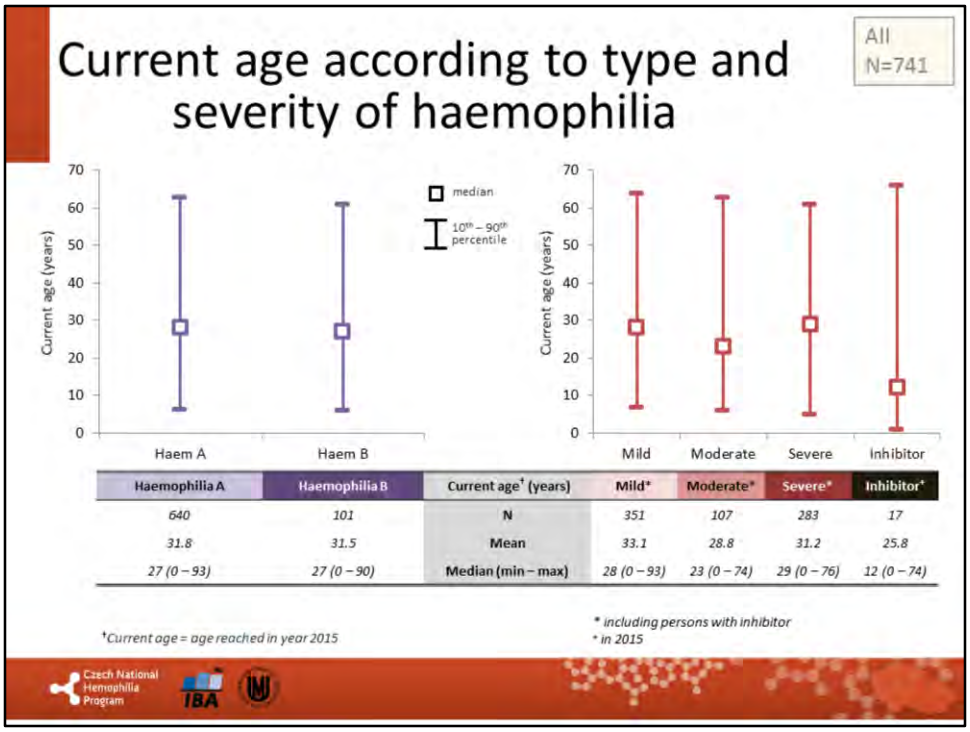
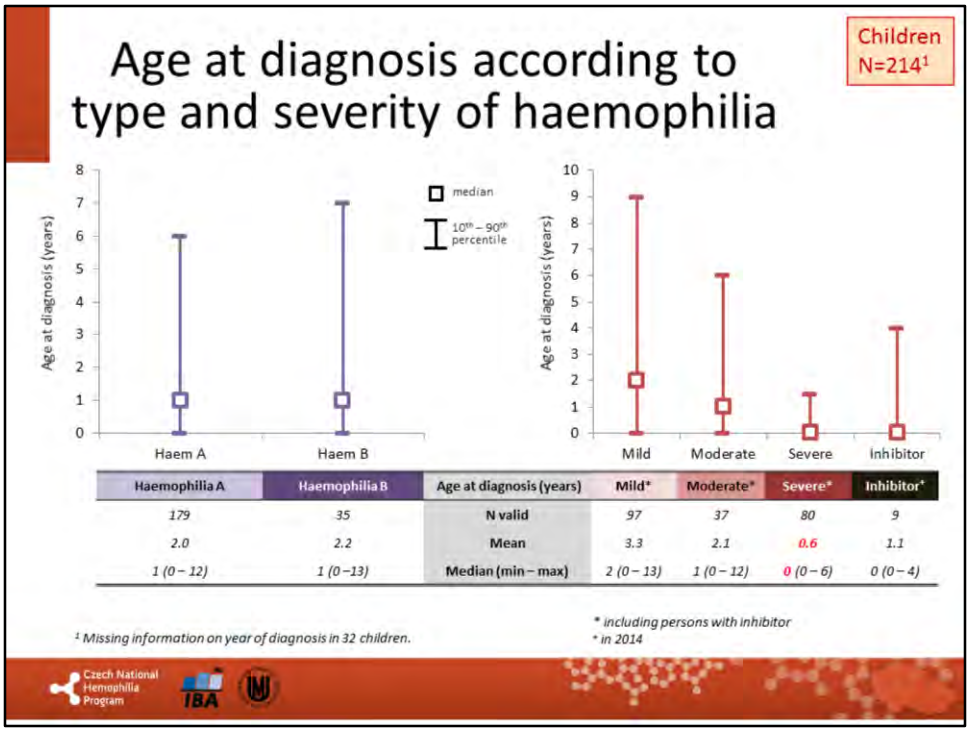


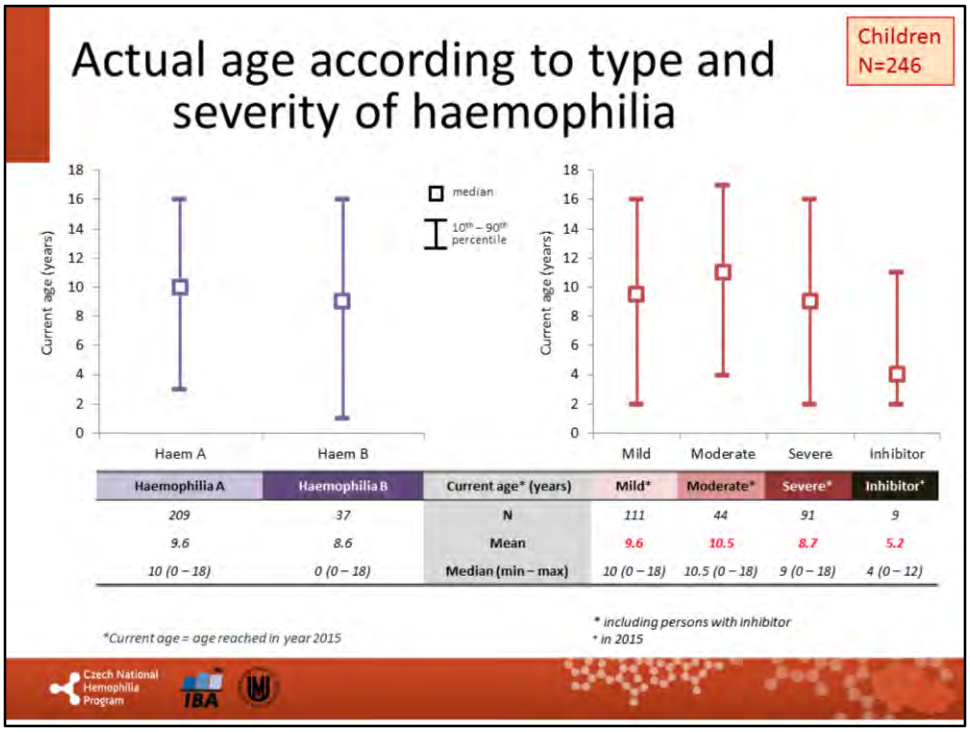
Median age at diagnosis of 1 year in severe haemophilia enables us to offer primary prophylaxis to our PUPs.



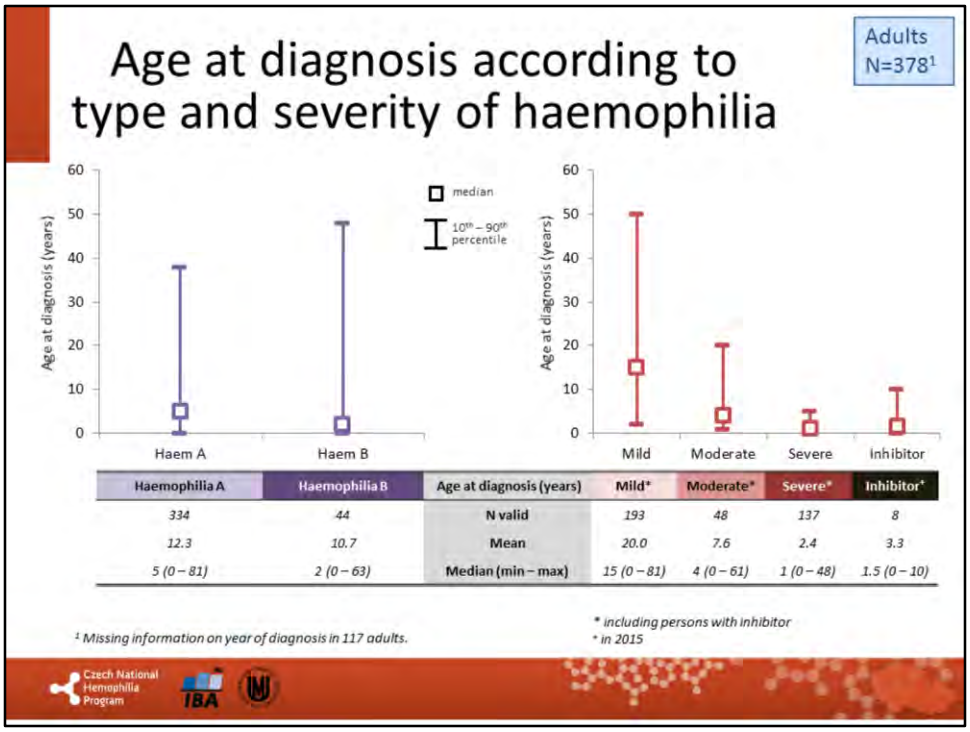
Our haemophilia population is relatively young. (Median age of Czech population is currently 42 years.)



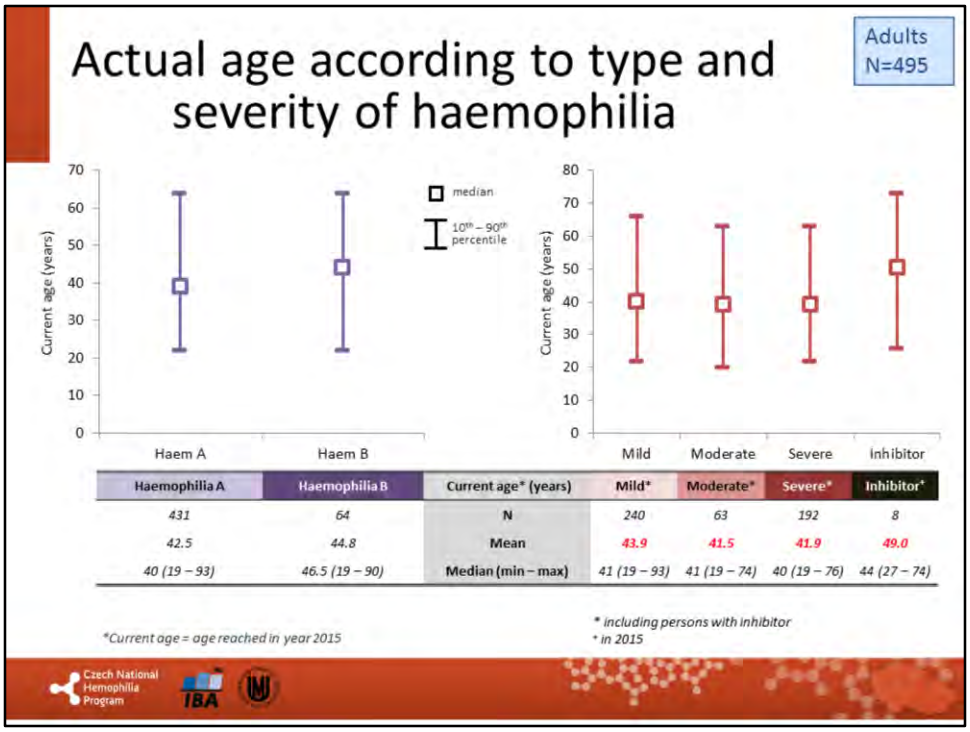
Median age at diagnosis below 1 year in severe haemophiliacs enables us to offer primary prophylaxis to all our PUPs. Even better seen within paediatric population.



Mean age of Czech paediatric haemophilia population is around 9 years. The decrease (from 10 in 2014) in this parameter during 2015 is caused by a number of new born haemophiliacs, registered in 2015.

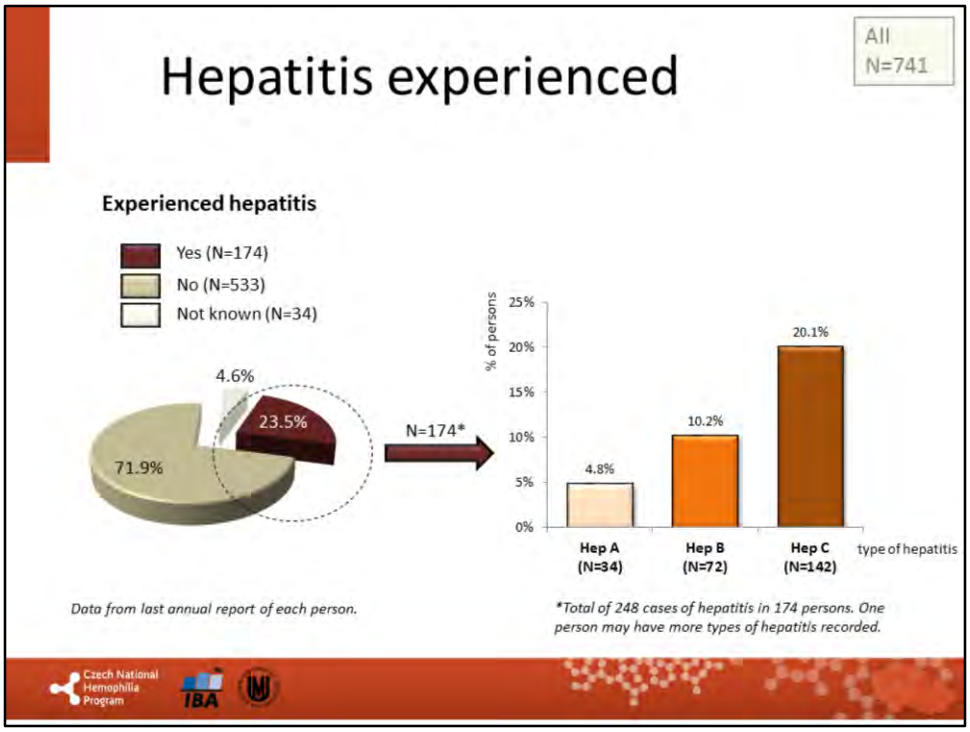


Even haemophiliacs who are adult in these days, were diagnosed early enough. However, for those, born before 1990, there was no chance for prophylaxis due to lack of concentrates behind the „iron curtain“. Though some of those, who are now adults were able to take advantage of prophylaxis, none of them had primary prophylaxis, which is a gold standard in these days. This is the major reason for higher annual bleeding rates in adult haemophiliacs as their joints have been significantly impaired during childhood (before 1990, when factor concentrates became available in CZ). See slides 61,62.

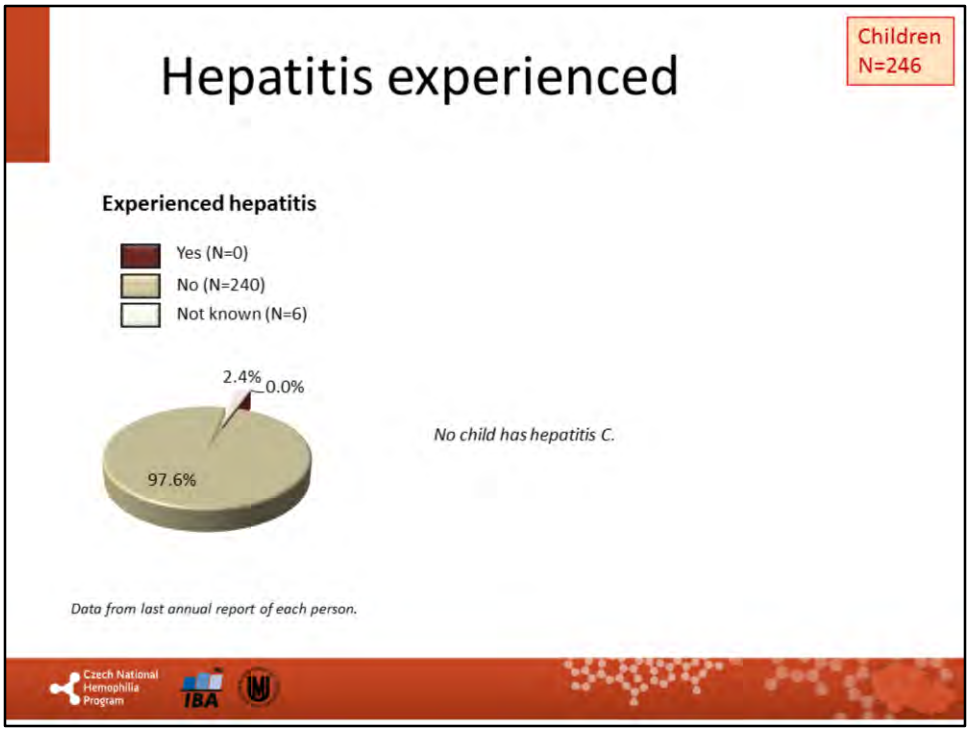


Haemophilia A	Haemophilia B	Current age* (years)	Mild*	Moderate*	Severe*	Inhibitor*
431	64	N	240	63	192	8
42.5	44.8	Mean	43.9	41.5	41.9	49.0
40 (19 – 93)	46.5 (19 – 90)	Median (min – max)	41 (19 – 93)	41 (19 – 74)	40 (19 – 76)	44 (27 – 74)

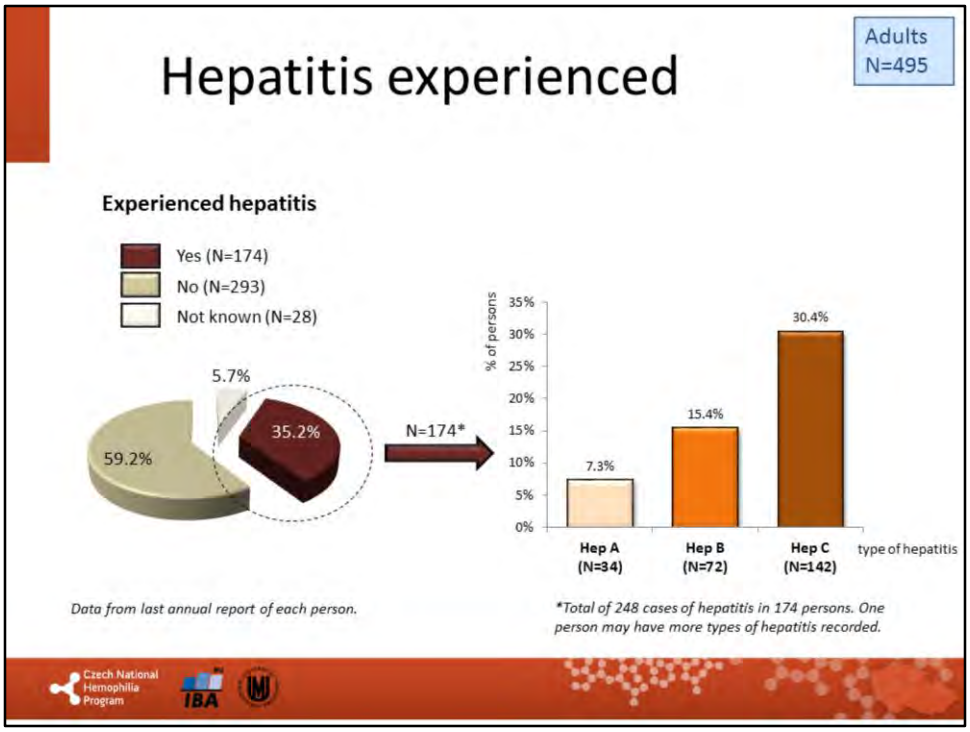
Mean age of Czech adult PWHs is around 43 years.



Relatively low prevalence of HepC compared to many other countries.
Please note, that increased number of PWHs with HepC (166 in 2014, 174 in 2015) is not caused by new infection, but reflects HepC positive adult PWHs who have not been registered before in some centres.
There has been NO NEW HepC infection in 2015.



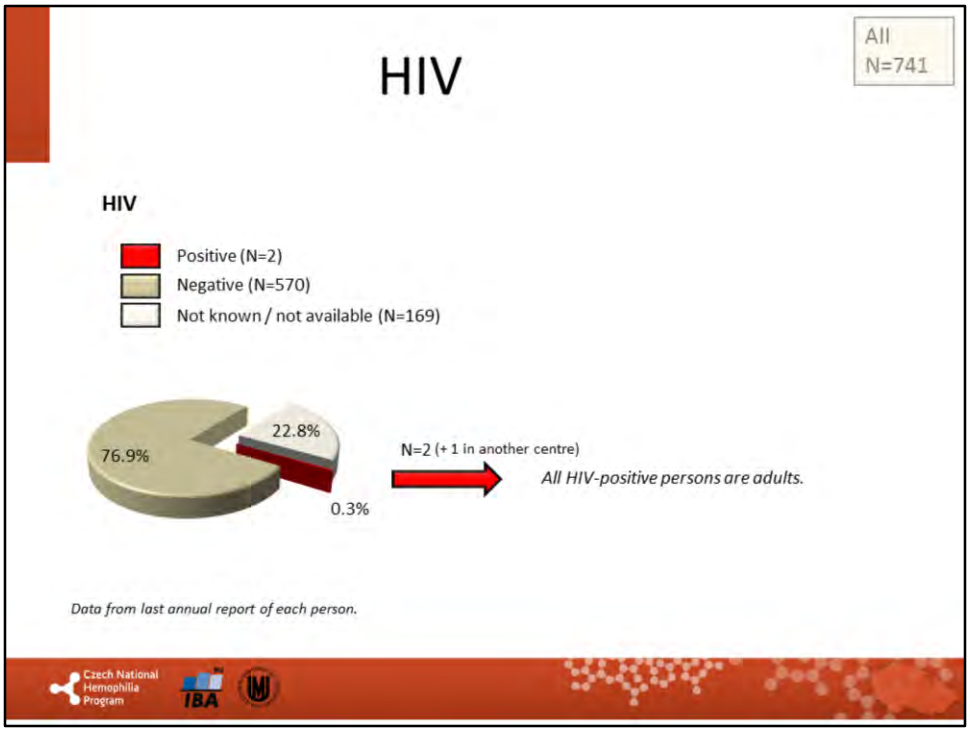
One child with previously acquired HepC infection was transferred to the respective adult center.
NO NEW HepC infection in children since late 90's.



Increased number of adult PWHs with HepC by 9 is not caused by new infection, but reflects 8 HepC positive adults who have not been registered before in some centres + 1 transferred child.

The number of adult PWHs within CNHP registry increased from 464 to 495 in 2015 due to improved data management in certain adult centres, which joined CNHP registry later.

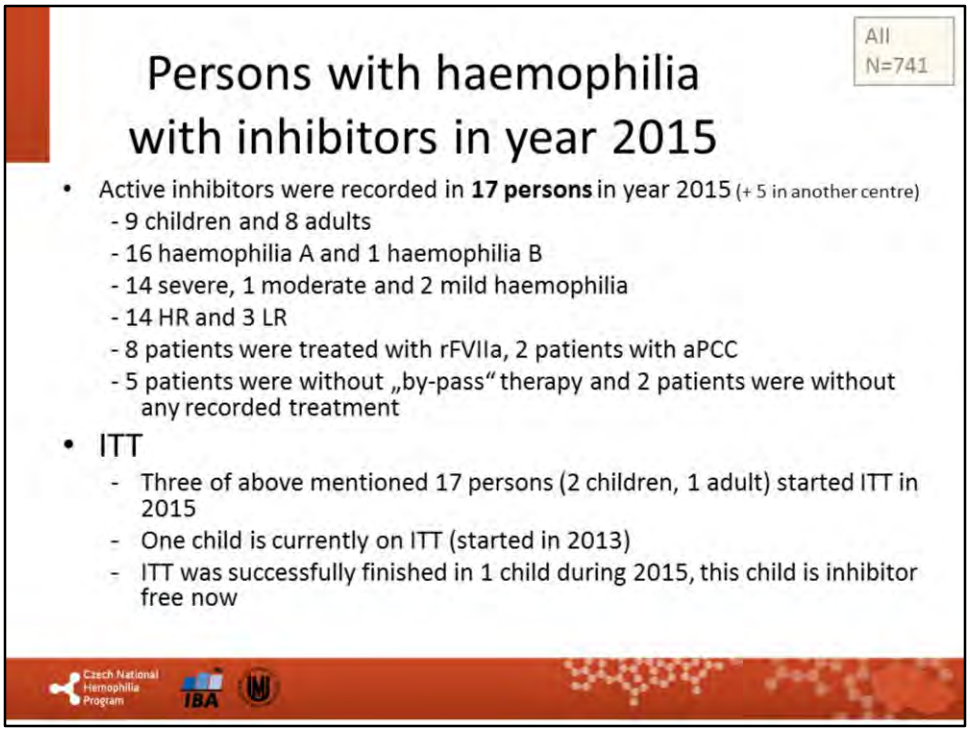
There has been NO NEW HepC infection in 2015.



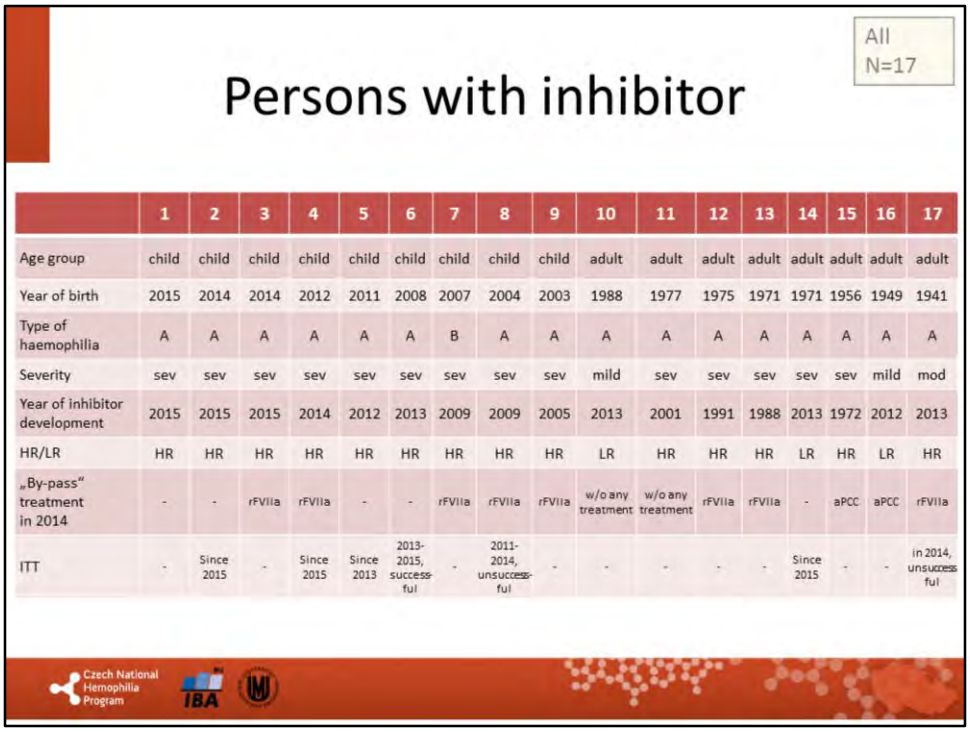
Very low number of HIV positive PWHs due to low/no access to contaminated concentrates in 80s and 90s. Our current treatment is on a very high safety level. No new HIV+ PWHs reported since late 90s.

Part A.2

Persons with haemophilia with inhibitor



Summary description of the PWHs with inhibitors within registry. There are five other PWHs with inhibitor in the center not participating in CNHP registry.
Please note increased number of PWHs with inhibitors in 2015, mainly 3 children with haemophilia A, who developed inhibitors in 2015. All were HR inhibitors.
It must be, however, put into the context with the information, that there were almost no PUPs with new inhibitors in several previous years and thus the overall relative incidence of inhibitors is not changed significantly comparing to Czech national data reported in Blood coagulation and Fibrinolysis in 2015.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age group	child	child	child	child	child	child	child	child	child	adult	adult	adult	adult	adult	adult	adult	adult
Year of birth	2015	2014	2014	2012	2011	2008	2007	2004	2003	1988	1977	1975	1971	1971	1956	1949	1941
Type of haemophilia	A	A	A	A	A	A	B	A	A	A	A	A	A	A	A	A	A
Severity	sev	sev	sev	sev	sev	sev	sev	sev	sev	mild	sev	sev	sev	sev	sev	mild	mod
Year of inhibitor development	2015	2015	2015	2014	2012	2013	2009	2009	2005	2013	2001	1991	1988	2013	1972	2012	2013
HR/LR	HR	HR	HR	HR	HR	HR	HR	HR	HR	LR	HR	HR	HR	LR	HR	LR	HR
„By-pass" treatment in 2014	-	-	rFVIIa	rFVIIa	-	-	rFVIIa	rFVIIa	rFVIIa	w/o any treatment	w/o any treatment	rFVIIa	rFVIIa	-	aPCC	aPCC	rFVIIa
ITT	-	Since 2015	-	Since 2015	Since 2013	2013-2015, success-ful	-	2011-2014, unsuccess-ful	-	-	-	-	-	Since 2015	-	-	in 2014, unsuccess-ful

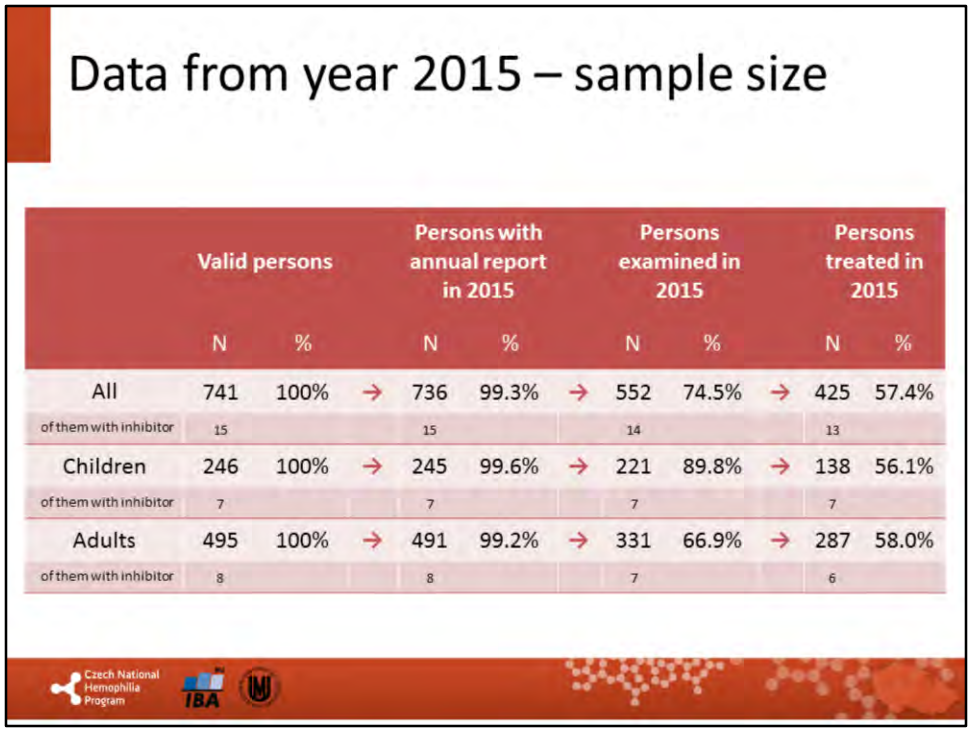
Information about PWHs with inhibitors and their treatment. Information reflects situation in December 2015.

Part A.3

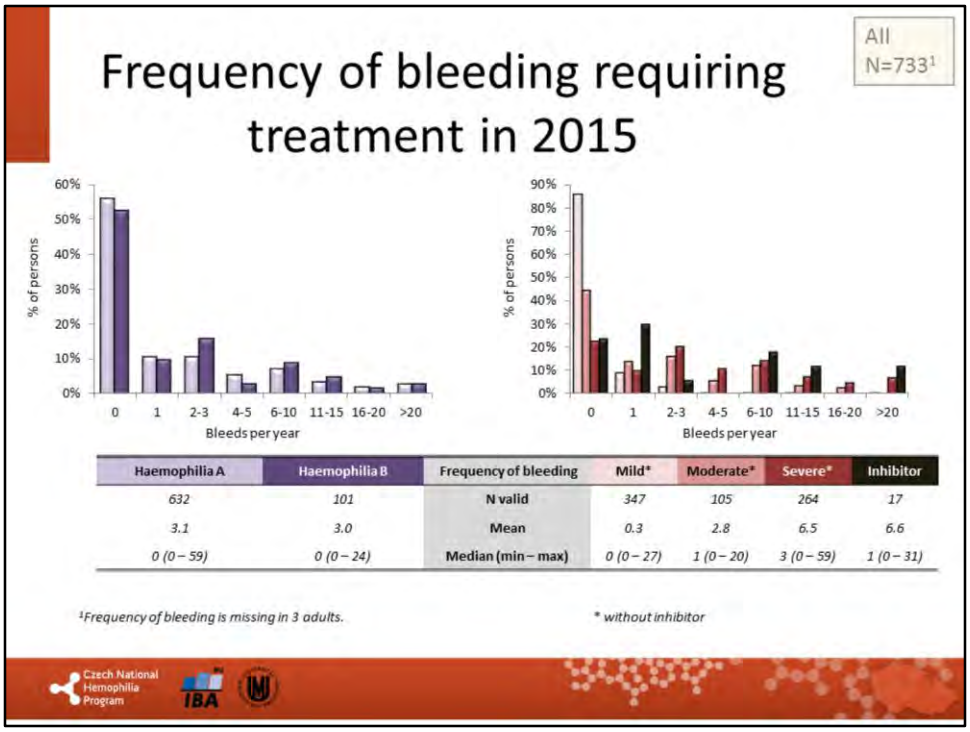
Treatment outcomes including bleeding frequency in persons with haemophilia 2015 data

Czech National Hemophilia Program

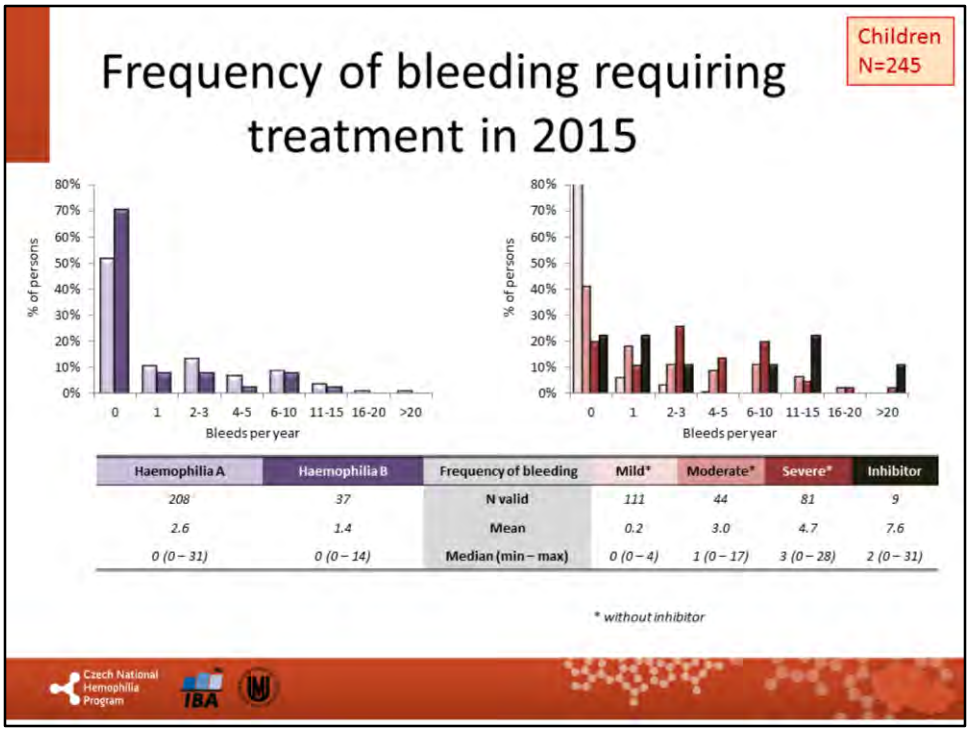
IBA



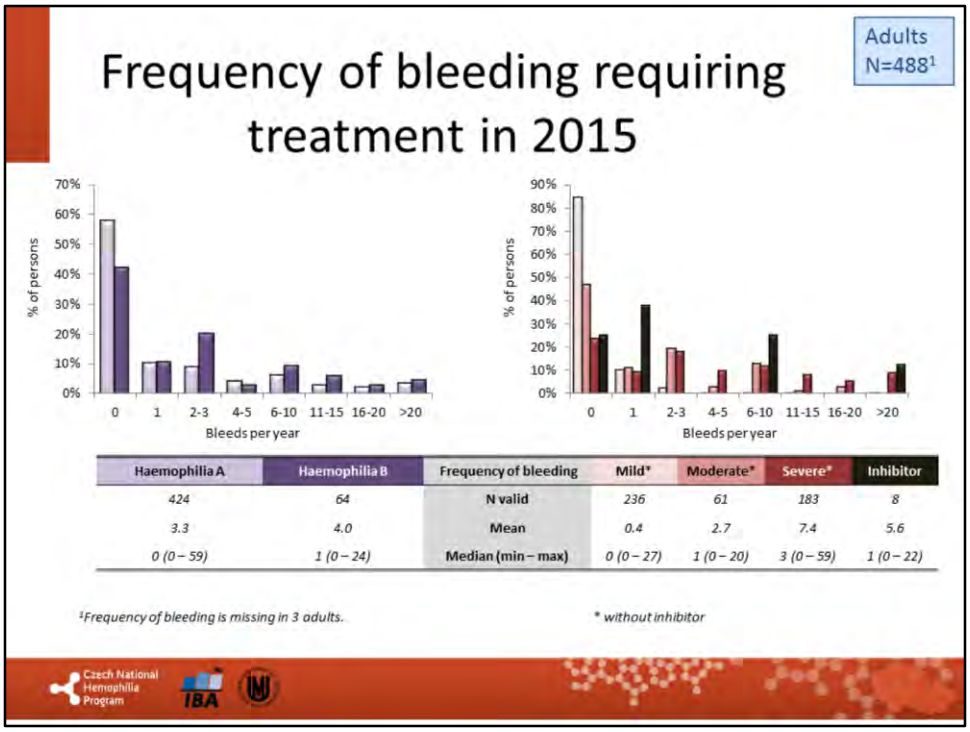
There are records of nearly 80% of all Czech haemophiliacs in total within the CNHP registry. As for paediatric population, ALL children are recorded. CNHP registry also houses records of over two thirds of adult haemophiliacs in Czech Republic. Further slides display analyses performed only on records, which were updated during 2015. Not all patients came to the centre (especially adults) and not all centres fully reported all data in 2015. Thus not all records have been updated and used for further analyses. Though the data completeness has further significantly improved in 2015 , it remains our task to get as close as possible to 100% in future years. This goal shall be reached by introducing of the data monitoring by designated CRO in 2016/2017. (Ideally, percentage of PWHs with annual report should be equal to PWHs examined and both should be 100%.)
Three treated adults are not included in further detailed analyses of treatment due to only partially filled annual report.



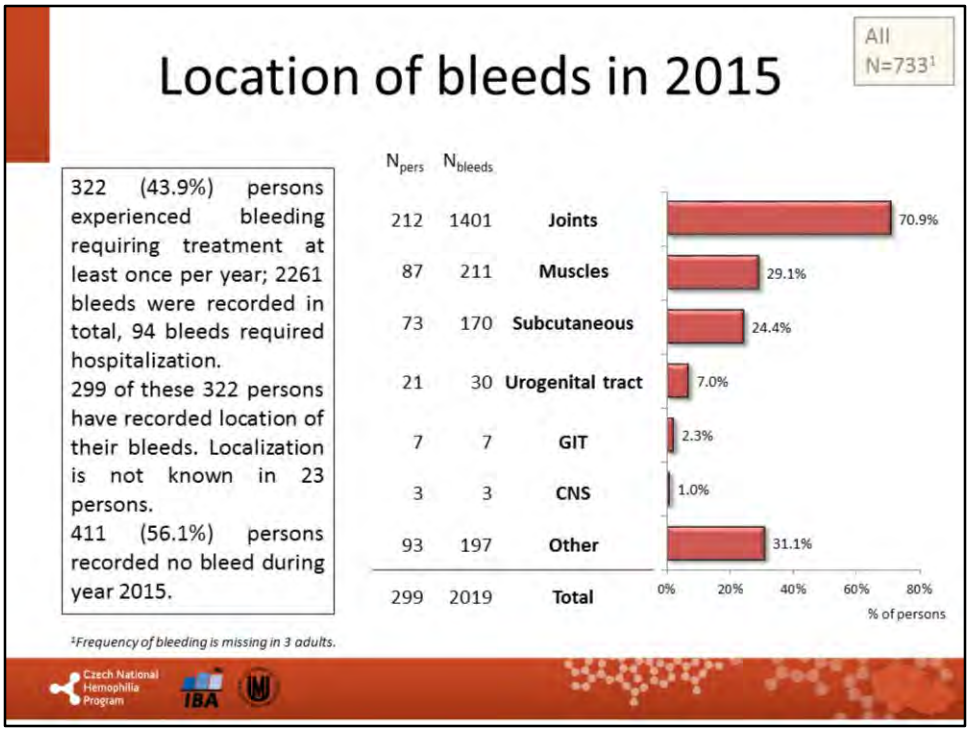
Data shown document good efficacy of care provided to Czech PWHs, no matter what age category they are. Mean number of bleedings per year (ABR) decreased from 9,4 (2014) to 6,5 (2015) in the whole severe haemophilia population regardless of prophylaxis. Median is 3.



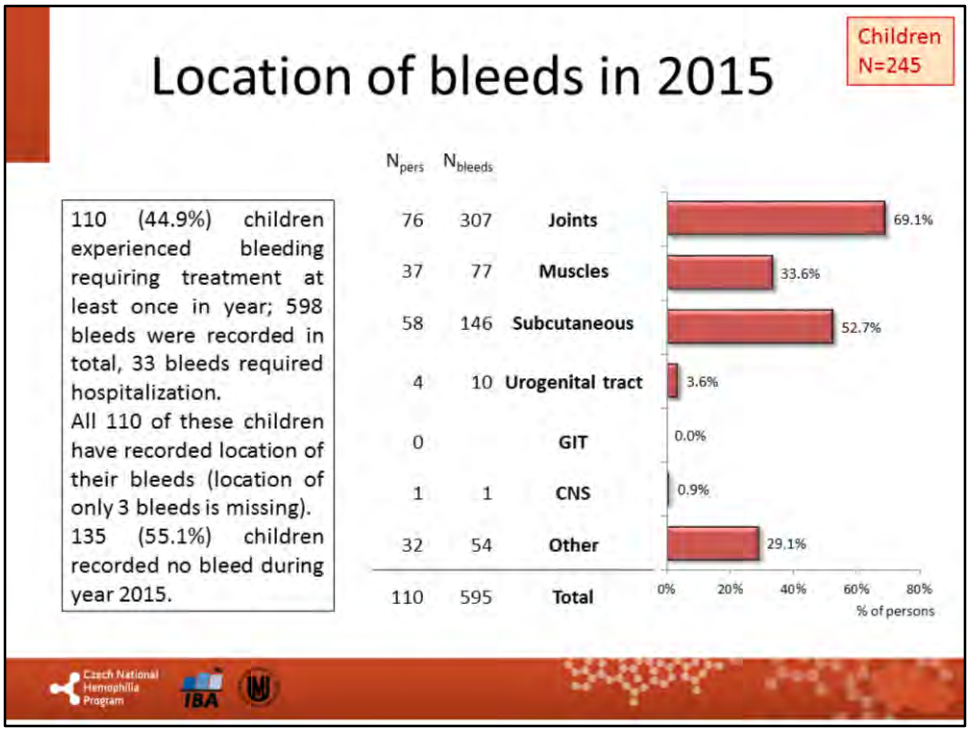
Median bleeding rate (all bleeds) in children with severe haemophilia decreased from 4 (2014) to 3 (2015) per year, regardless of prophylaxis.



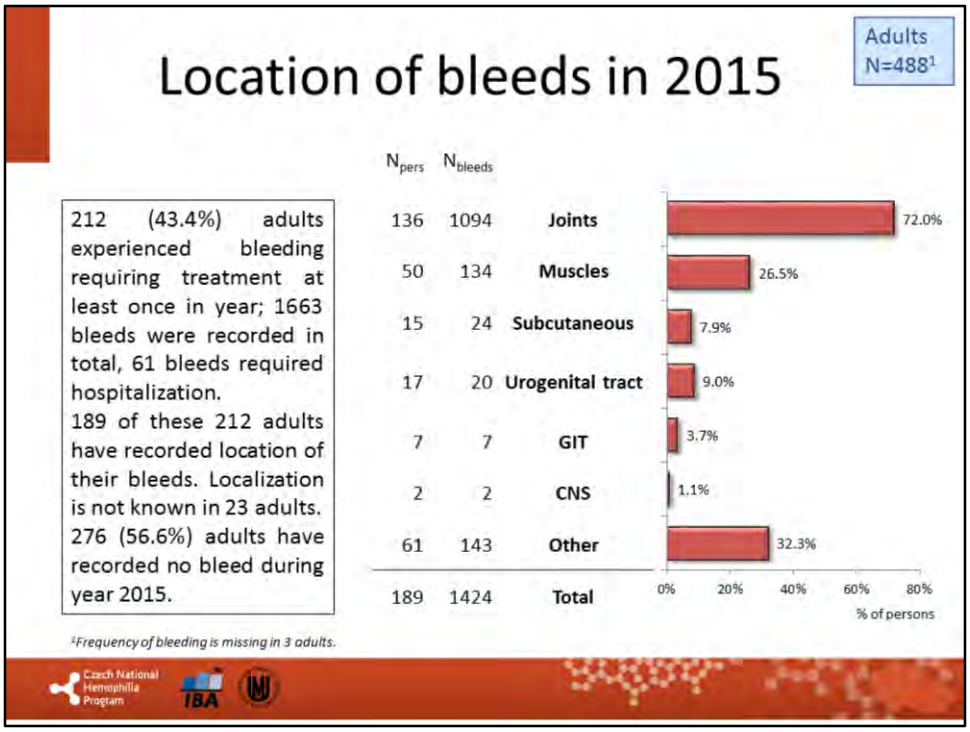
The same information for adult PWHs. Though also in this age category the ABR is improving (see following slides), there is still room for further improvement. Perhaps by broader introduction of tertiary prophylaxis in (older) adults.



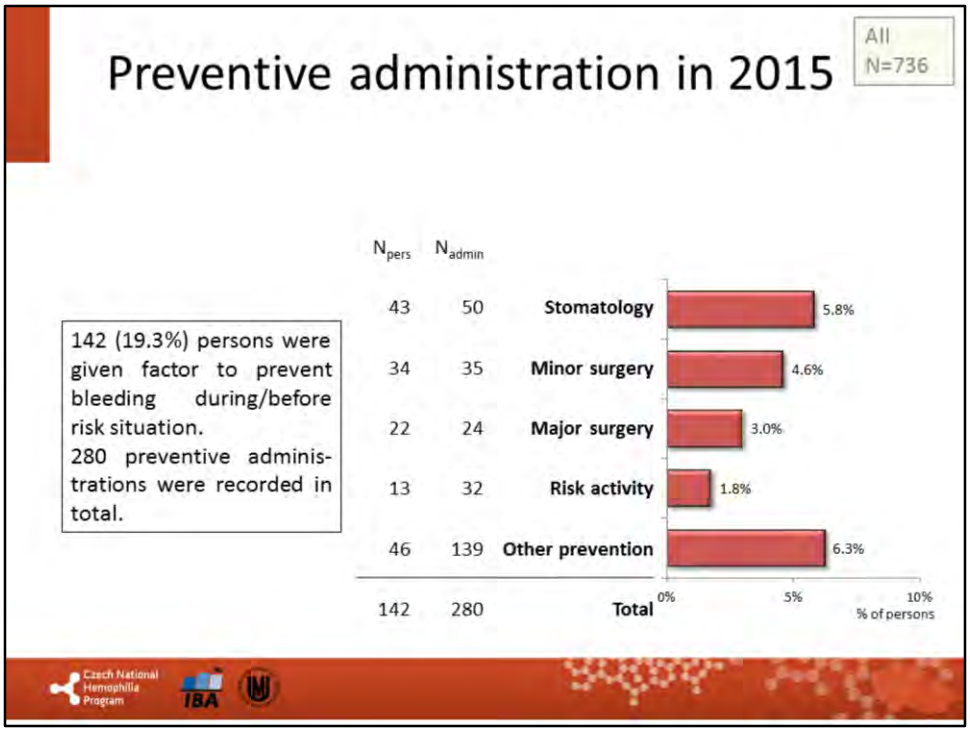
Over one half of all Czech PWHs did not experience any bleeding in 2015. Our aim should be to fully avoid CNS bleeds, though!



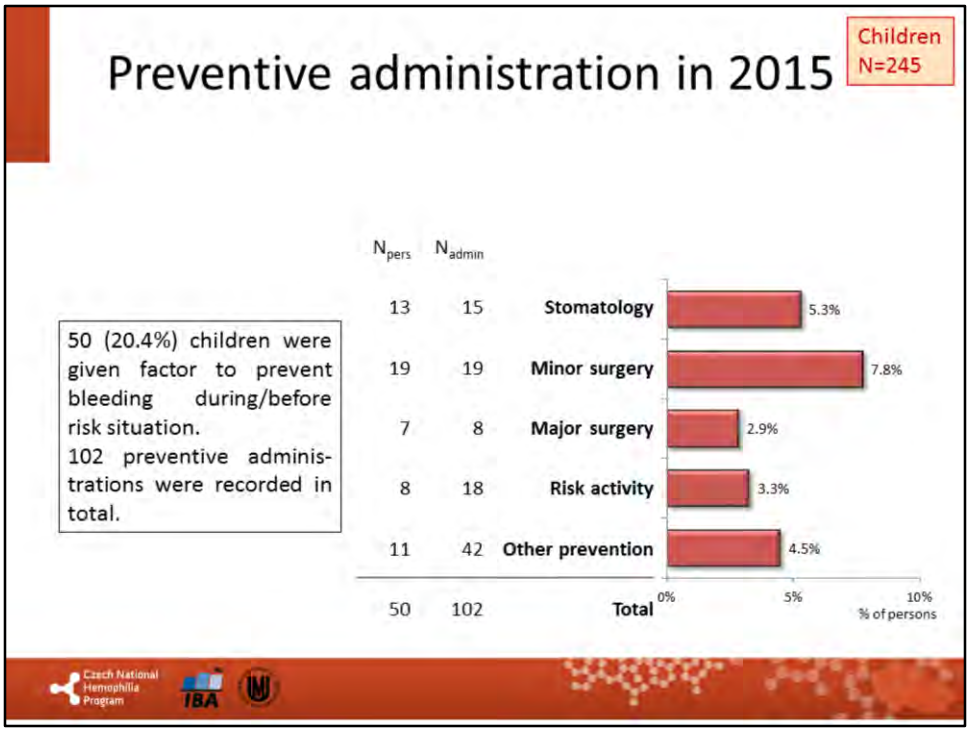
There was one CNS bleed in children with haemophilia in 2015. 55% of children had no bleed at all.



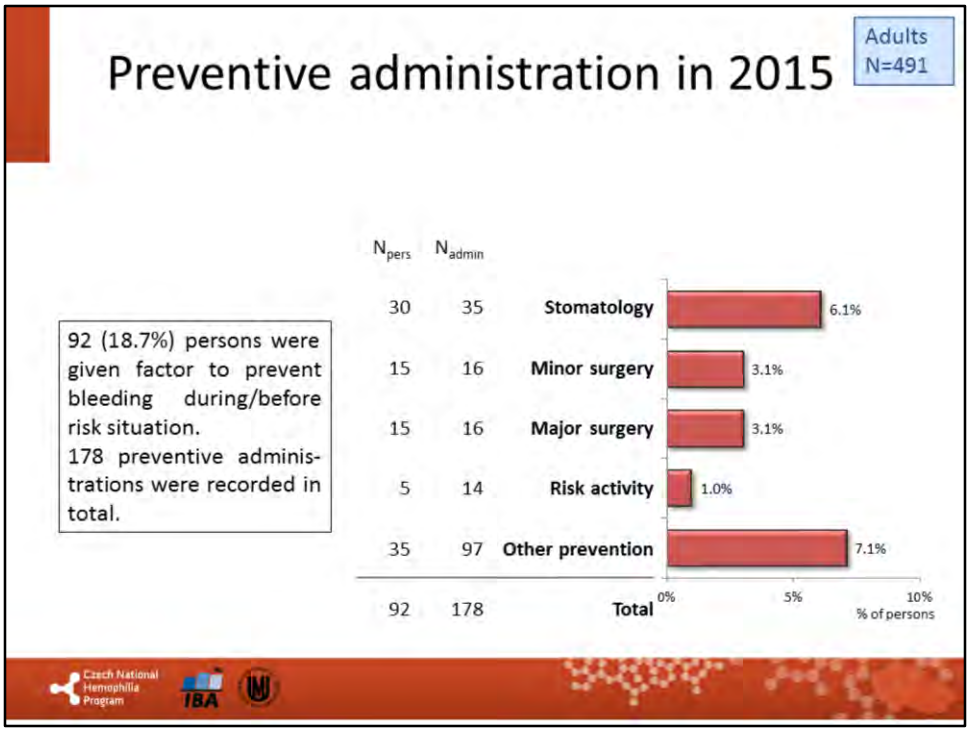
Bleeding events in adults.



Some PWHs were given factor concentrates not to treat bleeding, but to prevent bleeding during risk situations (i.e. surgeries, dental extractions, risk activities/sports etc…). These events were NOT counted/analyzed as bleeding episodes.



See comments on previous slide for explanation. This figure refers to paediatric population.



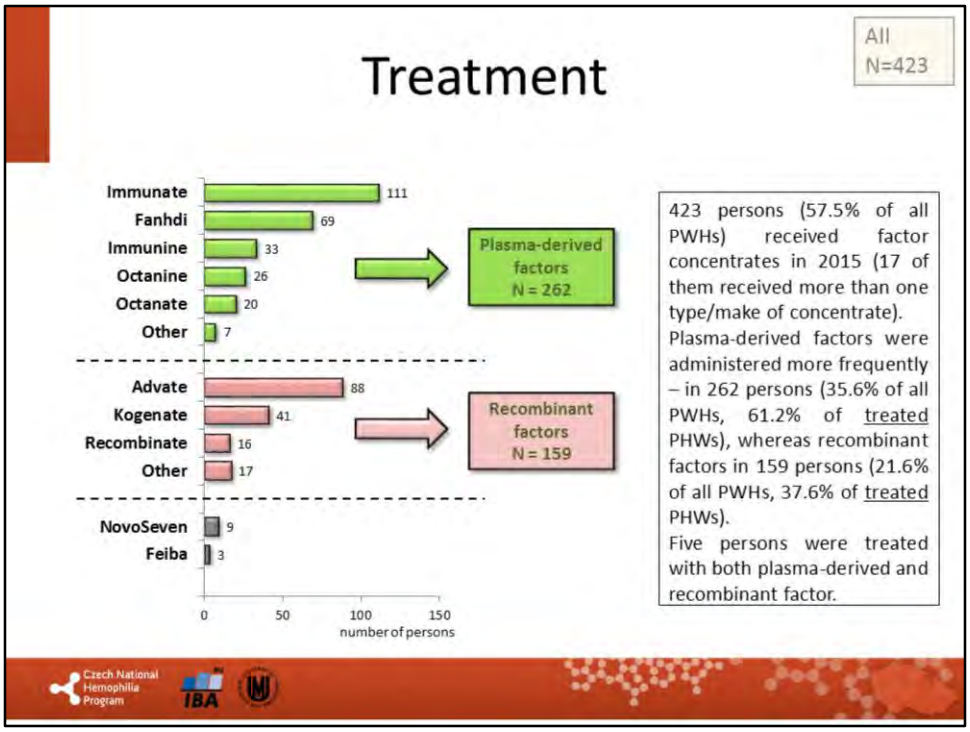
See comments on previous slide for explanation. This figure refers to adult population.

Part A.4

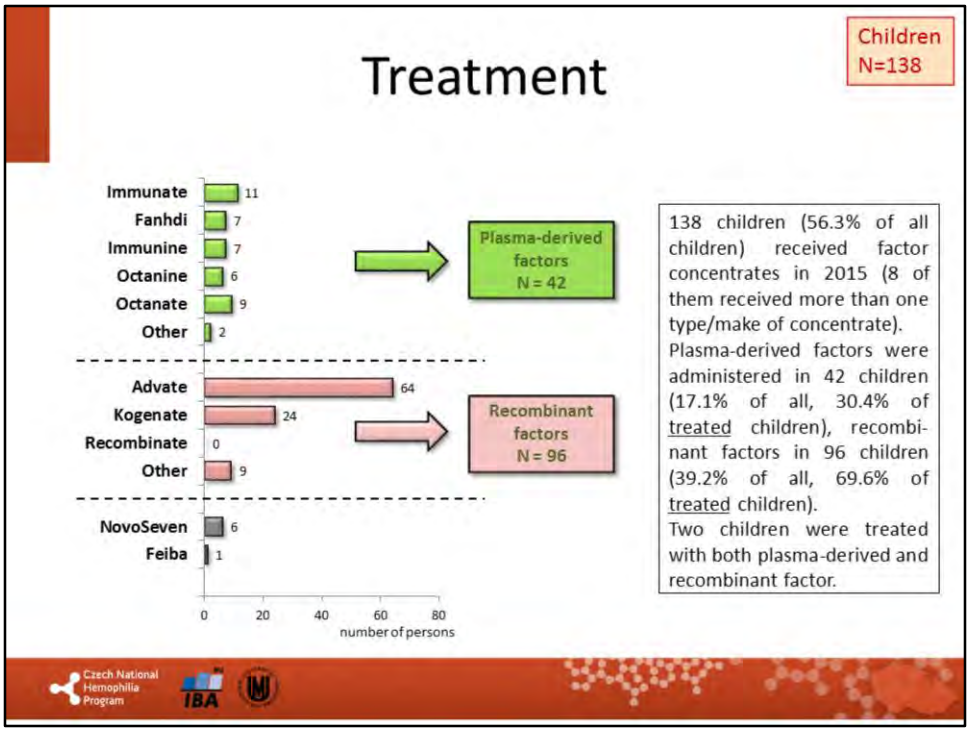
Treatment data and factor consumption 2015 data

Czech National Hemophilia Program

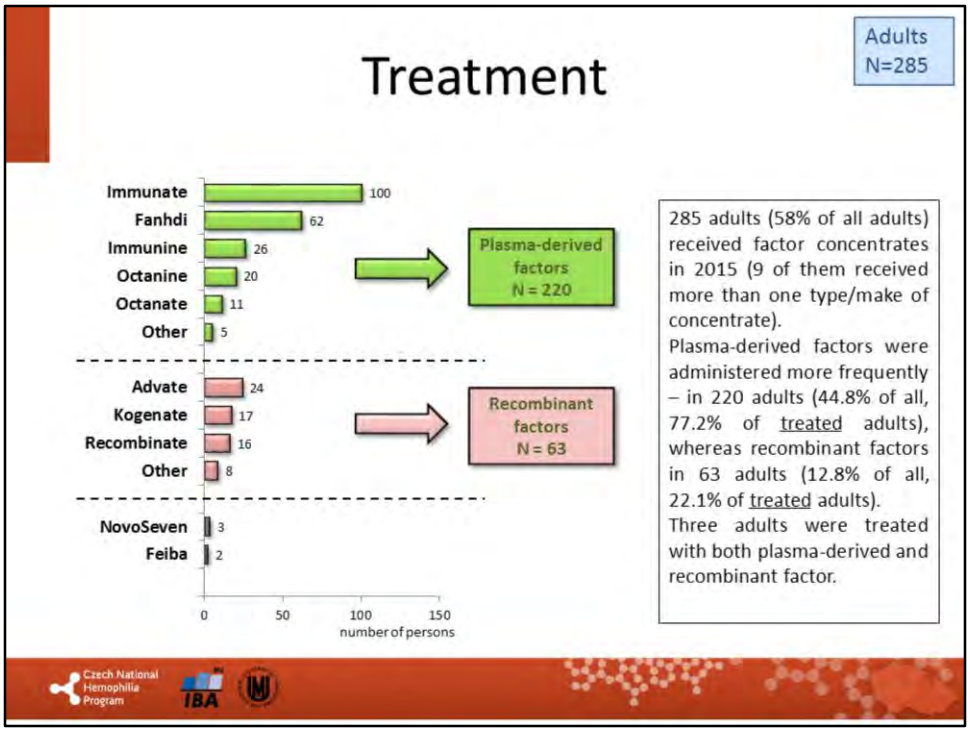
IBA



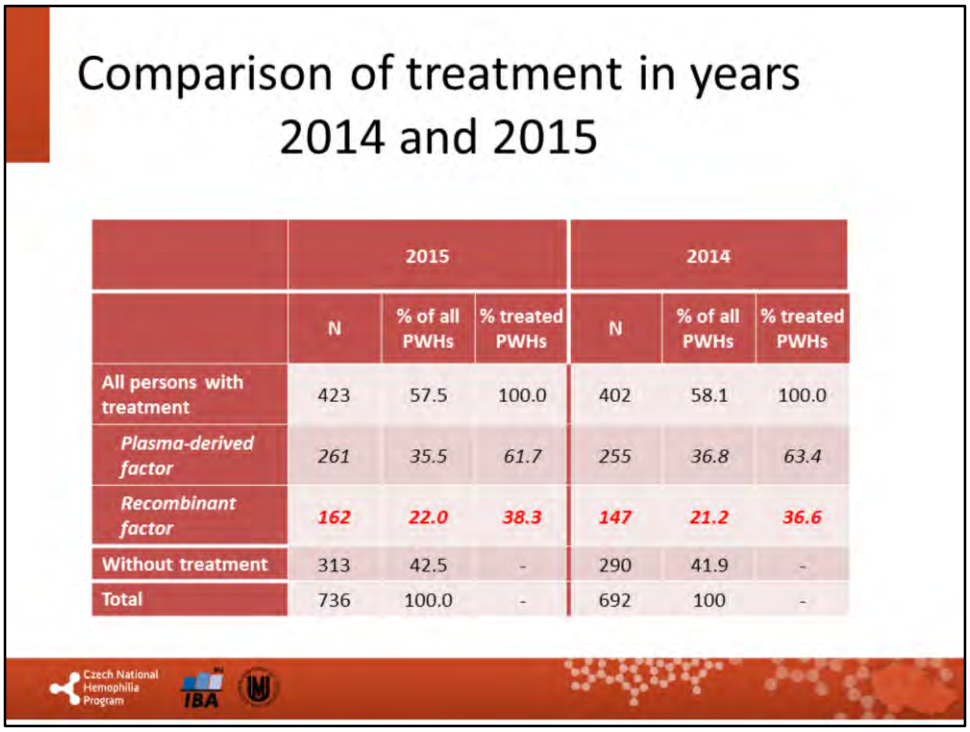
Over one third of PWHs registered in CNHP registry and treated with any factor concentrate were treated with recombinants in 2015. The number of PWHs treated with recombinants is gradually increasing over last several years. This is not only due to the recommendation of CNHP to treat PUPs with recombinants (since 2006), but also reflects switches of older children and adults to rFVIII in some cases.



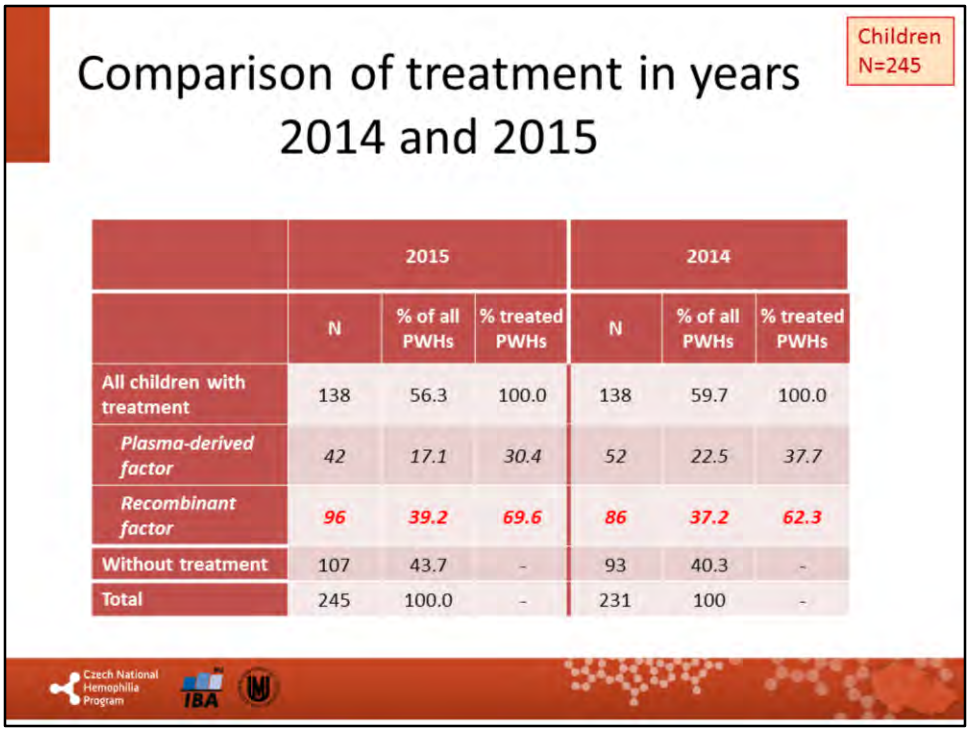
Over two thirds of children, who were given factor concentrate in 2015, were treated with recombinants.



Number of adult PWHs treated with recombinants is slowly increasing (currently 23% of those treated with factor concentrate in 2015 and registered within CNHP registry).

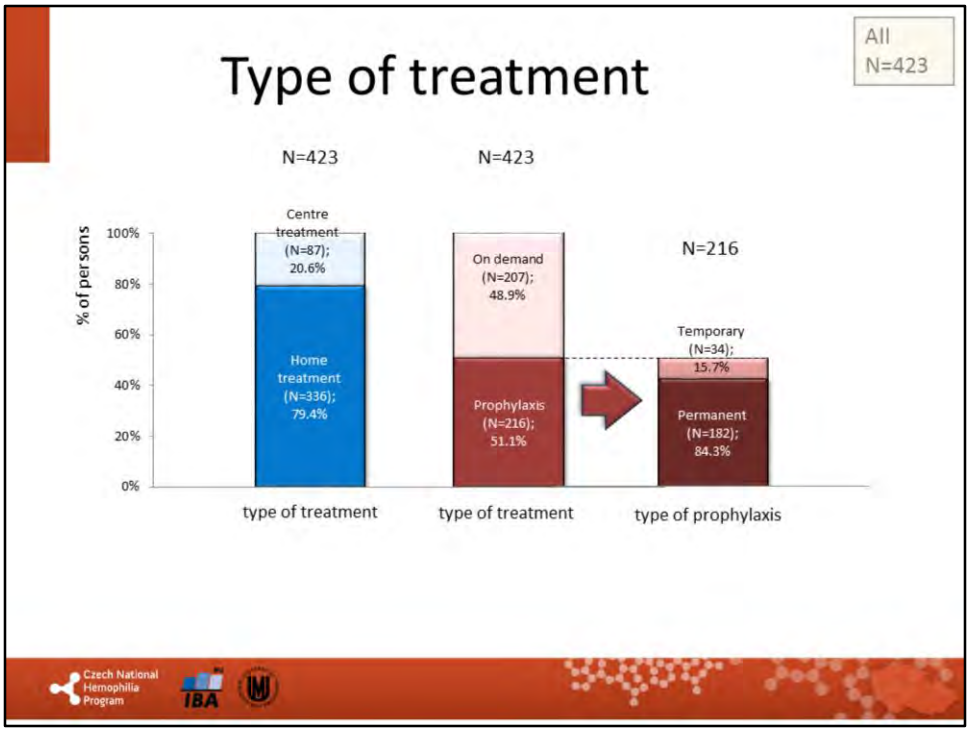


This table compares data between 2014 and 2015. E.g. you can see, that percentage of patients treated with recombinant concentrates and registered within CNHP registry changed from 36,6% in 2014 to 38,3% in 2015.

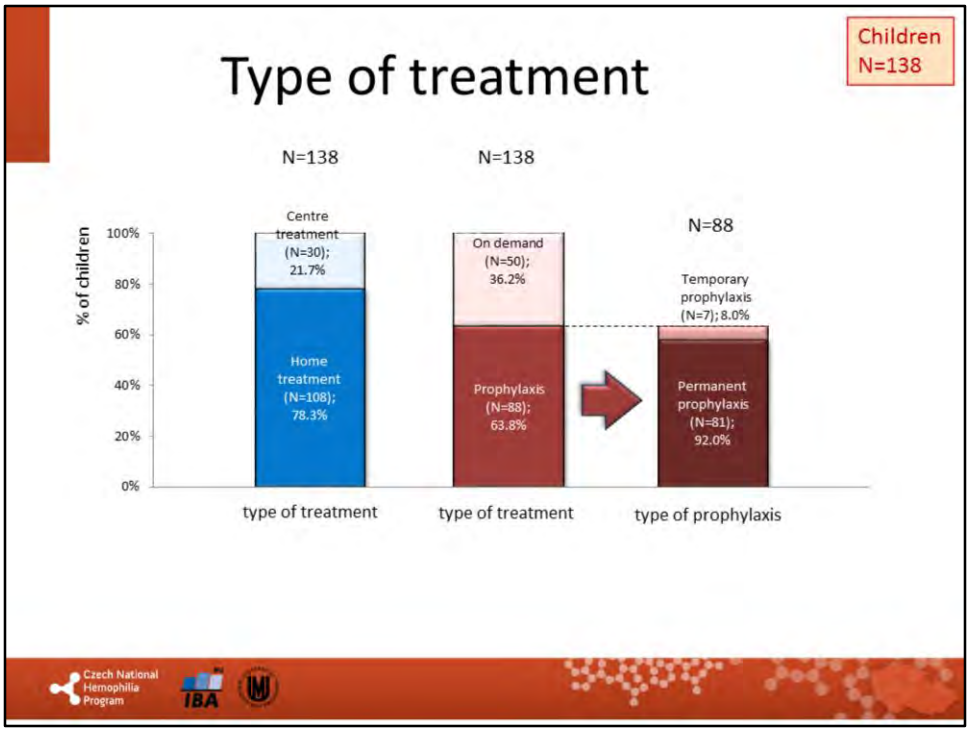


	2015			2014		
	N	% of all PWHs	% treated PWHs	N	% of all PWHs	% treated PWHs
All children with treatment	138	56.3	100.0	138	59.7	100.0
Plasma-derived factor	*42*	*17.1*	*30.4*	*52*	*22.5*	*37.7*
Recombinant factor	***96***	***39.2***	***69.6***	***86***	***37.2***	***62.3***
Without treatment	107	43.7	-	93	40.3	-
Total	245	100.0	-	231	100	-

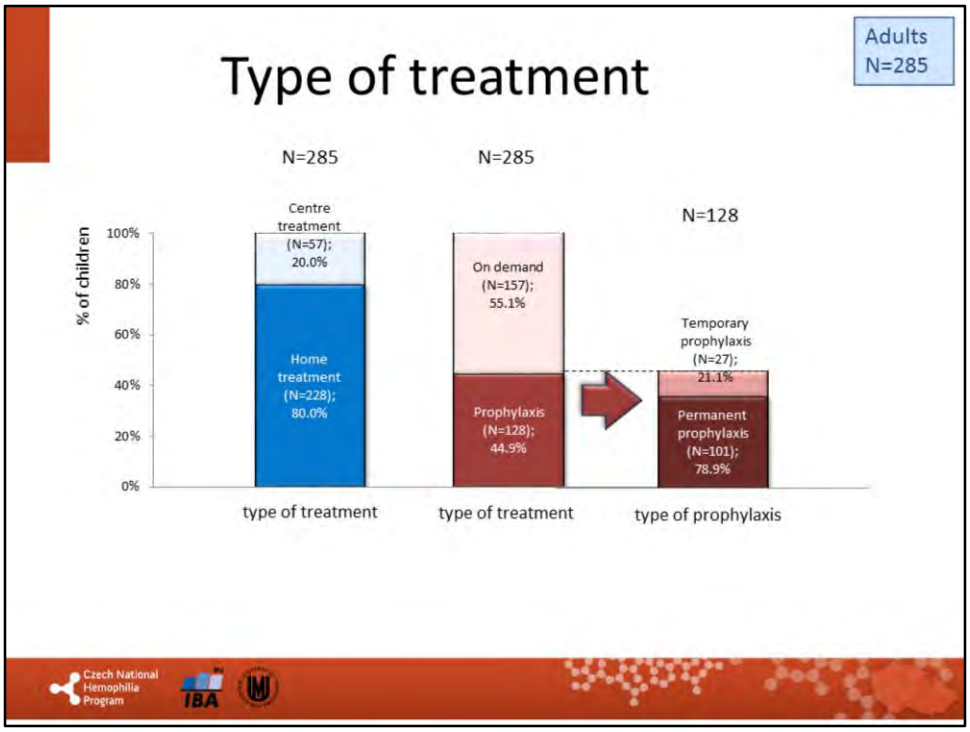
This table compares data between 2014 and 2015. E.g. you can see, that percentage of children treated with recombinant concentrates and registered within CNHP registry changed from 62,3% in 2014 to almost 70% in 2015.



Almost 80% of PWHs treated in 2015 took the advantage of home treatment. Half of treated PWHs were commenced on any type prophylaxis and 84% out of those on prophylaxis were on permanent prophy in 2015.



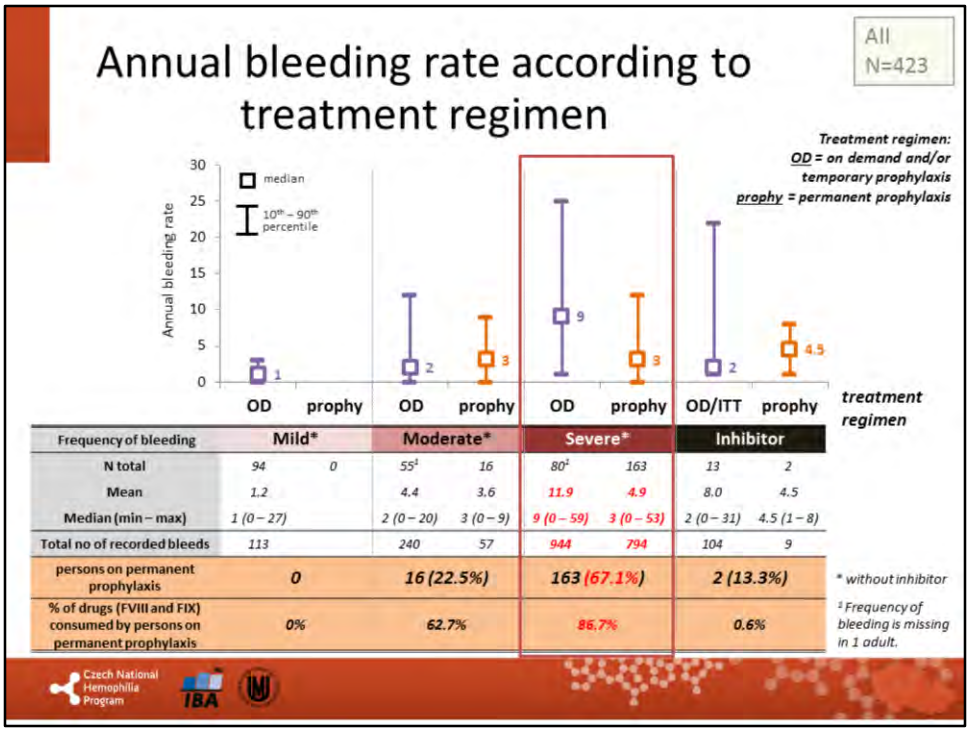
Almost 80% of children treated in 2015 took the advantage of home treatment. 64% of treated children were commenced on any type prophylaxis and 92% out of those on prophylaxis were on permanent prophy in 2015.



80% of adults treated in 2015 took the advantage of home treatment. 45% of treated adults were commenced on any type prophylaxis and 79% out of those on prophylaxis were on permanent prophy in 2015.

Part A.5

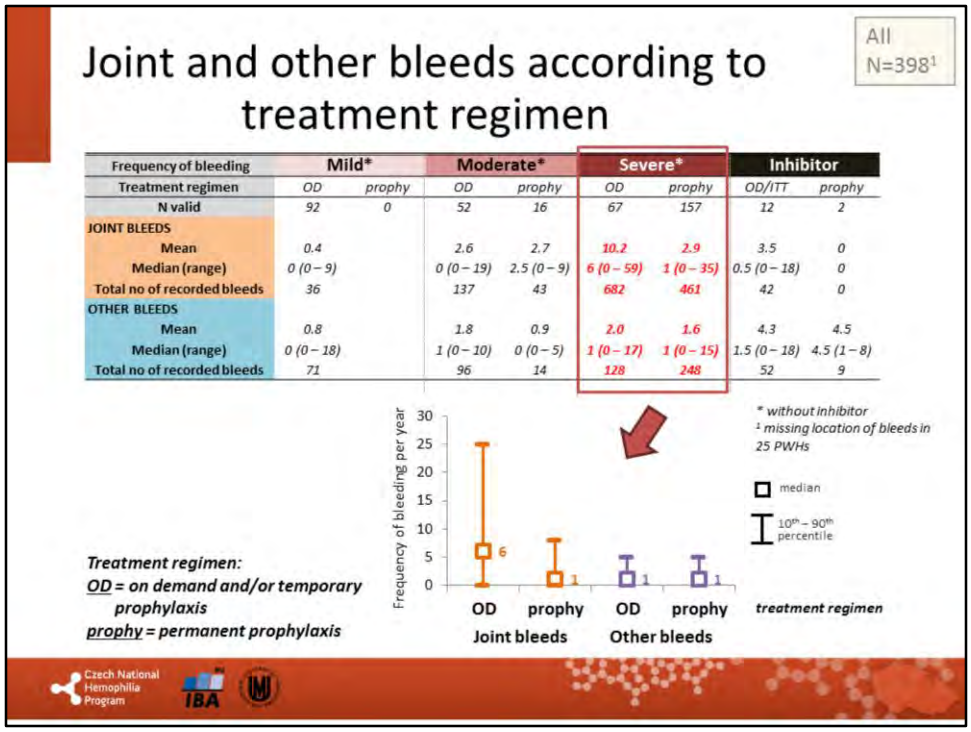
ABR in 2015 according to treatment regimen Haem A + Haem B



These data strongly support the positive effect of prophylaxis in Czech PWHs, no matter what age category they are. Rate of prophylaxis increased from 59,7% in 2014 to 67,1% in 2015 among Czech PWHs with severe haemophilia.

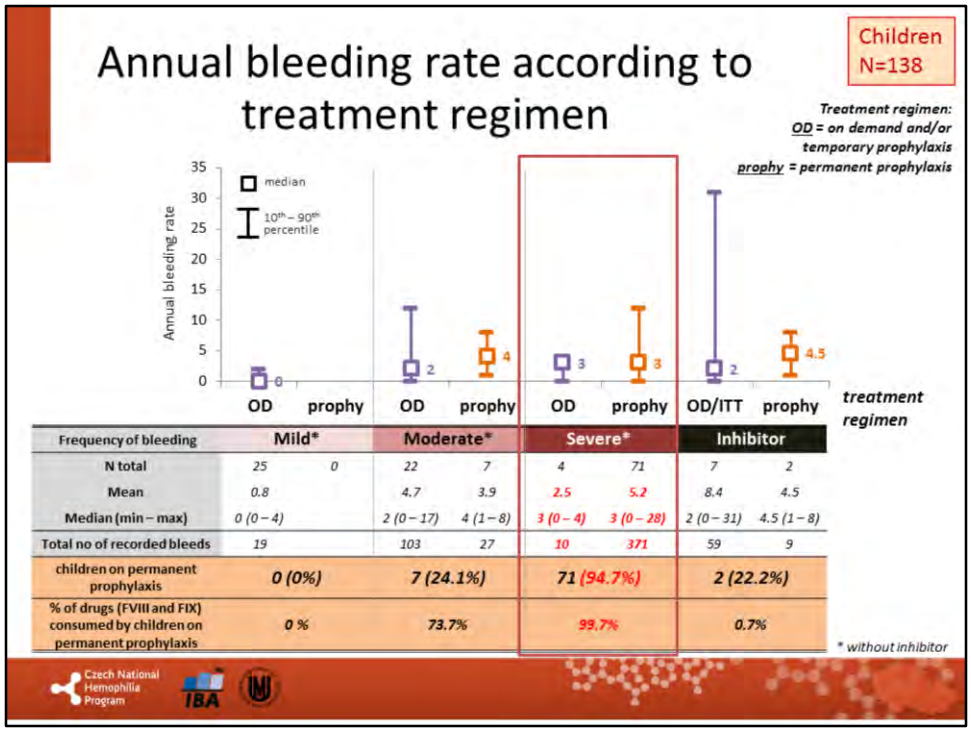
Median number of bleedings per year in severe haemophiliacs can be decreased from 9 in those without prophylaxis to 3 in those, who are taking the advantage of prophylactic factor application. The numbers also decreased compared to 2014 data (11,5 OD and 4 on prophy).

This table also shows, that, in general, consumption of factors is not significantly increased by using prophylaxis as 67,1% of treated persons with severe haemophilia were on permanent prophylaxis and they used 86,7% of total factor consumption for that particular group. Difference is thus rather small.



This important table shows, that the vast majority of bleeds in Czech PWHs which are influenced/diminished by prophylaxis are JOINT bleeds. The benefit of prophylaxis, leading to decrease of annual joint-bleeding rate from 6 to 1 (median) is undoubted.
Improvement can be seen between 2014 and 2015 (8 joint bleeds on OD, 2 on prophy in 2014).

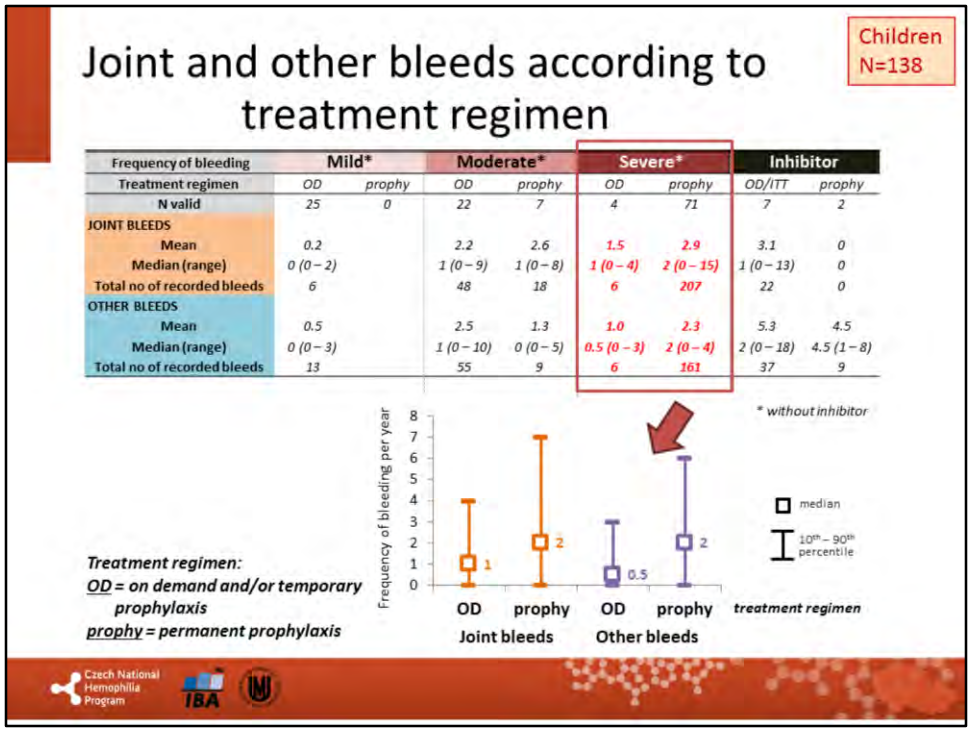
On the other hand, it is alarming to see, that vast majority of bleeds in Czech PWHS are still joint bleeds (up to 5/6).
If PWH has >1 joint bleed per year in a long term prospective, the locomotor apparatus deteriorates progressively.



This slide supports good effect of permanent prophylaxis in children. Rate of prophylaxis increased from 88,9% in 2014 to 94,7% in 2015 among children with severe haemophilia. However, those children with severe haemophilia, who are not on permanent prophylaxis yet shall be encouraged to do so. (see paragraph 3)

Number of bleeds per year (median) in severe haemophilacs on prophylaxis further decreased compared to 2014 from 4 to 3. ABR in children with severe haemophilia on OD decreased from 5,5 to 3. The same ABR for those on OD and on prophy suggests, that (almost) all children with severe haemophilia, who needed prophylaxis, already have it. Children with moderate haemophilia need our attention too, as they are currently having same or worse otcome, than severe ones.

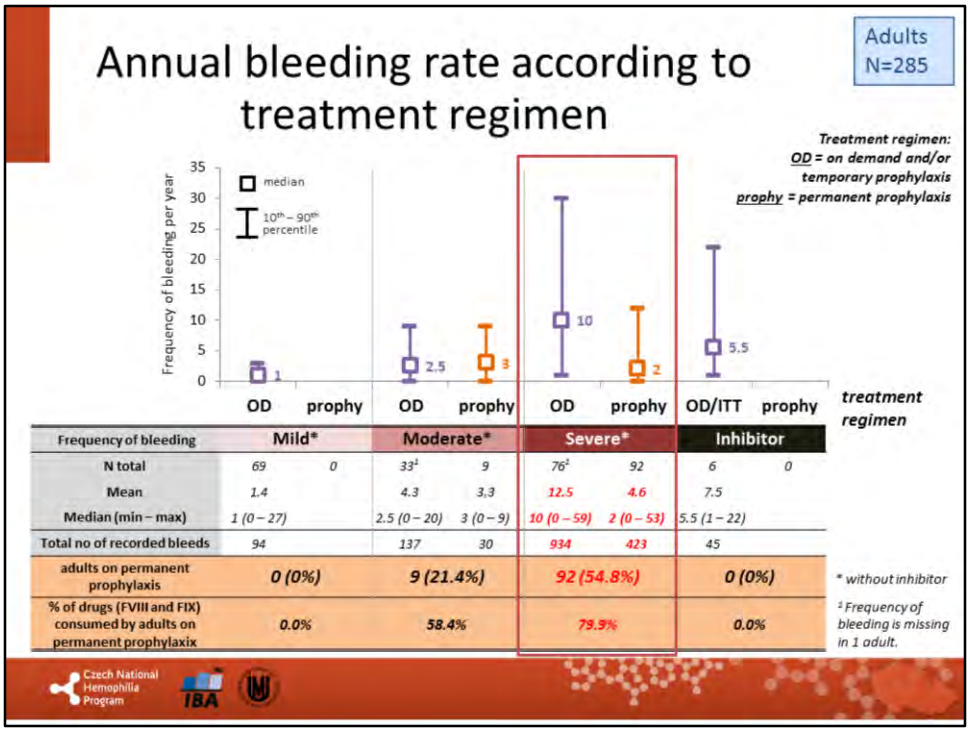
We should, however, still bear in mind, that over 2 bleeds/year lead to significant joint damage, and we shall further work on this issue! We are likely able to prevent almost all spontaneous bleeds, but we should focus on trauma bleeds in still more and more active children. This is true specially for children with severe haemophilia, regardless of their prophylaxis status in 2015.



This table shows, that in contrary to adult population, children with haemophilia in CZ do not have so many joint bleeds and its annual median bleeding rate is 2 (no change compared to 2014).
We, however, shall work together to get the median number of joint bleeds in children on prophylaxis below 2!!!
Perhaps, those children with severe haemophilia, who were not on prophylaxis in 2015, could have even 0 ABR when commenced on prophy??

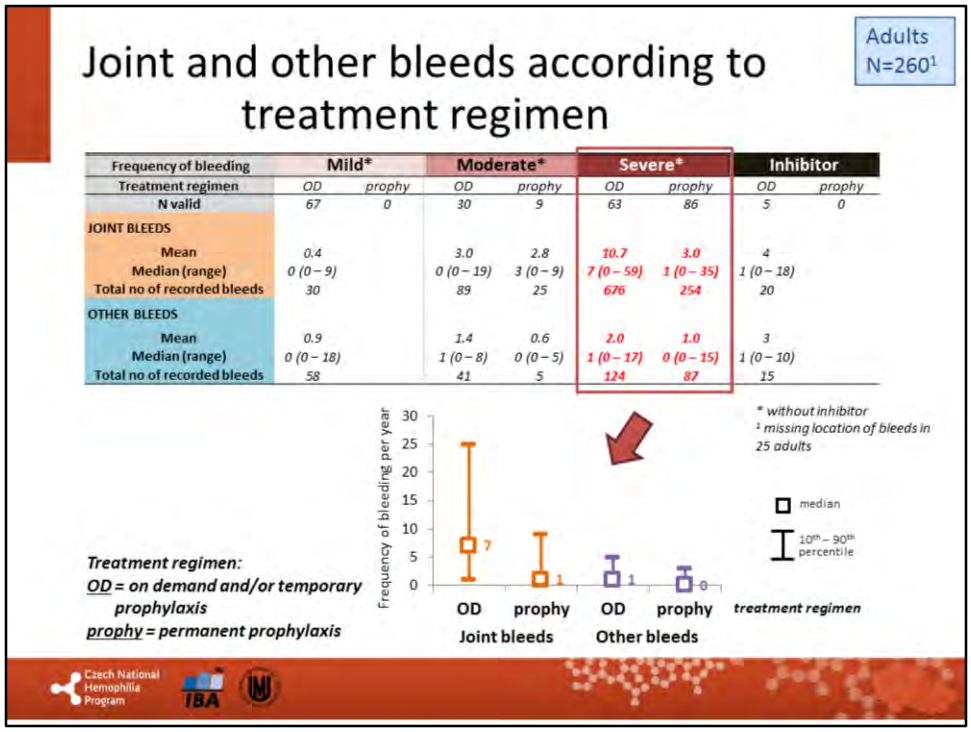
Median ABR of „other bleeds" for children with severe haemophilia treated OD decreased from 3 to 0,5 between 2014 and 2015

NB: Please note low joint - ABR in a patient with inhibitors on permanent prophylaxis with „by-pass" agents.



Prophylaxis works very well in Czech adult PWHs! It is able to decrease bleedings from 10 to 2 (median numbers). In 2014 median ABR in adult PWHs with severe haemophilia was 12 on OD and 3 on prophy.

Rate of prophylaxis increased from 47,6% in 2014 to 54,8% in 2015 among adults with severe haemophilia.
Use of prophylaxis will certainly increase the factor consumption in adults, but the benefit - shown as far less bleedings - is undoubted.

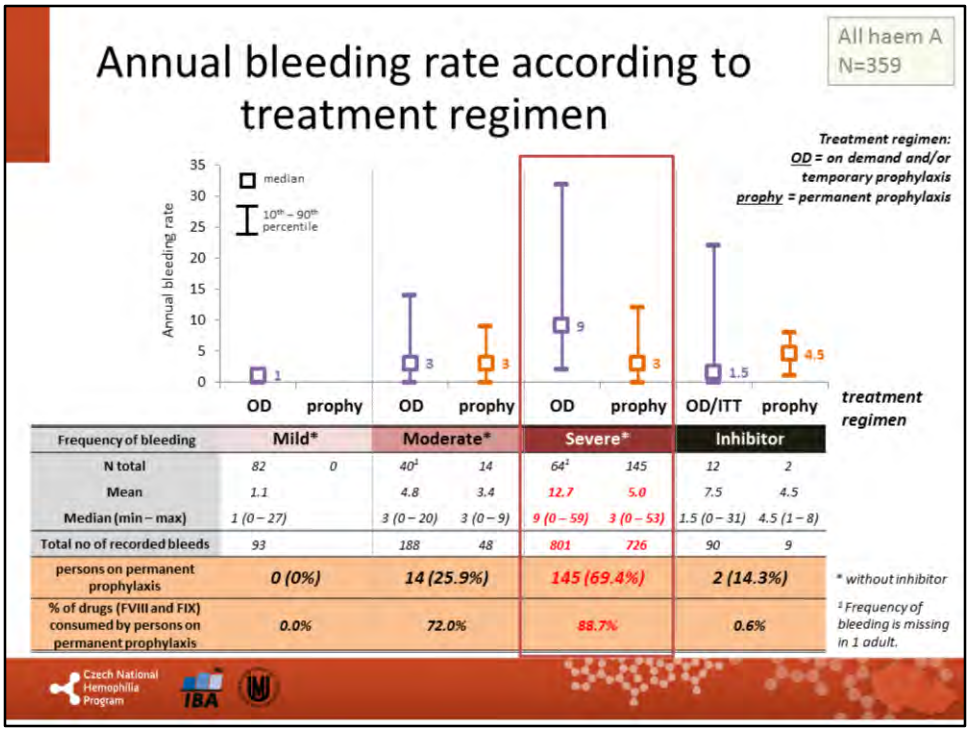


This table shows, that the vast majority of bleeds in Czech adult PWHs which are influenced/diminished by prophylaxis are JOINT bleeds.
The benefit of prophylaxis, leading to decrease of annual joint-bleeding rate in adults from 7 to 1 (median) is undoubted. In 2014, the joint ABR for adults was 9 on OD and 3 on prophy.

On the other hand, it is alarming to see, that vast majority of bleeds in Czech adult PWHS are joint bleeds (around 7/8). It applies mostly for those, who are not on prophylaxis!
If PWH has >1 joint bleed per year in a long term prospective, the locomotor apparatus deteriorates progressively. Prophylaxis in adults, can decrease the annual joint-bleeding rate down to 1 (median)!

Part A.6

ABR in 2015 according to treatment regimen Haemophilia A only



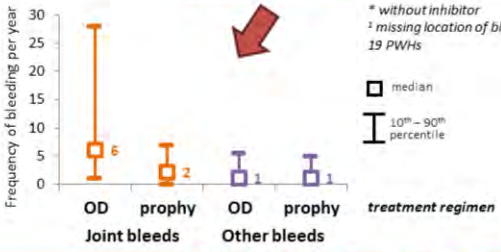
Similar data for Haemophilia A only.

Please note, that despite the significant and continuous improvement of haemophilia care in CZ, there are still people who bleed more than 50 times per year!, even when on prophylaxis!!! This number is not acceptable and shall be changed soon and rapidly.

Joint and other bleeds according to treatment regimen

All haem A
N=340[1]

Frequency of bleeding	Mild*		Moderate*		Severe*		Inhibitor	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy	OD/ITT	prophy
N valid	81	0	39	14	52	141	11	2
JOINT BLEEDS								
Mean	0.3		2.9	2.6	10.9	2.9	3.1	0
Median (range)	0 (0 – 9)		1 (0 – 19)	2 (0 – 9)	6 (0 – 59)	2 (0 – 35)	0 (0 – 18)	0 (0 – 0)
Total no of recorded bleeds	28		112	37	567	415	34	0
OTHER BLEEDS								
Mean	0.8		1.9	0.8	2.1	1.6	4.2	4.5
Median (range)	0 (0 – 18)		1 (0 – 10)	0 (0 – 5)	1 (0 – 17)	1 (0 – 15)	1 (0 – 18)	4.5 (1 – 8)
Total no of recorded bleeds	62		75	11	105	232	46	9



* *without inhibitor*
[1] *missing location of bleeds in 19 PWHs*

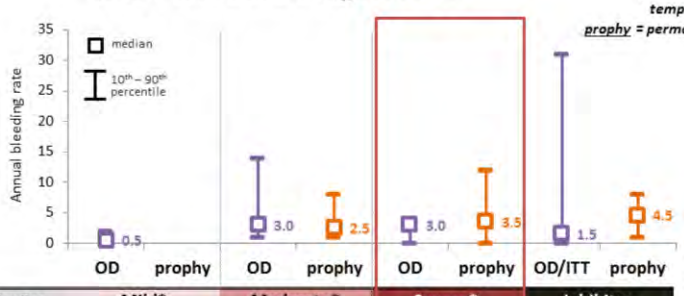
Treatment regimen:
***OD** = on demand and/or temporary prophylaxis*
***prophy** = permanent prophylaxis*

Czech National Hemophilia Program

Annual bleeding rate according to treatment regimen

Children (haem A) N=121

Treatment regimen:
OD = on demand and/or temporary prophylaxis
prophy = permanent prophylaxis



Frequency of bleeding	Mild*		Moderate*		Severe*		Inhibitor	
N total	20	0	19	6	4	64	6	2
Mean	0.7		5.4	3.3	2.5	5.4	7.5	4.5
Median (min – max)	0.5 (0 – 2)		3 (0 – 17)	2.5 (1 – 8)	3 (0 – 4)	3.5 (0 – 28)	1.5 (0 – 31)	4.5 (1 – 8)
Total no of recorded bleeds	13		102	20	10	347	45	9
children on permanent prophylaxis	0 (0%)		6 (24%)		64 (94.1%)		2 (25%)	
% of drugs (FVIII and FIX) consumed by children on permanent prophylaxis	0.0%		67.5%		99.6%		0.7%	

* without inhibitor

Czech National Hemophilia Program

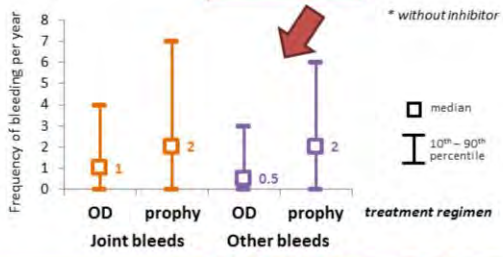
IBA

Joint and other bleeds according to treatment regimen

Children (haem A) N=121

Frequency of bleeding	Mild*		Moderate*		Severe*		Inhibitor	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy	OD/ITT	prophy
N valid	20	0	19	6	4	64	6	2
JOINT BLEEDS								
Mean	0.2		2.5	2.3	1.5	3.0	2.3	0
Median (range)	0 (0 – 2)		2 (0 – 9)	1 (0 – 8)	1 (0 – 4)	2 (0 – 15)	0 (0 – 13)	0 (0 – 0)
Total no of recorded bleeds	4		48	14	6	190	14	0
OTHER BLEEDS								
Mean	0.5		2.8	1.0	1.0	2.4	5.2	4.5
Median (range)	0 (0 – 2)		2 (0 – 10)	0 (0 – 5)	0.5 (0 – 3)	2 (0 – 14)	1 (0 – 18)	4.5 (1 – 8)
Total no of recorded bleeds	9		54	6	4	154	31	9

* without inhibitor

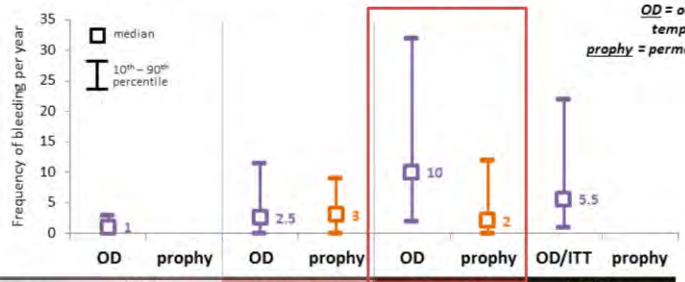


Treatment regimen:
<u>OD</u> = on demand and/or temporary prophylaxis
<u>prophy</u> = permanent prophylaxis

Czech National Hemophilia Program

Annual bleeding rate according to treatment regimen

Adults (haem A) N=238



Treatment regimen:
***OD** = on demand and/or temporary prophylaxis*
***prophy** = permanent prophylaxis*

Frequency of bleeding	Mild*		Moderate*		Severe*		Inhibitor	
N total	62	0	21[1]	8	60[1]	81	6	0
Mean	1.3		4.3	3.5	13.4	4.7	7.5	
Median (min – max)	1 (0 – 27)		2.5 (0 – 20)	3 (0 – 9)	10 (0 – 59)	2 (0 – 53)	5.5 (1 – 22)	
Total no of recorded bleeds	80		86	28	791	379	45	
adults on permanent prophylaxis	0 (0%)		8 (27.6%)		81 (57.4%)		0 (0%)	
% of drugs (FVIII and FIX) consumed by adults on permanent prophylaxix	0.0%		73.8%		82.6%		0.0%	

** without inhibitor*

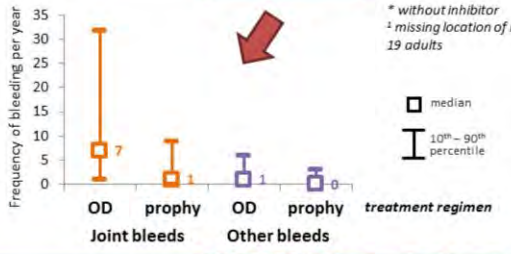
[1] Frequency of bleeding is missing in 1 adult.

Czech National Hemophilia Program

Joint and other bleeds according to treatment regimen

Adults (haem A) N=219[1]

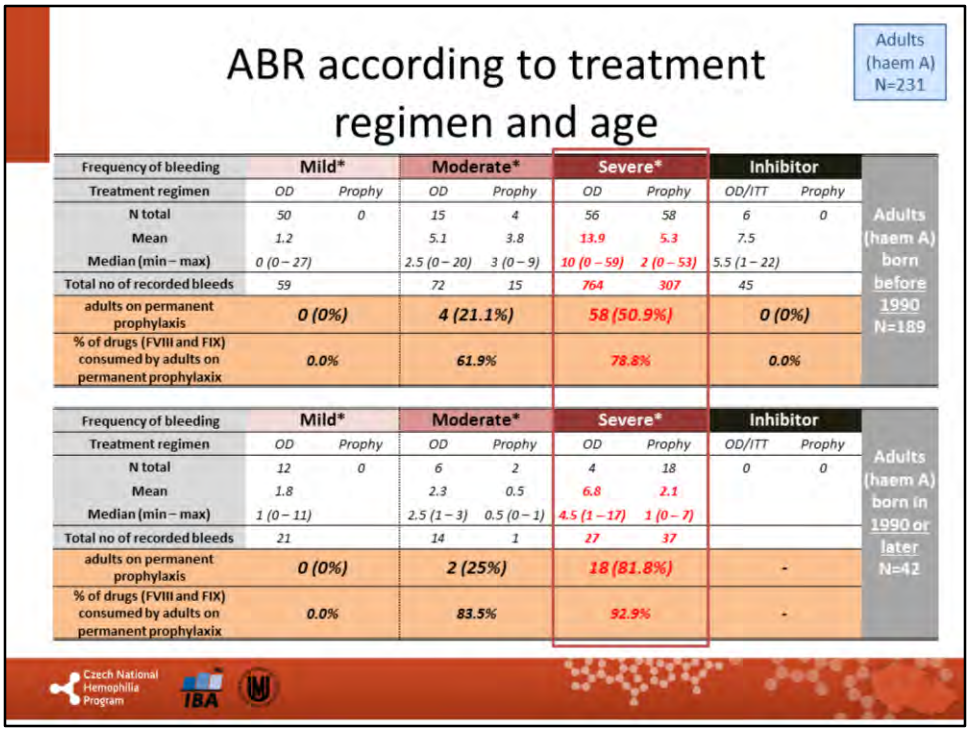
Frequency of bleeding	Mild*		Moderate*		Severe*		Inhibitor	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy	OD	prophy
N valid	61	0	20	8	48	77	5	0
JOINT BLEEDS								
Mean	0.4		3.2	2.9	11.7	2.9	4	
Median (range)	0 (0 – 9)		0.5 (0 – 19)	3 (0 – 9)	7 (0 – 59)	1 (0 – 35)	1 (0 – 18)	
Total no of recorded bleeds	24		64	23	561	225	20	
OTHER BLEEDS								
Mean	0.9		1.1	0.6	2.2	1.0	3	
Median (range)	0 (0 – 18)		1 (0 – 4)	0 (0 – 5)	1 (0 – 17)	0 (0 – 15)	1 (0 – 10)	
Total no of recorded bleeds	53		21	5	101	78	15	



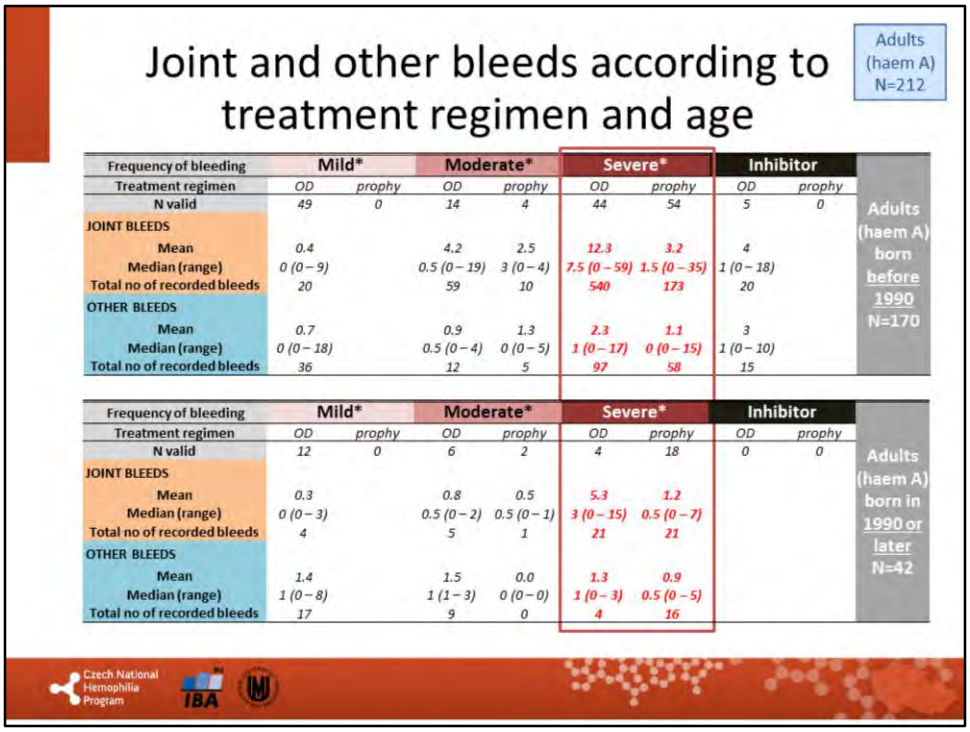
* *without inhibitor*
[1] *missing location of bleeds in 19 adults*

Treatment regimen:
***OD** = on demand and/or temporary prophylaxis*
***prophy** = permanent prophylaxis*

Czech National Hemophilia Program



This important table shows significant difference (approximately two fold) in bleeding rates between adult PWHs born before 1990 (when concentrates and thus also prophylaxis became available in CZ) and PWHs born later. Those, who were commenced on prophylaxis (at least secondary) during childhood have much better joints and much lower ABR. Please note especially the difference between ABR in younger group on permanent prophylaxis and older group without prophylaxis (1 versus 10 in median).



Frequency of bleeding	Mild*		Moderate*		Severe*		Inhibitor	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy	OD	prophy
N valid	49	0	14	4	44	54	5	0
JOINT BLEEDS								
Mean	0.4		4.2	2.5	12.3	3.2	4	
Median (range)	0 (0 – 9)		0.5 (0 – 19)	3 (0 – 4)	7.5 (0 – 59)	1.5 (0 – 35)	1 (0 – 18)	
Total no of recorded bleeds	20		59	10	540	173	20	
OTHER BLEEDS								
Mean	0.7		0.9	1.3	2.3	1.1	3	
Median (range)	0 (0 – 18)		0.5 (0 – 4)	0 (0 – 5)	1 (0 – 17)	0 (0 – 15)	1 (0 – 10)	
Total no of recorded bleeds	36		12	5	97	58	15	

Frequency of bleeding	Mild*		Moderate*		Severe*		Inhibitor	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy	OD	prophy
N valid	12	0	6	2	4	18	0	0
JOINT BLEEDS								
Mean	0.3		0.8	0.5	5.3	1.2		
Median (range)	0 (0 – 3)		0.5 (0 – 2)	0.5 (0 – 1)	3 (0 – 15)	0.5 (0 – 7)		
Total no of recorded bleeds	4		5	1	21	21		
OTHER BLEEDS								
Mean	1.4		1.5	0.0	1.3	0.9		
Median (range)	1 (0 – 8)		1 (1 – 3)	0 (0 – 0)	1 (0 – 3)	0.5 (0 – 5)		
Total no of recorded bleeds	17		9	0	4	16		

The difference mentioned in previous slide is mainly due to the different joint bleeding rate.

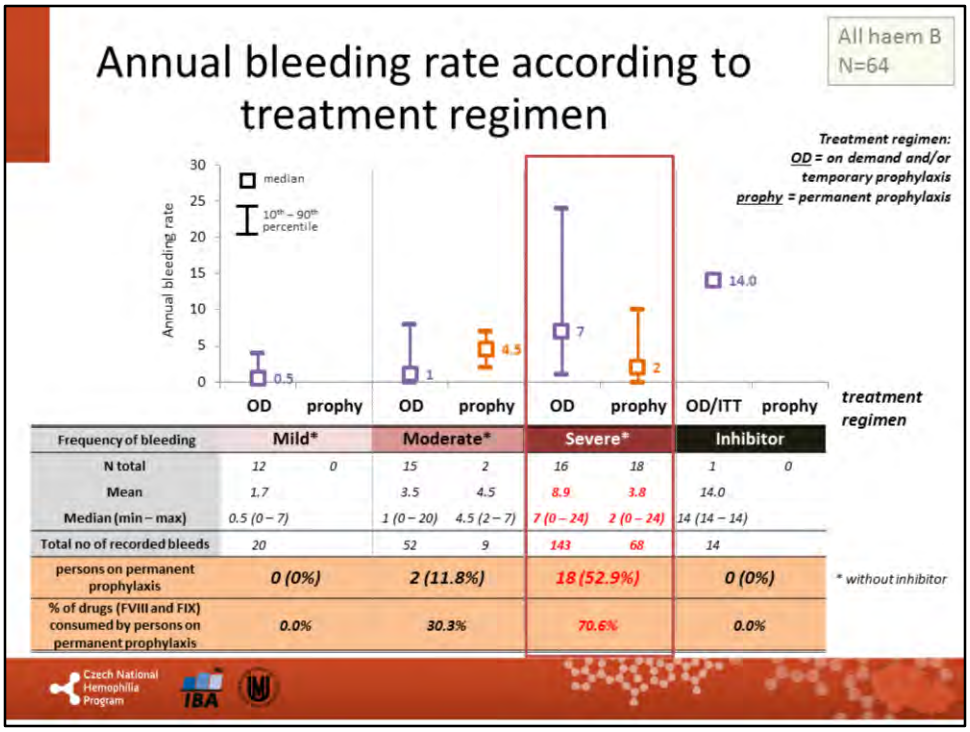
However, even in the older age group, prophylaxis can significantly decrease joint ABR in adult and elderly persons with haemophilia A (from 7,5 to 1,5, median).

Part A.7

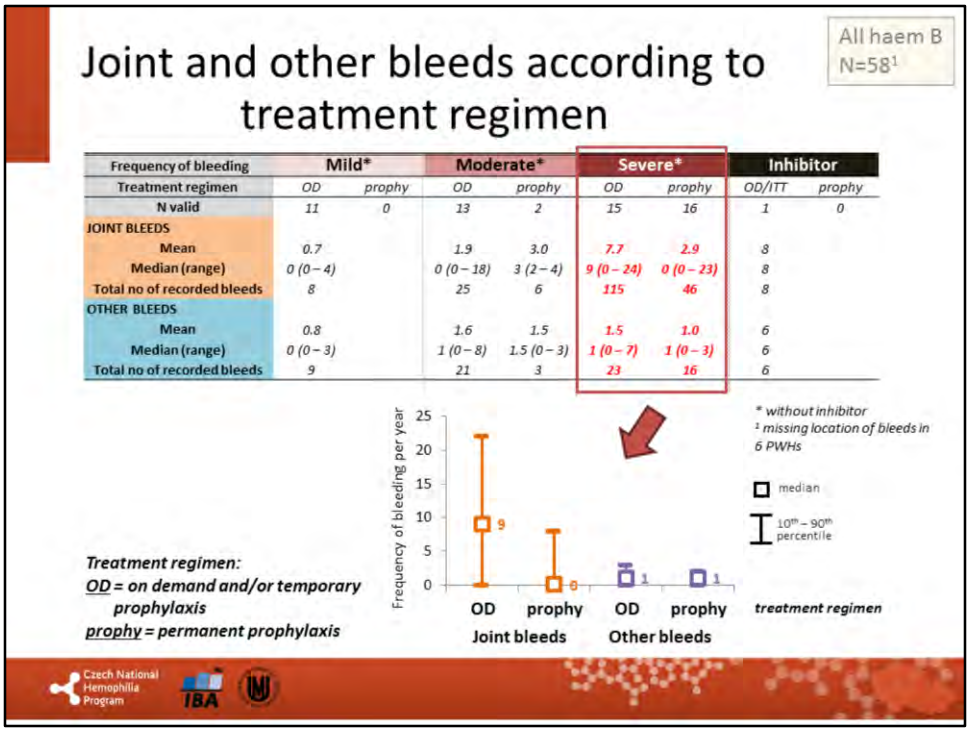
ABR in 2015 according to treatment regimen Haemophilia B only

Czech National Hemophilia Program

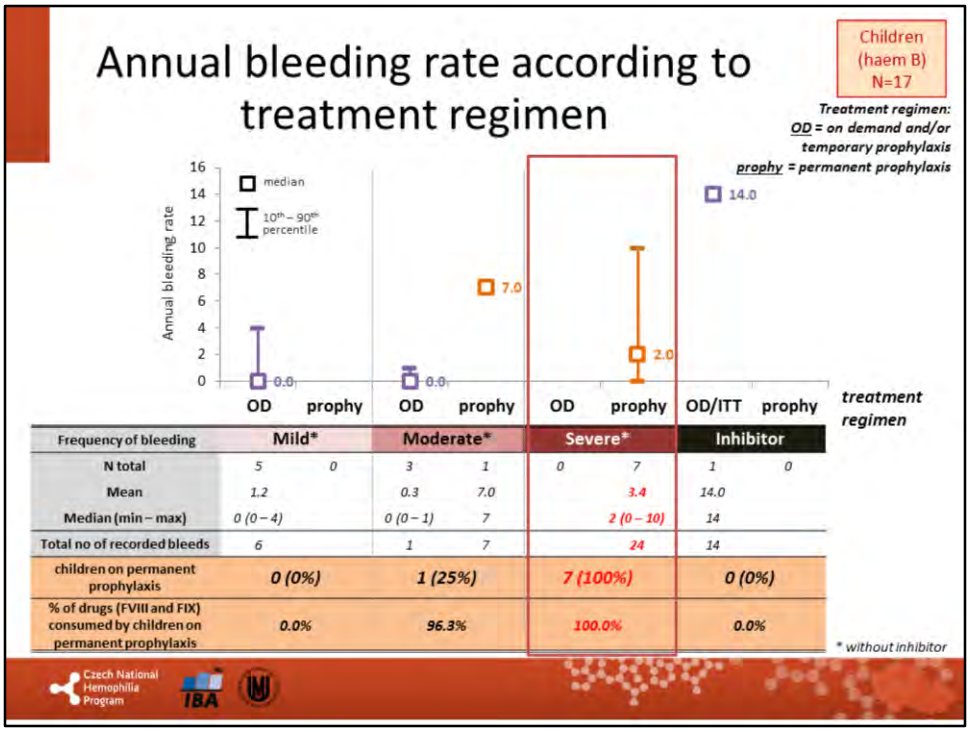
IBA



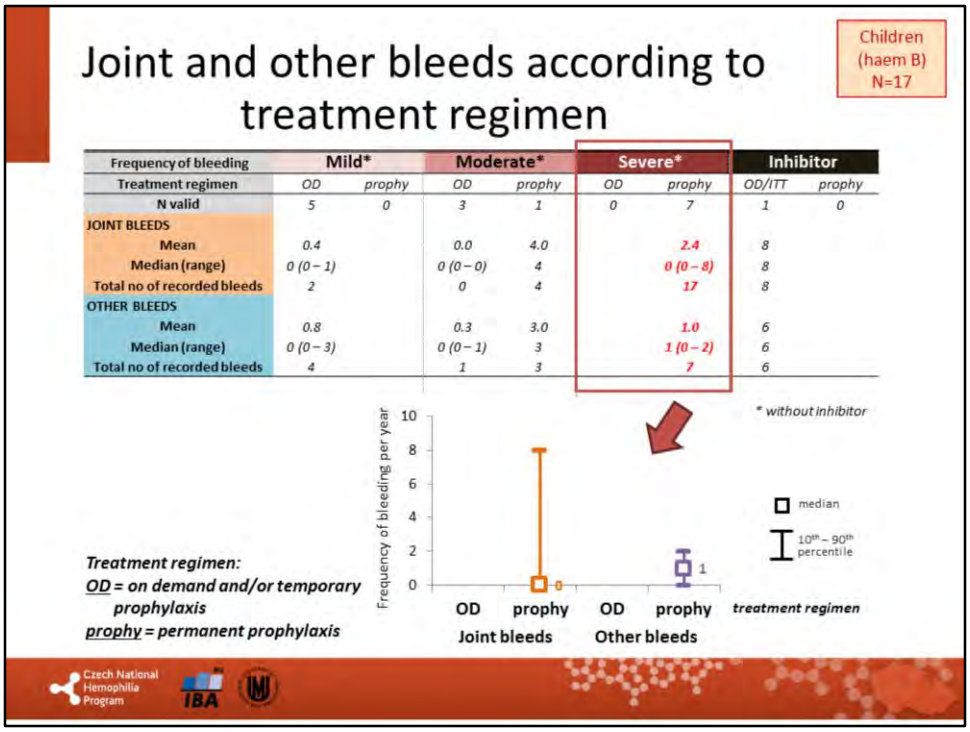
It is clearly seen, that haemophilia B has much less severe phenotype with significantly lower bleeding rates.
Though PWHs with severe haemophilia B do not bleed so often, prophylaxis can significantly decrease ABR also in these patients.
Less PWHs on permanent prophylaxis in haemophilia B population (52,9%) compared to haemophilia A (69,4%).



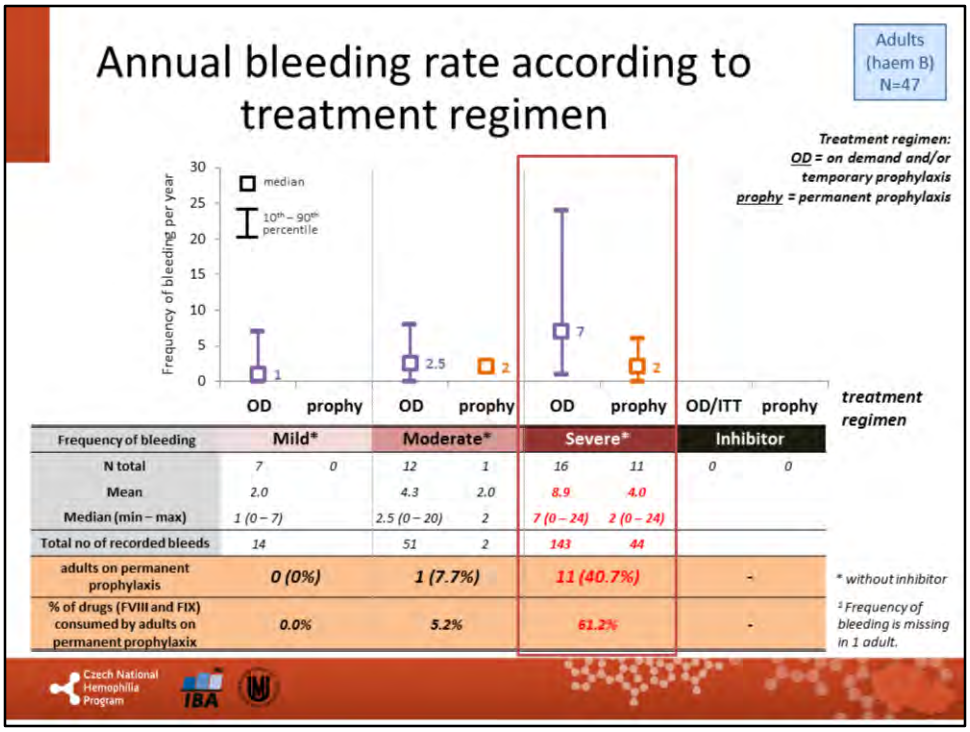
Lowering the ABR by prophylaxis is seen mostly in joint bleeds also in haemophilia B (from 9 to 0 median).



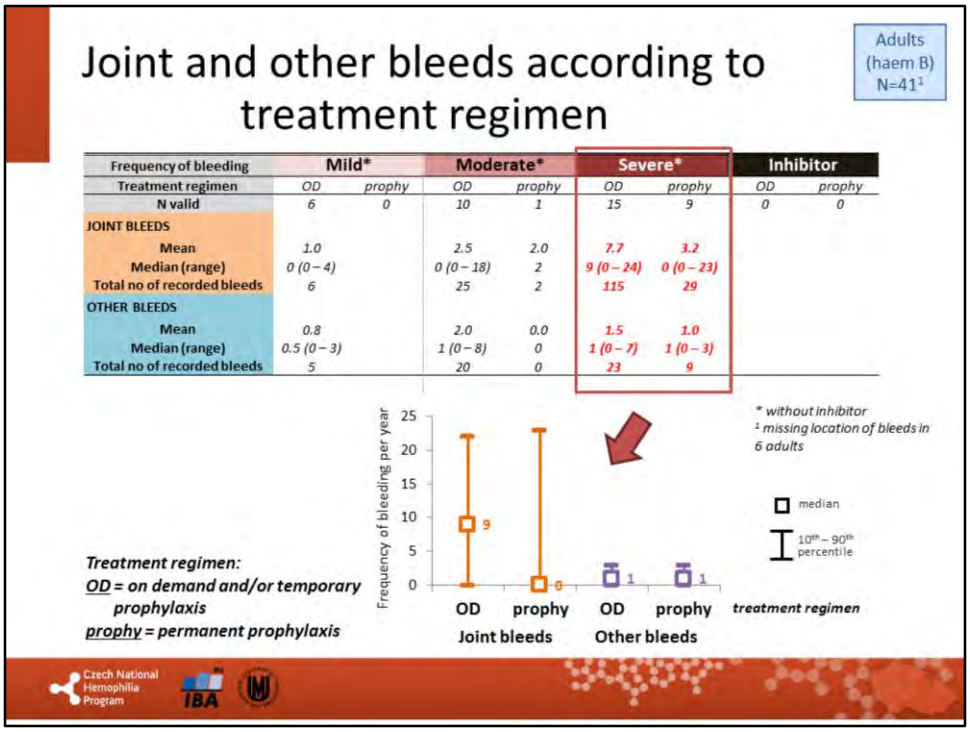
There are currently no children with severe haemophilia B without prophylaxis in CZ.



Median joint ABR in chidlren with severe haemophilia B is 0.



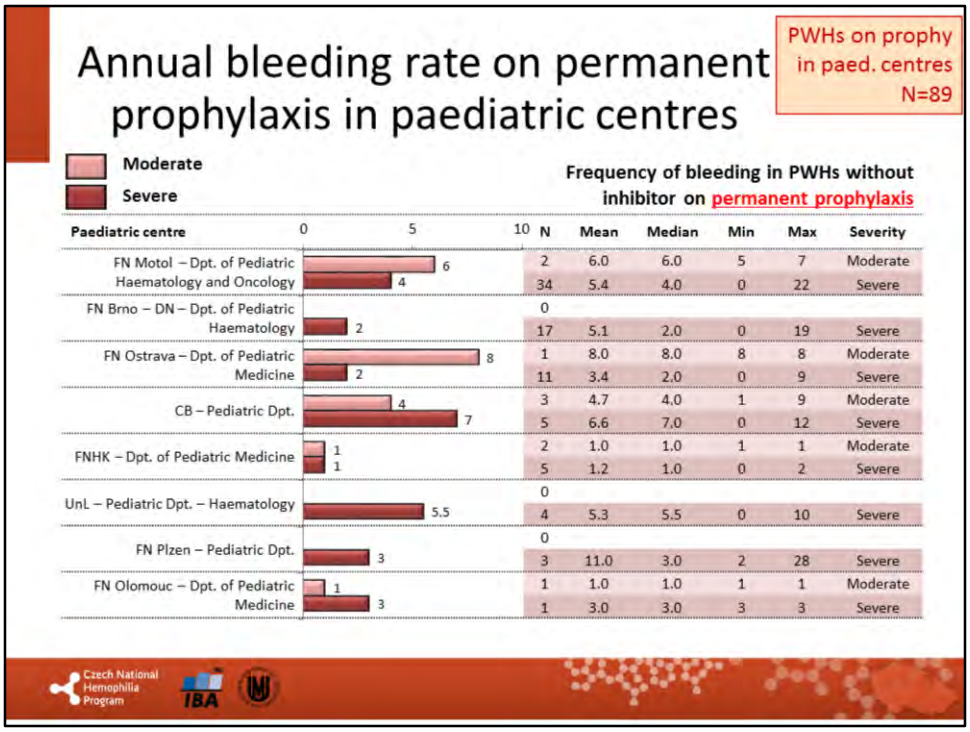
Small percentage of adults with haemophilia B (40,7%) were on permanent prophylaxis in 2015 despite the fact, than using prophylaxis can decrease ABR from 7 to 2, thus more than 3 times!
It should be our aim to offer prophylaxis (including tertiary) to all PWHs , who want it and in whom it can decrease the ABR and thus improve QoL.



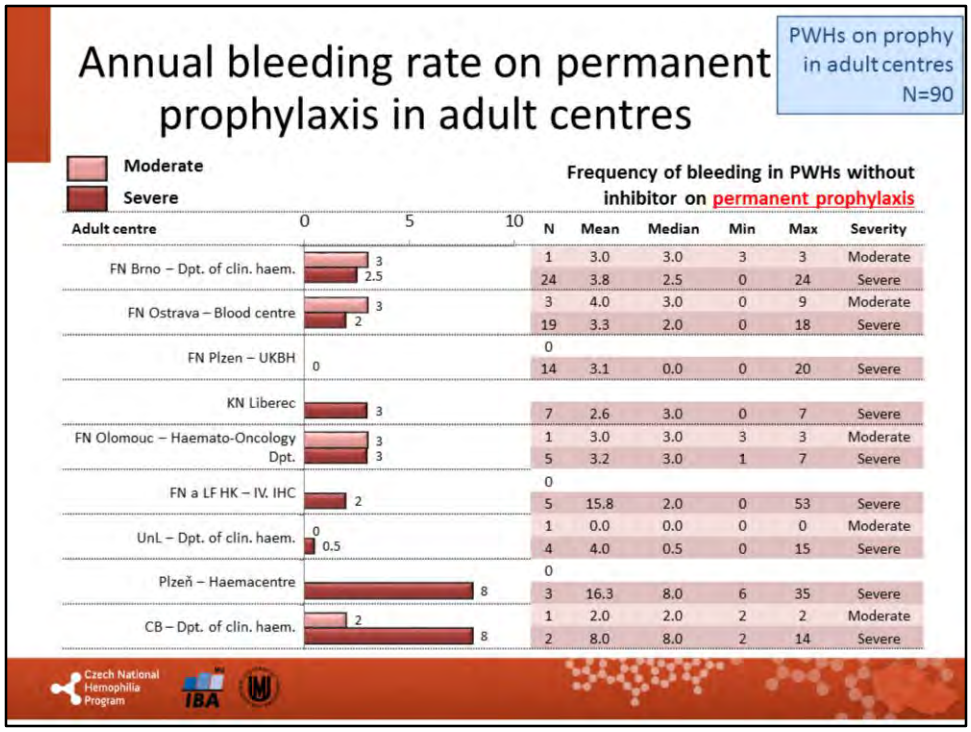
Like in haemophilia A, also in persons with haemophilia B the prophylaxis is mostly effective in reducing joint ABR (from 9 to 0 median).

Part A.8

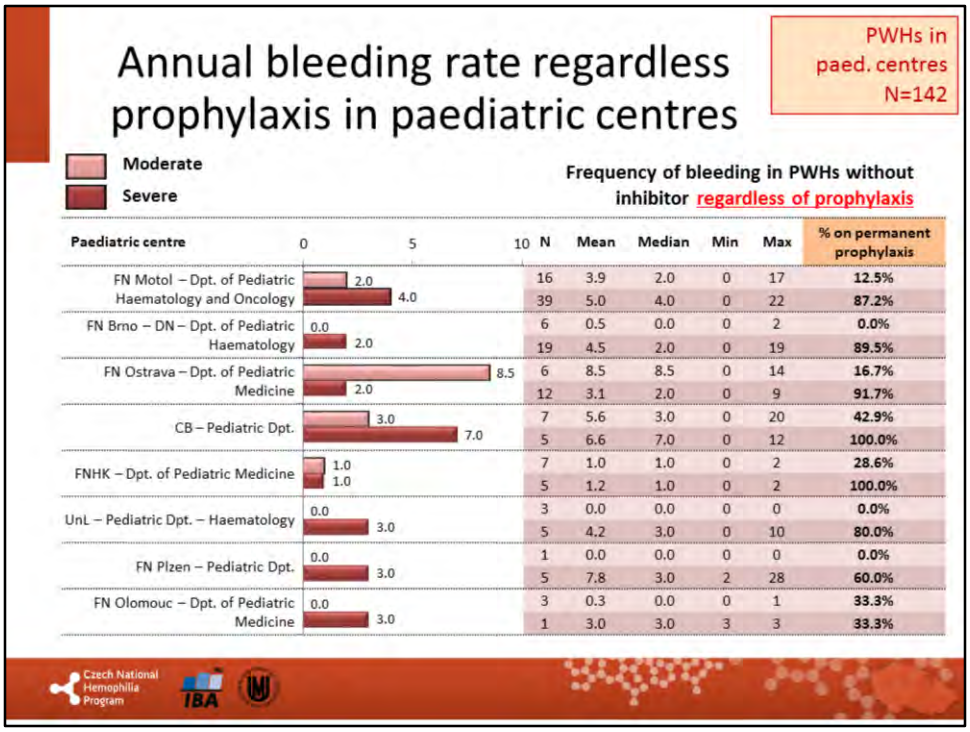
ABR in 2015 according to centres



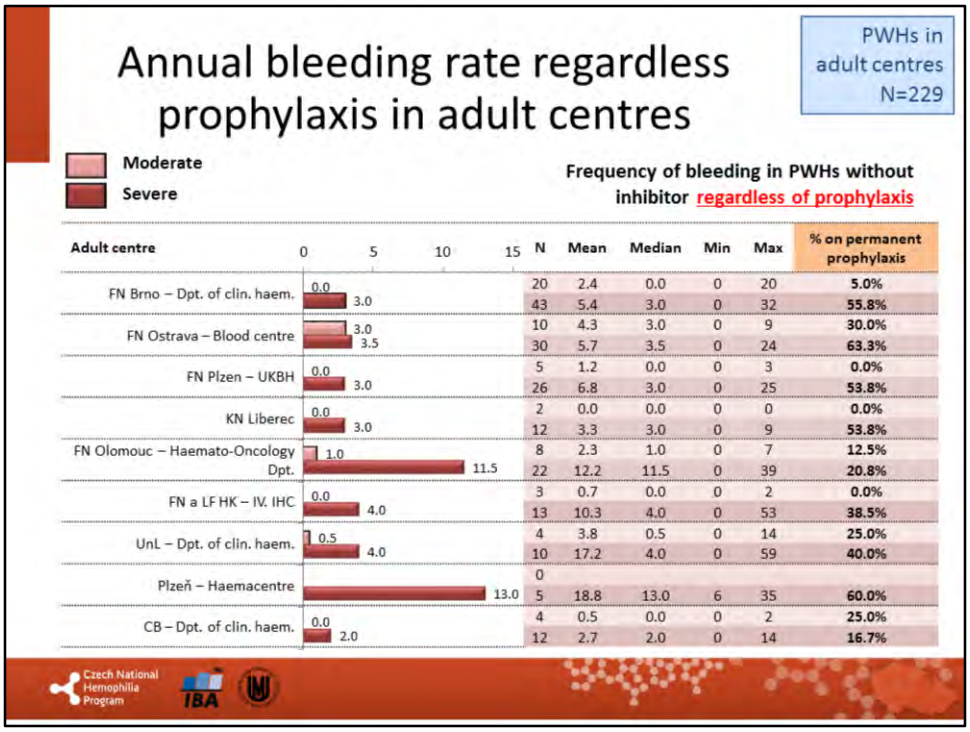
In vast majority of paediatric centres, severe haemophiliacs on prophylaxis bleed not more than 4 times per year (median). We should continue in our focus on individualized/tailored prophylaxis and shall offer it to all, who may benefit from this approach. This should also minimize the differences in ABR between centres. Though the situations improved since 2014, it is still an important challenge for all paediatric centres.



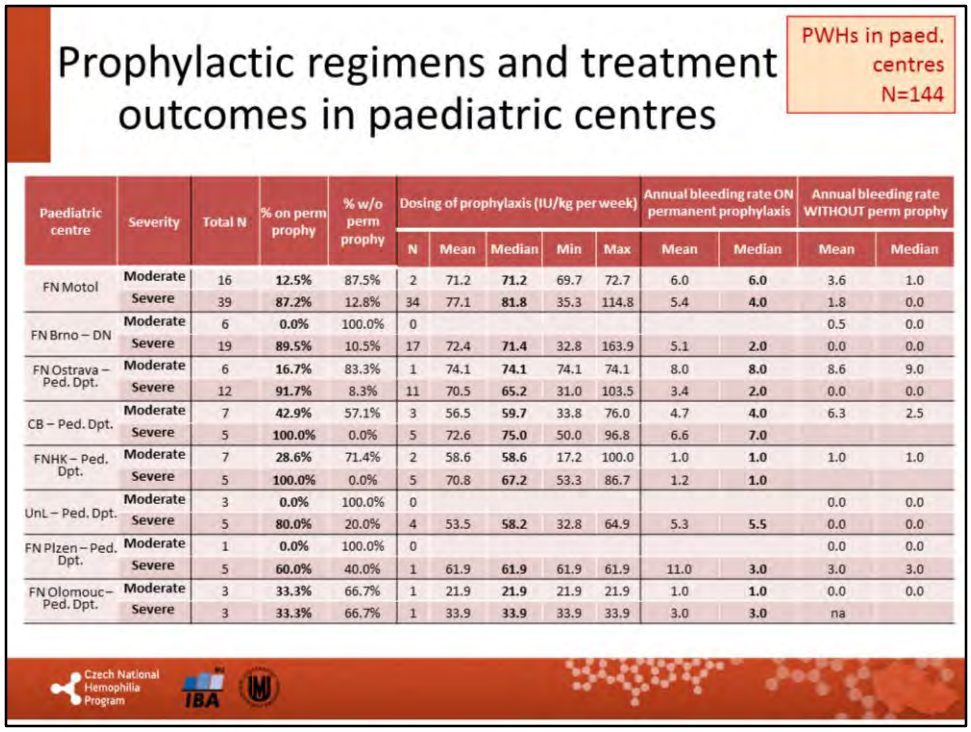
In centres using prophylaxis in adults, the ABR in severe haemophilia is often around 3. There are also adults with severe haemophilia, who have no bleed per year on permanent prophylaxis. This should encourage us to promote further prophylaxis in more adult PWHs.



Ideally, children on prophylaxis should have same (lower) bleeding pattern as/than those, who do not need prophylaxis. This is in fact the goal of prophylaxis! Those, who bleed, should be given prophylaxis to decrease the bleeding rate. Those, who have not more than one joint bleed per year without prophylaxis probably do not need it. Paediatric centres should work further on this issue to reflect the fact, that children in these days want to live very active life. The discrepancy between centres should be minimized or should even disappear to guarantee the same level of care nation-wide.



Similar information for adults. High ABR in some centres might be due to an individual with very severe phenotype and/or perhaps poor compliance. On the other hand, dealing with those patients should be a challenge for respective centres.



Paediatric centre	Severity	Total N	% on perm prophy	% w/o perm prophy	Dosing of prophylaxis (IU/kg per week)					Annual bleeding rate ON permanent prophylaxis		Annual bleeding rate WITHOUT perm prophy	
					N	Mean	Median	Min	Max	Mean	Median	Mean	Median
FN Motol	Moderate	16	12.5%	87.5%	2	71.2	71.2	69.7	72.7	6.0	6.0	3.6	1.0
	Severe	39	87.2%	12.8%	34	77.1	81.8	35.3	114.8	5.4	4.0	1.8	0.0
FN Brno – DN	Moderate	6	0.0%	100.0%	0							0.5	0.0
	Severe	19	89.5%	10.5%	17	72.4	71.4	32.8	163.9	5.1	2.0	0.0	0.0
FN Ostrava – Ped. Dpt.	Moderate	6	16.7%	83.3%	1	74.1	74.1	74.1	74.1	8.0	8.0	8.6	9.0
	Severe	12	91.7%	8.3%	11	70.5	65.2	31.0	103.5	3.4	2.0	0.0	0.0
CB – Ped. Dpt.	Moderate	7	42.9%	57.1%	3	56.5	59.7	33.8	76.0	4.7	4.0	6.3	2.5
	Severe	5	100.0%	0.0%	5	72.6	75.0	50.0	96.8	6.6	7.0		
FNHK – Ped. Dpt.	Moderate	7	28.6%	71.4%	2	58.6	58.6	17.2	100.0	1.0	1.0	1.0	1.0
	Severe	5	100.0%	0.0%	5	70.8	67.2	53.3	86.7	1.2	1.0		
UnL – Ped. Dpt.	Moderate	3	0.0%	100.0%	0							0.0	0.0
	Severe	5	80.0%	20.0%	4	53.5	58.2	32.8	64.9	5.3	5.5	0.0	0.0
FN Plzen – Ped. Dpt.	Moderate	1	0.0%	100.0%	0							0.0	0.0
	Severe	5	60.0%	40.0%	1	61.9	61.9	61.9	61.9	11.0	3.0	3.0	3.0
FN Olomouc – Ped. Dpt.	Moderate	3	33.3%	66.7%	1	21.9	21.9	21.9	21.9	1.0	1.0	0.0	0.0
	Severe	3	33.3%	66.7%	1	33.9	33.9	33.9	33.9	3.0	3.0	na	

More detailed description of prophylactic dosing/regimens used by different paediatric centres within CNHP and its correlation with annual bleeding rates in respective centres.

Prophylactic regimens and treatment outcomes in adult centres

PWHs in adult centres N=232

Adult centre	Severity	Total N	% on perm prophy	% w/o perm prophy	Dosing of prophylaxis (IU/kg per week)					Annual bleeding rate ON permanent prophylaxis		ON perm prophy	Annual bleeding rate WITHOUT perm prophy		W/O perm prophy
					N	Mean	Median	Min	Max	Mean	Median	Median age	Mean	Median	Median age
FN Brno – DCH	Moderate	20	5.0%	95.0%	1	42.9	42.9	42.9	42.9	3.0	3.0	26	2.4	0.0	44
	Severe	43	55.8%	44.2%	22	51.1	36.8	12.1	175.0	3.8	2.5	30	7.5	5.0	52
FN Ostrava – Blood centre	Moderate	10	30.0%	70.0%	3	45.9	50.0	24.4	63.2	4.0	3.0	63	4.4	3.0	62
	Severe	30	63.3%	36.7%	19	41.4	39.5	14.3	72.3	3.3	2.0	36	9.8	11.0	58
FN Plzen – UKBH	Moderate	5	0.0%	100.0%	0								1.2	0.0	39
	Severe	26	53.8%	46.2%	8	11.3	11.4	5.7	20.0	3.1	0.0	46	11.1	10.0	46
KN Liberec	Moderate	2	0.0%	100.0%	0								0.0	0.0	38
	Severe	13	53.8%	46.2%	7	41.2	40.3	21.4	62.7	2.6	3.0	37	4.2	3.0	47
FN Olomouc – HOC	Moderate	8	12.5%	87.5%	1	34.9	34.9	34.9	34.9	3.0	3.0	25	2.1	1.0	42
	Severe	24	20.8%	79.2%	5	34.4	42.9	14.1	52.0	3.2	3.0	25	14.8	13.0	51
FN a LF HK – IV. IHC	Moderate	3	0.0%	100.0%	0								0.7	0.0	20
	Severe	13	38.5%	61.5%	4	40.8	44.4	21.7	52.6	15.8	2.0	35	6.9	4.0	39
UnL – DCH	Moderate	4	25.0%	75.0%	1	75.0	75.0	75.0	75.0	0.0	0.0	23	5.0	1.0	23
	Severe	10	40.0%	60.0%	3	56.3	51.4	32.3	85.2	4.0	0.5	28	26.0	22.0	40
Plzeň - Haemacentre	Moderate	1	0.0%	100.0%	0								na		46
	Severe	5	60.0%	40.0%	1	25.0	25.0	25.0	25.0	16.3	8.0	42	22.5	22.5	34
CB – DCH	Moderate	4	25.0%	75.0%	0	na				2.0	2.0	49	0.0	0.0	62
	Severe	12	16.7%	83.3%	0	na				8.0	8.0	49	1.6	1.0	49

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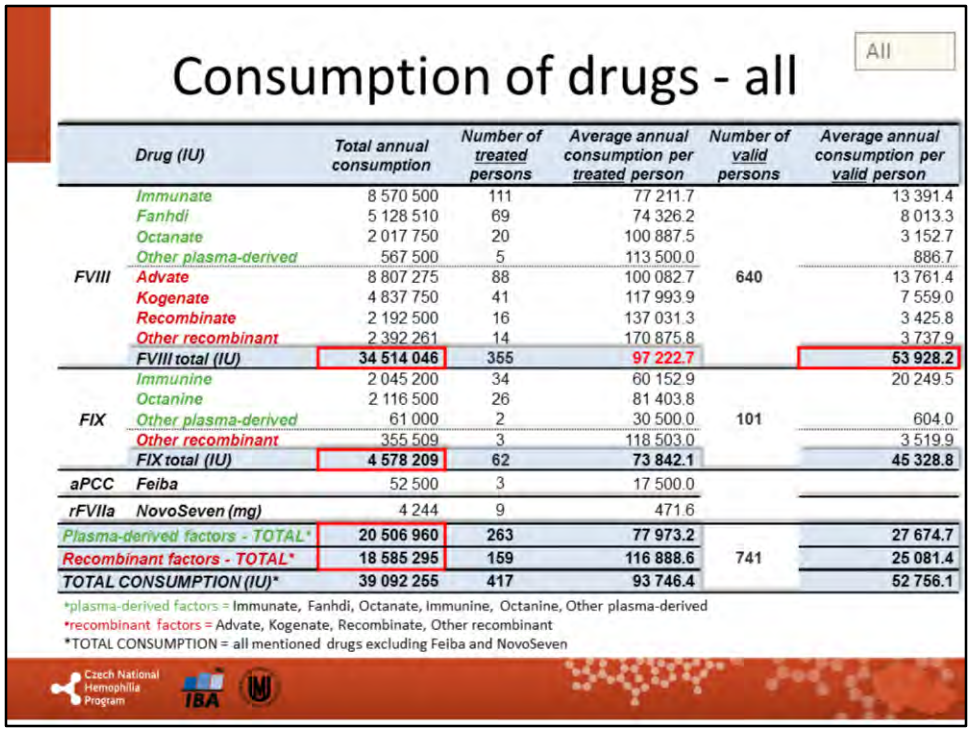
More detailed description of prophylactic dosing/regimens used by different adult centres within CNHP and its correlation with annual bleeding rates in respective centres.

Please note, that dosing used in adults (IU/kg/week) are often around ONE HALF of the dosing in paediatric haemophilia population! This fact deserves attention of treaters in adult centres as well as of regulators and health care payers.

Part A.9

Consumption of factor concentrates in 2015



Consumption of drugs - all

All

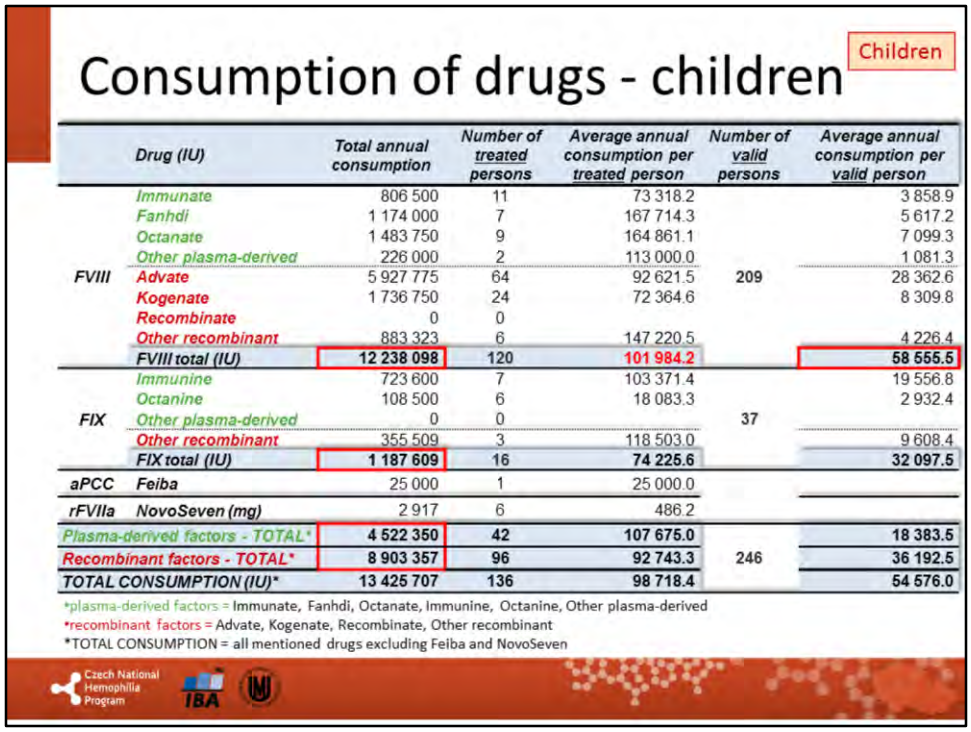
	Drug (IU)	Total annual consumption	Number of treated persons	Average annual consumption per treated person	Number of valid persons	Average annual consumption per valid person
	Immunate	8 570 500	111	77 211.7		13 391.4
	Fanhdi	5 128 510	69	74 326.2		8 013.3
	Octanate	2 017 750	20	100 887.5		3 152.7
	Other plasma-derived	567 500	5	113 500.0		886.7
FVIII	Advate	8 807 275	88	100 082.7	640	13 761.4
	Kogenate	4 837 750	41	117 993.9		7 559.0
	Recombinate	2 192 500	16	137 031.3		3 425.8
	Other recombinant	2 392 261	14	170 875.8		3 737.9
	FVIII total (IU)	34 514 046	355	97 222.7		53 928.2
	Immunine	2 045 200	34	60 152.9		20 249.5
	Octanine	2 116 500	26	81 403.8		
FIX	Other plasma-derived	61 000	2	30 500.0	101	604.0
	Other recombinant	355 509	3	118 503.0		3 519.9
	FIX total (IU)	4 578 209	62	73 842.1		45 328.8
aPCC	Feiba	52 500	3	17 500.0		
rFVIIa	NovoSeven (mg)	4 244	9	471.6		
Plasma-derived factors - TOTAL*		20 506 960	263	77 973.2		27 674.7
Recombinant factors - TOTAL*		18 585 295	159	116 888.6	741	25 081.4
TOTAL CONSUMPTION (IU)*		39 092 255	417	93 746.4		52 756.1

*plasma-derived factors = Immunate, Fanhdi, Octanate, Immunine, Octanine, Other plasma-derived
*recombinant factors = Advate, Kogenate, Recombinate, Other recombinant
*TOTAL CONSUMPTION = all mentioned drugs excluding Feiba and NovoSeven

Czech National Hemophilia Program IBA

Absolute numbers of respective concentrates in this figure refer ONLY to the records within CNHP registry, which have been updated in 2015. The most important information on this slide is „Average annual consumption per treated person“. This reflects nation-wide consumption of factor concentrate per treated PWH.

„Average annual consumption per valid person“ gives us an information on the consumption per patient, regardless of his treatment status. It also enables us to estimate the national-wide consumption of FVIII. As we do know, that there were 931 haemophilia A patients in 2015 (WFH survey 2015) the total consumption was approximately 50 207 154 IU of FVIII/year in the Czech Republic. (SUKL reported around 51 million units of FVIII purchased in CZ during 2015). In other words, it means, that the total consumption was about 4.76 IU/capita of FVIII in 2015.
Number of haemophiliacs B in the Czech Republic was 136 in 2015, the total consumption was approx. 6 164 717 IU of FIX/year, i.e. 0.58 IU/capita.



Consumption of drugs - children

Children

	Drug (IU)	Total annual consumption	Number of treated persons	Average annual consumption per treated person	Number of valid persons	Average annual consumption per valid person
FVIII	Immunate	806 500	11	73 318.2	209	3 858.9
	Fanhdi	1 174 000	7	167 714.3		5 617.2
	Octanate	1 483 750	9	164 861.1		7 099.3
	Other plasma-derived	226 000	2	113 000.0		1 081.3
	Advate	5 927 775	64	92 621.5		28 362.6
	Kogenate	1 736 750	24	72 364.6		8 309.8
	Recombinate	0	0			
	Other recombinant	883 323	6	147 220.5		4 226.4
	FVIII total (IU)	**12 238 098**	**120**	**101 984.2**		**58 555.5**
FIX	Immunine	723 600	7	103 371.4	37	19 556.8
	Octanine	108 500	6	18 083.3		2 932.4
	Other plasma-derived	0	0			
	Other recombinant	355 509	3	118 503.0		9 608.4
	FIX total (IU)	**1 187 609**	**16**	**74 225.6**		**32 097.5**
aPCC	Feiba	25 000	1	25 000.0		
rFVIIa	NovoSeven (mg)	2 917	6	486.2		
Plasma-derived factors - TOTAL*		**4 522 350**	**42**	**107 675.0**		**18 383.5**
Recombinant factors - TOTAL*		**8 903 357**	**96**	**92 743.3**	246	**36 192.5**
TOTAL CONSUMPTION (IU)*		**13 425 707**	**136**	**98 718.4**		**54 576.0**

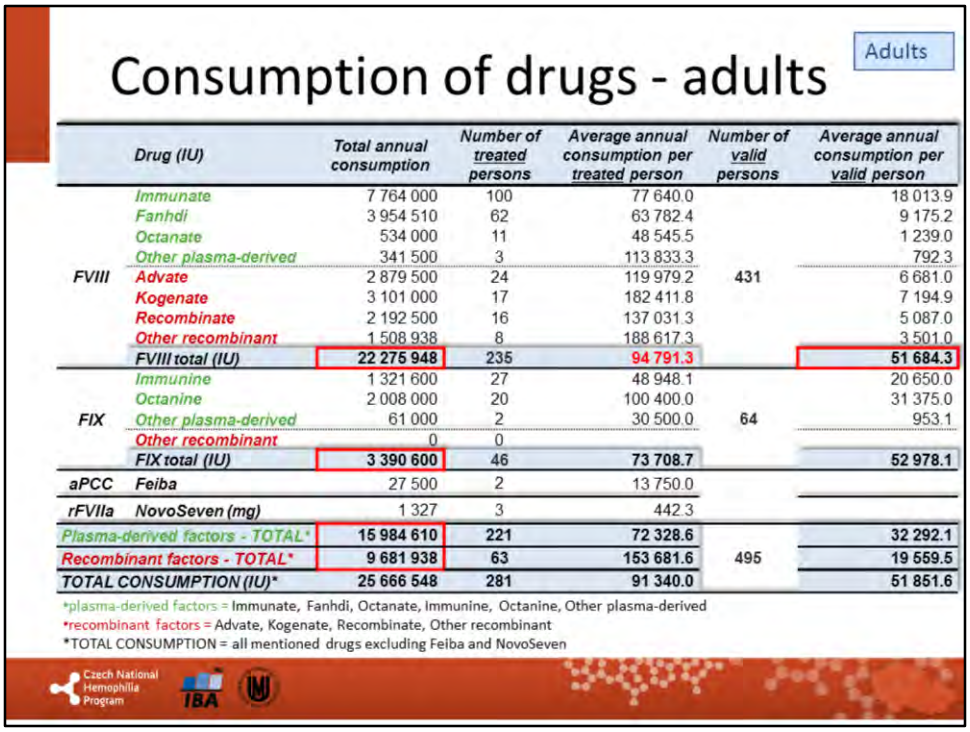
*plasma-derived factors = Immunate, Fanhdi, Octanate, Immunine, Octanine, Other plasma-derived
*recombinant factors = Advate, Kogenate, Recombinate, Other recombinant
*TOTAL CONSUMPTION = all mentioned drugs excluding Feiba and NovoSeven

Czech National Hemophilia Program IBA

Absolute numbers of respective concentrates in this figure refer ONLY to the records within CNHP registry, which have been updated in 2015. The most important information on this slide is „Average annual consumption per treated child“. This reflects nation-wide consumption of factor concentrate per treated child.

„Average annual consumption per valid child“ gives us an information of the consumption per child, regardless of his treatment status. It also enables us to estimate the national-wide consumption of FVIII in paediatrics. As we do know, that there were 209 boys (age 0-18 years) with haemophilia A in 2015 CNHP and WFH survey 2015, the total consumption will be approximately 12 238 099 IU of FVIII/year for children with haemophilia A in the Czech Republic. This represents around 24% of total national consumption, when children represent around 22 % of haemophilia population.

This information also suggests, that - in absolute numbers – on treatment in children we spend 10% more factor per patient, than on treatment in adults, though the difference in mean body weight between children and adults is three fold.



Consumption of drugs - adults

Adults

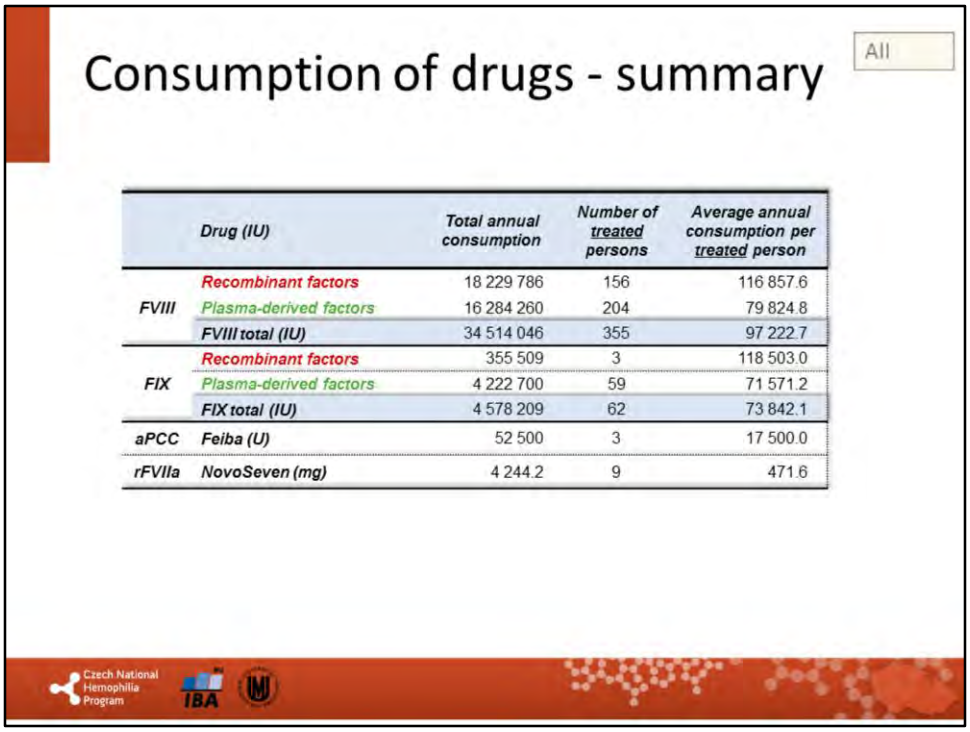
	Drug (IU)	Total annual consumption	Number of treated persons	Average annual consumption per treated person	Number of valid persons	Average annual consumption per valid person
	Immunate	7 764 000	100	77 640.0		18 013.9
	Fanhdi	3 954 510	62	63 782.4		9 175.2
	Octanate	534 000	11	48 545.5		1 239.0
	Other plasma-derived	341 500	3	113 833.3		792.3
FVIII	Advate	2 879 500	24	119 979.2	431	6 681.0
	Kogenate	3 101 000	17	182 411.8		7 194.9
	Recombinate	2 192 500	16	137 031.3		5 087.0
	Other recombinant	1 508 938	8	188 617.3		3 501.0
	FVIII total (IU)	22 275 948	235	94 791.3		51 684.3
	Immunine	1 321 600	27	48 948.1		20 650.0
	Octanine	2 008 000	20	100 400.0		31 375.0
FIX	Other plasma-derived	61 000	2	30 500.0	64	953.1
	Other recombinant	0	0			
	FIX total (IU)	3 390 600	46	73 708.7		52 978.1
aPCC	Feiba	27 500	2	13 750.0		
rFVIIa	NovoSeven (mg)	1 327	3	442.3		
Plasma-derived factors - TOTAL*		15 984 610	221	72 328.6		32 292.1
Recombinant factors - TOTAL*		9 681 938	63	153 681.6	495	19 559.5
TOTAL CONSUMPTION (IU)*		25 666 548	281	91 340.0		51 851.6

*plasma-derived factors = Immunate, Fanhdi, Octanate, Immunine, Octanine, Other plasma-derived
*recombinant factors = Advate, Kogenate, Recombinate, Other recombinant
*TOTAL CONSUMPTION = all mentioned drugs excluding Feiba and NovoSeven

Czech National Hemophilia Program IBA

Absolute numbers of respective concentrates in this figure refer ONLY to the records within CNHP registry, which have been updated in 2015. The most important information on this slide is „Average annual consumption per treated person“. This reflects nation-wide consumption of factor concentrate per treated adult.

„Average annual consumption per valid person“ gives us an information of the consumption per adult patient, regardless of his treatment status. It also enables us to estimate the national-wide consumption of FVIII in adults. As we do know, that there were 722 adult haemophiliacs A (over 18 years of age) in 2015 (WFH survey 2015) the total consumption will be approximately 37 316 064 IU of FVIII/year for adults with haemophilia A in the Czech Republic.



Higher consumption of recombinant FVIII compared to pdFVIII is due to the fact, that most rFVIII treated PWHs are children, having higher FVIII dosage (see previous slide).

All

Consumption of drugs

severe haemophilia (regardless of inhibitors)

	Total annual consumption	No of pts (sev haem)	Average consumption per patient	Average weight	Average annual consumption per kg/
FVIII total	29 688 296 IU	248	119 710.9 IU/pt	64.3 kg	1 863.0 IU/kg
FIX total	3 484 609 IU	38	91 700.2 IU/pt	70.4 kg	1 302.7 IU/kg

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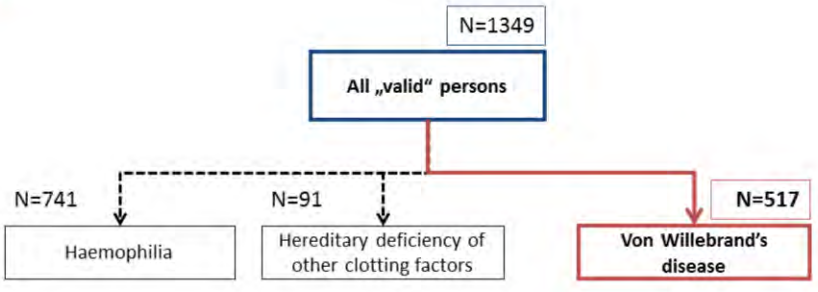
IBA

Part B

Persons with Von Willebrand disease

Sample size



Cca 1000 symptomatic vWDs should be in CZ
517 of them are in CNHP registry so far

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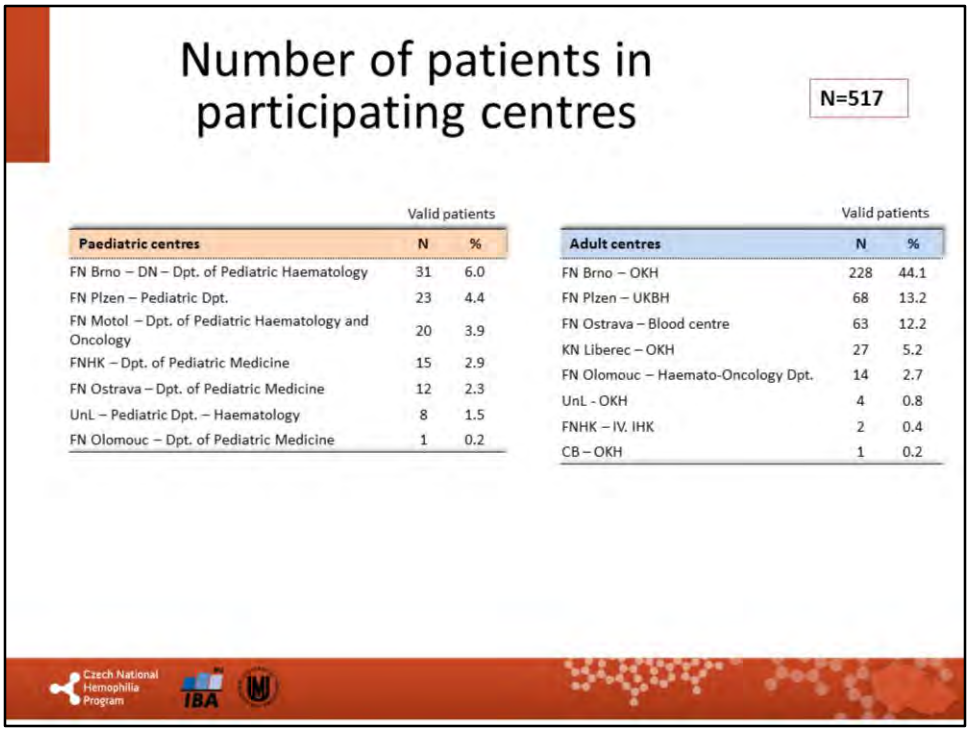
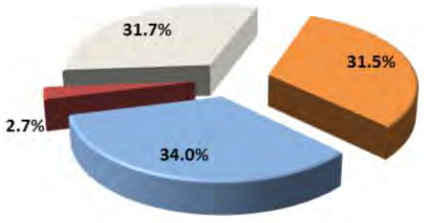


Centres participated in vWD survey within CNHP registry.

Type of Von Willebrand's disease

N=517



	Patients	
Type of disease	**N**	**%**
Type 1	163	31.5
Type 2	176	34.0
Type 2A	*74*	*14.3*
Type 2B	*11*	*2.1*
Type 2M	*26*	*5.0*
Type 2N	*11*	*2.1*
Type 2 (not specified)	*54*	*10.4*
Type 3	14	2.7
Type not determined / unfilled	164	31.7
Total	517	100.0

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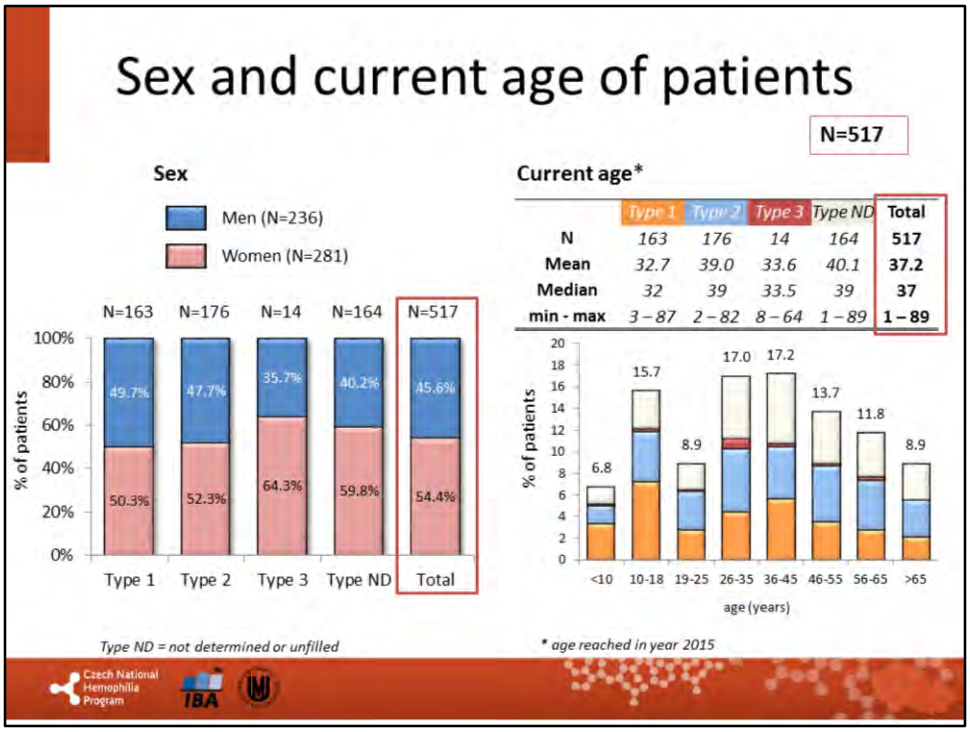
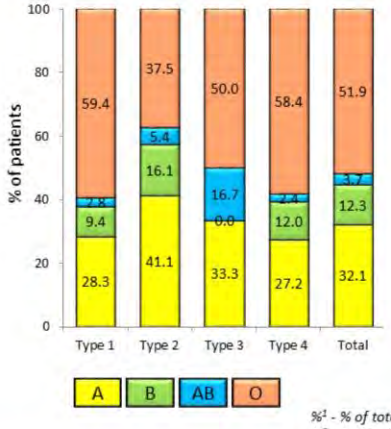
IBA



Median age of Czech vWDs is below 40 years.

Blood group

N=517



%¹ - % of total N
%² - % of valid N

Blood group		A	B	AB	O	ND	Valid N	Total N
Type 1	*N*	30	10	3	63	57	106	163
	%¹	18.4	6.1	1.8	38.7	35.0		100.0
	%²	28.3	9.4	2.8	59.4		100.0	
Type 2	*N*	46	18	6	42	64	112	176
	%¹	26.1	10.2	3.4	23.9	36.4		100.0
	%²	41.1	16.1	5.4	37.5		100.0	
Type 3	*N*	2	0	1	3	8	6	14
	%¹	14.3	0.0	7.1	21.4	57.1		100.0
	%²	33.3	0.0	16.7	50.0		100.0	
Type ND	*N*	34	15	3	73	39	125	164
	%¹	20.7	9.1	1.8	44.5	23.8		100.0
	%²	27.2	12.0	2.4	58.4		100.0	
Total	*N*	112	43	13	181	168	349	517
	%¹	21.7	8.3	2.5	35.0	32.5		100.0
	%²	32.1	12.3	3.7	51.9		100.0	

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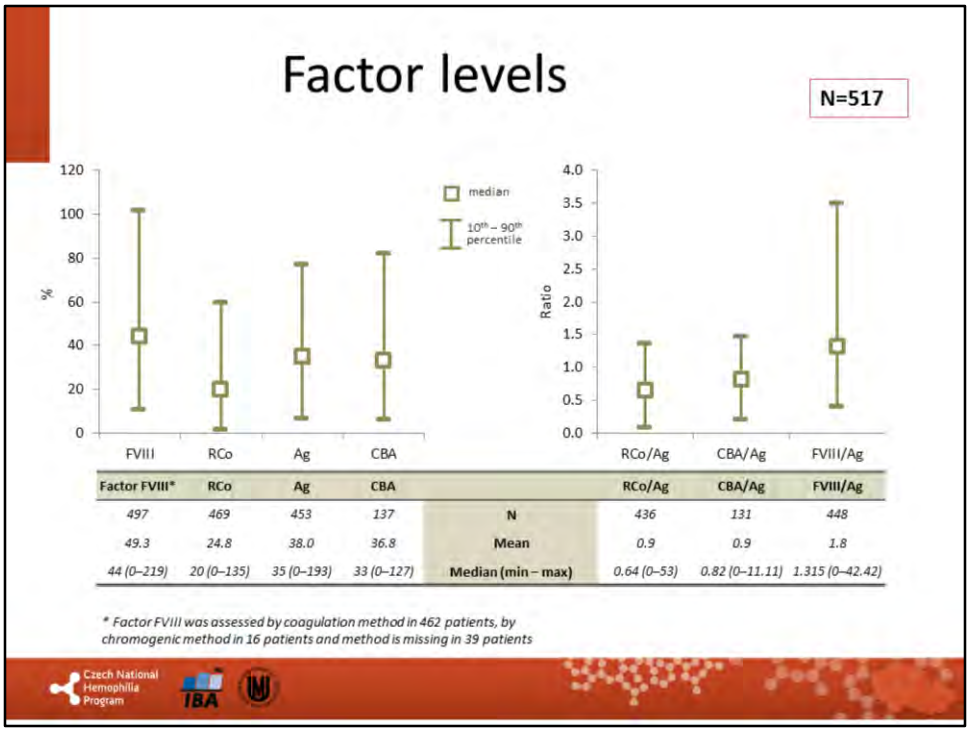
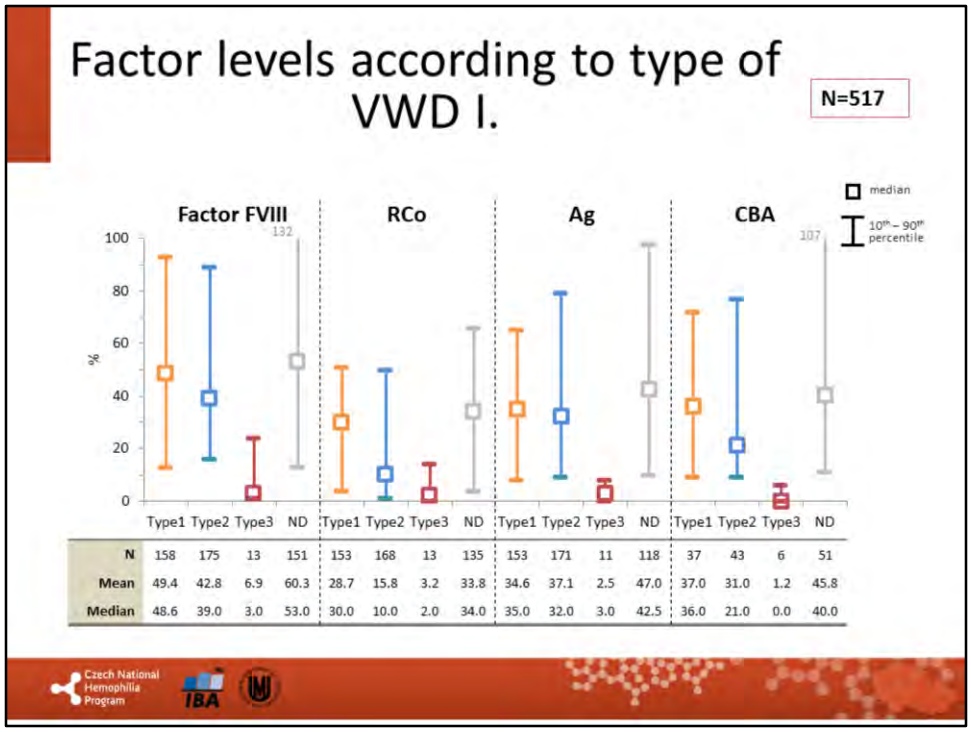
Well known predominance of BG 0 is confirmed within the registry.



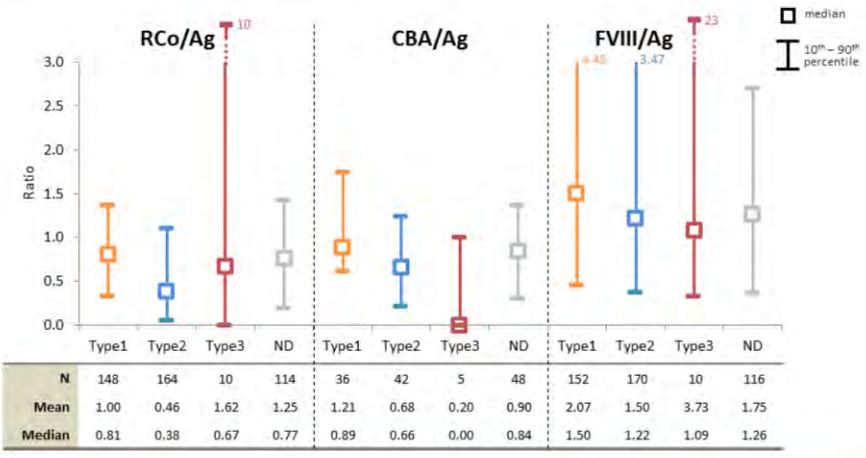
This slide is giving just general overview as it is not linked to different vWD subtypes.



This and further slides show factor levels in accord with respective vWD subtypes and correlate well with published data.

Factor levels according to type of VWD II.

N=517



	Type1	Type2	Type3	ND	Type1	Type2	Type3	ND	Type1	Type2	Type3	ND
N	148	164	10	114	36	42	5	48	152	170	10	116
Mean	1.00	0.46	1.62	1.25	1.21	0.68	0.20	0.90	2.07	1.50	3.73	1.75
Median	0.81	0.38	0.67	0.77	0.89	0.66	0.00	0.84	1.50	1.22	1.09	1.26

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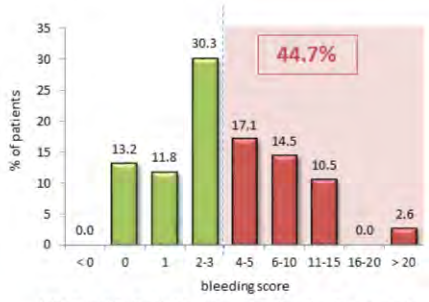
IBA

Bleeding score[1] according to sex

N=171[2]

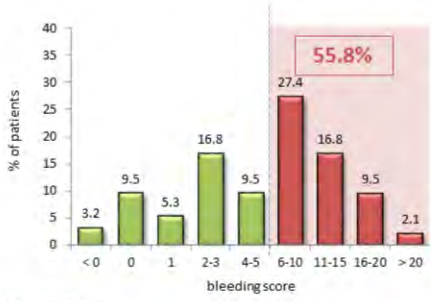
Men

N	*76*
Mean	*4.4*
Median (min - max)	*3 (0 – 25)*



Women

N	*95*
Mean	*7.1*
Median (min - max)	*6 (-3 – 23)*



[1] *Adult and Pediatric Vincenza VWD Bleeding Questionnaire and Scoring System*
[2] *Missing information on bleeding score in 346 patients.*

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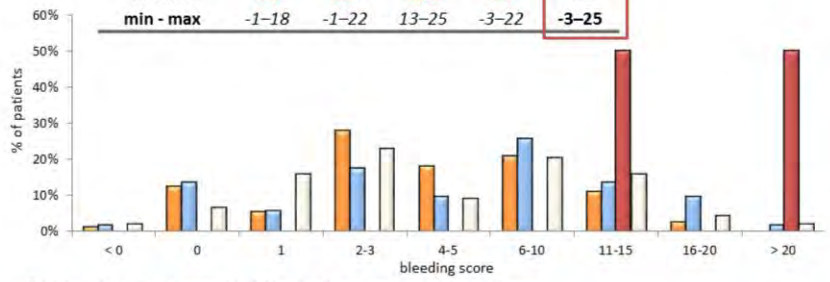
Bleeding score[1] according to type of disease

N=171[2]

Bleeding score

	Type 1	Type 2	Type 3	Type ND	Total
N total	163	176	14	164	517
N valid	72	51	4	44	171
Mean	4.8	6.7	18.8	5.7	5.9
Median	4.0	6.0	18.5	4.0	4.0
min - max	-1–18	-1–22	13–25	-3–22	-3–25



[1] Adult and Pediatric Vincenza VWD Bleeding Questionnaire and Scoring System
[2] Missing information on bleeding score in 346 patients.

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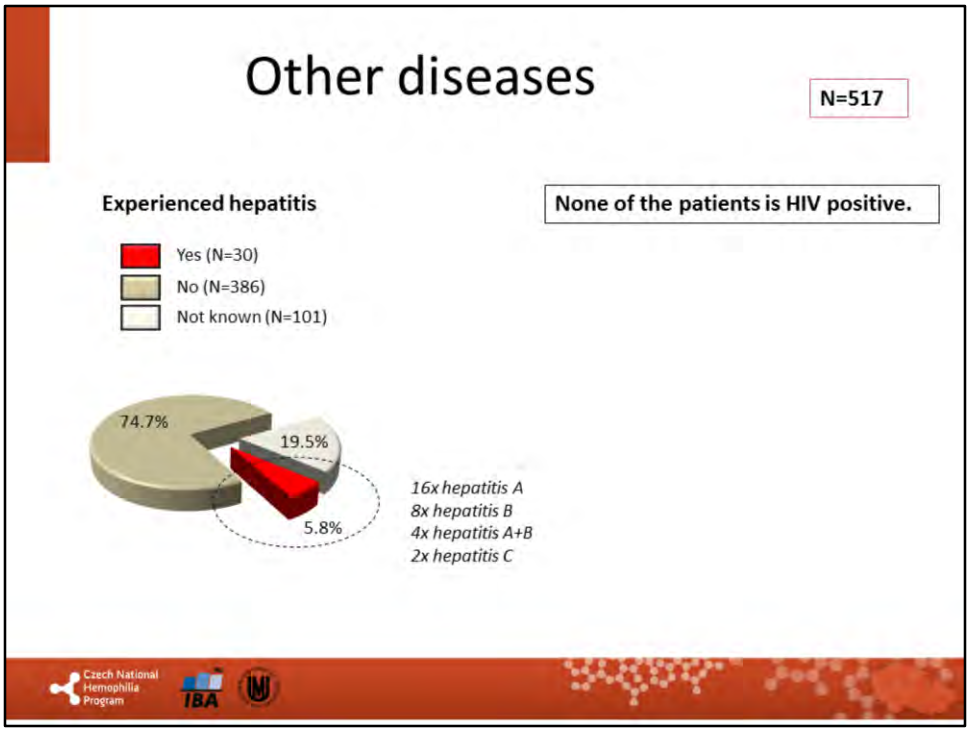
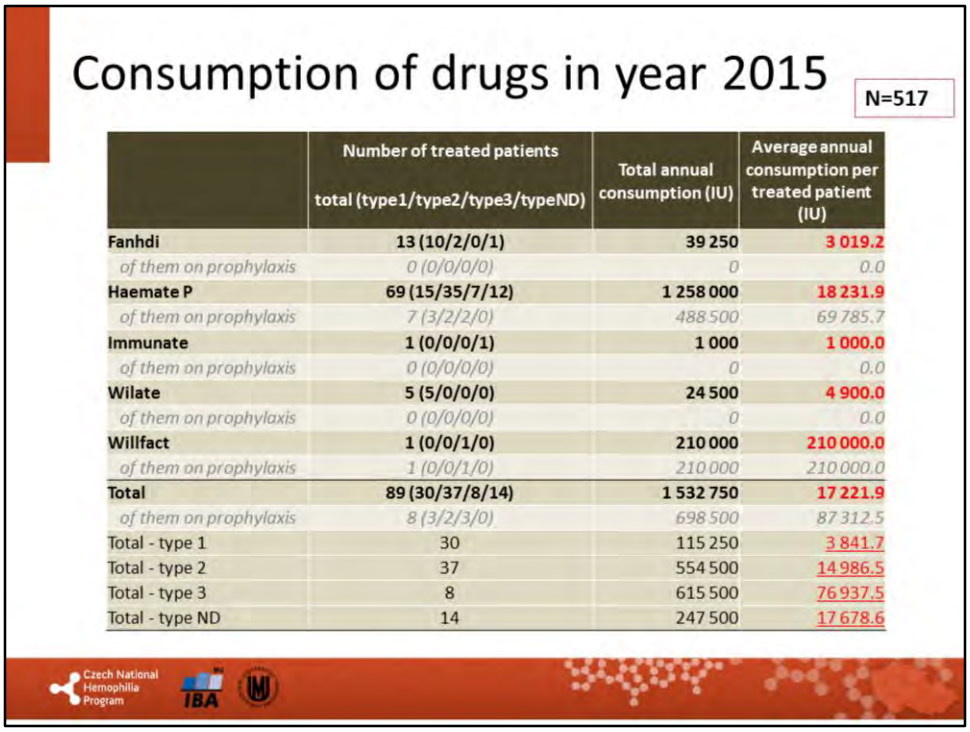
IBA

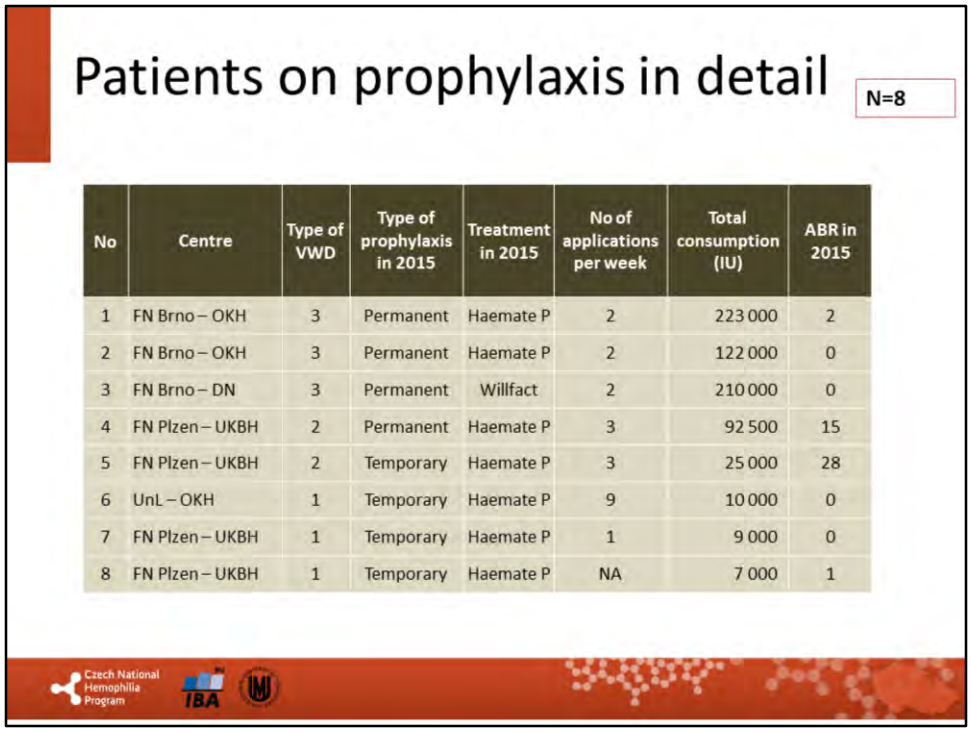
Type 3 has obviously the most heavy bleeding score.



Hepatitis and/or HIV prevalence in vWD patients within CNHP registry



Absolute numbers of respective concentrates consumption in this figure refer ONLY to the records within CNHP registry, which have been updated in 2015. The most important information on this slide is „Average annual consumption per treated person“. This aims to reflect nation-wide consumption of factor concentrate per treated patient. Shows well the highest consumption in type 3 vWD. Please note, that the numbers of treated patients are relatively small and do vary significantly between different concentrates. This is a source of potential bias. To increase the data validity, we have to increase the number of treated patients recorded within CNHP registry.
On the other hand, for vWD treated patients (excluding type 3 patients) the annual consumption per treated patient should reflect the real situation (between 14 000 – 17 000 IU/year) relatively well.



No	Centre	Type of VWD	Type of prophylaxis in 2015	Treatment in 2015	No of applications per week	Total consumption (IU)	ABR in 2015
1	FN Brno – OKH	3	Permanent	Haemate P	2	223 000	2
2	FN Brno – OKH	3	Permanent	Haemate P	2	122 000	0
3	FN Brno – DN	3	Permanent	Willfact	2	210 000	0
4	FN Plzen – UKBH	2	Permanent	Haemate P	3	92 500	15
5	FN Plzen – UKBH	2	Temporary	Haemate P	3	25 000	28
6	UnL – OKH	1	Temporary	Haemate P	9	10 000	0
7	FN Plzen – UKBH	1	Temporary	Haemate P	1	9 000	0
8	FN Plzen – UKBH	1	Temporary	Haemate P	NA	7 000	1

This slide shows consumption of factor concentrate in vWD patients on prophylaxis (permanent or temporary). Total annual consumption of 100 000 - 200 000 IU is related to those on long term prophylaxis (mostly type 3 vWD patients). Number of persons with vWD on prophylaxis is low in CZ.