The status of care for persons with haemophilia registered within CNHP registry
Annual Report 2016

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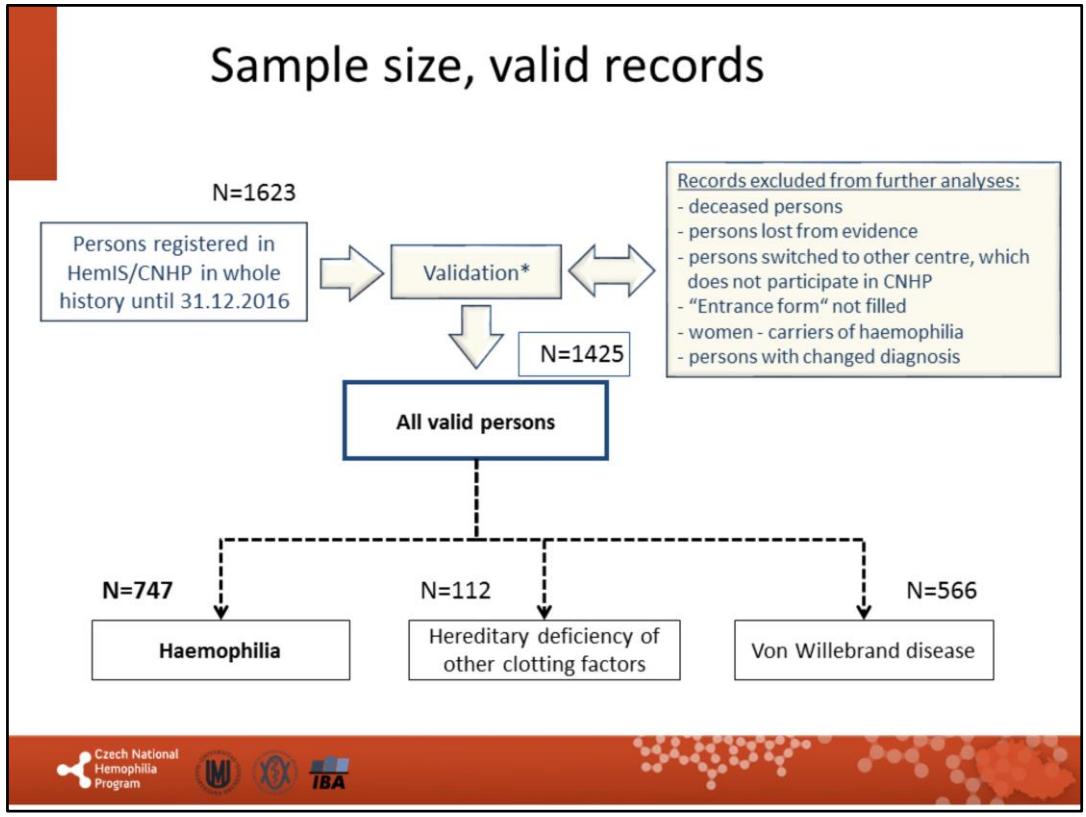
on behalf of
Centres contributing to CNHP registry
(Czech National Haemophilia Programme)

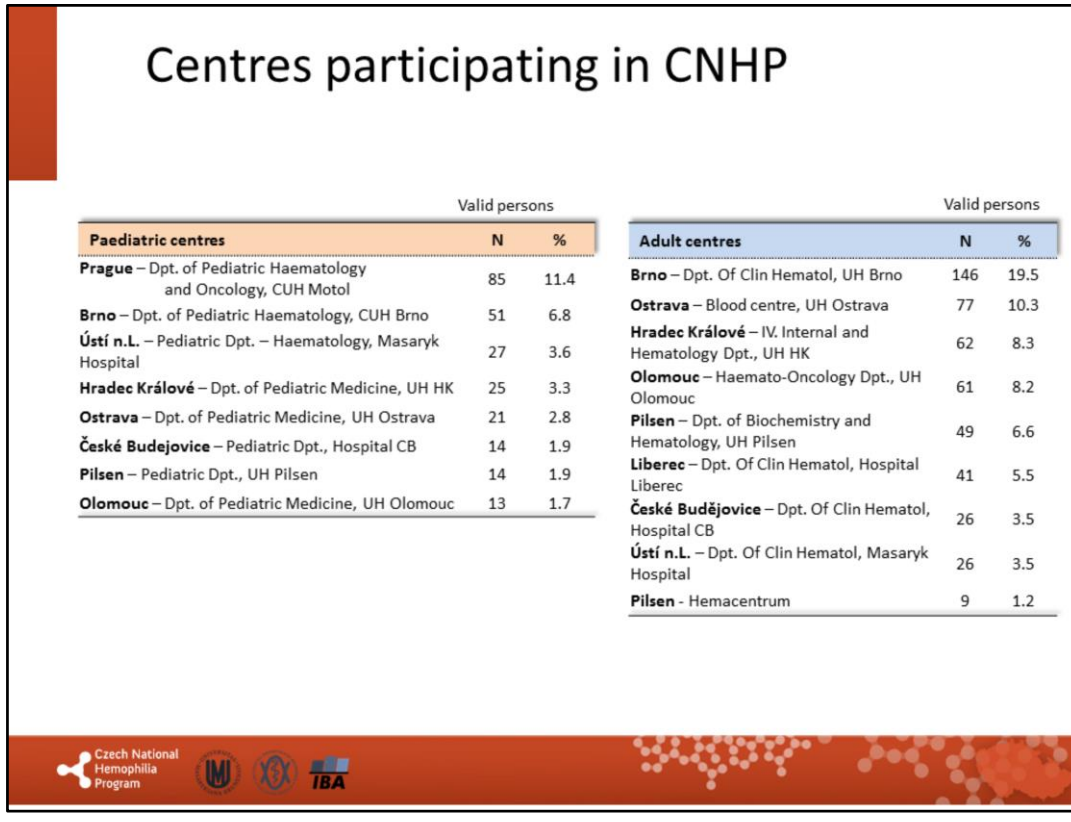
July 2017



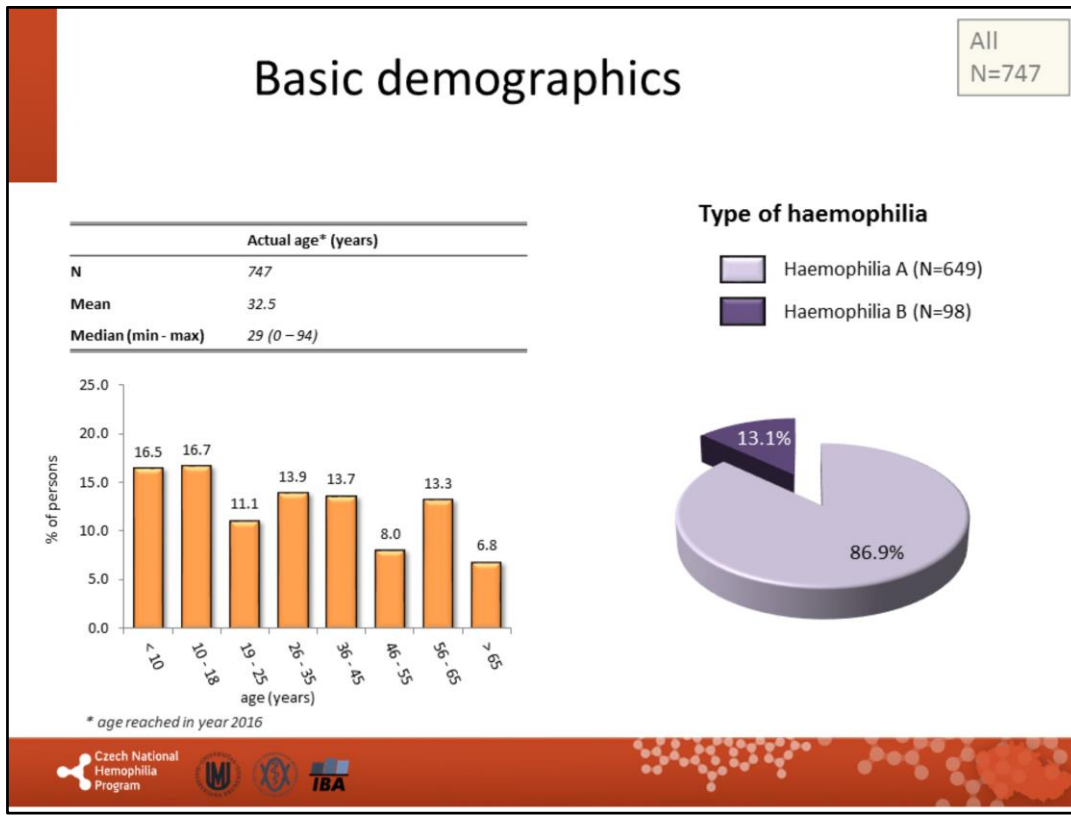
This slide describes the process of records' validation within the registry.

Part A

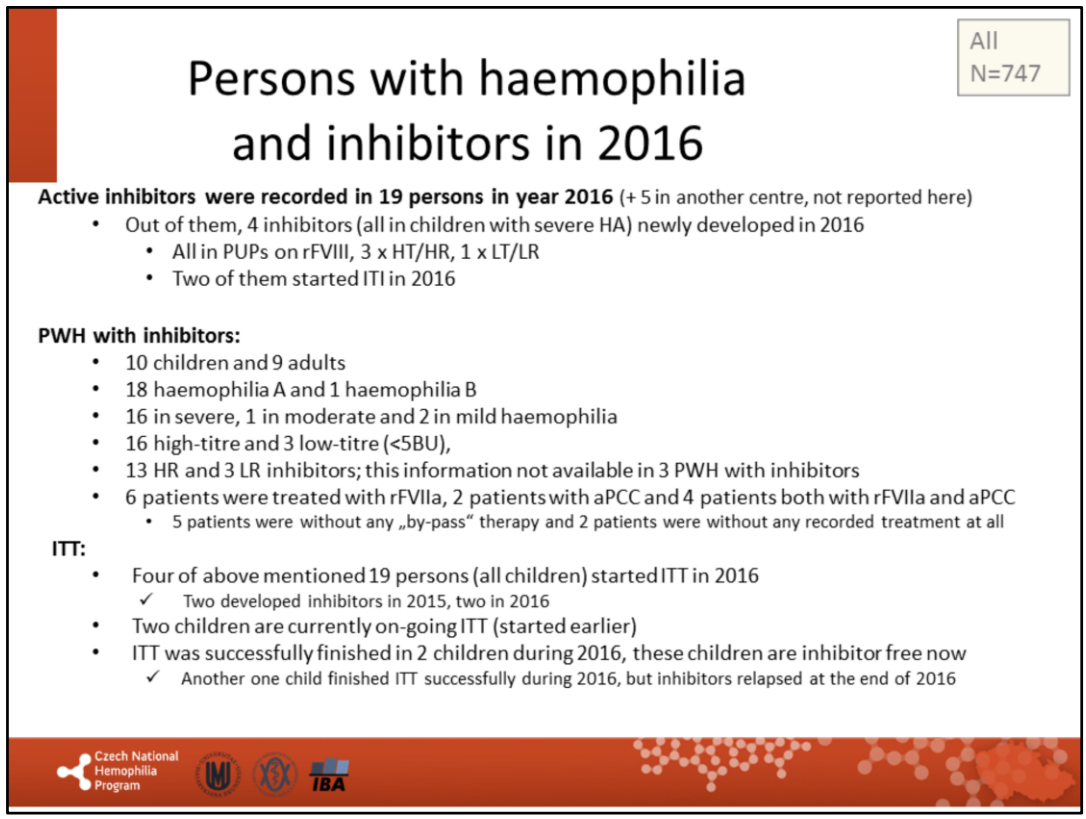
Persons with haemophilia (PWH)



Centres contributing to the CNHP registry.



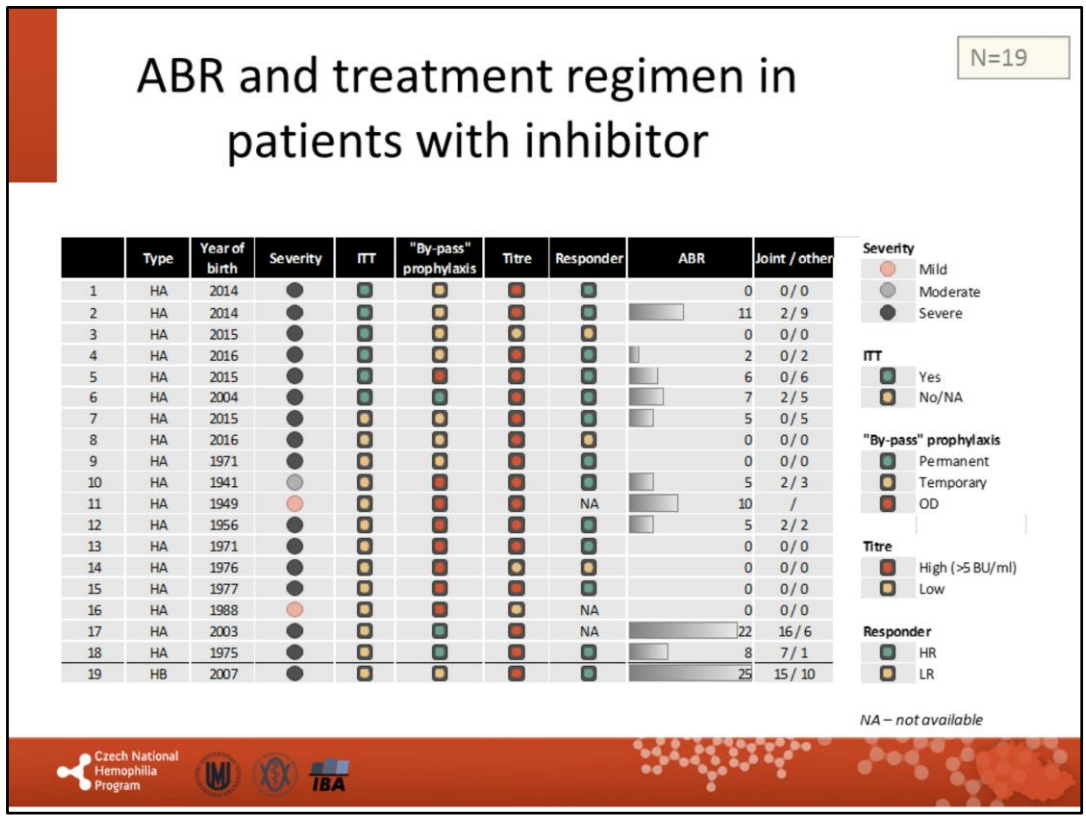
Though the percentage of PWH over 65 years has not been increasing dramatically over last several years, dealing with elderly people with haemophilia will be the challenge for treaters.



Summary description of the PWH with inhibitors within registry. There are five other PWH with inhibitors in the centre not participating in CNHP registry.

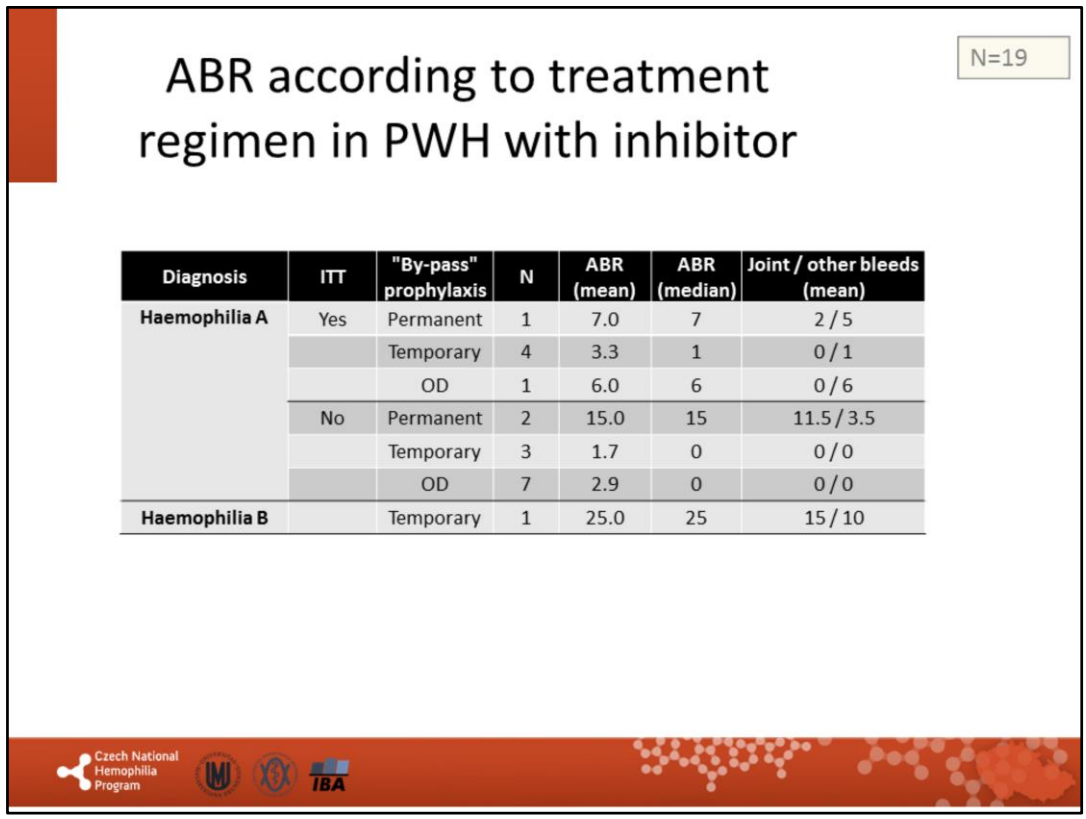
Please note further increased number of PWH with inhibitors in 2016. Four children with haemophilia A, (all severe PUPs) developed inhibitors in 2016. Most of them were HR inhibitors (only 1 was LR) . All inhibitors developed on rFVIII, as recombinant factors are treatment of choice in PUPs in Czech Republic

Six children were on ITI in 2016. Two of them started earlier, four started in 2016. ITI was successfully finished in 3 children in 2016, however, in one patient inhibitors relapsed at the end of 2016. No adults were on ITI in 2016.
The number of new inhibitors was thus higher, than the number of successfully achieved ITIs in 2016.



This slide describes in more details all PWH with “active” inhibitors within CNHP registry. Most, but not all of children with HT inhibitors are on ITI for different reasons. (Reasons not reported here, but often: previous ITI failure, waiting for inhibitors <10BU to start ITI, no consent for ITI provided by parents etc…) No adult PWH was on ITI in 2016.

Patients with inhibitors will be reported separately in details later in 2017.



Diagnosis	ITT	"By-pass" prophylaxis	N	ABR (mean)	ABR (median)	Joint / other bleeds (mean)
Haemophilia A	Yes	Permanent	1	7.0	7	2 / 5
		Temporary	4	3.3	1	0 / 1
		OD	1	6.0	6	0 / 6
	No	Permanent	2	15.0	15	11.5 / 3.5
		Temporary	3	1.7	0	0 / 0
		OD	7	2.9	0	0 / 0
Haemophilia B		Temporary	1	25.0	25	15 / 10

Patients with inhibitors, who have frequent joint bleeds, are on permanent prophylaxis with by-passing agents. Despite this, some of them have still high ABR.

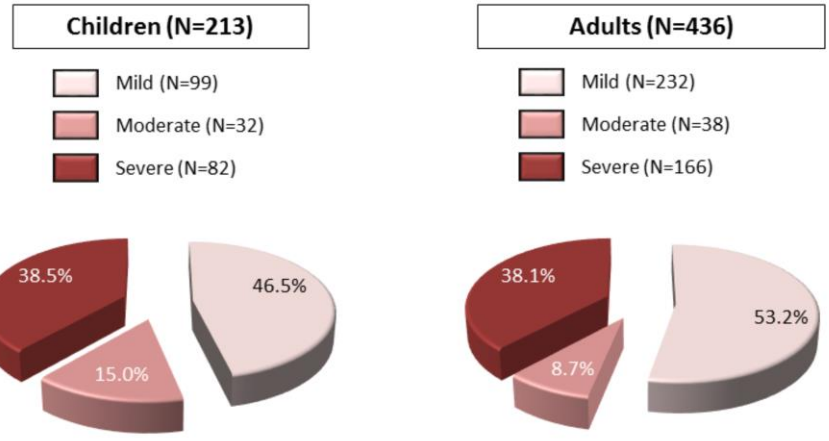
Part A.1

Demographic characteristics Haemophilia A

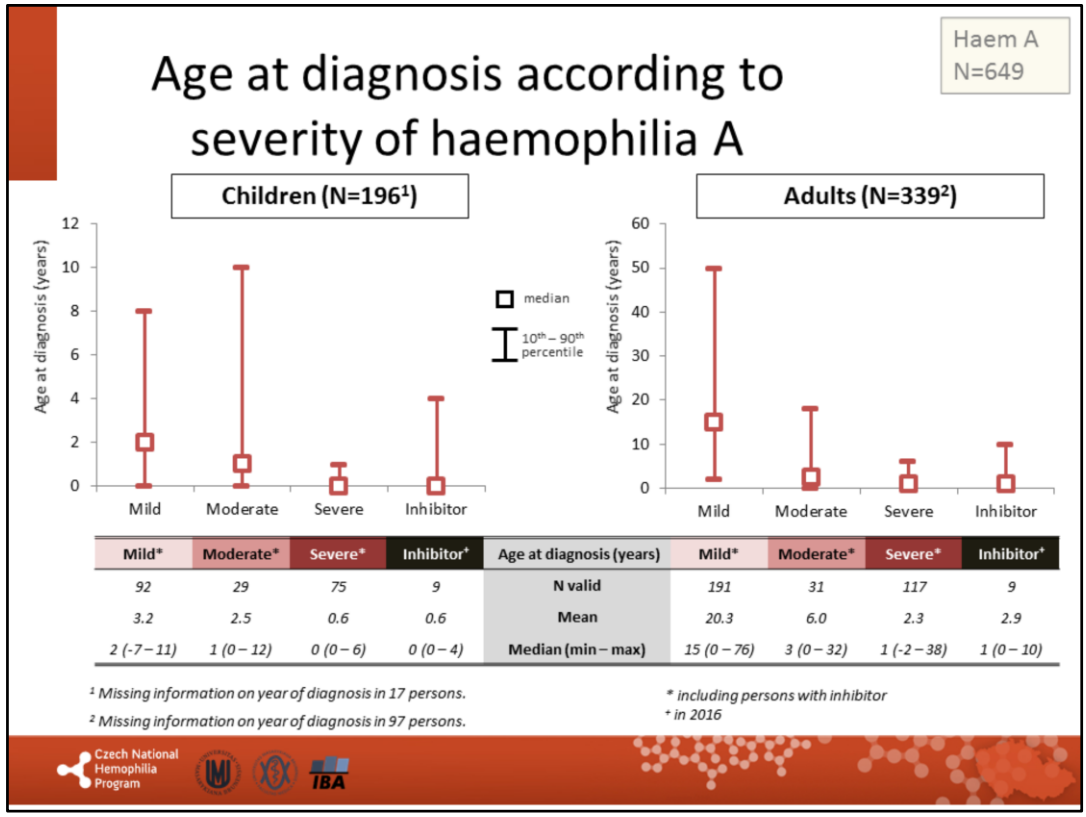
Czech National Hemophilia Program

Severity of haemophilia A

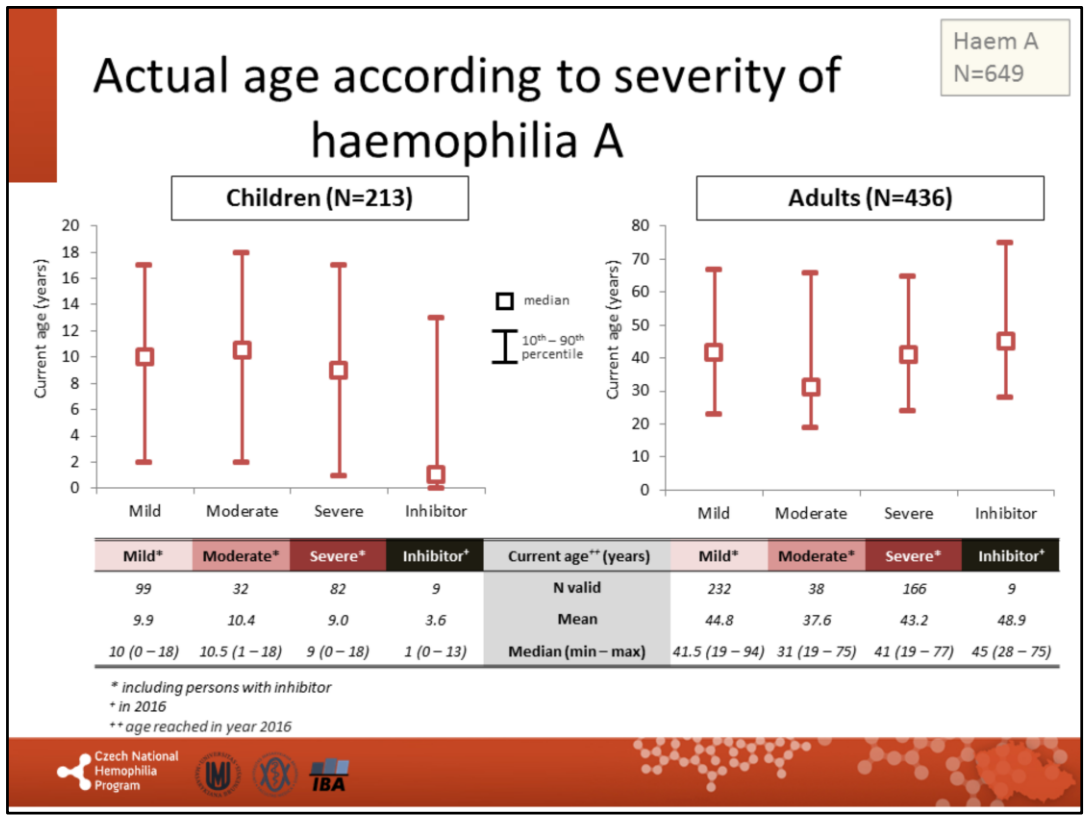
Haem A
N=649



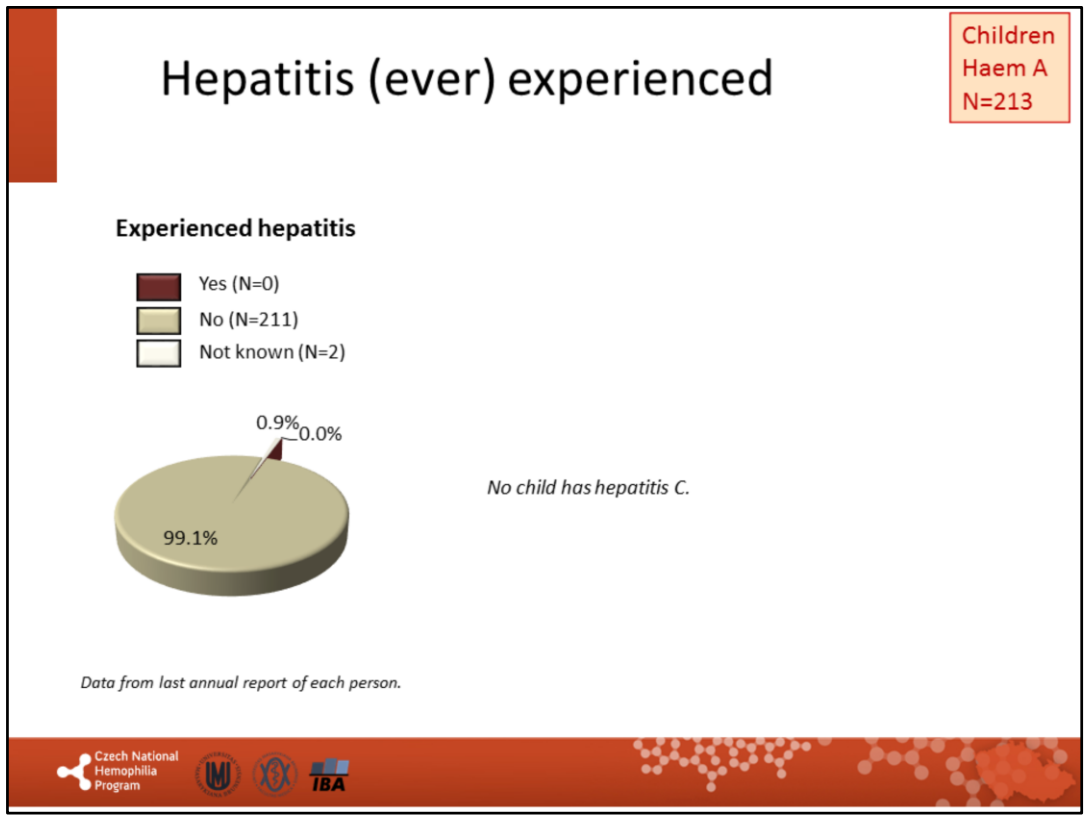
Czech National Hemophilia Program



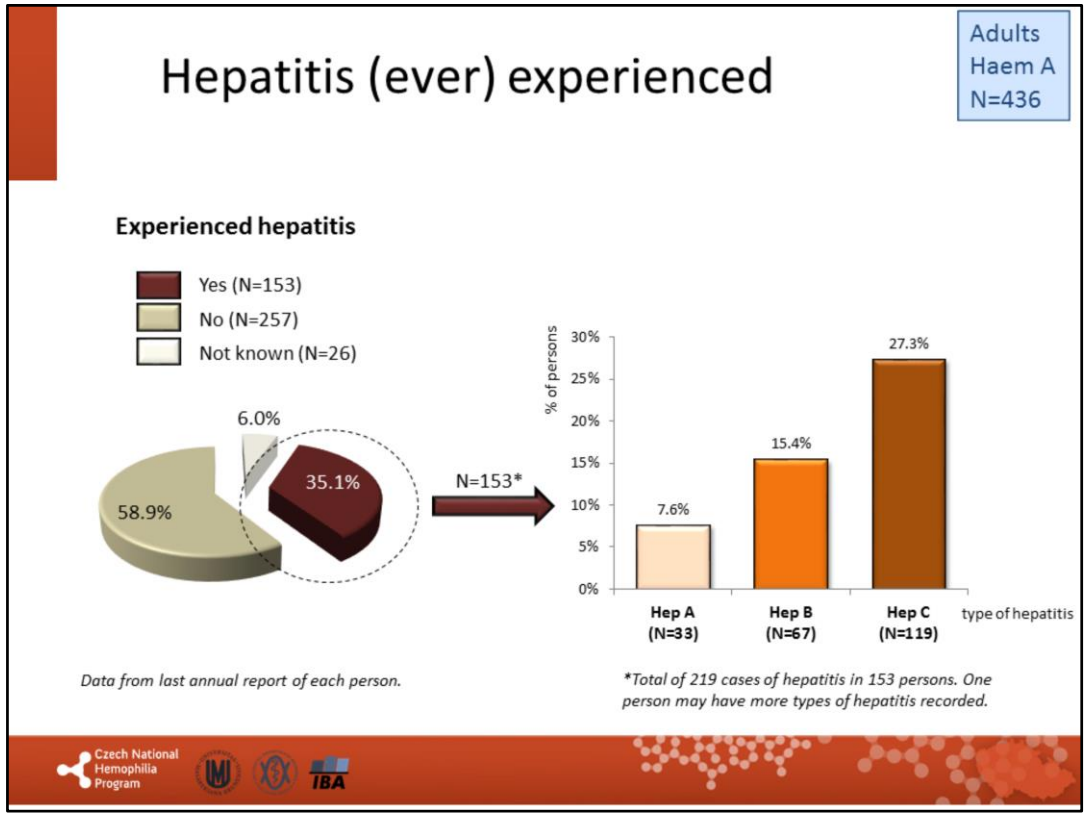
Median age at diagnosis is different for adults and children with HA. (In the past, the diagnostic options were worse, than they are today.)



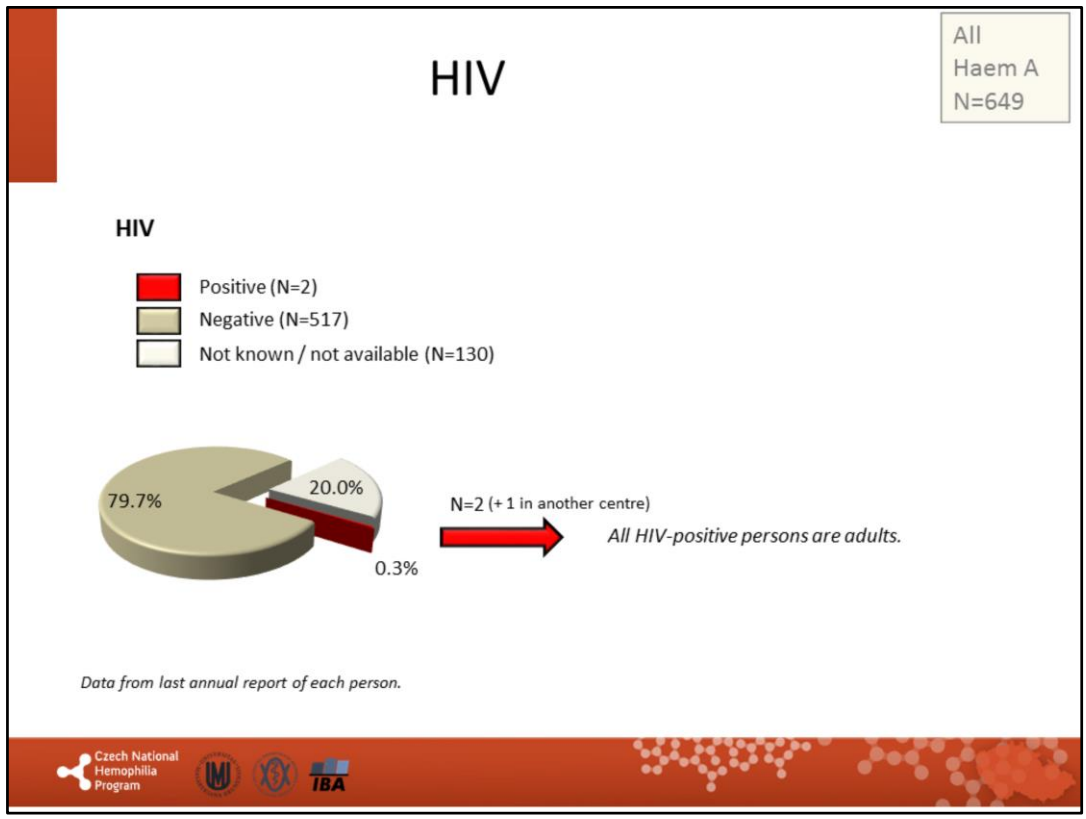
Mean age of Czech adults with HA is around 40 years. Mean age of children with HA is around 10 years.



No HepC infection in children since late 90's. None of Czech children with HA is infected with Hepatitis C.



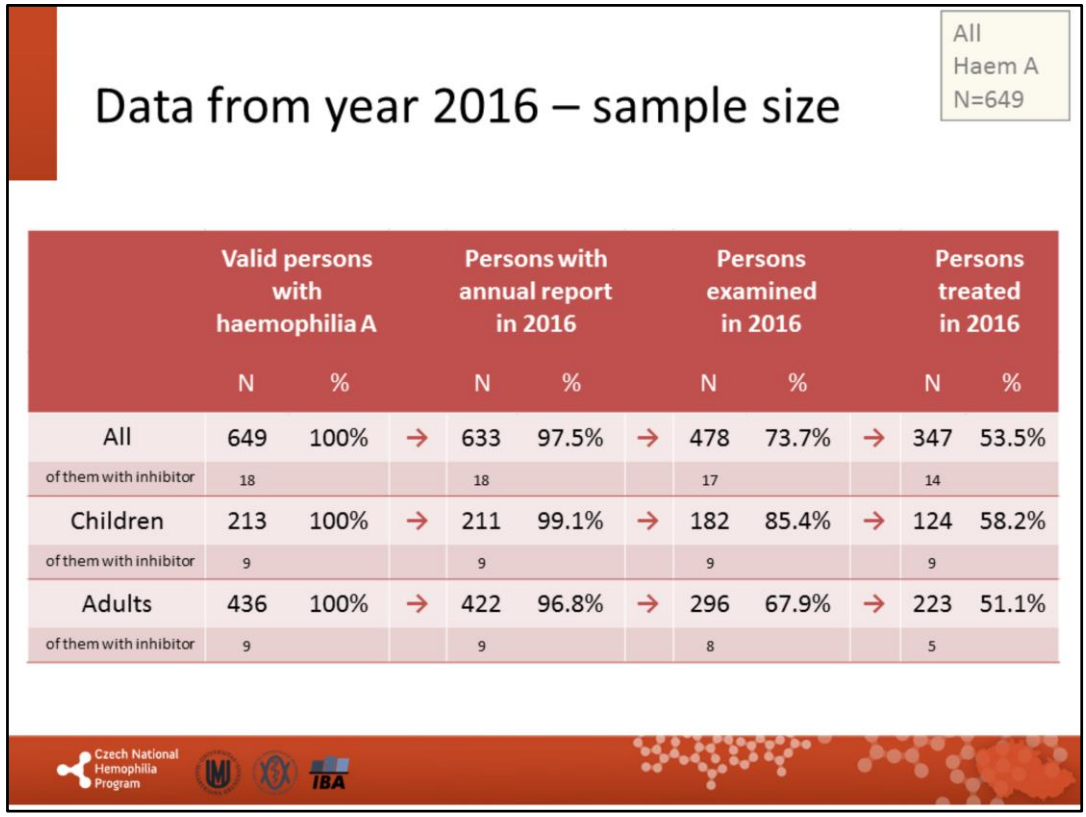
There has been NO NEW HepC infection in 2016.
119 PWHA ever experienced hepatitis, though some of them may have been successfully treated (numbers of successfully treated not shown here).



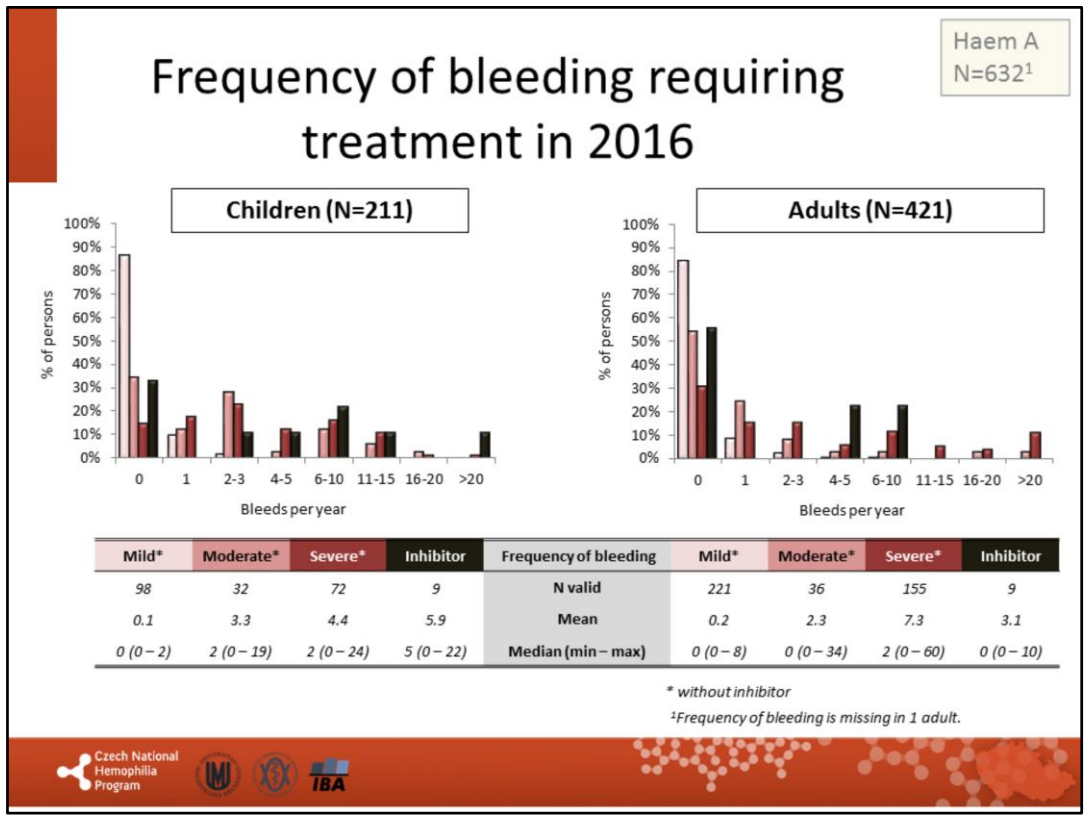
Very low number of HIV positive PWH due to low/no access to contaminated concentrates in 80s and 90s. Our current treatment is on a very high safety level. No new HIV+ PWH reported since late 90s.

Part A.2

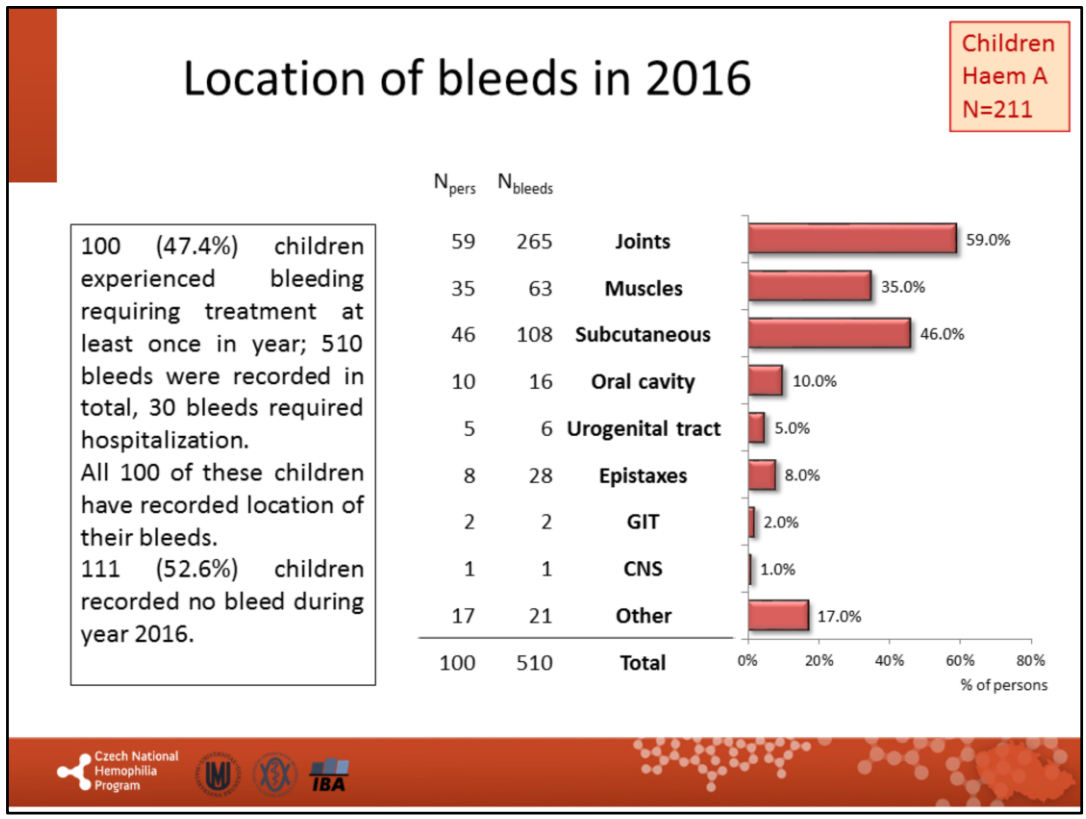
Treatment outcomes and bleeding frequency Haemophilia A



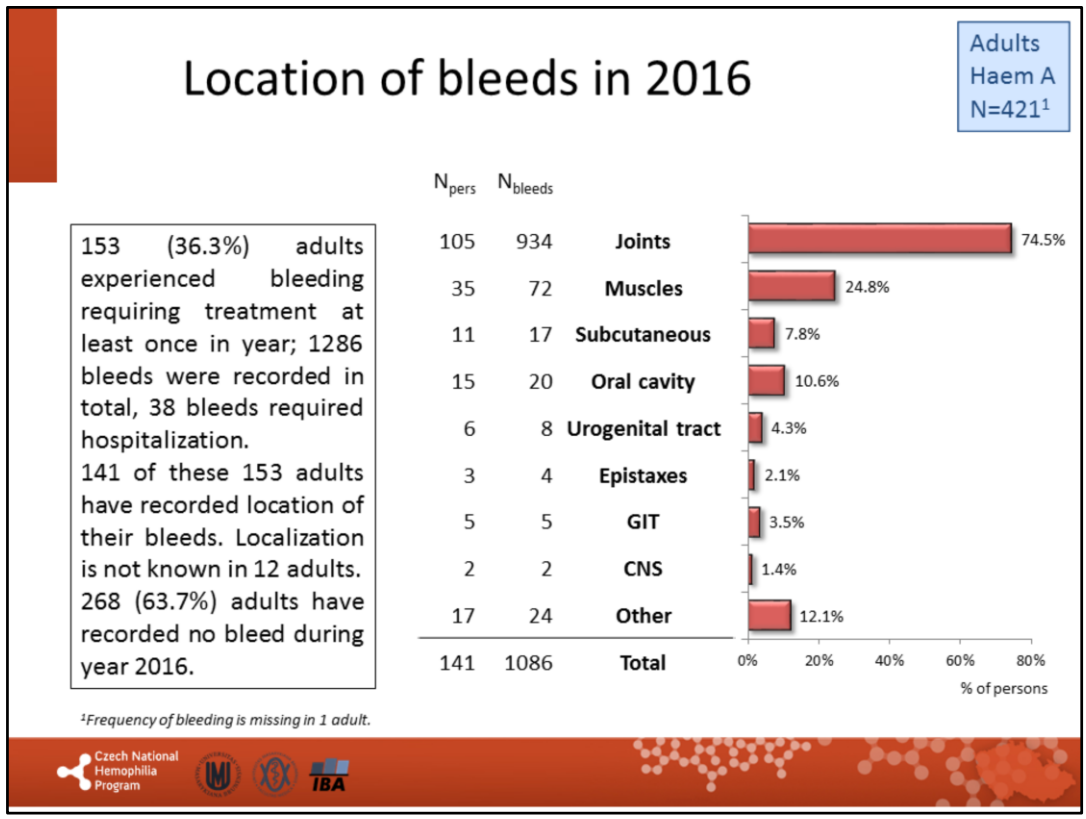
There are records of nearly 80% of all Czech haemophiliacs in total within the CNHP registry. As for paediatric population, ALL children are recorded. CNHP registry also houses records of over two thirds of adult haemophiliacs in Czech Republic. Further slides display analyses performed only on records, which were updated during 2016. Not all patients came to the centre (especially adults) and not all centres fully reported all data in 2016. Thus not all records have been updated and used for further analyses. Though the data completeness has further improved in 2016, 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 in 2017. (Ideally, percentage of PWH with annual report should be equal to PWH examined and both should be 100%.)
One adult is not included in further detailed analyses of treatment due to only partially filled 2016 annual report.



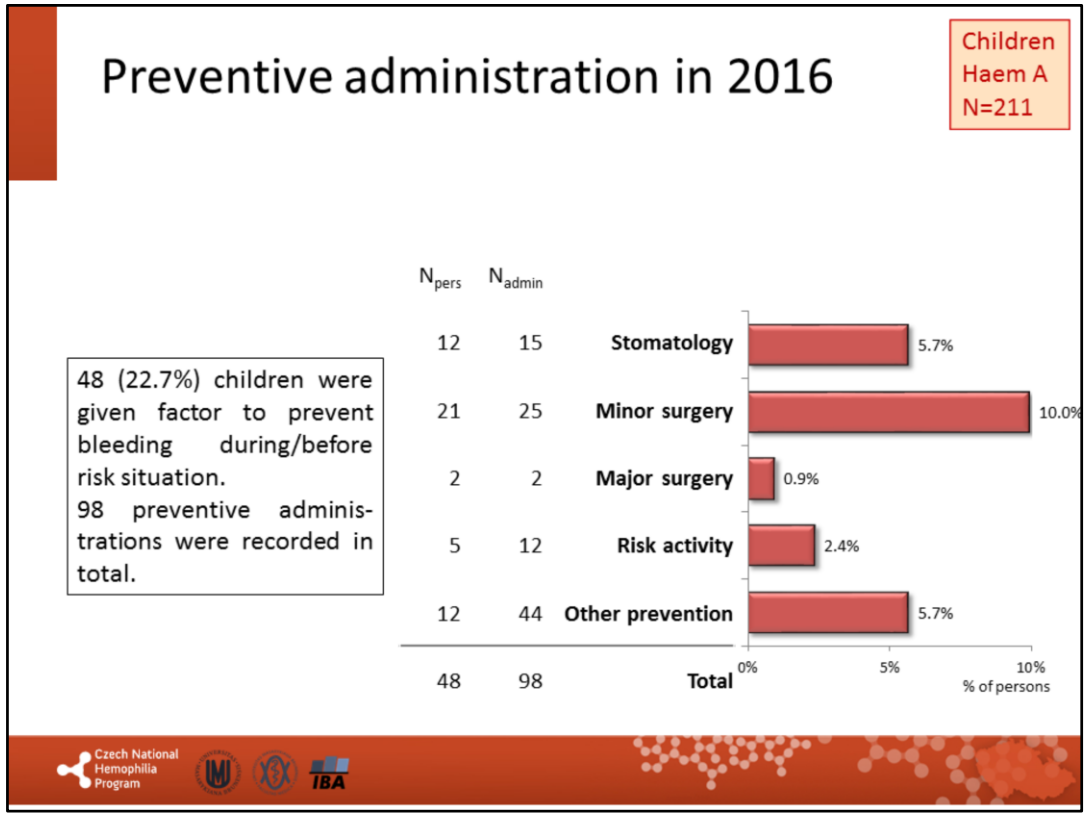
Data shown document good efficacy of care provided to Czech PWH, no matter what age category they are. Mean/Median number of bleedings per year (ABR) is 7,3/2 for adults and 4,4/2 in children with severe HA.
In 2015 the numbers for children were 4,7/3 and for adults 7,4/3.



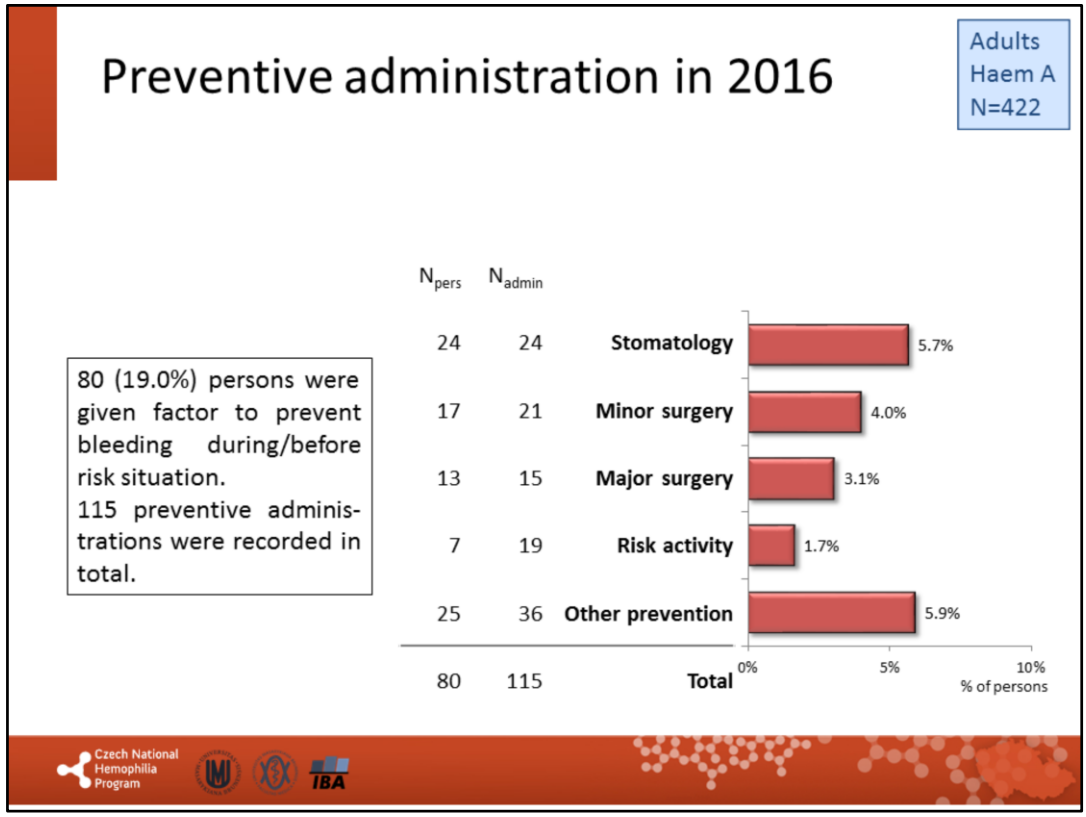
There was one CNS bleed in children with haemophilia in 2016. 52,6% of children had no bleed at all.



Bleeding events in adults.



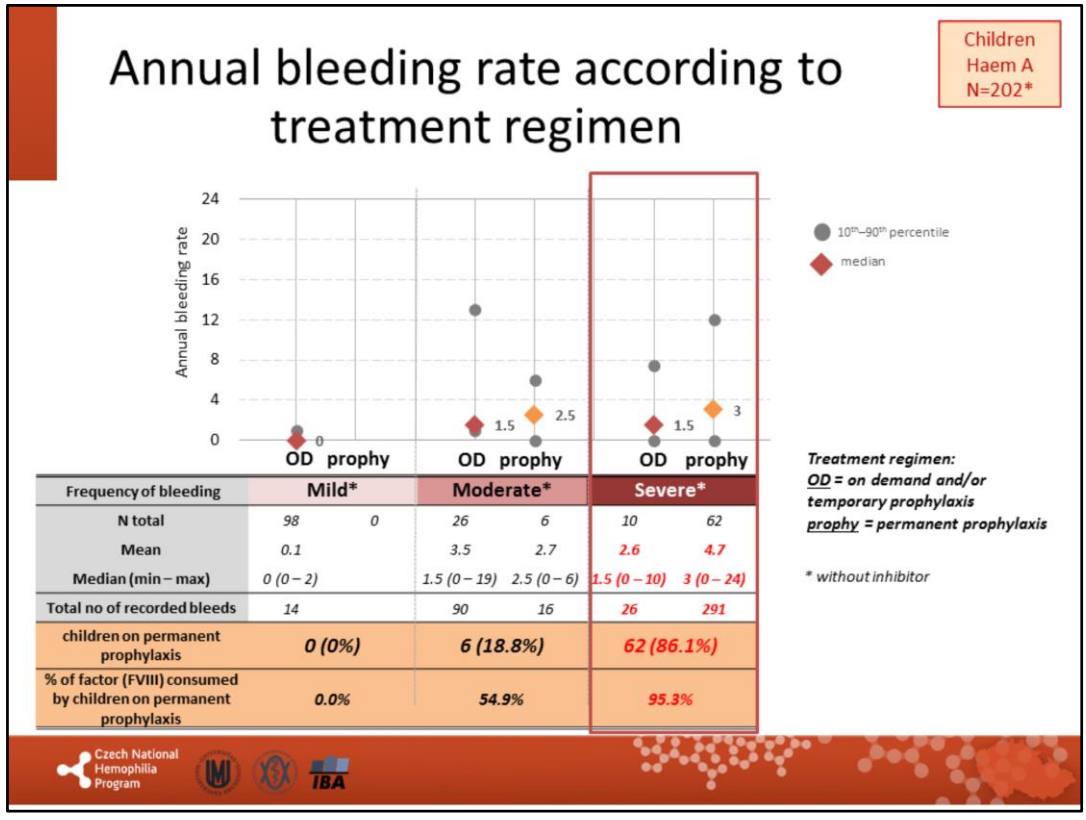
This figure refers to preventive factors administration in children with HA.



This figure refers to preventive treatment in adults with HA

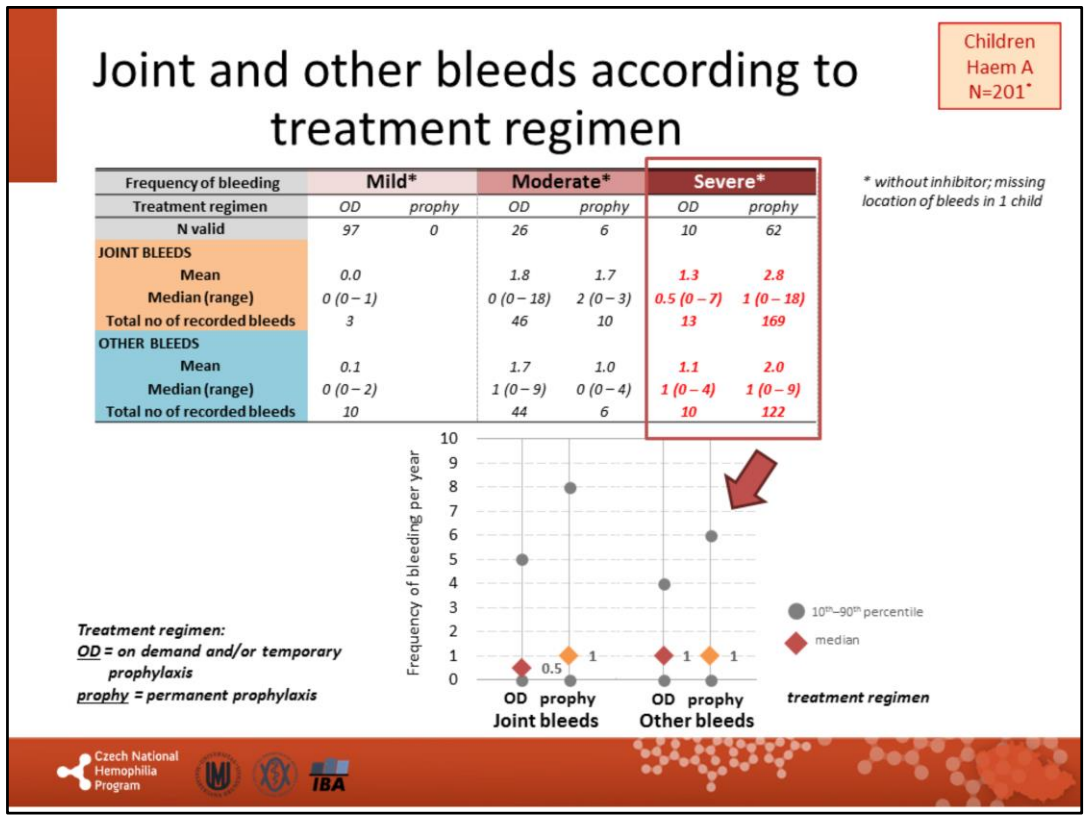
Part A.3

ABR according to treatment regimen Haemophilia A without inhibitor

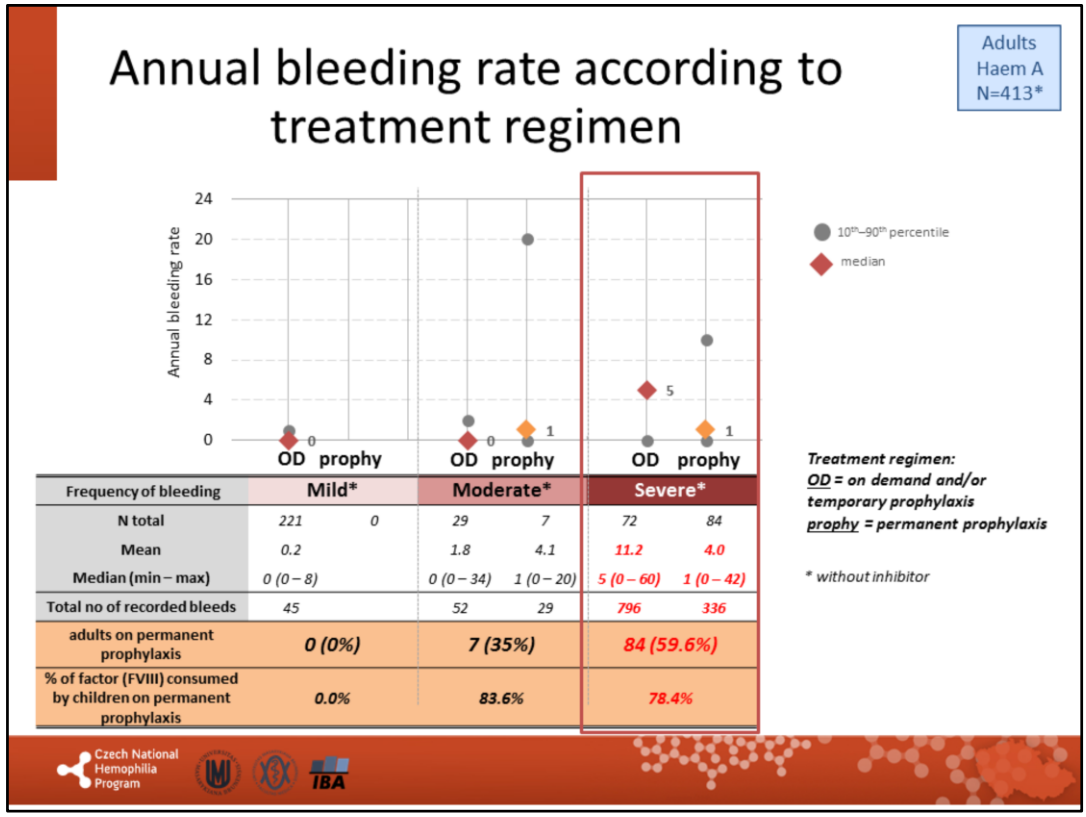


This slide supports good effect of permanent prophylaxis in children. Rate of prophylaxis decreased from 94,1% in 2015 to 86,1% in 2016 among children with severe haemophilia A. Those children with severe haemophilia, who are not on permanent prophylaxis yet shall be encouraged to do so. (see comment below) Number of bleeds per year (median) in severe haemophilacs A on prophylaxis decreased from 3,5 in 2015 to 3/year in 2016. ABR in children with severe haemophilia A on OD decreased from 3 to 1,5.

We should, however, still bear in mind, that over 2 bleeds/year may 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.



Children with HA on permanent prophylaxis had median of joint bleeds per year below 2 for the first time in the history of CNHP registry. This is, indeed, a great success, however, there are still children, who have over 10 joint bleeds per year! Please note also very high - and thus unacceptable - number of joint bleeds in some children with moderate HA, when treated „on-demand“ (interval range 0-18)! These children definitely deserve prophylaxis.

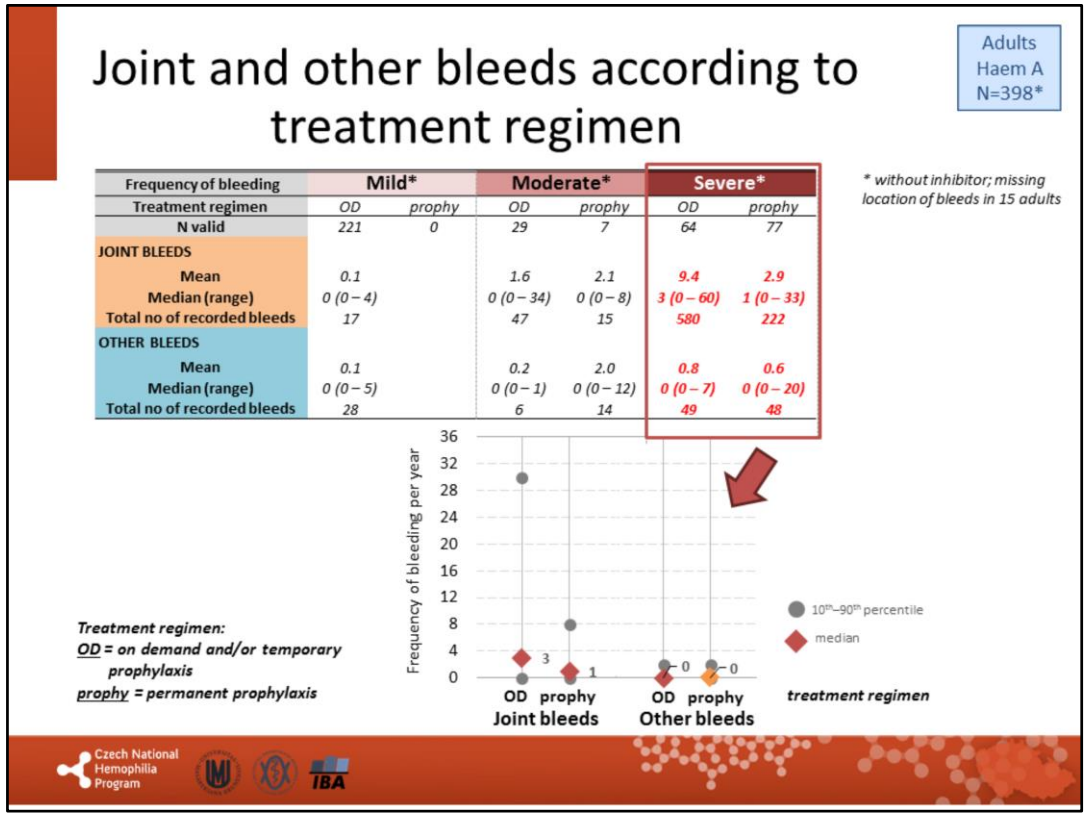


Frequency of bleeding	Mild*		Moderate*		Severe*	
N total	221	0	29	7	72	84
Mean	0.2		1.8	4.1	11.2	4.0
Median (min – max)	0 (0 – 8)		0 (0 – 34)	1 (0 – 20)	5 (0 – 60)	1 (0 – 42)
Total no of recorded bleeds	45		52	29	796	336
adults on permanent prophylaxis	0 (0%)		7 (35%)		84 (59.6%)	
% of factor (FVIII) consumed by children on permanent prophylaxis	0.0%		83.6%		78.4%	

Prophylaxis works very well in Czech adult PWHs! It is able to decrease bleedings from 5 to 1 (median numbers). In 2015 median ABR in adult PWHs with severe haemophilia was 10 on OD and 2 on prophylaxis.

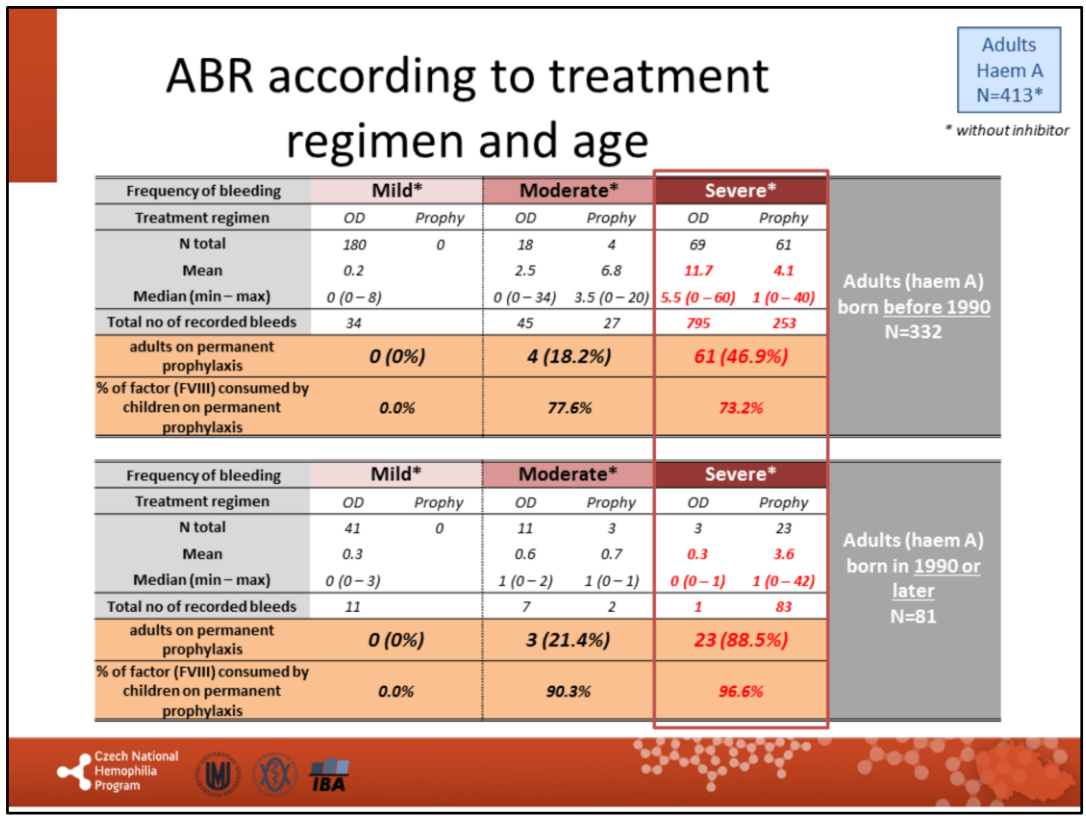
Rate of prophylaxis increased from 54,8% in 2015 to 59,6% among adults with severe haemophilia A.

Use of prophylaxis will certainly increase the factor consumption in adults, but the benefit shown as far less bleedings is undoubted.



Median of joint bleeds per year is below 2 also in adults with severe HA on prophylaxis. It is however seen, that some adult PWHA still have significant number of joint bleeds despite the prophylaxis. Wide interval range for those with severe and moderate HA treated “on demand” suggests, that more adults with HA should be commenced on prophylaxis.

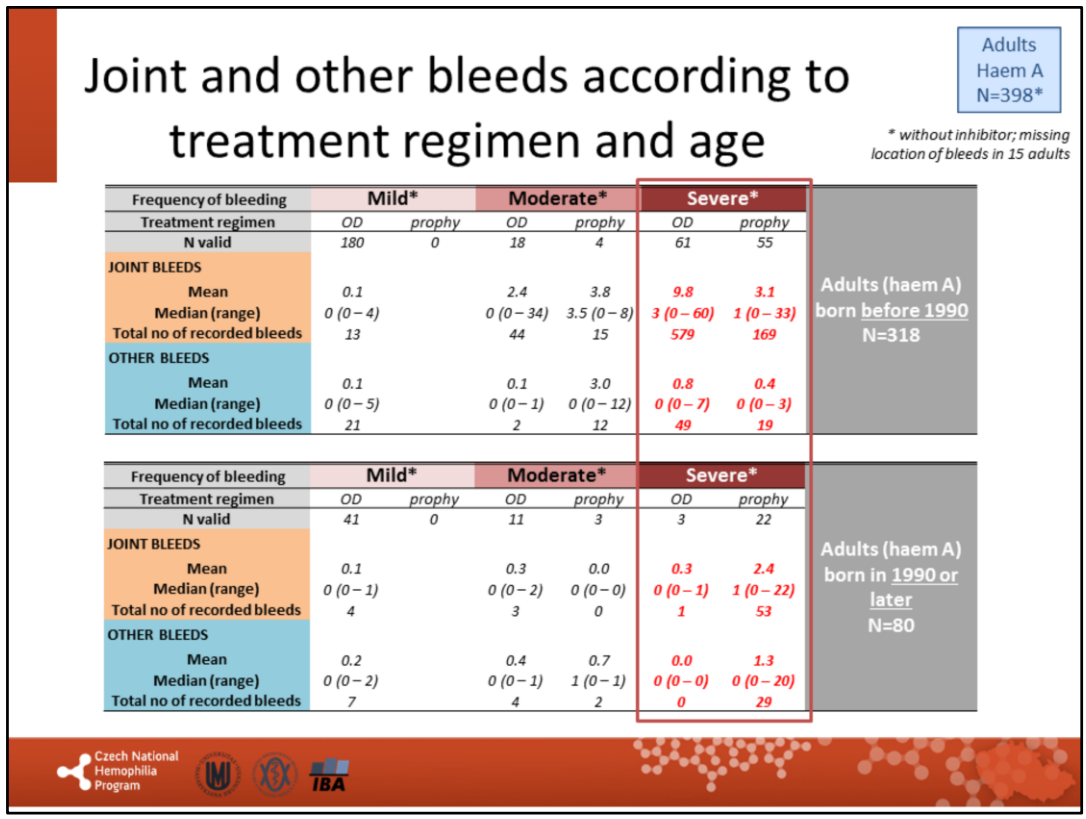
As described later in this report, doses for adults (in IU/kg/year) are still significantly lower, than in children with the same disease.



Frequency of bleeding	Mild*		Moderate*		Severe*	
Treatment regimen	OD	Prophy	OD	Prophy	OD	Prophy
N total	180	0	18	4	69	61
Mean	0.2		2.5	6.8	11.7	4.1
Median (min – max)	0 (0 – 8)		0 (0 – 34)	3.5 (0 – 20)	5.5 (0 – 60)	1 (0 – 40)
Total no of recorded bleeds	34		45	27	795	253
adults on permanent prophylaxis	0 (0%)		4 (18.2%)		61 (46.9%)	
% of factor (FVIII) consumed by children on permanent prophylaxis	0.0%		77.6%		73.2%	

Frequency of bleeding	Mild*		Moderate*		Severe*	
Treatment regimen	OD	Prophy	OD	Prophy	OD	Prophy
N total	41	0	11	3	3	23
Mean	0.3		0.6	0.7	0.3	3.6
Median (min – max)	0 (0 – 3)		1 (0 – 2)	1 (0 – 1)	0 (0 – 1)	1 (0 – 42)
Total no of recorded bleeds	11		7	2	1	83
adults on permanent prophylaxis	0 (0%)		3 (21.4%)		23 (88.5%)	
% of factor (FVIII) consumed by children on permanent prophylaxis	0.0%		90.3%		96.6%	

This important table shows in general significant difference in bleeding rates between adult PWH born before 1990 (when concentrates and thus also prophylaxis became available in CZ) and PWH born later.
This difference, however, disappears, when comparing adults with severe haemophilia A on prophylaxis. In both groups the medians and interval ranges are similar. In other words, prophylaxis works very well also in those, with already damaged joints. We advocate for more tertiary prophylaxis in adult PWH.



Frequency of bleeding	Mild*		Moderate*		Severe*	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy
N valid	180	0	18	4	61	55
JOINT BLEEDS						
Mean	0.1		2.4	3.8	9.8	3.1
Median (range)	0 (0 – 4)		0 (0 – 34)	3.5 (0 – 8)	3 (0 – 60)	1 (0 – 33)
Total no of recorded bleeds	13		44	15	579	169
OTHER BLEEDS						
Mean	0.1		0.1	3.0	0.8	0.4
Median (range)	0 (0 – 5)		0 (0 – 1)	0 (0 – 12)	0 (0 – 7)	0 (0 – 3)
Total no of recorded bleeds	21		2	12	49	19

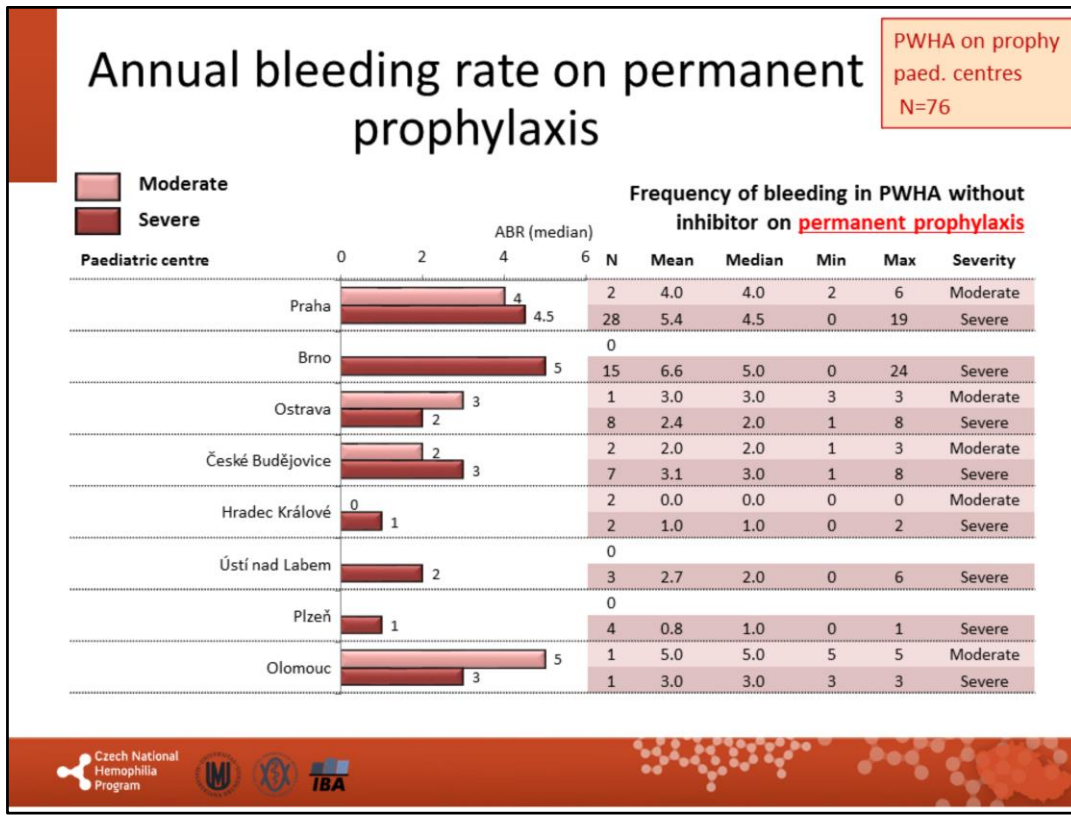
Frequency of bleeding	Mild*		Moderate*		Severe*	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy
N valid	41	0	11	3	3	22
JOINT BLEEDS						
Mean	0.1		0.3	0.0	0.3	2.4
Median (range)	0 (0 – 1)		0 (0 – 2)	0 (0 – 0)	0 (0 – 1)	1 (0 – 22)
Total no of recorded bleeds	4		3	0	1	53
OTHER BLEEDS						
Mean	0.2		0.4	0.7	0.0	1.3
Median (range)	0 (0 – 2)		0 (0 – 1)	1 (0 – 1)	0 (0 – 0)	0 (0 – 20)
Total no of recorded bleeds	7		4	2	0	29

The same is true for joint bleeds in adults. Situation significantly improved compared to 2015, some frequent bleeders however still remain, especially between adults with severe HA born before 1990 and still treated “on demand”. They are, indeed, the candidates for tertiary prophylaxis.

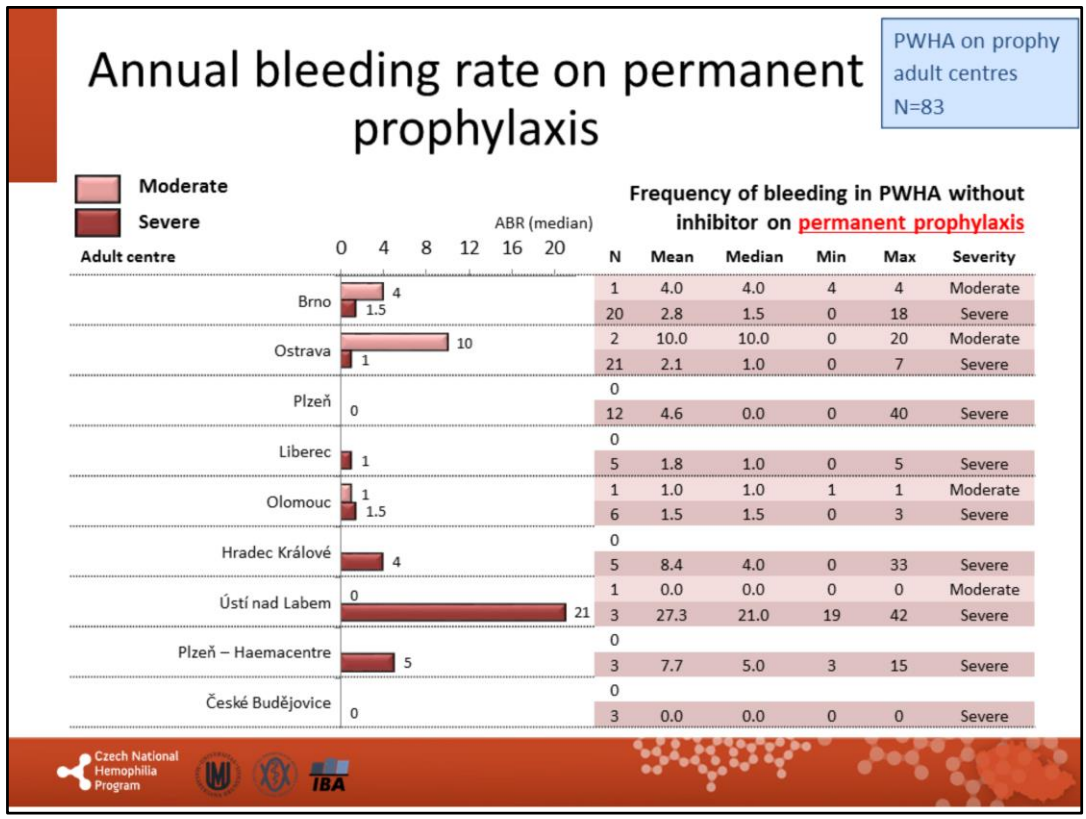
Part A.4

ABR according to centres Haemophilia A (PWHA)

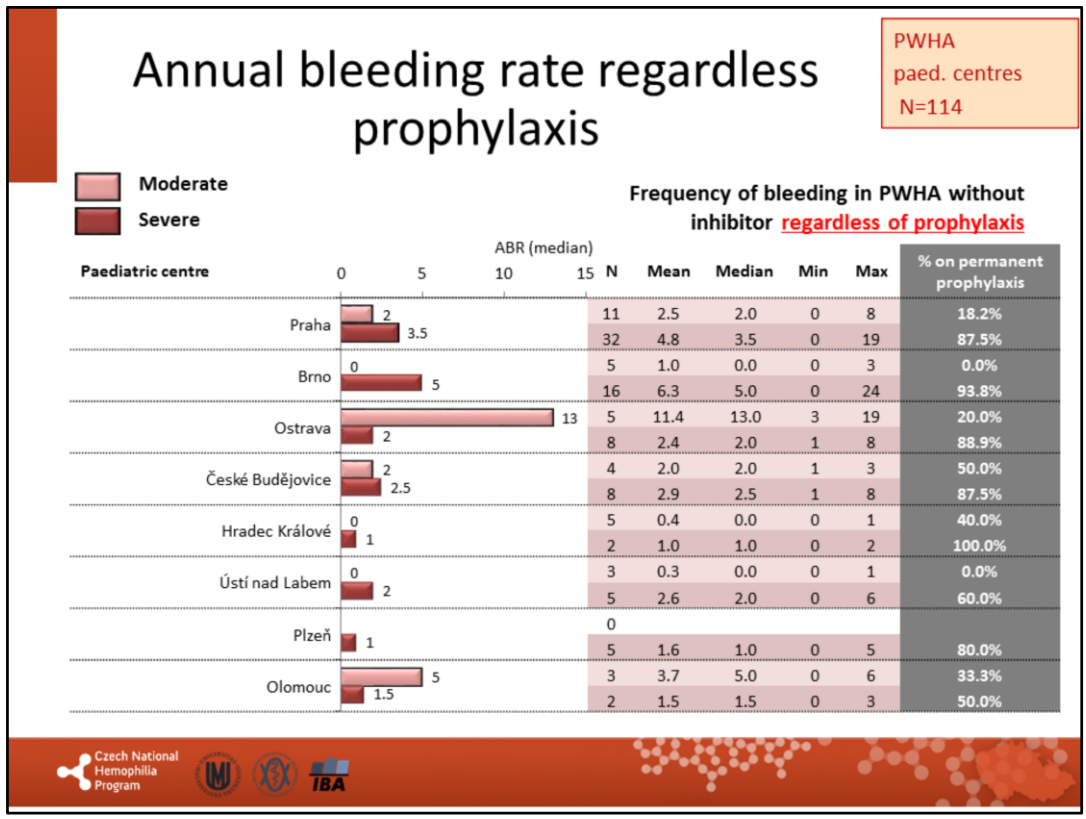
Czech National Hemophilia Program



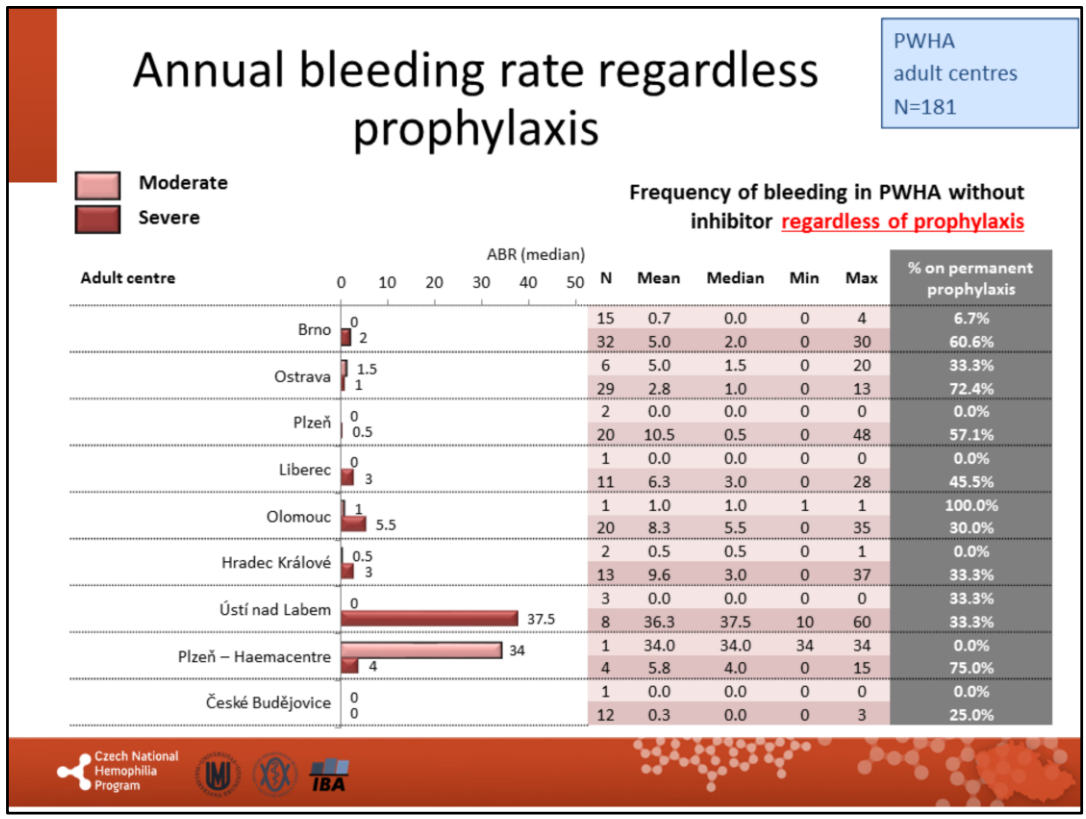
In vast majority of paediatric centres, severe haemophiliacs on prophylaxis bleed not more than 4 times per year (median). We should continue in our focus on individualized/tailored prophylaxis and shall offer it to all, who may benefit from this approach. This should also minimize the differences in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



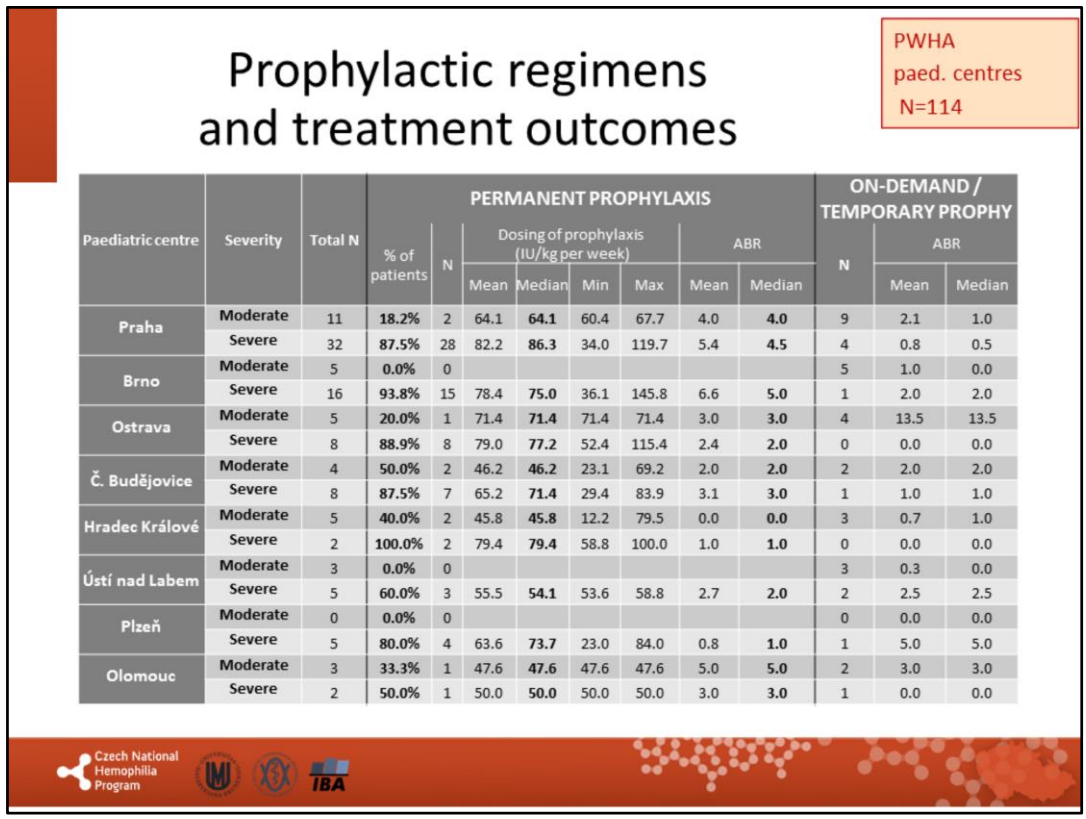
In centres using prophylaxis in adults, the ABR differs significantly. There are also adults with severe haemophilia, who have no bleed per year on permanent prophylaxis. This should encourage us to promote further prophylaxis in more adult PWH.



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.

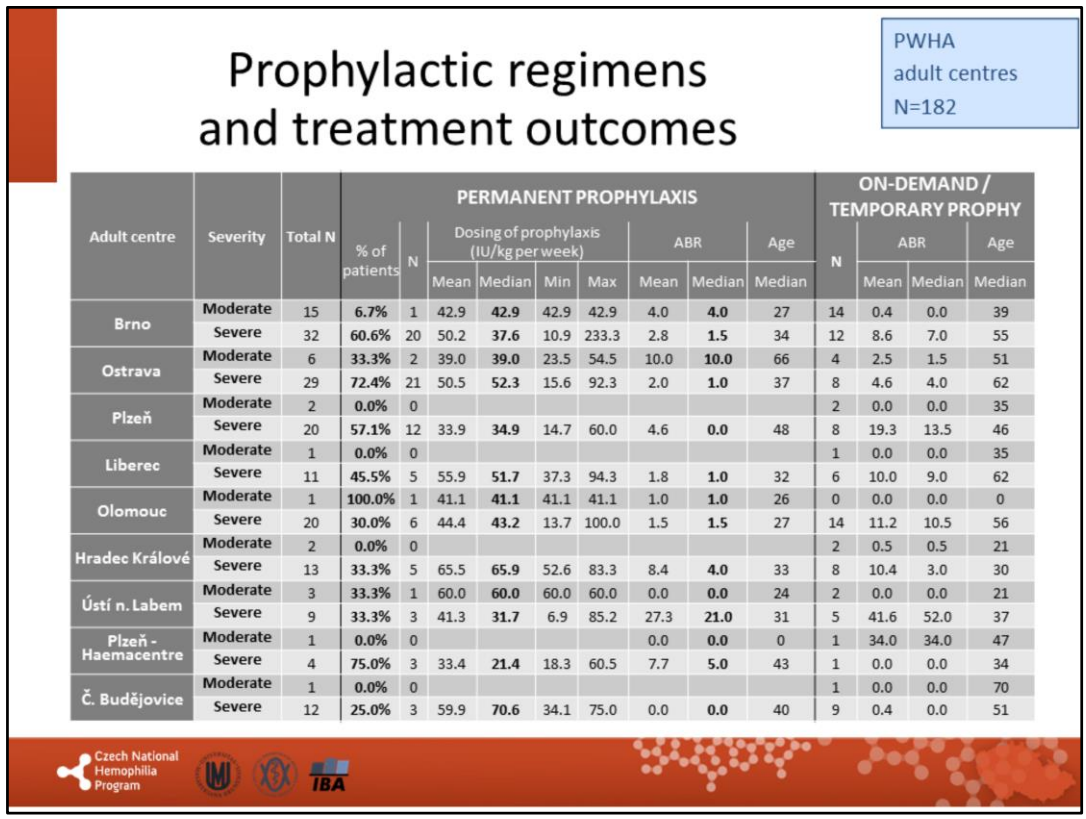


Similar information for adults. High ABR in some centres might be due to an individual with very severe phenotype and/or perhaps poor compliance. On the other hand, dealing with those patients should be a challenge for respective centres.



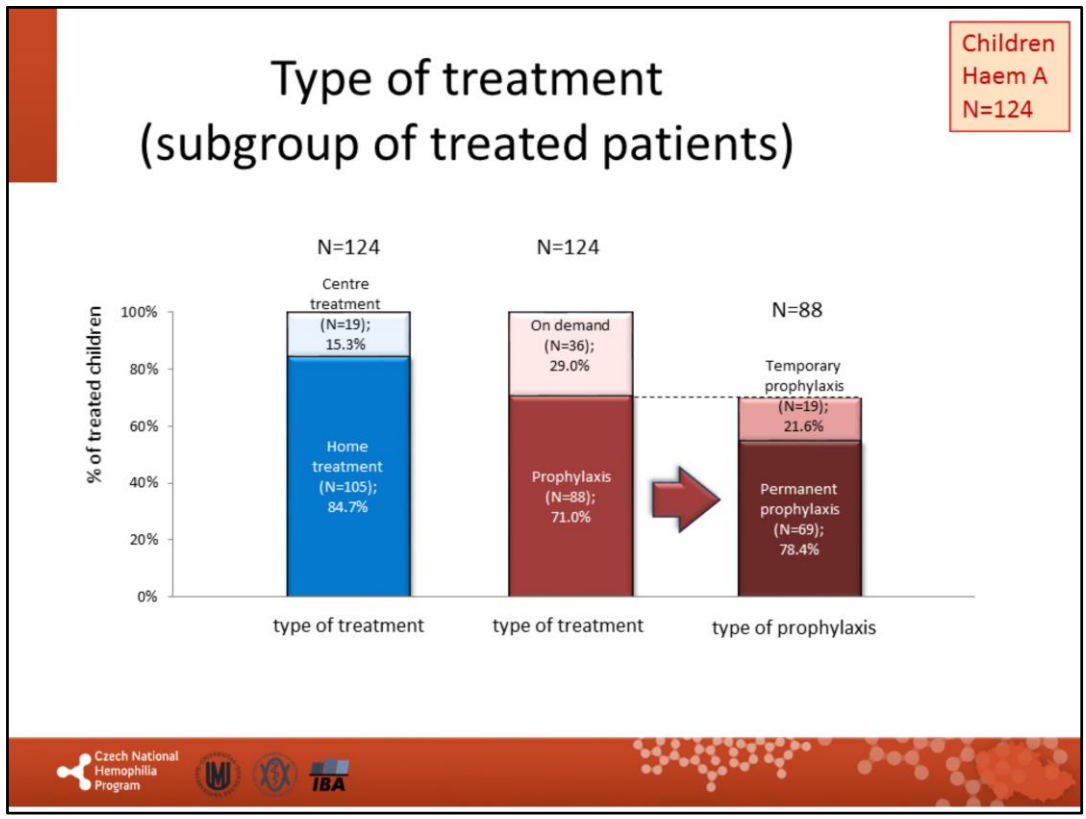
Paediatric centre	Severity	Total N	PERMANENT PROPHYLAXIS								ON-DEMAND / TEMPORARY PROPHY		
			% of patients	N	Dosing of prophylaxis (IU/kg per week)				ABR		N	ABR	
					Mean	Median	Min	Max	Mean	Median		Mean	Median
Praha	Moderate	11	**18.2%**	2	64.1	**64.1**	60.4	67.7	4.0	**4.0**	9	2.1	1.0
	Severe	32	**87.5%**	28	82.2	**86.3**	34.0	119.7	5.4	**4.5**	4	0.8	0.5
Brno	Moderate	5	**0.0%**	0							5	1.0	0.0
	Severe	16	**93.8%**	15	78.4	**75.0**	36.1	145.8	6.6	**5.0**	1	2.0	2.0
Ostrava	Moderate	5	**20.0%**	1	71.4	**71.4**	71.4	71.4	3.0	**3.0**	4	13.5	13.5
	Severe	8	**88.9%**	8	79.0	**77.2**	52.4	115.4	2.4	**2.0**	0	0.0	0.0
Č. Budějovice	Moderate	4	**50.0%**	2	46.2	**46.2**	23.1	69.2	2.0	**2.0**	2	2.0	2.0
	Severe	8	**87.5%**	7	65.2	**71.4**	29.4	83.9	3.1	**3.0**	1	1.0	1.0
Hradec Králové	Moderate	5	**40.0%**	2	45.8	**45.8**	12.2	79.5	0.0	**0.0**	3	0.7	1.0
	Severe	2	**100.0%**	2	79.4	**79.4**	58.8	100.0	1.0	**1.0**	0	0.0	0.0
Ústí nad Labem	Moderate	3	**0.0%**	0							3	0.3	0.0
	Severe	5	**60.0%**	3	55.5	**54.1**	53.6	58.8	2.7	**2.0**	2	2.5	2.5
Plzeň	Moderate	0	**0.0%**	0							0	0.0	0.0
	Severe	5	**80.0%**	4	63.6	**73.7**	23.0	84.0	0.8	**1.0**	1	5.0	5.0
Olomouc	Moderate	3	**33.3%**	1	47.6	**47.6**	47.6	47.6	5.0	**5.0**	2	3.0	3.0
	Severe	2	**50.0%**	1	50.0	**50.0**	50.0	50.0	3.0	**3.0**	1	0.0	0.0

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

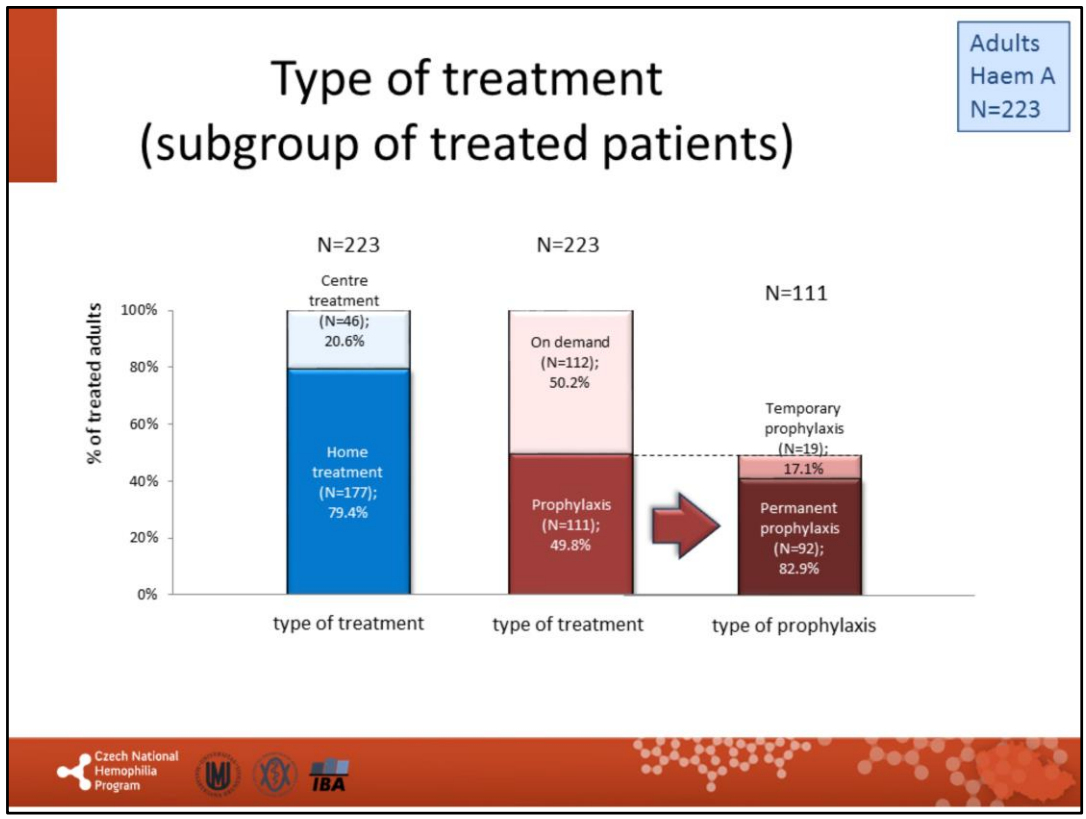


Adult centre	Severity	Total N	PERMANENT PROPHYLAXIS									ON-DEMAND / TEMPORARY PROPHY			
			% of patients	N	Dosing of prophylaxis (IU/kg per week)				ABR		Age	N	ABR		Age
					Mean	Median	Min	Max	Mean	Median	Median		Mean	Median	Median
Brno	Moderate	15	6.7%	1	42.9	42.9	42.9	42.9	4.0	4.0	27	14	0.4	0.0	39
	Severe	32	60.6%	20	50.2	37.6	10.9	233.3	2.8	1.5	34	12	8.6	7.0	55
Ostrava	Moderate	6	33.3%	2	39.0	39.0	23.5	54.5	10.0	10.0	66	4	2.5	1.5	51
	Severe	29	72.4%	21	50.5	52.3	15.6	92.3	2.0	1.0	37	8	4.6	4.0	62
Plzeň	Moderate	2	0.0%	0								2	0.0	0.0	35
	Severe	20	57.1%	12	33.9	34.9	14.7	60.0	4.6	0.0	48	8	19.3	13.5	46
Liberec	Moderate	1	0.0%	0								1	0.0	0.0	35
	Severe	11	45.5%	5	55.9	51.7	37.3	94.3	1.8	1.0	32	6	10.0	9.0	62
Olomouc	Moderate	1	100.0%	1	41.1	41.1	41.1	41.1	1.0	1.0	26	0	0.0	0.0	0
	Severe	20	30.0%	6	44.4	43.2	13.7	100.0	1.5	1.5	27	14	11.2	10.5	56
Hradec Králové	Moderate	2	0.0%	0								2	0.5	0.5	21
	Severe	13	33.3%	5	65.5	65.9	52.6	83.3	8.4	4.0	33	8	10.4	3.0	30
Ústí n. Labem	Moderate	3	33.3%	1	60.0	60.0	60.0	60.0	0.0	0.0	24	2	0.0	0.0	21
	Severe	9	33.3%	3	41.3	31.7	6.9	85.2	27.3	21.0	31	5	41.6	52.0	37
Plzeň - Haemacentre	Moderate	1	0.0%	0					0.0	0.0	0	1	34.0	34.0	47
	Severe	4	75.0%	3	33.4	21.4	18.3	60.5	7.7	5.0	43	1	0.0	0.0	34
Č. Budějovice	Moderate	1	0.0%	0								1	0.0	0.0	70
	Severe	12	25.0%	3	59.9	70.6	34.1	75.0	0.0	0.0	40	9	0.4	0.0	51

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



Over 80% of children treated in 2016 took the advantage of home treatment. 71% of treated children were commenced on any type of prophylaxis (was 64% in 2015) and 78% out of those on prophylaxis were on permanent prophy in 2016 (was 92% in 2015).



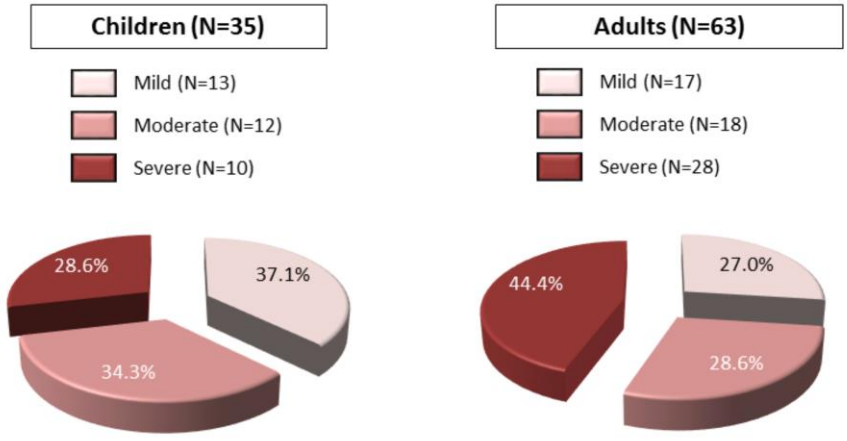
80% of adults treated in 2016 took the advantage of home treatment (no change compared to 2015). 50% of treated adults were commenced on any type of prophylaxis (was 45% in 2015) and 83% out of those on prophylaxis were on permanent prophy in 2016 (was 79% in 2015).

Part B.1

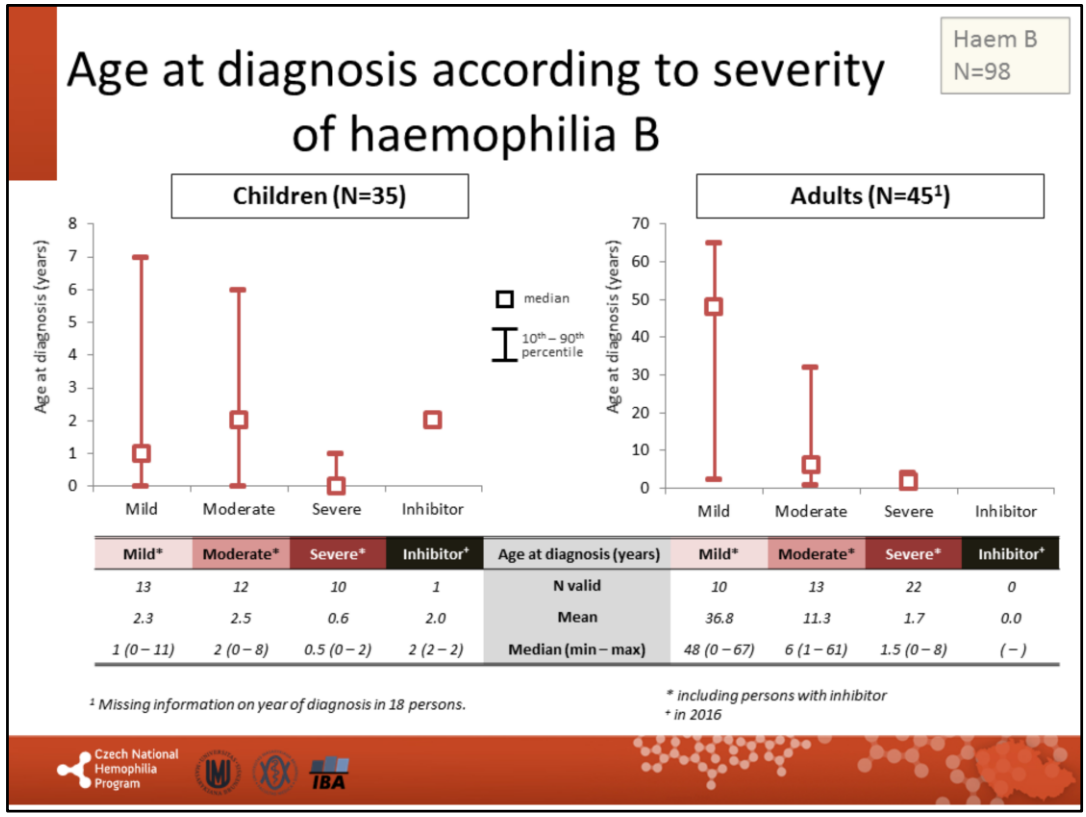
Demographic characteristics Haemophilia B

Severity of haemophilia B

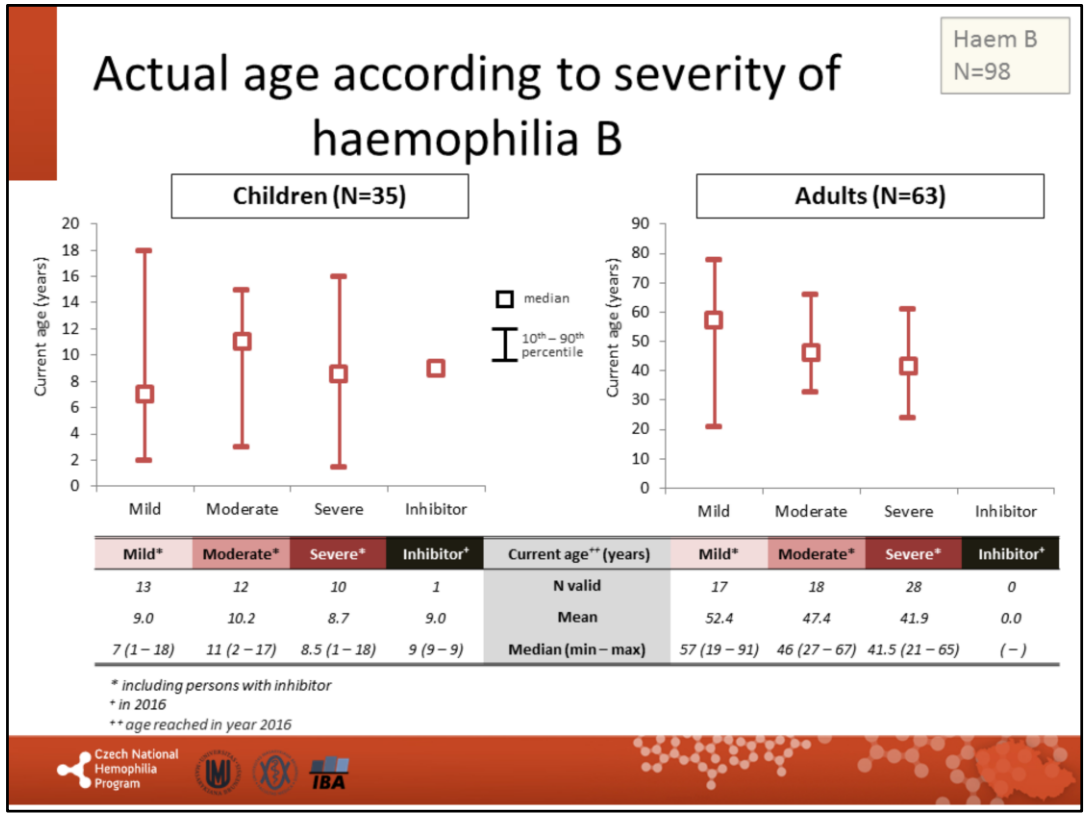
Haem B
N=98



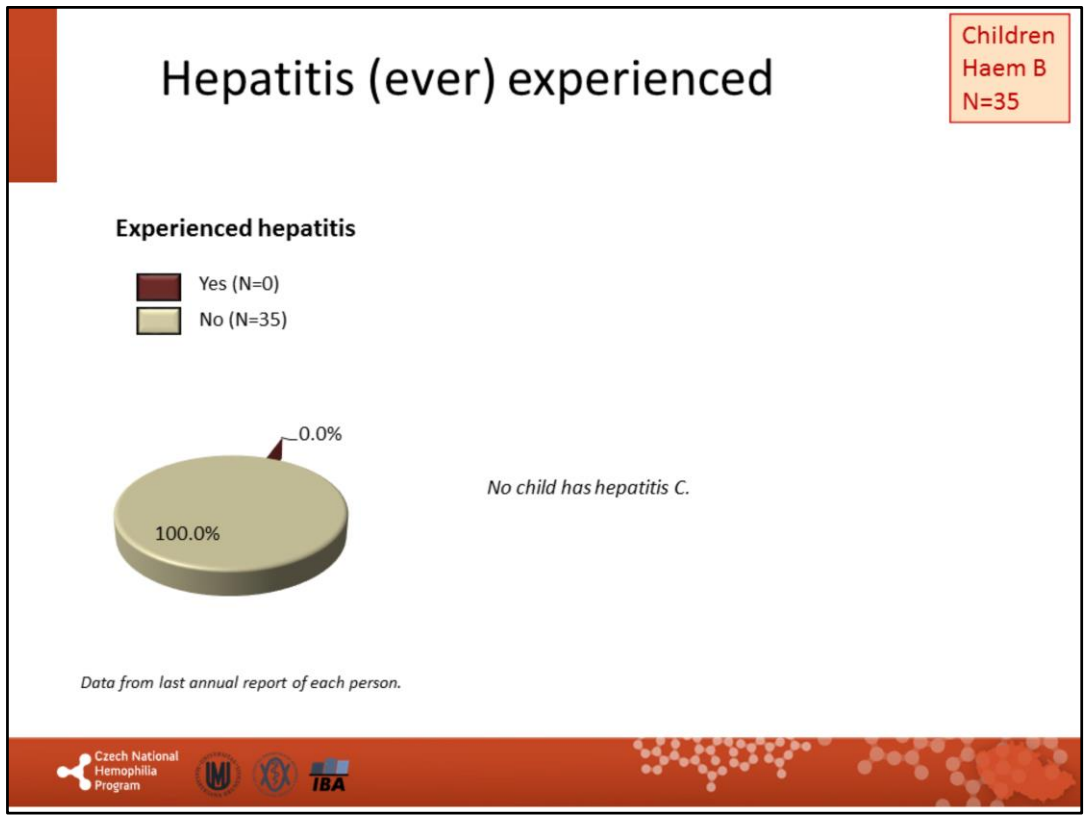
Czech National Hemophilia Program



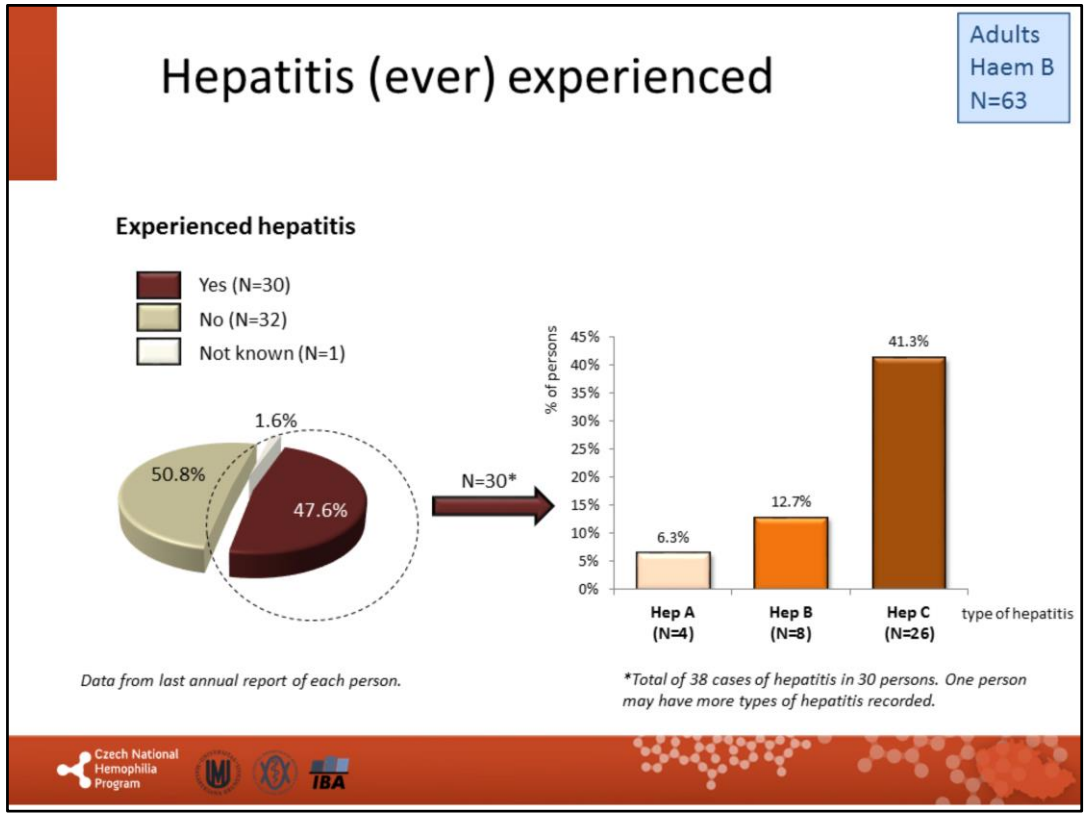
There is no major difference in demographics between HA and HB.



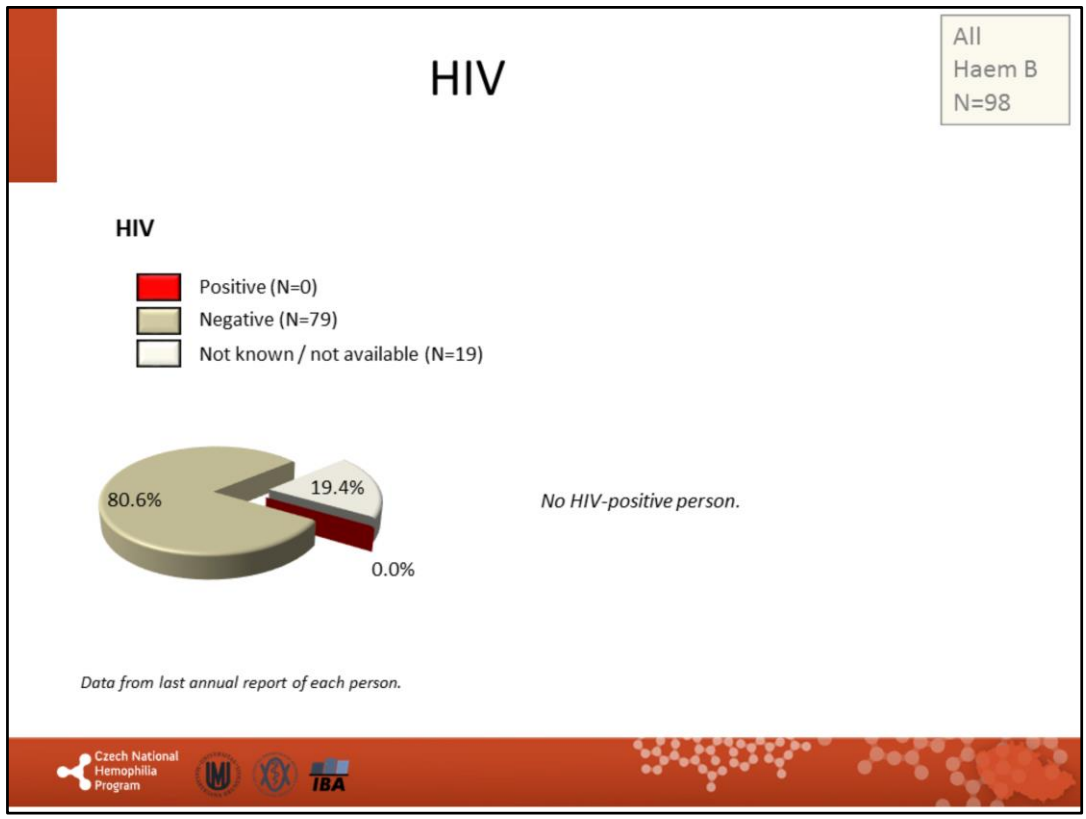
There is no major difference in demographics between HA and HB, perhaps adults with HB are slightly older than those, with HA.



NO HepC infection in children since late 90's. None of Czech children with HB is infected with Hepatitis C.



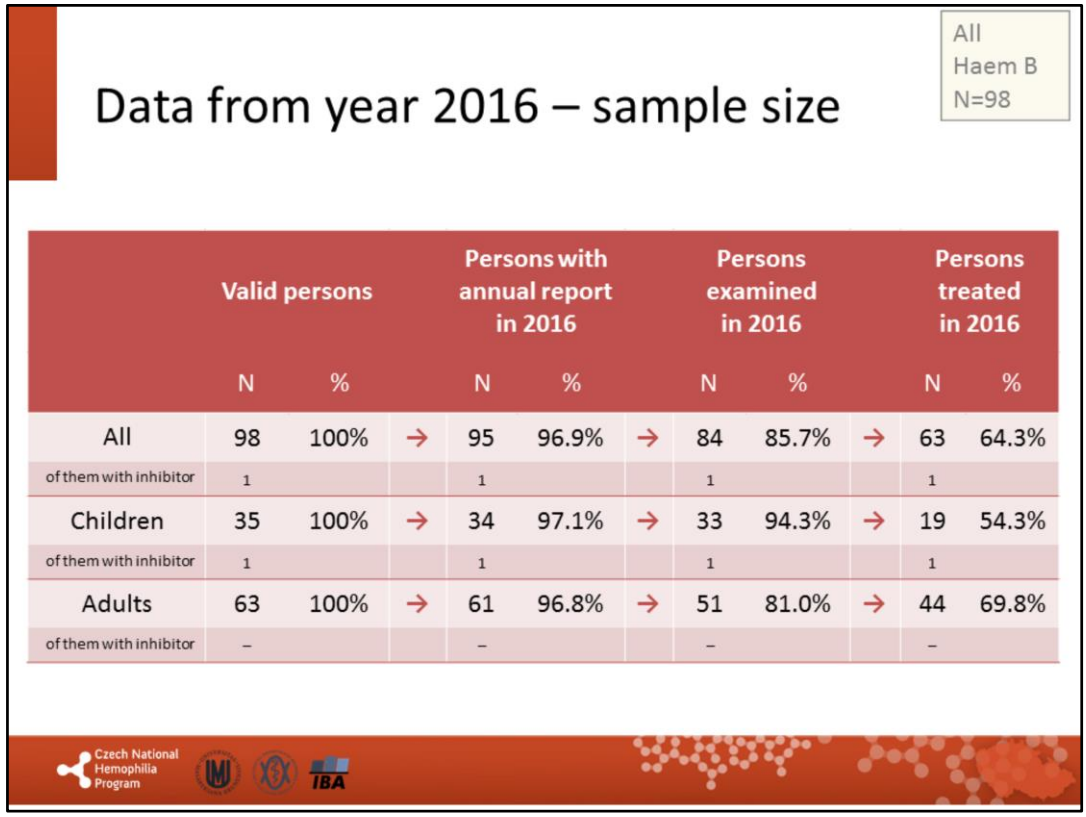
There has been NO NEW HepC infection in 2016.
26 PWHB ever experienced hepatitis, though some of them may have been successfully treated (numbers of successfully treated not shown here).



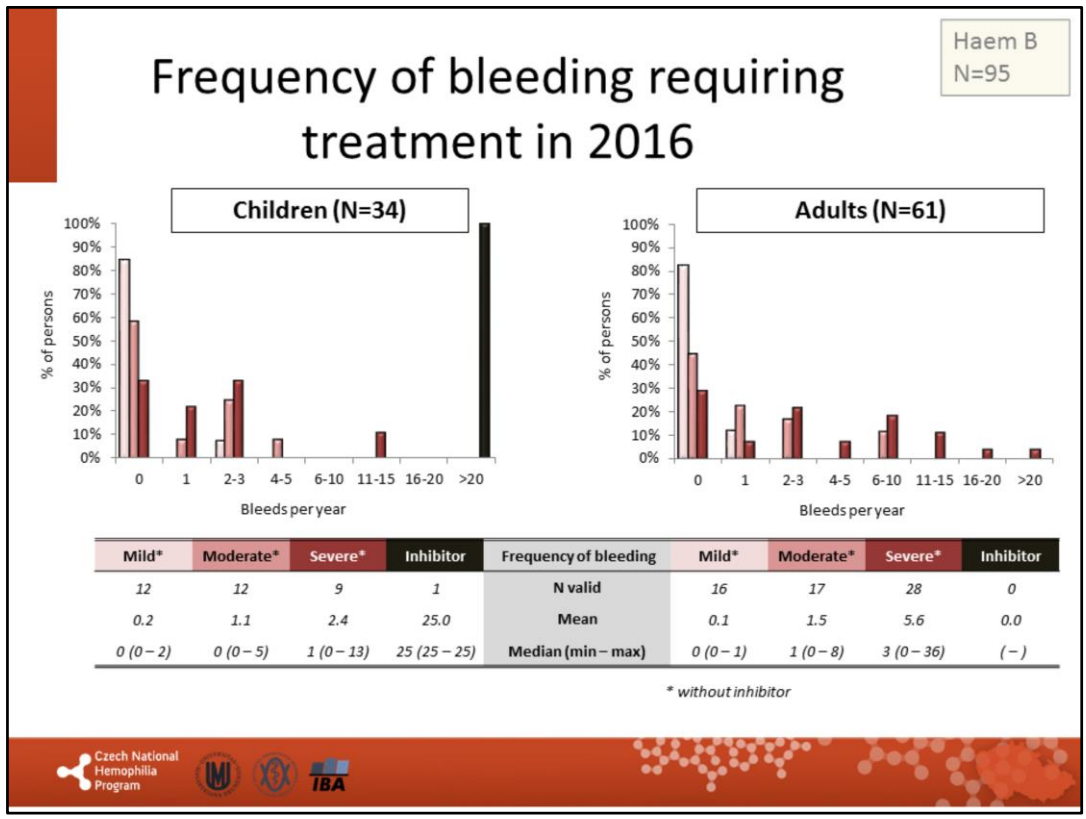
Very low number of HIV positive PWH due to low/no access to contaminated concentrates in 80s and 90s. Our current treatment is on a very high safety level. No new HIV reported in any PWH since late 90s.

Part B.2

Treatment outcomes and bleeding frequency Haemophilia B



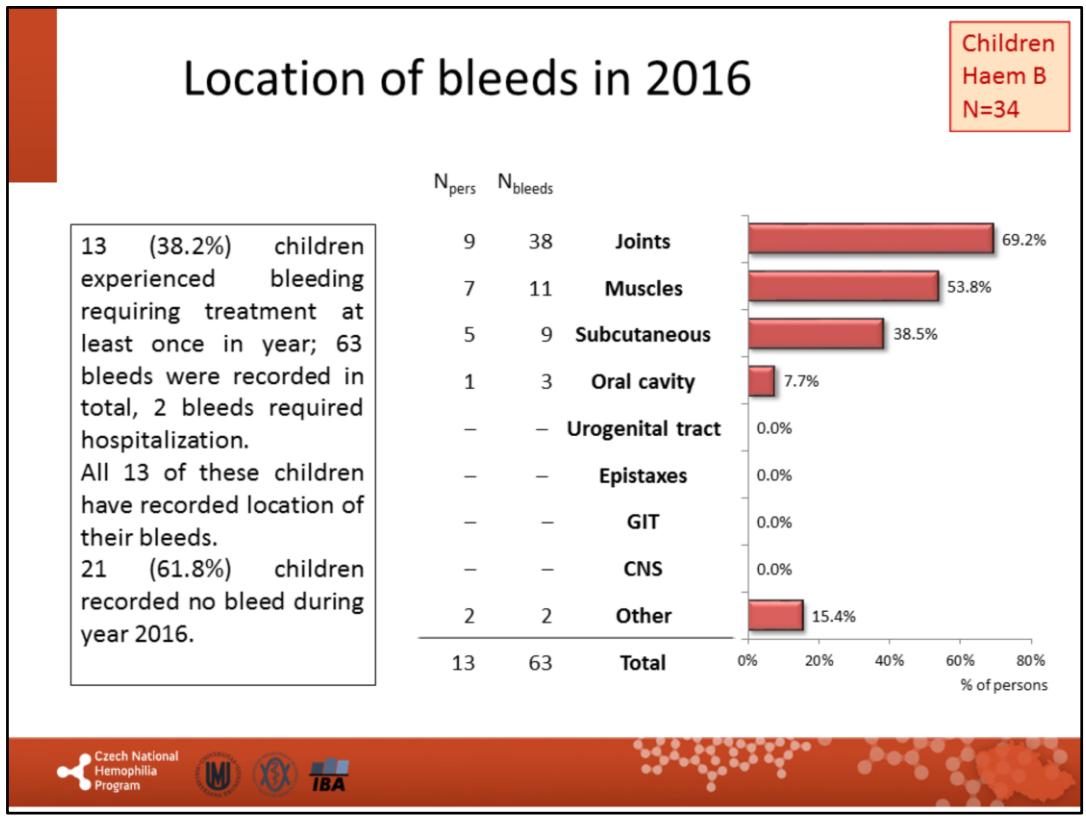
See previous comment for the same slide related to HA.



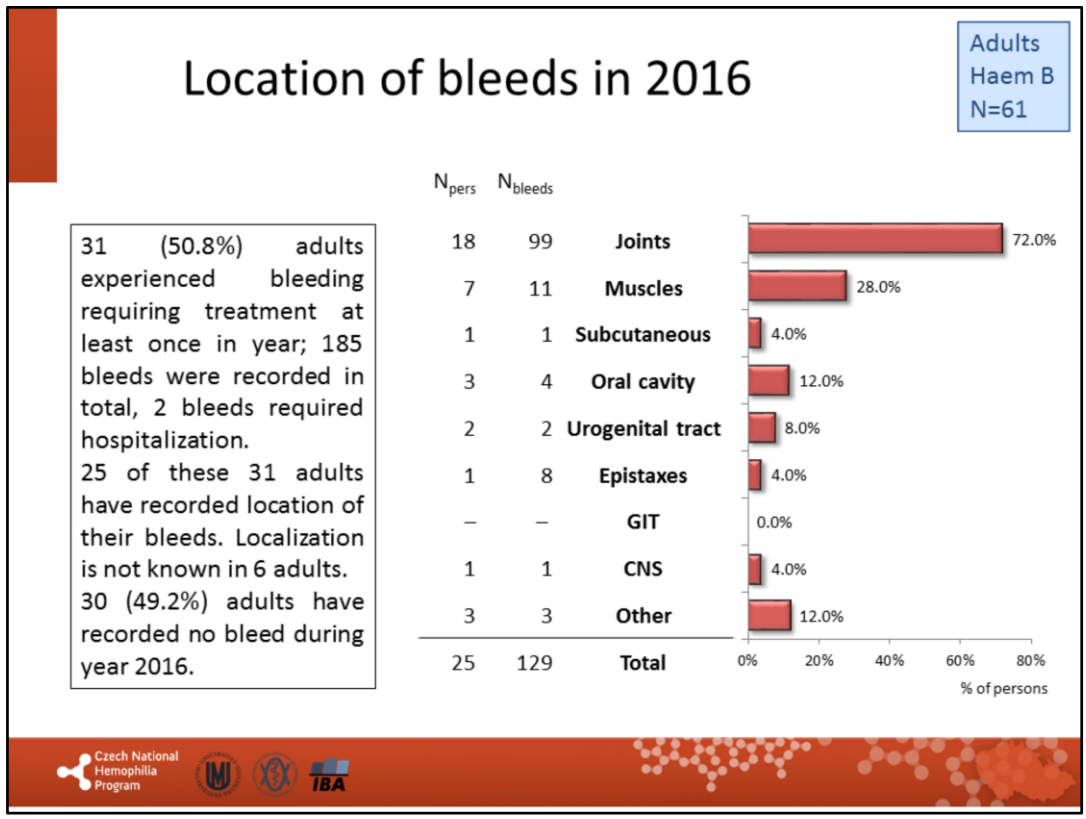
Mild*	Moderate*	Severe*	Inhibitor	Frequency of bleeding	Mild*	Moderate*	Severe*	Inhibitor
12	12	9	1	N valid	16	17	28	0
0.2	1.1	2.4	25.0	Mean	0.1	1.5	5.6	0.0
0 (0 – 2)	0 (0 – 5)	1 (0 – 13)	25 (25 – 25)	Median (min – max)	0 (0 – 1)	1 (0 – 8)	3 (0 – 36)	(–)

* without inhibitor

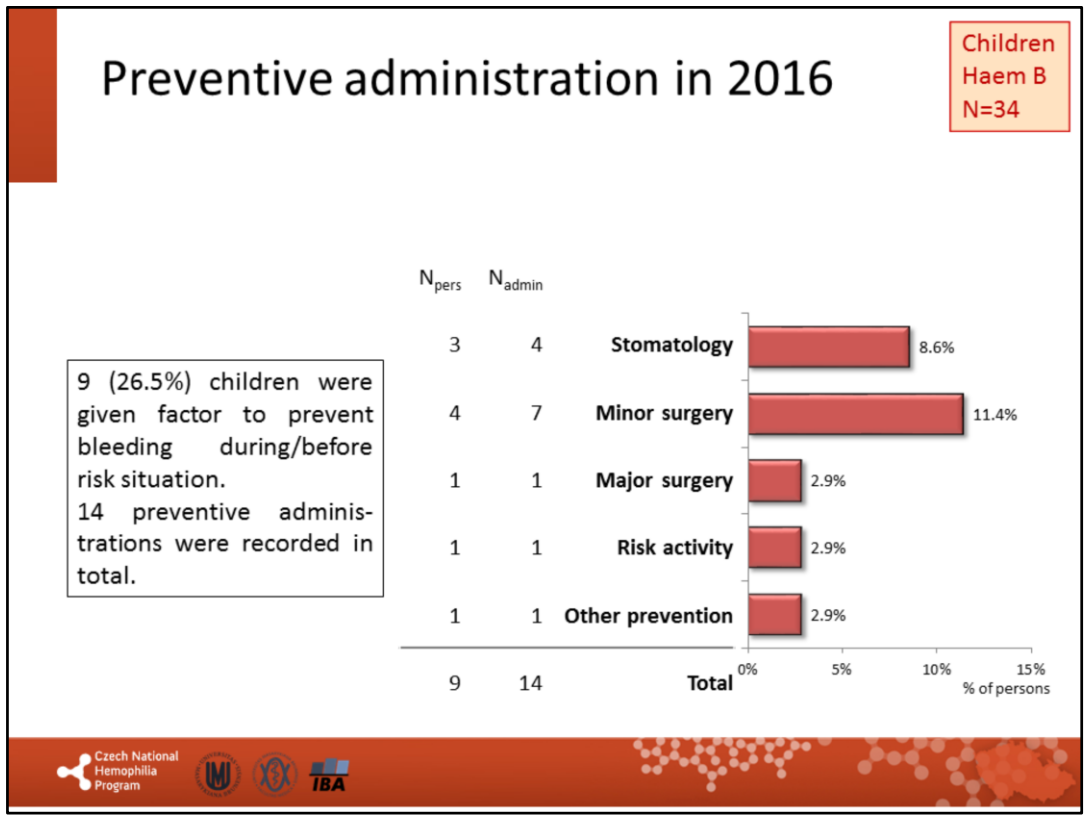
Data shown document good efficacy of care provided to Czech PWH, no matter what age category they are. Mean/Median number of bleedings per year (ABR) is 5,6/3 for adults and 2,4/1 in children with severe HB.



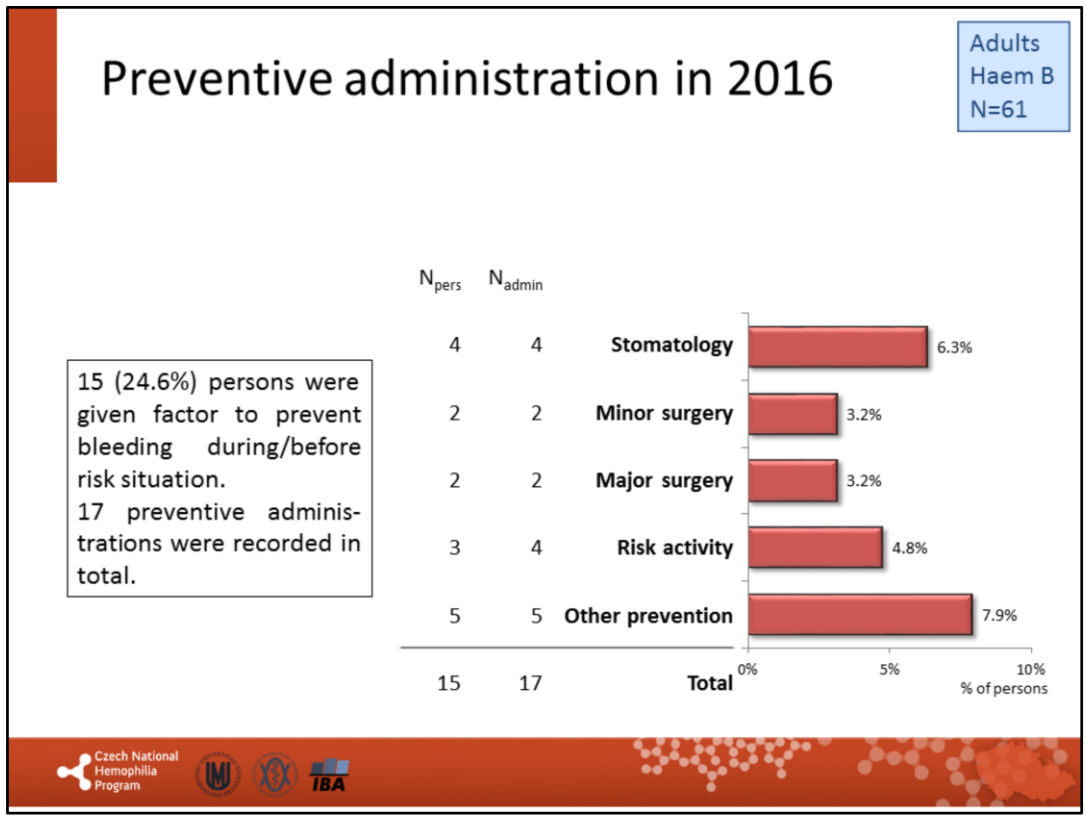
There was no CNS bleed in children with haemophilia B in 2016. 61,6% of children had no bleed at all.



Bleeding events in adults.



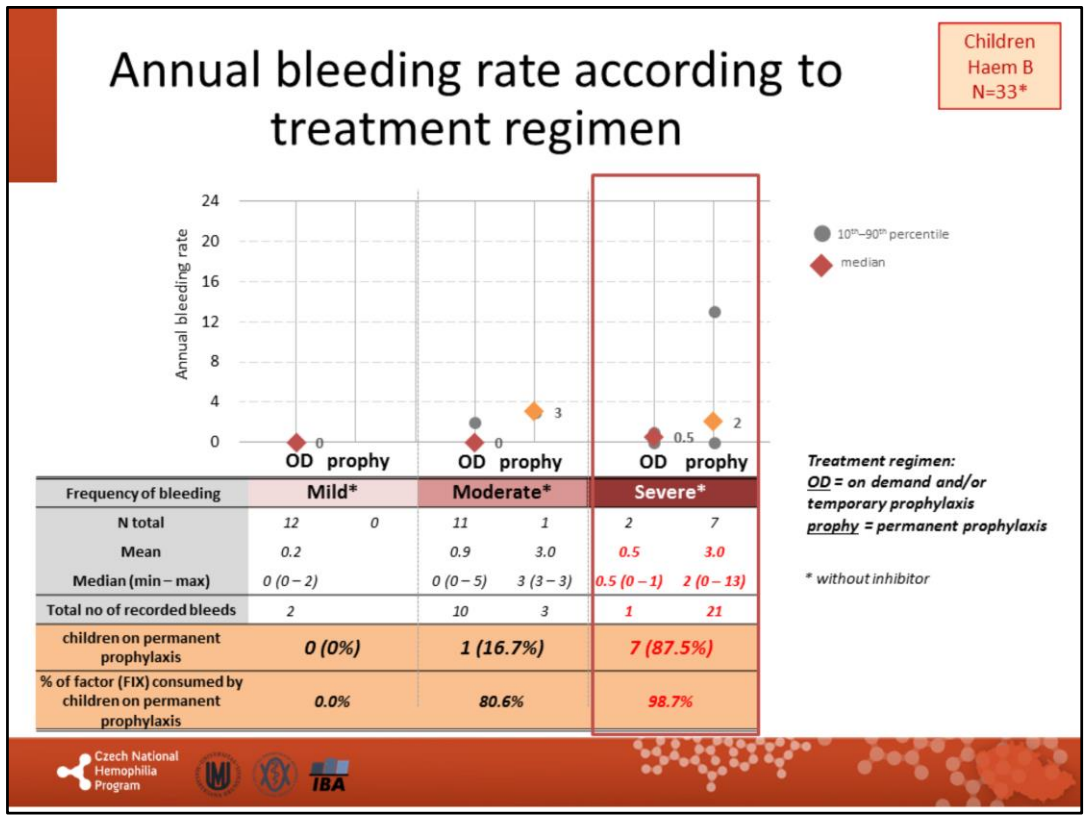
This figure refers to preventive factors administration in children with HB.



This figure refers to preventive factors administration in adults with HB.

Part B.3

ABR according to treatment regimen Haemophilia B without inhibitor



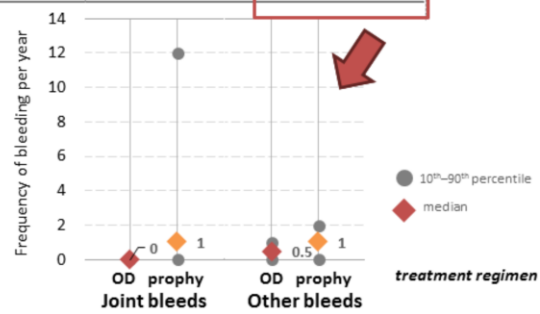
The data on bleeding rate in children with HB. The interval range in children with severe HB should be smaller, though. In general, less bleeds in children with HB.

Joint and other bleeds according to treatment regimen

Children
Haem B
N=33*

Frequency of bleeding	Mild*		Moderate*		Severe*	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy
N valid	12	0	11	1	2	7
JOINT BLEEDS						
Mean	0.0		0.4	3.0	0.0	2.3
Median (range)	0 (0 – 0)		0 (0 – 2)	3 (3 – 3)	0 (0 – 0)	1 (0 – 12)
Total no of recorded bleeds	0		4	3	0	16
OTHER BLEEDS						
Mean	0.2		0.5	0.0	0.5	0.9
Median (range)	0 (0 – 2)		0 (0 – 3)	0 (0 – 0)	0.5 (0 – 1)	1 (0 – 2)
Total no of recorded bleeds	2		6	0	1	6

** without inhibitor*



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

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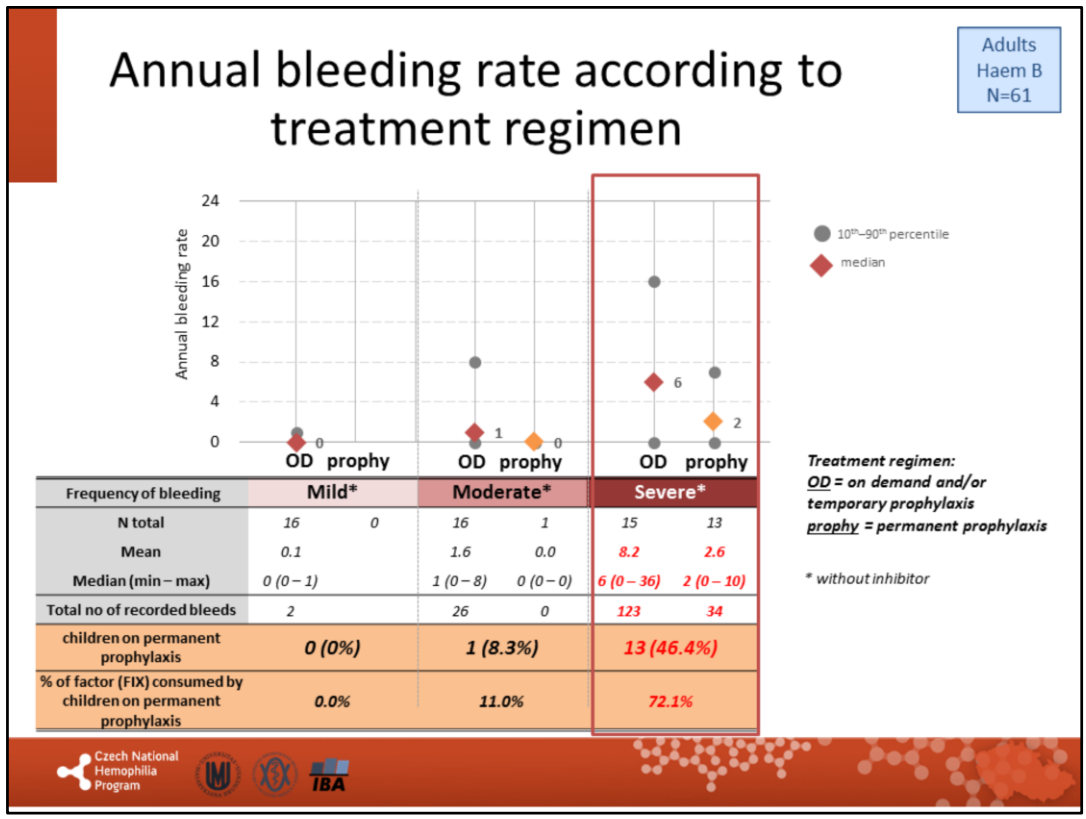
The same is true for joint bleeds.



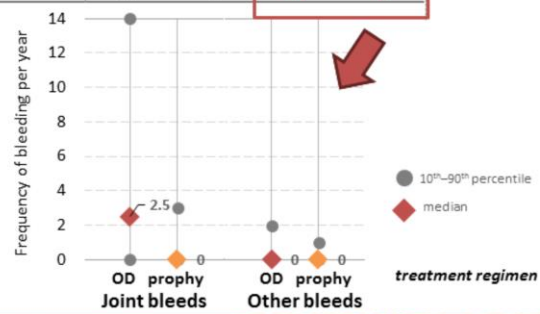
As well as in HA, adults with severe haemophilia B, who bleed frequently should be commenced on prophylaxis.

Joint and other bleeds according to treatment regimen

Adults
Haem B
N=55*

Frequency of bleeding	Mild*		Moderate*		Severe*	
Treatment regimen	OD	prophy	OD	prophy	OD	prophy
N valid	15	0	14	1	14	11
JOINT BLEEDS						
Mean	0.0		0.1	0.0	5.5	1.5
Median (range)	0 (0 – 0)		0 (0 – 1)	0 (0 – 0)	2.5 (0 – 15)	0 (0 – 7)
Total no of recorded bleeds	0		2	0	77	17
OTHER BLEEDS						
Mean	0.1		1.0	0.0	0.7	0.5
Median (range)	0 (0 – 1)		0 (0 – 8)	0 (0 – 0)	0 (0 – 5)	0 (0 – 2)
Total no of recorded bleeds	1		14	0	10	5

** without inhibitor; missing location of bleeds in 6 adults*



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

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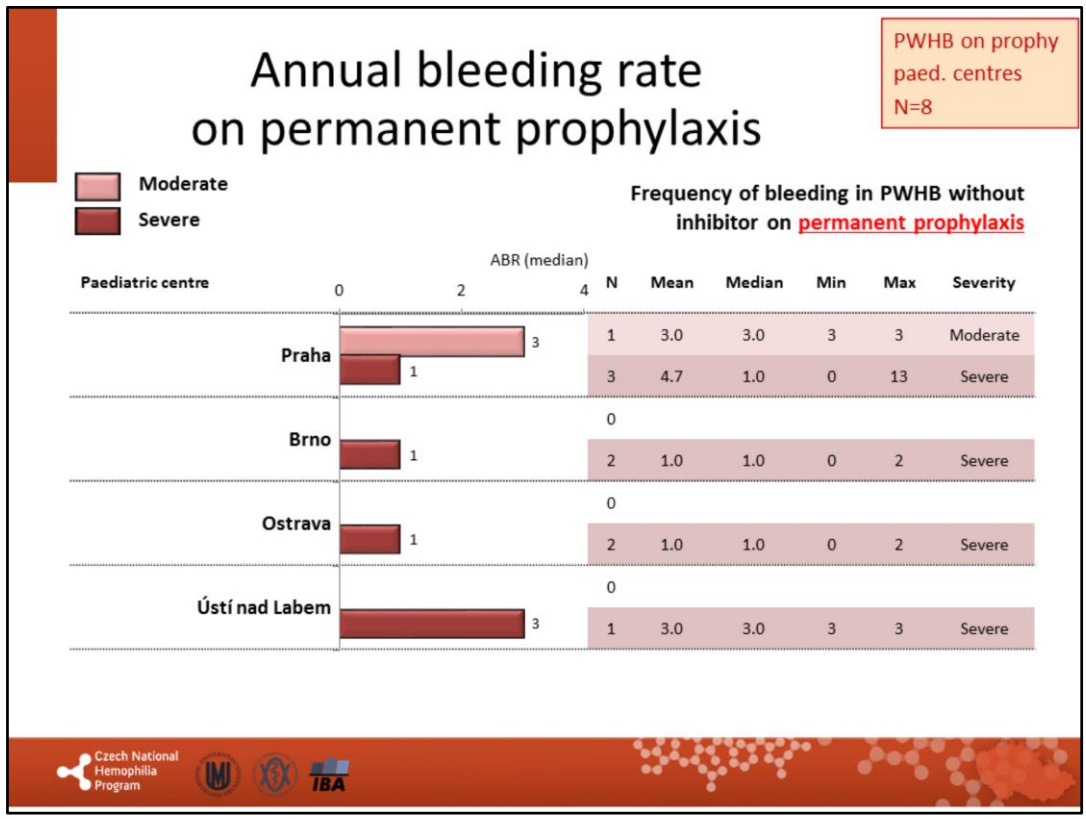
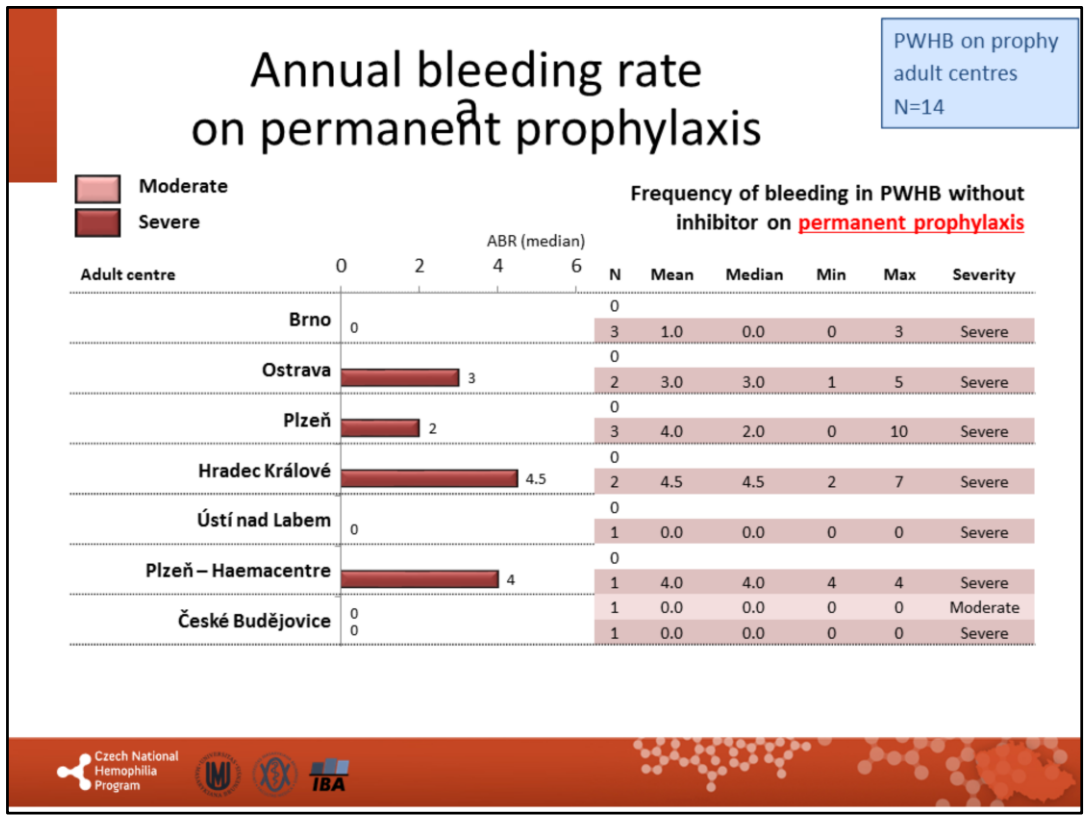
The same is true also for joint bleeds in PWHB.

Part B.4

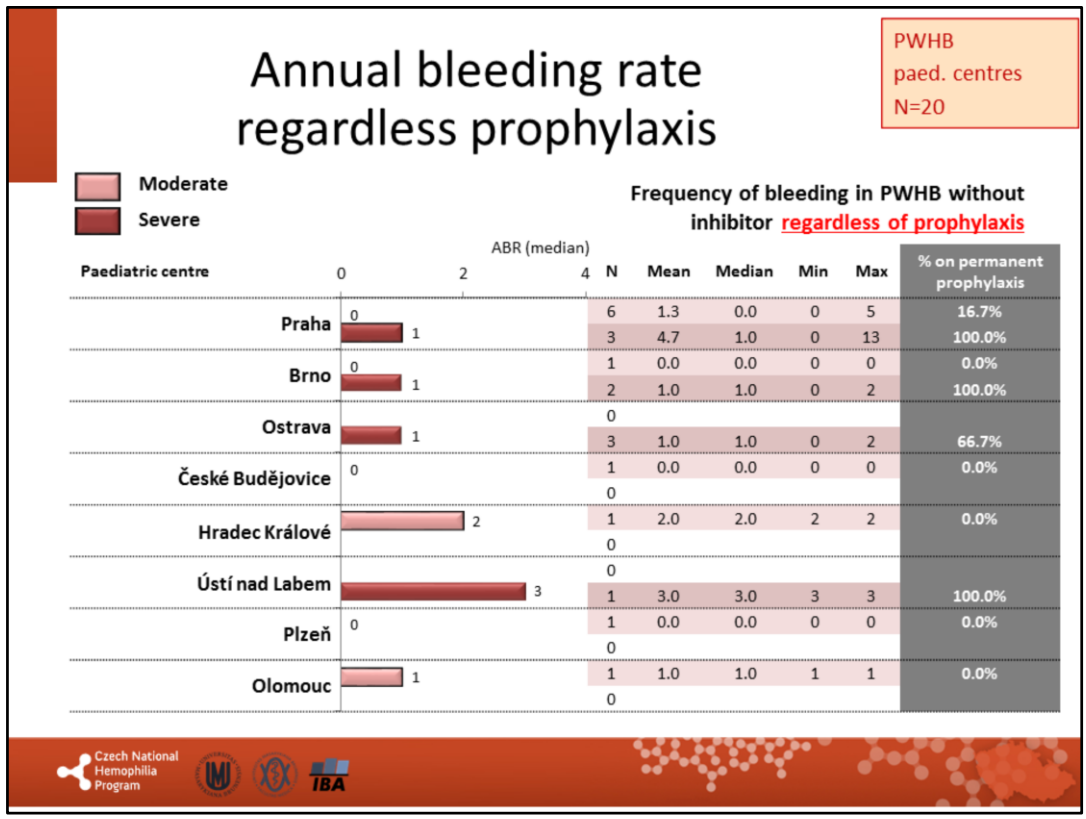
ABR according to centres Haemophilia B (PWHB)



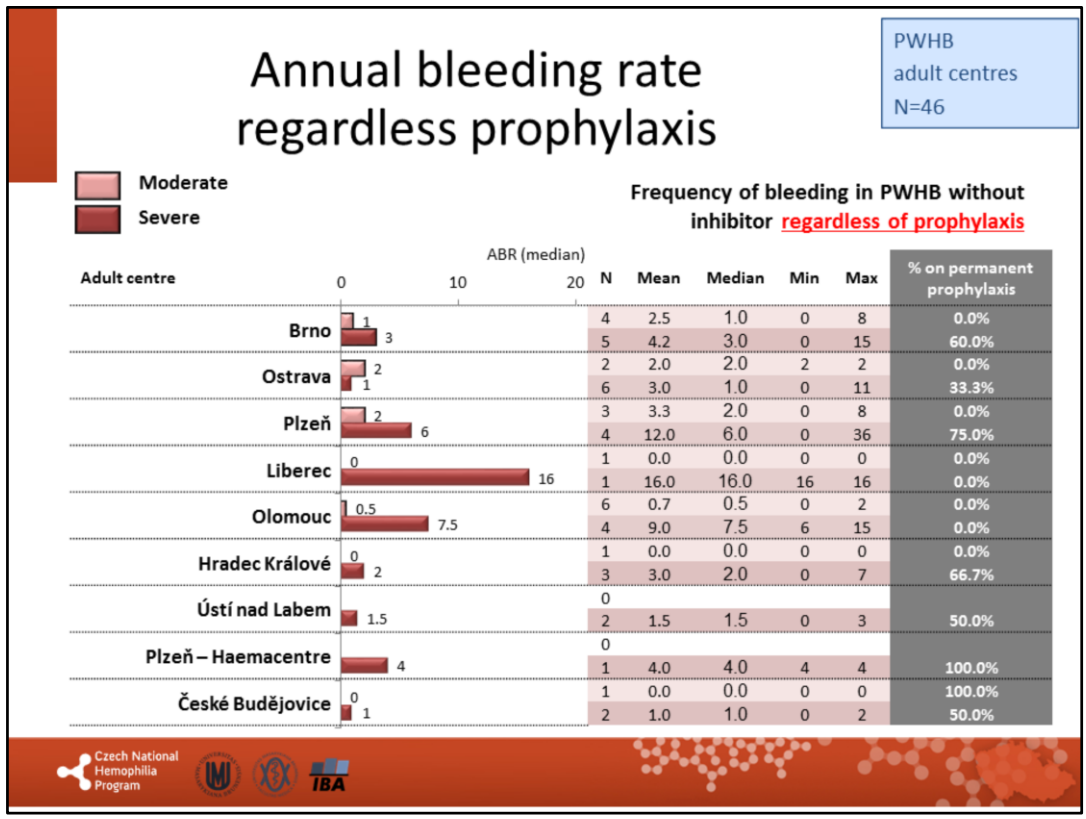
Not all centres treat children with HB. The median ABR is relatively low, but at least one child with severe HB has ABR over 10 despite of prophylaxis.



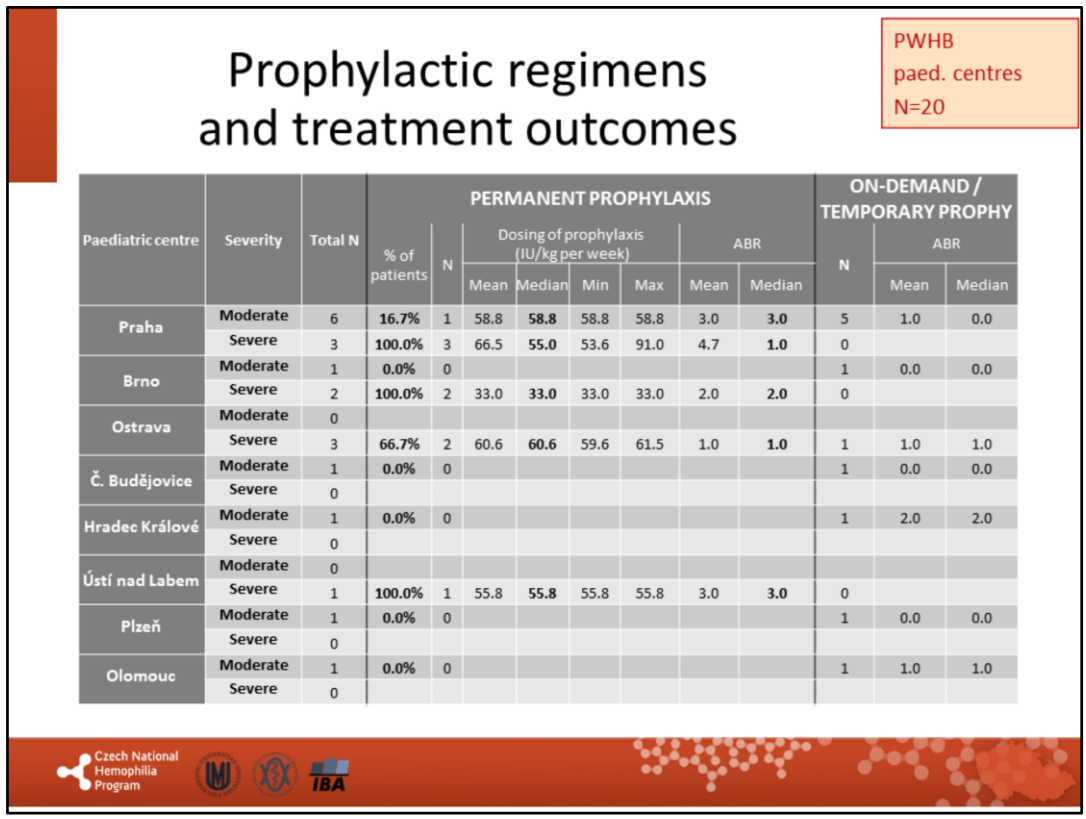
Similar situation for adults with HB. HB, though, means significantly less burden for patients, compared to adults with HA.



This slide describes the treatment of children with HB regardless of prophylaxis in those centres, which treat PWHB.



This slide describes the treatment of adults with HB regardless of prophylaxis in those centres, which treat PWHB.



Paediatric centre	Severity	Total N	PERMANENT PROPHYLAXIS								ON-DEMAND / TEMPORARY PROPHY		
			% of patients	N	Dosing of prophylaxis (IU/kg per week)				ABR		N	ABR	
					Mean	Median	Min	Max	Mean	Median		Mean	Median
Praha	Moderate	6	16.7%	1	58.8	58.8	58.8	58.8	3.0	3.0	5	1.0	0.0
	Severe	3	100.0%	3	66.5	55.0	53.6	91.0	4.7	1.0	0		
Brno	Moderate	1	0.0%	0							1	0.0	0.0
	Severe	2	100.0%	2	33.0	33.0	33.0	33.0	2.0	2.0	0		
Ostrava	Moderate	0											
	Severe	3	66.7%	2	60.6	60.6	59.6	61.5	1.0	1.0	1	1.0	1.0
Č. Budějovice	Moderate	1	0.0%	0							1	0.0	0.0
	Severe	0											
Hradec Králové	Moderate	1	0.0%	0							1	2.0	2.0
	Severe	0											
Ústí nad Labem	Moderate	0											
	Severe	1	100.0%	1	55.8	55.8	55.8	55.8	3.0	3.0	0		
Plzeň	Moderate	1	0.0%	0							1	0.0	0.0
	Severe	0											
Olomouc	Moderate	1	0.0%	0							1	1.0	1.0
	Severe	0											

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

PWHB
adult centres
N=46

Adult centre	Severity	Total N	PERMANENT PROPHYLAXIS									ON-DEMAND / TEMPORARY PROPHY			
			% of patients	N	Dosing of prophylaxis (IU/kg per week)				ABR		Age	N	ABR		Age
					Mean	Median	Min	Max	Mean	Median	Median		Mean	Median	Median
Brno	Moderate	4	0.0%	0								4	2.5	1.0	47
	Severe	5	60.0%	3	50.5	48.0	46.2	57.2	1.0	0.0	24	2	9.0	9.0	61
Ostrava	Moderate	2	0.0%	0								2	2.0	2.0	25
	Severe	6	33.3%	2	45.8	45.8	37.9	53.7	3.0	3.0	43	4	3.0	0.5	53
Plzeň	Moderate	3	0.0%	0					0.0	0.0	0	3	3.3	2.0	54
	Severe	4	75.0%	3	8.1	6.1	5.3	13.0	4.0	2.0	40	1	36.0	36.0	34
Liberec	Moderate	1	0.0%	0								1	0.0	0.0	43
	Severe	1	0.0%	0								1	16.0	16.0	24
Olomouc	Moderate	6	0.0%	0								6	0.7	0.5	43
	Severe	4	0.0%	0								4	9.0	7.5	49
Hradec Králové	Moderate	1	0.0%	0								1	0.0	0.0	62
	Severe	3	66.7%	2	108.2	108.2	108.2	108.2	4.5	4.5	38	1	0.0	0.0	60
Ústí n. Labem	Moderate	0													
	Severe	2	50.0%	1	49.3	49.3	49.3	49.3	0.0	0.0	21	1	3.0	3.0	45
Plzeň - Haemacentre	Moderate	0													
	Severe	1	100.0%	1	37.5	37.5	37.5	37.5	4.0	4.0	35	0			
Č. Budějovice	Moderate	1	100.0%	1	6.7	6.7	6.7	6.7	0.0	0.0	50	0			
	Severe	2	50.0%	1	42.1	42.1	42.1	42.1	0.0	0.0	53	1	2.0	2.0	43

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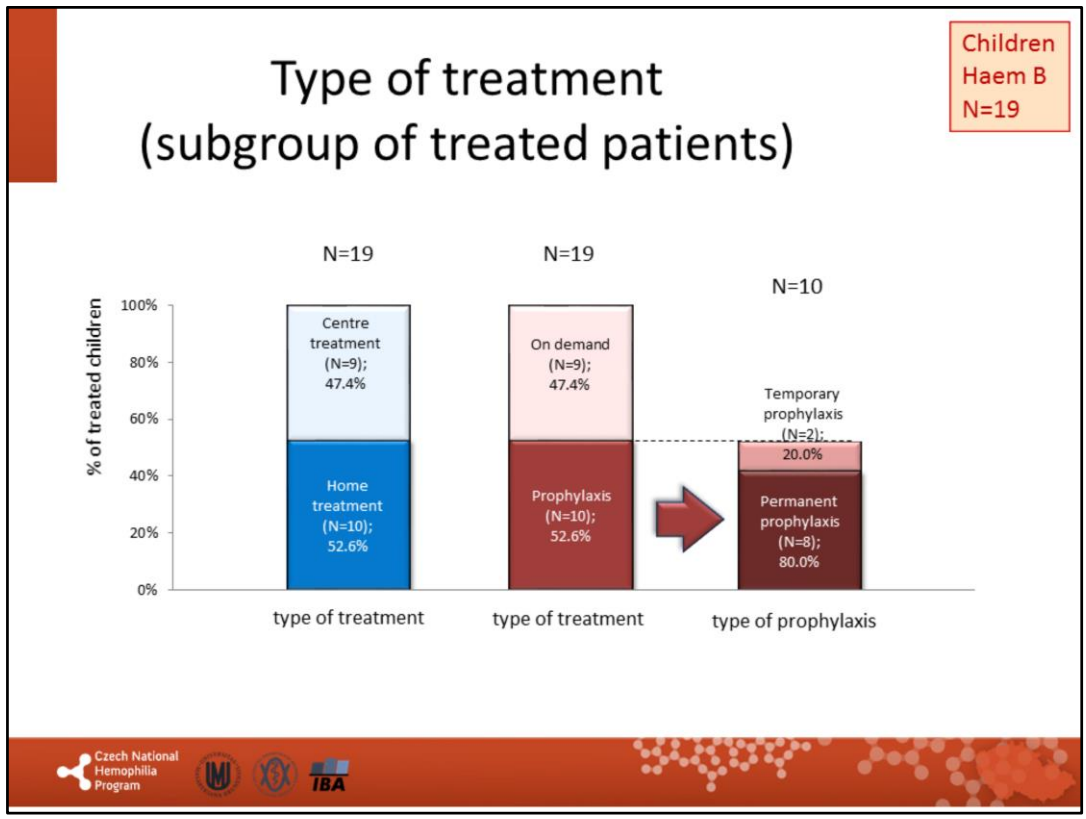
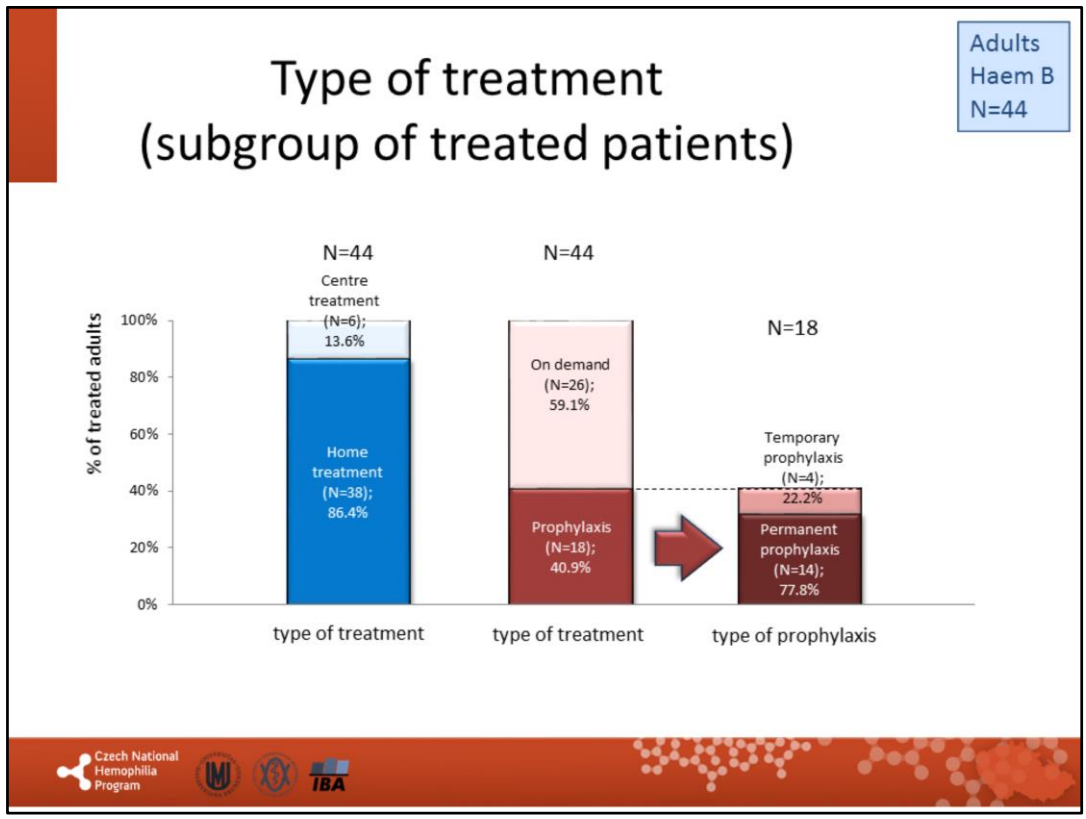
More detailed description of prophylactic dosing/regimens used by different adult centres within CNHP and its correlation with annual bleeding rates in respective centres.



Only 52,5% of children treated in 2016 took the advantage of home treatment. 52% of treated children were commenced on any type of prophylaxis and 80% out of those on prophylaxis were on permanent prophy in 2016.



86% of adults treated in 2016 took the advantage of home treatment. 40% of treated adults were commenced on any type of prophylaxis and 78% out of those on prophylaxis were on permanent prophy in 2016.

Part C.1

Treatment data and factor consumption Haemophilia A and B

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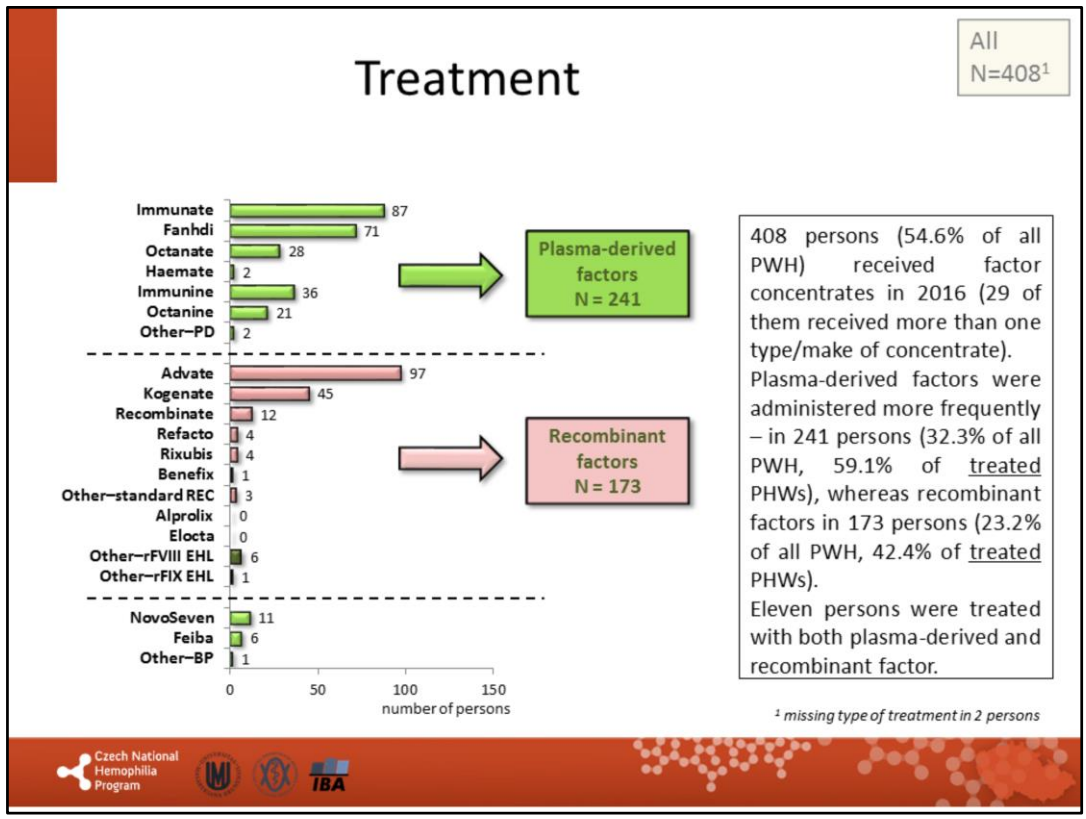
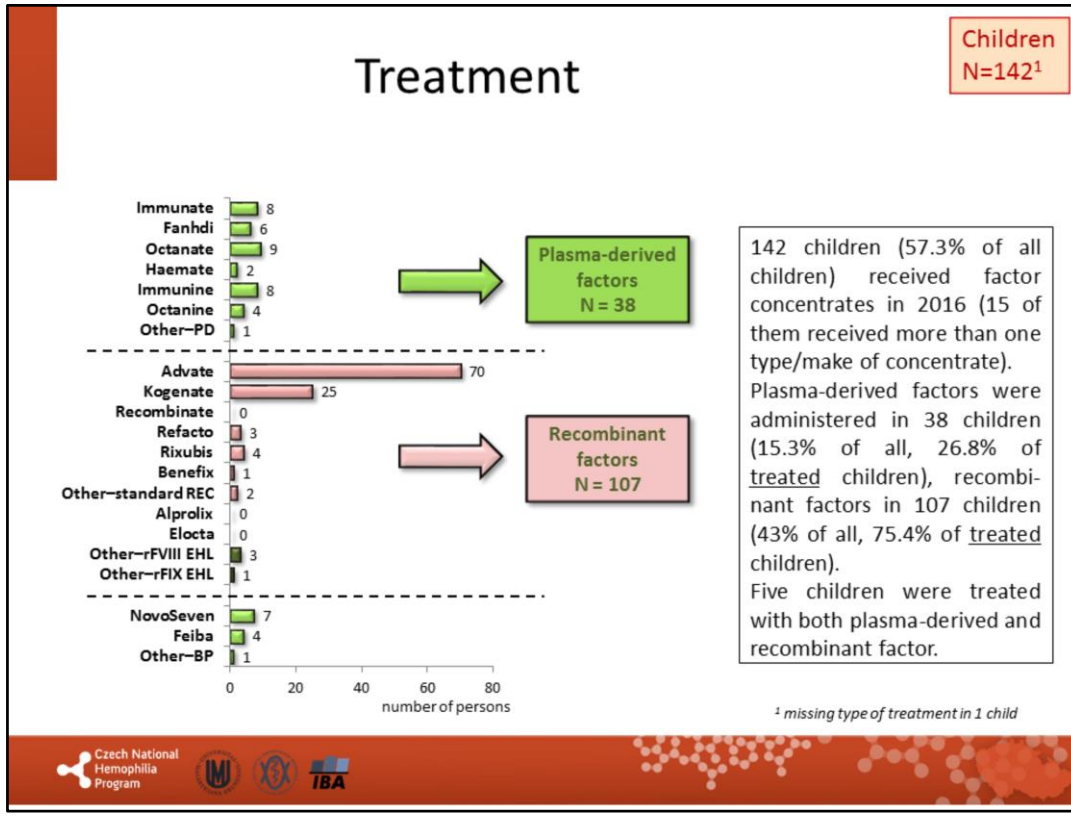
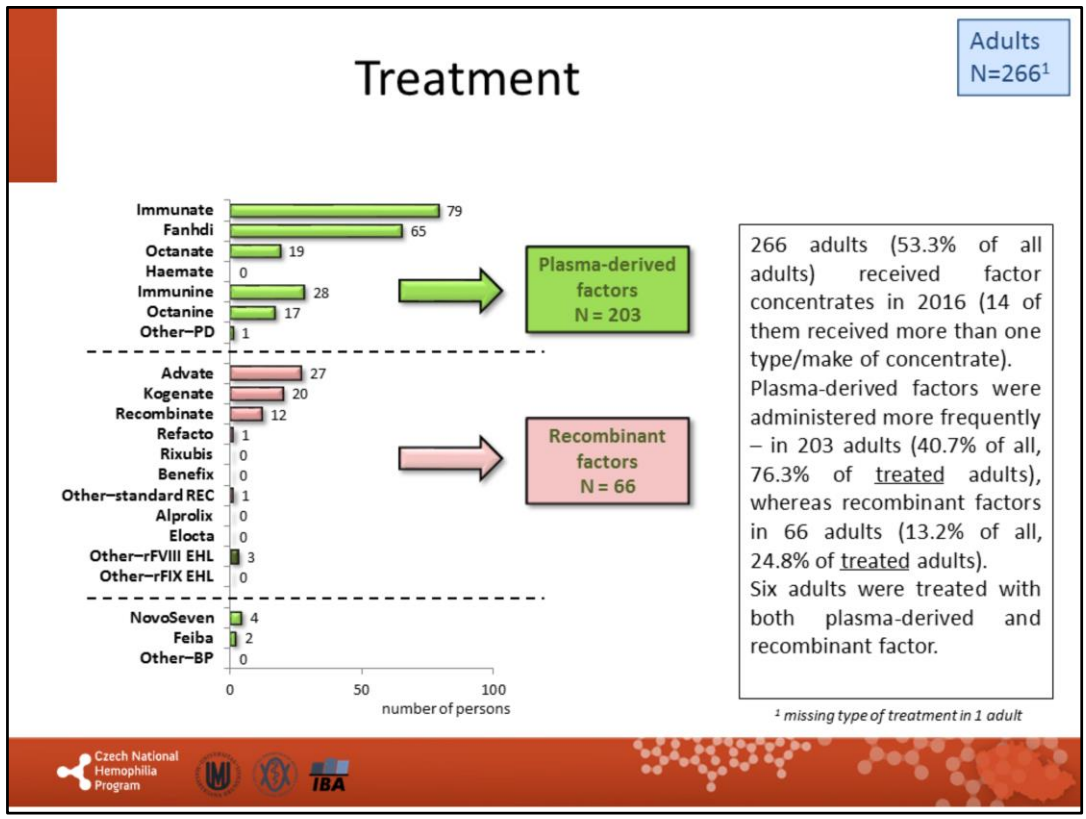


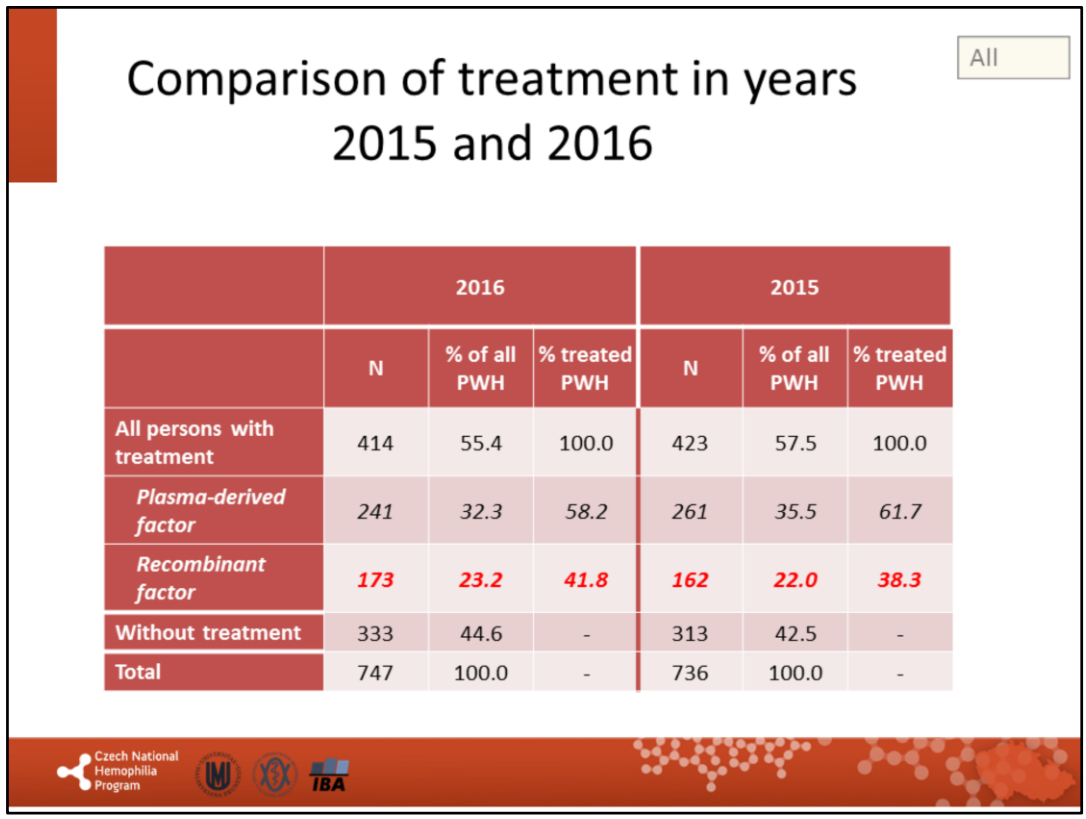
42% of PWH registered in CNHP registry and treated with any factor concentrate were treated with recombinants in 2016. The number of PWH treated with recombinants is gradually increasing over last several years. This is not only due to the recommendation of CNHP to treat PUPs with recombinants (since 2006), but also reflects switches of older children and adults to rFVIII in some cases.



Over 75% of children, who were given factor concentrate in 2016, were treated with recombinants.

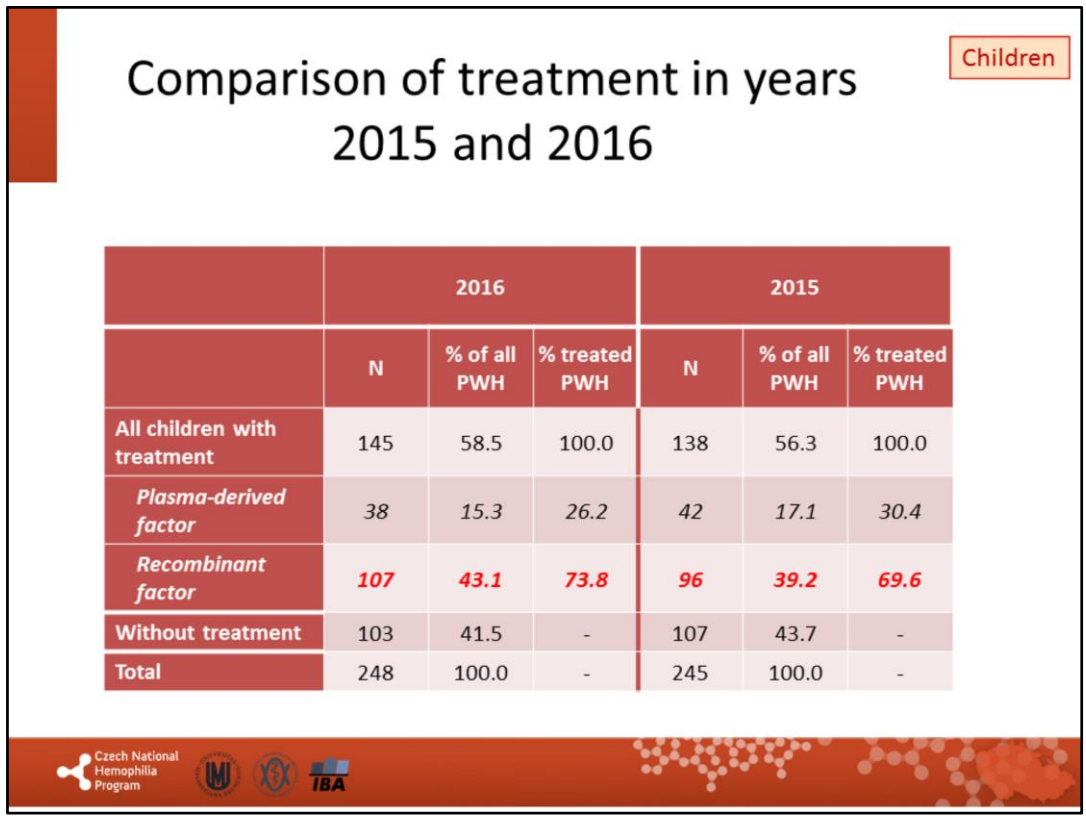


Number of adult PWH treated with recombinants is slowly increasing (currently 25% of those treated with factor concentrate in 2016 and registered within CNHP registry).



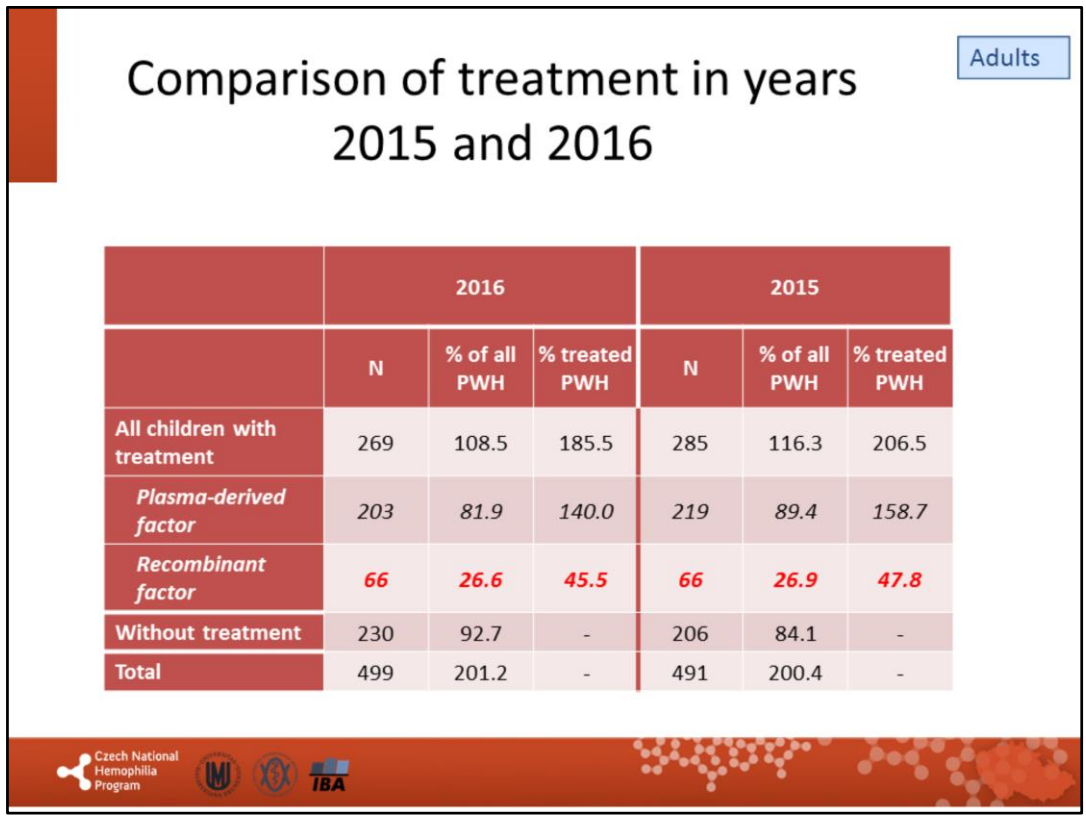
	2016			2015		
	N	% of all PWH	% treated PWH	N	% of all PWH	% treated PWH
All persons with treatment	414	55.4	100.0	423	57.5	100.0
Plasma-derived factor	*241*	*32.3*	*58.2*	*261*	*35.5*	*61.7*
Recombinant factor	***173***	***23.2***	***41.8***	***162***	***22.0***	***38.3***
Without treatment	333	44.6	-	313	42.5	-
Total	747	100.0	-	736	100.0	-

This table compares data between 2015 and 2016. E.g. you can see, that percentage of patients treated with recombinant concentrates and registered within CNHP registry changed from 38,3% in 2015 to 41,8% in 2016.



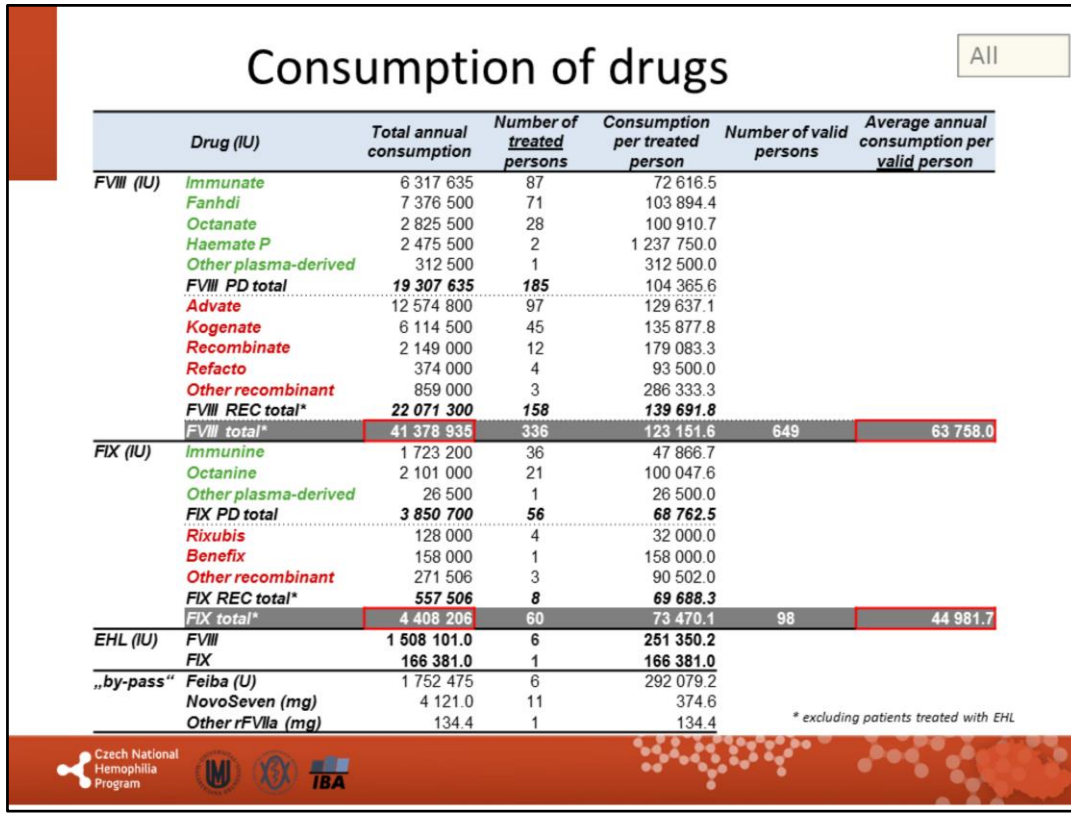
	2016			2015		
	N	% of all PWH	% treated PWH	N	% of all PWH	% treated PWH
All children with treatment	145	58.5	100.0	138	56.3	100.0
Plasma-derived factor	*38*	*15.3*	*26.2*	*42*	*17.1*	*30.4*
Recombinant factor	***107***	***43.1***	***73.8***	***96***	***39.2***	***69.6***
Without treatment	103	41.5	-	107	43.7	-
Total	248	100.0	-	245	100.0	-

This table compares data between 2015 and 2016. E.g. you can see, that percentage of patients treated with recombinant concentrates and registered within CNHP registry changed from 69,6% in 2015 to 73,8% in 2016.



	2016			2015		
	N	% of all PWH	% treated PWH	N	% of all PWH	% treated PWH
All children with treatment	269	108.5	185.5	285	116.3	206.5
Plasma-derived factor	*203*	*81.9*	*140.0*	*219*	*89.4*	*158.7*
Recombinant factor	***66***	***26.6***	***45.5***	***66***	***26.9***	***47.8***
Without treatment	230	92.7	-	206	84.1	-
Total	499	201.2	-	491	200.4	-

This table compares data between 2015 and 2016. E.g. you can see, that percentage of patients treated with recombinant concentrates and registered within CNHP registry changed from 47,8% in 2015 to 45,5% in 2016.



Consumption of drugs

All

	Drug (IU)	Total annual consumption	Number of treated persons	Consumption per treated person	Number of valid persons	Average annual consumption per valid person
FVIII (IU)	Immunate	6 317 635	87	72 616.5		
	Fanhdi	7 376 500	71	103 894.4		
	Octanate	2 825 500	28	100 910.7		
	Haemate P	2 475 500	2	1 237 750.0		
	Other plasma-derived	312 500	1	312 500.0		
	FVIII PD total	**19 307 635**	**185**	104 365.6		
	Advate	12 574 800	97	129 637.1		
	Kogenate	6 114 500	45	135 877.8		
	Recombinate	2 149 000	12	179 083.3		
	Refacto	374 000	4	93 500.0		
	Other recombinant	859 000	3	286 333.3		
	FVIII REC total*	**22 071 300**	**158**	**139 691.8**		
	FVIII total*	41 378 935	336	123 151.6	649	63 758.0
FIX (IU)	Immunine	1 723 200	36	47 866.7		
	Octanine	2 101 000	21	100 047.6		
	Other plasma-derived	26 500	1	26 500.0		
	FIX PD total	**3 850 700**	**56**	**68 762.5**		
	Rixubis	128 000	4	32 000.0		
	Benefix	158 000	1	158 000.0		
	Other recombinant	271 506	3	90 502.0		
	FIX REC total*	**557 506**	**8**	**69 688.3**		
	FIX total*	4 408 206	60	73 470.1	98	44 981.7
EHL (IU)	**FVIII**	**1 508 101.0**	**6**	**251 350.2**		
	FIX	**166 381.0**	**1**	**166 381.0**		
„by-pass"	Feiba (U)	1 752 475	6	292 079.2		
	NovoSeven (mg)	4 121.0	11	374.6		
	Other rFVIIa (mg)	134.4	1	134.4		

* excluding patients treated with EHL

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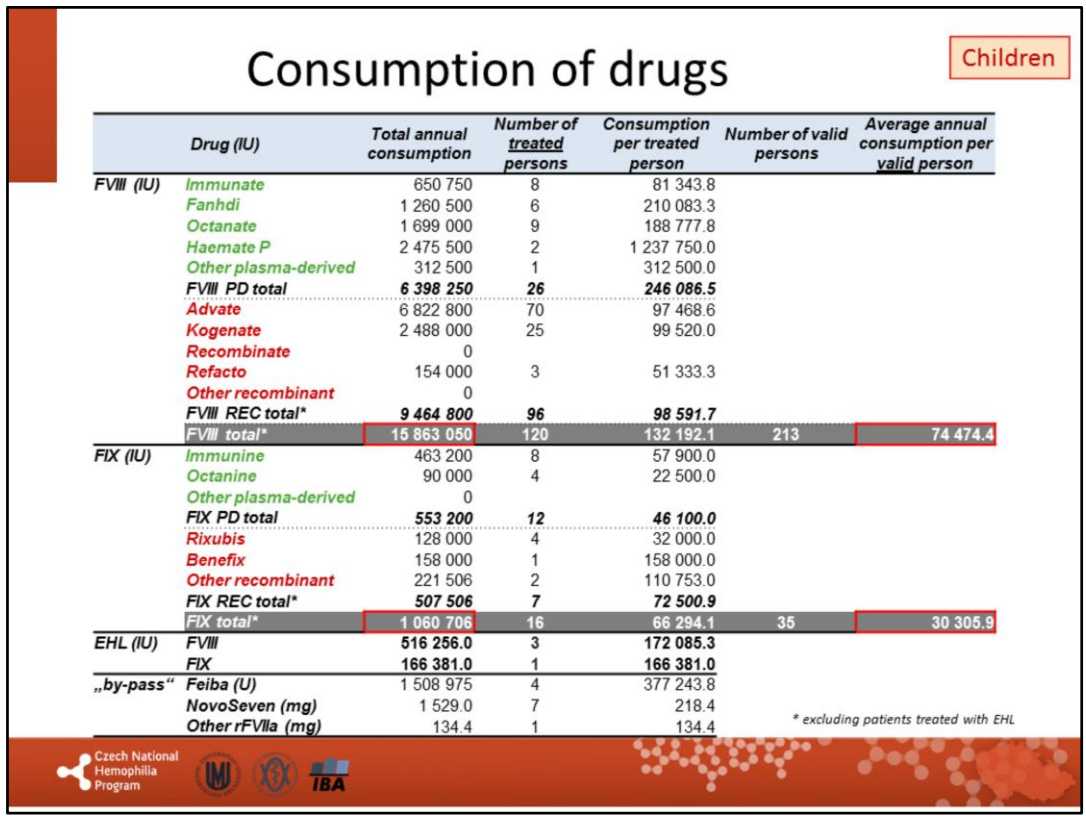
Absolute numbers of respective concentrates in this figure refer ONLY to the records within CNHP registry, which have been updated in 2016. The most important information on this slide is „Average annual consumption per treated person". This reflects nation-wide consumption of factor concentrate per treated PWH.

„Average annual consumption per valid person" gives us an information on the consumption per patient, regardless of his treatment status and severity of the disease. It also enables us to estimate the national-wide consumption of FVIII. As we do know, that there were 937 haemophilia A patients in 2016 (WFH survey 2016) the total consumption was approximately 59 741 246 IU of FVIII/year in the Czech Republic. (SUKL reported 64 235 500 units of FVIII purchased in CZ during 2016). In other words, it means, that the total consumption was about 5,6 IU/capita of FVIII in 2016 (SUKL reported 6 IU/capita). This is a significant increase (over 1IU/capita, cca 20%l) compared to 2015, probably due to 4 ITI (some of them high dosed) commenced in children in 2016 as well as increased number and perhaps dose of prophylaxis in adults.

Number of haemophiliacs B in the Czech Republic was 139 in 2016, the total consumption was approx. 6 252 498 IU of FIX/year, i.e. 0.59 IU/capita, thus no major change compared to 2015 (SUKL reported 6 944 750 IU of FIX purchased in 2016). New recombinant FIX were introduced in 2016.

EHL (Extended Half-Life) products are currently used only through clinical trials, though two of them were registered in CZ in 2016

Significant increase in aPCC consumption is caused mainly by aPCC prophylaxis in two children with inhibitors (in one as a part of Bonn ITI regimen), but more aPCC was used also in adults in 2016.



Consumption of drugs

Children

	Drug (IU)	Total annual consumption	Number of treated persons	Consumption per treated person	Number of valid persons	Average annual consumption per valid person
FVIII (IU)	Immunate	650 750	8	81 343.8		
	Fanhdi	1 260 500	6	210 083.3		
	Octanate	1 699 000	9	188 777.8		
	Haemate P	2 475 500	2	1 237 750.0		
	Other plasma-derived	312 500	1	312 500.0		
	FVIII PD total	**6 398 250**	**26**	**246 086.5**		
	Advate	6 822 800	70	97 468.6		
	Kogenate	2 488 000	25	99 520.0		
	Recombinate	0				
	Refacto	154 000	3	51 333.3		
	Other recombinant	0				
	FVIII REC total*	**9 464 800**	**96**	**98 591.7**		
	FVIII total*	15 863 050	120	132 192.1	213	74 474.4
FIX (IU)	Immunine	463 200	8	57 900.0		
	Octanine	90 000	4	22 500.0		
	Other plasma-derived	0				
	FIX PD total	**553 200**	**12**	**46 100.0**		
	Rixubis	128 000	4	32 000.0		
	Benefix	158 000	1	158 000.0		
	Other recombinant	221 506	2	110 753.0		
	FIX REC total*	**507 506**	**7**	**72 500.9**		
	FIX total*	1 060 706	16	66 294.1	35	30 305.9
EHL (IU)	**FVIII**	**516 256.0**	**3**	**172 085.3**		
	FIX	**166 381.0**	**1**	**166 381.0**		
„by-pass“	Feiba (U)	1 508 975	4	377 243.8		
	NovoSeven (mg)	1 529.0	7	218.4		
	Other rFVIIa (mg)	134.4	1	134.4		

* excluding patients treated with EHL

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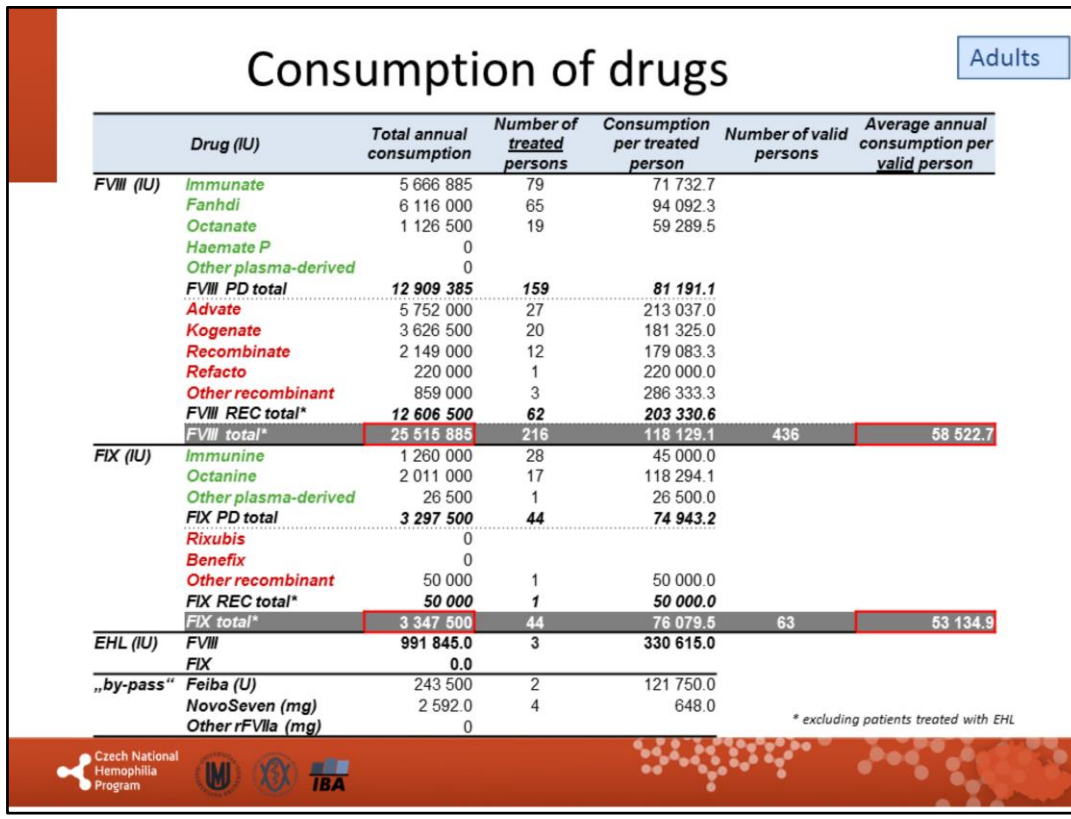
IBA

Absolute numbers of respective concentrates in this figure refer ONLY to the records within CNHP registry, which have been updated in 2016. The most important information on this slide is „Average annual consumption per treated person“. This reflects nation-wide consumption of factor concentrate per treated child with haemophilia.

Please note, that amount of FVIII is higher in children (median age 10 years), than in adults (median age around 40 years)! Thus, children with average weight around 25 kg had comparable or even higher consumption of FVIII to an adult weighting around 75 kg in average. Situation is similar for FIX



Consumption of drugs

Adults

	Drug (IU)	Total annual consumption	Number of treated persons	Consumption per treated person	Number of valid persons	Average annual consumption per valid person
FVIII (IU)	Immunate	5 666 885	79	71 732.7		
	Fanhdi	6 116 000	65	94 092.3		
	Octanate	1 126 500	19	59 289.5		
	Haemate P	0				
	Other plasma-derived	0				
	FVIII PD total	**12 909 385**	**159**	**81 191.1**		
	Advate	5 752 000	27	213 037.0		
	Kogenate	3 626 500	20	181 325.0		
	Recombinate	2 149 000	12	179 083.3		
	Refacto	220 000	1	220 000.0		
	Other recombinant	859 000	3	286 333.3		
	FVIII REC total*	**12 606 500**	**62**	**203 330.6**		
	FVIII total*	25 515 885	216	118 129.1	436	58 522.7
FIX (IU)	Immunine	1 260 000	28	45 000.0		
	Octanine	2 011 000	17	118 294.1		
	Other plasma-derived	26 500	1	26 500.0		
	FIX PD total	**3 297 500**	**44**	**74 943.2**		
	Rixubis	0				
	Benefix	0				
	Other recombinant	50 000	1	50 000.0		
	FIX REC total*	**50 000**	**1**	**50 000.0**		
	FIX total*	3 347 500	44	76 079.5	63	53 134.9
EHL (IU)	FVIII	991 845.0	3	330 615.0		
	FIX	0.0				
„by-pass"	Feiba (U)	243 500	2	121 750.0		
	NovoSeven (mg)	2 592.0	4	648.0		
	Other rFVIIa (mg)	0				

* excluding patients treated with EHL

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The same data for adults with haemophilia in 2016.