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Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres

John Michael Soucie[1,2], **Connie H. Miller**[1,2], **Brandi Dupervil**[1], **Binh Le**[1], **Tyler W. Buckner**[3]

[1]Division of Blood Disorders, Centers for Disease Control and Prevention, Atlanta, GA, USA

[2]Synergy America, Inc., Duluth, GA, USA

[3]Division of Hematology, University of Colorado School of Medicine, Aurora, CO, USA

Abstract

Introduction: Estimates of the size and characteristics of the US haemophilia population are needed for healthcare planning and resource needs assessment. A network of comprehensive haemophilia treatment centres (HTCs) located throughout the United States receives federal support for diagnosis and management of haemophilia and other rare bleeding disorders.

Aim: Estimate the incidence and prevalence of haemophilia among US males using the HTC network.

Methods: During the period 2012–2018, de-identified surveillance data were collected on all males who visited an HTC that included year of birth, gender, race, Hispanic ethnicity, residence zip code, haemophilia type and severity. Data from all patients were used to calculate period prevalence by haemophilia type, severity and state of residence. Data from a subset of patients born 1995–2014 were used to estimate incidence rates over the 20-year period.

Results: During the period, 21 748 males with haemophilia visited the HTCs resulting in an age-adjusted prevalence of 15.7 cases per 100 000 males (12 for haemophilia A and 3.7 for haemophilia B). Prevalence was higher among whites (15.1) than blacks (12.4) or Hispanics of either race (12.4). State-specific prevalence varied from 1.6 to 23.3 cases per 100 000. Based on 9587 males born during the index period, the average haemophilia incidence was 1 case per 4334 live male births.

Conclusion: Based on these data, we estimate that there are between 29 761 and 32 985 males with haemophilia living in the United States today, the majority of whom receive comprehensive care in specialized clinical centres.

Correspondence J. Michael Soucie, MS-S106-3, Centers for Disease Control and Prevention, 4770 Buford Highway, Atlanta, GA 30341-3717, USA. Msoucie@cdc.gov.

DISCLOSURES

JMS designed the study, performed analysis and wrote the paper. CHM designed the study and wrote the paper. BD and BL performed the analysis and wrote the paper. TWB designed the study and wrote the paper. TWB has acted as a paid consultant to BioMarin, Tremeau Pharmaceuticals, and uniQure and has participated in advisory boards with Takeda, Tremeau, Genentech/Roche, Spark, Pfizer, Bayer and Kedrion. All other authors stated that they had no interests which might be perceived as posing a conflict or bias.

Keywords

haemophilia; incidence; prevalence; registries

1 | INTRODUCTION

Haemophilia is an X-linked, inherited disorder that results from mutations in the genes that code for one of two proteins necessary for normal blood clotting, factor VIII (haemophilia A) or factor IX (haemophilia B). Haemophilia A (HA) is more common than haemophilia B (HB); however, both disorders primarily affect males and result in bleeding in organs, tissues and joints in response to trauma and surgery. Without treatment, repeated bleeding into joints leads to chronic debilitating joint disease. There are an estimated 20 000 men living with haemophilia in the United States, but the exact number is not known.

The US Centers for Disease Control and Prevention (CDC) conducted the first population-based assessment of the incidence and prevalence of haemophilia in the United States utilizing the Haemophilia Surveillance System (HSS) in the early 1990s.[1] However, the surveillance was conducted following a period of high mortality in the haemophilia population due to the HIV epidemic resulting from viral contamination of haemophilia treatment products. Although the incidence and prevalence numbers reported in the HSS were in the range of those previously reported, high mortality rates prior to the study period may have resulted in underestimates.

Due to the complex nature of the disorder, it is likely that the majority of people with haemophilia in the United States are seen in one of the approximately 140 federally supported specialized haemophilia treatment centres (HTCs) located throughout the United States as part of diagnosis and/or for routine follow-up care. At the time of the HSS, 67% of the identified population with haemophilia in the six-state surveillance catchment area received some care in an HTC during a three-year period.[1] A more recent population-based study conducted in Indiana found that 81.7% of males with haemophilia identified in that state had visited an HTC during the period 2011–2013.[2]

In 2012, in collaboration with the US HTC Network (USHTCN) and the American Thrombosis and Hemostasis Network (ATHN), CDC began collecting data on all people with bleeding disorders who received care at a network HTC at any time during each year through a surveillance programme called Community Counts.[3] Because routine treatment for the disorder is expensive and complications can be severe, estimates of the size and characteristics of the US haemophilia population are needed for healthcare planning and resource needs assessment. The surveillance project collects data that provide a unique opportunity to generate updated estimates of the incidence and prevalence of haemophilia among males in the United States.

2 | MATERIALS AND METHODS

Beginning in January 2012, a HIPAA-compliant de-identified data set that includes demographic and clinical information was collected on all people with bleeding disorders

who received care in the USHTCN in the portion of the Community Counts programme called the HTC Population Profile, which as such did not require informed consent. Specific data elements pertinent to this study include year of birth, gender, race, Hispanic ethnicity, primary bleeding disorder diagnosis, baseline factor activity level and residence 3-digit zip code. To assure confidentiality, data were sent to CDC using a unique identification key that can be linked to an individual patient only at the HTC.

We used data collected from all male individuals with a primary diagnosis of HA or HB who received care in 139 federally supported HTCs in the United States (Guam and Puerto Rico territories were excluded) during the period 2012–2018. Severity was classified as severe if the baseline factor activity level was <1%, moderate if between 1% and 5% and mild if >5% to 40% of normal.[4] The distributions of the patients according to clinical (haemophilia type and severity) and demographic (age, race and ethnicity) characteristics were used to describe the prevalent populations receiving care.

Haemophilia period prevalence was calculated by dividing the number of unique males with haemophilia who received care in the USHTCN during the period 2012–2018 by the average number of US male residents over the same time period.[5] The prevalence was expressed as cases per 100,000 (100K) males in the general US population. For each patient, age was calculated by subtracting the year of birth from the first year that the patient was reported in the surveillance data. Age-adjusted prevalence was calculated separately by haemophilia type by direct standardization to the age distribution of the US population in 2000.[6] Due to the lack of annual census estimates, haemophilia prevalence by race and ethnicity was calculated using the census populations estimated in 2015 as an approximation for the average general male population during the surveillance period. State-specific prevalence was determined using the 3-digit zip code of patient residence collected in the data set. For 20 subjects with missing zip code data, state of residence was assigned based on HTC location.

Using surveillance data on year of birth, annual incidence rates over the period 1995–2014 were calculated by dividing the number of male haemophilia births in a particular year by the number of male births among US citizens living in the states (excluding territories) in that year from the National Center for Health Statistics natality tables.[7] Incidence rates were expressed as one infant with haemophilia born per the number of live male infants born (e.g., 1 haemophilia birth per 5000 US male births). Rates were averaged over the entire 20-year period and separately over 5-year periods in order to examine trends. Rates were calculated for all males with haemophilia and separately by haemophilia type.

3 | RESULTS

During the period 2012–2018, 139 federally supported HTCs in the United States provided data on a total of 21 748 males with haemophilia. The demographic and clinical characteristics of the study population are shown in Table 1. Three-fourths had HA and just over 40 per cent overall had severe disease. The mean (median) age of the cohort was 23.5 (19) years, and 75 per cent were under the age of 35 years. Compared with US males, the age distribution of those with haemophilia was shifted towards younger ages with the

highest proportion under 25 years (Figure 1). Compared with the distribution of race in the United States, whites were over-represented (81% vs. 72.4%) while blacks (11.2% vs. 12.6%) and Asians (3.6% vs. 4.8%) were under-represented among those with haemophilia. The proportion of those with Hispanic ethnicity was the same among those with haemophilia and the general population (16% vs. 16.3%).

The distribution of severities varied by haemophilia type with a greater proportion of severely affected among those with HA and a greater proportion of moderately affected among those with HB (Table 2). The estimated prevalence of HA over the 6-year study period was 10.5 cases per 100K males which increased to 12 per 100K males after adjustment for the differences in the age distributions of the United States and haemophilia populations. The corresponding prevalence figures for the HB cohort were 3.2 cases per 100K which increased to 3.7 per 100K males after age adjustment.

State-specific haemophilia prevalence ranged from 1.6 per 100K in Delaware to 23.3 per 100K in Maine (Figure 2). There were also differences in prevalence by race and ethnicity. The prevalence of haemophilia for non-Hispanic whites, non-Hispanic blacks and for Hispanics of either race was 15.1, 12.4 and 12.4 cases per 100K, respectively.

Among all of the subjects who received care in the USHTCN during the period, 9587 (44%) were born during the period 1995–2014 and were used to estimate the incidence corresponding to their year of birth. The distribution of haemophilia type and severity of these patients was similar to that of the entire prevalent cohort; however, the proportion of Hispanics in this younger cohort was somewhat higher (Table 1).

Annual incidence rates over the 20-year period by haemophilia type are presented in Table 3. For HA, rates ranged from a low of 1 case per 7013 (1:7,013) live male births in 2014 to a high of 1:4906 in 2004. Corresponding ranges for HB were 1:24 265 in 2007 to 1:14 339 in 2003. Rates for haemophilia of either type ranged from 1:5193 in 2014 to 1:3834 in 2004. The overall average rate for all 20 years was 1:5617 for HA, 1:19 283 for HB and 1:4334 for both. Average rates for the four 5-year periods are shown in the last column of Table 3. While the rates were similar for the earlier two 5-year periods, rates appeared to be decreased for both HA and HB in the most recent two 5-year periods.

4 | DISCUSSION

Using data from a surveillance system that monitors people with haemophilia under care in federally supported HTCs, we found somewhat higher prevalence and incidence figures than those measured in the HSS. This finding was unexpected since the HSS provided more complete ascertainment in the states studied, and it is known that not all people with haemophilia in the United States receive care in these HTCs. While the exact proportion is unknown, estimates from a more recent study that used the same methodology as the HSS suggest that closer to 80% of the haemophilia population receive care in this HTC network versus the 67% measured in the HSS.[1,2] Based on the 21 748 patients we report in this study and our assumptions about the proportion of US haemophilia males who receive care in

HTCs (between 67% and 80%), we estimate that a total of between 29 761 and 32 985 males with haemophilia live in the United States today.

Other methodologic and ecologic differences between the current study and HSS may have contributed to the differences in rates. In HSS, an HTC patient was defined as having had an HTC visit during a 3-year period. The current study included all patients visiting an HTC over a 7-year period which may have increased the likelihood of enumerating patients with infrequent clinic visits. In addition, cases in HSS were defined as those with <30% factor activity level. However, our results were minimally affected when this lower cut-off value was used in a separate analysis (results not shown).

The state-specific prevalence in the six states that participated in HSS ranged from 12.8 to 13.7 per 100K and averaged 13.4 per 100K. In the current study, with patients from all 50 states, the state-specific prevalence ranged from 1.6 to 23.4 with an average of 14.4 per 100K. The somewhat lower average prevalence in the HSS states relative to the rest of the country based on our current data, if also present during the HSS study period, would have resulted in an underestimate of the national rate.

HSS was conducted when mortality rates from AIDS were still high.[8] Deaths occurring prior to the surveillance would have lowered the estimates of both prevalence and incidence since the incident cases were determined by using select birth years from among the prevalent cases. The younger overall age distribution of the patients in the current study relative to HSS (Figure 1) provides additional support for this possible explanation for the observed differences in rates found by the two studies.

As shown in the map, haemophilia prevalence varies markedly across the United States. State-specific prevalence variations were seen in both HA which ranged from 1.1 to 18.8 per 100K and in HB ranging from 0.7 to 10.4 per 100K males. HA prevalence was the highest in the country in New Hampshire, Vermont, Maine, West Virginia, Iowa and Pennsylvania. HB prevalence was highest in Ohio, Indiana, Iowa, Maine, West Virginia and Pennsylvania. These high prevalence states are reflected on the map in the Northeast and Midwest regions of the country and are consistent with founder effects present in both HA and HB combined with migratory patterns early in the country's history.[9–12]

A recent paper reported prevalence and incidence rates based on established registries in six countries that could be used to estimate the potential burden of haemophilia in other countries.[13] For ease of comparison, in Table 4 we have converted our incidence measures to the equivalent prevalence at birth measures used in the international study. In that paper, HA prevalence was 30% higher (17.1 vs. 12.0 cases per 100K males) while that for HB was nearly identical to the value reported here (3.8 vs, 3.7 cases per 100K). Similarly, estimates of incidence were about 35% higher for HA (24.6 vs. 17.9 cases per 100K live male births) but slightly lower than that for HB reported here (5.0 vs. 5.3 cases per 100K). The international data more closely match our upper estimates of the US male haemophilia population adjusted for the proportion of patients not seen at the HTCs (Table 4).

There are limitations that should be kept in mind when interpreting the findings that we report. First, as already mentioned, not all males with haemophilia receive care in the

federally supported HTC network covered by the surveillance. However, it is important to point out that 86% and 95% of males with severe haemophilia received care in an HTC during the 3-year periods monitored by the HSS and Indiana studies, respectively, while the proportions were lower for the milder severities. The longer surveillance period in the current study makes it likely that a higher proportion of males of all severities received care in an HTC and, therefore, contributed to the occurrence rates reported here. Nonetheless, the true occurrence rates of haemophilia are likely higher than those reported in this study.

Second, in order to contribute to the incidence rates, patients must have been old enough during the surveillance period to have been diagnosed with haemophilia. In our study, the youngest subjects had to have been diagnosed before the age of 5 years in order to be counted in the incidence estimate for 2014. We have previously reported median ages at diagnosis based on data from more than 13,000 participants of a similar surveillance system established in this same HTC network over the period 1998–2011 as 36 months for mild, 8 months for moderate and 1 month for severe cases.[14] It is likely that the lower incidence rates seen in the later years in Table 3 are due to higher numbers of primarily mildly affected patients who had not yet been diagnosed.

As shown in Figure 1, compared with the general population, the haemophilia population is younger in the HTC PR just as it was in HSS. Advances in haemophilia treatment options since the 1960s have reduced the risk of bleeding-associated mortality, but these improvements were offset by the increased mortality in persons with haemophilia due to HIV/AIDS and later HCV, both consequences of viral contamination of treatment products in the early 1980s. It is expected that as life expectancy has increased due to advances in therapy, the age distributions will likely more closely resemble that of the general US population over time. As has already been reported by others, issues of ageing in the haemophilia population including cardiovascular disease and other chronic disorders will become more prominent.[15,16]

Additionally, incidence rates may be affected by a number of factors, such as advances in or increased use of prenatal diagnosis leading to increased termination of affected pregnancies, ability to select female embryos after in vitro fertilization to avoid male offspring or select male embryos unaffected by haemophilia,[17] or even changes in the accuracy and/or timeliness of diagnosis if capabilities of HTCs are affected over time by changes in the treatment landscape.

Because haemophilia care in HTCs is potentially a regionalized phenomenon supported by the organizational structure of the USHTCN (ie regions meet and share clinical practices, difficult cases, quality improvement efforts, etc), it is important to continue to track the regional differences in the prevalence of haemophilia types and severities due to founder effects. It is possible that this variation in the epidemiology between states/ regions affects the care practices in those regions. For example, surgical procedures for arthropathy (eg joint replacement) could be less common in the Midwest due to a relatively higher proportion of moderate haemophilia patients (those with the less severe founder mutations) compared with other areas.

Finally, although we did not include women and girls in the data presented here, the HTC Population Profile provides an opportunity to characterize the female population with factor VIII/IX deficiency. The surveillance programme could help improve understanding of the scope of issues facing women with bleeding disorders and to determine the public health needs of this population. Recent publications[18–20] have documented the clinically significant bleeding among females with factor VIII and IX deficiency and highlight need for a more concerted effort to ensure the appropriate evaluation and management of women in the HTC system.

5 | CONCLUSIONS

We have found that occurrence rates of haemophilia in the United States are higher than previously measured by a population-based study conducted more than 20 years ago. The higher proportion of youth in the haemophilia population relative to the general population is indicative of the regeneration of a population decimated by the HIV epidemic in the 1980s. Improvements in treatment are expected to continue to extend the lifespan of people with haemophilia. Regional differences in the distribution and severity levels of the patient population may require closer monitoring to ensure that needed resources and services are available to maximize the health and quality of life of people with bleeding disorders. Continued surveillance in the USHTCN is important as advances in treatment are likely to affect both outcomes and care patterns. Longer acting and more effective treatment products as well as successful gene therapy will lead to decreased bleeding and other complications and may require less frequent follow-up care. Increases in life expectancy may result in changes in the care provided by the centres in order to deal with challenges of chronic diseases of ageing.

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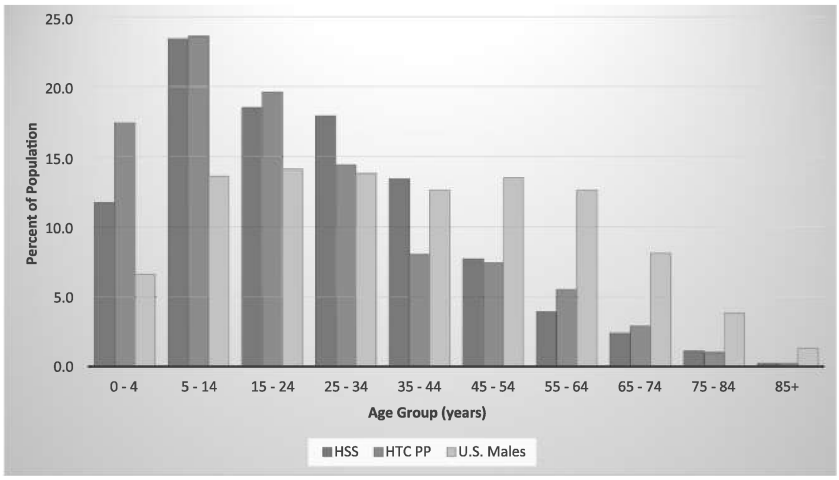

FIGURE 1.

Age distributions of HSS males (1998 study), HTC PP males (current study) and US males. HSS, Haemophilia Surveillance System; HTC PP, Haemophilia Treatment Center population profile. US male age distribution based on 2015 census estimate (https://www.census.gov/data/tables/2015/demo/age-and-sex/2015-age-sex-composition.htmlwileyonlinelibrary.com]) [Colour figure can be viewed at wileyonlinelibrary.com]

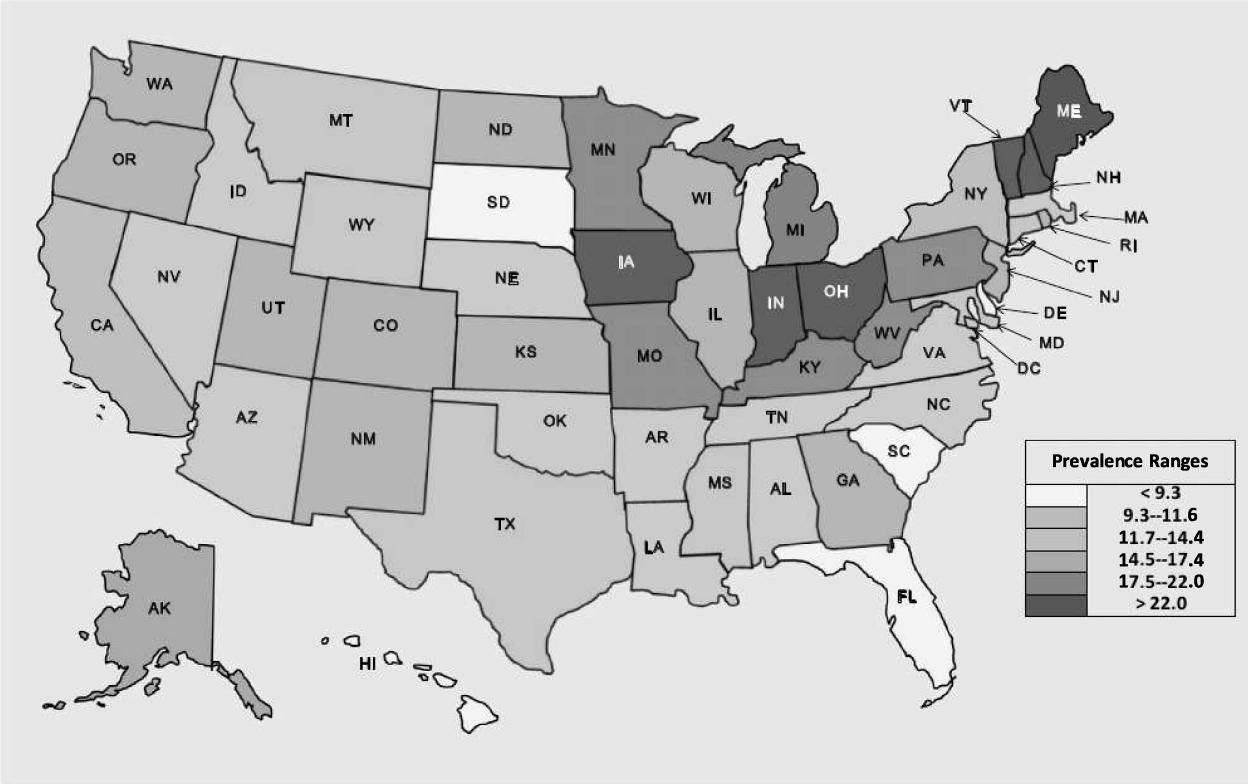

FIGURE 2.

State-specific prevalence of haemophilia per 100 000 population based on the number of males with haemophilia receiving care in 139 haemophilia treatment centres in the United States, 2012–2018 [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Characteristics of 21 748 males with haemophilia receiving care in 139 US haemophilia treatment centres, 2012–2018

	All		Born after 1994	
Characteristic	**N**	**%**	**N**	**%**
Haemophilia type				
A	16 642	76.5	7411	77.3
B	5161	23.5	2176	22.7
Severity				
Mild	6447	29.6	2776	29.0
Moderate	5427	25.0	2455	25.6
Severe	9478	43.6	4203	43.8
Unknown	396	1.8	153	1.6
Age (years)				
Under 1	1246	5.7	522	5.4
1–5	3032	13.9	2574	26.9
6–11	3099	14.3	3099	32.3
12–19	3839	17.7	3256	34.0
20–29	3670	16.9	136	1.4
30–39	2366	10.9	–	
40–49	1572	7.2	–	
50–59	1483	6.8	–	
60–69	935	4.3	–	
70+	506	2.3	–	
Race				
White	17 651	81.2	7653	79.8
Black	2432	11.2	1118	11.7
Asian	784	3.6	390	4.1
Other	407	1.9	192	2.0
Unknown	474	2.2	234	2.4
Ethnicity				
Non-hispanic	18 274	84.0	7618	79.5
Hispanic	3474	16.0	1969	20.5

TABLE 2

Period prevalence of haemophilia by type, 2012–2018

		Severity				Crude	Age-adjusted
Type	**Total N**	**Mild**	**Moderate**	**Severe**	**Unknown**	**Prevalence**[a]	**Prevalence**
A	16 642	5024 (30.2)[b]	3319 (19.9)	8011 (48.2)	288 (1.7)	10.5	12.0
B	5106	1423 (27.9)	2108 (41.3)	1467 (28.7)	108 (2.1)	3.2	3.7
Both A & B	21748	6447 (29.6)	5427 (25.0)	9478 (43.6)	396 (1.8)	13.7	15.7

[a]Prevalence expressed as the number per 100 000 US male population.

[b]Numbers in parentheses are percentages.

TABLE 3

Annual haemophilia incidence rates based on 9587 subjects born 1995–2014 and receiving care in 139 US haemophilia treatment centres, 2012–2018

	Haemophilia births				Incidence US Male births per each patient			Incidence 5-Yr period averages		
Year of birth	**HA**	**HB**	**All**	**US male births**	**HA**	**HB**	**All**	**HA**	**HB**	**All**
1995	363	102	465	1 996 355	5500	19 572	4293			
1996	359	107	466	1 990 480	5545	18 603	4271	**Average 1995–1999**		
1997	371	107	478	1 985 596	5352	18 557	4154	1:5377	1:18 503	1:4165
1998	390	121	511	2 016 205	5170	16 663	3946			
1999	381	106	487	2 026 854	5320	19 121	4162			
2000	413	92	505	2 076 969	5029	22 576	4113			
2001	387	105	492	2 057 922	5318	19 599	4183	**Average 2000–2004**		
2002	360	107	467	2 057 979	5717	19 233	4407	1:5304	1:18 657	1:4108
2003	377	146	523	2 093 535	5553	14 339	4003			
2004	429	120	549	2 104 661	4906	17 539	3834			
2005	381	128	509	2 118 982	5562	16 555	4163			
2006	384	100	484	2 184 237	5688	21 842	4513	**Average 2005–2009**		
2007	378	91	469	2 208 071	5841	24 265	4708	1:5590	1:20 329	1:4375
2008	415	113	528	2 173 000	5236	19 230	4116			
2009	376	107	483	2 113 856	5622	19 756	4377			
2010	351	100	451	2 046 935	5832	20 469	4539			
2011	349	110	459	2 024 052	5800	18 400	4410	**Average 2010–2014**		
2012	348	87	435	2 021 434	5809	23 235	4647	1:6198	1:19 643	1:4687
2013	308	125	433	2 012 954	6536	16 104	4649			
2014	291	102	393	2 040 701	7013	20 007	5193			

Note: Abbreviations: HA, haemophilia A; HB, haemophilia B.

TABLE 4

Comparison of findings between current study and a recent international study

	Current study	Current study plus 20% outside HTCs	Current study plus 33% outside HTCs	International study[14]
Period prevalence[a]				
Haemophilia A	12.0	14.4	16.0	17.1
Haemophilia B	3.7	4.4	4.9	3.8
Haemophilia A and B	15.7	18.8	20.9	20.9
Incidence/prevalence at Birth[b]				
Haemophilia A	17.9	21.5	23.8	23.2
Haemophilia B	5.3	6.4	7.0	4.7
Haemophilia A and B	23.2	27.8	30.9	27.9
Estimated US male haemophilia population	24 800	29 761	32 985	33 015

[a]Prevalence expressed as haemophilia patients per 100 000 male population.

[b]Incidence expressed as haemophilia patients per 100 000 male births.