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Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System

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Abstract

Aim—To describe the prevalence and complications in babies ≤2 years with haemophilia.

Methods—We used a standardized collection tool to obtain consented data on eligible babies aged ≤2 years with haemophilia enrolled in the Centers for Disease Control and Prevention Universal Data Collection System surveillance project at US Hemophilia Treatment Centers (HTCs).

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Disclosures

All authors except Dr. Prasad Matthew stated that they had no interests which might be perceived as posing a conflict or bias. Dr. Matthew is currently an employee of Bayer; at the time of the UDC project, he was a faculty at the University of New Mexico, Albuquerque, NM.

Results—Of 547 babies, 82% had haemophilia A, and 70% were diagnosed within one month of birth. Diagnosis was prompted by known maternal carrier status (40%), positive family history (23%), bleeding (35%) and unknown 2%; 81% bled during the first two years. The most common events were bleeding (circumcision, soft tissue, oral bleeding) and head injury. There were 46 episodes of intracranial haemorrhage (ICH) in 37 babies (7%): 18 spontaneous, 14 delivery related, 11 traumatic, 2 procedure related and 1 unknown cause. Of the 176 central venous access devices (CVADs) in 148 (27%) babies, there were 137 ports, 22 surgically inserted central catheters and 20 peripherally inserted central catheters. Ports had the lowest complication rates. Inhibitors occurred in 109 (20%) babies who experienced higher rates of ICH (14% vs. 5%; $P = 0.002$), CVAD placement (61% vs. 19%; $P < 0.001$) and CVAD complications (44% vs. 26%; $P < 0.001$). The most common replacement therapy was recombinant clotting factor concentrates.

Conclusion—Bleeding events in haemophilic babies ≤2 years were common; no detectable difference in the rates of ICH by the mode of delivery was noted. Neonatal factor exposure did not affect the inhibitor rates. Minor head trauma, soft tissue and oropharyngeal bleeding were the leading indications for treatment.

Keywords

babies; central venous access device; haemophilia; head trauma; inhibitors; intracranial hemorrhage

Introduction

A significant proportion of potentially preventable complications of haemophilia occur in early childhood, especially in children ≤2 years of age (hereafter referred to as baby/babies). These include bleeding events, falls and complications of treatment such as inhibitor formation that may have a lifelong impact. While joint disease is a hallmark of haemophilia in the older age groups, circumcision, head injury and intracranial haemorrhages (ICHs) due to delivery or trauma, and soft tissue/oral/nasal bleeding, are more likely to occur in early childhood [1–4]. Treatment for, and/or prophylaxis to prevent, bleeding episodes often necessitates the placement of central venous access devices (CVADs) because of difficulties in venous access [5]. However, early exposure to replacement therapy may lead to the development of alloimmune inhibitory antibodies (inhibitors), a challenging and costly complication of treatment [6].

The purpose of this study was to describe bleeding episodes and complications experienced by babies with haemophilia, enrolled in the Centers for Disease Control and Prevention (CDC) Universal Data Collection (UDC) System surveillance system and seen at the HTC network in the United States.

Materials and methods

From 1998 to 2011, the UDC project collected data from 135 federally funded Hemophilia Treatment Centers to monitor the health of people with bleeding disorders and the safety of blood products used for their treatment [1,6]. Babies less than 2 years of age were not eligible for inclusion in the UDC data until 2003. Enrolment was extended to babies (aged

≤2 years) in 2003 as a pilot project and nationwide enrolment began in 2004 [1]. Eligibility included either a congenital deficiency of any of the clotting factors at a level of <50% clotting factor activity, or the diagnosis of von Willebrand disease (VWD); data were collected at the registration visit and at subsequent visits at six-month intervals until the age of two. The target intervals for UDC visits were set up as frequent as once per 6 months for babies and 1 year for those >2 years of age and annually thereafter. Eligibility for this study required at least one UDC visit prior to age of 2 *and* one visit occurring between 24 and 30 months of age to capture all events occurring in the first two years of life. The Investigational Review Boards at CDC and participating institutions approved the protocol, and parent/guardian informed consent was obtained.

Data collection

Using standardized forms, HTC staff collected data at the time of a UDC visit, which was generally an annual comprehensive visit. All data were retrospectively extracted from the clinic and hospital charts/records and parental interview; the longest possible interval for birth history would be 1 year and 11 months. Most other data were collected within one year of the event. No children were excluded and only children with complete data (i.e. no missing data) were included in the analyses, as stated in the methods.

Information on race/ethnicity was based on self-report. Data regarding mother's haemophilia carrier status, family history, gestation period, prenatal testing, predelivery HTC contact, delivery method and the use of assistive devices (forceps or vacuum) were obtained by interview and/or review of the mother's medical record.

Data on the age at diagnosis, the reason for diagnostic testing and factor activity level (based on local laboratory results) were collected from the baby's medical record. Haemophilia severity level was defined on the basis of plasma factor VIII or IX activity (normal levels are 50–150%) as follows: <1% severe; 1–5% moderate; ≥5% mild [7,8]. The medical record was reviewed for vitamin K administration at birth and clotting factor concentrate administration during the first 24 hours of life.

During each clinic visit, detailed information was collected about all treatment products used during the previous interval and the treatment regimen prescribed was categorized as episodic if given in response to bleeding or prophylaxis if given on a regular continuous basis to prevent any bleeding episodes. Treatment products were categorized as recombinant or plasma-derived factor concentrates, bypassing agents, blood bank products (cryoprecipitate, fresh frozen plasma, packed red cells or whole blood) and non-plasma and topical products (desmopressin, antifibrinolytics, fibrin glue). The highest inhibitor titre was recorded based on the results of any inhibitor testing performed at the local laboratory, in the interval between UDC visits. For the analysis, patients with titres >1 Bethesda unit (BU) or who had received immune tolerance therapy were considered to have an inhibitor. The definitions of high (>5 BU)- and low (≤5 BU)-titre inhibitor were as described in the literature [7,8]. Information about the use of central lines such as totally implanted tunnelled central catheters (ports), transcutaneous, externalized tunnelled central catheters (externalized CVAD) and non-tunnelled peripherally inserted central catheters (PICC) and

any complications associated with the devices including infections, bleeding, mechanical problems, thrombosis or other was collected.

Information was collected about the numbers of head injuries, episodes/location of ICH, diagnostic confirmation method [e.g. magnetic resonance imaging (MRI), computed tomography (CT) scan] and any associated conditions (e.g. trauma, thrombocytopenia). Information about long-term effects, since birth or last visit, due to ICH or other bleeding (seizure disorders, focal neurological deficits, hydrocephaly, paralysis and neuropathy due to compartment syndrome) was also collected. The UDC baby registration and visit case report forms are available at http://www.cdc.gov/ncbddd/blooddisorders/udc/documents/udc-form-baby-registration_508.pdf and http://www.cdc.gov/ncbddd/blooddisorders/udc/documents/udc-form-baby-visit508.pdf.

Data analysis

Differences in the distribution of patient demographic and clinical characteristics by haemophilia type were assessed for statistical significance using chi-square or parametric or non-parametric tests of differences between means as appropriate.

Results

There were 547 male babies eligible for inclusion in the study. Female babies were excluded. Table 1 shows the demographic and clinical characteristics of the study subjects; 80% had haemophilia A and 60% had severe disease. Nearly 70% of babies were diagnosed within one month of birth and the mother was a known carrier in 40%; about 23% had some other family history of haemophilia and 35% had a bleeding symptom that prompted diagnosis. Seven per cent of the babies did not receive vitamin K at birth; 9% received clotting factor within 24 hours of birth for either prophylaxis or for the treatment of a bleeding event and 29% of mothers had contact with the HTC prior to the birth. Table 2 shows the age of diagnosis correlated with the severity of haemophilia; 60–70% of babies with all severities were diagnosed within one month of birth.

Bleeding sites and complications

During the first two years of life, 441 (81%) of the babies experienced at least one bleeding event. The most common site of bleeding during the newborn period was circumcision (20%); as the babies grew older, soft tissue/intramuscular haematomas (55.8%), oral/nasal bleeding (41.3%), head injuries (37.4%), joint haemorrhages (28.3%) and bleeding from the site of venepuncture (21%) were common (Table 3). Overall, there were 330 head injuries reported among 187 babies; 3 had associated skull fracture, and of those, 2 had a trauma-associated ICH.

Table 4 shows that the annual prevalence of ICH among babies with UDC visits (years 2003–2011) was 4% (0–6.8%) with no consistent trends over time. Table 5 shows that there were 46 ICHs in 37 babies during the first two years of life; 31 had a single episode of ICH; 4 had 2 ICHs; 1 had 3 ICHs; and 1 had 4 ICHs. Eighteen (39%) of the ICHs were spontaneous, 14 (30%) were associated with delivery, 11 (24%) were associated with trauma, 2 (4%) were associated with an unknown procedure and the cause of ICH was

unknown in 1 (2.2%). Only five babies with ICH were preterm and there was no statistical association between preterm birth and ICH. Most ICHs (76%) occurred in babies with severe disease, whereas 8% and 16% occurred in those with moderate and mild haemophilia, respectively. The most common ICH sites were subdural (57%) and intracerebral (30%). Computerized tomography (CT) was the most common imaging modality used for ICH confirmation. Seven (19%) of the 37 babies with ICH had one or more demonstrable long-term effects at the time of data collection: three with focal neurological deficits, two with both focal neurological deficits and paralysis, one with seizure disorder and one with neuropathy due to compartment syndrome.

The mode of delivery of the 547 babies was as follows: 348 vaginal, 182 Caesarean section (CS) delivery and 17 unknown. Of 13 babies with vacuum assist (all of whom had a negative family history of haemophilia), two (15.4%) had an ICH. Of four babies with forceps assist (one known carrier mother), none had an ICH. There was no significant difference in neonatal ICH by the mode of delivery; the neonatal ICH rate by delivery method was 3.2% among vaginal deliveries and 2.2% among caesarean section (CS) deliveries ($P = 0.5$). ICH in babies was associated with delivery in five (1.5%) of 344 women who were carriers or had some other family history of haemophilia when compared with nine (4.7%) of 190 women with no family history of haemophilia ($P = 0.02$).

CVAD complications

In their first two years of life, 148 (27%) babies had 193 CVADs placed. Of these, 112 (76%) babies had ports only, 11 (7%) had either a catheter or PICC placed and 25 (17%) had multiple CVAD types placed. Overall complication rates among the babies with CVADs were infections in 26%, bleeding in 8%, mechanical dysfunction in 6% and thrombotic complications in 1%. Figure 1 shows the distribution of complication rates by CVAD type. The average number of complications for each type of CVAD was 0.28 for the 130 ports, 0.58 for the 26 catheters and 0.76 for the 25 PICCs ($P < 0.001$, Kruskal–Wallis test).

Exposure to factor concentrates and blood products

During the first two years of life, 92.4% of these babies were exposed to factor concentrates, the vast majority of which were recombinant products (Table 6). About 10% of babies were exposed to bypassing agents (65% of these were recombinant), among whom 87% had evidence of an inhibitor as reported on the UDC form. A small proportion of babies were exposed to either plasma-derived concentrates or blood bank products. Babies with no family history of haemophilia were more likely to have received blood bank products (7.1% vs. 0.7%).

Inhibitory antibody development

Inhibitors occurred in 109 (20%) of the 547 babies; of these, 62 (11%) were low titre and 47 (9%) were high titre. Babies with inhibitors were more likely to have had an ICH (14% vs. 5%; $P = 0.002$) and a CVAD placement (61% vs. 19%; $P < 0.001$) and also experience a CVAD complication (44% vs. 26%; $P < 0.001$).

Inhibitors were much more common among babies with haemophilia A and severe disease (Table 7). The only infant populations at risk of developing inhibitors to FVIII and FIX are patients with haemophilia; therefore, mild haemophilia was used as a reference population. While some mutations predispose to inhibitor formation in patients with mild haemophilia, the data presented show a sixfold increased risk in severe patients, overall.

Inhibitor prevalence was significantly higher among babies born in families with no family history of haemophilia, but there was no relationship with race/ethnicity or factor exposure [administered for bleeding event or prophylaxis (1)], within the first 24 hours of life.

Discussion

This report describes the complications experienced by haemophilic babies ≤2 years of age diagnosed at HTCs that participate in the UDC surveillance. According to data collected by CDC, about 3% of people with hemophilia receiving care in US HTCs between 2012–2016 are ≤2 years old (http://www.cdc.gov/ncbddd/hemophilia/documents/a_mf_oakleym_htc-population-profile-report_508_final.pdf). Thus, the 547 boys with complete data and follow-up between 24 and 30 months correspond to about 4% of the total haemophilia population of 14, 910 patients enrolled in UDC between 2003 and 2011. While we have no data on bias regarding patients approached for enrolment or willingness to consent to UDC participation, our sample represents a substantial proportion of the babies seen at HTCs in the United States during the study years. In 70% of cases, the diagnosis of haemophilia was made within one month of birth. Only a third of the babies with haemophilia presented with bleeding, while nearly two-thirds were diagnosed based on a positive family history either with or without confirmed maternal carrier status. Although 40% of the mothers were carriers, only 29% had contact with HTC prior to delivery, and this may be because the carrier may not have lived in the state or the catchment area. This underscores the need for outreach and education of healthcare providers and families of patients with haemophilia to utilize HTCs for prenatal counselling and management of the pregnant carrier and her baby. Thirty-five per cent of diagnosed babies were other than white, non-Hispanic, possibly reflecting the increasing diversity in the United States.

Complications experienced in this age group were distinct from those seen in older children and adults and included (i) bleeding events secondary to delivery, or iatrogenic due to circumcisions, injections; (ii) a high frequency of head trauma as they learn to ambulate; and (iii) complications related to treatment including CVAD-related complications, exposure to blood and blood products and more importantly, the development of inhibitors.

Bleeding in the newborn commonly results from the birthing process or is associated with iatrogenic procedures such as circumcision and injections [1]. It is of concern that in the present study, 38 (7%) of 547 babies did not receive routine vitamin K injections despite the fact that such intramuscular injections are not associated with bleeding in the newborn period [1]. Whether a family history of haemophilia or carrier status of mother influenced refusal of vitamin K injection is difficult to determine due to the small numbers of babies (of the 38 babies, 12 (2.2%) had no family history, 14 (2.6%) had known carrier mother and 12 (2.2%) had other family history). Omission or refusal of prophylaxis with vitamin K at birth

sometimes results in late-onset vitamin K deficiency bleeding (VKDB) including ICH; thus, VKDB is still an important cause of neonatal haemorrhage [9].

ICH, one of the most dreaded complications of haemophilia, was surprisingly frequent in babies with haemophilia. Although the primary indication for the institution of routine prophylaxis in haemophilia is to prevent joint disease, the high rate of ICH observed in this surveillance study provides a compelling argument for the initiation of early prophylaxis to prevent ICH. It is not known whether the babies who experienced recurrent ICH episodes were on-demand therapy or did not receive vitamin K administration at birth. In the joint outcome study [10], three young children who suffered life-threatening haemorrhages were all in the on-demand.

In our cohort, delivery-associated ICH was seen in 33% of babies; although not statistically significant, ICH was more common with vaginal compared to CS delivery (3.2% vs. 2.2%, $P = 0.5$). The circumstances surrounding the delivery, whether some of the CS deliveries were unplanned and occurred following the onset of labour, were not known. Davies and Kadir [11] performed a meta-analysis of observational cohort studies and prospective imaging studies and reported that newborns with haemophilia were 44 times more likely to experience symptomatic ICH compared to the general population and the odds ratio of experiencing ICH were 4.4 (95% CI: 1.46–13.7, $P = 0.008$) following an assisted vaginal delivery and 0.34 (95% CI: 0.14–0.83, $P = 0.018$) following CS compared to vaginal delivery. This has implications especially in pregnant carriers where the avoidance of assisted deliveries is crucial. However, optimal obstetric management of potential carriers needs further study because it still remains controversial and our data did not support a significant benefit of CS for babies with haemophilia [12–14].

Beyond the newborn period, ICH was commonly associated with head injury and skull fractures and seen in all severities of haemophilia. Recurrent ICH needs to be studied further because as many as four episodes in an individual child were observed in our study. Subdural haematomas were the most common site and long-term neurological effects of ICH include seizure disorder, paralysis and focal neurological deficits.

Taken together, ICH and head trauma affected more than a third of the cohort; 187 of (34%) 547 babies had at least one episode of head trauma. Head trauma creates apprehension and often triggers replacement infusion of factor without waiting for symptomatic or radiologic evidence of internal bleeding, a biggest concern of medical staff and parents. The disproportionately large heads compared to the body, coupled with weak neck muscles and an unstable gait, make babies particularly vulnerable to head injuries. Head injuries are the leading cause of disability and death in babies with highest rates in the <4-year age group and are often related to falls [15,16]. Not all head traumas result in ICH and conversely not all ICHs are associated with head traumas; the relationship of preceding head trauma with the subsequent development of ICH is thus unclear. Witmer *et al.* [17] reported on 97 patients with haemophilia who had a total of 374 emergency department visits for head trauma. Of the 295 head CTs, nine (3%) episodes of ICH were identified, thereby exemplifying the need for further guidance on the indications for head CT vs. MRI in this population. Furthermore, 56% of patients with ICH had no clinical signs or symptoms. In a

more recent nested case–control UDC study [18] of 10 262 patients ≥2 years of age, 199 (1.9%) experienced ICH; head trauma occurred in 44% (88/199 cases). Other risk factors were inhibitors, haemophilia severity and prior ICH. Prophylaxis was associated with a significant risk reduction for ICH occurrence [18].

Musculoskeletal bleeding (soft tissue haematomas, muscle and joint haemorrhages) becomes more common by 6–12 months of age, as the child becomes more mobile. Unlike adults and older babies with haemophilia in whom muscle haematomas account for 10–25% and joint bleeding for 75% [19], in our study, soft tissue haematomas accounted for 40% and haemarthroses for only 9% of bleeding episodes in the first two years of life. Van Dijk *et al.* [20] reported the median age of first joint bleed was 1.8 years (range: 0.2–5.8). Oral or nasal bleeding was the second most common site of bleeding in the first two years of life, affecting 41% of babies, in contrast to this relatively infrequent site in older children and adults. Nasopharyngeal and tongue/oral haematomas can be life-threatening due to airway compression as a result of neck dissection [21,22].

Venous access whether required for replacement therapy, institution of prophylaxis or (in patients with inhibitors) for immune tolerance induction is challenging and necessitated CVAD placement in 27% of babies. It is well known that the use of long-term venous access systems in haemophilia is associated with complications such as infection, bleeding, mechanical malfunction and thrombosis. In our study and as reported previously [5,23], implantable devices such as ports had a much lower rate of complications than external devices or PICC lines.

For the treatment of bleeding events, most babies in our cohort received recombinant products, including bypassing agents (for those with inhibitors). Babies with no family history of haemophilia were more likely to receive blood and blood bank products. Awareness of manifestations of haemophilia in the babies coupled with early involvement/consultation of HTCs may result in the institution of appropriate therapy including prophylaxis with pathogen-safe plasma-derived or recombinant concentrates and prevent or reduce risk of exposure to blood and blood bank products [24].

Formation of inhibitors or alloantibodies related to factor exposure is one of the most serious complications and develops in 20–30% of patients with haemophilia [25–27]. A similar prevalence of 20% was seen in the babies enrolled in the UDC with 9% reporting high-titre and 11.3% low-titre inhibitors. It is not known whether the latter were transient inhibitors [28] or were of clinical relevance. Many risk factors, genetic and non-genetic, contribute to the development of inhibitors. In the UDC surveillance, inhibitors were strongly associated with ICH, CVAD use and CVAD complications and were more prevalent among those with severe haemophilia and those with no family history of haemophilia.

Study limitations

The UDC surveillance was designed as a minimal data set to capture the most significant issues in babies with haemophilia seen at the US HTC network. Detailed data regarding age and dates of specific bleeding episodes, genetic mutations, family history of inhibitors, exposure days, whether local inhibitor testing used the Nijmegen modification of the

Bethesda assay, transient nature of inhibitors, relationship of inhibitor development with the intensity of treatment and details of immune tolerance induction were not captured. Regarding recurrent ICH, it is not known whether these patients received prophylaxis or not at the time of the event because the information on treatment type was captured at the time of the annual visit. Dates of CVAD replacement, the number of days that catheters were in place and organisms causing CVAD infections were also not recorded. Kaplan–Meier analysis of bleeding and inhibitor complications could not be carried out because dates for bleeding events, inhibitors and CVAD insertions and complications were not captured to determine the relationships between exposures and outcomes. The UDC data were collected before the results of the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) study [29] were known; it would be interesting to determine whether the SIPPET study influences future treatment practices. Despite the limitations, the current surveillance results provide useful information regarding the complications experienced by this age group.

Conclusions

The UDC surveillance system demonstrated that babies with haemophilia experience bleeding events and head trauma in the first two years of life that require factor replacement therapy. Although not statistically significant, ICH was more common with vaginal compared to CS delivery. In this cohort, factor replacement/exposure within 24 hours of birth, whether for prophylaxis or for a bleeding event, was not associated with an increased inhibitor development. Continued surveillance is necessary to monitor the complications.

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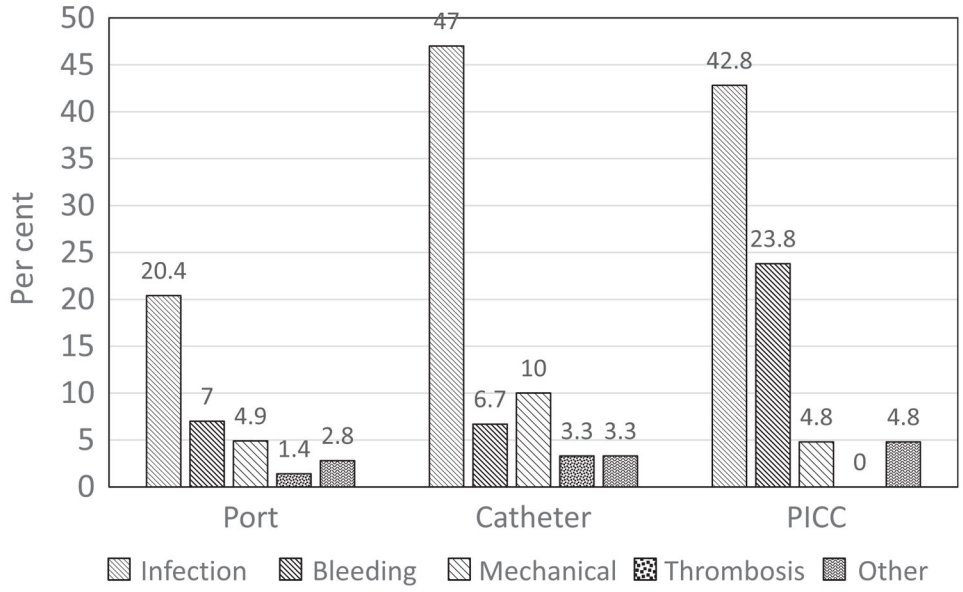

Fig. 1.

Complications of central venous access devices (CVADs) by CVAD type in babies with haemophilia. Some babies experienced more than one complication.

Table 1

Characteristics of 547 babies ≤2 years of age with haemophilia, 2003–2011.

Characteristics	Total *n*	%
Bleeding disorder		
Haemophilia A	450	82.3
Haemophilia B	97	17.7
Haemophilia severity		
Mild	89	16.3
Moderate	131	24.0
Severe	326	59.6
Unknown	1	0.1
Age at diagnosis		
<1 month	379	69.3
1–6 months	91	16.6
7–12 months	58	10.6
13–24 months	14	2.6
Race/ethnicity		
White	357	65.3
Black	56	10.2
Hispanic	83	15.2
Other	51	10.3
Reason for diagnosis		
Bleeding symptom	190	34.7
Mother known carrier	220	40.2
Other family history	124	22.7
Unknown	13	2.4
Vitamin K at birth		
Yes	365	66.7
No	38	7.0
Unknown	144	26.3
Clotting factor infused at birth		
Yes	49	9.0
No	474	86.6
Unknown	24	4.4
Haemophilia Treatment Centre contact prebirth		
Yes	159	29.1
No	374	68.4
Unknown	14	2.6

Table 2

Characteristics of babies: age of diagnosis correlated with haemophilia severity.

	Age at diagnosis (age in months when diagnosed) (%)						
Haemophilia severity level (mild, moderate or severe)	**Prenatal**	**<1 month**	**1–6 months**	**7–12 months**	**13–18 months**	**19–24 months**	**Total**
Mild	0 (0.00)	54 (60.67)	18 (20.22)	10 (11.24)	6 (6.74)	1 (1.12)	89
Moderate	3 (2.34)	89 (69.53)	21 (16.41)	12 (9.38)	1 (0.78)	2 (1.56)	128
Severe	15 (4.63)	217 (66.98)	52 (16.05)	36 (11.11)	1 (0.31)	3 (0.93)	324
Unknown	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1
Total Frequency missing = 5	18	361	91	58	8	6	542

Table 3

Sites of 2257 bleeding episodes in 547 babies ≤2 years of age enrolled in the Universal Data Collection system.

Sites of bleeding	The number of babies (%) with a bleeding episode[†]	The number of episodes (%)[†]
Soft tissue haematoma	246 (55.8)	904 (40.0)
Oral/nasal bleeding	182 (41.3)	335 (14.8)
Head injury	165 (37.4)	330 (14.6)
Joint bleeding	125 (28.3)	196 (8.7)
Intramuscular haematoma	99 (22.4)	140 (6.2)
Venepuncture/heel stick/surgical bleeding	91 (20.6)	152 (6.7)
Circumcision bleeding	88 (20.0)	92 (4.1)
Intracranial haemorrhage	37 (8.4)	48 (2.1)
Gastrointestinal	21 (4.8)	39 (1.7)
Umbilical bleeding	9 (2.0)	8 (0.4)
Genitourinary	6 (1.4)	8 (0.4)
Head injury with skull fracture	3 (0.7)	5 (0.2)

[†]Numbers and percentages do not total to 100% because a baby could have multiple bleeds.

Table 4

Intracranial haemorrhage (ICH) [†] prevalence by year and visits ($n = 46$).

Year	No. of ICH	No. of baby visits	Per cent
2003	0	12	0.0
2004	3	44	6.8
2005	8	133	6.0
2006	7	219	3.2
2007	11	203	5.4
2008	5	190	2.6
2009	9	171	5.3
2010	3	117	2.6
2011	0	48	0.0
Total	46	1137	4.0

[†]Some babies had more than one episode of ICH.

Table 5

Characteristics of 46 intracranial haemorrhages (ICHs) occurring in 37 babies during the first two years of life, 2003–2011.

	n **(%)**
ICH episodes associated with	
Spontaneous	18 (39.1)
Related to delivery	14 (30.4)
Traumatic	11 (23.9)
Procedure associated	2 (4.4)
Unknown	1 (2.2)
Location of ICH	
Subdural	22 (47.8)
Intracerebral	8 (17.4)
Epidural	6 (13.0)
Intra-/periventricular	2 (4.4)
Subarachnoid	1 (2.2)
Intracerebral + intra-/periventricular	3 (6.5)
Intracerebral + subdural	2 (4.4)
Subdural + subarachnoid	1 (2.2)
Intracerebral + subdural + subarachnoid	1 (2.2)
ICH Confirmed by: (sometimes more than one modality was used)	
Computerized tomography (CT)	38 (83.0)
Magnetic resonance imaging (MRI)	6 (13.0)
Physical examination only	3 (6.5)
Ultrasound	1 (2.2)
X-ray	1 (2.2)
Lumbar puncture	1 (2.2)

Table 6

Haemostatic products used by 547 babies with haemophilia during first two years.

Type of product	*n* (%)
Recombinant factor concentrates	499 (91.2)
Plasma-derived factor concentrates	20 (3.7)
Recombinant activated FVII	45 (8.2)
Activated prothrombin complex concentrates	23 (4.2)
Blood bank products	4 (0.7)
Nonplasma and topical products (antifibrinolytics, fibrin glue, desmopressin)	196 (35.8)
None	31 (5.7)

Proportions do not sum to 100% due to multiple product use by some babies.

Table 7

Associations between prevalent inhibitors and selected patient demographic and clinical characteristics in 547 children ≤2 years with haemophilia.

Characteristics	Total *n*	Inhibitor *n* (%)	OR (95% CI)	*P* value
Haemophilia type				
B	97	5 (5.2)	Ref	
A	450	104 (23.1)	5.5 (2.2–14.0)	<0.001
Severity[†]				
Mild	89	4 (4.5)	Ref	
Moderate	131	15 (11.4)	2.7 (0.9–8.6)	0.08
Severe	326	89 (27.3)	8.0 (2.8–22.4)	<0.001
Family history haemophilia				
No	203	65 (32.0)	Ref	
Yes	344	44 (12.8)	0.3 (0.2–0.5)	<0.001
Race/ethnicity				
White, non-Hispanic	357	61 (17.1)	Ref	
Black, non-Hispanic	56	15 (26.8)	1.8 (0.9–3.4)	0.08
White Hispanic	83	21 (25.3)	1.6 (0.9–2.9)	0.09
Other	51	12 (23.5)	1.5 (0.7–3.0)	0.3
Factor in first 24 hours				
No	474	95 (20.0)	Ref	
Yes	49	9 (18.4)	0.9 (0.4–1.9)	0.9

[†]Total does not sum to 100% due to missing data.