

# A STUDY OF VARIATIONS IN THE REPORTED HEMOPHILIA A PREVALENCE AROUND THE WORLD

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ORIGINAL ARTICLE *Clinical haemophilia*

## A study of variations in the reported haemophilia A prevalence around the world

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**Summary.** The objectives of this paper were to study the reported haemophilia A prevalence (per 100 000 males) on a country-by-country basis and address the following: Does the reported prevalence of haemophilia A vary by national economies? We collected prevalence data for 106 countries from the World Federation of Hemophilia (WFH) annual global surveys and the literature. We found that the reported haemophilia A prevalence varied considerably among countries, even among the wealthiest of countries. The prevalence (per 100 000 males) for high income countries was  $12.8 \pm 6.0$  (mean  $\pm$  SD) whereas it was  $6.6 \pm 4.8$  for the rest of the world. Within a country, there was a strong trend of increasing prevalence over time – the prevalence for Canada ranged from 10.2 in 1989 to 14.2 in 2008 ( $R = 0.94$  and  $P < 0.001$ ) and for the United Kingdom it ranged from 9.3 in 1974 to 21.6 in 2006

( $R = 0.94$  and  $P < 0.001$ ). Prevalence data reported from the WFH compared well with prevalence data from the literature. Patient registries generally provided the highest quality of prevalence data. The lack of accurate country-specific prevalence data has constrained planning efforts for the treatment and care of people with haemophilia A. With improved information, healthcare agencies can assess budgetary needs to develop better diagnostic and treatment facilities for affected patients and families and work to ensure adequate supplies of factor VIII concentrates for treatment. In addition, this information can help manufacturers plan the production of concentrates and prevent future shortages.

**Keywords:** economics, epidemiology, haemophilia A, prevalence, World Federation of Hemophilia

### Introduction

The reported *haemophilia A prevalence* (per 100 000 males) varies considerably among countries. For example, the reported haemophilia A prevalence in the early 1970s for the United Kingdom was approximately 10 per 100 000 males versus approximately 20 per 100 000 males in the United States [1]. Thirty years later the reverse is true – the

prevalence in 2006 in the United States was reported as 8.0 per 100 000 males versus 20.7 per 100 000 males in the United Kingdom [2]. The reported *haemophilia A prevalence* is the total number of reported or identified cases of haemophilia A in the population at a given time divided by the total number of males in that population. Inaccurate reporting practices would lead to differences in reported prevalence whereas poor availability of factor treatment resulting in death would lead to differences in actual prevalence. The reported haemophilia A prevalence accurately estimates the actual prevalence when all people with haemophilia A are counted (collectively exhaustive) and each person with haemophilia A is counted once (mutually exclusive).

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Accepted after revision 14 September 2009

The reported haemophilia A prevalence in lower income countries is often considerably less than that in higher income countries, and less than expected from average international incidence. The literature [3–7] suggests that the haemophilia A and B incidence is the same for all populations and racial groups and has been estimated to be 20 per 100 000 male births [8,9]. For example, people with haemophilia registered in the Haemophilia Federation of India account for only about 10% of what is expected, and registry data in Malaysia and South Africa account for less than 50% of expected cases [10]. Nathwani and Tuddenham [6] reported data on the haemophilia A prevalence for various lower income countries and found that only 5 of 11 countries in Africa reported data on the number of people with haemophilia A with prevalence ranging from 1.7 to 6.5 per 100 000 males; only four of nine countries in South America reported data where the prevalence ranged from 3.0 to 9.3 per 100 000 males; and only 3 of 10 countries in Asia reported data with prevalence ranging from 2.9 to 3.6 per 100 000 males.

There are many possible reasons for under-reporting cases of hemophilia A. Aledort [11] observed that the majority of haemophiliacs in the world have: (1) not been identified because of a lack of diagnostic capability, (2) no access to care, (3) no economic means, and (4) little to no available factor VIII (FVIII) replacement therapy. Without treatment, those with severe hemophilia often die in childhood or early adult life [12–15] thereby resulting in a decreased prevalence relative to the number of cases born. In addition, the reporting procedures in many countries have not accurately identified people with haemophilia A. Countries with marginal economies typically do not provide resources (both personnel and treatment products) for treating rare, chronic, and expensive conditions (e.g. haemophilia) since they focus their limited resources on public health issues that affect larger portions of the population, e.g. lack of sanitation, malnutrition, combating infectious diseases [4,5,7,10,16–22]. In association with the inadequate development of treatment resources, there has also been a lack of available supply of FVIII concentrates [23,24] perhaps mainly due to economic means, but also due to the difficulty in forecasting the demand [25]. The paucity of data about morbidity and mortality in haemophilia has hampered healthcare planning [5,18,26].

The primary aims of this research were to study reported haemophilia A prevalence on a country-by-country basis and to determine whether prevalence varied across national economies.

## Materials and methods

### *Economic classification*

We used the World Bank's economic classification to describe national economies for each country. These classifications are based on the World Bank's lending categories, which were established three decades ago and have been updated every year to incorporate the effect of international inflation [27]. To avoid countries shifting between economic categories annually and to allow for observation of trends in consistent groupings of countries over time, we applied the World Bank's 2006 economic classification to all years. Economies are classified according to 2006 gross national income (GNI) per capita (all in U.S. dollars) calculated using the World Bank's Atlas method [27]: low income, \$905 or less; lower middle income, \$906–\$3595; upper middle income, \$3596–\$11115; and high income, \$11116 or more. High income economies are further distinguished on whether the country is a member of the Organisation for Economic Co-operation and Development (OECD) [28].

### *Haemophilia A prevalence*

Data on the reported number of people with haemophilia A were obtained from the World Federation of Hemophilia (WFH) annual global surveys. Through its eight surveys, the WFH has reported haemophilia prevalence data on 106 countries from 1998 to 2006 [2,29–35]. Participation in the survey is voluntary and not all countries have provided prevalence data each year to the WFH. Data are collated in each country by the national member organizations (NMOs) in association with the clinicians and in some cases ministry of health officials. Countries use three data sources – registry, survey of haemophilia treatment centres (HTCs), and other approaches – to collect, record, and report prevalence data to the WFH. A national patient registry is a database or a collection of records of people with haemophilia A and B (PWH); it includes information on personal details (e.g., age, sex, type of bleeding disorder, severity), diagnosis, treatment and complications [2]. The HTC is a specialized medical centre that provides diagnosis, treatment, and care for people with PWH [2]. In a 1997 meeting of the World Health Organization and the WFH, the national patient registry was recommended as an essential step for improving the care and lives of PWH in the developing countries [36]. However, the quality of the data from national registries can have shortcomings when the registry is

not implemented properly. To improve the quality of data obtained from national patient registries, the WFH developed a guide for setting up and maintaining an effective national patient registry through collaborations between national patient organizations, healthcare professionals, treatment centres, and ministries of health [37]. The WFH also began in 2003 the Global Alliance for Progress (GAP) project to close the gap between the number of PWH counted and the actual number [38].

We investigated the quality of the reported prevalence data from the WFH annual global surveys. As an external validation of quality, we compared prevalence data from the literature for high income OECD countries to the WFH prevalence data. As an internal validation of quality, we used information from the WFH annual global surveys. The 2003–2006 surveys [2,33–35] asked NMOs to classify its data source (national patient registry, survey of HTC, and other approaches). We compared the reported prevalence data between data sources. The 2006 survey [2] asked NMOs to estimate what proportion (0–25%, 25–50%, 50–75% and 75–100%) of its country's population of PWH is covered by the numbers they reported. We compared these estimates between data sources. The 2005–2006 surveys [2,35] asked NMOs to estimate its age distribution of PWH (0–13 years, 14–18 years, and 19 years and older). We determined the percent of PWH in the 0–18-year age group by data source and compared it to the US male population.

The reported haemophilia A prevalence and incidence data for high income OECD countries were obtained from the literature, including the Canadian Hemophilia Registry and the United Kingdom Haemophilia Centre Doctors' Organization national database. We searched the literature using the following key terms: haemophilia, prevalence, and epidemiology. We used Medline, Cochrane Database of Systematic Reviews, and the Web of Science – Science Citation Index in our review. We also searched the following journals: *Acta Haematologica*, *American Journal of Hematology*, *Annals of Internal Medicine*, *Blood*, *Blood Coagulation and Fibrinolysis*, *British Journal of Haematology*, *British Medical Journal*, *Haemophilia*, *Haematologica*, *Journal of the American Medical Association*, *Journal of Clinical Epidemiology*, *Journal of Thrombosis and Haemostasis*, *Seminars in Hematology*, *Seminars in Thrombosis and Hemostasis*, *The American Journal of Pediatric Hematology/Oncology*, *The Lancet*, *The New England Journal of Medicine*, *Thrombosis and Haemostasis*, *Transfusion*, and *Vox Sanguinis*. Each retrieved article was reviewed for its relevancy.

Prevalence was either reported directly or required computation. When prevalence was reported, we recorded it directly. When the number of people with haemophilia A was reported, we calculated the prevalence for a country by dividing this number by the male population of that country in the appropriate year [39,40].

### Statistical analysis

We used the mean, standard deviation (SD), and coefficient of variation (CV) to describe the distribution of prevalence data for each country. The CV is the SD expressed as a percent of the mean and is useful for comparing the amount of variation in dissimilar data sets. An analysis of variance (ANOVA) compared the means of the reported annual haemophilia A prevalence data from the WFH (1) between economic classifications, (2) between data sources, (3) between the proportion categories, and (4) with the literature. We used time-series data from the WFH to determine whether lower income countries reported less prevalence data than higher income countries by comparing the number of times a country reported its prevalence data to the WFH and correlating this number with a country's GNI per capita [27]. We analysed the correlation between the reported haemophilia A prevalence with the percent of PWH in the 0–18 year age group. We also analysed the strength of the relationship between prevalence data from Canada, the Netherlands, and the United Kingdom with time.  $P \leq 0.05$  is considered statistically significant.

## Results

### World Federation of Hemophilia

Table 1 presents time-series data from 1998 to 2006 of the haemophilia A prevalence for countries reporting data to the WFH. For each country in Table 1 there were nine possible prevalence observations corresponding to the years 1998–2006, inclusive. The mean, SD, and CV are calculated from these observations. The mean prevalence among high income OECD countries ranged from 5.3 per 100 000 males in Korea to 38.6 per 100 000 males in Iceland whereas the haemophilia A prevalence (per 100 000 males) for high income non-OECD countries ranged from 1.0 in Saudi Arabia to 16.3 in Slovenia, upper middle income countries ranged from 2.9 in Lebanon to 17.5 in Hungary and, lower middle income countries ranged from 0.1 in Indonesia to 16.2 in Macedonia, and low income

**Table 1.** The reported haemophilia A prevalence (per 100 000 males) was determined from the reported number of patients with haemophilia A in a country from 1998–2006 [2,29–35] divided by its male population in the relevant year [39].

Country	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	Econ
Albania	16.3	14.9	15.1	16.1	NA	14.9	15.2	15.7	15.2	15.4	0.5	4%	4
Algeria	3.0	NA	NA	3.6	3.5	NA	5.0	NA	5.6	4.1	1.1	26%	4
Argentina	7.5	8.1	8.5	8.8	NA	8.9	9.1	9.1	8.9	8.6	0.6	7%	3
Armenia	NA	NA	8.1	9.7	NA	11.0	11.1	NA	NA	10.0	1.4	14%	4
Australia	10.8	10.6	10.5	10.4	NA	NA	8.8	12.8	13.5	11.1	1.6	14%	1
Austria	NA	8.4	8.4	NA	NA	8.7	8.7	NA	NA	8.5	0.2	2%	1
Azerbaijan	NA	NA	12.2	NA	NA	NA	19.6	NA	NA	15.9	5.2	33%	4
Bangladesh	0.2	0.2	0.2	0.2	NA	0.2	0.3	0.3	0.4	0.2	0.1	29%	5
Belarus	NA	NA	NA	10.0	NA	10.2	10.4	NA	10.2	10.2	0.2	2%	4
Belgium	10.5	11.8	12.1	12.4	12.4	12.3	NA	NA	NA	11.9	0.7	6%	1
Belize	NA	NA	1.6	2.4	NA	5.3	8.1	NA	NA	4.3	3.0	68%	3
Bolivia	NA	NA	NA	0.2	0.2	0.2	NA	NA	NA	0.2	0.0	2%	4
Bosnia -Herzegovina	NA	NA	6.5	5.3	NA	5.3	5.3	NA	5.2	5.5	0.5	10%	4
Brazil	NA	6.8	6.3	6.2	NA	6.0	5.9	5.9	7.4	6.4	0.5	9%	3
Bulgaria	11.4	12.4	13.1	13.2	NA	13.4	13.5	13.5	13.6	13.0	0.8	6%	3
Canada	11.9	13.1	12.6	12.5	12.4	NA	14.0	14.3	14.6	13.2	1.0	8%	1
Chile	8.2	9.8	10.5	11.6	11.5	11.4	NA	NA	NA	10.5	1.3	13%	3
China	0.3	0.5	NA	NA	NA	NA	0.4	NA	NA	0.4	0.1	31%	4
Colombia	2.7	2.9	3.1	2.4	NA	4.5	5.0	4.6	5.2	3.8	1.1	30%	4
Costa Rica	4.2	5.7	NA	6.3	NA	6.4	6.2	6.3	NA	5.9	0.8	14%	3
Croatia	NA	NA	NA	14.9	14.8	14.8	NA	20.2	17.1	16.3	2.3	14%	3
Cuba	NA	NA	3.9	4.0	NA	4.8	5.2	5.3	5.4	4.8	0.6	13%	4
Cyprus	6.1	11.0	10.6	11.0	NA	10.8	12.9	NA	NA	10.4	2.3	22%	2
Czech Republic	12.2	12.2	12.2	NA	NA	NA	NA	NA	NA	12.2	0.0	0%	1
Denmark	11.8	11.8	12.5	12.4	NA	12.6	12.1	13.1	NA	12.3	0.5	4%	1
Dominican Republic	NA	NA	2.8	3.9	3.9	3.8	NA	NA	NA	3.6	0.5	15%	4
Ecuador	NA	NA	NA	NA	NA	NA	NA	4.7	4.9	4.8	0.1	3%	4
Egypt	NA	7.5	7.5	10.4	10.2	NA	8.1	8.8	8.7	8.7	1.2	13%	4
El Salvador	3.7	NA	6.1	6.1	NA	6.4	7.1	NA	NA	5.9	1.3	22%	4
Eritrea	NA	NA	NA	NA	NA	NA	1.0	NA	1.3	1.2	0.2	19%	5
Estonia	NA	5.3	5.4	5.7	5.8	5.8	NA	NA	NA	5.6	0.2	4%	2
Finland	NA	NA	NA	NA	NA	8.6	NA	9.0	9.1	8.9	0.3	3%	1
France	12.7	12.7	14.8	NA	NA	NA	NA	9.8	11.0	12.2	1.9	15%	1
Georgia	NA	12.4	8.2	8.8	NA	6.5	8.2	8.8	NA	8.8	1.9	22%	4
Germany	NA	13.2	9.6	9.8	NA	10.0	10.0	10.0	10.0	10.4	1.3	12%	1
Greece	10.7	10.8	12.2	12.4	NA	12.4	12.8	13.0	13.0	12.2	0.9	7%	1
Guatemala	NA	NA	NA	NA	NA	NA	1.9	1.8	NA	1.9	0.0	2%	4
Honduras	1.7	1.3	NA	NA	NA	2.3	3.5	3.9	5.2	3.0	1.5	50%	4
Hungary	15.1	15.3	15.6	20.7	20.7	NA	18.2	18.2	16.5	17.5	2.3	13%	3
Iceland	37.7	NA	NA	39.4	NA	39.3	38.1	38.5	NA	38.6	0.8	2%	1
India	NA	NA	NA	0.6	NA	0.5	0.9	1.6	1.7	1.1	0.6	52%	5
Indonesia	0.2	0.1	0.1	0.1	NA	0.1	0.2	0.2	0.2	0.1	0.0	23%	4
Iran	8.6	9.1	8.5	8.5	NA	8.3	9.7	11.1	11.2	9.4	1.2	12%	4
Iraq	NA	NA	NA	NA	NA	NA	3.6	3.6	3.6	3.6	0.0	1%	4
Ireland	12.5	16.5	17.5	16.7	NA	16.6	17.8	18.9	18.3	16.8	2.0	12%	1
Israel	NA	NA	NA	NA	NA	NA	10.5	11.2	NA	10.8	0.5	5%	2
Italy	9.0	12.3	NA	NA	NA	NA	13.8	13.8	9.4	11.7	2.3	20%	1
Jamaica	6.1	6.9	7.0	7.7	NA	7.7	7.7	NA	NA	7.2	0.6	9%	4
Japan	5.3	5.5	NA	5.9	NA	6.2	NA	6.3	6.5	5.9	0.5	8%	1
Jordan	NA	NA	5.8	NA	NA	NA	NA	NA	6.9	6.4	0.7	11%	4
Kenya	1.0	2.5	2.4	2.4	2.4	NA	2.2	NA	2.1	2.1	0.5	24%	5
Korea	4.7	5.0	5.2	5.3	5.3	NA	5.5	5.8	5.9	5.3	0.4	7%	1
Latvia	4.4	6.1	6.4	6.9	NA	7.8	8.2	8.6	9.8	7.3	1.7	23%	3
Lebanon	NA	NA	NA	2.0	2.1	NA	4.5	NA	NA	2.9	1.4	50%	3



Table 1. (Continued)

Country	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	Econ
Lesotho	0.7	NA	NA	NA	NA	NA	NA	NA	1.7	1.2	0.7	59%	4
Lithuania	5.6	5.8	6.9	6.8	NA	6.9	NA	8.0	8.1	6.9	0.9	14%	3
Luxembourg	10.0	9.0	13.5	NA	NA	NA	NA	NA	NA	10.8	2.4	22%	1
Macedonia	NA	16.6	16.4	16.8	16.7	NA	14.7	NA	NA	16.2	0.9	5%	4
Malaysia	5.6	5.8	5.8	5.8	NA	5.7	5.8	6.5	6.6	5.9	0.4	7%	3
Malta	7.9	NA	NA	6.2	6.1	6.1	NA	NA	NA	6.6	0.9	13%	2
Mexico	NA	5.4	NA	3.0	NA	3.3	3.8	5.2	5.6	4.4	1.2	26%	3
Moldova	NA	NA	NA	NA	NA	9.5	NA	NA	NA	9.5	NA	NA	4
Mongolia	NA	NA	1.5	2.2	NA	2.3	2.7	NA	2.7	2.3	0.5	21%	5
Morocco	1.9	NA	NA	NA	NA	NA	NA	NA	NA	1.9	NA	NA	4
Nepal	0.3	0.4	0.5	0.5	0.5	0.5	NA	1.0	1.2	0.6	0.3	49%	5
Netherlands	15.3	16.0	15.9	17.7	NA	17.5	18.6	18.0	18.5	17.2	1.3	8%	1
New Zealand	18.5	17.0	16.7	21.6	NA	17.8	11.7	12.3	21.9	17.2	3.7	22%	1
Nicaragua	5.0	6.6	4.7	4.6	4.5	4.5	NA	NA	7.4	5.3	1.2	22%	4
Nigeria	NA	NA	NA	NA	NA	NA	NA	0.05	NA	0.05	NA	NA	5
Norway	11.6	11.5	11.6	NA	NA	11.9	NA	12.3	12.2	11.9	0.3	3%	1
Pakistan	NA	1.5	NA	NA	NA	0.5	0.5	0.8	1.6	1.0	0.5	53%	5
Palestine	NA	NA	8.6	NA	NA	NA	5.4	NA	5.3	6.4	1.9	29%	4
Panama	10.5	11.8	11.7	11.5	NA	13.1	13.5	12.4	13.1	12.2	1.0	8%	3
Paraguay	NA	2.3	NA	NA	NA	NA	NA	NA	NA	2.3	NA	NA	4
Peru	NA	NA	1.1	NA	NA	NA	1.8	2.5	3.2	2.2	0.9	41%	4
Philippines	0.3	NA	0.8	1.1	NA	1.3	1.6	NA	1.8	1.2	0.6	49%	4
Poland	9.7	10.0	10.1	10.4	NA	10.3	NA	11.6	11.2	10.5	0.7	7%	3
Portugal	8.7	8.7	8.7	8.6	NA	10.3	9.6	9.6	9.7	9.2	0.7	7%	1
Qatar	NA	NA	NA	NA	NA	NA	NA	NA	15.8	15.8	NA	NA	2
Romania	NA	11.4	11.4	11.5	NA	11.8	NA	12.1	12.7	11.8	0.5	4%	3
Russia	1.6	3.9	9.2	9.3	NA	11.1	9.5	5.9	6.6	7.1	3.2	45%	3
Saudi Arabia	NA	NA	NA	NA	NA	1.0	1.0	NA	NA	1.0	0.0	3%	2
Senegal	NA	2.0	NA	NA	NA	NA	2.4	NA	1.6	2.0	0.4	19%	5
Serbia*	9.4	9.8	8.2	8.0	NA	7.8	8.1	8.2	7.5	8.4	0.8	10%	3
Sierra Leone	0.2	NA	NA	NA	NA	NA	NA	NA	NA	0.2	NA	NA	5
Singapore	NA	NA	7.9	7.7	7.5	NA	NA	7.9	8.0	7.8	0.2	3%	2
Slovak Republic	17.1	17.2	16.2	16.1	NA	16.7	16.7	NA	17.2	16.7	0.5	3%	3
Slovenia	NA	NA	NA	NA	NA	16.3	16.3	NA	NA	16.3	0.0	0%	2
South Africa	NA	5.3	5.3	5.4	NA	5.3	5.7	5.8	6.0	5.5	0.3	5%	3
Spain	10.9	8.5	8.5	10.0	NA	9.7	7.6	7.6	7.6	8.8	1.3	14%	1
Sri Lanka	NA	NA	NA	NA	NA	NA	1.2	NA	NA	1.2	NA	NA	4
Sudan	NA	NA	NA	NA	NA	NA	1.4	NA	1.7	1.6	0.2	14%	5
Sweden	15.5	16.2	14.9	NA	NA	14.9	15.0	NA	NA	15.3	0.5	4%	1
Switzerland	14.5	13.3	14.6	11.9	NA	12.1	13.2	12.7	14.2	13.3	1.0	8%	1
Thailand	0.6	0.6	0.7	0.6	NA	0.7	0.9	1.3	3.6	1.1	1.0	91%	4
Togo	0.04	NA	NA	NA	NA	NA	NA	NA	NA	0.04	NA	NA	5
Tunisia	NA	NA	2.6	5.1	NA	4.7	NA	NA	4.3	4.2	1.1	27%	4
Turkey	0.7	1.0	1.1	2.2	NA	2.9	4.4	5.5	6.1	3.0	2.1	71%	3
Ukraine	1.0	0.4	NA	NA	NA	NA	NA	NA	NA	0.7	0.4	55%	4
United Kingdom	19.0	19.4	17.4	17.6	NA	17.2	NA	22.6	20.7	19.1	2.0	11%	1
United States	7.6	7.5	7.7	7.8	NA	7.6	7.8	7.9	8.0	7.8	0.1	2%	1
Uruguay	9.6	10.6	9.5	9.4	NA	9.5	9.5	NA	NA	9.7	0.5	5%	3
Uzbekistan	NA	NA	NA	5.6	NA	NA	4.8	6.0	7.6	6.0	1.2	20%	5
Venezuela	6.4	7.2	7.4	7.5	NA	8.0	8.6	9.4	9.8	8.0	1.2	14%	3
Vietnam	NA	NA	0.5	NA	NA	NA	0.4	1.7	2.0	1.2	0.8	68%	5
Zimbabwe	3.3	NA	NA	4.8	4.7	NA	4.6	NA	4.6	4.4	0.6	15%	5

\*In 1992, Yugoslavia was a federation of Serbia and Montenegro. In 2003, it was renamed the State Union of Serbia and Montenegro, and officially abolished the name Yugoslavia. In 2006, Serbia and Montenegro declared independence.

SD, standard deviation; CV, coefficient of variation; NA, not available, no data provided; Econ, Economic Classification [27]: 1: High income OECD (Organisation for Economic Co-operation and Development) [28]; 2: High income non-OECD; 3: Upper middle income; 4: Lower middle income; 5: Low income.

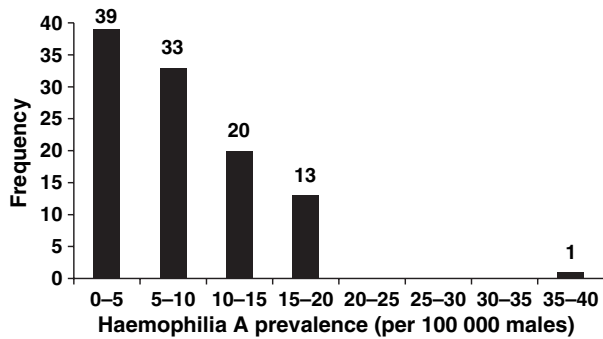


Fig. 1. Histogram for the mean haemophilia A prevalence (per 100 000 males) for each of the 106 countries reporting prevalence data to the World Federation of Hemophilia (Table 1). The numbers above each bar represents the number (frequency) of countries with mean prevalence in the range stated on the abscissa.

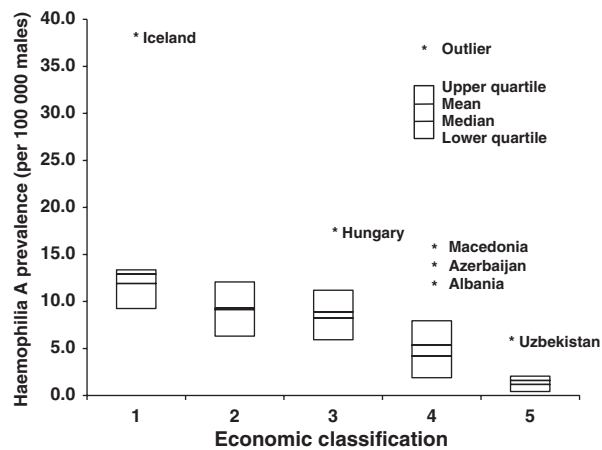


Fig. 2. Distribution plot with economic classification on the abscissa and haemophilia A prevalence (per 100 000 males) values on the ordinate. The prevalence values represent the mean prevalence for each of the 106 countries reporting prevalence data to the World Federation of Hemophilia (Table 1). The economic classification [27] is as follows: 1: High income OECD (Organisation for Economic Co-operation and Development) [28]; 2: High income non-OECD; 3: Upper middle income; 4: Lower middle income; 5: Low income.

countries ranged from 0.04 in Togo to 6.0 in Uzbekistan. Figure 1 is a histogram of each country's mean haemophilia A prevalence (Table 1). Nearly 70% of countries report prevalence (per 100 000 males) of 10 or less. Some countries had unusually high prevalence when compared to the countries within their economic classification (Fig. 2).

The reported haemophilia A prevalence varied considerably across economic classifications (Table 2). The mean haemophilia A prevalence was significantly different for all economic classification except the comparison between high income

non-OECD countries and upper middle income countries ( $P = 0.524$ ). On a country-by-country basis, the mean prevalence was moderately correlated ( $R = 0.53$ ) with GNI per capita [27].

The number of countries reporting [2,33–35] that they used a national patient registry has increased each year – 39 in 2003, 40 in 2004, 49 in 2005, and 57 in 2006 while at the same time the number of countries not reporting a data source decreased from 31 in 2003 to 14 in 2006. From 2003 to 2006, 44% of the countries reported using a registry whereas 26% reported surveying HTC, 11% used other approaches, and 19% did not report its data source to the WFH.

The mean of the prevalence data from registries was significantly higher than the mean of the prevalence data from surveying HTCs (Table 3). The mean prevalence increased with increasing economic capacity for registries and survey of HTCs. For registry-based data, the mean haemophilia A prevalence was significantly different for all economic classification except the comparisons between high income OECD countries and high income non-OECD countries ( $P = 0.624$ ) and high income non-OECD countries and upper middle income countries ( $P = 0.128$ ). The mean of the prevalence data for the proportion of PWH included in the prevalence data was significantly higher for the 75–100% category when compared to other proportion categories (Table 4).

The percent of PWH overall was 44% for the 0–18 years age group (meaning that 56% PWH were over 18 years) [2,35] whereas the US male population was 28% for the 0–18 years age group [39]. The percentages of PWH in the 0–18 years age group was moderately correlated ( $R = -0.60$ ,  $P < 0.001$ ) with the prevalence data [2,35]. On a country-by-country basis, the percent of PWH in the 0–18 years age group [2,35] was moderately negatively correlated ( $R = -0.52$ ,  $P < 0.001$ ) with GNI per capita [27] suggesting that in countries with a lower GNI fewer PWH survive into adult life.

There was no clear relationship among a country's frequency of reporting prevalence data and its economic capacity. We expected that lower income countries would report prevalence data less frequently than higher income countries. The number of times a country reported its prevalence data to the WFH was weakly correlated ( $R = 0.16$ ) with GNI per capita [27]. The results were not significantly different when we compared the frequency of reporting prevalence data between data sources. Experience at the WFH suggests that the level of resources available for data collection of individual



**Table 2.** Statistical analysis of the reported haemophilia A prevalence (per 100 000 males) by economic classification [27] for the annual prevalence data in Table 1.

Economic Classification	Mean	SD	CV	<i>n</i>	<i>N</i>	<i>P</i> compares economic classifications			
						(2)	(3)	(4)	(5)
High Income OECD countries (1)	12.8	6.0	47%	159	25	< 0.001	<0.001	<0.001	<0.001
High Income non-OECD countries (2)	8.4	4.0	47%	27	8		0.524	0.005	<0.001
Upper Middle Income countries (3)	9.0	4.2	47%	157	23			<0.001	<0.001
Lower Middle Income countries (4)	5.8	4.6	79%	152	35				<0.001
Low Income countries (5)	1.7	1.7	96%	61	15				
Countries in (2) – (5)	6.6	4.8	72%	397	81				
All countries	8.4	5.9	73%	556	106				

*P* compares the mean haemophilia A prevalence for economic classifications using an analysis of variance (ANOVA).

OECD, Organisation for Economic Co-operation and Development [28]; SD, standard deviation; CV, coefficient of variation; *n*, number of haemophilia A prevalence observations in Table 1 for each economic classification; *N*, number of countries in each economic classification.

**Table 3.** Statistical analysis of the reported haemophilia A prevalence (per 100 000 males) by data source (registry, survey of HTC, and other approaches) and economic classification [27] for the annual prevalence data from 2003–2006 [2,33–35].

Data Source	Mean	SD	CV	<i>n</i>	<i>P</i> compares data source		<i>P</i> compares data source and economic classification			
					(2)	(3)	(ii)	(iii)	(iv)	(v)
Registry (1)	9.3	6.8	73%	154	0.035	0.107				
Registry and High Income OECD (i)	14.7	8.1	55%	38			0.624	<0.001	<0.001	<0.001
Registry and High Income nonOECD (ii)	12.9	4.5	35%	5				0.128	0.007	<0.001
Registry and Upper Middle Income (iii)	9.8	4.3	44%	55					<0.001	<0.001
Registry and Lower Middle Income (iv)	6.3	4.9	78%	38						<0.001
Registry and Low Income (v)	1.7	1.7	100%	18						
Survey of HTCs (2)	7.4	4.6	62%	73		0.878				
Survey of HTCs and High Income OECD	10.9	3.3	30%	23						
Survey of HTCs and High Income nonOECD	10.8	0.5	5%	2						
Survey of HTCs and Upper Middle Income	9.0	2.4	26%	10						
Survey of HTCs and Lower Middle Income	6.1	4.5	74%	25						
Survey of HTCs and Low Income	2.2	1.8	84%	13						
Other (3)	7.3	4.9	48%	33						
Other and High Income OECD	11.4	5.2	45%	8						
Other and High Income nonOECD	6.4	6.3	99%	4						
Other and Upper Middle Income	7.4	3.3	45%	10						
Other and Lower Middle Income	6.3	3.7	58%	7						
Other and Low Income	1.3	1.0	75%	4						

*P* compares the mean haemophilia A prevalence for data source using an analysis of variance (ANOVA).

*P* compares the mean haemophilia A prevalence for data source and economic classification using an analysis of variance (ANOVA).

HTCs, haemophilia treatment centres; OECD, Organisation for Economic Co-operation and Development [28].

Survey Question B4 – What is the source of the numbers provided above? Check one:

Hemophilia registry of people with hemophilia (PWH) and other inherited bleeding disorders in your country.

Survey of your country's hemophilia treatment centres.

Other (Describe).

SD, standard deviation; CV, coefficient of variation; *n*, number of haemophilia A prevalence observations in Table 1 for each data source from 2003 to 2006.

NMOs plays as great a role as economic sophistication in determining frequency of data reporting.

#### *Literature (high income OECD countries)*

Prevalence varied considerably by country and by year. Table 5 presents the prevalence and incidence

in the literature for high income OECD countries. For most of the countries, the prevalence data were obtained infrequently with exceptions being Canada, the Netherlands, and the United Kingdom. There was a strong trend of increasing haemophilia A prevalence over time for Canada ( $R = 0.94$  and  $P < 0.001$ ), the Netherlands ( $R = 0.85$ ,  $P = 0.004$ )

**Table 4.** Statistical analysis of the reported haemophilia A prevalence (per 100 000 males) (Table 1) by the reported proportion of a country's patient population that is included in the 2006 prevalence data [2].

Proportion of patients included	Mean	SD	CV	N	Registry	HTCs	Other	<i>P</i> compares proportion of patients included		
								(2)	(3)	(4)
75–100% (1)	11.2	4.9	44%	34	29	3	2	0.008	0.017	<0.001
50–75% (2)	6.7	1.9	29%	10	6	4	0		0.376	0.029
25–50% (3)	5.5	3.3	59%	5	1	2	2			0.321
0–25% (4)	3.4	4.2	125%	16	10	3	3			

*P* compares the mean haemophilia A prevalence for the proportion of a patient population included in the prevalence data using an analysis of variance (ANOVA).

Survey Question B5 – Please assess what proportion of your country's patient population is included in the numbers provided for questions B1–3.

0–25%

25–50%

50–75%

75–100%

SD, standard deviation; CV, coefficient of variation; N, number of countries in each proportion category; HTCs, haemophilia treatment centres.

and the United Kingdom ( $R = 0.94$  and  $P < 0.001$ ) (Figs 3–5). The prevalence (per 100 000 males) for Canada was  $12.9 \pm 1.5$  (mean  $\pm$  SD),  $9.8 \pm 2.2$  for the Netherlands, and  $16.8 \pm 2.9$  for the United Kingdom. There was also a strong trend of increasing prevalence of severe haemophilia A in Canada ( $R = 0.89$ ,  $P = 0.003$ ) that was not observed in the United Kingdom ( $R = 0.64$ ,  $P = 0.048$ ). The prevalence of severe haemophilia A (per 100 000 males) over the period for Canada was  $4.0 \pm 0.3$  (mean  $\pm$  SD) in contrast to  $6.7 \pm 0.9$ , for the United Kingdom. The proportion of severe patients averaged 31% for Canada and 34% for the United Kingdom. We expected there to be less variability in the prevalence of severe haemophilia A when compared to the overall prevalence because under-diagnosed mild cases would affect the latter and not the former. This was the case for Canada, but not for the United Kingdom.

#### *Comparing prevalence data from the WFH annual surveys with prevalence data in the literature*

We compared on an annual basis the reported prevalence data for high income OECD countries from the WFH (Table 1) and from the literature (Table 5). There were 14 comparisons. The reported prevalence (per 100 000 males) data from the WFH was  $16.0 \pm 4.2$  (mean  $\pm$  SD) and  $15.8 \pm 3.9$  for the reported prevalence data from the literature and the means were not statistically significant ( $P = 0.880$ ). The WFH-reported prevalence in 1998 for the United States [29] was 36% less than the reported prevalence in the literature [79]. The WFH-reported

prevalence in 2001 for the Netherlands [32] was 34% higher than reported in the literature [59].

#### *Discussion*

This research aims to study the reported haemophilia A prevalence around the world and to determine whether prevalence varied across national economies. The WFH annual global surveys are currently the best available source of such information. However, the prevalence data provided by countries to the WFH can be of variable quality [26,38]. The problem is identifying which data are of high quality and which are not.

Data collection is time-consuming and expensive, and accuracy potentially limited by delays or lack of access to data. There can be duplication of entries or failure to register deaths or emigration resulting in an inflated prevalence. Lack of standardized data forms, definitions, and data collection procedures can greatly affect county-to-county comparisons. Some countries have sophisticated registries, while others can only collect limited data from some geographical areas. Even though a national patient registry is a key priority to improve haemophilia care, the type of registry used by a country, if not implemented properly, can affect the quality of its reported prevalence [37, B.L. Evatt, pers. comm.]. For example, patient organization registries may have limited information about total number of patients and correct diagnosis, if detailed clinical information is not shared by physicians. Likewise medical registries may be restricted to a specific class of patients; managers of medical registries may have a

**Table 5.** Reported haemophilia A prevalence (per 100 000 males) in the literature for high income Organisation for Economic Co-operation and Development (OECD) countries [28].

Country	Year	Prevalence		Incidence	Note	Source
		Overall	Severe			
Canada	2008	14.3	4.3	NA	C	[41]
Canada	2007	14.0	4.3	NA	C	[42]
Canada	2006	13.7	4.1	NA	C	[43]
Canada	2005	13.6	4.1	NA	C	[44]
Canada	2004	13.3	4.1	NA	C	[45]
Canada	2003	13.2	3.9	NA	C	[46]
Canada	2001	14.2	NA	NA	C	[47]
Canada	1995	11.2	NA	NA	C	[48]
Canada	1993	11.2	3.4	NA	C	[49]
Canada	1989	10.2	3.7	NA	C	[50]
Finland	1989	7.3	4.6	NA	C	[51,52]
Finland	1979	NA	4.3	NA	C	[14]
France	2001	15.0	NA	18.5	R	[53]
Greece	1992	12.0	3.6	19.3	R	[54]
Greece	1975	7.4	NA	NA	C	[55]
Italy	2006	9.5	4.8	NA	R	[56]
Italy	1991	8.2	NA	NA	R	[57]
Italy	1987	NA	NA	15.0	R	[57]
Italy	1981	NA	NA	12.0	R	[57]
Italy	1971	NA	NA	12.5	R	[57]
Italy	1961	NA	NA	9.5	R	[57]
Japan	1997	5.3	NA	NA	C	[58]
Netherlands	2001	11.7	NA	NA	C	[59]
Netherlands	1992	10.6	NA	NA	C	[60]
Netherlands	1992	11.4	NA	NA	C	[59]
Netherlands	1992	10.6	4.2	NA	C	[61]
Netherlands	1985	11.2	NA	NA	C	[59]
Netherlands	1985	11.2	NA	NA	C	[62]
Netherlands	1978	8.9	4.0	NA	C	[63]
Netherlands	1978	6.9	NA	NA	C	[59]
Netherlands	1972	5.7	NA	NA	C	[59]
Spain	1974	5.3	NA	NA	C	[64]
Sweden	1980	11.0	3.3	NA	C	[65]
Sweden	1974	10.7	3.6	NA	C	[66]
United Kingdom	2008	21.5	7.1	NA	C	[L. Dewhurst, pers. comm.]
United Kingdom	2007	21.2	7.0	NA	C	[67]
United Kingdom	2006	21.6	7.5	NA	C	[68]
United Kingdom	2005	21.0	7.0	NA	C	[69 and L. Dewhurst, pers. comm.]
United Kingdom	2004	20.7	6.9	NA	C	[69 and L. Dewhurst, pers. comm.]
United Kingdom	2003	19.2	6.6	NA	C	[70]
United Kingdom	2002	19.2	7.6	NA	C	[71]
United Kingdom	2001	19.0	6.6	NA	C	[72]
United Kingdom	2000	18.8	6.5	NA	C	[72]
United Kingdom	1999	17.5	4.3	NA	C	[73]
United Kingdom	1998	17.5	NA	NA	C	[74]
United Kingdom	1997	17.6	NA	NA	C	[75]
United Kingdom	1996	17.1	NA	NA	C	[76]
United Kingdom	1995	17.4	NA	NA	C	[76]
United Kingdom	1994	17.7	NA	NA	C	[76]
United Kingdom	1993	17.3	NA	NA	C	[76]
United Kingdom	1992	17.2	NA	NA	C	[76]
United Kingdom	1991	17.1	NA	NA	C	[76]
United Kingdom	1990	17.0	NA	NA	C	[76]
United Kingdom	1989	17.0	NA	NA	C	[76]
United Kingdom	1988	16.8	NA	NA	C	[76]

Table 5. (Continued)

Country	Year	Prevalence		Incidence	Note	Source
		Overall	Severe			
United Kingdom	1987	16.6	NA	NA	C	[76]
United Kingdom	1986	16.3	NA	NA	C	[76]
United Kingdom	1985	16.2	NA	NA	C	[76]
United Kingdom	1984	15.9	NA	NA	C	[76]
United Kingdom	1983	15.4	NA	NA	C	[76]
United Kingdom	1982	14.9	NA	NA	C	[76]
United Kingdom	1981	14.4	NA	NA	C	[76]
United Kingdom	1980	15.8	NA	NA	C	[77]
United Kingdom	1979	15.0	NA	NA	C	[77]
United Kingdom	1978	14.3	NA	NA	C	[77]
United Kingdom	1977	12.9	NA	NA	C	[77]
United Kingdom	1976	11.7	NA	NA	C	[77]
United Kingdom	1975	10.4	NA	NA	C	[77]
United Kingdom	1974	9.3	NA	NA	C	[78]
United States	1998	10.4	4.4	NA	C	[79]
United States	1994	10.5	NA	15.6	R	[9]
United States	1978	8.3	2.8	NA	R	[80]
United States	1971	20.5	12.3	NA	R	[81]

Overall – haemophilia A prevalence (per 100,000 males), includes people with severe, moderate, and mild haemophilia A.

Severe – severe haemophilia A (per 100,000 males), clotting activity level  $\leq 1\%$  normal.

Incidence – haemophilia A incidence or prevalence at birth (per 100,000 males).

NA, not available; C, calculated preference, reported number of people with haemophilia A in a country (source) divided by its male population in the appropriate year [39,40]; R, reported what was recorded in the source.

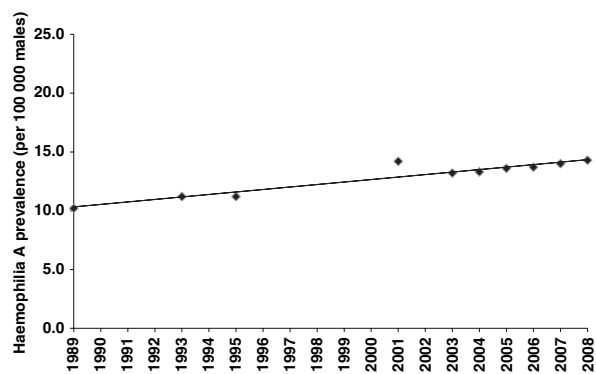


Fig. 3. Trend analysis ( $R = 0.94$ ,  $P < 0.001$ ) of the registry data for the haemophilia A prevalence in Canada (Table 5).

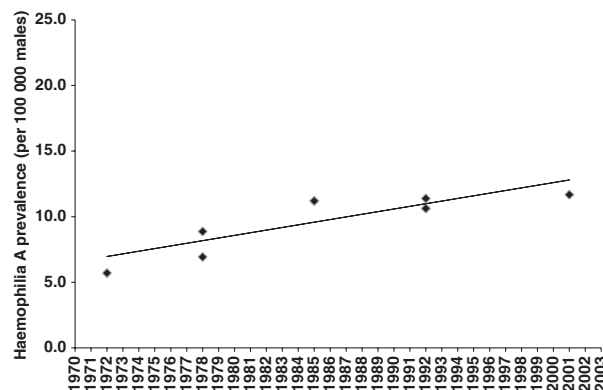


Fig. 4. Trend analysis ( $R = 0.85$ ,  $P = 0.004$ ) of the data for the haemophilia A prevalence in the Netherlands (Table 5).

proprietary attitude toward the data. Health ministry registries can be limited by a lack resources devoted to obtaining data, inability to verify the data and privacy laws limiting the distribution of patient information.

Incomplete ascertainment of cases, non-representative samples, and survey non-response may result in under-reporting of the number of people with haemophilia A in all of the studies (Tables 1 and 5). An incomplete ascertainment of cases, especially mild cases, occurs when countries count only patients that use their HTC or other care sources [2,14,29–35,41–52,55,57,58,76,78,79]. For

example, the WFH data for the United States is based solely on patients who use federally supported haemophilia treatment centres for care which accounted for about 70% of all patients identified in a more complete sample [9]. A non-representative sample occurs when the respondents from the sample do not match the desired target population. Some countries sampled a subset of its population to estimate prevalence [9,53–55,79,81] while others are old studies, and the prevalence reported for the 1970s may not represent the observed prevalence today [14,55,62–66,77,78,80,81]. A survey non-response occurs when a respondent does not respond

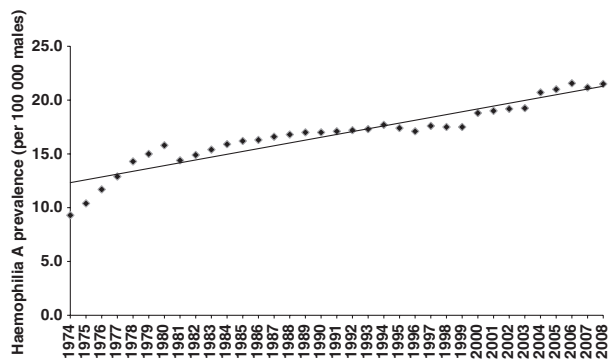


Fig. 5. Trend analysis ( $R = 0.94$ ,  $P < 0.001$ ) of the data for the haemophilia A prevalence in the United Kingdom (Table 5).

to a survey request. Some studies reported non-responding centres or hospitals [56,57,64,67–75] or non-responding individuals [59–63,65]. There is also substantial variation in the age distributions among countries which would contribute to variations in reported prevalence.

While there remain challenges in collecting reliable prevalence data, especially in countries without basic data collection tools, considerable progress has been made each year in both quantity and quality of the WFH prevalence data [18,26,38,82] as well as the prevalence data reported in the literature [9,49,56,59,76,83,84]. For high income OECD countries, our research shows that the reported prevalence data from the WFH compares well with the reported prevalence data from the literature. Our research also shows that national registries provide higher quality prevalence data than the other data sources. The distribution of patients in 0–18 years age groups from registries is closer to the age distribution in the general US male population when compared to the other data sources. Higher prevalence is associated with a smaller percent of PWH in the 0–18 years age groups as more PWH survive into adult life.

The reported haemophilia A prevalence is significantly different across national economies, even among the wealthiest countries. The reported haemophilia A prevalence in the high income OECD countries is significantly greater than the rest of the economic classifications. Similarly, for registry data, the mean prevalence increases with increasing economic capacity. On a country-by-country basis, the reported prevalence in the WFH annual surveys shows an increasing prevalence over time for nearly 80% of the countries. For example, there is a strong trend of increasing prevalence over time, as reported for Canada, the Netherlands, and the United

Kingdom. The increasing prevalence over time could reflect increased survival, improved diagnosis and classification brought about by worldwide improvement in the access of care for haemophilia, the effect of migration of patients from areas of poorer care to those with better care, and more countries using a national patient registry. The quality of data from registries is an improvement over the other data sources, but there can still be shortcomings with national patient registries. Further research is needed to investigate the data sources used by countries and the resulting quality of its prevalence data. For example, does the type of healthcare system influence data quality? Will a country with universal state-of-the-art healthcare identify more PWH even if they do not require treatment? Given the variability of the reported prevalence, further research is also warranted on investigating what the actual prevalence is and whether the incidence is the same for all populations and racial groups. Is there a biological explanation for this variability?

Some countries have higher prevalence when compared to the countries within their economic classification: Iceland, Hungary, Albania, Azerbaijan, Macedonia, and Uzbekistan. Iceland – the least populated high income OECD country – stands out for having the highest prevalence. This can be explained by a founder effect [85]. The other countries – Hungary (upper middle income), Albania, Azerbaijan, Macedonia (lower middle income), and Uzbekistan (low income) – have primarily used a registry as their data source with one exception: Macedonia, which surveyed HTC. Finally the blood borne epidemics which are associated with clotting factor treatment products played out differently in neighbouring or economically similar countries. Some countries had higher rates of infections depending on the source of clotting factor concentrates, domestic production and prevalence of infections in donor pools, and when inactivation and screening measure were introduced.

With treatment advances and improved reporting procedures, there will likely be an overall increase in the number of reported cases of haemophilia A relative to that observed today. Such epidemiological information will be important for national healthcare agencies to determine realistic budget priorities in planning for HTCs and for an increased use of FVIII concentrates in the treatment of haemophilia [5,82,86,87]. This information is also important for manufacturers in planning for adequate production of FVIII concentrates [25] to help prevent future shortages.



## Acknowledgements

We thank the president of the WFH, Mark W. Skinner, and Dr Bruce L. Evatt for their helpful review of the manuscript. We thank the chairman of the UKHCDO, Dr Charles R. M. Hay, for permission to publish its data. We thank Lynne Dewhurst in providing annual UKHCDO reports for 2004, 2005 and 2008. We thank Ben Palmer for providing statistical expertise. Professor Stonebraker received research grants from the University of Denver.

## Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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