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Jeffrey S. Stonebraker
North Carolina State University
College of Management
Raleigh, NC, U.S.A.

Mark Brooker
World Federation of Hemophilia
Montreal, QC, Canada

Robert E. Amand
Biotherapeutic Modeling Group, Inc.
Cary, NC, U.S.A.

Albert Farrugia
Plasma Protein Therapeutics Association
Annapolis, MD, U.S.A.

Alok Srivastava
Department of Haematology
Christian Medical College
Vellore, India

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FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
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World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel. : (514) 875-7944
Fax : (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

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A study of reported factor VIII use around the world

J. S. STONEBRAKER,* M. BROOKER,† R. E. AMAND,‡ A. FARRUGIA§ and A. SRIVASTAVA¶
**North Carolina State University, College of Management, Raleigh, NC, USA; †World Federation of Hemophilia, Montréal, QC, Canada; ‡Biotherapeutic Modeling Group, Inc., Cary, NC, USA; §Plasma Protein Therapeutics Association, Annapolis, MD, USA; and ¶Department of Haematology, Christian Medical College, Vellore, India*

Summary. The effect of replacement therapy has significantly improved the morbidity and mortality of people with haemophilia A in high income countries, a recent socio-economic development as the availability of safe concentrates has been matched by a willingness for their provision through reimbursement. In the developing world, however, this state has not been achieved, primarily because of the low visibility of haemophilia coupled with its expense, leading to inadequate treatment with its sequelae of severe pain, joint deformities, arthropathy, disabilities, and even death in childhood or early adult life. The objective of this paper was to study the reported factor VIII (FVIII) use on a country-by-country basis. Data on the reported FVIII use for 104 countries were obtained from the Marketing Research Bureau, Inc. and the World Federation of Hemophilia. The results show that FVIII use varies considerably among countries, even among the wealthiest of countries. The use of FVIII concentrate increases as economic capacity increases; in addition, consumption of FVIII has been increasing at a greater rate in high income countries. Given these trends, there probably will be a global increase in FVIII concentrates usage. Such information is critical for national healthcare agencies to determine realistic budget priorities in planning for an increased allocation of resources required to improve the treatment of patients with haemophilia A. This information is also important for pharmaceutical manufacturers to adequately plan for increased production of FVIII concentrates.

Keywords: economics, factor VIII (FVIII) use, FVIII concentrate, haemophilia A, national healthcare planning, production planning, World Federation of Hemophilia

Introduction

The availability of factor VIII (FVIII) concentrates affects lifespan and lifestyle for people with haemophilia A [1]. The effect of replacement therapy has improved significantly the life expectancy and quality of life of patients with haemophilia A in high income countries [2,3]. Before the development of replacement products for haemophilia in the 1960s, there was little difference in haemophilia care between the developed world and the developing world [4], with inadequate treatment resulting in terrible pain, joint deformities, arthropathy, disabilities, and death in childhood or early adult life [5–10]. It has been estimated that 70–80% of people with haemophilia globally, primarily in the developing world, receive inadequate or no treatment [11,12] because of unavailable and/or unaffordable factor concentrates [12–19]. Increasing the availability and use of FVIII concentrates will improve the mortality and morbidity outcomes for people with haemophilia A.

Effective national healthcare policy requires the rational economic allocation of scarce resources to a set of healthcare needs that are infinite [20]. National healthcare agencies in lower income countries are often slow to establish haemophilia care programs because they believe that there will be insufficient economic resources available to successfully establish such programs. Lower income countries typically do

Correspondence: Jeffrey S. Stonebraker, North Carolina State University, College of Management, Raleigh, NC 27695-7229, USA.
Tel.: +1 919 515 0155; fax: +1 919 515 6943;
e-mail: jeff_stonebraker@ncsu.edu

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not provide resources for treating rare, chronic, and expensive conditions (such as haemophilia) since they focus their limited resources on public health issues that affect larger portions of the population, e.g. family planning, sanitation, malnutrition, combating infectious diseases [12,13,16,21–24].

The primary aims of this research were to study the reported FVIII use on a country-by-country basis and determine whether the amount of FVIII used in the treatment of haemophilia A varied across national economies. Previous research has shown that the usage of FVIII concentrates tends to increase as economic resources increase [1,12,17,22,25–30]. In this study, we analysed FVIII use in terms of international units (IUs) per capita and IUs per person with haemophilia A (PWHA). Both can be useful for national healthcare planning and production planning. FVIII use (IUs per capita) can be useful for production planning when the vast majority of PWHA have been identified and are being treated. It must be remembered that in populations with significant early mortality in the haemophilia population due to under-treatment, the FVIII consumption per capita does not necessarily reflect the overall quality of care because available products are being provided only to the small population of survivors. When the vast majority of PWHA in a country (e.g. China, India, etc.) have not been identified or treated, FVIII use (IUs per capita) does not reflect the care that identified patients receive and can show an unrealistic burden of FVIII concentrate expense with the result that a country may not consider allocating funds for the treatment of haemophilia A. The identification and quantification of the haemophilia population is therefore a critical element in planning and delivering care.

Methods

Economic classification

We used the World Bank's economic classification [31] to describe national economies. Economies are classified according to the 2006 gross national income (GNI) per capita (all in US dollars) as determined from the World Bank Atlas method [31]: low income, $905 or less; lower middle income, $906–$3595; upper middle income, $3596–$11 115; and high income, $11 116 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) [32]. 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 2006 economic categories to all years.

FVIII use

We obtained data on the reported number of IUs of FVIII used for 104 countries from the Marketing Research Bureau, Inc. (MRB) and the World Federation of Hemophilia (WFH). MRB is a market research firm that tracks the annual number of IUs sold for FVIII concentrates at the country level on a worldwide basis [33–37]. MRB obtains these data through industry and government interviews. MRB does not collect FVIII use data annually for each country. The WFH is a non-profit organization that tracks the availability of clotting factor concentrates through its annual global surveys [38–42]. Each year survey questionnaires are sent to national member organizations (NMOs) linked with the WFH. The WFH reviews the completed questionnaires for inconsistencies and follows-up with NMOs when necessary. Participation in the questionnaire is voluntary and self-reported. Countries do not provide FVIII use data each year to the WFH. While there remain challenges in collecting reliable data, especially in countries without basic data collection tools, considerable progress has been made each year in both quantity and quality of data [17,22,26,43]. We averaged the reported FVIII use (IUs) from MRB and WFH when available in the same year and compared these data using percent difference:

$$\text{Percent difference} = \frac{|x - y|}{\left(\frac{x+y}{2}\right)} \times 100$$

where x is the reported FVIII use (IUs) from MRB and y is the reported FVIII use (IUs) from the WFH. The FVIII use (IUs per capita) for a country was calculated by dividing the reported number of IUs of FVIII used by its total population in the appropriate year [44]. The FVIII use (IUs per PWHA) for a country was calculated by dividing the reported number of IUs of FVIII used by the reported number of PWHA [38–42,45–47].

Statistical analysis

For each country in our study, we used the mean, standard deviation (SD), and coefficient of variation (CV) to describe its distribution of FVIII use. 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 FVIII use between economic

classifications. Regression analyses were performed on a country-by-country basis to examine the association between FVIII use and GNI per capita [31] and the association of FVIII use over time. The strength of the association between these variables was assessed by its correlation coefficient (R). In addition, the slope of the regression line (m) for FVIII use over time provided a measure of annual growth of FVIII use for a country. $P \leq 0.05$ is considered statistically significant.

Results

Data on the reported number of IUs of FVIII used were obtained for 104 countries from MRB and WFH. MRB reported data on 74 countries, whereas the WFH reported data on 87 countries. Out of the 104 countries considered in the study, 57 countries reported FVIII use data to both WFH and MRB, 17 countries reported data to MRB only and 30 countries to WFH only.

Of the countries reporting FVIII use data to both MRB and WFH, there were differences in what was reported annually by each country. We compared on an annual basis the reported FVIII use (IUs) data from MRB with the WFH. There were 64 comparisons. MRB reported higher levels of FVIII consumption than WFH in 35 instances, with an average difference of 44%; whereas WFH reported higher levels of FVIII consumption than MRB in 29 instances, with an average difference of 29%. We also compared, using ANOVA, the means of FVIII consumption from MRB and WFH by economic classification and the means were not statistically different. There was a clear trend with the reported FVIII use data from either MRB or WFH: the use of FVIII concentrate for a country increased as its economic capacity increased.

FVIII use (IUs per capita)

Table 1 presents time-series data from 1996 to 2006 of the FVIII use (IUs per capita) for 104 countries reporting data to MRB and WFH. There were eleven possible FVIII use observations corresponding to the years 1996–2006, inclusive. The mean, SD, CV, R and slope (m) were calculated from these observations. Figure 1 is a histogram of each country's mean FVIII use (Table 1). Sixty-four percent of countries reported FVIII use (IUs per capita) of 1.0 or less (Fig. 1) with Iceland reporting the highest use. The 1 IU per capita is approximately the 20 000 IUs per patient, which the WFH suggested as a minimum clinical target for haemophilia care [26]. The mean FVIII use (IUs per capita) among high income OECD countries ranged from 1.2864 in Korea to 9.0261 in Iceland whereas the FVIII use for high income non-OECD countries ranged from 0.2326 in Trinidad & Tobago to 4.6512 in Slovenia, upper middle income countries ranged from 0.2125 in Romania to 3.3948 in Hungary and, lower middle income countries ranged from 0.0069 in Armenia to 0.9680 in Iran, and low income countries ranged from 0.0004 in Nigeria to 0.1287 in Eritrea. Some countries had unusually high FVIII use (IUs per capita) when compared to the countries within their economic classification (Fig. 2).

FVIII use (IUs per capita) increased over time with 90% of countries having positive R and m values (Table 1). The average slope (m) for high income OECD countries was 0.1543 IUs per capita per year in contrast to 0.0556 IUs per capita per year for high income non-OECD countries, 0.1141 IUs per capita per year for upper middle income countries, 0.0299 IUs per capita per year for lower middle income countries, and 0.0182 IUs per capita per year for low income countries. Similar results were obtained for countries with FVIII use of least 1 IU per capita (m = 0.1560 IUs per capita per year) versus m = 0.0474 IUs per capita per year for countries consuming less than 1 IU per capita. There are many countries that have annual growth rates exceeding 0.2 IUs per capita, primarily in the high income OECD countries. The few exceptions include: Hungary (m = 0.4205, R = 0.95) and Slovak Republic (m = 0.2815, R = 0.98).

The reported FVIII use (IUs per capita) varied considerably across economic classifications. Table 2 presents the mean, SD, and CV of each observation in Table 1 by economic classification and ANOVA results. The FVIII use increased with increasing economic capacity – FVIII use for the high income OECD countries was 3.8312 ± 1.9691 IUs per capita (mean ± SD) whereas the FVIII use for the other economic classifications was 0.6008 ± 0.8618 IUs per capita (mean ± SD). The FVIII use was significantly different for all economic classification (Table 2). On a country-by-country basis, the mean FVIII use (IUs per capita) was strongly positively correlated (R = 0.81) with mean GNI per capita [31]. The variability (CV) of FVIII use decreased with increasing economic capacity. The CV was moderately negatively correlated (R = –0.55) with GNI per capita [31].

FVIII use (IUs per PWHA)

Table 3 presents time-series data from 1998 to 2006 of the FVIII use (IUs per PWHA) for 88 countries

Table 1. The reported factor VIII (FVIII) use (IUs per capita) was determined from the reported number of FVIII international units (IUs) used in the treatment of haemophilia A for a country from 1996 to 2006 [33–42] divided by its total population in the relevant year [44].

Country	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	R	m	Econ
Albania	NA	NA	NA	NA	NA	0.2269	NA	0.2568	0.2712	0.2536	0.2522	0.2522	0.0160	6%	0.59	0.0049	4
Algeria	NA	NA	NA	NA	NA	NA	0.0795	NA	NA	NA	0.2699	0.1747	0.1346	77%	NA	NA	4
Argentina	NA	NA	0.7011	NA	NA	0.8692	0.7306	0.6578	1.3004	NA	NA	0.8518	0.2630	31%	0.53	0.0608	3
Armenia	NA	NA	NA	NA	NA	NA	NA	0.0039	0.0099	NA	NA	0.0069	0.0042	61%	NA	NA	4
Australia	NA	2.3565	NA	NA	2.9260	2.9793	3.0096	3.8450	4.1930	4.6323	4.6030	3.5681	0.8627	24%	0.95	0.2822	1
Austria	2.6251	NA	NA	3.6063	NA	NA	3.7934	NA	NA	3.7506	NA	3.4438	0.5517	16%	0.83	0.1188	1
Azerbaijan	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.0499	NA	0.0499	NA	NA	NA	NA	4
Bangladesh	NA	NA	NA	NA	NA	0.0008	0.0018	0.0032	0.0021	0.0039	0.0044	0.0027	0.0014	51%	0.91	0.0007	5
Barbados	NA	NA	0.3521	NA	NA	NA	NA	NA	NA	NA	NA	0.3521	NA	NA	NA	NA	2
Belarus	NA	NA	NA	NA	NA	0.2000	0.2010	1.5153	0.2031	NA	0.2869	0.4813	0.5792	120%	0.00	−0.0012	4
Belgium	2.9586	NA	NA	3.1481	NA	NA	3.1156	NA	NA	6.3474	5.7526	4.2645	1.6450	39%	0.85	0.3379	1
Belize	NA	NA	NA	NA	NA	NA	0.1539	0.4183	0.2602	NA	NA	0.2775	0.1330	48%	0.40	0.0532	3
Bosnia & Herzegovina	NA	NA	NA	NA	NA	NA	NA	NA	0.0768	NA	0.7132	0.3950	0.4500	114%	NA	NA	4
Brazil	NA	NA	0.7432	NA	NA	0.8368	0.9056	0.8802	1.0913	1.1989	1.1832	0.9770	0.1796	18%	0.93	0.0621	3
Bulgaria	0.1209	NA	NA	0.1736	NA	1.1075	0.7537	1.0199	1.1161	1.1750	1.1933	0.8325	0.4449	53%	0.90	0.1210	3
Canada	2.7983	NA	3.1301	NA	4.0275	NA	NA	NA	3.9118	4.1673	4.3896	3.7374	0.6286	17%	0.91	0.1405	1
Chile	NA	NA	0.0826	NA	NA	0.7252	0.8240	NA	0.8698	NA	NA	0.6254	0.3669	59%	0.93	0.1366	3
China	NA	0.0080	NA	NA	0.0252	NA	NA	0.0247	NA	NA	0.0371	0.0237	0.0120	50%	0.94	0.0029	4
Colombia	NA	NA	0.0345	NA	NA	0.0756	0.1162	0.4121	0.4864	0.6118	0.7463	0.3547	0.2821	80%	0.93	0.0971	4
Costa Rica	NA	NA	0.5736	NA	NA	1.9432	NA	1.2093	0.9922	1.4014	NA	1.2239	0.5064	41%	0.34	0.0629	3
Croatia	NA	NA	NA	NA	NA	NA	1.1096	1.1057	NA	1.0108	2.4502	1.4191	0.6889	49%	0.69	0.2586	3
Cuba	NA	NA	0.0108	NA	NA	NA	0.0268	0.0222	0.0712	NA	0.0233	0.0309	0.0233	76%	0.44	0.0035	4
Czech Republic	1.2528	NA	NA	1.4653	NA	NA	2.0584	NA	NA	2.5903	NA	1.8417	0.6044	33%	0.98	0.1535	1
Denmark	4.0960	NA	NA	3.6124	NA	4.0157	3.7975	3.9532	3.9793	2.8798	NA	3.7620	0.4206	11%	−0.49	−0.0664	1
Dominican Republic	NA	NA	0.0045	NA	NA	0.0088	0.0277	NA	0.0107	NA	0.0321	0.0167	0.0123	73%	0.71	0.0029	4
Ecuador	NA	NA	0.0031	NA	NA	NA	NA	NA	0.0062	0.0389	0.0116	0.0149	0.0164	109%	0.50	0.0023	4
Egypt	0.0125	NA	NA	NA	0.0120	0.1033	0.1014	0.0121	NA	NA	NA	0.0483	0.0494	102%	0.37	0.0067	4
El Salvador	NA	NA	0.0628	NA	NA	0.4018	NA	0.0800	0.5322	NA	NA	0.2692	0.2346	87%	0.55	0.0491	4
Eritrea	NA	NA	NA	NA	NA	NA	NA	NA	0.2255	NA	0.0318	0.1287	0.1370	106%	NA	NA	5
Estonia	NA	NA	NA	NA	NA	0.9538	1.1864	NA	NA	NA	NA	1.0701	0.1645	15%	NA	NA	2
Finland	2.0878	NA	NA	2.9435	NA	NA	3.5749	NA	NA	4.4444	4.4346	3.4970	1.0093	29%	0.99	0.2415	1
France	2.3454	NA	NA	3.0538	NA	2.8575	3.2498	NA	6.5980	5.6984	5.0555	4.1227	1.6403	40%	0.82	0.3813	1
Georgia	NA	NA	NA	NA	NA	0.2936	0.2059	0.2521	0.2147	0.4139	NA	0.2760	0.0845	31%	0.47	0.0249	4
Germany	4.4561	NA	NA	4.9140	NA	5.4615	5.4555	5.4501	NA	6.4487	6.7763	5.5660	0.8101	15%	0.96	0.2253	1
Greece	0.9218	NA	NA	1.0065	NA	1.1776	1.2907	1.5048	1.6082	2.1577	2.5861	1.5317	0.5784	38%	0.89	0.1554	1
Guatemala	NA	NA	0.0644	NA	NA	0.1678	NA	NA	0.3227	NA	NA	0.1849	0.1300	70%	0.99	0.0430	4
Honduras	NA	NA	0.0129	NA	NA	NA	NA	0.1369	0.1576	0.1910	0.0005	0.0998	0.0873	87%	0.35	0.0097	4
Hong Kong	NA	0.6876	NA	NA	1.0207	NA	NA	1.9117	NA	NA	2.2434	1.4658	0.7319	50%	0.98	0.1853	2

Table 1. (Continued)

Country	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	R	m	Econ
Hungary	1.4156	NA	NA	1.9043	NA	2.4276	3.1189	NA	5.0727	4.7244	5.1004	3.3948	1.5622	46%	0.95	0.4205	3
Iceland	NA	NA	NA	NA	NA	NA	8.3868	11.034	9.2491	7.4341	NA	9.0261	1.5304	17%	−0.39	−0.4643	1
India	NA	NA	0.0058	NA	0.0069	0.0052	0.0065	0.0057	0.0089	0.0149	0.0075	0.0077	0.0031	41%	0.56	0.0007	5
Indonesia	NA	0.0016	NA	NA	0.0024	0.0140	0.0032	0.0055	NA	0.0109	0.0165	0.0077	0.0060	78%	0.70	0.0014	4
Iran	NA	NA	NA	NA	0.9074	0.4493	0.8904	0.9338	0.8738	1.4405	1.2808	0.9680	0.3188	33%	0.75	0.1102	4
Iraq	NA	NA	NA	NA	NA	NA	NA	NA	0.0146	NA	NA	0.0146	NA	NA	NA	NA	4
Ireland	6.8700	NA	NA	3.4639	NA	3.2367	4.5593	4.8315	5.1143	4.4865	5.3542	4.7396	1.1369	24%	−0.19	−0.0646	1
Israel	2.1142	NA	NA	NA	2.3011	NA	NA	3.3308	NA	NA	NA	2.5820	0.6551	25%	0.89	0.1669	2
Italy	1.9344	NA	NA	2.4403	NA	NA	3.1350	NA	NA	4.8597	5.1039	3.4946	1.4255	41%	0.97	0.3332	1
Jamaica	NA	NA	NA	NA	NA	NA	0.0419	NA	NA	NA	NA	0.0419	NA	NA	NA	NA	4
Japan	NA	1.6354	NA	NA	1.9522	NA	NA	1.9491	NA	2.2780	1.9511	1.9532	0.2272	12%	0.76	0.0466	1
Jordan	0.1407	NA	NA	NA	0.3126	NA	NA	0.2593	NA	NA	0.2924	0.2512	0.0769	31%	0.72	0.0130	4
Kenya	NA	NA	NA	NA	NA	NA	0.0001	NA	0.0263	NA	NA	0.0132	0.0185	140%	NA	NA	5
Korea	NA	1.1514	NA	NA	0.9384	0.8885	1.0790	1.2718	1.1382	1.7219	2.1016	1.2864	0.4170	32%	0.71	0.1013	1
Kuwait	0.6902	NA	NA	NA	0.4039	NA	NA	0.8100	NA	NA	NA	0.6347	0.2086	33%	0.21	0.0123	2
Latvia	NA	NA	NA	NA	NA	0.5421	0.5786	0.6223	0.8197	1.4492	1.5439	0.9260	0.4532	49%	0.92	0.2234	3
Lebanon	NA	NA	NA	NA	0.4507	NA	0.3877	0.1748	0.5923	NA	NA	0.4014	0.1736	43%	0.06	0.0065	3
Lesotho	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.1837	0.1837	NA	NA	NA	NA	4
Lithuania	NA	NA	NA	NA	NA	0.4163	0.5450	NA	NA	NA	1.1074	0.6896	0.3675	53%	1.00	0.1389	3
Luxembourg	NA	NA	NA	NA	NA	7.4830	7.4157	NA	NA	NA	NA	7.4494	0.0476	1%	NA	NA	1
Macedonia	NA	NA	NA	NA	NA	0.0992	0.1236	NA	0.4433	1.2291	NA	0.4738	0.5274	111%	0.89	0.2580	4
Malaysia	NA	0.3600	NA	NA	0.7820	0.4458	0.4161	0.5257	0.3894	0.4090	0.3881	0.4645	0.1377	30%	−0.23	−0.0110	3
Mexico	NA	NA	0.1257	NA	NA	0.2876	0.2359	0.3180	0.3377	0.3999	0.4939	0.3141	0.1173	37%	0.95	0.0416	3
Moldova	NA	NA	NA	NA	NA	NA	NA	NA	0.0275	NA	NA	0.0275	NA	NA	NA	NA	4
Mongolia	NA	NA	NA	NA	NA	NA	0.0275	0.0249	0.1941	NA	NA	0.0822	0.0969	118%	0.86	0.0833	5
Nepal	NA	NA	NA	NA	NA	0.0070	0.0063	NA	NA	0.0071	0.0118	0.0081	0.0025	31%	0.73	0.0008	5
Netherlands	4.2492	NA	NA	4.8061	NA	NA	4.6575	NA	NA	5.4508	NA	4.7909	0.4990	10%	0.89	0.1152	1
New Zealand	NA	4.2405	NA	NA	5.1459	2.6883	6.3724	10.656	4.4421	10.338	9.7556	6.7049	3.1165	46%	0.66	0.7056	1
Nigeria	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.0004	NA	0.0004	NA	NA	NA	NA	5
Norway	2.7372	NA	NA	3.2056	NA	2.6947	3.0432	NA	NA	3.5568	NA	3.0475	0.3554	12%	0.68	0.0723	1
Pakistan	NA	0.0019	NA	NA	0.0028	0.0020	0.0020	0.0029	NA	0.0087	0.0029	0.0033	0.0024	72%	0.53	0.0004	5
Palestine	NA	NA	NA	NA	NA	NA	NA	NA	0.4044	NA	0.5143	0.4593	0.0777	17%	NA	NA	4
Panama	NA	NA	0.7825	NA	NA	0.9564	0.0816	0.0802	0.3470	NA	0.8441	0.5153	0.3949	77%	−0.18	−0.0259	3
Peru	NA	NA	0.0469	NA	NA	0.1654	NA	NA	0.1975	0.1650	0.1087	0.1367	0.0595	44%	0.55	0.0099	4
Philippines	NA	0.0056	NA	NA	0.0052	NA	0.0126	0.0096	0.0111	NA	0.0072	0.0086	0.0030	35%	0.46	0.0004	4
Poland	0.4844	NA	NA	1.1901	NA	1.0942	1.6042	1.3905	NA	1.6494	1.5732	1.2837	0.4113	32%	0.90	0.1068	3
Portugal	1.1932	NA	NA	1.5527	NA	2.1768	2.1451	2.8904	2.8427	2.5867	2.9989	2.2983	0.6586	29%	0.94	0.1886	1
Puerto Rico	NA	NA	NA	NA	NA	NA	NA	NA	1.9898	NA	NA	1.9898	NA	NA	NA	NA	2
Romania	NA	NA	NA	0.3597	NA	0.0817	0.1323	0.0916	NA	0.2242	0.3855	0.2125	0.1341	63%	0.17	0.0089	3
Russia	0.1714	NA	NA	0.4736	NA	NA	0.4446	0.2724	0.1685	1.5678	2.9182	0.8595	1.0293	120%	0.63	0.1827	3
Saudi Arabia	1.7615	NA	NA	NA	0.9516	NA	NA	1.0320	NA	NA	NA	1.2484	0.4462	36%	−0.86	−0.1095	2

Table 1. (Continued)

Country	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	R	m	Econ
Senegal	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.0029	0.0029	NA	NA	NA	NA	5
Serbia*	NA	NA	NA	NA	NA	0.1798	0.2358	0.3277	0.2128	0.5062	0.8489	0.3852	0.2558	66%	0.84	0.1155	3
Singapore	NA	0.7642	NA	NA	0.3236	0.6102	0.4803	0.5686	NA	NA	0.9299	0.6128	0.2129	35%	0.33	0.0230	2
Slovak Republic	NA	NA	NA	1.5964	NA	2.5241	2.4777	2.7474	2.9516	3.4713	3.6841	2.7789	0.6932	25%	0.98	0.2815	3
Slovenia	NA	NA	NA	NA	NA	NA	NA	3.5495	NA	5.7529	NA	4.6512	1.5580	33%	NA	NA	2
South Africa	NA	NA	NA	NA	NA	NA	0.5152	0.5097	0.4838	0.6154	0.5915	0.5431	0.0570	10%	0.72	0.0258	3
Spain	2.4827	NA	NA	2.8839	NA	2.1231	2.9477	2.4464	2.0563	3.0474	3.6897	2.7097	0.5416	20%	0.38	0.0630	1
Sri Lanka	NA	NA	NA	NA	NA	NA	NA	0.0527	NA	NA	0.0781	0.0654	0.0179	27%	NA	NA	4
Sudan	NA	NA	NA	NA	NA	NA	NA	NA	0.0332	0.0593	0.0846	0.0591	0.0257	44%	1.00	0.0257	5
Sweden	5.6171	NA	NA	6.0404	NA	7.5541	6.7981	6.9895	NA	6.8903	NA	6.6482	0.7001	11%	0.74	0.1634	1
Switzerland	2.6220	NA	NA	2.7766	NA	2.8113	2.8113	3.0295	3.1614	3.1555	3.6511	3.0023	0.3249	11%	0.87	0.0862	1
Syria	0.1085	NA	NA	NA	0.2301	NA	NA	0.1509	NA	NA	NA	0.1632	0.0618	38%	0.42	0.0074	4
Taiwan	NA	0.9428	NA	NA	1.2210	NA	NA	1.4820	NA	NA	1.5693	1.3038	0.2825	22%	0.98	0.0713	NA
Thailand	NA	0.0238	NA	NA	0.0824	NA	NA	0.0563	NA	NA	0.0079	0.0426	0.0333	78%	−0.29	−0.0025	4
Trinidad & Tobago	NA	NA	0.2326	NA	NA	NA	NA	NA	NA	NA	NA	0.2326	NA	NA	NA	NA	2
Turkey	0.1854	NA	NA	NA	0.7556	0.2284	0.4793	0.3693	0.5831	0.6852	0.9537	0.5300	0.2660	50%	0.68	0.0568	3
Ukraine	NA	NA	NA	NA	NA	NA	0.0167	NA	NA	NA	0.3222	0.1694	0.2160	128%	NA	NA	4
United Arab Emirates	NA	NA	NA	NA	0.8469	NA	NA	NA	NA	NA	NA	0.8469	NA	NA	NA	NA	2
United Kingdom	2.8563	NA	NA	3.7341	NA	3.1695	3.7529	3.2676	NA	4.7089	4.1855	3.6678	0.6365	17%	0.76	0.1395	1
United States	2.7349	2.9090	3.3302	3.7851	3.7598	3.8720	3.8424	4.6488	4.5782	5.0859	5.3196	3.9878	0.8402	21%	0.98	0.2471	1
Uruguay	NA	NA	0.3693	NA	NA	0.8195	1.3857	1.1544	1.1419	NA	NA	0.9742	0.3936	40%	0.85	0.1457	3
Uzbekistan	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.0018	0.0018	NA	NA	NA	NA	5
Venezuela	NA	NA	0.3054	NA	NA	NA	0.2718	0.9701	0.4579	0.8357	1.9137	0.7924	0.6182	78%	0.69	0.1518	3
Vietnam	NA	0.0008	NA	NA	0.0025	0.0187	0.0184	NA	NA	NA	0.0035	0.0079	0.0053	105%	−0.02	−0.0001	5
Zimbabwe	NA	NA	NA	NA	NA	0.1188	0.0097	NA	NA	NA	0.2410	0.1232	0.1157	94%	0.78	0.0340	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; *R*, correlation coefficient; *m*, slope of regression line; *Econ*, Economic Classification [31]: 1: High income OECD (Organisation for Economic Co-operation and Development) [32]; 2: High income non-OECD; 3: Upper middle income; 4: Lower middle income; 5: Low income. Taiwan was not classified economically by the World Bank.

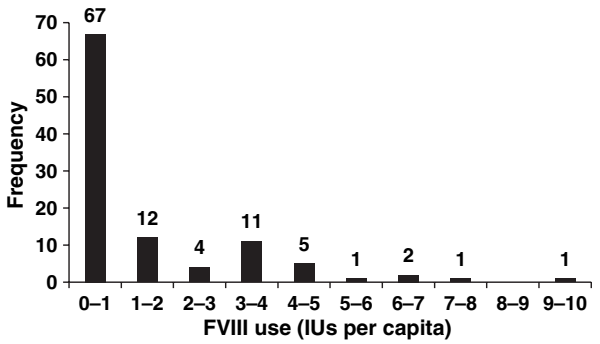

Fig. 1. Histogram for the factor VIII (FVIII) use (IUs per capita) for each of the 104 countries in Table 1. The numbers above each bar represents the number (frequency) of countries with mean FVIII use in the range stated on the abscissa.

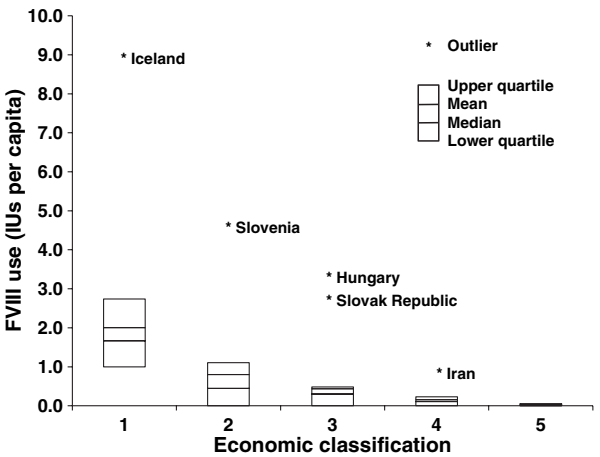

Fig. 2. Distribution plot with economic classification on the abscissa and factor VIII (FVIII) use (IUs per capita) on the ordinate. The FVIII use values represent the mean FVIII use for each of the 104 countries in Table 1. The economic classification [31] is as follows: 1: High income OECD (Organisation for Economic Co-operation and Development) [32]; 2: High income non-OECD; 3: Upper middle income; 4: Lower middle income; 5: Low income. *An outlier falls outside two standard deviations from the mean.

reporting data to MRB and WFH. There were nine possible FVIII use observations corresponding to the years 1998–2006, inclusive. The mean, SD, CV, *R*, and slope (*m*) were calculated from these observations. Figure 3 is a histogram of each country's mean FVIII use. Fifty-three percent of countries reported FVIII use (IUs per PWHA) of 20 000 or less (Fig. 3) with Saudi Arabia reporting the highest use. The mean FVIII use (IUs per PWHA) among high income OECD countries ranged from 24 712 in Czech Republic to 114 333 in Germany whereas the FVIII use for high income non-OECD countries ranged from 14 940 in Singapore to 191 736 in Saudi Arabia, middle upper income countries ranged from 3913 in Romania to 43 907 in Turkey, middle lower income countries ranged from 133 in Armenia to 35 088 in Guatemala, and low income countries ranged from 48 in Uzbekistan to 24 721 in Eritrea. Some countries had unusually high FVIII use (IUs per PWHA) when compared to the countries within their economic classification (Fig. 4).

FVIII use (IUs per PWHA) increased over time with 74% of countries having positive *R* and *m* values (Table 3). The average slope (*m*) for high income OECD countries was 2906 IUs per PWHA per year in contrast to 2198 IUs per PWHA per year for high income non-OECD countries, 1184 IUs per PWHA per year for upper middle income countries, –213 IUs per PWHA per year for lower middle income countries, and 271 IUs per PWHA per year for low income countries. Similar results were obtained for countries with FVIII use of least 20 000 IUs per PWHA (*m* = 2233 IUs per PWHA per year) versus *m* = 503 IUs per PWHA per year for countries consuming less than 20 000 IUs per PWHA. The growth rate in Italy was the highest at 8378 IUs per PWHA per year, followed by France at 8204 IUs per PWHA per year, Germany at 7899 IUs per PWHA per year, and Hungary at 6,345 IUs per PWHA per year.

The reported FVIII use (IUs per PWHA) varied considerably across economic classifications. Table 4 presents the mean, SD and CV of each observation in Table 3 by economic classification and ANOVA results. The FVIII use increased with increasing economic capacity – for the high income OECD countries FVIII use was 64 111 ± 27 792 IUs per PWHA (mean ± SD) whereas the FVIII use for the remaining economic classifications was 16 449 ± 19 695 IUs per PWHA (mean ± SD). The FVIII use was significantly different for all economic classification except for the comparison between high income OECD countries and high income non-OECD countries. On a country-by-country basis, the mean FVIII use (IUs per PWHA) was moderately positively correlated (*R* = 0.69) with mean GNI per capita [31]. The variability (CV) of FVIII use decreased with increasing economic capacity. The CV was moderately negatively correlated (*R* = –0.56) with GNI per capita [31].

Discussion

Treatment strategies for prophylaxis, surgery, and inhibitors vary from country to country and have an impact on the level of FVIII use. Therefore, care must be taken when making policy conclusions concerning

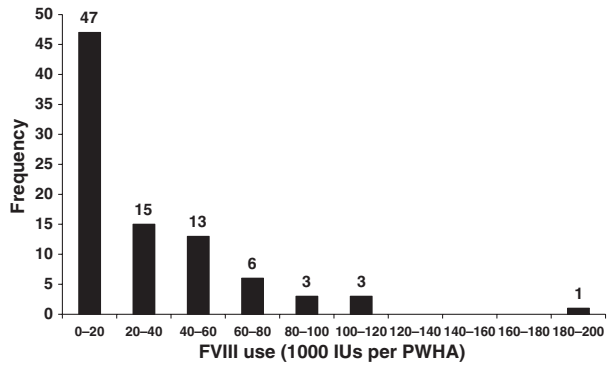

Fig. 3. Histogram for the factor VIII (FVIII) use (IUs per person with haemophilia A (PWHA)) for each of the 88 countries in Table 3. The numbers above each bar represents the number (frequency) of countries with mean FVIII use in the range stated on the abscissa.

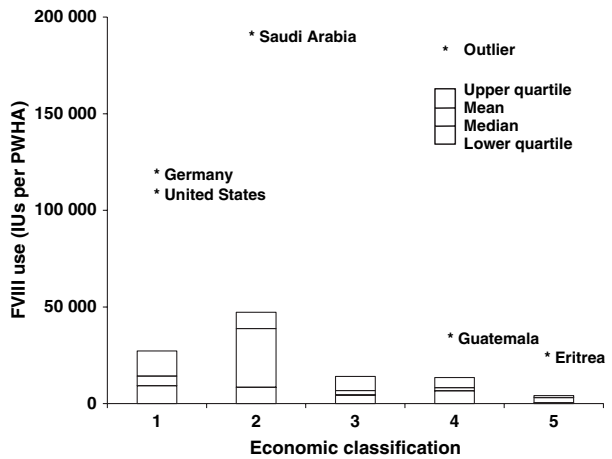

Fig. 4. Distribution plot with economic classification on the abscissa and factor VIII (FVIII) use (IUs per person with haemophilia A (PWHA)) on the ordinate. The FVIII use values represent the mean FVIII use for each of the 88 countries in Table 1. The economic classification [31] is as follows: 1: High income Organisation for Economic Co-operation and Development (OECD) [32]; 2: High income non-OECD; 3: Upper middle income; 4: Lower middle income; 5: Low income. *An outlier falls outside two standard deviations from the mean.

FVIII use for a country without reviewing its standard of treatment. For example, when the number of PWHA is under-reported in a country and its standard of care for treating inhibitor patients is to administer large amounts of FVIII, the reported FVIII use (IUs per PWHA) may be higher than what is actually used per patient. One could argue higher IUs per PWHA mean better care is being delivered. On the other hand, higher FVIII use could mean that there is over-treatment. We just don't know what is right from the reported data without understanding the treatment modalities of a country. However, factor use per capita and per patient are pieces of the overall picture and the global trends of FVIII use are clear.

The reported FVIII use is significantly different across national economies, even among the wealthiest countries. The reported FVIII use in the high income OECD countries is significantly greater than high income non-OECD, upper middle income, lower middle income, and low income countries. Factor VIII replacement therapy is available in high income OECD countries, but often times not available in less economically-developed countries, with some exceptions, because of the inability/unwillingness of governments/health insurance companies to pay for treatment and/or lack of available supply of FVIII concentrates.

Some countries are consuming more FVIII concentrates when compared to the countries within their economic classification – for FVIII use (IUs per capita): Iceland, Slovenia, Hungary, Slovak Republic, and Iran, and for FVIII use (IUs per PWHA): Germany, United States, Saudi Arabia, Guatemala, and Eritrea. Iceland – the least populated high income OECD country – stands out for using a huge amount of factor per capita. This can be explained by the fact that Iceland treats its patients using the standards of Northern European countries (i.e. among the highest in the world) combined with the fact that Iceland has the highest reported haemophilia A prevalence of 38.6 per 100 000 males [48]. Iceland is a small, isolated population in which the founder effect [49] is likely contributing to its high prevalence levels. The FVIII use (IUs per PWHA) of Iceland is less than the mean FVIII use (IUs per PWHA) for high income OECD countries. Slovenia, Hungary and the Slovak Republic are intriguing examples that definitely merit further research. Consanguineous marriages are common in Iran and, therefore, coagulation disorders are observed more frequently than in many other countries [50,51]. This large patient population is accompanied by one of the highest FVIII IUs per PWHA for its economic classification (Table 3), suggesting that the identification of large patient population and advocacy through the Iran Hemophilia Center has influenced the consumption of FVIII to levels higher than expected based on economic status [52]. Saudi Arabia is consuming the most FVIII IUs per PWHA. This could be attributed to its low reported haemophilia A prevalence of 1.0 per 100 000 males [48]. It should be noted that Saudi Arabia reported PWHA for one year (2003), whereas the FVIII use (IUs per capita) was reported as 1.7615 in 1996, 0.9516 in

Table 2. Statistical analysis of the reported factor VIII (FVIII) use (IUs per capita) by economic classification [31] for the annual FVIII use data in Table 1.

						P compares economic classifications			
Economic Classification	Mean	SD	CV	*n*	*N*	(2)	(3)	(4)	(5)
High Income OECD countries (1)	3.8312	1.9691	51%	158	25	<0.001	<0.001	<0.001	<0.001
High Income non-OECD countries (2)	1.4000	1.2381	88%	27	11		0.042	<0.001	<0.001
Upper Middle Income countries (3)	0.9665	0.9481	98%	134	23			<0.001	<0.001
Lower Middle Income countries (4)	0.2130	0.3073	144%	114	31				<0.001
Low Income countries (5)	0.0274	0.0564	206%	46	13				
Countries in (2)–(5)	0.6008	0.8618	143%	321	78				
G7 countries	3.8964	1.3051	33%	48	7				
All countries	1.6633	2.0125	121%	483	104				

P compares the mean FVIII use for economic classifications using an analysis of variance (ANOVA).
OECD, Organisation for Economic Co-operation and Development [32]; SD, standard deviation; CV, coefficient of variation; *n*, number of annual FVIII use observations in Table 1 for each economic classification; *N*, number of countries in each economic classification; G7 countries include: Canada, France, Germany, Italy, Japan, United Kingdom, and United States.
Taiwan was not economically classified by the World Bank, but was included in All countries analysis.

2000, and 1.0320 in 2003. Given its consistency of consumption over this time period, Saudi Arabia has probably been at the same levels of FVIII use (IUs per PWHA) since 1996. Germany and the United States also stand out for using a huge amount of FVIII IUs per PWHA. Similarly, the reported haemophilia A prevalence for Germany and the United States are 10.0 per 100 000 males and 8.0 per 100 000 males, respectively [48]. For the United States, the reported prevalence is based solely on patients who use federally supported haemophilia treatment centres for care which accounted for about 70% of all patients identified [53].

Sweden, one of the pioneers in the treatment of haemophilia, has seen remarkable growth in its demand for FVIII use over the last three decades. 'In Sweden we have sufficient amounts of factor VIII and factor IX concentrates available, and for the Haemophilic Centres there are no restrictions on the use of such treatment [54, p. 515].' In 1974, Sweden used 3.25 million IUs of FVIII [54], which is 0.40 IUs per capita or 7,454 IUs per PWHA. The FVIII use (IUs per capita) in Sweden was 6.89 in 2005 (Table 1), a 17-fold increase – a 10% growth per year since 1974. Similarly, the FVIII use (IUs per PWHA) in Sweden was 94 427 in 2003 (Table 3), a 12-fold increase – a 9% annual growth since 1974. The GNI per capita for Sweden has increased fivefold or 5% growth per year from $8,130 in 1974 to $40 950 in 2005 [31]. This phenomenal growth raises the following questions: Has Sweden reached a steady-state of FVIII use? Will countries currently consuming at Sweden's 1974 FVIII use levels grow at the same rate over the next 30 years? Is there a target level of demand for FVIII use for each country? How could this impact national healthcare planning and production planning? The evolution of care is dramatically demonstrated in Sweden, where a consumption of 0.40 IUs per capita in 1974 led to no restriction in the allocation of treatment. This means that, as supply is a function of demand, so is the converse true. In Australia, the target FVIII level in 2003 was 3.3 IUs per capita [55]. A year later, the Australian government approved the provision of recombinant products, freeing patient access to product from the constraints of a self-sufficiency policy for plasma products [56]. The current usage is 4.6 IUs per capita, and is still growing as clinicians and patients access treatment options unfettered by the constraints imposed by limitations in the supply of plasma products. Analysis of the evolution of care reveals the relative cost-effectiveness of different levels of treatment, leading to the situation in developed economies where 70% of factor is consumed by approximately 25% of patients, i.e. through inhibitor tolerisation and prophylaxis [15,57]. Such information is of great importance in allocating resources, particularly in developing countries where the priority is to secure treatment levels ensuring not only patient survival, but good musculoskeletal health to allow an independent and productive life.

The real challenge is to provide a method to calculate 'target' demand in each country to enable improved supply planning of FVIII concentrate production capacity and use [58]. Most industry FVIII demand forecasts use historical sales data to forecast future market (sales) demand and, hence, FVIII production. Standard forecasting methods that assume past behavior is predictive of future behavior [59] are often suitable, but offer little guidance for forecasting demand in supply-constrained markets

Table 3. The reported factor VIII (FVIII) use (IUs per PWHA – person with haemophilia A) was determined from the reported number of FVIII international units (IUs) used in the treatment of haemophilia A for a country from 1998 to 2006 [33–42] divided by its reported number of people with haemophilia A in the relevant year [38–42,45–47].

Country	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	*R*	*m*	Econ
Albania	NA	NA	NA	2834	NA	3463	3571	3239	3333	3288	284	9%	0.56	83	4
Algeria	NA	NA	NA	NA	4458	NA	NA	NA	9615	7037	3647	52%	NA	NA	4
Argentina	19 189	NA	NA	20 237	NA	15 097	29 113	NA	NA	20 909	5 902	28%	0.39	864	3
Armenia	NA	NA	NA	NA	NA	76	191	NA	NA	133	82	61%	NA	NA	4
Australia	NA	NA	56 000	57 700	NA	NA	95 357	72 595	68 478	70 026	15 806	23%	0.57	3 454	1
Austria	NA	88 218	NA	NA	NA	NA	NA	NA	NA	88 218	NA	NA	NA	NA	1
Bangladesh	NA	NA	NA	698	NA	2 476	1 509	2 278	2 390	1 870	760	41%	0.75	295	5
Belarus	NA	NA	NA	4 274	NA	31 712	4 167	NA	6 037	11 547	13 471	117%	−0.11	−720	4
Belgium	NA	54 514	NA	NA	51 364	NA	NA	NA	NA	52 939	2 227	4%	NA	NA	1
Belize	NA	NA	NA	NA	NA	15 714	6 364	NA	NA	11 039	6 612	60%	NA	NA	3
Bosnia -Herzegovina	NA	NA	NA	NA	NA	NA	3 000	NA	28 000	15 500	17 678	114%	NA	NA	4
Brazil	NA	NA	NA	27 327	NA	29 569	37 174	41 397	32 525	33 599	5 708	17%	0.65	1 925	3
Bulgaria	NA	2 881	NA	17 221	NA	15 686	17 059	17 949	18 107	14 817	5 910	40%	0.80	1 803	3
Canada	53 097	NA	64 375	NA	NA	NA	56 281	58 700	60 877	58 666	4 307	7%	0.25	319	1
Chile	2 041	NA	NA	12 609	14 493	NA	NA	NA	NA	9 714	6 712	69%	0.99	3 207	3
Colombia	2 590	NA	NA	6 452	NA	18 595	19 685	27 067	29 285	17 279	10 775	62%	0.97	3 574	4
Costa Rica	26 543	NA	NA	60 938	NA	37 407	31 259	43 624	NA	39 954	13 376	33%	0.16	771	3
Croatia	NA	NA	NA	NA	15 528	15 528	NA	10 407	29 848	17 828	8 369	47%	0.51	2 352	3
Cuba	NA	NA	NA	NA	NA	922	2 753	NA	866	1 514	1 074	71%	−0.21	−151	4
Czech Republic	NA	24 712	NA	NA	NA	NA	NA	NA	NA	24 712	NA	NA	NA	NA	1
Denmark	NA	61 935	NA	65 549	NA	63 393	66 563	44 318	NA	60 352	9 144	15%	−0.48	−1 836	1
Dominican Republic	NA	NA	NA	446	1 429	NA	NA	NA	NA	937	695	74%	NA	NA	4
Ecuador	NA	NA	NA	NA	NA	NA	NA	1 667	475	1 071	843	79%	NA	NA	4
Egypt	NA	NA	320	1 983	1 983	NA	NA	NA	NA	1 429	960	67%	0.87	832	4
El Salvador	3 472	NA	NA	13 457	NA	2 544	15 284	NA	NA	8 689	6 613	76%	0.44	1 102	4
Eritrea	NA	NA	NA	NA	NA	NA	44 627	NA	4 815	24 721	28 152	114%	NA	NA	5
Estonia	NA	NA	NA	36 111	44 722	NA	NA	NA	NA	40 417	6 089	15%	NA	NA	2
Finland	NA	NA	NA	NA	NA	NA	NA	100 497	99 703	100 100	561	1%	NA	NA	1
France	NA	49 587	NA	NA	NA	NA	NA	119 804	93 899	87 763	35 508	40%	0.87	8 204	1
Georgia	NA	NA	NA	7 062	NA	8 162	5 510	9 953	NA	7 671	1 870	24%	0.38	414	4
Germany	NA	76 145	NA	113 924	NA	112 052	NA	131 443	138 101	114 333	24 090	21%	0.94	7 899	1
Greece	NA	18 836	NA	19 210	NA	24 475	25 381	33 544	40 288	26 955	8 435	31%	0.91	2 928	1
Guatemala	NA	NA	NA	NA	NA	NA	35 088	NA	NA	35 088	NA	NA	NA	NA	4
Honduras	1 530	NA	NA	NA	NA	11 842	9 028	9 886	18	6 461	5 318	82%	0.22	380	4
Hungary	NA	26 035	NA	24 636	31 574	NA	58 629	54 457	65 019	43 392	17 972	41%	0.93	6 345	3
Iceland	NA	NA	NA	NA	NA	56 140	48 393	38 605	NA	47 713	8 787	18%	−1.00	−8 768	1
India	NA	NA	NA	1 599	NA	2 128	1 918	1 770	854	1 654	487	29%	−0.48	−121	5
Indonesia	NA	NA	3 676	31 250	NA	9 205	NA	12 805	17 211	14 829	10 433	70%	0.03	143	4
Iran	NA	NA	20 994	10 453	NA	22 125	17 678	25 707	22 613	19 928	5 318	27%	0.54	1 234	4
Iraq	NA	NA	NA	NA	NA	NA	795	NA	NA	795	NA	NA	NA	NA	4
Ireland	NA	42 208	NA	39 063	NA	58 490	57 792	47 539	58 701	50 632	8 860	17%	0.71	2 412	1
Italy	NA	40 986	NA	NA	NA	NA	NA	72 686	111 235	74 969	35 180	47%	0.90	8 378	1
Japan	NA	NA	NA	NA	NA	64 780	NA	73 984	61 627	66 797	6 421	10%	−0.06	−243	1
Jordan	NA	NA	10 345	NA	NA	NA	NA	NA	8 292	9 318	1 452	16%	NA	NA	4
Kenya	NA	NA	NA	NA	8	NA	2 416	NA	NA	1 212	1 703	141%	NA	NA	5
Korea	NA	NA	36 102	33 387	40 748	NA	41 399	59 688	70 965	47 048	14 899	32%	0.90	5 637	1
Latvia	NA	NA	NA	17 067	NA	17 262	21 812	36 660	34 311	25 422	9 417	37%	0.86	4 206	3
Lebanon	NA	NA	NA	NA	38 462	NA	26 687	NA	NA	32 574	8 326	26%	NA	NA	3
Lesotho	NA	NA	NA	NA	NA	NA	NA	NA	22 906	22 906	NA	NA	NA	NA	4
Lithuania	NA	NA	NA	13 063	NA	NA	NA	NA	29 485	21 274	11 612	55%	NA	NA	3
Macedonia	NA	NA	NA	1 183	1 479	NA	6 040	NA	NA	2 901	2 723	94%	0.96	1 713	4
Malaysia	NA	NA	26 569	15 119	NA	18 284	13 150	12 387	11 556	16 178	5 629	35%	−0.82	−1 995	3

Table 3. (Continued)

Country	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	*R*	*m*	Econ
Mexico	NA	NA	NA	19 581	NA	19 463	18 008	15 683	17 930	18 133	1 575	9%	−0.70	−577	3
Mongolia	NA	NA	NA	NA	NA	2 175	14 177	NA	NA	8 176	8 487	104%	NA	NA	5
Nepal	NA	NA	NA	2 612	2 412	NA	NA	1 450	1 984	2 114	515	24%	−0.82	−177	5
Netherlands	NA	60 880	NA	NA	NA	NA	NA	61 379	NA	61 130	353	1%	NA	NA	1
New Zealand	NA	NA	30 696	24 350	NA	58 000	71 795	77 496	42 063	50 733	21 842	43%	0.64	6 017	1
Nigeria	NA	NA	NA	NA	NA	NA	NA	1 563	NA	1 563	NA	NA	NA	NA	5
Norway	NA	56 078	NA	NA	NA	NA	NA	58 304	NA	57 191	1 574	3%	NA	NA	1
Pakistan	NA	NA	NA	NA	NA	1 139	NA	2 189	353	1 227	921	75%	−0.25	−150	5
Palestine	NA	NA	NA	NA	NA	NA	14 705	NA	19 048	16 876	3 071	18%	NA	NA	4
Panama	14 800	NA	NA	16 523	NA	1 214	5 101	NA	12 731	10 074	6 600	66%	−0.42	−901	3
Peru	NA	NA	NA	NA	NA	NA	21 559	12 931	6 834	13 774	7 399	54%	−1.00	−7 362	4
Philippines	NA	NA	1 286	NA	NA	1 456	1 343	NA	785	1 217	297	24%	−0.62	−74	4
Poland	NA	24 610	NA	21 807	NA	27 761	NA	29 302	29 000	26 496	3 213	12%	0.82	916	3
Portugal	NA	37 176	NA	52 428	NA	57 863	61 002	55 463	63 705	54 606	9 419	17%	0.89	3 220	1
Romania	NA	6 462	NA	1 455	NA	1 594	NA	3 816	6 241	3 913	2 416	62%	0.05	46	3
Russia	NA	12 411	NA	NA	NA	2 867	3 932	27 651	52 499	19 872	20 760	104%	0.57	4 361	3
Saudi Arabia	NA	NA	NA	NA	NA	191 736	NA	NA	NA	191 736	NA	NA	NA	NA	2
Senegal	NA	NA	NA	NA	NA	NA	NA	NA	354	354	NA	NA	NA	NA	5
Serbia[1]	NA	NA	NA	4 839	NA	8 500	5 316	12 441	22 868	10 793	7 403	69%	0.81	3 105	3
Singapore	NA	NA	8 125	15 823	12 658	NA	NA	NA	23 153	14 940	6 322	42%	0.91	2 198	2
Slovak Republic	NA	19 069	NA	32 227	NA	33 945	36 384	NA	44 209	33 167	9 118	27%	0.96	3 240	3
Slovenia	NA	NA	NA	NA	NA	44 514	NA	NA	NA	44 514	NA	NA	NA	NA	2
South Africa	NA	NA	NA	NA	NA	19 512	17 358	21 707	20 028	19 651	1 793	9%	0.42	589	3
Spain	NA	68 986	NA	43 272	NA	51 372	55 000	81 335	98 438	66 400	20 721	31%	0.56	4 426	1
Sudan	NA	NA	NA	NA	NA	NA	4 633	NA	9 609	7 121	3 519	49%	NA	NA	5
Sweden	NA	75 565	NA	NA	NA	94 427	NA	NA	NA	84 996	13 337	16%	NA	NA	1
Switzerland	NA	42 675	NA	48 235	NA	51 361	49 095	51 149	52 750	49 211	3 594	7%	0.91	1 249	1
Thailand	NA	NA	25 381	NA	NA	16 509	NA	NA	454	14 115	12 635	90%	−0.99	−4 154	4
Turkey	NA	NA	135 526	20 708	NA	25 362	26 365	24 510	30 974	43 907	45 005	103%	−0.62	−12 059	3
United Kingdom	NA	39 467	NA	36 942	NA	38 953	NA	42 506	41 270	39 828	2 149	5%	0.69	515	1
United States	88 611	102 232	99 121	101 033	NA	123 833	119 075	130 778	135 378	112 508	16 969	15%	0.96	5 590	1
Uruguay	7 935	NA	NA	17 928	NA	25 253	24 971	NA	NA	19 022	8 131	43%	0.99	3 027	3
Uzbekistan	NA	NA	NA	NA	NA	NA	NA	NA	48	48	NA	NA	NA	NA	5
Venezuela	9 433	NA	NA	NA	NA	24 176	10 623	17 614	38 774	20 124	11 991	60%	0.64	2 445	3
Vietnam	NA	NA	966	NA	NA	NA	NA	NA	347	657	438	67%	NA	NA	5
Zimbabwe	NA	NA	NA	5 055	417	NA	NA	NA	10 556	5 342	5 076	95%	0.79	1510	5

[1]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; *R*, correlation coefficient; *m*, slope of regression line.

Econ, Economic Classification [31]: 1: High income Organisation for Economic Co-operation and Development (OECD) [32]; 2: High income non-OECD; 3: Upper middle income; 4: Lower middle income; 5: Low income.

[60] that have been limited by insufficient product availability. Recognizing that past sales were limited by FVIII supply and given the high level of variability of FVIII use among countries and the consequences of not adequately treating haemophiliacs, we recommend the development of country-specific latent therapeutic demand (LTD) models. We define LTD as the underlying demand representing how physicians would prescribe treatment and how patients would follow or comply with the prescribed treatment if ample supplies of FVIII were available and affordable. In constructing these country-specific LTD models, current barriers to wider use of FVIII concentrates could be identified by each country, and best-treatment practices could be shared with the global haemophilia community. A major impediment in this process, however, is the lack of adequate data correlating long-term musculoskeletal outcome with dosage. In spite of decades of experience worldwide with factor replacement therapy, the optimal dose to

Table 4. Statistical analysis of the reported factor VIII (FVIII) use (IUs per PWHA – person with haemophilia A) by economic classification [31] for the annual FVIII use data in Table 3.

						P compares economic classifications			
Economic Classification	Mean	SD	CV	n	N	(2)	(3)	(4)	(5)
High Income OECD countries (1)	64 111	27 792	43%	99	24	0.139	<0.001	<0.001	<0.001
High Income non-OECD countries (2)	47 105	60 130	128%	8	4		0.004	<0.001	<0.001
Upper Middle Income countries (3)	22 943	17 205	75%	104	23			<0.001	<0.001
Lower Middle Income countries (4)	9 658	9 479	98%	75	24				0.003
Low Income countries (5)	3 986	7 937	199%	33	13				
Countries in (2)–(5)	16 449	19 695	120%	220	64				
G7 countries	82 899	33 463	40%	32	7				
All countries	31 241	31 510	101%	319	88				

P compares the mean FVIII use for economic classifications using an analysis of variance (ANOVA).
OECD, Organisation for Economic Co-operation and Development [32]; SD, standard deviation; CV, coefficient of variation; *n*, number of annual FVIII use observations in Table 1 for each economic classification; *N*, number of countries in each economic classification.
G7 countries include: Canada, France, Germany, Italy, Japan, United Kingdom, and United States.

achieve the goal that a particular country may choose, such as avoiding major dysfunction alone at the lower end of usage versus preservation of as normal joints as possible with continuous prophylaxis at the upper end of usage, remains undefined. Wide variations in FVIII usage, even among the high income OECD countries, further reiterate the lack of evidence-based practice with regard to dosage. Therefore, until appropriate data becomes available, accurate projections of national requirements of clotting factor concentrates will remain difficult.

There will likely be an overall increase in the amount of IUs of FVIII concentrates used in the treatment of haemophilia A. Trends suggest that FVIII use has been increasing at a faster rate with increasing economic capacity. Trends also suggest that consumption of FVIII has been increasing at a greater rate for countries consuming more than 1 IU per capita or 20 000 IUs per PWHA. The question remains, as more FVIII is produced will it continue to go disproportionately to those countries that already use the most FVIII or will increased production allow the rest of the world to catch up? Such information is critical for national healthcare agencies to determine realistic budget priorities in planning for an increased allocation of resources required to improve the treatment of patients with haemophilia A [1,17,61]. This information is also important for pharmaceutical manufacturers in understanding demand to: (1) plan for adequate production of FVIII concentrates [62] and (2) help prevent future shortages in FVIII concentrates. The lack of healthcare data for treating people with haemophilia A has been an impediment to the resource planning efforts of national healthcare agencies worldwide [1,17,22,26]. Improved data collection and surveillance can lead to better management and planning of healthcare requirements and resources [1,17,26,61,63] by identifying trends and needs of patients, and highlighting best treatment practices among countries. An increased supply of FVIII concentrates that is better-matched with LTD, together with appropriate financing of haemophilia care, could help achieve the benefits of more aggressive treatment regimens such as prophylaxis throughout the world. Finally, while GNI correlates with FVIII usage, there are clearly other factors that explain the differences between economically similar countries. These factors likely include national attitudes about healthcare, organization of healthcare delivery and the role of patients in making decisions about their own care.

This analysis has not included the use of cryoprecipitate to treat haemophilia A, which is known to be considerable in poor and emerging countries. The effect of this on the progression of treatment to the route of choice – stable, safe concentrates is debatable. Neither does this analysis cover haemophilia B (factor IX use) and other bleeding disorders. In particular, we were not able to distinguish between the use of plasma-derived FVIII concentrates to treat Von Willebrand disease and haemophilia A. The recent reiteration by the World Health Organisation that factor concentrates for haemophilia are essential medicines [64,65] should contribute to ensuring that healthcare systems continue to strive to optimize treatments and address some of the anomalies visible through this paper.

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1425 René Lévesque Blvd. W., Suite 1010 Montréal, Québec H3G 1T7 CANADA
Tel.: +1 (514) 875-7944 Fax: +1 (514) 875-8916
www.wfh.org