A STUDY OF REPORTED FACTOR IX USE AROUND THE WORLD

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Treatment for All

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ORIGINAL ARTICLE *Treatment*

A study of reported factor IX use around the world

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Summary. Replacement therapy has significantly improved the life expectancy and lifestyle of people with haemophilia. The objectives of this article were to study the reported factor IX (FIX) use on a country-by-country basis and address the following question: Does the reported FIX use vary by national economies? We obtained data on the reported number of international units (IUs) of FIX used for 90 countries from the Marketing Research Bureau and the World Federation of Hemophilia. Results show that the reported FIX use varies considerably across national economies, even among the wealthiest of countries. Trends suggest that the reported FIX usage increases with increasing economic capacity and has been increasing over time. Trends also suggest that consumption of FIX has been increasing at a greater rate in high income countries.

Given these trends, there will likely be an overall increase in the amount of FIX concentrates used in the treatment of haemophilia B. We also found that FIX use both in terms of IUs per capita and IUs per person provide a complete picture of the level of haemophilia care within a country. Such information is critical for planning efforts of national healthcare agencies to determine realistic budget priorities and pharmaceutical manufacturers to determine adequate production levels of FIX concentrates. By improving the data collection and surveillance of FIX use for the treatment of people with haemophilia B, we can identify trends and needs of patients and highlight best treatment practices among countries.

Keywords: factor IX, haemophilia B

Introduction

Replacement therapy has significantly improved the life expectancy and lifestyle of people with haemophilia A and B. The prevalence of haemophilia A and B for a country increases with its economic capacity and factor concentrates are more readily available with increased economic resources [1–3]. There have been other studies that analysed and showed that the usage of factor VIII (FVIII) concentrates for a country increased as its economic resources increased [1–10], but none on factor IX (FIX) use. We believe this is the first study to analyse global usage of FIX concentrates. In the 1950s, there was little difference in haemophilia care worldwide [11–13] and inadequate treatment resulted in pain, joint deformities, arthropathy, disabilities and death in childhood or early adult life for those with severe haemophilia not receiving treatment [3,14–19]. Approximately 70–80% of people with haemophilia A and B globally, primarily in the developing world, receive inadequate or no treatment [7,20] because of unavailable and/or unaffordable factor concentrates [6,7,9,15,18,21–28]. Increasing the availability and use of FIX concentrates can improve the mortality and morbidity for people with haemophilia B. The primary aims of this research were to study the reported FIX use on a country-by-country basis and to analyse whether the amount of FIX used in the treatment of haemophilia B varies by national economy.

Methods

Factor IX use

We obtained data on the reported number of IUs of FIX used for 90 countries from the Marketing Research Bureau, Inc. (MRB) 1996–2006 [29–33] and the World

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Federation of Hemophilia (WFH) 2001–2006 [34–38]. MRB is a market research firm that tracks the annual number of international units (IUs) sold for FIX concentrates on a country basis. MRB obtains FIX use data through industry and government interviews, but they do not collect the data annually for each country. The WFH is a non-profit organisation that tracks the availability of clotting factor concentrates through its annual global surveys. WFH obtains FIX use (IUs) data through a survey questionnaire of its national member organisations, but these data are not provided each year to the WFH.

When the reported FIX use (IUs) data from MRB and WFH are available in the same year, we averaged it. We also compared these data using:

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

where x is the reported FIX use (IUs) from MRB and y is the reported FIX use (IUs) from the WFH.

We analysed FIX use in terms of IUs per capita and IUs per person with haemophilia B (PWHB). It is important to analyse both per capita and per patient measures since together they provide a complete picture of the level of haemophilia care within a country [39]. For example, when the vast majority of people with haemophilia B have been identified FIX use in IUs per capita closely reflects the actual amount available for each PWHB and can be useful for planning current requirements. Per capita is a better measure for the overall development trend of haemophilia care than per patient since the population is stable whereas number of patients identified is not stable. On the other hand, when the vast majority of people with haemophilia B in a country have not been identified, FIX use in IUs per capita will give a rather unrealistic picture of the actual amount available for each PWHB. In this situation using IUs per PWHB provides a better understanding of the actual requirements at any time. The FIX use (IUs per capita) for a country was calculated by dividing the reported number of IUs of FIX used by its total population in the appropriate year [40]. The FIX use (IUs per PWHB) for a country was calculated by dividing the reported number of IUs of FIX used by the reported number of people with haemophilia B [34–38,41–43].

Economic classification

We used the World Bank's economic classification [44] 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 [44]: 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) [45]. 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.

Statistical analysis

We used the mean, standard deviation (SD) and coefficient of variation (CV) to describe the distribution of FIX use for each country and each economic classification. 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 FIX use between economic classifications. On a country-by-country basis, we examined the correlation between FIX use and GNI per capita [44] and the correlation of FIX 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 FIX use over time provided a measure of annual growth of FIX use for a country. $P \leq 0.05$ is considered statistically significant.

Results

Data on the reported number of IUs of FIX used were obtained for 90 countries from MRB and WFH. MRB reported data on 63 countries, whereas the WFH reported data on 75 countries. Out of the 90 countries, 48 reported FIX use data to both WFH and MRB, 15 reported data to MRB only and 27 to WFH only.

The reported FIX use (IUs) from MRB differed from the reported FIX use from the WFH. There were 63 instances when the reported FIX use data were available from both MRB and WFH in the same year. MRB reported higher levels of FIX usage than WFH in 39 instances with an average difference of 53%; whereas WFH reported higher levels of FIX usage than MRB in 24 instances, with an average difference of 48%. We used ANOVA to compare the means of FIX usage from MRB and WFH by economic classification and the means were not significantly different.

FIX use (IUs per capita)

Table 1 presents time-series data from 1996–2006 of the FIX use (IUs per capita) for 90 countries reporting data to MRB and WFH. There were eleven possible FIX 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 FIX use (Table 1). Sixty-three percent of countries reported FIX use (IUs per capita) of 0.2 or less (Fig. 1) with Ireland reporting the highest use. The mean FIX use (IUs per capita) among

Table 1. The reported factor IX (FIX) use (IUs per capita) was determined from the reported number of FIX international units (IUs) used in the treatment of haemophilia B for a country from 1996 to 2006 [29–38] divided by its total population in the relevant year [40].

Country	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	R	m	Econ
Albania	NA	NA	NA	NA	NA	0.01621	NA	0.00642	0.02872	0.03171	0.09458	0.03553	0.0345	97%	0.76	0.0136	4
Algeria	NA	NA	NA	NA	NA	NA	0.02256	0.02222	NA	NA	0.04534	0.03004	0.0132	44%	0.97	0.0062	4
Argentina	NA	NA	NA	NA	NA	0.11939	0.10626	0.09209	0.32836	NA	NA	0.16153	0.1118	69%	0.71	0.0613	3
Australia	NA	0.59453	NA	NA	0.73149	0.44199	0.71414	1.33542	NA	0.75892	0.83536	0.77312	0.2790	36%	0.41	0.0371	1
Austria	0.21421	NA	NA	0.25936	NA	NA	0.37934	NA	NA	0.22914	NA	0.27051	0.0749	28%	0.28	0.0055	1
Bangladesh	NA	NA	NA	NA	NA	NA	NA	0.00035	0.00028	0.00014	0.00011	0.00018	0.0001	71%	-0.08	0.0000	5
Belarus	NA	NA	NA	NA	NA	0.04000	0.05025	0.03031	0.05077	NA	0.05492	0.04525	0.0100	22%	0.52	0.0027	4
Belgium	0.24738	NA	NA	0.29513	NA	NA	0.28722	NA	NA	NA	NA	0.29158	0.0366	13%	0.92	0.0087	1
Belize	NA	NA	NA	NA	NA	NA	0.36936	0.22814	0.44610	0.33660	NA	0.34786	0.1106	32%	0.35	0.0384	3
Bosnia-Herzegovina	NA	NA	NA	NA	NA	NA	NA	NA	0.02561	NA	0.03821	0.03191	0.0089	28%	NA	NA	4
Brazil	NA	NA	NA	NA	NA	0.17354	0.14829	0.11552	0.37435	0.32115	0.31692	0.24163	0.1085	45%	0.74	0.0427	3
Bulgaria	NA	NA	NA	0.02480	NA	0.05034	0.05384	0.02104	0.05773	0.04842	0.03900	0.03841	0.0170	44%	0.61	0.0032	3
Canada	NA	NA	NA	NA	NA	NA	NA	NA	0.97011	1.12891	1.16647	1.08850	0.1042	10%	0.94	0.0982	1
Chile	NA	NA	NA	NA	NA	0.13401	0.03803	0.03762	0.17986	NA	NA	0.09738	0.0713	73%	0.25	0.0137	3
China	NA	0.00453	NA	NA	0.02205	NA	NA	0.01118	NA	NA	NA	0.01258	0.0088	70%	0.38	0.0011	4
Colombia	NA	NA	NA	NA	NA	0.01864	0.03487	0.05724	0.04005	0.05562	0.05488	0.04355	0.0153	35%	0.79	0.0065	4
Costa Rica	NA	NA	NA	NA	NA	0.68510	NA	0.54885	0.05878	0.70615	NA	0.49972	0.3021	60%	-0.26	-0.0456	3
Croatia	NA	NA	NA	NA	NA	NA	0.06658	0.00663	NA	0.05383	0.25077	0.09445	0.1074	114%	0.71	0.0416	3
Cuba	NA	NA	NA	NA	NA	NA	0.00446	NA	0.00089	NA	0.00222	0.00252	0.0018	72%	-0.62	-0.0006	4
Czech Republic	0.20394	NA	NA	0.19537	NA	NA	0.22545	NA	NA	0.24529	NA	0.21751	0.0224	10%	0.89	0.0051	1
Denmark	0.68584	NA	NA	0.43274	NA	0.61636	0.86560	0.89087	0.64779	1.01532	NA	0.73636	0.1981	27%	0.58	0.0372	1
Dominican Republic	NA	NA	NA	NA	NA	0.00259	0.00332	0.00327	NA	NA	0.00208	0.00281	0.0006	21%	-0.59	-0.0002	4
Ecuador	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.00406	0.00644	0.00525	0.0017	32%	NA	NA	4
Egypt	0.00032	NA	NA	NA	0.00301	NA	NA	0.00142	NA	NA	NA	0.00158	0.0013	85%	0.48	0.0002	4
El Salvador	NA	NA	NA	NA	NA	0.03494	NA	NA	0.09124	NA	NA	0.06309	0.0398	63%	NA	NA	4
Estonia	NA	NA	NA	NA	NA	0.03698	0.07959	0.07988	NA	NA	NA	0.06548	0.0247	38%	0.87	0.0215	2
Finland	0.48780	NA	NA	0.34857	NA	NA	0.47088	NA	NA	0.53562	0.53597	0.47577	0.0767	16%	0.57	0.0105	1
France	0.37664	NA	NA	0.50897	NA	0.50427	0.52716	NA	1.00620	0.86898	NA	0.63204	0.2465	39%	0.85	0.0636	1
Georgia	NA	NA	NA	NA	NA	0.01715	0.03034	0.07252	0.02214	0.08037	NA	0.04450	0.0297	67%	0.63	0.0118	4
Germany	0.70809	NA	NA	0.63841	NA	0.60683	0.63709	0.60556	NA	0.60556	0.96804	0.68128	0.1316	19%	0.32	0.0124	1
Greece	0.09311	NA	NA	0.10980	NA	0.25842	0.16663	0.30339	0.26422	0.35563	0.36210	0.23916	0.1050	44%	0.91	0.0290	1
Guatemala	NA	NA	NA	NA	NA	0.02347	NA	NA	0.06453	NA	NA	0.04400	0.0290	66%	NA	NA	4
Hong Kong	NA	0.06876	NA	NA	0.45032	NA	NA	0.43447	NA	NA	1.26192	0.55387	0.5039	91%	0.91	0.1188	2
Hungary	0.18422	NA	NA	0.23438	NA	0.22377	0.20858	0.19726	0.44497	0.44121	0.44741	0.29772	0.1225	41%	0.77	0.0285	3
Iceland	NA	NA	NA	NA	NA	NA	0.06969	0.03448	0.06485	0.06757	0.05915	0.05915	0.0166	28%	0.19	0.0024	1
India	NA	0.00081	NA	NA	0.00296	0.00056	0.00092	0.00059	0.00124	0.00181	0.00121	0.00126	0.0008	63%	0.02	0.0000	5
Indonesia	NA	0.00010	NA	NA	0.00012	NA	0.00015	0.00089	NA	NA	NA	0.00031	0.0004	122%	0.67	0.0001	4
Iran	NA	NA	NA	NA	NA	0.07488	0.22261	0.19853	0.21844	0.28810	0.21346	0.20267	0.0699	34%	0.70	0.0260	4
Iraq	NA	NA	NA	NA	NA	NA	NA	NA	0.00325	NA	NA	0.00325	NA	NA	NA	NA	4
Ireland	NA	NA	NA	0.85265	NA	2.07147	2.50382	2.79858	2.60551	2.25290	2.03032	2.15932	0.6412	30%	0.57	0.1522	1
Israel	0.09035	NA	NA	NA	0.08218	NA	NA	0.07746	NA	NA	NA	0.08333	0.0065	8%	-1.00	-0.0019	2
Italy	0.26141	NA	NA	0.36474	NA	NA	0.34450	NA	NA	0.39730	0.85064	0.44372	0.2329	52%	0.73	0.0407	1
Japan	NA	0.22592	NA	NA	0.45657	NA	NA	0.26751	NA	0.31041	0.28253	0.30859	0.0882	29%	-0.02	-0.0004	1
Jordan	0.03603	NA	NA	NA	0.04168	NA	NA	0.03457	NA	NA	0.03491	0.03680	0.0033	9%	-0.35	-0.0003	4
Kenya	NA	NA	NA	NA	NA	NA	NA	NA	0.00322	NA	NA	0.00322	NA	NA	NA	NA	5
Korea	NA	0.15616	NA	NA	0.17484	0.15686	0.18024	0.18554	0.19093	0.27410	0.27658	0.19941	0.0485	24%	0.82	0.0136	1
Kuwait	0.18254	NA	NA	NA	0.26930	NA	NA	0.30423	NA	NA	NA	0.25202	0.0627	25%	0.99	0.0176	2

Table 1. (Continued)

Country	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	R	m	Econ
Latvia	NA	NA	NA	NA	NA	0.10589	0.06461	0.08326	0.12462	0.18189	0.13609	0.11606	0.0416	36%	0.70	0.0155	3
Lebanon	NA	NA	NA	NA	0.07953	NA	0.13957	0.08576	0.18401	NA	NA	0.12222	0.0492	40%	0.68	0.0197	3
Lithuania	NA	NA	NA	NA	NA	0.07465	0.08939	NA	NA	NA	0.15101	0.10502	0.0405	39%	1.00	0.0153	3
Luxembourg	NA	NA	NA	NA	NA	0.35147	0.34831	NA	NA	NA	NA	0.34989	0.0022	1%	NA	NA	1
Macedonia	NA	NA	NA	NA	NA	0.01488	0.01236	NA	0.02463	0.22124	NA	0.06828	0.1021	150%	0.76	0.0425	4
Malaysia	NA	0.09692	NA	NA	0.16757	0.07048	0.14300	0.27095	0.23814	0.24437	0.25657	0.18600	0.0773	42%	0.79	0.0209	3
Mexico	NA	NA	NA	NA	NA	0.04463	0.06389	0.03024	0.06677	0.11164	0.09755	0.06912	0.0309	45%	0.77	0.0127	3
Mongolia	NA	NA	NA	NA	NA	NA	NA	0.00592	NA	NA	NA	0.00592	NA	NA	NA	NA	5
Nepal	NA	NA	NA	NA	NA	0.00124	0.01853	0.00330	NA	0.00060	0.00237	0.00521	0.0075	144%	-0.37	-0.0013	5
Netherlands	1.02854	NA	NA	0.42314	NA	0.45653	0.52785	0.52493	NA	0.61244	NA	0.64799	0.2653	41%	-0.56	-0.0381	1
New Zealand	NA	1.28824	NA	0.44833	1.53846	0.49303	1.49322	NA	0.93866	1.78604	1.95658	1.24783	0.5584	45%	0.27	0.0524	1
Norway	0.41058	NA	NA	NA	NA	NA	0.46487	NA	NA	0.64669	NA	0.49270	0.0911	18%	0.89	0.0241	1
Pakistan	NA	0.00097	NA	NA	NA	0.00051	0.00050	0.00064	NA	0.00014	0.00007	0.00047	0.0003	70%	-0.93	-0.0001	5
Palestine	NA	NA	NA	NA	NA	0.07901	0.00816	NA	0.01168	0.01129	0.10285	0.04194	0.0528	126%	0.86	0.0456	4
Panama	NA	NA	NA	NA	NA	NA	NA	0.01443	0.07117	NA	0.02661	0.03988	0.0329	83%	-0.22	-0.0037	3
Peru	NA	NA	NA	NA	NA	0.05001	NA	NA	0.05889	0.03666	0.00145	0.03675	0.0252	69%	-0.68	-0.0079	4
Philippines	NA	NA	NA	NA	0.00013	NA	0.00144	0.00425	NA	NA	0.00174	0.00189	0.0017	91%	0.41	0.0003	4
Poland	0.07771	NA	NA	0.01039	NA	0.10421	0.11738	0.18280	NA	0.15708	0.15732	0.11527	0.0586	51%	0.75	0.0128	3
Portugal	0.19887	NA	NA	0.39308	NA	0.35643	0.41395	0.47949	0.45550	0.48915	0.49428	0.41009	0.0986	24%	0.93	0.0277	3
Puerto Rico	NA	NA	NA	NA	NA	NA	NA	NA	0.14955	NA	NA	0.14955	NA	NA	NA	NA	2
Romania	NA	NA	NA	NA	NA	0.00908	0.00912	0.03729	NA	0.01849	0.23221	0.06124	0.0963	157%	0.73	0.0339	3
Russia	0.02571	NA	NA	0.04292	NA	NA	0.05019	0.08868	0.04719	0.22295	0.34266	0.11719	0.1198	102%	0.72	0.0243	3
Saudi Arabia	0.14893	NA	NA	NA	0.13457	NA	NA	0.12455	NA	NA	NA	0.13602	0.0123	9%	-1.00	-0.0035	2
Serbia*	NA	NA	NA	NA	NA	0.02056	0.02544	0.02853	0.01905	0.08118	0.03827	0.03551	0.0234	66%	0.56	0.0070	3
Singapore	NA	0.09452	NA	NA	0.01743	0.12204	0.07205	0.13622	NA	NA	0.08558	0.08797	0.0419	48%	0.18	0.0025	2
Slovak Republic	NA	NA	NA	0.18378	NA	0.18560	0.22736	0.22276	0.24132	0.38983	0.30531	0.25085	0.0736	29%	0.80	0.0245	3
Slovenia	NA	NA	NA	NA	NA	NA	NA	0.27345	NA	0.22511	NA	0.24928	0.0342	14%	NA	NA	3
South Africa	NA	NA	NA	NA	NA	NA	0.08587	0.08495	0.06310	0.07718	0.06224	0.07467	0.0115	15%	-0.76	-0.0055	3
Spain	0.38507	NA	NA	0.36613	NA	0.34363	0.38417	0.40377	0.37388	0.40441	0.61682	0.40973	0.0860	21%	0.54	0.0142	1
Sudan	NA	NA	NA	NA	NA	NA	NA	NA	0.00207	0.00976	0.00702	0.00628	0.0039	62%	0.63	0.0025	5
Sweden	1.05108	NA	NA	1.12905	NA	1.12409	1.14630	1.18879	NA	1.39400	NA	1.17222	0.1175	10%	0.85	0.0317	1
Switzerland	0.33473	NA	NA	0.48349	NA	0.52798	0.53638	0.55208	0.59367	0.62009	0.68789	0.54204	0.1047	19%	0.98	0.0311	1
Syria	0.00334	NA	NA	NA	0.01817	NA	NA	NA	NA	NA	NA	0.01075	0.0105	98%	NA	NA	4
Taiwan	NA	0.26675	NA	NA	0.27383	NA	NA	0.38930	NA	NA	0.38467	0.32864	0.0675	21%	0.90	0.0156	NA
Thailand	NA	0.00850	NA	NA	0.01648	NA	NA	0.00563	NA	NA	0.00630	0.00923	0.0050	54%	-0.45	-0.0006	4
Turkey	0.05451	NA	NA	NA	0.11004	0.07085	0.06653	0.06883	0.11107	0.13704	0.11258	0.09143	0.0297	32%	0.67	0.0063	3
Ukraine	NA	NA	NA	NA	NA	NA	0.00208	0.00210	NA	NA	NA	0.00209	0.0000	1%	NA	NA	4
United Kingdom	0.44393	NA	NA	0.60019	NA	0.45416	0.66697	0.53623	NA	1.01192	0.76061	0.63914	0.1996	31%	0.72	0.0416	1
United States	0.62240	0.76075	0.75996	0.85137	0.85657	0.62535	0.63439	0.89846	1.06453	1.08722	1.24455	0.85505	0.2061	24%	0.76	0.0473	1
Uruguay	NA	NA	NA	NA	NA	0.03308	0.11906	0.09105	0.12004	NA	NA	0.09081	0.0408	45%	0.74	0.0233	3
Venezuela	NA	NA	NA	NA	NA	0.16548	0.09152	0.22586	0.16372	0.30798	0.18646	0.19017	0.0724	38%	0.51	0.0198	3
Vietnam	NA	NA	NA	NA	0.00051	0.00498	0.00491	NA	NA	NA	0.00139	0.00295	0.0023	79%	-0.18	-0.0002	5
Zimbabwe	NA	NA	NA	NA	NA	0.01567	0.00194	0.00193	NA	NA	NA	0.00651	0.0079	122%	-0.87	-0.0069	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 [45]; 1: High income OECD (Organisation for Economic Co-operation and Development) [45]; 2: High income non-OECD [44]; 3: Upper middle income; 4: Lower middle income; 5: Low income. Taiwan was not classified economically by the World Bank [44].
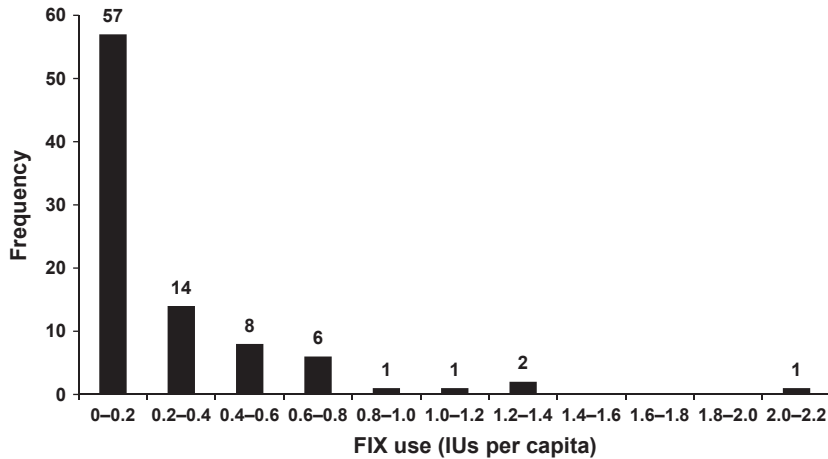
high income OECD countries ranged from 0.0591 in Iceland to 2.1593 in Ireland whereas the FIX use for high income non-OECD countries ranged from 0.0655 in Estonia to 0.5539 in Hong Kong, upper middle income countries ranged from 0.0355 in Serbia to 0.4997 in Costa Rica, lower middle income countries ranged from 0.0003 in Indonesia to 0.2027 in Iran and low income countries ranged from 0.0002 in Bangladesh to 0.0063 in Sudan. Some countries had unusually high FIX use (IUs per capita) when compared to the countries within their economic classification (Fig. 2).

The mean annual growth of FIX use (IUs per capita) increased over time with 78 percent of the countries having a positive slope of their regression line (m) (Table 1). Specifically, 22 of 24 (92%) high income OECD countries had positive growth, 4 of 6 (67%) high income non-OECD countries had positive growth, 20 of 23 (87%) upper middle income countries had positive growth, 12 of 17 (71%) lower middle income countries had positive growth and only 2 of 7 (29%) low income

countries had positive growth. The mean annual growth was positive for all economic classifications except for the low income countries. The mean growth of FIX use (IUs per capita per year) was 0.0312 for high income OECD countries, 0.0258 for high income non-OECD countries, 0.0179 for upper middle income countries and 0.0086 for lower middle income countries, whereas the low income countries had a negative growth that averaged 0.0009 IUs per capita per year. Countries with the largest mean annual growth of FIX use (IUs per capita per year) were Ireland at 0.1522, Hong Kong at 0.1188 and Canada at 0.0982.

The reported FIX use (IUs per capita) varied considerably across economic classifications with use increasing with increasing economic capacity. Table 2 Presents the mean, SD and CV of each observation in Table 1 by economic classification and ANOVA results. FIX use for the high income OECD countries was 0.6494 ± 0.4998 IUs per capita (mean ± SD) whereas the FIX use for the other economic classifications was 0.0997 ± 0.1376 IUs per capita (mean ± SD). FIX use was significantly different for all economic classifications (Table 2) except between high income non-OECD countries and upper middle income countries. On a country-by-country basis, the mean FIX use (IUs per capita) was moderately correlated ($R = 0.63$, $P < 0.001$) with the mean GNI per capita [44].
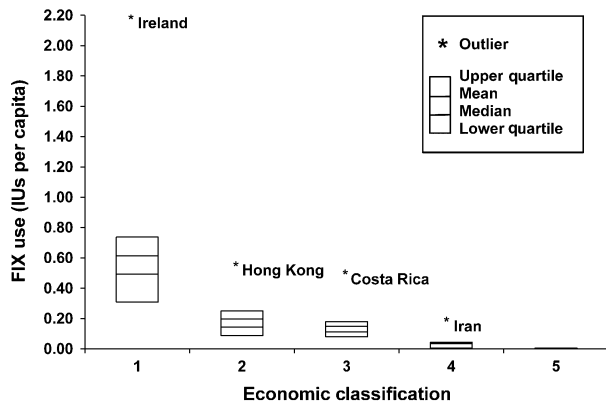
FIX use (IUs per PWHB)

Table 3 presents time-series data from 1998 to 2006 of the FIX use (IUs per PWHB) for 81 countries reporting data to MRB and WFH. There were nine possible FIX 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 FIX use (Table 3). Sixty percent of countries reported FIX use (IUs per PWHB) of 4,000 or less (Fig. 3). The mean FIX use (IUs per PWHB) among high income OECD countries ranged

Fig. 2. Distribution plot with economic classification on the abscissa and factor IX (FIX) use (IUs per capita) on the ordinate. The FIX use values represent the mean FIX use for each of the 90 countries in Table 1. The economic classification [44] is as follows: 1: High income OECD (Organisation for Economic Co-operation and Development) [45]; 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.

Table 2. Statistical analysis of the reported factor IX (FIX) use (IUs per capita) by economic classification [44] for the annual FIX use data in Table 1.

Economic Classification	Mean	SD	CV	Range		n	N	P compares economic classifications			
								(2)	(3)	(4)	(5)
High Income OECD countries (1)	0.6494	0.4998	77%	0.0591	2.1539	151	25	<0.001	<0.001	<0.001	<0.001
High Income non-OECD countries (2)	0.2001	0.2483	124%	0.0655	0.5539	25	8		0.117	<0.001	<0.001
Upper Middle Income countries (3)	0.1462	0.1317	90%	0.0355	0.4997	128	23			<0.001	<0.001
Lower Middle Income countries (4)	0.0399	0.0585	147%	0.0003	0.2027	83	24				<0.001
Low Income countries (5)	0.0028	0.0042	151%	0.0002	0.0065	36	9				
Countries in (2)–(5)	0.0997	0.1376	138%			272	64				
G7 countries	0.6697	0.2715	41%			44	7				
All countries	0.2962	0.4110	139%			427	90				

P compares the mean FIX use for economic classifications using an analysis of variance (ANOVA).
OECD–Organisation for Economic Co-operation and Development [45]; SD, standard deviation; CV, coefficient of variation; n, number of annual FIX 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 [44], but was included in the analysis for all countries.

from 289 in Iceland to 24,171 in the United States whereas the FIX use for high income non-OECD countries ranged from 1,908 in Singapore to 23,140 in Saudi Arabia, middle upper income countries ranged from 622 in Bulgaria to 15,574 in Costa Rica, middle lower income countries ranged from 58 in Cuba to 7,018 in Guatemala and low income countries ranged from 97 in Pakistan to 1,863 in Nepal. Some countries had unusually high FIX use (IUs per PWHB) when compared to the countries within their economic classification (Fig. 4).

The mean annual growth of FIX use (IUs per PWHB) increased over time with 79 percent of the countries having a positive slope of their regression line (m) (Table 3). Specifically, 16 of 16 (100%) high income OECD countries had positive growth, 2 of 2 (100%) high income non-OECD countries had positive growth, 15 of 20 (75%) upper middle income countries had positive growth, 8 of 10 (80%) lower middle income countries had positive growth and 0 of 4 (0%) low income countries had positive growth. The mean annual growth was positive for all economic classifications except for the low income and lower income countries. The mean growth of FIX use (IUs per PWHB per year) was 701 for high income OECD countries, 462 for high income non-OECD countries and 106 for upper middle income countries, whereas the lower middle income and low income countries had negative growth that averaged 278 and 190 IUs per PWHB per year, respectively. Countries with the largest mean annual growth of FIX use (IUs per capita per year) were Ireland at 1,541, United States at 1,309, Argentina at 1,259, Denmark at 1,173, Italy at 1,144, Canada at 1,110 and Brazil at 1,084.

The reported FIX use (IUs per PWHB) varied considerably across economic classifications with FIX use increasing with increasing economic capacity. Table 4 presents the mean, SD and CV of each observation in Table 3 by economic classification and ANOVA results. FIX use for the high income OECD countries was 11,383 ± 6,960 IUs per PWHB

(mean ± SD) whereas the FIX use for the remaining economic classifications was 2,898 ± 3,912 IUs per PWHB (mean ± SD). The FIX use was significantly different for all economic classification except for the comparison between high income non-OECD countries and upper middle income countries. On a country-by-country basis, the mean FIX use (IUs per PWHB) was moderately positively correlated ($R = 0.61$, $P < 0.001$) with the mean GNI per capita [44].

Discussion

The reported FIX use is significantly different across national economies, even among the wealthiest countries. The reported FIX use (IUs per capita and IUs per PWHB) in the high income OECD countries is significantly greater than high income non-OECD, upper middle income, lower middle income and low income countries. Replacement therapy is available in higher income countries, but often times not available in less economically-developed countries because of the inability/unwillingness of governments/health insurance companies to pay for treatment and/or unavailable supply of factor concentrates. While economic capacity correlates with FIX usage, there can be other factors–such as: number of PWHB, national attitudes about healthcare, organisation of healthcare delivery and the role of patients in making decisions about their own care–that could explain the differences between economically similar countries. Other sources of variation between countries of an upper economic status include the extent to which recombinant FIX has been introduced as a treatment modality; the lower recovery of FIX experienced with recombinant compared to plasma derived products [46] increases the amount of FIX used. In addition, patient-to-patient variation in recovery of FIX is notable in haemophilia B [47] and mutations such as haemophilia B Leyden [48] affect usage considerably. Thus, FIX usage is also a function of the product type and particular genetic profile of the individual population studied.

Table 3. The reported factor IX (FIX) use (IUs per PWHB–person with haemophilia B) was determined from the reported number of FIX international units (IUs) used in the treatment of haemophilia B for a country from 1998–2006 [29–38] divided by its reported number of people with haemophilia B in the relevant year [34–38,41–43].

Country	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	R	m	Econ
Albania	NA	NA	NA	202	NA	87	378	405	1,250	464	458	99%	0.76	181	4
Algeria	NA	NA	NA	NA	1,265	NA	NA	NA	1,615	1,440	248	17%	NA	NA	4
Argentina	NA	NA	NA	2,780	NA	2,114	7,351	NA	NA	4,081	2,851	70%	0.67	1,259	3
Australia	NA	NA	14,000	8,560	NA	NA	NA	11,893	12,428	11,720	2,289	20%	0.10	75	1
Austria	NA	6,344	NA	NA	NA	NA	NA	NA	NA	6,344	NA	NA	NA	NA	1
Bangladesh	NA	NA	NA	NA	NA	275	200	80	59	154	102	66%	−0.97	−77	5
Belarus	NA	NA	NA	855	NA	634	1,042	NA	1,156	922	228	25%	0.67	74	4
Belgium	NA	5,111	NA	NA	4,735	NA	NA	NA	NA	4,923	266	5%	NA	NA	1
Belize	NA	NA	NA	NA	NA	8,571	10,909	NA	NA	9,740	1,653	17%	NA	NA	3
Bosnia-Herzegovina	NA	NA	NA	NA	NA	NA	1,000	NA	1,500	1,250	354	28%	NA	NA	4
Brazil	NA	NA	NA	5,667	NA	3,881	12,752	11,089	8,712	8,420	3,679	44%	0.57	1,084	3
Bulgaria	NA	412	NA	783	NA	324	882	740	592	622	220	35%	0.32	27	3
Canada	NA	NA	NA	NA	NA	NA	13,958	15,902	16,177	15,346	1,210	8%	0.92	1,110	1
Chile	NA	NA	NA	2,330	669	669	NA	NA	NA	1,223	959	78%	−0.87	−831	3
Colombia	NA	NA	NA	1,592	NA	2,583	1,621	2,461	2,153	2,082	462	22%	0.42	101	4
Costa Rica	NA	NA	NA	21,484	NA	16,978	1,852	21,982	NA	15,574	9,421	60%	−0.26	−1,454	3
Croatia	NA	NA	NA	NA	932	93	NA	554	3,055	1,158	1,310	113%	0.66	471	3
Cuba	NA	NA	NA	NA	NA	NA	34	NA	83	58	34	58%	NA	NA	4
Czech Republic	NA	3,295	NA	NA	NA	NA	NA	NA	NA	3,295	NA	NA	NA	NA	1
Denmark	NA	7,419	NA	10,061	NA	14,286	10,836	15,625	NA	11,645	3,310	28%	0.85	1,173	1
Dominican Republic	NA	NA	NA	131	171	171	NA	NA	NA	158	23	15%	0.87	20	4
Ecuador	NA	NA	NA	NA	NA	NA	174	264	NA	219	64	29%	NA	NA	4
Egypt	NA	NA	80	NA	NA	NA	NA	NA	NA	80	NA	NA	NA	NA	4
El Salvador	NA	NA	NA	1,170	NA	NA	2,620	NA	NA	1,895	1,025	54%	NA	NA	4
Estonia	NA	NA	NA	1,400	3,000	3,000	NA	NA	NA	2,467	924	37%	0.87	800	2
Finland	NA	NA	NA	NA	NA	NA	NA	12,112	12,050	12,081	43	0%	NA	NA	1
France	NA	8,264	NA	NA	NA	NA	NA	18,270	NA	13,267	7,075	53%	NA	NA	1
Georgia	NA	NA	NA	412	NA	2,348	568	1,933	NA	1,315	970	74%	0.46	262	4
Germany	NA	9,893	NA	12,658	NA	12,450	NA	12,330	19,729	13,412	3,706	28%	0.76	987	1
Greece	NA	2,055	NA	4,216	NA	4,935	4,170	5,529	5,641	4,424	1,318	30%	0.90	456	1
Guatemala	NA	NA	NA	NA	NA	NA	7,018	NA	NA	7,018	NA	NA	NA	NA	4
Hungary	NA	3,204	NA	2,271	2,112	NA	5,143	5,086	5,703	3,920	1,583	40%	0.81	484	3
Iceland	NA	NA	NA	NA	NA	175	339	351	NA	289	98	34%	0.89	88	1
India	NA	NA	NA	174	NA	221	267	215	138	203	49	24%	−0.14	−3	5
Indonesia	NA	NA	184	NA	NA	1,496	NA	NA	NA	840	928	110%	NA	NA	4
Iran	NA	NA	NA	1,742	NA	4,704	4,420	5,141	3,769	3,955	1,334	34%	0.65	453	4
Iraq	NA	NA	NA	NA	NA	NA	177	NA	NA	177	NA	NA	NA	NA	4
Ireland	NA	10,390	NA	25,000	NA	33,880	29,442	23,871	22,260	24,140	7,955	33%	0.51	1,541	1
Italy	NA	6,126	NA	NA	NA	NA	NA	5,942	18,539	10,203	7,220	71%	0.60	1,144	1
Japan	NA	NA	NA	NA	NA	8,891	NA	10,081	8,924	9,299	678	7%	0.21	94	1
Jordan	NA	NA	1,379	NA	NA	NA	NA	NA	990	1,185	275	23%	NA	NA	4
Kenya	NA	NA	NA	NA	NA	NA	296	NA	NA	296	NA	NA	NA	NA	5
Korea	NA	NA	6,726	5,895	6,807	NA	6,945	9,501	9,339	7,535	1,506	20%	0.85	543	1
Latvia	NA	NA	NA	3,333	NA	2,310	3,316	4,601	3,024	3,317	829	25%	0.26	112	3
Lebanon	NA	NA	NA	NA	13,846	NA	8,291	NA	NA	11,069	3,928	35%	NA	NA	3
Lithuania	NA	NA	NA	2,342	NA	NA	NA	NA	4,021	3,182	1,187	37%	NA	NA	3
Macedonia	NA	NA	NA	178	148	NA	336	NA	NA	220	101	46%	0.89	59	4
Malaysia	NA	NA	5,693	2,391	NA	9,423	8,042	7,401	7,640	6,765	2,456	36%	0.60	639	3
Mexico	NA	NA	NA	3,038	NA	1,851	3,560	4,378	3,541	3,274	929	28%	0.53	255	3
Mongolia	NA	NA	NA	NA	NA	517	NA	NA	NA	517	NA	NA	NA	NA	5
Nepal	NA	NA	NA	463	7,050	1,282	NA	122	397	1,863	2,932	157%	−0.42	−597	5
Netherlands	NA	5,360	NA	NA	NA	NA	NA	6,897	NA	6,128	1,087	18%	NA	NA	1
New Zealand	NA	NA	9,177	4,135	NA	2,857	15,171	13,388	8,436	8,861	4,878	55%	0.40	842	1
Norway	NA	7,843	NA	NA	NA	NA	NA	10,601	NA	9,222	1,950	21%	NA	NA	1
Pakistan	NA	NA	NA	NA	NA	248	NA	35	8	97	131	135%	−0.97	−84	5
Palestine	NA	NA	NA	NA	NA	425	NA	3,810	NA	2,117	2,393	113%	NA	NA	4
Panama	NA	NA	NA	1,365	NA	218	1,046	NA	401	758	538	71%	−0.59	−153	3
Peru	NA	NA	NA	NA	NA	NA	6,427	2,874	91	3,131	3,176	101%	−1.00	−3,168	4
Philippines	NA	NA	32	NA	NA	641	NA	NA	190	288	316	110%	0.25	26	4
Poland	NA	215	NA	2,077	NA	3,650	NA	2,791	2,900	2,326	1,305	56%	0.78	353	3
Portugal	NA	9,412	NA	8,584	NA	9,599	9,775	10,488	10,500	9,726	721	7%	0.79	219	1
Romania	NA	NA	NA	162	NA	649	NA	315	3,759	1,221	1,704	140%	0.70	537	3
Russia	NA	1,125	NA	NA	NA	933	1,101	3,932	6,165	2,651	2,327	88%	0.70	605	3
Saudi Arabia	NA	NA	NA	NA	NA	23,140	NA	NA	NA	23,140	NA	NA	NA	NA	2
Serbia[*]	NA	NA	NA	553	NA	740	476	1,995	1,031	959	617	64%	0.55	177	3
Singapore	NA	NA	438	3,165	1,899	NA	NA	NA	2,131	1,908	1,124	59%	0.29	124	2
Slovak Republic	NA	2,195	NA	2,370	NA	2,752	2,975	NA	3,664	2,791	577	21%	0.97	206	3

Table 3. (Continued)

Country	1998	1999	2000	2001	2002	2003	2004	2005	2006	Mean	SD	CV	R	m	Econ
Slovenia	NA	NA	NA	NA	NA	3,429	NA	NA	NA	3,429	NA	NA	NA	NA	2
South Africa	NA	NA	NA	NA	NA	3,252	2,264	2,723	2,107	2,587	515	20%	−0.75	−298	3
Spain	NA	8,758	NA	7,004	NA	8,479	10,000	10,793	16,456	10,248	3,310	32%	0.74	939	1
Sudan	NA	NA	NA	NA	NA	NA	290	NA	797	543	359	66%	NA	NA	5
Sweden	NA	14,124	NA	NA	NA	16,060	NA	NA	NA	15,092	1,369	9%	NA	NA	1
Switzerland	NA	7,431	NA	9,059	NA	9,360	9,219	10,051	9,938	9,176	943	10%	0.92	332	1
Thailand	NA	NA	5,076	NA	NA	1,651	NA	NA	363	2,363	2,436	103%	−0.97	−786	4
Turkey	NA	NA	19,737	6,422	NA	4,728	5,022	4,902	3,657	7,411	6,103	82%	−0.76	−2,000	3
United Kingdom	NA	6,343	NA	5,293	NA	6,392	NA	9,134	7,500	6,933	1,457	21%	0.70	358	1
United States	20,221	22,995	22,582	16,318	NA	23,933	27,688	27,956	31,672	24,171	4,843	20%	0.79	1,309	1
Uruguay	NA	NA	NA	724	NA	1,992	2,625	NA	1,780	1,780	968	54%	1.00	634	3
Venezuela	NA	NA	NA	4,392	NA	5,629	3,798	6,491	3,778	4,818	1,200	25%	0.01	4	3
Vietnam	NA	NA	193	NA	NA	NA	NA	NA	139	166	38	23%	NA	NA	5
Zimbabwe	NA	NA	NA	667	83	NA	NA	NA	NA	375	412	110%	NA	NA	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 [44]: 1: High income OECD (Organisation for Economic Co-operation and Development) [45]; 2: High income non-OECD; 3: Upper middle income; 4: Lower middle income; 5: Low income.
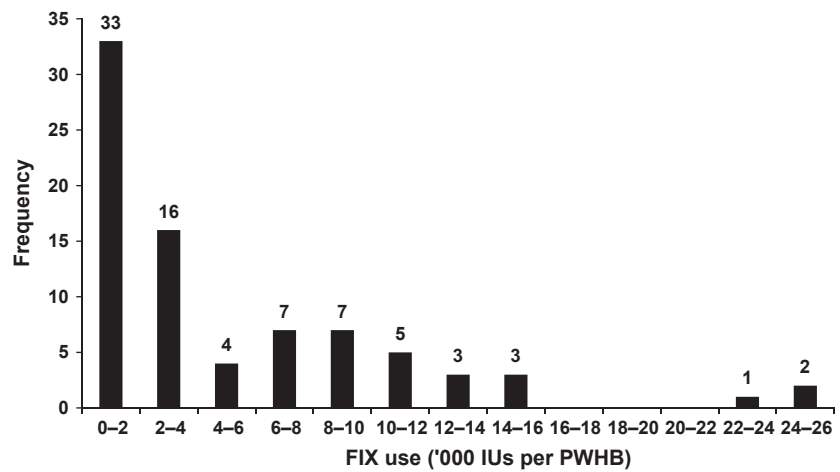

Fig. 3. Histogram for the factor IX (FIX) use (IUs per PWHB–person with haemophilia B) for each of the 81 countries in Table 3. The numbers above each bar represents the number (frequency) of countries with mean FIX use in the range stated on the abscissa.
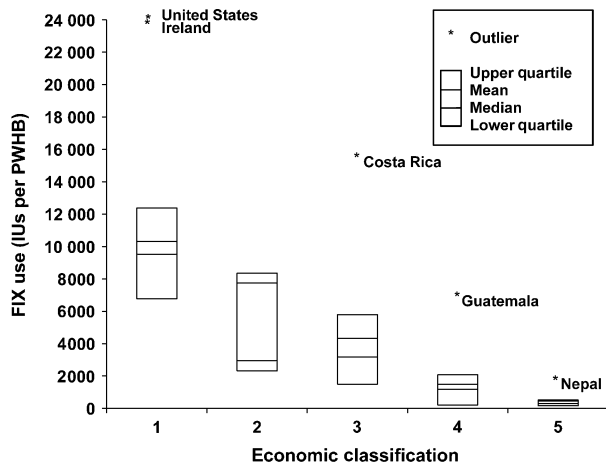

Fig. 4. Distribution plot with economic classification on the abscissa and factor IX (FIX) use (IUs per PWHB–person with haemophilia B) on the ordinate. The FIX use values represent the mean FIX use for each of the 81 countries in Table 1. The economic classification [44] is as follows: 1: High income OECD (Organisation for Economic Co-operation and Development) [45]; 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.

Some countries are consuming more FIX concentrates when compared to the countries within their economic classification–for FIX use (IUs per capita): Ireland, Hong Kong, Costa Rica and Iran and for FIX use (IUs per PWHB): United States, Ireland, Costa Rica, Guatemala and Nepal. Ireland stands out for its usage of FIX both in terms of IUs per capita and IUs per PWHB (Figs 1 and 3). This can be explained by the fact that Ireland treats its patients using the standards of Northern European countries, (i.e. among the highest in the world) combined with the fact that Ireland has the highest reported haemophilia B prevalence of 8.07 per 100 000 males [49]. The founder effect [50] is likely contributing to the high prevalence levels in Ireland. On the other hand, Iceland had the highest FVIII use [51] whereas its FIX use was the lowest for high income OECD countries. The United States also stands out for using a huge amount of FIX IUs per PWHB. The reported haemophilia B prevalence for the United States is lower than expected since it is based solely on patients who use federally supported haemophilia treatment centres for care which accounted for about 70% of all

Table 4. Statistical analysis of the reported factor IX (FIX) use (IUs per PWHB–person with haemophilia B) by economic classification [44] for the annual FIX use data in Table 3.

Economic Classification	Mean	SD	CV	Range		n	N	P compares economic classifications			
								(2)	(3)	(4)	(5)
High Income OECD countries (1)	11,383	6,960	61%	289	24,171	95	24	0.006	<0.001	<0.001	<0.001
High Income non-OECD countries (2)	4,622	7,011	152%	1,908	23,174	9	4		0.763	0.004	0.008
Upper Middle Income countries (3)	4,136	4,365	106%	622	15,574	99	23			<0.001	<0.001
Lower Middle Income countries (4)	1,495	1,688	113%	58	7,108	57	21				0.018
Low Income countries (5)	569	1,379	242%	97	1,863	25	9				
Countries in (2)–(5)	2,898	3,912	135%			190	57				
G7 countries	14,695	7,481	51%			29	7				
All countries	5,726	6,502	114%			285	81				

P compares the mean FIX use for economic classifications using an analysis of variance (ANOVA).
OECD, Organisation for Economic Co-operation and Development [45]; SD, standard deviation; CV, coefficient of variation; n, number of annual FIX use observations in Table 3 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.

patients identified [52]. Saudi Arabia had the third highest FIX use (IUs per PWHB) (Fig. 3). We believe that the high FIX usage (IUs per PWHB) for Saudi Arabia is attributed to its low-reported haemophilia B prevalence of 0.30 per 100 000 males [51]. This may also be a result of procurement of factor concentrates that is based on haemophilia B prevalence being estimated as one-fifth of the total number of people with haemophilia A and B when the actual number of people with haemophilia B in some countries is in fact much lower. However, over a period of time when this fact is better recognized, the actual use of FIX concentrate becomes very low in terms of per capita use as in Iceland while the per person use may still be much higher because of their treatment protocols. When compared to other upper middle income countries, Costa Rica is consuming more FIX concentrates both in terms of IUs per capita and IUs per PWHB. The Iran Hemophilia Center has identified a large haemophilia population which, in turn, has influenced the consumption of FIX (IUs per capita) to levels higher than expected based on economic status [53]. Other countries–Hong Kong, Guatemala and Nepal–having higher FIX use when compared to countries in their economic classification merit further research.

Treatment modalities vary from country to country and have an impact on the level of FIX use. Therefore, care must be taken when making policy conclusions concerning FIX requirements for a country without reviewing the actual number of PWHB identified at that time and its protocols of treatment. For example, when the number of PWHB is under-reported in a country, the reported FIX use (IUs per PWHB) may be higher than what is actually used per patient. It is difficult to know whether higher IUs per PWHB mean better care is being delivered to identified patients, or more patients are being treated than have been reported to the WFH or over-treatment is occurring, without a clear understanding of the treatment practices for a country. However, the global trends of FIX use are clear–there will likely be an overall increase in the amount of IUs of FIX concentrates used in the treatment of haemophilia B. Trends also suggest that FIX use has been increasing at a faster rate with increasing economic capacity. Such information is critical for planning. By improving the data collection and surveillance for the treatment of people with haemophilia B, trends and needs of patients can be identified and best treatment practices highlighted among countries and this, in turn, can lead to better management and planning of the requirements and resources for national healthcare agencies to determine budget priorities and for pharmaceutical manufacturers to determine adequate production of FIX concentrates [1,9,54].

Disclosures

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