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ORIGINAL ARTICLE *Clinical haemophilia*

Italian Registry of Haemophilia and Allied Disorders. Objectives, methodology and data analysis

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Summary. National haemophilia registries are powerful instruments to support health care and research. A national registry was established in Italy by the Ministry of Health until 1999. Since 2003 the Italian Association of Haemophilia Centres (AICE) started a new programme aiming at building up the Italian Registry of Haemophilia and Allied Disorders. The AICE identified an expert panel to steer the registry. A computer software to assist patient management was developed and all the AICE-affiliated haemophilia treatment centres (HTC) were prompted to adopt it. Twice a year a predefined set of anonymized data is centralized and merged into a national database. Duplicated entries are managed through a confidentiality sparing mechanism. The database covers sociodemographic, clinical, laboratory and treatment data. A subset of data are shared with the Ministry of Health (Istituto Superiore di Sanità, ISS). Overall, data were collected six times by 43 of 49 HTC; 41 centres updated their patients' records up to December 2006. The database contains 6632 unique records, 442 of them referring to dead patients. Database growth and missing data clearance showed a constantly positive trend over time. The database has collected records of the following alive patients – haemophilia A: 1364 severe, 398 moderate and 935 mild; haemophilia B: 231 severe, 138 moderate and 204 mild; von Willebrand's disease: 1208 type 1, 346 type 2 and 96 type 3. Inhibitor patients were 296 (of which 194 high responders and 65 low responders). The Italian registry run by AICE adds to the list of the available national haemophilia registries and is intended to establish treatment guidelines and foster research projects in Italy.

Keywords: haemophilia, registry, von Willebrand's disease

Introduction

The haemophilias are inherited bleeding disorders affecting about 400 000 persons worldwide. Deficiencies of factor VIII (haemophilia A, HA), FIX (haemophilia B, HB) and von Willebrand factor (von Willebrand's disease, VWD) are the most common, but rare defects of coagulation factors also occur. When left untreated, haemophilia causes crippling pain, severe joint damage, disability and death [1]. The development of national registries is a basic step to answer epidemiological questions on haemophilia, establish effective care programmes [2,3] and document the natural history of the disease with and without treatment [4–17]. A national registry may also allow the effective use of available resources [18], audit of clinical programmes [19,20], planning of research project and cross-evaluation of special sub-databases (for instance, on genetics [21–25] and inhibitors). Information supplied by a national registry may also help patients by increasing awareness and identifying shortcomings in the healthcare delivery system [2,3]. National registries can be valuable sovranationally for the same objectives, so that a sovranational programme of harmonization of haemophilia registries has been claimed in the past [26] and recently started by the FVIII/FIX Standardization Subcommittee of the International Society on Thrombosis and Haemostasis.

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The aims of this article were to describe the development of the Italian registry fostered by the Italian Association of Haemophilia Centres (AICE), and to report the main data from it so far extracted.

Methods

A national haemophilia registry in Italy was formerly maintained (up to 1999) through a collaboration between AICE and the Italian Ministry of Health (Istituto Superiore di Sanità, ISS). Since 2003 a new registry programme was independently developed by AICE. At the beginning, a working group of haemophilia treatment centre (HTC) directors set the goals of the registry and established the data to be collected. The goals were to determine prevalence and incidence of haemophilia, its management and complications. The Italian registry was conceived to be completely doctor-run, and to be regularly updated, and was named the Italian Haemophilia and Allied Disorders Registry.

The AICE organization and the registry steering bodies

Italian Association of Hemophilia Centre is a non-for-profit association of Italian doctors and carers involved in health care and research in haemophilia and other coagulation disorders. All the directors of the Italian HTC take part in AICE; they are actively involved in its management and meet twice a year. The main objectives of AICE are to prompt optimal health care delivery through the Italian HTC network; basic and clinical research on coagulation disorders; education of medical and related professionals involved in haemophilia care and collection of epidemiological data on coagulation disorders. First, each HTC Director is responsible for the collection and validation of patient data; then, a technical group, based at the University of Perugia, takes care of merging, analysing and reporting the database data; finally, a steering committee is responsible to evaluate and approve any request to access the database for research purposes. The central database, which is simply the merge of the anonymized replicates of all the local databases of each HTC, is stored at the University of Perugia. The Registry is not formally protocol driven, but all the details about data collection are agreed at each AICE general meeting and included in the corresponding minutes. An online help is available in the specific software employed for data collection (EMOCARD, see below).

*HTC management software (*EMOCARD)

The HTC directors chose to create a management software intended both to collect data for the registry and allow the clinical and administrative management of HTC. This plan led to EMOCARD, a management system developed by AICE and adopted by HTCs. EMOCARD was designed to support all the daily activities of HTCs, and covers all the relevant fields of haemophilia management (i.e. basic demographics, family and patient history of disease, vaccination, physical examination, HIV and HCV status, inhibitors, complete coagulation profile and other laboratory data, molecular diagnosis, type and mode of treatment, follow-up visits, hospitalization and surgical procedures). To improve homogeneity in data collection and minimize subjectivity, all the fields relevant to the registry were coded as yes/no or multiple choice variables; numerical data were preferred wherever possible [17]. EMOCARD is password protected, and it runs as a stand-alone programme or as a client-server application, available for the most common database services (MS-SQL and Oracle). The Italian HTCs were provided with a template consent form to be approved by each institutional review board and to be signed by each patient enrolled in the local database. The signed forms are peripherally stored.

Data centralization and merging

For each patient entered in the local database, EMOCARD generates a unique personal ID code (EMO-ID) to replace the patient's identity data when these are sent to the national database. Every 6 months each HTC centralizes anonymized records of patients through an automated procedure. After the information is gathered, the national database is updated according to the following rules: (i) each patient record in the national database is updated in accordance with the last patient record, (ii) any record referring to patients not already present in the national database is added as 'new patient' and (iii) any patient not present in the last data set sent to the national database is considered lost or withdrawn and is marked as 'deleted'. This routine is separately run for each data set sent by each HTC. Then a set of congruency checks is carried out on the newly merged national database. All the records not passing this stage are excluded from the analysis and queries are issued to the responsible HTC to fix them. This usually occurs before the next data collection.

A common bias occurs in similarly merged databases when a patient is entered twice or more often

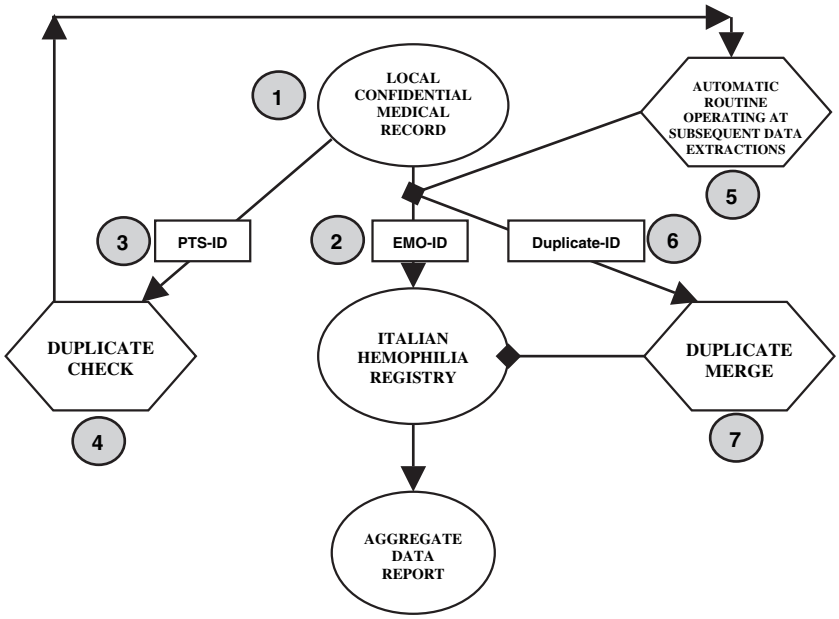

Fig. 1. Flow chart of the confidentiality sparing management of duplicated patients' records. Two independent sets of data are extracted from the confidential medical records of the haemophilia treatment centre (HTC) local databases (1): a set of relevant data, identified through a nationwide unique identifier [EMO-ID (2)] and a set of a unique patient identifiers, built up on patient sensible data [i.e. name initial, surname initial, birth date, code for birth place and sex; PTS-ID (3)]. The PTS-ID is unrelated to sensible clinical or demographic information and to the EMO-ID. Both the EMO-ID and PTS-ID are stored in the local database, but the EMO-ID only is included in the national data set. Then, a duplicate check routine (4) matches all the identical PTS-ID provided by different HTCs and produces a set of information that are embedded in an automatic routine (5) distributed to all HTC, which produces, in the following data extraction, a set of duplicate ID (6). The duplicate ID indicates different EMO-ID provided by different HTC but relative to unique duplicated patients. The duplicate ID is not stored in the local database, neither used when producing local reports, so that any duplicated patient is retained in any relevant local HTC database. Finally, a semiautomated duplicate merge procedure (7) is used to produce a national data report after merging of all records relative to unique patients.

because he is treated in different centres. A duplicate management routine was built up taking into account the need to preserve patient privacy [17,27]. This allows to merge records from different HTCs but referring to the same patient, and as the logic of the process does not imply any modification of the local database, patients' privacy is fully preserved (see Fig. 1 and legend for additional details).

Data analysis validation

A predefined set of database queries is then run on any newly updated national database (working database) to automatically produce national and local reports. These reports are published in password-protected pages on the AICE website (http://www.aiceonline.it), to allow each HTC to check and validate the local report. Any incongruence found by HTCs is evaluated, verified and eventually included in the working database that becomes definitive. The same set of queries is then run again on the final database version to produce the final reports.

Report distribution and website

The report is organized in sections (alive and dead patients, database updates, use of factor concentrates and other data) and subsections. Each subsection is made of summary and detail tables produced by direct analysis of the national database. To help data interpretation a series of calculated check cells are provided: lines for total and column for percentages. The report is a hypertextual page with a lateral flowing bar, several hyperlinks along the text, a menu on the left side of the page and can be completely printed out (with or without extended legends). The local report is very similar to the national one except for the presence of appendices produced by queries on data that require checking and rectifying. Final reports (local and national) are then published on the AICE website. Each HTC can access his own local report and the national one. The access to the local report is possible through a summary page listing the active centres, with information about the time of last data sent, number of patients provided and validation of the working report. The website stores all biannual

Table 1. Summary data for Italian male patients with haemophilia A as on December 2006.

		Age (years)				
Category	Number	0–9	10–24	25–44	45–64	65+
Haemophilia A severe	1100	122	267	465	217	29
Haemophilia A severe with inhibitor	261	54	60	91	49	7
Subtotal	*1361*	*176*	*327*	*556*	*226*	*36*
Haemophilia A moderate	377	35	94	143	78	27
Haemophilia A moderate with inhibitor	17	2	6	6	2	1
Subtotal	*394*	*37*	*100*	*149*	*80*	*28*
Haemophilia A mild	914	66	194	350	199	105
Haemophilia A mild with inhibitor	10	0	1	1	5	3
Subtotal	*924*	*66*	*195*	*351*	*204*	*108*
Total	2679	279	622	1056	550	172

Table 2. Summary data for Italian male patients with haemophilia B as on December 2006.

		Age (years)				
Category	Number	0–9	10–24	25–44	45–64	65+
Haemophilia B severe	223	34	64	84	31	10
Haemophilia B severe with inhibitor	7	4	2	0	1	0
Subtotal	*230*	*38*	*66*	*84*	*32*	*10*
Haemophilia B moderate	137	16	27	53	30	11
Haemophilia B moderate with inhibitor	1	0	0	1	0	0
Subtotal	*138*	*16*	*27*	*54*	*30*	*11*
Haemophilia B mild	199	24	49	66	46	14
Haemophilia B mild with inhibitor	0	0	0	0	0	0
Subtotal	*199*	*24*	*49*	*66*	*46*	*14*
Total	567	78	142	204	108	35

reports since July–December 2004, and allows comparisons between them.

Since only HTC directors have access to the full version of local and national reports, the AICE general assembly decided to publish online summary data for free access. These tables offer to anybody interested data on Italian patients with HA and HB grouped for age ranges, gender and presence or absence of inhibitor. The tables and their forecoming updates are accessible online at: http://www.aiceonline.it/indexEn.asp. A simplified version of the tables, referring only to male patients with HA and HB, is presented in Tables 1 and 2.

Data analysis

Common epidemiological measures were used in this report to summarize demographic and clinical data. The proportion of patients with a definite characteristic was expressed as percentage, and 95% confidence intervals were calculated for proportions when a subset of patients was considered. Age was analysed by calculating the percentage of patients within each age class, while the measures of central tendency chosen for age at diagnosis were mean and interquartile range and mode (the latter being the value occurring most frequently in the series of observations).

The growth of the database was measured by calculating the percentage increase in each data collection over the previous one, and by calculating the mean increase (mean of the semestral increases), cumulative increase (the sum of the semestral increases) and overall increase (the percentage increase of the last over the first data collection).

Results

Database growth and coverage

Since December 2004 five data extractions were carried out, so that at 6-month intervals the national database was updated. The number of active HTC involved in the registry project did progressively increase from 36 of 49 on December 2004 to 43 of 49 on December 2006.

The number of patients' records collected (total, alive and dead patients) increased during the period 2004–06. At the time of the first collection total patients included were 4222, 4055 alive and 167 dead. Nowadays total patients are 6632 after duplicate exclusion (7684 total records), 6190 alive and 442 dead. Database growth showed a constantly positive trend over time, with a mean increase rate over the five collections of approximately 12%. The rate of increase did progressively decrease with time, consistently with the consolidation of the progressive adoption of EMOCARD in the clinical practice of HTCs (18%: June 2005 vs. December 2004; 15%: December 2005 vs. June 2005; 12%: June 2006 vs. December 2005; 3%: December 2006 vs. June 2006). The cumulative and overall increases in the database over the five collections were 48.3% and 57.1% respectively.

The coverage by the registry of the actual Italian haemophilia population can be approximately estimated to be close to 90%. This figure was estimated by taking into account the number and size of HTCs not yet participating to the registry programme, and also by comparison with the number of patients previously enrolled in the official ISS database in 1999. Furthermore, the prevalence of HA and HB in

Italy calculated on the basis of registry data is 1 and 0.2 in 10 000 males, respectively, i.e. close to the expected theoretical prevalence of the diseases in the general population.

The following sections will report some of the main results from the last database collection of December 2006.

Demography

Of the 6190 living patients registered in the last reports 2697 (43.6%) had HA, 573 (9.3%) HB, 1650 (26.6%) VWD and 1270 (20.5%) other coagulopaties (not detailed in this report).

Haemophilia A

Patients with HA are stratified as severe (1364, 59.6%), moderate (398, 14.8%) and mild (935, 34.7%). Eighteen patients (0.7%) diagnosed with HA are females. One hundred and three patients are below 4 years of age (5.0% of severe patients, 3.5% of moderate and 2.0% of mild). Details on age distribution of male patients with HA are given in Table 1.

Age at first diagnosis for severe HA peaks in the first years of life and decreases thereafter, with fewer patients first diagnosed at an older age. The trend is opposite for mild HA, with an increasing rate from the class 4- to 10-years-old onwards, while patients with moderate HA show an intermediate trend (see Fig. 2, top panel). Median (interquartile range) age at diagnosis was 1.0 (0.6–6.0) years for severe, 4.0 (1.1–16.0) for moderate and 14.0 (4.2–30.0) for patients with mild HA. The mode of age at diagnosis was 1 for severe and moderate and 4 for patients with mild HA.

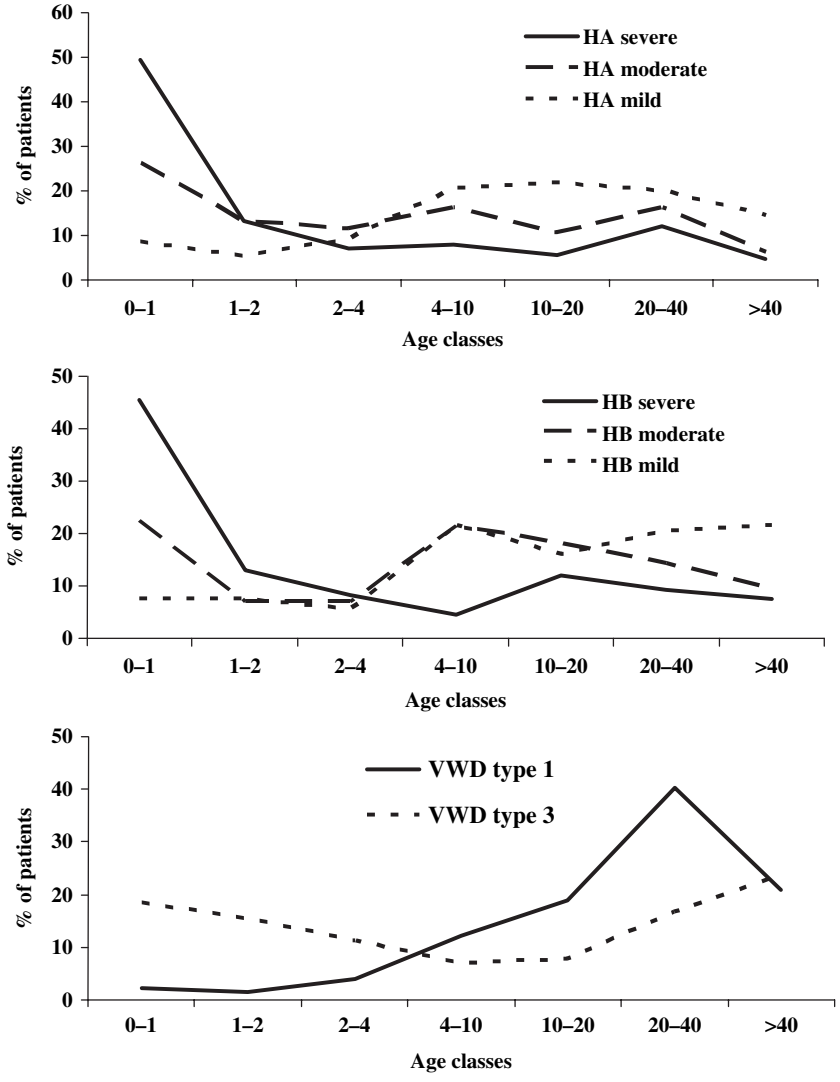

Fig. 2. Age of first diagnosis for patients with haemophilia A, haemophilia B and von Willebrand's disease. The figure shows the per cent of patients diagnosed in each age class.

In the last 11 years (1996–2006) the median annual number of newly diagnosed patients has been 18 (range: 6–26) for severe HA, 4 (range: 0–8) for moderate and 8 (range: 1–13) for mild disease.

The overall prevalence of the FVIII inhibitor was 10.7% in patients with HA, split in 19.2% of severe patients, 4.3% of moderate and 1.1% of mild. The inhibitor titre was specified in 88.2% of cases, high responders (peak titre ≥10 BU) being 75.2% and low responders (peak titre <10 BU) being 24.8%.

Data on the rate of HIV infection were reported for 77.3% of patients with HA enrolled in the registry. The percentage (with 95% confidence intervals) of infected patients were 13.5% (95% CI: 11.5–15.5), 3.6 (95% CI: 1.6–5.7) and 1.7 (95% CI: 0.7–2.7) for severe, moderate and mild patients respectively. Because concentrates virally safe from HIV transmission become widely available in Italy since 1985 and no infection occurred after this year, figures were recalculated considering patients born before 1986: 34.2% (95% CI: 29.8–38.7), 12.6% (95% CI: 6.0–19.3) and 8.3% (95% CI: 3.4–13.2) for severely, moderately and mildly affected patients respectively.

Data on the rate of HCV infection were reported for 73.2% of patients with HA enrolled in the registry. The observed rates of infection were 56.0% (95% CI: 53.2–58.9), 51.1 (95% CI: 45.5–56.7) and 42.4 (95% CI: 37.9–46.9) for severe, moderate and mild patients respectively. Because concentrates virally safe from HCV transmission became available in Italy since 1987, these figures were recalculated considering patients born before 1988: 75.5% (95% CI: 72.6–78.4), 75.4 (95% CI: 69.5–81.2) and 67.7 (95% CI: 61.6–73.3) for severely, moderately and mildly affected patients. Six cases of HCV infection were found in patients born after 1987 (four in severe, one in moderate and one in patients with mild HA), giving figures of 1.3% (95% CI: 0.0–2.6), 1.0 (95% CI: 0.0 to 3.0) and 0.5 (95% CI: 0.0 to 1.5) of severely, moderately and mildly affected patients. All these six cases were patients treated with plasma or cryoprecipitate outside Italy.

Haemophilia B

Patients with HB are stratified as severe (231, 40.3%), moderate (138, 24.1%) and mild (204, 35.6%). Six (1%) patients with HB are females. Thirty patients are below 4 years of age (6.0% of severe, 4.0% of moderate and 2.6% of mild patients). Details on age distribution of male patients with HB are given in Table 2. Age at first diagnosis shows trends similar to those of HA (see Fig. 2, middle panel). Median (interquartile range) age at diagnosis was 1.5 (1–10.0) years for severe, 8.0 (2.0–18.7) for moderate and 20.0 (6.2–39.5) for mild patients with HB. The mode of age at diagnosis was 1 for severe and moderate and 10 for mild patients with HB.

In the last 11 years (1996–2006) the median annual number of newborn patients has been 4 (range: 0–7), 2 (range: 0–3), 2 (range: 0–5) for severe, moderate and mild HB respectively.

Overall prevalence of FIX inhibitor was 1.4% in patients with HB. Inhibitors were reported in 3.0% of severe, 0.7% of moderate and in 0 mild patients with HB. Five of the eight inhibitors had the titre specified, that was high (≥10 BU) in three and low (<10 BU) in two. No cases of anaphylaxis were recorded upon treatment of these patients with concentrates.

Data about HIV infection were available for 74.7% of patients with HB enrolled in the registry. The percentage of infected patients were: 19.1% (95% CI: 13.4–24.8), 6.9 (95% CI: 2.3–11.5) and 3.1 (95% CI: 0.1–6.1) for severe, moderate and mild patients respectively. When considering only patients born before 1986, the figures were 38.9% (95% CI: 28.8–49.0), 21.9 (95% CI: 7.6–36.2) and 12.5 (95% CI: 1.0–24.0) for severely, moderately and mildly affected patients respectively.

Data about HCV infection were reported for 56.4% of patients with HB enrolled in the registry. The percentage of infected patients were 60.4% (95% CI: 52.3–68.6), 51.1 (95% CI: 40.8–61.4) and 32.6 (95% CI: 23.0–42.2) for severe, moderate and mild patients respectively. When considering only patients born before 1987, the figures were 65.9% (95% CI: 57.6–74.2), 68.7 (95% CI: 57.5–79.8) and 58.8 (95% CI: 45.3–72.3) for severely, moderately and mildly affected patients respectively. One patients with severe HB born after 1987 was positive for HCV (7.7%, 95% CI: 0.0–22.2). He presented other likely sources of infection.

Von Willebrand's disease

Patients with VWD are stratified as type 1 (1208, 73.1%), type 2 (346, 21.1%; 135 type 2A, 64 type 2B, 128 type 2M and 19 type 2N) and type 3 (96, 5.8%).

Age at diagnosis shows a progressive increase up to 40 years for VWD type 1, while a more constant rate can be observed for VWD type 3 (Fig. 2, bottom panel). Median (interquartile range) age at diagnosis was 25.0 (12.0–37.0) years for type 1 and 11.5 (2.2–31.0) for type 3 patients with VWD. The mode of age

at diagnosis was 5 for type 1 and 1 for type 3 patients with VWD.

Six inhibitors were recorded in 96 type 3 patients (6.2%). No inhibitors were found in other VWD types.

Discussion

Registries are often used to optimally manage genetically determined chronic diseases [28]. As an example, cystic fibrosis is usually managed through registries built up and run with the same scopes and methodology of the present Italian haemophilia registry [29,30]. In the haemophilia field, one of the first registries was set up in UK as early as in 1967 by 36 HTC (National Haemophilia Database) [31]. The UK database collates complete data on all new diagnoses of coagulation disorders, treatment, complications, viral transmission and mortality rates [4–7,32]. The database is regularly used for statistics on patients, healthcare planning and research. It is also used to advise the UK Department of Health and, in collaboration with the Purchasing and Supplies Agency, to inform, plan and audit a national tendering exercise for recombinant FVIII (rFVIII) products, and to advise the Health Department on the budget needed to support the switch of patients from plasma derived to rFVIII.

Another example is the Canadian registry (CHR) [33], operated by the Association of Hemophilia Clinic Directors with the support of the Canadian Association of Nurses in Hemophilia Care and the Canadian Hemophilia Society. The initial objective, in 1988, was to ascertain the number of patients with HA and HB; subsequently other data were added, including hepatitis C and HIV antibody status, the VWD registry and, recently, patients with rare bleeding disorders. Data are submitted anonymously by the 24 Canadian HTCs and updated annually. The clinic-based computer system, called CHARMS (Canadian Hemophilia Assessment and Resource Management System) and installed in all clinics, has been programmed in parallel and harmonized with the registry. The latter is used for epidemiological surveillance, planning research projects, evaluation of viral infections, causes of death and lobbying governments for resources. It has also aided in the struggle for compensation of patients with transfusion-transmitted virus infections [10,15,20]. Other national haemophilia registries are currently serving the haemophilia community [23,34–39].

The AICE chose to develop an information system network intended to collect data on patients with haemophilia and allied coagulation disorders both retrospectively and prospectively. The registry regularly updates information on patient demographics and clinical and laboratory phenotypes pertaining to 2697 patients with HA and 573 with HB. The prevalence and severity distribution of the disease is comparable to that of other European populations, even if the Italian registry still lacks a proportion of mild patients. The overall prevalence of HA (all degrees of severity) in the Italian registry is 0.95 per 10 000 males, while it is 2.06 in the UK database and 1.47 in the Canadian database. The prevalence of HB is 0.20 in the Italian database, 0.40 in UK and 0.36 in Canada. The prevalence of severe HA is 0.48 and 0.42 per 10 000 males in the Italian and Canadian registries, while for moderate HA they are 0.14 and 0.16 respectively. The prevalence of severe HB is 0.08 and 0.09 in the Italian and Canadian registries [32,40–43]. To our knowledge, no data are published from the UK registry about the prevalence of severe HA and HB. However, it appears that all the three registries cover a similar proportion of severe patients, while both the UK (older and based on a capillary network of HTC) and the CHR (serving a smaller population in the context of a very efficient epidemiological setting) collect a higher percentage of mild and moderate patients.

A puzzling finding in the Italian registry was that a significant proportion of patients, even severe ones, was apparently diagnosed later than expected, i.e. in the first few years after birth. A possible explanation is that in the past it was not unusual for a few patients to remain misdiagnosed or undiagnosed until they were referred to an HTC. For the data on HIV and HCV infections, it should be noted that the figures refer to the subpopulation of tested patients, and for these reasons percentages were given with their confidence intervals. Assuming that all the remaining patients with no information about infection status were negative and not yet recorded in the registry, the figures calculated on the subpopulation of tested patients must be considered the worst case scenario, i.e. likely to be higher than the actual ones. The seven cases of HCV infection found in patients born after 1987 occurred in patients treated with plasma or cryoprecipitate outside Italy (six patients with HA) or with other likely sources of infections (one patient with HB). In comparing the prevalence of HIV and HCV infection before and after the introduction of virally safe concentrates one must take into account also the higher early mortality rate for HIV-infected patients, which accounts at least in part for the higher prevalence of HCV infection in the total population. Unfortunately, registry data on

mortality causes are yet sparse and not enough to draw definite conclusions at the moment.

The Italian registry shares several characteristics with other aforementioned registries. It was conceived, planned and realized within the network of the AICE HTCs, it is not an initiative prompted by a regulatory agency, mainly or only aimed at cost control scopes. The principal objective of the registry is to develop a tool planned to be fully embedded in the routine daily clinical practice of each participating HTC. It was implemented as an open structure, and is currently being interfaced with several regulatory databases (i.e. the ISS-runned registry for surveillance of plasma-derived concentrates, the Ministry of Health National Database for rare disorders) and has a declared willingness to serve as health policy instrument. Finally, the Italian registry also shows a strong commitment to foster the continuous update of patients records, and heavily relays on web-based technology for most of its activities, i.e. data collection and clearance, report validation and spreadout [17,27,44].

From the research standpoint the Italian registry has the goals, within the frame of AICE-driven projects, to describe the natural history of haemophilia, to investigate epidemiological trends in demographic and clinically relevant outcomes, and to allow cross-match of information coming from multicentre studies (i.e. inhibitor phenotype characterization and genotyping of the population) by systematic use of the registry identifier. Clinical trials and epidemiological surveys now carried out in Italy include the registry identifier as a key to maximize the yield of any research project and to permit investigators to cross-match different sets of selected information.

The registry presents all the limitations of observational cohort studies, i.e. the risk of selection and inception bias, the absence of a concurrent control group, the non-randomized nature of intra-database subgroups comparisons and the retrospective nature of any inferential analysis performed on the database [28]. Another important limitation of the registry is the voluntary nature of underlying activities, left to the personal initiative of each HTC and to the resources that they are able to mobilize and devote to the project. As a matter of fact, only the centralized phase of data merging, clearing and reporting is managed through a grant issued by an Italian haemophilia patient organization. However, the Italian Ministry of Health, through the ISS, has repeatedly prompted local health authorities to facilitate data collection activities.

Finally, the Italian HTC directors chose to try to improve data yield and quality by two complementary action plans. The first one is to identify specific objectives to be reached in the next future (i.e. complete ascertainment of inhibitor cases and input of genetic mutations to the database). The second is to prompt the evolution of the system to allow patients to directly input their own data (mainly infusion and hemorrhage records) through a secured web-based application.

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Disclosures

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

References

1 Mannucci PM, Tuddenham E. The hemophilias – from royal genes to gene therapy. *N Engl J Med* 2001; **344**: 1773–9.
2 Evatt BL, Black C, Batorova A, Street A, Srivastava A. Comprehensive care for haemophilia around the world. *Haemophilia* 2004; **10**: 9–13.
3 Evatt BL. World Federation of Hemophilia Guide to Developing a National Patient Registry. *World Federation of Haemophilia* 2005. Available at http://www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/Registry_Guide_2005.pdf. (last accessed 07.09.2007).
4 Darby SC, Kan SW, Spooner RJ *et al.* The impact of HIV on mortality rates in the complete UK haemophilia population. *AIDS* 2004; **20**: 525–33.
5 Darby SC, Ewart DW, Giangrande PL *et al.* Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. *Lancet* 1997; **350**: 1425–31.
6 Darby SC, Ewart DW, Giangrande PL, Spooner RJ, Rizza CR. Importance of age at infection with HIV-1 for survival and development of AIDS in UK haemophilia population. UK Haemophilia Centre Directors' Organisation. *Lancet* 1996; **347**: 1573–9.
7 Wilde JT, Lee CA, Darby SC *et al.* The incidence of lymphoma in the UK haemophilia population between 1978 and 1999. *AIDS* 2002; **16**: 1803–7.

8 Hazewinkel MH, Hoogerwerf JJ, Hesseling PB *et al.* Haemophilia patients aged 0–18 years in the Western Cape. *S Afr Med J* 2003; **93**: 793–6.
9 Kar A, Potnis-Lele M. Descriptive epidemiology of haemophilia in Maharashtra, India. *Haemophilia* 2001; **7**: 561–7.
10 Walker IR, Julian JA. Causes of death in Canadians with haemophilia 1980–1995. Association of Hemophilia Clinic Directors of Canada. *Haemophilia* 1998; **4**: 714–20.
11 Ghirardini A, Schinaia N, Chiarotti F, De BR, Rodeghiero F, Binkin N. Epidemiology of hemophilia and of HIV infection in Italy. GICC. Gruppo Italiano Coagulopatie Congenite. *J Clin Epidemiol* 1994; **47**: 1297–306.
12 Schinaia N, Ghirardini AM, Mazzucconi MG, Tagariello G, Morfini M, Chiarotti F. Clinical factors associated with progression to AIDS in the Italian cohort of HIV-positive hemophiliacs. G.I.C.C. Gruppo Italiano Coagulopatie Congenite. *Thromb Haemost* 1994; **72**: 33–8.
13 Schinaia N, Ghirardini A, Chiarotti F, Gringeri A, Mannucci PM. Progression to AIDS among Italian HIV-seropositive haemophiliacs. Italian Group. *AIDS* 1991; **5**: 385–91.
14 Parameswaran R, Shapiro AD, Gill JC, Kessler CM. Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 2005; **11**: 100–6.
15 Arnold DM, Julian JA, Walker IR. Mortality rates and causes of death among all HIV-positive individuals with hemophilia in Canada over 21 years of follow-up. *Blood* 2006; **108**: 460–4.
16 Triemstra M, Rosendaal FR, Smit C, Van der Ploeg HM, Briet E. Mortality in patients with hemophilia. Changes in a Dutch population from 1986 to 1992 and 1973 to 1986. *Ann Intern Med* 1995; **123**: 823–7.
17 Arts DG, De Keizer NF, Scheffer GJ. Defining and improving data quality in medical registries: a literature review, case study, and generic framework. *J Am Med Inform Assoc* 2002; **9**: 600–11.
18 Szucs TD, Offner A, Kroner B, Giangrande P, Berntorp E, Schramm W. Resource utilisation in haemophiliacs treated in Europe: results from the European Study on Socioeconomic Aspects of Haemophilia Care. The European Socioeconomic Study Group. *Haemophilia* 1998; **4**: 498–501.
19 van Aken WG. The need for a national blood product monitoring system: role of hemophilia registries. *Transfusion* 1995; **35**: 540–1.
20 Walker I, Pai M, Akabutu J *et al.* The Canadian Hemophilia Registry as the basis for a national system for monitoring the use of factor concentrates. *Transfusion* 1995; **35**: 548–51.
21 Saad S, Rowley G, Tagliavacca L, Green PM, Giannelli F. First report on UK database of haemophilia B mutations and pedigrees. UK Haemophilia Centres. *Thromb Haemost* 1994; **71**: 563–70.
22 Belvini D, Salviato R, Radossi P *et al.* Molecular genotyping of the Italian cohort of patients with hemophilia B. *Haematologica* 2005; **90**: 635–42.
23 Fernandez-Lopez O, Garcia-Lozano JR, Nunez-Vazquez R, Perez-Garrido R, Nunez-Roldan A. The spectrum of mutations in Southern Spanish patients with hemophilia A and identification of 28 novel mutations. *Haematologica* 2005; **90**: 707–10.
24 Green PM, Waseem NH, Bagnall RD, Giannelli F. Mutation analysis and genetic service: the construction and use of national confidential databases of mutations and pedigrees. *Genet Test* 1997; **1**: 181–8.
25 Mukherjee S, Mukhopadhyay A, Chaudhuri K, Ray K. Analysis of haemophilia B database and strategies for identification of common point mutations in the factor IX gene. *Haemophilia* 2003; **9**: 187–92.
26 Dimichele D. In praise of long-term prospective data collection: questions and perspectives. *J Thromb Haemost* 2004; **2**: 1044–6.
27 Al-Shahi R, Warlow C. Using patient-identifiable data for observational research and audit. *BMJ* 2000; **321**: 1031–2.
28 Bolton-Maggs PH. Haemophilia – paucity of evidence, ways forward? *Blood Coagul Fibrinolysis* 2003; **14**: S7–9.
29 Leal T, Reychler G, Mailleux P, Gigi J, Godding V, Lebecque P. A specific database for providing local and national level of integration of clinical data in cystic fibrosis. *J Cyst Fibros* 2007; **6**: 187–93.
30 Metha G, Sims E, Culross F, McCormick J, Mehtha A. Potential benefits of the UK Cystic Fibrosis Database. *J R Soc Med* 2004; **97**: 60–71.
31 Hay CR. The UK Haemophilia Database: a tool for research, audit and healthcare planning. *Haemophilia* 2004; **10 (S3)**: 21.
32 Darby SC, Keeling DM, Spooner RJ *et al.* The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977–99. *J Thromb Haemost* 2004; **2**: 1047–54.
33 Walker I. The Canadian Hemophilia Registry. *Haemophilia* 2004; **10**: 21–2.
34 Lindvall K, Swedenborg N. UMAS Hemophilia Database. *Stud Health Technol Inform* 2006; **122**: 853.
35 Awidi AS. Inherited bleeding disorders in Jordan: an update of a 25 year registry. *Pathophysiol Haemost Thromb* 2006; **35**: 152.
36 Watling M. The European acquired haemophilia registry. *Blood Coagul Fibrinolysis* 2004; **15**: S29.
37 Kar A, Potnis-Lele M. Haemophilia data collection in developing countries: example of the haemophilia database of Maharashtra. *Haemophilia* 2004; **10**: 301–4.
38 Krebs H, Domsch C, Adelhard K *et al.* The national GTH haemophilia registry as database within the scope

of the German human genome project. *Hamostaseologie* 2003; **23**: 18–23.
39 O'Connor GI, Temperley IJ. A database for a National Haemophilia Centre. *Clin Lab Haematol* 1996; **18**: 195–200.
40 National Statistics. *Population Trends*. Hampshire, UK: Office for National Statistics; 2001. Available at: http://www.statistics.gov.uk/downloads/theme_population/PT106_v1.pdf (last accessed 07.09.07).
41 Canadian Hemophilia Registry – Factor VIII. *Haemophilia A*. 2007. Available at: http://fhs.mcmaster.ca/chr/2007_Reports/CHRVIII070427.pdf (last accessed 07.09.07).
42 Canadian Hemophilia Registry – Factor IX. *Haemophilia B*. 2007. Available at: http://fhs.mcmaster.ca/chr/2007_Reports/CHRIX070427.pdf (last accessed 07.09.07).
43 Statistiche demografiche ISTAT. Roma, Istituto Nazionale de Statistica; 2006. Available at: http://demo.istat.it/pop2006/index.html (last accessed 07.09.07).
44 Baker RI, Laurenson L, Winter M, Pritchard AM. The impact of information technology on haemophilia care. *Haemophilia* 2004; **10**: 41–6.

Appendix A. Co-authors of the study

All the Italian Hemophilia Centres Association sites participating at the registry programme are listed below, in alphabetical order with mention of the HTC director and of any other investigator directly involved in the project.

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