European Journal of Epidemiology (2019) 34:521–532
https://doi.org/10.1007/s10654-018-0468-7

DATA RESOURCES

FranceCoag: a 22-year prospective follow-up of the national French cohort of patients with inherited bleeding disorders

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Received: 29 June 2018 / Accepted: 20 November 2018 / Published online: 5 December 2018

Abstract
FranceCoag is an ongoing open prospective multicentre cohort project aimed at improving epidemiological knowledge about inherited bleeding disorders in France. The main objective of this article was to evaluate the project's progress as of the 30th December 2016. Between 1994 and this date, of the 10,047 patients included in the study, 384 (3.8%) were reported by clinicians to have died and 159 (1.6%) to be lost to follow-up. Among the remaining 9504 patients still being followed up, 5748 (60.5%) had haemophilia A, 1300 (13.7%) haemophilia B, 1980 (20.8%) von Willebrand Disease while 476 (5.0%) had another clotting factor deficiency (Factor I, II, V, combined V and VIII, VII, X, XI and XIII). The median age of the population was 32 years (Inter-quartile range (IQR) 18–50 years) at data extraction on December 30th, 2016. The subgroup of children (i.e., < 18 years old) with severe haemophilia and comprehensive information available since the first exposure to treatment was identified as the PUPs (Previously Untreated Patients) cohort. Data for the 643 children included in the PUPs' cohort had been collected since their birth. Follow-up data were collected by the clinicians in haemophilia treatment centres (HTC) every 12.9 months on median (IQR 11.4–21.3). In the PUPS cohort, data were updated every 6.2 months on median (IQR 3.7–11.7). A unique patient number assigned at study inclusion was kept at individual HTC by participating clinicians. The data collected included demographic, clinical, therapeutic and biological items on standard electronic forms. As of December 30th 2016, a plasma and serum samples was available for 2581 patients (27.1%).

Keywords Haemophilia · Rare inherited disease · Risk factor · Inhibitor · Prophylaxis

Introduction

The national French cohort project was set up in 1994 by the French National Institute of Health and Medical Research (Inserm) [1], to ensure pharmaco-epidemiological follow-up of patients with the most severe forms of haemophilia. This X-related recessive disease results from a deficiency in one of the proteins physiologically essential for coagulation (Factor VIII (FVIII) for haemophilia A (HA) and Factor IX (FIX) for haemophilia B (HB)). Patients experience recurrent episodes of bleeding with varying frequency, depending on the extent of the FVIII or FIX deficiency [severe form (< 1%), moderate form (1–5%), and mild form (5–40%)]. Bleeding usually occurs in muscles (haematoma) and joints (haemarthroses), and less frequently in more high-risk and possibly life-threatening locations (intracranial, organ and gastrointestinal bleeding, etc.). Repeated intravenous injections of anti-haemophiliac factor (AHF) replacement preparation is the standard treatment to prevent bleeding. However, this treatment exposes patients to risks, and consequently close monitoring is required. Until the late 1980s, infections transmitted by AHF of human plasma origin represented a major risk, mainly due to human immunodeficiency virus (HIV), viral hepatitis B (HBV) and viral hepatitis C (HCV). AHF concentrates available since the early 1990s (virus-inactivated plasma factors and recombinant factors, produced by genetic engineering) are devoid of these risks. However, careful surveillance is

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still required and remains a goal of FranceCoag, as the risk of transmission of infectious agents such as prions in the case of Creutzfeldt-Jakob disease and other emerging agents cannot be ruled out. Therefore, a protocol of enhanced neurological surveillance of patients with unusual neurological symptoms was implemented in 2015 as part of the FranceCoag cohort framework.

Currently, the most serious and common known complication of AHF treatment is inhibitor development (whereby an antibody directed against therapeutic FVIII or FIX inhibits their function). This complication has potentially devastating consequences on patient health, and also constitutes a major health economics issue. However, the non-genetic risk factors related to treatment type and to medical care protocol for patients treated with AHF remained highly debated and challenging issues during the two last decades. Accordingly, FranceCoag aims to identify and characterize the risks of inhibitor development and other possible adverse effects on patient health [2].

In 2003, the cohort study population was extended to exhaustively include all patients with inherited bleeding disorders having similar healthcare pathways, in order to improve epidemiological knowledge of these disorders and to assess clinical practices.

FranceCoag is fully funded by the French Ministry of Health. The French medical data protection authority approved its protocol. The project is supervised by a steering committee comprising healthcare professionals (including clinicians, pharmacists, biologists and geneticists) from haemophilia treatment centres (HTC), representatives of the French ministry of health, public healthcare agencies, research institutes and the national healthcare system users' association. Scientific experts and clinical research assistants (CRAs) contributing to the quality improvement of FranceCoag are also members of the committee.

Between 2004 and 2016, the coordinating team was located in Santé publique France (SpF), the national public health agency. Since January 2017, the cohort has been managed by Marseilles' University Hospital (Assistance-Publique - Hôpitaux de Marseille - AP-HM).

The objective of this article was to evaluate the project's progress and principal published results as of the 30th December 2016.

Cohort design

Population and recruitment

FranceCoag project is based on an open prospective cohort. From 1994 to 2002, only patients with haemophilia (HA or HB, including HB Leyden) were included. From 2003, after the cohort's objectives were amended, all patients with inherited clotting factor deficiency and meeting the following inclusion criteria became eligible:

- HA or HB with an FVIII or FIX level < 40% (patients < 18 years old with an FVIII/FIX level < 2% and for whom data has been recorded since their birth comprise the PUPs (Previously Untreated Patients) cohort)
- Type 2 or 3 von Willebrand Disease (vWD) and the most severe forms of type 1 vWD (von Willebrand factor antigen level < 30%)
- Afibrinogenemia (FI level < 0.2 g/l)
- Combined FVIII and FV deficiency (level < 30%)
- FXI deficiency (level < 20%)
- Other rare clotting factor deficiencies (FII, FV, FVII, FX, FXIII) with a level < 10%.

Almost all HTC (n = 33/36) identified by the national network of professionals healthcare in France territory (i.e., mainland France and French overseas territories) participate in the FranceCoag project. The participating HTC include all the 29 centres acknowledged by the French Ministry of Health as the main ones to be part of the national network for rare diseases related to: 1/the reference centre for haemophilia and allied rare bleeding disorders; 2/the reference centre for vWD. As of 30th December 2016, three of the initial 36 HTC were no longer active in FranceCoag (Fig. 1) but most of their patients were included and followed up in other participating HTC.

Clinicians from participating HTC include patients immediately upon deficiency diagnosis. In France, written consent is not required for such an observational study. Accordingly, clinicians provided an information leaflet to all patients (parents/legal guardians for children) presenting the cohort project's objectives and procedure, in accordance with the Helsinki Declaration.

Follow-up procedure

Patient follow-up in FranceCoag occurs as part of their usual medical care pathway trajectory. However, it is recommended that data be transmitted to the coordinating team at least once a year for the most severe forms of the diseases (i.e., those characterised by the total or near-total absence of coagulating factor in plasma, making them the most likely candidate to be treated according to a long term prophylactic regimen (e.g. severe haemophilia, vWD type 3, afibrinogenemia, FXIII deficiency)). For less severe forms (e.g. mild/moderate forms of haemophilia or vWD) presenting few spontaneous episodes of bleeding, the frequency of visits can be reduced to once every 2–3 years or even longer, as these patients do not feel the

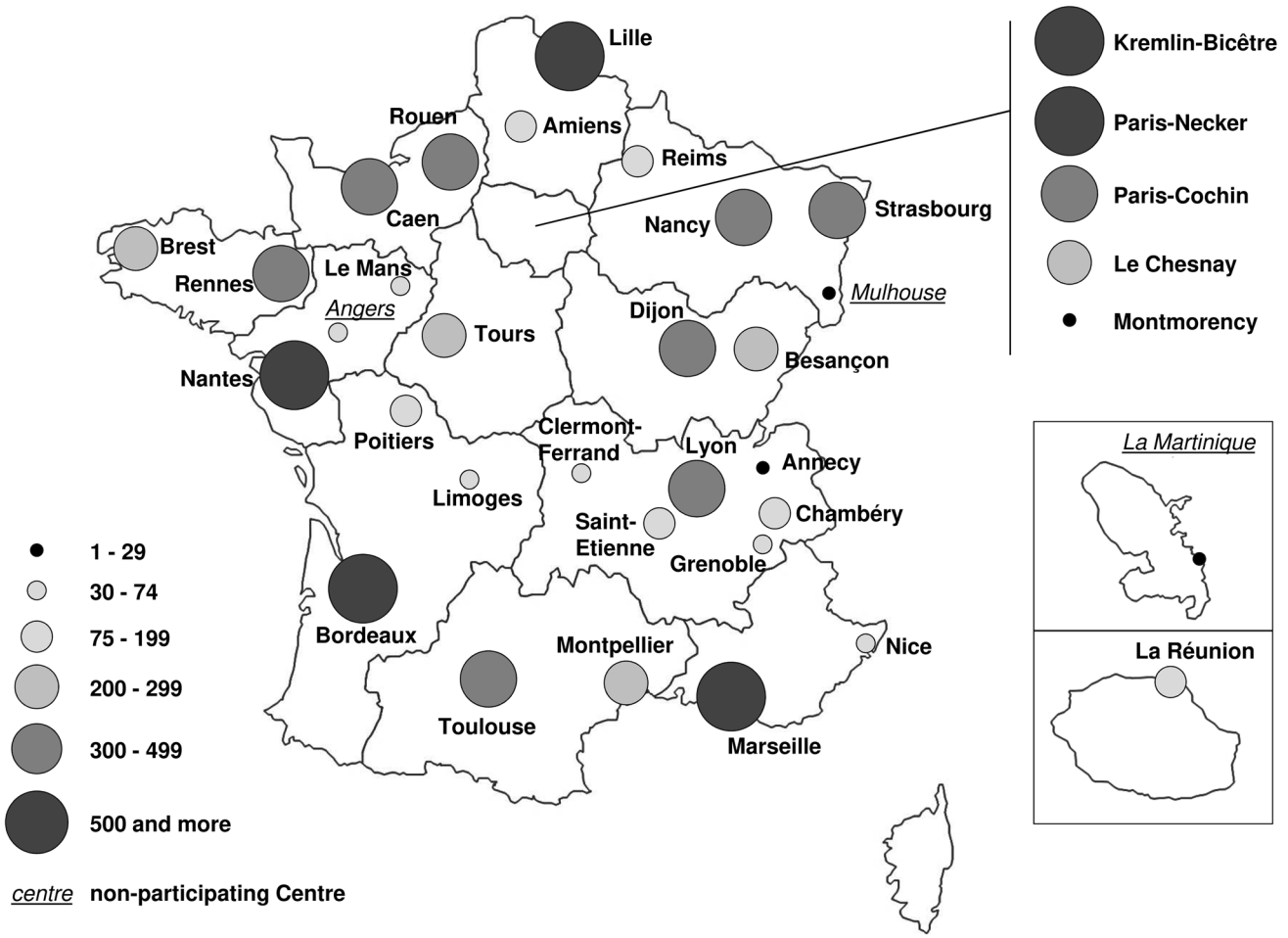

Fig. 1 Geographical distribution of the 9504 patients followed in the FranceCoag cohort as of 30th December 2016. Thirty-three haemophilia treatment centres (HTC) followed up 9504 patients. The total number of patients included in FranceCoag to that point were 10,047, of whom 384 (3.8%) were reported by clinicians to have died and 159 (1.6%) to be lost to follow-up (e.g. moved abroad, underwent liver transplant, did not respond to notifications to attend HTC). Some of the patients from three HTC no longer participating in the cohort were included and followed up in the other HTC

need for regular medical consultation. In the PUPs cohort, follow-up is encouraged from every three months till 150 cumulative exposure days of treatment by FVIII or FIX concentrates and then once a year. At 18 years of age, PUPs join the adult cohort.

The coordinating centre helps to improve the quality of follow-up by actively searching for patients with no information in the previous 3 years. It informs the HTC, and encourages the latter to actively seek out these patients in order to update their follow-up data. In accordance with applicable legislation in France, patients are entitled to exercise their right to leave the cohort at any point. However, this rarely occurs since only 2 patients did so in the first 22 years of follow-up (1994–2016).

Principal data collected

Data are collected using standard forms and cover various areas (demographic, clinical, genetic and biological information). Table 1 summarises the main information collected over the three following periods:

- 1994–2002: Data collection among patients with haemophilia only (Case Report Form).
- 2003–2009: Data collection among all patients, including those with vWD and other inherited bleeding disorders (electronic Case Report Form).
- From 2010 to present: Data collection with a more detailed electronic Case Report Form (with no change in inclusion criteria).

Table 1 Main data collected for patients followed in the FranceCoag cohort

Data type	Variables	Patients concerned by data collection over the following periods[a]		
		1994–2002	2003–2009	From 2010
Data collected at inclusion only				
ID	Unique patient number[b]	All	All	All
Demographic data	Date of birth/Gender	All	All	All
	Place of residence/Twins	–	All	All
	Ethnic origin	–	PUPs	PUPs
	Delivery maternity ward category	–	–	All
Clinical data	Deficiency type/Circumstances and date of diagnosis of the deficiency/Family history of haemophilia and inhibitors	All	All	All
	Haemophilia severity	–	–	All
Description of treatment received before inclusion in FranceCoag and a history of inhibitor development	Date of treatment initiation/treatment type/Number of days of injections	All	All	All
	Date and number of exposure days at the date of inhibitor detection/First and maximum titre of the inhibitor/History of immune tolerance	All	All	All
	Product injected on detection of inhibitor	–	–	All
History of diseases requiring long-term treatment but unrelated to the deficiency at inclusion		–	–	All
History of infection	Parvovirus B19/HAV/HBV/HCV/HIV[c]	All	All	All
Gene mutation		–	PUPs	PUPs
At each follow-up visit: Major events having occurred since the previous visit				
Level of schooling		–	PUPs	PUPs
Therapeutic treatment received	Treatment type/Number of days of injections and of units	All	All	All
	Date of first injections over the period	All	–	All
	Detailed description of the first 75 infusions[d]	–	–	All
Person administering the infusions	Professional/Father/Mother/Patient/Other	All	PUPs	PUPs
Treatment regimens	Prophylaxis regimen/Immune tolerance induction	All	All	All
	Treatment on demand	–	–	All
Detailed posology of prophylaxis and immune tolerance	Date of initiation, injection frequency and dose	–	PUPs	PUPs
Central venous devices	Insertion and removal of implantable chamber	All	PUPs	PUPs
	Cause for removal	–	PUPs	PUPs
Bleeding events	Surgical procedures (date and type) Central nervous system or life-threatening bleeding	All	All	All
Joint status	Haemarthrosis/Pednet score	–	PUPs	PUPs
Number of days in hospital		–	PUPs	PUPs
Haemostasis tests	Deficiency factor baseline level/Inhibitor assays	All	All	All
Description of discovery of the inhibitor	Number of EDs at the date of inhibitor detection	All	All	All
	Circumstances of the discovery	–	PUPs	All
	Circumstances likely to have triggered appearance Product injected upon detection of the inhibitor	–	–	All
Infectious status	New HAV or Parvovirus B19 infection[c]	All	All	–
	New HBV, HCV, HIV infection[c]	All	All	All
	Date and results of the most recent PCR-HCV[e]/ Treatment for Hepatitis C virus/Followed up by a hepatologist	–	–	All
Vaccination		All	PUPs	PUPs

Table 1 (continued)

Data type	Variables	Patients concerned by data collection over the following periods[a]		
		1994–2002	2003–2009	From 2010
Diseases requiring long-term treatment but unrelated to the deficiency at inclusion		–	–	All
Unexplained neurological symptoms appeared or aggravated		–	–	All
Patient lost to follow-up		–	All	All
Patient death	Date and causes of death	All	All	All
	Symptom of a neurological disease 6 months before follow-up	–	–	All

[a]All: information recorded for all cohort patients/PUPs: Information recorded only for patients in the PUPs cohort

[b]In the event of change of treatment centre, the patient keeps the ID allocated for reasons relating to data confidentiality

[c]Hepatitis A, Hepatitis B, Hepatitis C, Human immunodeficiency virus

[d]Additional data collected outside the computer application as part of an ancillary project

[e]Polymerase chain reaction detecting Hepatitis C virus RNA

Moreover, a biological blood sample collection was compiled over two distinct periods (note: blood samples harvesting for further banking has completely stopped since 2011):

- Between 1994 and 2000, serum, plasma and mononuclear cell straw preparations were collected from 1332 patients with haemophilia.
- Between 2008 and 2011, plasma and mononuclear cell straw preparations were collected from 1650 patients with bleeding disorders.

In addition to the agreement of applicable regulatory authorities, an ethical review of the protocol for the creation of the bank of blood samples demanded that written consent be provided for each collected blood sample.

Data management

FranceCoag data is kept in a centralized unique secure database. Data are transmitted by clinicians from the different HTC through a dedicated website in accordance with the security standards approved by the French medical data protection authorities. Confidentiality is ensured by a unique patient number (ID) assigned at study inclusion and stored in HTC by the relevant study clinician over the whole follow-up period. This ID remains unchanged even if the patient is later followed by another HTC, thereby ensuring patients can always be identified, not directly within the database, but via the HTC's workers.

Data quality control includes validity checks (i.e., the elimination of duplicates while saving data), additional automated inconsistency checks, and standard monitoring procedures (mainly through comparisons with patient records in hospitals, performed by CRA). These quality control procedures contain validation of gene mutations and identification of inhibitors by experts. Given that patients' full medical records are available at the HTC, additional information can be collected about certain health events, for the requirements of future studies (see Table 1—first 75 infusions). As regards clotting factor levels and inhibitor testings, the biological analyses are performed in the context of usual care, in the local laboratory associated to each HTC. Each lab of the French network uses an Internal Quality Control and participates to an external quality assurance. The local assessment of precision, both within and between run stands for guarantees of homogeneity for biological testings and validity of results.

As of 30th December 2016, clinicians typically completed the forms in a median period of 2.2 months (Inter-quartile range (IQR) 0.8–7.2). Median inclusion time of newly diagnosed cases was also very short (1.6 months (IQR 0.5–4.5) for patients with severe haemophilia diagnosed in 2014). Data were updated every 12.9 months in median (IQR 11.4–21.3) by the HTC during medical follow-up. Children in the PUPs cohort were followed up every six months in median (6.2; IQR 3.7–11.7).

Study progress and principal published results as of 30th December 2016

This cohort provided the first descriptive elements at a national level on the French population of people with bleeding disorders: demographic characteristics, prevalence of haemophilia, patient healthcare at birth and during follow-up, as well as major complications [3–9].

On 30th December 2016, 10,047 patients had been included in the cohort (Fig. 2), corresponding to a follow-up of 71,515 person-years.

Since 2009, the average inclusion rate has been stable with 42.8 new patients per month (standard deviation 4.2). For HA, HB, vWD and other bleeding disorders, the corresponding rates are 22.5, 5.5, 12.1, and 2.6 new patients per month, respectively.

Demographic characteristics

Three-hundred and eighty-four (3.8%) cohort participants were reported to have died between 1994 and 2016, with only 159 (1.6%) reported by clinicians as lost to follow-up (e.g. moved abroad, underwent liver transplant, did not respond to notifications to attend HTC). Therefore, in 2016, 9504 patients were considered as being followed up in FranceCoag (Fig. 1). The demographic characteristics of this population are provided in Tables 2 and 3.

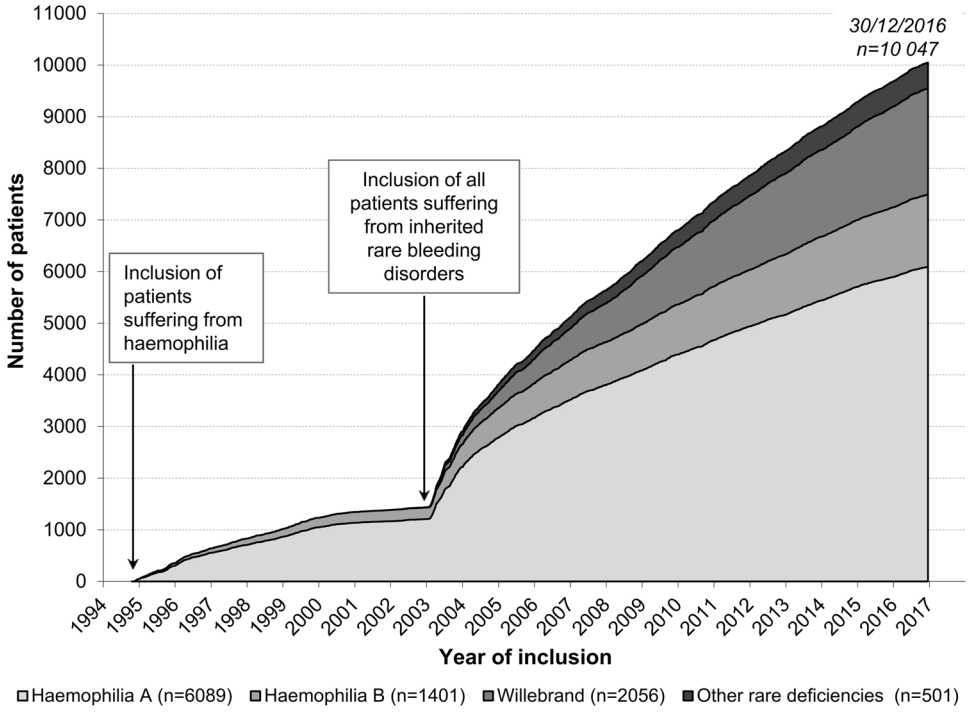

Fig. 2 Total number of patients included in the FranceCoag cohort between 1994 and 2016. This figure shows the timeline for inclusions in the FranceCoag cohort between October 1994 and December 2016. Four disease subgroups are shown: Haemophilia A, Haemophilia B, von Willebrand Disease and other rare deficiencies (FI, FII, FV, combined FV and FVIII, FVII, FX, FXI and FXIII). As of the 30th December 2016, 10,047 patients had been included in the FranceCoag cohort. From 1994 to 2003, only patients with haemophilia (A or B) were included. From 2003 onwards, the inclusion criteria were extended to include all patients with an inherited coagulation protein deficiency

Table 2 Demographic characteristics of patients with haemophilia followed up as of 30th December 2016

Bleeding disorder	All, (n)	Age[a], (years)		Gender, n (%)		PUPs[c], n(%)
		Median	IQR[b]	Male	Female	
Haemophilia A[d]	5748	31	17–49	5528 (96.2%)	220 (3.8%)	598 (10.4%)
Severe	1849	28	15–43	1842 (99.6%)	7 (0.4%)	541 (29.3%)
Moderate	803	33	17–49	797 (99.3%)	6 (0.7%)	57 (7.1%)
Mild	3089	33	19–52	2882 (93.3%)	207 (6.7%)	–
Haemophilia B[e]	1300	30	16–48	1212 (93.2%)	88 (6.8%)	121 (9.3%)
Severe	395	30	15–44	392 (99.2%)	3 (0.8%)	102 (25.8%)
Moderate	356	32	17–51	350 (98.3%)	6 (1.7%)	19 (5.3%)
Mild	548	30	16–50	469 (85.6%)	79 (14.4%)	–
All Haemophilia	7048	31	17–49	6740 (95.6%)	308 (4.4%)	719 (10.2%)

[a]Age calculated on 30th December, 2016

[b]Interquartile range

[c]Previously untreated patients: children suffering from haemophilia A or B with Factor VIII or IX activity < 2%

[d]Seven indeterminate severities

[e]One indeterminate severity

Table 3 Demographic characteristics of patients with von Willebrand Disease or other bleeding disorder followed up as of 30th December 2016

Bleeding disorder	All, (n)	Age[a], (years)		Gender, n (%)	
		Median	IQR[b]	Male	Female
Von Willebrand Disease	1980	36	19–53	877 (44.3%)	1103 (55.7%)
Other coagulation defects	476	35	20–55	226 (47.5%)	250 (52.5%)
Afibrinogenemia	40	29	15–52	21 (52.5%)	19 (47.5%)
FII deficiency	1	1	–	1 (100.0%)	–
FV deficiency	50	35	19–46	23 (46.0%)	27 (54.0%)
Combined FV and FVIII deficiency	12	33	17–49	5 (41.7%)	7 (58.3%)
FVII deficiency	155	31	21–46	68 (43.9%)	87 (56.1%)
FX deficiency	23	41	17–69	12 (52.2%)	11 (47.8%)
FXI deficiency	170	46	25–61	81 (47.6%)	89 (52.4%)
FXIII deficiency	25	22	17–41	15 (60.0%)	10 (40.0%)

[a]Age calculated on 30th December, 2016

[b]Interquartile Range

Patients with haemophilia constituted three quarters of the cohort. Women represented 4.4% of patients with haemophilia, most being haemophilia carriers with an FVIII or FIX level in the range]5%-40%[(i.e., mild form of haemophilia). With regard to age distribution, 1887 (26.8%) patients were < 18 years old, 719 (38.1%) of whom were being followed up in the PUPs cohort (Table 2).

Among patients with a different bleeding disorder from haemophilia, the M/F sex ratio was close to 1, as these diseases are not X-related. However, as already observed elsewhere, this ratio was less than 1 for those with vWD, as the disease is more frequently diagnosis in women (Table 3). Patients aged < 18 years accounted for 23.0% and 20.8%, respectively, of those with vWD and with a different coagulation deficiency.

Among the 9504 patients followed up (after exclusion of deaths and patients lost to follow-up, both reported by clinicians), 4142 (43.6%) had no follow-up data in FranceCoag for at least 3 years, and 2518 (26.5%) for at least 5 years. The majority of these patients had milder forms of the disease and did not feel the need for more frequent visits unlike patients with severe haemophilia. More specifically, they had few spontaneous bleeding symptoms episodes and consulted only under certain circumstances (e.g. surgery). Accordingly, 80.2% of haemophiliac patients not examined for 3 years had a mild/moderate form (Table 4). Only a minority of this patients were subsequently considered as lost to follow-up when this situation was assessed by the clinicians at the HTC level. Their characteristics in terms of sex ratio and age were comparable with the population who continued to be followed up more frequently.

Prevalence

FranceCoag data have been used to estimate the prevalence of haemophilia at birth, in particular haemophilia A, in previous studies (Table 5). Using data extraction from December 30th, 2016, the average prevalence at birth of this disease was updated through a 20 years period (1992–2012). It was estimated at 30.1 cases and 24.4 cases per 100,000 males born alive at birth, for haemophilia (HA and HB) and HA respectively. The latter was one of the highest prevalence estimates observed in industrialised countries [10, 11], suggesting that inclusion in FranceCoag was close to exhaustiveness at that point. With respect to other diseases, completeness had not yet been reached, notably for two reasons: first, as the eligibility of these diseases for inclusion in the cohort was more recent, clinicians were still focused on including patients diagnosed more than 3 years previously. Accordingly, in 2012 and 2013, 49.3% of the patients included had a diagnosis dating back more than 3 years. Second, some patients with mild forms of pathology (e.g. von Willebrand type 1) may have been followed up outside the French HTC network.

Medical care of patients

Thanks to the 22-year long follow-up, the work carried out in FranceCoag accurately described the diagnosis of haemophilia (age and circumstances), even in non-severe forms. Also, time to diagnosis of severe haemophilia was seen to improve over time (Table 5).

Data on the type of AHF concentrates used in the treatment of haemophilia helped describe AHF consumption as a function of the type of haemophilia. Accordingly, from the 2000s until end of 2016, the majority of patients with HA were treated with a recombinant FVIII concentrate, while plasma or recombinant factors remained equally distributed for patients with severe or moderate forms of HB (Table 5).

Moreover, the work of FranceCoag made it possible to assess the impact of treatment recommendations following haemophilia diagnosis. For example, it was demonstrated

Table 4 Demographic characteristics of patients with no follow-up visit form recorded for 3 years (not including patients reported as deceased or lost to follow-up) as of 30th December 2016

Bleeding disorder	Patients, n (%)			Age[a] (years)		Gender, n (%)	
	All	No follow-up visit form recorded for 3 years		Median	IQR[b]	Male	Female
All Haemophilia	7048	2964	(42,1%)	34	22–51	2815 (95.0%)	149 (5.0%)
Haemophilia A[c]	5748	2411	(41,9%)	35	22–51	2305 (95.6%)	106 (4.4%)
Severe	1849	464	(25,1%)	32	23–46	463 (99.8%)	1 (0.2%)
Moderate	803	310	(38,6%)	36	22–51	307 (99.0%)	3 (1.0%)
Mild	3089	1630	(52,8%)	35	21–52	1528 (93.7%)	102 (6.3%)
Haemophilia B[d]	1300	553	(42,5%)	33	22–51	510 (92.2%)	43 (7.8%)
Severe	395	114	(28,9%)	36	23–46	114 (100.0%)	–
Moderate	356	160	(44,9%)	34	24–53	158 (98.8%)	2 (1.3%)
Mild	548	278	(50,7%)	32	20–51	237 (85.3%)	41 (14.7%)
Von Willebrand Disease	1980	909	(45,9%)	38	22–53	404 (44.4%)	505 (55.6%)
Other coagulation defects	476	269	(56,5%)	38	23–58	125 (46.5%)	144 (53.5%)
Afibrinogenemia	40	17	(42,5%)	33	18–60	8 (47.1%)	9 (52.9%)
FV deficiency	50	28	(56,0%)	36	24–52	12 (42.9%)	16 (57.1%)
Combined FV and FVIII deficiency	12	3	(25,0%)	33	31–64	–	3 (100.0%)
FVII deficiency	155	98	(63,2%)	32	22–49	46 (46.9%)	52 (53.1%)
FX deficiency	23	12	(52,2%)	57	37–71	6 (50.0%)	6 (50.0%)
FXI deficiency	170	108	(63,5%)	42	23–62	51 (47.2%)	57 (52.8%)
FXIII deficiency	25	3	(12,0%)	18	18–41	2 (66.7%)	1 (33.3%)

[a]Age calculated on 30th December, 2016

[b]Interquartile Range

[c]Seven indeterminate severities

[d]One indeterminate severity

in the PUPs cohort that the availability of national medical guidelines on prophylaxis led to an improvement in clinical practice in France (Table 5).

Major complications

Inhibitor-based complications were effectively studied in severe HA using FranceCoag's PUPs cohort, especially through collection of detailed treatment information received in the first 75 days of treatment. More specifically, recent results published by Calvez et al. showed a significant association between the type of product infused and the risk of inhibitor development, within the recombinant class of FVIII concentrates, and between FVIII human coagulation and recombinant FVIII concentrates as well (Table 5).

The work of FranceCoag has also served to monitor infectious risk related to human parvovirus B19 (B19) (Table 5), HIV and HCV transmission. Overall, among the 10,047 patients included as of the 30th December 2016, 2204 (22.0%) were infected with HCV and 540 (6.5%) with HIV, 521 (5.2%) of the latter being co-infected with HCV. All these patients were infected before viral safety measures were implemented (in 1985 for HIV and in 1987 for HCV). No new treatment-related HIV/HCV infection was declared since 1994, the year FranceCoag was set up (unpublished observations).

FranceCoag is also part of a programme for prion-based disease risk surveillance (Creutzfeldt-Jakob and related diseases), based on a national protocol created by the French public authorities in July 2015. This protocol involves expert appraisal of the prion-based disease risk among patients presenting with unusual neurological symptoms. As of December 2016, no case had been detected (unpublished observations).

Discussion

FranceCoag is the only national, prospective, open cohort of patients with inherited bleeding disorders in France. It was set up with the triple aim to provide epidemiological evidence to public health authorities, clinicians, and patients, to contribute to pharmacosurveillance and to help to address research questions. This cohort exists thanks to the special contribution of motivated professionals from HTC and

Table 5 Principal published results from FranceCoag data

Topics	References	Year of birth	Population	Principal published results
Prevalence	Calvez et al. [10]	1991–2008	Haemophilia A	Overall: 23.3 cases per 10^5 male live births Severe forms: 8.8 cases per 10^5 male live births
Medical care of patients				
Diagnosis	Chambost et al. [14] Jousselme et al. [15]	1980–1994	Haemophilia A and B	Overall: 13,3 months (IQR: 3.2–56.5) Severe forms: 6.3 months (IQR: 0.3–10.8) Moderate forms: 13.7 months (IQR: 2.0–39.9) Mild forms: 58.9 months (IQR: 19.9–132.3)
		1980–2004	Severe haemophilia	1980–2004: 6.0 months (IQR: 0.1–10.6) 1980–1984: 8.6 months (IQR: 0.4–12.7)
Type of treatment	Institut de Veille Sanitaire [16]		Haemophilia A	Patients treated with recombinant FVIII concentrates: 1999–2001: 73% 2009–2011: 84%
Prophylaxis	Meunier et al. [17]	1996–2007	Severe haemophilia	Children ≥ 3 years old receiving prophylaxis according to year of follow-up: In 2001: 26.7% (8/30) In 2006: 79.4% (123/155) Median age at prophylaxis initiation according to year of birth for Haemophilia A and B respectively: 1996–1999: 4.0 years (IQR 3.3–6.1) and 6.1 years (IQR 2.5–6.6) 2004–2007: 1.8 years (IQR 1.3–2.3) and 1.4 years (IQR 1.1–2.7)
Major complications				
Inhibitor development	Calvez et al. [10]	1991–2013	Severe haemophilia A	High-titre inhibitors (titre > 5 Bethesda units) incidence: aHR*(second-generation full-length vs third-generation recombinant product): 1.6 (95% CI 1.2–2.1)
	Calvez et al. [18]		Severe haemophilia A	High-titre inhibitors (titre > 5 Bethesda units) incidence: aHR*(second-generation full-length recombinant vs human coagulation product): 1.64 (95% CI 0.82–3.25) aHR*(third-generation full-length recombinant vs human coagulation product): 2.81 (95% CI 1.44–5.49)
Infection	Gaboulaud et al. [19]	1994–2000	Haemophilia A and B	A higher prevalence of anti-B19 in children previously treated with solvent/detergent high-purity non-immunopurified and non-nanofiltered FVIII or IX concentrates than those treated with albumin- stabilized recombinant FVIII only (OR: 22.3; CI: 7.9–62.8), independently of the other factors studied

*Adjusted hazard ratio

patients. The professionals involved dedicate part of their time to the collection and improvement of data, and collaborate with epidemiologists in scientific projects to improve knowledge, with the goal of ameliorating their own clinical practices. With respect to the patients, they regularly record the details of therapeutic products received, bleeding events, and hospitalizations in a notebook. Furthermore, their representatives promote the project and participate in the cohort's steering committee.

At the international level, FranceCoag stands out from the few existing related national cohorts, as it includes all types and severities of haemophilia cases, as well as severe forms of all inherited bleeding diseases, except platelet disorders (as these diseases represent a much more heterogeneous group). Given the prevalence of haemophilia in France, one of the highest among national registries, the Demography and Data Committee of the World Federation of Haemophilia considers FranceCoag to be an extremely valuable tool

for epidemiological knowledge. Furthermore, FranceCoag is characterized by an especially long follow-up duration (as of 30th December 2016, 22 years follow-up) assessed by a follow-up of 71,515 person-years. The PUPs cohort is relatively unique in the world, in terms of numbers, quality, follow-up frequency and detailed individual information collected for the study of immunogenicity of new treatments and the impact of recommendations. It adds great value to FranceCoag. The latter contributes significantly to furthering knowledge of the risk factors of inhibitor development. For example, at a request of the European Medicines Agency, in 2015, FranceCoag data were used with data from two other cohorts [2, 12] in a meta-analysis of inhibitor incidence (manuscript for publication in progress).

Another important strength of this cohort is its high level of data quality. Thanks to controls developed in the web application for data entry, missing data are not permitted and there are increasingly fewer inconsistent data. To maximize homogeneity of the data collected by each treatment centre, the steering committee validates all collection procedures while the CRA check their application daily. A great deal of data are collected covering various areas (including demographic, clinical, biological and genetic information) and it is possible to easily collect complementary data for a subpopulation of interest.

Since January 2017, in agreement with the national health authorities, this cohort has been managed by an academic institution (Marseilles' University Hospital/AP-HM) as part of a project supported by a consortium of national partners. Some modifications are planned, especially:

- Cross-validation with other national medical and administrative databases (e.g. the national drug and medical procedure reimbursement database, molecular genetics laboratory databases, the national rare disease reference centre for vWD database), in order to assess the exhaustiveness of patient inclusion. As a matter of fact, for certain bleeding disorders other than haemophilia, completeness has not yet been confirmed;
- Collection of patients' first and last names, in an independent database, which is a mandatory step to facilitate the identification of duplicates and to improve the real time registration of the occurrence and the causes of deaths by cross-checking with the national mortality database. Accordingly, for patients with no new data for at least 3 years, the occurrence of death will be systematically checked and relative causes analysed.
- Comprehensive description of bleeding disorders in France: as yet, patients with inherited combined deficiency of vitamin K-dependent clotting factors and inherited platelet disorders are not included in the cohort. Official ethical authorisation for the inclusion of inherited combined deficiency of vitamin K-dependent clotting factors has already been granted, and data collection is planned in a new version of the software application used in the cohort;
- Patient involvement in self-completion of certain data in forms, especially regarding global health indicators health and quality of life;
- Linkage of FranceCoag data with the French database of rare diseases [13];
- Promotion of the use of the cohort's data for research projects and the development of partnerships.

FranceCoag data are available to all researchers whose study proposal has been validated by the scientific committee and approved by the FranceCoag steering committee. The study proposal procedure is available on request. It describes the terms and conditions of the data transfer agreement. Documentation for this cohort, including the case report forms, and publications are available at (www.francecoag.org). To find out more information, please, contact the coordinating centre: francecoag@ap-hm.fr

HTC collaborators (clinicians and non-clinicians) Abgraal JF, Adjaoud D, Albinni S*, Ancelet D, Aouba A*, Arab B, Ardillon L, Barbay V, Bariller E, Barro C, Bastenaire B, Bayart S, Beaussant-Cohen S, Behar C*, Belkaïd I, Benz-Lemoine E*, Berger C, Berny K, Bertrand MA, Beurrier P*, Bianchin M*, Biernat J*, Biron-Andreani C, Blanc M*, Bodet L, Borg JY*, Boulfroy E, Bovet J*, Briquel ME*, Brouk Z, Brunot A, Castet S, Chambost H, Chaminade A, Chamouni P, Charbonneau S, Chenuel C, Coatmelec B*, Codine P, Collet B*, Combe S, Dalibard V, De Lumley L*, De Raucourt E, Demay Y, Derlon A, Desprez D, Deville A, Dieval J*, d'Oiron R, Donadel Claeyssens S, Donadio D, Douay J, Drugmanne G, Dumesnil C, Dupont de Romemont C*, Durin-Assollant A*, Dutrillaux F*, Falaise C, Faradji A*, Ferré E, Ferrer AM*, Feugeas O, Fiks Sigaud M, Fimbel B*, Fonlupt J*, Fouassier M, Frenzel L, Fressinaud E*, Frotscher B, Gaboulaud V*, Gaillard S*, Gautier P, Gay V, Gembara P, Girault S, Gleizes E, Goesin I, Gorde S*, Goudemand J, Gourou K*, Grenetier S*, Gruel Y, Guérin V*, Guérois C*, Guezet-Souibri M*, Guillet B, Harroche A, Hassenboehler J, Hassoun A, Haya-Baviera G, Henni T, Henrio C*, Hézard N, Huguenin Y, Lambert E, Lambert T, Lartigue B, Laurian Y*, Lauroua P*, Le Cam Duchez V, Leclere A, Le Guyader M, Le Niger C*, Le François A*, Legrand F*, Lienhart A, Li-Thiao-Te V, Lutz P, Macchi L, Maire C, Marichez C, Marie-Cardine A, Marlu R, Marquès-Verdier A*, Martin M, Matingou M, Mahi Y*, Mercy J, Meunier S, Micheau M*, Milien V, Molho P*, Monlibert B, Monpoux F, Monmartin A, Moreau P, Munzer M*, Navarro R, Négrier C, Nemausat N*, Nguyen P, Normand C, Nyombe P, Oudot C, Ounnoughene N, Palamaringue P, Pan Petesch B, Paris C, Parquet A*, Paugy P*, Pautard B*, Pernod G*, Pertuiset N*, Peter O*, Peynet J, Pierre-Louis S, Pignon* B, Pincemaille O*, Pineau-Vincent F, Play B*, Polack B, Pouille Lievin O*, Pouymayou K, Pouzol P*, Rafowicz A, Ramassamy A, Rauch A, Regina S*, Renom P*, Reynaud J*, Ricard C, Risch J, Robert V, Roche M, Rosay A*,Rospide P*, Rothschild C, Rousseau F, Rugeri L, Sanderson F*, Savary I, Schneider P, Schved JF, Selva J, Sénéchal P, Sicardi F*, Sie P, Soler C*, Stieltjes N, Stoven C, Sultan Y*, Susen S, Tahiri C*, Tamburro M, Tardy B, Tarral E*, Ternisien C, Thiercelin Legrand MF, Thouvenin-Doulet S, Tintillier V*, Torchet MF*, Trillot* N, Tron P*, Trossaërt M, Uettwiller F, Valentin JB, Vanderbecken S, Vannier JP*, Vassilieff D*, Vicariot M*, Voisin S, Volot F, Voyer A, Wibaut B, * Collaborators no longer involved in FranceCoag cohort.

Funding FranceCoag is supported by French public health authorities.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest related to this description of the FranceCoag cohort.

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