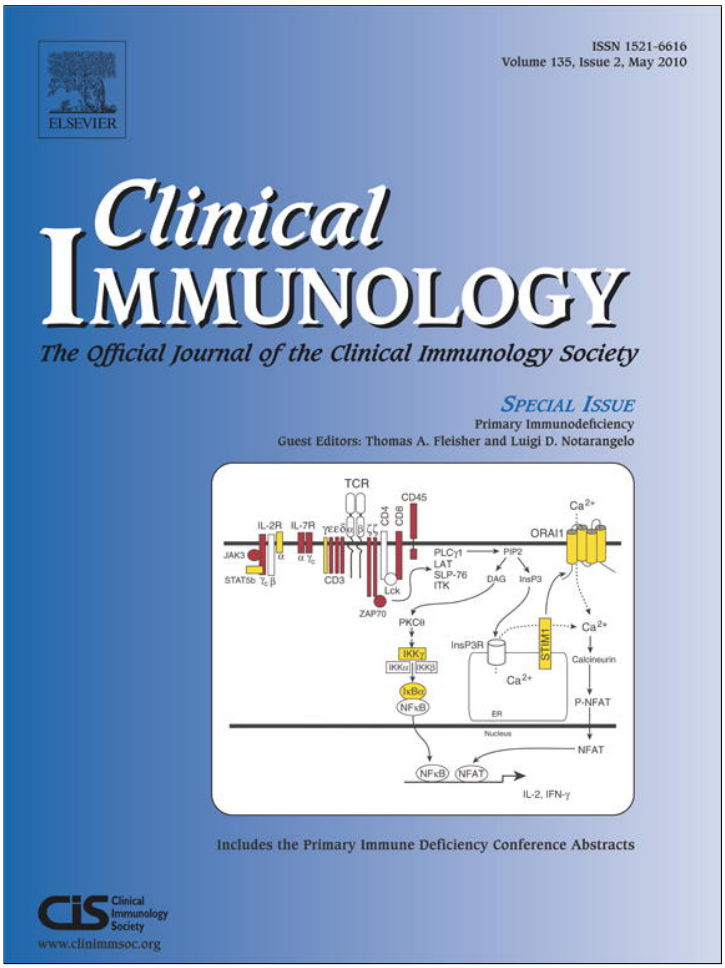

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The French national registry of primary immunodeficiency diseases

CEREDIH: The French PID study group [*,1]

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Abstract The French National Reference Center of Primary Immunodeficiencies (CEREDIH) was established in 2005 and now constitutes a nationwide network of pediatric and adult medicine departments in university medical centers. The registry comprises a total of 3,083 patients (mainly children), with an overall prevalence of 4.4 cases per 100,000 inhabitants. Predominantly B-cell immunodeficiencies are the most common diseases observed (43%). The proportion of common variable immunodeficiencies (CVIDs, 14%) is lower than reported by national registries in other developed countries. The data suggest that although referral to expert centers is fairly adequate for children, this is not yet the case in France for adults. The distribution of primary immunodeficiencies (PIDs) varied significantly across distinct geographical areas and this suggested regional differences in patient care. As the world's largest national registry of PIDs, CEREDIH provides a basis for both further studies and activities aimed at raising the physicians' awareness of PIDs (notably in adults).

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Background

Rare diseases such as primary immune deficiencies (PIDs) are increasingly being acknowledged as important medical and social issues by the health authorities and the medical community. Even though each rare disease affects a limited number of individuals (less than 200,000 individuals in the United States or, according to the European definition, fewer than 1 in 2,000 people), millions are concerned by the more than 6,000 different low-prevalence diseases identified to date [1]. In view of the scarce epidemiological data and the lack of available treatments, rare diseases are a tremendous challenge for the biomedical community [2,3]. Increasing awareness of rare diseases has prompted governments in Europe and North America to assign specific funds to rare diseases [4,5]. In November 2004, the French government put this issue on its agenda and implemented a National Plan for Rare Diseases [6]. Strategic priorities included better knowledge of the epidemiology of rare diseases, improved access to medical care and the promotion of research and innovation. The Plan also triggered the creation of a French National Center for Primary Immunodeficiencies (*Centre de Référence Déficits Immunitaires Héréditaires*, CEREDIH; www.ceredih.fr). In response to the Plan's strategic goals, the CEREDIH set up France's first National Registry of PIDs, in line with the PID registries established in other countries [7–12]. The long-term objective is to build a tool that provides retrospective and prospective data for the medical community, the health authorities and PID patients and their families, improves our knowledge of PID and raises French physicians' awareness of centers providing high-quality medical care in this field.

Methods

The CEREDIH network

The CEREDIH network was initiated in November 2005 and now comprises 58 medical departments with experience in the care of both children and adults with PID in 19 regional centers (Supplementary Table 1). All the various departments (mostly specializing in immunology, hematology, infectious diseases and/or internal medicine) are located in university medical centers. With the goal of registering all pediatric and adult PID patients in France, all immunologists, internal medicine specialists, infectious disease specialists, hematologists, lung specialists and other physicians (i) with experience in the care of PID patients (i.e. $\geq$ 5 patients for $\geq$5 years) or (ii) having attended PID meetings or (iii) having jointly or individually organized a PID clinic with an *ad hoc* immunology laboratory were contacted by the National Center and invited to collaborate within the network. The final list of participating physicians was drawn up by the CEREDIH Steering Committee (composed of 5 nationally acknowledged experts in the care of pediatric and adult PID patients, plus an immunobiologist and a biostatistician with expertise in the field of rare diseases). All diagnosed PID patients being monitored in university medical centers were thus identified. A CEREDIH member then made a site visit to collect data from the patients' medical records. For logistic reasons, centers from French overseas counties and territories were not included in this initial data collection stage. Written, informed consent was collected by the attending clinician, whereas deceased and lost-to-follow-up patients were anonymously registered. All data collection and analysis procedures were approved by the appropriate national and local regulatory authorities. Data from the existing French Registry for Severe Chronic Neutropenia [13] and the DEFicit-Immunoglobulin Study (a French nationwide study of adults with primary hypogammaglobulinemia [14]) were merged with the CEREDIH registry.

Data collection

The registry was launched in November 2005 and data collection continued until April 2009. Data were first collected on paper sheets and then entered into the European Society for Immunodeficiencies (ESID) online database (hosted by the Information Technology Center at University Hospital Freiburg (Freiburg, Germany)) [15]. The database included demographic information and key medical data such as the date of PID diagnosis, the date of symptom onset and a set of clinical laboratory results (see www.ceredih.fr for more information). These data relied on the ESID core dataset and were identical for all ESID participating centers. Collection of data on ethnicity is prohibited in France and so was not performed. Although the accuracy of PID diagnosis remained the responsibility of local physicians, all cases were validated by the CEREDIH Steering Committee. Primary immunodeficiencies were classified according to the International Union of Immunological Societies' (IUIS) criteria [16]. Given that the IUIS classifies diseases into 8 major groups and subgroups (including the so-called "autoinflammatory disorders", which are not considered to be immunodeficiencies and are not accompanied by increased susceptibility to infections or neoplasia), we simplified the classification by pooling conditions into 2 major groups. Thus, patients were referred to as having either an adaptive immune deficiency or an innate immune deficiency. Adaptive immune deficiencies encompass 2 major groups: predominantly T cell deficiencies (primarily severe combined immunodeficiencies (SCIDs)), well-defined T cell disorders, other known T cell disorders, unknown, predominantly T-cell disorders, familial hemophagocytic lymphohistiocytosis, autoimmune disorders, etc.) and predominantly B-cell deficiencies (primarily common variable immunodeficiency (CVID), agammaglobulinemia, hyper-immunoglobulin M (HIgM) syndromes and other hypogammaglobulinemias). Importantly, for patients with an IgA deficiency or IgG subclass deficiencies, only those exhibiting a clinically immunodeficient phenotype (i.e. recurrent infection, severe autoimmunity and/or neoplasia) were registered. The innate deficiencies included phagocytic disorders (severe congenital neutropenia, chronic granulomatous disease, leukocyte adhesion deficiencies, Mendelian susceptibility to mycobacterial infections, etc.) and complement deficiencies leading to increased susceptibility to infections (i.e. patients with C1 esterase inhibitor deficiency were thus not included).

Statistical analyses

Prevalence calculations were based on data provided by the French National Institute for Statistics and Economic Studies

(INSEE, http://www.insee.fr/fr/default.asp, last accessed on June 2nd, 2009). Patients aged 15 or under were categorized as children. Continuous variables are quoted as the median and interquartile range (IQR) or as the mean and standard deviation (SD). Variables were compared across groups by using the Mann-Whitney *U* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Statistical analyses were performed using SAS 9.1® software (SAS Institute Inc., Cary, NC, USA).

Results

Overall description of the French national registry of patients with PID

Between November 2005 and April 2009, 3,083 patients were registered in the database. The overall PID prevalence was estimated at 4.4 per 100,000 inhabitants (2,682 patients alive for 61,000,000 inhabitants in continental France). Predominantly B-cell and T-cell deficiencies were the most common PIDs, with prevalences of 43% and 38%, respectively (Table 1). An overview of the main PID diagnoses is given in Table 2, whereas Supplementary Table 2 provides a more detailed frequency distribution. IgA- and IgG subclass-deficient patients account for 31.3% of the patients with predominantly B-cell deficiencies. The gender distribution reflects the X-linked inheritance of some PIDs. We noticed a higher consanguinity rate than in the general population in France (below 1% [17]), reflecting the fact that most PID are rare diseases with an autosomal, recessive inheritance pattern. It is noteworthy that mutations in some of the 156 genes currently known to be associated with PIDs were found in 40% of all registered patients. Negative genetic tests may reflect a lack of information or (in most cases) as yet unidentified genetic causes (as it is the case for many B cell PIDs). Forty-two percent of all registered patients (1,112 out of 2,667) were receiving immunoglobulin (Ig) replacement therapy via intravenous infusion (74%) or subcutaneous infusion (26%). Sixty-four percent of patients with predominantly B-cell deficiencies and 31% of patients with predominantly T-cell deficiencies were undergoing Ig replacement therapy.

Distribution of patients by date of birth

The patients' distribution as a function of date of birth was then analyzed. In view of bias in survival and improvement in diagnostic accuracy over the last 30 years, most of the patients were found to be born in the last 2 decades (Fig. 1a). When this analysis was repeated in major PID subgroups, the patterns were different. For B-cell deficiencies (Fig. 1b), we observed a steady increase in identified cases between 1984 and 2000, although this finding was tempered by the fact that some B-cell PIDs (such as CVID) are mainly diagnosed in adults [18]. There were fewer patients with B-cell deficiencies born after 2000 than between 1992 and 2000. In contrast, for T-cell (Fig. 1c) and innate (Fig. 1d) immune deficiencies, the number of cases appeared to have remained fairly constant since 1988 - suggesting that most of these patients are now diagnosed and that the observed prevalence may correspond closely to the true incidence. The registry includes all patients with T cell and innate deficiencies who were cured by hematopoietic stem cell transplantation (HSCT). Overall, this suggests a steady increase in diagnosis. However, these data also point to the fact that there are still a number of patients with PID (mainly adults with predominantly B cell deficiencies) who are not diagnosed or not referred to university medical centers. A large number of patients had undergone HSCT (shaded area in Fig. 1), with a fairly constant annual rate since 1988. Most of these patients had predominantly T cell deficiencies. The patients with "B cell deficiencies" who underwent HSCT had an X-linked HIgM or immunodeficiency, centromeric region instability and facial anomalies (ICF) syndrome, which actually are also T-cell PID.

Table 1 Distribution of Primary Immunodeficiencies by main groups of diseases.

	N	%	Status (% alive)	Prevalence (/10^5 inhabitants)
Total registry	3083	100	87.0	4.40
Total adaptive	2492	80.8	86.4	3.53
B-cell deficiencies	1319	42.8	97.6	2.11
T-cell deficiencies	1173	38.0	73.7	1.42
Total innate	591	19.2	89.5	.87

Age at diagnosis and time to diagnosis

Table 3 depicts the median age at diagnosis for the different groups of PID. In the vast majority of cases, the PID was recognized during childhood (with the important and well-known exception of CVID). When analyzing the data as a function of date of birth, there appears to have been a significant reduction in the median age at diagnosis over the last 3 decades (Table 3b). In order to limit bias, we analyzed the median age at diagnosis according to the date of birth for patients born before 1998 and diagnosed before the age of 10. In fact, a significant difference was observed for T-cell immunodeficiencies only (Table 3c). A similar observation was made when analyzing median time to diagnosis, i.e. the time between disease onset and diagnosis (Table 4a-c).

Regional distribution

Based on the patients' place of residence, we determined the regional distribution of PID patients. The adjusted regional prevalence ranged from 2.1 to 6.7 per 100,000 inhabitants (Fig. 2a), with a trend towards higher values in the northern half of France. The regional distribution for PID prevalence in children $\leq$ 15 years of age showed a similar distribution, with a higher overall prevalence (Fig. 2b, range: 3.8-15.4 per 100,000 inhabitants) than in adults (Fig. 2c, range: 1.3-5.4 per 100,000 inhabitants). Significant differences between regional and national prevalence values are shown in Supplementary Table 3. Lastly, the prevalence of patients receiving Ig replacement therapy showed significant variations from one region to another, ranging from 0.74 to 4.56 per 100,000 inhabitants. The proportion of patients

Table 2 General characteristics by main Primary Immunodeficiencies diagnoses.

	N	Gender (% male)	Status (% alive)	Consang. (%)	Known Mutations (%)
Total registry	3083	58.8	87.0	15.0	40.0
Total adaptive	2492	58.4	86.4	14.3	38.1
B-cell deficiencies	1319	57.7	97.6	2.9	15.8
Agammaglobulinemia	161	95.0	99.4	4.7	72.7
CVID	441	46.9	96.6	3.4	10.2
Other hypogammaglobulinemia	654	53.1	98.6	2.5	1.7
Hyper IgM syndrome	63	85.7	90.5	0	55.6
T-cell deficiencies	1173	59.3	73.7	26.4	63.2
SCID	219	62.6	61.2	35.8	90.0
Ataxia-telangiectasia	250	49.2	62.0	27.8	76.3
Wiskott-Aldrich syndrome	139	97.1	83.5	*22.4	82.7
Hyper IgE syndrome	45	44.4	95.6	8.8	48.9
HLH	141	58.2	69.5	30.2	52.5
Autoimmune	63	61.9	90.5	12.5	74.6
Other T-cell deficiencies	316	50.3	82.6	22.8	37.0
Total innate	591	60.6	89.5	20.8	48.2
Phagocytic disorders	575	61.4	89.2	20.5	49.6
CGD	159	89.3	84.3	16.4	75.5
LAD	15	53.3	80.0	57.1	66.7
SCN	374	49.7	92.2	17.2	40.1
MSMD	7	57.1	85.7	57.1	85.7
Other phagocytic disorders	20	65.0	80.0	18.2	NA
Complement	16	31.3	100	25.0	NA

CGD: Chronic granulomatous disease.
Consang.: Consanguinity.
CVID: Common variable immunodeficiency.
HLH: Hemophagocytic lymphohistiocytosis.
LAD: Leukocyte adhesion deficiency.
MSMD: Mendelian susceptibility to mycobacterial diseases.
SCID: Severe combined immunodeficiency.
SCN: Severe congenital neutropenia.
NA: Not available.
*18/28 of patients with consanguineous parents were part of 2 families.

treated with subcutaneous (rather than intravenous) Ig therapy also varied greatly from one region to another (Fig. 2d) and ranged from 0% to 51.2%.

Comparison with other published national registries

The French data on the prevalence of PIDs in general and the major patient subgroups were then compared to the values reported in other countries where a PID national registry has been set up (Table 5). However, it must be born in mind that the registry methodologies differed from one country to another, with different data collection methods and the inclusion of centers with variable degrees of expertise in the care of immunodeficient patients. Major PIDs were assessed according to the classification used at the CEREDIH. The overall prevalence of PIDs was found to range from 2.5 (Ireland) to 5.3 per 100,000 inhabitants (Norway). The prevalence of CVID (0.7 per 100,000 inhabitants in France) ranged from 0.55 (Spain and Israel) to 2.1 (Norway). The prevalence of predominantly T cell disorders was 1.4 in France and 1.6 in Israel and ranged from 0.18 to 0.53 in other national registries.

Discussion

Here, we report on the distribution of PIDs in France for the first time. To the best of our knowledge, the French National Reference Centre for PIDs (CEREDIH) holds the largest national registry ever constituted. The CEREDIH registry is based on systematic, comprehensive in-situ data collection from university medical centers in continental France. In each center, all physicians known to have expertise in the care of children and adult patients with PID contribute to the registry within the very comprehensive CEREDIH framework. However, some physicians who care for PID patients outside these centers may have been missed. The CEREDIH network was set up in November 2005 and now encompasses 58 medical departments from 19 different regional centers distributed throughout continental France. We believe that this registry provides a fairly accurate representation of the

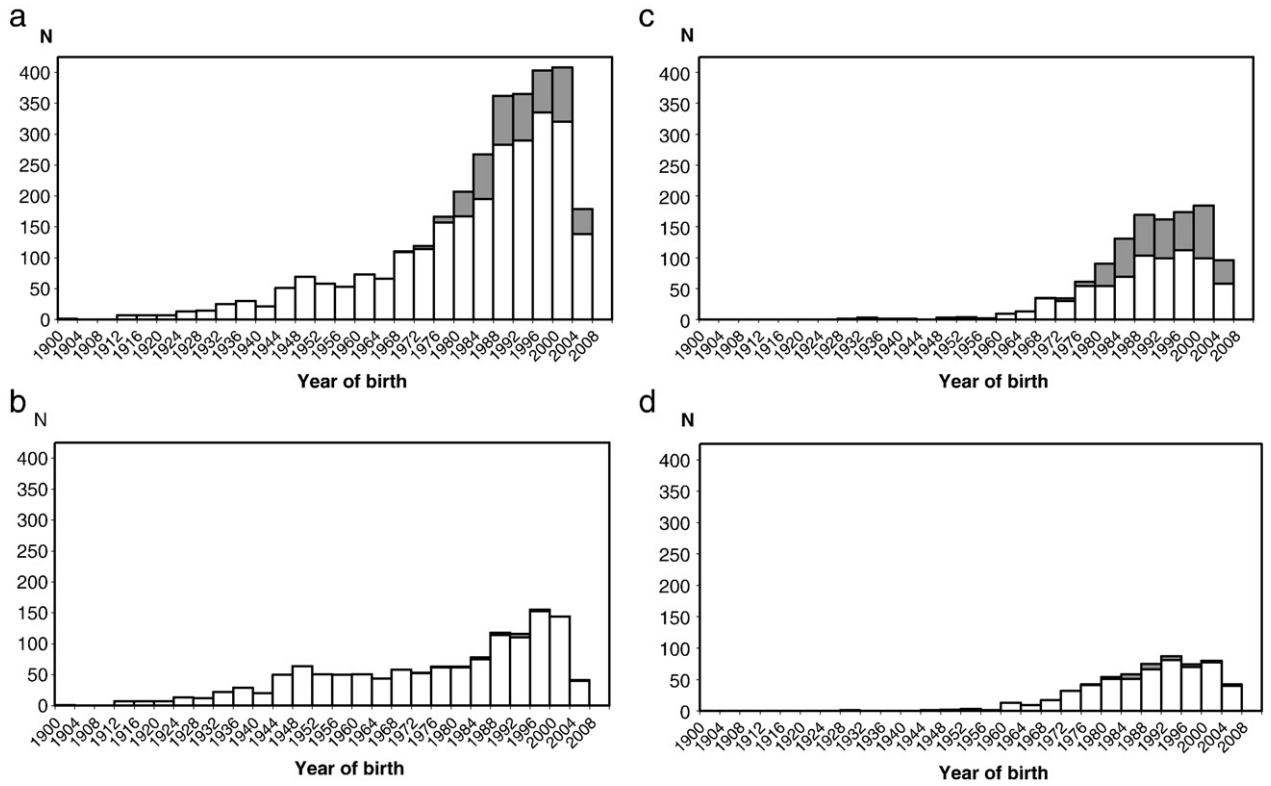

Figure 1 Distribution of patients with PID as a function of the year of birth. The proportion having undergone hematopoietic stem cell transplantation is shown by the shaded area. a. all PIDs (n=3,083), b. predominantly B-cell deficiencies (n=1,319), c. predominantly T-cell deficiencies (n=1,173), d. innate immunity deficits (n=591).

prevalence of PID patients receiving adequate diagnostic and therapeutic care in France. The data suggest a steady increase in PID diagnosis in France, with the notable exception of adult patients. Importantly, our registry analysis suggests that the prevalence of predominantly T cell immunodeficiencies and innate immune deficiencies will soon equate to the incidence.

It is remarkable to see that the overall prevalence of PIDs in France is similar to the values observed in other countries which have built a national registry, despite the presence of methodology differences [7–11]. Indeed, for all previous studies other than the Norwegian registry [12], the proportion of living patients was not reported. With a view to enabling further European-level studies, the data on French patients was entered in the ESID online database and then retrieved for analysis. At the time of writing, there were 10,279 patients registered in the ESID database [19], one third of whom come from France [15]. The overall prevalence in France was found to be consistent with (i) a previous local study based on the systematic collection of medical records in one county in Minnesota in the USA [20] and (ii) an international South American study [21]. Overall, these data differ from the estimation of 83 per 100,000 inhabitants made in a USA-based phone survey [22]. Although there are no clues to explain this very significant difference, we believe that based on age distribution, the European and Australian registry data are likely to provide a more realistic view of PID occurrence. Nevertheless, assessment of the prevalence of the major groups of PID shows that the observed prevalence of CVID in France is only about one third to one half of what was found in Norway or Australia. In contrast, the prevalences of other PIDs are variously higher than or similar to the Norwegian and/or Australian values. Inter-registry variability is also reflected by the relatively low observed prevalence of PIDs in adults in France. This difference is unlikely to reflect genetic disparity in France versus the inhabitants of Norway or Australia - particularly since CVID appears to be a genetically heterogeneous condition [18]. In fact, we believe that this disparity is related to either non-optimal referral of patients with PID to university medical centers and/or underdiagnosis of these conditions in France, with some regional variability (see below). However, when looking at the patients' age distribution and the decrease in age at diagnosis, it is clear that major improvements have occurred over the last few years. It will be important to assess the impact of family history on age at diagnosis and this analysis is now planned within the CEREDIH registry.

We are aware that there may have been data collection issues for adult patients with CVID. However, it is probable that these patients were not being cared for by physicians meeting the registry's criteria (see the Methods section). For B-cell deficiencies, data on the median age at diagnosis (Table 3) show a difference between patients born before

Table 3 Age at diagnosis.

a. Median age at diagnosis by group of diseases

	N	Median at diagnosis (years) age	Q1	Q3
Total	2648	3.3	.7	10.8
Total adaptive	2160	4.4	1.0	13.6
B-cell deficiencies	1099	9.3	3.2	32.6
Agammaglobulinemia	144	2.0	1.1	5.3
CVID	373	33.4	17.1	47.6
Other hypogammaglobulinemia	522	6.2	3.2	14.7
Hyper IgM syndrome	60	2.4	.8	6.1
T-cell deficiencies	1061	1.6	.4	5.6
SCID	203	.4	.2	.6
Ataxia-telangiectasia	244	5.5	2.9	8.1
Wiskott-Aldrich syndrome	124	.8	.3	2.0
Hyper IgE syndrome	40	4.0	1.3	6.7
HLH	126	1.0	.2	3.9
Autoimmune	45	5.6	.9	10.9
Other T-cell deficiencies	279	1.4	.3	5.6
Total innate	488	1.1	.3	3.6
Phagocytic disorders	474	1.1	.3	3.3
CGD	119	1.9	.7	5.4
LAD	14	.3	.2	1.1
SCN	318	.9	.2	2.3
MSMD	5	1.6	1.1	4.3
Other phagocytic disorders	18	2.9	.5	9.6
Complement	14	8.5	4.2	17.2

b. Evolution of median age at diagnosis by date of birth

	Before 1980	1981-1990	1991-2000	After 2000	p
Total registry	27.2	2.7	2.5	.9	<10-4
B-cell deficiencies	37.9	7.8	5.0	2.1	<10-4
T-cell deficiencies	7.2	2.0	1.5	.5	<10-4
Total innate	1.6	1.3	1.1	.7	<10-4

c. Evolution of median age at diagnosis by date of birth for patients with a diagnosis made before age of 10 and born before 1998

	Before 1983	1984-1988	1989-1993	1994-1998	p
Total registry	2.7	1.3	1.9	2.3	<10-2
B-cell deficiencies	4.9	3.7	3.9	4.9	NS
T-cell deficiencies	3.6	.9	1.5	1.3	<10-4
Total innate	1.0	.5	1.3	.9	NS

1980 and those born in subsequent decades. However, this difference was not present when the analysis was restricted to patients diagnosed below the age of 10. Given that CVID is diagnosed later in life, this finding might reflect a difference in the composition of the cohort, with a higher number of CVID patients born before 1980 and fewer born in subsequent decades.

Based on the patients' place of residence, the regional prevalence of PIDs was heterogeneous, with up to 3-fold variations from one region to another. This type of difference was also observed in the Norwegian, Spanish and Australian registries, with a higher prevalence in urban areas. There may be several explanations for this, including inadequate reporting. An uneven distribution of mutations in a given set of genes in distinct populations or an uneven distribution of populations with a high consanguinity rate are less likely explanations. In the CEREDIH registry, there was no obvious regional predominance of given sets of PIDs for patients with the same mutation. Furthermore, populations with distinct ethnic origins are fairly well dispersed across France. However, we were unable to verify this point because the collection of ethnic data is prohibited in France. Nevertheless, we believe that the heterogeneous distribution of PIDs is explained by a combination of misdiagnosis and lack of referral of diagnosed cases to university medical centers. In both instances, the quality of patient care is unsatisfactory. It will be important to determine the reasons for underrepresentation in the registry and to try to remedy this situation. It is our intention to perform in-depth surveys in selected regions of France by contacting physicians from

Table 4 Time to diagnosis.

a. Median time to diagnosis by group of diseases

	N	Median time to diagnosis (year)	Q1	Q3
Total registry	2516	1.0	.3	4.2
Total adaptive	2043	1.3	.3	5.1
B-cell deficiencies	1040	2.5	.7	7.8
Agammaglobulinemia	140	1.0	.4	3.3
CVID	356	6.0	1.3	15.0
Other hypogammaglobulinemia	487	2.3	.7	5.2
Hyper IgM syndrome	57	.9	.3	3.0
T-cell deficiencies	1003	.6	.2	3.1
SCID	201	.2	.1	.3
Ataxia-telangiectasia	202	2.9	1.3	6.0
Wiskott-Aldrich syndrome	124	.5	.2	1.4
Hyper IgE syndrome	39	1.5	.4	4.7
HLH	123	.2	.1	1.0
Autoimmune	44	2.1	.2	5.8
Other T-cell deficiencies	270	.7	.2	4.0
Total innate	473	.5	.1	1.1
Phagocytic disorders	459	.4	.1	1.1
CGD	114	.9	.3	3.0
LAD	14	.2	.1	1.0
SCN	310	.3	.1	.8
MSMD	5	.4	.3	.6
Other phagocytic disorders	16	.4	.1	4.7
Complement	14	2.8	.4	8.0

b. Evolution of median time to diagnosis by date of birth

	Before 1980	1981-1990	1991-2000	After 2000	p
Total registry	3.7	1.0	.8	.4	<10-4
B-cell deficiencies	5.6	2.6	1.8	1.0	<10-4
T-cell deficiencies	3.6	.8	.6	.2	<10-4
Total innate	.6	.5	.4	.3	<10-2

c. Evolution of median time to diagnosis by date of birth for patients with a diagnosis made before age of 10 and born before 1998

	Before 1983	1984-1988	1989-1993	1994-1998	p
Total registry	1.0	.5	.7	.8	<10-2
B-cell deficiencies	2.3	1.4	1.0	1.5	NS
T-cell deficiencies	1.7	.4	.5	.6	<10-4
Total innate	.5	.4	.6	.2	NS

non-university medical centers and those working in private practice and thus achieving more comprehensive reporting in these areas. In order to improve the detection of patients receiving immunoglobulin replacement therapy, further information could be retrieved from hospital pharmacies (the only ones in France authorized to deliver these medicines).

Registries are being increasingly acknowledged as powerful tools for enhancing our knowledge of many features of disease (especially rare diseases), such as epidemiology, natural history, access to care and improvements in healthcare. We firmly believe that the French CEREDIH PID registry will serve as a useful indicator of whether advances in PID care are taking place. Regional prevalences, the percentage of patients with a determined gene mutation, age at diagnosis and time to diagnosis are valuable markers for assessing these improvements. We also hope that this type of analyses could be performed at a broader level (at least Europe-wide); this endeavor would be facilitated by the implementation and use of a common database.

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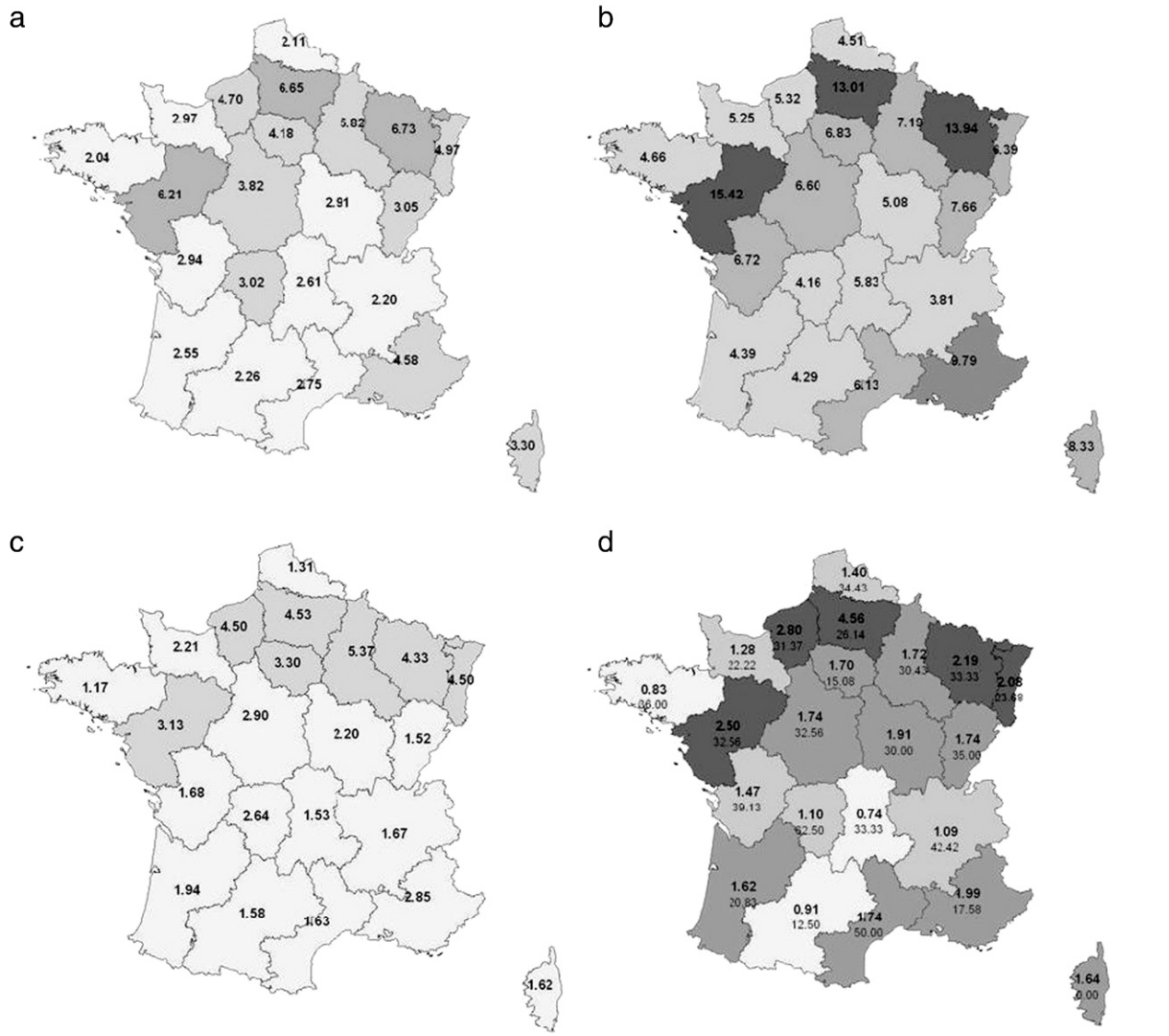

Figure 2 Regional distribution of PIDs. The adjusted prevalence is given per 100,000 inhabitants and for each administrative region. a. all ages, b. ≤15y., c. >15y., d. immunoglobulin replacement (subcutaneous/(intravenous+subcutaneous) in %).

Table 5 Estimated prevalences of major PID in six national registries (/105 inhabitants).

	Spain	Norway	Israel	Ireland	Australia	France
	1997 [3]	2000 [4]	2002 [5]	2005 [6]	2007 [7]	2009
	N=1015	N=237	N=292	N=99	N=1153	N=2682
Total registry	2.61	5.33	4.87	2.48	4.67	4.40
Total adaptive	2.37	4.02	3.15	1.73	4.40	3.53
B-cell deficiencies	1.94	3.55	1.55	1.55	3.87	2.11
CVID	.55	2.11	.58	.70	1.88	.70
Other hypogamma.	1.21	1.06	.55	.00	1.51	1.06
T-cell deficiencies	.42	.47	1.60	.18	.53	1.42
Total innate	.24	1.30	1.72	.75	.27	.87

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clim.2010.02.021.

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