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The European Society for Immunodeficiencies (ESID) Registry: recent advancements in the epidemiology of Primary Immunodeficiencies and how does that translate in clinical care

Nizar Mahlaoui [1,2,3], Benjamin Gathmann [4], Gerhard Kindle [4], Stephan Ehl [4], on behalf of the ESID Registry Working Party Steering Committee (Isabella Quinti, Italy, Bodo Grimbacher, Germany, Matthew Buckland, United Kingdom, Markus Seidel, Austria, Joris van Montfrans, The Netherlands) and the ESID Society.

[1]Centre de Référence Déficits Immunitaires Héréditaires (CEREDIH), Hôpital Universitaire Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France. [2]Unité d'Immuno-Hématologie et Rhumatologie pédiatrique, Hôpital Universitaire Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France. [3]Laboratoire de Génétique Humaine des Maladies Infectieuses, Branche Necker, Inserm U1163, Université Paris Descartes, Sorbonne Paris Cité, Institut Imagine, Paris, France. [4]CCI - Center for Chronic Immunodeficiency, University Medical Center Freiburg, Germany

INTRODUCTION

Primary Immune Deficiencies (PIDs) are a growing group of over 230 different inherited rare disorders caused by mutations in genes encoding proteins involved in the immune system. Left undiagnosed and untreated, PIDs are often chronic, serious or even fatal. The diagnosis of PIDs can be difficult due to lack of awareness and facilities for diagnosis, and management of PIDs is complex. Once recognised, these rare disorders are treatable and in some cases curable (by Hematopoietic Stem Cell Transplantation since 1968 and in some limited cases today by Gene Therapy since 2000). PID management highlights the role of specialised centres, the need for multinational research, the role of national and international patient organisations, the requirement for sustained access to all treatments including immunoglobulin (Ig) therapies and HSCT, which are important considerations for developing countries in terms of management and treatment options. Epidemiological data on PIDs are scarce highlighting the importance of national and international registries (such as the European Society for Immunodeficiencies (ESID) registry). Registries provide insight not only for healthcare professionals but also for patients and for healthcare policies makers, services and government agencies, particularly to ensure that PID patients world-wide have access to appropriate and sustainable medical and support services.

CORRESPONDING AUTHOR:

Dr. Nizar Mahlaoui , MD, MSc, MPH
Tel. +33 1 44 49 46 22
Fax: +33 1 44 49 46 25
Mail: nizar.mahlaoui@nck.aphp.fr

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METHODS

Since 2004, ESID (www.esid.org) runs a European-wide online registry for PID. The ESID Registry is based on contributions from the following national registries: CEREDIH (France), REDIP (Spain), PID-NET (Germany), UKPIN (UK), IPINET (Italy), AGPI (Austria), the Netherlands, Czech Republic. Additional contributions are received from the following countries: Turkey, Poland, Ireland, Portugal, Belgium, Switzerland, Slovakia, Sweden, Slovenia, Croatia, Serbia, Greece, Belarus, Russia, Hungary, Romania, Ukraine, Estonia, Lithuania, Egypt, Israel. In 2014, the technical backbone and user interface have been overhauled. All patients are now documented once per year and a three level registration concept has been implemented: Level 1 is mandatory for all centers participating in the registry project and aims at basic epidemiological features with yearly updates on survival and treatment. A genetics module will be implemented to be filled in by the genetics laboratories for consistent terminology. Level 2 foresees more detailed clinical and laboratory information and centers can choose to participate in certain disease categories according to their resources for documentation and scientific interests. Level 3 provides a platform for projects targeting individual diseases in even more detail. Level 3 studies have a defined endpoint (number of patients and/or period of observation) and offer opportunities for industry collaborations. Criteria for the clinical diagnosis of PID with unknown genetic cause have been elaborated and have to be confirmed for patients at registration. Built-in checks now validate all fields for consistency and completeness, and users are guided through the data entry process. Additional datasets are being programmed, data links to the Spanish and Italian registries have to be created, and the software will be "rolled out" to the UKPID and LASID registries. Importantly, data output for the centres will be extended, including an automatized annual report with benchmarking figures of the centre relative to national and European figures.

RESULTS

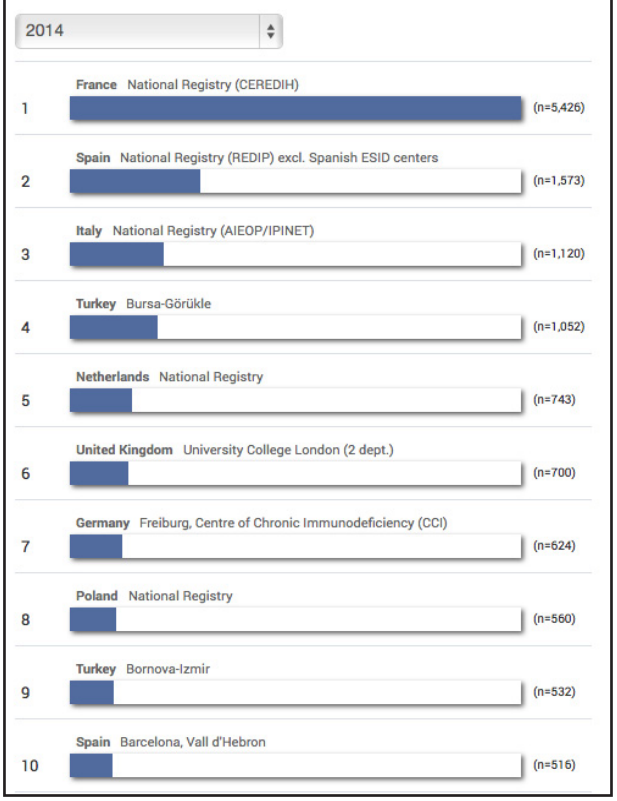
As of May 2014, the ESID Registry is the largest registry worldwide with 19,366 patients (both children and adults, see **Fig 1a and 1b**). Clinical diagnostic criteria have been developed for patients lacking a genetic diagnosis allowing an increased level of data quality. Data transfer from the original system to the new revised registry platform requires individual validation of these criteria.

Data on PID diagnosis both clinical and genetic, familial cases, consanguinity, presenting symptoms, diagnostic delay, type of treatments received (allowing a prospective data entry and follow-up), date of last news, clinical status… are available. Level 2 includes biological data for quality control (consistency of diagnosis with laboratory abnormalities), data monitoring and follow-up. The registry also encompasses data on therapy; especially on Ig replacement therapy, which is a lifelong maintained therapy for a majority of patients (see **Fig 1c**).

In a recently published study (1), registry analysis allowed to identify factors affecting the clinical presentation, association between clinical features, and differences and effects of immunoglobulin treatment in Europe in the most important group of PIDs (CVID, Common Variable ImmunoDeficiency). The data showed that and how patients with CVID are being managed differently throughout Europe, affecting various outcome measures.

PIDs are recognised as rare conditions and data on epidemiology of PIDs is scarce, although many countries across the EU and worldwide have implemented registries for PIDs. An example is the national registry established in France in 2005; the Reference Centre for PIDs (CEREDIH) runs the largest national PID registry worldwide, with dedicated and highly trained staff. It is based on a tight network of all university teaching hospitals, with 130 clinicians and at least 30 diagnostic immunology laboratories. National registries are important tools for assessing the proportion of affected individuals among the general population (prevalence) as well as measuring the number of new cases diagnosed each year (incidence), detection of areas of low diagnosis rates and provision of insights on diagnostic delay associated with increased morbidity and mortality. The registry also provides in-

Fig. 1a. Number of patients entered in the ESID Registry as of Jun. 25th, 2014 (only the first 10 centers are displayed, for more information, please visit www.esid.org)

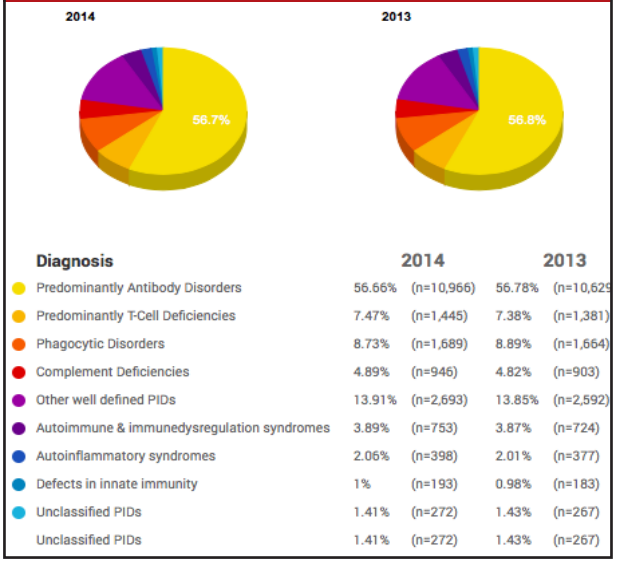


formation that is helpful to governments regarding estimates of those not diagnosed to aid planning of educational programs and provision of treatments and their costs. Presentation of this data to pharmaceutical industries helps to ensure that the supply of medical products meets demand. Thus a national registry is an important tool for health policy makers, stakeholders and health insurers, enabling plans for allocation of therapies and the development of innovative treatments, as also demonstrated in the UK Demand Management Plan. Prevalence of PIDs is at least 6 in 100,000 inhabitants although data provided by the ESID Registry shows variability most likely linked to lack of data entry is several countries (due to lack of manpower and money dedicated to data registration). Minimal incidence is still not accurately known but might be close to 1:3000 to 1:4000/year. These key indicators are useful especially in setting the frame for a pan-European newborn screening for Severe Combined ImmunoDeficiencies (including health economics).

CONCLUSION

Based on the ESID registry, more registries (local, regional or national) have been implemented in Europe and abroad, showing wider interest in the field and in this approach in trying to address clinical and scientific questions, suggesting that registries for rare diseases are widely considered as a valuable part of the toolbox to increase knowledge in the field (2).

Fig. 1b. PID main diagnostic categories of patients entered in the ESID Registry as of Nov. 15th, 2014.



Diagnosis	2014		2013	
Predominantly Antibody Disorders	56.66%	(n=10,966)	56.78%	(n=10,625
Predominantly T-Cell Deficiencies	7.47%	(n=1,445)	7.38%	(n=1,381)
Phagocytic Disorders	8.73%	(n=1,689)	8.89%	(n=1,664)
Complement Deficiencies	4.89%	(n=946)	4.82%	(n=903)
Other well defined PIDs	13.91%	(n=2,693)	13.85%	(n=2,592)
Autoimmune & immunedysregulation syndromes	3.89%	(n=753)	3.87%	(n=724)
Autoinflammatory syndromes	2.06%	(n=398)	2.01%	(n=377)
Defects in innate immunity	1%	(n=193)	0.98%	(n=183)
Unclassified PIDs	1.41%	(n=272)	1.43%	(n=267)
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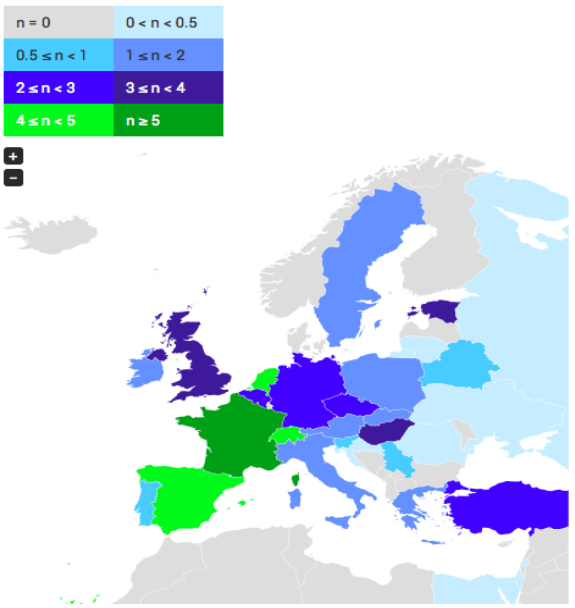
Fig. 1c. Frequency of Immunoglobulin replacement therapy (including route of administration) in the ESID Registry as of Jun. 25th, 2014.

2014

Additional statistics:	2014	
How many alive patients** overall are on Ig replacement?	(n=6,476)	50.36%
... alive patients** on IVIG	(n=4,239)	32.96%
... alive patients** on SCIG	(n=2,181)	16.96%
... alive patients** on IMIG	(n=22)	0.17%
Total number of alive patients**:	(n=12,860)	100%

**Alive patients with no information on therapy are excluded from this evaluation.

Fig. 2. Minimal prevalence map of PIDs in Europe (prevalence/100,000 inhabitants)



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