J Clin Immunol (2013) 33:1–7
DOI 10.1007/s10875-012-9751-7

ORIGINAL RESEARCH

Primary Immunodeficiency Diseases Worldwide: More Common than Generally Thought

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Received: 13 April 2012 / Accepted: 24 July 2012 / Published online: 31 July 2012

Abstract
Purpose Primary immunodeficiency diseases (PIDs) comprise at least 176 hereditary disorders that are thought to be individually and collectively rare. The actual prevalence and incidence of PIDs remains unclear, but recent epidemiologic studies have suggested that PIDs are more common than generally thought. Based on these studies, we attempted to estimate the worldwide prevalence and incidence of PIDs.
Methods Using data from registries and two recent epidemiologic surveys estimating the frequencies of PIDs, we extrapolated the frequencies reported for certain countries to the populations of continents and of the world.
Results Our upper estimates suggest that six million people may be living with a PID worldwide, whereas only 27,000–60,000 have been identified to date (all national registries and the Jeffrey Modell Centers Network, respectively). For Europe, our upper estimate was 638,000 cases, and 15,052 cases are currently registered (2.27 %). In Africa, up to 902,631 people may have a PID, whereas only 1,016 cases are currently registered. We also found that PIDs were prevalent not only in children, but also in adults, who were strongly underrepresented in registries.
Conclusion Specific, dedicated epidemiologic studies are required, to obtain more realistic statistics for PIDs and to increase the awareness of physicians and public health systems about these diseases. Furthermore, the field of PIDs is continually growing, and this is likely to lead to a revision of the definition of these conditions, potentially increasing estimates of their impact on both adults and children, at the population level.

Keywords Primary immunodeficiency · prevalence · incidence · mortality

Electronic supplementary material The online version of this article (doi:10.1007/s10875-012-9751-7) contains supplementary material, which is available to authorized users.

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Introduction

Primary immunodeficiencies (PIDs) constitute a large group of diseases, including at least 176 conservatively defined hereditary disorders [1] affecting the development of the immune system, its function, or both [2]. The number of known PIDs has increased considerably over the last 20 years, through two lines of research: the genetic dissection of known clinical phenotypes and the investigation of new clinical phenotypes [2–6]. Some of these clinical phenotypes are more common than traditional PID phenotypes.

In particular, new PIDs conferring a specific predisposition to infections with one or a few pathogens have been described [7], including genetic predisposition to EBV, *Neisseria*, papillomavirus, *Streptococcus pneumoniae*, weakly virulent mycobacteria, herpes simplex virus, and *Candida albicans* [8–15]. Mendelian predisposition to tuberculosis has even been reported [16, 17]. In addition, various non infectious phenotypes, as diverse as allergy, angioedema, hemophagocytosis, autoinflammation, autoimmunity, thrombotic microangiopathy and cancer, have been shown to result from inborn errors of immunity, in at least some patients [3]. The discovery of these new PIDs, infectious and otherwise, may necessitate a revision of previous estimates of the frequency of PIDs in the general population.

Meanwhile, conservatively defined PIDs are commonly thought to be individually and collectively rare. Rare diseases are defined as having an incidence of less than 1/2,000 live births in the EU [18] or a prevalence of less than 200,000 patients in the US. However, it remains unclear whether the prevalence and incidence of PIDs have been estimated accurately. Many studies, based on different methodologies, have attempted to estimate the prevalence of PIDs in various countries and have generated inconsistent results. For example, the most recent estimates obtained were 5.38/100,000 inhabitants in France in 2011 [19], 5.6/100,000 in Australia in 2007 [20], and 1.94/100,000 in the UK in 2011 [19]. These estimates of prevalence were based on data from registries (as defined below) and seem to be much lower than recently reported estimates based on specific population surveys in the US, such as the telephone survey carried out by Boyle & Buckley (prevalence of 86.3/100,000 inhabitants) [21] or the Mayo Clinic epidemiologic study by Joshi (incidence estimated at 10.3/100,000 person-years in recent years) [22]. We extrapolated these findings to the overall populations of continents, to assess the worldwide impact of PIDs and to evaluate the gap between our estimates and the number of registered cases in the regions concerned.

Methodology

We carried out a literature search on PubMed, using the keywords “incidence”, “prevalence” and “primary immunodeficiency”, to obtain the most recent and relevant data concerning PID prevalence and incidence. We narrowed down our search by considering only articles published in the last 10 years. We identified 169 articles, from which we selected those that appeared to be the most relevant [20–26]. Most of the available PID statistics are based on data from registries [19, 20, 23–26]. We assigned the highest priority to articles on registry data for entire continents (Europe, South America, Africa). In the absence of continental registries, we selected articles concerning the national registries that appeared to be the largest and most representative of the corresponding continent (e.g. Australia/New-Zealand, USA, Iran, Japan). We also consulted the websites of the national and international societies for immunodeficiencies responsible for managing these registries, such as the European Society for Immunodeficiencies [19], the US Immunodeficiency Network [27], the African Society for Immunodeficiencies [28] and the Primary Immunodeficiency Database in Japan [29]. These registries collect epidemiologic and clinical data for all patients with PIDs diagnosed in the corresponding region. We summarized the data collection methods used for these registries and the types of age data available (Suppl. Table 1). Finally, we used the most recent paper published by the Jeffrey Modell Foundation (JMF) [30], which provides an independent estimate based on a survey carried out for the Jeffrey Modell Centers Network, including data from 490 physicians at 192 academic teaching hospitals and medical school in 64 countries. Center directors were asked to give the number of patients with a specific PID managed at the center, but the correctness of the diagnosis was not checked.

We also identified two specific surveys conducted in the USA that aimed to provide a more exhaustive and accurate estimate of PID frequencies [21, 22]. The first was a telephone survey in a national, random sample of ~10,000 households in the US, corresponding to a total of ~27,000 household members [21]. In this study, all adult respondents were asked: “Has anyone in your household ever been diagnosed with a primary immunodeficiency disease, such as common variable immunodeficiency, IgA deficiency, IgG subclass deficiency or any other immunodeficiency? (This is not acquired immunodeficiency—AIDS).” If the respondent answered “yes”, he or she was asked how many people in the household had a primary immunodeficiency, their age, sex and the specific type of primary immunodeficiency. This survey estimated the overall prevalence of PIDs at 86.3/100,000 inhabitants. The second survey was an epidemiologic study providing an estimate of PID incidence in the USA based on a survey in Olmsted County, Minnesota [22]. The authors made use of the exhaustive medical records established in this county as part of the Rochester Epidemiology Project to obtain data for all patients treated between 1976 and 2006 whose medical records contained at least one of the ICD (International Classification of Diseases) codes relating to PIDs. Overall incidence was estimated at 10.3/100,000 person-years for the most recent period (2001–2006).

Our principal objective was to extrapolate the estimates obtained in these two American studies [21, 22] to various populations, to assess the worldwide impact of PIDs. We used, in particular, the data from the Australia/New Zealand registry, which gave the highest estimates for prevalence

[20]. We also evaluated the difference between our estimates and the numbers of patients currently listed in registries, as a function of age at diagnosis of the patients in particular.

Results

Estimates of PID prevalence from registry data (e.g. 5.38/100,000 in France [19], 5.6/100,000 in Australia [20]) were much lower than the estimates based on the data from Boyle and Buckley's survey (86.3/100,000) [21]. We calculated the number of PID cases that would be expected to occur worldwide on the basis of these prevalence estimates (Table I). Based on the Australian prevalence figures [20], there should be 390,546 PID patients worldwide. However, if we use the estimate from the telephone survey in US [21], the predicted total number of PID patients reaches six million. The available registries (ESID, LAGID, USIDnet, North Africa, Japan, Iran and Australia/New Zealand) [19, 20, 24–27] list 27,243 cases, corresponding to only about 0.45 % the number of cases expected based on this higher prevalence estimate [21]. The number of PIDs included in the JMF study was greater (60,364), but still accounted for only 1 % of the expected cases. Table I also provides data for the number of new PID patients expected each year, based on incidence data from Joshi [22]; this number could reach 718,326 worldwide.

Despite Africa being the second most populous continent, suggesting that it should have a large number of PID cases, its registry contained the smallest proportion of cases (see Table II). Indeed, in Africa, 58,572 PID cases would be expected on the basis of the prevalence reported for the Australian registry [20], and 902,631 cases would be expected based on US telephone survey prevalence data [21]. However, the ASID registry in North Africa, with only 1,016 registered cases in 2010 [26], covered only 8.52 % of the number of cases expected from Australian prevalence data and barely 0.55 % of that expected from US prevalence data. Overall, if we take prevalence estimates from the US survey as the reference, the coverage of the available registries seems to be very low, ranging from ~5 % (France, Australia) to less than 1 % (LAGID, ASID). Furthermore, the coverage of these registries may be overestimated, as registries generally contain both patients who are still alive and those who have already died, whereas prevalence estimates consider only people currently alive. For example, the ESID registry counts only 10,814 patients who were alive in 2011 (72 % of registered cases) [19]. Finally, the age distribution of the patients included in registries is also quite variable, with most of the cases diagnosed in children (e.g. the median age at diagnosis in the French registry is 3.3 years [23]) in some registries, whereas others have a majority of adult cases (e.g. the median age from date of birth in the Australian registry is 31 years [20]). The registries aim to cover all the cases occurring in the country, but another bias is introduced according to the types of specialists registering the patients.

We investigated this age effect further, by also calculating the expected number of new PID patients per year by age group for continents, based on the incidence by age group

Table I Estimation of the frequency of PIDs worldwide

Region/country	Estimated population 2011[a]	Estimate of the number of PID patients based on a prevalence of 5.6/100,000 inhabitants[b]	Estimate of the number of PID patients based on a prevalence of 86.3/100,000 inhabitants[c]	Estimate of the annual incidence of PID, based on an incidence of 10.3/100,000 person-years[d]
Europe	739,298,975	41,401	638,015	76,148
France	63,125,894	3,535	54,478	6,502
Africa	1,045,922,624	58,572	902,631	107,730
Morocco	32,272,974	1,807	27,852	3,324
North America	347,563,355	19,464	299,947	35,799
USA	313,085,380	17,533	270,193	32,248
South America	396,680,960	22,214	342,336	40,858
Asia	4,207,447,704	235,617	3,631,027	433,367
Japan	126,497,241	7,084	109,167	13,029
Iran	74,798,599	4,189	64,551	7,704
Oceania	37,174,805	2,082	32,082	3,829
Australia/New Zealand	27,020,241	1,513	23,318	2,783
Worldwide	6,974,036,375	390,546	6,018,593	718,326

[a] Estimation drawn from World Population Prospects, the 2010 Revision [31]

[b] Number of PID patients estimated from the prevalence data for the Australian registry [20]

[c] Number of PID patients estimated from the prevalence reported for the US telephone survey (Boyle & Buckley) [21]

[d] Number of PID patients per year estimated from the incidence estimated by Joshi et al. [22]

data of Joshi et al. [22] (see Table III). According to this approach, new PID cases in patients under the age of 15 years account for only 30.6 % of all PID cases, corresponding to ~230,000 expected cases. Thus, PIDs are not exclusively diseases of infancy, because incident cases in the worldwide population of adults over the age of 25 account for more than 50 % of all PID patients, with a total of ~400,000 new cases. However, this distribution may differ considerably between regions, due to demographic differences. For example, the populations of Africa, South America and Asia are younger and pediatric cases would therefore be expected to account for 47.6 %, 30.1 % and 29.7 % of PID cases, respectively. So, in these regions, and for the region covered by the ASID registry in particular, efforts should initially focus on raising the awareness of pediatricians concerning these conditions.

From the distribution of incident cases by age group provided in Table III, we determined the distribution of the prevalent cases listed in Table II by age at diagnosis (Table IV). This second distribution is comparable with registry data for age at diagnosis. The 5–14 age group was the most strongly represented group in the ESID registry, accounting for about 12.5 % of expected cases. By contrast, strong undercoverage was observed for the group of adults over the age of 50 years, as only 0.5 % of the expected number of cases for this age group were found in the registry. Overall, pediatric cases accounted for 45.7 % of the cases in the ESID registry, when they were expected to account for less than 17 % of the cases. This suggests that the diagnosis of PIDs in adults could be improved for ESID. A similar pattern was found in Japan, with a maximum coverage of 6.6 % for the 5–14 year age group and pediatric cases accounting for 57.1 % of the registered patients but only 15 % of the cases were expected to belong this group. In Morocco, we have similar coverage for the 0–4 and 5–14 year age groups (around 3 %), and really low coverage (less than 1 %) for other age groups (15 years and over). However, this distribution is easily accounted for by the collection of data from a pediatric ward. As a result, 92.4 % of our patients are under the age of 15 years at diagnosis, whereas we would expect only 32.4 % of the patients to belong to this group.

Discussion

Are PIDs really rare diseases? The estimated incidence and prevalence reported in the results section strongly suggest that PIDs are more common than generally thought. Based on the prevalence [21] estimated from the US telephone survey, 1/1,200 living people may harbor a PID. Overall, the two US surveys [21, 22] indicate that the prevalence and incidence of PIDs are similar to those observed for diseases such as leukemia (prevalence and incidence in the USA of 81.6/100,000 and 12.5/100,000, respectively [32]). Our estimates were based on two US-specific surveys aiming to provide a more exhaustive picture of the frequency of PIDs. These two studies are subject to several limitations, as pointed out by their authors [21, 22]. However, the 95 % confidence interval for the prevalence values provided by Boyle and Buckley remains reasonable (51 to 121.5/100,000) and the incidence estimates of Joshi et al. [22] are consistent with previously reported estimates [22]. In

Table II Registry coverage of expected prevalence and patient characteristics

Region/Country	Estimated prevalence[a]	Registry[b]	Registry coverage (%)[c]	Mean age at diagnosis (years)	Proportion of adult patients (% >15 years)
North Africa	183,808	1,016	0.55	NA	NA
Morocco	27,852	290	1.04	NA	NA
Europe	638,015	15,052	2.36	NA	67.43
France	54,478	3,340	6.13	3.3	NA
USA	270,193	2,804	1.04	NA	NA
South America	342,336	3,321	0.97	NA	NA
Japan	109,167	2,911	2.67	NA	42.8
Iran	64,551	930	1.44	4.75	40.7
Australia/New Zealand	23,318	1,209	5.18	NA	NA
World (JMF)	6,018,593	60,364	1.00	NA	NA

NA not available

[a] Estimated prevalence based on the US telephone survey [21] drawn from Table I

[b] Number of patients registered in North Africa [26], Morocco [26], Europe (ESID database [19]), France (ESID database [19]), USA (USIDnet [27]), South America (LAGID [24]), Japan (PIDJ [29]), Iran (IPIDR [25]), Australia [20] and JMF [30]

[c] Registry coverage (percentage) of the number of cases expected on the basis of the prevalence for the US [21]

Table III Estimated number of new PID cases by age group in 2011, from the estimates of incidence by age group provided by Joshi et al. [22]

Age (years)	Estimated Incidence[a]	World N (%)	Europe (%)	Africa (%)	North America (%)	South America (%)	Asia (%)	Australia (%)
0–4	21.9	139,886 (18.8)	8,757 (10.4)	34,582 (30.8)	5,183 (13.1)	7,377 (17.8)	78,956 (18.0)	326 (12.8)
5–14	7.2	87,338 (11.8)	5,356 (6.4)	18,840 (16.8)	3,223 (8.2)	5,127 (12.4)	51,553 (11.7)	201 (7.9)
15–24	9.7	117,679 (15.9)	8,862 (10.5)	20,275 (18.1)	4,652 (11.8)	6,738 (16.2)	73,003 (16.6)	307 (12.1)
25–49	6.8	166,499 22.4)	18,182 (21.6)	20,434 (18.2)	8,014 (20.3)	9,723 (23.4)	104,644 (23.8)	541 (21.3)
50–74	15.2	189,772 (25.6)	31,901 (37.9)	16,062 (14.3)	13,941 (35.3)	10,341 (24.9)	111,702 (25.4)	879 (34.6)
75+	12.7	40,762 (5.5)	11,173 (13.3)	1,999 (1.8)	4,438 (11.2)	2,203 (5.3)	19,542 (4.4)	289 (11.4)

[a] Approximate incidences (per 100,000 person-years) by age group from Joshi et al. [22]

any case, the estimates from these two studies are certainly more accurate than those based on registry data.

Our results were based on the extrapolation to other populations of estimates obtained in two US studies. This extrapolation appears to be reasonable for populations principally of European origin (e.g. Europe, Australia), but it is more questionable for other regions, in which PIDs are clearly underdiagnosed. The few registries available for these regions show a distribution of PIDs different from that in Europe, with an apparent predominance of autosomal recessive forms, probably due to higher rates of consanguinity in the countries concerned, particularly in the Arab world [33] and in Muslim populations generally. It must therefore be borne in mind that the extrapolation of estimates for countries with low rates of consanguinity to other regions may result in a major underestimation of the frequency of PIDs in these other regions. For example, founder effects have been found for MHC-II deficiency in Morocco [34], IL12B deficiency in Saudi Arabia [35], leukocyte adhesion deficiency in Tunisia [36] and ADA deficiency in Somalia [37]. Some of these PIDs are therefore much more common in these regions than elsewhere. For example, 31 of the 43 HLA-II-deficient patients identified in 1994 were of North African decent [38]. Similarly, Sanchez et al. [37] estimated that 1 in every 5,000–10,000 Somali children was likely to be born with adenosine deaminase (ADA) deficiency. Even more striking is the presentation of two autosomal recessive PID diseases, ataxia-telangiectasia and IL12RB1 deficiency, in a girl from Qatar [39].

The worldwide frequencies of PIDs estimated from the two US specific surveys are clearly very different from estimates based on registry data, the difference being largest for adults. Indeed, registry data acquisition is based largely on voluntary reporting by physicians and/or clinical centers

Table IV Estimation of registry coverage by age group for ESID, PIDJ and Moroccan registries

Region	Europe			Japan			Morocco		
Age group	Expected number of prevalent cases by age at diagnosis[a]	ESID registry	Registry coverage (%)	Expected number of prevalent cases by age at diagnosis[a]	PIDJ registry	Registry coverage (%)	Expected number of prevalent cases by age at diagnosis[a]	Morocco registry[b]	Registry coverage (%)
0–4	66,331	985	1.48 %	9,573	169	1.77 %	5,501	176	3.20 %
5–14	40,569	5,210	12.84 %	7,214	344	4.77 %	3,531	126	3.57 %
15–24	67,126	3,294	4.91 %	12,150	120	0.99 %	5,019	14	0.28 %
25–49	137,721	2,160	1.57 %	23,323	264	0.33 %	6,456	8	0.12 %
50–74	241,637	1,838	0.56 %	48,302	264	0.33 %	6,423	3	0.05 %
75+	84,631	1,838	0.56 %	8,604	264	0.33 %	922	0	0.00 %
Total	638,015	13,487	2.11 %	109,167	897	0.82 %	27,852	327	1.17 %

[a] The number of prevalent cases by age group is calculated by applying the proportion of incident cases by age group (obtained from Table III) to the total estimated number of prevalent cases provided in Table II

[b] Unpublished data

and its reliability and coverage therefore depend on the willingness of specialists to participate in the process and to cooperate, and PID awareness within the medical community. The observed differences, particularly in developing countries, may also result from the limited resources available for the precise diagnosis of PIDs, leading to an underestimation of the real number of PID cases in these countries [24]. Overall, it is clear that the identification of PID patients is far from complete, with both underreporting and ascertainment bias, leading to the overrepresentation of very active clinical centers and also of the most severely affected patients [40]. Moreover, age distribution in registries depends on the nature of the contributing centers, introducing another source of bias. Indeed, the mean/median age observed in most registries, except in that of Australia/New Zealand, is under 16 years, and even around 4 years for France and Iran (supplementary table 1), because many of the contributing centers are pediatric centers. This bias may account for some of the variations with age of the differences observed between registries and our estimates, as shown in Table IV (pediatric coverage is about twice the level of general coverage).

In an attempt to report all PID cases diagnosed worldwide, the JMF launched a survey in their Centers Network. This survey reported a higher level of coverage than observed for the collection of registries considered here (1 % versus 0.45 %). Clearly, not all patients are included in registries and epidemiologic studies should also include patients from the Jeffrey Modell Centers Network. The method on which the JMF survey is based is subject to certain limitations, but this survey is relevant and provides a first indication of the situation worldwide, with data from countries or regions that do not have a registry. Major efforts should be made to increase the awareness and diagnosis of PIDs. The "10 Warning Signs" of the JMF are one of the most widely promoted tools for PID prediction. However, a recent study showed that only three of these 10 signs are actually effective for PID prediction [41]. Arkwright and Gennery [42] used the data from this previous study and advances in our understanding of PIDs to draw attention to the need for a new paradigm for PID prediction.

Finally, our estimates do not take into account most of the newly discovered forms of PID [3]. For example, the genetic dissection of the syndrome of Mendelian susceptibility to mycobacterial diseases (MSMD, MIM # 209950) over the last decade has provided evidence for a genetic predisposition to the most severe forms of tuberculosis [43]. In particular, Boisson-Dupuis et al. [16] found IL12RB1 deficiency in two of 50 children with severe tuberculosis from Iran, Morocco and Turkey. Tabarsi et al. [17] also reported IL12RB1 deficiency in an adult with disseminated tuberculosis. The actual prevalence of other PIDs conferring a selective predisposition to a given infection is currently difficult to evaluate, because the exploration of these conditions has only recently begun [3]. This is the case for predisposition to invasive pneumococcal diseases [11], *Herpes simplex* encephalitis [14] and chronic mucocutaneous candidiasis [15]. In addition, multiple non infectious phenotypes have been shown to result from inborn errors of immunity (e.g. autoimmunity, angioedema, granuloma, autoinflammation, hemophagocytosis, and thrombotic microangiopathy) [3]. Efforts should therefore now focus on the investigation of these new PIDs, and such investigations may lead to an increase in the estimated frequency and impact of these conditions at the population level.

Conclusion

This overview of the epidemiology of PIDs highlights striking findings concerning the prevalence and incidence of PIDs. Two studies [21, 22] based on different methods provided consistent results, suggesting that PIDs are not rare diseases, with 1/1,200 people worldwide potentially living with a PID. Moreover, those estimates do not take into account the newly discovered forms of PID conferring a selective predisposition to a given microbe or with no associated infectious phenotype. PIDs may play an important role in mortality, particularly that due to infectious diseases, that has yet to be elucidated by the medical community. However, despite these gaps in our knowledge, PIDs are clearly more common than generally thought, indicating a need for improvements in public health policy in this field.

Conflict of Interest The authors declare that they have no conflict of interest.

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