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Issue: *The Year in Human and Medical Genetics: Inborn Errors of Immunity***Advances in primary immunodeficiency diseases in Latin America: epidemiology, research, and perspectives**Paolo Ruggero Errante,¹ José Luis Franco,² Francisco Javier Espinosa-Rosales,³ Ricardo Sorensen,⁴ and Antonio Condino-Neto¹¹Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil. ²Group of Primary Immunodeficiencies, School of Medicine, University of Antioquia, Medellín, Colombia. ³Immunodeficiency Research Unit, National Institute of Pediatrics, Mexico City, Mexico. ⁴Department of Pediatrics, Louisiana State University Health Science Center, New Orleans, Louisiana

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Primary immunodeficiencies (PIDs) are genetic disorders of the immune system comprising many different phenotypes. Although previously considered rare, recent advances in their clinical, epidemiological, and molecular definitions are revealing how much we still need to learn about them. For example, geographical and ethnic variations as well as the impact of certain practices influence their frequency and presentation, making it necessary to consider their study in terms of regions. The Latin American Society for Immunodeficiencies was established as an organization dedicated to provide scientific support for basic and clinical research and to develop tools and educational resources to promote awareness in the medical community. Initiatives such as these are positively influencing the way PIDs are tackled in these countries, as shown by recent reports and publications. This paper provides a historical compilation and a current view of the many issues faced by scientists studying these diseases in these countries, highlighting the diverse scientific contributions and offering a promising perspective for the further developments in this field in Latin America.

Keywords: primary immunodeficiency; Latin America; LASID; immunodeficiency epidemiology; PID registry; Latin American Society for Immunodeficiencies

Introduction

Primary immunodeficiencies (PIDs) are inborn errors of the immune system currently comprising almost 200 different phenotypes that predispose affected individuals not only to recurrent infections but also to chronic and systemic inflammation, hypersensitivity reactions, autoimmunity, and cancer.^{1,2} Their frequency in the general population is approximately 1:2,500 live newborns, and their global prevalence is currently unknown but is estimated to vary from 1:5,000 to 1:500,000 depending on the specific disease and the population under study.³⁻⁵ The International Union of Immunological Societies (IUIS) Expert Committee for Primary Immunodeficiency currently classifies PIDs in eight groups based on the affected immune

component and the genetic defect.³ These groups range from well-recognized antibody and complement deficiencies (and the combined cellular and phagocyte defects), to recently added categories that include diseases of immune regulation, innate immunity, and autoinflammatory syndromes, and to the more complex well-defined syndromes with immunodeficiency. This classification is updated every two years to adjust for the continuous and rapid evolution of the field, as advances in biological sciences and biotechnology are revealing new insights into the nature of PIDs and their actual contribution to human pathology.

Better tools for early diagnosis, such as neonatal screening with T cell receptor excision circles (TRECS) and Kappa-deleting recombination excision circles (KRECS), and even the possibility

of having an entire genome sequenced in a cost-effective manner, are influencing our ability to reduce the morbidity and mortality related to these diseases. There is the hope that these advances will help us to circumvent the complications and sequelae that are so common to patients with a PID by reducing disabilities related to school and/or work attendance, improving productive capacity, and decreasing costs to health care systems.^{6,7}

Proper knowledge of PIDs remains relatively scarce among medical communities in many countries around the globe, reflecting, in some cases, lack of awareness and in other cases apathy, as the field of immunology is often mistakenly considered too complicated to be useful for daily practice. In addition, health authorities in these countries are poorly informed and often underestimate the epidemiologic, social, and economic impact of PIDs compared to other more common diseases, making it more difficult for physicians working in this field to provide quality care for patients.

Delay in diagnosis of PIDs, as a consequence of lack of knowledge about them, is evident in countries of disadvantaged regions; but interestingly it also occurs in developed countries. Thus, research of and education in PIDs must be implemented as a public health policy universally, since the prognosis of many patients can be improved by early diagnosis and appropriate access to care and treatment.^{7,8} In general, when evaluating a patient for a suspected PID, the assessment of the immune system can be performed with inexpensive, simple, and reliable tests. Under specific circumstances, however, this might require more sophisticated and expensive laboratory tests, with delay in diagnosis often associated with limited access to these specialized resources.^{9,10} For example, in Finland, the diagnosis of common variable immunodeficiency (CVID) was delayed by 5 years in two-thirds of the patients and by 10 years in one-third of them.¹¹ In the United Kingdom, a delay of 6.2 years evident between 1989 and 1995 decreased to 3.5 years after the implementation of a government program directed at early recognition and diagnosis of PIDs.¹²

One possibility for establishing diagnostic performance tools for certain diseases is to evaluate patient registration data. Registries are designed to study the behavior of diseases in certain populations, and they are also very useful for improving patient care by providing epidemiological data that helps to mon-

itor health policies. In Europe, the PID registry is carried out by the European Society for Immunodeficiencies (ESID) (<http://www.esid.org/>), a non-governmental organization that emerged in 1994 to promote the exchange of information among doctors, nurses, investigators, patients, and their families.^{13–16} ESID continuously receives data from 85 specialized centers, and their entries in 2011 included 14,506 patients, implying an approximate prevalence of 4–47/1,000,000.^{16,17}

The Latin American Group for Immunodeficiencies (LAGID) was created in 1993 to study prevalence and to promote awareness about PIDs in Mexico and Central and South America. In 2009, LAGID became the Latin American Society for Immunodeficiencies (LASID) and established an online registry (<http://imunodeficiencia.unicamp.br:8080/>). The progress of PID registry in Latin America is shown in Table 1 and currently includes 1,888 cases, since April 2009.

Early and proper diagnosis and access to treatments remain the main problems that PID patients face in Latin America. These can be partly explained by the lack of proper training of general practitioners and medical specialists (mainly pediatricians), leading to misdiagnosis or late diagnosis. However, there are also difficulties in accessibility to screening tests, educational programs, and treatment centers.^{18–20} Therefore, special programs and focused policies must be implemented with the support of governments to overcome these difficulties.

PID diagnosis, treatment, and education in Latin America

Argentina

The main diagnostic centers in Argentina are public and located in Buenos Aires, and there are other less specialized centers in La Plata, Rosario, Cordoba, and Mendoza; they are all accessible at no cost. Private hospitals in Argentina only offer limited diagnosis because they do not have specialized laboratories and professionals dedicated to PIDs. In addition, patients from Paraguay, Bolivia, and Uruguay are usually diagnosed and treated in Buenos Aires since these countries have few resources.²¹ Regarding treatment, patients with PIDs who are in need of intravenous immunoglobulin (IVIG) are usually sent to Buenos Aires; however, infusions are often discontinued once pediatric patients become

Table 1. Participating countries in the LASID PID registry program

Countries	July 2009	December 2009	July 2010	December 2010	May 2011	September 2011
Argentina	2	45	178	229	456	700
Brazil	201	257	319	385	470	539
Chile	2	5	11	12	17	31
Colombia	87	127	136	136	136	204
Costa Rica	0	0	0	0	72	94
Honduras	0	9	10	10	11	32
Mexico	12	42	163	194	231	250
Paraguay	0	0	0	1	1	2
Peru	0	0	0	10	11	24
Uruguay	0	0	0	1	1	5
Venezuela	0	0	0	0	3	7
Total	304	485	818	978	1,409	1,888

LASID progress since start. From July 2009 until September 2011, LASID registered 1,888 cases from 12 countries.

adults.²² One issue that further complicates the picture is that in Argentina immunologists are not recognized as specialists by the Ministry of Health, and only two hospitals in Buenos Aires offer training in immunology.^{19,23} To partly overcome these problems, this year, the Jeffrey Modell Foundation established a diagnostic center at the Hospital “Ricardo Gutierrez” in Buenos Aires, to provide PID patient management, stimulate patients’ social and educational activities, and disseminate a national medical education program on PIDs.

Brazil

It is estimated that Brazil has 2,000 PID patients under treatment and that approximately 18,000 patients with PIDs are still waiting for diagnosis and proper management.²⁴ Immunological diagnosis is supported by several centers located in São Paulo, Minas Gerais, Paraná, Rio Grande do Sul, Bahia, and Rio de Janeiro.^{19,24,25} Centers in the southeast region of the country have specialized professionals with structure and access to molecular and genetic diagnosis. In Brazil, the federal government covers patients’ referrals to specialized centers when necessary.^{26–28} Still, high cost and poor access to specialized laboratories are considered by doctors to be the major problems in the diagnosis of PID (results available at <http://www.bragid.org.br/download/graficos.pps>). Highly specialized PID diagnostic centers in Brazil are sup-

ported by the Ministry of Health and the government research agencies Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and recently by the Jeffrey Modell Foundation.

The Brazilian Group of Primary Immunodeficiencies was established in 1997. Activities of this group take place in parallel with those of LASID and the Brazilian Society of Allergy and Immunopathology (ASBAI), including the first and second LASID Summer Schools, the implementation of the online LASID registry (<http://imunodeficiencia.unicamp.br:8080/>), two LASID scientific meetings, and a continuous medical education (CME) program throughout the country. The Federal University of São Paulo-UNIFESP, in partnership with the Jeffrey Modell Foundation, created the first Jeffrey Modell Diagnostic Center for PID in Latin America in April 2009 to enable physicians to diagnose and treat patients earlier, and to promote patient social activities and education. In Brazil, there are numerous funded residency programs in allergy and immunology, although only few centers train professionals in PID, mostly in the southeast region of the country.^{19,25}

A pilot program for newborn screening for severe combined immunodeficiency (SCID), T cell deficiencies, and DiGeorge syndrome began in 2010 at the Institute of Biomedical Sciences at the

University of São Paulo, in cooperation with the Federal University of São Paulo Medical School. This program, screening all newborns from a large public hospital in the city of São Paulo, is expected to run for at least three years.

Bacillus Calmette-Guérin (BCB) is a mandatory vaccine for tuberculosis given to all newborns in Brazil. The city of São Paulo reports approximately 80 cases per year of BCG-adverse reactions that require specific antibiotic therapy. This motivated professionals from both of the above universities to start a second pilot PID screening program based on the investigation of PIDs in all patients presenting with BCG-adverse reactions requiring antibiotics.

CNPq, FAPESP, and Baxter Bioscience, are supporting both projects. The newborn screening program, together with the study of PIDs in patients with BCG-adverse reactions in the city of São Paulo—a large Latin American urban center of approximately 20 million inhabitants—should provide useful information about some of the most relevant PIDs in the first year of life.

Chile

Laboratories for diagnosis of PIDs in Chile are available in Santiago, Temuco, Valparaiso, and Concepción. Basic screening tests for PIDs can be performed in large hospitals, although they receive little government financial support.²⁹ As in most developing countries in Latin America, the diagnosis of PID is often suspected and performed only after patients have suffered numerous infections and failed treatments, leading to their referral to an infectious diseases clinic or other specialists, and finally to an immunology center. Chile has a three-year medical residency program in immunology at the University of Santiago, providing training and care for adult and pediatric patients.¹⁹ The Jeffrey Modell Foundation also established a network in Chile in 2010 with similar goals to advance the PID field in this country. An advanced molecular diagnostic center is under construction at the University of La Frontera in Temuco, which is intended to take care of most of the molecular genetic diagnoses in Chile.

Colombia

In Colombia, several cities such as Medellín, Bogotá, Cali, and others, have well-equipped clinical laboratories that are able to perform tests for screening of common PIDs, but highly specific and specialized tests in immunology, molecular biology, and

genomics are only available at the only national PID referral center located in the University of Antioquia in Medellín.^{30,31} The national PID registry is carried out by this center and, interestingly, it shows that about 80% of PID cases come from the state of Antioquia,^{30,32} although this territory harbors less than 20% of the Colombian population. This reflects a distortion in the distribution of diagnosed cases in this country. To circumvent this problem, this referral center has established a network of physicians in other major cities, and is providing assistance for the development of other specialized centers and programs connected in a network in Bogotá, Cali, Cartagena, and other cities around the country.

In Colombia, every citizen is entitled to a basic health plan that is subsidized by the government (the Plan Obligatorio de Salud (POS)) and that provides basic coverage for most diseases including PIDs.^{33,34} To get additional health coverage, however, people are required to buy health plans that are available through private health care providers. Most patients in need of IVIG get their treatment from their respective health care provider at no cost as the cost is refunded through a government national fund (fondo de solidaridad y Garantía (FOSYGA)). In terms of awareness and education, the national patient organization Diana García de Olarte Primary Immunodeficiency Foundation (FIP) supports and develops educational programs, provides professional advice for IVIG treatments in specialized centers, and offers legal advice for patients on issues related to diagnosis and treatment.³⁵ Only the University of Antioquia in Medellín has an immunology program for medical residents, but, as in other Latin American countries, these physicians prefer to specialize in other medical areas, since the financial return is greater.¹⁹ In 2010, the Jeffrey Modell Foundation also established a research and diagnostic center at the University of Antioquia in Medellín.

Honduras

Honduras has two major health systems: public health and social security, which provide coverage for approximately 70% and 25% of the population, respectively, while 5% of individuals have private insurance. PID patients in this country are diagnosed after referral to major centers in Tegucigalpa or San Pedro Sula, with access to these centers available to all patients. The greatest challenges to diagnosis are

laboratory access and the costs related to testing. The only immunology laboratory able to support a PID diagnosis is in Tegucigalpa.¹⁹

Latin American reality, aiming to improve the management of patients with these diseases.

Mexico

In Mexico it is estimated that each year more than 4,000 children are born with PIDs and 250 will present with severe forms. Mexico has specialized centers for PID diagnosis and treatment in Mexico City, Monterrey, and Guadalajara. Molecular and genetic diagnosis for several PIDs can only be performed at the Jeffrey Modell Diagnostic Center at the National Institute of Pediatrics in Mexico City. Treatment with IVIG is covered by the public health system and is administered at no cost by public hospitals and clinics, but there are no specific national guidelines for IVIG administration. In Mexico, there are several residency programs in allergy and immunology, with an emphasis on allergy. Only the National Institute of Pediatrics in Mexico City has a more balanced program in pediatric allergy and clinical immunology, with an emphasis on PIDs.¹⁹

In summary, the conditions for PID diagnosis and management are heterogeneous in Latin America. Some countries have already joined the network to advance this field in our continent. Some medical centers in these countries have residency and/or postgraduate training programs in immunology. One issue affecting government programs on PID management is the lack of guidelines adapted for Latin American countries. Immunologists generally follow North American or European guidelines. LASID is currently adapting those guidelines to the

LASID activities

A major problem in developing countries has been the lack of registries for rare diseases; because of this the number of patients diagnosed does not reflect their actual prevalence. This problem is compounded by the wide distribution of diagnostic capabilities present in each country's regions and provinces, and PIDs are no exception (Table 2). Moreover, the lack of standardized case definitions makes it impossible to calculate rates of the healthy population from this source, by only reporting positive cases without referencing population data.¹⁹

In Latin America, countries participating in LAGID have published two reports about PIDs. The first was in 1998 and included 1,428 patients from eight countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Paraguay, and Uruguay). Predominantly, antibody deficiencies were reported in 58% of patients, followed by cellular and antibody immunodeficiencies associated with other abnormalities in 18%, immunodeficiency syndromes associated with granulocyte dysfunction in 8%, phagocytic disorders in 9%, combined cellular and antibody immunodeficiencies in 5%, and complement deficiencies in 2% of patients.³⁶

A second report in 2007 documented 3,321 cases from 12 Latin American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Peru, Paraguay, Uruguay, and Venezuela), again with predominantly antibody deficiencies in 53.2% of the patients, followed by other

Table 2. Current and expected PID prevalence in Latin America

Countries	Number inhabitants/ million 2006	PID 2006	Frequency	Expected number of PID patients
Argentina	39.5	1,246	1:30,000	3,900
Brazil	186.1	790	1:235,000	18,600
Chile	16	279	1:58,000	1,600
Colombia	42.9	145	1:300,000	4,200
Mexico	106.2	399	1:265,000	10,600
Peru	27.9	17	1:1,600,000	2,800

The minimal incidence of PID cases in Latin American countries was estimated by calculating the average of cases in 2006. Each value was divided by the country's birth rate in this period, and the result was multiplied by 100,000. From Leiva, *et al.*²⁴

well-defined PID syndromes in 22.6%, combined T and B cell immunodeficiency in 9.5%, phagocytic disorders in 8.6%, disorders of immune dysregulation in 3.3%, and complement deficiencies in 2.8% of the patients. All countries that participated in the first publication in 1998 reported an increase of PID cases, ranging between 10% and 80%.²⁴

These two reports highlight that, predominantly, antibody deficiencies remain the main PIDs registered in Latin America, with similar trends in other countries such as Australia,^{37,38} China,^{39,40} Egypt,⁴¹ France,⁴² Hong Kong,⁴³ Iran,^{44–46} Italy,⁴⁷ Kuwait,⁴⁸ the Netherlands,⁴⁹ Norway,⁵⁰ Poland,⁵¹ Republic of Ireland,⁵² Spain,^{53,54} Switzerland,⁵⁵ Taiwan,⁵⁶ Thailand,⁵⁷ Tunisia,⁵⁸ and the United States.^{59,60} However, other well-defined PID syndromes, such as ataxia-telangiectasia, have been reported more frequently, especially in Mexico and Central America. A higher incidence of certain PIDs has also been reported in other countries, such as India⁶¹ (phagocyte disorders) and Turkey⁶² (combined T and B cell immunodeficiencies).

The LASID online registry

The online PID registry program for Latin America (LASID registry) was officially launched on April 28, 2009 in São Paulo (Brazil) with the participation of 90 representatives from Argentina, Brazil, Chile, Colombia, Honduras, and Mexico, and faculty members from the United States and Europe. This registry was adapted from the ESID registry and is currently supported by the Jeffrey Modell Foundation (www.jmfworld.org), CNPq-Brazil, and the pharmaceutical companies Baxter, CSL Behring, Octapharma, Grifols, and LFB. It is available at <http://imunodeficiencia.unicamp.br:8080/> and as of September 2011, it contains information about 1,888 patients contributed by 40 centers from 11 Latin American countries (Tables 1 and 3, Fig. 1).^{15,16,63} Up-to-date data on this registry can be obtained on a regular basis at http://imunodeficiencia.unicamp.br:8080/estatistica_mensal.html.

In April 2011, the LASID registry Program Committee started three collaborative clinical epidemiological studies focusing initially on chronic granulomatous disease, agammaglobulinemia, and hyper-IgM syndrome. The preliminary results point to some specific characteristics, such as the high incidence of fungal infections in patients with

Table 3. Participating centers in the LASID registry program

Countries	April 2009	May 2011	September 2011
Brazil	14	17	18
Argentina	5	6	7
Chile	1	1	1
Costa Rica		1	1
Colombia	1	1	1
Mexico	1	4	5
Honduras	1	1	1
Paraguay	0	1	1
Peru	0	3	3
Venezuela	0	1	1
Uruguay		1	1
Total	23	37	40

The number of LASID registry participating centers increased to 40 centers in two years. Brazil, Argentina, and Mexico represent the countries with the most referral centers. Centers > 100 cases in Argentina, Brazil, Mexico, and Colombia.

X-linked hyper-IgM syndrome, and the incidence of BCG adverse reactions in 17% of the patients with chronic granulomatous disease. These results were presented and discussed in detail during the LASID meeting in Mexico in October 2011 and should progress toward more comprehensive studies during 2012. Initiatives such as these are motivating doctors to investigate and register their patients in our online database.

On October 14, 2009, experts from Argentina, Brazil, Chile, Colombia, Honduras, and Mexico and representatives of LAGID met in Cartagena de Indias in Colombia for the first time to discuss the particular needs of each country with respect to PIDs. This led to an initiative to publish the proceedings of this meeting and to date, LASID has published four reports and proceedings; the first two papers focused on the prevalence and characteristics of PID patients in Latin America,^{24,36} and the third and fourth summarized deficiencies in PID diagnosis and treatment in Latin America and described features of an educational outreach program, an immunology fellowship program, and a laboratory network aimed at overcoming the current deficiencies.^{19,20} More than compiling data, the LASID registry brings an educational perspective,

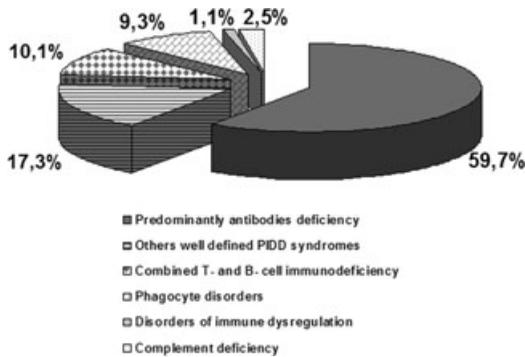


Figure 1. Distribution of PID among 1,888 patients from 12 countries in the new LASID registry. Predominantly antibody deficiencies were reported in 59.7% patients, followed by other well-defined PID syndromes in 17.3%, combined T and B cell immunodeficiency in 10.1%, phagocytic disorders in 9.3%, disorders of immune dysregulation in 1.1%, and complement deficiencies in 2.5% of patients. From <http://www.bragid.org.br>.

as doctors must know first how to diagnose and manage their patients before registering them. Thus, registering patients will benefit doctors and patients.

Educational programs

To improve the diagnosis, medical care, and research on PIDs in Latin America, the LASID Advisory Board has established several initiatives that include a CME program based on the PID warning signs, a LASID fellowship program, a Latin American laboratory network, summer school programs, and LASID scientific meetings.^{19,20,64} The main goal of the educational programs is to increase the capability of pediatricians, general practitioners, and some specialists to diagnose and manage patients with PIDs, as well as to train laboratory professionals to establish and develop diagnostic tests for PID patients. The fellowship program and summer schools are targeted to the younger generations that will multiply this network. It is expected that these initiatives will lead to a higher number of diagnosed patients, facilitating basic and clinical research.

LASID Summer School program

The LASID Summer School program has been an opportunity to promote scientific interaction and standardization of PID knowledge among different member countries, as the educational resources differ between participating countries.^{19,20} In 2006, the first LAGID summer school took place in São Paulo (Brazil) based on the ESID and the Clinical

Immunology Society (CIS) models. Experts from LAGID, ESID, CIS, and 36 students attended this meeting and discussed the diagnosis of the major PIDs in Latin America, IVIG therapy guidelines and bone marrow transplantation, and a LAGID communication network. Additional meetings took place in 2008 in Temuco (Chile) and more recently in 2010 in Bahia (Brazil) with 90 students from several Latin American countries.

The LASID fellowship program

The LASID Advisory Board established the LASID Fellowship program that will be starting in 2012. This program is funded by Baxter Bioscience and will include five fellows who will be selected on the basis of the scientific merit of the proposals and the commitment of the candidate to advance the PIDs filed in Latin America.²⁰ This program should help motivate young professionals to pursue the field of PID in Latin America and to serve as multipliers of PID educational programs.

The creation of PID reference centers

Education and training are necessary for general practitioners, pediatricians, and specialists from other areas of medicine to ensure that they are able to take care of PID patients. The first Jeffrey Modell Center for Latin America was established in April 2009 at the Federal University of São Paulo-UNIFESP. This center played a key role in education, patient activities, and PID registry,^{65,66} and now other centers sponsored as well by the Jeffrey Modell Foundation have been established in Mexico (2009), Colombia (2010), and Argentina (2011) with similar purposes. In addition, a network of clinical centers and molecular diagnostic laboratories was established in Chile in 2010. All of these centers and networks have implemented educational programs and organize workshops in the main cities of their countries to train physicians in the proper diagnostic approaches and treatments of patients with PIDs. Simultaneously, these centers are developing public relations campaigns in their areas of influence through radio, TV, and newspapers to bring their messages to the general community as well. A testimony to the success of this strategy is that in Mexico, for example, more than 1,500 participants have received basic training in PIDs, and patient referrals to the Jeffrey Modell diagnostic center in Mexico City have increased up to 40% in only one year since the start of this program. Moreover, other

Jeffrey Modell centers in Latin America are describing similar experiences.

Research development in PID in Latin America

LAGID was created in 1993 with the goals of spreading educational and awareness programs, establishing PID registries, and promoting annual scientific meetings with the participation of well-recognized international authorities in the PID field. This environment made possible important collaborations among Latin American doctors who, in turn, interacted with foreign investigators to create a network that advanced scientific developments in PID in Latin America. This collaboration has resulted in several publications, beginning with the clinical studies based on the LAGID registries.^{24–36}

Research groups from Argentina, Brazil, Colombia, Mexico, and Costa Rica have performed studies in some well-known PIDs, such as CGD, agammaglobulinemia, hyper-IgM syndrome, Wiskott–Aldrich syndrome, and ataxia-teleangiectasia, resulting in several publications that pointed to particular phenotypes and novel genotypes.^{67–76} These studies have contributed new insights about PID clinical presentation and have had a positive impact on the molecular diagnosis of PIDs. Specifically, these studies have shown that BCG complications are prevalent among SCID, T cell deficiency, and CGD patients; that fungal infections are highly prevalent among X-linked hyper-IgM patients; and that ataxia-teleangiectasia is exceptionally frequent in Mexico and Costa Rica. Currently, Chile is building a new diagnostic center at University La Frontera that will work with research centers in Argentina, Brazil, and Colombia. This strategy will strengthen even more the interactions among the several Latin American research centers. In addition, the University of Antioquia in Medellín has established a national genomic sequencing center that promises to bolster specific genomic studies in PIDs for the region.

Latin American investigators have also been involved in international studies leading to the discovery of novel diseases and molecular defects. These recent discoveries have led to major scientific advancements in PIDs that will likely have an impact on the management of patients worldwide, especially in Latin America where these diseases are prevalent.^{77–84} The benefit of this interaction

reaches doctors and patients with chronic mucocutaneous candidiasis, Mendelian susceptibility to mycobacterial diseases, antibody deficiencies, and hyper-IgE syndrome. It is expected that these contributions will encourage future generations of young Latin American scientists to continue to develop this research area in their own countries, stimulating professionals to stay and work in Latin America where research has been growing significantly in recent years.

In addition, some molecular discoveries and mechanistic studies with clinical implications have been achieved by Latin American groups not only as collaborative partners of European or North American research groups but also often as the leading teams. The contributions include major advancements in CVID, chronic granulomatous disease and disorders of the NADPH oxidase system, Mendelian susceptibility to mycobacterial infections, anhidrotic ectodermal dysplasia with immunodeficiency, hepatitis A, and complement and autoimmune disorders.^{85–90} We believe that research in Latin America will grow even more after the implementation of the online PID registry. Currently, there are ongoing studies on CGD, agammaglobulinemia, hyper-IgM, a prospective study on BCG adverse reactions, and the newborn screening of PIDs. These clinical–epidemiological studies will likely advance our understanding of PID clinical science and influence novel molecular and mechanistic studies and immunopathological pathways that help explain the prevalent phenotypes in Latin America. This should attract young investigators to stay and develop leading PID research teams in Latin America.

Concluding remarks

As the field of PIDs continues to grow, the countries of Latin America are undoubtedly making their own contribution. Nevertheless, there are challenges ahead that are not unusual in other countries around the world, even if individual countries have come to their own solutions. Basic aspects, such as improved diagnosis, availability of treatments, and government support, remain at the core of critical issues concerning PIDs that must be resolved. Moreover, issues such as incidence and prevalence and variations in phenotypes and molecular genotypes—increasingly recognized as unique to particular regions—must be taken into

account in Latin America in order to provide accurate information about how these diseases behave in this part of the world. To provide these solutions, LASID has been working recently to consolidate its agenda by establishing PID educational programs, registries, referral centers, and a network of laboratories throughout the continent. These initiatives have the support of other organizations such as ESID, the Jeffrey Modell Foundation, and CIS to name a few, providing an example of how the union of people brings synergy to the ideas. We are hopeful that they will have a positive impact on a greater number of diagnosed patients, increase scientific developments, expand professional networks, and generate greater awareness about PIDs.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Morimoto, Y. & J.M. Routes. 2008. Immunodeficiency overview. *Prim. Care Clin. Office Pract.* **35**: 159–173.
- Notarangelo, L.D. 2010. PIDs and cancer: an evolving story. *Blood* **116**: 1189–1190.
- Geha, R.S., L.D. Notarangelo, J.-L. Casanova, *et al.* 2007. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J. Allergy Clin. Immunol.* **120**: 776–794.
- Boyle, J.M. & R.H. Buckley. 2007. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. *J. Clin. Immunol.* **27**: 497–502.
- Notarangelo, L.D., A. Fischer, R.S. Geha, *et al.* 2009. Primary immunodeficiencies: 2009 update. International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies. *J. Allergy Clin. Immunol.* **124**: 1161–1178. Erratum in: *J. Allergy Clin. Immunol.* 2010; **125**: 771–773.
- Yarmohammadi, H., L. Estrella & C. Cunningham-Rundles. 2004. Diagnosis of primary immunodeficiency; can review of medical history help? *J. Allergy Clin. Immunol.* **113**: s47.
- Bonilla, F.A., I.L. Bernstein, D.A. Khan, *et al.* 2005. American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann. Allergy Asthma Immunol.* **94**(5 Suppl 1): S1–S63.
- Turvey, S.E., F.A. Bonilla & A.K. Junker. 2009. Primary immunodeficiency diseases: a practical guide for clinicians. *Postgrad. Med. J.* **85**: 660–666.
- Lindgren, M.L., L. Kobrynski, S.A. Rasmussen, *et al.* 2004. Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders. *MMWR Recomm. Rep.* **53**(RR-1): 1–29.
- Oliveira, J.B. & T.A. Fleisher. 2010. Laboratory evaluation of primary immunodeficiencies. *J. Allergy Clin. Immunol.* **125**: S297–S305.
- Kainulainen, L., J. Nikoskelain & O. Ruuskanen. 2001. Diagnostic finding in 95 Finnish patients with common variable immunodeficiency. *J. Clin. Immunol.* **21**: 145–149.
- Seymour, B., J. Miles & M. Haeney. 2005. Primary antibody deficiency and diagnostic delay. *J. Clin. Pathol.* **58**: 546–547.
- Sewell, W.A.C., S. Khan & P.C. Doré. 2006. Early indicators of immunodeficiency in adults and children: protocols for screening for primary immunological defects. *Clin. Exp. Immunol.* **145**: 201–203.
- de Vries, E. for the Clinical Working Party of the European Society for Immunodeficiencies (ESID). 2006. Patient-centered screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. *Clin. Exp. Immunol.* **145**: 204–214.
- Guzman, D., D. Veit, V. Knerr, *et al.* 2007. The ESID online database network. *Bioinformatics* **23**: 654–655.
- Gathmann, B., B. Grimbacher, J. Beauté, *et al.* 2009. The European internet-based patient and research database for primary immunodeficiencies: results 2006–2008. *Clin. Exp. Immunol.* **157**(Suppl 1): 3–11.
- Knerr, V., B. Gathmann, A.M. Eades-Perner, *et al.* 2008. The ESID online database for primary immunodeficiencies. First analyses with regard to Germany and Europe. *Med. Klin. (Munich)* **103**: 620–627.
- Pickett, D., V. Modell, I. Leighton & F. Modell. 2008. Impact of a physician education and patient awareness campaign on the diagnosis and management of primary immunodeficiencies. *Immunol. Res.* **40**: 93–94.
- Condino-Neto, A., J.L. Franco, C. Trujillo-Vargas, *et al.* 2011. Critical issues and needs in management of primary immunodeficiency diseases in Latin America. *Allergol. Immunopathol. (Madr.)* **39**: 45–51.
- Leiva, L.E., L. Bezrodnik, M. Oleastro, *et al.* 2011. Primary immunodeficiency diseases in Latin America: proceedings of the second Latin America Society for Immunodeficiencies (LASID) Advisory Board. *Allergol. Immunopathol. (Madr.)* **39**: 106–110.
- Maceira, D., G. Paraje, F. Aramayo, *et al.* 2010. Public financing of health research in five Latin American countries. *Rev. Panam. Salud Pública* **27**: 442–451.
- Krasovec, S., A. Ornani, M. Oleastro, *et al.* 2007. Efficacy and tolerability of an Argentine intravenous immunoglobulin in pediatric patients with primary immunodeficiency diseases. *J. Clin. Immunol.* **27**: 227–232.
- Galicchio, M.F., A. Ornani, L. Bezrodnik, *et al.* 2010. Guías de manejo: vacunas en pacientes con inmunodeficiencias primarias. *Arch. Argent. Pediatr.* **108**: 454–464.
- Leiva, L.E., M. Zelazco, M. Oleastro, *et al.* 2007. Primary immunodeficiency diseases in Latin America: the second report of the LAGID registry. *J. Clin. Immunol.* **27**: 101–108.
- Grumach, A.S., A.J. Duarte, R. Bellinati-Pires, *et al.* 1997. Brazilian report on primary immunodeficiencies in children: 166 cases studied over a follow-up time of 15 years. *J. Clin. Immunol.* **17**: 340–345.
- Ocké-Reis, C.O. & T.R. Marmor. 2010. The Brazilian national health system: an unfulfilled promise? *Int. J. Health Plann. Manage.* **25**: 318–329.
- Paim, J., C. Travassos, C. Almeida, *et al.* 2011. The Brazilian health system: history, advances, and challenges. *Lancet* **377**: 1778–1797.

28. Costa-Carvalho, B.T., G.F. Wandalsen, G. Pulici, *et al.* 2011. Pulmonary complications in patients with antibody deficiency. *Allergol. Immunopathol. (Madr.)* **39**: 128–132.
29. Goic, A. & R. Armas. 2010. The ALANAM statement on public health policy. *Rev. Med. Chil.* **138**: 1558–1560.
30. Montoya, C.J., J. Henao, H. Salgado, *et al.* 2002. Phenotypic diagnosis of primary immunodeficiencies in Antioquia, Colombia 1994–2002. *Biomédica* **22**: 510–518.
31. Díaz, M.A., D.M. Sarrazola & J.C. Orrego. 2008. Epidemiological, clinical and immunological characteristics of recurrent infection syndrome in individuals from low income neighborhoods from Cúcuta. *Infectio.* **12**: 254–263.
32. Enriquez, L.E., J.C. Orrego, J.L. Franco, *et al.* 2005. Epidemiologic characterization of patients with primary immunodeficiencies in the Program of Detection and Care of Recurrent Infections Syndrome at the Group of Primary Immunodeficiencies, University of Antioquia. *Revista de Inmunología.* **13**: 142–143.
33. Roa, H. & C. Roa. 2010. República de Colombia. Ley 100 de 1993. Sistema de Seguridad Social Integral. ECOE Ediciones. Colección Las Leyes de Colombia. Bogotá, 2010.
34. Cardona A.D. & C.A.M. Segura. 2011. Public health policies as regards the elderly in Colombia. *Rev. Esp. Geriatr. Gerontol.* **46**: 96–99.
35. Montoya, C.J. & R.U. Sorensen. Lecciones sobre el uso de gammaglobulina humana endovenosa. Boletín LAGID. 23 de Febrero de 2001. Available at: <http://www.lagid.lsuhs.edu/Tratamientos/971-010.htm>2001 (Accessed February 22, 2002).
36. Zelazko, M., M. Carneiro-Sampaio, M. Cornejo de Luigi, *et al.* 1998. Primary immunodeficiency diseases in Latin America: first report from eight countries participating in the LAGID. *J. Clin. Immunol.* **18**: 161–166.
37. Baumgart, K.W., W.J. Britton, A. Kemp, *et al.* 1997. The spectrum of primary immunodeficiency disorders in Australia. *J. Allergy Clin. Immunol.* **100**: 415–423.
38. Kirkpatrick, P. & S. Riminton. 2007. Primary immunodeficiency diseases in Australia and New Zealand. *J. Clin. Immunol.* **27**: 517–524.
39. Zhao, H.J., T.X. Chen, Y.Q. Hao, *et al.* 2006. Overview of clinical occurrence of primary immunodeficiency disorders in children. *Zhonghua Er Ke Za Zhi* **44**: 403–406.
40. Wang, L.L., Y.Y. Jin, Y.Q. Hao, *et al.* 2011. Distribution and clinical features of primary immunodeficiency diseases in Chinese children (2004–2009). *J. Clin. Immunol.* **31**: 297–308.
41. Reda, S.M., H.M. Afifi & M.M. Amine. 2009. Primary immunodeficiency diseases in Egyptian children: a single-center study. *J. Clin. Immunol.* **29**: 343–351.
42. CEREDIH: The French PIDD study group. 2010. The French national registry of primary immunodeficiency diseases. *Clin. Immunol.* **135**: 264–272.
43. Lam, D.S., T.L. Lee, K.W. Chan, *et al.* 2005. Primary immunodeficiency in Hong Kong and the use of genetic analysis for diagnosis. *Hong Kong Med. J.* **11**: 90–96.
44. Aghamohammadi, A., M. Moein, A. Farhoudi, *et al.* 2002. Primary immunodeficiency in Iran: first report of the National Registry of PIDD in Children and Adults. *J. Clin. Immunol.* **22**: 375–380.
45. Farhoudi, A., A. Aghamohammadi, M. Moin, *et al.* 2005. Distribution of primary immunodeficiency disorders diagnosed in the Children's Medical Center in Iran. *J. Investig. Allergol. Clin. Immunol.* **15**: 177–182.
46. Rezaei, N., A. Aghamohammadi, M. Moin, *et al.* 2006. Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. *J. Clin. Immunol.* **26**: 519–532.
47. Luzzi, G., L. Businco & F. Aiuti. 1983. Primary immunodeficiency syndromes in Italy: a report of the national register in children and adults. *J. Clin. Immunol.* **3**: 316–320.
48. Al-Herz, W. 2008. Primary immunodeficiency disorders in Kuwait: first report from Kuwait National Primary Immunodeficiency Registry (2004–2006). *J. Clin. Immunol.* **28**: 186–193.
49. Zegers, B.J., C.M. Weemaes, R.S. Weening, *et al.* 1994. Immunodeficiency in the Netherlands: clinical and immunological survey, 1970–1983. Interfacultaire werkgroep Immunodeficiëntie. *Ned Tijdschr Geneesk* **138**: 354–359.
50. Stray-Pedersen, A., T.G. Abrahamsen & S.S. Frøland. 2000. Primary immunodeficiency diseases in Norway. *J. Clin. Immunol.* **20**: 477–485.
51. Bernatowska, E., K. Madalinski, J. Michalkiewicz & H. Gregorek. 1988. Primary immunodeficiency diseases in children treated in the Children's Memorial Hospital, Poland. *Immunol. Invest.* **17**: 107–120.
52. Abuzakouk, M. & C. Feighery. 2005. Primary immunodeficiency disorders in the Republic of Ireland: first report of the national registry in children and adults. *J. Clin. Immunol.* **25**: 73–77.
53. Matamoros, F.N., B.S. Raga & C.G. Fontan. 1997. Primary immunodeficiency syndrome in Spain: first report of the national registry in children and adults. *J. Clin. Immunol.* **17**: 333–339.
54. Milá, L.J., G.A. Etxagibel & F.N. Matamoros. 2001. The Spanish Registry of Primary Immunodeficiencies (REDIP). *Allergol. Immunopathol. (Madr.)* **29**: 122–125.
55. Ryser, O., A. Morell & W.H. Hitzig. 1988. Primary immunodeficiencies in Switzerland: first report of the national registry in adults and children. *J. Clin. Immunol.* **8**: 479–485.
56. Lee, W.I., J.L. Huang, T.H. Jaing, *et al.* 2011. Distribution, clinical features and treatment in Taiwanese patients with symptomatic primary immunodeficiency diseases (PIDs) in a nationwide population-based study during 1985–2010. *Immunobiology* **216**: 1286–1294.
57. Benjasupattananan, P., T. Simasathein, P. Vichyanond, *et al.* 2009. Clinical characteristics and outcomes of primary immunodeficiencies in Thai children: an 18-year experience from a tertiary care center. *J. Clin. Immunol.* **29**: 357–364.
58. Bejaoui, M., M.R. Barbouche, A. Sassi, *et al.* 1997. Primary immunodeficiency in Tunisia: study of 152 cases. *Arch. Pediatr.* **4**: 827–831.
59. Javier, F.C. III, C.M. Moore & R.U. Sorensen. 2000. Distribution of primary immunodeficiency diseases diagnosed in a pediatric tertiary hospital. *Ann. Allergy Asthma Immunol.* **84**: 25–30.
60. Stiehm, R.E. 2007. The four most common pediatric immunodeficiencies. *Adv. Exp. Med. Biol.* **601**: 15–26.

61. Verma, S., P.K. Sharma, S. Sivanandan, *et al.* 2008. Spectrum of primary immune deficiency at a tertiary care hospital. *Indian J. Pediatr.* **75**: 143–148.
62. Shabestari, M.S., S.H. Maljaei, R. Baradaran, *et al.* 2007. Distribution of primary immunodeficiency diseases in the Turk ethnic group, living in the northwestern Iran. *J. Clin. Immunol.* **27**: 510–516.
63. Eades-Perner, A.M., B. Gathmann, V. Knerr, *et al.*; ESID Registry Working Party. 2007. The European internet-based patient and research database for primary immunodeficiencies: results 2004–06. *Clin. Exp. Immunol.* **147**: 306–312.
64. Maródi, L. & J.L. Casanova. 2009. Primary immunodeficiency diseases: the J Project. *Lancet* **373**: 2179–2181.
65. Modell, F. 2007. Immunology today and new discoveries: building upon legacies of Dr. Robert A. Good. *Immunol. Res.* **38**: 48–50.
66. Modell, V. 2007. The impact of physician education and public awareness on early diagnosis of primary immunodeficiencies: Robert A. Good Immunology Symposium, *Immunol. Res.* **38**: 43–47.
67. El-Hakeh, J., S. Rosenzweig, M. Oleastro, *et al.* 2002. Wiskott-Aldrich syndrome in Argentina: 17 unique, including nine novel, mutations. *Hum. Mutat.* **19**: 186–187.
68. Barese, C., S. Copelli, R. Zandomeni, *et al.* 2004. X-linked chronic granulomatous disease: first report of mutations in patients of Argentina. *J. Pediatr. Hematol. Oncol.* **26**: 656–660.
69. Danielian, S., M. Oleastro, M. Eva Rivas, *et al.* 2007. Clinical follow-up of 11 Argentinian CD40L-deficient patients with 7 unique mutations including the so-called “milder” mutants. *Clin. Immunol.* **27**: 455–459.
70. Roos, D., D.B. Kuhns, A. Maddalena, *et al.* 2010. Hematologically important mutations: X-linked chronic granulomatous disease (third update). *Blood Cells Mol. Dis.* **45**: 246–265.
71. Agudelo-Flórez, P., C.C. Prando-Andrade, J.A. López, *et al.* 2006. Chronic granulomatous disease in Latin American patients: clinical spectrum and molecular genetics. *Pediatr. Blood Cancer* **46**: 243–252.
72. Marques, O.C., P.V.S. Pereira, M.J. Hackett, *et al.* 2011. Expanding the clinical and genetic spectrum of human CD40L deficiency: the occurrence of Paracoccidioidomycosis and other unusual infections in Brazilian patients. *J. Clin. Immunol.* In press.
73. Patiño, P.J., J. Rae, D. Noack, *et al.* 1999. Molecular characterization of autosomal recessive chronic granulomatous disease caused by a defect of the nicotinamide adenine dinucleotide phosphate (reduced form) oxidase component p67-phox. *Blood* **94**: 2505–2514.
74. Patiño, P.J., J.E. Perez, J.A. Lopez, *et al.* 1999. Molecular analysis of chronic granulomatous disease caused by defects in gp91-phox. *Hum. Mutat.* **13**: 29–37.
75. Telatar, M., S. Teraoka, Z. Wang, *et al.* 1998. Ataxia-telangiectasia: identification and detection of founder-effect mutations in the ATM gene in ethnic populations. *Am. J. Hum. Genet.* **62**: 86–97.
76. Mitui, M., C. Campbell, G. Coutinho, *et al.* 2003. Independent mutational events are rare in the ATM gene: haplotype prescreening enhances mutation detection rate. *Hum. Mutat.* **22**: 43–50.
77. Liu, L., S. Okada, X.F. Kong, *et al.* 2011. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J. Exp. Med.* **208**: 1635–1648.
78. de Beaucoudrey, L., A. Samarina, J. Bustamante, *et al.* 2010. Revisiting human IL-12R β 1 deficiency: a survey of 141 patients from 30 countries. *Medicine (Baltimore)* **89**: 381–402.
79. Kumar, V., L.A. Pedroza, E.M. Mace, *et al.* 2011. The autoimmune regulator (AIRE), which is defective in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients, is expressed in human epidermal and follicular keratinocytes and associates with the intermediate filament protein cytokeratin 17. *Am. J. Pathol.* **178**: 983–988.
80. Bustamante, J., A.A. Arias, G. Vogt, *et al.* 2011. Germline CYBB mutations that selectively affect macrophages in kindreds with X-linked predisposition to tuberculous mycobacterial disease. *Nat. Immunol.* **12**: 213–221.
81. Hambleton, S., S. Salem, J. Bustamante, *et al.* 2011. IRF8 mutations and human dendritic-cell immunodeficiency. *N. Engl. J. Med.* **365**: 127–138.
82. Woellner, C., E.M. Gertz, A.A. Schäffer, *et al.* 2010. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. *J. Allergy Clin. Immunol.* **125**: 424–432.
83. Salzer, U., C. Bacchelli, S. Buckridge, *et al.* 2009. Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. *Blood* **113**: 1967–1976.
84. Gonzalez, B., S. Moreno, R. Burdach, *et al.* 1989. Clinical presentation of Bacille Calmette-Guérin infections in patients with immunodeficiency syndromes. *Pediatr. Infect. Dis.* **8**: 201–206.
85. Yancoski, J., C. Rocco, A. Bernasconi, *et al.* 2009. A 475 years-old founder effect involving IL12RB1: a highly prevalent mutation conferring Mendelian Susceptibility to Mycobacterial Diseases in European descendants. *Infect. Genet. Evol.* **9**: 574–580.
86. Kim, H.Y., M.B. Eyheramonho, M. Pichavant, *et al.* 2011. A polymorphism in TIM1 is associated with susceptibility to severe hepatitis A virus infection in humans. *J. Clin. Invest.* **121**: 1111–1118.
87. de Oliveira-Junior, E.B., J. Bustamante, P.E. Newburger & A. Condino-Neto. 2011. The human NADPH oxidase: primary and secondary defects impairing the respiratory burst function and the microbicidal ability of phagocytes. *Scand. J. Immunol.* **73**: 420–427.
88. Luengo-Blanco, M., C. Prando, J. Bustamante, *et al.* 2008. Essential role of nuclear factor-kappa B for NADPH oxidase activity in normal and anhidrotic ectodermal dysplasia leukocytes. *Blood* **112**: 1453–1460.
89. Condino-Neto, A. & P.E. Newburger. 2000. Interferon-gamma improves splicing efficiency of CYBB gene transcripts in an interferon-responsive variant of chronic granulomatous disease due to a splice site consensus region mutation. *Blood* **95**: 3548–3554.
90. Jesus, A.A., B.L. Liphhaus, C.A. Silva, *et al.* 2011. Complement and antibody primary immunodeficiency in juvenile systemic lupus erythematosus patients. *Lupus.* **20**: 1275–1284.