Algerian Registry for Inborn Errors of Immunity in Children: Report of 887 Children (1985–2021)

Abdelghani Yagoubi1 · Azzeddine Tahiat2 · Nabila Souad Touri3 · Mohamed Samir Ladj4 · Ouardia Drafi5 · Brahim Belaid6 · Ayda Mohand-Oussaid7 · Abdelhak Dekhim8 · Reda Belbouab9 · Yacine Ferhani9 · Souhila Melzi10 · Zohra Mansouri11 · Samir Iddir12 · Ouardia Khaled13 · Yacine Inouri13 · Yanis Meddour14 · Saadeddine Dib15 · Zohra Mansouri16 · Samir Iddir17 · Abderrahmane Boufersaoui18 · Houda Boudiaf19 · Abderrachid Bouhdjila20 · Ouardia Ibsaine16 · Hachemi Maouche21 · Djazia Dahlou21 · Azzedine Mekki5 · Belkacem Bioud8 · Zair Bouzerar10 · Zoulikha Zeroual11 · Fadila Benhassine18 · Dahila Bekkat-Berkani18 · Soumeya Naamoune22 · Samir Sofiane Salah22 · Samia Chaib14 · Nabila Atta123 · Nadia Bensaadi17 · Nadira Bouchair24 · Nacira Cherif12 · Leila Kedji1 · Salah Beneddouche25 · Mohamed Lamine Atif26 · Kamel Djenouhat2 · Nadia Kechout23 · Reda Djidjik6 · Keitoum Nafissa Benhalla7 · Leila Smaoui18 · Rachida Boukari9

Received: 9 February 2022 / Accepted: 3 July 2022 / Published online: 15 July 2022
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Abstract

Introduction  Inborn errors of immunity (IEI) represent a heterogeneous large group of genetic disorders characterized by susceptibility to frequent infections, autoimmune/inflammatory diseases, allergy, and malignancy. We aimed to report for the first time the Algerian registry for IEI in children.

Methods  We described the characteristics of IEI in Algerian children from the data collected in the Algerian registry for IEI between 1985 and 2021.

Results  Over a period of 37 years, we included 887 children (530 male, 59.6%) with a mean age at diagnosis of 3.23 years and a mean diagnosis delay of 2 years. The prevalence rate was estimated at 1.97/100,000 inhabitants or 5.91/100,000 children. The parental consanguinity was found in 52.6%. The most prevalent category was combined immunodeficiencies (CID) (35.5%), followed by predominantly antibody deficiencies (24.5%) and CID with syndromic features (18.3%). The most predominant diseases were severe CID (134 cases), MHC II deficiency (99 cases), agammaglobulinemia (82 cases), common variable immunodeficiency (78 cases), hyper IgE syndromes (61 patients), ataxia-telangiectasia (46 patients), Wiskott-Aldrich syndrome (40 patients) and chronic granulomatous disease (39 cases). The clinical presentation was dominated by lower respiratory tract infections (69%), failure to thrive (38.3%), and chronic diarrhea (35.2%). Genetic analysis was performed in 156 patients (17.6%). The global mortality rate was 28.4% mainly caused by CID.

Conclusion  This is the first report of the Algerian registry for IEI in children. Data is globally similar to that of the Middle East and North African (MENA) registries with high consanguinity, predominance of CID, and significant mortality. This registry highlights the weak points that should be improved in order to provide better patient care.

Keywords  Inborn errors of immunity · Registry · Children · Algeria
particularities, and prioritize efforts needed to improve diagnosis and treatment of IEI. Moreover, a national registry is very useful to identify all diagnosed patients, to estimate the prevalence of these disorders and to provide data for health-care professionals to improve patient care, and to perform scientific research, as well as it is an important tool to convince health authorities to set a national program of awareness and access to adequate management including bone marrow transplantation in children.

Although some specific aspects of IEI have been previously reported in Algerian patients [4–9], a global overview of IEI in Algeria has not been published yet. In this report, we describe epidemiological, clinical, etiological, management, and outcome data of IEI diagnosed in Algerian children.

**Materials and Methods**

**General Information About Algeria**

Algeria is the largest country in Africa with more than 2.3 million km². It includes three main geographical areas: The coastal band in the north; the highlands and steppe areas in the center; the Sahara in the south which covers 87% of the country’s surface. This year 2021, Algeria has a population of 45 million inhabitants with approximately 33% of children under 17 years old, and about 90% of this population lives in the north and the center [10]. Due to its history, Algeria is a rich ethnic mix with Berber, Arab, European, Turkish, and other origins. There are currently 17 university hospitals and about 10 public hospitals with academic departments of Pediatrics, most of them located in the north.

**The IEI Study Group**

The first Algerian child with IEI was registered in 1985. In 2015, a PID study group as a part of the Algerian Society of Pediatrics performed a retrospective multicenter study on PIDs in Algerian children. Data were collected from 13 pediatric departments and 4 immunology laboratories, and the results were reported in the 4th congress of the African Society for Immunodeficiency (ASID) [11]. This informal registry was updated prospectively with inclusion of newly registered patients from 18 pediatric centers (12 centers located in Algiers) and 5 immunology laboratories (all located in Algiers). In 2021, the members of the above-mentioned group (listed authors of this article) met to make this last update reported here and to create a formal registry.

**Data Collection and Content**

In the participating centers, all children aged less than 16 years at time of diagnosis of IEI between 1985 and May 2021 were included. Before 2015, data was obtained retrospectively from patient medical records and entered into a Microsoft Excel database. Since 2015, it has been collected prospectively on a standardized data form and then entered into the computerized database. Recorded information included demographical, clinical, biological (immunological, microbiological, and genetic, if available), treatment (antibiotics, immunoglobulin, bone marrow transplantation ...), and outcome data (complications and mortality). The data was regularly updated with a follow-up of patients every 3 to 6 months. All pediatric departments and immunology laboratories at Algerian University or teaching hospitals were invited to participate in this survey. A steering committee among authors reviewed the database to remove duplicates and to validate or correct diagnosis and category.

Data were collected and blood samples were analyzed after parent’s consent. The study was approved by the Ethics Committee of Mustapha Bacha University Hospital in Algiers, and it conforms to the provisions of the World Medical Association’s Declaration of Helsinki.

**Diagnosis and Classification**

Immunological workup was performed in five experienced laboratories, all of them located in Algiers. Complete blood count and serum immunoglobulin (Ig) measurement were performed in all patients after serological testing for human immunodeficiency virus to rule out a secondary immunodeficiency. Immunophenotyping of lymphocyte subpopulations by flow cytometry was included in the immunological workup since 2003. Other laboratory testing, including serum IgE level, serum IgG subclasses, antigenic and functional complement measurement, oxidative burst test, post-vaccination antibody response, were performed when needed. Before 2014, genetic analysis was performed only in few patients through a collaborative work with international centers (mainly from the USA and France), but currently Algerian laboratories are performing more frequently this analysis locally or in collaboration with international centers.

We used the ESID Registry-Working definitions based only on clinical and immunological criteria to diagnose the different IEIs in our patients [12, 13]. The genetic analysis when available was performed to support the diagnoses already established according to the ESID criteria. As we started registration of our patients in 2015, all diagnosed
IEIs were classified according to the Primary Immuno-deficiency Classification of the International Union of Immunological Societies Expert Committee updated in 2014 [14]. We have continued to use this classification for the following registered patients. IEIs were classified in nine categories: (1) Combined immunodeficiencies (CID), (2) CID with syndromic features, (3) predominantly antibody deficiencies, (4) diseases of immune dysregulation, (5) congenital defects of phagocyte number, function or both, (6) defects in innate immunity, (7) autoinflammatory disorders, (8) complement deficiencies, (9) unclassified PID (instead of phenocopies of PIDs).

Importantly, we did not include in our registry children with asymptomatic selective IgA deficiency or transient hypogammaglobulinemia of infancy.

Statistical Analysis

Basic descriptive statistical analysis was carried out using Microsoft Excel software.

Results

In a 37-year period, 887 children with IEI were collected from the different participating clinical pediatric centers (785 patients: 88.5%) and from immunology laboratories (102 patients: 11.5%). The prevalence rate was 1.97/100,000 inhabitants or 5.91/100,000 children. The number of included patients was steadily increasing, especially after 2017 with more than 100 cases per year (Fig. 1). Four hundred seventy-five patients (66% of the total number of included patients) lived in Algiers and neighboring provinces, and only 69 patients (7.8%) lived in the southern regions.

Demographic Data

Among the 887 included patients, 530 were male, and 357 were female (sex ratio was 1.48). Mean age at diagnosis was 3.23 years, and the mean age at onset was 1.22 years. These demographic characteristics are shown by IEI category in Table 1.

Parental consanguinity was found in 467 cases (52.6%), and a history of death in infancy was noted in 256 families (28.9%). This mortality involved 1 to 6 infants per family with a total of 394 deaths; most of them with the same clinical features of the index case.

Distribution of IEI

Patients were distributed into 9 categories as depicted in Fig. 2. The predominant categories were CID (35.5%), predominantly antibody deficiencies (24.5%), and CID with syndromic features (18.3%). The most predominant diseases were severe CID (SCID) (134 cases), MHC II deficiency (99 cases), agammaglobulinemia (82 cases), common variable immunodeficiency (78 cases), hyper IgE syndromes (61 cases), ataxia-telangiectasia (46 cases), Wiskott-Aldrich syndrome (40 cases) and chronic granulomatous disease (39 cases).

One hundred fifty-six children had complete lack of naive T cells including 134 patients with SCID, 18 patients with Omenn syndrome, and 4 patients with complete Di George syndrome. Only 27 (17.3%) children had an early FACS diagnosis including 17 children with SCID (12.7% of SCID patients), 8 children with Omenn syndrome (44.4% of Omenn syndrome patients), and 2 children with complete Di George syndrome (50% of complete Di George syndrome patients).
Furthermore, it is worth to be mentioned that 105 cases (11.8%) exhibited clinical features and immunological abnormalities compatible with IEI but could not be assigned to a given IEI category. They were considered, according to ESID registry-working definitions, as unclassified CID (47 cases), unclassified syndromic ID (5 cases), unclassified antibody deficiency (20 cases), unclassified disorders of immune dysregulation (5 cases), unclassified phagocytic disorders (3 cases), and unclassified immunodeficiencies (25 cases). The spectrum of the different identified IEI in our registry is shown in Table 2.

**Clinical Presentation**

The clinical presentation observed at diagnosis was dominated by lower respiratory tract infections (69%), failure to thrive (38.3%), and chronic diarrhea (35.2%). Of course, these clinical manifestations depended on the type of IEI. The main clinical signs observed in our registry are presented in Fig. 3.
Table 2 Different diseases diagnosed in Algerian IEI registry

| Diseases                                      | Number of patients | % Inside the registry | % Inside the category |
|-----------------------------------------------|--------------------|-----------------------|-----------------------|
| I. Combined immunodeficiencies (CID)          |                    |                       |                       |
| SCID                                          | 134                | 15.1                  | 42.5                  |
| T−B−NK−                                       | 15                 | 1.7                   | 4.7                   |
| T−B−NK+                                       | 73                 | 8.2                   | 23.2                  |
| T−B+NK−                                       | 14                 | 1.6                   | 4.4                   |
| T−B+NK+                                       | 32                 | 3.6                   | 10.2                  |
| Leaky SCID                                    | 10                 | 1.1                   | 3.2                   |
| MHC II deficiency                             | 99                 | 11.2                  | 31.4                  |
| Omenn syndrome                                | 18                 | 2.0                   | 5.7                   |
| CD40 ligand deficiency                        | 4                  | 0.4                   | 1.3                   |
| MHC I deficiency                              | 1                  | 0.1                   | 0.3                   |
| FCHO 1 deficiency                             | 2                  | 0.2                   | 0.6                   |
| Unclassified CID                              | 47                 | 5.3                   | 14.9                  |
| II. CID with syndromic features               |                    |                       |                       |
| Hyper IgE syndrome                            | 61                 | 6.9                   | 37.6                  |
| Ataxia-telangiectasia                         | 46                 | 5.2                   | 28.4                  |
| Wiskott-Aldrich syndrome                      | 40                 | 4.5                   | 24.7                  |
| Di George syndrome                            | 7                  | 0.8                   | 4.3                   |
| Vici syndrome                                 | 1                  | 0.1                   | 0.6                   |
| Hereditary folate malabsorption               | 1                  | 0.1                   | 0.6                   |
| Defective Arp2/3-mediated filament branching  | 1                  | 0.1                   | 0.6                   |
| Unclassified syndromic ID                     | 5                  | 0.5                   | 3.1                   |
| III. Predominantly antibody deficiencies       |                    |                       |                       |
| Agammaglobulinemia                            | 82                 | 9.2                   | 37.8                  |
| Common variable immunodeficiency              | 78                 | 8.8                   | 35.9                  |
| Hyper IgM                                     | 16                 | 1.8                   | 7.4                   |
| Selective IgA deficiency                      | 15                 | 1.7                   | 6.9                   |
| IgG subclass deficiency                        | 4                  | 0.5                   | 1.8                   |
| Selective IgM deficiency                      | 1                  | 0.1                   | 0.5                   |
| Specific antibody deficiency                  | 1                  | 0.1                   | 0.5                   |
| Unclassified antibody deficiency              | 20                 | 2.2                   | 9.2                   |
| IV. Diseases of immune dysregulation          |                    |                       |                       |
| Familial hemophagocytic lymphohistiocytosis    | 21                 | 2.4                   | 32.8                  |
| Chediak Higashi syndrome                      | 15                 | 1.7                   | 23.4                  |
| Griscelli syndrome                            | 8                  | 0.9                   | 12.5                  |
| ALPS                                          | 10                 | 1.1                   | 15.6                  |
| IPEX                                          | 4                  | 0.5                   | 6.2                   |
| IL10R deficiency                              | 1                  | 0.1                   | 1.6                   |
| Unclassified disorders of immune dysregulation| 5                  | 0.5                   | 7.8                   |
| V. Congenital defects of phagocyte            |                    |                       |                       |
| Chronic granulomatous disease                 | 39                 | 4.4                   | 54.9                  |
| Neutropenia                                   | 17                 | 1.9                   | 23.9                  |
| LAD 1                                         | 10                 | 1.1                   | 14.1                  |
| LAD 3                                         | 2                  | 0.2                   | 2.8                   |
| Unclassified phagocytic disorders             | 3                  | 0.3                   | 4.2                   |
| VI. Defects in innate immunity                |                    |                       |                       |
| Chronic mucocutaneous candidiasis             | 7                  | 0.8                   | 58.3                  |
| Mendelian susceptibility to mycobacterial disease | 5   | 0.5                   | 41.7                  |
| VII. Autoinflammatory disorders               | 16                 | 1.8                   |                       |
**Genetic Data**

Genetic analysis was performed in 156 patients (17.6%). The most frequently found mutations concerned 59 children (37.8%) with MHC II deficiency, 26 children (16.7%) with X-linked agammaglobulinemia, 14 children (9%) with SCID, and 10 children (6.4%) with CD18 deficiency.

Among patients with MHC II deficiency, a recurrent mutation of the $RFXANK$ gene, a 26-bp deletion at the boundary between intron 5 and exon 6 (also known as 752delG-25), has been found in 59 patients (i.e., in all patients with MHC II deficiency who had genetic analysis).

**Management**

Three hundred eighty-four out of the 690 children (55.6%) belonging to the three first categories (CID + CID with syndromic features + predominantly antibody deficiencies) included in our registry were under regular intravenous immunoglobulin (IV Ig) replacement therapy. This group included 201 patients with CID (63.8% of a total of 315 children with CID); 70 had CID with syndromic features (43.5% of 161 children of this category); and 113 had predominantly antibody deficiencies (52.1% of 217 children of this category) including 57 (69.5%) out of 82 agammaglobulinemia and 38 (48.7%) out of 78 common variable immunodeficiency. Immunoglobulin replacement therapy was well tolerated in almost all patients except for 13 (3.1%) children who had adverse events: rash (10/13), fever (1/13), seizure (1/13), and stroke (1/13).

Three hundred ninety-one (44%) children had microbiological data. Five hundred fifty-seven germs were identified and are detailed in Table 3. Curative antibiotics, antiviral, or antifungal therapies were used mostly on the basis of these microbiological data. Prophylactic antibiotic therapy, mainly

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**Table 2** (continued)

| Diseases                          | Number of patients | % Inside the registry | % Inside the category |
|-----------------------------------|--------------------|-----------------------|-----------------------|
| Familial Mediterranean fever      | 4                  | 0.4                   | 25.0                  |
| Hyper IgD                         | 7                  | 0.8                   | 43.7                  |
| CAPS                              | 5                  | 0.6                   | 31.2                  |
| VIII. Complement deficiencies     | 5                  | 0.6                   |                       |
| Unclassified ID                   | 25                 | 2.8                   |                       |
| Global                            | 887                | 100                   |                       |

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**Fig. 3** Main clinical signs observed at diagnosis

![Clinical Signs](image)

**Table 3** Isolated microbes in Algerian IEI registry

| Microbes                               | Number |
|----------------------------------------|--------|
| I. Bacteria                            | 338    |
| *Pseudomonas aeruginosa*               | 80     |
| *Staphylococcus aureus*                | 114    |
| Encapsulated germs                     | 75     |
| *Mycobacterium tuberculosis*           | 21     |
| Others                                 | 48     |
| II. Viruses                            | 62     |
| Cytomegalovirus                        | 28     |
| Ebstein Barr virus                     | 14     |
| Others                                 | 20     |
| III. Fungi                             | 157    |
| *Aspergillus*                          | 14     |
| *Candida*                              | 109    |
| *Pneumocystis jiroveci*                | 22     |
| *Cryptosporidium*                      | 12     |
| Global                                 | 557    |

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cotrimoxazole, was prescribed in 497/887 (56%) patients. It was different depending on the diagnostic category: 60.5% of patients with congenital defects of phagocyte, 39.8% of patients with CID, 27.2% of patients with syndromic CID, and 22.3% of patients with predominantly antibody deficiencies. Azithromycin prophylactic treatment was prescribed to patients with agammaglobulinemia and CVID presenting with bronchiectasis.

Hematopoietic stem cell transplantation (HSCT) was performed in 27 patients including 10 children with Wiskott-Aldrich syndrome, 3 children with MHC II deficiency, 3 children with chronic granulomatous disease, 3 children with Chediak Higashi syndrome, 3 children with CD40L deficiency, 2 children with SCID, 1 child with hyper IgE syndrome, 1 child with familial hemophagocytic lymphohistiocytosis, and 1 child with LAD1. This therapy was performed locally (single center of Pierre et Marie Curie University Hospital) in 9 children. A couple of 4-year-old twins with Wiskott-Aldrich syndrome underwent gene therapy at 20 months old performed in Italy. They are currently doing well.

### Mortality and Outcomes

Among the 887 patients, 10 (1.1%) had cancers, mainly lymphomas (70%). These children had mostly combined immune deficiencies. At the time of cancer onset, they were between 3 and 13 years old, and all of them were known as patients with immune deficiency, except one child in whom a gingival endothelioma was first diagnosed, and then exploration revealed a leaky SCID. Death occurred in 5 of them between 4 and 12 years old. These patients’ details are shown in Table 4.

In our registry, 201 (22.7%) children died with a median of 6 deaths/year (Q1 = 1, Q3 = 14); 180 (20.3%) children were lost to follow-up with a median of 11 months of follow-up before lost (Q1 = 4.5, Q3 = 30), and 506 (57%) children were alive and regularly followed up every 3 to 6 months, with a median follow-up of 13 months (Q1 = 6, Q3 = 36).

After exclusion of the 180 patients lost to follow-up, the mortality rate was estimated at 28.4% (201/707), but if we consider the likelihood of death of these lost to follow-up patients, the mortality rate could increase up to 43% (381/887). Children with CID had the most severe prognosis with 49.2% of mortality among which SCID were responsible for the highest mortality rate (64.9%). CID mortality was followed by diseases of immune dysregulation (44.2%), congenital defects of phagocyte (26.2%), CID with syndromic features (13.5%), and predominantly antibody deficiencies (8.2%). The main cause of death was severe infection in 144 patients (71.6%).

The transition of our patients from pediatric care to adult medicine is limited. Alive children with IEI who have reached 16 years old identified in our register are 68 patients. They mainly belong to the categories of predominantly antibody deficiencies and syndromic CID.

### Discussion

#### IEI Prevalence

We present the first report on the distribution of IEI in Algerian children. A total of 887 children were collected in a 37-year period, thus representing the largest published cohort of IEI patients in Africa and the third largest one in the Middle East and North Africa (MENA) [15, 16].

Based on a current population of 45 million inhabitants in Algeria, the estimated prevalence of IEI is approximately 2/100,000 inhabitants. However, since our registry includes only children, it would be more interesting to estimate the prevalence in this age group of population, and as this group represents about 33% of the general population, the estimated prevalence would be 6.6/100,000 inhabitants.

Table 4  Data of patients with immunodeficiency and cancer

| Patient | IEI                  | Age at IEI diagnosis (mo) | Cancer               | Age at cancer diagnosis (mo) | Status   | Age at death (mo) | Follow-up after cancer diagnosis (mo) |
|---------|----------------------|--------------------------|----------------------|-----------------------------|----------|------------------|--------------------------------------|
| 1       | CVID                 | 50                       | Hodgkin lymphoma     | NP                          | Died     | 65               |                                      |
| 2       | Ataxia-telangiectasia| 36                       | Non-Hodgkin’s lymphoma| 120                         | Died     | 146              |                                      |
| 3       | Ataxia-telangiectasia| NP                      | Non-Hodgkin’s lymphoma| 84                          | Alive    | 18               |                                      |
| 4       | SCID                 | 9                        | Myelodysplasia       | 45                          | Died     | 48               |                                      |
| 5       | Unclassified ID      | 9                        | Sarcoma              | 126                         | Died     | 134              |                                      |
| 6       | ALPS                 | 36                       | Hodgkin lymphoma     | 156                         | Alive    | 60               |                                      |
| 7       | Ataxia-telangiectasia| 36                       | Non-Hodgkin’s lymphoma| 48                          | Alive    | 108              |                                      |
| 8       | DOCK8                | 34                       | Non-Hodgkin’s lymphoma| 108                         | Died     | 120              |                                      |
| 9       | Ataxia-telangiectasia| 48                       | Hodgkin lymphoma     | 180                         | Alive    | 24               |                                      |
| 10      | Leaky SCID           | 48                       | Endothelioma         | 48                          | Alive    | 24               |                                      |
population in Algeria, the adjusted prevalence is approximately 6/100,000 children. This prevalence is greater than that found in Morocco (1.87/100,000) or Libya (1.65/100,000) but remains comparable to that reported in Tunisia (6.3/100,000), even though it should be noted that unlike the current Algerian registry, all other Maghreb registries include children and adults [17–19].

Although IEI are widely considered rare diseases, they could be more common than generally thought. Following the model proposed by Bousfiha et al. [20] based on an American epidemiological study with a prevalence of 86.3/100,000 inhabitants, the number of IEI patients in Algeria could be estimated at 38,835 with approximately 13,000 children, without taking into account the high rate of consanguinity in our population. Applying this model, we can estimate at 93.2% (13,000–887/13,000) the proportion of children who escaped inclusion. This high percentage is close to that of Maghreb countries [15]. It could be estimated at 93% in Tunisia and 97.8% in Morocco. Underestimation of the actual number of patients could be explained by several factors: (1) difficulty in accessing care for many patients due to the distance from diagnostic and treatment centers, mainly concentrated in Algiers; (2) likely existence of many cases died before being diagnosed. Indeed, dead infants in patients’ families (394 cases), as well as asymptomatic children in these families, were not counted. Currently, there is no systematic neonatal screening in Algeria, as in many North African countries, and family screening is not commonly carried out. Working to implement both practices will improve the capture of cases and their early management, (3) lack of awareness of IEI by the public and many health professionals leading to under diagnosis of these diseases, and finally (4) exclusion of children with asymptomatic selective IgA deficiency or transient hypogammaglobulinemia of infancy.

The documented incidence of IEI in Algeria has risen. The number of newly diagnosed IEI patients was less than 6 cases per year before 2003, whereas more than 100 new cases per year were diagnosed during the last 3 years. Such increase is mainly due to the performance of immunology laboratories which provided since 2003 the basic tests necessary for the diagnosis of the majority of IEI, and also to the improved awareness of physicians in diagnosing IEI since 2015, when the working group started collecting data to prepare the creation of this registry and reported the preliminary results during the fourth meeting of the African Society for Immunodeficiencies that took place in Algiers.

### Consanguinity

A high rate of consanguinity (52.6%) was found in our registry. Like in other IEI cohorts, this rate is higher than in Algerian general population where consanguinity was estimated at 25% [21]. However, this high consanguinity rate among IEI patients seems to be a commune feature of MENA region countries (58.2% in Tunisia, 43.2% in Morocco, 54.1% in Egypt, 78% in Kuwait, and 75% in Saudi Arabia) [17, 18, 22–24]. This high rate would explain the high number of autosomal recessive diseases in Algeria and other Arab countries.

### IEI Distribution

In our registry, CIDs were the most common (35.5%), followed by predominantly antibody deficiencies (24.5%) and CIDs with syndromic features (18.3%). Similar findings were also found in other Arab countries such as Tunisia [18], Egypt [22], Kuwait [23], and Saudi Arabia [24] with an estimated prevalence of CID of 28.6%, 30%, 31.8%, and 59.7%, respectively, whereas predominantly antibody deficiencies were the most common in Iranian [25], European [26], Latin-American [27], and American [28] registries with 30%, 50.5%, 52%, and 52%, respectively (Fig. 4). Such contrast between Arab and western countries may be explained by the high consanguinity rate promoting the emergence of autosomal recessive forms of CID, but it might be also related to a specific genetic background of Arab and North African countries. Indeed, 99 out of the 315 patients with CID had MHC class II deficiency (31.4% of CIDs and 11.2% of total IEI cases in our registry), caused mainly by a 26-bp deletion in RFXANK gene (i.e., 15E6−25_15E6+1, also known as 752delG26) [5, 6, 29]. The high frequency of 15E6−25_15E6+1 deletion among Algerian patients with MHC class II deficiency seems to be related to a founder effect in the North African population. Ouederni et al. showed that patients (most of them were Algerian) sharing 15E6−25_15E6+1 mutation had a common homozygous haplotype around the RFXANK gene locus [29]. The analysis in this study estimated the age of the most recent common ancestor (MRCA) of the patients to 90 generations. He lived 2250 years ago [29]. MHC class II deficiency is also common in other Arab countries, including Tunisia (7.9%), Morocco (6.7%), Kuwait (5.4%), and Saudi Arabia (12.4%), while its prevalence is very low in Iran (0.1%), Latin America (0.2%), and USA (0.04%). Another possible explanation for CID predominance is the absence of adult patients in our registry, knowing that the most frequent IEI type in adults is CVID.
**Genetic Diagnosis**

Although many IEIs can be characterized based on clinical and immunological data, genetic analysis remains a very useful diagnostic tool, especially in patients with confusing clinical and immunological picture. The access to genetic analysis depends on the human and laboratory resources of each country. Indeed, the percentage of genetic diagnosis ranged from 5.1 to 22.2% in Africa, 30.2 to 69% in the Middle East, 3.7 to 59.4% in the Far East, 8.8 to 57.3% in Europe, an average of 18% in Latin America and 45.8% in the USA [16]. In Algeria, the genetic diagnosis has increased from 11 patients (2.7%) in 2015 to 156 (17.6%) in this last report. This substantial increase of genetic testing in the last few years has been possible, thanks to the efforts of local immunology laboratories and to the collaboration with international teams. Further efforts are needed to raise awareness and improve collaboration with Algerian geneticists in the framework of the national registry. This will help to decrease the rate of unclassified IEIs.

**Management**

Infections are the most common cause of morbidity and mortality in children with IEI. Although IVIg replacement therapy decreases the frequency of invasive bacterial infections, it does not seem to completely prevent their occurrence; therefore, prophylactic antibiotics are commonly indicated [30]. We mainly used treatment by cotrimoxazole recommended in all CID, syndromic CID, predominantly antibody deficiencies, CGD, and congenital neutropenia. Antibiotic prophylaxis with azithromycin was used in predominantly antibody deficiencies expressed by respiratory manifestation with commonly associated bronchiectasis. In spite of the use of IVIg, antibiotic prophylaxis remains useful to slow down the progression and aggravation of bronchiectasis.

According to the classical indications of HSCT in IEI patients [31] including SCID, Omenn syndrome, MHC II deficiency, CD40 L deficiency, Wiskott-Aldrich syndrome, IPEX, familial HLH, Chediak Higashi syndrome, CGD, and LAD1, 384 children would have needed HSCT. However, only 27 patients (7%) underwent this therapy which is not yet sufficiently available in Algeria. Indeed, it has been performed locally in an adult HSCT center (Centre Pierre et Marie Curie — Algiers) only in 9 patients. Given that HSCT was not commonly performed in Algeria, some of our children with SCID took personal steps to access HSCT abroad. This was successful only for 2 patients.

**Mortality**

The overall mortality rate in our study was at least 28.4%. Similar mortalities were reported in other MENA registries, with 28.8%, 34.5%, 23.4%, and 26% in Moroccan, Tunisian, Egyptian, and Kuwaiti registries, respectively [17, 18, 23, 32]. Mortality was higher in CID patients than in patients from other IEI categories both in our cohort (49.2%) and other Arab registries; it ranged from 44 to 56% [17, 18, 23, 32]. SCID was responsible for the highest mortality rate (64.9%). In the CID category, 156 children had complete lack of naive T cells including 134 SCID, 18 Omenn syndrome and 4 complete Di George syndrome. Only 27 (17.3%) children had an early FACS diagnosis including 17 children with SCID (12.7% of SCID patients), 8 children with Omenn syndrome.
syndrome (44.4% of Omenn syndrome patients), and 2 children with complete Di George syndrome (50% of complete Di George syndrome patients), so the remaining 129 children (82.7%) would not have access to early FACS, and they could have been detectable through newborn screening. In contrast with our finding, the global mortality was low in Saudi Arabia registry (10.3%), and the mortality in the CID category was only 11.7% [24]. The high mortality rate in our data highlights the importance of an early and efficient management of patients with CID. In Europe, where antibody deficiencies are predominant (50.5% vs. only 10.3% for CID), the global mortality rate was 9.3% [26].

Limitations and Perspectives

This registry is a powerful tool to improve our knowledge on IEI. We believe that this work is the first step towards the implementation of a national registry of patients with IEI. The preparatory work for the development of this registry has created a multi-center network for the diagnosis and management of these patients and improved the collaboration between clinicians and immunologists. Progress was made as a result of the creation of this network, notably in terms of the number of diagnosed cases, which has increased from less than 6 cases per year before 2003 to more than 100 cases per year after 2017. This is mainly due to the considerable improvement in the immunological investigations (i.e., lymphocytes immune phenotyping by flow cytometry and functional analysis) and to the awareness of clinicians to recognize IEI through training.

We are aware that there are some limitations to this study including: (1) lack of adult cases, (2) use of the IUIS 2014 classification that does not include the later added categories of bone marrow failure syndromes and phenocopies of IEI, (3) underestimation of cases due to under-diagnosis of IEI and under-reporting of diagnosed cases that were sometimes recovered from laboratory lists, and (4) missing some information when collecting data retrospectively.

To address these shortcomings and to improve diagnosis and management of our patients, we plan to (1) move to an electronic registry that will be accessible and easy to use, thus facilitating the updating of patient data, (2) continue our efforts to raise awareness among physicians, including adult physicians, by training programs, (3) register all adult IEI patients in collaboration with immunologists and all relevant adult medicine specialists, (4) preparing and implementing a transition program to adult care will be a challenge for the next few years; with the improvement of care, there will be an increasing number of adolescents with IEI requiring the transition to adult-oriented care (internal medicine, pulmonology, and hematology). The main objective is to ensure the continuation of care and in particular the regular administration of IV Ig necessary to survive; (5) ensure availability of immunological tests in several regions of the country, (6) develop local molecular diagnosis and expand international collaboration, (7) implement SCID newborn screening, and (8) develop a pediatric HSCT center.

Conclusion

This registry provided an overview of the IEI situation in Algeria. Several similarities regarding the IEI epidemiology were found with other registries from the MENA region, such as high consanguinity rate, predominance of CIDs and significant mortality. Efforts should be made to strengthen the involvement of all physicians caring for these patients, increase the number of immunology laboratories to allow basic testing in the different regions of the country, improve collaboration with geneticists to better classify our patients, develop neonatal screening for SCID, make HSCT available for children with IEI, and develop home-based care. This will improve the quality of care, the quality of life for our patients, and reduce mortality. The current data is only for children; the involvement of adult physicians is needed to include adult patients and facilitate the child to adult transition. All these perspectives will be possible, if we convince policymakers and the health authorities of all these data, and steps have to be taken.

Acknowledgements

We want to pay tribute to the late Professor Mourad Baghriche, the first Algerian pediatrician who took a close interest in IEI. He was also the first reporter of our study group in international meetings. We would like to thank all the healthcare services involved in this study and our international collaborators. We express our deepest gratitude for all the patients and their families.

Author Contribution

(1) The conception and design of the study. (2) Acquisition of the data. (3) Analysis and interpretation of the data. (4) Drafting of the article. (5) Revising it critically for important intellectual content. (6) Approval of the final version to be submitted. (7) Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AY, LS, RBo (1, 2, 3, 4, 5, 6, 7); AT (2, 3, 4, 5, 6, 7); NST, MSL, OD, BB, AM, AD, RBe, YF, SM, AG, SH, OK, YI, YM, SN, SD, ZM, SI, ABoUf, HB, ABouh, OI, HM, DD, AM, BB, ZB, ZZ, FB, DB, SSS, SC, NA, NB, NBo, NC, LK, SB, KD, NK, RD (2, 3 ,5 ,6, 7); MLA (3, 5, 6, 7); KNB (1, 2, 3, 5, 6, 7).

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Declarations

Ethics Approval

This study involving human participants was reviewed and approved by Local Ethics Committee of Mustapha Bacha University Hospital and it conforms to the provisions of the World Medical Association’s Declaration of Helsinki.
Conflict of Interest

The authors declare no competing interests.

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Authors and Affiliations

Abdelghani Yagoubi1 · Azzeddine Tahiat2 · Nabila Souad Touri3 · Mohamed Samir Ladj4 · Ouardia Drali5 · Brahim Belaid6 · Ayda Mohand-Oussaid7 · Abdelhak Dekimi8 · Reda Beldoun8 · Yacine Ferhane9 · Souhila Melzi10 · Assia Guedour11 · Salima Hakem9 · Ouardia Khemici12 · Yacine Inouri13 · Yanis Meddour14 · Saadeddine Dib15 · Zohra Mansouri16 · Samir Iddir17 · Abderraouf Boufersaoui18 · Houda Boudiaf19 · Abderrahim Bouldjila20 · Ouardia Ibsaine16 · Hachemi Maouche21 · Djazia Douilou2 · Azzedine Mekki5 · Belkacem Biaoud · Zair Bouzerar20 · Zoulifka Zeroual11 · Fadila Benhassine18 · Dahla Bekka-Berkani18 · Soumeya Naamoune22 · Samir Sofiane Salah22 · Samia Chaib14 · Nabila Attal23 · Nadia Bensaadi17 · Nadira Bouchair24 · Nacira Cherif12 · Leila Kedji3 · Salih Bendeddouche25 · Mohamed Lamine Atif26 · Kamel Djemouha2 · Nadia Kechout23 · Reda Djiddik6 · Keltof Nafissa Benalla7 · Leila Smati18 · Rachida Boukari9

1 Pediatric Gastroenterology and Digestive Investigations, Centre Algérois de Pédiatrie, 57 Lotissement F, Draria 16050, Algiers, Algeria
2 Department of Medical Biology, Rouiba Public Hospital, Rue Larbi Abdesalam 16017, Algiers, Algeria
3 Department of Pediatrics, University Hospital Hassiba Ben Bouali, Rue Mohamed Boudiaf 09000, Blida, Algeria
4 Department of Pediatrics, Djilali Belkhenchir Public Hospital, El-Biar, Algiers, Algeria
5 Department of Pediatrics “B”, University Hospital Nafissa Hamoud, Rue Boudjemaa Moghi, Hussein Dey 16040, Algiers, Algeria
6 Department of Immunology, University Hospital Issaad Hassani, Beni Messous, 16206 Algiers, Algeria
7 Department of Pediatrics “A”, University Hospital Issaad Hassani, Beni Messous, 16206 Algiers, Algeria
8 Pediatric Division, University Hospital Abdenour Saadna, 19000 Setif, Algeria
9 Department of Pediatrics, University Hospital Mustapha Bacha, Place 1er Mai 1945, Sidi Mhamed, 16024 Algiers, Algeria
10 Department of Pediatrics, University Hospital Lamene Debaghine, Said Touati, Bab el Oued, 16009 BdAlgiers, Algeria
11 Department of Pediatrics “A”, University Hospital Nafissa Hamoud, Rue Boudjemaa Moghi, Hussein Dey 16040, Algiers, Algeria
12 Department of Pediatrics “B”, University Hospital Issaad Hassani, Beni Messous, 16206 Algiers, Algeria
13 Department of Pediatrics, Central Army Hospital, Ain Naadja 16205, Algiers, Algeria
14 Department of Immunology, Central Army Hospital, Ain Naadja 16205, Algiers, Algeria
15 Department of Pediatrics, University Hospital Dr Tidjani Damerdi, 05 Bd Mohammed V, Tlemcen, Algeria
16 Department of Pediatrics, Ain Taya Public Hospital, Ain Taya, Algiers, Algeria
17 Department of Pediatrics, University Hospital Nedir Mohamed, Tizi Ouzou, Algeria
18 Department of Pediatrics, Bologhine Ibn Ziri Public Hospital, Rue Abounoussa El Achaari Hammamet 16060, Algiers, Algeria
19 Department of Pediatric Oncology, University Hospital Mustapha Bacha, Place 1er Mai 1945, Sidi Mhamed, 16024 Algiers, Algeria
20 Department of Pediatrics “B”, University Hospital Ben Badis, Constantine, Algeria
21 Department of Pediatrics, Hassen Badi Public Hospital, El-Harrach, Algiers, Algeria
22 Department of Immunology, University Hospital Mustapha Bacha, Place 1er Mai 1945, Sidi Mhamed, 16024 Algiers, Algeria
23 Department of Immunology, Dely Brahim, Institut Pasteur d’Alger, Algiers, Algeria
24 Department of Pediatrics, Clinique Sainte Thérèse, Rue Calama, Annaba, Algeria
25 Department of Pediatrics, Mother and Child Specialized Hospital, Tlemcen, Algeria
26 Department of Epidemiology and Preventive Medicine, University Hospital Douera, Douera, Algiers, Algeria