Primary immunodeficiencies in Tygerberg Hospital and on the national PID Registry, South Africa

M van Velden

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Supervisor: Profs M Kruger and M Esser

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Mia van Velden

Date: December 2019

Abstract

Introduction: Little is known about the prevalence of primary immunodeficiencies (PID) in South Africa. The purpose of this study was to describe the profile and spectrum of patients affected by PID referred to the Tygerberg Hospital Immunology Service, situated in the Western Cape province of South Africa, during the past 25 years.

Methods: This study entailed a retrospective descriptive analysis of the epidemiological data of patients with suspected PID referred to Tygerberg Hospital Immunology Service between 1 January 1991 and 5 May 2016. Data collected included date of birth, diagnosis, age at diagnosis, geographic origin, ethnicity, referral site, family history of PIDs, presenting features, immunological tests done, and outcome (alive or dead). The diagnosis was classified according to the International Union of Immunological Societies (IUIS) published in April 2014 and the European Society for Immunodeficiency published in July 2016 or listed as 'other'.

Results: The patient cohort included 500 patients between 0 and 60 years with a median age of 5 years (interquartile range=10). The majority of patients (70%) were from the Western Cape and were referred by paediatricians not linked to tertiary institutions (43%). The most common clinical presentation was recurrent respiratory tract infections (60%). The male to female ratio was 1.2:1. The main categories of PID, according to the IUIS criteria, were antibody deficiencies (52,80%), followed by complement deficiencies (19,80%), combined immunodeficiencies (7,12%), combined immunodeficiencies with associated syndromic features (6,25%), autoinflammatory disorders (3,40%), congenital defects of phagocyte number and/or function (4,20%), and defects in innate immunity (1,26%). There were no patients with phenocopies of PID disorders. The majority of patients were Caucasian (59,40%), who had antibody deficiencies (39,00%) as most common diagnosis. This was followed by 24,80% mixed-race patients and 11,60% black African patients, who mostly had complement deficiencies (10,00% and 4,00%, respectively).

Conclusion: The median age of diagnosis of PID in this study was older than those in studies in other developing countries, but clinical presentation and types of PID were similar to reports from other developing countries with low rates of consanguinity. However, there was an increased number of patients diagnosed with complement deficiencies (specifically hereditary angioedema) in the Western Cape.

Opsomming

Inleiding: Daar is weinig studies aangaande die voorkoms van primêre immuungebreke (PIG) in Suid-Afrika. Die doel van dié studie was om die profiel en spektrum te bepaal van pasiënte met PIG wat oor die afgelope 25 jaar verwys is na die Tygerberg-immunologiekliniek in die Wes-Kaap.

Metodes: Die studie is ’n retrospektiewe beskrywende analise van die epidemiologiese data van pasiënte, vermoedelik met PIG, wat tussen 1 Januarie 1991 en 5 Mei 2016 na Tygerberg Hospitaal verwys is. Die ingesamelde data het die geboortedatum, diagnose, ouderdom ten tye van diagnose, geografiese oorsprong, etnisiteit, verwysingsbron, familiegeskiedenis van PIG, presenterende simptome, of daar immunologiese toetse gedoen is, en die uitkoms (of die pasiënt lewend is/ gesterf het) ingesluit. Die diagnose is geklassifiseer volgens die riglyne van die Internasionale Unie van Immunologiese Gemeenskappe (IUIG), wat in April 2014 gepubliseer is, sowel as dié van die Europese Gemeenskap vir Immuungebrekkigheid, in Julie 2016 gepubliseer, of as ‘ander’ uitgelig.

Resultate: Die pasiëntkohort het 500 pasiënte tussen 0 en 60 jaar met ’n mediane ouderdom van 5 jaar (interkwartiel variasie =10) ingesluit. Die meerderheid (70%) van die pasiënte was van die Wes-Kaap en is deur pediaters verwys wat nie verwant is aan tersiêre hospitale in die Wes-Kaap nie (43%). Die algemeenste presenterende klagte was herhalende respiratoriese infeksies (60%). Die verhouding van mans tot vrouens was 1.2:1. Volgens die IUIG klassifikasie was die hoofkategorieë van PIG antiliggaamdefekte (52,80%), gevolg deur komplementdefekte (19,80%), gekombineerde immuungebrekkigheid (7,12%), gekombineerde immuungebrekkigheid met geassosieerde sindromiese kenmerke (6,25%), outo-inflammatoriese defekte (3,40%), kongenitale defekte van fagosietgetal en/ of -funksie (4,20%), en defekte in aangebore immuniteit (1,26%). Daar was geen pasiënte met fenokopieë van PIG nie. Die meerderheid van pasiënte was van Kaukasiese herkoms (59,40%) met antiliggaam defekte (39,00%) as hoofdiagnose. Dit is gevolg deur 24,80% pasiënte van gemengde herkoms en 11,60% swart pasiënte – albei groepe het komplementdefekte (10% en 4% onderskeidelik) as hoofdiagnose gehad.

Gevolgtrekking: Die mediane ouderdom ten tye van diagnose met PIG in hierdie studie was ouer in vergelyking met studies in ander ontwikkelende lande. maar kliniese presentering en PIG-tipes was soortgelyk aan die van ander ontwikkelende lande met ’n lae voorkoms van bloedverwantskap. Daar is egter ’n groter aantal pasiënte met komplimentdefekte (spesifiek oorgeërfde angio-edeem) in die Wes-Kaap gediagnoseer.

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List of abbreviations

BCG	bacille Calmette-Guerin
BMT	bone marrow transplant
CGD	chronic granulomatous disease
CMV	cytomegalovirus
CNS	central nervous system
EBV	Epstein-Barr virus
ESID	European Society for Immunodeficiencies
GIT	gastrointestinal tract
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
Ig	immunoglobulin
IPIDR	Iranian Primary Immunodeficiency Registry
IUIS	International Union of Immunological Societies
LASID	Latin American Society for Immunodeficiencies
NHLS	National Health Laboratory Service
PID	primary immunodeficiency
REDCAP	research electronic data capture
SA PID Register	South African Primary Immunodeficiency Register
SCID	severe combined immune deficiency
TB	tuberculosis
WAS	Wiskott-Aldrich syndrome

Glossary

Gamma interferon – Macrophage-activating cytokine produced by T cells and natural killer cells.

Hematopoietic stem cell transplantation (**HSCT**) – The transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood. It may be autologous (the patient's own stem cells are used), allogeneic (the stem cells come from a donor) or syngeneic (the stem cells come from an identical twin).

Phenocopy – An environmentally induced, nonhereditary variation in an organism, closely resembling a genetically determined trait.

Chapter 1: Introduction

1.1 Background

Primary immunodeficiencies (PIDs) comprise nearly 300 different disorders in nine major categories.(1)(2) Very little is known of the prevalence of PID in Africa. Naidoo et al(3) concluded in a previous study of PIDs in the Western Cape, South Africa, that there was a need for research into the effective diagnosis of PIDs. Esser reported that PIDs were probably not only underdiagnosed, but were often diagnosed late.(4) Owen et al recently described the association of complement C5 and C6 deficiency in the mixed-race and African populations in the Western Cape, concluding that complement deficiencies in South Africa were not rare(5).Bacille Calmette-Guerin(BCG) disease in human immunodeficiency virus (HIV)-negative patients was also an indicator of underlying PID, which was important in the South African context, where all children were vaccinated with BCG at birth.(4)(6) Missed or delayed diagnoses of children with PIDs may lead to serious morbidity and mortality, and can lead to a missed opportunity to improve the quality of their lives and even save lives.(7)

South Africa has a high burden of infectious disease such as HIV and tuberculosis, which pose challenges for the diagnosis of PID.(8) These and other infectious diseases pose a limitation on resources available for rare diseases such as PIDs. They may also mask and delay a diagnosis of PID. This may result in the actual prevalence of PIDs in the country never being accurately determined.

1.2 Problem statement and aim of research project

The primary aim of the study was to describe the profile and spectrum of diagnoses of patients referred to Tygerberg Hospital immunology service during the past 25 years with suspected PID. This included the patients who were referred across the country to the Tygerberg Hospital immunology service and enrolled on the national PID Register.

1.3 Brief chapter overview

Chapter 2 reviews the literature, Chapter 3 describes the methodology including the study design, instruments used, data analysed, limitation of the data collection and ethical aspects of the data collection. Chapter 4 discusses the results and Chapter 5 draws conclusions based on the findings.

Chapter 2: Literature review

2.1 Introduction

Primary immune disorders are defects in the development and function of the human immune system. They are characterised by an increased susceptibility to infections, and some can present with autoimmunity or lymphoproliferation.(7)(9) Primary immunodeficiencies (PIDs) cause the patient to develop infections which are severe and persistent, presenting unusual types of organisms or course of illness, and may be associated with hypersensitivity reactions, autoimmunity and cancer.(10)(11)(12)

PIDs are relatively rare conditions and are frequently diagnosed only at a late stage.(13)(14)(15) PID is often not diagnosed because the patient may present with non-specific signs which may easily be ascribed to other more common diseases.(7)(6) A delay in diagnosis can cause mortality in the infant and serious morbidity in the older child, with permanent organ damage and suffering.(7)(16) Accurate diagnosis is crucial to allow the earliest institution of appropriate and often lifesaving therapy such as bone marrow transplants or long-term immune replacement, while an incorrect diagnosis may lead to unnecessary high-risk interventions or years on costly treatment.(17) It is therefore crucial that physicians are able to recognise the warning signs (18)(16) that can indicate PIDs so that the correct investigations and treatment may follow. Warning signs for PID vary in different regions of the world. In South Africa helpful indicators that warrant further investigation for PIDs are disseminated BCG, recurrent meningococcal infections and atypical mycobacteria.(19)(1)(20) Important warning signs include a family history of primary immunodeficiency or failure to thrive. Other warning signs are related to persistent, recurrent, severe or unusual infections (e.g. four or more ear infections within one year; two or more serious sinus infections or pneumonias within one year; two or more months on antibiotics with little effect or a need for intravenous antibiotics to clear infections; recurrent, deep skin or organ abscesses; or two or more deep-seated infections, including septicaemia, persistent thrush in the mouth and fungal infection on the skin).

Patient registries and databases constitute key instruments for the development of clinical research in the field of rare diseases, and the improvement of patient care and healthcare planning for better social, economic and quality of life outcomes. Such registries and databases are the appropriate way to pool scarce data for epidemiological and clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials, to support the enrolment of patients and to assess the impact of new interventions.(21) In order to increase awareness, diagnosis and reporting of PIDs, the South African PID Registry was established in 2008. Once an accurate estimate of the burden of a disease is known, resource allocation, essential drug list inclusions and treatment such as immunoglobulin replacement can be planned for PID patients in South Africa.

2.2 Broad theory base

2.2.1 Epidemiology

The global prevalence of PIDs varies between 0.3 and 12 per 100 000 population, and is higher in areas with high rates of consanguinity. The prevalence in South Africa is unknown, but according to data reported in the PID Register these diseases are either missed or not reported. The possible reasons for underdiagnosis are that patients presenting with recurrent, persistent, severe or even unusual infections are treated without investigating the underlying cause, or the diagnosis is missed in the face of the overwhelming burden of similar clinical presentations of infectious diseases such as HIV and tuberculosis.(22)

Data on epidemiology of PIDs are rapidly growing; however, as many countries have by now implemented registries for PIDs.(23) Registries are crucial to capture data on the spectrum of PID and treatment needs to inform healthcare providers and enable research collaborations.(8) Once an accurate estimate of prevalence of PIDs is known, it becomes a vital tool for advocacy for improved diagnostics and treatment. PID registries also allow identification of diseases more common in South Africa than elsewhere.(24)

Because of the limited resources to diagnose and treat PID, a group of immunologists from four Latin American countries formed an organisation in 1993 called the Latin American Group for Primary Immunodeficiency Diseases (LAGID – later LASID). One of its aims was to include other Latin American countries and to create registries of PID in each participating country. After more than a decade since the creation of this group and its PID Registry, the result is impressive. The membership of the group has grown from the initial four to a total of 14 countries. Awareness, diagnosis and treatment of PIDs have improved as a result of annual discussions with international speakers, educational programmes and national scientific meetings with paediatricians. LASID, in cooperation with scientists in countries with well-established immunology and molecular biology laboratories, helps other countries with limited resources in the diagnosis of PID. LASID has also developed a parent support group and an online forum to keep members up to date with discussions regarding diagnosis and treatment options.(23) Other examples of PID registries in developing countries include the African Society for Immune Deficiencies (ASID) and the Iranian PID Registry (IPIDR).(25)(26) Some examples of registries and databanks in developed countries include the Reference Centre for PIDs established in France in 2005 (Centre de Référence Déficits Immunitaires Héréditaires), the European Society for Immunodeficiencies (ESID), the Jeffrey Modell Foundation, the Asian Primary Immunodeficiency (APID) Network, and the United States Immunodeficiency Network (USIDNET).(25)

To date there is still limited information regarding PID in South Africa, a developing country with a population of about 55.7 million nationals across nine provinces. The 2016 midyear estimated figures for race distribution in South Africa were black African 80,60%, mixed race 8,80%, Caucasian 8,10%, and Asian 2,50%.

The South African PID Register was set up in affiliation with the paediatric PID clinical service in 2008 and is based at Tygerberg Hospital. The national registry is coordinated through the National Health Laboratory Service at Tygerberg Hospital with private secretarial funding.(24)(27) The registry includes patients from both the public and private sector of South Africa who have consented to their data being collected for registry purposes. The service was further improved by adding a genetic counselling service and a molecular identification study in 2013.

The only previous information on PID in South Africa was from an important study at a single institution, the Red Cross War Memorial Children's Hospital in Cape Town, which reported the epidemiology of PID over a 27-year period between 1983 and 2009, and included 168 patients. The most common PIDs were antibody deficiencies (51%) (of which common variable immunodeficiency was the most common), followed by well-defined syndromes (24%), combined B and T cell deficiencies (11%), phagocytic disorders (5%), predominantly T cell defects (5%), complement defects (4%) and disorders of innate immunity (0,60%). There was a male predominance in all categories, except in well-defined syndromes, where there was an equal gender distribution. There was a decline in the mean age of diagnosis of patients with PID (67 months to 35 months) over the period of 25 years.(3)

Comparing research from other developing countries like Iran and Tunisia, there is a similarity in mode of presentation. A large study in Iran between March 2006 and March 2013 of 731 patients from 14 medical centres predominantly had patients with antibody deficiency (32,30%). This was followed by combined immunodeficiencies (22,30%) and thereafter congenital defects of phagocyte number, function or both (17,40%), syndromes (17,20%), auto-inflammatory disorders (5,20%), immune dysregulation (2,60%), defects in innate immunity (1,60%) and complement deficiencies (1,40%).(26)

A report from Tunisia, covering 25 years (1988–2012) (Tunisian Registry of Primary Immunodeficiencies) included 710 patients. Of note was the high rate of consanguinity (58,20%) of families, as well as differences from Western countries owing to the large proportion of patients with combined immunodeficiencies and phagocyte defects in number and/or function. Combined immunodeficiency disorders were the most common (28,60%) followed by congenital defects of phagocyte (25,40%), immunodeficiency syndromes (22,70%), predominantly antibody deficiencies (17,70%), diseases of immune dysregulation (4,80%), defects of innate immunity (0,40%) and complement deficiencies (0,40%).(28) All three studies mentioned above (Tunisian, South African and Iranian studies) found the most common clinical presentation to be respiratory infections.

2.2.2 Classification of PID

The aim of the classification of PIDs in categories is to provide a framework that not only demonstrates the scientific basis of these conditions, but assists clinicians in diagnosis. Classification also contributes to advising on appropriate ICD10 coding (World Health Organization International disease codes). These codes form the basis on which funding for healthcare is provided.

The international classification, being the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency (see Appendix 2 for IUIS April 2014), defines nine categories which are distinguished according to which component of the immune system is affected.(29) For each category, the condition is listed, along with the genetic defect, if known, and the major immunological abnormalities (and for some conditions the non-immunological abnormalities) associated with the disease. Since 2013 the IUIS also instituted a phenotypic classification, and is revised every two years.

The nine IUIS categories are:(29)

1. Combined immunodeficiencies
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly antibody deficiencies
4. Diseases of immune regulation
5. Congenital defects of phagocyte number, function, or both
6. Defects in innate immunity
7. Autoinflammatory disorders
8. Complement deficiencies
9. Phenocopies of PID

Classification can be done by either using the IUIS or ESID criteria:

Table 2.1: Definition of IUIS and ESID

ESID (July 2016)	**IUIS (April 2014)**
▶ European Society of Immunodeficiencies (ESID; reviewed July 2016) ▶ 66 categories	▶ International Union of Immunological Societies Expert Committee for Primary Immunodeficiency (IUIS; reviewed April 2014) ▶ 9 categories

The extended classification and clinical diagnosis definitions of immunodeficiencies of the European Society of Immunodeficiencies (ESID) Registry (July 2016) has 66 categories (see Appendix 3). The ESID criteria are for patients with no genetic diagnosis, except for atypical severe combined immune deficiency (SCID) and DiGeorge syndrome where a known genetic defect and confirmation of criteria is mandatory.

2.2.3 The 10 warning signs of primary immunodeficiency are:(18)(30)(16)

1. One or more new ear infections within one year
2. Two or more serious sinus infections within one year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within one year
5. Failure of an infant to gain weight or grow normally
6. Recurrent, deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infection on skin
8. Need for intravenous antibiotics to clear infections
9. Two or more deep-seated infections including septicaemia
10. A family history of PIDs

Additional warning signs in use specifically to South African patients are:(13)

1. BCG dissemination
2. Recurrent meningococcaemia
3. Unusual or recurrent mycobacterial infections

2.2.4 Investigation of immunodeficiencies

Investigation is guided by an in depth detailed medical history, clinical presentation with thorough examination and consideration of a causative organism.(1)(30)(31) A practical way to investigate PID is provided in Table 2.2, which is adapted from the four-step Jeffrey Modell Foundation(JMF) approach, as the four steps procedure is not always feasible for patients who travel long distances in South Africa. Not all the recommended tests are available at the South African National Laboratory level.

Table 2.2: Primary Immunodeficiency investigation (modified from the Jeffrey Modell Foundation approach)

First-stage testing	Example
Exclude chronic infection	FBC and differential HIV, CMV, EBV, TB
Quantitative immunoglobulins	IgE, IgG, IgM, IgA
Sweat test	
Second- and third-stage testing	
Complement screen	CH50, C1qAb, C3, C4, C6, CH100, ACH 100, MBL, C1 inhibitor
Lymphocyte phenotyping	T helper cells, cytotoxic T cells, B cells, NK cells, Killer cells (using mAbs for CD3, CD4, CD8, CD19, CD16+56, CD18)
Humoral testing	IgG subclasses (IgG1, IgG2, IgG3, IgG4); B cell activation markers, memory B cells, specific antibody responses to protein antigens, response to polysaccharide vaccine
T Cell function	Mantoux skin test, Quantiferon gold TB test, T-spot TB test
Lymphocyte proliferation in response to mitogens	
Phagocyte function tests	Oxidative burst test, phagocytic index & chemotaxis, CD11, CD18, bacterial killing
Fourth-stage: Confirmatory / Genetic tests with some examples	
Agammaglobulinaemia Bruton's Tyrosine kinase; KRECS and TRECS (naïve B and T cells), common gamma chain, XLA gene BTK, CGD gene CYBB, XLP gene SH2D1A, NOD2 gene NOD2	

(i) First-stage testing

First-stage testing includes exclusion of chronic infection and causes of secondary immune deficiency such as human immunodeficiency virus (HIV), cytomegalovirus (CMV), Ebstein Barr virus (EBV), TB, coeliac disease, diabetes mellitus, cystic fibrosis and protein-losing states. First-line screening for primary immune defects includes a full blood count with a differential count and a smear, as well as testing of immunoglobulin levels.(32)(33) When evaluating the white cell subsets it is important to look at the absolute count rather than percentages and the respective ranges for age.(31) When measuring levels of major immunoglobulin classes (IgG, IgA, IgM and IgE), it is important to compare the results with age-matched reference intervals that are typically provided as 95% confidence intervals.(31)

(ii) Second- and third-line testing (34)

Second- and third-line testing should be dependent on suggestive history, symptoms and cultured organisms. Lymphocyte phenotyping by flow cytometry form part of the later screening tests of humoral, T cell and NK cell deficiencies. Absence of B cells with normal T cells and NK cells is found with agammaglobulinaemia, while reduced T cells are found in severe combined immunodeficiency syndrome (SCID).(35)

The best screening test for defects in the classical complement pathway is doing a haemolytic complement activity assay (CH50) (classical pathway), whereas the AH50 assay screens for defects in the alternative pathway.(31) When the total immunoglobulin levels are only modestly decreased (or even normal), measurement of specific antibody responses is useful in confirming defective antibody production.(31) Functional analysis of B lymphocyte and IgG subclasses involves the analysis of antibody responses to protein antigens (e.g. antibody response to tetanus vaccine) and polysaccharide antigens (e.g. antibody response to *Streptococcus pneumoniae* polysaccharide vaccine). If the antibody response to a vaccine antigen is low, the patient should be vaccinated to ensure appropriate exposure, and antibody levels should be retested four weeks after vaccination.(31)(1)

Immunoglobulin subclasses (IgG1, IgG2, IgG3 and IgG4) can be used in selected patients to delineate subclass deficiencies if IgG levels are normal but antibody responses are defective. Subclass deficiencies are also seen in patients with IgA deficiencies.(24) Functional analysis of T lymphocytes involve analysing cytokine production or proliferation. The Mantoux test is an in vivo delayed hypersensitivity response to a purified peptide derivative. T lymphocytes proliferate in response to antigens and mitogens.

Functional analysis of the innate immune system, including phagocytic defects, measures chemotaxis (ability of neutrophils to migrate to the site of infection), phagocytosis (engulfment of foreign

pathogens), and the oxidative burst (intracellular killing) functions of neutrophils and monocytes.(22)(31)

(iii) Fourth-line testing

Fourth-line testing should be guided by an experienced clinician and preferably with a genetic counsellor. These tests may include enzyme measurements, cytokine studies and genetic investigations. Examples include specific Bruton's tyrosine kinase assays to confirm agammaglobulinemia, CD40 ligand for hyper-IgM syndrome, CD 11/18 determination for leucocyte adhesion deficiency and common gamma chain detection for X-linked SCID and an increasing number of genetic investigations.(24)(36)

2.2.5 Treatment of immunodeficiencies

Treatment of immunodeficiencies include prevention and treatment of infections, boosting of the immune system and treatment of the underlying immune deficiency and associated conditions.(13) Prevention of infections include prophylactic antibiotics or antifungals as determined by the pathogens involved. Penicillin is commonly used for late complement factor deficiencies, co-trimoxazole and itraconazole for chronic granulomatous disease and cotrimoxazole for T cell defects.(22) The use of live attenuated vaccines, e.g. oral polio, BCG, measles, mumps, rubella, varicella or rotavirus, in any patient with T cell or severe immunodeficiency is strictly contraindicated to prevent vaccine-associated disseminated infections. Live polio virus vaccination is also contraindicated in agammaglobulinaemia. Live vaccines should be avoided whenever there is a family history of severe PID.(22)

Other general measures in treatment of patients with PID are prompt and aggressive treatment of infections, providing nutritional support (e.g. Zinc, Vit D and Vit A) and only using irradiated blood products for transfusions to prevent possible graft versus host disease, particularly for severe T cell defects.(22) Boosting or replacement of the immune system is done by subcutaneous or intravenous administration of gamma globulin (Ig) therapy (for patients with antibody and B lymphocyte deficiencies), gamma interferon (for patients with chronic granulomatous disorder with recurrent infections) and the very judicious use of growth factors.(37)(38)(39)

Bone marrow transplant (BMT), now mostly referred to as haematopoietic stem cell transplant (HSCT), is curative in almost 75% of children affected by severe PIDs. In recent years the outcome of BMT and cure for PID has increased dramatically in dedicated centres with earliest diagnosis and access to the international donor pool, even with matched unrelated donors (MUDs). Besides the conventional indications for BMT (profound or absent T cell function, profound or absent natural killer function, known syndromes with T cell deficiencies), indications to BMT for PIDs affecting quality of life or pointing to an expectation of life that does not exceed the third or fourth decade remain unclear.(40)

Access to HSCT in the public and private sector in South Africa is limited, as a consequence of the lack of availability of local donors and also a lack of dedicated facilities with expertise.(13) Other available treatments indicated in specific disorders include cytokine therapy, enzyme replacement, colchicine and interleukin 1-blocking agents and an emerging list of biologic drugs.(1)

The future of treatment of PID where molecular diagnosis can be confirmed (e.g. severe forms of T-cell-related PID) is with gene therapy.(34) Gene therapy has been shown to be successful, as immune reconstitution was achieved in children with SCID. However, it is not yet routinely used as a therapeutic modality as it has caused leukaemia in some recipients.(22)(41)(34). The initiation of these leukemias was related to vector-mediated insertional mutagenesis and vector lower respiratory tract enhancer activation of endogenous proto-oncogenes such as *LMO2, Bmi1* and *CCND2*(34). The first clinical trials performed with gamma retroviral vectors (c-RV) for adenosine deaminase severe combined immunodeficiency (ADA-SCID), X-linked SCID (SCID-X1) and Wiskott–Aldrich syndrome (WAS) showed that gene therapy is a valid therapeutic option in patients lacking an human leukocyte antigen-identical donor. The occurrence of insertional oncogenesis in SCID-X1, WAS and chronic granulomatous disease (CGD) RV of earlier clinical trials prompted the development of safer vector construct based on self-inactivating (SIN) retroviral or lentiviral vectors (LVs).(42) No insertional mutagenesis events have been observed in more than 40 ADA-SCID patients treated so far in the context of different clinical trials worldwide, suggesting a favourable risk–benefit ratio for this disease. Gene editing for the defective gene is another future option of treatment which is already being trialled.

2.3 Conclusion

A review of PIDs diagnosed will give an indication of the profile of the patients in the Western Cape with PID. This will also increase awareness of PIDs in South Africa which will – it is hoped – result in earlier diagnosis and subsequent improvement in morbidity and mortality rates of patients.

Chapter 3: Method

3.1 Research design

The study is a retrospective descriptive analysis of the cohort of patients referred to the Tygerberg Hospital Immunology Service over the past 25 years (1 January 1991 to 5 May 2016). Tygerberg Hospital is one of two tertiary-level hospitals in the Western Cape, South Africa, and mainly receives referrals from the Western Cape, but also from the other eight provinces in the country. The patients were between the ages of birth and 73 years and were referred for suspected PID. Patient records were excluded from the study if age, presenting complaint or diagnosis were not captured.

3.2 Data capture

Data were obtained from the hard copies of the clinical records of patients seen at Tygerberg Hospital Immunology Service and from the South African PID Register. The data were de-identified, electronically captured by using REDCAP (research electronic data capture) offline on the Tygerberg Hospital premises, and later uploaded to the central REDCAP database.

Diagnosis of immunological abnormalities was obtained from laboratory data retrieved from the National Health Laboratory Services (NHLS) and affiliated referral laboratories and interpreted by the clinician in charge of the service. PIDs were classified according to the nine categories as set out by the IUIS classification published April 2014 and the more extended classification of the ESID, published 2016. The patients who could not be classified according to the IUIS or ESID classification were excluded, and an alternate diagnosis was captured.

The variables that were captured included age; geographic origin; ethnicity; clinical presentation; source of referral; whether the patient was seen at Tygerberg Hospital (either in the clinic or in the ward) or consulted via telephone or email; whether there was a known family history of PIDs; diagnosis (IUIS/ ESID/ other); age of patient at diagnosis; whether immunological tests were done; date of first and last contact with the patient; and whether the patient was still alive (Table 4.1).

Table 3.1: Thirteen variables were captured from 871 patients

Patient profile	Immunology Service
▶ Sex ▶ Age at diagnosis ▶ Geographic origin ▶ Ethnicity ▶ Family history ▶ Presenting features ▶ Diagnosis (IUIS and ESID) ▶ Outcome	▶ Source of referral ▶ Mode of referral ▶ Date of diagnosis ▶ Immunological tests done ▶ Whether patient is registered on the SA PID Register

The exported data de-identified patient name, date of birth and folder number, linking the record to a unique study number and all data analyses were done without identifying data. The log identification key was securely kept, with access available only to the principal investigator, who had the use of a password-protected computer.

Statistical analysis

Descriptive statistics such as means, standard deviations, and proportions were calculated. Cross-tabulation was done for categorical risk factors and outcomes such as clinical diagnosis and primary immune deficiency (PID). The association between these risk factors (i.e. sociodemographic and clinical presentations) and the various outcomes were assessed by a chi-square test.

The prevalence of PID in the study group was estimated overall and reported with 95% confidence intervals. The time to PID diagnosis was calculated from the clinical records, and Kaplan-Meier graphs were used to compare graphically the time-to-event profile for various risk factors such as the sex of the patient.

For ease of interpretation, the visual representation of the results were converted to a flowchart for the number of patients included, a histogram for the age of diagnosis, family history represented in a pie chart, source of referral and PID classification was converted to bar charts, pie charts and tabulations.

Stata 15 was used for the calculations.

3.3 Ethics

The ethics status of the research protocol was approved by the Health Research Ethics Committee (approval number S15/10/260) of the Stellenbosch University Faculty of Medicine, which allowed a

waiver of individual consent for patients that could not be traced. Permission was granted by the chief executive officer of Tygerberg Hospital to review the patient folders. The custodian of the PID Register gave consent for access to the records of patients who were referred to Tygerberg Hospital. The South African PID Register had already given ethics approval for data analysis (approval number N08/09/264) ("SA PID Register"). The exported data de-identified patient name, date of birth and folder number. The patients were assigned a unique study number in order to maintain anonymity. The log identification key was securely kept, with access available only to the principal investigator, who had the use of a password-protected computer.

Chapter 4: Results

4.1 Section 1: Family history, sex and number of patients analysed

Tygerberg Hospital received referrals from both the state and private healthcare sectors in the country. Over the past 25 years, 876 patients were referred to the immunology service with suspected primary immunodeficiency. Five patient files were excluded as they contained insufficient data (Figure 4.1). Of the 871 patients, 371 (42,59%) did not meet the criteria of PID in either the ESID or IUIS classification, though 14% had a positive family history of having a PID. The final study population of 500 patients was further analysed and 22,40% had a family history of PID (Figure 4.2), with a male to female ratio of 1.2:1 (sex was unknown in 0,40% of the cases). Of the 500 patients with PID, 316 were registered on the South African PID Registry.

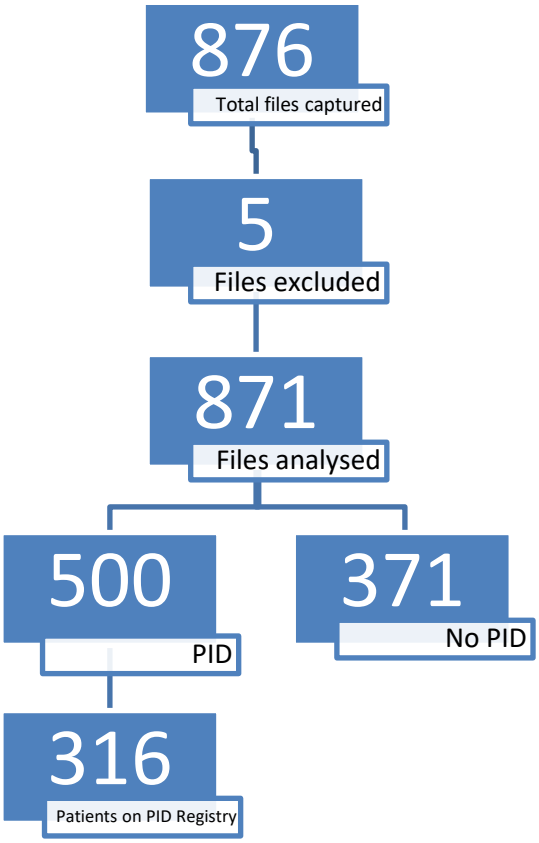


Figure 4.1: Number of patients in the study: Of the 876 files captured, 5 were excluded due to insufficient data. Of the remaining 871 files, 500 patients were classified with a PID, and 316 of these patients were registered on the South African PID Registry

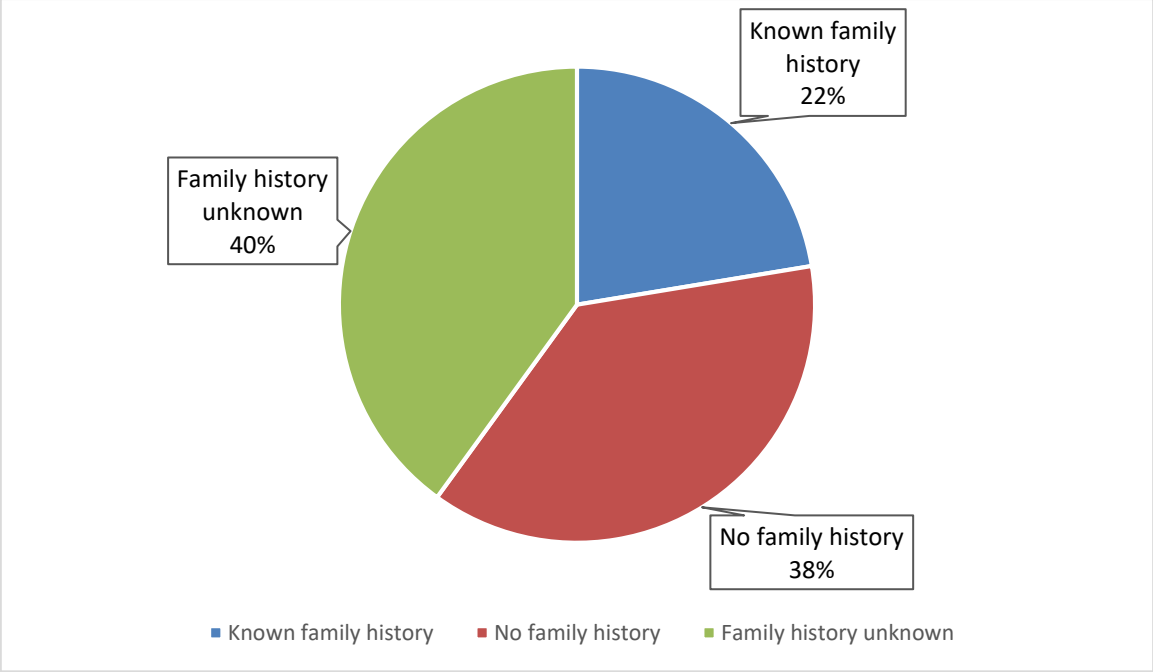


Figure 4.2: Family history of patients referred to the clinic with confirmed primary immunodeficiency (n=500): in 40% of patients with PID it was not noted whether there was a family history of PID or not, 38% had no family history and 22% had a known family history of PID

4.2 Section 2: Age distribution of patients

The median age of patients with PID was five years (interquartile range=10) (mean: 10 years; range: 1 year 9 months till 60 years; Standard Deviation 12,6). The majority (60%) of patients were diagnosed before 20 years of age.

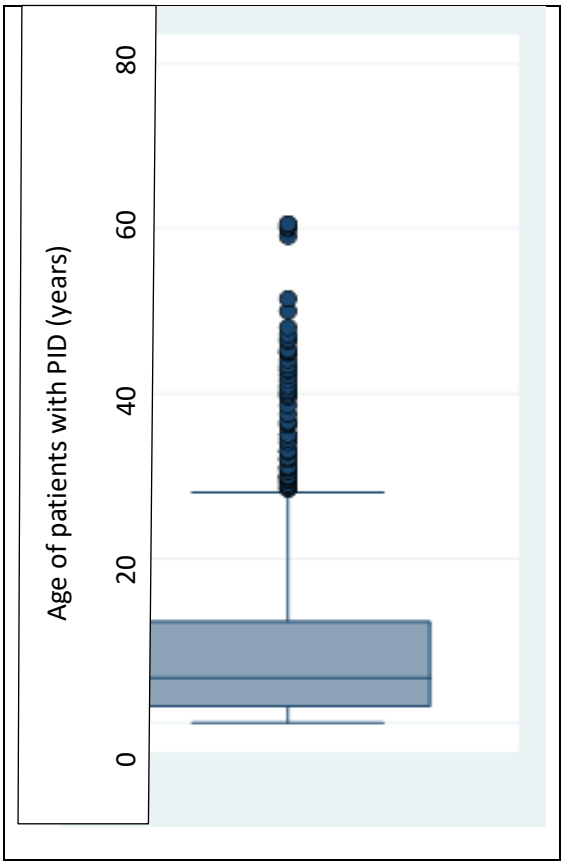


Figure 4.3: Box Plot of patients with PID (median age 5 years, interquartile range=10, 25th quartile=2 years, 75th quartlile=12 years, minimum age=0, maximum age=60years)

4.3 Section 3: Region of referral of patients

The majority of patients with confirmed PID were from the Western Cape (69,60%), while 15% were from Gauteng, 4,80% from KwaZulu-Natal, 3% from Free State, 2,80% from Eastern Cape, 1,60% from Mpumalanga, 1,20% from Northern Cape, 1,20% from non-South African citizens, 0,60% from North West and only 0,20% from Limpopo.

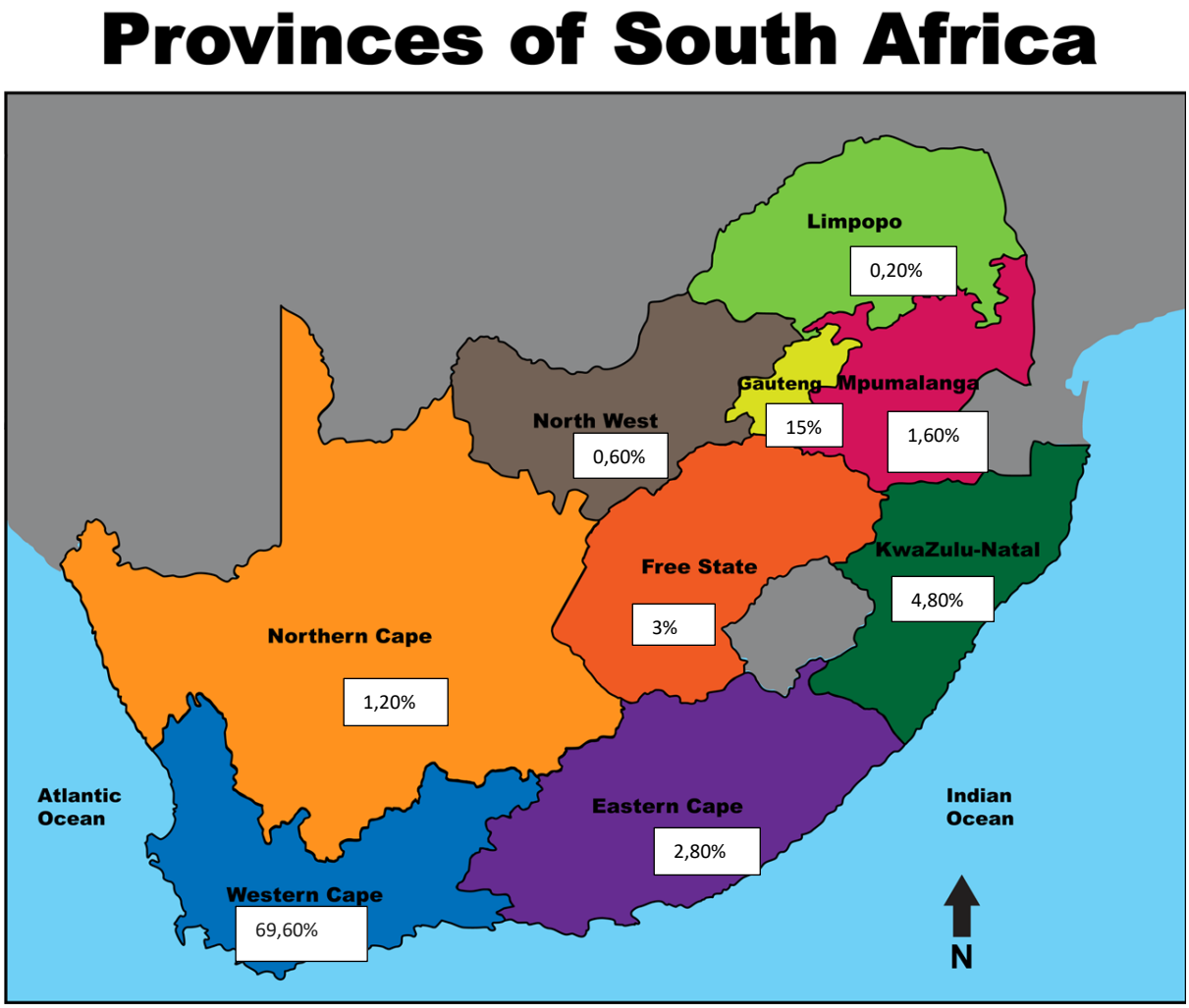


Figure 4.4 Region of referral of patients

4.4 Section 4: Source of referral

As depicted in Figure 4.5, the majority (43%; n=216) of patients were referred by paediatricians not linked to tertiary institutions, while 26% (n=133) were referred by a paediatrician in a tertiary institution, 18% (n=90) by physicians in tertiary institutions, 8% (n=42) patients from physicians other than from tertiary institutions, 1% (n=6) from general practitioners, and 2% (n=13) from other (e.g. pathologists and patient support groups).

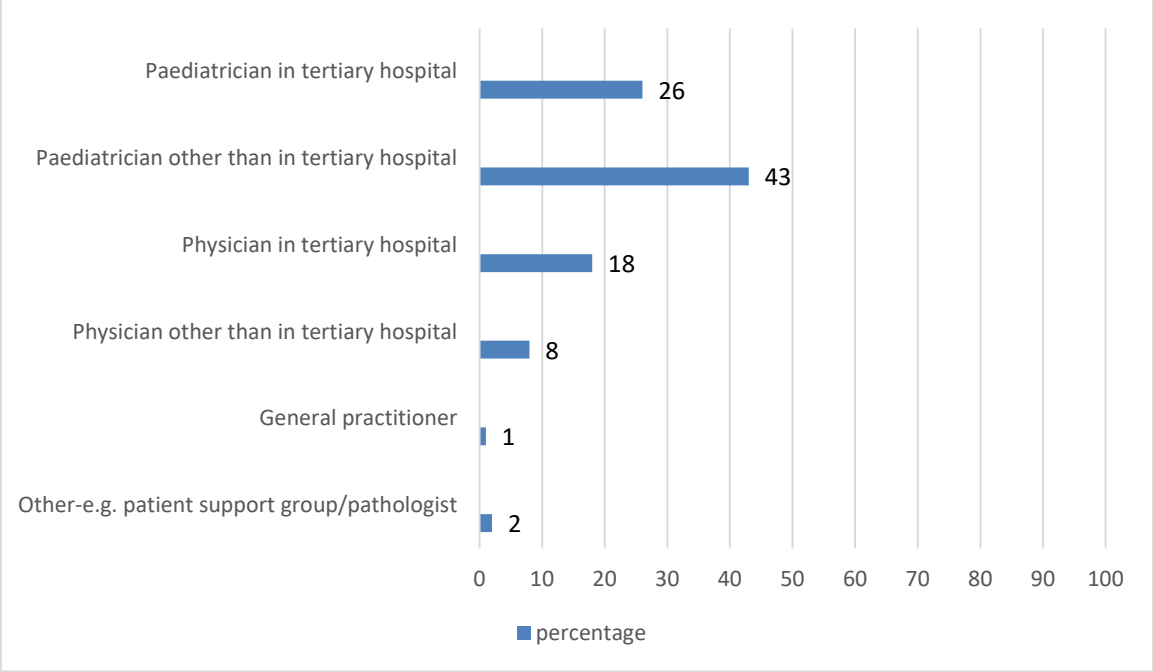


Figure 4.5: Source of referral of patients for evaluation of suspected primary immunodeficiency

4.5 Section 5: Presenting features

The presenting features were classified according to a selection of 10 common modes of presentation. The most common presentations were respiratory complaints (n=304;60%), followed by oedema (n=52;10%); gastrointestinal-related symptoms (GIT) (n=41;8%); central nervous system (CNS) disorders (n=38;7,5%); and skin infections or eczema (n=36;7%). The other modes of presentation included patients (n=32; 6%) who could not be classified in the nine common modes of presentation: namely patients who presented with septicaemia (n=25; 5%), those who were asymptomatic/carriers (n=17; 3,4%), those who had bone and joint complaints (n=17; 3,4%), and those who presented with pyrexia (n=15; 3%) (Figure 4.6).

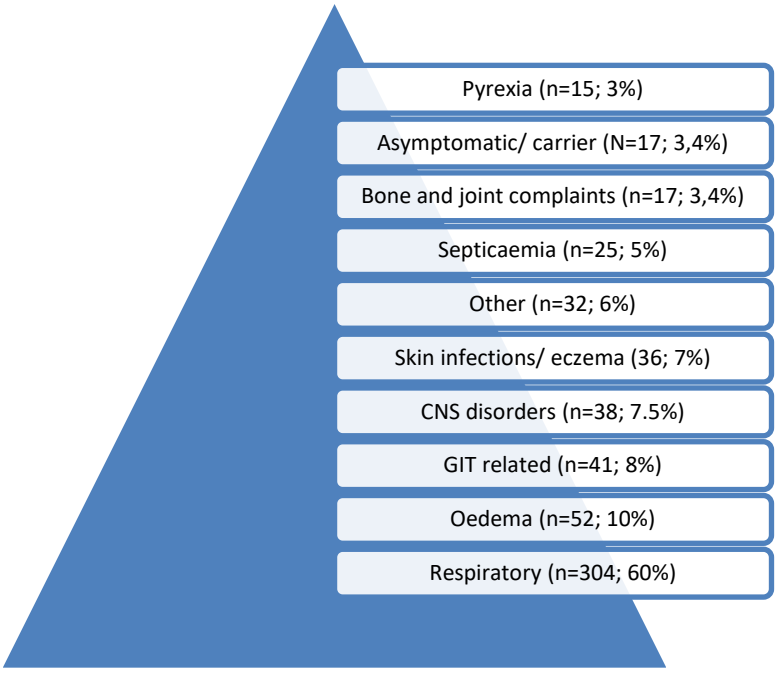
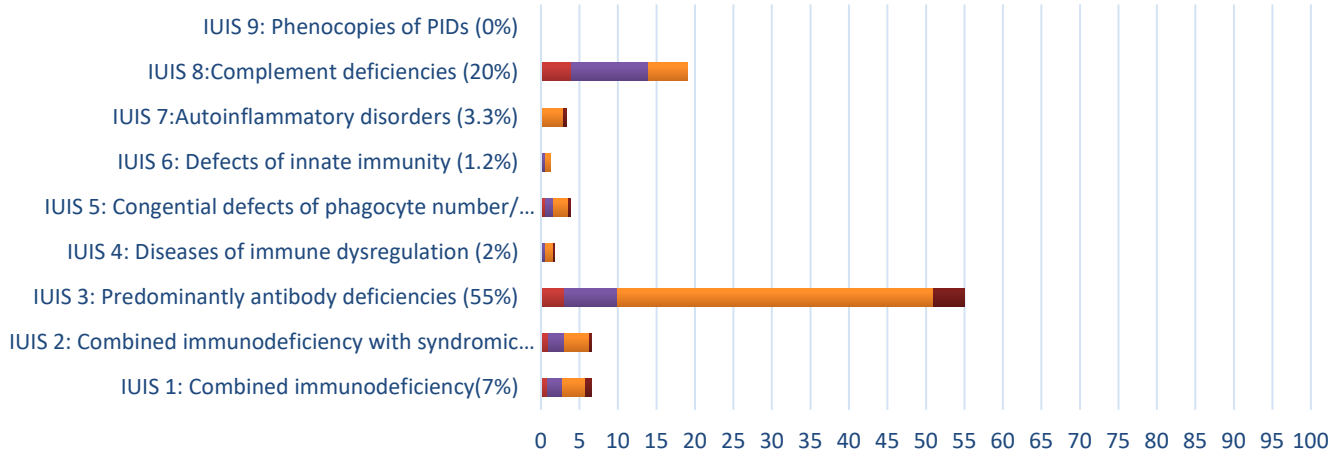


Figure 4.6: Presenting features of patients with Primary Immunodeficiency Disorders. The presenting features were classified in these 10 categories as it was the most common groups. Some patients presented with more than one of the presenting features, thus the total percentages does not add up to 100%.

4.6 Section 6: Classification (International Union of Immunological Societies Expert Committee for Primary Immunodeficiency

The patients were classified according to the 10 categories of the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency (IUIS) classification, of which the 10th category was classified as 'none of the above', and the 67 categories of the European Society for Immunodeficiencies (ESID) classification, of which the 67th category was 'none of the above'. The majority (n=473; 95%) of the 500 patients could be analysed according to IUIS criteria 1 to 9. According to IUIS criteria the majority of patients (n=264; 52%) predominantly had antibody deficiencies (IUIS 3), followed by complement deficiencies (IUIS 8) in 20% (n=94); a further 7% (n=33) had combined immunodeficiencies (IUIS 1); 6% (n=30) had combined immunodeficiencies with associated syndromic features (IUIS 2); and 4% (n=20) had congenital defects of phagocyte number, function or both (IUIS 5). The smallest three groups were 3,3% (n=16) of patients who had autoinflammatory disorders (IUIS 7); 2% (n=10) of patients with diseases of immune dysregulation (IUIS 4); and 1% (n=6) had defects in innate immunity (IUIS 6). There were no patients with phenocopies of primary immunodeficiency disorders (IUIS 9) (Figure 4.7).



	IUIS 1: Combined immunodeficiency(7%)	IUIS 2: Combined immunodeficiency with syndromic features (6%)	IUIS 3: Predominantly antibody deficiencies (55%)	IUIS 4: Diseases of immune dysregulation (2%)	IUIS 5: Congential defects of phagocyte number/ function or both (4%)	IUIS 6: Defects of innate immunity (1.2%)	IUIS 7:Autoinflammatory disorders (3.3%)	IUIS 8:Complement deficiencies (20%)	IUIS 9: Phenocopies of PIDs (0%)
African	0,8	1	3	0	0,6	0,2	0	4	0
Mixed Race	2	2	7	0,6	1	0,4	0,2	10	0
Caucasian	3	3,3	41	1	2	0,6	2,7	5	0
Unknown	0,8	0,2	4	0,2	0,2	0	0,4	0	0

Figure 4.7: Ethnicity and primary immunodeficiency according to the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency criteria

4.7 Section 7: Ethnicity of patients

Table 4.2 and Figure 4.8 summarises the PIDs in the different ethnic groups (n=473) according to the IUIS classification. Two Asian patients were not diagnosed according to IUIS criteria, leaving 473 for further analysis according to IUIS. The majority of patients with PID, 57,40%, were Caucasian, followed by 24,80% mixed race, 11,60% African, and 0,40% Asian, while race was unknown in 5,70% (Figure 4.6). The mixed-race and African population mostly had complement deficiencies (9,80% and 3,80% respectively), followed by antibody deficiencies (3,20% and 6,80% of total PIDs) and combined immunodeficiencies with syndromic features (1,20% and 2%). The majority (42%) of the Caucasian patients with PID had antibody deficiencies (39% of total PIDs), followed by complement deficiencies (5,20%), combined immunodeficiencies (3%) and autoinflammatory disorders (2,60%).

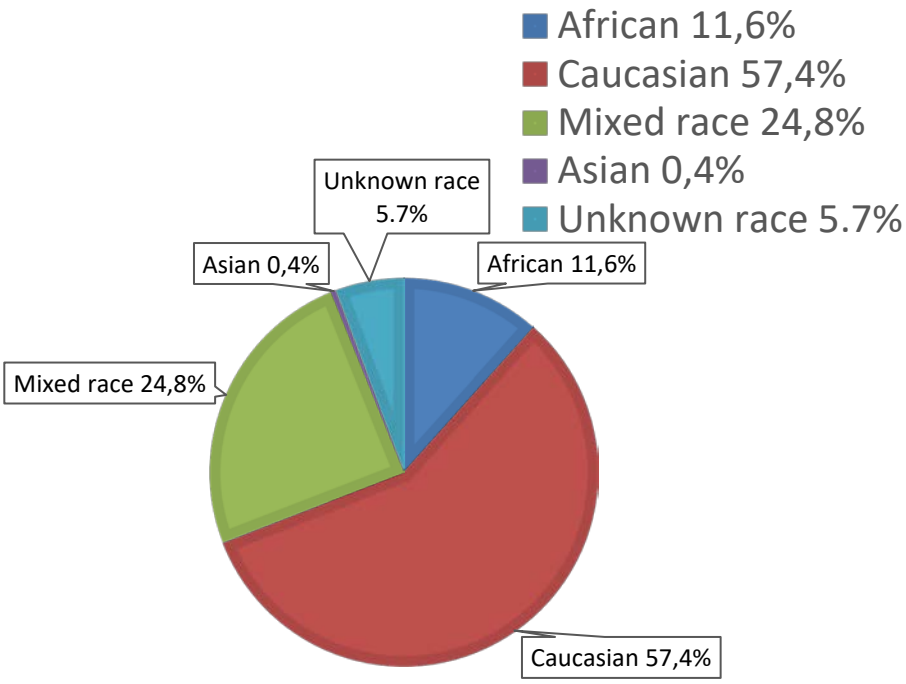


Figure 4.8: Ethnicity and primary immunodeficiency (percentage)

Table 4.1: Ethnicity and Primary Immunodeficiency Disorders (International Union of Immunological Societies Expert Committee for Primary Immunodeficiency criteria)

IUIS criteria	African	Caucasian	Mixed race	Unknown	Total
1 Combined immunodeficiencies	4	15	10	4	33 (7%)
2 Combined immunodeficiencies with syndromic features	6	13	10	1	30 (6%)
3 Predominantly antibody deficiencies	16	195	34	19	264 (56%)
4 Diseases of immune dysregulation	0	6	3	1	10 (2%)
5 Congenital defects of phagocyte number, function or both	3	10	7	0	20 (4%)
6 Defects of innate immunity	1	3	2	0	6 (1%)
7 Autoinflammatory disorders	0	13	1	2	16 (3%)
8 Complement deficiencies	19	26	49	0	94 (20%)
9 Phenocopies of primary immune deficiency disorders	0	0	0	0	0 (0%)
Total: absolute (percentage)	49 (10,0%)	281 (59,40%)	116 (24,5%)	27 (0.05%)	473

4.8 Section 8: European Society for Immunodeficiencies (ESID) classification

Nearly all patients (n=495; 99%) could be diagnosed with PID using the ESID classification. The most common diagnosis in 108 patients (21,7%) was antibody deficiency; 57 patients (11,4%) had hereditary angioedema; 46 patients (9,2%) had common variable immunodeficiency disorders; 35 patients (7%) had unclassified complement deficiencies; and 31 patients (6,7%) had well-defined immunodeficiency syndromes. There were 17 (3,5%) patients with SCID – an important group because of the high morbidity and mortality if diagnosed late. Because of routine vaccination with BCG at birth and the high incidence of tuberculosis in South Africa,(43) an important group was the patients with Mendelian susceptibility to mycobacterial diseases (n=7; 1,4%). The remaining five patients with PID were classified under the IUIS classification.

Table 4.2 European Society for Immunodeficiencies (ESID) classification

PID category (ESID)	Total number of patients	Percentage
Unclassified antibody deficiency	108	21,7
Hereditary angioedema	57	11.4
Common variable immunodeficiency disorder	46	9.2
Agammaglobulinemia	35	7,0
Unclassified complement deficiencies	35	7,0
Transient hypogammaglobulinaemia of infancy	33	6,6
Selective IgA deficiency	20	4,0
Unclassified autoinflammatory disease	18	3.6
Severe combined immunodeficiency	17	3.4
Unclassified immunodeficiencies	16	3.2
Specific IgG deficiency	14	2.8
DiGeorge syndrome	13	2.6
Combined immunodeficiency	11	2.2
Chronic granulomatous disease	10	2,0
HyperIgE syndrome	8	1.6
Unclassified phagocytic disorders	7	1.4
Defects with susceptibility to mycobacterial infection	7	1.4
Isolated IgG deficiency	7	1.4
Unclassified disorders of immune dysregulation	6	1.2
Wiskott-Aldrich syndrome	6	1.2
Unclassified defects of innate immunity	4	0.8
Ataxic telangiectasia	3	0.6
Cyclical neutropenia	2	0.4
One patient (0,2%) in each of the following categories:	12	2.4
- Autoimmune lymphoproliferative syndrome - Chronic mucocutaneous candidiasis - complement component 2 deficiency - class switch recombination defects and hyperimmunoglobulin M syndromes - congenital neutropenia - familial hemophagocytic lymphohistiocytosis syndromes - FOXP3 deficiency - IPEX-like disease - mannose-binding lectin deficiency - Omenn syndrome - Selective CD4 cell deficiency - unclassified syndromic immunodeficiency		
Total	**495**	**99,10**

4.9 Section 9: Immunological tests done

The majority of patients (88%) were investigated with immunological tests, while 2% did not have any investigations done (already done prior to referral) and in 10% of patients the results were not recorded in the notes.

4.10 Section 10: PID Registry

Only 63% (n=316) of the 500 patients with PID were registered in the national PID register. Of the patients on the PID Registry, 90,5% (n=286) were still alive, 9,1% (n=29) were deceased and 1 patient's status was unknown at the time of this review.

Chapter 5: Discussion

5.1 Summary of findings

This is the first review of the patients referred to the Tygerberg Immunology Service over the past 25 years, and adds to the knowledge of the patient profile of South African patients with PID. Since the study focused on patients referred to Tygerberg Hospital Immunology Service, the epidemiological information obtained provided data from a single, central hospital in South Africa. It is noteworthy that the increase in the number of diagnoses (n=500) in the 25-year study period, which took place 25 years after the previously reported study done in Cape Town with only 168 PID-diagnosed patients over a 26-year period.(3) The increase is probably due to improved diagnostic ability and recording, but prevalence and the burden of PID is probably still underestimated in South Africa.(44) Another South African publication documented the lack of dedicated immunologists and unavailability of a screening programme in South Africa.(1)

The median age of patients at diagnosis, namely 5 years, was older than that of patients in other comparative studies in Iran (median age of 3 years and 6 months) and in both Oman and Tunisia (median age of 2 years).(28)(45)(46) The majority of patients (60%) presented with respiratory symptoms. This was a similar finding to the earlier Cape Town study (95,4%), as well as the report from Iran (33.5%) and Oman (47%).(45)(46)(3) Only 3% of patients in the present study were referred for evaluation because of a family history, despite family history being one of the strongest predictors of PID.(30) The predominantly male distribution (55%) was similar to studies in the Middle East (61%), North Africa (58%), Europe (60,8%) and the United States of America (58%).(28)(45) (47)(48). The male predominance could be explained by some PID conditions that are inherited in a X-linked pattern.

The diagnostic spectrum compares to reports from Europe, the United States of America, Latin America, China and the Middle East with regard to the most common PID being antibody deficiency.(49)(50)(51)(26)(52)(48)(53) The most common specific disorder was common variable immunodeficiencies (9,2%), which was also similar to the findings in the previous reports from Cape Town (11,3%), Egypt (18,7%) and Europe (20,7%), while severe combined immunodeficiency was more common in Iran, Saudi Arabia and Tunisia. In Oman, phagocytic disorders were predominant.(54)(3)(26)(45)(51)(28)(47) A surprising finding of this study was the high percentage of complement deficiencies (10,8%) in comparison to other studies in Europe (1%), the United States (2,6%), Latin America (2,8%), Tunisia (0,4%), Iran (2,4%) and Oman (6%).(28)(45)(46)(48)(55) The high percentage of complement deficiencies is probably attributable to the special research interest in this medical condition in the Western Cape.

The number of African and mixed-race patients referred for evaluation of suspected PIDs has dramatically increased in the past two decades, but has still been severely underrepresented in terms of the racial demography of South Africa. The increase could be due to an improved awareness and diagnosis of PIDs. Caucasian patients have had mostly antibody deficiency (60%), which is similar to two reports from the USA.(56)(57)

There is limited information regarding the Asian population and PIDs in South Africa. In a report by Wang et al(53) on the distribution and clinical features of primary immunodeficiency diseases in Chinese children from 2004 to 2009, the findings similar to this study included a male predominance (5.29:1), with antibody deficiency disease as the most common category (48,2%), with pneumonia being the most common manifestation. The spectrum of PID included well-defined immunodeficiency syndromes (20,5%), combined T and B cell immunodeficiencies (16,9%), congenital defects of phagocyte number and/or function (10,8%) and diseases of immune dysregulation (3,1%). Agammaglobulinemia was the most frequent disease type.(53)

Autoinflammatory conditions were mostly seen in the Caucasian population. The African patients (11,6%) and mixed race (4,8%) mostly had complement deficiencies (4% and 10% respectively) (of which hereditary angioedema was the most common diagnosis), followed by antibody deficiency (3% and 7%) and combined immunodeficiencies with syndromic features (1% and 2%). There was a smaller percentage of congenital defects of phagocyte number, function, or both in South Africa (4,2%) compared to 17,5% in Iran, 42% in Oman and 56% in Europe.(46)

PID is still regarded as a rare disease in South Africa, as it is in the rest of the world, partly because of lack of data especially from Africa. A disease is considered rare when it affects fewer than 200 000 individuals in the United States or fewer than one in 2 000 people in Europe (58). In South Africa, which is still a developing country with limited resources for patients with PID, research is limited, expertise is sparse and the diagnosed patients are few in number. It is important, however, to advocate for better access to specialty care including psychological support to improve quality of life.

Areas that need development in South Africa include an online national register, national and international research collaboration and implementation of formal subspecialty training in clinical immunology for paediatric and adult immunologists. Government funding or health insurance needs to improve to ensure that patients are entitled to long-term follow up and appropriate essential treatments. Awareness and care will also improve if South Africa can establish more specialist PID centres with reasonable accessibility for all patients in different provinces. In the context of rare diseases, disease-specific registries form a vital component of a public health programme, providing data necessary for planning services, monitoring public health and improving patient care. Patient registries can help to provide the basis for this by collecting data over a longer period of time and by connecting centres nationally or even internationally.(59) The ESID online registry is an example of an international

organisation that started to run an online registry (initiated in 2004). The advantage of this most up-to-date form of data storage is the ease of accessibility for users worldwide without necessarily needing additional technical equipment or software.(59) If a standardised database or register were to be used for all patients with PID in South Africa, it would serve as a platform for epidemiological analysis and for the review and development of new diagnostic and therapeutic strategies for patients with PID in South Africa. The design, realisation, curation and documentation in a database is, however, time consuming and requires dedication and funding. A lack of time, funding and manpower thus poses a challenge for maintaining a register.

With the advances in molecular, whole genome and exome sequencing techniques in South Africa, additional patients with defects should be identified. A protocol for selecting patients who will need molecular or genetic testing would aid in earlier diagnosis of patients with PID. An example of improving clinical and genetic data collection by pooling resources and using research collaborations is the Asian Primary Immunodeficiency (APID) Network. APID was established in 2009 at the University of Hong Kong, and has a genetic diagnostic laboratory. The aim is the promotion of knowledge in terms of scientific discovery, clinical management and service needs of PID in Asian countries. The genetic diagnostic laboratory has offered free of charge genetic tests for patients from over 50 hospitals in mainland China, Taiwan, the Philippines, Singapore, Thailand, Malaysia, Vietnam, India and the Kingdom of Bahrain. In 4 years, the APID Network received 1 300 referrals and PID was genetically confirmed in 455 patients.(60)

Newborn screening in 11 programmes in the United States identified a surprisingly high number of SCID, namely 1 in 58 000 infants, with high survival due to early diagnosis and treatment.(61) Newborn screening for the detection of severe forms of PID manifest through T and/or B cell lymphopenia using T cell receptor excision circles (TREC), and kappa-recombining excision circles screening has been established in many countries.(62) Unfortunately South Africa does not have a newborn screening protocol for PIDs. A review of the national registry for patients with PID maintained by the United States Immunodeficiency Network (USIDNET) found that 28% of African-American patients had recorded neutropenia, while only 17% of Caucasians and 2% of Asian/Pacific Islanders were neutropenic ($p=0.005$).(63) Further investigation for PID in African patients with neutropenia in South Africa could potentially increase the diagnostic yield of PIDs in this racial group.

Even in South Africa, with limitations on healthcare spending, it was reported that hematopoietic stem cell transplantation is feasible and offers many patients the opportunity for cure or long-term survival.(64) The ESID keeps record of treatment modalities (e.g. immunoglobulin therapy and stem cell treatment) as well as whether it is administered as in- or outpatient.(55) These data aid in assessment of quality of life. If treatment modalities are recorded in a similar manner in South Africa, it would aid in motivating for resources, depending on the measured burden and need for resources.

5.2 Limitations and strengths of this study

Not all hospitals and medical practitioners in South Africa contribute to the South African PID Registry, which leads to under-reporting of PIDs. Furthermore, the division of private and state medical care causes a scattered network of information regarding PID incidence and prevalence.

A shortcoming of this study is the underrepresentation of less well known or less severe categories of PIDs owing to suspected lack of reporting or lack of enough criteria to confirm a diagnosis for inclusion in the South African PID Registry. There is still a serious lack of data on African patients and their profiles. There is also a lack of accuracy of diagnoses in the hard copy notes, and definite molecular diagnoses of patients only emerged in the past 10 years (mostly funded by research collaborations). Owing to the limited availability of genetic testing, most of the patient diagnoses were based on clinical grounds.

Notwithstanding these shortcomings, this study provides a retrospective review of the local epidemiology of PID in the Western Cape and adds to the existing knowledge on PIDs in South Africa.

A strength of the study lies in having one dedicated reviewer to review the data and similarities and differences found in the comparative review of the PID profile in the Western Cape with international and African countries.

5.3 Conclusions

This study is the first review of Tygerberg Hospital's Immunology Service, which is also the main feeder for the national PID Registry, and described the spectrum of patients referred to a single tertiary centre in South Africa. It includes findings regarding mode of presentation and types of PIDs, and the results were found to be similar to the results from other developing countries, except that the Western Cape had the highest reported frequency of complement deficiencies (specifically hereditary angioedema) in the world.

The Western Cape median age of diagnosis was older, compared to other developing countries, and attempts should be made to improve awareness and encourage early diagnosis. Further significant aspects noted in the study were the lack of data on African patients and their profiles, the importance of a PID suggestive family history, and the need to consider PID as a differential diagnosis in HIV-negative patients with chronic or unusual respiratory disease.

5.4 Future research

Though telephonic and email consultations, extent of special investigations and treatment provided were not analysed in this study, these tasks are known to contribute significantly to the workload of any

paediatric immunology service. The availability of special investigations and the treatment of PIDs in South Africa could be areas for future research. Such research would give an indication of whether improvements have been made in the referral system and would furthermore assess figures on the morbidity and mortality of patients with PID in this country. Electronic data capturing with guidance on salient aspects in history and investigations into when patients are referred will also improve the service and subsequent data analysis.

The rapid drop in price of molecular diagnostics and improved data analysis, as also the ease with which DNA samples can be shipped in countries with extremes of temperature, will make an attractive second-line investigation into PID in the future. Furthermore, the comprehensive history of patients with suspected PID, together with genetic counselling, is of paramount importance for targeted and ethical molecular investigation. Molecular diagnosis of PID in South Africa should improve with the increased availability of these tests.

Improved awareness of PID and registration of patients with PID will provide a basis for the implementation of government policies to improve access to treatment and supportive care for patients with rare diseases in resource-limited settings, and subsequently improve their quality of life.

Appendices

1. Data collection sheet

2. IUIS classification (April 2014)

3. ESID classification (July 2016)

1. Data collection sheet

2.	Variable / Field Name	Field Label *Field Note*	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: **Record number** (record_number)			
1	record_id	Record ID	text
2	surname_name	Surname, Name	text, Required, Identifier
3	folder_number	Folder number	text, Identifier
4	dob	Date of birth	text (date_dmy, Min: 1800-01-01), Identifier
5	gender	Gender	dropdown (autocomplete), Required 1 Male 2 Female 3 Unkown
6	geographic_origin	Geographic origin	radio 1 Northern Province/ Limpopo 2 North West Province 3 Mpumalanga 4 Gauteng 5 Freestate 6 Kwazulu-Natal 7 Northern Cape 8 Western Cape 9 Eastern Cape 10 Not South African
7	ethnicity	Ethnicity	radio 1 Black 2 White 3 Coloured 4 Asian 5 Unknown
8	family_history	Family history	dropdown (autocomplete), Required 1 Yes 2 No 3 Unknown
9	iuis_category	IUIS category	checkbox, Required 1 iuis_category___1 Combined immunodeficiencies 2 iuis_category___2 Combined immunodeficiencies with associated syndromic features 3 iuis_category___3 Predominantly antibody deficiencies 4 iuis_category___4 Diseases of immune dysregulation

				5	iuis_category___5 Congenital defects of phagocyte number, function or both
				6	iuis_category___6 Defects of innate immunity
				7	iuis_category___7 Autoinflammatory disorders
				8	iuis_category___8 Complement deficiencies
				9	iuis_category___9 Phenocopies of primary immunodeficiency disorders
				10	iuis_category___10 None of the above
10	esid		European Society of immunodeficiencies category (2016)	dropdown (autocomplete)	
				1	Agammaglobulinaemia
				2	Asplenia syndrome (Ivemark syndrome)
				3	Ataxia telangiectasia (ATM)
				4	Autoimmune lymphoproliferative syndrome (ALPS)
				5	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED/ APS1 with CMS)
				6	Barth syndrome
				7	Bloom syndrome
				8	Cartilage hair hypoplasia (CHH)
				9	Chronic mucocutaneous candidiasis (CMC)
				10	Complement component 2 deficiency
				11	Complement component 3 deficiency (C3)
				12	Class switch recombination (CSR) defects and hyper- immunoglobulin M (HIGM) syndromes
				13	Chediak Higashi syndrome (CHS)
				14	Chronic granulomatous disease (CGD)
				15	Clericuzio-type poikiloderma with neutropenia syndrome
				16	COHEN syndrome
				17	Combined immunodeficiency (CID)
				18	Common variable immunodeficiency disorders (CVID)
				19	Congenital neutropenia
				20	Cyclical neutropenia
				21	Defects of TLR/NFkappa-B signalling
				22	Defects with susceptibility to mycobacterial infection (MSMD)

23 Deficiency of specific IgG (Specific antibody deficiency- SPAD)
24 DiGeorge syndrome
25 Dyskeratosis congenita
26 Factor D deficiency
27 Familial hemophagocytic lymphohistiocytosis syndromes (FHLH)
28 FOXP3 deficiency (IPEX)
29 Glycogen storage disease type 1b (GS1b)
30 Griscelli syndrome type 2
31 Hereditary angioedema (C1 inh)
32 Hermansky-Pudlak syndrome (type 2)
33 HLA class I deficiency
34 HLA calss II deficiency (MHC2)
35 Hoyeraal-Hreidarsson syndrome
36 Hyper IGE Syndromes (HIES)
37 IgA with IgG subclass deficiency
38 Immunodeficiency centromeric instability facial anomalies syndrome (ICF)
39 IPEX-like disease
40 Isolated IgG subclass deficiency
41 Isolated congenital asplenia
42 Mannose-binding lectin deficiency (MBL)
43 Nijmegen breakage syndrome
44 Omenn syndrome
45 Partial albinism and immunodeficiency syndrome
46 Properdin P factor complement deficiency (PFC)
47 Schimke disease
48 Seckel syndrome
49 Selective CD4 cell deficiency
50 Selective IgA deficiency
51 Selective IgM deficiency
52 Severe combined immunodeficiency (SCID)
53 Shwachman-Diamond-syndrome
54 Thymoma with immunodeficiency
55 Transient hypogamma-globulinaemia of infancy
56 Warts hypogammaglobulinemia infections and myelokathexis (WHIM)
57 Wiskott-Aldrich syndrome (XLT/WAS)

			58 X-linked lymphoproliferative syndrome (XLP)		
			59 Unclassified antibody deficiency		
			60 Unclassified phagocytic disorders		
			61 Unclassified disorders of immune dysregulation		
			62 Unclassified defects of innate immunity		
			63 Unclassified complement deficiencies		
			64 Unclassified autoinflammatory disease		
			65 Unclassified syndromic immunodeficiencies		
			66 Unclassified immunodeficiencies		
			67 None of the above		
11	diagnosis_icd10	Diagnosis ICD10	text BIOPORTAL:ICD10 CM	BIOPORTAL:ICD10 CM	
12	diagnosis_other	Diagnosis (other)	notes		
13	referral_date	Date of referral	text (date_dmy)		
14	source_of_referral	Source of referral	dropdown (autocomplete) 1 Paediatrician Tertiary Hospital 2 Paediatrician other than Tertiary 3 Physician in Tertiary hospital 4 Physician other than tertiary 5 General practisioner 6 Other- eg Patient support Group and Pathologist		
15	type_of_referral	Type of referral	dropdown (autocomplete) 1 Telephonic 2 Inpatient 3 Email		
16	date_of_diagnosis	Date of diagnosis	text (date_dmy)		
17	age_diagnosis_years	Age at diagnosis(years)	text		
18	age_diagnosis_months	Age at diagnosis (months)	text		
19	presenting_features	Presenting features	checkbox		
			1	presenting_features___1	Respiratory
			2	presenting_features___2	Skin infections/ eczema
			3	presenting_features___3	Pyrexia
			4	presenting_features___4	GIT related
			5	presenting_features___5	Swelling of body
			6	presenting_features___6	CNS infection

			7 presenting_features___7 Septicaemia
			8 presenting_features___8 Bone and joint
			9 presenting_features___9 Asymptomatic / carrier
			1 presenting_features___1 Other 0 0
20	immunological_tests_done	Immunological tests done	dropdown (autocomplete) 1 yes 2 no 3 unknown
21	first_seen_by_immunology_service	First contact with immunology service	text (date_dmy)
22	last_seen	Last contact with immunology service	text (date_dmy)
23	statute	Statute	dropdown (autocomplete) 1 Alive 2 Dead 3 Unknown
24	sa_pid_register	Registered on SA PID Register	dropdown (autocomplete), Required 1 Yes 2 No
25	record_number_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete

2. IUIS classification

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3. ESID classification

See reference(66)

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