Section A-Research Paper

Review of Primary Immunodeficiency Diseases (PIDs): Attention and Awareness is Critical for Proper Management

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Abstracts:
Primary immunodeficiency diseases (PIDs) are diverse genetic disorders mainly responsible for severe and recurrent infectious diseases such as ear infections, sinus infections, pneumonias, deep skin or organ abscesses, persistent thrush in mouth etc. PIDs may also be responsible for many life threatening syndromes such as DiGeorge syndrome, Wiskott-Aldrich syndrome, Ataxia-Telangiectasia, Ivemark syndrome, polyendocrinopathy syndrome etc. Defects occurring at any stage of development, differentiation and maturation of innate immune and adaptive immune cells may be responsible for such PIDs as they failed to perform their defensive function. Latest publication of the International Union of Immunological Societies (IUIS) in 2022 described 485 inborn errors of immunity under 10 broad classification. The increasing nature of PIDs observed in different medically developed countries is alarming for the rest of the world. Though the disease is directly related to the immune system which is developed at an early stage after birth, it may have a correlation with the under-five year's mortality rate of several regions. This scenario is observed in most of the developing and under developed countries of Asia and Africa region. It was observed from a literature survey that there are a number of authentic and flexible techniques for rapid identification of the PIDs suspects. In this context, JMF suggested 10 warning signs for PIDs may be used for preliminary screening out the PIDs suspects from the general group of population with the help of concerned parents and relatives. Earlier the disease was rarely diagnosed due to its wide genetic level variation in the genome, however, improvement in the diagnostic apparatus such as flow-cytometer, genomic PCRs, gene scan analysis, RT-PCR, next-generation sequencing (NGS) techniques make this disease understandable to the medical world. Not only that, nowadays there are many authentic treatment options such as HSCT, BMT, Ig etc. developed for PIDs sufferers. In developing and underdeveloped countries, PID is still being neglected by health professionals. Therefore, a proposal of combined treatment strategy for preventing this diseases morbidity is necessary.

Key words: immunodeficiency, innate, adaptive, immunity, flow-cytometer, next-generation sequencing.

Abbreviations:
AH50 (Alternative Complement assay); APAAACI (Asia Pacific Association of Allergy, Asthma, and Clinical Immunology); APAPARI (Asia Pacific Association of Pediatric Allergy, Respirology and Immunology); APSID (Asia Pacific society for Immunodeficiencies); APSID (Asia Pacific society for Immunodeficiencies); BMT (Bone marrow transplant); CBC (Complete Blood Cell Count); CGD (Chronic Granulomatous Disease); CH50 (Haemolytic Complement assay); CVID (Common variable immunodeficiency); ESID (European Society for Immunodeficiencies); FPID (Foundation for Primary Immunodeficiency); HLH (Hemophagocytic lymphohistiocytosis); HSCT (Haematopoietic Stem Cell Transplantation); IEI (Inborn Errors of Immunity); IUIS (International Union of Immunological Societies); IVIg (Intravenous immunoglobulin);

ISPID (Indian Society for primary immune deficiency); JMF (Jeffrey Model Foundation); KRECs (kappa deleting-recombination excision circles); LASID (Latin American Society for Immunodeficiencies); LPI (Legatum Prosperity Index); MyPIN (Malaysian Primary Immunodeficiency Network); NGS (Next-Generation Sequencing); PCR (Polymerase Chain Reaction); PEPAC (JMF Physician Education and Public Awareness Campaign); PID (Primary immunodeficiency diseases); RT-PCR (Reverse Transcription Polymerase Chain Reaction); SCID (severe combined immunodeficiency); SCIG (Subcutaneous Immunoglobulin); TRECs (T-cell receptor excision circles); USIDNET (United States Immunodeficiency Network); WAS (Wiskott-Aldrich Syndrome); WAS (Wiskott-Aldrich syndrome); WHO (World Health Organisation); XLA (X-Linked Agammaglobulinemia)

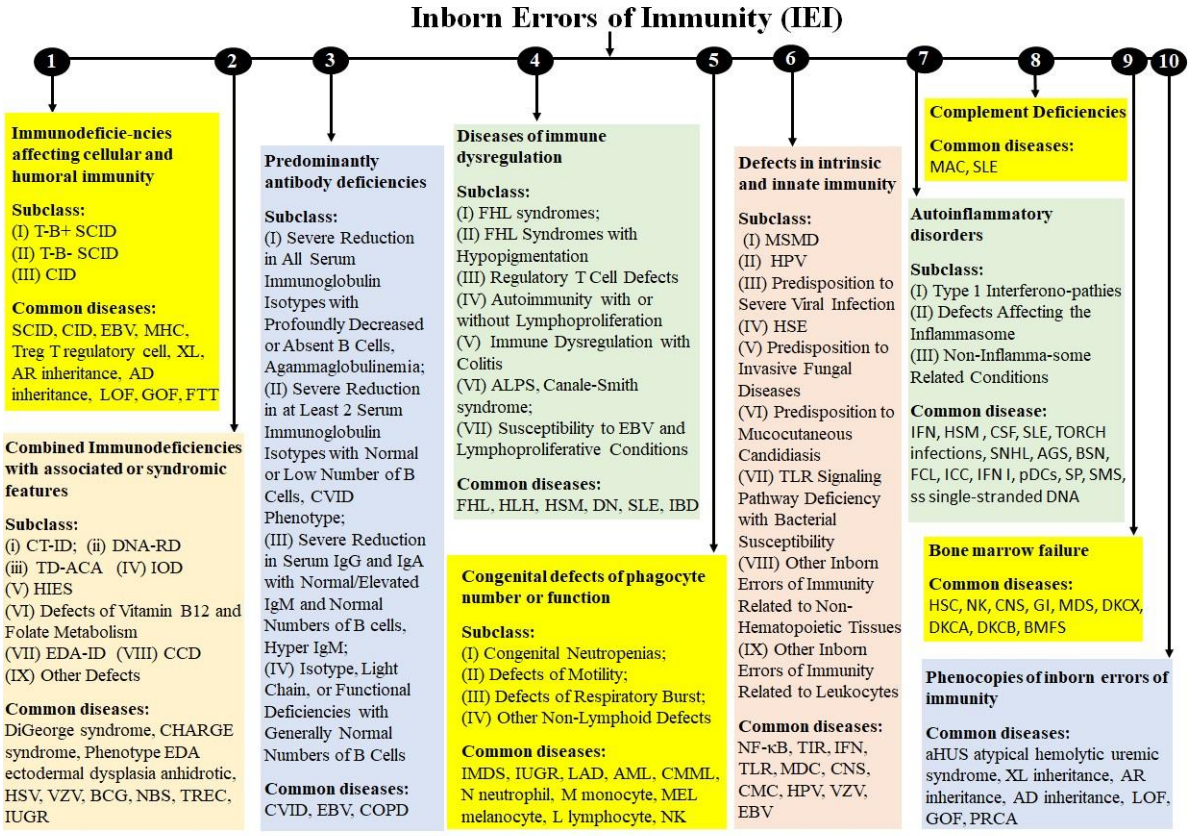
Introduction:

Primary immunodeficiency diseases (PIDs) are solely associated with the defective functions of the immune system [1-4]. The disease is broadly described under the "Inborn Errors of Immunity (IEI)" [4]. The disease PID was projected by the medical world in the early 50's of last century and recognised as a rare disease [3, 5]. As per the published report on 2022, the International Union of Immunological Societies (IUIS) identified 485 IEIs under 10 broad classification (Chart-1) [6]. The exact diagnosis of PIDs may be precarious due to its wide spectrum of signs and symptoms alongside the lack of concrete relationship between the clinical manifestations and the underlying etiology [7]. Continuous development in the field of genetic research specially increased access to the next-generation sequencing (NGS) has a probability to add more PIDs variants in the next IUIS issue [2, 8]. Previously, it was observed that 65 new variants were added in 2018 and 55 variants in 2020 issue of IUIS [6, 9]. Due to this rapid discovery of the new variants of PIDs, several PIDs seem to be individually rare but its aggregated numbers will represent a significant worldwide health burden in the near future [6]. An appropriate worldwide strategy is required to prevent the PIDs related upcoming health and growing economic losses in different developed countries like the USA and several European countries.

PIDs are generally developed immediately after birth or in the early stage of life due to abnormalities in the innate and/or adaptive (acquired) immune system [10]. Genetic defects is generally the prime reason for such abnormalities in WBC (mostly T- and/or B- lymphocytes), which is generally developed during birth or at several months old [10]. Such defects may be responsible for getting sick faster and for longer periods of time from usual childhood infections. The common symptoms of PIDs are diverse types of repeatedly occurring symptoms which, when severe, might lead to death at an early age (Chart-2) [1]. In such cases, the child survival rate of a country, namely neonatal mortality rate, infant mortality rate, under five years' mortality rate etc. are key demographic indicators and should have a relation with the frequency of PIDs' occurrence. Unfortunately, till to date, it is very difficult to establish any statistical relationship between the frequencies of PIDs with the key demographic data of a country (Table-1). According to the IUIS 2022 report only 80 countries in the world mostly from American and European subcontinents where there exists a developed healthcare system have successfully reported PIDs [1]. However, only 4509 PIDs patients have been registered from 7 African countries representing 240 million people which is only 17.9% of the total population (around 1339.85 million) living in 54 countries [1]. Similarly, in the case of Asia which is the most populous continent (4561 million), out of 48 countries only18 countries registered 15939 PIDs patients [1]. Statistically the above numbers do not represent the exact scenario of those two continents as it is well known that many of the Asian and African countries have a poor healthcare system, high rate of infectious diseases and poor child survival rate (Table-1). Whereas, medically advanced countries like the USA, France, Canada, UK, Sweden, China etc. countries have successfully detected a huge number of PIDs (Table-2). It raises questions of seriousness when some of the top most populated countries such as Indonesia, Pakistan, Nigeria etc. still failed to diagnose a single case of PIDs (Table-1). It is

surprising and raises questions regarding the existing overall management of PIDs in the world, when some of the top most populated countries with high child mortality rate, such as, Indonesia, Pakistan, Nigeria etc. fails to diagnose a single case of PIDs. Even in Bangladesh where infectious disease is a common scenario, only 13 PIDs patients have been detected so far. The above information indicates PIDs are totally overlooked in some regions in the world. The probable reasons for such ignorance may include its clinical heterogeneity, knowledge gaps among physicians and insufficient diagnostic knowledge along with lack of proper uses of existing expensive diagnostic facilities including flow-cytometer and lack of accessibility to genetic testing such as next generation sequence [11-12]. A massive awareness program is required for both health professionals as well as for general people for early detection and treatment of PIDs in all over the world, especially those countries that have suffered from unsatisfactory treatment facilities and have high child mortality rate.

Chart 1: Classification of Inborn Errors of Immunity as per IUIS'2022 [6].



Here, **AD** =autosomal dominant, **AGS** = Aicardi-Goutières syndrome, **aHUS** = atypical hemolytic uremic syndrome, **ALPS** = Autoimmune Lymphoproliferative Syndrome, **AML** = acute myelogenous leukemia, **AR** = autosomal recessive, **BCG** = Bacillus Calmette-Guerin, **BMFS** = bone marrow failure syndrome, **BSN** = bilateral striatal necrosis, **CCD** = Calcium Channel Defects, **CHARGE** = coloboma, heart defects, atresia choanae (choanal atresia), growth etardation, genital abnrmalities and ear abnormalities, **CID** = Combined Immunodeficiency, **CMC** = chronic mucocutaneous candidiasis, **CMML** = chronic myelomonocytic leukemia, **CNS** = central nervous system, **COPD** = chronic obstructive pulmonary disease, **CSF** = cerebrospinal fuid, **CT-ID** = Immunodeficiency with Congenital Thrombocytopenia, **CVID** = Common variable immunodefciency disorders, **DKCA** = autosomal dominant dyskeratosis congenita, **DKCB** =autosomal recessive dyskeratosis congenita, **DKCX** = X-inked dyskeratosis congenital, **DN** = double-negative, **DNA-RD** = DNA Repair Defects Other Than Those Listed in group 1, **EBV** = Epstein-Barr virus, **EDA** = Ectodermal Dysplasia Anhidrotic, **EDA-ID** = Anhidrotic Ectodermodysplasia with Immunodeficiency, **FCL**= familial chilblain lupus, **FHL** = Familial Hemophagocytic Lymphohistiocytosis, **FTT** = failure to thrive, GI = gastrointestinal, **GOF** = gain-of-function, **HIES** = Hyper IgE Syndromes, **HLH** = hemophagocytic lymphohistiocytosis, **HPV** = human papillomavirus, **HSC** = hematopoietic stem cell, **HSE** = Herpes Simplex Encephalitis, **HSM** = hepatosplenomegaly, **HSV** = herpes simplex virus, **IBD** = infammatory bowel disease, **ICC** = intracranial calcifcation, **IFN** = interferon, **IMDS** = myelodysplastic syndrome, **IOD** = Immuno-osseous Dysplasias, **IUGR** = intrauterine growth retardation, **LAD** = leukocyte adhesion defciency, **LOF** = loss-of-function, **MAC** = membrane attack complex, **MDC** = myeloid dendritic cell, **MDS** = myelodysplastic syndrome, **MHC** = major histocompatibility complex, **MSMD** = Mendelian Susceptibility to mycobacterial disease, **NBS** = newborn screen, **NF-κB** = nuclear factor kappa B, **NK** = natural killer, **pDCs** = plasmacytoid dendritic cells, **PRCA** = pure red cell aplasia, **SCID** = severe combined immunodefciency, **SLE** = systemic lupus erythematous, **SMS** = Singleton-Merten syndrome, **SNHL** = sensorineural hearing loss, **SP** = spastic paraparesis, ss = single-stranded, **TD-ACA** = Thymic Defects with Additional Congenital Anomalies, **TIR** = Toll and interleukin 1 receptor, **TLR** = Toll-like receptor, **TORCH** = toxoplasmosis, other, rubella, cytomegalovirus, and herpes infections, **TREC** = T cell receptor excision circle (biomarker for low T cells used in NBS), **VZV** = varicella zoster virus, **XL** = X-linked inheritance

PIDs will have a critical impact on worldwide health in the near future and will act as a barrier to achieve Sustainable Development Goals (SDGs) (GOAL 3: Good Health and Well-being)

proposed by the United Nations. To overcome the situation, the World Health Organisation (WHO) and its associates need to take the leading position to develop appropriate strategies for promoting PIDs related knowledge including identification, diagnosis, knowledge sharing and developing treatment facilities among the member countries. Not only that, WHO has to supervise all these countries to develop their own national level policies for assuring appropriate training to the general physicians among PIDs, maintain proper registry for PIDs, treatment outcomes, and reporting system to the international bodies.

The objective of the present study is to focus on the disease nature, worldwide situation of PIDs, available diagnosis strategy and intended approaches for the treatment. The study also tries to justify the importance of creating a nationwide database, bi-lateral and uniform sharing of knowledge, maintaining registry, etc. In the present study, a specific management approach for overcoming the present and upcoming situation of PIDs has also been proposed.

Table 1: List of top 10 populated countries in the world with some key demographic indicators for PID

Population Rank	Country	Current Population (Million) in 2023 [13]	Registered PIDs patients (IUIS 2022 report) [1]	Mortality Rate Per 1,000 Live Births (as per 2021 statistics) [13]			Percentage of care-seeking children (under age 5) for infectious diseases [13]	
				Neo-natal	Infant	Under five years	Acute respiratory infection	Diarrhoea
1st	India	1428.6	778	19	25	30.6	56	61
2nd	China	1425.7	2487	3	5	6.9	-	-
3rd	USA	339.9	30227	3	5	6.2	-	-
4th	Indonesia	277.5	-	11	19	22.2	75	36
5th	Pakistan	240.5	-	39	53	63.6	71	37
6th	Brazil	216.4	1878	8	13	14.4	50	-
7th	Nigeria	223.8	-	35	71	110.8	40	40
8th	Bangladesh	172.9	13	16	23	27.3	46	72
9th	Russia	144.4	204	2	4	5.1	-	-
10th	Mexico	128.46	1744	8	11	13.2	73	61

Table 2: Top 10 PID detection countries with their population, mortality rate, economical position and healthcare facilities.

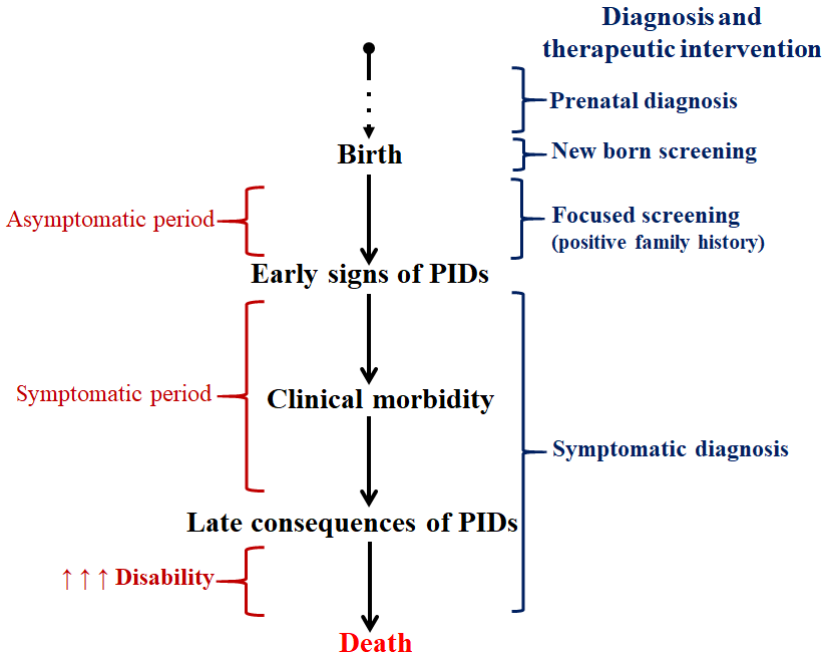
World-wide Position of PID detection	Name of the Country	No. of registered PIDs patients [1]	Current Population '2023 [13]		Under Five Mortality Rate in 2021 (Per 1,000 Live Births) [13]			Economical position [14]	World ranking in the Health Care System LPI* 2020 Ranking [15]
			Million	Rank as per population	Neo-natal mortality rate	Infant mortality rate	Under five mortality rate		
1st	USA	30227	339.9	3rd	3	5	6.2	1st	18th
2nd	France	6602	64.8	23rd	3	3	4.4	6th	22nd
3rd	Turkey	6392	85.8	18th	5	8	9	17th	94th
4th	UK	4758	67.7	21st	3	4	4.2	5th	13th
5th	Poland	4099	41.03	36th	3	4	4.3	23rd	36th
6th	Iran	3056	89.2	17th	13	11	12.6	25th	120th
7th	Canada	3047	38.8	37th	3	4	5	10th	14th
8th	Argentina	2730	45.8	32nd	5	6	6.9	21st	63rd
9th	Sweden	2727	10.6	85th	1	2	2.5	22nd	4th
10th	China	2487	1425.7	2nd	3	5	6.9	2nd	54th

* Legatum Prosperity Index

Diagnosis challenges for PIDs:

Primary immunodeficiency disorders (PIDs) are diagnostically challenging chronic disorders. It is connected to the defective immune system which may be observed at any age and have an association to the genetic predilection and environmental exposures [4, 12]. Signs and symptoms may differ on the basis of PID specific types and individual sufferers. However, frequent and longer lasting or harder-to-treat infections may also be used as the marker signs for PIDs. The Jeffrey Model Foundation in association with International Patient Organisation for Primary Immunodeficiencies and Primary Immunodeficiency Association developed "10 warning signs of primary immunodeficiency" (Figure-1), which is widely promoted in most of the European countries for developing awareness in the general population [16]. Diagnostic success mostly depends on critical observation of symptomatic warning symptoms of PIDs (Figure-1) and successive further applications of diagnostic tools and methods (Figure-2). A child who has been bearing only one of these signs (Figure-1) is unlikely to have PIDs. But the probability of having PIDs increases when a child suffers from several of the symptoms listed in Figure-1, or has repeated symptoms of the same infections in a short period of time. Above them, there are many remarkable visible and internal signs including family history that may be considered for detecting the PIDs suspects from the general groups (Figure-1). PIDs make individuals more susceptible to a wide range of diseases including allergy, autoimmunity, skin infection, intestinal infection, sinopulmonary infection, inflammation, malignancy, physical disability, permanent organ damage, or even death etc. [4]. Presently around 485 genetic defects (Chart-1) are identified [6] that have specific association on one or more components (mainly cells and proteins) of the innate or adaptive immune system, which make these diseases challenging for diagnosis and may be responsible for inadequate treatment facilities. An experienced or trained physician may correlate the PID by minutely observing history, and the nature of infectious disease (Figure-2). Clinical suspicion is vital for timely diagnosis of these disorders and to postulate appropriate treatment facilities. Generation of clinical suspicion from general people and general physicians will be helpful for overcoming the present situation of failure to detect PIDs.

Chart 2: The consequences of PIDs and diagnostic opportunities



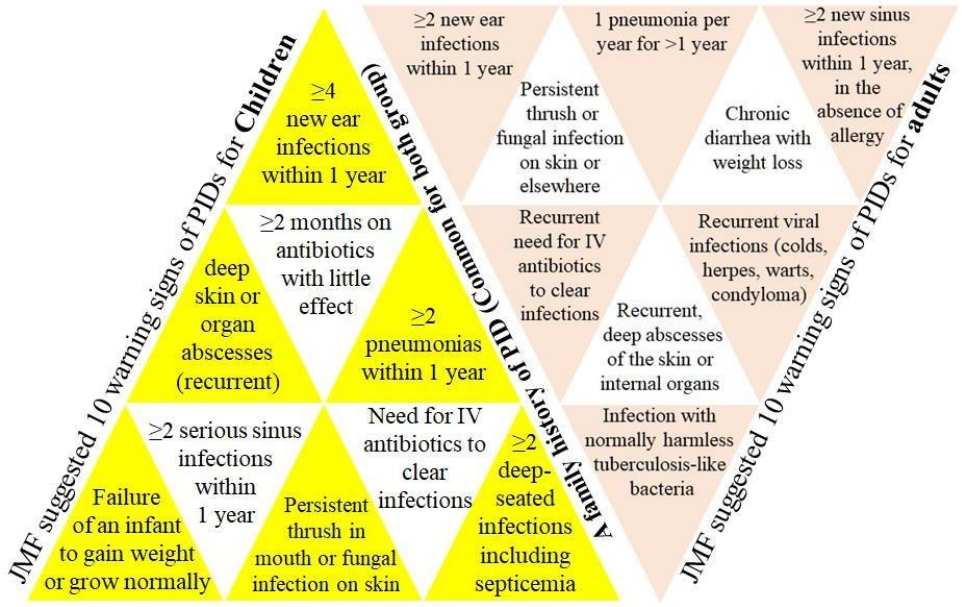


Figure 1: Simple screening procedures of PIDs [17-19]

Diagnostic difficulties of PID:

It is very difficult to identify exact types of PIDs by using conventional biomedical analysis. Advanced technology such as next generation sequencing (NGS), Genomic PCR, RT-PCR, flow-cytometer etc. may be used for detection purposes. Flow-cytometer and NGS techniques are suitable for diagnosis of difficult PIDs, but both techniques are expensive and demands advance level knowledge of the investigators [11]. Flow-cytometer is comparatively rapid detection process of specific cell populations or subpopulations mainly responsible for the immune system such as T-cell, B-cell, NK cell etc. Flow-cytometer may also be suitable for screening the altered expression of a specific protein (both extracellular and intracellular), assess for biological changes connected to the specific immune defects and evaluate certain characteristics of the functional immune system [20-21]. In-case of NGS, targeted gene panels are generally cost effective for patients having a predictable clinical profile [11].

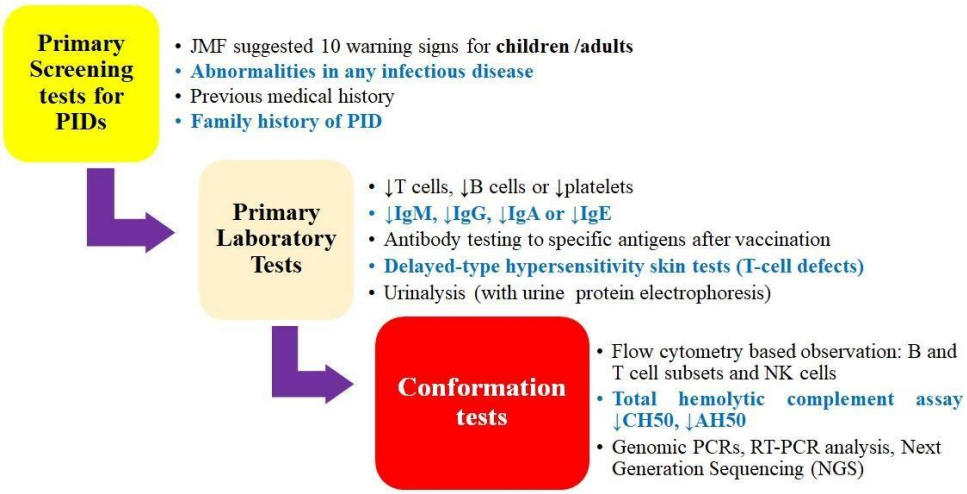


Figure 2: Diagnosis procedures of PIDs [11, 22, 23]

It is expected that physicians will initially assess the suspects by a series of commonly practiced laboratory investigations before going through the flow cytometer or NGS techniques. For PIDs, there are several laboratory investigations are recognised such as (i) a complete blood cell count (CBC): decreased number of T-cell and B-cell may be alarming, (ii) measurements of serum immunoglobulins: decreased in any or all of IgG, IgM, and IgA levels may be alarming (iii) measurements of functional antibodies against immunized antigens after vaccination: decreased or absent antibody response to vaccination is alarming, (iv) delayed-type hypersensitivity skin tests for screening out the T-cell defects: negative result indicate possible impaired T-cell response, (v) total haemolytic complement assay (CH50) for screening out the complement deficiencies: decreased or absent proteins is alarming, (vi) nitroblue tetrazolium test for screening out the phagocytic disorders etc. [22].

Detection of PIDs may be started by new-born screening by quantifying T-cell receptor excision circles (TRECs) or kappa deleting-recombination excision circles (KRECs) [24]. For this purpose dried blood spots (DBSs) have to be collected from all new-born babies on day 3 of life [11, 24]. TRCEs are the small pieces of DNA generally found in specific naïve T-cells [24]. RT-PCR is used to quantify the number of copies of TRECs. The level of TRCEs normally decline in healthy individuals with age or in case of HIV patients [24]. In case of severe combined immunodeficiency (SCID) and other T-cell lymphopenia the level of TRCEs are observed to reduce or absent [17, 24]. KRECs are the products of the B-cell immunoglobulin kappa gene which may be used for identifying XLA and XLA-like diseases in neonates [24].

Treatment options for PIDs:

Untreated PIDs may be responsible for developing life-threatening conditions such as infections, chronic organ injuries, disabling disorders etc. that could result in diminishing quality of life and life expectancy [7]. An early detection (Chart-2) and prompt action could reduce complications and save lives by administering appropriate treatment [11, 25]. Currently, there are many treatment options for PIDs that are introduced and frequently practiced in different countries [Figure-3]. PIDs may be responsible for developing different life threatening syndrome (Chart-1) such as DiGeorge syndrome (associated with congenital heart disease, hypoparathyroidism, abnormal facies etc.), Wiskott-Aldrich syndrome (WAS) (associated with thrombocytopenia, eczema etc.), Ataxia-Telangiectasia, Ivemark syndrome (associated with congenital heart disease, bilateral 3-lobed lungs etc.), polyendocrinopathy syndrome (associated with endocrine organ dysfunction) [16]. Treatment approaches of most of the above syndromes are case specific and treatment approaches are mostly targeted to manage rather than totally cure. The root cause of most of the above syndromes are associated with the genetic defects probably developed before or after birth. So, early detection, such as new-born screening as well as successive treatment will increase the probability of surviving the PIDs sufferers.

There are many treatment options available for PIDs (Figure-3). HSCT, BMT, thymus transplant may be considered as the definitive cure for many PIDs exclusively SCID, WAS, CGD, HLH, etc. HSCT are usually curative for several PIDs and the facilities have been practiced in Japan since the year 1991 [11]. However, the best outcomes of HSCT are observed if the treatment approach is applied at a young age (<3 months) and prior to any infectious complications of SCID [26-27]. Intravenous immunoglobulin (IVIg) is one of the costly and standard treatment approaches for different PIDs especially XLA, CVID etc. [11]. Subcutaneous route of Immunoglobulin replacement (SCIG) therapy is the standard practice for PIDs treatment in the United States and European countries [11]. Bone marrow transplants from HLA-identical donors may be another curative approach to treat PID patients with cellular

immune deficiencies such as SCID, WAS, DiGeorge syndrome, and also favourable for patients with chronic granulomatous disease [22]. When frequent infections are a problem, many PID patients are managed with antibiotics alone or in combination with IVIg [22]. Sometime enzyme replacement therapy is recommended for adenosine deaminase deficiency (a subtype of SCID) and cytokine therapy for chronic granulomatous disease [22].

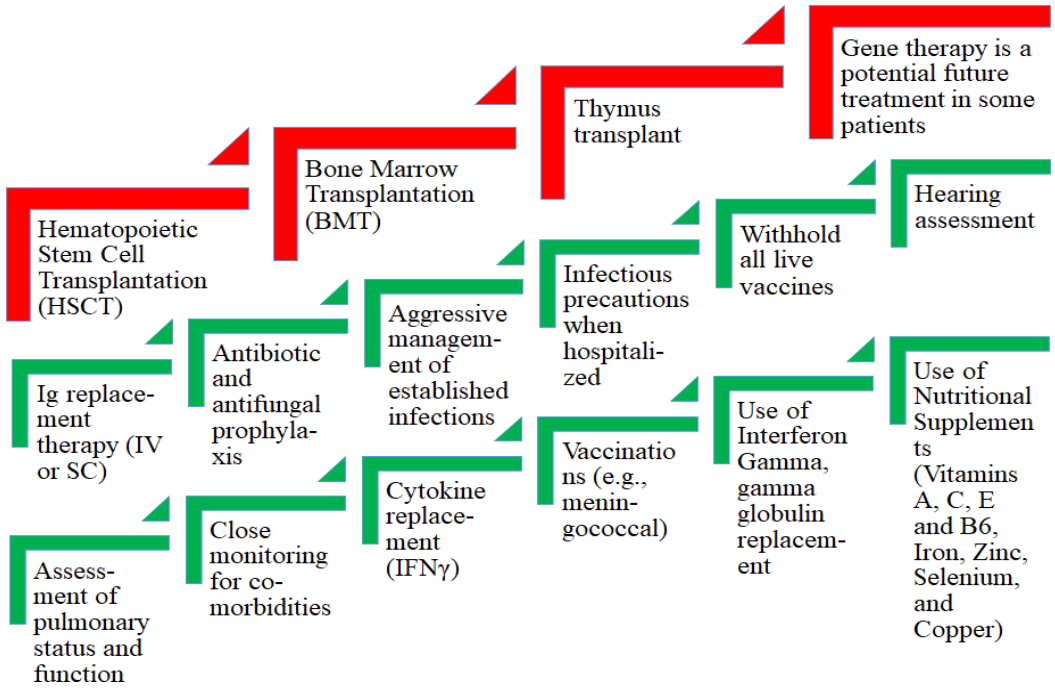


Figure 3: Possible treatment options for PIDs. Here, Red bar indicates definitive therapy and Green bar indicates supportive therapy [17, 26-27]

Approaches of overcoming PIDs morbidity:

There is no correct estimation of the global PID prevalence in different regions and ethnicities [1]. Since the first report of PID in 1952 in Japan till to date around 104614 PIDs patients were registered in 80 countries in the world from the periods of January 1981 to June 2020 [1]. But the number is not representative as most of the populated and medically backward countries failed to register PIDs, which is outrageous in contest with their under-five mortality rate (Table 1). Though the prevalence of PIDs differs from one region to another, few studies assume that nearly 1% of the population may be suffering from PIDs [24]. Early detection and treatment may improve the overall quality of the life as well as reduce the overhead treatment cost. Diagnostic delay, which is defined as the elapsed time between the onset of PID symptoms and the establishment of diagnosis, may be reduced by increasing awareness of PID among physicians and the public [1]. In this regard, a widespread awareness is necessary to avoid the serious morbidity due to late diagnosis of the wider spectrum of PID and prevent premature death [19].

Till to the date, the global problem of PID is clearly misjudged and now it demands keen concentration for managing the complex heterogeneous genetic disorders [1]. Without government level interest, it will be difficult to adopt the whole treatment facilities of PIDs in medically backward countries. Nationwide awareness will be required for identifying PIDs and developing treatment facilities. WHO and its associates may take a leading role to create government level awareness as well as in the health professionals. They may take help from the J Project which was conducted in several European countries to increase physician

awareness and promote the genetic testing for diagnosis of PIDs [5]. The outcome of the J Project drastically improved the diagnosis and medical care of PID patients in Europe.
In the present context, a cyclic five steps strategy (Figure-4) is proposed for setting the sequential activities of a particular government who are interested in developing a proper management system on PIDs.

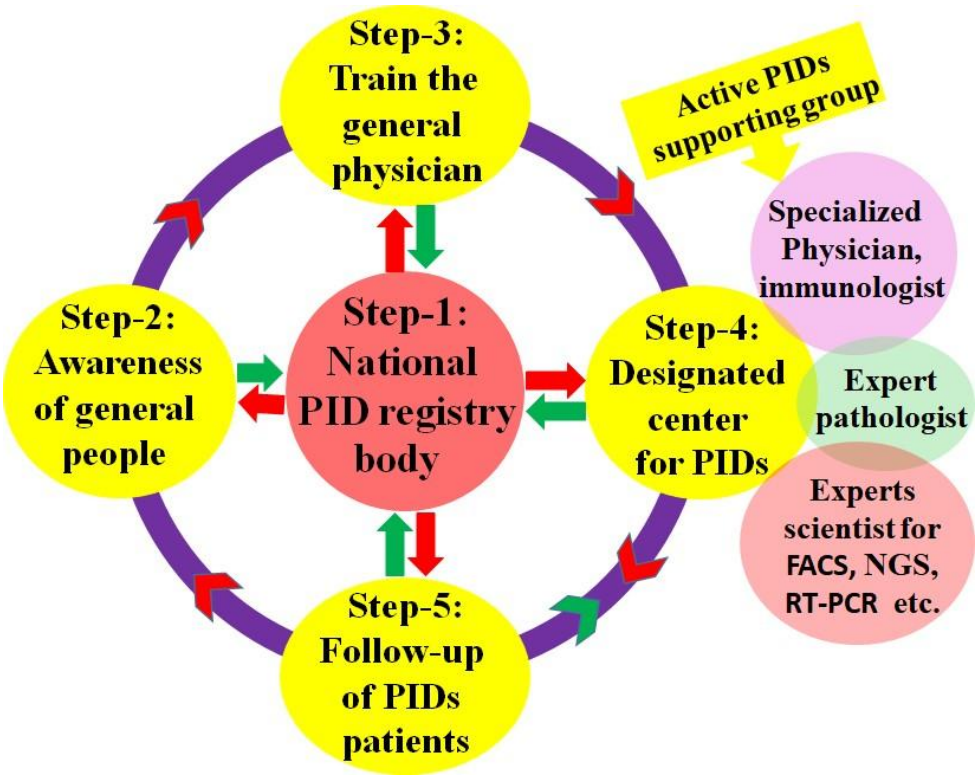


Figure 4: Proposed management approaches of PIDs for medically back-warded countries (here, red arrow indicates "forward activities" and green arrow indicates "feedback").

First of all, each nation has to develop a dedicated "national PIDs registry body" under a research institute funded by the government. The organization will act as the heart of monitoring all PIDs cases in that particular nation. Presently there are many regional registry body has functioning in different parts of the world such as the ESID, LASID, USIDNET, APSID, PEPAC, APSID, ISPID, FPID, APAAACI, APAPARI, MyPIN etc. are working to register the case of PIDs [1, 11, 28]. However, the performance of the United States Immunodeficiency Network (USIDNET) databases is outstanding as this registry system solely concerns a particular nation [1]. So, any country who wants to concentrate on PIDs, needs to establish a central registration system (organization) first. Country wise dedicated PIDs registry body (organization) will take necessary action to promote the information among the root level of people to identify the suspects. The prime objective of this organization would be to register the primary suspects of PIDs, differentiate confirmed cases, monitor the intended treatment approaches, follow-up the treatment outcomes, rate of recovery, rate of failure, rate of developing new variants, family history of all cases etc. As the PIDs are genetic problems, a worldwide database will be helpful for managing the disease. Bilateral and multilateral information sharing tendency will reduce the gap between developed and underdeveloped countries' treatment approaches for PIDs. Generally PIDs information is updated every two years by the IUIS. Active participation of each nation will enrich the database and active

supporting groups will easily identify the treatment strategy for an existing or a new case. A dedicated cell may be opened by the health ministry to monitor the activities of "national PIDs registry body" and the progress of the existing situation of PIDs. An artificial (AI software) registry system may be developed for auto ascertaining PIDs suspects from the hospital registry from different primary, secondary or tertiary levels of the healthcare system.

After establishing a national PID registry body, the cell should take necessary steps to create awareness (in step 2) regarding PIDs. The awareness strategy may be started considering the general people as the integrated part. Concerned general people will be an important resource to combat against the PIDs. Because general people are the ultimate contact person who will primarily suspect the PIDs patients based on their medical history and symptoms and ultimately bring them into the health care system to conform. In this regard, JMF suggested 10 warning signs for PIDs for children and adults (Figure-1) may be used as the baseline for detecting the PIDs suspects. Government should take necessary steps to educate the general people regarding PIDs by using available primary health education programs, leaflets, talk shows etc.

General physicians who are dealing in the primary level health care facilities may act as the focal person to deal with the primary suspects. But this group of health professionals have to be trained (in step 3) on PIDs before enrolling in the system. Without proper knowledge, PIDs may be overlooked due to their common nature match with different simplified infectious diseases. General physicians need to be concerned enough to register the case history as such that PIDs warning signs are not overlooked. Though the infection is the common symptom of PIDs, general physicians have to collect detailed medical history of such patients. Presence of two or more symptoms listed in Figure-1 will be helpful to identify the PID suspects. However, the physicians have to educate more details regarding those signs and diagnostic approaches to conform the suspects. Lectures, workshops and training may be arranged for primary care physicians including pediatricians and general practitioners for early finding of PIDs from every part of a country. Many countries already have started adopting formal training programs to educate young doctors, such as in India initiated this training program in the year 2014, and to date, many trained immunologists have started providing care to patients with PIDs across different parts of that country [11]. Awareness programs in physicians may be started by conducting a survey to know their basic knowledge about PIDs. This type of survey was conducted in the USA in the year of 2008 [26] and in Ukraine in 2016 [5] by developing specific questionnaires including warning signs in children and adults, general signs of PIDs, specific signs of PIDs, treatment strategies and immunization of patients with PID etc. On the basis of the outcome, a training module may be designed for individual groups of physicians to perform their job at the root level. This group will act as the active force for confirming the PID patients from the general suspects detected in step-2 by the general people.

In Step-4, a government have to establish a 'designated center for PIDs' under a mainstream government hospital with a group of specialized physician, immunologist, pathologist, biochemist who are able to diagnosis PIDs by using advanced level of analytical equipments such as flow-cytometer, NGS, genomic PCRs, gene scan analysis, RT-PCR analysis etc. All personnel in these groups may be designated as the "active PIDs supporting group". The center has to have sufficient facilities for diagnosing and provide relevant treatment support. However, Specific in-depth training program is required for these specialized groups. The prime objective of this center is to acquire knowledge of recent development of PIDs and capable themselves to offer such treatment in their own establishment. They have to develop a warm connection with the international expert group along with the regional and international PID centers for sharing knowledge, treatment facilities, and consultation.

Step-5 is the follow-up strategy of the conformed PID patients. Once a case is confirmed by the 'designated center for PIDs', it demands special care from the government as the treatment

procedure is complex and expensive. Government subsidies will be appreciated for some extent of the treatment. Many Asian countries like Malaysia, Thailand etc. give subsidies for most of the patients for IVIg therapy [11]. The 'national PID registry body' has to maintain the follow-up report of each and every PID patient. If necessary, the national PID registry body can communicate with different Professional bodies dealing with PID for offering appropriate treatment, such as, ESID, LASID, USIDNET, APSID, PEPAC, APSID, ISPID, FPID, APAAACI, APAPARI, MyPIN etc. [1, 11, 28]. In this step, through the 'national PID registry body' PID patients will also have a chance to get suggestion from different PID advocacy organizations, such as, IPSPI, PiDPWs from India, ThaiPOPI, PID Care China, PPIPI, PID Korea, PID Tsubasa-noKai in Japan, Persatuan Pesakit Imunodefisiensi Primer Malaysia (Malaysian Patient Organisation For Primary Immunodeficiencies) [11].

PID will be a manageable disease in case of early detection and application of proper treatment strategy. However, due to its complex nature and expensive diagnosis and treatment facilities, proper motivation and knowledge sharing among the patient group is important. By implementing the five step strategy proposed in this article will be helpful for medically back warded countries to initiate the treatment facilities of PID.

Conclusion:

Though there are several diagnosis alternatives introduced for PODs, still in many countries numerous suspects stay without confirmation tests. The prime reason may be due to the insufficient awareness of PIDs amongst both physicians and the general public in most of the developing and under developing countries. National level policy is required for all such countries to develop awareness programs for targeting both the physician and general public which may change the present shortcoming regarding PIDs. Not only that, government level schemes should develop for educating short listed physicians to manage the PIDs. Government should allocate sufficient funds for conducting PIDs related research to improve awareness programs, to improve diagnosis setup, to develop treatment facilities, to maintain the proper registry for all PIDs suspects and patients. Research may also focus on identifying the new variants, their diagnosis approach, treatment facilities as well as their applications in the root level people. Formatted questionnaires may be developed for quick measuring the understanding level of general physicians working in the root level regarding PIDs. Training modules may be developed for different levels of personnel who will be involved in the PIDs identifications, treatment and awareness program. Online reporting system may be developed for immediate entry of the PIDs suspect from the root level physicians. Moreover, a government level supervision is necessary to monitor all PIDs related issues including diagnosis, treatment, success history, and follow-up history by using a digital or artificial registry system.

Conflict of interest statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Author contribution statement:

Sadat, Karmaker, and Pasha proposed the idea. Sadat, Karmaker, and Khan drafted the manuscript. Sadat, Karmaker, Razu, and Barua reviewed the manuscript. Sadat, Karmaker and Pasha wrote the initial draft of the manuscript. Sadat, Karmaker and Khan revised the manuscript. All authors read and approved the final submitted version of the manuscript.

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