PID
PRIMARY IMMUNODEFICIENCIES

European Primary Immunodeficiencies Consensus Conference

Consensus Report and Recommendations

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

efis

ESID

International Nursing Group iNGID for Immunodeficiencies

European Commission

EDF.IPI CENTRE FOR TRAINING AND RESEARCH Founded in 1999

European Primary Immunodeficiencies Consensus Conference Report

Contents

	Page
Foreword	3
Executive Summary	4
Consensus Statement and Recommendations	6
Session 1: An EU Public Health Issue	12
Overview of PIDs in the EU, Goals and Objectives of the Meeting	12
The Benefits on an EU approach to Rare Diseases	13
Addressing Inequalities of Access to Healthcare in an Extended Europe	15
PIDs – a Public Health Issue?	17
Session 2: What are Primary Immunodeficiencies?	19
Overview of PIDs in Adults and Children	19
Prevalence, Screening and Diagnosis of PIDs in the EU	20
Treatment Options: Immunoglobulin Therapy – the Major Therapy Choice in PID	22
Treatment Options: Bone Marrow Transplants/ Gene Therapy	24
Disparity of Diagnosis, Treatment and Care for PIDs between Member States of the EU	26
Session 3: Consequences Of Missed Or Delayed Diagnosis	28
Consequences of Missed/Delayed Diagnosis: Mortality/Morbidity	28
Consequences of Missed/Delayed Diagnosis: Quality of Life	30
Consequences of Missed/Delayed Diagnosis: A Patient's Story	31
Consequences of Missed/Delayed Diagnosis: Health Care Costs	33
Session 4: Public Health Interventions to Address PIDs	35
Evaluating Strategies for Early Identification of People with PIDs	35
Genetic Testing and Early Detection	37
The Role of Nurses in Recognising PIDs	38
The Importance of Patient Registries in Rare Diseases	40
Educational Outreach Efforts by:	
• Physicians: The J-Project – An Eastern European Initiative	41
• Patients: Physician & Public Awareness Campaigns in the US	43
• Patients: Patient Organisation Activities in Europe	45
• Nurses: Educational Outreach Efforts by Nurses	47
What Can We Learn from the US – The Positive Effects from the US Consensus Conference?	48
Conference Organising Partners, Sponsors and Partners	50
Glossary of Terms	51

The EU PID Consensus Conference was held in June 2006. This Conference along with the resulting Statement, Report and Recommendations have been produced as part of a project supported by funding from the EU Public Health Programme.

The project has been jointly led by ESID, IPOPI, EFIS and INGID with the support of the European Commission. Many thanks to the representatives from these organisations as well as the JMF and the ECE IPI CTR, who have collectively worked tirelessly to ensure this project came to fruition.

- Bianca Pizzera, Chairman IPOPI
- David Watters, Executive Director IPOPI
- Dr Ann Gardulf, President INGID
- Amena Warner, Vice President & Treasurer INGID
- Prof Luigi Notorangelo, President ESID
- Dr Esther de Vries, Treasurer ESID
- Dr Helen Chapel, ESID
- Prof Reinhold E Schmidt, Treasurer EFIS
- Vicki Modell, Founder JMF
- Prof László Maródi, Chairman ECE IPI CTR

Thanks also go to those who worked so hard on the translations of this document. They include Dr Teresa Espanol, Elizabeth Galkina, Martine Pergent, Anneli Larsson, Bianca Pizzera, Prof Reinhold E Schmidt, Kees Waas, Susanna Lopes da Silva, Prof Bernatowska and Prof László Maródi.

Further copies of this document are available in English, Dutch, German, Italian, French, Spanish, Portuguese, Hungarian, Polish and Swedish at www.eupidconference.com. Further information can found by emailing david@ipopi.org.

Foreword

In the European Union any disease suffered by fewer than 1 in 2000 people is considered a “rare disease”. With levels of diagnosis currently estimated at 1 in 10000, Primary Immunodeficiencies (PIDs) are classified as rare diseases. The lack of information about rare diseases often means that sufferers, who together represent more than 7% of the total EU population, do not always benefit from the health services they need. Yet it is often these frequently life-threatening or chronically debilitating diseases that require combined efforts to prevent citizens suffering from a reduced quality of life or dying early.

Rare diseases are already a priority in the Community Public Health Programme, which aims to complement national policies at European level by improving information, sharing good practice and reporting on health across the Union. The Commission is pleased to support the EU PID Consensus Conference through the Public Health Programme and commends the efforts of the partners involved in organising the conference to promote awareness among the medical community and the general public about PIDs. We hope that as a result of the conference they will also be well placed to disseminate new systems that reduce unequal access to diagnosis and treatment across Europe and to ensure that information produced by registries on PIDs can be utilised effectively by clinicians.

EU action in the field of rare diseases can only be efficient if large scale networks involving patients’ organisations, health professionals and other stakeholders from several EU Member States are created. The Commission welcomes the positive steps in this direction from the International Patient Organisation for Primary Immunodeficiencies, the European Society for Immunodeficiencies, the European Federation for Immunological Societies, the International Nurses Group for Immunodeficiencies and the East-Central-European Infectious and Paediatric Immunology Centre for Training and Research and the potential for these organisations to encourage the support of the Community for Primary Immunodeficiencies and other rare diseases in coming years.

Andrzej Rys
Public Health Director
Directorate General Health and Consumer Protection
European Commission
Brussels

October 2006

Executive Summary

On 19-20 June 2006, the International Patient Organisation for Primary Immunodeficiencies (IPOPI), the European Society for Immunodeficiencies (ESID), the International Nurses Group for Immunodeficiencies (INGID) and the European Federation for Immunological Societies (EFIS) in partnership with the European Commission, held a two-day Consensus Conference on Primary Immunodeficiencies (PIDs) at the Paul-Ehrlich-Institut in Langen, Germany.

More than 100 experts in clinical immunology, PID care, public health, genetics, EU/national ministries of health and agencies, academic centres, public health laboratories, industry, professional organisations and patient groups were brought together to identify and develop public health strategies for PID.

PIDs are a diverse group of more than 100 immune disorders, many of which result from single-gene defects. The defects lead to increased susceptibility to recurrent and persistent infections. If PIDs are left un/misdiagnosed, the immune system remains compromised leading to chronic illness, disability, reduced working capacity, decreased quality of life for patients and families, permanent organ damage or even death.

At the conference, the multi-discipline experts concluded that;

- PIDs are widely undiagnosed and there is a lack of awareness of PID among the general public, healthcare professionals, healthcare policy makers and implementers.
- Effective therapies for PIDs exist and early treatment saves lives, prevents morbidity and improves quality of life. There is also evidence that early treatment is cost effective.
- There is a significant disparity of care within and across EU member states.

The multi-discipline experts developed a Consensus Statement containing these conclusions and also approved a series of recommendations that focus on three key areas where priority action is needed to be taken by Member State governments of the EU;

Awareness and education

- Clinical protocols to reliably identify PIDs
- Epidemiological studies into the prevalence and incidence of PIDs and their impact on public health and costs.
- International patient registries expanded to assess the clinical presentation, natural history and genetic patterns of PIDs.

- Health campaigns developed to raise awareness of PIDs among the general public.
- Education programmes targeting the general public, healthcare professionals and healthcare policy makers and implementers.

Screening and diagnosis.

- Practical tools for efficient diagnosis of PID made available in every country.
- Evaluation of diagnostic tools for PID and research into the feasibility of screening programmes to prevent damage.

Treatment and management.

- EU guidelines developed to provide equal access to treatment and assure an optimum standard and quality of patient care in the appropriate treatment setting.
- Cross country initiatives set up to allow exchange of expert experience and education.
- EU treatment centre networks established in order to determine disease outcomes.
- Safe immunoglobulin treatments available to all patients who require antibody replacement.

The following report includes the full Consensus Statement and summaries of the presentations given at the EU PID Consensus Conference. Full copies of the presentations and further details can be found at the conference web site: www.eupidconference.com.

European Primary Immunodeficiencies Consensus Statement

In partnership with the European Commission, the International Patient Organisation for Primary Immunodeficiencies (IPOPI), the European Society for Immunodeficiencies (ESID), the International Nurses Group for Immunodeficiencies (INGID) and the European Federation for Immunological Societies (EFIS) held a two-day EU Consensus Conference on Primary Immunodeficiencies (PIDs) on 19-20 June 2006 at the Paul-Ehrlich-Institut in Langen, Germany.

Attending this conference were representatives drawn from physician, patient, nurse, industry and health policy maker networks from across the EU. Together, the expert attendees of this conference agreed this Consensus Statement on PIDs which focuses on:

- The extent of the negative impact PIDs currently have on healthcare systems and undiagnosed patients.
- The disparities of care and treatment that exist for people with PIDs across the EU.
- Examples of immediate actions and initiatives that EU Member State governments can take to reduce the burden of PIDs in three key areas:
  1. Awareness and Education
  2. Screening and Diagnosis
  3. Treatment and Management

1. Awareness & Education

Consensus Statement

I. General public

- There is a lack of awareness of PIDs amongst the general public,
- There is misunderstanding of the impact of PIDs on schooling, work and social life of individual patients,
- The huge differences between PIDs and HIV/AIDS are not understood.

II. Healthcare professionals

- Due to a failure to include applied Immunology within professional training programmes, there is a lack of awareness of PIDs by:
    - First line healthcare professionals (family GPs, doctors, nurses, midwives) i.e. lack of awareness of symptoms,
    - Secondary healthcare professionals (doctors in community and teaching hospitals) i.e. lack of understanding of availability and efficacy of treatments,
    - Allied professionals (physiotherapists, dieticians, genetics nurse specialists, pharmacists, psychologists, dentists).

III. Healthcare policy makers and implementers

- There is a lack of awareness among healthcare policy makers, at national and EU level of the negative impact on healthcare resources caused by the chronic under diagnosis of PIDs,
- There is a lack of understanding of the level of disease prevention that could be obtained if PIDs were adequately diagnosed.

Recommendations for Action:

I. General public

To increase awareness of PIDs, public health campaigns and educational programmes are needed; this is enabled by development, implementation and evaluation of:

- Updated, translated (for non-native speakers) and adjusted (for special groups) material used for the recognition of potential patients,
- Material suitable for primary school curricula, including books, leaflets, letters for parents and information for school nurses to distribute,
- Material suitable for public health campaigns worldwide; this might include awareness days, as well as standard TV, print and internet advertisements to be used (with translations) in all EU member states,

- Inclusion of a PIDs story line in national TV soap-operas.

II. Healthcare professionals

To increase awareness of PIDs, better education is needed; this is enabled by:

- Provision of standards for basic and applied immunology training in the core content for medical & nursing schools, with particular emphasis on PIDs,
- Coupling nurse education with protocols for vaccine failures and recognition of excessive numbers of infections,
- Integrating basic and applied immunology teaching, particularly alongside immunisation, into programmes for training fellows in general paediatric internal medicine, rheumatology, respiratory medicine, and infectious disease,
- Distribute information used for education of all groups on accessible websites,
- Enabling accrual of educational credits from shared material,
- Reciprocation of information on PIDs, including guidelines and education, at professional meetings of related medical specialties,
- Including PIDs as a topic in continued professional development for related medical specialists in career posts, physiotherapists, nurses and midwives.

III. Healthcare policy makers and implementers at EU and national levels i.e. EU level: Institutions, Parliament, Member states, EMEA. National level: regulators, legislators, national advisory bodies, Insurers. Worldwide level: WHO, pharmaceutical companies, vaccine manufacturers

To increase awareness of PIDs by:

- Studies on impact of diseases and therapy, coupled with epidemiology, public health impact and cost effectiveness studies to demonstrate savings and improvement in quality of life,
- Strong patient organisations in all EU countries, with identification of prominent patient advocates,
- Easily accessible information for health managers/insurers,
- Regular publications from national registries.

2. Screening & Diagnosis

Consensus Statement

PIDs are widely under diagnosed.

Early identification of PIDs will:
- Save lives,
- Improve health, quality of life, and lifespan in identified patients through adequate treatment,
- Enable genetic counseling and prenatal diagnosis within the family.

Tools for identification of PIDs are:
- Diagnostic guidelines for recognition of symptomatic patients,
- Appropriate immunologic and genetic laboratory tests,
- Screening tests for suitable diseases.

Recommendations for Action:

I. Gathering Information

Clinical protocols are needed to reliably identify PIDs; these can be created by development, implementation and evaluation of:
- Diagnostic guidelines on a scientific basis,
- Standardised diagnostic criteria for PIDs.

Assessment of the impact of PIDs on the community is needed; this is enabled by epidemiologic studies to assess:
- The prevalence and incidence of PIDs in the population,
- The impact of PIDs on public health,
- The impact of PIDs on health care costs.

International PID registries enable future diagnostic processes by identifying:
- The pattern of clinical presentation of these diseases,
- The natural history of the various PIDs (morbidity, mortality, complications),
- Relationships between clinical disease patterns and genetic backgrounds.

II. Appropriate Diagnostic Tools

Practical tools for efficient diagnosis of PIDs are needed in every country; this is enabled by availability of:
- Simple diagnostic tests at the local level,
- Immunologic tests in specialist diagnostic centres at the national level,

- Elaborate tests through networks of excellence across Europe.

Appropriate evaluation of diagnostic tools is needed; this is enabled by:
- Development of age-matched reference values for all diagnostic immunologic tests,
- Regular quality control of immunologic laboratories.

Research on the feasibility of screening programmes for PIDs is needed to prevent damage, including:
- Development of suitable tests,
- Assessment of costs and benefits,
- Evaluation of ethical aspects,
- Development of management guidelines for identified patients.

3. Treatment & Management

Consensus Statement

Effective therapies for PIDs exist.

Early treatment saves lives, prevents morbidity and improves quality of life.

Experts have reported that early treatment of PIDs is cost effective.

Safety of immunoglobulin treatments are a priority.

There is a significant disparity of care within and across EU Member States:
- There is a lack of specialised care in many countries,
- There are wide variations in the availability and funding of existing therapies,
- The availability of self treatment at home is inconsistent throughout the EU.

There are not enough trials for new therapeutic strategies.

Variation in methods in post marketing surveillance trials of products makes effective comparative analysis difficult.

Recommendations for Action:

I. Guidelines

Develop and implement European guidelines to ensure equal access to treatment within the EU for those with PIDs, assuring an optimum standard and quality of patient care in the appropriate treatment setting.

II. Education & Expertise Exchange

Cross country initiatives should be developed to allow the exchange of expert experience and education in order to:

- Organise specialist nurse/midwife training courses in the EU,
- Fund medical & nurse specialists to visit other immunology centres,
- Educate related healthcare professionals,
- Support the on-going development of the ESID registry.

III. Centre Networks

EU diagnosis and treatment centre networks should be established to develop methods in order to determine disease outcomes through:

- Standardising clinical trials and post marketing surveillance,
- Using the online professional registry facility from ESID.

IV. Treatment

Adequate funding should be made available to provide:

- Optimum levels of treatment in each EU Member State,
- Safe immunoglobulin treatments,
- The appropriate supply of treatment, specifically immunoglobulins, for PID patients requiring this life saving therapy.

Session 1:
An EU Public Health Issue

Overview of PIDs in the EU, Goals and Objectives of the Conference

Professor Reinhold Schmidt
Director, Department of Clinical Immunology, Hannover Medical School, Germany.

Summary
Professor Schmidt outlined the goals and objectives of the Conference, emphasising that Member State Governments of the EU need to take urgent action to address PIDs as a public health issue.

Key Points

- PIDs are suffered by people who have an inherent defect in their immune system. Sufferers are susceptible to recurrent, persistent, severe or unusual infections.
- Thousands of people with PIDs are being treated for the infections rather than for the underlying immune deficiency. This failure to diagnose is having a negative impact on the lives of sufferers and healthcare systems.
- The EU PID Conference was developed as joint initiative between the key organisations of the PID community in Europe as a culmination of a number of activities intended to raise PID as a public health issue.
- Funding of the conference by the EU Commission is itself recognition of PID as an important public health issue. The aim is to ensure that this public health priority is now recognised by national EU Member State governments.

With the help of the conference participants, the aim is to develop a consensus statement of recommendations that supports the EU PID community to:

- Communicate to EU governments the extent of the negative impact PIDs currently have on healthcare systems and undiagnosed patients.
- Demonstrate the disparities of care and treatment that exist for people with PIDs across the EU.
- Provide examples of immediate actions and initiatives Member State governments can take to reduce the burden of PIDs.

The Benefits of an EU Approach to Rare Diseases

Daniel Mann
Health Information Unit, Directorate General for Health and Consumer Protection, European Commission (EC)

Summary
Mr Mann explained how the EC considers PID to be a public health priority. He also described how the EU has taken several steps to improve the awareness, diagnosis and treatment of PID as part of a wider public health campaign for rare diseases.

Key Points

- PIDs are an obvious area where lack of information/knowledge among physicians, patients and the public is a barrier to the promotion of health and disease prevention.

The EU's public health priorities include;

- Improving information and knowledge for the development of public health strategies
- Promoting health and so preventing disease

The public health priority of PID was first recognised in the Community Action Programme, established in 1999. EU research grants have so far;

- Enabled setting up of a pan-European patient register for PIDs.
- Linked experts centres in Europe for sharing data, describing new diseases and coordinating treatments.
- Improved understanding of disease mechanisms.

One important element of the EU's public health programme has been to develop a network of "Centres of Reference" across the EU. With this in mind, several recommendations were made;

- Existing expert centres to be drawn up to help patients and health professionals know where diagnosis and appropriate management can be procured.
- Financial support for networks of centres across Europe to encourage the exchange of knowledge and best practice.
- Financial support to develop computerised systems for sharing medical files and for experts to meet and discuss clinical cases.
- A system of designated European "centres of reference" should be developed, in the long term, in collaboration with national health authorities.

PIDs are considered a priority within the 2005 Work Plan of the Public Health Programme and the latest Research Framework Programme. Continued support from the EU will;

- Improve the exchange of information using existing EU networks and promote better classification.
- Create links between existing research programmes.
- Promote awareness among the medical community and the general public.
- Set up systems that reduce unequal access to diagnosis and treatment across Europe.
- Monitor efficacy and safety of interventions by building on registries already in place and ensure that information produced by these can be utilised effectively by physicians.

Addressing Inequalities of Access to Healthcare in an Extended Europe

François Houÿez
Health Policy Officer, European Organisation for Rare Diseases (EURORDIS).

Summary
Dr Houÿez's presentation explained how patient access to treatments for rare diseases (orphan drugs) varies significantly across the EU and depends primarily on the healthcare systems of individual Member States.

Key points

- There is considerable variability in the availability, price and reimbursement status of drugs for rare diseases between Member States.
- EU regulations that aim to improve access to drugs for rare diseases exist but they are rarely applied.
- There is little or no long-term financial support for chronic conditions.
- Richer nations, and particularly wealthier individuals in those nations, are more likely to have access to treatments and quality care, exaggerating further inequalities with poorer nations.
- Measures can be taken at EU and national level to reduce inequalities and harmonise care. Patient associations play a crucial role in influencing health care choices and policies.

EU legislation and incentives have helped to improve the development of orphan drugs. However, access to treatments largely depends on individual Member States, since national governments are responsible for assessment of therapeutic value, pricing and reimbursement. However, national governments often do not have the expertise to conduct therapeutic value assessments. Distribution and tax systems can result in price differences of as much as 70% between countries, despite the fact that most product prices set by manufacturers are broadly the same. As a consequence, treatments for rare diseases are made available in a timeframe and under conditions of access that are worse than for other drugs; this means that patients cannot access potentially life-saving treatments.

To improve patient access to these treatments, the EU strategy is to develop initiatives to reduce inequalities. These include;

- Development of care management consensus conferences and "best practice" treatment guidelines.
- Establishment of a pan-European working group responsible for therapeutic value assessment.

- Referring cases to national courts when a Member State is in breach of EU orphan drug legislation.

PIDs – a Public Health Issue?

Professor Edvard Smith
Karolinska Institutet, Stockholm

Summary
Professor Smith explained why PID is an unaddressed public health issue in the EU.

Key Points

- PIDs are currently an unaddressed public health issue in the EU.
- The aim is to improve patient quality of life while reducing healthcare costs.
- PID serves as a model for all rare diseases

PIDs affect up to 1.5million people across Europe, with an estimated 60,000 severe cases. A large number of children and adults are suffering from recurrent infections within the Member States without being diagnosed and therefore offered treatment. Effective diagnosis and treatment results in improved quality of life for sufferers and reduces costs for healthcare providers. As research methods have developed, more PIDs have been identified and defined. Currently, 128 different forms have been identified but, at the current rate of discovery, it is estimated that over 300 will have been identified by 2020.

PIDs serve as a model for all rare diseases for several reasons;

- European research into PID is world-leading and has developed technology (e.g. screening tools, gene therapy) and helped to improve understanding of genetics and immunology.
- The European Initiative on Primary Immunodeficiencies (EURO-PID), an EU funded collaborative research project has characterised over 20 molecular defects in five years and received an award from the EC in recognition of its achievements.
- The PID community has started to develop instruments for patient data handling
- Excellent collaboration channels exist between key PID organisations that provide an optimal link between doctors and scientists (ESID), nurses (INGID) and patients (IPOPI).

ESID is a non-profit organisation. The society has the following objectives;

- To facilitate the exchange of ideas and information among physicians, scientists and other investigators who are concerned with PID
- To promote research on the causes and mechanisms of these disorders

- To encourage clinicians and investigators in research institutions or private industry to share their knowledge of diagnostic and management procedures, and of immunologically active drugs
- To promote the application and the dissemination of recent advances in biomedical science for the prevention, diagnosis and treatment of immunodeficiency diseases
- To foster excellence in research and medical practice
- To promote interaction with nurses and patient associations, so as to increase exchange of information among patients, parents of patients, nurses, doctors and researchers

Although PIDs are *currently* an un-addressed public health issue in the EU, through the EU PID Consensus Conference, the European Commission is supporting EU PID patient, physician and nurse networks to:

- Communicate to EU governments the extent of the negative impact PIDs currently have on healthcare systems and undiagnosed patients.
- Demonstrate the disparities of care and treatment that exist for people with PIDs across the EU.
- Provide examples of immediate actions and initiatives Member State governments can take to reduce the burden of PIDs.

Session 2:
What are Primary Immunodeficiencies?

Overview of PIDs in Adults and Children

Dr Helen Chapel
Head of Clinical Immunology, Nuffield Department of Medicine, University of Oxford.

Summary
Dr Chapel's presentation provided an overview of PIDs in adults and children and specifically covered the key characteristics of PIDs and the impact of undiagnosed/poorly treated PIDs on patients, families and healthcare systems.

Key points

- PIDs are a diverse group of immune system disorders.
- The majority of PIDs are genetic and therefore inherited and, unlike HIV/AIDS, PIDs are not caused by a virus; patients do not "catch" these disorders.
- PID patients are susceptible to recurrent and persistent infections.
- Undiagnosed or poorly treated PIDs have a devastating effect on the lives of patients and their families and place significant strain on health care systems.

PIDs result whenever one or more essential parts of the immune system are missing or not working properly due to an intrinsic or genetic defect.
Over 100 different types of PIDs have been identified which range in severity from life-limiting to life threatening and vary in nature and incidence, but all forms of PIDs leave the patient susceptible to frequent, persistent and recurrent infections. Whatever the age of onset, PIDs are life-long conditions. PIDs are treatable and yet the majority of patients remain undiagnosed and untreated.

Symptoms of PIDs are often overlooked by physicians because they resemble common illnesses (e.g. sinus/ear infections, pneumonia, fever or bronchitis). If left undiagnosed or poorly treated, PIDs can have a devastating effect on the lives of patients and their families. Recurrent infections are painful, frightening and frustrating and cause permanent damage to vital organs, resulting in disability or death. Child patients miss time from school and study while adult patients are forced to take time off work and may require care workers to look after them. Undiagnosed patients become sick and reliant members of society and are a significant burden on healthcare systems requiring a lifetime of repeated hospital visits, hospital admissions and possibly intensive care.

Prevalence, Screening and Diagnosis of PIDs in the EU

Professor Lennart Hammarström
Professor, Karolinska Institutet, Stockholm, Sweden

Summary
Professor Hammarström explained why patient prevalence data proves that PIDs are widely undiagnosed. He also described the methods used to diagnose PID and explained how diagnosis can be improved.

Key points

- PIDs are considered rare diseases and yet it is estimated that the real prevalence in the EU maybe as high as 1 in 250-500.
- Diagnosis of PIDs is often simple and inexpensive but the necessary tools are not always available.
- Diagnosis rates could be increased through population-based or neonatal screening programs.
- ESID have introduced a new patient database that should improve knowledge of PIDs over the long term.

It is estimated that the real prevalence of PIDs in the EU maybe as high as 1 in 250-500 and yet they are considered rare diseases by the majority of the medical community. In reality, PIDs maybe more common than diseases such as insulin-dependent diabetes, haemophilia and multiple sclerosis.

A pan-European PID registry was set up by ESID in 1994 in order to determine the true number of PID patients and raise awareness. There are currently only about 10 thousand patients on the registry, which underlines the lack of awareness and the extent of under-diagnosis of PIDs. Prevalence figures for PIDs vary significantly between different Member States, suggesting a major disparity in the quality of diagnosis and care across the EU. Prevalence figures for one Member State, Sweden, show considerable variation in success in diagnosis of different forms of PID.

Diagnosis first of all depends on awareness by the physician that these diseases exist and are not uncommon. Tools for diagnosis exist but are not always available. A simple and inexpensive blood test can detect 95% of PIDs. Sophisticated immunological and genetic tools can be employed to achieve a more specific diagnosis, but these are generally restricted to specialist centres of care and are not available in all Member States.

In order to increase rates of diagnosis, population-based or neonatal screening programs need to be introduced. However, this would require accurate and cost- effective diagnostic tools that could simultaneously screen

large numbers of patients. The development in Sweden of a large-scale screening tool for detecting certain antibodies is a promising development.

ESID have recently replaced the registry with an online database system. This new, secure, internet-based patient database, will store much more information about each patient than the previous registry. By bringing together clinical and laboratory data of PID patients, this database should improve diagnosis, classification, prognosis and therapy. Data from different centres will be more easily accessible to others and detailed long-term documentation will enable the research community to develop large genetic and therapeutic trials.

Treatment Options: Immunoglobulin Therapy – The Major Therapy Choice in PID

Dr Hilary Longhurst
Consultant Immunologist, Barts and The London NHS Trust

Summary
Dr Longhurst's presentation explained how replacement antibody therapy is an effective treatment for most PID patients

Key points

- Most cases of PID are due to inadequate production of antibodies to microbial agents.
- It is now possible to replace or supplement these antibodies that the patient is unable to produce. Such treatment is, essentially, lifesaving.
- Scientific studies show that patient-reported health and quality of life is significantly improved by optimal antibody treatment for PID. Home-therapy has been shown to further improve the quality of life of patients and their families.

Adults with PID disorders, if not diagnosed and properly treated, have a significantly worse quality of life compared with healthy individuals. Untreated PID patients are constantly fatigued and susceptible to repeated infections of the chest, gastrointestinal system, joints and skin, which may lead to chronic scarring of the lungs and other organs and eventual disability and death. Overall, they have worse mobility, poorer emotional wellbeing, decreased ability to engage in social activity, and decreased capacity to work and study or participate in recreational and leisure activities.

The two commonly used methods of antibody replacement therapy are intravenous (injection into the vein) and subcutaneous (under the skin) infusions. If treatment is instituted early and tailored for the needs of the individual, replacement therapy is effective in preventing infections and consequent damage due to repeated infections. Infection rates in people undergoing antibody replacement therapy are similar to infection rates of the normal population and scientific studies have shown that patient-reported health and quality of life for patients with PID are significantly improved. Studies have also shown that effective therapy significantly reduced missed days at school or work and the duration of antibiotic use.

The availability of subcutaneously infused immunoglobulin has opened up the opportunity for home therapy for many patients because it easier to administer. Home therapy largely avoids the regular trips to the hospital for intravenous treatment, further reducing the time patients have to take off from school and work, giving them a sense of being less sick and disabled. Home therapy has worked very well in young persons and children. The parents of

children with PIDs report significantly less disruption in family activities, work and social life. Patients report greater independence, freedom and flexibility.

Treatment Options: Bone Marrow Transplants/ Gene Therapy

Professor Christine Kinnon
Head of Infection and Immunity, UCL Institute of Child Health, London

Summary
Professor Kinnon outlined advances in the treatment of a form of PID with Bone Marrow Transplant (BMT) and gene therapy.

Key points
- Patients with Severe Combined Immunodeficiency (SCID), a severe form of PID, die within the first two years of life unless treated.
- SCID can be treated by BMT or gene therapy.
- BMT is successful in 90% of cases if a matching donor is found.
- Gene therapy remains an experimental treatment but clinical trials show promise.

Bone marrow contains specialised haematopoietic stem cells that are responsible for the production of the constituents of blood, immune cells and antibodies. During a BMT, bone marrow is taken from a healthy donor and infused into a patient with SCID. If a matching donor is found, bone marrow transplantation is successful in 90% of cases. However, for 60% of cases there is no matching donor and cells from a non-matching, or mismatched, donor has to be used, which reduces the success rate to less than 60%. Measures need to be developed to improve the success rate for children with no matched donor.

Since 2000, scientists at the Hospital Necker in Paris, France have carried out gene therapy on 11 patients with SCID. In each case, scientists took bone marrow from the patients and obtained a set of blood stem cells from the marrow. The cells were infected with a virus carrying the correct replacement gene and these “transfected" cells were then transplanted back into the patients. These stem cells then divide to form daughter cells and develop into immune cells bearing the correct version of the gene. All patients showed a good response to therapy in terms of improved immune response. However, three of the patients have since developed leukaemia-like disease, 30-36 months after treatment. These three patients have been treated by conventional anti-leukaemia therapy, chemotherapy and bone marrow transplantation. Two of the patients recovered while unfortunately the third relapsed and died.

Similar gene therapy treatments have been performed at Great Ormond Street Hospital in London. Preliminary investigations indicate that the

treatment was successful in each case and none of the patients have as yet developed the complications that were encountered in the French trials. It is not yet known whether these adverse events will also occur in the UK trials, but all four patients involved have successfully passed the 30-36 month interval when a minority of patients in the French trial started to develop the leukaemia-like disease. The UK trial adopted a slightly different virus for delivery and a slightly different procedure; it is unclear whether this could explain the differing outcomes.

There are still questions concerning the safety of gene therapy but of the 19 patients successfully treated by gene therapy so far, there has only been one fatality. This compares favourably to the outcome for a mismatched bone marrow transplant where five of the patients would have been expected to die in the first 3 years.

Additional clinical trials of gene therapy for other forms of PID have been performed. The techniques that have been developed to treat SCID and other PIDs could possibly be used to treat other diseases such as leukaemia, haemophilia and sickle cell anaemia. There is a still a long way to go to make gene therapy successfully applicable to a wide range of disorders and work must continue in these fields.

Disparities of Diagnosis, Treatment and Care for PIDs between Member States of the EU

Professor Anna Sediva
Vice-Head, Institute of Immunology, University Hospital Motol, Prague, Czech Republic

Summary
Professor Sediva's presentation provided an overview of the current inequalities in PID diagnosis, treatment and care in the EU. She then described measures that could reduce these disparities.

Key points

- Significant disparities exist in the diagnosis, treatment and care of PID patients between the 25 Member States (MS) of the EU.

Data from the ESID register show the disparity in recorded incidence of PID between MS – chiefly indicating differences in awareness of the conditions. There are socio-economic reasons, as well as biological reasons for these differences.

Diagnosis – Diagnosis guidelines for PID exist in 24 MS, but compliance varies. Molecular diagnoses are available in all MS except Estonia, Lithuania and Romania. However, the number of PIDs that can be detected by molecular diagnosis in each MS varies significantly. Access to prenatal diagnosis is patchy.

Treatment – Antibody replacement therapy is available in all countries, although access to home based therapy is limited to a minority of MS. Bone marrow transplants are available in all but Lithuania and Romania and gene therapy is only available in four MS (France, Germany, Italy, and UK). Only three MS have developed national guidelines for PID management (Netherlands, Romania, and UK).

Care – Policies on insurance coverage and financial reimbursement of PID therapies vary considerably between MS.

Steps have been taken by ESID to try and reduce the differences in awareness and treatment of PID in MS. These include;

- An online pan-European patient database.
- Working parties and summer schools that facilitate exchange of knowledge and best practice between researchers and practitioners in different MS.
- Meetings in each MS that enable national experts to discuss ways of improving the standard of care in their country.

Additional steps need to be taken in the future to further address the inequalities

Diagnosis

- Encourage full application of ESID guidelines in all MS.
- Ensure that patients in each MS have access to centres providing molecular diagnoses of PID.
- Increase the availability of all types of testing techniques.
- Increase financial coverage for diagnosis and treatment by MS health systems (e.g. reimbursement of intravenous antibody replacement).

Care and Treatment

- Improve awareness of therapeutic guidelines
- Ensure re-imbursement for Intravenous Immunoglobulin (IVIG) treatments
- Improve local and EU-wide awareness
- Improve the availability of other treatments and care, including home therapy

Session 3:
Consequences Of Missed Or Delayed Diagnosis

Consequences of Missed or Delayed Diagnosis: Mortality/Morbidity

Dr Fulvio Porta
Head of Bone Marrow Transplant and Oncohaemotology Unity, Spedali Civili, University of Brescia, Italy

Summary
Dr Porta's presentation described the problems of missed/delayed diagnosis and outlined how a network established in Italy has helped to address some of these problems.

Key Points

- It is often more difficult to diagnose mild forms of PID in comparison with severe forms.
- Patients with severe PID present symptoms and require hospital admission before the second decade of life. Patients with mild forms of PID can present symptoms and require hospital admission but are often undiagnosed.
- First symptoms of PID tend to present later now compared to the past, due to improved sanitation and prompt use of antibiotics.
- All Severe Combined Immunodeficiency (SCID) patients die within the first three years of life unless treated. Bone Marrow Transplant (BMT) ensures a very high rate of survival, which is still good even when a matching donor cannot be found. However, success of BMT depends on an early diagnosis.
- Late diagnosis leads to more severe complications and higher risk of death.
- A national network in Italy has helped to standardise diagnosis and treatment across the country.
- The Italian PID network looks to collaborate with ESID and find ways of replicating this system in other member states.

The relatively small PID community established the Italian PID Network in 1999 after collaborating with the much larger oncohaematology community. The PID community took advantage of the wider presence (57 specialist centres) and greater resources available in oncohaematology. The aim of the network was to improve the awareness of PID among physicians, and improve treatment and care of patients in non-specialist hospitals.

The network developed therapeutic guidelines for several forms of PID including XLA, CGD and CVID. These protocols detailed diagnostic criteria and treatment guidelines that could be adopted by all Italian doctors caring for PID patients. For example, for XLA and CVID patients, the guidelines outlined indications on the administration, dosage and interval of antibody replacement therapy as well as practical indications on how to avoid and/or treat adverse effects and minimize risk of viral infections. To access these protocols, medical doctors are requested to compile a detailed questionnaire on enrolment and each year after enrolment.

Since the Italian PID Network was established there has been;

- A significant increase in the number of registered PID patients.
- Improved knowledge of patient demographics and availability/location of physicians.
- Improved access to genetic diagnosis.
- Physicians nationwide using the diagnostic and therapeutic approaches recommended by the network.
- A fall in the mean age at diagnosis for XLA patients from 3 years (1971-1999) to 1.5 years in 2000-2005.
- More frequent treatment for patients in a local hospital, avoiding the psychological and social burden associated with frequent travel to distant specialist centres.
- Optimal treatment for XLA; almost all patients receiving antibody replacement therapy for XLA are receiving optimal doses of antibody. Previously many patients were receiving antibody doses that were too low.

This network has made significant progress in improving diagnosis and treatment of PID. However, there is still significant work to do. For example, for a form of PID called Wiskott Aldrich Syndrome (WAS), patients are now being diagnosed who would previously have been missed. However, there is still a gap and the situation is worse for XLA where the median age at diagnosis is 5 years, despite the fact that onset of first symptoms is noted at a median of 6 months.

Since patient records have been well organised across the country, they have been easily transferred to the pan-European registry. There are now more Italian patients per centre in the European register from than any other country.

However, for the EU as a whole, PIDs frequently remain undiagnosed or are diagnosed too late:

- In SCID cases, the time interval from first symptoms to BMT is far too long (4 months)
- In non-SCID severe PID the time interval from diagnosis to BMT is 11 months
- Forms of PIDs which are not candidates for BMT often remain undiagnosed.

Consequences of Missed or Delayed Diagnosis: Quality of Life and Health Service Costs - Why Diagnosis and Optimal Treatment is Good for the Patient and Good for Healthcare Systems

Dr Ann Gardulf
President, International Nursing Group for Immunodeficiencies (INGID)
Associate Professor, Karolinska University Hospital and Institutet in Stockholm

Summary
Dr Gardulf explained how, using the example of antibody replacement therapy, diagnosis and appropriate treatment of PID can lead to significant benefits for both patients and healthcare systems.

Key points

- Adults with untreated PID have a significantly worse quality of life compared to healthy individuals.
- Scientific studies show patient-reported health and quality of life are significantly improved by optimal antibody treatment.
- Home therapy has been shown to further increase the quality of life for patients and leads to substantial savings for healthcare services, patients and their families.
- Mechanisms are needed to ensure that learnings of new treatment developments can be effectively shared & utilised by physicians and nurses throughout the European Union

A number of studies have demonstrated that home therapy brings substantial direct and indirect cost savings in terms of social and healthcare services. A 1995 Swedish based study demonstrated that Subcutaneous Immunoglobulin (SCIG) antibody therapy at home instead of intravenous immunoglobulin (IVIG) at the hospital reduced the annual cost to the health-care sector per patient by US $10,100 in that country (1993 prices). A study comparing the patient-borne costs of lifelong SCIG antibody therapy at the hospital and self-therapy at home demonstrated that home therapy reduced the total yearly costs by approximately 50% and the out-of-pocket expenses for the patients by 85%.

Consequences of Missed or Delayed Diagnosis: A Patient's Story

Mrs Jose Drabwell
Trustee of PIA and Treasurer & Trustee of IPOPI

Summary
Mrs Drabwell, drawing from her own experience, provided an insight into the suffering that PID patients have to endure and how appropriate diagnosis and treatment can be life transforming.

Key Points

- For many years Jose suffered with debilitating infections that could have been avoided if only the medical professionals treating her had been aware of PID.
- Diagnosis and treatment has transformed her life.

Patients with PID get a wide range of debilitating infections that tend to recur despite treatment with antibiotics. One common problem is chronic sinusitis (infection and inflammation of the sinuses, air passages in bones of the cheeks, forehead, and jaw). Another common problem is chronic bronchitis (infection and inflammation of the airways leading to the lungs).

PID patients can develop more serious infections such as pneumonia, meningitis and osteomyelitis. Pneumonia is an infection of the smallest airways and air sacs in the lungs, which prevents oxygen from reaching the blood and makes breathing hard. Meningitis, an infection of the membranes that surround the brain and spinal cord, causes fever and severe headache, and can lead to seizures, coma, and even death. Osteomyelitis is an infection that invades and destroys bones.

Some PID patients are infected with germs that a healthy immune system would hold in check. These are known as "opportunistic" infections. One example is toxoplasmosis, a life-threatening infection of the brain that can cause confusion, headaches, fever, paralysis, seizures, and coma.

Jose's story is an all too familiar example of unnecessary suffering. Throughout her childhood and early adult life, Jose was plagued by many different recurrent infections. She would recover from one infection only to fall ill with another one. She was left feeling exhausted and miserable, frustrated that nobody could explain what was wrong with her.

For years, Jose was regularly visiting clinics, going to hospitals, receiving treatment and undergoing surgery for her symptoms from specialists in several different fields; pulmonary specialists, ENT specialists, gastroenterologists, ophthalmic surgeons, audiologists, dentists and

dermatologists. Considerable amounts of time, money and resources were spent trying to treat Jose's symptoms and none of the specialists that she was referred to considered the possibility of PID. ENT specialists thought that she may have asthma. Her dermatologist thought that her skin rash was due to an allergic reaction and her dentist thought that her tooth decay and ulcers were due to incorrect brushing.

It was fortunate for Jose that a friend was aware of PID and suggested that she underwent tests. She managed to see a specialist who finally established the cause of her suffering; a PID called CVID. Within 3 months of receiving antibody replacement therapy, she reported feeling like a different person; frequent infections no longer plagued her and she was able to live a normal life.

In some ways, Jose was lucky. For many patients with PID, late diagnosis results in unnecessary organ damage, permanent disability, hospitalisation, inability to work, dependency on social welfare, low quality of life and in some cases death.

Consequences of Missed or Delayed Diagnosis: Health Care Costs

Professor Thomas Szucs
Health Economics, Institute of Social and Preventative Medicine, University of Zurich

Summary
Professor Szucs's presentation explained the importance of health economic evaluation studies in demonstrating the cost effectiveness of therapies for PID.

Key points

- Analyses of the consequences of new and existing therapies, both in terms of benefits and costs, are crucial for decisions on resource allocation.
- Purchasers of health care are increasingly requesting proof of the value for money for competing treatments in order to decide on their reimbursement status.
- Cost effectiveness has become an important criterion for selection of therapies by providers and payers of health care.
- Economic evaluation studies have therefore become an important source of information to aid decision making by purchasers and providers of care.
- There is currently only limited economic evaluation data available for PID.
- The cost of treating PID is expensive. However, the cost of failing to treat PID is significantly higher. This has already been demonstrated to some extent but further assessments are needed.

An economic evaluation involves assessment of both all inputs and outcomes of a health care programme.
The inputs include;

- The direct medical costs (e.g. cost of drugs, analytical procedures required, hospitalisation costs, staff time, and equipment)
- The direct non-medical costs (e.g. patients' out-of-pocket expenses, expenses, transportation costs, community support services)
- The indirect costs (e.g. production losses) due to patients being off work due to illness.
- The intangible costs (e.g. pain, suffering) associated with the therapy.

The outcomes are measured as health improvements, expressed in one or more of the following;

- Natural units (that is, health effects such as cases successfully treated, life-years gained etc),

- Utilities (that is, preference weights such as quality adjusted years)
- Associated economic benefits (that is, production gains, savings and intangible benefits)

One of the aims of the PID community should be to use economic evaluations to support the early diagnosis of patients. There are certain prerequisites for early detection measures

- Detectable, asymptomatic disease stage.
- Availability of a suitable test.
- Effective and appropriate treatment available, with potentially life-prolonging effect.
- Politically realisable.

An early diagnosis should be sought if;

- Diagnosis leads to improved clinical outcome (survival, quality of life).
- It is possible to manage the additional clinical time required to confirm the diagnosis and provide long term care to those who screen positive.
- The patient in whom an early diagnosis is achieved will comply with subsequent recommendations and treatment options.
- The burden of disability from the target disease warrants action.
- The cost, accuracy and acceptability of the screening test are adequate for the purpose.

Currently, only empirical data are available for health economic assessments of PIDs. However, it has been determined that the introduction of self-therapy at home reduced the total yearly costs by approximately 50% and the out-of pocket expenses for the patients by 85%. A study of PID costs in Germany conducted by Högy (Eur J Health Econ, 2005, 50, 24–29) also showed that treatment with Subcutaneous Immunoglobulin (SCIG) is cost saving from the perspective of the German statutory health insurance.

Session 4:
Public Health Interventions to Address PIDs

Evaluating Strategies for Early Identification of People with PIDs

Professor Reinhold Schmidt
Director, Department of Clinical Immunology, Hannover Medical School, Germany.

Summary
Professor Schmidt explained how early identification of PID relies on improving awareness and understanding among the general public, healthcare professionals and healthcare policy makers and implementers.

Key Points

- Various strategies have been used by some NMOs to raise awareness of PIDs among the general public. These strategies should continue and need to be replicated across the EU.
- A limited number of strategies to improve awareness among healthcare professionals have been developed in certain Member States.
- European and national organisations need to pool resources and develop strategies to improve awareness and understanding of PID among healthcare professionals, policy makers and implementers.
- Patient registries play a vital role in any attempt to diagnose PID earlier.

Strategies that have been used to increase public awareness of PIDs include;

- Distribution of the “10 Warning Signs” posters originally developed by the JMF.
- Awareness campaigns as part of the first European Day of Immunology held by EFIS in 2005.
- Advertisement campaigns in magazines, newspapers, newsletters, radio and television.
- PID education as part of primary school curricula.

Strategies that should be developed to increase awareness of PID among healthcare professionals include;

- Education workshops for nurses and midwives
- Clinical immunology modules as part of medical courses

Strategies that should be developed to increase awareness of PID among Healthcare Policy Makers and Implementers include;

- Collection of epidemiological data and studies of disease impact on public health
- Studies on the outcome of therapy and its cost effectiveness.

The information collected through patient registries will help in the early diagnosis of PID patients. This is because registries can;

- Identify clinical presentation patterns
- Identify the natural history of different PIDs
- Identify genetic patterns

Genetic Testing and Early Detection

Professor Jennifer Puck
Professor of Paediatrics, University of California, San Francisco, USA

Summary
Professor Puck explained the importance of early diagnosis of PID and how genetic testing plays a vital role in achieving this goal.

Key points
- Genetic tests for PID would enable early detection of PIDs
- Genetic tests could be done as part of prenatal, newborn and carrier screening programs.

PIDs are largely caused by structural defects or “spelling mistakes” in the genes that encode for components of the immune system. Tools have been developed that can detect these errors.

It is vital that certain forms of PID are detected as early as possible to avoid permanent damage and death. However, detection is often difficult since patients may not show definitive symptoms before developing irreversible damage. Under such circumstances, genetic testing is the best method of ensuring an accurate and early diagnosis.

Some individuals with a family history of PID may be carriers of the genetic defect without suffering from the disorder. Carrier screening determines whether the individual could pass a copy of a defective gene to his/her child. Individuals can then be offered genetic counselling so that they understand the risks involved.

One form of PID, such as Severe Combined Immunodeficiency (SCID), can be caused by one of thousands of possible errors at the DNA level. The goal is to create a single accurate test screen that can detect these myriad defects. Continued research is essential to achieve this objective.

The Role of Nurses in Recognising PIDs

Ms Amena Warner
Clinical Nurse Specialist in Immunology and Allergy, Treasurer & Vice President for the International Nurses Group in Immunodeficiency (INGID)

Summary
Ms Warner's presentation provided an insight into the important role nurses play in the diagnosis and care of PID patients.

Key points

- Nurses in all areas of health care play a vital role in the direction of care of patients with PID.
- Nurses are often the first health care professionals to come into contact with PID patients and spend more time with patients and their families than any other health care professional.
- Community and public health nurses visiting schools and clinics can help to spot individuals who may have a PID; for example, if an infant is not gaining weight or growing normally. The observant and well-informed nurse can take a proactive role in recognising signs of PID and ensure its early detection.
- Nurses specialising in immunology can liaise with nurses in other areas of health care and improve awareness of PID.

Nurses also play a crucial role at every stage in the care of PID patients;

- Helping PID patients to understand and come to terms with the need for lifelong treatment.
- Providing emotional support to patients and families to minimise distress associated with a chronic condition such as PID.
- Educating patients to care for themselves. For example, nurse run therapy training programmes have been set up to train patients on how to self-administer subcutaneous antibody replacement at home.
- Administering intravenous antibody replacement to patients and carrying out liver function tests and blood tests to check antibody levels.
- Participating in genetic, quality of life and health economic research in the field of PID.

INGID was formed in 1994, with the aims of improving and extending the quality of nursing care of patients with PID, and increasing the awareness and understanding of PID amongst nurses. This is being achieved by:

- Forming international networks of nurses working with patients who have PID in order to share knowledge, experience, information, and research.
- Creating a base within the specialty for international collaboration between nurses in research/quality assurance projects.

- Working closely with ESID (the European Society for Immunodeficiencies), IPOPI (the International Patient Organisation for Primary Immunodeficiencies), EFIS (the European Federation of Immunology Societies), and with others who have an interest in primary immunodeficiency disorders.
- Organising biennial INGID meetings, held concurrently with the ESID and IPOPI biennial meetings.

The Importance of Patient Registries in Rare Diseases

Mr Brian O'Mahony
Irish Haemophilia Society (IHS); Chairman of the IHS between 1987 and 2003, President of World Federation of Haemophilia from 1994 to 2004.

Summary
Mr O'Mahony's presentation provided an overview of the importance of patient registries in improving the provision of care for rare diseases.

Key points
- Patient registries are a vital tool in raising awareness of public health issues associated with diseases that would otherwise be overlooked.
- Registries have helped to improve treatment of haemophilia.

Patient registries for a particular condition provide data on the size and characteristics of a patient population and the existing standard of care. Armed with this knowledge, caregivers can demonstrate the public health needs to governments. Funding and resources can be allocated, organised and distributed based on priorities and unmet needs, ensuring that government investment is cost effective.

With a continually updated registry, caregivers can monitor trends and identify where and how the organisation of care should be modified. Further down the line, registries can be used to protect and defend government budgets by demonstrating how investment translates into improved care in terms of increased survival and reduction in hospitalisation, expensive complications and avoidance of more expensive treatments.

A patient registry also provides demographic information of use to patient organisations that can organise their services based on this information. Global databases allow inter-country comparisons that enable national governments to identify where other countries may have a better approach.

Haemophilia, a rare blood clotting disorder, requires life-long and expensive therapy. By setting up registries, haemophilia organisations have succeeded in demonstrating that it is possible even for countries with limited resources to provide an organised system of adequate haemophilia care.

Development of existing PID patient registries in Europe are essential for effective planning and gathering accurate data.

Educational Outreach Efforts: The J Project - An East European Initiative

Professor László Maródi
Head, Department of Infectology and Paediatric Immunology, University of Debrecen, Hungary.

Summary
Professor Maródi's presentation provided an overview of the foundation and the aims of the J project – a programme which could be used as a model in other areas of the EU.

Key points

- Development of a specialist diagnostic centre for PID in Hungary has enabled physicians in several East European countries to obtain a more precise diagnosis for their patients.
- The J project has improved awareness, diagnosis and treatment of PID in several East European countries.

The problem of under-diagnosis and lack of treatments for PID in Eastern European countries was identified by Prof Maródi who, together with the Jeffrey Modell Foundation (JMF) organised a conference to address these issues. The three-day conference in Hungary brought together more than 100 physicians from 12 Eastern European countries. There was consensus among the attendees that a single, fully developed Diagnostic Centre would be able to serve this group of member states.

The JMF presented a comprehensive proposal designed specifically for these countries and a JMF Diagnostic Centre was established in Prof Maródi's department at the University of Debrecen. From this centre, a physician education program called the J Project was established.

The aim of the J Project is to increase awareness of PID among the medical profession and the general public in several East-European countries including Bulgaria, Hungary, Poland and Romania.

To achieve this goal, the project organizes several meetings on PID each year in the individual countries. This gives national opinion leaders an opportunity to discuss diagnostic and therapeutic practices and problems, and to define specific areas to be improved and to be supported by other European groups, institutions, companies, and foundations. The project also aims to update national PID registries, develop PID professional working groups and establish PID patient support groups.

The total number of PID registered patients in the 10 countries that are part of the J Project has risen to nearly a thousand. In each state, basic diagnostic

tools are now available to physicians but they rely on the JMF Centre in Debrecen for more detailed and definitive molecular genetic analyses. The Centre currently has the expertise to identify 16 different PIDs. As awareness improves and more diagnoses are made, the long-term goal is to establish similar diagnostic centres in each individual member state.

Educational Outreach Efforts: Physician Education and Public Awareness Campaigns in the US

Mr Fred Modell
Jeffrey Modell Foundation (JMF). Mr Modell together with his wife Vicki established the JMF in memory of their son who died at the age of 15 of a PID.

Summary
Mr Modell outlined the success of a national education and awareness campaign in the US and described how similar campaigns could be supported in the EU.

Key points
- The US government has recognized PID as a public health issue.
- The government collaborated with the JMF to fund a national education and awareness campaign, which has been a success.
- The JMF encourage EU Member States to develop a similar education and awareness campaign.

After a request from US Congress, the JMF and the Centres for Disease Control and Prevention (CDC) held a fact-finding consensus conference in Atlanta, USA in 2001. The two day conference concluded that PID is a serious public health concern in the US and recommended a scientific framework to advance physician education and public awareness of PID. A Congressional Committee provided funding for a national education and awareness campaign, which included distribution of a “10 Warning Signs of PID” poster and other related materials to physicians, day care programs, public health departments, clinics, third-party payers and others. The goal of the campaign was to identify patients with PID, refer “at risk” patients to specialised “Centres of Excellence”, properly diagnose the patients to identify the specific defect and treat the disorder effectively.

A media campaign has been in place since 2003, in television, radio and print. The campaign received government financial support but the majority of the funding came from the private sector. To date, television, radio, newspapers, magazines and other media organizations have donated over $53 million to run the advertisements. It is estimated that every household in the USA has been reached by the campaign.

Based on 88 reports from Global Jeffrey Modell Referral and Diagnostic Centres (including those located in Europe itself), since the beginning of the campaign there has been a;
- 79% increase in the number of diagnosed patients,
- 58% increase in the number of patients receiving treatment,

- 54% increase in the number of patients receiving antibody replacement therapy,
- 57% increase in the number of patient referred to one of these centres
- 256% increase in the number of diagnostic tests performed.
- JMF website traffic has increased from 54,103 hits per month (when there was no awareness campaign) to 665,617 hits per month.

It has been demonstrated that the Physician Education and Public Awareness Campaign has been effective in improving diagnosis and care for those with PIDs. The JMF encourages EU Member State governments to support national patient organisations and IPOPI in the same way as the US Congress, the US National Institute for Health (NIH) and the US Centre for Disease Control (CDC) supports the JMF. Now that PIDs have been recognised as a public health issue by the European Commission, JMF encourages Member State governments to also recognise the public health issues associated with PIDs and support improvements in diagnosis and care that reverberate at every level; the health ministry, hospitals, medical schools, primary physicians, specialists, patients, nurses, schools and the work place in order to improve diagnosis and care for those with PIDs in Europe.

Educational Outreach Efforts: Patient Organisation Activities in Europe

Mrs Anneli Larsson
Chair PIO, Primar Immunbrist Organisationen, Sweden
Vice Chair, IPOPI

Summary
Mrs Larsson's presentation explained the role of IPOPI and National Member Organisations (NMOs). She also outlined how these organisations have developed education outreach efforts aimed at improving awareness of PID.

Key points

- IPOPI is an international patient organisation for PID. By providing support to NMOs, IPOPI aims to ensure;
  - Access to quality health care, treatment, medicines and safe blood products to all individuals with a PID.
  - Access to educational materials, information and support for every individual with a PID.
  - Recognition of PID in each country's health planning policies, to allow for early diagnosis and improved treatment.

According to a recent survey in Denmark, the greatest difficulty facing PID patients is lack of awareness among the general public, leading to discrimination and feelings of isolation.

A number of educational outreach efforts have already been instituted by IPOPI and certain NMOs to raise awareness of PID among the general public;

- Press releases, articles and advertisements in newspapers and magazines.
- Information material developed for schools and community centres.
- Lectures by experts to staff at hospitals and lectures held by patients at medical congresses.
- In Sweden, an education campaign has been designed to reach all primary healthcare centres, primary clinics and schools.
- "10 Warning Signs of PID" posters and leaflets, as produced by the Jeffrey Modell Foundation (JMF) in the United States, are distributed to surgeries, clinics and schools in several member states.
- IPOPI organise biennial meetings with ESID and INGID. This gives members of the entire PID community the opportunity to discuss developments in this fast moving field and draw up future approaches.
- In France, a consensus meeting on PID was held and a statement was produced that was distributed to primary care centres.
- Patient surveys have been completed in Denmark and France to assess the issues facing PID patients.

- Events have been organised that bring patients together to discuss and share their experiences.

Patient organisations would like to carry out national awareness campaigns, similar to the media campaigns established by the JMF in the US, and to be able to measure the outcome of these campaigns in the EU.

Educational Outreach Efforts by Nurses

Dr Peter Vickers
Senior Lecturer, University of Hertfordshire
Dr Vickers has set up the first course (via distance learning) for nurses in immunology at undergraduate and Masters levels.

Summary
Dr Vickers' presentation highlighted the important role of nurses in the management of PID and reviewed the education programmes available to nurses.

Key points

- Nurses play a vital role in the recognition, care and treatment of patients with PID.
- Nurses need to be well educated in the discipline but there are currently very few opportunities to gain adequate training.
- Mechanisms are needed to ensure that education reaches out to all nurses within the EU member states.

Nurses spend more time with patients and families than any other health care professionals and are often the first to hear parents or patients describe a family history of recurrent infections. Nurses can offer high-quality and cost effective care to PID patients provided they receive adequate training to;

- Improve the early suspicions they may have of a PID and in turn help to improve the rate of early diagnosis.
- Improve the care of patients with PIDs and their families.
- Help patients to come to terms with, and to live with, their condition.
- Help patients to comply with their treatment and understand the consequences of treatment.

There are currently very few training courses available to nurses in the EU and many nurses have to try and learn about these disorders on their own in order to be able to give the optimum care. Some introductory training is provided as part of basic nursing courses at some Swedish and UK universities. A 10-week course in immunology is available at the Karolinska Institute, Sweden and advanced-level specialist courses are available at the University of Hertfordshire, UK. Other education initiatives include a nurse education interactive CD-ROM developed by Baxter, a UK-based web based learning package, an education section in the INGID online journal and tutorials at nursing conferences. Expanding these education programmes is often hampered by a lack of qualified and experienced teachers and by difficulties in recruiting young nurses due to poor awareness of the opportunities already available.

What Can We Learn from the US – The Positive Effects from the US Consensus Conference?

Dr Hans Ochs
Professor of Paediatrics, University of Washington School of Medicine and Children's Hospital & Regional Medical Centre

Summary
Dr Ochs described the various steps that have been taken to improve research in the field of PID since the US Consensus Conference in 2001

Key Points
The US Consensus Conference held in Atlanta in 2001 recognised the need to improve basic and clinical research in PID and recommended organising research networks similar to those established by ESID.
The NIH sponsored a $12.8 million initiative to address these shortcomings and as part of this, a research consortium, the US Immunodeficiency Network (USIDNET), was established. USIDNET aims to improve PID research by;

- Identifying the genetic bases of newly defined PID
- Studying the molecular, cellular and clinical characteristics of genetically determined PID.
- Identifying gaps in research such as gene therapy, QoL studies and long-term outcome studies.
- Identifying ways of improving existing therapies (e.g. role of antibiotics, tailoring immunoglobulin administration protocols).
- Advancing the discovery of new therapies.

To achieve this, USIDNET has undertaken several measures:

Education

- Summer schools have been established to train new investigators.
- Stipends are offered to selected doctors and PhD candidates, enabling them to spend time at medical centres which specialise in the study of one or more aspects of PID. This provides researchers with first-hand observation of patient evaluation and treatment, or familiarisation with useful laboratory technologies.
- Travel scholarships are awarded to PID investigators to attend national and international meetings with a strong component devoted to PID.

Data

- Cell and tissue samples obtained from PID donor patients are stored on a central repository where they are made available to PID investigators. Steps are taken to ensure patient confidentiality.

- Investigators are encouraged to use the PID patient registry that has existed in some form since 1992. This web-based database is now a part of USIDNET and is currently being redesigned to expand its usefulness and scope to include over 30 different PIDs.

Research

- Two-year grants of between $50,000 and $150,000 per annum are awarded to competent research projects in the US and elsewhere. Steps are taken to ensure that these funds allocated for PID are not used for other disease areas. These grants are designed to recruit new investigators and help to maintain and expand existing research investigations.
- A mentoring program is available that allows investigators new to the field to gain consultation from established investigators to help with the preparation of grant applications.
- Collaboration between PID research groups is encouraged to share resources and knowledge.

The strategies adopted by USIDNET set an example for national governments that could be applied to help PID patients, and their doctors and carers, throughout the EU.

EU PID Consensus Conference Partners

The European Commission

International Patient Organisation for Primary Immunodeficiencies

International Nursing Group for Immunodeficiencies

European Society for Immunodeficiencies

European Federation of Immunological Societies

EU PID Consensus Conference Sponsors

Conference Diamond Sponsor: Baxter

Dinner and Accommodation Diamond Sponsor: Talecris

Platinum Sponsor: ZLB Behring

Premium Sponsor: Octapharma

Classic Sponsor: Grifols

Classic Sponsor: LFB

EU PID Consensus Conference Endorsers

Clinical Immunology Society (CIS)

East-Central-European Infectious and Pediatric Immunology Centre for Training and Research

German Federal Institute for Drugs and Medical Devices

International Council of Nurses

AIEOP-Italian Network of Primary Immunodeficiencies

Glossary of Terms

AIDS - Acquired Immunodeficiency Syndrome

BMT – Bone Marrow Transplant

CDC – Centre for Disease Control (US)

ECE IPI CTR - East-Central-European Infectious and Pediatric Immunology Centre for Training and Research

EFIS – European Federation for Immunological Societies

ESID – European Society for Immunodeficiencies

EURO-PID - European Initiative on Primary Immunodeficiencies

HIV - Human Immunodeficiency Virus

IPOPI – International Patient Organisation for Primary Immunodeficiencies

IVIG – Intravenous Immunoglobulin

JMF – Jeffrey Modell Foundation

NIH – National Institute for Health (US)

NMO – National Patient Member Organisation

PIDs – Primary Immunodeficiencies

QoL – Quality of Life

SCID – Severe Combined Immunodeficiencies

SCIG – Subcutaneous Immunoglobulin

USIDNET - US Immunodeficiency Network

WFH – World Federation of Hemophilia