



Primary immunodeficiencies in Central and Eastern Europe—the power of networking *Report on the activity of the Jeffrey Modell Foundation Centers Network in Central and Eastern Europe*

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Abstract

Jeffrey Modell Foundation centers' network activities in Central and Eastern Europe (JMF CEE) have contributed to the development of care for patients with primary immunodeficiencies. On the data continuously collected from individual centers in participating countries since 2011, we demonstrate a steady improvement in a number of aspects concerning complex care for patients with primary immunodeficiencies. The presented data show an improvement of awareness about these rare diseases across the whole Central and Eastern European region, an increase in newly diagnosed patients as well as genetically confirmed cases, earlier establishment of diagnosis, and improved access to clinical treatment. We also present an active patient involvement that is reflected in the expansion of patient organization centers and their activities. The cooperation within the JMF CEE network has also contributed to greater international exposure of participating centers and further to the gradual development of research activities in the rapidly evolving field of primary immunodeficiencies. The improvement of all important aspects of the complex field of primary immunodeficiencies within the JMF CEE network documents the strength and advantages of the joint and coordinated networking.

Keywords Primary immunodeficiency · Jeffrey Modell Foundation · Jeffrey Modell Centers Network · Awareness · Education · Diagnosis · Treatment

Introduction

Primary immunodeficiencies (PIDs) are genetically inherited disorders of the immune system that encompass a range of inborn errors of immunity [1], from specific disorders affecting selective immune defense mechanisms to serious, even life-threatening diseases characterized by a profound lack of immune functions. The clinical history of these disorders

dates back to the 1950s, when the first clinical entity, Bruton's agammaglobulinemia, was identified and gave rise to the field of PIDs [2]. Since then, the field has grown enormously in unprecedented leaps. To date, up to 400 well-defined PIDs have been described, and our knowledge of their etiology continues to expand. Similar progress is ongoing in the diagnostic and therapeutic algorithms of these disorders, thus significantly improving the clinical outcome [3, 4].

While historically, some important discoveries in the field of immunology have been made in Eastern Europe, such as the discovery of phagocytes and phagocytosis by Elie Metchnikov, Ukrainian and Russian scientist; the beginning and early development in the field of PIDs in the second half of the twentieth century found countries of Eastern Europe in information isolation with restrained access to scientific knowledge. However, at the turn of the millennium, new connections with colleagues and centers in Western Europe and the USA have been driving forces behind the

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progress in Eastern Europe. While such contacts are important for individual centers, they were not sufficient for the systematic development of the whole field. Individual internal efforts arose in Eastern European countries that strengthened the cooperation within centers in these countries. The first pioneering activity was the initial organization and cooperation of some countries in Central and Eastern Europe under the J Project, a successful educational project that still exists that created the foundation for future activities [5–7]. Progressive cooperation within the J Project and the establishment of relations with the Jeffrey Modell Foundation (JMF) led to the formation of the JMF Central and Eastern European network (JMF CEE network). This unique situation gave the countries in the Central and Eastern European regions the opportunity to join the global community of JMF Centers that aimed to better identify, diagnose, and treat patients with PIDs at the global scale. The beginning of this program in 2011 marked an era of new possibilities for the involved centers and countries.

Here, we describe the principles of the structure and function of the JMF Centers Network in Central and Eastern Europe and give a report on the progress of the field in involved countries as it was achieved in multiple relevant areas characterizing the complex principles of care in PIDs.

Methodology

The JMF Centers Network is represented by a global network of JMF Centers that specialize in advancing the diagnosis and treatment of PIDs. The network currently includes nearly 400 centers in 86 countries, spanning 6 continents (for a recent review, see 7).

JMF Centers in Central and Eastern Europe

JMF started to prepare their organized involvement in the Central and Eastern European region around 2010, and the first centers were launched in 2011. Due to the many complex issues comprising the different histories, healthcare systems and presence or absence of centers already established in the field and to improve patient care in individual countries, the whole process started with the identification and inclusion of individual centers. Centers were then allowed entry into the network based on mutual JMF and center contracts that specified, in detail, the activities of a particular center. The list of participating centers is shown in Table 1, and their geographical distribution is shown in Fig. 1. The involvement of the centers in the network is not uniform and reflects various specific aspects of individual

Table 1 The list of centers within the JMF Central Eastern European Network

Centers participating in the publication (13)	
- Baku	Azerbaijan
- Vienna	Austria
- Minsk	Belarus
- Sofia	Bulgaria
- Zagreb	Croatia
- Prague	Czech Republic
- Tallinn	Estonia
- Debrecen	Hungary
- Kaunas	Lithuania
- Vilnius	Lithuania
- Timisoara	Romania
- Bratislava	Slovakia
- Ljubljana	Slovenia
Centers not participating in the publication (11)	
- Sarajevo	Bosnia Hercegovina
- Almaty	Kazakhstan
- Astana	Kazakhstan
- Oslo	Norway
- Krakow	Poland
- Russia (5)	Russia
- Belgrade	Serbia

institutions or countries. Some centers represent a whole country, while others cover parts of the population of their respective countries. The differences between centers also reflect the fact that individual centers represent countries with greatly dispersed populations. Relatively few patients referred to small countries have relationships with larger centers in regard to patients/population ratios.

JMF Centers: function, tasks, and aims

JMF Centers in the global network aim to improve the clinical care of patients with PIDs, placing a special emphasis on early and precise diagnosis as well as on access to appropriate medical care. These core tasks are accompanied by other activities, such as education of professionals, patients, parents, and the public; the support of and cooperation with patient groups; negotiations with national healthcare authorities; and interacting and networking at the international level. All of these tasks are being carried out in the JMF Central and Eastern Europe Centers Network. The follow-up is a subject of regular quarterly reporting as well as the annual reports presented during JMF Network meetings. Individual centers alternate in the organization of these

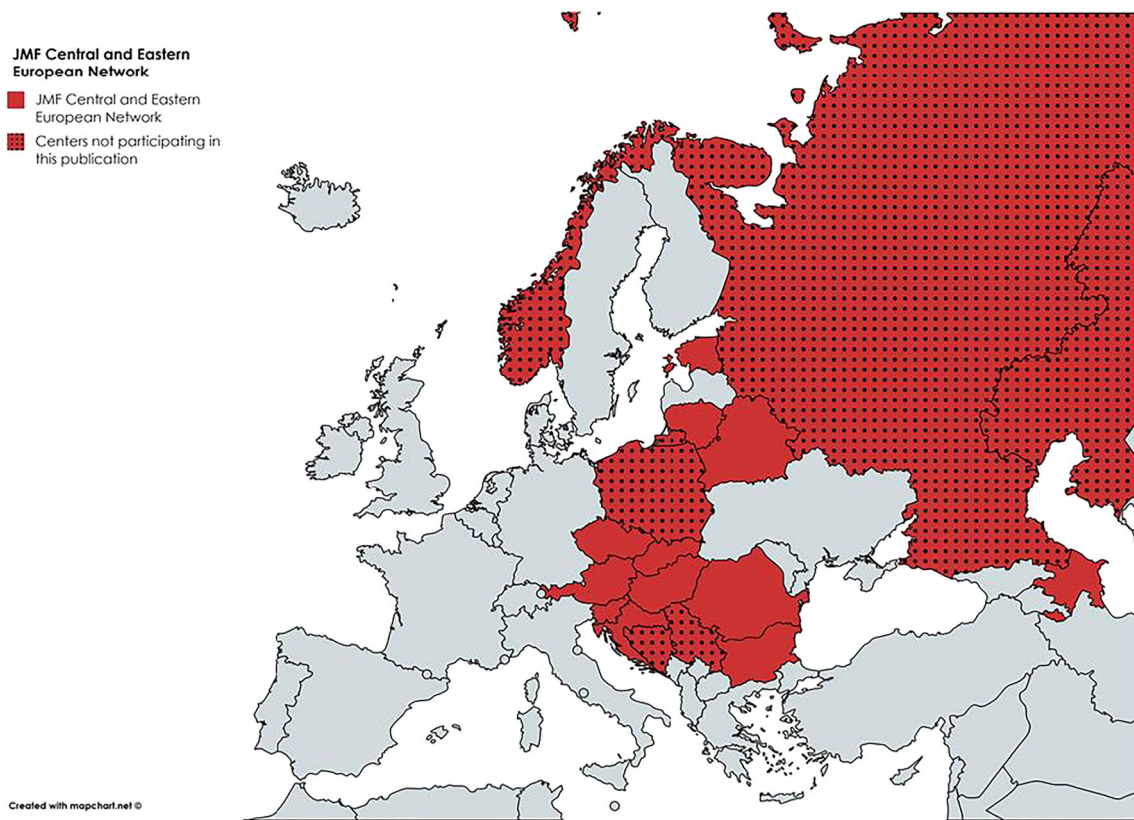


Fig. 1 Geographical distribution of JMF CEE network countries

meetings, which also traditionally include a site visit to the hosting center.

JMF Centers: follow-up variables

Reports on the activities of each center include the following variables:

- Number of patients in follow-up, including newly diagnosed patients
- Stratification of patients according to their PID classification and age
- Mode of treatment, number of patients on immunoglobulin therapy, and mode of therapy
- Number of patients who underwent hematopoietic stem cell transplantation (HSCT)
- Access to genetic diagnosis for PIDs
- Early diagnosis of severe forms of immunodeficiencies and availability of neonatal screening for severe combined immunodeficiency (SCID)
- Participation in national and international registries
- Existence and cooperation with national and international patients organizations
- Educational activities
- Public awareness campaigns

- Organization of referral care in the country
- Reimbursement policies

We also note the research activities in the centers, the future perspectives, and the education and support of prospective leaders in the field.

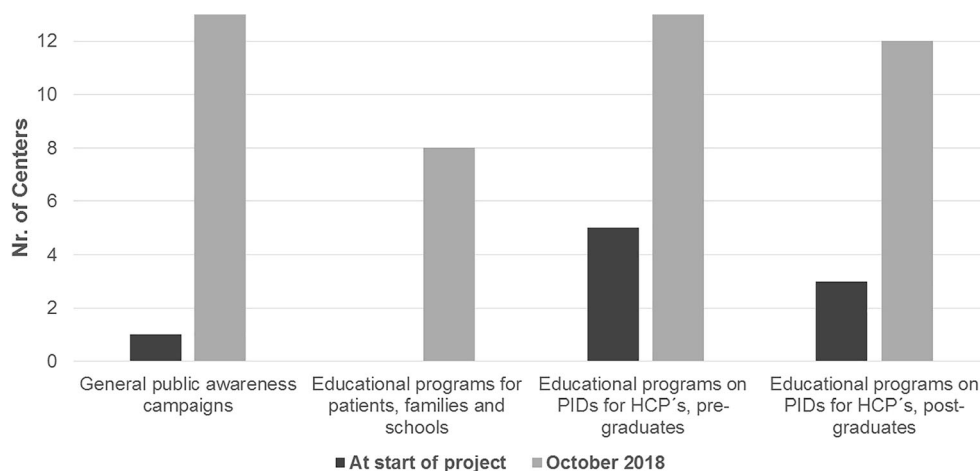
Results

In the following section, data effective until October 2018 are presented.

PID awareness

Patients with PIDs are the core of JMF Centers' activities. Therefore, at the beginning of their operation, the centers focused on patient identification. To manage this task, all centers initiated a variety of activities to increase the awareness of these disorders not only among the general public but also among medical professionals who are not specifically trained on PIDs but who care for PID patients on a regular basis, such as general practitioners in pediatrics and internal medicine. The summary of these efforts is shown in Fig. 2, awareness of PID. The figure shows a dynamic development, from

Fig. 2 PIDs awareness. Increased awareness-related activities and number of raised educational programs in JMF CEE



practically non-existent activities on PIDs to a rise of events organized by the cooperating centers, targeting the public, patients and their families, healthcare professionals, and also medical students. The rise of activities aimed at increasing awareness closely corresponds with the growing number of PID patients registered in individual centers.

Patients and registries

The number of patients followed by each individual center is shown in Table 2. The table illustrates the dynamics very clearly, demonstrating the particular additional value provided by the JMF Center Network. The number of patients at the start line corresponds to the cumulative number of patients followed in centers in previous years. Due to targeted

awareness campaigns, the number of patients has substantially grown in all centers. For some centers that only had a very few patients diagnosed at the beginning of the center's existence, their participation in the JMF Center Network provided the opportunity to establish the diagnosis in a previously unattainable number of PID patients. The total number of patients followed by the network was initially 1536 and increased to 3400 by the end of 2018.

Immunology laboratories and genetic testing

PIDs represent a challenge for making an appropriate medical diagnosis. Accessibility to immunological investigations and genetic testing remain the core function of the centers. While the majority of centers was able to

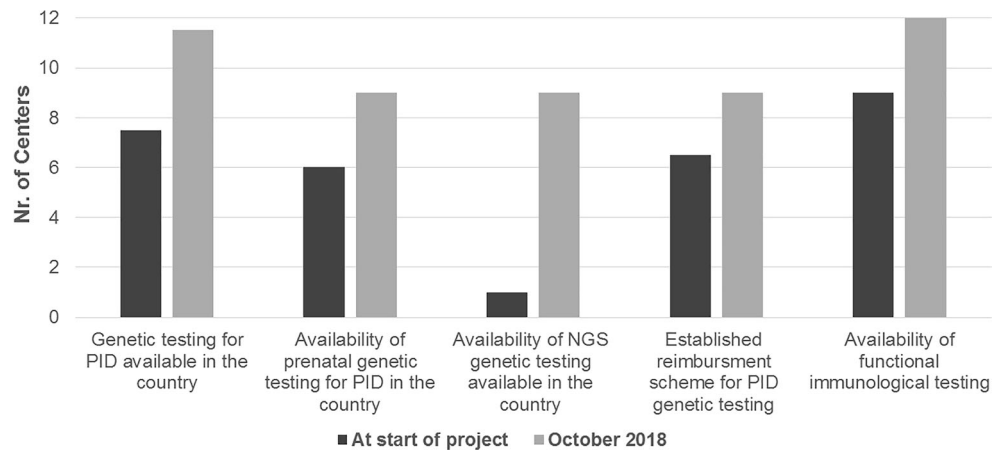
Table 2 JMF CEE network registry

Participating centers	Country	Country population/ millions	No. of patients/ (start)	No. of patients/ 2018	% increase
Baku*	Azerbaijan	10.0	38 (2013)	100	263
Vienna	Austria	8.7	241 (2014)	312	129
Minsk*	Belarus	9.4	171 (2012)	436	255
Sofia*	Bulgaria	6.9	77 (2015)	143	186
Zagreb*	Croatia	4.1	64 (2011)	226	353
Prague	Czech Rep.	10.6	221 (2011)	461	209
Tallinn*	Estonia	1.3	10 (2011)	99	990
Debrecen	Hungary	9.6	325 (2010)	730	225
Kaunas	Lithuania	2.8	52 (2014)	91	175
Vilnius	Lithuania	2.8	20 (2014)	81	405
Timisoara	Romania	19.4	132 (2012)	222	168
Bratislava	Slovakia	5.4	67 (2011)	227	339
Ljubljana*	Slovenia	2.0	118 (2011)	272	231

The table shows the number of patients per center, together with the documented increase of registered patients in individual centers

Centers marked with * serve as national centers exclusively covering the whole population, and centers without * cover PID patients population in their respective countries only partly

Fig. 3 Immunology laboratory and genetic testing. Increased availability of genetic testing for PIDs including next-generation sequencing methods, improvement in the availability of functional tests



provide routine immunological investigations at the beginning of the JMF Center project, the availability of genetic testing was limited. Figure 3 shows an improvement in this regard that reflects the situation in most but not all centers. Indeed, a precise genetic diagnosis still represents a challenge for some centers, placing an increased emphasis on the need for international cooperation. While access to genetic testing has led to an indisputable breakthrough in the elucidation of the causes of some PID patient’s disease, recent data have shown that even the most sophisticated genetic testing does not always establish a clear diagnosis. Moreover, genetic testing has to go hand-in-hand with a functional analysis that maps, in detail, the immune functions affected by the particular defect in the immune-related genes. The availability of such tests has also improved in the centers over the time, and in some centers, efforts to design optimal functional assays have paved the way to brand new research activities and, in some cases, enabled the choice of a tailored therapeutic approach.

Centers within the JMF Central and Eastern European Network proved to be quite successful in establishing a

precise diagnosis of PID patients, including genetic testing, as shown in Fig. 4.

International Union of Immunological Societies classification

The correct and verified diagnosis of PID patients allows for their classification into well-defined sub-categories. In that respect, JMF Centers use a recent classification published and regularly revised by IUIS [1]. Figure 5 documents the situation in the network that corresponds to large international registries, with antibody deficiencies being the most prevalent form of PIDs. As expected, the relative ratios of the PID categories have remained more or less unchanged over time regardless of the increase in the number of patients.

Access to treatment

PIDS, in general, represent complex diseases with multiple clinical presentations. Correspondingly, the treatment of these disorders is also complex, either targeting a specific dysregulation due to a known genetic defect or tailored to the clinical

Fig. 4 Number of patients with a genetically confirmed diagnosis. Increased number of genetically confirmed PIDs

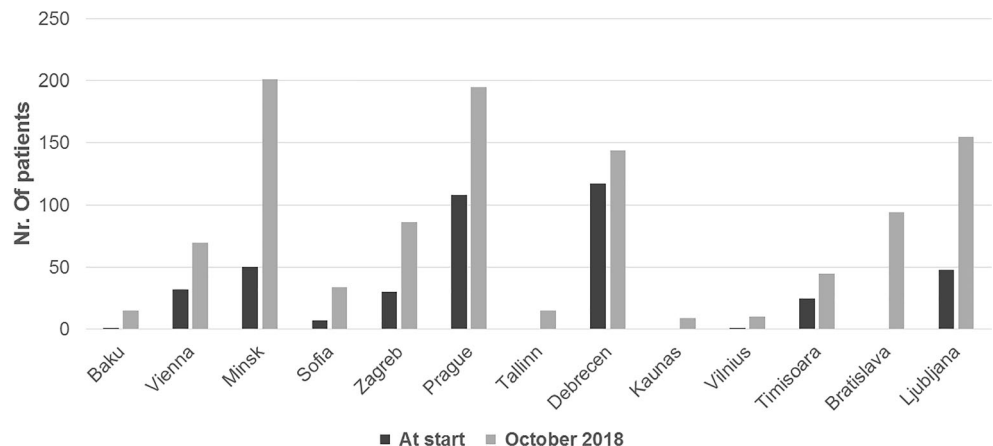
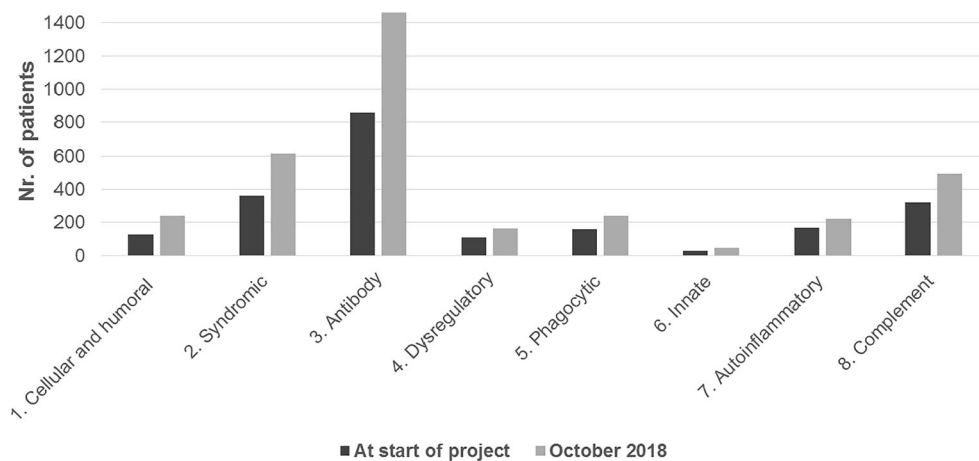


Fig. 5 Number of patients in disease subgroups according to the IUIS classification. Spectrum of followed PID patients corresponds to subgroups in other large registries, with the majority of cases representing antibody deficiency. JMF CEE network registers more complement deficiencies, mostly patients with hereditary angioedema. The spectrum remains constant even with an increasing number of patients being followed.



presentation of a particular patient. Since antibody deficiencies represent the most frequently diagnosed causes of PIDs, regular substitution with immunoglobulins (Ig) has become the most basic and readily available management strategy. Figure 6 shows an improvement of access to immunoglobulin therapy in all centers. This is due to both an increase in the overall number of patients and a slight increase in the percentage of patients treated with immunoglobulins, i.e., from 19 to 23% in the cumulative view of all centers over the duration of the JMF CEE Network. The same graph also reflects the dynamic trend of subcutaneous immunoglobulins (SCIGs) replacing intravenous immunoglobulins (IVIGs) at a large scale. A significant increase in the use of SCIGs in our centers resonates with the global shift towards personalized care for patients, giving them the option to adjust their treatment to fit their lifestyles as best as possible.

While immunoglobulin replacement therapy is the most widely used treatment modality in patients with a dominant antibody deficiency, some combined and especially more severe forms of SCID require a causal solution in the form of hematopoietic stem cell transplantation (HSCT). HSCT units

do not exist in all centers within the network. Some centers have well-established transplantation centers with a longstanding tradition, for example, Prague center reports 13% and Ljubljana center 9% transplanted patients among their PID cohort. Some of the smaller centers transplant only 2% of their PID patients in their historic cumulative data. However, as Fig. 7 shows, the situation is improving in those centers. Indeed, only a fraction of patients had to seek care abroad.

Additionally, exceptional cases (in total 2) of athymia associated with complete DiGeorge syndrome received thymic transplants in the European Center for Thymic Transplants in the Great Ormond Street Hospital for Sick Children in London.

Health economy is always a crucial factor that dictates the level of healthcare. Financial aspects have always represented crucial limiting factors for Central and Eastern European countries. Table 3 summarizes the reimbursement policies in these countries with regard to treatment options and shows the secure reimbursement policies for immunoglobulin therapy as well as the access to HSCT.

Fig. 6 Access to treatment. Significantly improved access to immunoglobulin therapy for patients followed in centers associated with JMF CEE network

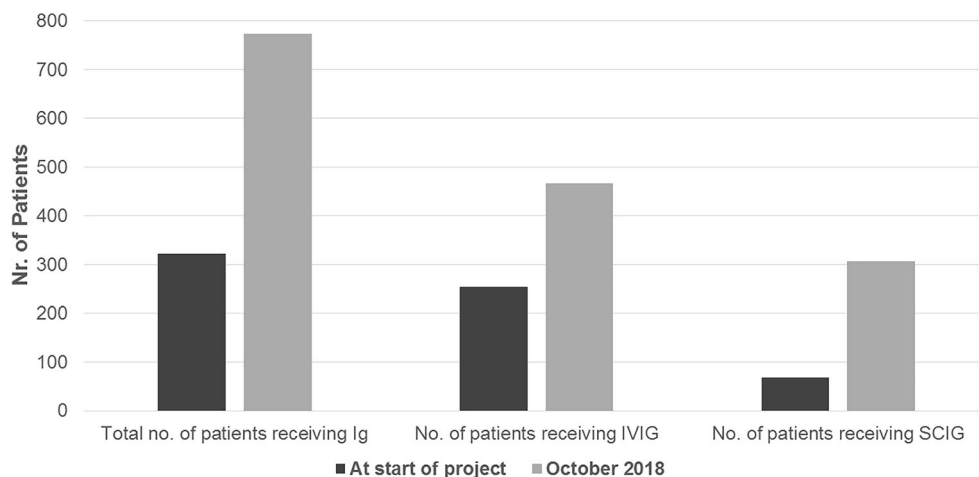
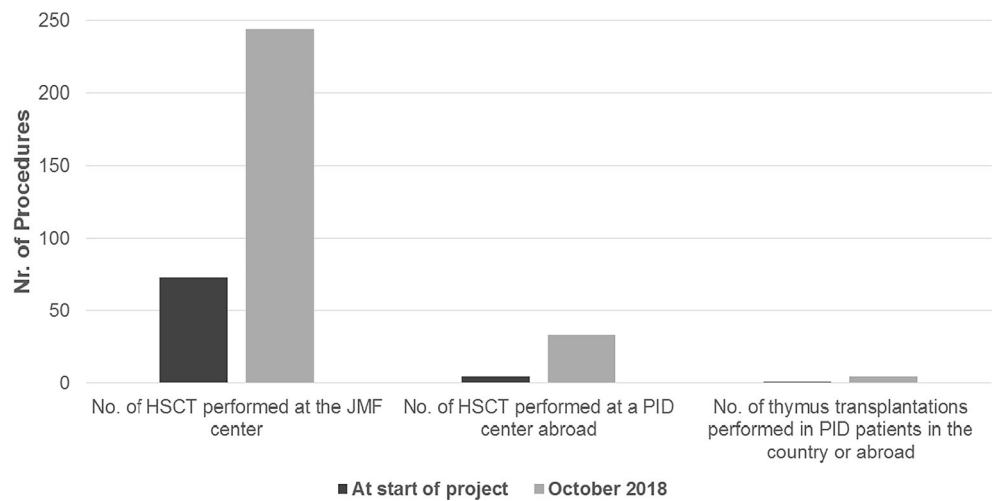


Fig. 7 Transplantation. Increased number of HSCT within the JMF CEE network. Two thymic transplants were performed in the Great Ormond Street Hospital in London, European Center for thymic transplants, for patients diagnosed with athymia from the network



Sadly, treatment availability fluctuates depending on the political and economic situation of the individual countries, which also affects the healthcare sector.

Centers, personnel, and PhDs

As PIDs are rare diseases that are extremely complex, care has to be provided in highly specialized centers. Highly trained specialist care providers are therefore an invaluable asset. Table 4 illustrates an improvement in the recognition of JMF Centers since the formation of the network. All centers serve as national referral centers for PID patients, and the majority of them are part of a wider international collaboration. Similarly, cooperation with international registries, such as the European Society for Immunodeficiencies (ESID) registry, has significantly grown, and a vast majority of patients are now registered in the ESID registry.

Together with recognition of centers comes the need for specialists in every aspect of PID care. Table 5 demonstrates the growing number of highly specialized staff working in all involved centers. Among them, we especially value young PhD students with international connections, open possibilities, and a dedication to push the whole field forward.

Research

International collaborations and the involvement of young students seem to be the driving force behind research

activities. Research seems to represent the most challenging part for centers in Central and Eastern Europe, mostly due to a lack of leaders in the field in individual countries and also due to low financial support at the national level. Nevertheless, even at this level, the situation seems to be slowly improving. Figure 8 illustrates the cumulative effort of centers in international publication and grant activities. We listed the best publications that have separately originated in individual centers (Supplementary Table 1).

Support for young professionals

Due to the importance of continuous training of highly qualified specialists with national and international experience, the network organizes an annual Spring School in PIDs as an educational platform with the opportunity to meet international faculty and colleagues. The school preferentially accepts junior immunologists from the network but is open to a wider international audience. Since 2011, the school was attended by 210 participants from 17 countries, led by 25 faculty members. The network also encourages young colleagues to participate in a regular ESID Summer School and apply for ESID short- and long-term scholarships.

Patient organizations

As the patient is the core of PID care, cooperation with patient organizations has always been one of the priorities of the

Table 3 Access to healthcare

Access to healthcare	At start of project	Today
Centers with established reimbursement: IVIG	11/13	12/13
Centers with established reimbursement: SCIG	5/13	12/13
Centers with HSCT available within the country	7/13	11/13
Centers with thymus transpl. available within the country	0/13	0/13

Improved access to healthcare for PID patients

Table 4 JMF Centers' recognition

JMF Centers recognition	At start of project	Today
Recognized national referral center for pediatric patients	6/13	12/13
Recognized national referral center for adult patients	3/13	11/13
Centers with established programs for transition of care from pediatric to adult service	1/13	8/13
Centers with formally recognized referral pathways for PID patients and/or national recommendations	1/13	5/13
Centers with established links with international PID reference centers/networks including the reimbursement scheme	4/13	10/13

Markedly improved recognition of JMF CEE centers in individual countries and improved organization of care for PID patients, including programs for transition from pediatric to adult care

network. Almost all centers cooperate with patient organizations as they become established in individual countries. Some of these organizations are members of international networks (Fig. 9).

Discussion

The field of PIDs has recently experienced unprecedented development, mainly due to the rapid introduction of novel diagnostic and treatment options. New trends, collaborations, and recommendations around the world are orchestrated by societies for PIDs, such as the ESID in Europe, the Clinical Immunology Society (CIS) in the USA, the Latin American Society for Immunodeficiencies (LASID), the African Society for Immunodeficiencies (ASID), and the Asia-Pacific Society for Immunodeficiencies (ASPID). Similar professional international coordinating activities have been put into place for nursing staff in association with the International Nursing Group for Immunodeficiencies (INGID) and patients collaborating through the International Patient Organization for Primary Immunodeficiencies (IPOPI). In addition to these professional societies, the field is fortunate to benefit from the activities of several great foundations for PIDs that are active in many countries. Prominently, the international dimension of the PID field is encompassed by the worldwide network of the JMF foundation and its centers located in all continents.

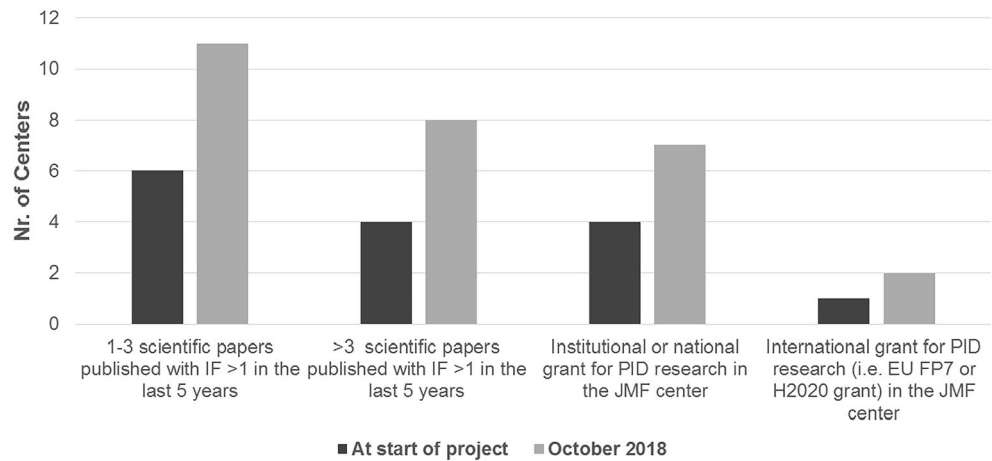
The region of Central and Eastern Europe was historically set aside from all these activities and only started to slowly join at the beginning of the twenty-first century. Here, we demonstrate that the JMF Network for Central and Eastern Europe is complementing the J Project which was already active in the geographical area and that recently celebrated its 15th anniversary [7]. The JMCN provided further impulse for Eastern European countries to develop and improve the care of patients with PIDs and to connect with the worldwide field of PIDs. The existence of the JMF Network in the region brings an additional value on top of the natural progress in the field. While in the region of Central and Eastern Europe, JMF Centers working on individual basis had existed previously and encompassed larger regional area including Russia; it was the creation and internal organization of JMF CEE network that added further value for comprehensive development of participating centers. JMF CEE network thus represents more tightly cooperating subset of Eastern European JMF Centers reported in JMF global report on primary immunodeficiencies [8]. The abovementioned internal organization of the network facilitated the internal reorganization of individual centers and inspired continuous progress and development. Regular reporting and participation in network activities also contributed to the centers' internal structural organization and further translated to better care for patients in the respective countries, which was shown by an improvement in nearly all of the measured parameters. Currently, after ongoing continuous efforts targeted at education in the field, the clinical

Table 5 Personnel

Personnel	At start of project	Today
No. of trained subspecialists dedicated to clinical care of PID patients	53	81
No. of trained laboratory workers dedicated to immunological diagnostics of PID patients	36	52
No. of trained geneticists dedicated to molecular genetic diagnostics of PID patients	15	24
No. of PhD students who successfully defended their PhD thesis in the field of PhD research in the last 5 years	6	26

Increased number of specialists in the field in all centers, increase of PhD students within JMF CEE network

Fig. 8 Research. Increased research activity in centers with access to national or international funding



care of patients with PIDs in countries involved in the network is at the level of the latest knowledge and in line with international guidelines. It is, however, also clear that the achieved state and level of care may not be permanent as much still depends on varying circumstances, such as the economic and political situation in individual countries. A reminder of this instability recently occurred in Romania, where the power of international networking averted the government’s decision to withdraw funding for immunoglobulin treatment and restore it to its original extent.

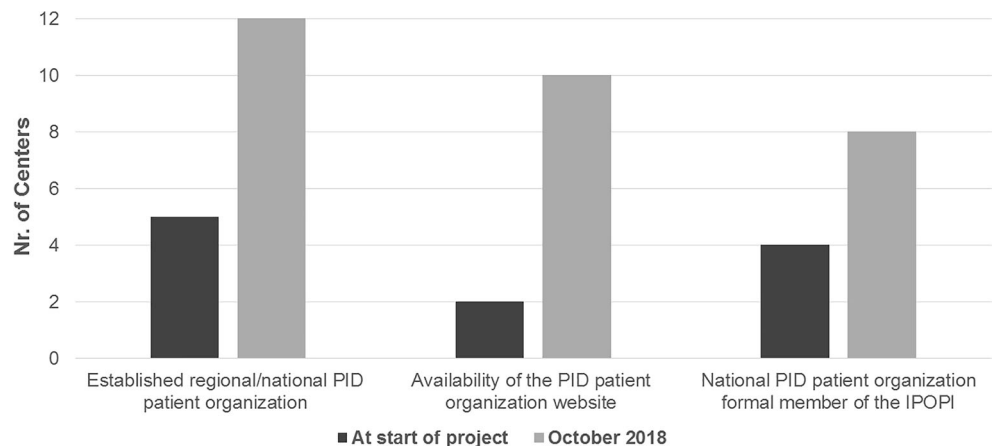
Despite the progress especially in the clinical care of PID patients, the PID Centers of Central and Eastern Europe are still somewhat falling behind the traditional Western centers, particularly in research, which is one of the most important aspects in the rapidly developing field of immunodeficiencies. Experience has shown how difficult obstacles may arise from the interruption of research continuity, especially in the already economically disadvantaged countries of Eastern Europe. Overcoming these obstacles requires long and systematic work, mainly involving young colleagues, which is particularly facilitated by engagement in international networks. Indeed, we showed a gradual improvement

in research activities documented by publications from individual centers as well as in those involving joint publications arising from the network. Nevertheless, there is still an additional scope for improvement, and overcoming the gap between Eastern and Western Europe will require continuous future efforts, for example, the engagement of Eastern European Centers in international research activities organized by the EU.

Conclusion

We showed a major overall improvement in the complex area of PIDs in Central and Eastern Europe to which the JMF Network has considerably contributed. The principles of the organization and activities of the entire network described here have proven to be very effective and beneficial to the participating countries, PID centers, and their patients. The scheme has initiated a long-term project heading towards self-sustainability and has laid the foundation for knowledge transfer within the field and across other areas.

Fig. 9 Patient organizations. Cooperation with the established patients’ organization in the majority of centers



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Compliance with ethical standards

Conflict of interest Activities of all centers involved in Jeffrey Modell Centers Network in Central and Eastern Europe are or have been financially supported by both JMF and Octapharma.

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