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EDITORIAL

Social/economic costs and health-related quality of life in patients with rare diseases in Europe

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Although there is no single commonly accepted definition worldwide for rare diseases [1], the European Commission has agreed that rare diseases are life-threatening or chronically debilitating conditions affecting no more than 5 in 10,000 people in the European Union (EU) [2]. Despite the low frequency of each single rare disease, it is estimated that between 5000 and 8000 rare diseases have been described, affecting 6–8 % of the population in the course of their lives, for a total number of people ranging between 27 and 36 million in the EU [3–5].

While the effects of rare diseases are varied, many have serious health consequences, a high proportion being degenerative and life-threatening. About 80 % of rare diseases have a genetic origin. Approximately 50 % have a childhood onset and it is estimated that over one-third of deaths of children under the age of 1 year are due to rare diseases [6]. It is also worth noting that due to their low prevalence, the correct diagnosis of rare diseases is complex and subject to significant delays. Moreover, despite significant advances brought about by specific health policies in recent years [2, 7], not only do most rare diseases have no cure but, for many, there is no effective treatment available or, if treatments exist, there is no guarantee of improvement in life expectancy or quality of life. The combination of these elements—severity of illness, diagnostic uncertainty, lack of effective treatments—has a strong social impact that rests largely on patients and their families.

Two insufficiently examined issues with rare diseases are (i) the economic impact caused to society, and (ii) the loss of health-related quality of life (HRQOL) for affected patients and their caregivers. Although some country-specific research on a limited set of rare diseases has been done on HRQOL and cost-of-illness [8–12], cross-national research on the socio-economic impact of rare diseases is still lacking in the EU.

The "Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe" (BURQOL-RD) project was a 3-year project under the framework of the Second Programme of Community Action in the Field of Public Health, which began in April 2010, and was promoted by the Directorate General for Health and Consumer Affairs (DG Sanco) [13]. Its objective was to develop a disease-based model capable of quantifying the socio-economic burden and HRQOL of patients suffering from ten rare diseases and their caregivers in Europe (reference year: 2012). Hence, BURQOL-RD can help to set the basis for an integrated and harmonised approach to assess public policies and interventions for rare diseases in the EU. The availability of these approaches and their application will be crucial to define the current consequences of rare diseases on society, and to assess the effectiveness of new policies and interventions [14], opening a channel for studying the cost-effectiveness of new treatments (e.g. orphan drugs).

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BURQOL-RD was made up of 12 associated partners and 8 collaborating partners, including the European alliance of patient organisations, EURORDIS (Rare Diseases Europe). The partners were from eight EU member states: Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden and the UK. Twelve participating organisations were non-profit, four were governmental, and three academic. A two-round Delphi process in combination with Carroll's diagram was used to generate consensus in the selection of the ten rare diseases among the project participants [13]. A final set of rare diseases was obtained to be targeted in the pilot study of BURQOL-RD: cystic fibrosis (CF), Prader-Willi syndrome (PWS), haemophilia, Duchenne muscular dystrophy (DMD), epidermolysis bullosa (EB), Fragile X syndrome (FXS), scleroderma, mucopolysaccharidosis (MPS), juvenile idiopathic arthritis (JIA) and histiocytosis.

Patient recruitment is a common barrier that limits the power and validity of research findings in research into rare diseases. To overcome this barrier, the BURQOL-RD research team developed a successful recruitment strategy based on online questionnaires distributed by patient organisations using e-mail [14].

The prevalence of CF was estimated in Europe at 12.6 per 100,000 inhabitants, with sharp variations between countries. Indeed, in BURQOL-RD participating countries, the reported prevalence ranged from 5.9 to 21.0 cases per 100,000 inhabitants, with additional disparities between regions within a same country [15]. Chevreul et al. [16] estimated that the total average annual cost per patient with CF varied from €21,144 in Bulgaria to €53,256 in Germany. Direct healthcare costs ranged from €12,161 (Bulgaria) to €28,827 (Germany). Direct non-healthcare costs ranged from €6313 (Hungary) to €21,528 (UK). Loss of labour productivity ranged from €1094 (Bulgaria) to €12,443 (UK). In adults, mean EQ-5D index score fell between 0.640 and 0.870, and the EQ-5D VAS score was between 46.0 and 69.7.

PWS is a rare neuro-genetic disorder resulting from a genetic defect affecting imprinted genes on chromosome 15 at q11–13. Though epidemiological information is scarce and of limited validity for PWS worldwide, European data from the UK and Belgium provides estimates for a birth incidence of 1 case per 26,000–29,000 inhabitants, and a population prevalence of 1 case per 52,000–76,000 inhabitants [17, 18]. López-Bastida et al. [19] estimated that the average annual costs per patient with PWS ranged from €3937 to €67,484 in the participating countries. Direct healthcare costs ranged from €311 to €18,760, direct non-healthcare costs ranged from €1269 to €44,035, and loss of labour productivity ranged from €0 to €2255. The mean EQ-5D index score for adult PWS patients ranged from 0.40 to 0.81 between countries, and the mean EQ-5D VAS score was estimated to range from 51.3 to 90.

Reported figures suggest that in high-income countries belonging to the Organisation for Economic Co-operation and Development (OECD), the prevalence of haemophilia A is 14 per 100,000 males [20–23], while the yearly World Federation of Hemophilia (WFH) survey covering 106 countries, including all of Europe, estimated the prevalence of haemophilia A and B at 2.6 per 100,000 in the general population [21]. Cavazza et al. [24] showed that the lowest average annual cost per patient with haemophilia was reported in Bulgaria (€6660) and the highest in Germany (€194,490). Drugs represent nearly 90 % of direct healthcare costs in the majority of countries analysed (Hungary, Italy, Spain and Germany). In Bulgaria, France and Sweden, however, healthcare services (visits, tests and hospitalisations) prevail. The mean EQ-5D index score for adult patients was 0.69, and mean EQ-5D VAS was 66.6. The mean EQ-5D index score for caregivers was 0.87, and mean EQ-5D VAS was 75.5.

DMD is a rare disease that has a pooled prevalence of 4.8 per 100,000 males and an incidence ranging from 10.7 to 27.8 per 100,000. DMD is a rapidly progressive form of muscular dystrophy, causing increasing loss of muscle function and weakness [25–27]. Cavazza et al. [28] estimated an average annual cost per patient with DMD that ranged from €7657 in Hungary to €58,704 in France. Direct non-healthcare costs are the main component of costs, and informal care is its main driver. With regard to adult patients, the EQ-5D VAS score and EQ-5D index scores were 50.5 and 0.24, respectively. The corresponding EQ-5D VAS and EQ-5D index scores for caregivers were 74.7 and 0.7, respectively.

EB is a family of rare genetic dermatological conditions. EB consists of a group of inherited connective tissue disorders characterised by the absence of a particular cohesion protein in the skin that results in the defective connection of its outer and inner layers (epidermis and dermis) making it fragile. The estimated prevalence of EB in European Union countries is 2.4 cases per 100,000 inhabitants [29, 30]. Angelis et al. [31] estimated average annual costs per patient with EB that ranged between countries from €9509 to €49,233. Direct healthcare costs ranged from €419 to €10,688, direct non-healthcare costs ranged from €7449 to €37,451, and loss of labour productivity ranged from €0 to €7259. The mean EQ-5D index score for adult EB patients was estimated between 0.49 and 0.71 and the mean EQ-5D VAS score was estimated at between 62 and 77.

FXS is the leading cause of inherited intellectual disability, and results from mutations on the fragile mental retardation 1 (FMR1) gene of the X chromosome [32]. This disease affects males more often, and more severely, than females, with an estimated incidence of 1 in 5000 males and 1 in 9000 females [33]. In Europe, the overall

prevalence of the disease is estimated at 20 cases per 100,000 inhabitants [34]. Chevreul et al. [35] estimated that the total average annual cost per patient with FXS varied from €4951 (Hungary) to €58,862 (Sweden). Direct non-healthcare costs represented the majority of costs in all countries but there were differences in the share incurred by formal and informal care among those costs. Mean EQ-5D index score for adult patients varied from 0.52 in France to 0.73 in Hungary, while for caregivers this score was consistently below 0.87.

Systemic sclerosis (SSc; scleroderma) is a multisystem, heterogeneous and progressive disorder of unknown origin with no effective treatment or cure, resulting in disability and reduced life expectancy. The incidence and prevalence of SSc varies from 0.6 to 19 and 4 to 242 cases per million inhabitants, respectively, depending on methodological differences in case definition and ascertainment, the time period studied and/or differences in genetic and ethnic backgrounds [36–44]. Lopez Bastida et al. [45] estimated average annual costs per patient with SSc that ranged from €4607 to €30,797 in the BURQOL-RD participating countries. Estimated direct healthcare costs ranged from €1413 to €17,300, direct non-healthcare costs ranged from €1875 to €4684, and labour productivity losses ranged from €1701 to €14,444. The mean EQ-5D index score for adult SSc patients was estimated at between 0.49 and 0.75, and the mean EQ-5D VAS score was estimated at between 58.7 and 65.9.

The prevalence data on MPS varies substantially across Europe and studies are often poorly reported in terms of diagnostic methods and patient characteristics. According to a review by Jurecka et al. [46], the prevalence of MPS (all types) per 100,000 live births was 4.5 in the Netherlands, 3.7 in the Czech Republic, 3.5 in Germany, 3.1 in Norway, 1.8 in Denmark, 1.8 in Sweden and 1.8 in Poland. Pentek et al. [47] estimated a mean yearly total cost per patient with MPS that ranged from €24,520 (Hungary) to €209,420 (Germany). Direct healthcare costs ranged from €275 per patient in France to €206,283 in Germany and direct non-healthcare costs ranged from €24,066 per patient in Italy to €201,371 in Sweden. Patients' and caregivers' average EQ-5D index scores were 0.23 and 0.75, respectively.

JIA is a general term for a group of conditions characterised by chronic arthritis with no defined cause. The disease commonly occurs in children before the age of 16, and lasts for a minimum of 6 weeks. The prevalence in Europe ranges from 4.2 to 20.5 per 100,000 inhabitants depending on the specific subtype [34, 48]. Kuhlmann et al. [49] estimated average annual total costs per patient with JIA that ranged from €27,634 to €36,396 between countries. Estimated direct healthcare costs ranged from €14,508 to €22,138; direct non-healthcare costs ranged from €7837 to €14,155 and labour productivity losses ranged from €0 to €8715. The mean EQ-5D index score for JIA patients was estimated at between 0.44 and 0.88 and the mean EQ-5D VAS score was estimated at between 62 and 79.

Histiocytoses are a group of rare heterogeneous diseases that are characterised by proliferation and accumulation of reactive or neoplastic histiocytes within various tissues. Langerhans cell histiocytosis (LCH) is the most common type, with an estimated prevalence of about 1 case per 50,000 to 1 case per 200,000 inhabitants. Recent studies indicated an incidence of around 0.9 LCH cases per 100,000 children per year [50–52]. Iskrov et al. [53] estimated average annual costs per patient with histiocytosis that ranged from €6832 to €33,283 between countries. Direct healthcare costs ranged from €1698 to €18,213, direct non-healthcare costs ranged from €2936 to €17,622 and labour productivity losses ranged from €1 to €8855. The mean EQ-5D index score for adult histiocytosis patients was estimated at between 0.32 and 0.85 and the mean EQ-5D VAS score was estimated at between 50.0 and 66.5.

Overall, the set of research articles contained in this special issue of the European Journal of Health Economics represents the broadest, most realistic research exercise providing valid information on the burden of rare diseases performed in European countries to date. The main strength of the study lies in the use of a common methodology to assess costs and HRQOL in a wide spectrum of rare diseases in different EU countries. The combination of the bottom-up approach to costing with the estimation of costs over a 1-year period provides a more robust and accurate picture of the medium-term burden of rare disease. These results show that, despite the relevancy of studying direct healthcare costs incurred by rare diseases, social costs are even higher, due to the loss of labour productivity and formal or informal care involved.

While there are important differences between countries depending on the degree of development of formal care provided by social services, informal care is presented as the main social resource involved in the care of people with rare and debilitating diseases. More intense use of informal care can be observed in southern European countries.

In each of the diseases analyzed, there are sharp differences in the estimated costs between countries. This may be due to several causes, including the different unit costs of resources, but also differences in the intensity of resource utilisation. For example, in health treatments, there are important differences between approved and publicly funded drugs in each country. Logically, a third source of variability to note is the heterogeneity of an analysis on small samples where the uncertainty of the

analysis is high. Away from the dimension of costs, the HRQOL of respondents affected by any of the studied rare diseases is considerably lower than that of the general population.

A clear understanding of the current patterns of resource use, costs and HRQOL in patients with rare diseases is needed in order to aid in the appropriate planning of health services. Cost-of-illness studies need to be updated to understand the economics of diseases and their changing cost structures so as to enable policymakers to better understand the factors that impact rare disease-related expenditure, as well as a better-informed distribution of resources.

This research has also shown that patient organisations can effectively and efficiently participate in social research projects with researchers and academic health economists, enabling these professionals to get closer to the patients and offering a unique perspective for data interpretation [14].

The results of this research are clearly reproducible as they are intended to be used for long-term monitoring of rare diseases. The protocols established can be readily transferred to other rare diseases for which no information on social economic costs and HRQOL is currently available, as well as extending such analysis to other countries. There is a clear interest in the future application of these tools in research projects focused on the burden of rare diseases in Europe. In addition, they will be crucial for further studies on the cost-effectiveness and patient preferences for new treatments, diagnosis or better healthcare for patients with rare diseases.

It would also be necessary to increase the efforts devoted to improving epidemiological information on rare diseases. Given the high social costs identified, it would be very useful to use the social perspective in economic evaluations of new treatments. We must also emphasise the need to increase resources dedicated to social support for families (including reinforcement of formal care), and to improve visibility and social protection of informal caregivers, while also improving the social recognition of their work.

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