

Why rare diseases are an important medical and social issue

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Rare diseases affect a limited number of individuals (defined as no more than one in 2000 individuals in the European Union and no more than about one in 1250 in the USA),¹ but the number of disorders that fit this definition is very large (>5000 according to WHO). Therefore, the number of patients affected by a rare disease could be about 30 million in Europe and 25 million in North America.²⁻⁵ The true burden of rare diseases in Europe and elsewhere is difficult to estimate, since epidemiological data for most of these diseases are not available.

Rare diseases are an important public-health issue and a challenge for the medical community. They are called health orphans, because rare diseases were neglected for many years. Similarly, before the USA passed the Orphan Drug Act in 1983, the pharmaceutical industry had neglected the development of treatments for rare diseases, hence the name orphan drugs. Public awareness about the difficulties of patients with rare diseases was first raised by the report of the National Commission on Orphan Disease of the US Government in 1989.⁶ The Commission's hearings with hundreds of stakeholders highlighted issues that affected patients' care, such as little information on rare diseases, difficulties of financing research, drawbacks of providing adequate health insurance and coverage of medical expenses, and the limited availability of effective treatments.

The International Classification of Diseases (ICD) that is used in most countries is not convenient for rare diseases.⁷ The absence of a universally recognised coding system is an obstacle for reliable registration of patients in national or international databases, preventing assessment of the economic and social effects of rare diseases. For some disorders, national or international registries are available, which have been set up and maintained by researchers, patients' associations, public institutions, or drug companies. The European Rare Disease Task Force of the Health and Consumers Protection Directorate General of the European Commission has set up a working group to collaborate with WHO on ICD-10, and is considering all other existing classifications to provide the rare-diseases community with a uniform system.

Assessment of the prevalence of rare diseases was attempted by the European Organization for Rare Diseases (Eurordis), and Orphanet, with the support of the European Commission.⁸ This study not only provided an estimate of the prevalence of several rare diseases (table), but also showed the absence of reliable data, low consistency between sources of information, and poor methodological quality of epidemiological studies. Additionally, facilities for biochemical or genetic testing are scarce.

We use the collective term of rare diseases to include a very heterogeneous group of disorders that can affect any system. Most rare diseases are genetic disorders, which are often severely disabling, substantially affect life expectancy, and impair physical and mental abilities. These disabilities result in reduced quality of life, and affect an individual's potential for education and earning capabilities. One example is inborn errors of metabolism, most of which are rare (prevalence between 1 in 1400 and 1 in 5000 livebirths).⁹ An Italian prospective study (1985-97) on patients aged 0-17 years revealed that, of the 1935 newborn babies with inborn errors of metabolism identified by the study, only 11% reached adulthood.¹⁰

Rare diseases also pose a considerable burden on the affected families. This burden was assessed by sending a questionnaire to 2500 patients with chronic diseases (8.2% of which were rare diseases).¹ Patients with rare disorders had the worst experience in terms of loss of social and economic opportunities, and of medical care.¹

Patients with rare diseases face diagnostic delays. This issue was shown in a survey of eight rare diseases (Crohn's disease, cystic fibrosis, Duchenne muscular dystrophy, Ehlers-Danlos syndrome, Marfan's syndrome, Prader-Willi syndrome, tuberous sclerosis, and

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See Editorial page 1972

See Comment page 1978

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	Estimated prevalence (per 100 000)
Brugada syndrome	50
Erythropoietic protoporphyria	50
Guillain-Barré syndrome	47
Familial melanoma	46
Autism, genetic types	45
Tetralogy of Fallot	45
Scleroderma	42
Great vessels transposition	32.5
Focal dystonia	30
Marfan's syndrome	30
Non-Hodgkin malignant lymphoma	30
Retinitis pigmentosa	27.5
Gelineau's disease	26
Multiple myeloma	26
α1 antitrypsin deficiency	25
Congenital diaphragmatic hernia	25
Juvenile idiopathic arthritis	25
Neurofibromatosis type 1	25
Oesophageal atresia	25
Polycythaemia vera	25

Adapted from reference 8.

Table: Rare diseases with the highest estimated prevalence

For more on Eurordis see <http://www.eurordis.org>

For more on Orphanet see <http://www.orpha.net/>

fragile X syndrome) in 17 European countries.¹¹ To identify the main causes of diagnostic delay, 18 000 questionnaires were mailed to organisations dealing with rare diseases. In 25% of the patients, 5–30 years had elapsed from the time of first symptoms to the correct diagnosis. Before final diagnosis, 40% of the patients were diagnosed incorrectly and the others had no diagnosis. Incorrect diagnosis led to futile medical interventions: 16% of the patients had surgery, 33% did not receive appropriate medical treatment, and 10% were given psychological care on the assumption that symptoms were psychosomatic. 25% of the respondents travelled to another region to obtain a confirmatory diagnosis and 2% travelled abroad. A third of the patients noted that the method of communicating the diagnosis was unsatisfactory. Despite limitations to the methods, this study showed that appropriate information and medical expertise on rare diseases are often insufficient, and access to care is difficult. Therefore, the consequences include increased risk of medical complications and late sequelae.

To improve patients' access to expert care, the need to promote a network of reference centres for rare diseases has been thought to be a priority in several countries. An expert group of the European Commission recommended that a network for diagnostic testing of rare genetic disorders be established in Europe, emphasising that a regulatory framework for genetic testing should be developed. The expert group also recommended that European member states introduce universal neonatal screening to possibly prevent or attenuate rare diseases by early diagnosis.¹² Expert reference centres for rare diseases exist, but many patients might not know about their existence.

The European Rare Disease Task Force has surveyed the existing reference centres in Europe.¹³ Sweden, the UK, Denmark, Belgium, France, and Italy have adopted plans to designate reference centres for rare diseases, or set up national networks of centres. The criteria for defining the role and characteristics of these centres vary between the countries, and so do the number of reference centres. A commonly accepted definition of reference centres and information about how to set up these centres are needed.

Public awareness of rare diseases has increased in recent years because of the work done by patients' support groups. Set up in 1983, the National Organisation of Rare Disorders (NORD) in the USA was instrumental in the approval of the Orphan Drug Act.¹⁴ In 1986, the Genetic Alliance was set up to increase the capacity of genetic advocacy groups. NORD now consists of more than 2000 organisations and the Genetic Alliance more than 600.

In Europe, Eurordis is an alliance of patients' associations dedicated to improving the quality of life of all people living with rare diseases. It was created in 1997 based on the model of NORD, and it has been a driving

force in advocating the adoption of the European Regulation on Orphan Drugs. The role of patients' and parents' support groups is indeed growing beyond the boundaries of initiatives aimed at raising public awareness, and promoting social care and benefits. These aims are very important, since patients with rare diseases in most health-care systems face inadequate social and health care. Although most European health-care systems cover treatment costs, the coverage might not be complete and the economic burden on the patients is tremendous. Moreover, caring for a person with a severe disabling disorder often implies that families see a drop in their incomes, especially if one family member has to reduce work hours or stop it altogether.

With increasing awareness of the difficulties associated with rare diseases and the value of solving them, it has become important to collaborate internationally to address these problems and their treatments. With that aim, the International Conference on Rare Diseases and Orphan Drugs was first held in 2005 in Stockholm, Sweden, covering a range of issues with support from the Office of Rare Diseases at the National Institutes of Health, USA, and the European Commission.⁵ This international collaboration still continues, and one of many important issues is improved alignment, coordination, and harmonisation of European and US orphan drug designations, leading to more cooperation in the approval process of novel treatments.

The European Platform for Patients' Organisations, Science and Industry is a partnership between patients, industry, and scientists, set up in 1994 to exchange information and discuss policies on health-care promotion. Its primary mission is to establish a strong European alliance of patients' organisations, researchers and clinicians, and industry, and has made the development of new medicines for rare diseases one of its most important goals.

The logo of NORD represents a person slowly emerging from darkness into light. This is exactly what has happened to rare diseases in the past decade. The problems of patients with one of these conditions have surfaced and are now firmly present on the agenda of health-care providers, public-health authorities, and policy makers who decide future investments for medical research.

Indeed, during the past two decades, recognition that rare diseases are an important medical and social issue has been constantly growing in the public consciousness as a result of work by active advocacy groups that include academics (clinical and basic researchers) and politicians. Moreover, the unmet needs of patients with rare diseases offer new avenues of investment, as shown by the interest of the pharmaceutical industry.

However, almost all the rare diseases still have no cure. The advances in our understanding of mechanisms of many diseases, and the explosion of knowledge in

For more on the ICORD collaboration see <http://www.icord.se>

For more on the National Organization for Rare Disorders see <http://www.rare-diseases.org>

For more on the Genetic Alliance see <http://www.geneticalliance.org>

genetic medicine, indicate that it is time for a leap forward. Crucial to this aim is that public-research programmes for rare diseases are increased, and that drug development to treat a substantial number of affected patients is boosted by public and private initiatives.

Conflict of interest statement

We declare that we have no conflict of interest.

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Does orphan drug legislation really answer the needs of patients?

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Orphan-drug legislation (panel)¹ was intended to make drugs for rare diseases sufficiently profitable to bring to the market. Legislation in both the USA and in the European Union has been effective in meeting that goal. Since the passage of the US Orphan Drug Act in 1983, more than 300 products for rare diseases have received market approval from the US Food and Drug Administration (FDA).² This number compares with only ten products approved to market in the preceding decade.³ But does this mean that the legislation has met patients' needs? Although the number of marketed orphan products has increased, there has also been a steady increase in the time⁴ and expense⁵ needed for product development; yet the overall number of products approved to market has decreased.⁶ In this essay, we will consider criticism from interested parties in both the USA and European Union.^{7–9}

The most common criticism of the orphan-product legislation has been the very high cost of treatment with some of the drugs. Drugs such as imiglucerase, an enzyme replacement therapy developed by Genzyme to treat Gaucher's disease, and other orphan blockbuster drugs have led to calls for modification of the legislation. Treatment with imiglucerase might cost as much as US\$400 000 per year for an adult patient.¹⁰ Although

Gaucher's disease affects fewer than 20 000 patients in the USA,¹¹ Genzyme reportedly received more than \$800 million in revenue in 2004 from this product alone.¹² Some would like to see a cap placed on revenues from orphan drugs, shortening of exclusivity provisions, or review of exclusivity provisions when profitable.¹³

Orphan blockbuster drugs such as epoetin alfa (Epogen) and recombinant human-growth hormone (Genotropin, Humatrope, Nutropin) have been criticised because much of their post-market revenue has come from off-label use. Such outcomes are rare; however, orphan-product exclusivity does not preclude off-label use for highly prevalent diseases. Orphan legislation considers the relevant population for an orphan drug on the basis of the action of the drug. From the perspective of the patient with a rare disease, whether a drug is also effective in treating a more prevalent disorder is irrelevant. Of more importance to these patients is the knowledge that the product is safe and effective for their treatment.

The development of any new medication is a long, risky, and costly undertaking, and drug companies are naturally impatient to recover their investment once the drug is marketed. However, despite the highly publicised cases above, there are many examples of orphan drugs

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