Health Policy 119 (2015) 964–979

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

Review

Socio-economic burden of rare diseases: A systematic review of cost of illness evidence

Aris Angelis*, David Tordrup[1], Panos Kanavos

Medical Technology Research Group, LSE Health, London School of Economics and Political Science, Houghton Street, WC2A 2AE London, United Kingdom

ARTICLE INFO

Article history:
Received 21 March 2014
Received in revised form
25 November 2014
Accepted 17 December 2014

Keywords:
Cost of illness
Rare diseases
Socioeconomic impact
Systematic review
Orphan drugs
BURQoL-RD

ABSTRACT

Cost-of-illness studies, the systematic quantification of the economic burden of diseases on the individual and on society, help illustrate direct budgetary consequences of diseases in the health system and indirect costs associated with patient or carer productivity losses. In the context of the BURQOL-RD project ("Social Economic Burden and Health-Related Quality of Life in patients with Rare Diseases in Europe") we studied the evidence on direct and indirect costs for 10 rare diseases (Cystic Fibrosis [CF], Duchenne Muscular Dystrophy [DMD], Fragile X Syndrome [FXS], Haemophilia, Juvenile Idiopathic Arthritis [JIA], Mucopolysaccharidosis [MPS], Scleroderma [SCL], Prader-Willi Syndrome [PWS], Histiocytosis [HIS] and Epidermolysis Bullosa [EB]). A systematic literature review of cost of illness studies was conducted using a keyword strategy in combination with the names of the 10 selected rare diseases. Available disease prevalence in Europe was found to range between 1 and 2 per 100,000 population (PWS, a sub-type of Histiocytosis, and EB) up to 42 per 100,000 population (Scleroderma). Overall, cost evidence on rare diseases appears to be very scarce (a total of 77 studies were identified across all diseases), with CF ($n = 29$) and Haemophilia ($n = 22$) being relatively well studied, compared to the other conditions, where very limited cost of illness information was available. In terms of data availability, total lifetime cost figures were found only across four diseases, and total annual costs (including indirect costs) across five diseases. Overall, data availability was found to correlate with the existence of a pharmaceutical treatment and indirect costs tended to account for a significant proportion of total costs. Although methodological variations prevent any detailed comparison between conditions and based on the evidence available, most of the rare diseases examined are associated with significant economic burden, both direct and indirect.

1. Introduction

Most rare diseases are associated with high unmet need due to the lack of available and effective treatments and the relative lack of research to discover and develop such treatments. In the European Union (EU), a rare disease is defined as one affecting less than 1 in 2,000 people, and it is estimated that over 6,000 different, life-threatening or chronic, rare diseases exist today [1]. Although rare diseases are by definition associated with low prevalence, considering that 6–8% of the population are affected by a rare disease, the total number of patients in the EU is estimated to be between 27 and 36 million [2]. With the majority of rare disease patients suffering from less frequent conditions with a prevalence of 1 in 100,000 population, and

* Corresponding author at: London School of Economics and Political Science, Houghton Street, King's Chambers, 3.02, WC2A 2AE London, United Kingdom. Tel.: +44 207955 6842.
E-mail address: a.n.angelis@lse.ac.uk (A. Angelis).
[1] Present address: World Health Organisation, Representation to the EU, Rue Montoyer, 141,000 Brussels, Belgium.

http://dx.doi.org/10.1016/j.healthpol.2014.12.016
0168-8510/

with many rare diseases being of genetic origin, there is a strong public health interest relating to their cost and broader socioeconomic impact in order to develop sustainable health policy options.

Cost-of-illness (COI) studies measure the socio-economic burden of a disease and can be used as a public policy tool to assist in prioritisation and justification of healthcare and prevention policies [3]. COI studies can indicate which interventions are more valuable by comparing averted economic burden, and consequently lead to shifts in distribution of public and private investments. Different stakeholders can utilise COI studies differently. Governments can estimate the financial impact of a disease on public budgets for resource allocation purposes, whereas pharmaceutical corporations can identify diseases with high management costs to direct research and development (R&D) investments towards accordingly.

In addition, COI studies provide information for other types of economic evaluations, including a framework for cost estimation in cost-utility and cost-effectiveness analyses, frequently used by policy makers [3,4]. They are increasingly cited in clinical and epidemiological research to emphasise the importance of studying a particular disease and the scale of a health-related problem, conveying the aggregate burden of illness on society by estimating the maximum amount that could potentially be saved if a disease were to be eradicated [5,6].

While COI studies can identify and measure all costs of a particular disease, they do not address issues of inefficiency or waste; nor do they weigh up costs and benefits of interventions [6]. Caution is also advisable when interpreting COI estimates as potential savings if a disease were systematically targeted, because not all conditions can be fully eradicated, and some proportion of economic burden will remain despite effective interventions [6]. For optimal resource allocation, COI studies should be used in combination with full economic evaluations such as cost-benefit or cost-utility analyses which assess both costs and outcomes [7].

COI studies employ a wide range of different designs and methodologies, often limiting comparability and usefulness of results [8]. Variations include data sources, perspectives (healthcare, societal, etc.), cost types, costing approach and discount rate [9]. While standardisation of methodology through implementation of guidelines is becoming increasingly important, some flexibility may be required for diseases with special characteristics to be adequately described [3,9].

Numerous COI studies have been conducted over the past three decades across a range of diseases, however few have addressed rare diseases. In this context, the aim of the BURQOL-RD project ("Social Economic Burden and Health-Related Quality of Life in patients with Rare Diseases in Europe") was to provide new tools and knowledge for 10 rare diseases (RDs), including socio-economic burden and health related quality of life for patients and their caregivers [10].

As part of this initiative, the objective of this study is to systematically review the relevant literature on the socio-economic burden of RDs and identify all costs, both direct and indirect, related to ten specifically identified RDs from the perspective of patients, families and society.

2. Data and methods

The BURQOL-RD project participants adopted a Delphi consensus approach in combination with a Carroll diagram for the selection of the 10 RDs to be studied [10]. An expert panel involved 23 individuals as representatives of each associated and collaborating project partner. Initially, the selection criteria for the potential RDs were defined and were summarised under the acronym BOSCARE and included: a *broad* spectrum of RDs being suitably represented, including some ultra-rare and less frequently researched RDs; the availability of strong and well-*organised* patient associations for specific RDs in most participating Member States, ensuring adequate recruitment and participation rates; taking advantage of previous *studies* carried out by Eurordis and other national/regional patient associations, to consider at least some of the RDs included in such studies for which a minimum threshold of participation was obtained; select RDs where in the absence of effective therapies a professional network can offer integrated advice, *care* and support for the affected families; and availability of rare disease *registries*, European research networks financed by the European Union DG-Sanco or networks of reference centres. Subsequently, a two-round Delphi panel process yielded a prioritised list of diseases. A questionnaire was administered to all experts via e-mail. In the first round, the questionnaire offered the BOSCARE criteria and an initial set of candidate RDs; each expert was asked to select 10 diseases according to the BOSCARE criteria and rank them by importance. In the second round, members were provided with their own rankings as well as with the overall results of the first round for the panel, and a revision of their ranking was requested. Based on this approach a shortlist of 36 RDs emerged following the end of the first round, and a total of 33 RDs were shortlisted following the end of the second round. The following step involved a joint discussion among the expert panel, where six potential determinants were identified, notably (a) prevalence of $\geq$1/10,000 or <1/10,000; (b) age at onset and whether this was during adulthood or childhood; (c) the extent to which the disease was genetic or had other origin; (d) whether or not the disease resulted in physical impairment and/or mental impairment; (e) whether or not there exist valid diagnostic tests; and (f) whether or not there is availability of effective therapies to modify the disease course. Experts provided a ranking for the conditions based on these determinants. Finally, in the group of shortlisted conditions from the above step, a Carroll trilateral diagram was applied taking into account three determinants, namely (a) prevalence, (b) availability of effective treatments and (c) need for carer.

The final set of 10 rare conditions included Cystic Fibrosis (CF), Duchenne Muscular Dystrophy (DMD), Fragile X syndrome (FXS), Haemophilia (HAE), Juvenile Idiopathic Arthritis (JIA), Mucopolysaccharidosis (MPS), Scleroderma (SCL), Prader-Willi Syndrome (PWS), Histiocytosis (HIS) and Epidermolysis Bullosa (EB). In selecting the final list