Evaluation of orphan diseases global burden

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Abstract

Orphan diseases is a significant socio-economic burden for both global and Russian health care systems. The global burden of disease metrics introduced by WHO, such as DALY, QALY, HALE, can be a useful tool for building economic models and prognoses, as well as medicine funding distribution. However, it is very difficult to standardize a heterogeneous group of rare diseases and it is difficult to talk about the cost-effective treatment options search, in cases where patients with an orphan disease may have only one pathogenetic therapy option. Much work needs to be done to find optimal treatment options and establish the standards of care necessary to maintain physical health, work capacity and quality of life.

Key Words: Orphan diseases; rare diseases; global disease time; disability; quality of life; DALY; QALY; HALE.

Modern world is changing rapidly and dynamically whit increasing population and duration of life. In these conditions, maintenance of a person's legal capacity and quality of life is of particular importance. Thanks to modern advances in medical science, it has become possible to reduce mortality and to treat or compensate for diseases previously considered incurable. These undoubtedly positive changes, nevertheless, are associated with increasing number of patients with functional limitations, of burden on health care and difficulties in budget planning. Country leaders, ministries and public organizations have a serious interest in maintaining health of citizens and their ability to work, both for ethical and financial reasons. That is why today socio-demographic characteristics are carefully studied and analyzed, which make it possible to form impression of the health of the population, to assess contribution of individual diseases to permanent and temporary disability, the so-called global burden of disease (GBD). GBD – is the basis for compiling economic models, forecasting spending and distributing financial resources in health care.1 Unfortunately, information on mortality and health of the population in all regions of the world is very fragmentary and quite contradictory. This highlights the need to use common terms, metrics and criteria to describe and analyze public health problems and burden of different diseases, injuries and risk factors. Introduction of common framework for collecting, integrating, validating, analyzing, and benchmarking data would be of great benefit. Availability of objective and comprehensive data on socially significant GBD indicators would give the authorities not only the opportunity to comprehensively consider the current picture and emerging trends in the health status of the population, but to implement effective programs to preserve health and to eliminate identified problems.

Orphan diseases

Orphan diseases are an important problem of modern healthcare that requires a special approach and careful budget planning. "Orphan", or rare diseases, - is an umbrella term for a group of nosologies that are less common than the frequency established by the legislation of each country.2,3 There is no standard definition of a rare disease; on average, a disease is considered rare if it affects fewer than 7 out of 10.000 people.4,5 Between 5000 and 8000 rare diseases have been identified in the world, about 80% of them are of genetic origin.
Although the peculiarity of these diseases is that they have a low incidence, they are numerous and their overall share in the statistics of disability and mortality is very high. Consequently, the socio-economic burden of orphan pathology for society and the state is also high. In Russia, at the end of 2019, the list of rare diseases, whose treatment is covered by the state, was expanded to 14 conditions (hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, malignant neoplasms of lymphoid, hematopoietic and related tissues, multiple sclerosis, hemolytic uremic syndrome, juvenile arthritis with systemic onset, mucopolysaccharidosis I, II and VI type II, hereditary anemia, non-aplastic factors (fibrinogen), VII (labile), X (Stuart-Prower),5 and budgetary funding was increased yearly to 2 billion rubles (32.300000 USD) as of December 2019. Comparative analysis of the dynamics of the prevalence of rare (orphan) diseases in children, both in general and by individual nosological forms according to 2015 and 2018 data, showed that the prevalence of rare (orphan) diseases in children as a whole increased from 234.76 to 283.65 per 1 000 000 of the child population (by 20.8%) (1: 4250 and 1: 3520, respectively). This happened due to the majority of nosological forms (Figure 1 and Tables 1 and 2).6 Depending on the type of disease, a monthly course of treatment and / or rehabilitation costs from 100.000 rubles (1400 USD) up to several million of rubles.6 The cost of orphan drugs, according to European colleagues, exceeds the cost of conventional drugs by 13.8 times.7 Due to the local and small sales market, it is not profitable for pharmaceutical companies to develop new drugs and spend them on clinical trials. For very few rare diseases, specific drugs have been developed, although the use of specific therapy can significantly affect the disability, mortality and quality of life of such patients.2 There are practically no data on the economic burden and global health indicators in people with rare diseases in Russian scientific sources. As an example, we can take the data on hemophilia A: the course of treatment for which for a child ranges from 21040 USD to 1000 000 USD per year per patient, and for an adult from 42700 USD to 2140000 USD per year per patient. The cost varies depending on the drug, weight, type of disease and the presence of complications.8 Kolbin A.S. et al. (2018)9 provides figures for the cost of treating Pompe disease. The cost of providing patients with the specific drug alglucosidase alfa as enzyme replacement therapy for a child is 10131952 rubles or 131264 USD per year per patient, and for an adult 34596 912 rubles or 448219 USD per year per patient. At the same time, it

Fig 1. Increase in the number of patients with rare diseases in Russian Federal Registry.
was concluded that the use of a specific drug is an economically feasible treatment option being 11.4% cheaper in comparison with symptomatic therapy. The costs of the health care system due to the progression of the disease and severe complications in patients with Pompe disease up to 12077545 rubles or 156470 USD per person lower when using alglucosidase alfa. On the contrary, the increase in the costs of diagnostic and rehabilitation measures in patients on symptomatic therapy determines a significant burden on the budget of medical institutions, given the severity of the course and the deterioration of patients' condition. Moreover, this is just a small fraction of the numbers and needs of patients with rare diseases. According to various estimates, from 15000 to 1.5 million people in Russia suffer from orphan pathology. Such a scatter of figures is due to the

| Disease |
|---------|
| Hemolytic uremic syndrome |
| Paroxysmal nocturnal hemoglobinuria (Markiafava-Micheli) |
| Aplastic anemia, unspecified |
| Hereditary deficiency of factors II, VII, X |
| Idiopathic thrombocytopenic purpura (Evans syndrome) |
| Defect in the complement system |
| Premature puberty of central origin |
| Disorders of aromatic amino acid metabolism (classical phenylketonuria, other types of hyperphenylalaninemia) |
| Tyrosinemia |
| Maple Syrup Disease |
| Other types of branched-chain amino acid metabolism disorders (isovalerian acidemia, methyl malonic acidemia, propionic acidemia) |

*Prevalence data abroad is derived from information provided by European Orphanet Information System (2019).
difficulties of the epidemiological assessment of this group of diseases, due to its heterogeneity, difficulties in diagnosis and statistical accounting for public health. Walker C.E. et al. (2016) made an attempt to assess the problem of the global burden of rare diseases for Australia, when analyzing medical databases, 441 rare disease codes and a cohort of 45,213 people with these diagnoses were identified. This represented approximately 2% of the population of Western Australia. Walker and colleagues also calculated the impact of rare diseases on the Australian health system: hospital stays associated with rare diseases were on average 3 days longer than the average hospital stay. Two percent of the population suffering from rare diseases accounted for 4.6 to 10.5% of total hospitalization costs. The American researchers confirm these results. Yoon et al. report that codes of birth defects and genetic diseases accounted for 2.5% of childhood diseases and accounted for 9 to 12% of hospital admissions to pediatric departments, which corresponded to 16 to 28% of total costs of inpatient treatment. In pediatric practice, rare diseases are believed to account for a higher proportion of hospitalizations and costs than adults do. Research data from Walker C.E. confirm this hypothesis. The work of his colleagues can be extrapolated to other health care systems for rare diseases.

### Table 2. Absolute numbers of patients and prevalence (per 100 000) of the most common rare diseases in Russia (according to Federal Register)

| Disease Category                                      | Code   | Number | Prevalence |
|-------------------------------------------------------|--------|--------|------------|
| Fatty acid metabolism disorders                       | Е71.3  | 30     | 0.04       |
| Homocystinuria                                        | Е72.1  | 15     | 0.02       |
| Glutaricaciduria                                      | Е72.3  | 40     | 0.02       |
| Galactosemia                                           | Е74.2  | 267    | 0.29       |
| Other sphingolipidosis: Fabry (Fabry-Anderson) disease, Niemann-Pick | Е75.2  | 66     | 0.10       |
| Mucopolysaccharidosis, type I                         | Е76.0  | 66     | 0.07       |
| Mucopolysaccharidosis, type II                        | Е76.1  | 98     | 0.08       |
| Mucopolysaccharidosis, type VI                        | Е76.2  | 46     | 0.04       |
| Acute intermittent (hepatic) porphyria                | Е80.2  | 50     | 0.07       |
| Copper metabolism disorders (Wilson's disease)        | Е83.0  | 602    | 0.55       |
| Incomplete (imperfect) osteogenesis                   | Q78.0  | 560    | 0.50       |
| Pulmonary (arterial) hypertension (idiopathic) (primary) | I27.0  | 519    | 0.51       |
| Systemic-onset juvenile arthritis                     | М08.2  | 1058   | 0.96       |
| Total                                                 |        | 12029  | 11.56      |

* Prevalence data abroad is derived from information provided by European Orphanet Information System (2019).
The Global Burden of Disease

In 1990, the World Health Organization (WHO), together with the World Bank, initiated the Global Burden of Disease (GBD) project.\textsuperscript{12,13} The purpose of those studies were to solve three main tasks: i) Provide information on non-fatal disease outcomes for international health policy discussion; ii) Develop objective epidemiological assessment criteria; iii) Quantify the burden of disease and its economic significance. A number of metrics have been introduced as quantitative assessment criteria. One of the main ones was QALY (quality adjusted life-years) – years of life adjusted for quality. QALY is a score calculated to compare different diseases and health interventions, which takes into account the average quality of life expectancy. For example, one year of ideal health equals one QALY, deaths equals zero QALY, and a year lived in a worse than ideal condition is graded from 0 to 1. The cost of QALYs for each individual nosology is of great importance for the distribution of health care resources. DALY (Disability adjusted life-years) - years of life adjusted for disability, has become another concept for assessing global health in research. One DALY represents one wasted year of healthy life. DALY indicator can be viewed as the gap between the current state of health and the ideal situation when the entire population survives to old age, without limiting its functionality. For illness, condition or injury, DALYs are calculated as the sum of years of life lost (YLL) due to premature mortality of lost years due to disability (YLD). Thus, \textbf{DALY} = \textbf{YLL} + \textbf{YLD}. \textbf{YLL} is the number of deaths from a specific disease times the average life expectancy. YLL considers cause of death, age and gender. \textbf{YLL} = \textbf{N} x \textbf{L}, where: \textbf{N} = number of deaths and \textbf{L} = average life expectancy in years. To determine the \textbf{YLD} for a specific condition over a certain time period, the number of cases of the disease in that period is taken, multiplied by the average life expectancy with this disease and a coefficient reflecting the severity of the disease on a scale from 0 (ideal health) to 1 (death). Basic formula for \textbf{YLD} is: \textbf{YLD} = \textbf{I} x \textbf{DW} x \textbf{L}, where: \textbf{I} = number of cases, \textbf{DW} = weight of disability, \textbf{L} = mean duration of illness before remission or death (years). Examining current DALYs and their dynamics allows you to quickly compare the burden of different diseases and injuries. For a complete picture, the researchers additionally use the opposite parameter - \textbf{HALE} (Healthy Life Expectancy), which reflects the expected healthy life expectancy and is calculated using the Sullivan method.\textsuperscript{12} HALE is a single aggregate indicator of population health expressed in years lived to death without disease and functional limitations. In 2016, this indicator, averaged over the world, was 63.3 years.\textsuperscript{15} It is the most significant for assessing global human health. Together, the DALY and HALE scores allow comparisons of the extent of functional health loss due to illness and injury across countries and across different social groups. They can be used to assess the effectiveness of health systems and understand the needs of the population in providing medical care. In Russia for 2016 the HALE indicator was 66.09 (61.24 - 70.37) years for women and 57.78 (53.22 - 62.52) years for men, which is on average two years more than in 1990 and about 10 years less than the average life expectancy for men and women.\textsuperscript{14}

Global burden of orphan diseases assessment

Estimating the global burden of orphan diseases is challenging. The existing criteria for assessing the global burden of disease are poorly applicable to rare pathologies, primarily for a number of technical reasons.\textsuperscript{15} Clearly identify and count the rare disease is a daunting task. Significant difficulties arise already at the stage of collecting statistical data, due to problems with the accuracy of the final diagnosis, imperfections in registers and reporting systems. In addition, different countries have adopted different definitions of a "rare disease"; new conditions are detected every year, which add to the list, while others may go off the list due to an increase in prevalence. Thus, due to the heterogeneity of the group of orphan diseases itself, all epidemiological data and global estimates are very approximate.\textsuperscript{15} The possibilities for using GBD metrics are quite narrow. For example, the formulas do not take into account the stages of the disease and the long-term prospects of its development, do not assess the economic benefit that can be obtained through early treatment, which will exceed (for example, type 1 Gaucher disease) expensive blood transfusions, splenectomy, pain relief, hospitalizations, endoprosthetics and other operations at a later age. While these procedures themselves are considered cost-effective for the untreated patient, they can be very costly for the healthcare system.\textsuperscript{16} Splenectomy, in particular, impairs the long-term perspective by increasing the risk of osteonecrosis.\textsuperscript{17} GBD metrics ignore the economic benefits of early, effective treatment that allows the patient and family to participate in working life. As calculated by Dr. Hyru and colleagues,\textsuperscript{17} a young married specialist with a diagnosis of type 1 Gaucher disease, who is in his twenties, undergoing enzyme replacement therapy, together with his wife, will bring about 100000 British pounds a year to the state in tax payments, which will fully cover the cost of the medicine. Thus, we would like to emphasize not only the ethical underpinnings of effective treatment, but also the savings that healthcare can receive.

Ethical issue of application of global burden of disease metrics in patients with Orphan Pathology

Speaking of rare diseases, it is difficult to use standard metrics for assessing GBD for a number of ethical reasons, as it forces one to think in accordance with a utilitarian approach and puts financial benefits as its goal, which inevitably pushes the value of human life and its quality to second place. According to British researchers, for example, the cost of 15 years of therapy for one
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orphan diseases compared to more studied conditions, as the results of decades of research are often not used for orphan conditions. Much of the debate about health priorities takes the following form: “Patients A and B need 100 ml of medicine, while Patient C 200 ml. Should we treat A and B or C?” – this is unfair because for many people in need of life-saving therapy, the effective dosage and cost are morally completely arbitrary. After all, the amount of medicine they need and its cost did not directly skyrocket from them. Perhaps the only adequate question, regardless of cost and dosage, is: whether the drug can improve health or at least stabilize the manifestations of the disease? If yes, the drug must be covered for all three patients A, B and C.

Russian government policies, problems and solutions

In Russian Federation 14 nosologies are included to the «Register of patients with life-threatening and chronic progressive rare (orphan) diseases leading to a reduction in the life expectancy of citizens or their disability», treatment of these patients comes at the expense of the federal budget. Among these patients, there are no priorities in age, type or stage of the disease for medical care and drug provision. In accordance with the legislation, all patients must receive treatment. Since orphan conditions. Much of the debate about health priorities takes the following form: “Patients A and B need 100 ml of medicine, while Patient C 200 ml. Should we treat A and B or C?” – this is unfair because for many people in need of life-saving therapy, the effective dosage and cost are morally completely arbitrary. After all, the amount of medicine they need and its cost did not directly skyrocket from them. Perhaps the only adequate question, regardless of cost and dosage, is: whether the drug can improve health or at least stabilize the manifestations of the disease? If yes, the drug must be covered for all three patients A, B and C.

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**List of acronyms**

DALY - disability adjusted life years  
GBD - global burden of disease  
HALE - healthy life expectancy  
WHO - World Health Organization  
QALY - quality adjusted life years

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