Zdrowie Publiczne i Zarządzanie 2021; 19 (3–4): 104–111
www.ejournals.eu/Zdrowie-Publiczne-i-Zarzadzanie, doi:10.4467/20842627OZ.21.014.16419

Global access to medicines: An uphill struggle

Costase Ndayishimiye https://orcid.org/0000-0003-1829-0037
Desmond A. Aji

Europubhealth+, Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland

Address for correspondence: Costase Ndayishimiye, Health Economics and Social Security Department, Institute of Public Health, Jagiellonian University, Skawinska 8, 31-008 Kraków, Poland, costase.ndayishimiye@doctoral.uj.edu.pl

Abstract

Background: The study originated from the authors' coursework in health technology assessment and rational pharmaceutical policy. Purpose: To respond to the question of whether there is a global problem of access to medications by providing differentiated backgrounds and possible solutions or mitigation strategies for boosting the population's access to medications. Method: Thematic content analysis (TCA) was performed on paper-based data. Findings: 39 documents were included, including 22 articles, eleven technical reports, two books, one book chapter, and three websites. Drug accessibility issues affect four major categories – essential, innovative, orphan, and highly-priced medicines. Access to these medications is nevertheless hampered for several reasons, including patents; prohibitive costs; fluctuating production; market unprofitability for rare diseases; and delays in innovative treatments, even in developed countries. Conclusion: Efforts to boost drug access should target all sectors – public, private, and non-governmental – and should forge ties with pharmaceutical firms and key health care institutions.

Key words: **access to drug, drug patent, essential medicine, human right, innovative drug, medicine, orphan drug, rare disease**

Słowa kluczowe: **choroby rzadkie, dostęp do leków, leki, leki podstawowe, leki sieroce, patenty lekowe, prawa człowieka**

Introduction

Access to medications – as an essential tool for ensuring basic human rights to health – has been the subject of much attention for several decades. On the other hand, billions of people around the world lack access to life-saving drugs [1]. The World Health Organization (WHO) indicates that one-third of the world's population lacks access to medicines [2]. In developing communities, avoidable and curable diseases, including communicable diseases like tuberculosis and AIDS, continue to be major causes of morbidity and mortality due to a lack of access to medicines.

Inequitable access to essential medicines affects around 30% of the world's population, with the percentage rising to over 50% in the poorest countries of Africa and Asia [3]. There are several indices that might demonstrate disparities in population access to medications around the world, but the current huge disproportionate spending on drug prescriptions may be one of them. Globally, spending on drug prescriptions in 2020 was estimated at $1.3 trillion, of which the United States alone spent $350 billion [4]. In the coming years, these high drug expenditure rates are even predicted to rise at a global annual rate of 3–6% [5].

This research grew out of a mini project for the authors' health technology assessment (HTA) and rational pharmaceutical policy (RPP) coursework that focused on the broad question "Analysis and discussion of the issue: Is there a global problem of access to medicines?" The authors sought to answer this question by elaborating on the reasons why global access to medicine remains a challenge, highlighting context and exploring potential solutions or mitigation strategies. As a result, the researchers remain broad in their approach to the subject while providing in-depth analysis of key issues and potential solutions or mitigations.

Methodology

Purposive sampling was used by the authors to identify and judge which documents were required to answer the research question, "Is there a global problem of access to medicines?" According to the literature, documents can be

a valuable source of information for research, especially when other sources are unavailable [6]. For example, historians are highly reliant on documents to gather information [7]. Documents can also be used as primary sources, providing the whole or majority of the data needed for contemporary research [6].

Researchers looked up (problem* OR challenge* OR issues* OR difficult* OR obstacle*) AND (access* OR availabilit*) AND (medicine* OR drug* OR medication*) in PubMed, Scopus, Web of Science, and the Cochrane Library. They also conducted manual searches on Google Scholar and on websites. Due to the low sensitivity of the Cochrane CENTRAL index and the fact that Hunter et al. (2022) claim that "register records as they appear in CENTRAL are less comprehensive than the original register entry, and thus are at a greater risk than other systems of being missed in a search," [8] researchers additionally searched the clinicaltrials.gov and ICTRP registries.

Iteratively, the researchers created larger categories, "themes," and subcategories, "sub-themes," using manual inductive coding. As soon as the first documents were retrieved, the analysis of the contents and themes (thematic content analysis, or TCA) began. Finally, as "presentation of the results," the themes were reported, along with supporting excerpts and descriptions of those themes and subthemes in relation to the study questions.

Results and discussions

Overview of Analyzed Documents

Over 45 documents were retrieved, but by the 39th, further coding was no longer possible, and no new meaning to previously identified information was discovered. The 40th and 41st documents confirmed this, thus allowing the researchers to judge the research question as sufficiently answered. These 39 documents include 22 scientific articles [2, 4, 5, 9–27], eleven technical reports [1, 3, 28–36], two books [7, 37], one book chapter [38], and three websites [39–41].

Global challenges

Is access to essential medicines "a lost battle"?

The WHO [3] defines essential medications as those that address the population's most critical health-care needs. They are chosen based on scientifically evidenced public health significance, efficacy, safety, and comparative cost-effectiveness. Within the framework of functioning health systems, essential medications should be available at all times in sufficient quantities, in the right dose forms, with good quality and reliable information, and at an affordable price for both individuals and communities.

Essential drugs constitute the foundation for practically every public health initiative seeking to lower morbidity and death. However, accessibility gaps still exist. In a world divided into wealthy and poor countries, there are several reasons why populations lack access to basic drugs or vaccines. Yet everything, directly or indirectly, revolves around economic considerations.

Studies demonstrate that there is still a problem with access to essential medicines in poor countries [22–25]. Four main issues seem to contribute to the inaccessibility of essential drugs for a population in great need. First is the fluctuation in production. This is particularly due to the eradication of some diseases in some parts of the world, which makes the drug market for those diseases commercially unprofitable. Essential medications required for curing some tropical diseases have started to disappear from the market due to their commercial unprofitability. The invention of these medications was in the 1950s and 1960s or perhaps earlier [25]. In wealthy countries, these drugs are currently rarely or never prescribed [25]. The disease caused by *Neisseria meningitidis*, which is endemic in Sub-Saharan Africa, is a good example. Its treatment, oily suspensions of chloramphenicol, is no longer guaranteed. Roussel-Uclaf, the leading manufacturer, has transferred its technology to another laboratory in order to generate more profitable medications [25]. As a result, outbreaks caused by *N. meningitides* have increased. For example, in Nigeria, nearly 100,000 cases of meningitis caused by *N. meningitides* have been registered [26].

The second issue is low-quality and counterfeit pharmaceuticals. This is a problem because, in most cases, drugs should be manufactured to high standards. However, many underdeveloped countries lack the technological, financial, and human resources needed to implement such standards. Even some developed countries may be less stringent when manufacturing drug products for export [25]. As a result, the market for counterfeit and inferior pharmaceuticals is showing an increasing trend. Inferior medications are those manufactured with little or no regard to proper production standards, whereas counterfeit drugs are ones that mimic genuine drugs.

The third problem is the prohibitive cost. Many examples of drugs that are just unaffordable due to prohibitive costs may be found in the literature. Most of them have been marketed and are thus still protected by patents. Furthermore, creating field-based drug research to assess optimal use and remotivating research and development programs for novel essential pharmaceuticals for the poor world remains a difficulty.

Finally, issues of access to essential pharmaceuticals cannot be left without addressing drug and globalization-related questions and concerns. Agreements regarding the availability of old and new medications (such as the World Trade Organization accord) may have some unintended implications that hinder the availability of essential drugs in the developing world [25].

Access to innovative medicines is a very different dynamic. Why?

An innovative drug is a new medication that is prescribed to a patient to treat a specific disease [39]. Innovative drugs

contribute to the delivery of novel solutions to patients for the treatment of diseases for which no satisfactory treatment is currently available on the market. Diseases, such as cancer, osteoarthritis, etc., can be treated with novel drugs. However, there is significant unavailability and delays in acquiring novel medicines, even in industrialized countries.

The amount of time it takes for novel medications to become available has been studied across the European Union (EU) Member States. The 2019 Patients Waiting to Access Innovative Therapies (WAIT) Indicator Survey [37] shows that the average time in EU and European Economic Area (EEA) nations is 504 days, ranging from 127 days in Germany to over 823 days in Poland [37]. If this is the case in well-established and financially secure health systems, it would be logical to assume the situation is even worse in less developed countries. Slow regulatory processes, such as late market access assessment, duplicative evidence requirements, reimbursement delays, and local formulary determinations, could be worse in poor countries and thus hinder the availability and accessibility of innovative pharmaceutical medicines if the cost is supposed to be affordable.

Often, however, several interrelated factors affect the availability and accessibility of innovative drugs. These factors vary depending on different aspects; for instance, the country's policies, such as those governing market authorization and prices, among others. According to the European Federation of Pharmaceutical Industries Associations (EFPIA) [37], there are ten factors affecting the availability and delay of novel pharmaceuticals from five different perspectives. While the whole list is summarized in Table 1, these five primary categories are: (1) time until market authorization; (2) price and reimbursement procedures; (3) value evaluation criteria; (4) readiness of the health system; and (5) the delay from national to regional approval.

Gaps in access to highly priced medicines leave the poor vulnerable

The lack of access to medicines is also fueled by high prices. To date, there is no internationally or European agreed definition of a "high-priced" medicine (i.e., the price point at which a medicine can be considered high-priced). However, the 2015 report by the WHO defines a medicine as high-priced if the therapy for one patient exceeds €10,000/year to be reimbursed by a public payer [30]. Highly priced medicines disrupt the financial sustainability of health care systems as a huge proportion of the national and international budget is consumed. Numerous reasons exist for the lack of access to highly priced medicines, but they can be categorized broadly into three: infrastructure [27], costs of medications [38], and research and development [38].

Firstly, due to poorly developed health infrastructure locally, such as loopholes in storage and supply chain management, inaccessibility could result. The availability of some medicines is hampered as they require a cold chain and are kept in stringent storage conditions (a specific temperature, for example) during transportation. Deficiencies in infrastructure are of great concern, even though improvement in this area might not necessarily lead to a price reduction in drugs worldwide or the establishment of effective treatment of diseases in low-income countries. On the other hand, the accessibility and availability of medicines depend on several factors combining together to determine the cost, such as the conditions in which the medicines are developed and the market for the sale of those medicines. The situation is further compounded by the pursuit of gain by pharmaceutical companies [9]. Grover et al. [27] commented that "in most of the developing world, it is more profitable to sell drugs to the very wealthy at high prices than it is to sell cheaper drugs to a greater number of people."

In addition, research institutions involved in the development and production of (up-to-date) pharmaceutical products contribute to price increases. Because conducting pharmaceutical research is often costly but necessary, pharmaceutical companies tend to recoup their costs by

Table 1. The main issues associated with the inaccessibility of innovative medicines

Grouping	Main causes
Period preceding market approval	(1) The pace with which the approval system progresses (2) Accessibility of drugs before branding permissions
Procedures for determining cost and reimbursement	(3) Initiation of the procedure (4) Timeliness and adherence to country-specific deadlines
Steps to assess a drug's value	(5) Inconsistency in the evidentiary requirements (6) Inconsistent value and pricing (7) Importance placed on product differentiation and selection
Readiness in healthcare settings	(8) Budgetary restrictions in the implementation of decisions (9) Diagnosis, support facilities, and adaptability to patient preferences
Delays from national levels downwards or vice versa	(10) Multi-layered decision-making systems

Source: adjusted from EFPIA [37].

selling pharmaceutical products at a high price. This is often seen during clinical trials, and experts have even gone further to warn against the current rising clinical research trial costs [10]. "Reducing the cost of trials is absolutely crucial for the public good," says Dr. Claiborne Johnston, director of the University of California, San Francisco Neurovascular Disease and Stroke Center. Research shows that the average cost of developing a drug had, over the previous 20 years, risen at a rate that was 7.4% higher than inflation and that clinical trials were responsible for most of the increase [11]. As a result, society bears the burden of high development costs through higher drug prices [10].

Furthermore, the public health and human rights issues surrounding worldwide access to medicines are magnified by intellectual property and international trade. The right of intellectual property grants companies, according to the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS), exclusive control of the property designated for a certain time period. Under TRIPS, pharmaceutical companies have the right to patent medications and gain exclusive control of patented drugs for about 2 decades or more. This results in a monopoly and the likelihood of an increase in price with no competition as manufacturers of generic drugs are excluded [40].

Securing access to orphan medicines for the less wealthy is currently too arduous

"An *orphan drug* can be defined as any medicinal product intended for a rare disease or a disease with no existing satisfactory method of diagnosis, prevention, or treatment" [12, 31]. The definition of uncommon or rare infections differs across nations and organizations but regularly takes into account the severity, the presence of different treatment options, and disease prevalence. In the United States, rare diseases are defined as "diseases or conditions that affect fewer than 200,000 patients in the country (6.4 in 10,000 people)" [13], while in the EU, a rare disease is defined as "a life-threatening or chronically debilitating condition that affects no more than 5 in 10,000 people" [13]. Examples of rare illnesses include degenerative diseases, rare cancers, genetic diseases, and infectious tropical diseases.

There are currently 6000–8000 rare diseases affecting 6-8% of the global population [13, 16]. Although they are rare individually, these diseases collectively affect about 300 million people globally; 50% of those affected are children, with a 30% likelihood of passing away before reaching their fifth birthday [17]. Owing to the fact that these diseases are more common in low-income countries, this brings about a huge disparity and poor quality of health.

On the other hand, pharmaceutical companies strongly lack interest in the drug market for rare diseases [18]. Between 1975 and 2004, over 1500 medicines have been approved; about 1% of these drugs are related to neglected diseases (NTDs) [32]. Nonetheless, patient access to orphan drugs is hindered by several factors, including clinical challenges, disease awareness, and high cost, amongst others. The latter is very critical because orphan medications are sometimes associated with high prices. This roots into major problems because such high costs, with a limited number of patients, attract no investors. This leads to the unavailability of drugs or – if they are available – makes them unaffordable. Also, due to the limited number of patients, the investment is hardly recoverable. As such, it deters companies from developing new medications. In addition, manufacturers are further scrutinized by the public due to the high value of some of the orphan drugs. Furthermore, the background information about these diseases, such as the epidemiology, treatment pathway, and patient subgroups, is scarce, and the science associated with them is quite complex and/or expensive [41].

Well, as we know, global access to medicines is still a challenge. What can be done next?

Basic or essential medicines

Access to essential drugs remains a key pressing concern in the world, even if there is somehow a progress currently. Different programs intend to increase access and there are a variety of strategies applied. The WHO has developed a four-part framework [3] to guide and organize collaborative efforts on essential drug access. These are as follows: (1) rational selection, (2) sustainable financing (3), affordable prices, and (4) reliable health and supply systems. Firstly, rational use of medicines is when "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community," according to the WHO [33]. On the other hand, what constitutes the rational use of medicines can differ significantly across continents, within continents, across regions, and within regions, between countries. However, the WHO [34] suggests up to twelve core components (Table 2) to consider when promoting the rational use of medicine everywhere.

As described previously, the high cost makes some essential drugs unaffordable for patients. Therefore, the second key element to boosting access to essential medicines is to ensure affordable prices [34]. This can be done through: utilizing readily available and unbiased price information; allowing price competition in the local markets; promoting bulk procurement; adopting and implementing generics policies; negotiating equitable pricing for new essential medicines for priority diseases; negotiating prices for newly registered essential medicines; duties, tariffs, and taxes on essential medicines should be eliminated; reducing mark-ups through more efficient distribution and dispensing systems; encouraging local production of essential drugs of assured quality when appropriate and feasible; and including and implementing the WTO/TRIPS-compatible safeguards in national legislation.

The third element that seeks to increase access to essential medicines is sustainable financing. This may apply to all other types of drugs and incorporates the following: increasing public funding for health, including essential

Table 2. Twelve principal interventions to promote rational use of medicines

Number	Strategies
1	Multifaceted committees to develop policies on drug use
2	Clinical protocols
3	List of essential drugs should be based on the treatment preferences
4	Establishing task forces responsible for medicines and therapeutics at hospital levels
5	Incorporating problem-oriented training sessions on pharmacotherapy during undergraduate studies
6	Integrating continuous in-service medical training as a prerequisite to obtain a license
7	Supervision, auditing and feedback
8	Independent information on medical products
9	Educating the public about pharmaceutical products
10	Avoidance of perverse financial incentives
11	Suitable and enhanced regulations
12	Proper government funding to guarantee drugs' availability and staffing

Source: adjusted from WHO [33].

medicines; reducing out-of-pocket spending, particularly among the poor; expanding health insurance through national, local, and employer schemes; external funding (grants, loans, and donations) should be directed toward specific diseases with a high public health impact; and exploring other financing mechanisms, such as debt-relief and solidarity funds.

The final suggested, but critical, component of the framework for collective action to improve access to essential medicines is a reliable supply system. This takes into account: integrating medicine into the development of the health sector; creating efficient public-private-non-governmental organization (NGO) supply-chain approaches; assuring the quality of medicines through regulatory control; exploring various purchasing schemes; procurement co-operatives; and incorporating traditional medicines into health-care delivery.

In addition, the WHO has elaborated a strategic program aimed at increasing equitable access to essential drugs [29]. It's called "*Towards access 2030: WHO essential medicines and health products strategic framework 2016–2030*." This is recognized in the Sustainable Development Goals (SGDs) and is represented across the agency through regional and country-level programs. Its future work is structured according to two broad trajectories: (1) fostering needs-based innovation and reinforcing health products' selection, use, and supply systems to increase access; and (2) strengthening regulatory capacity and practices to ensure the quality, safety, and efficacy of products and improve the efficiency and regulatory systems to secure health gains.

Highly priced medicines

In an effort to combat several challenges that plague the management of high-priced medicines by countries, different country-led partnerships were enforced. In addition to data collection, financial agreements, and HTA, different nations have adopted several strategies to mitigate the cost of high-value medicines, including price negotiations, pooled procurement collaboration on horizon scanning, and policy exchanges [35].

In order to improve access to highly priced medicines, there is a need to promote competition in the supply chain management system while distinguishing between medicines that are patent protected and their generic equivalent upon expiration of the patent protection [36].

Engage in pro-competition strategies, especially in markets where there is the absence of patent protection. Examples of such strategies include improvement in market transparency; information dissemination regarding price, cost-effectiveness, and efficacy; and incentives for the rational prescription of drugs based on cost and quality [36].

Strategies that can be used to improve access to high-cost medications could simply include the following: development of integrated policies geared at promoting access and innovation; management of intellectual property to foster public health and innovation; evaluation of innovation and the incorporation of new health technologies; promotion of the specific financing of drugs; negotiation and regulation of prices; management of procurement in the public sector; implementation of the rational use of medications; and development of intervention tools [36].

Innovative medicines

The root causes of inaccessibility to innovative drugs are multifactorial. As a result, they can only be solved by various stakeholders working together. We believe that collaborative work could address both the root causes of unavailability and delay. Various proposals exist on how to achieve this. Among these are the EFPIA's suggestions [37]: proposals to expedite the regulatory process in order to provide patients with safe and high-quality diagnostics, vaccines, and treatments as soon as possible; proposals aimed at increasing information transparency regarding the

placement of centrally approved products on the market; proposals to facilitate a process in which prices are aligned with value and ability to pay; suggestions for increasing the efficiency and quality of value assessment; and proposals to ensure access equity and solidarity across countries, e.g., EU member states.

Orphan drugs

Policy frameworks geared toward optimizing licensing, reimbursement processes, pricing, and research and development (R&D) have been impactful in addressing the unmet needs of patients with uncommon illnesses. Several countries, such as the USA, the EU, and Japan, have adopted orphan drug legislation (ODL) and the Orphan Drug Act (ODA) and offer regulatory as well as financial incentives to institutions to venture into orphan drug development [19].

There is a need for the anticipation of potential funding loopholes by manufacturers and to address them accordingly by engaging with regional, local, or national funding institutions. For example, producers can enhance forecasting, partake in advocacy meetings, and seek innovative mechanisms of payment to address budgetary concerns. Conditional licensing, the management of entry agreements, and early access programs can support the access of medication to patients. Payers' concerns about clarifying clinical and economic uncertainties can be addressed by linking registries to the collection of real-world data. For example, "recent orphan medicine launches have offered retroactive rebates, deferred payments, and installment options, as well as outcomes-based/pay-for-performance contracts" [41].

HTA and collaboration with international bodies are very important and can provide support to organizations seeking to venture into new orphan drugs. For instance, there have been several publications on the evaluation of the high-priced disease sector by the European Network for Health Technology Assessment (EUnetHTA). After regulatory approval, there is the provision of an assessment, pooling of resources, setting standards using evidence and advanced evaluations, and access to patients in different locations.

A coordinated and thoughtful plan of engagement is imperative in several disease sectors to handle ethical, geographical, and legal hurdles. This will broaden the coordination strategy globally while aligning with the regional context and affiliate strategy and incentives.

Although R&D is super costly in the field of uncommon infections, researchers should look at both sides in terms of costs and revenues. The expenditure incurred by pharmaceutical organizations in R&D is about $60 billion, while the yearly revenue of these organizations surpasses/exceeds about $300 billion [20], [28]. As such, the cost is easily covered.

Finally, challenges associated with access to orphan medications can be managed if producers engage proactively through public-private partnerships (PPPs).

The study's limitations and areas for future research

The study may have a limitation in that it relied only on documents. This source of data is primarily limited by the fact that researchers can only access what is documented and accessible. Some researchers [7] claim that documents can be the only accessible sources of information, while others [6] agree that they can be used to conduct primary research. However, qualitative researchers who use the same methodology prefer to obtain information from the participants' "words" or by observing them doing what they do in their natural environment, "observation" [42]. Other researchers suggest using multiple data sources to get a more complete picture, also known as "triangulation of methods" [43].

Additionally, the authors took a broad view of the drug accessibility issues to ensure that they addressed the general inquiry and adhered to the specified academic requirements. Future studies should use narrowed research questions for in-depth answers to specific questions. These may, for instance, be studies on the challenges associated with access to cancer medications between wealthy and developing nations over time.

Conclusions

- This study revealed that there are still access challenges to drugs globally in all four main categories: essential medications, innovative medicines, highly priced drugs, and orphan medicines.
- Drugs may not be available due to a lack of effective treatments, prohibitive costs, fluctuations in production, and delays. The unprofitability of medicines to treat rare diseases and diseases that mainly affect poor countries means that manufacturers are less interested in their production. R&D also plays an important role in the global pharmaceutical market. Additionally, patents are still one of the main global barriers to the development and distribution of new drugs, although this is further aggravated by poor quality and counterfeit drugs.
- The aforementioned problems are not independent and unrelated. They are complicated by the fundamental nature of the pharmaceutical market and the way it is regulated. Therefore, the solutions or strategies to solve these challenges require collaborative efforts at all levels, in all domains, and in all sectors – public, private, and non-governmental. Pharmaceutical organizations and key health institutions, including the WHO and health ministries, should work as an inseparable team.

Declarations

The authors declare no conflict of interest.

Authors' contribution: C.N: methodology, writing – original draft preparation, visualization; C.N. and D.A.A.: conceptualization, data acquisition, formal analysis, writing – review and

editing. Both authors have read and aproved a final version of manuscript to submission.

Acknowledgements

The authors thank their supervisor, Dr. Tomasz Bochenek, for his support. His enthusiasm, experience, and attention to detail were an inspiration and helped make this project a reality. Dr. Michał Zabdyr-Jamróz provided crucial oversight and technical assistance, and the authors are extremely grateful for his persistent support.

Disclaimer

This study arose from the authors' coursework "Health Technology Assessment and Rational Pharmaceutical Policy" for the European Public Health Master: Europubhealth+ Studies, which was funded by the European Union's Erasmus+ Program.

References

1. World Health Organization, *WHO Medicines Strategy 2004–2007: Countries at the Core*, World Health Organization, Geneva PP – Geneva 2004: 12, https://apps.who.int/iris/handle/10665/68514 (accessed: 27.09.2022).
2. Ozawa S., Shankar R., Leopold C., Orubu S., *Access to Medicines through Health Systems in Low-and Middle-Income Countries*, "Health Policy and Planning" 2019; 34, no. Supplement 3: III1–III3, doi: 10.1093/heapol/czz119.
3. World Health Organization, *Equitable Access to Essential Medicines: a Framework for Collective Action*, "WHO Policy Perspectives on Medicines" 2004; 4: 1–6.
4. Aitken M., Kleinrock M., Simorellis A., Nass D., *The Global Use of Medicine in 2019 and Outlook to 2023*, "IQVIA Institute for Human Data Science" 2019; January: 1–56.
5. Rajkumar S.V., *The High Cost of Prescription Drugs: Causes and Solutions*, "Blood Cancer Journal" 2020; 10 (6), doi: 10.1038/s41408-020-0338-x.
6. Miller F.A., Alvarado K., *Incorporating Documents into Qualitative Nursing Research*, "Journal of Nursing Scholarship" 2005; 37 (4): 348–353.
7. Howell M.C., Prevenier W., *From Reliable Sources: An Introduction to Historical Methods*, Cornell University Press, 2001.
8. Hunter K.E. et al., *Searching Clinical Trials Registers: Guide for Systematic Reviewers*, "BMJ" 2022; 377: e068791, doi: 10.1136/bmj-2021-068791.
9. Flynn S., Hollis A., Palmedo M., *An Economic Justification for Open Access to Essential Medicine Patents in Developing Countries*, "Journal of Law, Medicine & Ethics" 2009; 37 (2): 184–208.
10. Collier R., Rapidly Rising Clinical Trial Costs Worry Researchers, "CMAJ" 2009; 180 (3): 277–278, doi: 10.1503/cmaj.082041.
11. Johnston S.C., Hauser S.L., *Clinical Trials: Rising Costs Limit Innovation*, "Annals of Neurology" 2007; 62 (6): 6–7, doi: 10.1002/ana.21329.
12. Sharma A., Jacob A., Tandon M., Kumar D., *Orphan Drug: Development Trends and Strategies*, "Journal Pharmacy Bioallied Sciences" 2010; 2 (4): 290, doi: 10.4103/0975-7406.72128.
13. Franco P., *Orphan Drugs: The Regulatory Environment*, "Drug Discovery Today" 2013; 18 (3–4): 163–172, doi: 10.1016/J.DRUDIS.2012.08.009.
14. Blankart C.R., Stargardt T., Schreyögg J., *Availability of and Access to Orphan Drugs: An International Comparison of Pharmaceutical Treatments for Pulmonary Arterial Hypertension, Fabry Disease, Hereditary Angioedema and Chronic Myeloid Leukaemia*, "Pharmacoeconomics" 2011; 29 (1): 63–82, doi: 10.2165/11539190-000000000-00000.
15. Aagaard L., Kristensen K., *Access to Cross-Border Health Care Services for Patients with Rare Diseases in the European Union*, "Orphan Drugs: Research and Reviews" 2014; 4: 39, doi: 10.2147/ODRR.S58268.
16. Garau M., Mestre-Ferrandiz J., *Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries*, "OHE Briefing" 2009; 52: 1–32.
17. *Diabetes TL. Spotlight on Rare Diseases*, "The Lancet Diabetes & Endocrinology" 2019; 7 (2): 75.
18. Villa S., Compagni A., Reich M.R., *Orphan Drug Legislation: Lessons for Neglected Tropical Diseases*, "International Journal Health Planning and Management" 2009; 24 (1): 27–42, doi: 10.1002/HPM.930.
19. Chan A.Y.L. et al., *Access and Unmet Needs of Orphan Drugs in 194 Countries and 6 Areas: A Global Policy Review With Content Analysis*, "Value Healthcare" 2020; 23 (12): 1580–1591, doi: 10.1016/J.JVAL.2020.06.020.
20. Ahmadiani S., Nikfar S., *Challenges of Access to Medicine and The Responsibility of Pharmaceutical Companies: a Legal Perspective*, "DARU Journal of Pharmaceutical Sciences" 2016; 24 (1): 1–7, doi: 10.1186/S40199-016-0151-Z.
21. Kantarjian H., Rajkumar S.V., *Why are Cancer Drugs so Expensive in the United States, and What are The Solutions?*, "Mayo Clinic Proceedings" 2015; 90 (4): 500–504, doi: 10.1016/j.mayocp.2015.01.014.
22. Masiga J., *Essential Drugs Concept: Is It Still Relevant in Our Situation Today*, "Meds Updat." 2010; 17: 2–8.
23. Loyse A. et al., *Cryptococcal Meningitis: Improving Access to Essential Antifungal Medicines in Resource-Poor Countries*, "Lancet Infectious Diseases" 2013; 13 (7): 629–637.
24. Nchako E., Bussell S., Nesbeth C., Odoh C., *Barriers to The Availability and Accessibility of Controlled Medicines for Chronic Pain in Africa*, "International Health" 2018; 10 (2): 71–77.
25. Pe B., Chirac P., Trouiller P., Pinel J., *Access to Essential Drugs in Poor Countries*, "JAMA" 1999; 281 (4): 361–367.
26. Pécoul B. et al., *Long-acting Chloramphenicol versus Intravenous Ampicillin for Treatment of Bacterial Meningitis*, "The Lancet" 1991; 338 (8771): 862–866, doi: 10.1016/0140-6736(91)91511-R.
27. Grover A., Citro B., Mankad M., Lander F., *Pharmaceutical Companies and Global Lack of Access to Medicines: Strengthening Accountability under The Right to Health*, "Journal of Law, Medicine & Ethics" 2012, 40 (2): 234–250, doi: 10.1111/J.1748-720X.2012.00661.X.

28. World Health Organization, *Pharmaceutical Industry, Trade, Foreign Policy, Diplomacy and Health*, Geneva 2013.
29. World Health Organisation (WHO), *Towards Access 2030: WHO Medicines and Health Products Programme Strategic Framework 2016–2030*, Geneva 2017.
30. EUROPE and WHO, *Access to New Medicines in Europe: Technical Review of Policy Initiatives and Opportunities for Research*, Copenhagen 2015.
31. European Organisation for Rare Dieases, *Rare Diseases: Understanding This Public Health Priority*, Paris 2005.
32. Toreele E., Usdin M., Chirac P., *A Needs-Based Pharmaceutical R&D Agenda for Neglected Diseases*, Geneva 2004.
33. World Health Organization, *The Rational Use of Drugs: Report of the Conference of Experts, Nairobi, 25–29 November 1985*, Geneva 1985.
34. World Health Organization, *Promoting Rational Use of Medicines: Core Components*, Geneva 2002.
35. WHO and Europe, *Expert Meeting on Market High-priced Innovative Medicines*, Brussels 2020.
36. Pan American Health Organization and Regional Office of the World Health Organization, *Access to High-Cost Medicines in the Americas: Situation, Challenges and Perspectives*, Washington 2010.
37. European Federation of Pharmaceutical Industries and Associations, *The Root Cause of Unavailability and Delay to Innovative Medicines: Reducing the Time before Patients Have Access to Innovative Medicines*, Brussels 2020.
38. Pogge T., Rimmer M., Rubenstein K., *Introduction: Access to Essential Medicines: Public Health and International*, in: *Incentives for Global Public Health: Patent Law and Access to Essential Medicines Connecting International Law with Public Law*, T. Pogge, M. Rimmer, and Rubenstein, eds., Cambridge University Press, 2010: 1–32.
39. Persistent Market Reaserch, *Innovative Drugs Market: Global Industry Analysis and Forecast to 2020*, https://www.persistence-marketresearch.com/market-research/innovative-drugs-market.asp (accessed: 8.01.2022).
40. UN Human Rights Office of the High Commissioner, *Special Rapporteur on the Right to Physical and Mental Health*, *Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health*, 2020, https://www.ohchr.org/en/special-procedures/sr-health (accessed: 8.01.2022).
41. Mtech Team, *Challenges for Orphan Medicines Entering the European Market – Part 4: Operational Challenges*, 2021, https://mtechaccess.co.uk/orphan-medicines-europe-operational-challenges/ (accessed: 8.01.2022).
42. Hodder I., Hutson S., *Reading the Past: Current Approaches to Interpretation in Archaeology*, Cambridge University Press, 2003.
43. Thurmond V.A., *The Point of Triangulation*, "Journal of Nursing Scholarship" 2001; 33 (3): 253–258.