International Journal for Equity in Health

RESEARCH

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Rare disease challenges and potential actions in the Middle East

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Abstract

Background Rare diseases, defined variably by global regions, collectively impact approximately 300 million individuals despite affecting small population segments individually. Historically there were no treatments developed for these conditions, leading to significant care challenges. Public interventions have incentivized treatment development, yet up to this day, many rare disease patients are deprived of timely diagnosis and treatment in comparison to patients with more common diseases. This study evaluates the challenges that rare disease patients and healthcare systems face in the Middle East and North Africa (MENA), seeking strategies to enhance treatment accessibility.

Methods We followed a three-step approach for the study. First, we searched scientific publications and grey literature for the global challenges faced by rare disease patients. Our search also collected information on orphan drug regulations implemented in different countries. Subsequently, we used the findings to conduct a survey to pharmaceutical company representatives across three countries in the region (The Kingdom of Saudi Arabia, Egypt, and the United Arab Emirates). The survey assessed the challenges facing rare disease patients in the MENA region and the policies that have been implemented to overcome these challenges. The survey was then followed by governmental expert interviews to validate the survey responses and provide recommendations to mitigate the challenges.

Results The literature and survey results revealed several challenges facing rare diseases, including lack of awareness, difficulty in acquiring marketing authorization and reimbursing orphan drugs. Validation meetings provided recommendations to mitigate such challenges in the selected countries. For instance, the collaboration between the Ministry of Health and pharmaceutical companies was recommended to improve rare diseases care. A separate registration process for orphan drugs with clear criteria and timelines was suggested. A differential cost-effectiveness threshold for orphan drugs was recommended. It was also recommended to establish a definition for rare diseases and to increase the utilization of managed entry agreements for orphan drugs.

Conclusions Rare diseases present challenges in the MENA region and globally, requiring focused attention and innovative solutions. By implementing comprehensive strategies that consider both economic efficiency and fairness, healthcare systems can better serve rare disease patients and improve their quality of life.

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Keywords Rare diseases, Orphan drugs, Challenges, Policies, Middle East, Egypt, United Arab Emirates, Kingdom of Saudi Arabia, KSA, UAE

Background

Rare diseases are defined as conditions that affect only a small number of people predominantly based on the prevalence or incidence within a specific country or geographical region [1].

Although each disease is considered rare on its own, when taken together, rare diseases are more common than one might think [2]. There are an estimated 6,000 to 8,000 rare diseases worldwide [3, 4] collectively affecting a significant number of people [3, 5]. For example, in Europe, it was estimated that 8% of people have at least one rare disease [5] and around 25 million people in the United States have rare diseases [3]. Worldwide, around 300 million patients are affected with a rare disease, half of them are children, with around 30% likely to die by age 5 [2, 6, 7]. It is important to note that 80% of rare diseases are genetic in origin [3, 5]. This means that most rare diseases are caused by changes or mutations in an individual's DNA [3, 5].

Many patients with rare diseases face difficulties in accessing timely medical care due to the low prevalence of these conditions. In the past the low prevalence discouraged the pharmaceutical industry from investing in the development of new treatments, as the potential financial returns did not justify the substantial costs involved. These drugs became "orphaned" as companies were reluctant to pursue them under normal market conditions [6].

In a global healthcare system operating solely on market principles (not considering issues of equity or fairness), it would be possible that patients with rare diseases may not receive the treatment they need [8]. Due to the life-threatening and/or chronically debilitating nature of rare diseases, many individuals affected by these conditions may not survive to adulthood [9]. However, from an equity perspective, rare disease patients should have the same opportunities to access treatment as patients with common diseases. As a result, addressing the needs of patients with rare diseases has been more and more considered as a public health priority [9].

In the 1970s, the availability of drugs to treat rare diseases was limited to only 10 drugs [3]. The global healthcare system failed to adequately address the needs of patients with rare diseases, leaving them underserved due to their small numbers.

In response to the challenges faced by patients with rare diseases, various governments and international organizations have initiated potential solutions to incentivize pharmaceutical companies to invest in the development of treatments for rare diseases [10]. To this end, legislative measures such as the Orphan Drug Act (ODA) in the United States were enacted to facilitate the development and availability of treatments for rare diseases [3]. The public interventions to facilitate the development of orphan medicines can be allocated to push and pull incentives [11]. Push incentives include public grants to conduct research in rare diseases or establishing patient registries, tax credits for research and development expenses, reduction of regulatory fees or assistance in writing clinical trial protocols. Pull incentives include accelerated centralized regulatory procedure, increased market exclusivity period, automatically assumed reimbursement or higher willingness to pay thresholds for orphan medicines [12–14]. Similarly, the European Union and Japan have implemented rare disease legislation aimed at reducing the administrative burden and encouraging collaboration [13]. The introduction of public interventions reshaped the landscape of pharmaceutical R&D where the cost of developing rare disease treatments significantly dropped to about 25% of the cost associated with developing treatments for more common conditions [15]. Furthermore, the extended market exclusivity, simplified regulatory reviews, as well as the limited price control mechanism for orphan drugs, coupled with the low operational costs (i.e. less dependency on sales representatives) increased the operating profit of orphan drug manufacturing more than 5 times that of non-orphan drugs [16]. Orphan drugs created a new era of "nichebuster" therapies where manufacturers focus on less prevalent diseases with no direct competitors rather than medicines in highly competitive market segments of more prevalent diseases [17]. As a consequence of increased profitability boosted by public incentives the number of orphan drug designations increased from 531 to 3633 (by 584%) and orphan approvals increased from 80 to 470 (by 486%) between the first decade after the ODA was enacted (1983–1992) to the recent decade (2013–2022) [18].

Despite the notable advances in rare disease treatments, the access to the currently available treatments for patients is still compromised owing to significant obstacles facing rare diseases and orphan drugs [1, 4]. Yet up to this day, many rare disease patients are deprived of timely diagnosis and treatment in comparison to patients with more common diseases [6].

Using the United Nations' prevalence rate of 0.7% for rare diseases, it is estimated that the number of rare disease patients in Middle Eastern countries such as Egypt, the Kingdom of Saudi Arabia (KSA), and the United Arab Emirates (UAE) may have reached up more than 750,000,

250,000, and 65,000 in 2021 respectively [19]. As interest in improving healthcare is a priority in many countries, there is a growing focus on addressing the global problem of rare diseases and orphan drugs [19]. Initiatives such as pre-marital genetic screening - which is offered in countries including Saudi Arabia and the UAE- have already been implemented to keep track of patients with rare diseases [19]. However, given the increasing number of rare disease patients and challenges in accessing therapy, there is a clear need for further research to identify the specific obstacles facing these patients and to propose potential solutions to improve access to treatment.

The objective of our research is to achieve a unified understanding of the most common challenges that impede access to innovative treatments for rare disease patients, and to propose solutions to these challenges in three Middle Eastern countries: Egypt, KSA, and UAE. Such solutions can be further translated at a later stage into future policies.

Methods

We conducted a non-systematic review to gather evidence on the most common global challenges facing rare diseases, and policies that have been implemented to mitigate those challenges. Furthermore, we investigated the different types of special access programs as they represent one of the important potential pathways for patient access to treatment due to unmet medical needs and the low number of patients. Finally, the search was complemented by exploring orphan drug regulations in different countries.

To assess the local challenges in the Middle East region, the search results were enriched by local insights from private and public sector representatives in three selected Middle Eastern countries: Egypt, KSA and UAE. We created a survey to be disseminated among pharmaceutical companies' market access leads to collect local information about the rare diseases challenges they face and to provide their insights into potential solutions. The survey results were summarized and consolidated for each country.

Later, the survey findings were validated through interviews with governmental healthcare sector stakeholders who provided their insights and proposed similar or different potential solutions. The final interview results provided a local insight into rare diseases most common challenges and potential solutions in each country, as they included aggregated data from 3 sources: international literature, local pharmaceutical industry representatives and the public healthcare sector.

Literature search

We searched scientific publications and grey literature for the most common challenges facing rare diseases globally, and we also searched for potential policies that have been implemented to mitigate the burden. This search was not confined to a specific geographical area. We searched PubMed, Google Scholar, and Google search engine using the following keywords: "rare diseases" and "orphan drugs". The search was not limited by publication time and only English language articles were reviewed.

The search resulted in identifying several challenges and policies related to rare diseases. We used qualitative thematic analysis to categorize the data into five domains: disease awareness, marketing authorization, reimbursement, pricing and HTA, orphan drug designation, and policy incentives and special access programs.

Furthermore, we explored the regulations of different countries regarding rare diseases. This was accomplished by using the following keywords: "rare diseases" and "regulations" to identify pertinent information.

The scope of our search was not exhaustive, as we aimed to identify only the most common challenges and potential solutions to create a comprehensive and practical survey, so the search may have not encompassed every single challenge or solution in the literature.

Survey

Based on the literature search findings, a survey was developed to discover the potential challenges facing rare disease patients and healthcare systems in each of the three countries, and to assess the presence of policies designed to mitigate these challenges. The survey also sought to gather recommendations for how to address the challenges in these countries. The aim of the survey was to identify the current state of the rare disease landscape in selected Middle Eastern countries and to develop recommendations aimed at improving care and outcomes for individuals affected by rare diseases.

The survey was distributed electronically through Google Forms™ among representatives of pharmaceutical companies who were leaders of market access departments in their companies. We received responses from 11 representatives from Egypt, 14 from KSA, and 9 from UAE. Each response did not reflect the answer of only one individual in each company but represented an internal consensus of all market access leads in the company. Pharmaceutical companies included in the survey were orphan drugs marketing authorization holders. A total of 25 questions were included in the survey grouped into 5 sections: disease awareness, marketing authorization, reimbursement, pricing and HTA, orphan drug designation, and policy incentives and special access programs. Two additional questions were used to gather data.

The survey included both multiple-choice (13 questions) and open-ended questions (12 questions). Some of the open-ended questions were placed at the end of each

domain, allowing respondents to provide their insights in an unrestricted form. Examples of questions included in the survey the level of awareness among stakeholders (in the rare disease awareness domain), the time needed for the marketing authorization (in the marketing authorization domain), and the reimbursement of orphan drugs (in reimbursement, pricing, and HTA domain). A complete list of questions included in the survey can be found in Additional file 1.

The responses to multiple-choice questions were aggregated and the mean values were calculated for continuous variables, while for categorical, and Boolean questions, the frequency per choice was determined. Finally, the survey results were presented graphically as represented in Additional file 2. In addition, responses to open-ended questions were compiled to provide insights into each domain. The research team then presented such insights and recommendations to governmental experts.

Governmental sector experts' validation meetings

As the survey results represented only the perspective of pharmaceutical companies, it was necessary to validate these findings by conducting interviews with public sector experts. Meetings held included payers and policymakers working in governmental entities of each country. Experts included representatives from Egypt's Universal Procurement Authority (UPA) and the Universal Health Insurance Authority (UHIA), Saudi Arabia's Ministry of Health, and the UAE's Department of Health (DOH) and Dubai Health Authority (DHA). These validation interviews were conducted online where it started by presenting the survey results of each domain to experts and soliciting their feedback. The experts were also asked to provide their recommendations for addressing the challenges in each domain identified in the survey.

Based on the input from the validation meetings and survey analysis, we adjusted the results to incorporate the opinions of public stakeholders and to provide a more comprehensive understanding of the challenges. Additionally, potential recommendations were discussed and suggested based on this input, resulting in a list of recommendations.

Results

The findings presented below outline the outcomes of our literature search with respect to challenges, policies, and orphan drug regulations. Subsequently, a section dedicated to region-specific findings, derived from survey data and validation meetings is provided for each of the 5 domains.

Literature search

The sections below present the findings of our search into the challenges facing rare diseases and the policies implemented to mitigate them. Data were categorized into five domains: disease awareness, marketing authorization, reimbursement, pricing and HTA, orphan drug designation, and policy incentives and special access programs. Additionally, we provide an overview of orphan drug regulations in various countries.

Challenges & related policies

Disease awareness

There are several interrelated challenges associated with the recognition and diagnosis of rare diseases. Lack of awareness about a disease can impact both patients and physicians where patients who are unfamiliar with the specific signs and symptoms may not seek medical advice in a timely manner [20, 21]. Additionally, clinicians who lack awareness of rare diseases may be more likely to misdiagnose these conditions or delay making an accurate diagnosis [20, 21]. This is reflected in the significant delay in diagnosis experienced by many rare disease patients, with an average delay of 7.6 years in the United States and 5.6 years in the United Kingdom before getting the correct diagnosis [22]. On average, patients visit more than seven physicians before an accurate diagnosis is made [23].

Market authorization

Due to the rarity of such diseases, the available clinical evidence for these conditions is often limited. Therefore, decision-makers and regulators may be reluctant to grant approvals for rare disease treatments with such limited evidence [24]. In low and middle income countries, where awareness of rare diseases is even more limited, the approval process for these treatments can be slower than in higher income countries. Additionally, many Middle Eastern countries base their marketing authorization for rare disease treatments on approvals from the European Medicine Agency (EMA) and the FDA, which can further delay the initiation of the approval process and its regulation [1].

Policies to mitigate marketing authorization challenges of orphan drugs included the establishment of clear provisions and timelines for obtaining marketing authorization. For example, some countries provides fast-track approval for orphan drugs [6, 25].

Reimbursement, pricing, and HTA

The rarity of such diseases and difficulties facing pharmaceutical industries in developing their treatments drives industries to ask for high prices for their orphan drugs [26]. Some countries use external price referencing to determine the price of orphan drugs [27]. In response to that, pharmaceutical companies may employ a strategy known as "price sequencing," which involves delaying the introduction of orphan drugs in lower economy markets

to prevent other countries from referencing their lower prices which negatively affects patients access to treatment [27].

Regarding HTA, one major challenge for rare disease technologies is the absence of a tailored method for evaluating these technologies [28]. This can be attributed to several factors, including the lack of sufficient and robust clinical data [26], no established standard of care [29], insufficient knowledge of the natural history of these conditions, a lack of validated instruments for assessing efficacy and effectiveness endpoints, and the absence of an incremental cost-effectiveness threshold specifically designed for rare diseases [28, 30].

Another significant challenge is the uncertainty faced by HTA authorities when evaluating rare disease technologies. These technologies often have major uncertainties related to their real-world efficacy, effectiveness, cost-effectiveness, and added value [31]. Other uncertainties include the potential of the treatment to address unmet medical needs and the lack of strong evidence regarding the number of patients who may benefit from the treatment. This can result in uncertainty about the budget impact of these technologies, making it more difficult to inform decision-making and determine the value of orphan drugs [1, 24, 32].

To mitigate challenges related to the pricing and reimbursement of orphan drugs, pricing and reimbursement guidelines should be established. Furthermore, managed entry agreements and special access programs use should be increased to improve patient access to treatment [6]. Roessler et al. [33] reported methods that can be employed to control the high costs of orphan drugs such as the repurposing of drugs for new indications. However, this approach may be hampered due to financial considerations and difficulty in conducting clinical trials. Additionally, procurement mechanisms as price control, centralised purchasing and value-based procurement were utilized to reduce the economic impact of rare disease treatments. In an attempt to reduce the cost of the drug, partnerships and programs in collaboration with key stakeholders (such as the industry) may be established [34].

Since HTA is difficult to implement for orphan drugs due to very limited and non-robust data, Zelei et al. considered criteria to assess the value of orphan drugs. These criteria were classified into: disease-related criteria, treatment-related criteria, economic factors and societal factors [35]. These criteria can be translated into a tool to assess the value of orphan drugs.

Orphan drug designation

One of the challenges that faces rare disease and orphan drug designation is the lack of a universal accepted definition for rare diseases and orphan drugs [1]. The US FDA and the European Union (EU) define a drug intended to treat a rare disease as an orphan drug [5]. However, the threshold for what is considered a rare disease varies between regions.

Several policies were reported to regulate orphan drugs and mitigate such challenges. One of the policies included the establishment a formal definition and an official list for rare diseases [6]. The European Union (EU) defines rare diseases as life-threatening or chronically debilitating conditions affecting no more than 5 in 10,000 people [36]. However, in the United States, the Food and Drug Administration (FDA) strictly defines rare diseases based only on their prevalence as any disease affecting fewer than 200,000 people [5].

Furthermore, establishing clear criteria for the drugs to be considered orphan (known as orphan designation) was stated in some countries [5, 6]. Criteria for granting orphan status to the drug mainly revolves around the intent of the drug to treat, prevent, diagnose a rare disease. For that reason, it is important to set a definition for rare disease.

Policy incentives & special access programs

Conducting research and clinical trials for rare diseases face several challenges, one of them is the limited number of patients and their dispersion across different geographic locations [37–39]. This makes it difficult to identify and recruit patients for clinical trials. Additionally, the limited number of rare disease experts and the heterogeneity of these conditions in terms of pathogenesis, symptom presentation, natural history, disease severity, and progression results in misdiagnosis and an underestimation of the true frequency of these diseases [1, 37, 40].

To address the challenges in research, several policies have been implemented to promote research and development. For instance, the EMA and FDA provide market exclusivity to orphan drugs for a period of 10 and 7 years, respectively [25, 41]. The EMA also offers assistance with clinical trial protocols and scientific advice to pharmaceutical companies developing orphan drugs [42]. In addition, some countries have established funding programs to support research and development in the field of rare diseases [6]. Research-related incentives also included protocol assistance, scientific advice, and clinical research subsidies [25].

There were also policy incentives related to increasing the market availability of orphan drugs. Payers can contribute to reducing the co-payment value incurred by patients. Furthermore, a funding program is also of great importance to increase access to orphan drugs. If the therapy is not provided in the country, then financial assistance for cross-border access may be beneficial. Tax credits for orphan drug sales are offered as an incentive

for pharmaceutical industries. Furthermore, waiving fees or a fee refund for orphan drug submission files is also offered.

Special access programs play an increasingly important role in improving patient access to treatments for rare diseases. Several types of special access programs exist, each designed to increase patient access in different ways.

One type of special access programs is the early access program, which is implemented for patients after the discontinuation of a clinical trial. Under this type of program, the product is partially or fully funded from public funds, while the manufacturer gains additional data for marketing authorization purposes.

Another type of special access program is compassionate use, which allows an investigational product to be given to a group of patients who have a disease with no satisfactory authorized therapies and where there are no ongoing clinical trials [43].

Other types of special access programs include named patient basis early access, where the drug is designated for use by an individual patient, typically after the discontinuation of a clinical trial and before the drug is reimbursed [44].

In some cases, a product may be authorized for use in one indication but may also offer beneficial effects in another indication (off-label use). This is considered another form of special access programs [45].

Finally, coverage with evidence development is a form of special access programs, where payers agree to reimburse the drug, either as part of a clinical trial or through registered centres, while the manufacturer collects additional data [46].

Orphan drug regulations in different countries

In recent years, countries around the world started to pass laws and regulations aimed at improving patient access to orphan drugs. In the United States, for example, the Orphan Drug Act [47] provides incentives such as market exclusivity and tax credits to encourage the development of treatments for rare diseases [25]. Similarly, in Europe, incentives were provided, and in 2008, the European Union launched a project to facilitate the development of national plans for rare diseases [48]. In addition to these efforts, the European union launched a screening project with the goal of reducing the time required for diagnosis and enabling more efficient intervention through the use of genetic newborn screening and advanced analysis methods [49].

Non-EU countries also have national regulations to ensure coverage of orphan drugs. In Russia, for example, there is a special program that provides financing for 12 high-cost diseases at the federal level [50]. Countries like Australia, Japan, and Taiwan, offer incentives focusing on research and development where they provide financial and marketing incentives to develop and produce rare diseases medicines [25]. Incentives includes grants, fast-track approval, protocol assistance, and market exclusivity [50]. Similarly in Japan, it provides regulatory fee waivers, research grants, tax credits, and reductions, tools to reimburse medical costs, and funding to encourage research and orphan drug development [51, 52].

However, policies vary greatly between countries, for example, some countries in Latin America already have comprehensive rare disease policies such as the presence of healthcare plans with national centres and facilities to support disease management and guarantee access to health services. While other countries in Latin America, have only basic protective laws that do not necessarily guarantee funding or financial protection for patients, nor do they regulate access to treatments [25, 37, 47, 53, 54].

Rare diseases in the Middle East

The scientific literature describes numerous challenges related to managing rare diseases in the Middle East, especially a lack of access to genomic diagnostic tools and personalized care plans [55]. These challenges are exacerbated by the region's high consanguinity rates and larger family sizes, which contribute to the elevated prevalence of rare conditions, especially Mendelian disorders [55]. Patients typically endure extended diagnostic journeys, averaging six to eight years, involving numerous hospital visits and redundant diagnostic tests [55]. This situation is further compounded by the shortage of skilled healthcare professionals, insufficient awareness of rare diseases, and inadequate reimbursement for genetic testing, resulting in delayed diagnosis and treatment and creating significant socio-economic burdens [19].

Efforts are underway to address these issues, such as the establishment of clinical genomic centers in some Middle Eastern countries, along with initiatives for genetic screening and counseling. For instance, a pilot project created the Catalogue of Transmission Genetics in Arabs (CTGA) database to improve education, raise public awareness, and track patients with rare diseases [19].

Collaborative efforts have also gained momentum, for instance, the UAE's Rare Disease Society was formed to foster global scientific collaboration and promote awareness and prevention strategies [56]. Similarly, the Saudi Rare Disease Summit, held under the Saudi Ministry of Health, emphasizes multi-stakeholder collaboration to enhance patient care [57]. Additionally, the MENA Congress for Rare Diseases facilitates knowledge sharing and innovative strategies across the region, while the Centre for Arab Genomic Studies (CAGS) plays a pivotal role in characterizing genetic disorders and promoting research across Arab nations [58, 59].

In addition to the mentioned initiatives, Saudi Arabia has initiated programs to train nationals abroad to mitigate the shortage of skilled healthcare professionals in rare diseases [19].

There is a growing commitment to increasing the private sector's role in healthcare. Pharmaceutical companies focus on marketing and distributing orphan drugs within the region.

On the policy front, the establishment of cost-effectiveness thresholds (CET) for orphan drugs in Egypt and the UAE have been introduced to prioritize and improve access to rare disease treatments. The Egyptian CET was established where the score of a Multi-Criteria Decision Analysis (MCDA) tool was translated into a multiplier of the conventional threshold to estimate a threshold for orphan drugs [60]. Additionally, the UAE has recently introduced its CET, incorporating a two-times multiplier specifically designed for treatments targeting rare diseases [61].

Local insights- survey and validation meetings

Disease awareness

Survey The first section of the survey was "disease awareness". Respondents were asked to rate the level of awareness of different stakeholders on a scale from 1 (low) to 5 (high). The highest level of awareness for rare diseases in all countries was observed among healthcare and service providers. KSA had the highest level of awareness among healthcare providers, and the least among patients, and patient access groups for all countries combined. On the other hand, Egypt and UAE's awareness levels were closely related as shown in Fig. 1.

Regarding national programs, almost 95% of respondents in all countries combined reported the absence of a national registry program. Additionally, more than 70% reported that there was no national screening program applied in their respective country or they weren't aware of any. For diagnostic tools, most respondents (70%) in all countries combined indicated that diagnostic tools required were either lacking or not known to be readily available.

Validation meeting

Experts agreed with the survey results illustrating that the general level of awareness in all three countries is relatively low. They also stated that the highest level of awareness is observed among healthcare providers as they are in direct contact with patients. In Egypt, experts expected higher awareness among patients due to efforts by manufacturers to raise awareness.

In terms of national registries, KSA already deployed patient registries for some rare diseases. Egypt lacked a unified registry for rare disease patients and only has separate ones, such as the Health Insurance Organization's (HIO) registry. While in UAE, experts stated that there are currently no known registries due to the lack of a surveillance system, but a new initiative using the International Classification of Diseases (ICD) codes 10 & 11 will be announced on the UAE national day.

Regarding the screening for rare diseases, experts in KSA indicated that newborn screening for hemophilia and spinal muscular atrophy is mandatory in both

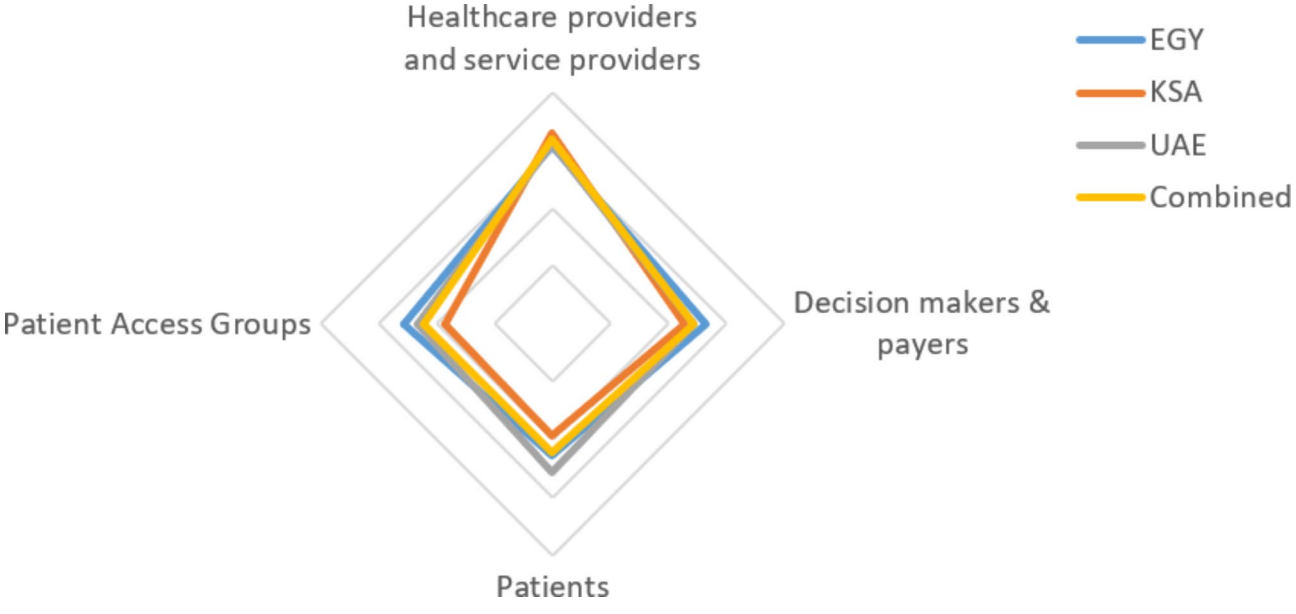

Fig. 1 Disease Awareness Level

Table 1 Summary of proposed recommendations

Survey domain	Recommendations
Disease awareness	Collaboration between the Ministry of Health (MoH) and pharmaceutical companies to improve rare disease policies, registries, awareness, and diagnosis
	Increasing centers for diagnosis of rare diseases
	Training healthcare professionals on using diagnostic tools
	Establishing patient registries to reduce uncertainty in clinical evidence and improve patient access to drugs (UAE)
Marketing authorization	Developing a separate registration process for orphan drugs with clear requirements and timelines
Reimbursement, pricing, & HTA	Establishing a pricing process for rare diseases which does not depend on external price referencing
	Introducing a cost-effectiveness threshold for non-orphan drugs and a differential higher cost-effectiveness threshold for orphan drugs
	Creating affordability programs to improve patients' access to orphan products
	Supporting patient advocacy groups to allow for patients' engagement in decision-making in the long run
Orphan designation	Developing a guideline that considers how to identify rare diseases and implementing such guidelines in registration, pricing, and reimbursement
Policy incentives & special access programs	Increasing the use of managed entry agreements for orphan drugs
	Increase the use of outcomes-based managed entry agreements (Egypt)

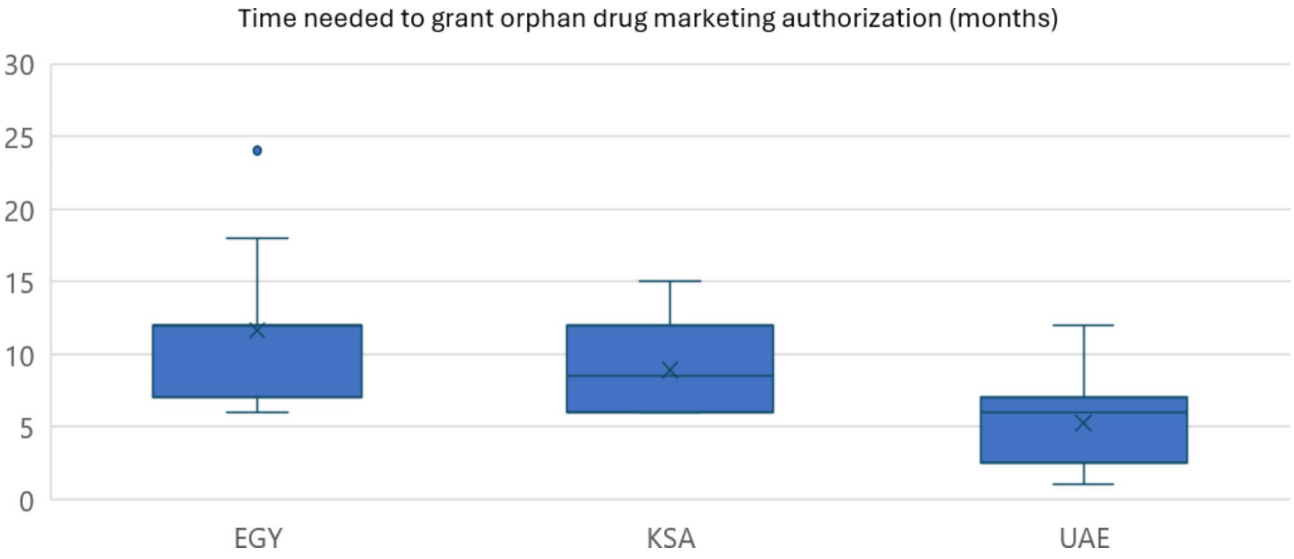

Fig. 2 Market Authorization Time in Months (median)

the public and private sectors. Experts in all countries reported that the availability of diagnostic tools varies as it is influenced by factors such as the existence of screening programs and availability of treatment. In UAE, if the required diagnostic tool is not available, the patient may be sent abroad for diagnosis.

Recommendations

Recommendations included the collaboration between the Ministry of Health (MoH) and pharmaceutical companies to improve rare disease policies, registries, awareness, and diagnosis. This can be achieved by increasing centers for diagnosis of rare diseases and training healthcare professionals on using diagnostic tools. In Egypt, it was recommended to develop a national plan aiming to mitigate rare diseases challenges. While in UAE, development of patient registries was recommended to decrease uncertainty in clinical evidence and improve patient access to drugs (Table 1).

Market authorization

Survey

More than half of the respondents reported that orphan drugs gain marketing authorization in a faster time compared to non-orphan drugs. Egypt was the slowest to acquire market authorization (12 months), while UAE was the fastest (6 months). The following figure shows the time needed by each country to grant orphan drug marketing authorization from the perspective of pharmaceutical companies (Fig. 2).

Concerning clinical evidence, more than half of pharmaceutical companies representatives in all countries

reported that uncertainty in clinical evidence poses a hurdle in acquiring marketing authorization for rare diseases. Furthermore, more than 60% reported that regulatory bodies do not request local clinical evidence for orphan drugs.

As for the requirements of marketing authorization, more than 90% of respondents in all countries reported that FDA and/or EMA approvals were essential for orphan drugs to acquire marketing authorization locally. In KSA, approvals from the United Kingdom, Switzerland or Australia were considered in addition to the FDA or EMA. While in UAE, Japan approvals were considered on top of the FDA or EMA.

Validation meeting

In Egypt, experts reported that the marketing authorization process for orphan drugs takes either the same amount of time or even longer than non-orphan drugs. This is due to performing external price referencing (EPR) to set a price for orphan drugs. However, when EPR is not feasible, regulators may use value-based pricing, which takes even longer. In contrast, experts in UAE and KSA reported that marketing authorization for orphan drugs is faster than for non-orphan drugs.

In KSA, despite limited evidence for orphan drugs, they undergo a fast-track review and are authorized more quickly than non-orphan drugs. Egyptian experts reported the time required for marketing authorization to take is at least 18 months. While KSA experts reviewed 8.5 months reported by survey respondents as a reasonable duration, UAE experts indicated a maximum of 1 year for marketing authorization.

Experts in all countries agreed that uncertainty in clinical evidence poses a challenge in marketing authorization and an even greater issue in coverage and reimbursement of orphan drugs. According to experts, local evidence is not mandatory for market authorization in any of the three countries. However, experts in Egypt suggested that requesting local evidence could facilitate coverage and reimbursement decisions. For marketing authorization, all three countries mainly depend on submissions to the EMA or FDA.

Recommendations

Recommendations included the development of a separate registration process for orphan drugs with clearly identified requirements and timelines in all three countries (Table 1).

Reimbursement, pricing, and HTA

Survey

More than 80% of pharmaceutical companies representatives in the region reported the absence of provisions and guidelines for orphan drugs in both pricing and reimbursement. Regarding price referencing methodology for orphan drugs, all respondents agreed that external price referencing is applied to orphan drugs each in their respective country. Furthermore, 70% of respondents in the region mentioned that orphan drugs follow the regular process of formulary listing without any exemptions.

The shortest time needed for orphan drugs to be reimbursed was reported in the UAE with a median of 6 months while the longest time was reported in Egypt with a median of 18 months. In KSA, a median of 12 months was reported to reimburse orphan drugs.

Concerning the implementation of HTA for orphan drugs, half of the respondents in KSA reported that HTA is not used for orphan drugs. A similar percentage was reported in the UAE. However, in Egypt, more than 80% indicated that HTA is currently used for orphan drugs. Cost-effectiveness analysis was the most frequent component considered by respondents followed by budget impact analysis in all countries combined.

Regarding the cost-effectiveness threshold (CET), more than 70% in the region reported that CET is not applied for orphan drugs, or even if it is applied no special threshold is provided for orphan drugs.

Validation meeting

In Egypt, all respondents indicated that orphan drugs are priced according to EPR, but experts stated that when EPR is not feasible, value-based pricing may be used instead. In KSA, experts agreed with survey results that EPR is applied to orphan drugs. Experts also agreed with survey results that there are no pricing and reimbursement regulations for orphan drugs in the three countries. In terms of formulary listing, orphan drugs in Egypt follow the same process but are often rejected and fail to be listed. In that case, patients may access these drugs through media pressure or court orders. While, in KSA, orphan drugs can follow a different track depending on the authority listing them.

The time it takes for an orphan drug to be reimbursed after being authorized varies by country. In Egypt, experts considered 18 to 24 months a reasonable duration. In KSA, it may take less than 12 months to be reimbursed but longer to be listed. In UAE, experts agreed that it takes about 6 months for reimbursement, but timing also depends on the sector issuing the reimbursement decisions.

In Egypt, HTA is currently not used for assessing orphan drugs and UAE does not have an HTA process. Experts in all countries indicated that budget impact analysis is the most important criterion from the payer perspective. In Egypt, a differential threshold has been developed where multipliers of the cost-effectiveness threshold were used to determine the differential

threshold for orphan drugs, but not yet implemented [60]. In the UAE, a recently established CET has been introduced, incorporating a differential threshold for rare diseases. For ultra-rare diseases, no threshold is required, and interventions are directly reimbursed for the individual [61]. In KSA, experts agreed on the importance of applying a higher value for orphan drugs when developing a threshold. Currently, the Saudi cost-effectiveness threshold has been published and is based on opportunity costs [62].

Recommendations

Recommendations for all three countries included establishing a pricing process for rare diseases that does not rely on external price referencing. It was also recommended to establish well-founded patient advocacy groups to allow for patient engagement in decision-making. In UAE and KSA, it was recommended to develop a cost-effectiveness threshold for non-orphan drugs and a higher differential cost-effectiveness threshold for orphan drugs. Furthermore, affordability programs to improve patient access to orphan drugs were also recommended. (Table 1)

Orphan drug designation

Survey

Most of the pharmaceutical companies representatives in the region responded that in their respective markets there are neither a definition nor a designation for rare diseases or orphan drugs. As for criteria required for orphan designation, nearly 90% of respondents indicated that there are no published criteria or procedures for orphan drug designation.

Validation meeting

Experts agreed with the survey results regarding the absence of an official definition and designation for rare disease or orphan drugs in their respective country. In KSA, experts stated that authorities follow the FDA definition for rare disease and orphan drugs.

Recommendations

Recommendations included the development of a guideline that considers how to identify rare diseases and implementing such guidelines in registration, pricing, and reimbursement. Since Egypt usually adopts the FDA or EMA for designation, it was recommended to formally announce it (Table 1).

Policy incentives & special access programs

Survey

Most of the policy incentives addressed in the survey were not applied in the region. Most respondents indicated that regulatory bodies neither grant market exclusivity for orphan drugs nor waive fees for orphan drug file submission each in their respective countries. A similar percentage of respondents reported that regulatory bodies do not provide tax credits or exemptions for orphan drug sales. Furthermore, almost all respondents indicated that orphan drugs follow regular price regulations with no exemptions. On the other hand, half the respondents supported the availability of funding programs for rare disease patients.

For special access programs implemented in the region, named patient basis early access was the most frequently implemented followed by compassionate use access schemes. While outcome-based managed entry agreements were known to be implemented by 50% of pharmaceutical companies' representatives (Fig. 3).

Validation meeting

In terms of funding programs, experts in Egypt confirmed the existence of programs for rare diseases, such as the well-known initiative by the Egyptian president to provide free treatment for spinal muscular atrophy patients. In UAE and KSA, experts agreed with survey responses that there are no policy incentives in either country.

Regarding special access programs, experts in Egypt reported that there is currently no specific program for orphan drugs. Based on their experience, the most commonly implemented programs were patient early access and compassionate use. However, drugs are usually dispensed as a result a court order rather than a government decision.

Experts indicated that outcome-based agreements and coverage with evidence development are not implemented in Egypt. While in UAE, financial-based agreements are most commonly used. In KSA, early access programs are often used for rare diseases and outcome-based agreements are conducted for a small number of patients where a patient registry is formed, and physicians follow the patients while outcomes are collected by a third party.

Recommendations

Recommendations included increasing the use of MEAs and special access programs for orphan drugs in all countries. Since Egypt is a lower-middle income country, the use of outcome-based agreements to reduce the uncertainty in clinical evidence is recommended. Furthermore, combining outcome-based agreements with other agreements that mitigate the risk in the number of patients having the disease is suggested (Table 1).

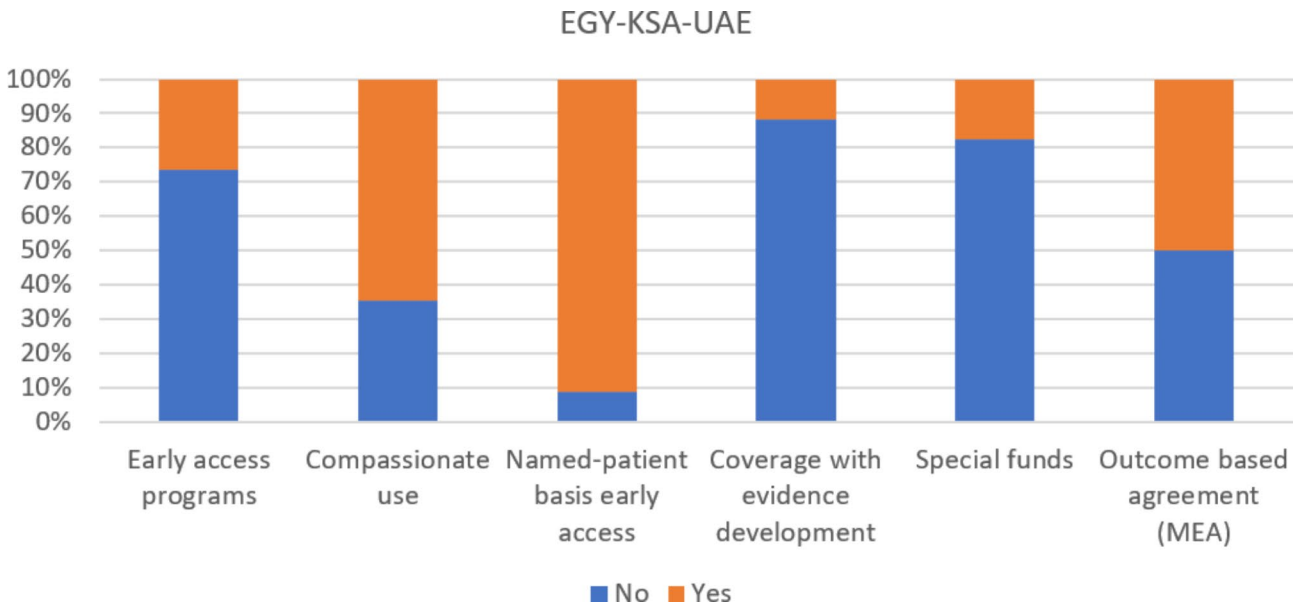

Fig. 3 Implemented Special Access Programs

Summary of recommendations for all domains (based on surveys and validation meetings)

A summary of proposed recommendations is summarized in Table 1.

Discussion

Despite advances in orphan drug development due to international public push and pull incentives, access to health technologies for rare diseases remains a significant challenge [1, 4]. To address this issue, several countries have implemented policies to mitigate the challenges accompanying rare diseases [3]. Countries created policies aimed at improving coordination of care and diagnostic resources allowing specialists to share information about rare diseases and create comprehensive care plans [47]. Additionally, the adoption of agile procedures for orphan drug registration and the creation of reference centers for rare diseases was one of the recommendations for better outcomes [63].

Some countries have used their strengths in science and research to advance the understanding and treatment of rare diseases. For instance, the UK launched Genome UK, while China initiated a national precision medicine program, both aimed at improving health outcomes for patients with rare diseases [64].

These examples illustrate the diverse approaches that different countries have taken to address issues related to rare diseases. However, there is no one-size-fits-all solution, and it is important to tailor policies and programs to the specific context and needs of each country. In our study, recommendations were aligned with some of the world's best practices such as establishing a definition for rare diseases, increasing awareness of rare diseases, and improving diagnostic centers.

This research represents an important step towards improving patient access to rare disease treatments. Establishing a national or regional registry for rare diseases with the coordination of regulatory bodies, health care payers or other public institutes can be pivotal in identifying underdiagnosed cases and facilitating comprehensive care. Such registries enable collaboration across borders, particularly in the Middle East, where shared resources like a centralized laboratory for genetic studies can significantly enhance diagnostic capabilities. The recommendations generated by this study can be translated into potential actions or policies to mitigate the challenges facing rare diseases and orphan drugs. Further steps could include developing strategies for implementing these recommendations at the national level and evaluating their effectiveness in improving patient outcomes.

Limitations

The survey results were obtained from a single perspective, that of pharmaceutical companies. However, meetings were conducted with governmental experts to validate the findings. Another limitation of the study was the small sample size. Despite the low number of responses per country (11 in Egypt, 9 in the UAE, and 14 in KSA), each response represented the consensus of market access leads within each company and not an individual respondent. Although not all companies were represented in the survey, the proportion of companies holding orphan drug marketing authorization that were included can be considered representative especially with

our aim being to collect the most common challenges and policies implemented in selected countries.

Conclusion

In conclusion, our research has highlighted the challenges facing patients with rare diseases in Egypt, KSA, and UAE. To address these challenges, policies need to be implemented to increase awareness of rare diseases and establish guidelines for their pricing and market authorization. Furthermore, rare diseases should be on the public health priorities list, with a focus on reducing the burden of these conditions on patients and society. By taking action to address the challenges facing patients with rare diseases in these countries, we can work towards a more equitable healthcare system that meets the needs of all patients.

Abbreviations

CET	Cost-Effectiveness Threshold
CTGA	Catalogue of Transmission Genetics In Arabs
EMA	European Medicine Agency
EPR	External Price Referencing
EU	European Union
FDA	Food and Drug Administration
HIO	Health Insurance Organization
HTA	Health Technology Assessment
ICD	International Classification of Diseases
KSA	The Kingdom of Saudi Arabia
MENA	Middle East and North Africa Region
MoH	Ministry of Health
ODA	Orphan Drug Act
UAE	United Arab Emirates

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12939-025-02388-4.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We are thankful to the respondents of the survey for their time and opinion.

Author contributions

ZK, AF, SAl, and AA contributed to the study's conception. AF, SAb, AS, HAb, Hal, MJ, MG, and SF contributed to the study's design. Acquisition of the data was performed by AF. Data analyses and interpretation were performed by AF and NK. The first draft of the manuscript was written by NK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

The work is published with the support of PhRMA Middle East.

Data availability

The data supporting the findings of the study are available within the paper and its Supplementary Information files. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request.

Declarations

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Syreon Middle East was a contractual partner of PhRMA Middle East. AF and SA are shareholders in Syreon Middle East. NK is an employee in Syreon Middle East. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.Funding: The work is published with the support of PhRMA Middle East.

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Received: 23 May 2024 / Accepted: 10 January 2025
Published online: 26 February 2025

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