Advancing rare disease policy in Latin America: a call to action

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Summary

People living with a rare disease are amongst the most vulnerable groups in society. They have been historically marginalised and systematically stigmatised. It is estimated that 300 million people worldwide live with a rare disease. Despite that, many countries today, especially in Latin America, still lack consideration of rare diseases in public policies and national laws. Based on interviews with patient advocacy groups in Latin America, we aim to provide recommendations for lawmakers and policymakers in Brazil, Peru, and Colombia on how to improve public policies and national legislation for persons living with rare diseases in these three countries.

Keywords: Rare diseases; Orphan drugs; Right-to-Health; Health policy; Public policy

Introduction

On 16 December 2021, the UN adopted the first-ever UN Resolution on "Addressing the Challenges of Persons Living with a Rare Disease and their Families." This milestone is the outcome of coordinated and robust advocacy from global rare disease civil society groups led by Rare Diseases International (RDI), the NGO Committee for Rare Diseases, and EURORDIS – Rare Diseases Europe. The text was proposed by three UN Member States – Spain, Brazil, and Qatar – and was co-sponsored by 54 countries. It was adopted unanimously by all 193 UN Member States. This is the first ever UN text to give full visibility to the over 300 million persons living with a rare disease worldwide.[1] It encourages countries to promote public policies, patient-centred programs, and initiatives that would strengthen health systems and calls for action to address the specific challenges faced by individuals living with rare diseases and their families.[1] Therefore, this article aims to advise lawmakers and policy makers in Latin America on the creation of new laws and policies for the rare disease community.

Definition of rare diseases

Up until May 2022, there was no internationally recognized definition of rare diseases. After the adoption of the UN Resolution on People Living with rare diseases, RDI held a side-event at the World Health Assembly (WHA) in Geneva, where they proposed a universal description of rare diseases. According to its core definition, "a rare disease is a medical condition with a specific pattern of signs, symptoms, and clinical findings affecting less than or equal to 1 in 2000 people living in any WHO region."[2]

However, despite the support to establish an internationally recognized RD definition, each country has still adopted its own. In the Latin American region, there is a wide range of classifications. For example, in Brazil, a disease is considered rare when it affects 65 or fewer inhabitants per 100,000. In Colombia, the range is 2 per 10,000 individuals. Other countries such as Argentina, Chile, Mexico, Panama and Uruguay consider a disease to be rare when it affects 5 in 10,000 individuals.

Table 1 shows the difference between rare disease definitions around the world.

Not having a universal definition negatively impacts the lives of people with rare diseases. It disrupts clinical trial operations, governmental funding, international partnerships for research and development, and market access. Standardising rare disease definitions is and must remain the main priority for rare disease advocacy groups in Latin America.

Overview

Brazil

Until the early 1980s, there were almost no initiatives in Brazil that considered rare diseases a public health issue. In light of that, patient advocacy organisations and social movements pressured the national government toward the formulation of public policies and national legislation that would protect the rights of the rare disease community.[3] In 2014, the Ministry of Health established Ordinance No. 199, which included two landmark provisions: 1) National Policy for Comprehensive Care for People with Rare Diseases; 2) Guidelines for Comprehensive Care for People with Rare Diseases within the scope of the Public Health System

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Country	WHO Region	Definition of rare diseases (prevalence)	Definition of rare diseases (fixed no.)	Persons per 10,000
Argentina	AMR	5/10,000	–	5
Brazil	AMR	65/100,000	–	6.5
Peru	AMR	1/100,000	–	0.1
Chile	AMR	5/10,000	–	5
Colombia	AMR	2/10,000	–	2
Ecuador	AMR	1/10,000	–	1
Mexico	AMR	5/10,000	–	5
Panama	AMR	5/10,000	–	5
European Union (EU)	EUR	5/10,000	–	5
United States of America	AMR	–	200,000	5.9

The table shows the difference in "Rare Diseases" definitions in Latin America, the European Union, and the United States. It highlights the importance of effectively implementing the universal description of rare diseases, proposed by Rare Diseases International (RDI) in May 2022, at the World Health Assembly (WHA).

Table 1: **Definition of rare diseases in various countries.**

(SUS).[4] Although a step forward, implementing the Ordinance is lacking. This is due to two main factors: 1) lack of appropriate funding; 2) lack of normative enforcement, given that ordinances from the Ministry of Health do not have legal status.[5]

To increase funding and awareness of rare disease advocacy, the Chamber of Deputies established the Parliamentary Front to Combat Rare Diseases. Once the Front gained recognition in 2019, two new governmental programs were created. The Federal Senate installed a sub-commission dedicated to rare diseases, and the Ministry of Women, Family, and Human Rights created the General Coordination of Persons living with Rare Diseases.[6] In 2020, this same Ministry established the Inter-ministerial Committee on Rare Diseases, which aims to act in the development of policies for the rare disease community.[7] Although these committees exist, there are still few public policies and laws for people living with a rare disease in Brazil.

In addition, the existing policies have shown numerous flaws and inconsistencies. For example, Ordinance 2305/2001 establishes guidelines for medical assistance to people living with *osteogenesis imperfecta*-a rare disorder also known as brittle bone disease. Its implementation has been widely criticized by public health experts because it does not grant patient-centred therapeutic decisions.[8]

In Brazil, the main Rare Disease patient advocacy organization is called *Casa Hunter*. Besides helping to enact laws and public policies for the Brazilian Rare Disease community, the non-profit also has several projects, such as the House of the Rare (in Portuguese, *Casa dos Raros*): the first-ever healthcare institution in Latin America entirely focused on providing comprehensive care, research and training in Rare Diseases. Casa Hunter also provides financial aid to low-income people living with rare diseases; offers psychological assistance to rare disease patients, and their relatives, who do not have financial conditions; provides the means for rare disease patients to be consulted by a medical specialist, and helps them to access the necessary diagnosis and treatment.

Peru

The first national law in Peru concerning persons living with a rare disease was only developed in 2011 (Law 29.698).[9] This law declares national interest and preferential attention to the treatment of persons living with a rare disease. One of the main demands of the Peruvian Federation of Rare Diseases (FEPER) is to transform this legislation into a framed law.

Another initiative developed by the Peruvian government is the *Fondo Intangible Solidario de Salud* (FISSAL).[10] FISSAL is a special fund that aims to assist individuals who cannot afford their high-cost treatments. It covers diseases like cancer, chronic kidney failure, and rare diseases. Rare diseases were only included in FISSAL in 2021, after persistent advocacy from FEPER. Despite that, many patient advocacy groups urge FISSAL to increase both its budget for rare diseases and monetary coverage of treatments and orphan drugs.

A promising landmark in Peru is the 2021–2024 National Plan for Rare Diseases. It aims to establish strategies to improve the quality of life of the rare disease community.[11] The National Plan for Rare Diseases implements an epidemiological and management information system, promotes education and training of health professionals in rare diseases and fosters the development of research on rare diseases. It seeks to improve patients' access to comprehensive care, with safe and quality care per lifetime. The National Plan also encourages the participation of the rare disease community in the articulation of actions to be developed on a national level.[9]

Colombia

In 2010, Colombia established the first national legislation in Latin America targeted for the rare disease community: Law 1392. This legislation provides guidelines to increase access to orphan drugs.[12] Colombia's law is a social protection measure that considers rare disease patients as a protected class. Although some cities in Colombia, like Bogotá, have used Law 1392 as a model for local policy, it has not been effectively implemented across the country.[13]

Six Decrees were added to Law 1392 to streamline the process of regulating the identification and registration of rare diseases in the nationwide registry program.[14] Decree 1954, established in 2013, was created to consolidate the information in the national registration of rare disease patients. The Department of Municipal Health and Health Promotion Entities, two governmental departments in Colombia, were able to gradually accomplish the consolidation.

The creation of a centralised bargaining system is another initiative established by Law 1932. It reduces costs and increases transparency in the purchasing process of orphan drugs. However, it has not been implemented.[14] The main issue with rare disease advocacy in the country is not the scarcity of laws and policies for the rare disease community, but their ineffective implementation. For instance, Colombia has one of the most well-developed Patient Registry Programs in the region, however it is often outdated. This problem can lead to a variety of negative consequences, such as misallocation of the public health budget.

Colombia also has a considerable patient advocacy network. The Federación Colombiana de Enfermedades Raras (FECOER) has worked for the inclusion, integration, and attention of more than one million people with rare diseases living in Colombia.[15] For example, in 2019, FECOER launched a book called "*Enfermedades Raras: Del Diagnóstico a Las Políticas Públicas,*" which spreads awareness around rare diseases in the country.[15] FECOER also engages in advocacy. They helped to draft the *Plan Decenal de Salud Pública* 2012–2021, which aims to promote health equity for the rare disease community.[15]

Barriers to healthcare

Lack of access to diagnosis

Prior to the pandemic, roughly 40% of European, rare disease patients lacked a specific, medical diagnosis.[16] In Latin America, a staggering 75% of rare disease patients remained undiagnosed.[16] This difference is due to many factors, which includes: lack of research, shortage of patient registration, scarcity of new-born screening tests and few effective public policies for rare diseases in Latin America. Moreover, developed countries have national departments to address the needs of rare disease individuals. In contrast, mainly civil associations, federations, and patient groups assist people with rare diseases in Latin America. Adding to the health disparity, the COVID-19 pandemic caused the number of rare disease patients without a confirmed diagnosis to increase significantly.[15]

Taking Peru as a case study, FEPER received large amounts of mail from undiagnosed people asking for help to identify their disease. FEPER diverted them to international groups of rare disease patients because there was no established state department in Peru charged with diagnosis assistance. FEPER was asked to help because of their active status as an advocate for people with rare diseases. Since 2011, FEPER has helped hundreds of people obtain their diagnoses abroad. In 2017, FEPER and Peruvian Associations of Rare Diseases coordinated an operation in partnership with international governments, airline companies, geneticist physicians, and a Peruvian university. They sent blood samples to France and Chile to find accurate diagnoses for rare disease patients in Peru. This process took over a year, but they were able to obtain hundreds of diagnoses.[17]

Among those diagnoses, 120 were *Trimethylaminuria* (TMAU), a rare disorder with high prevalence in women.[18] Due to the diseases' metabolic effects, the bodies of individuals with TMAU emit an intense and unpleasant fishy odour.[19] Many TMAU patients are presumed to have poor hygiene, causing social isolation, depression, rejection and high suicide rates.[18] In some cases, gender bias leads doctors to assume TMAU's symptoms are "imaginary." Many women are wrongly prescribed antidepressants or antipsychotics. These incorrect prescriptions are socially harmful and may even lead to fatal outcomes.[18]

FEPER also carried out public health awareness campaigns to increase and improve the diagnosis of rare diseases. These events happened in communities far from the capital, where health disparities are larger. Through FEPER's campaigns, a variety of health professionals engaged with thousands of people seeking a diagnosis.[17] In each event, more than 3000 people showed up.[17] However, due to the pandemic, these campaigns have been suspended.

Diagnostic odyssey

Diagnostic odyssey is defined as "the time between when a symptom or feature of a genetic or rare disease is noted to the time when a final diagnosis is made."[20] The last section discussed the difficulties of being diagnosed in Latin America. However, there are many obstacles' persons living with rare diseases face even if they can be diagnosed by a doctor. Many patients are diagnosed incorrectly. The diagnostic odyssey is exacerbated by lack of funding from governments or medical providers towards medical technology and genetic counselling. Many physicians are not equipped with the tools to properly diagnose patients, and genetic testing or counselling is not accessible.

Maria Isabel Acevedo, a Colombian mother of two children with spinal muscular atrophy type 2 (*SMA2*), struggled to get her children diagnosed.[21] In the early 2000s, Maria gave birth to her first daughter. After a few months, she started showing symptoms of *SMA2*. Unfortunately, Colombia didn't have genetic counselling or testing available. Maria thus had to travel to the United States to get her daughter tested.[21] When Maria's second child was developing symptoms of spinal muscular atrophy, her doctors refused to believe her.[21] Spinal muscular atrophy is caused by autosomal recessive inheritance of the gene *SMN1*, meaning both parents have to carry the gene. Since Maria's children have different fathers, geneticists thought it was impossible that both her children inherited the same rare disease.[21] It took over a decade for the genetic tests to be confirmed.[21]

Lack of interest and transparency by pharmaceutical industries

Drugs targeted to treat rare diseases, also known as orphan drugs, are placed in a limited market. Therefore, the vast majority of them present an extremely high price. A study conducted in 2020 reveals that orphan drugs are on average 25 times more expensive than non-orphan drugs.[22] Nowadays, 88% of orphan drugs cost more than $10,000.00 per year, per capita.[22]

Due to the lack of incentives for the production and commercialization of orphan drugs in Latin America, several pharmaceutical industries do not have an interest in filing a patent request in these countries. A compelling illustration of this scenario is the Trikafta case (*2020*).[23] Trikafta is a promising orphan drug that can significantly improve the quality of life of those living with Cystic Fibrosis.[24] It is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[25,26] However, the American biopharmaceutical company that produces Trikafta, Vertex Pharmaceuticals, was not interested in requesting the registration of Trikafta in the Brazilian regulatory agency (ANVISA). Therefore, patient advocacy organizations of people living with Cystic Fibrosis, such as *Instituto Unidos Pela Vida* (United for Life Institute), decided to write an online petition to pressure the pharmaceutical company to file a registration request of Trikafta in ANVISA. The campaign was known as *#RegistraVertex* (#RegisterVertex).[27] It had more than 163 thousand signatures.[27] Due to the petition, Vertex announced that it would request the registration of Trikafta in the first quarter of 2021.[28] The application was submitted to ANVISA on March 26, 2021.[28] Trikafta was approved by ANVISA on March 2, 2022.[29]

Another barrier to the registration and incorporation of new treatments for rare diseases into Latin American health systems is that payers tend to be more interested in funding randomized controlled experiments, and the classical randomized controlled trial (RCT) cannot always be conducted in rare disease research due to small numbers of eligible patients and the heterogeneity of the patient groups. Therefore, developing efficient trial designs relevant to small populations, as well as promoting international collaboration, is necessary to advance rare diseases research worldwide.[30]

Right-to-health litigation

The right-to-health litigation, also known as judicialization of health, is characterised by legal actions that demand access to high-cost medical treatments and drugs. It mainly occurs when the government refuses to bear the costs of a certain drug or treatment, and the plaintiff claims its constitutional right-to-health, mandating the government to subsidize the high-cost medical care needed. This phenomenon has significantly increased in Latin America over the past years.[31]

According to Octavio Luiz Motta Ferraz, the most challenging type of judicialization of health in Brazil occurs when a rare disease patient requests an intervention not provided by the public health system but is safe and effective according to the regulatory authorities yet is extremely expensive and has no cheaper therapeutic alternative.[32]

Colombia has had similar complications with the judicialization of health. With the enactment of Law 1751, Colombia has recognised the right-to-health for its citizens. It has allowed Colombians to file lawsuits (*tutelas*) against the government, upholding their right to request access to drugs and treatments.[32] In many right-to-health litigation cases, the government has used the argument that "not providing access to treatments wouldn't worsen the condition of the disease holder."[32] This is a very weak argument and rarely accepted in court. Another strategy the government uses to avoid providing treatments to litigants is assigning them to doctors extremely far from their hometown. Since transportation is unaffordable, many patients cannot reach their doctor and continue to lack access to diagnosis and treatments.[32]

Medical tourism and migration

The vast majority of those who can obtain diagnosis and access to treatments are in the middle and upper classes. These individuals can afford medical tourism to a developed country. Anel Townsend, former Minister of Women's Affairs and Social Development in Peru and mother of a boy with Duchenne's Muscular Dystrophy, stated, "I consulted five doctors in Peru until I reached the preliminary diagnosis of muscular dystrophy. Since one of my sisters lived in Washington DC, I had the necessary financial resources to travel and pay for the medical appointment and biopsy my son needed at Johns Hopkins Hospital. I was lucky to start an early battle against his disease and resort to palliative treatments" (translated from Spanish).[17] If her son did not travel, he would have had to undergo surgery in Peru. The surgeon would take a sample of his muscle tissue,

send it to Germany or the United States, and wait several months for the results. On the other hand, if Anel couldn't afford it, she would have to wait for six years, or more, to obtain the diagnosis in Peru.

Eduarda, a Brazilian teenager living with Cystic Fibrosis, is another medical tourist. Eduarda studied law in Brazil, as she dreamed of becoming a lawyer. However, Cystic Fibrosis made it almost impossible to continue her academic journey. The one drug that could significantly improve her quality of life, Trikafta, is still not available in Brazil. Therefore, Eduarda had to leave her family, friends, and studies in Brazil to access Trikafta in the United States. Besides the burden of living in a new country, Trikafta costs more than $300,000.00 annually. Fortunately, Eduarda can access Trikafta through the University of Miami Cystic Fibrosis Center, but she is one of the only Brazilians with Cystic Fibrosis who have had this chance.[33]

Less than 3% of the Latin American population can afford to travel for medical treatment.[34] Medical tourism is not a viable option for most people who need accessible and affordable medical attention. There needs to be reform within Latin America to improve its treatment and care of people with rare diseases.

Recommendations

People living with rare diseases are entitled to their right to health and to life. These are two fundamental human rights. There should not be a debate over whether it is cost-effective to make a person's life better, nor should proper care be inaccessible. To promote accessible healthcare for the rare disease community, we propose the following public policies in order of greatest importance:

Recommendations for Latin America

Standardise the definition of rare diseases

Not having a unified definition for rare diseases in Latin America is harmful for the rare disease community. A standardisation would remove discrepancies for partnerships in research and development, funding opportunities, and market access.

Promote regional research partnerships for scientific and clinical collaboration

Latin American countries should work together to facilitate clinical research and improve access to orphan drugs. For example, the government could provide a waiver on a customs tariff for the importation of orphan drugs. Governments could also promote tax exemptions to pharmaceutical companies that price their orphan drugs below a certain range. Other effective incentives to produce orphan drugs are providing regulatory fee waivers, 50% tax credit in clinical expenditure, grants for clinical research, and seven-year market exclusivity. It is vital to promote rare disease research because it may improve scientists' understanding of all diseases in the future.

Develop a regional rare disease registry program

It is essential to develop a regional rare disease registry program for both diagnosed and undiagnosed rare disease patients to identify the exact number of rare disease patients in the region, their socio-economic and demographic profiles, and other relevant information. This program should be inspired by efficient models of Rare Diseases Registry Programs around the world, such as those adopted in the United States and Italy. It would help to inform and shape medical research, support evidence-based public health policies, as well as advance product development.

Recommendations for Brazil

Expand prenatal screening, diagnostic exams, and genetic tests for rare disease diagnoses into the Brazilian Public Health System (SUS)

It is essential to guarantee affordable and universal access to early diagnosis, through the expansion of prenatal screening, diagnostic exams, and genetic tests for rare disease diagnoses. Usually, it takes about five to seven years to diagnose a rare disease.[35] During this time, individuals undergo innocuous treatments and ineffective medical-hospital visits. This not only damages the patients' physical and mental health, but also generates significant expenses for the health system. Thus, the expansion of prenatal diagnostic tests and the encouragement of DNA sequencing and genetic mapping research are fundamental measures to avoid the diagnostic odyssey.

Establish an Office of Rare Diseases within the Ministry of Health

Creating an Office of Rare Diseases within the Brazilian Ministry of Health is extremely important because it would acknowledge the specific challenges associated with rare diseases and orphan drugs. The Office would develop strategic action plans to address these issues and effectively guarantee the right to health for the rare disease community.

Develop a new Health Technology Assessment (HTA) process for the assessment of orphan drugs, within the National Commission for the incorporation of Technologies in the Unified Health System (Conitec)

The current cost effectiveness threshold for the assessment of rare disease therapies in Brazil (3 X PIB per capita/QALY) is extremely prejudicial for the incorporation of orphan drugs. Cost-effectiveness should not be a metric to assess health technologies for rare diseases, and QALY cannot be used as the only measure of health outcomes for rare disease patients. Multi-Criteria Decision Analysis (MCDA) approaches targeted toward orphan drugs are needed to inform the determination of

value of rare disease therapies and identify benefits not captured in the QALY.

Recommendations for Colombia

*Improve the effective implementation of the Colombian Newborn Screening Law (*Ley de tamizaje neonatal*)*

Expanding and improving the newborn screening program is crucial because it allows medical professionals to immediately identify at-risk babies and provide the proper treatment plans. Providing newborn screening and genetic testing at birth also leads - in the medium and long term - to an economy in Colombia's public health budget because it avoids the diagnostic odyssey, misdiagnosis, and missed diagnosis; prevents the need for complex interventions, and the use of high-cost treatments.

Provide workshops and educational courses about rare diseases to medical professionals—especially those working in primary care—and to medical students

Teaching about rare diseases in hospitals and medical universities is essential. It increases awareness on rare diseases and educates health workers on the protocols and guidelines to care for both diagnosed and undiagnosed rare disease patients.

Update the Colombian National Patient Registry Program

There is a need to update and improve the Colombian National Patient Registry Program. The use of outdated data can lead to a variety of negative consequences, such as misallocation of the public health budget and, therefore, an increase in the right-to-health litigation in the country. A real-time updated registry program creates a better system with more reliable data.

Recommendations for Peru

Adoption of agile and unbureaucratic procedures in the registration of orphan drugs

People living with rare diseases can die waiting for orphan drugs to be registered through the current slow and bureaucratic registration process in Peru. Adopting equally safe, but more agile procedures, can potentially save many lives.

Creation of reference centres for rare diseases

Specialized centres would aim to provide integral and holistic medical assistance to rare disease patients, especially those who are low-income. These centres would serve as a communal area for research, extension, and education in rare diseases.

Provide a special pension to low-income mothers whose children live with a chronic and/or rare disease

It is common for mothers to fully dedicate themselves to the feeding, hygiene, and transportation of their child with a rare disease. Because of this commitment, mothers (or guardians) are unable to engage in paid work. Mothers should have the ability to apply for a special pension and maintain decent living conditions for her and her child.

Conclusion

This paper summarises public policies and national laws related to rare diseases in three Latin American countries: Brazil, Colombia, and Peru. Based on interviews with patient advocacy organizations, we propose recommendations to policy makers and lawmakers that aim to improve access to diagnosis, drugs and treatments for people living with a rare disease. The right to health is a fundamental human right, and the rare diseases community cannot be left behind. The time to act is now.

Contributors

The co-authors, DW and AK, have made equal contributions to the manuscript. Each author helped with ideation, literature search, study design, interview process, writing, analysis, editing, and approval of the manuscript.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

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