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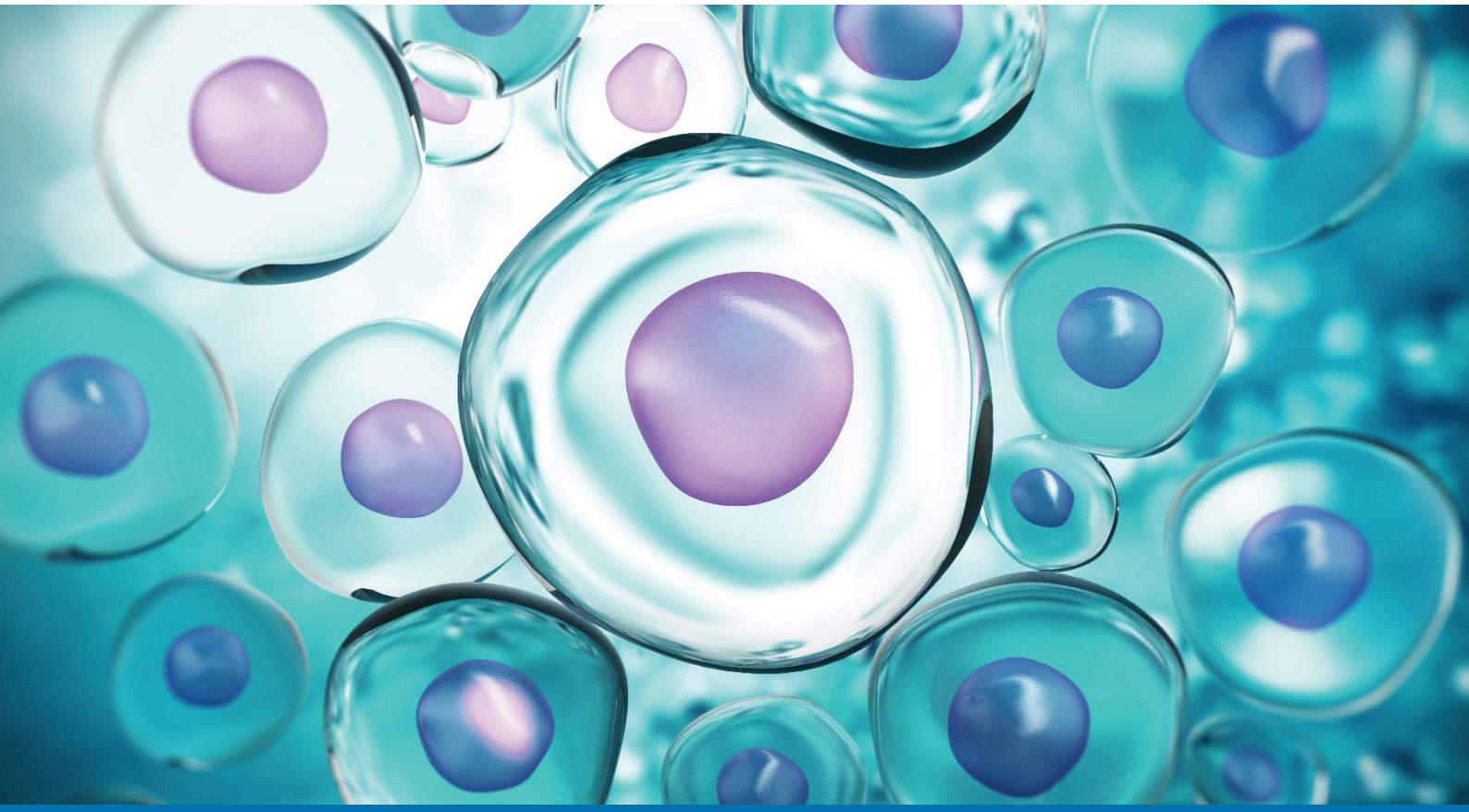

The socioeconomic impact of rare diseases: An analysis of the evidence in middle-income countries

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Executive Summary

Worldwide, it is estimated that over 300 million persons are living with one or more of the 6,000 to 8,000 identified rare conditions. While progress has been made in the last decade to improve the health and quality of life of persons living with a rare disease (PLWRD), many PLWRD remain undiagnosed, receiving no treatments or care. The purpose of this research is to describe the socioeconomic impact of different rare diseases on PLWRDs and their families and on society across different countries, with a focus on lower-middle- and upper-middle-income countries (defined collectively as middle-income countries (MICs)) relative to high-income countries (HICs).

The assessment of socioeconomic impact of disease can play a significant role in policymakers' allocations of healthcare resources. Ideally, decisions should be based on a multitude of impacts to the family, including direct medical and non-medical costs, indirect costs, and social and psychological impacts, as well as direct costs (of treatment) and indirect costs to society. A preliminary literature review found few studies on the social and economic impacts of rare disease (RD) for families in middle-income countries (MICs) and even fewer in low-income countries (LICs). Moreover, even the data on societal cost for RD treatment in MICs were limited and of uneven quality. Using a case study approach, this study examines the potential influence of country income level, disease, standard of care, cost of treatment, and health system financing on access to treatment and socioeconomic impact in selected MICs.

To this end, this study sets out a research framework to address the following questions:

- Are there significant differences in the prevalence of different rare diseases across countries? Does this have implications for societal impact?
- Are there differences in access to care and in healthcare provision, and what are the implications for magnitude and composition of socioeconomic impact? Does this affect the impact on people's working lives, on caregivers, and on society more broadly?
- Does the composition of the socioeconomic impact affect rare diseases policy?
- What are the policy recommendations to improve the current level of understanding of the socioeconomic impact of rare diseases in MICs?

Study scope and approach

The impact of rare diseases is poorly understood due to the lack of data in LICs and MICs. This makes it difficult to perform analyses similar to those conducted in HICs. To deal with this limitation, it was necessary to adopt a case-study approach, analyzing the evidence across a set of rare diseases and MICs where more information is available. Therefore, the findings from this analysis should be regarded as the first step in fully characterizing the socioeconomic impact of rare diseases in MICs, and their generalization should be considered carefully and subject to further investigation.

Specifically, this study focuses on estimating the socioeconomic impact of six rare diseases—Gaucher disease (GD), mucopolysaccharidosis II (MPS II), hemophilia, idiopathic pulmonary fibrosis

(IPF), multiple myeloma (MM), and myasthenia gravis (MG)—representing different categories of disease (metabolic, hematologic, pulmonary, oncology, and inflammatory/neurologic). These diseases also differ in terms of prevalence, age of onset, complexity of diagnosis, and the degree to which effective treatments exist.

Evidence on the scale of the socioeconomic impact was collected in 12 countries with different income levels, levels of investment in the healthcare system, and prioritization of rare diseases (Executive summary table 1). This list includes two HICs as a reference point but focuses on MICs.

Executive summary table 1: Countries included in the study

Lower-middle-income countries (LMICs): Egypt, Ghana, Kenya

Upper-middle-income countries (UMICs): Brazil, Chile,[i] China, Colombia, Malaysia, South Africa, Thailand

High-income countries (HICs): Australia and Taiwan (included in the analysis to provide perspectives from more established economies)

A literature review was conducted and public databases were searched to collect evidence on direct costs (inpatient, outpatient, and medical costs) and indirect costs (levels of labor force participation, absenteeism and presenteeism, and early retirement for both PLWRD and their caregivers). These were used to estimate the total socioeconomic impact. To account for additional significant aspects of the burden of rare diseases, available evidence on quality of life, cost of transportation, and cost in terms of reduced life expectancy also are presented. The analysis of the evidence across the rare diseases and countries studied leads to five key findings, listed below. Given these results are based on a limited number of case studies and a relatively small number of data points, we need to be cautious about generalizing from these findings, but they should form working hypotheses for future study.

Finding 1: Existing information on the socioeconomic impact of rare diseases is limited, particularly in MICs

Despite careful selection of therapy areas and countries to be included in the analysis, the amount of available data is still limited. This affects the ability to produce accurate estimates of the impact of rare diseases. Data are least available in LMICs, and, although availability is greater in UMICs, it is still weaker than in HICs.

- **Prevalence:** It was possible to identify evidence of prevalence for all the countries included in the study, but there was variation in the number of diseases covered. Data availability ranged from all six diseases in China, Colombia, and Taiwan, to only three diseases in Ghana.
- **Direct costs:** The evidence on medical costs is also sparse, and the quality of data varies across countries. MM and hemophilia are the diseases with the best data quality and availability. Hence, this analysis of direct costs is focused on these diseases.

i Although in 2013 the World Bank categorized Chile as a high-income country, it still exhibits some elements of an upper-middle-income country in its healthcare system—thus, it was not used as a high-income comparator country.

- **Indirect costs:** Quantifying all the indirect cost elements is difficult and many studies in HICs exclude them. The best data available are for hemophilia, MM, and MPS II.

Finding 2: The prevalence of rare diseases is underestimated in MICs

The first element examined in most studies of the socioeconomic impact of a disease is the number of persons affected. This statistic is commonly measured in terms of the prevalence of the disease. It is clear in every disease examined in this study that the prevalence reported in MICs is substantially lower than that reported in HICs. There is a large variation in reported prevalence across the diseases, with the largest variation in GD (from 0.02 to 1.26 per 100,000 persons in South Africa and Taiwan, respectively) and MM (from 0.76 to 28.11 per 100,000 persons in Ghana and Australia, respectively). If the observed prevalence rates from the two HIC comparators—Australia and Taiwan—were applied to the MICs in the study, this would equate to over 30 million unreported PLWRD across all six diseases (or approximately 50% of all those affected).

In MICs, the prevalence rates are likely to under-report the number of patients because of the following:

- **Insufficient awareness of rare diseases and limited ways to report them:** In some MICs the prevalence figures for some diseases are based on hospitalization records, only capturing the most severe cases of rare diseases in a population (for example, China and Thailand for MG). In countries where the public and healthcare providers (HCPs) have more awareness of rare diseases, reported prevalence is greater, likely because people seek medical care and are diagnosed.
- **Insufficient diagnostic testing:** Prevalence figures are reported based on people who have been diagnosed. A confirmed diagnosis by a specialist may be required for people to enter the treatment pathway and be included in registries and public databases. Although there are challenges to providing a correct diagnosis in HICs, the problem is exacerbated in MICs where patients face difficulties accessing a specialist for diagnosis. For instance, some of the diseases studied (GD and MPS II) can be diagnosed through Newborn Screening (NBS). However, its use is more limited in MICs, even where NBS programs have been implemented in some regions of the country or for other rare diseases for a significant period of time.

Underreporting of prevalence masks the impact of rare diseases on unidentified RD populations in MICs (where the impact could be greater than in HICs).

Finding 3: The estimated impact of rare diseases is significant across all countries, regardless of their income level

This study estimated the socioeconomic impact associated with direct and indirect costs for persons diagnosed with a rare disease. There is considerable variation in the quality of the data, but, after allowing for inflation and exchange rates, it is possible to make some comparisons across diseases and countries. Unsurprisingly, the nominal total impact per person diagnosed is much higher in HICs. For instance, the total estimated annual impact for a diagnosed patient with hemophilia is approximately 10 times higher in Australia (USD 91,400) than in Thailand (USD 9,700).

However, when this impact is considered in terms of a measure of average income, a different picture emerges. The total impact of hemophilia is approximately 1.8 times the average income in Australia and 1.4 times the average income in Thailand. On this measure, the impact is of the same order of magnitude. Similarly, while the total estimated impact per person living with MM in Australia is about twice that in China—USD 44,500 as compared to USD 19,200, respectively—this cost represents 0.9 times the average income in Australia but double that or 1.8 times the average income in China.

There is considerable variation across countries and diseases, but across the six diseases in our study, the ratio of the total impact to average income is similar across MICs and HICs.

These results need to be considered carefully. Clearly, the number of persons (as a proportion of the population) diagnosed with a rare disease is much lower in MICs than in HICs, but where impacts can be observed, the per-person impacts are of the same magnitude in MICs as in HICs, once normalized by income.

Finding 4: There are differences in the composition of direct and indirect costs across diseases and countries, which are driven by access to care for rare diseases

To understand the factors driving the composition of the socioeconomic impact of rare diseases, this study considered the care pathway, clinical guidelines, and access to treatment. Across diseases and countries, there is variation in the availability of and adherence to clinical guidelines as well as in the standard of care (SoC) available and received:

- **Limited access to specialists:** In many MICs, access to specialists is limited by low total availability of specialists and by regional and rural disparities. After an initial diagnosis, there can be long wait times to see a specialist. For instance, for MM, patients wait an average of six months to see a hematologist in the Brazilian public sector, while only 13% of patients in Australia wait more than two months. This aligns with general data on per capita specialist availability, which is six times higher in HICs compared with MICs in this study.[ii]
- **Lack of harmonized clinical guidelines:** There are significant differences across the set of countries regarding the existence of clinical guidelines and the SoC received. Even when clinical guidelines are available, access to the best treatment options remains limited in practice. Many MICs rely on older, generic treatments instead of newer, targeted therapies. For example, Brazil, China, Colombia, and South Africa rely on older therapies for treating the majority of persons with MM, even though all the countries except for South Africa have developed clinical guidelines. However, country-specific guidelines can positively impact treatment access, particularly if they account for healthcare system characteristics and constraints. For example, the country-specific guidelines for MPS II in South Africa were instrumental in ensuring that enzyme replacement therapy (ERT) was made available for the majority of the population.
- **Inconsistent access to treatment and SoC:** The SoC accessible to patients varies significantly across countries, with some providing the most up-to-date treatments while others rely on older, less effective alternatives. For example, persons with hemophilia across nearly all the countries reviewed have limited access to treatment with the optimal SoC, extended half-life (EHL) factor replacement therapy in prophylaxis. Taiwan, Brazil, and Colombia typically provide prophylactic treatment but with standard half-life clotting factor concentrates (SHL CFCs). Cryoprecipitate and fresh frozen plasma (FFP) treatments are more commonly used in China and Thailand and on-demand treatment with CFCs was found to be the dominant SoC in Egypt.

Where countries have invested in improving the provision of care, this appears to reduce the indirect impact associated to PLWRD and their caregivers. This is illustrated by hemophilia: in China, 34.8% of the total estimated impact is indirect (PLWRD and caregivers); in comparison, around 10% of the total impact is indirect in Colombia and Brazil, where more updated SoCs are provided. There are, of

ii Excluding China, Malaysia, and Taiwan, for which data were not available.

course, many other factors that affect this ratio, but this is consistent with the finding that indirect impact is higher for countries investing less in rare diseases.

There is also an association between access to treatment and the composition of direct medical costs. Comparing the data for MM in Latin America with the data in Australia, there are higher hospitalization costs and lower medicines costs due to reduced availability of effective treatments and poorer health outcomes in Latin America. For example, drug therapies for MM amount to an average of 67% of the medical costs in Australia, compared with only 54% in Brazil. As a result, 37% of medical costs in Brazil are attributed to hospitalizations and the remainder attributed to other outpatient costs.

Finding 5: The impact on patient and caregiver experience is challenging to quantify but remains critical

Some of the most important elements of the socioeconomic impact of rare diseases are those that fall on PLWRD, their families, and their caregivers, but these cannot easily be quantified and compared due to a lack of standardized data. They include:

- **Higher mortality rates:** There are considerable data to suggest that the level of investment in diagnosis, treatment, and management of diseases impacts life expectancy. A higher mortality rate, compared with the total population, is a key feature in rare diseases. Life expectancy is further reduced in MICs compared with HICs, likely due to lower investment in healthcare. For example, when hemophilia is well managed through adequate access to innovative therapies, mortality is low. However, in countries where access to innovative therapies is poor and only a sub-optimal SoC is available, the life expectancy of persons with hemophilia compared with the general population is notably reduced.
- **Poorer quality of life**: PLWRD and their caregivers are at higher risk of experiencing poor quality of life, including increased mental health issues and social isolation, as well as a negative impact on career. These consequences are exacerbated when the level of care is not aligned with international standards. For example, in Malaysia, persons living with more severe MG experienced reduced quality of life, and in South Africa, persons with the disease experienced higher levels of anxiety, tension, fatigue, and confusion compared with the general population. Depression and other mental health issues are more common in PLWRD, who often encounter social stigmatization and suffer from a wide range of comorbidities, including pain. This not only affects their ability to engage in productive work and their earning capacities but also means they face higher expenses for healthcare services, including assistance for daily living. Furthermore, caregivers face financial strains because they can dedicate less time to work and are not financially compensated for their caregiving responsibilities, an issue that is exacerbated in MICs.
- **More direct costs for PLWRD:** A separate and important consideration is the direct medical cost borne by PLWRD. In many MICs, where the public sector does not provide sufficient coverage of treatment and care for those who need it, people are more likely to face catastrophic out-of-pocket expenditures. Many PLWRD, particularly in rural areas, are burdened with additional travel time and costs to receive a timely diagnosis and treatment. Although our research shows this to be the case, it was not possible to systematically document these costs in the countries in scope.

While these components cannot be estimated, it is clear that the socioeconomic impact on PLWRD, their caregivers, and, ultimately, on society, is significant in MICs.

Conclusions

The socioeconomic impact of rare diseases in MICs is significant. This is often less visible due to the underreporting of prevalence, which can result from factors such as diagnostic challenges, a different composition of medical costs (with lower treatment costs but higher emergency and hospitalization costs), and higher costs imposed on PLWRD and caregivers by the impact on their ability to participate in employment. Five main themes apply to the countries and diseases investigated (Executive summary table 2).

Executive summary table 2: Cross-cutting themes

1. The data on the prevalence of rare diseases in many MICs reflect only some of the PLWRD. Therefore, improving the collection of data on prevalence is valuable to ensure that the complete socioeconomic impact is understood and that policies are planned accordingly.
2. Low diagnosis rates do not reduce the socioeconomic impact but only hide the costs. It is also important to underscore that screening and early diagnosis have important clinical benefits and can reduce the socioeconomic impact on PLWRD, caregivers, and societies, especially in diseases with a childhood onset. Investment in NBS programs and periodical reviews of the diseases included in testing improve the rates of accurate and timely diagnosis.
3. The magnitude of the socioeconomic impact of rare diseases per diagnosed person is similar across countries, once normalized by income level. For this reason, RD should be given the same priority across any economy, although the specific actions to address it will need to take into account national contexts.
4. Globally, the implications of poor access to RD care are complex. The evidence suggests that the cost associated with no diagnosis or misdiagnosis, the corresponding treatment delay, and the challenge of finding and traveling to a specialist are more pronounced in MICs, given the small number of specialist centers and geographical dispersion. Investing in the training of specialists and improving HCP awareness, including general healthcare practitioners for referral, is particularly important for rare diseases that are not screenable via NBS and/or manifest later in life. The establishment of national reference centers can expand access to diagnosis and treatment by providing support to associated centers.
5. Investment to ensure adherence with country-specific guidelines and investment into effective RD diagnostics and treatments is often seen as challenging, given budget restrictions. This study shows that investing in effective diagnostics and treatment can help reduce the impact on other parts of the healthcare system and on PLWRD and their caregivers. Moreover, this would have an invaluable benefit on the quality of life and life expectancy.

Developing more robust and granular data on rare diseases at the country level will be important to accurately capturing the number of people affected, the cost to PLWRD and their families, and wider socioeconomic costs. Further research to understand the composition of the socioeconomic impact could drive local policies and investments that improve health and well-being outcomes for PLWRD and their families, as well as use healthcare resources more effectively and improve the economic participation of the entire population.

Glossary

ASCT	Autologous Stem Cell Transplant
CFC	Clotting factor concentrates
CHE	Catastrophic health expenditure
CRA	Charles River Associates
EHL	Extended half-life
ERT	Enzyme replacement therapy
EURORDIS	European Organisation for Rare Diseases
FFP	Fresh frozen plasma
GD	Gaucher disease
GDP	Gross domestic product
GNRD	Global Network for Rare Diseases
hATTR	Hereditary transthyretin-mediated
HCP	Healthcare provider
HCPA	Hospital de Clínicas de Porto Alegre
HIC	High-income country
HQMS	Hospital Quality Monitoring System
HRCT	High-resolution computed tomography
HTA	Health technology assessment
ICU	Intensive care unit
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IPF	Idiopathic pulmonary fibrosis
LFP	Labor force participation
LMIC	Lower-middle-income country
MG	Myasthenia gravis
MGS	Medical Genetics Service
MIC	Middle-income-country
MM	Multiple myeloma
MPS	Mucopolysaccharidosis
MPS II	Mucopolysaccharidosis type II

NBS	Newborn screening
NORD	National Organization for Rare Disorders
PE	Plasmapheresis
PKU	Phenylketonuria
PLWRD	Persons living with a rare disease
RD	Rare disease
RDI	Rare Diseases International
SHL	Standard half-life
SMA	Spinal muscular atrophy
SoC	Standard of care
TPE	Therapeutic plasma exchange
UHC	Universal healthcare
UMIC	Upper-middle-income country
UN	United Nations
USD	United States Dollars
YLL	Years of Life Lost

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IFPMA, in collaboration with Rare Diseases International (RDI), engaged Charles River Associates (CRA) to investigate the broad socioeconomic impact of rare disease, drawing upon the evidence for a diverse set of conditions, with a focus on lower-middle and upper-middle-income countries. The data collection and analyses were conducted by the CRA team with regular feedback from IFPMA members and RDI representatives. Additional guidance was provided by Professor Steven Simoens (Professor of Health Economics at KU Leuven, Belgium).

1. Introduction

Worldwide, it is estimated that over 300 million persons are living with one or more of the 6,000 to 8,000 identified rare conditions, most of which are complex, chronic, degenerative, and often life-threatening.[1,2,3,iii] Collectively, this represents at least 4% of the worldwide population; however, only a small percentage of these persons receive adequate care.[4] Persons living with a rare disease (PLWRD) typically encounter what is referred to as a "diagnostic odyssey," facing significant diagnosis delays and/or misdiagnosis—on average for more than six years—before arriving at an accurate diagnosis.[5,6,7] Even after receiving a diagnosis, most patients will not receive treatment: only 6% of diagnosable rare diseases have a specific treatment, and many of these do not fully address the needs of PLWRD.[iv,8,9] Access to treatment remains a significant challenge for PLWRD, and this is exacerbated for those in low- and middle-income countries.[10] As a result, PLWRD and their families across the globe face extensive challenges, not only in managing their health but in experiencing social and economic inequalities with regard to social inclusion, financial stability, access to education, and employment.[11,12]

Although there have been many studies on the socioeconomic impact of rare diseases, the focus has generally been on high-income countries (HICs) (mostly the United States and European countries) or particular diseases. To date, there has not been a study that has reviewed the evidence of socioeconomic impact, focusing on countries with fewer resources and drawing conclusions across different types of rare diseases affecting persons living in these countries. To address this gap, his study considers the evidence (to the extent that it is available) on the wider socioeconomic impact of a set of rare diseases, to assess the impact on PLWRD, their caregivers, healthcare systems, and society as a whole in lower-middle and upper-middle-income countries (defined collectively as middle-income countries (MICs)). On the basis of the evidence, the study concludes with common themes that are associated to lessening the socioeconomic impact of rare diseases, especially in MICs, and recommendations for future evidence collection and analysis.

1.1 Context: The global debate on rare diseases

The calls for policymakers to address the challenges facing PLWRD intensified in the early 1980s with the recognition of poor diagnostic processes, limited access to specialists, few available treatment options, and a lack of understanding of the social and economic impacts. The National Organization for Rare Disorders (NORD), founded in the United States in 1983, was the first national non-profit organization to represent PLWRD and their families.[13] NORD was instrumental in the passing of a landmark bill in that same year, the Orphan Drug Act, which created financial incentives for the development of rare disease (RD) treatments in the US.[14] In Europe, the European Organisation for Rare Diseases (EURORDIS) was founded in 1997, playing a significant role in the adoption of the first European legislative text concerning rare diseases.[15,16] In subsequent years, international organizations including Rare Diseases International (RDI) have been highlighting the need for a

iii The estimate excludes rare cancers, infectious diseases, and poisonings. Rare diseases currently affect at any point in time 3.5%–5.9% of the worldwide population. See: Nguengang Wakap, S., Lambert, D. M., Olry, A., Rodwell, C., Gueydan, et al. (2020). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *European Journal of Human Genetics*, 28(2), 165–173.

iv As of 2020, 564 orphan drugs have been approved by the FDA to treat 838 rare diseases, and as of 2021, in the EU only 260 medicinal products are approved in rare disease indications. See, for example: Zanello, G., Chan, C. H., Pearce, D. A., & IRDiRC Working Group. (2022). Recommendations from the IRDiRC Working Group on methodologies to assess the impact of diagnoses and therapies on rare disease patients. *Orphanet Journal of Rare Diseases*, 17(1), 181.

global policy focus on rare diseases.[17,18] These efforts and commitment have led to a better understanding of the RD landscape.

At country and regional levels, a range of policy initiatives have been introduced, from the establishment of national plans that prioritize the diagnosis and treatment of rare diseases to streamlined regulatory pathways to encourage the development of orphan medicines.[19] Furthermore, the patient voice has been strengthened through global, regional, and national-level patient organizations working together to generate greater action and awareness for rare diseases.[20]

While there has been a relatively greater policy focus in high-income countries, particularly the US and European countries, progress to prioritize rare diseases has been made in MICs through locally adapted strategies and initiatives to engage the community and recognize the unmet need for rare diseases. The result of these efforts was the first ever UN Resolution on rare diseases adopted in 2021.[21] The Resolution placed a series of requests upon UN Member States and agencies to ensure PLWRD have "equal opportunities to achieve their optimal potential development and to fully, equally and meaningfully participate in society."[22] Given the opportunity to focus global policymakers on the specific needs of PLWRD across all countries, it is important that the scale and composition of the socioeconomic impact of rare diseases are understood in different healthcare settings.[23,24]

1.2 An overview of the global evidence on the socioeconomic impact of rare diseases

Most of the existing studies on the socioeconomic impact of rare diseases focus on higher-income settings, such as the US, where more robust sources, such as registries and patient medical claims data, are readily available.[25] For instance, recent analyses have shown that, in the US, the socioeconomic impact of rare diseases is approximately 10 times higher than that of non-rare diseases.[26] Furthermore, the socioeconomic impact of rare diseases without any treatment options available—the current state for most rare diseases—was estimated to be 21.2% higher than that of rare diseases for which treatment is available.[27] The economic impact of rare diseases in the US in 2019, including medical and indirect costs, was estimated to be USD 997 billion.[v] Hospital inpatient care and prescription medication were the key drivers for medical costs, while labor market productivity losses were the key drivers of indirect costs.[28] Other estimates have included mortality costs; when these are considered, the impact was estimated to be even higher: USD 2.2 trillion per year for 8.4 million people (compared with an estimated USD 3.4 trillion per year for 133 million patients with non-rare diseases in the US).[29] Studies estimating the cost of RD in Europe are in development.

Other studies have described a significant socioeconomic impact of rare diseases in specific countries or cities, or for a specific rare disease. Many of these focus on clinical aspects rather than economic data. For example, a study looking at the global burden of multiple myeloma (MM) found access to effective care to be limited in LICs and MICs, particularly in sub-Saharan Africa.[30] However, these studies do not report global estimates of the socioeconomic impact of rare diseases and, if they do consider the cost burden, tend to focus on medical costs, with indirect costs incorporated where the data are available to support such estimates.

[v] Includes USD 449 billion (45%) in direct medical costs, USD 437 billion (44%) in indirect costs, USD 73 billion in non-medical costs (7%), and USD 38 billion (4%) in healthcare costs not covered by insurance. See: Yang, G., Cintina, I., Pariser, A., Oehrlein, E., Sullivan, J., & Kennedy, A. (2022). The national economic burden of rare disease in the United States in 2019. *Orphanet Journal of Rare Diseases*, 17(1), 1–11.

Studies estimating the socioeconomic cost outside of the US and Europe are rare and focus on individual countries. A study from Hong Kong estimated total inpatient cost for the RD population, finding the cost to constitute 4.3% of total inpatient cost in the year of the study (2015/16).[31] In Shanghai, a study looked at a set of 23 rare diseases and estimated the mean direct medical cost to be USD 2.4 million per year across all RD inpatients and outpatients. Another study from Hong Kong—the first in the Asia Pacific region to assess both societal costs and financial hardship resulting from rare diseases—collected socioeconomic data through a survey approach validated specifically for rare genetic diseases. They found the total socioeconomic cost to be higher in the pediatric population than the adult population— due to the higher cost of health services and total direct healthcare costs as well as a higher cost of informal care support.[32] Other studies have also estimated or described specific elements of the socioeconomic impact, such as the fiscal impact of a specific disease,[vi] caregiver burden,[vii] or healthcare experiences and needs of PLWRD.[viii] The current picture is therefore highly fragmented in terms of both country coverage and the impacts assessed.

1.3 The value of studying the socioeconomic impact of rare diseases in middle-income countries

The value of studies that estimate the socioeconomic cost of disease is that they provide a comprehensive assessment of the impact of diseases on patients, caregivers, the healthcare system, and the economy.[33] These assessments can play a significant role in policymakers' allocations of healthcare resources, by creating awareness of existing gaps in healthcare provision and making the case for investing in preventing, treating, and managing the disease.[34]

Given the different structures of the healthcare system and healthcare provision, there is reason to believe that the scale of the socioeconomic impact and its composition in MICs is likely to be different to that in HICs, and, consequently, that policy planning needs to be tailored accordingly.[35] Drawing on the existing limited literature on the impact of rare diseases, specifically in MICs, we developed a set of high-level hypotheses around the core components of socioeconomic impacts established in the literature (Table 1).

vi For example, Connolly (2019) estimates the fiscal life course of an individual with hereditary transthyretin-mediated (hATTR) amyloidosis in the Netherlands, finding that lifetime taxes are reduced by €180,812 by the age of 45 and government transfers reach €111,695. Halting disease progression early would generate fiscal benefits in addition to the health benefits for the persons with hATTR. See: Connolly, M. P., Panda, S., Patris, J., & Hazenberg, B. P. C. (2019). Estimating the fiscal impact of rare diseases using a public economic framework: a case study applied to hereditary transthyretin-mediated (hATTR) amyloidosis. *Orphanet Journal of Rare Diseases*, 14(1), 220. https://doi.org/10.1186/s13023-019-1199-x

vii For example, Días et al. (2023) describe the indirect burden placed on caregivers of PLWRD in Latín America. They find that caregivers are primarily women, and they experience a physical, social, and economic burden in their caregiving roles including physical pain, social isolation, and substantial out-of-pocket expenses. See: Dias, A. G., Daher, A., Barrera Ortiz, L., Carreño-Moreno, S., Hafez H, S. R., Jansen, A. M., Rico-Restrepo, M., & Chaparro-Diaz, L. (2023). Rarecare: A policy perspective on the burden of rare diseases on caregivers in Latin America. *Frontiers in public health*, 11, 1127713. https://doi.org/10.3389/fpubh.2023.1127713

viii For example, Molster et al. (2016) assessed the healthcare needs of PLWRD in Australia, finding that most face high unmet needs such as wait times of over five years for a diagnosis (30%), or experience problems in the transition from pediatric to adult care (52.8%). See: Molster, C., Urwin, D., Di Pietro, L. et al. (2016). Survey of healthcare experiences of Australian adults living with rare diseases. *Orphanet J Rare Dis 11*, 30. https://doi.org/10.1186/s13023-016-0409-z

Table 1: Existing evidence and hypotheses for the socioeconomic impact of rare disease in middle-income countries (MICs)

Existing evidence from MICs	Hypothesis for MICs
• Understanding the prevalence of rare disease depends on diagnosis. Diagnosing RD is challenging and depends on an efficient referral system and access to specialist centers.[36] In many MICs, such RD networks are still in development.[37] • Many rare diseases (80%) are genetic, yet in many MICs there is a lack of access to diagnostic testing.[38,39]	**Hypothesis 1:** Prevalence of RD in MICs may be less understood due to lack of access to the diagnostic infrastructure and specialists required to diagnose and report the disease.
• Treatments for rare diseases are not equitably available worldwide, and there are significant access disparities across geographies and income levels.[40,41] • Out-of-pocket spending on both medical and non-medical costs required for PLWRD often results in catastrophic expenditures for people living in MICs and their households.[ix,42]	**Hypothesis 2:** Direct treatment costs may be lower in MICs due to a lack of access to the most effective treatments. As a result of lower access to effective treatments, health outcomes may be worse in MICs: this would have implications for other elements of the socioeconomic impact, such as non-treatment related components of the direct medical costs.
• Existing evidence from MICs demonstrates poor access to diagnosis and treatment as well as a lack of social security mechanisms or universal health coverage. The loss of caregiver productivity for chronic and debilitating diseases is considerable, especially if informal care is around-the-clock and lifelong.[43] • Especially for patients living in rural areas, there are significant differences in costs associated to gaining a diagnosis and ongoing treatment and access to hospitals, specialists, or disease support networks.[44]	**Hypothesis 3:** The indirect impact could constitute a larger proportion of the total socioeconomic impact of RD in MICs, especially in countries with poor access to healthcare services, infrastructure, and treatments.

CRA analysis of multiple sources

To test our hypotheses and further elucidate the critical unmet needs faced by PLWRD and their families, this study sets out a research framework to address the following questions:

- Are there significant differences in the prevalence of different rare diseases across countries? Does this have implications for societal impact?

ix Economic burden becomes catastrophic if the ratio of direct cost to the total annual income of the household exceeds 10%. See: Wang, L., Zou, H., Ye, F., Wang, K., Li, X., Chen, Z., ... & Shen, M. (2017). Household financial burden of phenylketonuria and its impact on treatment in China: a cross-sectional study. *Journal of Inherited Metabolic Disease*, 40, 369–376.

- Are there differences in access to care and in healthcare provision, and what are the implications for magnitude and composition of socioeconomic impact? Does this affect the impact on people's working lives, on caregivers, and on society more broadly?
- Does the magnitude and composition of the socioeconomic impact have implications for RD policy?
- What are the policy recommendations to improve the current level of understanding of the socioeconomic impact of RD in MICs?

1.4 Structure of the report

The remainder of the report is structured as follows:

- **Section 2** describes this study's approach to data collection and estimation of the socioeconomic impact, summarizing the selection of the diseases and countries as well as the analysis of qualitative and quantitative evidence.
- **Section 3** outlines the key findings from the quantitative and qualitative analysis of the socioeconomic impact of rare diseases in MICs.
- **Section 4** reviews a set of cross-cutting themes resulting from the findings of our study, with examples from MICs.

2. The research approach

The research follows a five-step approach (Figure 1).

Figure 1: Five-step approach to estimating the socioeconomic impact of rare diseases

Source: CRA analysis

2.1 Framework to characterize socioeconomic impact

The framework to estimate the socioeconomic impact of rare diseases draws on the components included in previous studies but with the expectation that the data in MICs are limited and that some elements of the socioeconomic impact can be discussed only qualitatively (Table 2).

Table 2: Socioeconomic framework to estimate the socioeconomic impact of rare diseases

Component	Elements estimated quantitatively	Elements assessed qualitatively
Direct medical costs	Inpatient stay (acute and non-acute) Outpatient care Prescription medication	Out-of-pocket costs and catastrophic expenditures
Indirect costs	Absenteeism/presenteeism (PLWRD and their caregivers) Early retirement (PLWRD and their caregivers)	Transportation costs Quality of life (for example, mental health, physical pain)
Mortality impact	*Not quantified*	Impact on life expectancy for PLWRD

Source: CRA analysis

2.2 Rare diseases and countries included in the study

Rare diseases included in the study

The rare diseases were selected to include diseases with a known diagnostic and treatment pathway, available prevalence data, and differentiation in the age of onset, type of disease, and requirements of diagnostic infrastructure. A final list of six diseases—Gaucher disease (GD), Mucopolysaccharidosis II (MPS II), hemophilia, idiopathic pulmonary fibrosis (IPF), multiple myeloma (MM), and myasthenia

gravis (MG)—was compiled, representing different categories of disease (metabolic, hematologic, pulmonary, oncology, and inflammatory/neurologic) (Table 3).[x]

Table 3: High-level characterization of the diseases

Disease	Characteristics and impact
GD (1) [xi]	GD is a lysosomal storage disorder with three distinct types causing anemia, bone pain, fatigue, and organ enlargement.[45] Type 1 GD is the most prevalent form of the disease, making up approximately 95% of cases, while type 2 is the most severe. Type 3 is intermediate between type 1 and type 2.[46]
	For types 1 and 3, enzyme or substrate replacement therapy are the standard of care, reducing symptoms and allowing persons living with GD to live full and active lives. Type 2 is not treatable and generally progresses to death in early childhood.[47] Without treatment, symptoms are poorly managed and disease complications may result in irreversible organ damage or shortened life expectancy.[48]
Hemophilia A & B [xii]	Hemophilia is an x-linked blood disorder affecting mostly males. Low levels of clotting factor lead to excessive bleeding, bruising, and internal bleeding into joints and the brain.[49]
	The predominant standard of care treatment is replacement clotting factor, either plasma-derived or recombinant, to manage bleeding episodes and allow persons with hemophilia to live full and active lives.[50] Without treatment, an uncontrolled bleeding episode may be fatal.[51]
IPF	IPF is a type of interstitial lung disease causing impaired lung function such as shortness of breath and cough.[52]
	Anti-fibrotic agents are the standard of care, which can slow disease progression, reduce exacerbations, and maintain quality of life, but they do not have a significant impact on mortality.[53]

x The diseases reviewed and selected aligned with the definition of rare disease developed by RDI: "A rare disease is a medical condition with a specific pattern of clinical signs, symptoms, and findings that affects fewer than or equal to 1 in 2000 persons living in any World Health Organization (WHO)-defined region of the world." See: Rare Diseases International. Operational Description of Rare Diseases. https://www.rarediseasesinternational.org/description-for-rd/ Accessed 15 February 2024.

xi We assume all cases are for Gaucher disease type 1 only, in this study. GD type 2 is very rare, with an incidence of approximately 5% of all GD patients, and has a prevalence of virtually zero, considering its severity and the resulting early death. GD type 3 accounts for 5% of all patients with GD, but studies have found it is much more prevalent in Asian populations. For this reason, we may have underestimated the socioeconomic burden—particularly indirect and mortality costs—in Asian countries, as GD3 has a more variable prognosis depending on disease severity. See: Orphanet (2012). Gaucher disease. https://www.orpha.net/en/disease/detail/355; https://www.sciencedirect.com/science/article/pii/S2214426917301416

xii As noted in the methodology section, for hemophilia, either we use data reporting an average impact across hemophilia type A or B or we apply weighting based on distribution of disease type and severity reported by the World Federation of Hemophilia.

	Without treatment, there is rapid decline in lung function and mortality.[54]
MPS II	MPS II is a progressive x-linked lysosomal storage disorder that affects males. It is caused by the lack of an enzyme, leading to accumulation of waste materials in tissues and organs. Symptoms include skeletal deformities, joint stiffness, organ damage, and sometimes cognitive impairment.[55]
	There is no curative treatment for MPS II. The standard of care treatments are enzyme replacement therapy and stem cell transplant, which can improve neurocognitive symptoms.[56] Without treatment, life expectancy is reduced due to irreversible clinical progression.[57]
MM	Multiple myeloma is a hematological cancer that affects white blood cells and is generally diagnosed in older adults. Risks include both genetic and environmental factors. Symptoms include bone pain, fatigue, anemia, and kidney problems.[58]
	Standard of care treatment includes chemotherapy, targeted immunotherapies, radiation, and stem cell transplant, which extend survival, although MM remains incurable.[59] Without treatment, symptoms are poorly managed and life expectancy is reduced.[60]
MG	MG is an autoimmune disorder characterized by fluctuating weakness of voluntary muscles, causing difficulties in performing everyday activities.[61]
	Enzyme inhibitors and immunosuppressive agents are the standard of care for managing symptoms of MG.[62] Without treatment, an exacerbation of symptoms—myasthenic crisis—may be fatal.[63]

GD = Gaucher disease, IPF = idiopathic pulmonary fibrosis, MPS II = mucopolysaccharidosis type II, MM = multiple myeloma, MG = myasthenia gravis

Source: CRA analysis of multiple sources

Countries included in the study

The aim of the study was to look at the socioeconomic impact of RD in lower-middle and upper-middle countries across different regions (Africa, Asia, Latin America, and Oceania).[xiii] To optimize the likelihood of gathering disease and socioeconomic data, the countries prioritized for selection were those with a larger population size, published studies on rare diseases, a relevant RD patient organization, and evidence of policies supporting rare diseases or orphan drugs.[xiv] It was also taken into account that countries vary in the level of RD policy prioritization, evidenced by the establishment

[xiii] Countries from North America and Europe were not included as these have already been the focus of other socioeconomic studies.

[xiv] Importantly, these criteria were used to support the selection process and were not applied as exclusion criteria. As a result, the selected countries may meet some but not all of these criteria.

of national plans or RD committees.[xv] Ten countries were selected, most of which have not been covered in any major socioeconomic study to date: Brazil, China, Chile, Colombia, Egypt, Ghana, Kenya, South Africa, Malaysia, and Thailand. Australia and Taiwan were also included as HIC comparators, which have strong healthcare systems and RD policies (Figure 2).[xvi]

Figure 2: Existence of rare disease specific policies in the countries in the study

Source: CRA analysis of multiple sources

2.3 Literature review and approach to data collection

A structured literature review of the socioeconomic studies published between 2018 and 2023 was conducted on the factors impacting the socioeconomic impact of disease; specific to the countries in scope, or low-middle-income countries; and specific to the diseases in scope, or rare diseases generally.[xvii] As a result, 35 socioeconomic studies were found focusing on one of the six diseases in scope in one of the 12 countries.

In addition to the results drawn from published studies, a hand-searching process was applied to collect data for each country and disease. This evidence and data provided inputs for both the quantitative and qualitative analysis of each rare disease, medical costs, indirect costs, and mortality and quality of life impacts. Overall, 302 relevant sources were retrieved.

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xv This study recognizes that these proxies are imperfect—policies do not necessarily translate into PLWRD having access to rare disease services and treatments. Likewise, the lack of an official plan does not preclude good practices. Therefore this has been augmented with an analysis of health spending, with relevant data points documented in Appendix A.

xvi Although Chile has been categorized as a high-income country in 2013 by the World Bank, it still exhibits some elements of an upper-middle-income country in its healthcare system—thus, it was not used as a high-income comparator country.

xvii For instance, research terms included components of socioeconomic costs: *"economic burden"* or *"economic impact*" or *"medical costs"* or *"caregiver"* or *"out-of-pocket costs"* or *"productivity loss"*; research terms included the name of the country or a more general reference to lower-income settings: *"Brazil"* or *"Colombia"* or *"Chile"* or *"South Africa"* or *"low-middle-income countries"* or *"upper-middle-income countries"*; and research terms included an understanding of the characteristics of the disease and the treatment approach, such as *"multiple myeloma"* and *"diagnosis"* and *"factor replacement therapy"* or *"myasthenic crisis."*

3. Evidence and findings from the analysis of the socioeconomic impact

This chapter presents the five overarching findings resulting from the analysis of the quantitative and qualitative evidence on the socioeconomic impact of the relevant rare diseases across the countries in scope.[xviii]

- **Finding 1:** Existing information on the socioeconomic impact of rare diseases is limited, particularly in MICs
- **Finding 2:** The prevalence of rare diseases is underestimated in MICs.
- **Finding 3:** The estimated impact of rare diseases is significant across all countries, regardless of their income level.
- **Finding 4:** There are differences in the composition of direct and indirect costs across diseases and countries, which are driven by access to care for rare diseases.
- **Finding 5:** The impact on patient and caregiver experience is challenging to quantify but remains critical.

The aim was to develop findings that go beyond the individual diseases and countries, but given these results are based on a limited number of case studies and a relatively small number of data points, generalizations from these findings should be made carefully. Outcomes from the research are therefore presented as working hypotheses requiring validation in future studies.

3.1 Finding 1: Existing information on the socioeconomic impact of rare diseases is limited, particularly in MICs

Despite careful selection of therapy areas and countries to be included in the analysis, the available data remained limited. This affects the ability to produce accurate estimates of the impact of rare diseases. Data are least available in the lower-middle-income countries reviewed, and, although availability is relatively improved in the upper-middle-income countries, it remains weaker in comparison to HICs.[xix]

Evidence available on direct and indirect costs is sparse, and the quality of data varies across countries

Data availability ranged from all six diseases in China, Colombia, and Taiwan, to only three diseases in Ghana. Even across the six diseases, there are not always national or regional studies to draw on (with studies focusing on individual hospitals or particular funding channels), and the strongest disease areas are multiple myeloma and hemophilia (Table 4). For example, in MM, five sources were identified describing the medical costs across a set of five countries, but these ranged in time frame from 2015 to 2021. Although most estimated all healthcare system related costs, none covered the out-of-pocket cost to patients. Studies from South Africa and China only covered second-line treatment costs, requiring evidence-backed extrapolations to arrive at a final cost estimate. The medical cost data for hemophilia were more complete, and 12 studies were retrieved describing the

[xviii] For a complete summary of data outputs and references used, see: Appendix A: Outputs from the estimation of the socioeconomic burden; Appendix B: Sources used to define the socioeconomic framework and to estimate socioeconomic burden.

[xix] Low-income countries (LICs) were excluded from the study at the outset due to insufficient existing information for these countries.

medical costs across a set of seven countries, all of which reported a total direct cost figure.[xx] Given the limited data availability, quantitative conclusions could not be derived on the out-of-pocket costs faced directly by patients and their families, so this is discussed qualitatively in Finding 5.

Table 4: For illustration—countries with sufficient medical cost data available for each disease

	GD	Hemophilia	IPF	MG	MM	MPS II
Brazil						
Colombia						
Chile						
South Africa						
Kenya						
Egypt						
China						
Thailand						
Malaysia						
Taiwan						
Australia						

Shaded in Green, Blue, or Red = sufficient local data available

Green = Good quality: Complete local data available, only adjustment for inflation / currency conversion

Blue = Medium quality: Only partial cost data (for example, treatment costs, medicine costs, or hospitalization costs) across the country in focus. Some scaling (for example, assumptions of the proportions of cost components reported in other studies, not necessarily from the country in focus) required to arrive at complete cost

Red = Low quality: Only partial cost data (for example, treatment, medicine, or hospitalization costs) from a region or site of care in the country in focus. Some scaling (for example, assumptions of the proportions of cost components reported in other studies) required to arrive at complete cost

Source: CRA analysis of multiple sources (See Appendix A, B)

[xx] In some countries, this was reported for both hemophilia A and B individually, requiring some weighting (using data on the distribution of patient severity and hemophilia type) to arrive at a total cost figure.

On top of the direct medical costs identified in the last section, there are indirect costs associated to the impact on employment, productivity, and travelling for care).[xxi] Across the diseases, comparable data were available across countries on the disability-adjusted life years or estimates from the literature on the impact of the disease on employment. This could be used to estimate how the severity of the disease was impacting the ability of patients and caregivers to work. Data on absenteeism and the likelihood of a PLWRD requiring support from a caregiver were also considered, to refine our analysis. The best data available are for hemophilia, MM, and MPS II. However, as discussed in Finding 5, standardized data on several aspects—such as quality of life, life expectancy disadvantage, and transportation costs—could not be found even though these are recognized as some of the most important elements of the socioeconomic impact of rare diseases.

3.2 Finding 2: The prevalence of rare diseases is underestimated in MICs

An important element examined in most socioeconomic studies is the number of patients affected. This is commonly measured with disease prevalence.[xxii] While there are prevalence data for all the countries studied, there was significant variation in the number of diseases covered in each country. This ranged from all six diseases in Colombia, China, and Taiwan, to only three diseases in Ghana (Figure 3). There was also considerable variation in where the data came from, with international databases and global disease studies for MM, hemophilia, and IPF (the only three diseases reporting prevalence figures in all our countries in scope), or estimated prevalences based on prevalence per live births and incidence, or data from peer-reviewed studies specific to a single country or disease.

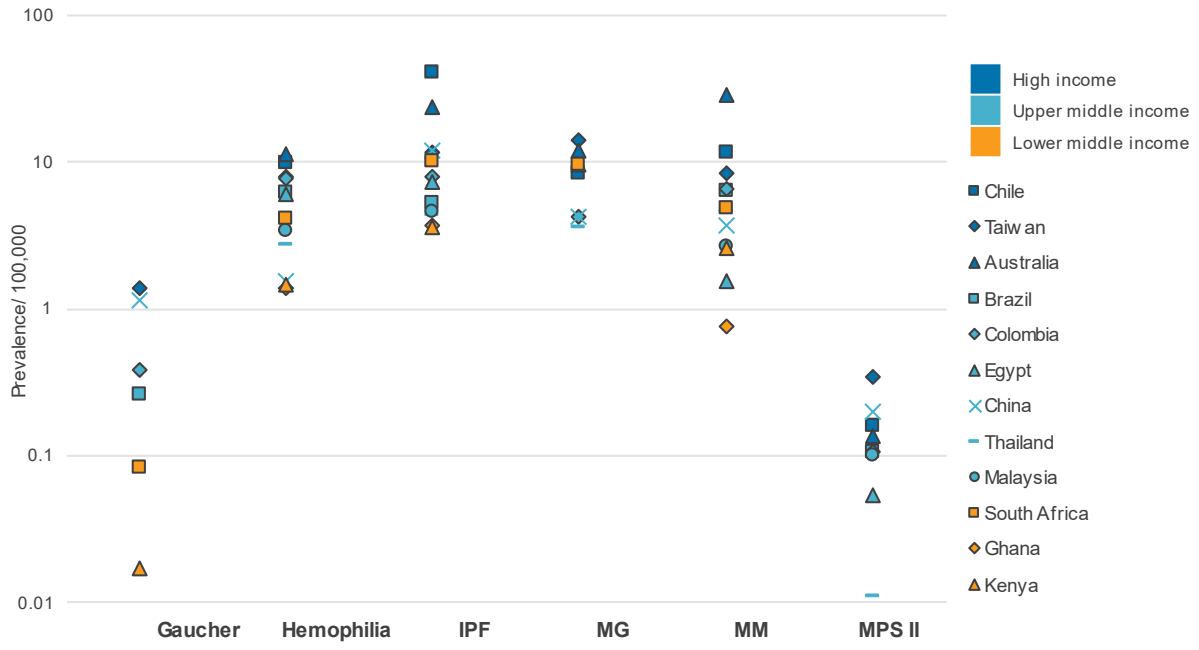
There is large variation in prevalence within each disease, with the largest variation in GD (ranging between and 0.017 in Kenya and 1.356 in Taiwan per 100,000) and MM (ranging between 0.758 in Ghana and 28.111 in Australia per 100,000). However, as can be seen in Figure 3, the reported prevalence in MICs is substantially below that reported in HICs. This is common across most diseases[xxiii] and consistent with the wider literature on prevalence rates and the burden of disease.[64]

xxi The absolute estimates of indirect costs are presented in Appendix A. The analysis focuses on hemophilia (four papers provided specific data allowing for the calculation of indirect costs), MM (eight papers retrieved), and MPS II (two papers), as these diseases present the most reliable data. Altogether, the indirect costs are considered for 10 countries, although with different levels of completeness across diseases. For hemophilia the indirect costs are analyzed for seven countries, while for MPS II and MM, five and four countries are analyzed, respectively (the results are presented in Table 4).

xxii Defined as the proportion of a population who have a specific disease in a specific period of time

xxiii Apart from MPS II where we do not have data on lower-middle-income countries

Figure 3: Disease prevalence, per 100,000, by income status



Source: CRA analysis of multiple sources; data sources vary, and some countries do not have prevalence data for all diseases[xxiv]

The lower levels of prevalence in MICs reflects how the data are collected

In many MICs, prevalence data are only being collected in some sites of care. In China and Thailand, prevalence data for MG are based on hospitalization records, only reflecting persons with MG experiencing severe symptoms.[65,66] For example, the Hospital Quality Monitoring System (HQMS) was used to establish the incidence of MG in China. While the HQMS provides a valuable source of national, population-based data, outpatient data are excluded, leaving many living with a milder form of MG uncaptured.[67] As a result, China and Thailand have some of the lowest prevalence numbers reported for MG (Figure 3). The same challenge is observed with the prevalence data for MM, where prevalence is only captured in some countries when a patient seeks specialist care.

The lower levels of prevalence data can be further explained by the relationship between the reported prevalence and the diagnostic pathway

As is the case in HICs, prevalence data are also dependent on rates of diagnosis. While misdiagnosis is common in every country, it is higher in MICs, often as a result of limitations in healthcare infrastructure and services available.[68,69] In Brazil, there is low awareness of MM across patients and physicians. In a patient survey, 98% of persons with MM had not heard of the disease before being diagnosed. There is also a low level or awareness among primary care physicians, and nearly a third of patients waited for more than a year to receive an accurate diagnosis. Low awareness, and the fact that MM is a great mimicker of other, benign conditions, means that patients are often treated symptomatically for a significant period of time before MM is suspected and confirmed.[70]

A similar picture is seen for hemophilia. Based on global prevalence estimates for hemophilia, the proportion of persons receiving an accurate diagnosis of hemophilia also varies significantly

xxiv See Appendix A for all estimates of patient prevalence.

depending on the healthcare infrastructure available, from nearly 100% of persons with hemophilia identified in HICs to less than 12% in lower-income countries.[71] While some countries utilize laboratory screening to identify persons with hemophilia, others only document persons with hemophilia who seek treatment, leaving as many as 66% of persons with hemophilia unidentified globally.[72]

The diagnosis of IPF is universally challenging due to similarities in the clinical presentation of interstitial lung diseases; even in well-resourced countries such as the US, over half of persons living with IPF receive at least one misdiagnosis, with an average time to diagnosis of 2.7 years.[73] In Australian clinical guidelines, a diagnosis of IPF can be categorized as "definite," "probable," "possible," or "inconsistent with" IPF, reflecting the complexity of diagnosis.[74] Limited access to high-resolution computed tomography (HRCT) imaging and the absence of multi-disciplinary diagnostic teams further intensify the challenges of IPF diagnosis in lower-income countries.[75] Many primary hospitals in China cannot perform HRCT, driving a wide gap in diagnostic capabilities; across 14 primary hospitals in China, the overall IPF diagnostic accuracy was 66%, in comparison with 96% at a specialist respiratory center with HRCT capabities.[135]

For lysosomal storage disorders such as GD and MPS II, bone marrow aspiration is now widely considered an obsolete diagnostic method since it is less sensitive, less specific, and more invasive than enzymatic assays. However, since gold-standard diagnostic techniques (enzymatic assay availability) are not universally accessible in LICs and MICs, such as Kenya, bone marrow aspiration remain the primary method of GD diagnosis.[76]

This results in an underestimate of prevalence across MICs. For example, in Colombia, a case of MM is only registered once a patient seeks care from a hematologist (of which there are shortages); as a result, the prevalence is likely underestimated.[77] Prevalence figures for hemophilia are also reported based on identified persons with hemophilia who entered the care pathway.[78] This observation is not new. The World Federation of Hemophilia (WFH) published a study in 2019 that demonstrated true prevalence is significantly higher than previous estimates, but despite such growing awareness of underreporting, many persons with hemophilia remain unidentified.[79]

Higher, more accurate estimates of prevalence are available in countries with newborn screening (NBS) programs, but access to NBS varies in MICs

Some genetic rare diseases can be diagnosed through NBS. For instance, of the diseases in scope of this report, GD and MPS II can both be diagnosed through NBS. Taiwan is the only country in our sample for which NBS has been available for both GD and MPS II since 2015. As a result, we observe significantly higher prevalence figures reported for both diseases in Taiwan (Figure 3).[80,81,82] In particular, NBS for MPS II was found to lead to better long-term clinical outcomes in Taiwan as an early diagnosis meant that enzyme replacement therapy (ERT) could be initiated early, with treatment provided before irreversible organ damage occurs.[83] Conversely, in China, NBS has not yet been implemented for GD. For persons with GD and their caregivers, the diagnostic odyssey poses a significant impact, with an average of five misdiagnoses before an accurate diagnosis.[84]

Globally, many countries have implemented NBS programs. However, the number of diseases included in testing may be more limited in MICs due to economic, technical, and logistical constraints.[85] For example, Colombia and Egypt both have national NBS programs but only include two and six diseases, respectively.[xxv] There is limited uptake of organized NBS across the African

[xxv] None of the rare diseases covered in these NBS programs are included in this study.

continent, with the exception of some countries along the northern coast.[86,87] In contrast, a notably higher number of diseases are covered in Australia's NBS program—twenty-seven disorders—although GD and MPS II are not covered in the panel.[88,89,90] There are also challenges with the level of population coverage for NBS in MICs, even when NBS programs have been implemented for a significant period of time. In Brazil, nationwide coverage approached 85% in 2006 but has plateaued since, despite the continued expansion of NBS into all states by 2014. While NBS coverage in the wealthiest Sao Paulo State now exceeds 95%, disparities persist across other states.[91]

Prevalence rates can increase over time due to improved diagnosis and reporting. For example, in Taiwan, increased disease awareness and improved diagnosis have seen the reported prevalence of MG nearly doubling from 2000 to 2007—from 8.4 to 14.0 cases per 100,000. Committed advocacy efforts from the Myasthenia Gravis Association of Taiwan, active since 1993, have supported these improvements.[92,93]

This analysis indicates prevalence rates underestimate the impact and scale of RD in MICs, due to low awareness, a limited number of ways to report the disease, and resources constraints across the diagnostic pathway. Conducting a scenario analysis by applying the observed prevalence rates from the two HIC comparators—Australia and Taiwan—to the MICs in the study indicates that there are approximately 30 million unreported cases across the six diseases and 10 MICs (Table 5).

Table 5: Potential underreported cases per 100,000 in MICs compared with average prevalence in higher-income countries

		Difference, HIC comparator (average: Australia, Taiwan) **and MICs**									
	HIC average (2/3 avg.)	**Brazil**	**Colombia**	**Chile**	**South Africa**	**Ghana**	**Kenya**	**Egypt**	**China**	**Thailand**	**Malaysia**
GD	**1.356** (0.904)	**1.098**	**1.356**		**1.273**		**1.339**		**0.227**		
Hemo-philia	**9.614** (6.409)	**3.391**	**1.983**	**-0.179**	**5.541**	**8.24**	**8.154**	**3.66**	**8.087**	**6.91**	**6.219**
IPF	**17.540** (11.693)	**12.309**	**9.723**	**-22.557**	**7.375**	**3.702**	**3.594**	**7.258**	**11.767**	**4.352**	**4.561**
MG	**12.855** (8.57)		**8.665**	**4.495**	**3.378**			**3.285**	**8.657**	**9.306**	
MM	**18.202** (12.135)	**11.838**	**11.644**	**6.767**	**13.372**	**17.444**	**15.659**	**16.659**	**14.563**	**13.591**	**15.542**
MPS II	**0.236** (0.157)	**0.132**	**0.130**	**0.076**				**0.183**	**0.041**	**0.225**	**0.137**

Key:	***Criteria***
Underreporting unlikely	*Difference with HIC comparator is negative*
Underreporting likely	*Difference with HIC comparator is less than 2/3 the average HIC prevalence figure*
Significant underreporting likely	*Difference with HIC comparator is greater than 2/3 the average HIC prevalence figure*
Missing data	*n/a*

Source: CRA analysis of multiple sources (see Appendix B for complete list of sources)

There are several implications of underestimated and underreported prevalence for any estimate of socioeconomic impact:

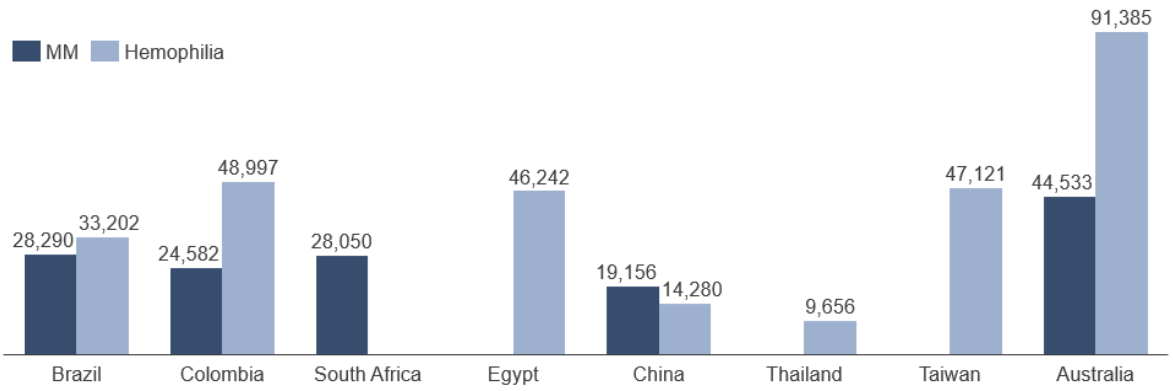
- It is not possible to estimate an absolute socioeconomic economic impact (that is, to total the socioeconomic impact for the country), nor is it possible to make a direct comparison of the level of absolute disease impact across countries. Therefore, the per patient socioeconomic impact is assessed (that is, the socioeconomic impact of the disease on an "average" patient).
- Existing studies that estimate absolute impact or cost based on reported prevalence will likely significantly underestimate the socioeconomic impact as there are many PLWRD who are undiagnosed and untreated.
- The differing characteristics of each rare disease also has implications for underreporting of prevalence and the socioeconomic impact.
    - Differences in prevalence estimates for genetic diseases such as GD are primarily attributable to variation in the efficiency of the diagnostic pathway across countries.
    - For non-genetic diseases with a late age of onset, such as MM or MG, differences in prevalence can also be due to the demographic composition of the population and access to healthcare services.

While reported prevalence directly affects the accuracy of a total estimated socioeconomic impact there are other important implications. Delays in diagnosis can result in disease progression and complications, amplifying the socioeconomic impact and composition of both direct medical costs and indirect costs for identified PLWRD. These impacts are examined in more detail in the subsequent sections.

3.3 Finding 3: The estimated impact of rare diseases is significant across all countries, regardless of their income level

Drawing on published studies and national data sources, it was possible to develop estimates of the annual total socioeconomic cost per patient for the six diseases across most countries in the study (this cost is illustrated for MM and Hemophilia in Figure 4 below). The nominal impact per patient of quantifiable costs (both direct and indirect costs) of RD is nearly always higher in HICs. For instance, the total estimated annual impact for a diagnosed patient with hemophilia is approximately 10 times higher in Australia (USD 91,400) than in Thailand (USD 9,700). However, this is not comparing apples with apples, as the countries do not have the same level of wealth and the nature of healthcare provision varies significantly from country to country (and even within countries).

Figure 4: Average annual total socioeconomic costs per patient (MM, Hemophilia; USD, 2020)



Source: CRA analysis of multiple sources (see Appendix A, B)

The magnitude socioeconomic impact of RD is better understood when accounting for differences in a country's income level

One way to take into account the differences in income between countries is to look at the socioeconomic impact as a ratio with the gross domestic product (GDP) per capita (a measure of average income). When socioeconomic impact is considered in terms of a measure of average income, a different picture emerges. The total impact of hemophilia is approximately 1.8 times the average income in Australia and 1.4 times the average income in Thailand (Table 6). On this measure, the magnitude of the impact is similar between HIC and MICs. While the total estimated impact per person living with MM in Australia is about twice that in China—USD 44,500 and USD 19,200, respectively—this cost represents 0.86 times the average income in Australia and 1.8 the average income in China. There is considerable variation across countries and diseases, but across the six diseases in our study, we conclude the ratio of the total impact to average income is similar across MICs and HICs and, on average, the normalized impact is higher in MICs. The same analysis for the other diseases supports this conclusion.

Table 6: Average total socioeconomic costs per patient, as a proportion of GDP per capita (MM, Hemophilia; USD, 2020)

Total costs per patient (USD)	Brazil	Colombia	South Africa	Egypt	China	Thailand	Taiwan	Australia
Hemophilia	33,202	48,997		46,242	14,280	9,656	47,121	91,385
/GDP per capita	4.80	**9.24**		**12.95**	1.37	1.38	1.65	1.76
MM	28,290	24,582	28,050		19,156			44,533
/GDP per capita	**4.09**	**4.63**	**4.89**		1.84			0.86

Source: CRA analysis of multiple sources (see Appendix B for complete list of sources); bolded figure represents highest cost figure proportional to the GDP per capita. Blank indicates no data available. No data available for Chile, Ghana, Kenya, or Malaysia for both Hemophilia and MM.

These results need to be considered carefully. Clearly, the number of persons (as a proportion of the population) diagnosed with a rare disease is much lower in MICs than in HICs, but where impacts can be observed, they are of the same magnitude in MICs as in HICs. Moreover, this statistic is looking at the cost relative to average income and not looking at the income of the patients who are actually treated.[xxvi]

Moreover, these findings require to be further contextualized by examining the evidence available on the composition of the costs (direct and indirect costs) and the qualitative literature on their relationship with SoC, which can provide further insights on why the magnitude of the costs is comparable across different countries (this analysis is provided in Finding 4).

3.4 Finding 4: There are differences in the composition of direct and indirect costs across diseases and countries, which are driven by access to care for rare diseases

The total socioeconomic costs estimated above are composed of direct and indirect costs. Given the hypothesis that this would be affected by standard of care (SoC), it is useful to first compare how the SoC varies across countries and then investigate whether we can observe any correlation to composition of the costs.

There is significant variation in the SoC received across the countries in the study

To understand the estimated socioeconomic impact, it is important to first consider evidence on the SoC received and the clinical guidelines available in each country for each rare disease.[xxvii] Across the diseases and countries, only 23 clinical guidelines were identified describing the SoC. Out of the 23 guidelines, 19 are country specific: in Brazil, all five of the diseases for which costs were estimated had country-specific guidelines, compared with no evidence of any local clinical guidelines in Kenya.

[xxvi] While it was not possible to consider income of patients who are treated, given the data available, this is a separate but interesting question to consider as it would provide more information about affordability rather than comparing socioeconomic impact.

[xxvii] Due to data limitations, this analysis is restricted to countries and rare disease for which medical cost data were available (See Finding 1).

In general, the availability of clinical guidelines and the type of treatment protocol vary considerably across countries and diseases. Unsurprisingly, Australia is the country where the SoC reflects more frequently the international best practice. Egypt and Kenya are the countries where the SoC is more frequently outdated (Table 7).

Further, adherence to guidelines and timely access to treatment with the SoC also vary, due to limited access to specialists in many MICs. For example, after the initial diagnosis of MM, the wait time to see a hematologist in the Brazilian public sector was as long as six months.[125] By contrast, in Australia, most patients are seen by a specialist shortly after symptom onset. A minority of 13% of persons with blood cancer in Australia reported that it took more than two months to be referred to a specialist after their initial symptoms.[94] Delays in diagnosis also lead to disease progression and poorer health outcomes. In China, the majority of persons with MM were not diagnosed until severe complications occurred, with 85.8% of patients diagnosed at stage III of disease progression.[95] Moreover, these issues have consequences on the possibility to determine the socioeconomic impact of the disease, as well as the composition of socioeconomic costs.

Table 7: Clinical guidelines and most used standard of care (SoC) across diseases and countries *(analysis covering countries/diseases where data on medical costs are also available to document some observable use of treatment)*

	Gaucher	Hemophilia	IPF*	MG*	MM	MPS II
Brazil	Only low-dose ERT generally available	Prophylaxis; limited EHL	Anti-fibrotics available with limited access		Low ASCT rates, poor access to novel agents	ERT are available
Colombia	ERT	Prophylaxis; limited EHL		Various therapeutics**	Low ASCT rates, poor access to novel agents	
Chile			Anti-fibrotics available with limited access			ERT
South Africa	Low-dose ERT				Poor access to ASCT, novel agents, maintenance	
Kenya	Supportive care					
Egypt		On-demand				
China		Plasma-derived CFC	Anti-fibrotics available with limited access	Various therapeutics**	Low ASCT rates, poor access to novel agents	Supportive care
Thailand		Plasma-derived CFC		Various therapeutics**		
Malaysia				Various therapeutics**		Supportive care, minority ERT
Taiwan	ERT	Prophylaxis; limited EHL				ERT

				Various therapeutics**		
Australia		Prophylaxis; good access to EHL	Anti-fibrotics available; evidence of reimbursement	Various therapeutics; good access to innovative agents, IVIg, TPE**	High ASCT rates; good access to novel agents	

Key:	SoC reflects international best practice	SoC is relatively up to date but with remaining deficiencies across the countries in scope	SoC is outdated across the countries in scope

Country-specific guidelines or guidance from professional association		References made to international guidelines		No icon—no guidelines identified	Not reviewed—no medical cost data available

* For IPF and MG, there is evidence describing which treatments are available but little evidence indicating the most used SoC or what proportion of patients are receiving the most effective therapies.

** Guidelines for most countries indicate that various therapeutics are available for persons with MG, including cholinesterase inhibitors, immunosuppressive drugs, intravenous administration of g-globulin, plasmapheresis, thymectomy, and thymus radiotherapy. However, there is only evidence on the average breakdown of therapeutics provided to patients in Australia and Taiwan.[xxviii,xxix]

MM = multiple myeloma; IPF = idiopathic pulmonary fibrosis; MG = myasthenia gravis; MPS II = mucopolysaccharidosis type II; SoC = standard of care; ASCT = autologous stem cell transplant; EHL = extended half-life; CFC = clotting factor concentrates; ERT = enzyme replacement therapy.

Source: CRA analysis of multiple sources (see Appendix B for complete list of sources)

The most consistency in availability of clinical guidelines was seen for MM and hemophilia. However, it is important to be cautious about drawing conclusions regarding a causal relationship between the existence of clinical guidelines and SoC used in the country. In some countries, international guidelines will be commonly used (and the relevant SoC), even if not directly referred to. In many cases, clinical guidelines take time to update, even in HICs, and this does not necessarily mean that the approach to treatment has not changed in the meantime.

The evidence on the SoC for each disease is also non-uniform, especially when multiple treatments exist for some diseases. For example, for MG and IPF, there is evidence describing what treatments are available in each country. However, the evidence does not indicate the most frequently used SoC or the proportion of patients who are able to access the most innovative therapies. For other diseases, the evidence specific to these parameters is available and it is possible to observe differences in the SoC across countries and patients. As a result, due to such differences in the availability of effective treatments across countries, it is reasonable to expect different medical costs

[xxviii] In Taiwan, first-line treatment for persons with MG was with pyridostigmine (82%), steroids (58%), and azathioprine (11%). See: Herr, K. J., Shen, S. P., Liu, Y., Yang, C. C., & Tang, C. H. (2023). The growing burden of generalized myasthenia gravis: a population-based retrospective cohort study in Taiwan. *Frontiers in Neurology,* 14, 1203679. https://doi.org/10.3389/fneur.2023.1203679

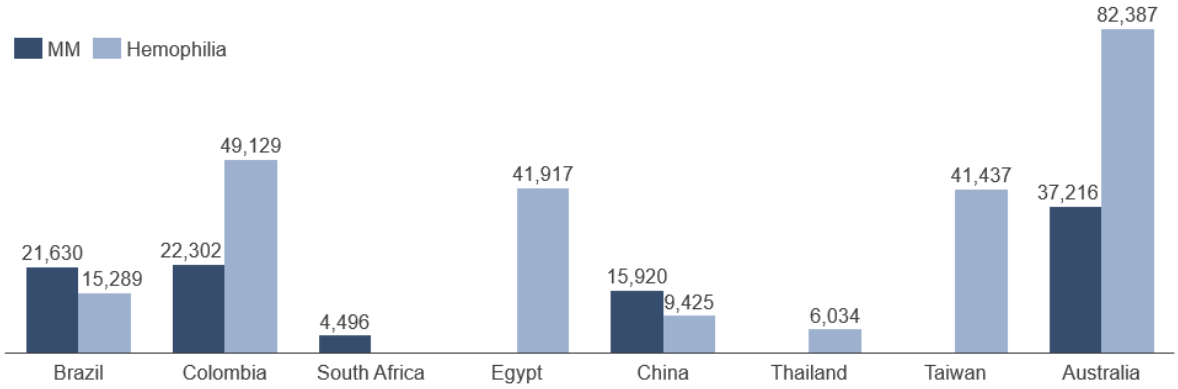
[xxix] In Australia, a study of persons with MG found there was a high rate of oral corticosteroid use (66%), a lower use of IntraVenous Immunoglobulin (IVIg, 47%) and a small percentage of Therapeutic Plasma Exchange (TPE, 4.5%). See: Sansoni, J., Menon, N., Viali, L., White, S., & Vucic, S. (2023). Clinical features, treatments, their impact, and quality of life for Myasthenia Gravis patients in Australia. *Journal of clinical neuroscience,* 118, 16–22. https://doi.org/10.1016/j.jocn.2023.09.023

and health outcomes for patients, with broader consequences to PLWRD, healthcare systems, and caregivers.

The access to effective treatments impacts the composition of the estimated direct cost of rare disease

MM and hemophilia are the diseases with the best data quality on the medical costs. The average annual medical costs per patient treated for MM and hemophilia are illustrated in Figure 5. It would be expected that the absolute medical expenditure would be higher in HICs, reflecting higher investments in healthcare and the use of a more cutting-edge SoC. However, this is not always the case. For hemophilia, Australia has significantly higher costs than the other countries, but Taiwan has comparable costs to some MICs (Figure 5).

Figure 3: Average annual medical costs per patient (MM, Hemophilia; USD, 2020)

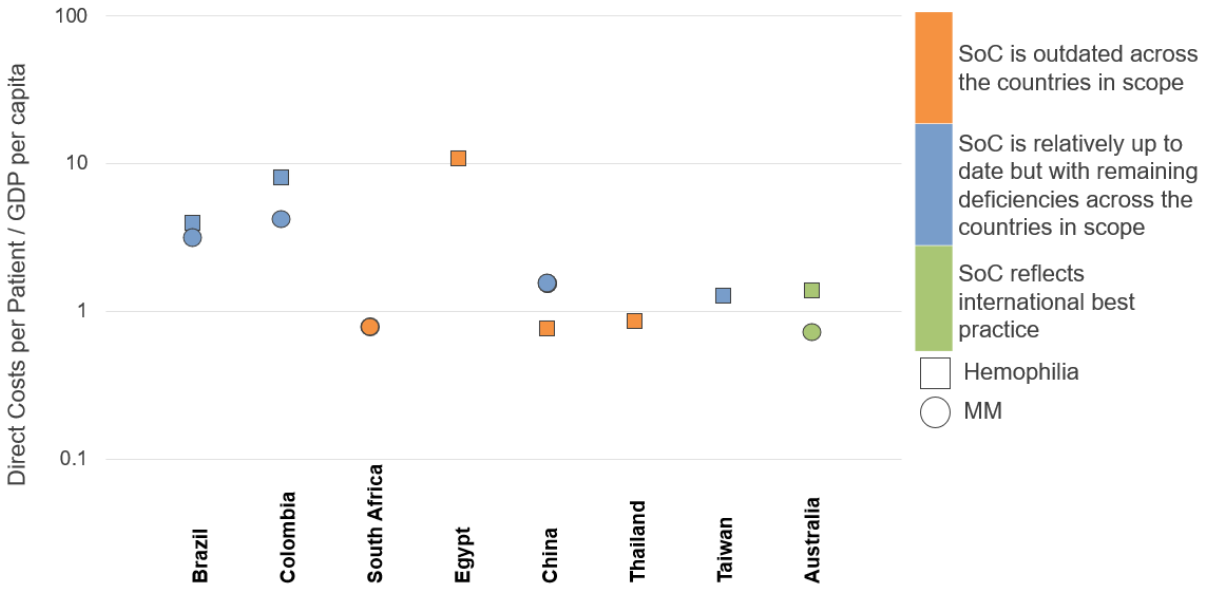


Source: CRA analysis of multiple sources (See Appendix B for complete list of sources)

It could be expected that a SoC consisting of the most effective therapies has higher prescription medicine costs, but also that this leads to improved health outcomes, which can reduce medical costs and healthcare resource utilization, including hospitalizations. One way to investigate this is to look at whether there is a relationship between overall medical costs and SoC.

Comparing a country such as Australia, where there is good access to the most effective treatments, to the MICs such as Brazil, Colombia, South Africa, and China, where treatments diverge from best practices, an association cannot be observed between medical costs as a proportion of GDP per capita and the quality of SoC (Figure 4). For example, in Brazil, medical costs are 3.12 times the GDP per capita, whilst in Australia, medical costs are only 0.72 times the GDP per capita.[96] We do not find that where less effective treatments are used as the SoC, the medical cost data as a proportion of GDP per capita is lower.

Figure 4: Average direct costs per patient/ GDP per capita (MM, Hemophilia; USD, 2020)



Source: CRA analysis of multiple sources (see Appendix B for complete list of sources); no direct costs data available for Chile or Malaysia for Hemophilia or MM

However, further insights can still be learned, looking at the available evidence for the diseases in scope.

MM

Studies on MM in Australia, China, and Latin America provide information into the relationship between the SoC and the composition of healthcare costs (Table 8). In Australia, drug therapies for MM amount to 67% of the medical costs, on average.[97] Comparing this to other HICs the largest expenditures for MM are also attributed to pharmaceuticals but demonstrate offsetting costs for hospitalization. For example, in New Zealand, approximately 58% of the medical costs are attributed to pharmaceuticals and only 20% to hospital admissions.[98] For MM patients in France, the evidence shows the proportion of the cost attributed to medications increases with each line of treatment received, ranging between 39% of costs for first line patients and 71% for patients on fourth and later lines of therapy. However, hospitalization costs are proportionately low, approximately only 22% of the total medical costs for first line patients.[99] Studies looking at medical costs in the US also find that prescription drugs are the largest cost drivers across disease phases, with variation across different phases of the cancer care continuum.[100] On average, one study found that pharmacy drugs accounted for 32.9% of total medical costs while and hospital outpatient care (mostly driven by provider-administered drugs) were 26.2% of total medical costs while hospital inpatient visits were only 29.3% of total medical costs.[101]

In Latin America, there are higher hospitalization costs and due to reduced availability of effective treatments and delayed diagnosis.[102] In Brazil, 37% of medical costs are attributed to hospitalizations, while a relatively high proportion (54%) of the costs remain attributed to medications, and the remainder attributed to other outpatient costs.[103] Other studies on the hospitalization costs for MM provide additional insight on the drivers of these differences in cost composition. In China, pulmonary infection and suppressed bone marrow function were significantly associated with increased direct medical costs.[104] A late diagnosis therefore implies a more advanced stage of the disease at the time

of diagnosis and treatment and, as a result of the complications of disease progression, higher hospitalization costs for MM.

Table 8: Multiple myeloma average annual medical costs per patient

	Brazil[xxx]	Colombia	South Africa	China	Australia
Medical costs (USD, 2020)	21,630	22,302	4,496	15,920	37,216
Medical costs / GDP per capita*	3.12	**4.20**	0.78	1.53	0.72

Key:	SoC reflects international best practice	SoC is relatively up to date but with remaining deficiencies across the countries in scope	SoC is outdated across the countries in scope

*For example, in Brazil, medical costs are 3.12 times the GDP per capita

*Source: CRA analysis of multiple sources (See Appendix B for complete list of sources); **bolded figure** represents highest cost figure proportional to the GDP per capita*

Hemophilia

As characterized earlier, hemophilia manifests at an early age and requires lifelong preventative treatment. Overall, we observe that the medical costs are the key driver of socioeconomic impact for this condition, but the SoC can dictate how efficient these medical costs are.[xxxi] For hemophilia**,** Australia has a relatively low medical cost as a proportion of GDP per capita (1.36), but it is the only country providing an optimal SoC, that is, where most persons with hemophilia are treated prophylactically, with good access to extended half-life (EHL) factor replacement therapy.[105] In all of the other countries, there is only limited access to treatment with EHL prophylactically. Taiwan, Brazil, and Colombia typically provide prophylactic treatment but with standard half-life clotting factor concentrates (SHL CFCs). Where a less optimal SoC is provided, we observe that medical costs as a proportion of GDP per capita are at the same level (1.25 in Taiwan) or significantly higher (3.89 and 7.95 in Brazil and Colombia, respectively) compared with Australia. Cryoprecipitate and fresh frozen plasma (FFP) treatments are more commonly used in China and Thailand. Egypt, where on-demand treatment with CFCs is the dominant SoC, is the country in our sample with the highest medical costs as a proportion of GDP per capita (10.78) (Table 9).

The literature shows what is not captured in the higher medical costs, including the differences in the impact on health systems and patients. Persons with hemophilia receiving on-demand treatment, the SoC in Egypt, have a higher risk of developing inhibitors compared with those treated prophylactically.[106] Prophylactic treatment has been shown to be cost-effective compared with on-demand treatment and delivers additional savings to healthcare systems.[107] In Colombia, as prophylaxis increasingly became adopted as the SoC in recent years, hospitalizations for bleeding decreased by 9% (from 2015 to 2020) and provision of medical care by interdisciplinary teams

xxx Private sector medical costs are estimated to be higher, at USD 55,178 or 7.97 times the GDP per capita.

xxxi The analysis for hemophilia was restricted to the following countries based on availability of medical cost data: Brazil, Colombia, Egypt, China, Thailand, Taiwan, Australia.

increased by 9% (from 2019 to 2020).[xxxii] However, some of the most severe patients with hemophilia have significantly higher costs. For example, the total average annual medical cost for hemophilia A patients with high titer inhibitors (who are refractory to factor VIII or factor IX and therefore require an alternate SoC) to be 521,762 USD[xxxiii] (approximately 23 times higher than the average cost per patient).[108] 99.8% of this cost was directly related to the cost of the alternate SoC, coagulation factors and bypassing agent.[109]

Studies have also found that the annual amount of CFC use is similar whether treatment is received prophylactically or on-demand.[110] Cryoprecipitate and FFP treatments, while more affordable and more commonly provided in MICs, carry greater risks of blood-borne diseases and volume overload.[111] The additional medical costs resulting from such adverse events, which are more likely to occur in patients treated in countries like China and Thailand due to the SoC used, may not be fully captured in our data.

Table 9: Hemophilia average annual medical costs per patient

	Brazil	Colombia	Egypt	China	Thailand	Taiwan	Australia
Medical costs (USD, 2020)	30,021	46,627	44,130	9,309	6,390	43,200	81,424
Medical costs / GDP per capita	4.34	8.79	**12.36**	0.89	0.91	1.51	1.57
Key:	*SoC reflects international best practice*		*SoC is relatively up to date but with remaining deficiencies across the countries in scope*			*SoC is outdated across the countries in scope*	

Source: CRA analysis of multiple sources (See Appendix B for complete list of sources); bolded figure represents highest cost figure proportional to the GDP per capita

MG and IPF

For the remaining diseases, comparisons across countries show similar trends. Lessons can be drawn from national studies.[xxxiv] For MG**,** international studies show that approximately 15%, on average, of patients will have a myasthenic crisis, requiring hospitalization.[112] Inpatient treatment for such crises often involves acute care in the intensive care unit and immunologic therapies such as plasmapheresis (PE), immunoglobulin (IVIg), and corticosteroids.[113,114] Access to long-term immunosuppressant treatment reduces the probability of a myasthenic crisis and therefore the impact of hospitalization. As a result of the intensive healthcare required for myasthenic crises, this is the key driver of medical costs. We would expect countries with lower access to long-term immunosuppressant treatment to have higher hospitalization costs, but we were not able to substantiate this assumption.

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xxxii Hospitalizations decreased from 19% in 2015 to 10% in 2020, and medical care by interdisciplinary teams increased from 39% in 2019 to 48% in 2020. See DiMinno, G. G., Araujo Cabrera, L. M., Loayza Urcia, N., Bordone, R., Murillo, C. M., Beltran, J. C., & Mathew, P. (2022). Prophylaxis and hemophilia care in LATAM: Baring it all—Highlights from the CLAHT 2021 symposium. *EJHaem*, 3(4), 1287–1299.

xxxiii Original cost reported in USD 2018 (498,947) and has been updated to USD 2020 for consistency with this study's estimates reported across diseases and countries.

xxxiv All estimates of medical costs for the diseases described in the remainder of this section—MG, IPF, GD, and MPS II—are reported in Appendix A.

With IPF, the costs related to hospitalization, emergency room visits, and acute exacerbation can be expected to be the largest contributor in MICs. Anti-fibrotic therapies reduce the risk of hospitalizations for persons with IPF by slowing the decline in lung function and development or exacerbation of comorbidities.[115,116] In Australia, a HIC, nearly 70% of medical costs are from medication, while a much smaller 18% of medical costs are due to hospitalizations. Furthermore, the average length of stay in hospital for persons with IPF admitted to hospital in Australia was 2.8 days.[117] By contrast, in China, prior to the availability of anti-fibrotic medications, the average length of stay in hospital for IPF patients was 10 days.[xxxv,xxxvi] This provides evidence to support the hypothesis that treatment in MICs changes the composition of medical costs.

GD and MPS II

Regarding GD and MPS II, in countries providing access to ERT as the SoC, medical costs are significantly higher compared with countries primarily or exclusively providing supportive care and treatment. In these countries, ERT represents the key cost driver and almost the entire composition (> 99%) of all of this study's estimates of the medical cost of GD.[118] In countries with limited access to ERT for GD, a larger proportion of the medical cost is attributed to inpatient and outpatient care, while treatment costs constitute a smaller proportion (~72%). Similarly, for MPS II, despite clinical guidelines recommending ERT, its high cost prevents the majority of patients in MICs from accessing it, thereby restricting treatment options to supportive care and symptomatic treatment. A study in China of persons with lysosomal storage disorders found that while the direct medical costs of patients receiving ERT were significantly higher than those of patients who did not receive ERT, the indirect costs were nearly tenfold higher for patients not receiving ERT, attributed to higher rates of absenteeism and greater need for caregiver support.[119]

A separate and important issue that deserves consideration is the direct medical cost borne by patients. In many MICs, where the public sector is usually under-resourced to provide effective coverage of treatment to all PLWRD, patients are more likely to face catastrophic out-of-pocket expenditure.[120] While we were not able to quantify this cost, we can assess its impact from the literature. For instance, in Colombia, a study showed that the total direct costs of multiple myeloma for 2,132 patients was USD 188 million, of which 75% was attributed to expenses not covered by the Health Benefit Package.[121,122] In China, for hemophilia,[123] the majority of persons with hemophilia and their families encounter catastrophic health expenditure (CHE), and many persons with hemophilia require hospitalization. One study suggested that over 80% of persons with hemophilia encountered CHE and 25% were hospitalized in the past year.[xxxvii] Another study from China found that the costs from IPF could impoverish 121.98 thousand urban and 94.62 thousand rural residents, respectively.[124] Despite the important implications this has for equality in access to care, with wealthier PLWRD having better opportunities,[125] data granularity across diseases and countries is sparse and does not sufficiently document the burden to patients and their families.

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xxxv The study looked at IPF patients discharged from the Beijing Chao-Yang Hospital between 2012 and 2015. See: Zheng, Xiao-Fen, Bing-Bing Xie, Yan Liu, Ming Zhu, Shu Zhang, Cheng-Jun Ban, Jing Geng et al. Direct medical costs of hospitalized patients with idiopathic pulmonary fibrosis in a tertiary hospital in China. *Chinese Medical Journal* 133, no. 20 (2020): 2498–2500.

xxxvi Access to anti-fibrotic medication has improved in China in recent years. This is reflected in our estimates of the medical costs in China. See, for example: Richeldi, L., Rubin, A. S., Avdeev, S., Udwadia, Z. F., & Xu, Z. J. (2015). Idiopathic pulmonary fibrosis in BRIC countries: the cases of Brazil, Russia, India, and China. *BMC Medicine*, 13(1), 1–9.

xxxvii CHE is defined as where annual hemophilia related costs exceeded 40% of annual non-food household expenditure. See, for example: Wang, X., Zhang, L., Zhang, P., & Chen, W. (2022). EE502 Economic Burden of Patients with Hemophilia in China. *Value in Health*, 25(7), S433.

The access to effective treatments has implications for the composition of the estimated indirect cost of rare disease

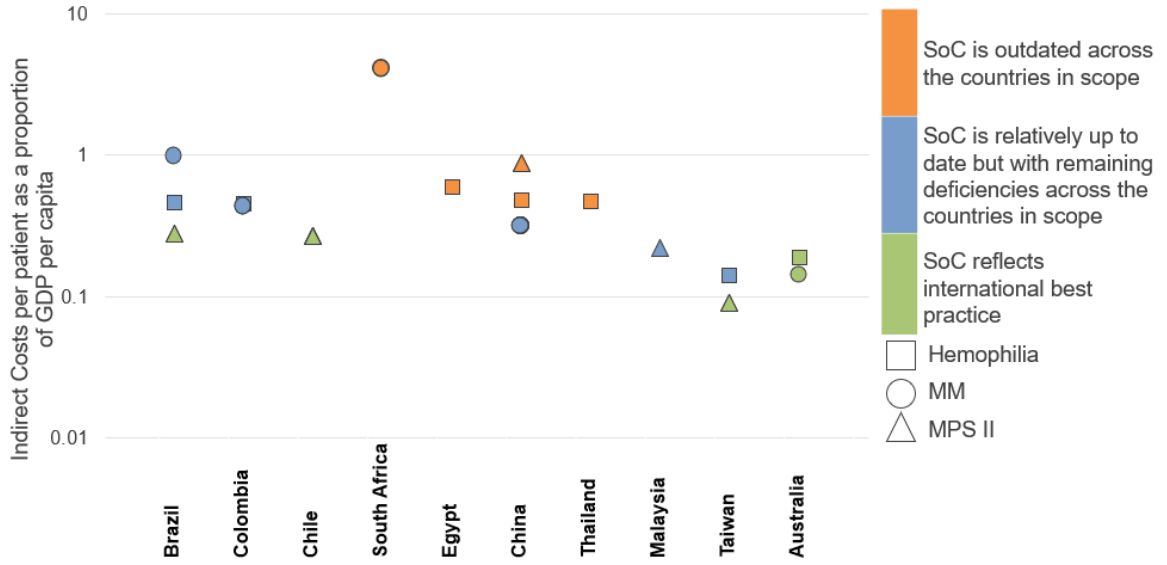
It is also possible to compare the indirect costs if countries have a SoC that reflects international best practice. For hemophilia, MM, and MPS II, the absolute and relative indirect costs, which account for the country's average income, are reported in Table 10 and depicted graphically in Figure 7 below. For all three diseases, a higher proportional indirect impact is observed in countries with an outdated SoC (South Africa, Egypt, and China, respectively).

Table 10: *Average indirect costs per patient, as a proportion of GDP per capita (MM, Hemophilia, MPS II; USD, 2020)*

Indirect costs per patient (USD)	**Brazil**	**Colombia**	**Chile**	**South Africa**	**Egypt**	**China**	**Thailand**	**Malaysia**	**Taiwan**	**Australia**
Hemophilia	3,181	2,370			2,112	4,971	3,265		3,921	9,961
/GDP per capita	0.46	0.45			**0.59**	0.48	0.47		0.14	0.19
MM	6,660	2,280		23,555		3,236				7,317
/GDP per capita	0.96	0.43		**4.10**		0.31				0.14
MPS II	2,148		3,532			3,428		2,717	5,304	
/GDP per capita	0.28		0.27			**0.88**		0.22	0.09	
Key:	*SoC reflects international best practice*		*SoC is relatively up to date but with remaining deficiencies across the countries in scope*				*SoC is outdated across the countries in scope*		*Not estimated*	

Source: CRA analysis of multiple sources (See Appendix B for complete list of sources); bolded figure represents highest cost figure proportional to the GDP per capita

Figure 7: Average indirect costs per patient / GDP per capita (MM, Hemophilia, MPS II; USD, 2020)



Source: CRA analysis of multiple sources (see Appendix B for complete list of sources)

There is some supporting evidence that improved access to the most effective treatments reduces unplanned hospitalizations and comorbidities from the disease, therefore alleviating some of the indirect impact of hospitalizations placed on persons with MM and their caregivers.[126] Furthermore, access to maintenance therapy extends remission and enables productivity of both persons with MM and their caregivers.[127] Hemophilia can be well managed when there is access to the most effective therapies. However, complications from the disease—such as recurrent or prolonged bleeding—are exacerbated when persons with hemophilia do not receive the optimal SoC, affecting the productivity of both persons with hemophilia and their caregivers.[128] Access to the most innovative therapies, such as extended half-life recombinant therapies, also allows for self-administered and less frequent subcutaneous injections, alleviating some of the time impact of treatment on patients and healthcare systems.[129]

For MPS II, ERT improves symptoms and delays disease progression; therefore, this treatment can reduce the impact placed on caregivers and their productivity loss.[xxxviii] Higher proportional indirect costs can be observed in China, which does not provide access to the most innovative SoC compared with countries where ERT is available. The indirect costs are likely higher due to reduced access to diagnosis for MPS II.

Although the indirect cost analyses for MG, IPF, and GD are not included in the main analysis, similar qualitive evidence exists and there is a similar pattern (Appendix A). For MG, indirect cost estimates due to lost productivity and early retirement of both patients and caregivers represent a significant proportion of the total socioeconomic impact. This is particularly high in countries such as China, Thailand, and Malaysia, where there is a lower relative expenditure on healthcare.[xxxix] Similarly, for IPF, a high indirect impact on persons with IPF and their caregivers can be estimated, due to severity

[xxxviii] Indirect costs to persons living with MPS II are not estimated as the life expectancy with the disease—even when the optimal SoC is received—is approximately 16 years.

[xxxix] See Appendix A.

of the disease and the lack of access to anti-fibrotic medication (for example, in China).[xl] In GD, if patients can access ERT, symptoms manifestation and disease progression are reduced.[130] As a result, patients are more likely to be able to maintain employment—although only evidence in high income countries could be identified in this study.[xli]

As the indirect costs depend on the impact of the disease on life expectancy and quality of life, and on how the treatment can minimize this impact, the composition of these costs varies considerably across diseases. For instance, in severe and life-shortening childhood-onset diseases, the driver of indirect costs is likely to be the impact on missed productivity. In adult-onset diseases, the indirect costs are more likely to reflect the impact on family and caregivers' lives. This is consistent with the data collected:

- The highest impact on employment is expected to be for persons with GD, given a relatively longer life expectancy.[131] There is a minimal impact on employment for MPS II, as even with an effective SoC uptake, the average age of mortality for these patients is 16 years, below the average working age.[132,xlii]
- Looking at the impact on caregivers, we observed data from an upper-middle income country (Turkey), where it was reported that 55% of persons with hemophilia require a non-formal caregiver, with 41% of these caregivers missing an average of 98.4 working days.[133]
- Data on the average labor force participation of PLWRD in each country also provide insight into the socioeconomic impact. For example, for the age groups impacted by MM (determined by average age of onset of the disease in each country or region), labor force participation ranged from only 15% in Australia to 83.5% in Kenya.[xliii,134]
- Finally, the data shows that the aggregated labor force participation (LFP) for people in MICs is higher relative to HICs for the post-retirement (65+) age group. This means that the indirect impact due to lost productivity is higher for persons with diseases with an older age of onset—such as MM, IPF, and MG—as more persons diagnosed with these diseases are still active participants in the labor force in MICs compared with those diagnosed in HICs.[135]

3.5 Finding 5: The impact on patient caregiver experience is challenging to quantify but remains critical

Some of the most important elements of the socioeconomic impact of diseases are those that fall on patients, their caregivers, and their families. Overall, it is difficult to quantify and compare all the indirect cost elements given the lack of necessary standardized data. However, the available information suggests that the magnitude of these (relative to income) is similar to the one observed in HICs, and qualitative evidence suggests these represent the tip of the iceberg.[136]

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xl See Appendix A.

xli A study in the UK found that 69% of respondents were receiving ERT and 27% receiving oral SRT; only 4% were untreated. In this study population, only 16% reported not being able to work due to their health. The remaining 19% worked full time, 28% worked part-time, and 36% were retired. Gauchers Association. (2019, June). https://www.gaucher.org.uk/storage/files/An_Insight_from_Gaucher_patients_aged_45_and_over_in_the_UK.pdf

xlii See Appendix B for a complete list of sources used to estimate the indirect and mortality impact.

xliii A limitation for the indirect costs is the use of labor participation rates for this calculation, which does not incorporate the informal labor sector. In lower-income countries, the informal labor sector tends to absorb most of the expanding labor force in the urban areas.

There is a relationship between the investment in healthcare and mortality outcomes

It would be ideal to estimate the mortality costs associated with all the diseases, but it was possible to collect data only for some of the diseases in scope. There are also methodological challenges in making these comparisons, because although some countries, especially HICs (such as Australia), commonly use lost years of life in economic evaluations, in many other countries the value of lost years of life is not seen as a useful or appropriate metric.

However, some observations can be made, as although there are many factors affecting mortality across countries, there is considerable evidence to suggest that the level of investment in diagnosis, treatment, and management of diseases in MICs lowers life expectancy:

- Mortality rates for MM are higher in South Africa, reflecting the delayed diagnosis and outdated SoC available.[137]
- For hemophilia, when there is high quality healthcare and adequate access to innovative therapies, mortality is low.[138] However, in countries where access to innovative therapies is limited and a sub-optimal SoC is available, the life expectancy disadvantage is high—64%, 77%, and 93% in upper-middle-, lower-middle- and low-income countries, respectively.[139]
- For IPF, earlier deaths could be reduced in MICs by improving access to anti-fibrotic medicines.[140]
- For MG, the mortality impact is almost zero if it is well managed. Approximately 10%–20% of persons with MG will have a myasthenic crisis, requiring hospitalization. In the 1960s, such a crisis would lead to mortality in as many as 80% of cases. However, with the development of and access to novel therapies and intensive care techniques, this figure is now lower than 5%.[141] While treated persons with MG have a normal life expectancy, many persons living with MG in MICs remain unidentified until reaching a critical level of illness.[142] A study in China describes that more than half of hospitalized persons with MG were newly diagnosed and the resultant admission mortality rate among all admitted persons with MG was as high as 14.7%.[143]
- For MPS II, although the treatment uptake can have a significant impact on the severity of symptoms, progression of the disease, quality of life, and well-being, the evidence suggests that it has no impact on life expectancy.[144]

Ultimately, it is likely that a higher mortality rate is one of the most significant consequences associated with rare diseases, especially in MICs. However, it is challenging to quantify this. There is, however, compelling evidence that the difference in investment in health and social care provision has an impact on life expectancy for many patients.

The impacts on quality of life and transportation costs are significant, but challenging to quantify

To understand the impacts on quality of life and the level of transportation costs it was also necessary to draw on the available literature, as it is not possible to compare data across countries and regions. There are a range of estimates from patient surveys or established patient registries, which may guide the development of statistics that could be used in future research.

There is evidence that PLWRD and their caregivers are at higher risk of experiencing poor quality of life, increased mental health issues, social isolation, and poor work-life balance.[145,146] For example, a study of persons with lysosomal storage disorders in China, including GD and MPS, found that their quality of life was impacted, with 80.6% of persons experiencing pain and/or discomfort, and 74.2%

experiencing anxiety and/or depression.[147] Studies in both Egypt and Australia found that depression was common in persons with IPF.[148,149]

Similarly, for MM, persons with the disease suffer from a wide range of comorbidities, experiencing physical pain as well as mental and emotional disorders. This not only affects their earning power and ability to engage in productive work but also means that most require significant levels of physical assistance, often from informal caregivers.[150] A Brazilian study on MM found that 85% of the surveyed physicians highlighted that they consider the impact of treatment on quality of life during decision-making.[151] A Malaysian study considering the quality of life of persons living with MG found that those with more severe disease experienced reduced quality of life.[152] Furthermore, a study in South Africa found that persons with MG experienced higher levels of anxiety, tension, fatigue, and confusion than did controls.[153]

Looking at hemophilia, a study in China found that the health-related quality of life of persons with hemophilia is impacted, and those with severe hemophilia reported a lower utility score than those with mild or moderate hemophilia.[154] A similar study focused on the impact of hemophilia on children aged 3-16 years and their caregivers in Egypt, finding that 20% were “dissatisfied or very upset,” and an additional 36% of the were “neither satisfied nor upset.” Furthermore, family caregivers face financial strains because they are not financially compensated for their caregiving responsibilities.[155]

These studies provide useful data points but illustrate the challenge of estimating the socioeconomic impact of RD based on the existing publications:

- They use different metrics to measure quality of life, with some studies using the standard metrics used in cost-effectiveness studies, and others using ad hoc surveys or patient and caregiver self-reported outcomes. In some studies, caregivers report that their quality of life has been impacted (emotional, social, or financial impacts).[156] In other studies, patients respond to surveys according to standardized scales, such as the Hamilton Anxiety Rating Scale (HARS) or Hamilton Depression Rating Scale (HAMD). [157]
- The counterfactual of these studies varies, with some studies reporting the result for PLWRD, whilst others compare this to a population “average.”

A similar result is found when we look at transportation costs. Various approaches were employed across studies. Some focused on self-reported outcomes of the financial impact: they show that patients living in rural areas are burdened with additional travel time and costs to receive treatment. This is particularly important in MICs, where the distance traveled to receive treatment can be significant. For instance, in Latin America, many PLWRD must travel long distances to access care, but a study has shown that less than 3% of the Latin American population is financially able to travel for medical treatment.[158,159]

Other have captured the length of travel time required and the associated costs. A study in hemophilia has shown that, on average, persons with hemophilia travel for 79.4km to receive treatment in South Africa: the mean transportation costs were evaluated to be around USD 13 per visit, which corresponds to 1.4% of the mean family monthly income.[160] Often these studies focused on geographically similar countries. There are similar results reported for Algeria, India, Morocco, and Oman.[161]

In some cases, publications described the consequence of the travel costs. Their findings show that the unaffordability of travel can have implications on timely diagnosis. For instance, a large proportion (43.5%) of persons living with GD in China reported that they had to travel to the tertiary hospitals in other provinces to get a confirmed diagnosis.[162]

4. Conclusions: Cross-cutting themes

The purpose of this report is to review the evidence on the socioeconomic impact of rare diseases across MICs. Evidence shows that the socioeconomic impact of rare diseases in MICs is significant (and relative to GDP of a similar order of magnitude to HICs). It is also clear that this impact is often less visible in MICs due to underreporting of cases, diagnostic weaknesses, and a different composition of medical costs (with lower treatment costs but higher emergency and hospitalization costs), including higher costs imposed on carers due to productivity loss.

Five main themes have been derived across the countries and diseases investigated:

1. **The data on prevalence reflect only part of the population living with rare diseases.** Improving data collection on prevalence is valuable, especially to accurately evaluate the population impact and include rare diseases in policy planning. Estimation of prevalence will improve with better diagnosis. Looking at the data sources, the estimation of prevalence has also improved by expanding data collection across multiple sites of care (not just specialist hospitals) and by establishing standardized and linked patient registries. Registries take time to design, initiate, and build, but add value over time. Improved prevalence data allow stakeholders to better understand the impact of rare diseases, to define the most appropriate approach to address them, and to help governments develop policy planning tools. For example, some studies have used population-based registries to estimate the socioeconomic impact of MM.[163,164,165,166] Patient organizations and industry could support the establishment of registries on a global scale. For instance, the WFH launched the World Bleeding Disorders Registry in 2018, a global registry collecting standardized clinical data of persons with hemophilia; as of 2023, over 70% of participants in the registry are from low- or lower-middle-income countries.[167] Furthermore, the International Collaborative Gaucher Group Gaucher Registry, established in 1991, provides data on demographic, genetic, and clinical characteristics of more than 6,000 persons with GD across the world, including MICs such as South Africa, the Philippines, and Lebanon.[168,169] The registry was the result of a collaborative effort across international experts and industry.

2. Low diagnosis rates do not reduce the socioeconomic impact but hide the costs. In this study, the quantitative analysis focused on the cost of diagnosed and treated patients. However, the literature suggests that the cost of the undiagnosed—and therefore untreated—patients is sometimes higher than treated patients. Furthermore, an early diagnosis has important clinical benefits and reduces the socioeconomic impact to patients and caregivers, especially in diseases with a childhood age of onset (publications on GD and MPS II support this). **Investment in newborn screening (NBS) programs and periodical review of the diseases on the panel improve accurate and timely diagnosis rates**. As seen in the literature review (see Chapter 3), the number of diseases considered and NBS coverage vary significantly across countries. NBS programs in HICs usually provide support along the patient journey to ensure the diagnosis confirmation and timely treatment and care.[170] For example, in Australia, NBS is fully covered in public hospitals, testing for 27 conditions, with 5 further conditions now being incorporated.[171] New conditions proposed for inclusion in the NBS panel are reviewed by an independent non-statutory committee; MPS II is currently under review.[172] There is a clear approach defined in Australia's NBS National Policy Framework to respond to abnormal NBS results, including timely confirmatory diagnostic testing, documentation of results, and follow-up care for the family.[173] Further, implementation of NBS takes place in stages and does not require an immediate rollout of a comprehensive NBS platform. The Philippines NBS program serves as a model of successful implementation in an MIC.[174] From a pilot in 1996 to a sustainable program covered by national insurance, the program's success can be attributed to national policies, dedicated partners, and continuous education of HCPs to perform NBS.[175] Several pilot programs of NBS for lysosomal

storage disorders (for example, MPS II and GD), have been implemented in Brazil.[176,177] One such pilot demonstrated the viability of a digital microfluidics method performed in a standard clinical biochemistry laboratory, demonstrating its feasibility in a resource-constrained setting with less advanced laboratory infrastructure.[178] While this approach may not translate to a reduced socioeconomic impact in the short term, it highlights the value of adapting strategies to local needs.

3. **The magnitude of the socioeconomic impact of rare diseases per diagnosed person is similar across countries, once normalized by income level.** For this reason, rare disease should be given the same priority across any economy, although the specific actions to address it will need to consider national contexts. Prioritization of universal healthcare (UHC) is critical to alleviate this impact. In 2019, countries adopted the UN Political Declaration on UHC, which includes PLWRD, as a first step towards ensuring no person is left behind.[179] However, in MICs, achieving UHC remains challenging due to a lack of funding, inequitable and inadequate access to health insurance coverage, and amplification of health system vulnerabilities due to public health emergencies and climate change related natural disasters.[180] These challenges will need to be addressed as countries seek to demonstrate their commitment to UHC, and may require more efficient and equitable fundraising and pooling of resources. As this research demonstrates, these investments can have offsetting costs and benefits which should be accounted for when making funding decisions. To reduce the global magnitude of the socioeconomic impact of RD, greater investment into strengthening health systems and ensuring dedicated funding for RD will be required to improve health and social services for PLWRD.

4. **Globally, the cost of misdiagnosis or late diagnosis and the challenge of accessing and traveling to a specialist is often overlooked. The literature suggests that these costs are greater in MICs than in HICs.** Investing in the training of specialists and improving other HCP awareness would support adequate and timely diagnosis for the rare diseases that are not diagnosable via NBS and/or manifest later in life. In HICs this is organized through centers of excellence, offering regular free trainings to educate physicians. Although this may not be directly replicable in MICs, there are significant benefits in training sessions organized by multidisciplinary teams to cover all aspects of diagnosis and treatment, from raising awareness of early symptoms to providing tools for physicians to diagnose in a timely fashion. For instance, the Taiwan Foundation for Rare Disorders has organized training courses for medical personnel, social workers, and patient groups since 2000, covering the use of specific medical equipment.[181] Establishing national or regional reference centers can ensure quality and timely diagnosis and treatment. For example, Brazil has a well-established diagnostic pathway for all types of MPS. The Medical Genetics Service of Hospital de Clínicas de Porto Alegre (MGS/HCPA) is a well-known national reference center that has received samples from persons with suspected MPS since 1982.[182] Where resource constraints are severe, it may be possible to extend these reference centers beyond the borders of a single country, which would facilitate regional outcomes for PLWRD. The European Reference Networks demonstrate the value in virtually connecting HCPs to exchange knowledge and therefore improve patient care.[183] In that spirit, the Global Network for Rare Diseases (GNRD), led by RDI, aims to connect existing networks to form a global network, improving health equity, RD awareness, and coordination of care.[184]

5. **Investment in country-specific guidelines and in effective RD diagnostics and treatments is often seen as challenging, given budget restrictions**. The quantitative and qualitative results (see Chapter 3) show that there are significant variations in clinical guidelines and SoC across MICs. Multi-stakeholder collaboration across the industry, academia, patient organizations, and healthcare professionals can inform country-specific guidelines, with best practice sharing

facilitated by the establishment of reference centers (Theme 3).[185] This study shows that investing in effective diagnostics, treatment and healthcare infrastructure (including patient registries and HCP training) can have offsetting costs, both in terms of the costs on more emergent areas of the healthcare system and the costs placed on PLWRD and their caregivers. Moreover, this would have an invaluable benefit on the quality of life and life expectancy. This is a common finding across diseases, although the types of cost offsets vary from one disease area to another.

In conclusion, this study shows that the scale of the socioeconomic impact of rare diseases in MICs per patient is significant (and comparable to that in HICs). It was not possible, however, to develop aggregate estimates of the socioeconomic impacts, as in many cases, the data are imperfect. It will be important to develop more robust and granular data on rare diseases, as existing evidence misrepresents the number of people affected, overlooking the cost to patients and families as well as wider socioeconomic costs. It will also be important to further understand the composition of the socioeconomic impact, in order to drive policies and investments that can reduce the impact on patients and their families, use healthcare resources more effectively, and have a positive impact on economic participation.[186]

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A.1 Outputs from the estimation of the socioeconomic burden

Patient prevalence

The patient prevalence of each rare disease was used to assess the impact of the disease in each country, and in the next tables the cost per patient and the cost across each population are reported.

Appendix Table 1: Patient prevalence, per 100,000

	Brazil	Colombia	Chile	South Africa	Ghana	Kenya	Egypt	China*	Thailand	Malaysia	Taiwan	Australia
GD	0.258	0.375		0.083		0.017		1.129			1.356	
Hemophilia	6.168	7.528	9.290	4.022	1.234	1.406	5.800	1.528	2.558	3.434	7.900	11.019
IPF	5.231	7.817	40.097	10.165	3.702	3.594	7.258	11.767	4.352	4.561	11.492	23.588
MG		14.190	8.360	9.477			9.570	4.198	3.549		14.000	11.710
MM	6.364	6.558	11.435	4.830	0.758	2.543	1.543	3.639	4.611	2.660	8.293	28.111
MPS II	0.104	0.106	0.160				0.053	0.195	0.011	0.099	0.339	0.133

Key: **Based on international databases**; **Based on prevalence per live births**; **Based on incidence figures**; **Prevalence from peer-reviewed academic articles**; **Missing data**

**No prevalence data was reported for hemophilia in China for the year 2020, so the total cost applies prevalence for 2021*

Source: CRA analysis of multiple sources

Estimated cost outputs by disease

All costs reported are in USD for the year 2020. For costs where the source reported a different currency and/or year, the cost value was converted to USD using the average exchange rate for the local currency in the reported year and/or then adjusted to the year 2020 using the average USD inflation rates for the relevant previous years.[1,2,3,4]

A complete list of sources used as inputs to the estimates are presented in Appendix B.

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Appendix Table 2: Multiple myeloma (MM) cost outputs (USD)

	Brazil	Colombia	South Africa	China	Australia
Medical cost per patient	21,630	22,302	4,496	15,920	37,216
Indirect cost per patient	6,660	2,280	23,555	3,236	7,317
Total cost per patient	28,290	24,582	28,050	19,156	44,533
Total cost (million)	383.8	82.1	79.7	983.7	321.2

Source: CRA analysis of multiple sources

Appendix Table 3: Hemophilia cost outputs (USD)

	Brazil	Colombia	Egypt	China*	Thailand	Taiwan	Australia
Medical cost per patient	30,021	46,627	44,130	9,309	6,390	43,200	81,424
Indirect cost per patient	3,181	2,370	2,112	4,971	3,265	3,921	9,961
Total cost per patient	33,202	48,997	46,242	14,280	9,656	47,121	91,385
Total cost (million)	436.6	187.9	288.2	307.9	17.7	87.7	258.3

*No prevalence data was reported for hemophilia in China for the year 2020, so the total cost applies prevalence for 2021

Source: CRA analysis of multiple sources

Appendix Table 4: Idiopathic pulmonary fibrosis (IPF) cost outputs (USD)

	Brazil	Chile	China	Australia
Medical cost per patient	13,606	6,393	12,760	22,404
Indirect cost per patient	1,720	3,484	2,128	11,219
Total cost per patient	15,325	9,877	14,888	33,624
Total cost (million)	171.8	77.2	2,473.7	203.7

Source: CRA analysis of multiple sources

Appendix Table 5: Myasthenia gravis (MG) cost outputs (USD)

	Colombia	China	Thailand	Malaysia	Taiwan	Australia
Medical cost per patient	7,965	1,026	2,561	3,345	4,460	14,423
Indirect cost per patient	1,691	3,076	2,141	2,889	5,623	12,423
Total cost per patient	9,656	4,103	4,702	6,234	10,084	26,846
Total cost (million)	69.8	243.1	11.9	0.9	33.3	69.1

*The increased risk of mortality resulting from unmanaged symptoms of MG is qualitatively described; however, as overall mortality is low and the disease is not systematically life-shortening, mortality costs are not quantified.

Source: CRA analysis of multiple sources

Appendix Table 6: Mucopolysaccharidosis type II (MPS II) cost outputs (USD)

	Brazil	Chile	China	Malaysia	Taiwan
Medical cost per patient	289,810	605,384	5,205	42,073	306,226
Indirect cost per patient	2,148	3,532	3,428	2,717	5,304
Total cost per patient	291,958	608,916	8,633	44,790	311,531
Total cost (million)	65.0	18.8	23.7	1.5	24.9

Source: CRA analysis of multiple sources

Appendix Table 7: Gaucher disease (GD) cost outputs (USD)

	Brazil	Colombia	South Africa	Kenya	China	Taiwan
Medical cost per patient	167,735	458,245	48,363	2,024	44,111	297,874
Indirect cost per patient	6,787	4,975	5,409	1,768	9,644	17,594
Total cost per patient	174,523	463,220	53,772	3,792	53,755	315,468
Total cost (million)	96.2	88.5	2.6	0.03	856.4	100.8

Source: CRA analysis of multiple sources

A.2 Sources used to define the socioeconomic framework and to estimate socioeconomic burden

This appendix provides the references used to define the socioeconomic framework and to calculate the socioeconomic burden across the rare diseases. The sources are grouped by the type of information they were used for: (i) socioeconomic studies, (ii) prevalence, (iii) to estimate medical costs, (iv) indirect costs, and (v) mortality costs. Some of the sources are further subdivided across the rare disease they correspond to; however, when a source was relevant across various rare diseases, it was grouped into a general heading.

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