

FINAL REPORT
BREAKING DOWN THE BURDEN OF RARE DISEASES
IN SOUTH AFRICA

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Commissioned & Funded by the
Innovative Pharmaceutical Association
South Africa (IPASA)

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The final version this report will be made available online at: <https://ipasa.co.za/resource-centre/> and <https://rdai.co.za/>

Executive Summary

Rare diseases (RD) comprise a diverse group of over 6 000 conditions that collectively affect more than 350 million people globally. While each condition is individually rare, the collective burden is substantial. In South Africa (SA), the burden of RD has been poorly quantified due to a lack of national surveillance, limited diagnostic capacity, and fragmented healthcare responses. The globally accepted estimate that 6–8% of a population may be affected by RD has often been used in South Africa, equating to 4.2 million individuals. However, this broad estimate lacks granularity, limiting its usefulness for policy planning, resource allocation, and advocacy.

Aim

This study was commissioned by the Rare Disease Access Initiative (RDAI) and funded by the Innovative Pharmaceutical Association South Africa (IPASA), following a request from the South African National Department of Health, to provide a more accurate and detailed estimate of the burden of RD in SA. It aimed to determine the point prevalence of RD in SA, identify affected subgroups (e.g., by age, inheritance, disability), and estimate the number of patients requiring high-cost therapies, thereby enabling targeted policy and service responses.

Method

The study applied the Orphanet epidemiological methodology, which has been previously used internationally to estimate RD prevalence. Using four curated Orphanet datasets (epidemiology, natural history, functional consequences, and medical domains), the study applied inclusion/exclusion criteria to identify 3 728 unique RDs. Microsoft Power BI and Excel were used to integrate and analyse these datasets against South African population statistics (2024). Point prevalence estimates were divided into direct (based on population-level data) and indirect (based on individual case and family reports). Additional analyses covered age of onset, inheritance, disability, medical domain and high-cost treatments for the sub-set of included RD.

Key Results

Estimated National Burden: The mean RD point prevalence in SA was estimated as 4.8% (range: 3.7–5.9%), equating to 3 030 204 RD patients (min: 2.3M; max: 3.7M).

Distribution of Burden:

- Just 404 RDs (11%) account for 98% of affected individuals.
- Most RDs are autosomal recessive (42%) or autosomal dominant (27%).

Age of Onset: 77% of RDs begin in childhood, with 7% presenting antenatally and 11% in adulthood.

Disability: Over **1.3 million South Africans** with RD experience functional limitations or participation restrictions.

High-Cost Drug Need: Of the subset of Orphanet RD included in this study, less than 5% of RD patients require high-cost drugs. Of 59 RD with such therapies, only 25

treatments are approved in SA, of which only a limited number are accessible and available to RD patients.

Implications

- The RD burden in SA is significant, widespread, and largely paediatric in onset, underscoring the urgency of investing in early diagnosis, comprehensive newborn screening, and community genetic services.
- Given the concentration of disease burden in a limited subset of RDs, prioritising these 400+ conditions could provide a high-impact entry point for service expansion.
- Only a small fraction of patients require expensive treatments, debunking the myth that RD care is unaffordable by default. Further detailed analysis is required to quantify the specific burden of patients requiring high-cost treatments. Strategic access to high-cost drugs remains essential but should not overshadow the need for low-cost, high-yield, available interventions.
- The use of population prevalence estimates may underestimate the true burden of RD due to high early mortality; future efforts should include birth prevalence and local empiric studies, especially for vulnerable and underdiagnosed groups.

Conclusion

This study offers the first detailed, evidence-based estimate of the RD burden in South Africa using internationally recognised data and methodology. The findings support the need for urgent action to improve diagnostic capacity, workforce development, policy alignment, and equitable access to care. It provides a strong foundation for national planning, international reporting obligations, and achievement of the Sustainable Development Goal (SDG 3) targets in 2030 and the other recent World Health Assembly commitments to RD.

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Introduction

The Rare Disease Challenge

Rare diseases (RD) collectively represent a significant burden of diseases, with over 350 million of the global population impacted by these conditions (1-3). The majority of RD are the result of genetic or partially genetic causes, while a small proportion may be acquired through environmental exposure, infection etc (4). As a result, most RD are present from birthⁱ, although they may only manifest later in childhood or adulthood. The collective of RD is highly heterogeneous and is currently estimated to include between 6000 to 7000 conditions (7).

The Diagnostic Odyssey

Despite the heterogeneity of the RD collective, these conditions share common challenges that set them apart from other diseases - related to diagnosis, treatment and care (8). This includes an extended diagnostic journey or “odyssey”, taking an average of >5 years for an accurate diagnosis (9), and even longer in severely resource constrained settings, such as many low- and middle-income countries (LMIC). This journey often includes several misdiagnoses, extended hospital stays and multiple visits to specialists and other health care professionals (HCP), before a correct diagnosis is received (10, 11). Consequently, due to unhampered disease progression, many RD patients die prematurely before receiving an accurate diagnosis - and those that do survive, often live with preventable, unmitigated lifelong disability and poor quality of life, unable to access timely, appropriate healthcare services and often require life-long, full-time care. A high proportion of RD affect children early in infancy/childhood and these diseases progress rapidly, preventing a third of paediatric RD patients, the most vulnerable of society, from reaching their 5th birthday (12).

While it is impossible for HCP to have in-depth knowledge of all 6000+ RD, a major contributor to inadequate diagnostics is the lack of knowledge, awareness and education of HCP, who receive minimal undergraduate training on these conditions. Generally, HCP are taught to think of more obvious, common diagnostic possibilities before thinking of the unlikely, which is said best in the aphorism coined in the 1940's by Dr Theodore Woodward, “when you hear hoofbeats, think of horses not zebras” (13).

Substantial lay-expertise is accumulated by RD patients and caregivers living 24/7 with these conditions. However, this is often disregarded and not always considered by HCP. Many RD patients, caregivers and their families also face extensive social exclusion, marginalisation and stigma (8), which combined with a lack of social support, directly impacts their quality of life.

ⁱ Most rare diseases are also considered as congenital disorders (also known as birth defects), since they are present from birth (congenital). They may be function or structural disorders (5, 6).

Few Treatment Options

The widespread myths that “nothing can be done” for RD patients and “all RD treatments are expensive” continue to persist today, despite the fact that many RD, if accurately diagnosed and referred timeously, can be well managed with low-cost treatment options. Some RD are managed by implementing strict dietary modification, such as low phenylalanine diets for patients with phenylketonuria (PKU). Similarly, some RD have low-cost treatments, such as congenital hypothyroidism (CH), which is affordably treated by a daily levothyroxine dose to replace the lacking thyroid hormone. If diagnosed early in life, this treatment prevents irreversible disease progression of CH, which causes severe cognitive and physical development issues, often requiring full-time, lifelong care.

For many RD however, there are no approved treatments available, with only 5% having a drug approved by the Food and Drug Administration (FDA) (14). Consequently, many RD patients use medicines approved for other conditions, off-label. A small proportion of RD patients require high-cost, lifesaving treatment, such as enzyme replacement therapy (ERT) and gene therapy (14). Despite their availability, many of these high-cost treatments remain inaccessible and/or unaffordable to the majority that need them, especially in resource-limited populations.

Lack of Data

One of the key stumbling blocks in quantifying the burden of RD globally is the lack of data (8). The scarcity of individual RD often limits the implementation of clinical trials and generation of real-world data, which further hinders the development of new treatments. Diagnostic challenges, including the lack of diagnostic capacity and infrastructure, misdiagnosis and a portion of RD patients remaining undiagnosed, further contributes to underreporting and subsequent inadequate corresponding political commitment to this group of conditions globally. For evidence-based healthcare systems such as in South Africa (SA), policy makers require empiric data to quantify the burden of disease and inform policy decisions and resource allocations to generate an appropriate healthcare response for those affected (8). Without this evidence-base there is no accurately perceived healthcare issue, and subsequently inadequate relevant services are deployed. This leaves many of those impacted by these conditions without access to the care they require.

However, increased worldwide recognition of RD is beginning to emerge as a result of consolidated efforts by the global RD disease community, across a wide range and at varying levels of stakeholders. This is reflected in several World Health Assembly (WHA) Resolutions, including: WHA Resolution 76.132 of 2021 addressing the challenges of persons living with a RD and their families (15); and WHA resolution 77.5 of 2024, to accelerate progress towards reducing maternal, newborn and child mortality in order to achieve the United Nations (UN) Sustainable Development Goal (SDG) targets 3.1 and 3.2 (16). A further resolution, “Rare diseases: a global health priority for equity and inclusion”, ratified at the 78th WHA in May 2025, declared RD as a global health priority under the UN Universal Health Coverage (UHC) and equity agenda. It focuses on reducing delays in diagnosis, fragmented care, and addressing the high financial/social burden faced by over 300 million people globally with RD. WHO member countries, including SA, are required to implement and report back on WHA Resolution activities and progress. Other recent global initiatives and publications also highlight a renewed RD global

impetus and focus, including the implications of this collective burden of disease and the potential consequences of not addressing the RD collective as a healthcare priority (12, 17-20).

A Global Definition of Rare Diseases

A recent key initiative by a global expert consensus study addressed existing confusion around the definition of RD, since a range of different definitions for RD have been used historically across the world. A global panel of experts, led by Rare Diseases International (RDI), developed an operational description of RD describing: 1) Which diseases are considered rare; 2) How many people are affected; and, 3) A broader context on why this impacted population demands specific attention (21). The output of this study defines RD as 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*” (21).

This milestone publication provides a reference for decision-makers across the world - enabling them to better understand, address and plan an appropriate healthcare response and a shared starting point for developing population estimates of those impacted by RD (21).

The South African Context

Located at the southern tip of Africa, SA is an upper-middle-income country according to World Bank Classification (22). In mid-2024, the South African population was just over 63 million people, distributed across nine provinces occupying an area of 1.2 million km² (23). An estimated 68% of the population reside in urban areas, with Gauteng and KwaZulu-Natal (KZN) contributing 25%, and 20% of the population respectively (23). The country sees just over one million live births annually, and in 2023 this included 168 535 (18%) births to mothers aged ≥35 and 131 609 (11.5%) to mothers aged 10-19 (24).

The neonatal mortality rate (NMR), infant mortality rate (IMR), and under-5 mortality rate (U5MR) were 12, 21, and 28 per 1,000 live births respectively, in 2020 (25). The fertility rate averages 2.41 children per woman and in 2024, life expectancy at birth was 69.2 years for women and 63.6 years for men (23). The country has been heavily impacted by HIV/AIDS, with an estimated 12.7% of the population (around eight million people) living with HIV in 2024, with the highest number of patients on antiretroviral treatment (ART) documented worldwide. The combination of high numbers of AIDS-related deaths, followed by an ongoing, successful HIV prevention programme for mother-to-child transmission (PMTCT) has led to a young population demographic today, with 27.5% (17,33 million) of the population <15 and only 9.7% (6,13 million) aged ≥60 (23). However, this is set to change in the coming century as communicable diseases continue to be better controlled, and as people live longer and face more chronic health conditions as the country transitions epidemiologically (4, 26).

Rare Diseases in South Africa

The burden of RD is yet to be quantified in SA and currently, there is no nationally coordinated surveillance of this collective by the National Department of Health (NDOH) (Personal Communication H. Malherbe, 2021). The current paper-based national

surveillance system implemented since 2006 for more obvious, common congenital disorders (CD), AKA birth defects, is estimated to be under-reporting by >95%, highlighting the lack of resources allocated to this collective of conditions, including the majority of RD (27). Modelled estimates of a sub-set of endogenous congenital disorders, including RD, have also been developed for SA, including more common early onset conditions due to chromosomal disorders, congenital malformations and single gene disorders (28).

Due to the lack of available RD data both in SA and globally, the widely cited figure of 6-8% of a population affected by RD, based on a RD definition of 1 in 2000, has been used historically to generate a rough estimate of the associated burden of disease (29). In 2022, the estimated number of South Africans affected by RD was calculated based on 7% of the population, ranging from 3.6 to 4.8 million people, with an average of 4.2 million or 1 in 15 affected by RD in the country. While this statistic has been a useful starting point for advocacy activities to motivate generally for improved health services for RD, greater granularity of the burden of RD is required for this to be more meaningful. As RD increasingly emerge as a global public health and as a national health priority in SA, it is crucial to offer a more accurate, evidence-based estimate of their prevalence, thus setting the context for this study.

Study Aim

At a meeting held on 8th March 2024 between the South African Rare Disease Access Initiative (RDAI) (30) and the National Department of Health (NDOH), a more detailed breakdown of the burden of RD was requested by Dr Lesley Bamford, Chief Director of Child, Youth and School Health and Acting Chief Director: Women's, Maternal and Reproductive Health. To enable a comprehensive response to this request, RDAI commissioned this study, funded by the Innovative Pharmaceutical Association South Africa (IPASA).

This study aimed to provide greater granularity of the burden of RD in SA, currently estimated at 4.2 million. This should provide a more accurate number of South Africans impacted by RD, including sub-categories of patients requiring different types of care, such as those living with disability and the portion requiring high-cost treatments. The result of this study should help incentivize both the national and provincial governments in SA to improve healthcare services for those impacted by these conditions.

Method

Methodology Identification

To ensure an evidence-based response to the request for more granular data on the burden of RD in the country, a preliminary literature review was undertaken in July/August 2024 to identify key publications on RD epidemiology that could potentially be applied to the South African population. Few relevant publications were identified. While several previous studies (31, 32) have generated estimates to describe the epidemiology of the RD collective - these were not comprehensive and were based on smaller groupings of

RD with limited population coverage and data, which are likely to have led to overestimates (1).

This absence of data specifically relating to RD in SA culminated in the decision to use a key, globally accepted, existing data source offering a suitable approach for this study. Within this context, studies undertaken by Orphanet epidemiologists in 2020 and 2024 using the Orphanet database were identified as offering a suitable methodology for this South African study (1, 2, 33, 34). This approach may serve as a tool for other populations to generate RD estimates, as has been undertaken by the Model Global Database for a subset of CD (28).

Orphanet and Previous Studies

Orphanet (www.orpha.net), co-founded by the European Commission (EU), is a global database dedicated to sharing knowledge on RD to improve diagnosis, care and treatment of those affected (35). It includes data on >6000 RD and is manually curated and continually updated via multiple sources including comprehensive, collaborative ongoing literature reviews collating data from scholarly sources (scientific journals, clinical research, case reports etc); national and international RD experts; specialised centres of expertise; RD registries; patient organisations and advocacy groups; clinical trials and research databases.

Since 2005, Orphanet has included annotated RD information including epidemiologic indicators and was revised in 2021 to include additional data indicators available in separate, downloadable files on functional consequences (disability), natural history and linearization (medical domains). These datasets are publicly available online from <https://www.orphadata.com/orphanet-scientific-knowledge/> and updated datasets are uploaded twice annually. Each individual RD entity included in Orphanet is identified across the different datasets by an ORPHAcode - a unique and time stable numerical identifier that is randomly assigned by the database upon creation of the entity.

Studies previously undertaken by the Orphanet team used these datasets to estimate the global point prevalence of a sub-set of RD included in the database (1,2,34). The sub-set of RD was selected by applying a series of filters or inclusion/exclusion criteria to RD entities in the Orphanet database. The total point prevalence rate for RD for this sub-set of conditions was then applied to the global population, highlighting the potential application of this approach for other populations.

Point prevalence is the proportion of a population with a specific health event or disease (in this case, RD) at a certain point in time. It is considered the most appropriate indicator for RD, *“since it provides a measure of the population burden of disease and can thus inform focused service delivery targeted at the specific needs of RD patients, pharmacoeconomic evaluation of orphan drugs, appropriate health and social service commissioning, and facilitation of clinical trials”* (1).

The latter part of this Method section details the application of this previous methodology to the South African population, based on the publications emanating from this earlier work, together with additional discussions with the Orphanet team in 2024 and 2025 to clarify the methodology and to enable Orphanet to confirm generated estimates for SA.

Dataset Selection

The four required Orphanet files were downloaded in Microsoft Excel file format from the Orphanet website (<https://www.orphadata.com/orphanet-scientific-knowledge-files/>) on 21 October 2024, together with relevant online supporting documentation (36-38). Specific datasets (dated 31 July 2024) downloaded included:

- Epidemiology of rare diseases;
- Natural history of rare diseases;
- Rare diseases and functional consequences, and;
- Linearisation of rare diseases.

Software Used

Solely using Microsoft Excel was found to be cumbersome and error prone due to the multiple datasets and data complexity of this study, highlighting the need for a more powerful data analysis tool. Specifically:

- 1) The four dataset files were downloaded from the Orphanet website in Microsoft Excel format.
- 2) Microsoft Power BI desktop software (Version: 2.137.1102.0 64-bit (October 2024) was used to import, manipulate and link the multiple downloaded Orphanet datasets using the ORPHAcode as a common data indicator.
- 3) The linked Orphanet dataset was imported back into Microsoft Excel and combined with South African population data (23) for further analysis as detailed in subsequent sections of the method.

Data Inclusions and Exclusions

Filters (inclusion and exclusion criteria) were applied to the whole Orphanet database in Excel as shown in Figure 1, to limit the analysis to the same sub-set of RD used previously by Wakap et al (1) and Yamazaki et al (2, 33, 34).

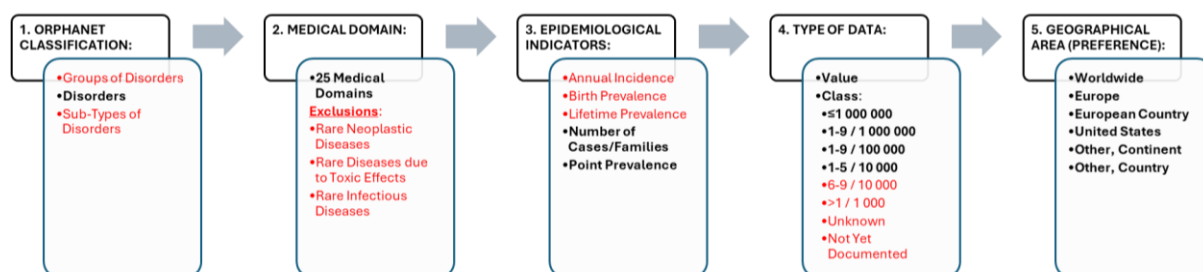


Figure 1: Selection of Orphanet data using applied inclusion/exclusion criteria as filters. Note: Red text indicates excluded Orphanet data indicators; black text indicates included Orphanet data indicators.

The inclusion and exclusion criteria were specifically applied as follows:

- 1) **Orphanet Classification:** Data for “Groups of disorders”² and “Subtypes of Disorders”³ were excluded to avoid duplicate counts. Only data for unique clinical RD entities were included, specified in Orphanet as “Disorders”. These include rare-: diseases, malformation syndromes, morphological anomalies, biological anomalies, clinical syndromes and particular clinical situations (37).
- 2) **Excluded Medical Domains:** Orphanet assigns a single "preferential parent" classification to each active, clinical entity in the linearisation dataset file. This sorts each entry (ORPHAcode) by medical specialty and prevents multiple counting of entities classified under multiple categories. Of the total 28 Orphanet medical domains, entities primarily assigned to three medical domains were excluded, specifically: rare neoplastic disease (i.e. rare cancers); rare disorders due to toxic effects (i.e. poisonings with acute/subacute clinical course); and infectious diseases.
- 3) **Epidemiological Indicators:** Only disorders with associated epidemiological data were included and of these, those specifically described by “point prevalence” were included. All disorders described by “annual incidence”, “birth prevalence”, “incidence” or “lifetime prevalence” and those with no point prevalence value (unknown or not yet documented) were excluded.
- 4) **Type of Epidemiological Data:** Only disorders with a point prevalence of ≤ 1 in 2000 (equivalent to 5 in 10 000 or less) were included. Disorders with a higher point prevalence, specifically 6-9 per 10 000 and >1 per 1000, were excluded.
- 5) **Geographical Area:** Data registered in Orphanet is collectively analysed and only the most accurate data sources meeting specific quality criteria⁴ are kept for further calculation. An average value is calculated and extrapolated to the closest larger geographical area. In this study, only one point prevalence rate or range was included per disorder. For disorders with more than one recorded geographic point prevalence listed, only one value or range was selected and used from the dataset, in the following order of preference⁵:
 - a. Worldwide;
 - b. Europe;
 - c. European Country;
 - d. United States;
 - e. Other, continent;
 - f. Other, country.

Point Prevalence Data Type

The point prevalence descriptors in Orphanet include three data types:

² Groups of Disorders: A collection of clinical entities sharing a set of common features.

³ Subtypes of Disorders: Subdivision of a disorder according to a positive criterion.

⁴ Orphanet quality criteria: Study design based on population, study with case ascertainment established using the most recent internationally accepted diagnostic criteria, and case finding method including administrative databases or hospital medical records.

⁵ Only three of the records in the Orphanet included data sources for South Africa and these were all based on individual cases and families, highlighting the need to rely on prevalence data from elsewhere.

- 1) **Class and Value:** For RD with both a numerical point prevalence value and a prevalence range, the “ValMoy”⁶ value in the Orphanet dataset (reported per 100 000 population) was used as the minimum, maximum and mean value.
- 2) **Class only:** For RD with a prevalence range, a minimum, maximum and mean value were assigned, specifically:
 - a. <1 per 1 000 000: Minimum, maximum and mean all assigned as 0.1 per 100 000.
 - b. 1-9 per 1 000 000: Minimum = 0.1 per 100 000; maximum = 0.9 per 100 000; mean = 0.5 per 100 000.
 - c. 1-9 per 100 000: Minimum = 1 per 100 000; maximum = 9 per 100 000; mean = 5 per 100 000.
 - d. 1-5 per 10 000: Minimum = 10 per 100 000; maximum = 50 per 100 000; mean = 30 per 100 000.

To prevent duplication, only one value was included per disorder (ORPHAcode), either from class and value (ValMoy), or class only (mean) as described in 1) and 2) above.

Resulting values from these two types of data (class and value, and class only) were then summed to calculate the direct point prevalence per 100 000 population.

This direct point prevalence was then used to calculate the number of South African patients using the total population (63 015 904) (23), as follows:

$$\begin{aligned} & \text{Number of South African patients} \\ &= \text{Direct Point Prevalence} \times \frac{\text{South African Population}}{100\,000} \end{aligned}$$

- 3) **Case and family reports:** For RD where there is no population-based study, Orphanet collects the number of cases or families from published case report(s), case series or recent review of the worldwide literature - and calculates the total number of cases or families reported (37). The lowest point prevalence range (<1/1,000,000) is assigned to the disorder.

In this study, for RD described by case or family reports, individual point prevalence values were not calculated. Instead, these cases were tackled as a group to calculate an indirect point prevalence, as previously described by Orphanet (1, 2, 34). To minimize the effect of changing family size this analysis was repeated using ten cases per family. Specific steps included:

- a. The global indirect point prevalence was first calculated by summing the total number of cases (ValMoy⁶) reported by cases/families, divided by the global population (8 200 000 000).

⁶ ValMoy is the mean value of a given prevalence type in Orphanet.

$$\begin{aligned} & \text{Global indirect point prevalence} \\ &= 100\,000 \times \frac{\sum \text{of cases and families (x10) reported}}{\text{Global Population}} \end{aligned}$$

- b. The resulting global indirect point prevalence rate per 100 000 population was then applied to the 2024 South African population (63 015 904) (23) to calculate the number of patients in South Africa using the previously outlined method (above) for the direct point prevalence.

Calculation of Overall Point Prevalence

The total South African point prevalence value was calculated by summing the direct and indirect point prevalences. Point prevalence estimates were summarized descriptively and presented as the number of cases per 100 000 of the population. From this, the number of RD and the number of patients for each of the point prevalence ranges were calculated.

Additional Analyses

Other analyses of the dataset were undertaken in Microsoft Excel using filters and count formula's, specifically:

Age of Onset

The distribution of the RD included in the study were counted across Orphanet age of onset categories across the life course, specifically: Antenatal: Before birth; Neonatal: Birth to four weeks of life; Infancy: 5 weeks to 23 months; Childhood: 2-11 years; Adolescent: 12-18 years; Adult: 19-65 years; Elderly: >65 years; All ages: across life course with no peak. For RD where there is no age of onset available: No information on the age of onset of first clinical manifestation is available in the scientific literature or included in Orphanet. These age categories are not mutually exclusive and a RD may have more than one age of onset reported.

Type of Inheritance

The number and proportion of type of inheritance patterns were identified for all the RD included in the study.

Medical Domain

For each of the 25 Orphanet medical domains (linearisation) included in this study, the number (and proportion) of RD assigned to each of these as a preferential parent were counted - to prevent multiple counting of entities classified under multiple categories.

Functional Consequences (Disability)

The Orphanet functional consequences dataset provides information relating to activity limitation/participation restriction, frequency, temporality, degree of severity and type of

loss of ability. For the purpose of this study, only an initial analysis was undertaken to count the number of included Orphanet RD and the associated number of RD patients with disability data i.e. activity limitation/participation restriction, those RD with no associated functional disability, and RD that were not applicable (due to early mortality etc).

High-Cost Drugs for Rare Diseases

Orphanet is still in the process of developing a list of orphan drugs, as outlined online (<https://www.orpha.net/en/other-information/about-orphan-drugs?stapage=countries>). Until this is completed, a detailed list of Orphanet RD treatable with approved, high-cost drugs remains unavailable and is not comprehensively offered elsewhere.

To begin to address this information gap within the context of this South African study, a list was manually compiled using the sub-set of Orphanet RD with an indicated high-cost therapy approved by at least one regulatory body globally. This involved a brief desktop study undertaken in early 2025 using several key, recent articles (14, 39) as a starting point. For the purpose of this study, high-cost drugs were defined as medications developed for a disease that affects a small number of people, often with significant costs associated with development and limited market size.

This preliminary list was circulated to key, local stakeholders in the country and relevant experts for further input, including the Rare Disease Access Initiative (RDAI) (30), the National Bioproducts Institute (Personal Communication L. Kwaan, May 2025) and the International Rare Disease Research Consortium (<https://irdirc.org/>). Relevant input, including regulatory approval and availability in SA was incorporated and the list was updated to serve as a dynamic tool for South African policy makers.

Results

Orphanet contains descriptions of 6 147 clinically unique RD (disorders). After all filters were applied to exclude specific characteristics as detailed in the method, a total of 3 728 RD remained that met the study inclusion criteria.

As detailed in Figure 1, from the initial 6 417 unique clinical RD “disorders” in Orphanet and excluding “disorder groups” and “sub-groups” to prevent duplication, 5 733 RDs remained once cancers, infectious diseases and poisonings were excluded (n=684). Further exclusions included: 1 025 RD with no epidemiological data; 3 RD with no point prevalence values, 10 RD requiring internal quality control by Orphanet; and 963 RD with a point prevalence of >1 per 2 000.

Following all exclusions, a total of 3 728 RDs with point prevalence data were included in this analysis, representing 58% of unique clinical RD (“disorders”) in Orphanet. Of these 3 728, a total of 781 (21%) RD had a point prevalence value or class used to calculate the direct point prevalence; 2 610 (70%) RDs were described by reports of single cases, and 337 (9%) described by reports of families and were collectively used to calculate the indirect point prevalence.

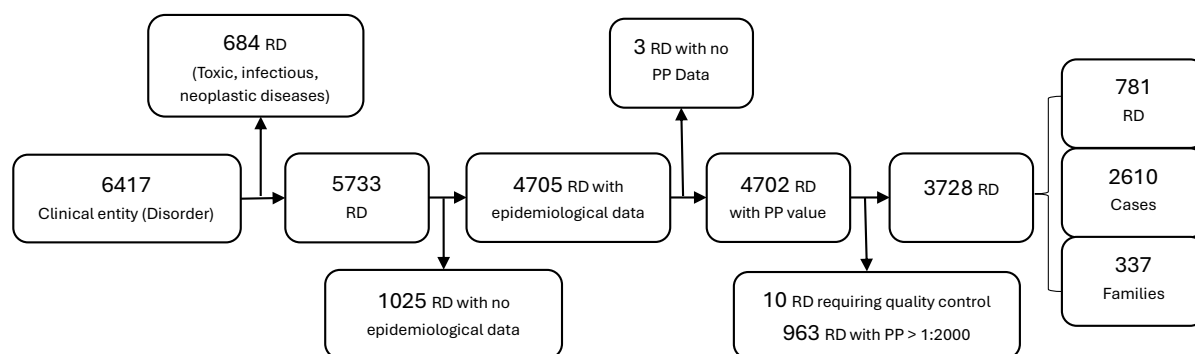


Figure 1. Selection process of point prevalence data from Orphanet's epidemiological file (31 July 2024) used for analysis.

South African Point Prevalence

An estimated average of 4.8% (ranging from minimum 3.7 to 5.9% maximum) of the South African and global populations are affected by the **sub-set of RD** included in this study. In SA, this equates to a mean of 3 030 204 RD patients (ranging from a minimum of 2 321 906 to a maximum of 3 738 503). See Table 1 for details.

The direct point prevalence for 781 (21%) RD described by value and class, or class only, equated to a mean of 4 807 per 100 000 of the population or 3 029 175 South Africans. The indirect point prevalence for the 2 947 (79%) of RD described by 2 610 cases and 337 families equated to 1.63 per 100 000 of the population, or 1 030 South Africans.

Table 1: Derivation of global and South African point prevalence from case reports, family reports, pre-established ranges and numerical values. a) Indirect point prevalence if number of families $\times 10$ to account for changing family size; b) Total number of patients divided by the global population (8 200 000 000) and resulting rate per 100 000 used to calculate number of patients for South African population (63 015 904)(23); C) Mean point prevalence per 100 000.

Indicators	Rare Diseases (Number)	Rare Diseases (%)	Number of Patients: Global	Number of Patients: South Africa	Point Prevalence per 100 000
Indirect Point Prevalence^{a)}					
Cases	2610	70%	99 795	767	1,22
Families	337	9%	34 230	263	0,42
Sub-Total: Indirect	2 947	79%	134 025	1 030	1,63
Direct Point Prevalence^{b)}					
Value & Class (ValMoy)	433	12%	261 252 000	2 007 687	3 186
Class Only:					
Minimum			40 754 000	313 189	497
Mean	348	9%	132 922 000	1 021 488	1 621
Maximum			225 090 000	1 729 787	2 745
Total (Min)	3 728	100%	302 140 025	2 321 906	3 685
Total (Mean)^{c)}	3 728	100%	394 308 025	3 030 204	4 809
Total (Max)	3 728	100%	486 476 025	3 738 503	5 933

As shown in Figure 2, a small proportion (4%, n=148) of the more common RD (1-5 per 100 000) included in this study account for 78% (n=2 365 617) of the South African patient population. At the other end of the scale, a large number of RD (84%, n=3 135) occurring at ≤ 1 per 1 000 000 of the population, equate to a very small proportion (<1%, n=11 743) of RD patients in the country. Figure 3 shows the same analysis for the direct point prevalence only, demonstrating a similar trend with a smaller proportion (19%) of more common RD accounting for a significant proportion (78%) of RD patients.

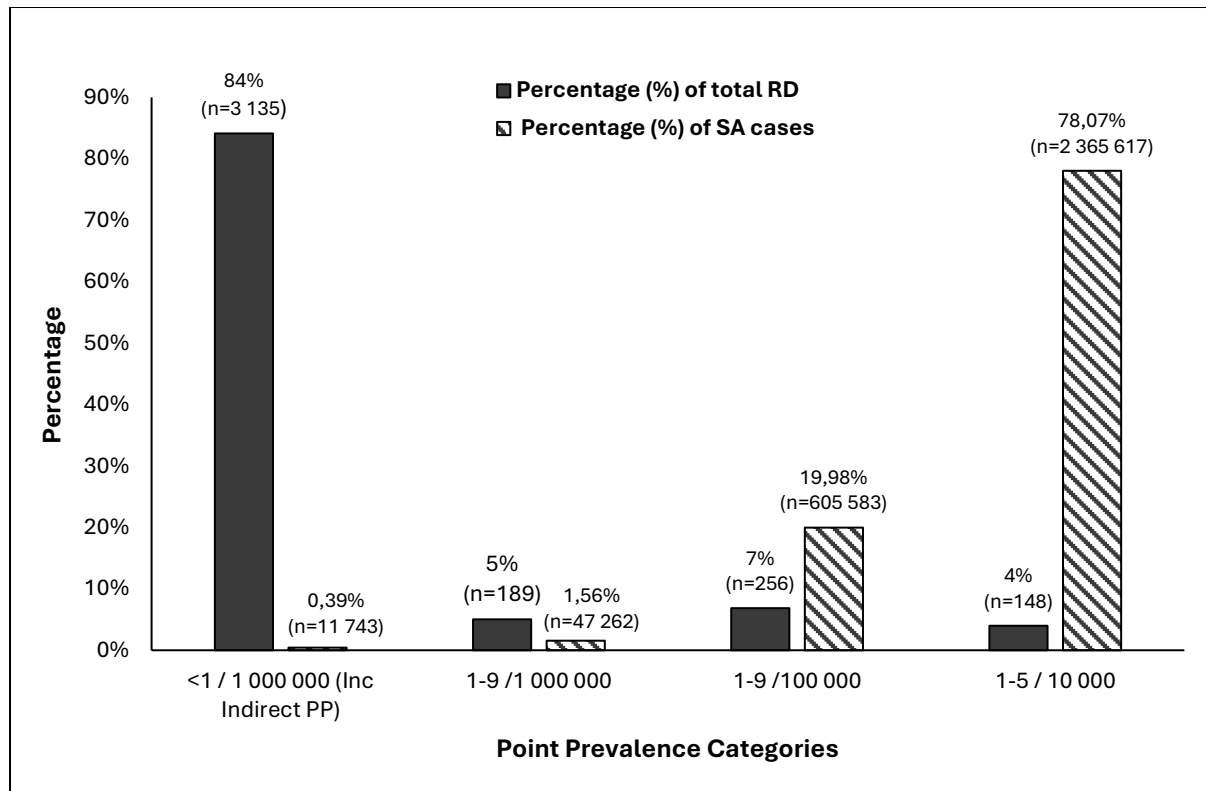


Figure 2. Distribution of rare diseases (proportion and number) and South African patients (proportion and number) for all 3 728 rare diseases across point prevalence categories.

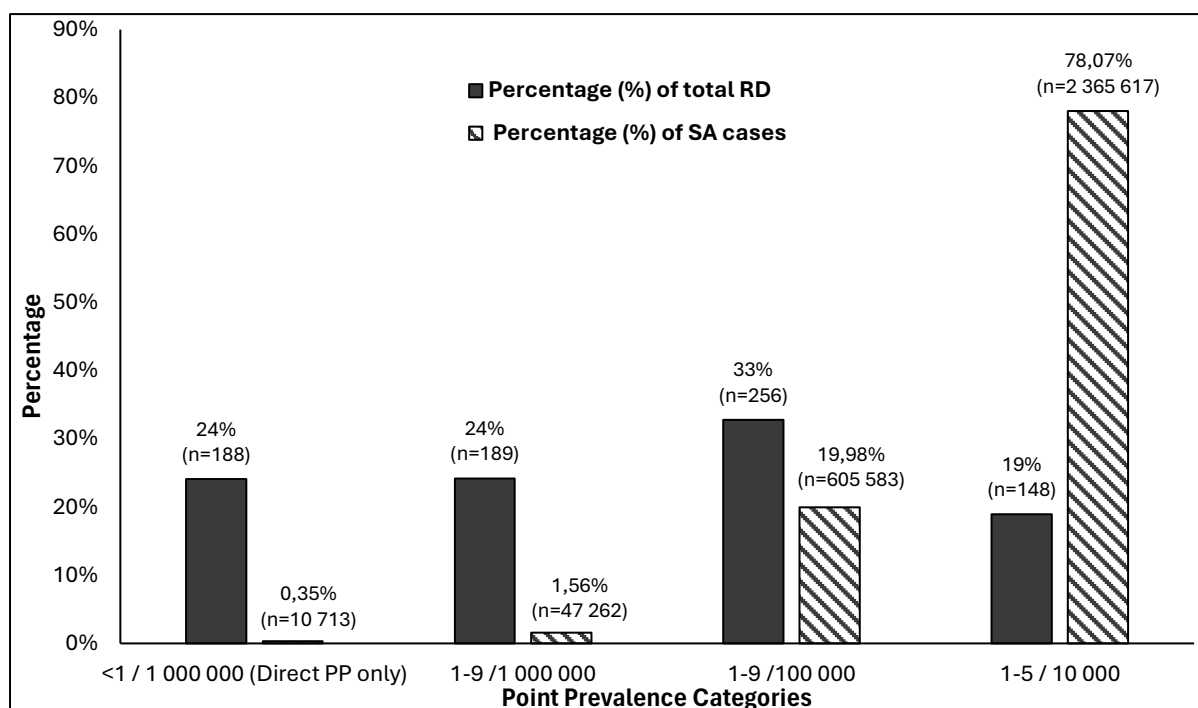


Figure 3. Distribution (proportion and number) of 781 rare diseases and South African patients (proportion and number) across point prevalence categories described by direct point prevalence only.

Age of Onset

Figure 2 summarises the age of onset of RD described for 3 728 RD extracted from the natural history Orphanet dataset. The age categories used are detailed in Orphanet supporting documentation on ontology (40).

The majority (77%) of the 3 728 RD included in this study have onset during childhood⁷, with 11% occurring in adulthood⁸, 7% presenting antenatally (before birth) and 4% across all age ranges.

⁷ Paediatric onset includes neonatal, infancy, childhood and adolescent ages of onset.

⁸ Adulthood includes adult and elderly age of onset categories.

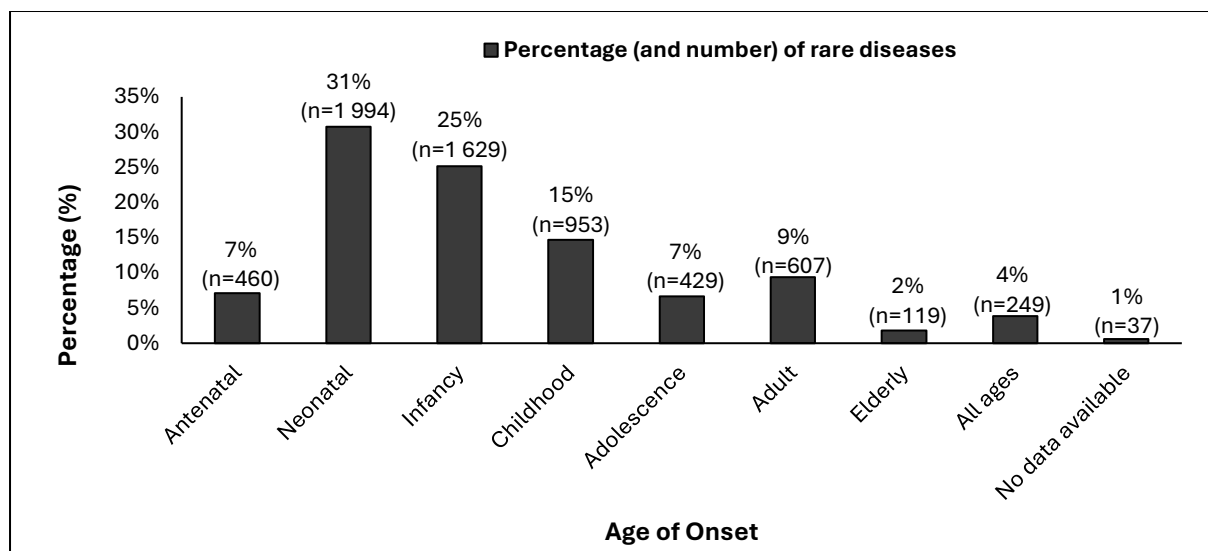


Figure 4. Age of onset for the 3 728 rare diseases included in this analysis across the life course, specifically: Antenatal: Before birth; Neonatal: Birth to four weeks of life; Infancy: 5 weeks to 23 months; Childhood: 2-11 years; Adolescent: 12-18 years; Adult: 19-65 years; Elderly: >65 years; All ages: across life course with no peak; No age of onset available: No information on the age of onset of first clinical manifestation is available in the scientific literature. Age categories are not mutually exclusive.

Inheritance Patterns

Analysis of the epidemiological and natural history data found that of the 3 728 RD included in this study, 3 669 RD (99%) had one or more inheritance patterns indicated in the Orphanet dataset (40).

The mode of inheritance for most of the RD was autosomal recessive (n=1 527, 42%) or autosomal dominant (n=998, 27%), with the least number of diseases for semi-dominant (n=4, 0.1%), Oligogenic or Y-linked inheritance patterns (n=1, 0.03% each), as described in Figure 2. For 21% (n=777) of RD included, inheritance patterns were indicated as unknown or not available in the Orphanet database. For detailed explanations of these inheritance types and other categories, refer to Orphanet supporting documentation on ontology (40).

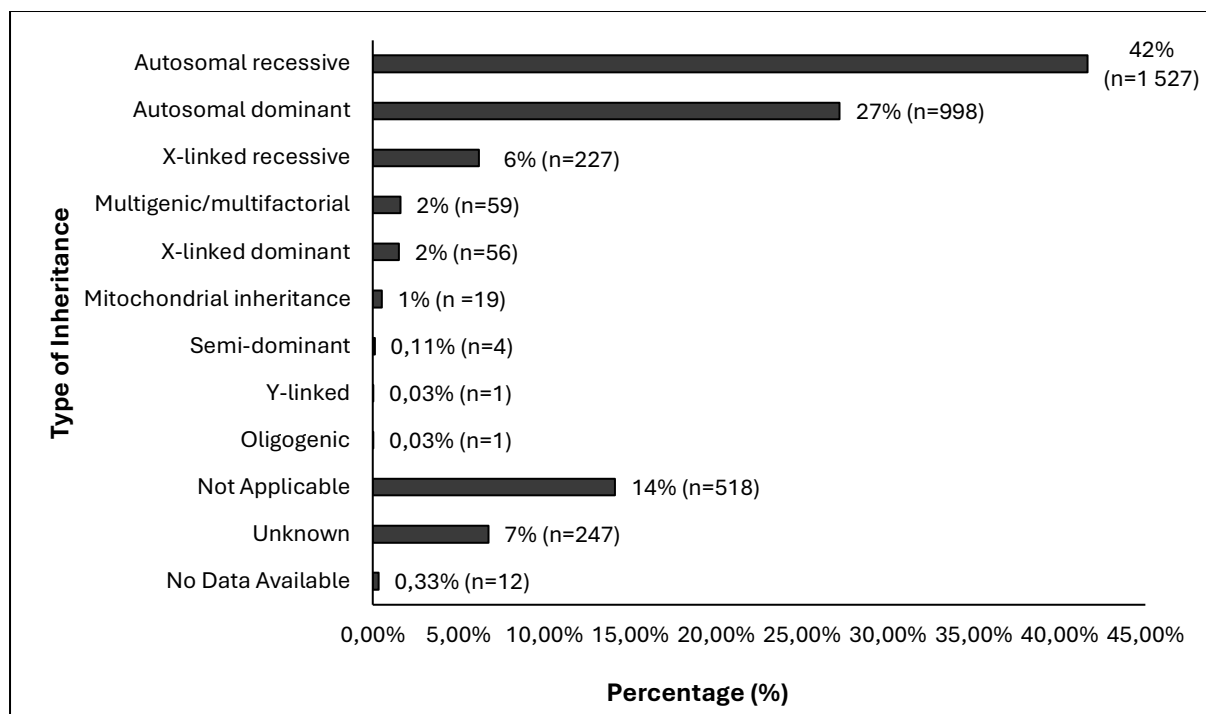


Figure 5. Distribution of inheritance patterns of 3 728 rare diseases extracted from Orphanet (31 July 2024 dataset). Note: The mode of inheritance categories are not mutually exclusive, with some conditions presenting in multiple inheritance types.

Medical Domain

The 3 728 RD included in this study are categorised according to the 25 medical domains in the Orphanet linearisation file, as shown in Figure 6. The majority (37%) of the RD included are primarily classified as rare developmental defects occurring during embryogenesis, followed by rare neurological diseases (20%) and rare inborn errors of metabolism (IEM) (8%).

The “other” category in Figure 6 includes 15 medical domains comprising <100 RD in each, i.e. rare- gastroenterologic, renal, respiratory, cardiac, hepatic, otorhinolaryngologic, circulatory system, odontologic, gynaecologic/obstetric, infertility, urogenital, maxillo-facial surgical, genetic, abdominal surgical diseases and rare disorders potentially indicated for transplant or complication after transplantation.

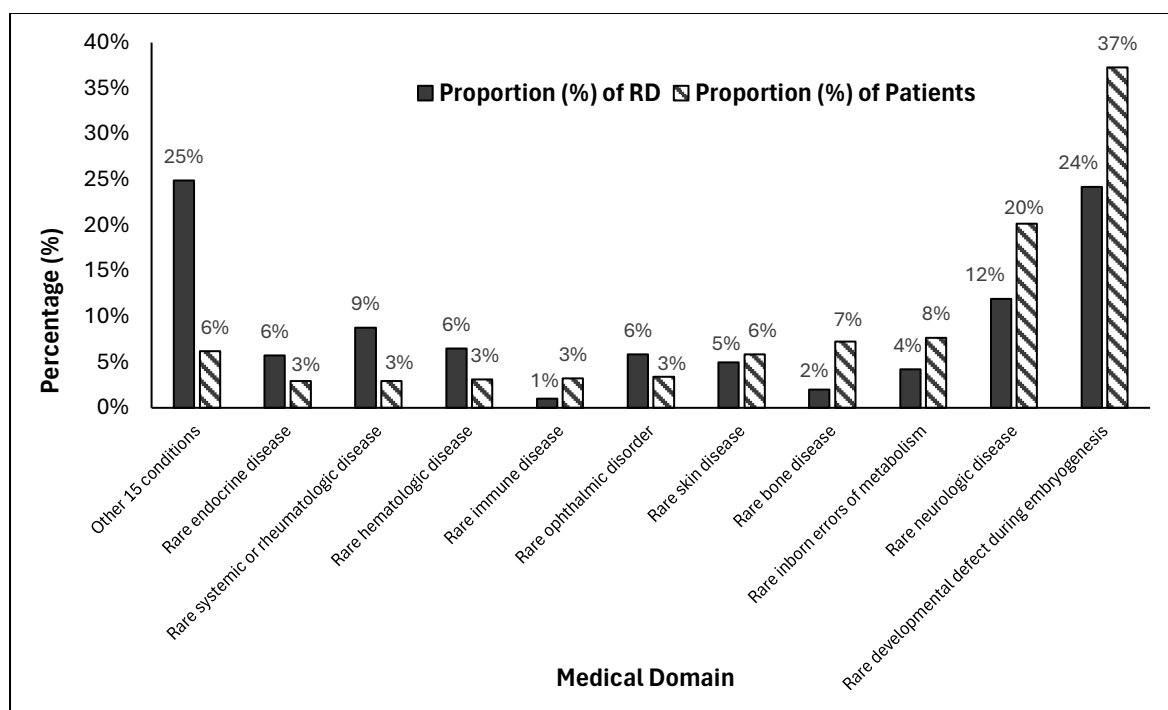


Figure 6. The 3 238 rare diseases included in this study ranked by the top 10 medical domains classified by Orphanet based comparing the proportion of rare disease per category to the proportion of RD patients in South Africa. The “other” category comprised 15 categories of rare disease, each including <50 diseases.

In Table 2, the types of clinical specialties and allied health care professionals (HCP) are listed per medical domain.

Table 2. Number of rare disease patients per medical domain in South Africa and required cadres of clinical specialists and allied healthcare professionals.

Medical Domain	Number of patients	Clinical Specialties Required	Specialised Allied Healthcare Required
Rare abdominal surgical disease	0	General/abdominal surgeon, paediatric surgeon, gastroenterologist, intensivist, radiologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, post-op care, palliative care
Rare genetic disease	2	Medical geneticist, other	Genetic counsellor, specialist nurses, palliative care
Rare maxillo-facial surgical disease	1	Oral and maxillofacial surgeon, intensivist, paediatrician, medical geneticist	Genetic counsellor, specialist nurses, post-op care, palliative care
Rare disorder potentially indicated for transplant or complication after transplantation	6 081	Transplant surgeon, specialised physician, intensivist, immunologist, medical geneticist, paediatrician	Genetic counsellor, pharmacist, social worker, bone marrow transplant coordinator, dietician, physiotherapy, specialist nurses, palliative care
Rare infertility	13 107	Reproductive endocrinologist, gynaecologist, urologist, medical geneticist	Genetic counsellor, specialist nurses, palliative care
Rare urogenital disease	22 056	Urologist, paediatrician, endocrinologist, medical geneticist	Genetic counsellor, specialist nurses, palliative care
Rare gynecologic or obstetric disease	76 882	Gynaecologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, palliative care
Rare odontologic disease	13 613	Oral medicine, orthodontics, oral and maxillofacial surgery, endodontics, periodontics, medical geneticist, paediatrician	Genetic counsellor, physiotherapist, speech therapist, feeding specialist, specialist nurses, palliative care
Rare circulatory system disease	10 151	Cardiologist, vascular surgeon, haematologist, rheumatologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, post-op care, palliative care
Rare otorhinolaryngologic disease	30 695	Otorhinolaryngologist (ENT specialist), medical geneticist, paediatrician, other sub-specialties	Genetic counsellor, audiologist, specialist nurses, palliative care
Rare hepatic disease	57 013	Hepatologists, gastroenterology, transplant surgeon, intensivist, immunologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, post-op care, palliative care
Rare cardiac disease	86 847	Cardiologist, cardiac surgeon, intensivist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, post-op care, palliative care
Rare respiratory disease	184 433	Pulmanologist (respiratory physician), medical geneticist, paediatrician	Genetic counsellor, specialist nurses, palliative care
Rare renal disease	68 887	Nephrologist, radiologist, transplant surgeon, intensivist, immunologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, palliative care
Rare gastroenterologic disease	184 080	Gastroenterologist, GI surgeon, hepatologist, endocrinologist, rheumatologist, medical geneticist, paediatrician	Genetic counsellor, nutritionist/dietician, specialist nurses, post-op care, palliative care
Rare endocrine disease	173 145	Endocrinologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, palliative care
Rare systemic or rheumatologic disease	265 743	Rheumatologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, palliative care
Rare hematologic disease	195 981	Haematologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, palliative care
Rare immune disease	29 593	Rheumatologist, immunologist, endocrinologist, haematologist, dermatologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, palliative care
Rare ophthalmic disorder	177 133	Ophthalmologist, relevant sub-specialists, medical geneticist, paediatrician	Genetic counsellor, optician, specialist nurses, palliative care
Rare skin disease	151 470	Dermatologist, haematologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses, palliative care
Rare bone disease	60 405	Orthopaedic surgeon, rheumatologist, endocrinologist, medical geneticist, paediatrician	Genetic counsellor, physiotherapist, biokineticist, specialist nurses, post-op care, palliative care
Rare inborn errors of metabolism	128 343	Endocrinologist, chemical pathologist (metabolic specialist) neurologist, endocrinologist, medical geneticist, paediatrician	Genetic counsellor, specialist nurses nutritionist/dietician, physiotherapist, palliative care
Rare neurologic disease	361 100	Neurologist, medical geneticist, paediatrician	Genetic counsellor, physiotherapist, specialist nurses
Rare developmental defect during embryogenesis	733 746	Fetal medicine specialist, obstetrician, neonatologist, paediatric surgeon, medical geneticist, paediatrician	Occupational therapist, physiotherapist, speech therapist, feeding specialist, specialist nurses
Total	3 030 509		

Functional Consequences (Disability)

The Orphanet Rare Diseases “Functional Consequences” dataset includes annotations for activity limitations and participation restrictions (i.e., disability) using the Orphanet Functioning Thesaurus (41), which is derived and adapted from the WHO's International Classification of Functioning, Disability and Health – Children and Youth version (42). These data were applied to the South African population (23) to estimate the number of RD patients for each category where these were recorded.

Functional consequences in Orphanet are organised by their frequency in the patients’ population and is assessed using the whole patient population affected by the disease, receiving standard care and management (specific and/or symptomatic management, prevention and prophylaxis, devices and aids, care and support) (43).

Disability Category

For the 3 728 RD included in this study, 569 had associated Orphanet Functional Consequences data. An average of 1 334 231 of patients in SA experience loss of ability⁹ associated with the RD, i.e. disability of some kind, versus 114 983 with no loss of ability and 40 366 were not applicable.

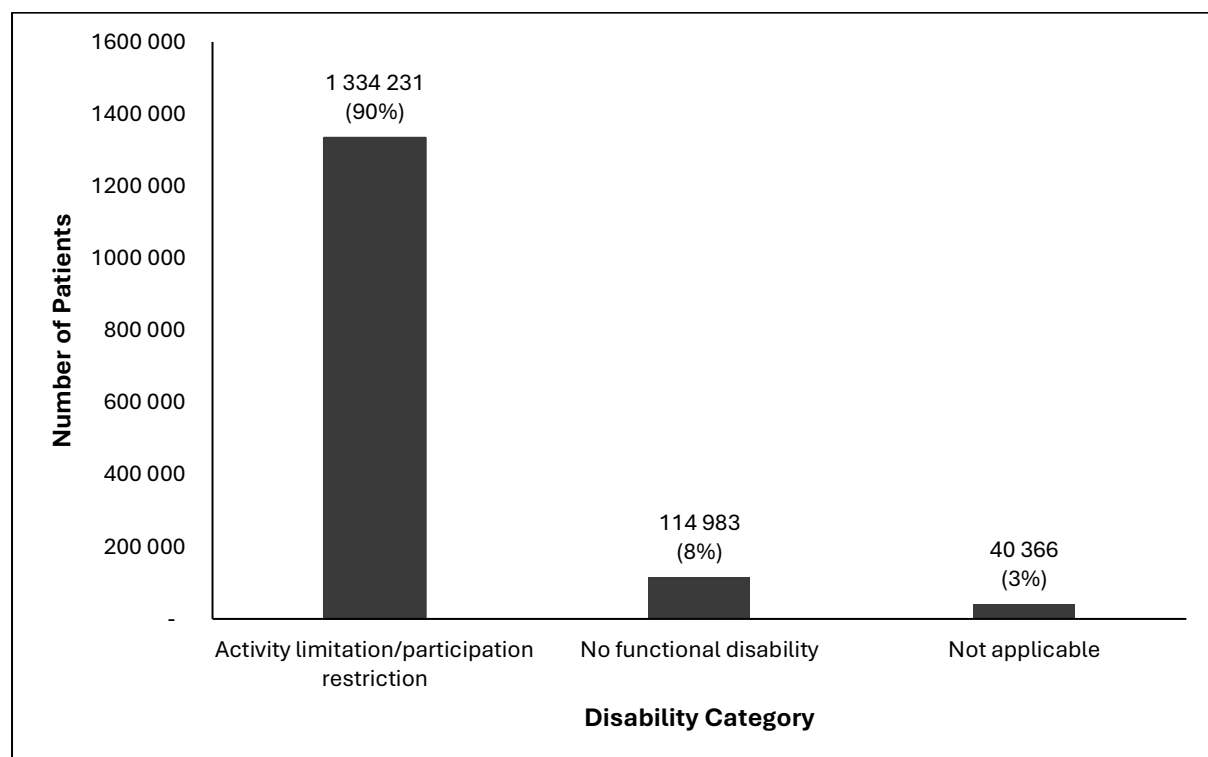


Figure 7. Column chart showing the estimated mean number and proportion (%) of rare disease patients in South Africa for Orphanet disability categories for 569 rare diseases with associated disability category data. Note: “Not applicable” means: 1) Patients die prematurely; 2) Patients experience hypervariable functioning (abilities vary over time and situationally); and, 3) Other reasons for not applicable.

⁹ Loss of ability is defined by Orphanet as the progressive and definitive loss of a skill or participation over the course of the disease (<https://www.orpha.net/en/disease/disability>).

Patients Requiring High-Cost Drugs

Table 3 is a preliminary list compiled solely for Orphanet RD included in this study where a high-cost drug has been indicated and approved by at least one regulatory body worldwide. These results show that for 59 RD included, there are 57 indicated high-cost drugs of which 25 are approved in SA. Of these 59 RD, most are categorised by Orphanet as IEM (n=14), followed by rare immune diseases (n=9), rare neurologic diseases (n=9) and rare hematologic diseases (n=8). For the 57 indicated high-cost drugs, the most common classes of therapies are Enzyme Replacement Therapy (ERT) with 18 drugs for 25 RD; gene therapy with four drugs for 11 RD; and monoclonal antibodies with four drugs for five RD.

Table 3. List of RD requiring high-cost drugs included in this study with an indicated, approved high-cost drug available globally and in South Africa.

Disorder Name	Orphanet Medical Domain	Potential number of patients in SA	Type of Therapy	Approved Therapeutic	Approved in South Africa
Metachromatic leukodystrophy	Rare neurologic disease	63	Gene Therapy	Lenmeldy, Libmeldy (Atidarsagene Autotemcel)	x
Lysosomal acid lipase deficiency (Wolman Disease)	Rare inborn errors of metabolism (IEM)	1 260	Enzyme Replacement Therapy (ERT)	Kanuma (Sebelipase alfa)	x
Atypical hemolytic uremic syndrome	Rare renal disease	630	Terminal Complement Inhibitor	Soliris (Eculizumab)	x
			Terminal Complement Inhibitor	Ultomiris (Ravulizumab)	✓
Proximal spinal muscular atrophy	Rare neurologic disease	3 151	Gene Therapy	Zolgensma (Onasemnogene abeparvovec)	x
Retinitis pigmentosa	Rare ophthalmic disorder	16 825	Gene Therapy	Luxturna (voretigene neparvovec)	x
Leber congenital amaurosis	Rare ophthalmic disorder	1 575	Gene Therapy	Luxturna (voretigene neparvovec)	x
Gaucher disease	Rare IEM	630	Substrate Reduction Therapy	Cerdelga (Eliglustat)	x
			ERT	Cerezyme (Imiglucerase)	✓
			ERT	VPRIV (Velaglucerase alfa)	✓
			ERT	ElELYso (Taliglucerase alfa)	✓
Mucopolysaccharidosis type 2	Rare IEM	126	ERT	Elaprase (Idursulfase)	✓

(Hunter syndrome)					
Fabry disease	Rare IEM	18 905	ERT	Fabrazyme (Agalsidase beta)	✓
Mucopolysaccharidosis type 1 (Hurler's syndrome)	Rare IEM	315	ERT	Aldurazyme (Laronidase)	✓
Morquio syndrome type A (Mucopolysaccharidosis type 4A)	Rare IEM	17 392	ERT	Vimizim (Elosulfase alfa)	x
Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI)	Rare IEM	101	ERT	Naglazyme (Galsulfase)	x
Sly syndrome (mucopolysaccharidosis type VI)	Rare IEM	6	ERT	Mepsevii (Vestronidase alfa)	x
Alpha-mannosidosis	Rare IEM	63	ERT	Lamzede (Velmanase alfa)	x
Glycogen storage disease due to acid maltase deficiency (Pompe Disease)	Rare IEM	1 890	ERT	Myozyme (Alglucosidase alfa)	✓
Phenylketonuria (PKU)	Rare IEM	2 607	ERT	Palynziq (Pegvaliase)	x
Chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type A/B)	Rare IEM	63	ERT	Xenpozyme (Olipudase alfa)	x
Infantile neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type A)	Rare IEM	63	ERT	Xenpozyme (Olipudase alfa)	x
Argininemia (Arginase 1 Deficiency)	Rare IEM	63	ERT	Loargys (Pegzilarginase)	x

T-B+ severe combined immunodeficiency due to gamma chain deficiency	Rare immune disease	3 151	ERT	Polyethylene glycol-conjugated ADA (Pegademase)	x
Severe combined immunodeficiency due to adenosine deaminase deficiency	Rare immune disease	126	ERT	Polyethylene glycol-conjugated ADA (Pegademase)	x
Severe combined immunodeficiency due to complete RAG1/2 deficiency	Rare immune disease	630	ERT	Polyethylene glycol-conjugated ADA (Pegademase)	x
Congenital sucrase-isomaltase deficiency	Rare gastroenterologic disease	12 603	ERT	Sacrosidase (Sucraid)	x
Hypophosphatasia	Rare bone disease	13	ERT	Strensiq (Asfotase Alfa)	x
Acute peripheral arterial occlusion	Rare circulatory system disease	10 083	Enzyme-based medication	Collagenase Clostridium histolyticum (CCH)	x
Cystic fibrosis	Rare respiratory disease	7 015	Mucolytic	Pulmozyme (Dornase alfa)	✓
			CFTR potentiator	Kalydeco (Ivacaftor)	x
			CFTR modulator (corrector/potentiator combination).	Orkambi (Lumacaftor/Ivacaftor)	x
			CFTR modulator (corrector/potentiator combination).	Symdeko (Tezacaftor/Ivacaftor)	x
			CFTR modulator (corrector/potentiator combination).	Trikafta (Elexacaftor/Tezacaftor/Ivacaftor)	x Section 21 (genotype specific)
Beta-thalassemia	Rare hematologic disease	315	Iron chelator	Desferal (Deferoxamine mesylate)	✓
				Exjade, Jadenu (Deferasirox)	✓

				Ferriprox (Deferiprone)	✓
Neuromyelitis optica spectrum disorder	Rare neurologic disease	1 305	Monoclonal Antibodies	Blitzima, Mabthera, Ristova, Rixathon, Rituxima (Rituximab)	✓
				Ocrevus (Ocrelizumab)	✓
				Bonspri (Ofatumumab)	✓
Myasthenia gravis	Rare neurologic disease	4 896	Monoclonal Antibodies	Soliris (Eculizumab)	x
Acquired hemophilia A	Rare hematologic disease	193	Monoclonal Antibodies	Soliris (Eculizumab)	x
Congenital factor V deficiency	Rare hematologic disease	63	Hormone	DDAVP, Minirin, Despress (Desmopressin)	✓
Congenital factor XI deficiency	Rare hematologic disease	63	Antifibrinolytic agent	Tranmenxid IV, Fibtin, Morwak, Transun IV, Tranic, Cyklokapron, Cynex, Immatra, Rubinex, Cyklocloot, Zamicron, Stranan (Tranexamic Acid)	✓
Hemophilia A	Rare hematologic disease	3 056	Clotting Factor	Factor VII Concentrate	x
			Monoclonal Antibodies	Hemlibra (Emicizumab)	✓
			Clotting Factor	NovoSeven (Recombinant activated Factor VII - rFVIIa)	✓
Hemophilia B	Rare hematologic disease	1 890	Clotting Factor	Factor IX Replacement	x
			Gene Therapy	Hemgenix (etranacogene dezaparvovec-drib)	x
			Clotting Factor	NovoSeven (Recombinant activated Factor VII - rFVIIa)	✓
Central retinal vein occlusion	Rare ophthalmic disorder	17 644	Anti-VEGF drug	Avastin, Mvasi, Riqviva (Bevacizumab)	✓
				Lucentis (Ranibizumab)	✓
				Eylea (Aflibercept)	✓
Paroxysmal nocturnal hemoglobinuria	Rare hematologic disease	1 260	Monoclonal Antibodies	Soliris (Eculizumab)	x
				Ultomiris (Ravulizumab)	✓

Spinal muscular atrophy with respiratory distress type 2	Rare neurologic disease	63	Gene Therapy	Zolgensma (Onasemnogene AOP105)	x
Spinal muscular atrophy with respiratory distress type 1	Rare neurologic disease	63	Antisense oligonucleotide (ASO)	Spinraza (Nusinersen)	x
Brachydactyly-short stature-retinitis pigmentosa syndrome	Rare bone disease	63	Gene Therapy	Luxturna (voretigene neparvovec)	x
Congenital bile acid synthesis defect type 4	Rare hepatic disease	63	Gene Therapy	Luxturna (voretigene neparvovec)	x
Polyneuropathy-hearing loss-ataxia-retinitis pigmentosa-cataract syndrome	Rare neurologic disease	63	Gene Therapy	Luxturna (voretigene neparvovec)	x
Retinitis pigmentosa-hearing loss-premature aging-short stature-facial dysmorphism syndrome	Rare developmental defect during embryogenesis	63	Gene Therapy	Luxturna (voretigene neparvovec)	x
Retinitis pigmentosa-intellectual disability-deafness-hypogonadism syndrome	Rare neurologic/ophthalmic disease	63	Gene Therapy	Luxturna (voretigene neparvovec)	x
Retinitis pigmentosa-juvenile cataract-short stature-intellectual disability syndrome	Rare ophthalmic disorder	63	Gene Therapy	Luxturna (voretigene neparvovec)	x
Severe combined immunodeficiency due to FOXP1 deficiency	Rare immune disease	63	ERT	Polyethylene glycol-conjugated ADA (Pegademase)	x
Short-limb skeletal dysplasia with	Rare immune disease	63	ERT	Polyethylene glycol-conjugated ADA (Pegademase)	x

severe combined immunodeficiency					
Combined immunodeficiency due to IKK2 deficiency	Rare immune disease	63	ERT	Polyethylene glycol-conjugated ADA (Pegademase)	x
Severe combined immunodeficiency due to CTPS1 deficiency	Rare immune disease	63	ERT	Polyethylene glycol-conjugated ADA (Pegademase)	x
Severe combined immunodeficiency due to LAT deficiency	Rare immune disease	63	ERT	Polyethylene glycol-conjugated ADA (Pegademase)	x
Intellectual disability-seizures-hypophosphatasia-ophthalmic-skeletal anomalies syndrome	Rare neurologic disease	63	ERT	Strensiq (Asfotase alfa)	x
Lung fibrosis-immunodeficiency-46,XX gonadal dysgenesis syndrome	Rare respiratory disease	63	Anti-fibrotic agent	Ofev, Vatrana (Nintedanib)	✓
				Esbriet/Pirfenidone (Pirfenidone)	✓
Multiple sclerosis-ichthyosis-factor VIII deficiency syndrome	Rare hematologic disease	63	Monoclonal Antibodies	Blitzima, Mabthera, Ristova, Rixathon, Rituxima (Rituximab)	✓
				Ocrevus (Ocrelizumab)	✓
				Bonspri (Ofatumumab)	✓
Hepatic veno-occlusive disease-immunodeficiency syndrome	Rare immune disease	63	Antithrombotic agent	Defibrotide	x
			Enzyme-based medication	Collagenase Clostridium histolyticum (CCH)	x
Acute peripheral arterial occlusion	Rare circulatory system disease	18 905	Antiplatelet	Pletal (Cilostazol)	x

Neuronal ceroid lipofuscinosis type 2	Rare neurologic disease	63	ERT	Brineura (Cerliponase alfa)	x
Congenital Short Bowel syndrome	Rare developmental defect during embryogenesis	63	Glucagon-like peptide-2 (GLP-2) analogs	Gattex, Revestive (Teduglutide)	x
Homozygous Familial hypercholesterolemia	Rare endocrine disease	201	Protein Inhibitor	Juxtapid, Lojuxta (lomitapide)	x
			Monoclonal Antibodies	Repatha (evolocumab)	✓
Congenital generalized lipodystrophy (Berardinelli-Seip syndrome)	Rare endocrine disease	315	Hormone replacement therapy	Myalept, Myalepta (metreleptin)	x
Hereditary angioedema with C1Inh deficiency	Rare genetic disease	315	Complement Inhibitor	Cinryze (human C1 esterase inhibitor)	x
Total		150 971		57	27

Notes:

- This table may exclude some high-cost drugs approved in SA but are indicated for RD excluded from this study, eg. Evrysdi (risdiplam) indicated for specific types of SMA.
- Approval of a drug in SA does not mean it is available or accessible in the country. E.g. Ferriprox is registered and approved in SA but is not available.
- Section 21 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) allows treating clinicians to apply for special permission so patients can get medicines not yet registered in South Africa, though access is limited and often costly. E.g. Trifakta has been granted Section 21 access for patients with specific CF genotypes.
- The patient numbers presented here are intended as initial, approximate estimates only for use as a starting point for further analysis. While these estimates serve to demonstrate that a small proportion of RD patients require high-cost drugs, they should not be considered definitive patient population numbers. More detailed analyses are required to integrate specific epidemiological factors including age related prevalence, age of onset, age-stratified population groups etc, and survivorship to generate accurate patient numbers requiring these specific drugs.

Discussion

The aim of this study was to provide greater granularity of the estimated burden of RD in SA. Since RD encompass a heterogeneous group of >6000 conditions, detailed epidemiological description of this collective has been lacking. In SA and other LMIC, competing health priorities often take precedence in terms of allocated resources and

services provided - as they are more easily diagnosed and treated. This data deficit has led to reliance on the widespread understanding that RD affect 6-8% of the global population (29) – and while this approach has offered a starting point in terms of the overall burden of RD, it offers little guidance for policy makers on how to develop an appropriate healthcare response.

Recent studies by Orphanet have combined the point prevalence of a sub-set of Orphanet RD with global demographic data to develop a more evidence-based estimate of the global point prevalence of RD (1, 2, 34). These previous studies, which include a sub-set of RD in Orphanet, offer further insights into the burden of RD, by breaking it down into more tangible, evidence-based groups – and offered a suitable methodology for this study.

South African RD Point Prevalence

The South African RD point prevalence resulting in this study, ranging from 3.7-5.9%, with a mean of 4.8% of the population affected align with the previous Orphanet studies indicating 3.3-5.9% in 2020 by Wakap et al (1) and 4.14-5.28% in 2024 by Yamazaki (2, 34). Slight differences reported between these studies may be attributed to the continual updating of the Orphanet dataset over time.

In SA, 4.8% of the population equates to an estimated 3 030 204 patients, ranging from 2.3 to 3.7 million South Africans affected by the RD included in this study. Similar to Orphanet studies, the results indicate that a relatively small number of RD, specifically 404 of the 3 728 included in the study, account for 98% of RD patients. Conversely, 3 324 of the 3 728 RD included in this study account for less than 2% (n=59 005) RD patients in the country.

With such a high proportion of RD patients being impacted by a relatively small number of RD, this sub-set of conditions may offer an initial list of RD to prioritise resource allocation to generate an appropriate healthcare response. While these estimates may serve as a starting point for consolidated, targeted efforts in the country in the absence of empiric RD data, with only 58% of unique clinical RD in Orphanet included in this study, the total cumulative point prevalence of total RD is likely much higher.

Natural History

Age of Onset

The results of this study support the widely cited principle that most RD present in childhood, with 77% of RD included having pediatric onset, spanning neonatal (first 28 days of life), infancy (first 2 years of life) and childhood stages of life. Such a substantial proportion of the burden of RD emerging in children, equating to over 5 000 of the most vulnerable in society, highlights the need for early identification, accurate diagnosis and referral for relevant, accessible care. South Africa currently has a very “young” population, with 40% of the population aged <20 years of age and with around a million births annually, the health care system requires appropriate capacity, infrastructure and resources to provide the care required by those impacted by RD (23, 24).

The importance of seeking early antenatal care (ANC), particularly before 20 weeks of pregnancy, is also demonstrated through the 7% (n=460) of estimated RD presenting

antenatally. Factors limiting prenatal diagnosis of RD include late access and poor ANC compliance, particularly in the public healthcare sector; inadequate infrastructure and lack of skilled clinical expertise, including high resolution ultrasonographers and other key cadres of HCP, including paediatricians, clinical medical geneticists and genetic counsellors.

The estimated 11% of RD in this study manifesting in adulthood, spans a period 40 years from the age of 19 – 65+, when citizens are most likely to reproduce and significantly contribute to society as part of the workforce. Timely, accurate diagnosis and referral to relevant, accessible care and psychosocial support at the key points of care across this part of the life course is essential to optimize the quality of life of those affected and to maximise societal participation.

Type of Inheritance

Unsurprisingly, the majority of genetic RD are inherited via autosomal recessive and dominant inheritance. The finding highlights the importance of similar work in populations where high rates of consanguinity are practiced since resulting pregnancies will be at higher risk from these recessive conditions.

This predominantly monogenic mode of inheritance highlights the importance of, and need for, better coding of these conditions. The currently implemented 10th revision of the International Classification of Diseases (ICD-10) is inadequate in the coding of these conditions, limited to chapter XVII which includes only the more obvious structural congenital malformations, deformations and chromosomal abnormalities, with the remaining 40-50% of RD scattered across other ICD-10 chapters.

An array of expertise is required to identify, diagnose and treat this collective of RD, ranging from community health workers equipped to identify basic red flags during post-delivery community visits, to highly trained clinical medical geneticists and genetic counsellors. Many such opportunities can be integrated into existing primary healthcare, such as vaccination schedules or piggyback onto other established programmes, such as HIV Prevention of Mother-to-Child (PMTCT). However, the current capacity of skilled HCP, both in the specialized field of community genetic services as well as other specialised clinical cadres has been found to be completely inadequate (44, 45).

Medical Domains

Based on the analysis of the Orphanet dataset using medical domains - while most RD are caused during embryogenesis, neurological causes and IEM, the number and range of specialties required to diagnose and treat these conditions is vast. Most RD require a multidisciplinary team of HCP for optimal medical management as indicated in Table 2, but such coordinated care is seldom implemented currently in either healthcare sector in the country. The imperative to address this lack of expert capacity is essential – not only for the sake of the patients but also to prevent underreporting, since if a RD is not accurately diagnosed it cannot be counted or included in surveillance programmes. This results in inadequate health policy and insufficient services being implemented in response to an inaccurately quantified burden of disease.

Across healthcare, the multidisciplinary team also needs to consider the patients family comprehensively rather than treating the patients in isolation. This is both due to the inherited cause of many of these RD requiring extended screening interventions and the significant caregiving role undertaken by the family, which has implications for social support and respite care services to prevent caregiver burnout.

Functional Consequences (Disability)

RD contribute significantly to the burden of disease, including both mortality and morbidity in SA, with >90% of RD patients, equating to 1 334 231, mainly children, being affected by disability of some type and frequency. Early identification and diagnoses of RD can enable timeous referral to relevant rehabilitative care, including physiotherapy, speech-, feeding- and occupational therapies to mitigate disability. Patients living with complete or severe disabilities often require full-time, lifelong care – with significant implications for family members who carry the burden of caregiving, without government-supported mental health support or respite care.

A proportion of RD patients die prematurely because of their RD. This has implications for palliative care, which should be provided from the point of diagnosis to ensure optimal quality of life of the RD patient and their family, with end-of-life care to ensure a pain free, dignified death. In SA, the lion's share of palliative care is directed to cancer and HIV/AIDS patients – with little recognition of the specific needs of the significant RD pediatric community.

As RD become more timeously diagnosed and treated, the burden of disability due to these conditions will increase as more patients survive – highlighting the importance of addressing this growing societal need. Primary preventative efforts can reduce the number of affected pregnancies by converting them to unaffected pregnancies, exemplified by folic acid supplementation and mandatory folate fortification of staple crops to reduce the number of pregnancies affected by neural tube defects. Secondary prevention to reduce the number of affected births includes screening, diagnosis and genetic counselling during pregnancy, and contributes towards informed decision making around continuing the pregnancy. In some populations where diagnosis in utero and legal Termination of Pregnancy has become commonplace for specific conditions, the birth prevalence of some RD has decreased substantially. Early, accurate diagnosis and referral at birth (i.e. tertiary prevention) for relevant treatment can help mitigate disability and decrease mortality through life saving interventions and rehabilitative care that can directly impact the quality of life of a RD patient.

High-Cost Drugs

Many medications indicated to treat RD come at a high cost because they are designed to treat diseases affecting a small population, often with prices reaching tens or hundreds of thousands of dollars per patient per year, sometimes even millions. The preliminary list of RD with high-cost treatments compiled in this study does not attempt to address the complex issue of drug costing – it rather serves to demonstrate the limited treatment options available for patients represented by the sub-set of RD included in this study. It also dispels the myth that all RD treatments are expensive – with only 150 971

(<5%) of the 3 030 204 RD patients estimated to potentially require high-cost treatments¹⁰. Disappointingly, of the 59 RD listed, treatments for only 25 are approved in SA, and many of these approved drugs are unavailable or remain inaccessible to the patients due to high cost.

Limitations

Methodology

Since this study was based on the Orphanet methodology (1, 2, 34), it is subject to the same limitations — notably that only diseases classified as rare in Europe are included in Orphanet. Additionally, only 58% of Orphanet RD are included, with RD described by other, excluded prevalence and incidence measurements. RD caused by infections, toxins and rare cancers which combined represent a notable burden of disease, are also excluded. Since Orphanet is an ongoing systematic review of available data for RD, the different epidemiological methods used in population studies varies, and confusion and inconsistent use of measurement descriptors and the use of unsubstantiated data hinders the collection of RD data.

Use of Population Prevalence

Population prevalence counts the number of individuals with a specific condition within a defined population at a particular point in time. It includes individuals who were born with the condition and those who have acquired it later in life. If a condition is associated with high infant mortality, such as the majority of early onset RD included in this study, many individuals born with these conditions will not survive to be counted in the population prevalence later in childhood. While population prevalence is useful for generating estimates across the entire life course (as was intended by the earlier Orphanet efforts), this can lead to an underestimate of the true burden of a condition with high early mortality.

Birth prevalence is a more accurate and stable indicator of conditions associated with high, early mortality, especially RD and congenital disorders - because it focuses on the number of births affected by a condition as a proportion of total births, rather than tracking its presence in a changing population over time. It essentially provides a snapshot of the initial occurrence rate at birth, before mortality or other factors (i.e. Termination of Pregnancy) can influence the population and remove cases before they are fully counted, leading to an underestimate of the true incidence of the condition at birth and the total burden of disease. Birth prevalence is less susceptible to the influence of mortality and other demographic factors that affect population prevalence, as it isolates the initial occurrence rate from the complexities of population dynamics.

¹⁰ The patient numbers presented here are intended as initial, approximate estimates only. They should not be considered definitive patient population numbers, as more detailed analyses at the sub-population level are required. Such analyses would need to integrate specific epidemiological factors including age related prevalence, age of onset, age-stratified population groups, and survivorship etc.

The difference between birth prevalence and population prevalence is more significant in LMIC where relevant diagnostic expertise, infrastructure and therapeutics are often lacking for these conditions, preventing early, accurate diagnosis and referral for care. Thus, it is a limiting factor that the population prevalence is used as the sole indicator in this study, due to the high mortality rates of most RD - which is further exacerbated by the reliance on rates from other, mainly high-income populations included in the Orphanet dataset. This means that the results presented in this study for SA are the “**potential**” population prevalence rates, since they assume early diagnosis and referral for all those affected, based on available care offered in high-income settings. This serves to highlight the need for local empiric RD studies that include actual available care in SA, and across the African continent and in other LMIC to develop more accurate estimates for resource-constrained populations.

While low levels of consanguinity have been documented for SA (28), for populations with high rates of consanguineous unions, further adjustments would be required to generate estimates that better reflect the higher risks and subsequent higher prevalence of RD (especially autosomal recessive) in these populations.

Definition of Rare Diseases

While the recent publication of the Operational Description of RD (21) is a tool to help standardize the use of a shared global definition of RD, the historic use of broader or more narrow definitions of RD may prevent this approach being immediately implemented by other populations. In SA, although the RDI definition is yet to be implemented officially, many RD stakeholders are already using the definition of $<1/2000$ of the population. This study therefore offers a starting point for further studies in SA to assist policy makers in making informed policy and resource allocation decision-making relating to RD.

Conclusions & Recommendations

With such a significant proportion of the population affected by these conditions, there is an urgent need for improved community genetic services to address the genetic health of the South African population. While recent publications have highlighted the decline of these services over the last 20 years to address the HIV/AIDS epidemic (46, 47), attention is now shifting to other health priorities, especially those contributing to neonatal, infant and under-5 deaths, both because of the recent WHA Resolution 77.5 (16) and the impending 2030 targets of Sustainable Development Goal 3 (48). Current community genetic services are only effectively able to function at 10% of the required capacity, resulting in the majority of the population being unable to access the care required (44).

While addressing the burden of RD will undoubtedly come with a cost – the default decision of not diagnosing and caring for those affected is already coming at a much higher cost for the country, both socioeconomically and personally. This highlights the urgent need to implement interventions such as comprehensive newborn screening (NBS), which has been tried, tested and proven extensively elsewhere in the world, including other LMIC, where the health outcomes and economic societal savings clearly demonstrated the benefits. Comprehensively addressing the burden of RD is a key

component to further significantly reducing child mortality in the country, particularly within the context of the Sustainable Development Goal 3 targets (48).

This study has implemented a pioneering approach to obtain more granular data on the proportion of the South African population affected by RD. To build on the foundational work in this study and address its limitations, the following areas are recommended for future research:

- 1) **Developing more focused estimates using birth prevalence.** Including:
 - a. The sub-group of early-onset RD with high, early mortality.
 - b. Provincial and Geographic Distribution: Estimate RD prevalence and access to care at provincial level to inform regional planning and resource allocation.
- 2) **Health Economic Evaluations**, including conduct cost-benefit and cost-effectiveness studies on:
 - a. Societal costs of interventions for RD, including the cost of “no care”.
 - b. Early diagnosis interventions (e.g., NBS).
 - c. Delayed diagnosis and treatment.
 - d. Long-term caregiving and disability support costs.
- 3) **Equity and Access Mapping:** Evaluate disparities in access to diagnostics, treatment, and specialist clinical care between public and private sectors, and rural vs. urban populations.
- 4) **RD Policy Environment in South Africa:** Assess current policy gaps, regulatory barriers, and potential incentives for RD drug access, health workforce development, and surveillance systems.
- 5) **Expanded Functional Impact Analysis:** Deepen the analysis of functional consequences (disability) using Orphanet's data on severity, temporality, and management, including the cost and availability of rehabilitation services.
- 6) **Local Validation of Orphanet Estimates:** Initiate empirical RD registries and pilot surveillance studies in South African clinical settings to validate and refine estimates generated through global datasets.

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