Review of: "The Plight of Rare Diseases in Southern Africa: Health and Social Services Policy Recommendations"

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Potential competing interests: No potential competing interests to declare.

Firstly, I would like to congratulate the authors on the exceptionally good oversight of the issues facing rare disease patients in Sub Saharan Africa.

My comments are purely to enhance the publication as I have been privileged to have worked in High-, Middle- and Low-Income countries and hope the perspective will help readers.

My comments will follow statements from the publication in context.

> *Adachi et al. (2023) suggested that a higher prevalence of rare diseases in South Africa compared to other African and **neighbouring** countries may be due to a more developed tracking system.*

I think the statement can be enhanced as the lack of diagnostics is a main contributor the higher incidence of patients identified in South Africa. The diagnostic capabilities in South Africa is currently much better developed than other parts of Africa. It is very difficult when most rare disease are diagnosed on clinical findings rather than laboratory confirmation. It is important for future developments that diagnostics networks are developed inside the continent and the reliance and sending of diagnostic samples to external providers are complex and have multiple confounders. One such example is that genetic panels have become available to many African countries through charitable programs however they were generated from mostly European decent populations and not capturing the unique genetics of the local population leading to false assurance that some conditions has been excluded.

> *However, these represent only a few cases, as the majority of rare diseases remain undiagnosed or misdiagnosed due to limited information about their associated symptoms and a lack of guidelines for capturing their information within the healthcare systems of the SADC region.*

There is a common saying in medicine that you only diagnosis the conditions you think of and for which the diagnostics re available. This statement is interconnected as health care providers firstly needs to be educated to have the knowledge to consider rare diseases and then the diagnostic facilities need to be there to support them. The best educators of rare disease are the patients themselves and patient organisations should be actively encouraged to be involved in the process of policy development. Sadly, Patient Organisations (PAG) are poorly supported by government? Health

insurance funding systems driving them to find support from the public and the pharmaceutical industry which then creates the impression of bias and a frequent reason for governments and health funders to then minimise their contributions. Joint collaboration is needed to develop unbiased clinically relevant guidelines to serve these rare disease patients which should include disease awareness, phenotypes and collecting of appropriate samples for diagnostics.

> *Most initiatives are country-wise, such as those making up this coalition (Appendix 1).*
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> *Most initiatives are **country-wide**, such as those making up this coalition (Appendix 1).*

> *We propose using the most widely accepted definition of a rare disease, i.e., a condition that affects 1 person per 2,000.*

It is a very good starting point to have a universal definition, but Africa has a few unique situations which needs to be considered. Due to limited diagnostics and very few newborn screening programs the rare disorders are accumulated around those which can be easily diagnosed clinically or those for which diagnostics are available. Population data is also frequently out of date and migration pattern also influence the composition of populations.

In the future it maybe pragmatic to either redefine the definition to a specific number like the USA definition which is disorders which affects less than 200 000 of the population or have some methods to have conditions move out of the rare disease definition as the diagnostics improve. A very practical example is that Tuberculosis would be considered a rare disease in some high-income countries where it is endemic and parts of Africa and as therapeutics improve and access the health care the same situation may develop. The lack of genetic testing, prenatal testing and genetic counselling will also skew the data towards a composition of rare diseases which are very different to other continents.

We propose policies that will foster collaborative research to understand genetic factors and heredity patterns of rare diseases, the development of diagnostic tools, and the discovery and development of orphan drugs by:

> 1. *Allocating funding for research on rare diseases diagnosis, heredity, and treatment*
> 2. *Creating a harmonious research environment in the region with shared resources, protocols, databases, and discoveries.*
> 3. *Harmonization of the regulatory environment for research, clinical trials, and drug development for rare diseases.*
> 4. *Incentivizing and encouraging the development of orphan drugs by fast-tracking the approval of protocols, waiving fees associated with the discovery and production of orphan drugs and centralizing the processes and protocols for drug development. We also propose tax incentives for drug development companies, such as a certain level of tax credits and tax reduction for preclinical research, as well as market exclusivity for a number of years.*

5. ***Enhancing the knowledge of ethics in rare disease and how ethical decision making should be included in developing policies and treatments.***

> *Partly because they affect few people, approved treatments are currently available for only 2.5-5% of rare diseases, many of which are prohibitively priced and often not registered for use in SADC countries.*

The perception that all rare diseases have expensive treatments is untrue and should be actively used in examples with health care policy maker and funders. For context Galactosemia is a rare disorder which is prevalent in Sub Saharan Africa and has a milder phenotype than the European common mutation and can be treated by simply lactose free diet. If untreated many of these infants will die with acute liver failure in infancy or E.Coli sepsis but simple modification to diet will secure healthy adulthood with minimal cost to the health care system. There are multiple similar examples but until the SSA epidemiology has been established it will be difficult to predict the potential cost of therapies and true budget impact.

> *Rare diseases receive limited attention in the SADC region, resulting in significant costs not only to healthcare systems but also to individuals living with these conditions. With no clear guidelines, the diseases are often misdiagnosed or completely undiagnosed, exacerbating the situation. We propose a unified policy framework for health and social services to address the gaps in rare disease diagnosis, treatment, and management in the SADC region. This approach has been shown to improve health outcomes for PLRDs by collectively addressing the burden and ensuring the effective utilization of resources, rather than tackling individual diseases in small geographical areas.*

Some of the lack of attention to rare disease is the perception that they only influence a small percentage of the population so can be forgotten. As the authors suggested the key is collaboration and make health care policy makers and funders aware that the disorders are collectively common 1 in every 17 people, not all are expensive to treat, preventative therapies, genetic and prenatal counselling are essential, they are a benefit to society rather than a burden and are entitled to the same access to health care than all other individuals. Patient advocacy groups are a major source of education and support and should be part of the rare disease health care policy.