UMEÅ UNIVERSITY

RHEUMATIC HEART DISEASE IN NAMIBIA

Evaluating the Burden and the Cost-Effectiveness of a Preventive Strategy

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Poverty Breaks Heart – Bongani Mayosi

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Abstract

Background: Rheumatic Heart Disease (RHD) is a neglected public health problem, which is most prevalent in low-and middle-income countries. It affects over 460 million people and causes about 390,000 deaths annually, predominantly children, young adults, and women. This thesis aimed to assess the burden of Rheumatic Heart Disease in Namibia and to evaluate the cost-effectiveness of a preventive strategy.

Methods: Data was obtained from primary and secondary sources in four distinct studies. The first study analysed the RHD outpatient and inpatient data from 2010-2020. The second employed a cross-sectional survey, incorporating a questionnaire with the EQ-5D-5L tool, to assess the health-related quality of life and healthcare usage pre- and post-RHD diagnosis. A systematic review was conducted in the third study synthesising preventive interventions, while the fourth study used a Markov model to evaluate the cost-effectiveness of a secondary prevention strategy in Namibia.

Results: The clinical RHD prevalence was estimated at 28 per 100,000 cases. From the survey, 83 RHD patients participated, predominantly women (77%) and primarily young adults aged 20-29 (41%). The majority (84%) had received surgical treatment. Notably, there was a significant increase in mean QALY from 0.773 pre-diagnosis to 0.941 post-diagnosis ($p<0.001$). The systematic review underscored the effectiveness of school and nurse-led prevention programmes. The health economic evaluation demonstrated that echocardiographic RHD screening was cost-effective, with an Incremental Cost-Effectiveness Ratio of N$ 28,516.75 per QALY gained, which falls below Namibia's GDP per capita.

Conclusions: The findings highlight a significant gap in RHD data, particularly in high-endemic regions like Sub-Saharan Africa, emphasising the need for enhanced data quality and surveillance. The effectiveness of school-based and community-led programmes is apparent, but the scarcity of data from diverse regions limits a comprehensive understanding of optimal prevention strategies. Echocardiographic screening is identified as a feasible component of RHD secondary prevention in Africa, pointing towards a policy need for improved surveillance and data quality. Future research should investigate the impact of various interventions on RHD incidence and prevalence.

Key Words: Rheumatic Heart Disease, Prevention, Cost-effectiveness, Namibia

Abbreviations

A.S.A.P.	Awareness Surveillance Advocacy Prevention
ARF	Acute Rheumatic Fever
CET	Cost-effectiveness Threshold
ICER	Incremental Cost Effectiveness Ratio
GAS	Group A Streptococcus
HRQoL	Health-related Quality of Life
LMICs	Low-and Middle-Income Countries
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjusted Life Years
RF	Rheumatic Fever
RHD	Rheumatic Heart Disease

Simple Summary

Title: Heart Damage from a Sore Throat and How We can Prevented it

Rheumatic Heart Disease (RHD) is a serious heart condition that can develop after a sore throat caused by a bacteria, mainly in children and young adults. Sometimes the body's immune system, trying to fight off the infection, mistakenly damages its own tissues including the heart, joints, and skin. This is called rheumatic fever, and it can lead to RHD, where the heart valves get permanently damaged. Worldwide, over 460 million people have RHD, and it causes more than 390,000 deaths every year, mostly in low-and middle-income countries. In Namibia, about 1% of people might have RHD, but it's hard to know for sure because we don't have enough data.

Detecting and treating the sore throat early with antibiotics can stop rheumatic fever and prevent RHD. This research looked into how big of a problem RHD is in Namibia, what can be done to prevent it, and whether those prevention methods are worth the cost.

We found that RHD mainly affects young people in Namibia, especially in the north. Research from around the world shows that checking and treating kids for sore throat at school works well to stop RHD. Also, having community health workers teach families about RHD helps people get treatment early. However, when we looked at Namibia's health data, we saw it was missing key details needed to understand the full impact of RHD. Again, the information is mainly kept at the main heart clinic in Windhoek, and not much is done to educate the wider community. This problems are common in many other countries like Namibia.

Sometimes people have RHD without ever knowing they had a throat infection, or show symptoms until the damage is worse. It's important to find these people early to prevent the condition from worsening and requiring major expensive treatment like heart surgery. Scanning hearts with special machines in schools and communities can find RHD even if there are no symptoms. We looked at the costs and benefits of doing this in Namibia and found that the benefits outweigh the costs, making it a good investment.

These findings are important not just for Namibia but for other similar countries. We need to get better at collecting RHD data and educating both the public and health workers about the disease. Early treatment for throat infections and heart screenings are crucial in managing RHD. We need more information to understand RHD better and to find effective ways to prevent it. Including RHD services in existing healthcare and using available community health workers can help manage resources better.

Original Papers

Paper I

Shimanda PP, Söderberg S, Iipinge SN, Neliwa MN, Shidhika FF, Norström F. Rheumatic heart disease prevalence in Namibia: a retrospective review of surveillance registers. *BMC Cardiovascular Disorders*. 2022;22:266. https://doi:10.1186/s12872-022-02699-2

Paper II

Shimanda PP, Söderberg S, Iipinge SN, Shidhika FF, Norström F. Health-related quality of life and healthcare consultations among adult patients before and after diagnosis with rheumatic heart disease in Namibia. *BMC Cardiovascular Disorders*. 2023;23:456. https://doi:10.1186/s12872-023-03504-4

Paper III (a)

Shimanda PP, Shumba TW, Brunström M, Söderberg S, Lindholm L, Iipinge SN, Norström F. Preventive interventions to reduce the burden of rheumatic heart disease in populations at risk: a systematic review protocol. *Systematic Reviews*. 2021;10:200. https://doi:10.1186/s13643-021-01748-9

Paper III (b)

Shimanda PP, Shumba TW, Brunström M, Söderberg S, Lindholm L, Iipinge SN, Norström F. Preventive interventions to reduce the burden of rheumatic heart disease in populations at risk: a systematic review. *Journal of the American Heart Association.* 2024;13:e032442. https://doi.org/10.1161/JAHA.123.032442

Paper IV

Shimanda PP, Lindholm L, Söderberg S, Norström F. Rheumatic Heart Disease School-Based Echocardiographic Screening: A Cost-Effectiveness Markov Model. *(Manuscript*)

Background

Introduction

Rheumatic Heart Disease (RHD) is a severe, yet preventable, chronic heart condition resulting from untreated Acute Rheumatic Fever (ARF).[1] It leads to significant health issues like significant heart failure and stroke, profoundly impacting daily activities, education, and work. RHD is one of the most common acquired cardiovascular diseases and cause of morbidity and mortality in children and young people under the age of 25 years, predominantly women. The prevention of RHD hinges on early treatment of ARF. However, in areas where RHD is endemic, inadequate healthcare often leads to many cases remaining undiagnosed. Early detection, crucial for halting its progression, is achievable through techniques such as echocardiography and the establishment of patient registries for ongoing care.

RHD is associated with poor socio-economic conditions and social determinants of health, e.g., overcrowding, poor sanitation, inequitable access to healthcare in poor and socially disadvantaged settings are partially attributable to the aetiology of ARF and RHD, in addition to genetic predisposition.[2] While the prevalence of RHD is easier to establish, the prevalence of ARF is still incompletely understood as it is only present in a subset of patients and only a minority of the patients with RHD recall a preceding ARF episode.

Rheumatic Heart Disease

RHD continues to be a global health problem, affecting approximately 460 million people worldwide and causing around 390,000 annual deaths, predominantly among children and young adults.[3] However, these estimates heavily rely on mathematical models and may underestimate or overestimate the true disease burden due to limited data, systematic surveillance programmes, and healthcare resources in low-and middle-income countries (LMICs) where the disease is prevalent. RHD is most prevalent in the Oceania, South Asia, and Sub-Saharan Africa.[4]

RHD is a chronic consequence of an autoimmune-mediated inflammation to the heart and cardiac valves following infection by Group A b-haemolytic Streptococcus (GAS), mostly in the pharyngeal.[1] ARF is a multisystem autoimmune response presumed to arise from antigenic mimicry to certain GAS antigenic proteins in genetically predisposed individuals.[5,6] Antibodies developed in response to GAS pharyngitis cross-react with cardiac proteins through a process termed 'molecular mimicry'. ARF develop in about 0.3-3% of individuals with untreated GAS pharyngitis.[1,7] However, the natural history and progression of ARF and RHD still remain not completely understood.

Inflammation of the heart valves leads to progressive damage with fibrotic changes, resulting in chronic RHD.[8,9] The Mitral valve is most commonly affected compared to the Aortic valve, while mixed valvular involvement is also common. The left-sided

valves are mostly affected due to high haemodynamic shear forces, relative to the right sided valves (Tricuspid and Pulmonary). The Tricuspid valve is less structurally involved but more commonly functionally involved as a haemodynamic consequence of left heart disease. Presentations range from subclinical to severe clinical disease with symptoms such as heart failure, atrial fibrillation, subacute bacterial endocarditis (SBE), stroke/cerebrovascular accident (thrombo-embolic complications), poor maternal outcomes, progressive morbidity/disability, reduced quality of life, and premature mortality.

Clinical Presentation and Diagnostic of RHD

GAS pharyngitis, often resembling viral infections, presents with symptoms such as a sudden sore throat, pain upon swallowing, fever, red and swollen tonsils, and tender lymph nodes in the neck, usually without a cough. Due to its similarity to viral respiratory infections, laboratory confirmation, typically through throat swab cultures, is essential for accurate diagnosis. Rapid Antigen Detection Tests (RADTs) are also used for their speed, although their sensitivity varies.

ARF, an acute illness, usually manifests 2-4 weeks after GAS pharyngitis with symptoms including fever, carditis, arthritis, chorea, subcutaneous nodules, and erythema marginatum. Carditis is the most common initial presentation, occurring in about 50-70% of patients.[10] ARF diagnosis is based on a combination of clinical signs and laboratory findings, following the Jones Criteria, as it lacks a singular diagnostic feature.

RHD symptoms vary depending on the affected heart valves and the severity of the valvular lesions, commonly including activity-related shortness of breath, bodily swelling, palpitations, and chest pain.[11] Clinical examination may reveal cardiac murmurs, altered heart sounds, signs of fluid overload, and cardiac chamber enlargement. Despite these symptoms, compensatory haemodynamic changes can lead to a prolonged symptom-free period. RHD diagnosis often follows a confirmed ARF episode, but particularly in LMICs, patients may present without prior ARF symptoms, often with severe complications. Diagnosing RHD involves comprehensive clinical assessments, including an Electrocardiogram (ECG), chest X-ray, and crucially, echocardiography, which confirms clinical assessments and assists in managing the disease.[12]

Echocardiography significantly improves the diagnosis of RHD and ARF as it can detect valvular pathology and dysfunction with mild and moderate stenosis and/or regurgitation, which might be missed during auscultation. The integration of echocardiographic findings into the diagnostic criteria for both ARF and RHD has led to increased detection of subclinical cases of rheumatic carditis and RHD, thereby enhancing the accuracy of prevalence estimates.[13] Early and precise diagnosis is vital for the timely initiation of suitable antibiotic prophylaxis, which is crucial in halting disease progression and improving patient prognosis.

The 2023 World Health Federation guidelines on echocardiographic diagnosis of RHD, alongside the 2015 Jones Criteria for ARF diagnosis, provide comprehensive

recommendations for utilising echocardiography in diagnosing, classifying, and assessing the risk of ARF and RHD.[10,14]

Subclinical carditis, characterised by echocardiographically detected valvulitis without clinical signs of carditis, is found in up to 53% of ARF cases.[10] The 2015 revision of the Jones Criteria formally recognised the importance of echocardiography in diagnosing rheumatic carditis.[10] Subclinical carditis, identified through echocardiographic valvulitis, is now considered a major diagnostic criterion for ARF. Consequently, echocardiography is strongly recommended for patients suspected of having ARF, particularly in high-risk areas.

Improving access to echocardiography in LMICs is crucial. Strategies such as task-shifting, the use of handheld devices, and simplified diagnostic protocols are key to facilitating early diagnosis of ARF and RHD, which can significantly enhance patient outcomes.[15]

Management and Prevention of RHD

RHD prevention requires multi-modal interventions including primordial, primary, secondary, and tertiary prevention. This requires collaboration across various sectors.[16,17]

Primordial prevention targets reducing GAS infection risks through improved living conditions, nutrition, and equitable healthcare access. Strategies include enhancing sanitation and housing, nutritional programmes, and public education about GAS symptoms and treatments. These measures are complemented by policy efforts addressing social determinants like housing and education.

Primary prevention focuses on preventing ARF by early detection and treatment of GAS pharyngitis using penicillin. This involves educating healthcare professionals and the public about GAS symptoms and the importance of antibiotic completion. Integrating primary prevention into healthcare systems, schools, and community initiatives is vital.

Secondary prevention aims to prevent ARF recurrence and RHD progression in individuals with a history of ARF or RHD. Central to this is regular administration of benzathine penicillin G, typically every 3-4 weeks, to maintain effective serum levels against GAS infections. This approach includes systematic screening, regular follow-ups, and patient education about the importance of ongoing antibiotic prophylaxis.

Tertiary prevention manages established RHD to prevent further deterioration and improve quality of life. This includes medical management with appropriate medications, regular monitoring, and possibly surgical interventions for severe valve damage. Lifestyle modifications, patient education, and support groups are also important components.

Impact of RHD on the Health-Related Quality of Life

Health-Related Quality of Life (HRQoL) plays a crucial role in informing treatment decisions and deriving quality-adjusted life years (QALYs), a key measure in

economic evaluations for health resource allocation.[18,19] QALYs incorporate individual preferences, assigning weights to different health states, ranging from 0 (death) to 1 (perfect health), to reflect the value individuals place on being in a specific health state.[20] HRQoL assessments often employ standardised tools, like the EQ-5D, developed by the EuroQol group.[21]

In the context of RHD, assessing HRQoL is essential to understand the disease's multifaceted impact on patients. This multidimensional concept includes self-perceived health status affected by impairments, functional status, personal perceptions, and social opportunities influenced by the disease, injury, treatment, or policy.[18]

The RHD-related morbidity significantly impairs the physical, social, and psychological well-being of patients. This includes fears such as the prospect of death and potential complications.[22] These factors collectively affect the HRQoL of individuals living with RHD. Heart failure and congestive heart failure, severe complications of RHD, are known to contribute to psychological stress in cardiac patients broadly.[23–25] Beyond these direct complications, various treatment measures such as surgery, regular intramuscular injections of Benzathine Penicillin for secondary prophylaxis, ongoing medication, and anticoagulants also play a role in influencing HRQoL in RHD patients.[26]

When considering the influence of long-term treatment for ARF or RHD patients on the HRQoL, QALY scores can be suitable as they offer a comprehensive patient-centred measure of health outcomes, including both the quality and quantity of life.[20] However, QALY weights in RHD research are seldom measured and validated.

Global Resolution on RF and RHD

RHD remains a significant concern in LMICs and among indigenous populations in some high-income settings nations, despite its near eradication in high-income countries.[27] This disparity led to its neglect in global health policy from the late 20th century, but it has re-emerged as a priority in the early 21st century.

The resurgence of interest in RHD has incited increased research, action, and advocacy across affected regions. A pivotal moment was in 2006, when a resolution for controlling Rheumatic Fever and RHD in the African region was adopted. This resolution advocated for comprehensive programmes incorporating a multifaceted strategy labelled "Advocacy, Surveillance, Awareness, Prevention (A.S.A.P)".[28]

In 2013, the World Heart Federation set goals to reduce premature deaths from cardiovascular diseases by 25% among individuals under 25 years by 2025.[29] This goal marked a significant step in re-establishing RHD as a global health concern. In 2018, the World Health Organization (WHO) adopted a Global Resolution on ARF and RHD declaring them as global health prioritie.[30] This resolution was significant for establishing key actions, advocating for resource mobilisation, and renewing global commitment towards eradicating ARF and RHD. The increased focus on RHD at a global level reflects a renewed understanding of its impact and the need for concerted efforts to eradicate it.

RHD in Namibia

The prevalence of RHD in Namibia, as estimated by the Global Burden of Disease (GBD) study, stands at 1.09% and equating to approximately 25,200 prevalent cases.[31] The disease is more common in the northern regions of the country, and predominantly among women.[32–34] RHD is also ranked among the three most common causes of cardiovascular death in children in the ages 5-14 years, in addition to Congenital Heart Disease.[35]

Preventive measures, surveillance activities, and cardiac surgery have been in place since 2010. Surgical intervention for RHD, including both valve replacement (utilising biological and mechanical prostheses) and valve preservation strategies, is central to treatment.[35] However, due to limited human and infrastructural resources, there are extensive waiting times, ranging from weeks to years. An equity-based prioritisation system is employed, focusing on clinical severity and prognosis, yet the efficiency and fairness of this system merit further examination.

Treatment protocols heavily rely on penicillin for ARF and as secondary prophylaxis for RHD.[36] Post-surgical care includes Aspirin for patients with biological prostheses and Warfarin for those with mechanical ones. Continuous monitoring and dosage adjustment of Warfarin is a critical aspect of care, conducted at the cardiac Warfarin clinic.[37] Women, especially those of reproductive age on long-term anticoagulation therapy, receive specialised counselling and family planning services, including the provision of progesterone-derived transdermal patches. This gender-specific approach to RHD treatment, particularly for women opting to start families, demonstrates an integrated care model. However, supporting data on the efficacy and outcomes of these tailored approaches would provide a more comprehensive understanding of their impact.

Health Economics Aspect in RHD

Health economic evidence is crucial in guiding decision-makers to allocate resources efficiently and effectively, especially in regions facing resource and budget constraints. While health economic evaluations are often more informative for health and social care decisions, as they consider both costs and outcomes simultaneously compared to other alternatives, conducting such analyses within the RHD population presents challenges. These include the limited range of implemented interventions, scarce data, and decisions on prioritising funding for RHD over other prevalent diseases.[38,39]

Although, previous economic evaluations demonstrated that preventive interventions for RHD are cost-effective, offering potential long-term benefits.[40–47] Both primary and secondary prevention strategies are demonstrated to be cost-effective in different countries, but most of the evidence is from high-income countries.[42] Notably, a combination of prevention strategies is often reported as the most cost-effective and cost-saving approach in the long term.[42,44,47] Additionally, echocardiography screening as part of secondary prevention for active RHD case

finding has been shown to be cost-effective and important for early detection of patients with trivial disease.[48–50]

Furthermore, RHD poses significant socioeconomic challenges to the patients and healthcare systems.[51,52] However, most research on RHD-related costs has been conducted in high-income countries, leading to a data gap in LMICs.[53] This gap is more pronounced in community-level costs data, compared to the medical costs associated with RHD, highlighting a need for more comprehensive socioeconomic research in these settings. RHD-related costs are crucial to information economic evaluations to guide and support policy decisions in RHD care and management.

Rationale for the Thesis

Rheumatic Heart Disease inflicts a significant societal burden, characterised by high morbidity and mortality rates, predominantly affecting the younger population. The disability and premature deaths of children and young adults have profound implications for the workforce in developing countries, where RHD is more prevalent. This not only strains the healthcare systems due to the demands of treatment and management but also places a considerable economic burden on these societies.

In Namibia, the burden of RHD is estimated to affect approximately 1% of the population.[31] However, with fewer than 1,000 patients diagnosed and registered at the national cardiac clinic, the prevalence estimates are likely an underrepresentation of the true impact. This discrepancy highlights a critical gap in the identification and management of RHD, in addition to the absence of population-based preventive interventions.

Furthermore, there is a notable paucity in scientific knowledge regarding RHD's impact on the well-being of patients and the healthcare system. The disease's effect on health-related quality of life, a crucial aspect of patient care, remains under-researched. Additionally, there is a lack of comprehensive studies evaluating the cost-effectiveness and overall worth of interventions aimed at preventing and controlling RHD.

Addressing these critical gaps is essential for the global fight against RHD. It necessitates a focused effort to generate robust data and evidence that can guide more informed and strategic health policy and intervention planning, ultimately mitigating the burden of RHD in Namibia and beyond.

Aims

The primary aim of this thesis is to evaluate the burden of RHD and to identify and evaluate preventive strategies that are both effective and economically feasible for implementation in Namibia.

Specific Aims

Sub-aim 1: Aimed to estimate the prevalence of RHD and the RHD-related health care systems in Namibia (*Paper I*).

Sub-aim 2: Aimed to assess the Health-related Quality of Life and healthcare consultations among adult RHD patients in Namibia before and after diagnosis (*Paper II*).

Sub-aim 3: Aimed to synthesis the effectiveness of preventive interventions in reducing the incidences of ARF and/or RHD among populations at risk of the disease (*Paper III a & b*).

Sub-aim 4: Aimed to evaluate the cost-effectiveness of an echocardiography screening intervention for RHD in Namibia (*Paper IV*).

Materials and Methods

Research Setting

The research was conducted in Namibia, an upper-middle-income country located in South-west Sub-Saharan Africa, covering an area of 825,419 km^2. The country has an estimated population of 3.02 million, predominantly young people under the age of 30 years.[54] Namibia is characterised by its sparse population distribution across 14 regions, with a population density of less than 3 people per km^2. The life expectancy at birth is 64.6 years, while the healthy life expectancy stands at 56.1 years.[55]

Namibia's public healthcare system operates on a three-tier structure: primary (consisting of 37 healthcare centres and 289 clinics), secondary (including 3 intermediate hospitals and 30 district hospitals), and tertiary (with 1 referral hospital). Specialised cardiac care within the public health services, including cardiac surgery, is only available at tertiary hospital.

Public health services are largely subsidised by the government, ensuring citizens fair and reasonable access to care. The total government health expenditure accounts for approximately 16.6% of the total budget and 8.5% of the Gross Domestic Product (GDP). Despite substantial government subsidisation, the out-of-pocket expenditure (OOP) for public care still averages around 8.2% and N$542.50 per capita. Notably, over 70% of the health expenditure is allocated towards curative and clinical healthcare, rather than preventive services. Additionally, a significant portion of this expenditure (27.3%) is directed towards non-communicable diseases.[55]

Research Design

The research was characterised by a comprehensive and multifaceted quantitative methodology, divided into four sub-studies. The initial phase involved a retrospective analysis, using data extracted from outpatient RHD register and inpatient hospital admission records. This was followed by a cross-sectional survey conducted among adult RHD patients, who were receiving routine follow-up care at an outpatient cardiac clinic. The third phase of the study comprised a systematic review of the existing literature on preventive interventions implemented for RHD. The final phase employed a Markov model to assess the cost-effectiveness of secondary prevention strategies for RHD in Namibia.

Paper I

This study employed a retrospective approach, examining secondary data extracted from health record registries.

Data were sourced from two secondary records: the outpatient cardiac clinic's Rheumatic Heart Disease (RHD) register and the inpatient hospital admission database, covering the period from January 2010 to December 2020. Sociodemographic data (age, gender, and region) and clinical characteristics were collected from both registers.

In this study, the heart valve diseases in the outpatient register were classified into four categories: (i) mitral, (ii) aortic, (iii) tricuspid, and (iv) mixed. Mitral valve disease encompassed mitral regurgitation and stenosis, either in isolation or combined with tricuspid valve anomalies. A similar definition was applied to aortic valve disease. Tricuspid valve disease was identified by tricuspid regurgitation or stenosis alone. Mixed valve disease referred to cases involving both aortic and mitral, or these combined with tricuspid valve disease.

Hospital admission data was retrieved using the 2016 fifth edition International Statistical Classification of Disease and Related Health Problems (ICD-10) codes.[56] Acute Rheumatic Fever was retrieved with I00-I02 ICD-10 codes. Rheumatic Mitral valve disease was defined by code I05, Rheumatic Aortic valve disease by code I06, Rheumatic Tricuspid valve disease by code I07, multiple Rheumatic valve diseases by code I08, and other Rheumatic valve diseases by code I09. Non-rheumatic valve diseases were retrieved with I34-I38 codes.

Descriptive statistical analyses were conducted using STATA 14.2 and Office 365 Microsoft Excel, with results presented as frequencies and percentages.

Paper II

A cross-sectional survey was conducted with adult RHD patients at an outpatient cardiac clinic between June 2019 and March 2020.

Patients were recruited during their routine follow-up visits within the study period. Those aged 18 years or older who provided informed consent were enrolled. Participants completed a self-administered questionnaire, with the researcher available to explain and interpret questions as needed.

The self-administered questionnaire incorporated the EuroQol 5 dimensions instrument with 5 response options (EQ-5D-5L).[21] The first section gathered sociodemographic characteristics and clinical data of the patients. The second section inquired about healthcare visit frequency, hospital admissions, missed work or school days, travel distance and mode to the health facility, and duration of stay. Participants provided retrospective information for the year before their RHD diagnosis and the preceding 12 months.

The EQ-5D-5L assessed the HRQoL for the year before RHD diagnosis and at the survey time. It includes five dimensions: Mobility, Self-care, Usual activities, Pain or discomfort, and Anxiety or depression, each with five response levels that correspond to no problems, slight, moderate, severe, and extreme problems. The

second part of EQ-5D-5L features a Visual Analogue Scale (VAS), where patients rate their quality of life from 0 to 100.

The questionnaire was developed in English and also translated into Oshiwambo, the most spoken local language in Namibia.

Survey data was captured and managed using Office 365 Microsoft Access and Excel, then exported to STATA 14.2 for analysis. Descriptive analyses included percentages, means, medians with standard deviations (SD), and 25th and 75th quartiles. The Wilcoxon signed-rank test was applied for pairwise comparisons of QALY scores before diagnosis and at the time of the study. The Mann–Whitney U rank sum tests were used to compare QALY scores between groups.

EQ-5D-5L responses are presented by dimension for each patient group and subgroup. These responses were converted into QALY scores using the Ethiopian population EQ-5D value set in a decremental approach.[57] The QALY score, ranging from 0 (death) to 1 (full health), measures health-related quality of life. The Ethiopian tariff was selected as the most suitable for Namibia, considering its Sub-Saharan African context.

Paper III (a & b)

A systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[58] Initially, a protocol developed and subsequently registered with the International Prospective Register of Systematic Reviews (PROSPERO) - **ID: CRD42020170503**, peer-reviewed, and published (Paper III a).

Eligibility criteria

Studies were selected based on criteria including: (i) evaluation of the effectiveness of preventive interventions with reported outcomes on the incidence or prevalence of Group A Streptococcus (GAS), Acute Rheumatic Fever (ARF), and Rheumatic Heart Disease (RHD); (ii) intervention implementation from January 2000 onwards; (iii) clear description of interventions aimed at reducing the incidence or prevalence of GAS, ARF, and/or RHD; (iv) intervention studies focusing on populations not at risk of ARF or RHD, based on prevalence rates or non-endemic status. Studies not in English were categorised as "awaiting classification" due to translation constraints and were not included in the analysis.

For this study, an intervention was defined as any activity or strategy undertaken to lower the incidence or prevalence of GAS, ARF, and/or RHD within populations identified as at high risk of RHD, based on global prevalence estimates.[59]

Information sources

A comprehensive search was performed in electronic databases including PubMed, Scopus, and Web of Science, covering publications from January 2000 to February 2023. Additionally, manual searches were conducted in the reference lists of relevant articles.

Search strategy

The search strategy incorporated Medical Subject Headings (MeSH) terms and keywords such as "Rheumatic Heart Disease", "Acute Rheumatic Fever", "Rheumatic Fever", "Group A Streptococcus", "Intervention", and "Program".

Study selection process

One reviewer imported the retrieved studies into Clarivate Endnote 20 and screened titles for selection. Subsequently, two independent reviewers screened abstracts and full texts for relevance. A third reviewer was involved in cases of ambiguity regarding study relevance.

Quality appraisal

The methodological quality of the included studies was evaluated by two independent reviewers using the Joanna Briggs Institute (JBI) critical appraisal checklists for non-randomised intervention studies.[60,61] These JBI checklists were considered appropriate for addressing the methodological heterogeneity among the included studies which are mainly observational and epidemiological studies.[61]

Data synthesis

Given the heterogeneity in methodology, outcomes, and contexts among the included studies, a synthesis without meta-analysis (SWiM) approach was adopted.[62] As a result, the review findings were articulated through a narrative synthesis and presented descriptively.

Paper IV

This study employed a Markov model to assess the cost-effectiveness of an echocardiographic screening programme for RHD in school children, compared to a 'do-nothing' strategy (**Figure 1**). The model aims to capture the long-term health and economic impacts of RHD screening.

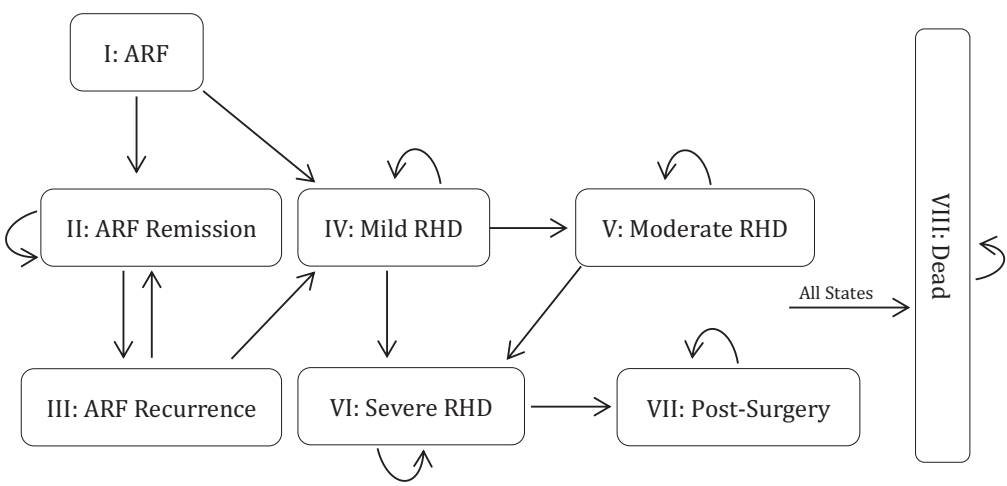


Figure 1 Markov model framework

Model and perspective

The Markov model adopted a societal perspective, comparing incremental costs and quality-adjusted life years (QALYs) over a 100-year horizon. This extended timeframe is crucial for understanding the lifetime implications of RHD and its interventions. In scenario without screening, children are typically diagnosed during routine care at moderate or severe RHD stages. The parameters used in the model were either extrapolated from the literature or assumed based on clinical relevance.

Model states

The Markov model outlines the progression of RHD through eight distinct states (**Figure 1**). *State I, ARF*, includes children with subclinical carditis identifiable by echocardiography, characterised by pathological regurgitation of the mitral or aortic valve, but without the classic signs or symptoms of ARF as defined by the Jones criteria. *State II, ARF Remission*, includes children who have recovered from an ARF episode. *State III, ARF Recurrence*, contains children who experience a subsequent ARF episode, increasing their risk of developing RHD compared to their initial episode.

State IV, Mild RHD, encompasses children displaying trivial or mild valvular pathology identified by echocardiography, characterised by morphological changes in the mitral and/or aortic valve and pathological regurgitation and/or stenosis. *State V*, Moderate RHD, includes children with established valvular disease but no clinical complications, while *State VI, Severe RHD*, encompasses those with significant valvular disease presenting with clinical complications such as heart failure, arrhythmia, stroke, or requiring cardiac surgery. All children in this state will undergo valve replacement surgery. *Post-surgery, State VII*, represent the post-operative phase. The final dead state, *State VIII*, is an absorbing state indicating mortality, accounting for both disease-related deaths and deaths from other causes.

Transition probabilities

Transition probabilities, modelled on yearly cycles, were derived from existing literature, or assumed based on clinical relevance. Baseline probabilities were used in both scenarios, with risk reduction adjustments applied in the screening scenario (**Table 1**).

Table 1 Transition probabilities used in the model

Transition	Probability	Source(s)
ARF to Mild RHD	0.324	Coates[47]
ARF to Dead	0.010	Watkins[42]
ARF Remission to ARF Recurrence	0.086	Coates[47]
ARF Remission to Dead	0.005	Assumed
ARF Recurrence to Mild RHD	0.643	Coates[47]
ARF Recurrence to Dead	0.020	Coates[47]
Mild RHD to Moderate RHD	0.210	Beaton[13]
Mild RHD to Severe RHD	0.041	Beaton[13]
Mild RHD to Dead	0.008	Dixit[44]
Moderate RHD to Severe RHD	0.025	Zachariah[49]
Moderate RHD to Dead	0.013	Dixit[44]
Severe RHD to Surgery (100% get surgery)	0.750	
Severe RHD to Dead	0.250	Coates[47]
Risk of death from valve surgery	0.030	Coates[47]
Post-Surgery to Dead	0.017	Coates[47]
Risk reduction from secondary prevention	0.55	Coates[47]
Risk reduction from valve surgery	0.85	Coates[47]
Risk reduction from heart failure management	0.60	Coates[47]

Costs

Costs included RHD-related healthcare expenses and patient costs incurred during visits, calculated in Namibian Dollars using local sources and published research (**Table 2**).[53] In the 'do-nothing' scenario, costs for non RHD-related healthcare utilisation were considered for all health states except moderate RHD, severe RHD, and post-surgery states. Screening costs encompassed equipment, salaries, and confirmatory screening for positive cases detected in initial screenings. Staff salaries were estimated based on the Namibian public health salary scales, while the cost for equipment were estimated based on market values.

Table 2 Healthcare cost per state and total screening cost

State	No Screening (N$)	Screening (N$)
ARF Remission	1,740.56	8,764.88
ARF Recurrence	1,740.56	17,582.00
Mild RHD	1,740.56	11,194.43
Moderate RHD	14,347.05	14,347.05
Severe RHD	184,013.25	184,013.25
Post-Surgery	12,518.27	12,518.27
Dead	0	0
Total Screening Cost		4,493,593.20

Health utility

Health outcomes (**Table 3**), expressed as QALYs, were taken from the survey study (Paper II) and the study by Dixit *et al*. in India.[63] These are further described in Paper IV in the appendix.

Table 3 Health utility

State	QALY	Source(s)
ARF	0.937	Irlam[43]
ARF Remission	0.955	Dixit[63]
ARF Recurrence	0.937	Dixit[63]
Mild RHD	0.941	Shimanda[33]
Moderate RHD	0.773	Shimanda[33]
Severe RHD	0.658	Dixit[63]
Surgery	0.962	Shimanda[33]

Discount rate

A standard 3% discount rate was applied to both costs and outcomes, adjusting for the time value of money and future uncertainties. This rate is widely used in global health cost-effectiveness studies as recommended by different panels on Cost-Effectiveness in health and medicine.[64]

Outcome

The primary outcome measure was the Incremental Cost-Effectiveness Ratio (ICER), indicating the cost per QALY gained in each scenario. In the absence of a cost-effectiveness threshold (CET) for Namibia, we used the one-to-three times the GDP per capita threshold as recommended by the World Health Organization for countries without an official CET.[65]

Sensitivity analysis

Deterministic sensitivity analyses were performed to evaluate the influence of uncertainties in model inputs on the overall cost-effectiveness results. Each analysis involved varying a single key parameter while maintaining the others at their baseline values. Transition probabilities were modified according to the 95% confidence intervals obtained from the primary sources. Costs were altered by either halving or doubling the initial estimates. In the base case, it was assumed that all patients with severe RHD underwent surgery, but this assumption was adjusted to 50% and 80% for the sensitivity analyses. Additionally, the discount rate was varied between 0% and 5%.

Data analysis

The analyses were performed in Office 365 Microsoft Excel.

Ethical Consideration

The research was conducted in adherence to the ethical principles of the World Medical Association's Helsinki Declaration. Ethical approval was obtained from the Biomedical Research Ethics Committee (BREC) and the Research Management Committee (RMC) at the Namibian Ministry of Health and Social Services (**Study Approval Reference: 17/3/3 PPS**) for secondary data in sub-study I and for the survey in sub-study II. Following, permissions for data collection were secured from each hospital's superintendent.

Informed consent was obtained from participants, ensuring voluntary participation without prejudice for refusal or withdrawal. Participants were fully informed about the study's objectives and their rights, with confidentiality and anonymity strictly maintained.

For the systematic review and cost-effectiveness analysis, ethical clearance was not required as these parts involved no primary data collection.

Results

The main results comprised the estimated RHD prevalence and characteristics of RHD patients (Paper I), the impact on Health-related Quality of Life (HRQoL) and healthcare utilisation from RHD (Paper II), the effectiveness of various preventive interventions for RHD (Paper III), and the cost-effectiveness of RHD echocardiography screening interventions (Paper IV).

Paper I

The outpatient register contained 718 patients with clinical RHD regarded as active at the time of the study. The estimated prevalence of clinical RHD was 28 cases per 100,000. The prevalence is disproportionally high in the northern regions, with Oshana region having the highest prevalence of 124 cases per 100,000 (**Table 4**).

Table 4 Number of clinical Rheumatic Heart Disease cases per region between 2010-2020

Region	Population+	RHD Cases	Prevalence/100,000
Namibia	***2,550,226***	***718***	***28***
Omusati	249,885	6	2.4
Oshikoto	195,165	13	6.7
Ohangwena	255,510	23	9.0
Kavango	237,779	32	13
Omaheke	74,629	11	15
Erongo	182,402	27	15
!Karas	85,759	13	15
Zambezi	98,849	20	20
Otjozondjupa	154,342	32	21
Hardap	87,186	19	22
Kunene	97,865	31	32
Khomas	415,780	213	51
Oshana	189,237	235	124

RHD Rheumatic Heart Disease
+ Population estimates for 2016

Majority of the registered patients were young people under 30 years old (72%), predominantly women (65%) (**Table 5**). Mitral valve disease was the most common (58%), followed by mixed valve disease (19%) and aortic valve disease (13%), respectively. Only 19 patients (2.3%) had a history of ARF recorded in the register. Also, 288 patients (36%) were reported to have undergone heart surgery.

Table 5 Characteristics of patients with clinical Rheumatic Heart Disease in the cardiac outpatient register between 2010-2020 (n=812)

Variables	**n**	**%**
Sex (n=808)		
Women	523	65
Men	285	35
Age Group (n=802)		
0 – 19 years	431	54
20 – 39 years	258	32
≥ 40 years	113	14
Valvular Disease (n=467)		
Aortic Valve Disease	59	13
Mitral Valve Disease	269	58
Tricuspid Valve Disease	23	4.9
Mixed Valve Disease	90	19
Unclassified Valve Disease	26	5.6
Other Clinical Information		
Surgery	288	36
Warfarin	164	21
Acute Rheumatic Fever/Rheumatic Fever	19	2.3
Atrial Fibrillation	35	4.3
Congenital Heart Disease	5	0.6
Hypertension	22	2.7
Stroke	14	1.7
Death	74	9.1

A total of 1,463 hospital admissions were recorded, with most of them attributed to ARF (51%) (**Table 6**). The median number of admission days was 4 days. A total of 44 deaths were recorded during this period.

Table 6 Hospital admissions related to Acute Rheumatic Fever & Rheumatic Heart Disease between 2010-2020 (n=1,463)

Variables	**n**	**%**
Sex		
Women	883	60
Men	580	40
Age Group		
0 – 19 years	555	38
20 – 39 years	495	34
≥ 40 years	413	28
Clinical Diagnosis		
Acute Rheumatic Fever/Rheumatic Fever	739	51
Rheumatic Aortic Valve Disease	31	2.1
Rheumatic Mitral Valve Disease	72	4.9
Rheumatic Tricuspid Valve Disease	10	0.7
Multiple Valve Disease	16	1.1
Other Rheumatic Heart Disease	481	33
Non-rheumatic Valve Disease	114	7.8
Surgery		
Yes	75	5
No	1,388	95
Death		
Yes	44	3
No	1,419	97
Days spent in Hospital		
0 – 14 days	1,280	88
15 – 29 days	137	9
≥ 30 days	46	3
	n	**1st&3rd quartile**
Median Admission Days	4	2&9
Median Acute Rheumatic Fever Admission Days	4	2&8
Median Valvular Heart Disease Admission Days	5	2&10

The study identified several limitations in the RHD-related healthcare practices. The inpatient register lacks patient unique identifiers while the outpatient register contains a single entry per patient and not capturing information per visit. In addition, the outpatient register has missing data on the sociodemographic and clinical information of the patients. Another limitation is the accuracy of the data with possible misreporting in the inpatient register based on the data compared

with local cardiology experts opinions. RHD awareness activities are clinic-based with minimal community level activities.

Paper II

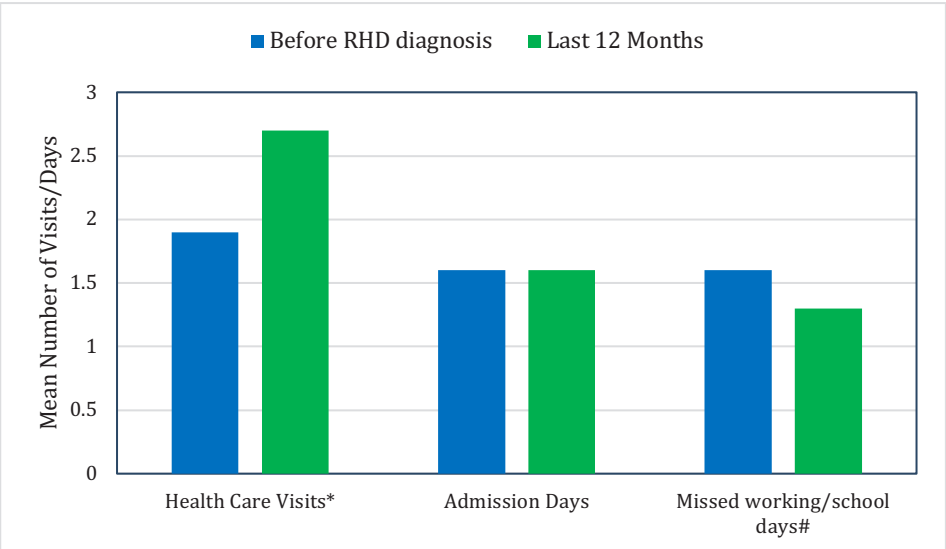
In the survey, 83 patients with rheumatic heart disease (RHD) participated. A significant proportion (77%) were women, with the largest age group being young adults between 20 and 29 years (41%). The majority of these patients (84%) had undergone surgery, with a mean of 7 years from surgery to the time of the survey.

There was a significant improvement in the mean quality-adjusted life year (QALY), which increased from 0.773 in the year prior to RHD diagnosis to 0.941 at the time of the survey ($p<0.001$) (**Table 7**). Similarly, the EQ-VAS rating showed a significant increase from 66 prior diagnosis to 79 during the study ($p=0.005$). Approximately 62% of patients reported experiencing problems in at least one dimension before diagnosis, which decreased to 45% at the time of the survey. Notably, patients most experienced problems in the usual activities dimension (28%) at the time of the survey (*available in Paper II*).

Table 7 Sociodemographic characteristics and QALY score prior RHD diagnosis and during the survey (n=83)

	Before Diagnosis		Time of Survey		
Variable	**n (%)**	**Mean (SD)**	**n (%)**	**Mean (SD)**	**p-value**
Mean QALY	78	0.77 (0.31)	83	0.94 (0.16)	<0.001
Sex					
Women	59 (76)	0.74 (0.34)	64 (77)	0.95 (0.11)	0.002
Men	19 (24)	0.87 (0.21)	19 (23)	0.91 (0.26)	0.23
Age					
18 – 19 years	4 (5)	0.90 (0.16)	4 (4.8)	0.95 (0.75)	NC
20 – 29 years	32 (41)	0.77 (0.32)	35 (42)	0.95 (0.12)	0.01
30 – 39 years	24 (31)	0.76 (0.26)	25 (30)	0.94 (0.12)	0.008
40 – 49 years	12 (15)	0.70 (0.48)	13 (16)	0.89 (0.32)	NC
≥ 50 years	6 (8)	0.90 (0.19)	6 (7.2)	0.98 (0.03)	NC
Place of residence					
Rural	67 (86)	0.78 (0.29)	72 (87)	0.94 (0.17)	<0.001
Urban	11 (14)	0.72 (0.48)	11 (13)	0.97 (0.05)	NC
Education					
No formal education	2 (3)	1	2 (2.4)	0.98 (0.23)	NC
Primary education	15 (19)	0.85 (0.23)	16 (19)	0.96 (0.08)	0.17
Secondary education	49 (63)	0.73 (0.35)	52 (63)	0.92 (0.19)	0.003
Tertiary education	12 (15)	0.83 (0.30)	13 (16)	0.99 (0.01)	NC
Employment					
Employed	31 (40)	0.72 (0.38)	34 (41)	0.95 (0.10)	0.01
Student	7 (9)	0.75 (0.41)	7 (8.0)	0.95 (0.06)	NC
Unemployed	40 (51)	0.82 (0.24)	42 (51)	0.93 (0.20)	0.009
Years with RHD					
<10 years	50 (64)	0.77 (0.33)	53 (64)	0.92 (0.19)	0.019
≥ 10 years	28 (36)	0.78 (0.30)	30 (36)	0.98 (0.03)	<0.001
Surgery					
Yes	66 (85)	0.75 (0.34)	70 (84)	0.96 (0.09)	<0.001
No	12 (15)	0.92 (0.13)	13 (16)	0.82 (0.32)	NC
Years after Surgery					
<10 years	53 (85)	0.79 (0.27)	56 (81)	0.96 (0.10)	0.001
≥ 10 years	12 (15)	0.66 (0.37)	13 (19)	0.99 (0.01)	NC
Heart Valve Disease					
Mitral	31 (40)	0.66 (0.34)	34 (41)	0.94 (0.14)	<0.001
Aortic	14 (18)	0.91 (0.18)	14 (17)	0.94 (0.08)	NC
Mixed	33 (42)	0.82 (0.31)	35 (42)	0.94 (0.20)	0.032

The frequency of healthcare visits also increased, from an average of 1.6 days before diagnosis to 2.7 days in the 12 months preceding the survey (p<0.001) (**Figure 2**). The mean travel distance to the healthcare facility was reported as 55 km (standard deviation: 189 km). A significant majority of the patients (78%) used paid transport, incurring an average cost of N$65 (standard deviation: N$99) (**Table 8**).



* p<0.001 # p=0.138

Figure 2 Healthcare consultations among the RHD patients

Table 8 Factors regarding access to healthcare facility for RHD care

Factor	n	%
Distance to health facility (Mean=55 km; SD=189 km)		
0-9 kilometres	24	29
10-19 kilometres	18	22
20-29 kilometres	7	8.0
≥30 kilometres	34	41
Travel time to health facility (Mean=2.1 hours; SD=1.2 hours)		
<30 minutes	34	41
30-60 minutes	19	23
1-2 hours	16	20
2-3 hours	10	12
>3 hours	3	4.0
Transport to health facility for RHD care		
Own car	7	8.4
Taxi	65	78
Bicycle	1	1.2
Walking	10	12
Cost of transport to health facility (Mean=N$65; SD=N$99)		
No cost	18	22
≥24 NAD	30	36
25-49 NAD	7	8
≥50 NAD	28	34

km – Kilometres, **N$** – Namibian Dollar, **SD** – Standard Deviation

Paper III

Study selection

Seven studies were included in the systematic review. Initially, a comprehensive search yielded 3,037 studies from various databases. Of these, 516 duplicates were removed. Subsequently, the titles and abstracts of the remaining 2,520 studies were screened for relevance to the study's objectives, leading to the exclusion of 2,485 studies. A detailed full-text review was then conducted on 35 studies, out of which 28 were excluded for not meeting the inclusion criteria (**Figure 3**).

The reasons for exclusion varied. Seventeen studies failed to report the impact of the intervention on the incidence or prevalence of the disease. Five studies described interventions implemented before the year 2000. Two studies focused on interventions that did not target ARF or RHD, or were aimed at populations not at risk. Another two were limited to describing clinical activities, and the final two were not published in English.

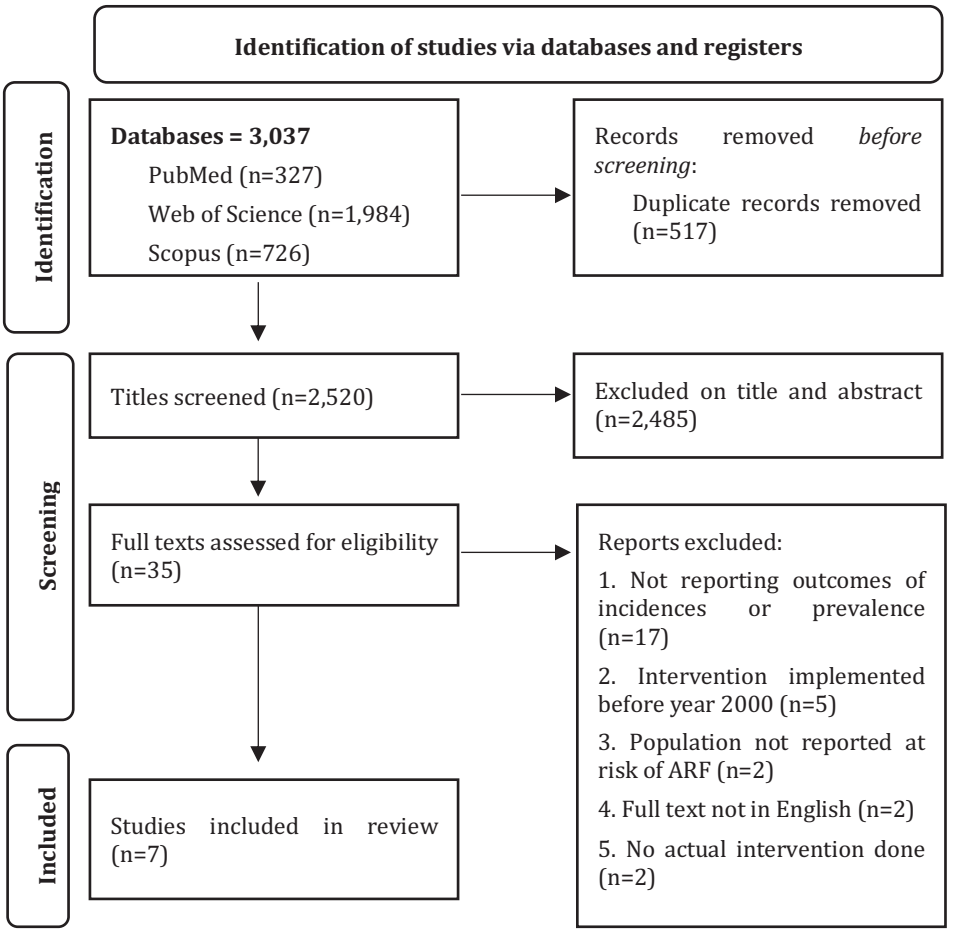


Figure 3 PRISMA flow diagram for study selection

Characteristics of included studies

The included studies were all descriptive in nature, comprising five cross-sectional and two cohort studies (**Table 9**). Five studies were conducted in high-income countries, one in Australia and four in New Zealand, while two were from low-to-middle income countries (Sudan and Nepal). The New Zealand studies primarily described school-based, nurse-led clinics for the primary and secondary prevention of RHD, showing up to a 60% reduction in ARF incidence and prevalence. The Australian study reported reduced ARF cases with a community-based primordial and primary prevention programme led by community workers.

In contrast, the studies from Nepal and Sudan presented detailed comprehensive programmes integrated within existing health systems, both reporting reductions in RHD prevalence rates.

Table 9 Summary of the included studies

Population	Intervention	Comparator	Outcome	Reference
Community Health Workers	Comprehensive programme	None	Developed surveillance registers and integrated programme into existing services.	Ali & Subahi, 2020[66] Sudan
School children	Sore throat clinic in schools, and create awareness.	Pre-intervention	Declining GAS prevalence rates and improved health literacy.	Anderson, et al., 2016[67] New Zealand
School children	School-based sore throat clinic	Pre-intervention	Declining ARF incidence rates.	Jack, et al., 2018[68] New Zealand
School children	School-based sore throat clinic	Pre-intervention	Reduced ARF incidences and GAS prevalence.	Lennon, et al., 2017[69] New Zealand
Community	Comprehensive programme	Pre-programme	Reduced RHD prevalence.	Regmi PR, 2016[70] Nepal
School children	School-based sore throat clinics.	Cohort 1: School clinic supported by GP Cohort 2: No school clinic Cohort 3: Limited school services	ARF prevalence reduced in cohorts with school clinics	Walsh, et al., 2020[71] New Zealand
Community	Community based programme supported by community health workers.	Pre-intervention	Reducing ARF incidences	Ralph, et al., 2022[72] Australia

GP: General practitioner

Quality appraisal

Potential risks of bias were noted, relating to methodological descriptions, sample sizes, and control for confounding factors. Given the heterogeneity of the studies and the complexity inherent in evaluating RHD interventions, no studies were excluded based on the quality appraisal.

Paper IV

The discounted Incremental Cost-Effectiveness Ratio (ICER) for an echocardiographic screening for RHD was estimated to be N$ 28,516.75 per QALY gained (**Table 10**). This ICER is deemed cost-effective when compared to the N$269,335.68 standard threshold in Namibia, which is three times the GDP per capita.

Adjusting key parameters in the model confirmed that screening for RHD continues to be cost-effective. A decreased likelihood of progression from mild to advanced RHD states resulted in a higher ICER than the baseline, yet it remained within cost-effective bounds. Furthermore, lowering the rate of surgical interventions to 50% or 80% for patients with severe RHD led to reduced ICERs relative to the baseline scenario.

Table 10 Incremental Cost-Effectiveness Ratio (ICER) and sensitivity analyses

	Screening	**No Screening**	**Difference**
Baseline			
Cost (discount)	N$ 702,987.39	N$ 662,108.71	N$ 40,878.68
Cost (no discount)	N$ 351,873.22	N$ 320,392.93	N$ 31,480.29
QALY (discount)	39.00	37.87	1.14
QALY (no discount)	39.66	38.55	1.10
ICER (discount)			**N$ 35,943.86**
ICER (no discount)			**N$ 28,510.43**

Sensitivity Analyses	**Lower Case ICER**	**Upper Case ICER**
ARF to Mild RHD	N$ 28,887.91	N$ 28,010.28
ARF Recurrence to Dead	N$ 28,685.86	N$ 28,193.58
Mild RHD to Moderate RHD	N$ 90,960.50	N$ 10,639.62
Mild RHD to Severe RHD	N$ 30,898.75	N$ 16,320.68
Mild RHD to Dead	N$ 30,831.70	N$ 27,528.02
Severe RHD to Surgery	N$ 617.53	N$ 14,244.92
Risk of death from valve surgery	N$ 28,527.44	N$ 28,448.76
Post-Surgery to Dead	N$ 28,737.16	N$ 28,403.65
Risk Reduction from Secondary Prevention	N$ 11,742.39	N$ 66,951.90
Risk Reduction from Heart Failure Management	N$ 28,983.51	N$ 28,205.22
Discount Rate	N$ 27,680.03	N$ 26,036.74

Discussion

Perspective

Rheumatic Heart Disease is preventable, yet a persisting significant public health problem in low-to-middle income countries and in indigenous populations in high-income countries characterised by health and social inequities.[73] The burden of RHD has substantially declined over the past century in high countries, a trend largely attributed to economic advancements and targeted health interventions.[74] However, evidence suggests a recent increase in RHD incidence rates in some high-income countries, possibly due to rising global migration trends.[27]

Following successful programmes implemented in the 1980s-90s, several resolutions and guidelines have been developed in the early 2000s targeting the elimination of RHD through directed and comprehensive interventions. A key component in the resolutions is advocacy for policies and resource allocation decisions towards the prevention and control of RHD.[75]

While solutions for preventing and controlling RHD are known, the main barriers to their implementation are lack of prioritisation, resources, and gaps in scientific evidence.[76–78] Firstly, there is a scarcity of epidemiological data from endemic regions. Secondly, there is a limited understanding of transferable successful prevention practices across diverse contexts. Thirdly, there is lack of value economic evaluations to guide resource allocation decisions. Addressing these gaps is crucial for the development of informed policies, programme design, and for the effective monitoring and evaluation of RHD prevention strategies.

Context

This thesis investigates RHD care in Namibia to inform intervention advocacy, incorporating a clinical data review, assessment of RHD impact on patients, evidence synthesis on effective prevention practices, and an evaluation of a prevention strategy's potential cost-effectiveness. The findings offer valuable insights for Namibia and comparable settings on RHD management.

Findings

Using the best available clinical information sources (Paper I), the estimated clinical prevalence of RHD was identified as 28 cases per 100,000, markedly lower than the 1,048.7 cases per 100,000 estimated by the Global Burden of Disease (GBD) study by IHME for Namibia.[31] This significant variance may largely stem from the GBD's inclusion of extrapolated undiagnosed cases, in contrast to our reliance solely on clinical data. Even though, found systemic issues in health information systems, notably the lack of data verification processes, absence of unique patient identifiers, and data recording inconsistencies limit accurate estimation of the prevalence. These findings highlight the persistent barriers in disease surveillance and the

critical shortage of reliable data from RHD-endemic regions, which limits the accurate assessment of RHD's burden in low-to-middle-income countries.

In the survey (Paper II), there was an increase in quality-adjusted life year (QALY) to 0.941 from 0.773 before RHD diagnosis. The improvement is likely attributable to the efficacious management and treatment of RHD, particularly surgical interventions, as the majority had undergone such procedures[79]. This aligns with findings from a similar study in India, which also reported similar QALY values among RHD-treated adult patients.[63] On the other hand, the lower QALY prior to diagnosis may reflect the period during which patients lived with undiagnosed RHD. This situation is common in RHD-endemic regions with scarce resources and limited cardiac expertise, where diagnoses often occur at advanced disease stages.

Overall, RHD in Namibia predominantly affects individuals under 30 years, especially women, and is more common in areas characterised by low socioeconomic conditions (Papers I & II). Patients incurred additional healthcare costs associated with ongoing care and monitoring, underscores RHD's substantial socioeconomic repercussions on predisposed populations.[80]

The synthesis of evidence on effective RHD prevention practices (Paper III) suggests that implementing school-based primary prevention services, strengthening community-based programmes supported by community health workers, integrating RHD services into existing health care systems in collaboration with local health governance, and conducting rigorous evaluations are crucial steps toward preventing and reducing the burden of the disease. These findings complement existing literature, where a prior meta-analysis have shown primary prevention in schools or community can have an efficacy of about 60% to reduce ARF cases.[81] Similarly, another meta-analysis has concluded that integration of programmes into existing healthcare services can improve a range of intermediate health outcomes.[82]

In addition, the review (Paper III) also identifies a significant limitation in the evidence base, predominantly derived from studies in indigenous populations in Australia and New Zealand, which may limit the generalisability of these practices to other contexts.[66–72] Nevertheless, the identified good practices are broadly applicable and should be advocated for within existing infrastructures like school-based health services, which are prevalent globally.[83] Notably, the review also highlights a lack of rigorous evaluations of RHD interventions' impact on disease incidence and prevalence, pointing to a substantial knowledge gap in effective and universally applicable practices. This lack of robust evidence underscores the need for focused research to inform policy and interventions, especially in resource-limited settings tailored approaches could enhance practicality and effectiveness.

Active case finding through echocardiographic screening is an effective model to determine the disease burden and enhance secondary prevention of RHD, feasibly conducted by non-specialist health personnel in diverse settings.[13,14] However, empirical evidence on the cost-effectiveness of these active case-finding models, especially in the African context, is still scarce.

This thesis (Paper IV), utilising a case study from Namibia, demonstrated the cost-effectiveness of echocardiographic screening conducted by nurses using portable hand-held devices in school settings, with support from echocardiogram technicians and paediatric cardiologists. This result is consistent with three prior modelling studies that identified echocardiographic screening among children as a cost-effective strategy in Australia and Brazil.[48–50] This finding is significant for policy development and research on RHD interventions aimed at determining the disease burden and improving preventive measures, particularly for individuals in the early stages of the disease, where treatment is most beneficial. However, the limited data on the natural and clinical progression of RHD and the effectiveness of interventions continue to constrain economic evaluations.

Policy Implications & Recommendations

A principal objective of this thesis is to inform advocacy for RHD policy and interventions in endemic countries similar to Namibia. The findings provide diverse insights into RHD-related healthcare and surveillance systems in LMICs, implemented preventative measures, and the potential cost-effectiveness of active case findings in such settings. By applying the universal "Advocacy", "Surveillance", "Awareness", and "Prevention" (A.S.A.P) framework, this thesis proposes key recommendations for policy development and research concerning RHD prevention and control.[84]

Advocacy

Integrating RHD services into existing health systems is essential for eradication efforts. Yet, challenges such as systemic weaknesses, data scarcities, and a lack of evidence on effective preventive measures hinder RHD's prioritisation in globally, leading to its relative underfunding despite its substantial burden.[38] A multi-sectoral approach involving various stakeholders is necessary, underpinned by robust evidence to advocate for RHD prioritisation.

Papers I and II emphasise the need for action-oriented research to enhance RHD-related healthcare systems, particularly in improving data systems to provide accurate disease burden estimates. Furthermore, there is a clear gap in evidence on effective preventive practices, necessitating further research to determine and evaluate the impact of interventions on disease burden, as highlighted by findings from Paper III.

Additionally, assessing the cost-effectiveness of various strategies is crucial for guiding prioritisation efforts. Paper IV indicated that active case finding could be cost-effective in LMICs, underscoring the importance of further research, including comparative economic analyses of RHD interventions vis-à-vis existing healthcare services, to inform health financing decisions.

Overall, this thesis advocates for broad stakeholder engagement to strengthen data systems and mobilise the necessary investments for expanding RHD care to the community level and integrating it into existing health services. Policies should be informed by evidence of effective and cost-efficient strategies, with a priority placed

on generating longitudinal data on RHD progression, patient outcomes, and mortality risks.

Surveillance

Surveillance is an important pillar in understanding the disease outcome and effectiveness of interventions. Findings (Paper I) highlighted several weaknesses within existing surveillance mechanisms, notably the absence of integration, no individual identifying information, and lack of validation protocols, all of which compromise data quality.

It is important to advocate for the enhancement of the current data systems via multi-stakeholder engagement. The digitisation of surveillance registries promises to optimise data collection and linkage across various sites and healthcare system levels. Previous evidence supports the viability of electronic registers.[85] Together with the national health information databases, surveillance registers should incorporate unique patient identifiers to facilitate thorough data verification and validation, thus strengthening system-wide monitoring and evaluation.

The establishment of sentinel surveillance linked to the primary register at the cardiac clinic is essential. Such integration will ensure comprehensive data capture from both primary healthcare and community levels, thereby broadening our understanding of disease burden.[86]

Moreover, the inclusion of surveillance registers in future active finding initiatives is crucial for strengthening secondary prevention strategies[13]. This thesis (Paper IV) demonstrates the cost-effectiveness of echocardiographic screening that include surveillance registers, highlighting their role in enhancing patient engagement and continuity of care. Investigating the feasibility of integrating these registries within existing primary healthcare frameworks is a necessary future recommendation, aiming to broaden their utility beyond mere diagnostic screenings.

Awareness

Public health initiatives must prioritise education and the creation of awareness among both the community and health providers to facilitate the early recognition and effective management of RHD. Utilising community healthcare workers for awareness campaigns within communities, as supported by the findings of Paper III, is a practical strategy.

The findings from Papers I and II indicate potential issues with the awareness levels among healthcare providers across different tiers of the healthcare system, highlighting the need for further investigation in this area. For example, Paper I found that all hospital admissions from 2010 to 2017 were solely due to rheumatic fever, pointing to a possible neglect of RHD. Similarly, the low QALYs reported by patients prior to their RHD diagnosis in Paper II suggest periods of undiagnosed disease, highlighting the need for increased awareness.

These findings highlight the crucial need for awareness and education among healthcare workers to enhance timely and accurate detection of RHD. Continuous education initiatives, as part of prevention strategies, are essential for maintaining sustained effectiveness.[87]

Public health initiatives and research should embrace a multi-stakeholder approach to extend the reach of awareness efforts across varied platforms, thereby enhancing the accessibility of information to a broader audience.

Enhancing awareness is vital in influencing health-seeking behaviours, enabling patients to identify symptoms promptly and access timely medical care, thereby meriting priority in public health agendas.

Prevention

Findings from Paper III highlighted the persisting gap in evidence supporting effective prevention practices across various contexts. Nevertheless, school-based interventions, particularly those administered by nurses, have shown promise in diminishing the incidence and prevalence of ARF and RHD, especially within indigenous populations in high-income countries.[88] This thesis advocates for the adoption of such strategies within LMICs, integrating them into existing school health services.[89] It is imperative for future studies to assess the cost-effectiveness of these interventions to inform their implementation across diverse environments. Paper IV presents evidence that targeted secondary prevention strategies, such as screening programmes within schools, can be economically viable, suggesting a potential cost-benefit of integrating RHD prevention into school health services.

Furthermore, public health initiatives should prioritise primordial prevention at the community level. This could involve mobilising community healthcare workers to deliver services and enhance living conditions at the household level. To improve our understanding of primordial prevention's efficacy, community-based research is essential. Such studies should examine how social determinants of health interact with preventive measures, thereby optimising the effectiveness of these initiatives.

Another important component is to include confirmatory tests for GAS in the primary prevention care to ensure correct treatment and possibly curb over usage of antibiotic.

To mitigate the substantial costs associated with tertiary care for RHD, enhancing prevention strategies is crucial. Consequently, research should focus on identifying and addressing obstacles to effective prevention, including challenges in supply chains, access to healthcare services, and issues with patient compliance.

Strengths & Limitations

The thesis possesses several strengths and limitations. A significant limitation concerns the validity and reliability of secondary data from registries, limiting accurate estimations of the RHD burden. The uncertainty regarding the inclusion of data from primary and private healthcare facilities adds to this issue. Despite these challenges, the thesis utilised the best available data, highlighting deficiencies in data systems and emphasising the need for community-based studies for precise disease prevalence assessment.

Another limitation is the survey's focus on patients attending follow-up care, which might skew the representation of the broader RHD patient population by excluding those missing follow-up appointments. Recall bias constitutes an additional

limitation due to the reliance on patients' recollection of their HRQoL before RHD diagnosis. The lack of a comparison group also restricts definitive conclusions about the overall impact of RHD on HRQoL. However, the pre- and post-diagnosis approach is a notable strength, providing valuable insights into the changes in patients' HRQoL following treatment. Furthermore, this study is among the few that have assessed and estimated the QALY for RHD patients, contributing significantly to the field.

The systematic review's exclusion of non-English studies may narrow the scope of its conclusions. The diversity of the reviewed studies prevented detailed analyses of intervention efficacy, and the potential oversight of relevant studies in grey literature or those with unclear outcomes further limits the review. Nevertheless, the review offers a comprehensive analysis of RHD intervention research, providing a critical overview of current preventive practices.

Lastly, the cost-effectiveness analysis is limited by the scarcity of data on RHD's long-term progression and associated costs, leading to uncertainties in the model's assumptions. The model's assumption of echocardiographic detection of ARF presents practical challenges due to limited cardiac expertise, yet this assumption is crucial for widening the scope of screening beyond confirmed cases of valvular damage. Despite these limitations, altering various key parameters in the sensitivity analyses consistently demonstrated that screening remains cost-effective.

Conclusions

This thesis has provided a comprehensive analysis of Rheumatic Heart Disease (RHD), encompassing epidemiology, health-related quality of life (HRQoL), the effectiveness of preventive interventions, and the cost-effectiveness of echocardiographic screening. The multifaceted approach of this research offers a holistic view of RHD, highlighting its prevalence, impact, and management strategies.

The epidemiological aspect of the study reveals a significant discrepancy in RHD prevalence estimates, underscoring the need for improved data quality and surveillance systems, particularly in high-endemic regions like Sub-Saharan Africa. The effectiveness of preventive interventions, particularly school-based and community-led programmes, has been shown to be significant in various settings. However, the lack of data from regions with high RHD endemicity limits our understanding of the best practices for RHD prevention, especially in diverse health system contexts.

The cost-effectiveness analysis of echocardiographic screening, particularly in the context of Namibia's GDP per capita, supports its inclusion in RHD secondary prevention strategies in the African region. This thesis addresses the gap in economic evaluations for such initiatives, especially in low-to-middle-income countries, providing recent data on disease progression and costs from an African perspective.

Based on this research, policy recommendations emphasise the need to enhance data collection and improve quality, advocating for the establishment of standardised national and regional RHD registries. It is imperative to reinforce surveillance systems for early detection and monitoring, integrating these within existing public health infrastructures, supported by technological solutions like mobile health applications. Prioritising healthcare accessibility and early detection in high-endemic areas is crucial, necessitating increased funding, community outreach, and educational initiatives.

Assessing the effectiveness of preventive interventions, particularly those based in schools and communities, and evaluating their cost-effectiveness in comparison to existing healthcare services will inform the allocation of resources. The development of comprehensive RHD management protocols, training of healthcare professionals, and ensuring access to necessary treatments are paramount. International collaboration and the exchange of best practices are vital for a global approach to RHD management and awareness. The implementation of these recommendations is expected to significantly enhance outcomes and quality of life for individuals affected by RHD, especially in areas with limited resources.

Epilogue

Reflecting on the transformative journey of a PhD, it was a path both challenging and enlightening. Initially, my passion for helping others inspired my dream of becoming a Medical Doctor. However, attention deficits, which I later discovered during my PhD to be ADHD, diverted this path as I could not achieve the necessary scores for admission. Instead, I found my calling in Nursing, a profession that aligned with my passion and offered a deeper, more profound opportunity to care for people than I had imagined possible in medicine.

As a nursing student, a simple yet profound interaction during a home visit, where a patient shared the relief they found in a traditional remedy, incited my curiosity in cardiovascular disease. My career as a Registered Nurse, particularly in the area of internal medicine, exposed me to the realities of cardiovascular diseases, notably Rheumatic Heart Disease (RHD), among young people and set the stage for my academic pursuit. Driven by this newfound interest, I embarked on a Master's in Public Health & Health Economics at Umeå University, later ending in a PhD focused on RHD. This was not just an academic exercise; it was a personal mission to shed light on a disease that, despite its severity, remained under-researched in Namibia.

My PhD journey was about filling this gap, about bringing RHD into the spotlight and advocating for better data and policies. Throughout this journey, the practical aspects of research, from collecting primary data to obtaining ethical clearances, have been invaluable learning experiences. They have not only enhanced my research skills but also deepened my understanding of public health and health economics methodologies.

Now, as I stand at the crossroads, post-PhD, I find myself contemplating my identity and the future. "Who am I?" "What have I become?" These questions, while rhetorical, do not overshadow the clarity of my purpose. I remain a nurse at heart, with a renewed purpose in public health and a keen interest in utilising my expertise in health economics to strengthen health systems. Research in RHD is predominantly led by medical and cardiology experts. I aim to bring a nurse's and public health perspective to the forefront, addressing crucial gaps in RHD patient care and community-based health. This inspiration represents a commitment to inspire more nurses into the realms of research and science.

Thus, this thesis marks not an end but a gateway to new beginnings. It signifies a transition from exploration to application, from student to scholar, and from aspiration to action. The journey continues, driven by the quest for discovery and the desire to contribute meaningfully to the field of healthcare.

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Appendix

Appendix 1 Questionnaire for data collected in sub-study II

PARTICIPANT ID.: ☐ **DATE:** _____

RHEUMATIC HEART DISEASE

FINANCIAL BURDEN AND HEALTH-RELATED QUALITY OF LIFE

1. **Name and Surname: .....**
2. **Age: .....**
3. **What is your sex?**

   Male ☐
   Female ☐
4. **What is your <u>current marital status</u>?**

   Married/Living together ☐
   Single ☐
   Divorced/Widowed ☐
5. **When was your Rheumatic Heart Disease diagnosed?**

   Year: **.....**
6. **Before your Rheumatic Heart Disease was diagnosed, did you have any of the following symptoms?**

   For any symptom you experienced, please specify the year when it first appeared.

   <u>Symptoms</u>

   Sore or swollen ankles, knees or elbows (called arthritis)

   Yes ☐ Year ..... Did you seek health care due to the problem: Yes / No
   No ☐

   Sore throat

   Yes ☐ Year ..... Did you sought health care due to the problem: Yes / No
   No ☐

   Jerky uncontrolled movements of the arms or legs (called chorea)

   Yes ☐ Year ..... Did you seek health care due to the problem: Yes / No
   No ☐

   Fast breathing

   Yes ☐ Year ..... Did you seek health care due to the problem: Yes / No
   No ☐

   Feeling short of breath

   Yes ☐ Year ..... Did you seek health care due to the problem: Yes / No
   No ☐

   Chest pain with exertion

   Yes ☐ Year ..... Did you seek health care due to the problem: Yes / No
   No ☐

7. Think of the <u>year prior</u> to when your Rheumatic Heart Disease symptoms appeared

a) How often did you visit health care professionals? ..... ☐ times
e.g. doctor, nurse

b) How many days were you hospitalised? ..... ☐ days

c) How often did you miss working days, school days and similar? ..... ☐ days

8. Think of your situation <u>during the last 12 months</u>.

a) How often did you visit health care professionals? ..... ☐ times
e.g. doctor, nurse

b) How many days were you hospitalised? ..... ☐ days

c) How often did you miss working days, school days and similar? ..... ☐ days

9. How many kilometres do you travel to your nearest healthcare facility when you seek Rheumatic Heart Disease care?

☐ Kilometres

10. How long time does it commonly take you to get to the cardiac clinic?

5 – 30 minutes ☐
30 – 60 minutes ☐
1 – 2 hours ☐
2 – 3 hours ☐
More than 3 hours ☐

11. What is your mode of transport to the healthcare facility?

Own car ☐
Taxi ☐ ..... N$
Bicycle ☐
Walking ☐

12. On average, how many hours do you spend at the healthcare facility when you seek care for Rheumatic Heart Disease?

☐ Hours

What time did you arrive at cardiac clinic today? .....

13. Have you used any of the following medication in the last week? Tick all that applies

	Yes	No	I don't know
Asthma-/allergy medication	☐	☐	☐
Diabetes medication	☐	☐	☐
High blood pressure medication	☐	☐	☐
Anti-depressive medicine	☐	☐	☐
Cholesterol medicine	☐	☐	☐
Other medicine	☐	☐	☐

14. Do you currently smoke any tobacco products?

No ☐
Yes, 1 – 10 times per day ☐
Yes, 11 – 20 times per day ☐
Yes, More than 20 times per day ☐

15. Do you drink alcohol?

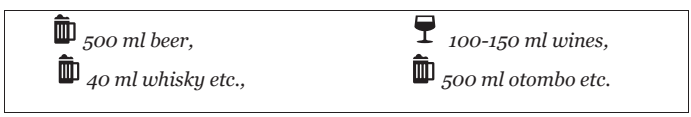
Yes ☐
No ☐

16. How often do you drink alcohol in a month?

4 times per week or more ☐ 2-3 times per week ☐
2-4 times per month ☐ 1 time per month or rarely ☐
I don't drink alcohol ☐

17. How many glasses do you drink in a typical day when you drink alcohol?

With one glass we mean:



1-4 glasses ☐ 5-9 glasses ☐
10 or more glasses ☐ Don't know ☐
I don't drink alcohol ☐

18. By ticking in each group below, please indicate which statements best describe your own health state during the year prior to when your Rheumatic Heart Disease symptoms appeared and today.

Under each heading, please tick the ONE box that best describes your health.

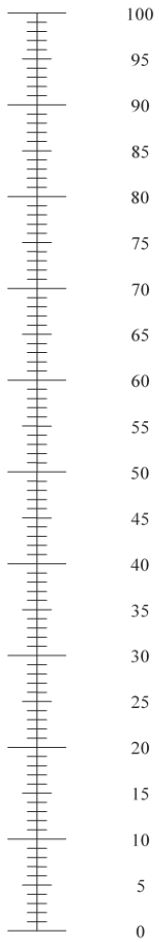
MOBILITY	**Year prior**	**Today**
I have no problems in walking about	☐	☐
I have slight problems in walking about	☐	☐
I have moderate problems in walking about	☐	☐
I have severe problems in walking about	☐	☐
I am unable to walk about	☐	☐
SELF-CARE		
I have no problems washing or dressing myself	☐	☐
I have slight problems washing or dressing myself	☐	☐
I have moderate problems washing or dressing myself	☐	☐
I have severe problems washing or dressing myself	☐	☐
I am unable to wash or dress myself	☐	☐
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*		
I have no problems doing my usual activities	☐	☐
I have slight problems doing my usual activities	☐	☐
I have moderate problems doing my usual activities	☐	☐
I have severe problems doing my usual activities	☐	☐
I am unable to do my usual activities	☐	☐
PAIN / DISCOMFORT		
I have no pain or discomfort	☐	☐
I have slight pain or discomfort	☐	☐
I have moderate pain or discomfort	☐	☐
I have severe pain or discomfort	☐	☐
I have extreme pain or discomfort	☐	☐
ANXIETY / DEPRESSION		
I am not anxious or depressed	☐	☐
I am slightly anxious or depressed	☐	☐
I am moderately anxious or depressed	☐	☐
I am severely anxious or depressed	☐	☐
I am extremely anxious or depressed	☐	☐

The best health you can imagine year before symptoms appeared

19. To help people say how good or bad a health state is, we have drawn a thermometer-like scale on which <u>the best state you can imagine is marked 100</u> and the <u>worst health status you can imagine is marked 0</u>.

The best health you can imagine today

The best health you can imagine



The worst health you can imagine

We would like to know how good or bad your health was, in your own opinion, **the year prior to your Rheumatic Heart Disease symptoms appeared.**

Mark an X on the scale on the **left** to indicate how your health was.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH YEAR BEFORE SYMPTOMS APPEARED =

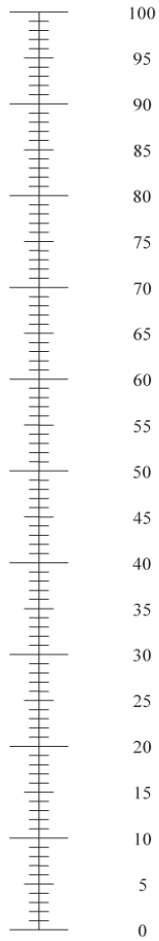
We would like to know how good or bad your health is, in your own opinion, **today**.

Mark an X on the scale on the **right** to indicate how your health is.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health you can imagine



The worst health you can imagine

21. Which is your hometown/city? .....

22. Where did you grew up as your place of residence?

Rural area	☐
Urban area	☐

23. In which region did you grow up?

Erongo	☐	Hardap	☐	Kavango	☐	Khomas	☐
Kunene	☐	Ohangwena	☐	Omaheke	☐	Omusati	☐
Oshana	☐	Oshikoto	☐	Otjozondjupa	☐	Zambezi	☐

24. What is your home language?

English	☐	Oshiwambo	☐	Afrikaans	☐
Silozi	☐	Damara/Nama	☐	Otjiherero	☐
Rukwangali	☐	Other:			

25. What is the <u>highest level of education</u> that you have completed?

Never went to school	☐
Primary education (Grade 1 – 7)	☐
Secondary education (Grade 8 – 12)	☐
Tertiary education (Diploma, Degree from university or college)	☐

26. What is your current job?

Employed	☐
Self-Employed	☐
Housewife	☐
Student	☐
Unemployed	☐
Pre-retired because of RHD	☐
Retired	☐
Other	☐

27. What is your most recent occupation? .....

28. Could we contact you for participation in an interview study, which would focus on your experiences living with RHD?

Yes	☐
No	☐

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