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STATE-OF-THE-ART REVIEW

Rheumatic Heart Disease Burden in Africa and the Need to Build Robust Infrastructure

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ABSTRACT

Rheumatic heart disease (RHD) is an important public health problem in Africa. Mapping the epidemiology of RHD involves elucidating its geographic distribution, temporal trends, and demographic characteristics. The prevalence of RHD in Africa varies widely, with estimates ranging from 2.9 to 30.4 per 1,000 population. Factors contributing to this burden include limited access to health care, poverty, lack of research interest, and genetic fragility. Studies have highlighted differences in group A Streptococcus (GAS) incidence among different African countries, emphasizing the importance of effective monitoring and intervention strategies. RHD epidemiological mapping in Africa indicates regional differences and socioeconomic determinants. The high prevalence among females in most studies and among children underscores the urgency for targeted interventions. Diagnosing RHD in Africa faces challenges of inaccessibility of health facilities and trained personnel. Efforts to develop cost-effective and accessible diagnostic tools, such as mobile/portable echocardiography machines, molecular biomarkers such as Tenascin-C and microRNA expression profile shows promise for accurate diagnosis of RHD, but their validation and utilization is limited due to resource constraints. Furthermore, lack of an effective licensed vaccine for GAS causes significant retardation in RHD control in Africa. Addressing the burden of RHD in Africa and other low- and middle-income countries requires robust RHD biomarkers and effective vaccines. This review provides a comprehensive overview of the landscape of RHD in Africa, covering the bacteriology of GAS, the burden of GAS infections, exploring diagnostic avenues, challenges, and opportunities in RHD biomarkers, diagnosis, effective prevention strategies, and RHD management in Africa. (JACC Adv. 2024;3:101347)

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ABBREVIATIONS AND ACRONYMS

GAS = group A Streptococcus

iGAS = invasive group A Streptococcus

LMICs = low- and middle-income countries

miRNA = microRNA

PAH = pulmonary hypertension

RHD = rheumatic heart disease

TnC = Tenascin-C

Rheumatic heart disease (RHD) is emerging as a significant public health concern in Africa, coinciding with a paradigm shift in the continent's health landscape.[1] Africa is now experiencing a growing burden of several diseases, such as RHDs that may lead to consequences of cardiovascular diseases. RHD is the end result of an infectious disease, promulgated by poverty and overcrowding, with a later sequalae of cardiovascular consequence; therefore, it merits attention separately to the usual cardiovascular disease. This epidemiological transition presents a unique challenge for addressing the burden of RHD in Africa. These challenges include limited health care resources, complex diagnostic pathways, and a scarcity of skilled health care professionals.[2] However, the inconsistent data on infectious burden and RHD across Africa have been identified as a limitation in developing a continent-wide solution. In addressing RHD in Africa requires better access to penicillin prophylaxis, percutaneous valve interventions, cardiac surgery, and specialized care for pregnant women with heart conditions. These essential services are often lacking, highlighting the need for improved health care access and infrastructure.[3]

Understanding the role of group A Streptococcus (GAS) in RHD pathogenesis is crucial. Analyzing the genetic diversity, virulence factors, and antibiotic resistance profiles of African GAS strains is essential for effective prevention and control. Evaluating GAS infection burden and its sequelae especially RHD, is vital for understanding its epidemiology in Africa. Current data on GAS-related disease prevalence, incidence, and distribution across African regions are fragmented, hindering efforts to identify disparities and target interventions. Mapping GAS infection and its sequelae like RHD epidemiology involves clarifying its geographic distribution, temporal trends, and demographic characteristics. Access to accurate, affordable diagnostic tools—clinical, echocardiographic, and laboratory-based tools—are imperative for early detection of GAS infection and its sequelae like RHD management in Africa.[4]

While molecular biomarkers hold promise for enhancing RHD diagnosis, their integration into routine clinical practice in Africa faces challenges. Therefore, this review aimed to provide a broad overview of the landscape for burden of RHD in Africa, encompassing the bacteriology of GAS, the burden of GAS infections, mapping the epidemiology of RHD, exploring diagnostic avenues, and discussing challenges and opportunities in RHD diagnosis. Thus, will ultimately help to the development of an effective policies for preventing, diagnosing, and managing RHD in Africa.

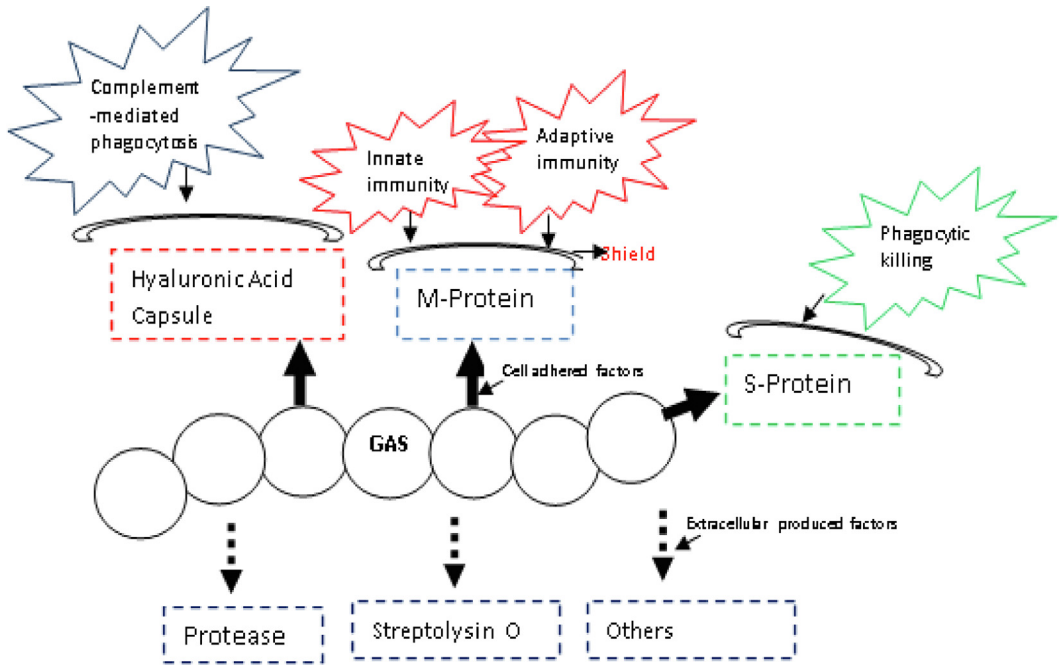
HIGHLIGHTS

- GAS infection and its sequelae possess a significant public health challenge in Africa, demanding immediate action to address its persistent burden.
- The epidemiology of RHD varies across African regions on account of geography, time, as well as socioeconomic factors which necessitates tailored intervention strategies.
- There are limited health care facilities and trained personnel which hinder RHD diagnosis, thus necessitating innovative and resource-efficient diagnostic approaches such as molecular biomarkers as the potential for improved diagnostic accuracy and accessibility.
- The absence of an effective GAS vaccine impedes RHD control efforts, underlining the need for vaccine development to reduce RHD incidence and prevalence.
- The need of focusing reasonable resources on developing robust and strong health care infrastructure, including early detection of GAS infection and strategic policy recommendations and practical steps for health system strengthening to address RHD in Africa.

THE COMPLEX IMMUNOLOGICAL MECHANISMS OF GAS INFECTIONS IN HUMANS. The mechanisms of human infection by GAS is complex and multifaceted, involving intricate interactions between host and bacterial factors that contribute to the development of infection. GAS produces an array of virulence factors, both cell wall-associated and secreted, which exert diverse effects on tissues, cells, and components of the immune response. Some of these components (virulence factors) that play essential roles in epithelial tissue colonization and the progression of invasive disease are highlighted in **Figure 1**.

GAS BURDEN IN AFRICA. According to the World Health Organization, GAS is the ninth leading cause of global mortality, with invasive infections and RHD as the major causes. High-income nations have seen a decline in acute rheumatic fever (acute rheumatic fever [ARF])/RHD due to better living conditions and

FIGURE 1 Representative Examples of GAS Cell-Associated and Secreted Virulence Factors, including Hyaluronic Acid Capsules, M Proteins, S Proteins, Streptolysins O, Proteases, and Other Immunoglobulin-Degrading Enzymes



The figure also highlights the interactions of these virulence factors with the innate and adaptive immune systems, complement fixation pathways, and the phagocytic cell system. GAS = group A Streptococcus.

penicillin use. Low-income countries, with 80% of the global population, still suffer from ARF/RHD, with 2.4 million affected children aged 5 to 14 years.[5] GAS prevalence significantly impacts Africa, though the full burden is unclear due to limited health care access, resources, and timely management. **Table 1** summarizes the studies on the burden of GAS infection in Africa. The prevalence of GAS infection in Africa is poorly documented due to limited surveillance. However, some studies have estimated the incidence of GAS sore throat and invasive disease. Examples in Uganda there were an incidence of sore throat episodes of 540 per 100 person-years while in Zambia 32 per 100 person-years were recorded.[6] Similarly, study from Ethiopia reported 7.8 cases of invasive GAS (iGAS) disease per 100,000 population.[7]

A study in rural Kenya reported 1.8 cases of iGAS per 100,000 person-years, with skin infections, pneumonia, and bacteremia as common symptoms, and 88 diverse emm types of GAS strain.[5] In Uganda, 15.9% of children carried β-hemolytic streptococci, with 41.8% being GAS-associated disease. A 2019 review by Barth et al[8] revealed a 21% prevalence of GAS pharyngitis in Africa, highlighting regional and urban-rural differences. The study discloses a substantial overall prevalence of GAS pharyngitis in Africa, with a pooled estimate of 21%, underscoring the ongoing burden of these infections. Noteworthy regional differences show Central Africa has a lower prevalence compared to other regions. Urban areas have a higher prevalence (32%) than rural areas (12%), highlighting the impact of socioeconomic factors like overcrowding on infection rates. Limited data on GAS skin infections show a prevalence of 74%. Molecular studies suggest promising vaccine coverage for pharyngitis (75% and 88% cross-reactivity) but pose challenges for iGAS with a potential coverage of 57%. Comparisons with previous studies in children show lower overall prevalence in Africa, and no significant differences are found in GAS prevalence across different age groups. These findings stress the need for more research into regional disparities and a nuanced approach to vaccine development for GAS infections in Africa, highlighting the need for targeted interventions.

TABLE 1 Summary of GAS Burden in Africa

Country	Incidence Rate	Year	Ref #
South Africa	22.1	2022	9
Ethiopia	7.8	2022	6
Kenya	0.6	2016	10
Uganda	41.8	2020	2
East Africa	17.9	2017	7
Egypt	42.2	2015	11
South Africa	3.0	2023	12
Nigeria	0.0	2013	13
Nigeria	5.0	2019	14
Nigeria	3.3	2021	15
Gabon	5.8	2014	16
Tanzania	6.9	2016	17
Cameroun	22.5	2011	18
Mali	25.5	2015	19
Morocco	6.2	2021	20

GAS = group A Streptococcus.

MAPPING THE EPIDEMIOLOGY OF RHD IN THE AFRICAN CONTEXT. RHD in Africa occurred among several populations including children, a study among East African school children, indicated a high prevalence rate as reported WHO in which that the East Africa's prevalence exceeded that of developed countries like the United States, showing RHD is more common in poorer areas. Regional analyses showed lower RHD prevalence in the Horn of Africa, likely due to varying diagnostic sensitivity. Notably, studies published after 2015 recorded a lower RHD prevalence, possibly reflecting improved health care services, technological advancements, and interventions aimed at reducing RHD in Africa (**Figure 2**). Highlighting the pattern of the distribution of RHD in Africa. RHD epidemiology in Africa is influenced by regional variations, socioeconomic factors, and health care access. Prevalence rates vary, with poverty, limited education, and poor health care infrastructure perpetuating RHD in vulnerable populations.

The prevalence of RHD in Ethiopia, Uganda, Tanzania, and Sudan was reported to be 56.74%, 56.7%, 33.7%, and 61.5%, respectively. Furthermore, study in Mali reported a prevalence of 20% among adults and 4% among children.[19] In other studies conducted in the region, RHD prevalence among African children aged 6 to 10, was found to be as high as 26%, with females often outnumbering males 2:1.[19] However, a study by Nkereuwem in North Central Nigeria found a higher incidence among boys.[21]

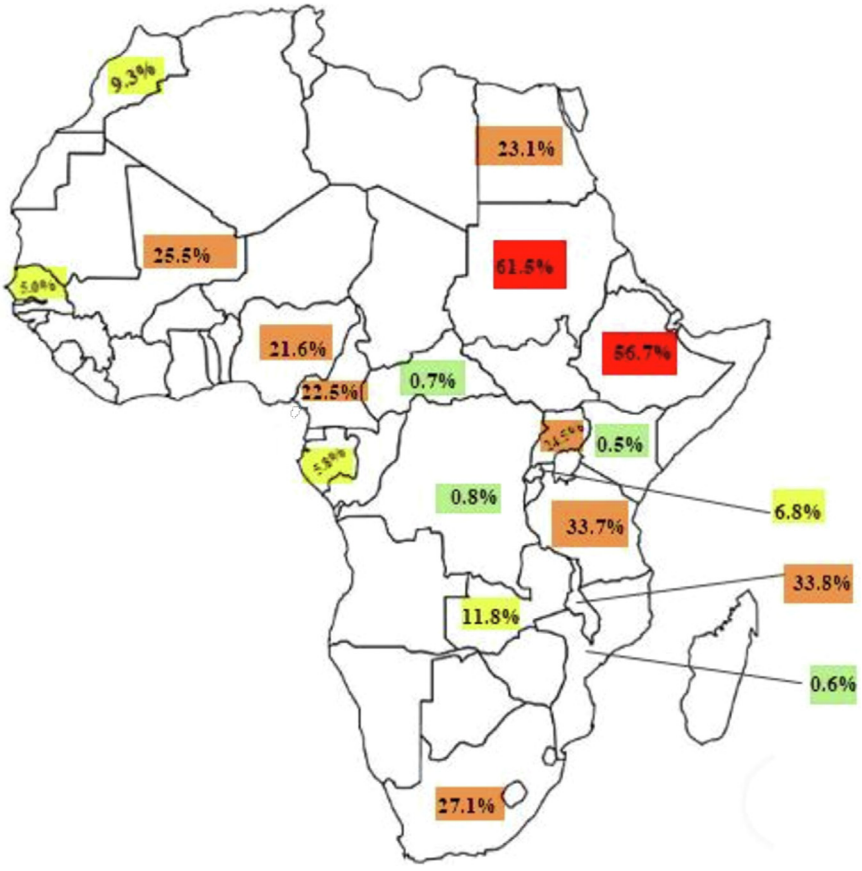
Recent data show a 14.6% prevalence in East Africa,[7] while in Uganda 14.8 RHD cases per 1,000 children have been reported,[22] 6 years later it rises to 24.5% as reported by Amy Scheel et al.[23] Malawi's 2014 study reported 3.4% latent, 0.7% definite, and 2.7% borderline RHD cases.[7,23] Two years later, Amy et al.[23] reported 33.8%. A Zambian survey found 3 definite RHD cases among 1,102 students.[7] Other factors might have influenced RHD distribution in some African countries. Kingué et al[24] found low education levels among RHD patients in 7 western and central African countries: 41.5% had no formal schooling, 6.4% only received Qur'anic schooling, 32.8% completed primary school, 15.3% secondary school, and 2.8% reached university level. Households averaged 6 children. RHD led to school delays (66.2%) and prolonged work absences (62%) or job termination (51%) in adults. Ekure et al[25] found a 2.7 per 1,000 prevalence of RHD among 4,107 children in Lagos, Nigeria.

Africa bears a large share of the global RHD burden, with 32.9 million cases and over 319,000 new cases annually. The lack of RHD infrastructures exacerbates early detection, diagnosis, and management challenges.[2] Investing in infrastructure for the prevention, diagnosis, and treatment of RHD aligns with the principles of precision medicine and can significantly reduce the societal and economic impacts of the disease. Precision medicine, which tailors health care based on individual genetic, environmental, and lifestyle factors, can improve the effectiveness of interventions for RHD. Studies have shown that early detection and treatment of GAS infections, which can lead to RHD if untreated, are crucial for preventing the progression of the disease.[26]

Strategic investments in health care infrastructure, such as the development of robust diagnostic facilities, improved access to antibiotics, and comprehensive follow-up care systems, can help mitigate health disparities associated with RHD. For instance, the integration of echocardiographic screening in primary health care settings have been shown to be effective in early detection and management of RHD in high-risk populations.[27]

Furthermore, public health initiatives that promote awareness and education about the importance of early treatment of GAS infections can play a significant role in reducing the incidence of RHD. By addressing the socioeconomic and environmental factors that contribute to the prevalence of GAS infections.[28] Ultimately, strategic investments in

FIGURE 2 A Map of Africa and Overlying the Most Recent Incidence Rate and Pattern of Rheumatic Heart Disease in Africa



The red colors indicate countries with high burden of recorded cases while green showed the countries with low disease burden. brown and yellow shows a moderate and low cases respectively.

RHD-related health care infrastructure not only align with the goals of precision medicine but also provide a sustainable approach to reducing the burden of RHD, thereby improving health outcomes and quality of life for affected individuals.[29]

EXPLORING DIAGNOSTIC AVENUES FOR RHD IN AFRICA. Effective RHD management requires accurate diagnosis, but Africa faces challenges due to limited health care access and awareness. RHD diagnosis often uses cardiovascular imaging, including echocardiography, cardiovascular magnetic resonance, and computed tomography, to assess cardiac structure and function.[23,24] However, these tools are scarce in low-income countries. While low-income countries focus on RHD treatment, secondary prevention relies on proper case detection. Echocardiography is crucial for visualizing valve damage,[24] but its cost and need for trained physicians limit its use in many African communities. Hence, the need to seek for a cheaper, robust RHD detection method. Conventional methods like throat cultures and serological tests should be available in resource-limited settings. Gardezi et al[30] compared low-cost handheld echocardiography and auscultation for RHD detection in Uganda, finding handheld echocardiography more sensitive and specific than auscultation.[29] Furthermore, both methods need expert cardiologists, making them less favorable in low-income countries. In Ethiopia, trained nonexpert nurses achieved reasonable sensitivity and specificity in RHD screening, showing nurse involvement's

potential. Addressing these challenges requires exploring cost-effective, accessible diagnostic tools for Africa. Developing point-of-care diagnostics for remote areas and expanding access to cardiac surgery, especially valvular surgery, is crucial.[24]

For GAS, diagnostic avenues include but not limited to conventional methods like throat cultures. Special procedures have been developed to optimize the identification of the bacteria (*Streptococcus pyogenes*) in throat cultures. Lancefield antigen determination first develop as a method for distinguishing β-hemolytic streptococci into different species by determining the presence of Lancefield antigens on streptococcal surfaces through antibodies.[31]

Serological tests are utilized in the diagnosis of GAS infections. In comparison with throat culture, serological rapid antigen detection tests, offer diagnosis at the point of care often within 5 to 10 minutes, the result can be obtained. These tests are mostly common in resource-limited settings. These techniques aided the diagnosis by the detection of certain streptococcal antibodies. It's rare and useful in acute infections, since antibody development takes about 1 to 2 weeks after the onset of acute infection to be detectable in serum samples. Rising antibody levels only occur in patients suffering from *S pyogenes* infections and streptococcal carriers do not experience an increase of antibody titers,[31] when acute and convalescent sera are compared. A 4-fold rise in antibody titers is regarded as a definitive proof of antecedent GAS infection.

Methods based on nucleic acid detection was first introduced for direct *S pyogenes* diagnosis from clinical throat swabs. The GAS Direct test identifies specific rRNA sequences of *S pyogenes* in pharyngeal specimens by a single-stranded chemiluminescent nucleic acid probe. Other Molecular detection methods utilizing either real-time polymerase chain reaction (PCR)[32] or selected biomarkers were also available on other several platforms.

CHALLENGES AND OPPORTUNITIES IN RHD DIAGNOSIS THROUGH MOLECULAR BIOMARKERS. RHD continues to pose a significant public health challenge in Africa, where research on biomarkers for early detection and management is crucial but fraught with numerous obstacles. Some of which are as follows: the vast genetic diversity within African populations poses a challenge in identifying universal biomarkers for RHD.[33] Moreover, environmental factors, including the prevalence of coinfections and variations in climate, can influence biomarker expression and complicate the establishment of reliable diagnostic markers.[34] Access to state-of-the-art technologies for biomarker research is often restricted in African institutions. This limitation extends to a lack of technical expertise necessary to utilize these advanced techniques effectively.[35] Training and capacity building are urgently needed to bridge this gap. Socioeconomic factors, such as limited access to health care, result in delayed diagnoses and treatment, which affect the availability of early-stage disease samples crucial for biomarker discovery.[36] Furthermore, the dearth of advanced research infrastructure in many African countries severely hampers the progress of biomarker studies. Laboratories often lack the essential equipment and facilities required for cutting-edge genomic, proteomic, and metabolomic analyses.[37] Another factor might be fragmentation of research efforts and limited collaboration among institutions impede the progress of RHD biomarker studies.[34] Additionally, logistical, legal, and privacy issues constrain the sharing of data across borders, which is essential for large-scale studies.[38] And lastly, funding constraints further restrict the ability to undertake large-scale or longitudinal research projects.[39]

The evolving landscape of molecular diagnostics introduces opportunities in RHD diagnosis. Molecular biomarkers promise precise, early detection of GAS infections, providing insights into disease progression. However, integrating molecular diagnostics in resource-limited regions is difficult due to infrastructure, financial, and personnel constraints.

Despite these hurdles, molecular biomarkers present avenues for advancing RHD diagnosis in Africa. Research and development endeavors should concentrate on devising molecular diagnostic tools that are not only cost-effective but also user friendly, facilitating their deployment across diverse settings.

THE URGENT QUEST FOR RELIABLE MOLECULAR SIGNATURES DISEASE BIOMARKERS FOR RHD DIAGNOSIS ESPECIALLY IN AFRICA. Diagnostic challenges persist in diagnosing GAS pharyngitis, with throat swabs for culture being the primary method. Skin lesion isolation is difficult due to *Staphylococcus aureus* colonization. Serological diagnosis relies on detecting immune responses to bacterial enzymes like anti-streptolysin O, anti-DNase B, anti-hyaluronidase, anti-NADase, and anti-streptokinase. GAS pharyngitis is often indistinguishable from viral pharyngitis, necessitating throat culture as the gold standard. Rapid antigen detection tests are also useful, albeit, less sensitive than throat culture.[40]

Significantly lower serum Tenascin-C (TnC) levels was found in acute carditis patients compared to

TABLE 2 Molecular Biomarkers for Diagnosis and Prognosis of RHD and Related Diseases

S/N	Name of the Molecular Biomarker	Type of Markers	Biological Function	Role in RHD Diagnosis/Prognosis	Ref #
1	Intracellular adhesion molecule-1 and vascular cell adhesion molecule-1	Endothelial dysfunctions protein	Endothelial dysfunctions protein	Upregulation in RHD patients indicate endothelial activation and inflammation. Potential marker for early diagnosis	46
2	C-reactive protein	Inflammatory protein	inflammation	Upregulation indicates early stage of either ARF or RHD	47
3	Galactin-3	Carbohydrate binding proteins	Inflammation and fibrosis	Potential biomarker for RHD (upregulation indicates bad prognosis)	43
4	Brain natriuretic peptide and N-terminal pro B-type natriuretic peptide	Cardiomyocyte hormones	Known to be associated with cardiac dysfunction and heart failure	Diagnosis, prognosis of RHD, and risk stratification of heart failure	48
5	Matrix Metalloproteinases	Extracellular matrix enzymes	Known for cardiac remodeling	Upregulated in patients with RHD	49
6	miR-1183 and miR-1299	Small noncoding RNAs	Regulate gene expression	Dysregulated in patients with RHD	44
7	GWAS	Specific genes	Allele of certain genes are associated with increased risk of disease or disease severity	?	22,41
8	HLA-DR7/DR53	HLA variant	HLA variant	Haplotypes associated with risk of diseases or extravasation	45
9	IGHV4-61 gene	Immunoglobulin heavychain gene	GWAS study	Signals associated with ~2-fold increase risk of RHD	50
10	Tenascin-C	Extracellular matrix proteins	Pleotropic protein	Upregulation associated with ARF and CRHD diagnosis	41

ARF = acute rheumatic fever; HLA = human leukocyte antigen; RHD = rheumatic heart disease.

controls, suggesting TnC significance in the diagnostics, predictions and prognosis of rheumatic carditis. Another study in Egyptian children indicated elevated TnC levels in ARF and chronic rheumatic heart disease (CRHD) groups, with lower levels linked to severe mitral valve insufficiency.[41] Elevated serum TnC can serve as a diagnostic marker for ARF and CRHD, surpassing C-reactive protein, ESR, and antistreptolysin O titer. However, while this biomarker shows potential, it is still under investigation and not widely adopted in clinical practice.

Among 93 CRHD patients undergoing elective valve surgery, subclinical inflammation was found in 31.4% of cases. Although inflammatory biomarkers (high-sensitivity C-reactive protein, interleukin-2, interleukin-6, tumor necrosis factor-α, interferon-γ) were elevated, they were not reliably linked to histologically confirmed subclinical inflammation, and Gallium-67 scintigraphy imaging also failed to detect inflammation (**Table 2**).[42]

Kirvan et al.[42] introduced GlcNAc-specific IgG2 as a novel biomarker for ARF, RHD, and Sydenham's chorea (SC). This biomarker differentiates between uncomplicated pharyngitis and ARF, offering insights into GAS infection sequelae and enhancing understanding of ARF pathophysiology. Th1/Th17 cells in RHD and SC might trigger organ-specific autoimmune T cell responses, with Th1 interferon-γ promoting the switch to the IgG2 subclass. Increased GlcNAc-specific IgG2 levels might be useful for the development of ARF diagnostics, therapeutics and Streptococcal vaccine development.[43]

In another study involving 215 African patients with severe RHD and 230 controls, quantitative proteomics and machine learning identified 56 key proteins linked to RHD. Notably, adiponectin, complement component C7, and fibulin-1 were elevated in RHD patients, while ficolin-3 was lower. These biomarkers showed strong discriminatory power (area under the curve of 0.90) between cases and controls, highlighting ongoing inflammation in RHD that may be related to disease severity.[44]

MicroRNA (miRNA) expression profiles are key in RHD biomarker studies. Comparing miRNA expression between RHD patients and healthy controls showed 133 miRNAs (including miR-1183 and miR-1299) upregulated and 137 miRNAs (including miR-4423-3p and miR-218-1-3p) downregulated in RHD patients. Quantitative real-time PCR confirmed miR-1183 and miR-1299 differential expression in tissue and plasma. Bioinformatics and GO/pathway analysis suggest these miRNAs as potential RHD biomarkers,

FIGURE 3 DNA Nudge Box Rapid Point of Care Device Demonstrating the Test Flow of the Strep a group A Streptococcus Test Screening, With Results in 90 minutes which Include Antimicrobial Resistance Targets

offering pathways for novel therapeutics.[45] RHD patients with secondary pulmonary hypertension (PAH) show miR-1299 as a direct RHD regulator. Variation in miR-1183 expression among RHD-PAH patients with different pulmonary artery pressures suggests a role in pulmonary artery remodeling. These findings highlight miR-1183 and miR-1299's distinct roles in RHD pathogenesis, especially in secondary PAH, positioning them as potential disease markers.[45]

The pressing health challenges of RHD in Africa and other LMICs highlight the urgent need for accessible biomarkers. Identifying reliable biomarkers for GAS infection sequelae, like RHD, can revolutionize early detection and monitoring, improving diagnostic accuracy and treatment efficacy. This pursuit is not just scientific but a compassionate call to address unmet needs in resource-limited settings, aiming to improve health outcomes, reduce mortality, and foster a healthier future for vulnerable populations.

An Imperial College London spin off, DNA Nudge, medical device technology company, with Nant Nudge LLC, have a rapid, accurate, portable, battery/solar powered lab-free RT-PCR device, under development is one of such potential novel assays with great promise for diagnosis of GAS in resources limited health care facilities, it can delivers results at the point of need, in just over an hour, even in remote areas of Africa. Health care professionals or technicians can easily be trained to carry out the simple swab to result test. Doctors or lead clinicians can receive the results to any device such as iPad, mobile phone or computer, immediately on completion of the test, even if they are not present on site. The small award-winning Nudge Box RT-PCR machine is CE Marked as seen in (**Figure 3**).

The current DNA Nudge medical platform tests have 95%+ specificity and 100% sensitivity.[51,52] The StrepA (GAS) test will hopefully follow suit and provide a much-awaited solution for the countries of Africa. Not only will the test provide diagnosis of Strep A (GAS) but also has molecular anti-microbial resistance targets within the same test, to enable targeted treatment.[51,52] Fortunately, no confirmed penicillin resistance in GAS has been reported, though it remains a future concern. The DNA Nudge Strep A (GAS) test addresses this, including tetR, emm, ermB, mefA, tetM, tetO, tetK, tetL, and RNAseP control. Antimicrobial resistance targets for azithromycin and doxycycline are included for cases where penicillins cannot be used, per WHO guidelines for LMIC settings treating GAS/long-term RHDs.[52]

Tetracycline resistance is addressed by tetM and tetO (ribosomal tetracycline resistance) and tetK and tetL (efflux pump mediated resistance).[52]

NEED FOR INCORPORATION OF SOCIAL DETERMINANTS OF HEALTH (SDH) INTO THE MANAGEMENT OF RHD IN AFRICA. In addressing RHD in Africa, it is imperative to recognize the need for integrating SDH to comprehensively manage this complex health issue. By understanding and addressing the broader social factors influencing RHD, we can enhance prevention, treatment, and outcomes in affected populations.[51] Many African countries have limited access to health care facilities, particularly in rural areas, this poses a significant barrier to RHD management. Efforts to improve health care infrastructure, increase in the number of trained health care professionals, and implement innovative programs like telemedicine initiatives can enhance access to care for individuals with RHD, as reported in some African countries.[53]

Africa boasts of the most diverse cultural beliefs and language barriers but also has low health literacy levels. These social factors can significantly impact awareness and understanding of RHD among African populations.[47] Therefore, RHD control and management in Africa require tailored health education programs delivered through community health workers, schools, and religious institutions to increase awareness of RHD risk factors, symptoms, and preventive measures. This empowerment enables individuals to seek timely care and adhere to treatment regimens, thereby improving disease management outcomes[52] Such interventions must be culturally sensitive and respectful of traditional healing practices to effectively engage individuals with RHD and their families.

Furthermore, economic disparities and poverty contribute to RHD in Africa. Addressing socioeconomic determinants like unemployment, food insecurity, and lack of clean water and sanitation is crucial for preventing RHD and improving outcomes. Improving housing, nutrition, and economic stability can indirectly influence disease outcomes by reducing stress and improving health.[54] Advocacy is needed to prioritize RHD on the public health agenda, advocate for increased funding for RHD prevention and control programs, and policies to improve housing, education, and access to essential health care services.[55]

Moreover, social support networks are crucial for adherence to treatment and promoting healthy behaviors among those with RHD. Community-based programs offering emotional support, peer mentoring, and practical assistance can positively impact disease management and well-being.[56]

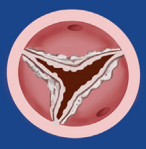
Further research is needed to understand the specific social determinants influencing RHD outcomes in African populations. Collecting data on social, economic, and environmental factors, along with clinical outcomes, can inform targeted interventions and policy development tailored to the needs of diverse African communities.[14,55]

The RHD in Africa is exacerbated by several SDH. Poverty and overcrowding are key contributors, as these conditions increase the risk of streptococcal infections, which lead to ARF. Limited access to primary health care services further hampers early detection and treatment, worsening outcomes. Additionally, poor public health education contributes to the lack of awareness around prevention and management. Insights from the 2020 Australian Guideline for RHD emphasize addressing these social determinants as critical in reducing the disease burden. For instance, the guidelines stress improving hygiene, reducing household crowding, and increasing health literacy, particularly in underserved communities. This holistic approach has proven successful in Australia and can be adapted to the African context. By focusing on these factors, robust infrastructure—encompassing health care access, education, and improved living conditions—can be built to effectively control RHD. Therefore, there is a need to address these social disparities and the importance of strengthening health care systems across Africa to curb the rising prevalence of RHD.

FUTURE DIRECTION IN RHD IN AFRICA. Developing molecular biomarkers to detect RHD early is crucial for effective management. Research in Africa and elsewhere in LMIC should focus on identifying genetic, epigenetic, or protein biomarkers that indicate RHD before severe symptoms. These biomarkers can stratify patients by their risk of disease progression, guiding African clinicians in resource allocation and identifying those needing intensive monitoring or early intervention. Future research should also identify molecular biomarkers for personalized treatment tailored to individual patients. This involves selecting medications or interventions based on genetic predisposition or RHD molecular subtype, emphasizing in-depth studies like GWAS and other omics research in RHD.[24,43,51,55]

Additionally, future research should focus on molecular signatures to monitor disease progression and treatment response over time, indicating disease activity or treatment efficacy to help clinicians adjust strategies. These signatures may also aid in

CENTRAL ILLUSTRATION **Infrastructure Needs Required for Effectively Managing and Mitigating the Impact of the Burden of Rheumatic Heart Disease on the Continent of Africa**



Rheumatic Heart Disease (RHD) Burden in Africa; Challenges and Way Forward

1. Burden of RHD in Africa

- Africa bears a significant burden of RHD largely caused by Group A Streptococcus (GAS)
- High burden attributable to untreated or inadequately treated GAS infection
- Prevalence rates varies across African countries, with some regions experiencing higher burdens than others

2. GAS Infection in Africa

- The prevalence in Africa is not well documented due to lack of surveillance data
- Scattered data on invasive GAS are available among children and immune compromised patients

3. Diagnosis

- Early detection is crucial for management of GAS
- Unmet need for surgical correction due to the scarcity of cardiac surgical care in most parts of LMICs with RHD prevalence

4. Epidemiology of RHD in Africa

- Factors affecting RHD in Africa are: incomplete disease understanding, insufficient advocacy, poverty, overcrowding, inadequate sanitation, limited healthcare access, and genetic predispositions
- Primordial prevention strategies are crucial for reducing exposure to GAS and lowering the risk of RHD

5. Vaccine Development/New Therapeutic Targets

- Studies on GAS vaccine candidates specifically in Africa are very scarce
- Lack of funding and collaboration with local research institutions, international organizations, and pharmaceutical companies play a crucial role

6. Challenges and Way Forward

- Collaboration between institutions from HIC and LMIC should be encouraged, as it can help address challenges in understanding and diagnosing RHD in Africa
- Increased funding is essential to better understand burden and improve diagnostic capabilities, paving the way for effective interventions
- Integration of social determinants of health, improvement of healthcare access, and provision of culturally sensitive education is very crucial to enhance prevention and management

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discovering novel therapeutic targets for RHD, elucidating the molecular mechanisms, and identifying new pathways or molecules for intervention.

Furthermore, large-scale studies are needed to validate molecular biomarkers in diverse African populations. These can identify biomarkers specific to ethnic groups or regions and ensure diagnostic and treatment strategies are applicable across populations. Integrating molecular biomarkers into Africa's health care systems may involve training providers and ensuring infrastructure and resources are in place (**Central Illustration**).

Lastly, emphasizing early diagnosis and timely treatment of GAS infections is a cost-effective strategy to reduce the RHD burden. Early intervention has been shown to lower long-term health care costs and improve patient outcomes.[57] Encouraging collaborations between the public and private sectors to pool resources for vaccine development is also essential. Successful models, such as the GAVI Alliance, have demonstrated enhanced vaccine access in low-income countries.[58] Promoting partnerships between African and international research institutions to accelerate vaccine R&D, as exemplified by the MRC Unit The Gambia at LSHTM,[59] is another critical step.

Furthermore, establishing biobanks and data repositories to support genomic research could be highly beneficial. The H3Africa Initiative is a good model that has advanced genomics research in Africa.[60] Learning from successful control strategies, such as the Rheumatic Heart Disease Program in Uganda, which showcased the effectiveness of integrated RHD control measures,[61] is also crucial. Implementing these strategies may ensure practical and impactful measures, reducing health disparities and improving health outcomes.

RHD remains an important health issue for indigenous women of child-bearing age in northern Australia. However, the influence of RHD on maternal outcomes with current clinical practice is unclear, highlighting the importance of cardio-obstetric care in this condition (or screening for RHD in obstetric care) Typical pregnancy haemodynamic changes include a 40% to 50% increase in blood volume and cardiac output by midterm, accompanied by vasodilation and an increase in heart rate of 10 to 15 beats/min.[62] Labor and delivery pose an additional cardiovascular burden due to contractions, pushing and the autotransfusion that occurs after delivery.[62,63] Although these changes are well tolerated by most women, in those with significant RHD, there may be adverse cardiovascular effects that can result in maternal or fetal morbidity or even death.[64] Specific factors on history or echocardiography have been identified as risk factors for adverse outcomes.[65] Recommendations for management of RHD in pregnancy include a multidisciplinary approach by obstetricians, cardiologists, and anesthetists, with specific measures to prevent cardiac decompensation.[63,66] There is no previously published research that has evaluated the outcomes of patients with RHD in pregnancy in an Australian context.

CONCLUSIONS

The urgent call for action on RHD in Africa is clear. There is an immediate need to prioritize RHD on national and international health agendas by strengthening health care systems, fostering research collaborations, and integrating RHD prevention and management into public health frameworks. Understanding the socioeconomic determinants of RHD epidemiology is crucial for effective prevention and intervention strategies. Educational programs on GAS infections, RHD, and the importance of timely treatment are vital to mitigating the disease's impact in Africa.

Biomarkers play a crucial role in the fight against RHD, offering insights into genetic, epigenetic, and proteomic factors in disease susceptibility and progression. These biomarkers can aid in early diagnosis, risk stratification, and targeted therapies, particularly for advanced RHD, by identifying specific pathways and molecular targets for intervention. This approach enables more personalized and effective treatments, improving patient outcomes. Although this is vital, RHD control in Africa most be done in the context of comprehensive, multimilitary approach including basic science, clinical research, and population-based interventions with support in socioeconomic programs.

Biomarker discovery and vaccine innovation can empower African health care systems to combat GAS and RHD effectively, however, early research and development efforts must be intensified to overcome the challenges associated. Promoting partnerships between African and international research institutions, can accelerate vaccine R&D.

In conclusion, addressing RHD in Africa requires a multifaceted approach, including biomarker discovery, vaccine innovation, and strategic investments in health care infrastructure. Collaborative research, community engagement, and sustained efforts in these areas will help achieve equitable health outcomes and disease control in Africa.

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