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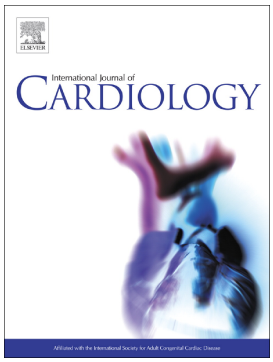

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Babu Muhamed, Daniel Mutithu, Olukayode Aremu, Liesl Zühlke, Karen Sliwa

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RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE: FACTS AND RESEARCH PROGRESS IN AFRICA

Babu Muhamed[1], Daniel Mutithu[1], Olukayode Aremu[1], Liesl Zühlke[1,2] and Karen Sliwa[1]

[1]Hatter Institute for Cardiovascular Diseases Research in Africa, Department of Medicine, University of Cape Town, Cape Town, South Africa.

[2]Division of Paediatric Cardiology, Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa.

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Corresponding author for this submissions is:

Prof. Karen Sliwa, MD, PhD
Hatter Institute for Cardiovascular Research in Africa
Chris Barnard Building
Faculty of Health Sciences, University of Cape Town
3, Anzio Road, Observatory, 7935
E-mail: Karen.Sliwa-Hahnle@uct.ac.za

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Key words : Rheumatic Fever, Rheumatic Heart Disease, Africa

KEY POINTS

- RHD remains a public health priority in Africa, despite being nearly eliminated in high-income countries.
- The prevalence of RHD in Africa has been estimated through screening of school-aged children, retrospective and prospective assessment of hospital records and active surveillance among community members.
- Several approaches have been used to increase RHD awareness among the general public, school-going children, teachers and tertiary heath care givers.
- Basic science research remains critical in understanding the unexplained susceptibility seen in some individuals who proceed to develop RHD.
- Adherence to penicillin prophylaxis remains a major concern in Africa.
- Multidisciplinary cooperation, preconception and antenatal care have been proposed as the key measures to improve the pregnancy outcomes of RHD patients.
- Training of cardiac surgeons and other specialised care givers is recognised as one of the essential means of improving accessibility and availability of cardiac surgery in Africa.

Abstract

In recent years, the devastating effect of rheumatic fever (RF) and rheumatic heart disease (RHD) in Africa has been acknowledged by Institutions such as the Pan-African Society of Cardiology, the African Union Commission, and the World Health Organization. Key priorities set to eradicate RF and RHD include diagnosing and managing RF and RHD, building registries, improving adequate supplies of benzathine penicillin, reproductive health services, and cardiac surgery, developing multi-sectoral RHD awareness programmes, understanding RHD pathogenesis and fostering international partnership for resource mobilization. There were volumes of peer reviewed publications focusing on the key priorities to fight RHD in different parts to Africa; both individually as well as through international collaborations. This article analyzed findings and reports from 1961 to 2018 on efforts to eradicate RF and RHD in Africa.

Introduction

Rheumatic heart disease (RHD) is a chronic condition resulting from untreated beta-hemolytic streptococci. More than 33 millions individuals are affected globally; Africa is among endemic regions [1]. RHD remains a public health priority in Africa, despite being nearly eliminated in high-income countries [2, 3]. The effort to control the burden of RHD have gained momentum in recent years following the Drakensberg declaration which galvanised research interest in RHD [4]. Data on RHD remains scanty in some part of the African continent although interest in RHD research have increased in the last decade [5]. This review highlights studies that have been conducted in the African continent by reviewing published articles.

RHD observational registries

A registry of existing RHD cases is a critical step on identifying and assessing the disease burden. Multicenter registries help in tailored clinical care and contribute to understanding disease outcomes [6]. The Global RHD registry (REMEDY) is the largest international multicenter study to emerge in Africa [7]. Clinical outcomes of 3,343 RHD patients (IQR 15 to 52 years) from 14 low and middle-income countries, 12 in Africa were followed up for 24 months [7]. Some of the key highlights from the REMEDY study are the high mortality and morbidity rate among patients with clinical RHD. It is also noteworthy that individuals with post-primary education were associated with lower risk of death. In addition, higher levels of education were associated with RHD awareness and decline in RHD prevalence [7].

The VALVAFRIC study, registry in Western and Central Africa (2004 to 2008) provided prospective and retrospective data on the clinical characteristics and treatment of 3,441 RHD patients [8] Patients with higher education had lower NYHA class. Additionally, the study highlighted scarcity of cardiac surgery which was afforded to only 27 individuals out of 1,200 who required surgery [8].

The Uganda Rheumatic Heart Disease registry is an initiative of the Uganda Heart Institute (UHI) established in 2010 to facilitate a database of all patients diagnosed with RHD. By the

year 2013, over 900 patients were enrolled in the registry [9]. The registry identified 398 patients requiring invasive intervention, which was not easily accessible [9].

RHD patients have also featured in other cardiovascular disease registries. These include the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF), Tanzanian Heart Failure (TaHef), Abeokuta Heart Failure registry, The RE-LY Atrial Fibrillation Registry, Registry of Pregnancy and Cardiac Disease (ROPAC), Pan African Pulmonary Hypertension Cohort (PAPUCO) Registry and Tunisian multicenter registry [10-14].

Prevalence of RHD in Africa

RHD prevalence in Africa has been estimated through screening of school-aged children, retrospective and prospective assessment of hospital records and active surveillance among community members. The Institute of Health Metrics (IHME) and the Global Burden of Disease (GBD) has used detailed modelling (DISMOD) to compare endemic regions of the world. Watkins and colleagues (2017) suggests that the Democratic Republic of Congo is the most affected African country with an estimated 805,000 RHD cases as at 2015 [1]. The Heart of Soweto study in Gauteng, South Africa showed incidence of new-onset RHD cases at 23.5/100,000 per annum among patients aged >14 years [15]. Echocardiographic screening in Ugandan, Ethiopian, and South African school-aged children have reported 40.2/1,000 (10.9/1,000 definite), 30.5/1,000 (16.5/1000 definite) and 20.2/1,000 (3.4/1,000 definite) RHD prevalence, respectively [16]. The prevalence of RHD among school children in other African countries ranges between 0.3 - 31/1,000 (Table 1).

RHD awareness in Africa

Awareness have been recognised as a critical step on combating and managing RHD [4]. A study conducted at Buea Regional hospital in Cameroon reported approximately 70 to 95% of respondents had little or no knowledge of RHD [17]. Lack of adequate knowledge on RHD could be a contributor to delayed seeking of medical care which heightens the risk of developing chronic RHD [18]. Previous studies have shown dismal levels of rheumatic fever (RF) and RHD awareness amongst primary healthcare givers in Cape Town, South Africa and Khartoum, Sudan [19, 20]. A meta-analysis of data from Tanzania and Uganda showed that lack of RF/RHD awareness among caregivers was one of the major impediments towards successful RHD control [21].

Several approaches have been used to increase RHD awareness among the general public, school-going children, teachers and tertiary heath care givers. Public medical camps and training [22], awareness to women of reproductive age [23] and empowering the general population on health risks of RHD [24] are some of the approaches employed. Other strategies include partnership with influential films stars and famous sports men and women to educate and create awareness within communities [25]. In addition, multimodal media approaches such as brochures, documentaries, short films and social media platforms have been used [26]. RHD awareness and health promotion programs have been underpinned to potentially help in RHD management [25]. Existing healthcare systems can be leveraged to access government resources and improve awareness of RHD, which can contribute to reducing RHD deaths [27]. A collective effort towards creating awareness should be created to control and reduce cases of RHD related mortality.

Basic science research in Africa

Basic science research remains critical in understanding the unexplained susceptibility seen in some individuals who proceed to develop RHD [28]. In Africa, several publications have investigated pathogenesis of RHD (Table 2).

Knowledge on the role of inflammatory response in RHD remains poorly understood. In Egypt, elevated levels of C-reactive proteins (CRP) confirming active inflammation in chronic RHD was correlated with mitral valve regurgitation [29]. High sensitivity C-reactive protein (hsCRP) have been associated with RHD pathogenesis and is a potential biomarker for RHD mitral stenosis (MS), mitral regurgitation (MR) and successful valvuloplasty [30]. The role of hsCRP and CRP in elevated inflammation in RHD remains elusive [30].

Aschoff nodules in RHD patients associated with macrophages and lymphocytes have shown variations in inflammation cytokines and lymphocytes expression levels at different stages of the nodules [31]. In addition, TNF-α and IL-1 cytokines were associated with macrophages while IL-2 were associated with lymphocytes [31]. CD4+ T cells are also highly expressed in RF valves with few CD8+ T cells involvement. Importantly, TNF-a and IL-1 cytokines were found in all aschoff nodules stages while IL-2 was only found in stage 3 or the lymphocytes rich lesions [31].

Expression of specific molecules have been used and proposed as biomarkers of RHD pathogenesis. B cells surface alloantigen D8/17 have been associated with cases of RHD susceptible patients. Despite D8/17 alloantigen being used as RHD infection biomarker in other countries, it's expression among South African population was not significant and was not considered as a potential biomarker [32]. Other molecules proposed as potential RHD biomarkers include Atrial Natriuretic peptide (ANP) [33], B-type Natriuretic peptides (BNP) [34], Amino-terminal pro-brain natriuretic peptides (NT-pro BNP) [35] and Cellular adhesion molecules (CAMs) [36].

Evidence of genetic susceptibility to RHD have been shown in genes located in the human leucocyte Antigens (HLA) and elsewhere in the genome [37]. In Africa, HLA typing studies conducted using serological methods revealed no differences in HLA-a, HLA-B, and HLA-DQ frequencies between RHD patients and controls [38-40]. However, a different study showed a significant association between RHD and HLA-B8 [41]. HLA-DR1 antigens have been predominantly observed in RHD cases signalling genetic susceptibility to chronic RHD [38].

Molecular HLA typing studies have shown significant association between HLA-DR molecules and RHD in Egypt (HLA-DR*04, HLA-DR*13 and HLA-DR*10) and Uganda (HLA-DR*11 and HLA-DR*1), respectfully [42, 43].

Genes located elsewhere in the genome that have been explored in the African population include, *TNF-α*, *IL-4, IL-10, IL-6, IL-1Ra^{VNTR}, ecNOS4, TGF-β1, ACE* and *MBL2* (Table 1) [44-49]. Associations were reported in the *TNF-α* (rs1800629), *IL-10* (rs1800896), *TGF-β1* (rs1800470 and rs4803457), *ACE* and *MBL2* (rs1800450) *genes* [46-49]. However, small sample sizes (*n* = ~ 100 cases) remain a major limitation. Reappraisal of candidate genes associations in RHD have not prevailed in large multicenter studies [50]. Current literature show that only Egypt have reported on non-HLA genes (Table 1). Future genetic studies in the African continent should tap on the richly diverse African population to understand the genetic susceptibility to RHD.

Penicillin prophylaxis

Primary and secondary prevention of recurrent streptococcal infection and RF through prophylactic penicillin is the preferred preventive medical intervention. Yet, adherence to penicillin prophylaxis remains a major concern in Africa. Prophylaxis remains the most cost effective means of treating suspected pharyngitis in children [51]. Factors that attribute to poor adherence include distance from health facility, pain associated with penicillin injection, waiting times, and level of education [52]. In Egypt, patients with advanced knowledge on RHD understood the consequences of missing their monthly penicillin and had improved adherence to RHD prophylaxis compared to the less informed patients [53]. Other motivations for adherence include fear of disease worsening associated with perceived missing injection, family support, and supportive health care providers [54].

Reproductive health care in RHD patients

RHD still constitutes a major cause of maternal and foetal morbidity and mortality [55-59]. Peripartum cardiomyopathy (PPCM) and complications of RHD are the most important causes of maternal mortality [60]. There is increased efforts to focus on RHD patients of childbearing age for better outcome and empowerment. Multidisciplinary cooperation, preconception and antenatal care have been proposed as the key measures to improve the pregnancy outcomes of RHD patients [55]. Factors such as infrastructural changes, use of appropriate referral algorithm and training of primary, secondary and tertiary staff in cardiovascular diseases are likely to improve patient care [60, 61].

Poor outcomes have been predicted following the maternal cardiovascular hemodynamic changes with more women suffering from stenotic lesions (mitral and aortic), pulmonary hypertension, previous heart failure, receiving cardiac medications and higher NYHA class (III and IV) ($p<0.001$) [62, 63]. Maternal age above 28 years, body mass index higher than 28, mean pulmonary artery pressure higher than 50 mmHg, NYHA class III-IV and development of heart failure or cyanosis are predictors of poor outcomes in pregnancy [62].

Cardiac Surgery

Cardiac surgery remains a challenge in Africa (Fig. 1) [64]. However, efforts to avail surgical services across the African continent have gained momentum in recent years [65]. The Cape Town Declaration proposed establishment of an international working group to evaluate and endorse development of cardiac surgical care [65]. Additionally, training of cardiac surgeons and other specialised care givers was recognised as one of the essential means of improving accessibility and availability of cardiac surgery in the continent [65].

Summary

RHD is a neglected disease in Africa. Early detection of RHD is vital in the successful management of the disease. Poor infrastructure and lack of RHD awareness among patients and health care workers have led to a significant portion of the population being deprived of the lifesaving diagnoses and management of the disease. There is a paucity of published literature on RHD in many African nations. The momentum built following the global resolution on RF and RHD at the 71st World Health Assembly in Geneva, needs to be sustained and should encourage more research on RHD in Africa.

Review Data

PubMed, Scopus, Web of Science and African Journals online were searched in November 2018 using combined key terms such as “rheumatic fever” or ”rheumatic heart disease” AND “each of the African states (e.g. Angola)”. The search was not restricted to full-text or language.

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Table 1: Publications reporting on prevalence of RHD in Africa.

Country	Prevalence %	Prevalence Per 1,000	Sample size (*n*)	Study setting	Study design	Screening tool	Mean age (SD)	Study duration	Year	Reference*
Botswana	8.4	-	179	Hospital	Cross-sectional	Echocardiography	34 ± 14.7 32 ± 15.5	2007 - 2008	2012	[1]
Cameroon	3.1	-	669	Hospital	Prospective	Echocardiography	47.8 ± 20.3	2016 - 2017	2018	[2]
Cameroon	6.7	-	239	Hospital	Cross-sectional	Echocardiography	-	2016 - 2017	2017	[3]
Cameroon	5.8	-	1,130	Hospital	Prospective	-	11.8 years	2003 - 2013	2016	[4]
Cameroon	48	-	1,666	Hospital	Cross-sectional	Echocardiography	-	2006 - 2014	2016	[5]
Cameroon	20.3	-	158	Hospital	Cross-sectional	-	-	2003 - 2013	2015	[6]
Cameroon	3.4		1,252	Hospital	Prospective	Echocardiography		2008 - 2010	2013	[7]
Cameroon	14.6	-	462	Hospital	Prospective	Echocardiography	-	2002 - 2008	2011	[8]
Cameroon	64.5	-	262	Hospital	Retrospective	Echocardiography	-	2005 - 2007	2009	[9]
Congo	-	3.5	2,232	School	Screening	Echocardiography	-	2005	2008	[10]
Democratic Republic of Congo	-	14.03	4,848	School	Screening	Echocardiography	-	1996	1998	[11]
Djibouti	6%	-	32	Hospital	Prospective	Echocardiography	-	2009 - 2010	2013	[12]
Egypt	-	19.6 (Definite) 11.4 (Borderline)	3,062	School	Screening	Echocardiography	10 ± 2.6	2009 - 2014	2017	[13]
Egypt	0.37	-	5,609	School	Screening	Echocardiography	-	-	2016	[14]
Egypt	-	6.2	5,465	School	Screening	-	-	-	1998	[15]
Egypt		3.2	8,000	School	Screening	-	-	1990 - 1991	1994	[16]
Eritrea	4	-	684	School	Screening	Echocardiography	-	-	2014	[17]
Eritrea	2.3		348	Hospital	Prospective	Echocardiography		2008	2011	[18]
Ethiopia	5.6	56.7	987	Community	Screening survey	Echocardiography	13.2 ± 4.7	-	2017	[19]
Ethiopia	86		2,541	Hospital	Prospective	Echocardiography	-	2015	2017	[20]
Ethiopia	11.8		862	Hospital	Retrospective	Echocardiography		2010 - 2015	2017	[21]
Ethiopia	-	19	3,238	School	Screening	Echocardiography	13.2 ± 3.2	2013 - 2014	2016	[22]

Ethiopia	57	-	106	Hospital	Retrospective	-	-	2012 - 2015	2016	[23]
Ethiopia	-	31	2,000	School	Screening	Echocardiography	10.7 ± 2.5	2008 - 2012	2015	[24]
Ethiopia	32.8	-	781	Hospital	Prospective	-	31.4 ± 13.2	2003 - 2008	2010	[25]

***Supplementary reference**

Table 1*: Continued…*

Country	Prevalence %	Prevalence per 1,000	Sample size (n)	Study setting	Study design	Screening tool	Mean age (SD)	Study duration	Year	Reference*
Ethiopia	-	6.4	9,388	School	Screening	Echocardiography	-	1999	1999	[26]
Ethiopia	54.9	-	448	Hospital	Retrospective	-	-	1989 - 1992	1993	[27]
Ethiopia		4.6	3,235	School	Screening	Echocardiography		1989 - 1990	1992	[28]
Ethiopia	54.5	-	365	Hospital	Retrospective	-	<18	1981 - 1988	1990	[29]
Ethiopia	45		338	Hospital	Prospective	Auscultation		1995 - 1986	1988	[30]
Ethiopia		0.49	1,212	School	Screening	Auscultation		-	1978	[31]
Ghana	17.3	-	708	Hospital	Prospective	-	36.3 ± 1.6	1992 - 1995	2000	[32]
Ghana	20.1	-	572	Hospital	Retrospective	Echocardiography	36.2 ± 1.7	1992 - 1995	2000	[33]
Ivory coast	1.1		126	Hospital	Retrospective	Echocardiography	15 ± 6.7	2000 - 2009	2013	[34]
Ivory Coast	28	-	217	Hospital	Retrospective	Echocardiography	58.9	1995 - 2005	2010	[35]
Ivory Coast	-	1,9	9,484	School	Screening	Auscultation	-	1977 - 1978	1979	[36]
Kenya	0.32	-	8,011	Hospital	Retrospective	Echocardiography		2011 - 2014	2017	[37]
Kenya	64	-	937	Hospital	Retrospective	Echocardiography	-	-	2016	[38]
Kenya	6.7	-	134	Hospital	Retrospective	Autopsy records	-	2005 - 2009	2011	[39]
Kenya		27	1,115	School	Screening	Echocardiography	-	-	1996	[40]
Kenya	40.7	-	211	Hospital	Retrospective	Echocardiography	-	1992 - 1994	1996	[41]
Libya	4	-	200	Hospital	Prospective	Echocardiography	-	-	1989	[42]

Madagascar	2.1	-	859	Schools and hospital	Observational screening	Echocardiography	20.1 ± 15.1	2014 - 2015	2017	[43]
Malawi	10.1	-	71	Hospital	Prospective	Echocardiography	3.1 ± 9	2017	2018	[44]

***Supplementary reference**

Table 1: ***continued..***

Country	Prevalence %	Per 1,000	Sample size (n)	Study setting	Study design	Screening tool	Mean age (SD)	Study duration	Year	Reference*
Malawi	3.4	-	1,450	School and community	Cross-sectional	Echocardiography	-	2014	2016	[45]
Malawi	22.4	-	250	Hospital	Prospective	Echocardiography	137.8 ± 30.4 (months)	2009 - 2011	2013	[46]
Malawi	34	-	3,908	Hospital	Retrospective	Auscultation, Chest radiography, ECG, echocardiography	39.9 ± 32.4	2001 - 2005	2008	[47]
Malawi	2	-	114	Hospital	Prospective	Auscultation, Chest radiography, ECG	-	-	1975	[48]
Morocco	-	-	359	School Hospital	Prospective	-	-	1969 - 1970	1974	[49]
Morocco	80	-	171	School	Screening	-	-	1965 - 1969	1973	[50]
Mozambique	0.69	-	2,170	School	Retrospective	Echocardiography	10.6	2005	2012	[51]
Mozambique	-	7.8 and 30.4	2,170	School	Screening	Echocardiography	11 ± 2.5 and 11.4 ± 2.0	2005	2009	[52]
Mozambique	-	2.3	2,170	Schools	Prospective	Clinical examination	10.6 ± 2.5	2005	2007	[53]
Mozambique	-	30.4	2,170	School	Screening	Echocardiography	10.6 ± 2.5	2005	2007	[53]

Nigeria	2.6	-	1,364	Hospital	Prospective	Echocardiography	9.12 ± 2.75	2007 - 2016	2018	[54]
Nigeria	25.6	-	125	Hospital	Prospective	Echocardiography	9.49 ± 3.01	2007 - 2016	2017	[55]
Nigeria	26.32	-	163	Hospital	Retrospective	Echocardiography	45.1 ± 18.6	-	2015	[56]
Nigeria	42.7	-	3,810	Screening	Prospective	Echocardiography	10.4 ± 3.4	2009 - 2014	2015	[57]
Nigeria	42.7		110	Hospital	Prospective	Echocardiography		2009 - 2014	2015	[57]
Nigeria	1.3	-	159	Hospital	Retrospective	Review of post-mortem records	-	2001 - 2010	2014	[58]
Nigeria	17.4	-	116	Hospital	Prospective	Echocardiography	6.7 ± 5.7	2009-2012	2014	[59]
Nigeria		0.57	1,764	Screening	School	Echocardiography		2011 - 2012	2013	[60]
Nigeria	57.7	-	580	Hospital	Retrospective	Echocardiography	-	1999 - 2009	2013	[61]

***Supplementary reference**

Table 1*: Continued…*

Country	Prevalence %	Prevalence per 1000	Sample size (n)	Study setting	Study design	Screening tool	Mean age (SD)	Study duration	Year	Reference*
Nigeria	1.7	-	2501	Hospital	Prospective	2D colour Doppler echocardiography	-	2002 - 2010	2013	[62]
Nigeria	8.6	-	475	Hospital	Prospective	Echocardiography 12-lead - ECG	-	2006 - 2010	2013	[63]
Nigeria	-	0.16 and 1.2	9,423	Hospital	Retrospective	Echocardiography	25.64 ± 9.65	2003 - 2011	2013	[64]
Nigeria	1.4	-	208	Hospital	Retrospective	ECG and clinical investigation	-	2005 - 2008	2012	[65]
Nigeria	6.7	-	120	Hospital	Prospective	Echocardiography, baseline blood chemistry and full blood count	-	-	2012	[66]
Nigeria	4	-	234	Hospital	Prospective	Echocardiography	-	2009 - 2010	2012	[67]
Nigeria	2.9	-	391	Hospital	Retrospective	Echocardiography and plain chest radiology	-	2007	2010	[68]

Nigeria	3.1	-	913	Hospital	Prospective	Echocardiography	-	2004 - 2007	2009	[69]
Nigeria	4.3	-	423	Hospital	Retrospective	Echocardiography	-	2001 - 2005	2009	[70]
Nigeria	59	-	2,527	Hospital	Retrospective	Echocardiography	-	1991 - 2001	2008	[71]
Nigeria	8.3	-	277	Hospital	Retrospective	Echocardiography	-	2006 - 2007	2008	[72]
Nigeria	3.7	-	1,441	Hospital	Retrospective	Echocardiography	54.4 ± 14.3	2005 - 2007	2008	[73]
Nigeria	1	-	109	Hospital	Prospective	Echocardiography	-	2002 - 2003	2007	[74]
Nigeria	9.8	-	1,499	Hospital	Retrospective	Echocardiographic	24 ± 12.75	2002 - 2006	2007	[75]
Nigeria	11.2	-	594	Hospital	Prospective	Echocardiography	-	2002 - 2004	2007	[76]
Nigeria	9.2	-	141	Hospital	Prospective	Echocardiography	-	2000 - 2003	2006	[77]
Nigeria	14.4	-	4,456	Hospital	Retrospective	Auscultation	-	1975 - 1976	1979	[78]
Nigeria	0.03	-	12,755	School	Prospective	Auscultation	-	1970 - 1974	1978	[79]

***Supplementary reference**

Table 1*: Continued…*

Country	**Prevalence %**	**Prevalence Per 1000**	**Sample size (n)**	**Study setting**	**Study design**	**Screening tool**	**Mean age (SD)**	**Study duration**	**Year**	**Reference***
Rwanda	36 (Childrenn) 27 (Adults)	-	259 Children 460 Adult	Hospital	Retrospective	Echocardiography	-	2006 - 2017	2018	[80]
Rwanda	-	6.8	2,501	School	Screening	Echocardiography	12.2	-	2017	[81]
Rwanda	32	-	192	Hospital	Retrospective	Echocardiography	-	2006 - 2011	2013	[82]
Senegal	-	4.95	2,019	School	Screening	Echocardiography	-	2011	2015	[83]
Senegal	-	4.9	2019	Schools	Prospective	echocardiography	9.7 ± 3.3	2011	2015	[84]

Senegal	25.6	-	18,815	Hospital	Prospective	echocardiography	-	2009 - 2012	2015	[85]
Senegal		5.4 (5-15 years) 10.1 (16-18 years)	1,116 (5-15 years) 888 (16-18 years)	School	Screening	Echocardiography	-	2010	2013	[86]
South Africa	-	20.2	2,720	School	Screening	Echocardiography	12.2 ± 4.2	2008 - 2012	2015	[24]
South Africa	36	-	960	Hospital	Prospective	Echocardiography	-	2006 - 2007	2010	[87]
South Africa	63	-	493	Hospital	Retrospective	-	-	1993 - 1995	2006	[88]
South Africa	15.6	-	102	Hospital	Prospective	Echocardiography	-	1986	1989	[89]
South Africa		1	4,408	School	Prospective	Auscultation		1884	1987	[90]
South Africa	42.3	-	5,725	Hospital	Retrospective	Electrocardiography Radiography ultrasonography	-	1963 - 1974	1984	[91]
South Africa		6.9	12,050	School	Prospective	Auscultation		1975	1975	[92]
Sudan		2.3	2,129	School	Prospective	Echocardiography	-	2016 - 2018	2018	[93]
Sudan		0,3	3,000	School	Prospective	Echocardiography		2015 - 2016	2018	[94]
Sudan		19	1,515	School	Prospective	Echocardiography		2015 - 2016	2018	
Sudan	17.89	-	123	Hospital	Prospective	Medical history questionnaire	-	2014	2018	[95]
Sudan	-	2.3	2,302	School	Prospective	Handheld echocardiography	-	2016 - 2018	2018	[93]

***Supplementary reference**

Country	Prevalence %	Prevalence Per 1000	Sample size (n)	Study setting	Study design	Screening tool	Mean age (SD)	Study duration	Year	Reference*
Sudan	39	-	179	Hospital	Prospective	Auscultation		1991 - 1993	1994	[96]
Sudan	-	11	13,322	School	Prospective	Auscultation	-	1986 - 1989	1992	[97]
Sudan	25.4	-	958	Hospital	Prospective	-	-	1957 - 1960	1961	[98]
Tanzania	12	-	427	Hospital	Prospective	Echocardiography	-	2012 - 2013	2014	[99]
Uganda	1.5	-	993	Hospital	Prospective	Echocardiography	-	2009 - 2010	2019	[100]

Uganda	2.45 (Borderline) 1.26 (Definite)	-	2,453	Community	Screening	Echocardiography	-	-	2019	[101]
Uganda	-	18.3 (Definite) 35.2 (Borderline)	1,365	School	Screening	Echocardiography	-	-	2018	[102]
Uganda	1.2 (Definite) 3.3(Borderline)	-	956	School	Screening	Echocardiography	-	2014	2016	[103]
Uganda	1.1-2.6	-	4,773	School	Screening	Echocardiography	(5 - 15)	2018	2014	[104]
Uganda	30	-	97	Hospital	Prospective	Echocardiography	-	2009 - 2010	2012	[105]
Uganda	55.4	-	130	School	Screening	Echocardiography	-	2010	2012	[106]
Uganda	35	-	58	Hospital	Prospective	Echocardiography	-	2007	2007	[107]
Uganda	12	-	500	Hospital	Prospective	Echocardiography	-	1993 - 1994	1996	[108]
Uganda	26	-	449	Hospital	Prospective	Auscultation	-	1962 - 1963	1966	[109]
Zambia	-	11.8	1,102	School	Screening	Echocardiography	15.3 ± 1.9	2015	2018	[110]
Zambia	18.2	-	170	Hospital	Retrospective	-	-	1969	1976	[111]
Zimbabwe	16		236	Hospital	Retrospective	Echocardiography	52.1 ± 21.2	2012	2015	[112]
Zimbabwe	-	11.9	50	Hospital	Prospective	Two-dimensional (2D) paediatric echocardiography	7.5 ± 10.5	2012 - 2013	2015	[113]
Zimbabwe	7	-	411	Hospital	Prospective	-	-	-	1991	[114]
Zimbabwe	38.3	-	564	Hospital	Retrospective	Auscultation	-	1957 - 1960	1963	[115]

Table 1*: Continued…*

***Supplementary reference**

Table 2: Summary of RHD basic science studies in Africa.

	Pathogenesis	Type of study	Clinical marker	Validated	Country	Year	Reference*
Inflammation	**High sensitivity CRP (hsCRP)**	Case study	Yes	No	Egypt	2016	[116]
	C-reactive proteins (CRP)	Case study	yes	Yes	Egypt	2011	[117]
	Aschoff nodules' cytokines and lymphocytes	Case study	No	No	South Africa	1997	[118]
	Oxidation associated IgM anti-PC & anti-MDA IgG Abs	Case control	No	No	Uganda	2016	[119]
Haemodynamic factors	**Human urotensin II**	Case control	Yes	No	Egypt	2017	[120]
Cell-surface and circulatory molecules	**B-type natriuretic peptides (BNP)**	Case control	Yes	Yes	Egypt	2016	[121]
	Cellular adhesion molecules (ICAM-1, VCAM-1, E-selectin	Case control	No	No	Egypt	2013	[122]
	Atrial natriuretic peptide (ANP)	Case control	Yes	Yes	Egypt	2013	[123]
	B cells surface alloantigen D8/17	Case control	No	No	South Africa	2011	[124]
	NT-pro BNP	Case study	No	No	Uganda	2016	[125]

IgM - immunoglobulin M, **IgG** - Immunoglobulin G, **Abs** - antibodies, **Anti-PC** - antibodies against phosphorylcholine, **anti-MDA** - antibodies against malondialdehyde, **ICAM-1 –** intercellular adhesion molecule 1, **VCAM-1 –** vascular cell adhesion molecule 1, ***Supplementary reference**

Table 3: HLA and Candidate gene studies emerging from African continent.

HLA Class/Genes	HLA Alleles/Variant	Association	Phenotype	Cases	Mean age ± SD	Female	Male	Controls	Country	Year	Reference*
IL-4 ***IL-10***	Intron 3	No No	RHD	140	12.2 ± 3.4	68	72	100	Egypt	2016	[126]
Class II	DRB1*11	Yes	RHD	96	29.6 ± 10.2	46	50	103	Uganda	2014	[127]
ACE	DD	Yes	RHD	139	9.5 ± 2.2	91	48	70	Egypt	2011	[128]
TNF-α	-308G/A (rs1800629) -238G/A (rs361525)	Yes Yes	RHD	80	11.8 ± 4.2	52	28	50	Egypt	2010	[129]
TGF-β1	869T>C (rs1800470) -509C>T (rs4803457)	Yes Yes	RHD	73	31.7 ± 14.7	53	20	55	Egypt	2010	[130]
TNF-α ***IL-10***	-308G/A (rs1800629) -1080 (rs1800896)	Yes Yes	RHD	20	11.5 ± 2.6	7	13	10	Egypt	*2010*	[131]
‡**Class I** **Class II**	B5 DRB1*04-02 DRB1*1309	Yes Yes Yes	RHD	100	17.5 ± 5.6	41	59	71	Egypt	2010	[132]
ecNOS4a	b/a	No	RHD	139	9.5 ± 2.2	91	48	79	Egypt	2009	[133]
‡**Class I** ‡**Class II**	A B DR DQ	No No Yes No	RHD	120	27.6 ± 14.5	80	40	1,416 (HLA A and B) 20064	South Africa	1987	[134]
TNF-α ***IL-10*** ***IL-6*** ***IL-1Ra^{VNTR}***	-308G/A (rs1800629) -1080 (rs1800896) *-174* (rs1800795) A1/A1	Yes Yes No Yes	RHD	50	12.2 ± 3.4	21	29	98	Egypt	*2007*	[135]

‡**Class II**	DRB1*0701 DQA1*0201	Yes Yes	RHD	88	14.3 ± 9 (n=53) 11.5 ± 4 (n=35)	52	36	59	Egypt	1999	[136]
‡**Class I** ‡**Class II**	A B DR1 DQ	No No No No	RHD	59	32.9	33	26	1,416 (HLA A and B) 20064	South Africa	1997	[137]

‡HLA typed using two stage micro-lymphocytotoxicity method, *Supplementary reference


TUNISIA
MOROCCO
ALGERIA
LIBYA
EGYPT
WESTERN SAHARA
MAURITANIA
MALI
NIGER
CHAD
SUDAN
ERITREA
CAPE VERDE
SENEGAL
THE GAMBIA
GUINEA-BISSAU
GUINEA
BURKINA FASO
BENIN
NIGERIA
DJIBOUTI
SOMALIA
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Figure 1