



Incidence and characteristics of newly diagnosed rheumatic heart disease in Urban African adults: insights from the Heart of Soweto Study

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Aims

Little is known on the incidence and clinical characteristics of newly diagnosed rheumatic heart disease (RHD) in adulthood from urban African communities in epidemiologic transition.

Methods and results

Chris Hani Baragwanath Hospital services the black African community of 1.1 million people in Soweto, South Africa. A prospective, clinical registry captured data from all *de novo* cases of structural and functional valvular heart disease (VHD) presenting to the Cardiology Unit during 2006/07. We describe in detail all cases with newly diagnosed RHD. There were 4005 *de novo* presentations in 2006/07 and 960 (24%) had a valvular abnormality. Of these, 344 cases (36%) were diagnosed with RHD. Estimated incidence of new cases of RHD for those aged >14 years in the region was 23.5 cases/100 000 per annum. Most were black African females ($n = 234 - 68\%$) with a similar age profile to males [median 41 (interquartile range 30–55) years vs. 42 (interquartile range 31–55) years]. The predominant valvular lesion ($n = 204, 59\%$) was mitral regurgitation (MR), with 48 (14%) and 43 (13%) cases, respectively, having combination lesions of aortic plus MR and mixed mitral VHD. Impaired systolic function was found in 28/204 cases (14%) of predominant MR and in 23/126 cases (18%) with predominant aortic regurgitation. Elevated right ventricular systolic pressure >35 mmHg (62 cases), atrial fibrillation (34 cases), and anaemia (27 cases) were found in 18, 10, and 8% of 344 RHD cases, respectively. Subsequent valve replacement/repair was performed in 75 patients (22%). A total of 90 cases (26%) were admitted within 30 months of initial diagnosis for suspected bacterial endocarditis.

Conclusion

These data reveal a high incidence of newly diagnosed RHD within an adult urban African community. These data argue strongly for the first episode of RHD to be made a notifiable condition in high burden countries in order to ensure control of the disease through register-based secondary prophylaxis programmes.

Keywords

Africa • Rheumatic heart disease • Valve disease • Epidemiologic transition

Introduction

The World Health Organisation (WHO) estimates that acute rheumatic fever (ARF) and subsequent rheumatic heart disease (RHD) affect about 15.6 million people worldwide.^{1,2} Acute rheumatic fever following a group A streptococcal infection of the tonsillo-pharynx leads to an inflammatory reaction that involves many organs including the heart, joints, and central nervous system. The most important complication is fibrosis of the heart

valves. Patients with severely damaged valves leading to altered haemodynamics, chamber remodelling, and the clinical syndrome of heart failure (HF) require open heart surgery to replace or repair the damaged heart valves. If left untreated, subsequent HF and/or death is almost inevitable. As such, it is estimated that RHD causes more than 200 000 deaths annually; predominantly children and young adults living in developing countries. However, cases in children 5–14 years of age are likely to represent only 15–20% of all cases within all age groups of vulnerable

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populations.³ In the recently published *Heart of Soweto Study*, an ongoing registry of heart disease in one of Africa's largest urban concentrations of black Africans, we have provided evidence of an epidemiologic transition, with the emergence of the types of heart disease seen in more affluent countries⁴ together with a large burden of diseases of poverty. The latter included a significant component of RHD, tuberculous pericarditis, and idiopathic-dilated cardiomyopathy (CMO).⁵

It is within this context that we used the Heart of Soweto Clinical Registry to examine the incidence and clinical characteristics of newly diagnosed RHD presenting in adulthood in an urban African community in epidemiologic transition. Information on the burden and features of RHD will assist in the development of appropriate public health programs for the early detection, treatment, and prevention of the disease.^{6,7}

Methods

Study setting

The Heart of Soweto Study is an ongoing survey initiated in 2006 to investigate emergent heart disease and its antecedents in the geographically compact townships that comprise Soweto (population of 1.1 million) in South Africa. The purpose and methods of this multi-faceted study, including a detailed clinical registry of nearly all newly diagnosed cardiologic cases presenting to the Chris Hani Baragwanath Hospital, have been described in detail previously.^{4,8}

Like other urban regions within Sub-Saharan Africa, many individuals within Soweto have adopted western lifestyles due to urbanization and are, therefore, in epidemiologic transition. With the exception of dyslipidaemia, we have documented highly prevalent modifiable cardiovascular risk factors in Soweto usually associated with high income countries.⁹ At the same time, Soweto is being populated by a steady number of migrants from rural regions where traditional lifestyles remain the norm. South Africa has a population of different ethnic backgrounds encompassing Blacks, Europeans, Asians, and Coloureds (Khoi San European-African-Malay South African of mixed ancestry) and this is reflected in our study cohort.

The 3500 bed Chris Hani Baragwanath Hospital provides most specialist cardiac services and treatment (via the Cardiology Unit) for Soweto and surrounding communities. Annually, the hospital admits around 130 000 patients; around one-third of whom are managed by the Department of Medicine. It is within this context that the Cardiology Unit (staffed by internal medicine specialists in cardiology training and supported by experienced cardiologists) manages around 21 000 cases per annum; its case-load representing a 'barometer' of the underlying spectrum of cardiovascular disease (mild to severe) within the community.⁴ The Cardiology Unit applies gold-standard cardiologic expertise and advanced diagnostic investigations to provide definitive diagnostic and treatment services.

Study cohort

This paper provides a detailed description of the clinical and demographic characteristics of the 960 cases of newly diagnosed adult patients with valvular abnormalities presenting to the Cardiology Unit in the calendar years 2006 and 2007. This includes all patients presenting to the dedicated cardiology outpatient department via a combination of sources including those directly referred for a cardiac assessment from the 12 local Soweto primary care clinics (specifically 509 cases—53%) in addition to all those referred from the general

medical outpatient facilities, the specialist medical registrar clinic, and diabetic clinic with the hospital (365 cases—38%). It also comprises patients initially admitted to the general medical or any other ward at the hospital referred for a cardiologic consultation (86 cases—9%). All patients aged 14 years and above are considered 'adult' and are managed by the adult Cardiology Unit rather than paediatric cardiologists. There is no upper age limit.

Study data

In addition to a comprehensive range of demographic and clinical data (including blinded Minnesota coding of a 12-lead electrocardiogram),¹⁰ all 960 patients ultimately diagnosed with a valvular heart abnormality in 2006–2007 were identified via systematic screening program of all new case presentations to both confirm clinically indicated cardiac dysfunction (based on a patient's past history and/or clinical presentation) and asymptomatic forms of the same. This involved a detailed echocardiographic assessment of ventricular function, valvular integrity, and function and regional wall abnormalities [specific measurements were available in all but six of *de novo* cases of RHD (2%)]. Specifically, two-dimensional targeted M-mode echocardiography with Doppler colour flow mapping was performed using a Hewlett Packard Sonos 5500 echocardiograph attached to a 2.5 or 3.5 MHz transducer. All echocardiographic procedures were undertaken by trained operators and measurements made according to the American Society of Echocardiography guidelines.¹¹

In order to exclude an ischaemic aetiology, every patient (regardless of age) with clinical suspicion of coronary artery disease based on ECG (e.g. pathological Q waves) and echocardiography (e.g. regional wall motion abnormalities) is routinely subjected to a stress test, cardiac nuclear imaging, and, if indicated, cardiac catheterization.

Case definition

Rheumatic heart disease

Rheumatic heart disease was diagnosed on the basis of a medical history of ARF, and/or praecordial abnormalities including presence of a cardiac murmur plus standard echocardiographic criteria.¹² Rheumatic heart disease predominantly affects the mitral valve leading to commissural fusion, which results in bowing or doming of the valve leaflets in diastole. Rheumatic mitral stenosis was typically diagnosed on the basis of thickening or calcification of the leaflets, especially the posterior leaflet and by involvement of the sub-valvular region leading to fusion, shortening, fibrosis, and calcification of the mitral chordae. Isolated or concomitant mitral regurgitation (MR) was diagnosed by any definitive evidence of regurgitation seen in two planes by Doppler evaluation using semi-quantitative measures. Multiple views allowed detection of eccentric jets. Severe MR was diagnosed by detection of additional systolic flow reversal in the pulmonary veins. Patients with trivial MR and no structural valve changes were excluded.

Rheumatic aortic stenosis or regurgitation (AR) was diagnosed on the basis of commissural fusion of the aortic leaflets, possible increased echogenicity along the leaflet edges, and systolic doming of the aortic leaflets. The shape of the continuous-wave Doppler was taken into consideration in the differential diagnosis (e.g. sub-aortic membrane or hypertrophic CMO and measurement of maximum *trans*-aortic pressure gradient).

Changes in left atrial and left and right ventricular geometry were taken into consideration prior to making a definitive diagnosis of relevant rheumatic cardiac lesions.

Degenerative (calcific valve disease)

Degenerative valvular heart disease (VHD) was defined according to the echocardiographic criteria¹² for calcific valve disease. The age of presentation was taken into consideration for the sometimes difficult differential diagnosis of calcific bicuspid aortic VHD presenting in those aged 45–65 years¹² or degenerative aortic VHD typically presenting in those aged 65 years or more. A high percentage of degenerative mitral VHD with typical mitral annular calcification was diagnosed by isolated area of calcification on the left ventricular side of the posterior annulus or in more severe disease involving the entire posterior annulus. In severe mitral VHD, the extension of the calcification to the base of the mitral leaflets resulting in functional mitral stenosis due to narrowing of the diastolic flow area was demonstrated. The leaflets remain thin and mobile in contrast to RHD.

Degenerative changes of calcific aortic VHD are detected on two-dimensional echocardiography via increased echogenicity of the leaflets with reduced systolic opening. The calcific masses are usually on the aortic side of the leaflet resulting in increased leaflet stiffness without commissural fusion. Calcific shadowing and reverberation typically limit the image quality.

Aortic regurgitation was semi-quantitatively assessed in two planes and confirmed by signal intensity and shape of the continuous-wave Doppler.

Study follow-up

Applying standard clinical and echocardiographic criteria¹³ for suspected bacterial endocarditis, we identified all patients with RHD admitted for antibiotic treatment to Chris Hani Baragwanath Hospital within 30 months of initial diagnosis. Blood culture results from the National Health Laboratory Service, Johannesburg, South Africa were evaluated for all cases. In this same patient group and timeframe, we identified all those who underwent valve replacement/repair at Johannesburg Hospital. Surgical referral was based on standard criteria for cardiothoracic surgery using a combination of symptoms and cardiac dimensions by echocardiography.

Ethical considerations

Ethical approval for the study was sought from the local Ethical Committee and permission confirmed through the relevant administrative bodies. The study conformed to the principles outlined in the Declaration of Helsinki. Each patient in the study is assigned a unique identifying code (9 digits) and all documents labelled accordingly to maintain anonymity and verbally agreed to participate at the time of data collection.

Statistical analyses

All study data were documented and entered into the study database by a dedicated team of experienced cardiac nurses. Each patient receives a unique study number (9 digits). Data were then verified and analysed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Normally distributed continuous data are presented as the mean \pm standard deviation and non-Gaussian distributed variables as the median plus interquartile range (IQR). Percentages are presented with 95% confidence intervals (CI) where appropriate. Comparisons according to demographic and clinical profile involved Chi-square (χ^2) analysis with calculation of odds ratios (OR) and 95% CI for discrete variables and Student's *t*-test and analysis of variance for normally distributed continuous variables. Multiple logistic regression analyses (entry model) were performed on age, sex, ethnic origin, and risk factors to derive adjusted OR's. The rate of incident case presentations per annum of RHD was calculated on an age- and sex-specific basis

using the most up-to-date Census data for the Baragwanath Hospital catchment area (including Soweto) with adjustment for the 2 year study period. Significance was accepted at the two-sided level of 0.05.

Statement of responsibility

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Classification of newly diagnosed valvular abnormalities

In 2006 and 2007, there were a combined total of 4005 *de novo* presentations of heart disease to the Cardiology Unit. Overall, 960 patients (24%) presented with some form of valvular abnormality or dysfunction. Women [570 cases (59%)] and black Africans [868 cases (90%)] predominated. Just over half (512–53%) of patients were specifically from Soweto and had lived there for a median of 42 (IQR 21 to 50) years. According to our prospectively applied criteria, there were three types of presentation; (i) 481 cases (50%) of structural VHD (including three cases in whom the exact cause was undetermined), (ii) 439 cases (46%) of functional VHD, and (iii) 40 cases (4%) in whom the underlying aetiology and type of valvular dysfunction remained undetermined.

Table 1 shows the underlying pattern of structural valve abnormalities found in the identified cases. The two largest sub-groups in these 481 patients being 344 patients (36% of total valve cases) who presented with newly diagnosed RHD and 101 patients (11% of total cases) with degenerative VHD. The secondary causes of functional VHD found in the majority of remaining cases ($n = 439$) included right HF/pulmonary hypertension ($n = 197$ –45% of this patient group), idiopathic-dilated CMO ($n = 119$ –27%), hypertensive heart disease ($n = 70$ –16%), ischaemic CMO ($n = 30$ –7%), and post-partum CMO ($n = 23$ –5%).

Figure 1 compares the overall pattern of abnormalities in those with structural or functional VHD according to gender ($n = 920$ excluding indeterminate cases). While the pattern of structural forms of VHD was similar in men and women, there were marked differences (notwithstanding the presence of post-partum CMO) in the pattern of functional VHD. For example, women were more likely to present with valvular dysfunction associated with an idiopathic-dilated CMO (OR 1.52, 95% CI 1.07–2.18; $P = 0.026$) or hypertensive heart disease (OR 1.70, 95% CI 1.03–2.81; $P = 0.042$). Alternatively, men were more likely to present with an associated ischaemic CMO (OR 3.56, 95% CI 1.62–7.88; $P = 0.026$) and RHF/Cor Pulmonale (OR 2.11, 95% CI 1.54–2.90; $P < 0.0001$).

Newly diagnosed rheumatic heart disease

Table 2 shows the demographic and clinical profile of the 344 newly diagnosed cases of RHD. Overall, black African females (68%) predominated and there was an early peak in all case presentations in the third decade of life; with a rising number of cases in the age groups 14–19 years (3% of RHD cases), 20–29 years (16%), and 30–39 years (24%) followed by a plateau of cases in the age groups 40–49 years (17%), 50–59 years (19%)

Table 1 Pattern of structural valve abnormalities in 481 de novo presentations of valve disease

Group	Aetiology	Sub-category	All (n = 481)	Women (n = 325)	Men (n = 156)
Structural valve disease	Rheumatic		344 (72%)	234 (72%)	110 (71%)
	Degenerative		101 (21%)	65 (20%)	36 (23%)
	Other structural abnormalities	Congenital heart disease	20	15	5
		Unclassified	3	2	1
		Marfan syndrome	1	1	0
		Sub-aortic aneurysm	1	1	0
		Sub-mitral aneurysm	2	1	1
		Myxomatous mitral valve	3	3	0
		Mitral valve prolapse	5	3	2
		Hypertrophic CMO	1	0	1
		Sub-total		36 (7%)	26 (8%)

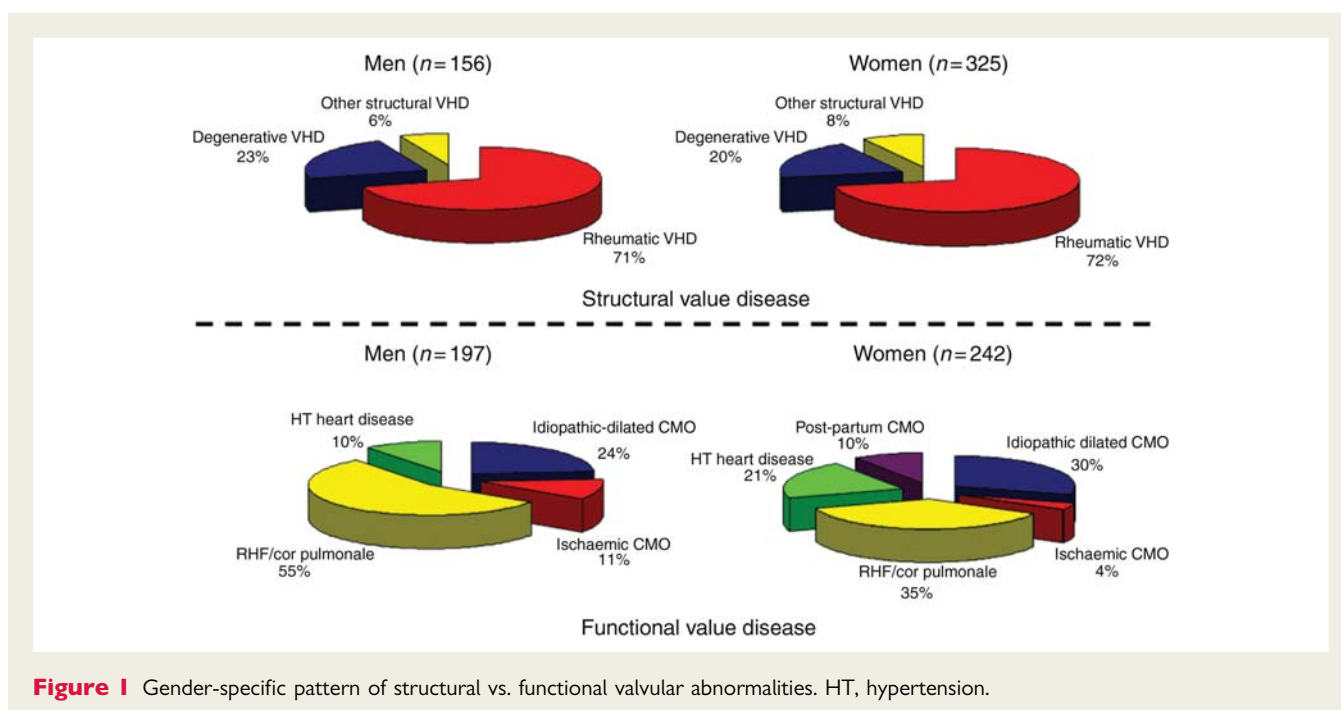


Figure 1 Gender-specific pattern of structural vs. functional valvular abnormalities. HT, hypertension.

and a declining number of case presentations thereafter in the age groups 60–69 years (12%) and 70 years and over (8%). The pattern of case presentation according to age was similar for both men and women, with the exception of a sharper decline in the proportion of patients aged 60–69 years in men compared with women (7 vs. 13% for that age group).

Based on the number of cases and age- and sex-specific population data, the estimated incidence of new cases of RHD for the population surrounding Chris Hani Baragwanath Hospital aged >14 years was 23.5 cases/100 000 per annum. In contrast to the absolute number of case presentations, a j-shaped distribution of incidence cases was evident with incidence rising from 15 to 53 cases/100 000 per annum between the ages of 19 and 60+ years (the highest point being in older cases) after an initial high of 30 cases/100 000 per annum in those aged 15–19 years (Figure 2). Figure 3 demonstrates the pattern of underlying mitral valve pathology according to age group with age-specific incidence

rates (men and women combined) provided. Younger patients in the age range 10–29 years presented predominantly with pure MR, whereas middle aged adult patients developed mitral stenosis (age range 20–39 years) taken over by mixed mitral VHD in older patients. There were no gender-specific statistical differences in symptoms of dyspnoea, peripheral oedema, resting heart rates, and blood pressure or education.

Concurrent anaemia and atrial fibrillation were found in 27 (8%) and 34 (10%) of the cases, respectively. Only 64 patients had a medical indication or gave consent for an HIV ELISA test and, of these, 23 (36%) tested positive.

Echocardiographic features

Table 3 shows the echocardiographic features of this cohort according to the predominant rheumatic valvular lesion (e.g. AR more significant than stenotic component in mixed aortic VHD). Patients having haemodynamically significant VD affecting two

Table 2 Socioeconomic data and clinical presentation of newly diagnosed rheumatic heart disease (n = 344)

	ALL (n = 344)	Women (n = 234)	Men (n = 110)
Socio-demographic profile			
Female	234 (68%)	234 (100%)	–
Median (IQR) age in years	43 (32 to 56)	41 (30 to 55)	42 (31 to 55)
Black African	314 (91%)	220 (94%)	94 (85%)
0–10 years standard education	314 (91%)	213 (91%)	101 (92%)
Median (IQR) years in Soweto	36 (20–50)	35 (20–49)	37 (20–50)
Clinical presentation			
Dyspnoea	226 (66%)	159 (68%)	67 (61%)
Palpitations/chest pain	227 (66%)	156 (67%)	71 (65%)
Raised jugular venous pressure	19 (5.5%)	12 (5.1%)	7 (6.4%)
NYHA Functional Class III/IV	61 (18%)	38 (16%)	23 (21%)
Peripheral oedema	94 (27%)	69 (29%)	25 (23%)
Mean heart rate (b.p.m.)	84 ± 17	86 ± 18	81 ± 16
Systolic blood pressure (mm Hg)	122 ± 24	122 ± 24	121 ± 24
Diastolic blood pressure (mm Hg)	69 ± 20	69 ± 21	67 ± 18
Clinical profile			
Renal dysfunction	57 (22%)	28 (17%)	29 (32%)
Anaemia	27 (8.2%)	23 (10%)	4 (4%)
Atrial fibrillation	34 (10%)	20 (9%)	14 (13%)

NYHA, New York Heart Association. Renal dysfunction defined = an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² (moderate to severe renal impairment): calculated in 254 cases using the modification of diet in renal disease abbreviated formula (estimated GFR mL/min/1.73 m²) = 186.3 × (serum creatinine mg/dL)^{-1.154} × (age)^{-1.154} × (0.742 female sex) × (1.21 if black African) using serum creatinine concentrations (μmol/L) converted to mg/dL. Anaemia defined as haemoglobin level < 11 d/L in men and < 10 d/L in women from 330 cases.

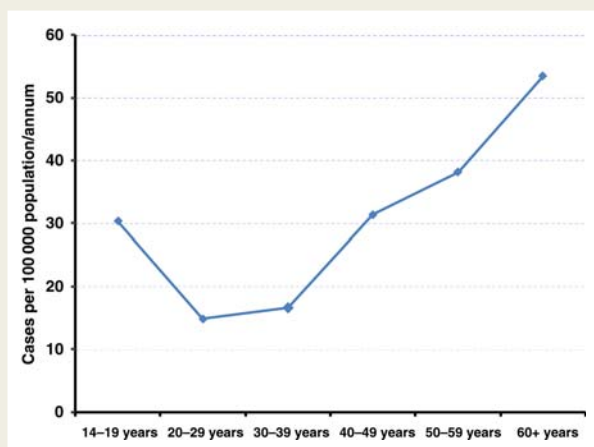


Figure 2 Estimated incidence of rheumatic heart disease (de novo hospital presentations).

valves (e.g. aortic and mitral VHD) were counted twice. The most common predominant valvular lesion was MR (204/344 cases) with 48/344 cases having combination lesions of AR and MR and mixed mitral VHD in 43/344. A mixed aortic VHD was diagnosed in 25/344 cases. Of the 31 cases diagnosed with rheumatic aortic valve stenosis, 25 patients had additional AR, 9 had additional mitral incompetence, and 2 patients had additional mitral stenosis.

Presentation with an impaired systolic function of a left ventricular ejection fraction < 45% was not uncommon: 28 of 204 cases (14%) presenting with MR and 23 of 126 cases (18%) presenting with AR. An elevated right ventricular systolic pressure > 35 mmHg was found in 62/344 (18%) cases.

Initial pharmacological treatment

At the time of clinical presentation, 247 patients (72%) were prescribed at least one form of cardiac-specific treatment (Table 4). In those with MR (n = 204), therapeutic agents typically prescribed to those in HF, including loop diuretics, angiotensin converting enzyme (ACE) inhibitor, beta-blockers, and aldosterone inhibitors, were prescribed in 57, 26, 22, and 14% of cases, respectively. Combined anti-platelet therapy (predominantly warfarin and aspirin—33%) and potassium supplements (30%) were other commonly prescribed agents. In those with AR (n = 126), loop diuretics, ACE-inhibitors, beta-blockers, and aldosterone inhibitors were prescribed in 69, 36, 19, and 16% of cases; with anti-platelet therapy (40%) and calcium antagonists (22%) also commonly prescribed.

Outcomes

A total of 90 out of 344 cases (26%) were admitted to the hospital within 30 months of initial diagnosis for suspected bacterial endocarditis (minimum of two sets of blood cultures obtained on every patient). Overall, 20 patients (22%) were treated for bacterial endocarditis fulfilling modified Dukes criteria after investigation

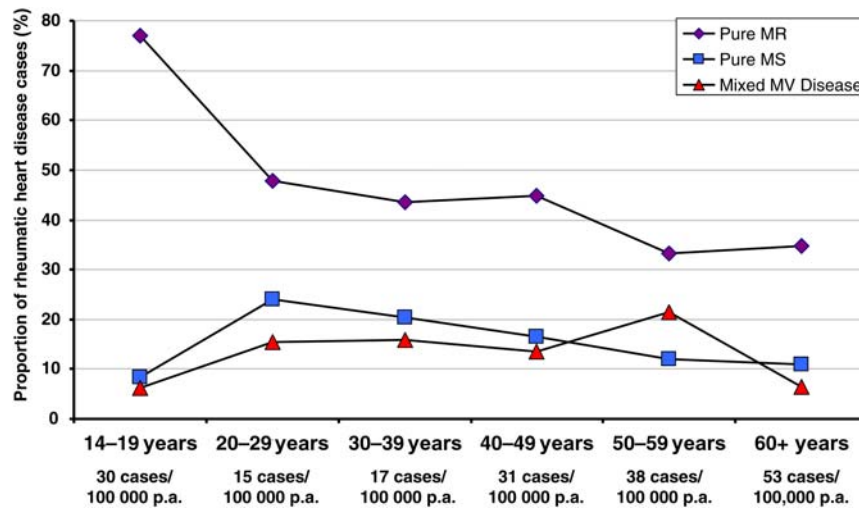


Figure 3 Pattern of underlying mitral valve pathology according to age group in rheumatic heart disease (n = 344). MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve.

Table 3 Echocardiographic features of 344 de novo adult cases of rheumatic heart disease in according to predominant valvular lesion

	All cases	Mitral stenosis	Mitral regurgitation	Aortic stenosis	Aortic regurgitation
Total cases	344 (100%)	103 (30%)	204 (59%)	31 (9%)	126 (37%)
Systolic function and dimensions					
Mean LVEF	58 ± 13	59 ± 11	58 ± 13	60 ± 13	56 ± 14
Systolic dysfunction (%)	50 (17%)	11 (9.2%)	28 (14%)	7 (23%)	23 (18%)
Mean LVEDD (mm)	49 ± 12	44 ± 10	51 ± 11	49 ± 14	51 ± 14
LVEDD > 55 mm	86 (25%)	7 (6.8%)	49 (24%)	6 (19%)	40 (32%)
Mean LVESD (mm)	36 ± 21	33 ± 13	38 ± 31	31 ± 14	37 ± 14
LVESD > 45 mm	55 (16%)	8 (7.8%)	27 (13%)	3 (10%)	22 (17%)
Valvular regurgitation (mild: moderate: severe)					
Mitral valve (%)	103 (30%)	20: 17: 4.9%	43: 40: 17%	19: 6.5: 3.2%	22: 8.7: 7.1%
Aortic valve (%)	126 (37%)	12: 6.8: 0%	12: 8.3: 3.4%	35: 32: 13%	45: 37: 18%
Tricuspid valve (%)	89 (26%)	8.7: 14: 11%	13: 9.3: 7.4%	13: 3.2: 3.2%	9.5: 9.5: 6.4%
Other abnormalities					
RVSP > 35 mmHg	62 (18%)	26 (25%)	40 (20%)	3 (10%)	19 (15%)

Systolic dysfunction defined as an LVEF < 45% (specific data available in 303 cases). LVEF, left ventricular ejection fraction; LVEDD, left ventricular diameter at diastole; LVESD, left ventricular diameter at systole; RVSP, right ventricular systolic pressure.

with transthoracic and/or transoesophageal echocardiography. Of those, eight patients (8.8% of those admitted) had positive blood cultures identifying Coagulase Negative Staphylococcus in six cases (including three patients with prosthetic valves) with singles cases of Staphylococcus aureus and Acinetobacter baumannii infection.

A total of 75 cases (22%) were sent for valve replacement/repair in a period of 30 months. Of these, 22 patients (29%) underwent aortic valve replacement, 32 patients (43%) mitral valve replacement/repair, and 21 patients (28%) double valve replacement.

Discussion

To the best of our knowledge, we present the first study of the incidence of new-onset RHD in patients above the age of 14 years in Africa.¹⁴ We show that RHD is common, and highlight the persistent burden of newly diagnosed cases within an African adult population. Overall, the volume and pattern of cases challenge the common assumption that chronic RHD presents predominantly in children.¹⁵ Our data indicate that the burden imposed by RHD is present throughout the life course, with a large majority

Table 4 Pattern of initial prescribed treatment for patients with rheumatic heart disease

	All cases	Mitral stenosis	Mitral regurgitation	Aortic stenosis	Aortic regurgitation
Total cases	344 (100%)	103 (30%)	204 (59%)	31 (9%)	126 (37%)
Loop diuretics	208 (61%)	69 (67%)	116 (57%)	22 (71%)	76 (69%)
Anti-platelet therapy	130 (38%)	45 (44%)	67 (33%)	12 (39%)	50 (40%)
Potassium supplements	103 (30%)	39 (38%)	61 (30%)	6 (19%)	31 (25%)
ACE-inhibitor	94 (27%)	26 (25%)	53 (26%)	10 (33%)	45 (36%)
Beta-blocker	89 (26%)	42 (41%)	44 (22%)	9 (29%)	24 (19%)
Aldosterone inhibitor	47 (14%)	13 (13%)	28 (14%)	6 (19%)	20 (16%)
Cardiac glycoside	43 (13%)	14 (14%)	24 (12%)	3 (9.7%)	16 (13%)
Calcium antagonist	39 (11%)	6 (5.8%)	16 (7.8%)	6 (19%)	28 (22%)

of cases presenting beyond middle age: our observations both support and contradict the proposition that the prevalence of RHD peaks in the fourth decade of life¹⁶ given that the peak age group (in terms of absolute numbers) in this study was 30–39 years (24%), but that the majority of cases (57%) were aged 40 years or more (Figure 2) reflecting prevalence of milder forms of RHD becoming symptomatic only in adulthood and poor antibiotic treatment decades ago. Indeed, peak incidence occurred in those aged 60 years or more.

Furthermore, we demonstrate a significant proportion of cases of degenerative VHD in Africa. It is significant that, not a single case of ARF, a previously common diagnosis in the region also in patients above the age of 14 years¹⁷ was observed in this series. This encouraging development most probably reflects better access to primary healthcare, less overcrowding, and better sanitation for children and young adults living in Soweto in the past 15 years of a new democratic government. However, only patients aged >14 years attend the adult cardiac clinic and this observation is not reflective of more rural areas of South African and neighbouring countries.¹⁸

Acute rheumatic fever is a notifiable condition in South Africa, a measure that is designed to ensure that cases are enrolled in registers and are offered secondary prophylaxis with regular penicillin injections. Secondary prophylaxis is a cost-effective and proven intervention for the prevention of progression of RHD. Our data that show a high incidence of RHD but a low or absent detection of ARF suggest that it is the first episode of RHD that should be made notifiable in order to ensure registration and follow-up of patients. It is of interest that in South Africa, the first episode of RHD was initially made notifiable, but this was rescinded in the early 1990s.¹⁹ Our study highlights the need to re-instate the first attack of RHD as a notifiable condition, not only in South Africa, but in other countries where RHD is endemic.

These data also reaffirm that primary VHD plays a pivotal role in the development of HF in Africa with around 1 in 10 cases of *de novo* HF attributable to primary valve abnormality (mostly RHD). However, our data also highlight the therapeutic challenges doctors in developing regions are faced when assessing patients presenting with cardiac murmurs. Of 4005 patients seen for the first time at this tertiary centre over a period of 24 months, 960 had some form of valvular abnormalities resulting in stenotic or

regurgitant lesions with more than 50% having functional VHD due to ischaemic, idiopathic, and other causes of CMO.

In describing complex cases within this cohort, it was essential to distinguish between primary as opposed to functional VHD (e.g. idiopathic-dilated CMO resulting in annular dilatation).⁵ Significantly, there is a paucity of HF studies and registries from high-income countries that make such a distinction.^{20,21} For example, the EHFS II²⁰ reported that 72% of the *de novo* acute HF patients had evidence of MR (moderate to severe in >40% of cases). However, they did not distinguish between MR due to primary VHD dysfunction to degeneration of valvular and cardiac structure with both cardiac remodelling and increasing age. In Africa, the therapeutic approach to HF due to severe rheumatic MR (surgery) vs. functional MR (e.g. in selected patients with idiopathic-dilated CMO who may benefit from a multi-site pacemaker)⁵ is of particular relevance.

Overall, these data have important clinical and public health implications for Sub-Saharan Africa, the wider African continent, and other parts of the world in epidemiologic transition. In high-income countries, VHD is typically degenerative and is regarded as an emerging public health problem.²¹ Generally, VHD is poorly represented in the international classification of disease, and its contribution to mortality and morbidity has to some extent been ignored.²¹ In recent years, a number of reports have been published investigating mechanism of functional MR in non-ischaemic and ischaemic CMO^{22,23} and their impact on subsequent HF and cardiac re-synchronization.²²

Our high number of newly diagnosed symptomatic RHD is confirmed by two recent South African studies investigating the aetiology of cardiac disease in pregnancy. Nqayana T *et al.*²⁴ reported on 77 cases with RHD of 95 women with cardiac diseases identified during the study period of 1 year at Inkosi Albert Luthuli Central Hospital in Durban, South Africa. A 4 year audit of cardiac disease in pregnancy at another South Africa Hospital found an aetiology of 63.5% of RHD and 20.1% of prosthetic VHD probably of rheumatic disease origin.²⁵ Sani and colleagues reported on prevalence and pattern of RHD in the Nigerian Savannah,²⁶ 9.8% of cases screened by echocardiography over a 4 year period had RHD with MR being the most common echocardiographic diagnosis in 38% of the cases. A large portion of the 129 patients with RHD had complications at diagnosis with 31.8% of the cases

demonstrating left ventricular systolic dysfunction. Screening for RHD in schoolchildren aged 6 to 17 years in Mozambique¹⁸ demonstrated mitral valve involvement in a great majority of cases (98.4%) and a prevalence rate of 30.4 cases per 1000 but 90% of cases were clinically silent, occurring in asymptomatic children. Our study, which shows that a third of new cases occur in patients over 50 years of age, suggests that the study of the whole population is required in order to gain a fair estimate of the burden of RHD in endemic regions.

Our study has a number of limitations. First, this study cohort only reflects those who are fortunate enough (or sick enough) to seek specialist care at the hospital and was always likely to describe those with more advanced forms of VHD; these data undoubtedly under-represent those adults in Soweto who are suffering from milder forms of VHD. Unfortunately, there are no gold-standard methods for definitively categorizing the aetiology and clinical characteristics of VHD. We applied a clinically orientated approach based on published criteria¹² and acknowledge that there may be inherent biases in our classification of cases. While providing some important outcome data, constraints in research capacity and the fact that many patients in South Africa often have no phone, incomplete addresses, or are forced to migrate for employment opportunities, limited our ability to undertake comprehensive follow-up of patients (i.e. beyond data on re-admission and surgical data). As a clinical registry, we did not systematically validate diagnostic data, but (wherever possible) have adhered to the recently published STROBE guidelines relating to the reporting of this type of study.²⁷ Our estimates concerning the incidence of new case presentations of RHD above the age of 14 years need to be interpreted cautiously given inherent difficulties in population estimates in South Africa and the fact that one in two case presentations were from the discrete boundaries of Soweto. Urban African cities as Soweto have a large migrant population and in particular those having migrated from rural to urban areas might have been previously had poor access to health care.

In conclusion, this study provides important insights into the still large and complex burden of newly diagnosed chronic RHD within an adult urban community, supporting recent statements^{3,28} that RHD is of sufficient importance to warrant urgent attention of the international public health and research community.^{28–30} The results argue strongly for the first episode of RHD to be made a notifiable or reportable condition in high burden countries, as a measure to ensure control of the disease through register-based secondary prophylaxis programmes.³¹

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