The severe presentation and poor outcomes of Rheumatic Heart Disease in Namibia: Lessons from the REMEDY study

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Abstract

Background: Rheumatic heart disease (RHD) is the most common form of acquired cardiovascular disease in children and young adults in developing countries. This paper reports baseline characteristics and outcome data for patients enrolled in the Global Registry for RHD (the REMEDY study) from Namibia.

Methods: The Namibian site recruited 266 patients between January 2010 and November 2012 who were followed for two years to assess clinical outcomes, intervention, morbidity and mortality.

Results: Patients were young; median age 22 years, 36% children and 72.6% less than 30 years of age. At baseline they had severe heart disease. Almost a third were in New York Heart Association (NYHA) Class III-IV. Two thirds had cardiomegaly and half were in congestive cardiac failure. The left ventricle was dilated in 41% and 32% of adults had reduced left ventricular function (ejection fraction). The majority had moderate to severe disease with respect to all valvular lesions (e.g. mitral regurgitation 69.8%, mitral stenosis 79.0%, aortic regurgitation 62.4% and aortic stenosis 58.8%). With reference to prevention and control, secondary prophylaxis was only being used by 34.2% of patients. Oral anti-coagulation (OAC) therapy was prescribed to 75.3% (64 /85) of patients with clinical indications but less than half (41.5 %) had international normalized ratio (INR) monitoring in the preceding six months. Almost a fifth (17.9%) of the patients died.

Conclusions: Patients with symptomatic RHD are young with severe disease and show inadequate use and access to both prevention and intervention. REMEDY Namibia highlights gaps in evidence-based solutions aimed at preventing and limiting the impact of RHD.

255 words.

Introduction

Rheumatic heart disease (RHD) is the consequence of acute rheumatic fever (ARF) which is caused by pharyngeal infection with Group A beta haemolytic streptococcus. [1] The Global Burden of Disease Study 2013 estimates that nearly 33 million persons living with RHD contribute to 275 000 deaths in every year.[2, 3] It the most common form of acquired heart disease among children and young adults in developing countries and affects approximately 0.5 – 3% of school-aged children in Africa.[3] [4] RHD is no longer a public health problem in most developed countries. [5] Historical studies from these countries describing clinical features, natural progression and outcomes may not be applicable to developing nations like Namibia where RHD remains a major cause of cardiovascular morbidity and mortality. [6] [7] [8]

Namibia is a large country in sub saharan Africa (824 292 km^2) with a population of only 2.3 million people.[9] There were no cardiology services prior to 2008 and without capacity to manage patients with established RHD, there were no data on prevalence or incidence and there was also no programme for the prevention of ARF or control of RHD.

A dedicated specialist RHD clinic was established in 2010 and Namibia was one of the sites in the Global Rheumatic Heart Disease Registry (REMEDY) a multi-centre, international prospective registry of patients with RHD conducted in 14 countries.[11] The aims of the study were to characterise hospital-based RHD in Namibia. The objectives were to comprehensively describe the patient demographics, the pattern and severity of disease, measure outcomes and complications, assess risk factors, audit contemporary practice (prevention and treatment) and evaluate public health control activities. [6] The baseline characteristics and two year follow up of individuals with RHD enrolled at the Namibia REMEDY site are reported here.

Methods

The study was conducted between July 2010 and November 2012 in the Rheumatic Heart Disease clinic at the Windhoek Central Hospital, the national referral centre for patients with RHD. All patients with a diagnosis of RHD (confirmed with echocardiography) were invited to participate in the study and this was done during their routine clinical visits. Enrolled patients were assessed and treated according to standard practices. This study was approved by the Permanent Secretary of the Ministry of Health and Social Services and informed consent was obtained from subjects or, their guardians in the case of children (less than 18 years). The study design, data collection and statistical considerations of REMEDY were applied to the Namibian patients as described previously.][11] [12]

Results

Baseline Characteristics

There were 266 patients enrolled in REMEDY in Namibia between January 2010 and November 2012. The geographic distribution indicated that the majority of patients were referred from regions in excess of 700 km from the referral centre (Figure 1). The patients were young; ninety-six (36.0%) were children under 18 years of age, and 72.6% were less than 30 years of age (Figure 2). The median age was 22 [IQR 15-32] years. Two hundred (60.5%) were female, a great proportion of whom were (87.6%) in childbearing age (between 12 to 51 years) and of those 4 were pregnant. Amongst the children, 7 (2.8%) were less than 5 years old (Figure 3). Only 32 (12%) were older than 40 years (Figure 2).

Geographical Distribution of REMEDY Namibia Participants

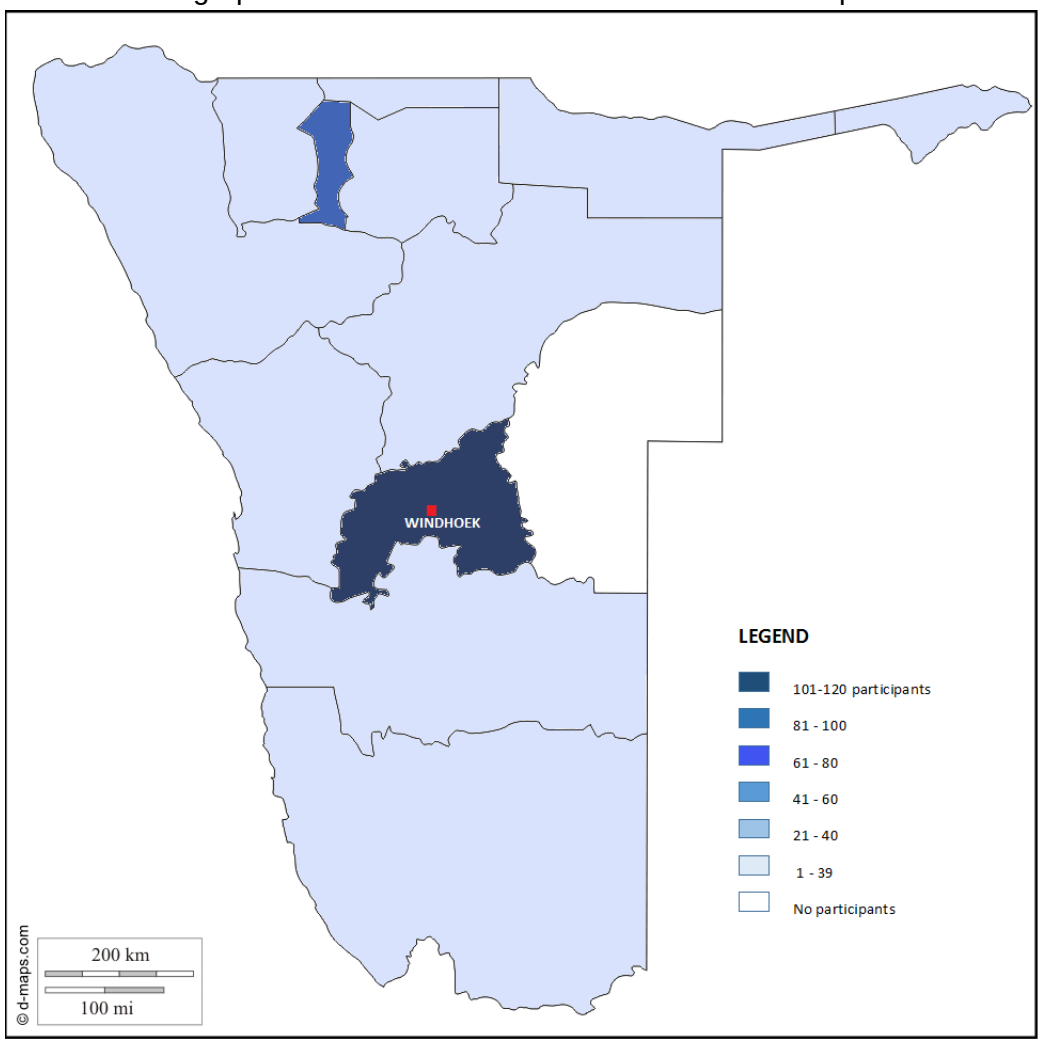

Figure 1. Geographic Distribution of REMEDY Namibia Participants

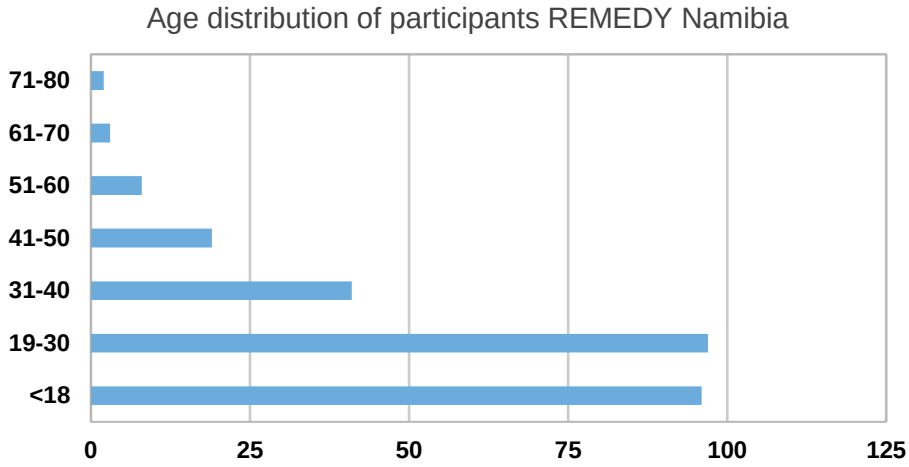

Figure 2. Age distribution of children (≤ 18) REMEDY Namibia

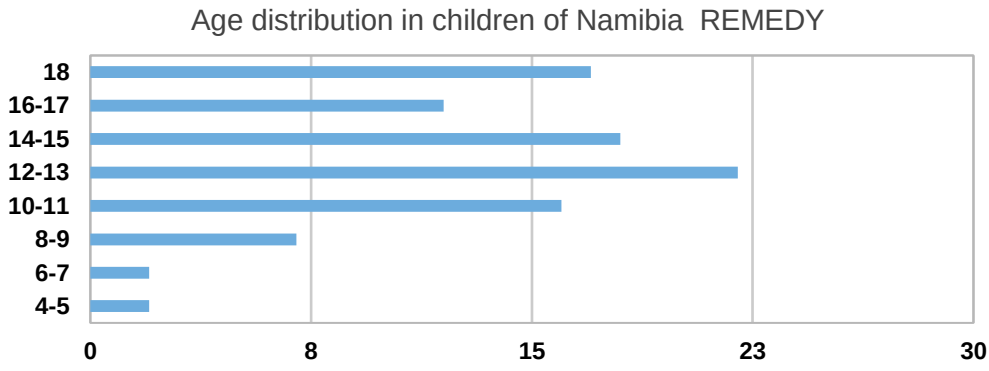

Figure 3. Age distribution at enrolment in children in REMEDY Namibia

The clinical features and investigations at enrolment are shown in Table 1. Less than half the patients (40.2%) reported a history of ARF. Almost a third of patients were severely symptomatic with 28.7% in New York Heart Association (NYHA) Class III-IV. Chest radiographs taken at baseline demonstrated cardiomegaly in two-thirds, pulmonary oedema in 8.3% and pleural effusions in 6.8%. At baseline there were 9 patients with a past history of infective endocarditis. In total, 47 patients had atrial fibrillation (AF) and 19 had cerebrovascular accidents (stroke).

Table 1. Baseline Characteristics of 266 REMEDY Namibia Participants

Baseline Characteristics of 266 children and adults with rheumatic heart disease in Namibia	
Clinical Characteristics and past medical history	Number of participants (%)
NHYA III &IV	75 (28.1)
Acute rheumatic fever*	107 (40.2)
Congestive heart failure	130 (48.9)
Stroke or transient ischaemic attack	19 (7.1)
Infective endocarditis	9 (3.3)
Major bleeding	3 (1.1)
Peripheral embolism	3 (1.1)
Atrial fibrillation**	47 (17.7)
HIV positive	10 (3.8)
Pulmonary Hypertension	105 (39.6)
Chest Radiograph	
Cardiomegaly	175 (65.8)
Pulmonary oedema	22 (8.3)
Pleural effusions	18 (6.8)
Echocardiography (n)	
Decreased LVEF in adults (170)	55 (32.4)
Decreased LVEF in children(96)	13 (13.5)
Dilated LVEDD in adults (170)	70 (41.2)
Dilated LVEDD in children (96)	59 (61.5)
Surgery	
Valve replacement	40 (15.0)
Mechanical valve replacement	35 (13.2)
Bio-prosthetic valve replacement	5 (1.9)
Valve repair	7 (2.6)
Percutaneous valvuloplasty	4 (1.5)
*Data available in 255 participants **Data available in 259 participants	

The mitral valve was the most commonly affected valve with mitral regurgitation in 92/266 (34.5%) and mitral stenosis in 95/266 (42.6%). Mixed mitral valve disease was described in 29 (13%). Aortic valve disease manifested as regurgitation in 133 (59.6%) and stenosis in 17 (7%). Mitral and aortic valve disease were found in combination in 101 (45.3%) whilst only two patients had isolated aortic valve disease. The majority of cases had moderate to severe disease with respect to all valvular lesions (e.g. mitral regurgitation 69.8%, mitral stenosis 79.0%, aortic regurgitation 62.4% and aortic stenosis 58.8%). In total, 167 (62.8%) were assessed as having severe disease. Myocardial function was impaired with decreased ejection fraction in 26.3%, of these 13 were children.

Of 266 patients, 47 had previous surgery with the majority having mechanical valve replacements 35/47 (74.5%). Only 5/47 (10.6%) had bio-prosthetic or tissue valve replacements and 7 had mitral valve annuloplasty with valve repair. Percutaneous valvuloplasty was performed for mitral stenosis in 4 patients.

At baseline, secondary penicillin prophylaxis had not been prescribed in 65.8% (173/263) of patients. Of those on prophylaxis, intramuscular benzathine long acting penicillin was the most common mode of administration 63/90 (70%). Oral anti-coagulation (OAC) therapy (Coumarin) was prescribed to 75.3% (64 /85) of patients with clinical indications for anticoagulation; thirty-one of thirty five (88.6%) patients with mechanical valves and thirty-three of fifty (66.0%) with atrial fibrillation or flutter. Of patients taking OAC regardless of indication less than half (41.5 %) had international normalized ratio (INR) monitoring in the preceding six months. The INR at enrolment was recorded for only 36.8% (25/65) of patients in which 8 were sub therapeutic, 13 were within therapeutic range and 4 above the therapeutic range. There was no INR result available for 40/65 of patients on Coumarin. The majority of participants (67.9%) were unaware of the therapeutic range of INR values.

Follow up

Vital status was known for 241 (90.6%) of the participants and clinical outcomes after 27 months follow up are shown in Table 2. Fourty-six patients (46 17.3%) died. The majority of deaths occurred in the first year of enrolment; 29 during the first 12 months (mortality rate 129.8/1000 patient years) compared to 17 in the subsequent 15 months (mortality rate 76.7/1000 patient years). The median age of death was 21.3 [IQR 15.3-27.1], the youngest recorded death in a 6 year old. The only risk factor at enrolment that was independently associated with mortality was severe disease (HR 4.9; 95%CI 1.50-15.98).

Table 2: Incidence of clinical outcomes at two years of follow-up in children and adults with rheumatic heart disease in Namibia (n=266 unless otherwise specified)

Outcome	Number of events over 27 months	Patient-years	Incidence rate per 1000	95% Confidence interval
Death				
In first 12 months	29	223.4	129.79	90.20 – 186.78
In second 15 months	17	221.7	76.68	47.67 – 123.35
Congestive heart failure	8	349.8	18.19	9.10 – 36.37
Stroke or TIA	3	2.2	1342.83	433.09-4163.54
Atrial fibrillation	4	442.9	9.03	3.39 – 24.06
Surgery	58	367.6	157.79	121.99 – 204.10
Valvuloplasty	7	434.1	16.13	7.69 – 33.83

During follow-up, there were no recurrences of ARF. Eight patients developed congestive heart failure (18.1 per 1000 patient years), four atrial fibrillation (9.03/1000 patient years), three stroke or TIA and three infective endocarditis. Seven pregnancies were reported during follow up. Sixty-five patients had intervention over the 27 month period. Seven received percutaneous valvuloplasty for mitral stenosis and 58 had valve repair or replacement surgery.

Table 3 : Predictors of mortality in 266 children and adults with rheumatic heart disease in Namibia followed up over two years

Baseline variable	Hazard ratio	95% Confidence interval	p value
Severe disease†	4.90	1.50 – 15.98	0.008
Age	1.00	0.96 – 1.03	0.796
Female sex	0.64	0.32 – 1.28	0.206
Atrial fibrillation	2.33	0.96 – 5.77	0.069
New York Heart Association functional class III/IV	1.16	0.51 – 2.64	0.725
On secondary antibiotic prophylaxis at enrolment	1.68	0.80 – 3.53	0.173
Prior valve intervention or surgery	0.88	0.26 – 2.93	0.832
Multi-valve disease	0.73	0.35 – 1.51	0.392
Congestive heart failure at enrolment	1.87	0.80-4.35	0.149
Prior infective endocarditis	2.57	0.72 – 9.19	0.146
Prior stroke	1.53	0.51 –4.61	0.448
Education beyond primary school	0.89	0.39 – 2.05	0.789

Discussion

The baseline and outcomes data for REMEDY grouped the 14 participating countries into three income categories according to the 2011 World Bank definitions of low-income, lower-middle income and upper-middle-income countries (Namibia and South Africa). [11] [12] [23] The presentation of the data in this manner masked several important differences between Namibia and South Africa. Firstly, the median age at presentation for upper middle income countries was 39 whereas the median age for Namibia at 22 years, is more congruent with that of low income countries in REMEDY. [11] Similarly, children less than 18 years of age represented 36 % of Namibian patients compared with 19.4% in the "upper-middle-income group", again more in keeping with low income countries. [11] Thirdly, the proportion of women of child bearing age in Namibia was 87%, vastly in excess of that for upper middle income countries (66.9%) and even exceeding that for low income countries. [11] Most importantly, the mortality rate at the end of follow up was 12.5% for the upper middle income cluster however, in Namibia, the reported rate of 17.9% is higher even than that observed in lower middle countries (16.8%) and closer to the rate observed in low income countries (20.8%). [12] The demographic, clinical and outcomes data presented in the REMEDY study has concealed these very important disparities.

Patients presented young and with advanced disease; almost half had a past history of congestive cardiac failure, a third were in NYHA III or IV, the majority with moderate to severe valvular heart disease and a quarter had objective evidence of impaired left ventricular function. Severe disease impacts survival where a staggering number, almost one-fifth of patients enrolled, died (17.6%). These patients were very young (median age of 21.3 years [IQR 15.3-27.1]. Whereas life expectancy in Namibia is 63.1 years for men and 68.5 years for women, only 10 % of patients at baseline were older than 40 years.[13] The significant drop in number of patients over the age of 40 years suggests early death could be a characteristic of RHD in Namibia. The numbers of patients that developed congestive heart failure, atrial fibrillation, infective endocarditis, were hospitalised or that received surgical intervention reflect significant morbidity from RHD.

RHD is known to show a female preponderance and this is confirmed in Namibia.[14] Almost 90% of women were in child-bearing age. Heart failure is an added risk factor for pregnancy.[15] There is high morbidity and mortality associated with rheumatic heart disease in pregnancy. [16] Work from Senegal has shown that rheumatic heart disease is associated with a maternal mortality rate of 34% in pregnancy and a high rate of foetal loss among survivors [17] Official figures reveal maternal mortality is 265 per 100,000 live births in Namibia and the contribution of RHD to maternal morbidity and mortality requires further investigation. [18].

There is irrefutable evidence that long acting benzathine penicillin administered three to four weekly by intramuscular injection reduces recurrent episodes of acute

rheumatic fever in people with established RHD. [19] It is also superior to twice daily oral penicillin. [20] The administration of and adherence to penicillin therapy is in many ways a barometer for prevention strategies within a health system.[19] [21] At baseline, penicillin had been prescribed in only one third of patients with RHD. Low usage of penicillin prophylaxis suggests a lack of awareness that penicillin prophylaxis is imperative for secondary prevention. The fact that almost 60 percent of patients or parents could not offer any history of RF or RHD also suggests a lack of awareness about RHD in the community. Collectively these data reflect health system weaknesses which demand enquiry and comprehensive intervention. [11]

Patients with atrial fibrillation or with prosthetic mechanical heart valves ought to be using oral anticoagulation medication, to prevent left atrial thrombus and prosthetic valve thrombosis. [22] The low numbers of patients on OAC and the lack of knowledge about target INR's, reflect a lack of awareness about good clinical practice. The fact that a third of patients on Coumarin had not had an INR for over 6 months shows significant non-compliance and a poor penetration of highly relevant clinical knowledge amongst health professionals. These data point the way to much needed targeted health education interventions.

The study was based in a tertiary referral hospital and in this context the severity of disease is not unexpected but reflects a great number of late presentations of severely affected patients. The geographic distribution of patients mimics the population distribution of Namibia. Although the majority of the patients were enrolled in Windhoek, more than half (60%) were referred from the northern regions (700 kilometres away). This results in significant health service challenges relating especially to access to surgery, safe and reliable anticoagulant monitoring and control and loss to follow-up.

There are important implications for clinical practice and health policy revealed in this study with red flags raised including low levels of awareness about RHD, delayed referral to a service capable of delivering tertiary interventions, suboptimal utilisation of penicillin prophylaxis within a health system which fails to deliver on secondary prevention. RHD is preventable with adequate medical care and is a mirror for the effectiveness of the primary health care system. This study has contributed to the development of a national programme for prevention and control of RHD(24) using the PASCAR-driven A.S.A.P. Programme, which calls for efforts to increase awareness of RF/RHD among the general public and practitioners; the establishment of surveillance programmes to measure the burden of disease in the population; advocacy to increase allocation of resources for the treatment of affected children and young adults; and the implementation of primary and secondary prevention schemes.[10] The importance of needs-driven health systems research cannot be under-estimated. REMEDY has proven that research is in itself an agent for change.

Conclusion

The Namibian patients enrolled in the REMEDY study present at an early age yet, they manifest with severe disease, require costly high-end surgical interventions and have a high mortality rate comparable with other low-middle income or event low-income countries. The REMEDY study in Namibia has highlighted the gaps existing in current health services and the urgent need for more robust application of known evidence-based solutions to prevent and manage the complications of RHD.

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