Clinical outcomes for young people with screening-detected and clinically-diagnosed rheumatic heart disease in Fiji

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TITLE PAGE

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Conflict of Interest

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ABSTRACT

Background

Echocardiographic screening is under consideration as a disease control strategy for rheumatic heart disease (RHD). However, clinical outcomes of young people with screening-detected RHD are unknown. We aimed to describe the outcomes for a cohort with screening-detected RHD, in comparison to patients with clinically-diagnosed RHD.

Methods

A retrospective cohort study included all young people with screening-detected RHD in the Central Division of Fiji in the primary cohort. Screen-negative and clinically-diagnosed comparison groups were matched 1:1 to the primary cohort. Data were collected on mortality, clinical complications and healthcare utilisation from the electronic and paper health records and existing databases.

Results

Seventy participants were included in each group. Demographic characteristics of the groups were similar (median age 11 years, 69% female, median follow-up 7 years). There were nine (12.9%) RHD-related deaths in the clinically-diagnosed group and one (1.4%) in the screening-detected group (Incident Rate Ratio: 9.6, 95% CI 1.3–420.6). Complications of RHD were observed in 39 (55.7%) clinically-diagnosed cases, four (20%) screening-detected cases and one (1.4%) screen-negative case. There were significant differences in the cumulative complication curves of the groups (p<0.001). Rates of admission and surgery were highest in the clinically-diagnosed group, and higher in the screening-detected than screen-negative group.
Conclusions

Young people with screening-detected RHD have worse health outcomes than screen-negative cases in Fiji. The prognosis of clinically-diagnosed RHD remains poor, with very high mortality and complication rates. Further studies in other settings will inform RHD screening policy. Comprehensive control strategies are required for disease prevention.

Abstract Word Count: 248

KEY WORDS:

Rheumatic heart disease; mass screening; echocardiography; complications; morbidity; mortality; survival analysis
1. INTRODUCTION

Rheumatic heart disease (RHD) is the chronic sequel of acute rheumatic fever (ARF), an autoimmune reaction to infection with the Group A Streptococcus bacterium. People with RHD are at increased risk of complications such as congestive heart failure (CHF), infective endocarditis, arrhythmia, stroke, complications of pregnancy and childbirth, and premature death.

Echocardiography is a sensitive test for the diagnosis of RHD (1). Screening using echocardiography may identify individuals with RHD that have not previously presented to clinical services, and echocardiographic screening research activities have been conducted in many countries for two decades (2, 3). There are an estimated 33 million prevalent cases of RHD globally (4), although this estimate does not include asymptomatic cases as uncovered in screening studies, suggesting the actual global burden may be considerably greater (5).

However, whilst data exist on the natural history of RHD for patients presenting with clinically-diagnosed ARF or RHD (6), data are limited on the clinical outcomes for people with screening-detected RHD. It is therefore not known whether echocardiographic findings on screening represent only trivial to mild disease, or if some predispose to serious complications, increased healthcare utilisation and premature death. These data are required for development of evidence-based policy for population-level screening.

We previously reported severe disease on echocardiography in some young people with screening-detected RHD in Fiji (7). In this study, we aimed to describe the clinical outcomes for a cohort of young people with screening-detected RHD, and to compare these outcomes to a cohort without RHD and to a cohort with clinically-diagnosed RHD.
2. METHODS

2.1 Design and setting

We used a retrospective cohort study to describe and compare the clinical outcomes of a screening-detected RHD cohort with two matched groups of screen-negative and clinically-diagnosed RHD participants.

This study took place in the Central Division of Fiji, a country in the South Pacific with a population of approximately 900,000. Forty-one percent of the population reside in the Central Division (8). Fiji has a very high prevalence of RHD (definite RHD 7 per 1000 school-aged children on echocardiography) (9). Fiji has conducted sporadic echocardiographic screening for RHD since 2006 and has an active RHD control program managed by the Ministry of Health and Medical Services. All inpatient and outpatient medical care for children and young adults with RHD in the Central Division is provided at the Colonial War Memorial Hospital in Suva.

2.2 Participants

Cases were defined by interrogating a database compiled from individual screening activity logs in Fiji, as previously described (10). All young people aged 5 – 15 years who were diagnosed with RHD on echocardiographic screening from 2006 – 2013 and recommended to commence secondary prophylaxis were included in the primary cohort (11-13). We excluded any child known to have RHD prior to screening, or who was later assessed to have a non-RHD diagnosis such as congenital heart disease. We also excluded cases assessed to have possible or probable RHD (14) or borderline RHD (15). We excluded cases screened outside the Central Division as data for other divisions were unreliable or unavailable.
We then defined two matched comparison groups: a control group of screen-negative participants, and a comparison group of participants with clinically-diagnosed RHD. Participants for these groups were matched 1:1 for each screening-detected case by date of screening/diagnosis, age, gender and ethnicity. Screen-negative cases were identified by manually searching the school screening enrolment logs for the child of the closest age to the case at the same school, where gender and ethnicity were matched. Echocardiography reports were then checked to ensure none had congenital or other abnormalities.

Clinically-diagnosed cases were identified by manually searching the Fiji National RHD register. At the time of the study, the register was a locally-stored, Microsoft Access database managed by the RHD control program, containing demographic and clinical information for all cases of ARF and RHD notified to the program since 2005. Patients without RHD (registered as ARF only) or residing outside the Central Division were excluded. Register data were filtered to display age and gender matched individuals with a clinical diagnosis date within 12 months of the screening date of the screening-detected case. The individual with the closest age was enrolled as the match. In the few instances where there was no available match for cases of other Pacific Islander ethnicity, a match was selected from the indigenous iTaukei population. Matching was performed blinded to any additional clinical or demographic information.

2.3 Outcomes

The study period was defined from the date of screening or clinical diagnosis until July 31 2015, or the date of death where applicable. Outcomes collected were known clinical complications of RHD (CHF, infective endocarditis, stroke, ARF recurrence, and death). Data were also collected on healthcare utilisation episodes including admissions, surgery and medication prescriptions. Documented prescription of a medical treatment for cardiac failure
was coded as CHF. Reliable data were not available for complications of pregnancy and childbirth.

2.4 Data collection

The main data source was the Fiji electronic health information system (PATIS Plus) which includes hospital admission coding according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) for the main divisional and subdivisional hospitals nationally, and detailed medication prescribing records. Coding data for hospital admissions are fairly reliable, although there are some known deficiencies (16). The second major source of data was individual patient files held at the Colonial War Memorial Hospital. These paper files were manually inspected page-by-page for details of admissions, surgery, medications and complications. Additional data were extracted from the Fiji National RHD Register and existing lists of cardiac surgical cases held by the RHD control program.

Two data collectors used a standardised data extraction tool to inspect the PATIS record, individual patient file and any other available data sources and reached consensus on items to include in the analysis. When assessing admission episodes for clinically-diagnosed cases, any admission where the initial diagnosis of RHD was made was excluded, and only subsequent admissions counted. All records were reviewed by an experienced paediatrician and reasons for admission, surgery and death were classified as RHD-related or not.

A list of participants who had died was compiled from all data sources. We then undertook a primary review of death certificates held at the Fiji Health Information Unit to determine cause of death. Death certificate information is generally available and reliable as reporting deaths is mandatory prior to burial or cremation (17).
2.5 Statistical analysis

Descriptive statistics were used to calculate frequency of clinical outcomes. Incident rates were calculated using the total period of observation of each group as the denominator. Incident rate ratios (IRR) with 95% confidence intervals were used to compare outcomes between the primary cohort (screening-detected) and the screen-negative and clinically-diagnosed groups. Kaplan-Meier failure curves were used to compare mortality and cumulative RHD complications, and the log-rank test used to assess for differences between groups. Results were analysed using Stata 14.2 (Statacorp, College Station, TX, USA).

2.6 Ethical approval

The study protocol was approved by the Fiji National Research Ethics Review Committee (2014.134) and the Royal Children’s Hospital Human Research Ethics Committee, Australia (2015-02).
3. RESULTS

3.1 Characteristics of cohort groups

Seventy screening-detected cases were included. The median age at screening was 10.9 years, median age at end of study was 17.6 years and median length of observation was 7.4 years. Females accounted for 69% of cases and 83% were iTaukei (indigenous Fijian). These cases were matched with 70 screen-negative and 70 clinically-diagnosed cases, and the demographic characteristics of the three groups were very similar (Table 1).

3.2 Healthcare interactions

There were 28 admissions (16 RHD-related) in the screening-detected group compared to 4 (none RHD-related) in the screen-negative group and 113 (78 RHD-related) in the clinically-diagnosed group (Table 2). Admission incident rates were higher in the screening-detected than screen-negative group (IRR 7.1, 95% CI 2.5–27.9) and higher in the clinically-diagnosed than screening-detected group for overall admissions (IRR 4.3, 95% CI 2.8–6.8) and RHD-related admissions (IRR 5.2, 95% CI 3.0–9.5). Admission bed days were higher in the screening-detected than screen-negative group (IRR 3.7, 95% CI 2.7–5.3) and higher in the clinically-diagnosed than screening-detected group (IRR 6.6, 95% CI 5.6–7.8).

Three screening-detected and fifteen clinically-diagnosed patients had cardiac valve surgery during the study. Surgical episodes were more frequent in the clinically-diagnosed group than the screening-detected group, both overall (IRR 7.5, 95% CI 2.6–29.2) and for RHD-related surgery (IRR 6.4, 95% CI 1.8–33.9, Table 2). There was only one episode of surgery (not RHD related) in the screen-negative group, although this result was not statistically significantly different to the screening-detected group with this sample size.
3.3 RHD complications

In the screening-detected group, 14 (20%) developed complications of RHD, particularly CHF (Table 2). There was one episode each of infective endocarditis, arrhythmia and ARF recurrence. The rate of complications was significantly higher than the screen-negative group (IRR 14.2, 95% CI 2.2–601.9) where only one complication was recorded (idiopathic supraventricular tachycardia). Complications were most frequent in the clinically-diagnosed group (IRR compared to screening-detected group: 3.0, 95% CI 1.6–5.9), with 39 (56%) cases developing complications, most commonly CHF (49%). There was a significant difference in the complication-free survival curves between the clinically-diagnosed and screening-detected group (p<0.001) and between the screening-detected and screen-negative groups (p<0.001, Fig. 1)

3.4 Mortality

There were two deaths (3%) in the screening-detected group, one due to RHD, which equates to an RHD-attributable death rate of 2.1 per 1000 person-years. There were nine deaths (13%) in the clinically-diagnosed group, all due to RHD, which equates to an RHD-attributable death rate of 20.5 per 1000 person-years (IRR compared to screening-detected group for overall mortality: 4.8, 95% CI 1.0–45.6; for RHD-related mortality: 9.6, 95% CI 1.3–420.6, Table 2). There were no deaths in the screen-negative group. There was a significant difference in the survival curves for mortality between the clinically-diagnosed and screening-detected groups (p=0.02) but not between the screening-detected and screen-negative groups (p=0.16, Fig. 2). Outcomes by sex are shown in Appendix Table A.1.
4. DISCUSSION

This cohort study provides several insights into the clinical outcomes of screening-detected and clinically-diagnosed RHD in this setting. Firstly, screening-detected RHD is associated with poorer health outcomes than for those without RHD, with a high complication rate of 20% over a median follow-up of 7 years. The predominant complication was CHF, and there were episodes of arrhythmia and endocarditis, three cases requiring valve surgery and one death from severe RHD. This suggests a health burden clearly in excess of the general child and adolescent population of Fiji, as evidenced by the incident rate ratio 14 times higher for complications, and 7 times higher for admissions, compared to the screen-negative group. There were no deaths or RHD-related healthcare episodes in the screen-negative group, which precluded calculation of incident rate ratios for these outcomes.

Secondly, we report a very high rate of complications in the clinically-diagnosed group, with more than half developing complications and a striking 13% mortality rate over the median 7 years of follow-up. These data provide further evidence of the devastating nature and poor prognosis of clinical RHD, even in this young age-group. The clinically-diagnosed group was 3 to 5 times more likely to develop complications or be admitted for RHD than the screening-detected group, and 10 times more likely to die from RHD. These differences may be due to clinically-diagnosed cases having a more severe form of disease, a more advanced stage of disease, or more cases with true disease rather than benign echocardiographic abnormalities. There were few recorded episodes of ARF in either RHD group, although under-diagnosis and under-reporting are known to be issues in Fiji (18).

There are few data on the clinical outcomes of screening-detected RHD available for comparison. Mirabel et al. followed 114 children with screening-detected RHD in New
Caledonia for a shorter period (median 2.5 years) and reported a mild spectrum of disease without significantly different outcomes to a matched screen-negative group (19). Only one child with screening-detected RHD developed heart failure and there were no deaths or episodes of cardiac surgery. In Uganda, two of 51 children with asymptomatic, screening-detected RHD developed ARF, including one with CHF, over a median follow-up of 25 months (20). In South Africa, two of 44 asymptomatic cases developed symptomatic CHF over five years (21). The differences between these studies and our results are consistent with the higher severity of the Fiji screening cohort on echocardiography (7) and may represent differences in the health systems and health-seeking behaviours of the population. It is likely that several screening-detected cases in our study who developed complications would have had clinical symptoms at time of diagnosis, and represent “missed” clinical cases rather than pre-symptomatic disease.

The richest contemporary data on the outcomes of clinically-diagnosed RHD is the multi-centre, prospective REMEDY cohort study which reported outcomes at 2 years for 3343 patients in low and middle income countries in Africa, Yemen and India (22). The cohort was considerably older (median age 28 years) and half had severe disease at baseline. The mortality rate over two years was 17%. CHF was found in 33% at baseline and a further 7% developed CHF over 2 years. Age, severe disease and CHF at baseline were predictors of mortality. The outcomes from the present study are comparable with the REMEDY data, and likely represent an even poorer prognosis, given the Fiji cohort was considerably younger and was selected from all new clinically-diagnosed RHD cases rather than symptomatic, hospital-based cases. A cohort of 396 new clinically-diagnosed cases of RHD admitted to a tertiary hospital in New Caledonia was also older than our cohort at baseline (median age 18 years, IQR 10-40). Cardiac complications were present in 27% at baseline (23). Of those followed for a median of 4 years, 2.4% died, a further 6% developed complications each year and 20%
required surgical or percutaneous intervention. A cohort of 1066 clinically-diagnosed, Indigenous RHD cases from the RHD registry of the Northern Territory of Australia (median age 22 years) found CHF in 14% at baseline and a further 13% within 5 years of diagnosis (24). All cause-mortality was 11.6% after 10 years in the Indigenous cohort, with a standardised mortality ratio of 1.56 compared to the Indigenous population of that region. By contrast, the all-cause mortality rate for all ARF/RHD patients in Fiji was previously estimated to be 3.7% per year (2% in 4-19 year olds).(17) In both the New Caledonian and Australian cohorts, outcomes were far poorer for those with severe disease, who had a low rate of complications. The better outcomes observed in Australia and New Caledonia, compared to REMEDY and Fiji cohorts may reflect the quality and availability of healthcare and surgical services, and the benefits of benefits of long-standing RHD control programs.

The study findings suggest that screening-detected RHD represents an earlier, or less severe form of RHD, with poor health outcomes compared to the unaffected population. However, there is likely variation among this group, and some cases may never develop clinical disease. It remains unclear whether there are characteristics identifiable at the time of screening which may predict which patients are more likely to progress to clinical complications. This should be the target of future research, although large, prospective cohorts will be required. These results add to the growing body of evidence around early case detection, and specifically echocardiographic screening, for the prevention of RHD. This evidence will assist in ongoing formulation of RHD screening policy, including the development of economic analyses.

4.1 Strengths and limitations

We provide the longest follow-up data on outcomes following echocardiographic screening, and the first data from a developing country. The three, well-matched cohort groups allow comparison with the health utilisation and clinical outcomes of a non-affected population and
a clinically-diagnosed group. Data were collected from multiple sources. However, there are several limitations to this study. Reliable details of disease severity at diagnosis were unavailable, and therefore it is not possible to determine the effect of severity on the observed differences between the clinically-diagnosed and screening-detected groups, or between our cohort and other international cohorts. It is likely that some clinically-diagnosed cases were misdiagnosed as RHD due to a low threshold for diagnosis in children admitted for illnesses such as sepsis or ARF in this high RHD-prevalence setting, particularly prior to the development of the 2012 World Heart Federation diagnostic criteria (15). However, all cases were taken from the RHD register and had been commenced on antibiotic prophylaxis. This misclassification would likely underestimate the complication rate in this group. The sample size was limited by the number of screening-detected cases, and incidence estimates of complications and mortality may be imprecise, as demonstrated by the wide confidence intervals for some results. This study did not evaluate outcomes for those with screening-detected borderline RHD, and the clinical prognosis of that group remains unclear. Data were collected retrospectively and limited by the availability and completeness of documentation. Due to data availability, participants were limited to those in the Central Division, and results may not be generalizable to more remote parts of Fiji or international settings.

Finally, secondary antibiotic prophylaxis adherence data for were not available over the period of follow-up, and it is not known what effect prophylaxis would have on clinical outcomes. Adherence is generally low in Fiji (10), and the poor outcomes observed in both RHD groups underlines the need to improve secondary prophylaxis delivery structures for all known cases. Screening will be ineffective without high levels of adherence, and should not be implemented without the fundamentals of a register-based control program and strong health systems for secondary prophylaxis and follow-up.
5. CONCLUSIONS

Young people with screening-detected, definite RHD in Fiji have worse health outcomes than screen-negative cases, with more morbidity and greater healthcare utilization. The prognosis of clinically-diagnosed RHD remains poor, with very high rates of mortality and complications. Further follow-up studies from a range of settings will inform RHD screening policy. Screening may detect sizeable numbers of cases who are either symptomatic at baseline or rapidly become so. Further studies from a range of settings are needed to guide how such patients should be managed and followed, and to inform broader RHD screening policy. Investment and implementation of comprehensive control strategies are required to prevent complications and mortality.

Abbreviations

ARF: acute rheumatic fever
CHF: congestive heart failure
RHD: rheumatic heart disease

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Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.
REFERENCES


TABLE 1 – Characteristics of participant groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Screening-detected</th>
<th>Screen-negative</th>
<th>Clinically-diagnosed</th>
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<tr>
<td>Median age at screening / diagnosis (IQR), yrs</td>
<td>10.9 (8.7, 12.4)</td>
<td>10.9 (8.8, 12.6)</td>
<td>10.9 (8.8, 12.9)</td>
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<td>Median age at end of study (IQR), yrs</td>
<td>17.6 (13.1, 20.1)</td>
<td>17.6 (13.1, 20.2)</td>
<td>17.8 (14.6, 20.2)</td>
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<td>Median length of observation (IQR), yrs</td>
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<td>7.4 (6.9, 8.9)</td>
<td>7.0 (5.1, 8.8)</td>
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<td>Sex – n (%)</td>
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<td>Male</td>
<td>22 (31.4)</td>
<td>22 (31.4)</td>
<td>22 (31.4)</td>
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<tr>
<td>Female</td>
<td>48 (68.6)</td>
<td>48 (68.6)</td>
<td>48 (68.6)</td>
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<td>iTaukei</td>
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<td>60 (85.1)</td>
<td>59 (84.3)</td>
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<td>Fijian of Indian Descent</td>
<td>10 (14.3)</td>
<td>10 (14.3)</td>
<td>10 (14.3)</td>
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<td>Other</td>
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<td>Total</td>
<td>70</td>
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TABLE 2 – Clinical outcomes of screening-detected RHD patients in comparison to screen-negative and clinically-diagnosed groups

<table>
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<tr>
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<th>Screening-detected (n = 70)</th>
<th>Screen-negative (n= 70)</th>
<th>Clinically-diagnosed (n = 70)</th>
<th>Incident Rate Ratio, screening-detected vs screen-negative (95% CI)</th>
<th>Incident Rate Ratio, clinically-diagnosed vs screening-detected (95% CI)</th>
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<td><strong>Health care interactions</strong></td>
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<tr>
<td>Total observation, p-y</td>
<td>468.2</td>
<td>476.1</td>
<td>439.1</td>
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<td>Admissions, n</td>
<td>28</td>
<td>4</td>
<td>113</td>
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<td>Admissions per 1000 p-y</td>
<td>59.8</td>
<td>8.4</td>
<td>257.4</td>
<td>7.1 (2.5, 27.9)</td>
<td>4.3 (2.8, 6.8)</td>
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<td>Admission bed days</td>
<td>172</td>
<td>47</td>
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<td>Admission bed days per 1000 p-y</td>
<td>367.3</td>
<td>98.7</td>
<td>2434.6</td>
<td>3.7 (2.7, 5.3)</td>
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<td>0</td>
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<td>34.2</td>
<td>0</td>
<td>177.6</td>
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<td>Surgery per 1000 p-y</td>
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<td>2.1</td>
<td>63.8</td>
<td>4.1 (0.4, 200.3)</td>
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<td>Surgery, RHD-related per 1000 p-y</td>
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<td>0</td>
<td>41.0</td>
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<td>6.4 (1.8, 33.9)</td>
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<td>34 (48.6)</td>
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<td>Any complication, n (%)</td>
<td>14 (20.0)</td>
<td>1 (1.4)</td>
<td>39 (55.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any complication per 1000 p-y</td>
<td>29.9</td>
<td>2.1</td>
<td>88.8</td>
<td>14.2 (2.2, 601.9)</td>
<td>3.0 (1.6, 5.9)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>2 (2.9)</td>
<td>0</td>
<td>9 (12.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality per 1000 p-y</td>
<td>4.3</td>
<td>0</td>
<td>20.5</td>
<td>--</td>
<td>4.8 (1.0, 45.6)</td>
</tr>
<tr>
<td>Mortality, RHD-related, n (%)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>9 (12.9)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Mortality, RHD-related per 1000 p-y</td>
<td>2.1</td>
<td>0</td>
<td>20.5</td>
<td>--</td>
<td>9.6 (1.3, 420.6)</td>
</tr>
</tbody>
</table>
p-y, person-years; RHD, rheumatic heart disease; ARF, acute rheumatic fever
APPENDIX

TABLE A.1 – Clinical outcomes by diagnosis and sex.

<table>
<thead>
<tr>
<th></th>
<th>Screening-detected</th>
<th>Screen-negative</th>
<th>Clinically-diagnosed</th>
<th>IRR clinically-diagnosed vs screening-detected (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants – n (observation p-y)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (152.0)</td>
<td>22 (152.0)</td>
<td>22 (147.1)</td>
<td></td>
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<tr>
<td>Female</td>
<td>48 (316.2)</td>
<td>48 (324.1)</td>
<td>48 (292.0)</td>
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</tr>
<tr>
<td><strong>Complications – n (per 1000 p-y)</strong></td>
<td>14 (29.9)</td>
<td>1 (2.1)</td>
<td>39 (88.8)</td>
<td>3.0 (1.6, 5.9)</td>
</tr>
<tr>
<td>Male</td>
<td>7 (46.1)</td>
<td>0</td>
<td>12 (81.6)</td>
<td>1.8 (0.6, 5.3)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (22.1)</td>
<td>1 (3.1)</td>
<td>27 (92.5)</td>
<td>4.2 (1.8, 11.4)</td>
</tr>
<tr>
<td><strong>Mortality – n (per 1000 p-y)</strong></td>
<td>2 (4.3)</td>
<td>0</td>
<td>9 (20.5)</td>
<td>4.8 (1.0, 45.6)</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>2 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (6.3)</td>
<td>0</td>
<td>7 (24.0)</td>
<td>3.8 (0.7, 37.4)</td>
</tr>
</tbody>
</table>

IRR, Incident Rate Ratio; p-y, person-years.
FIGURE LEGEND

Fig 1. Cumulative RHD complications by cohort group

Fig 2. Cumulative mortality by cohort group
Fig. 1
Fig. 2