Acute Rheumatic Fever and Rheumatic Heart Disease
Incidence and Progression in the Northern Territory of Australia, 1997 to 2010

Joanna G. Lawrence, BHB, MBCHB, FRACP; Jonathan R. Carapetis, MBBS, FRACP, PhD; Kalinda Griffiths, BBMSci, MPH; Keith Edwards, MBBS, DCH, FRCP(Edin), FRCPCFRACP; John R. Condon, FAFPHM, PhD

Background—Although acute rheumatic fever (ARF) and its sequel, rheumatic heart disease (RHD), continue to cause a large burden of morbidity and mortality in disadvantaged populations, most studies investigating the effectiveness of control programs date from the 1950s. A control program, including a disease register, in the Northern Territory of Australia where the Indigenous population has high rates of ARF and RHD allowed us to examine current disease incidence and progression.

Methods and Results—ARF and RHD incidence rates, ARF recurrence rates, progression rates from ARF to RHD to heart failure, and RHD survival and mortality rates were calculated for Northern Territory residents from 1997 to 2010. For Indigenous people, ARF incidence was highest in the 5- to 14-year age group (males, 162 per 100,000; females, 228 per 100,000). There was little evidence that the incidence of ARF or RHD had declined. The ARF recurrence rate declined by 9% per year after diagnosis. After a first ARF diagnosis, 61% developed RHD within 10 years. After RHD diagnosis, 27% developed heart failure within 5 years. For Indigenous RHD patients, the relative survival rate was 88.4% at 10 years after diagnosis and the standardized mortality ratio was 1.56 (95% confidence interval, 1.23–1.96).

Conclusions—For Indigenous Australians in the Northern Territory, ARF and RHD incidence and associated mortality remain very high. The reduction in ARF recurrence indicates that the RHD control program has improved secondary prophylaxis; a decline in RHD incidence is expected to follow. (Circulation. 2013;128:492-501.)

Key Words: Australia | incidence | recurrence | rheumatic fever | rheumatic heart disease

Clinical Perspective on p 501

Acute rheumatic fever (ARF) is an autoimmune phenomenon that occurs after infection with group A streptococcus. Inflammation of the joints, heart, and brain results in the common clinical manifestations of arthritis, carditis, and chorea. Although now rare in developed countries, ARF maintains a noteworthy presence in economically disadvantaged populations, driven by factors that include household overcrowding and poor hygiene.1 The major morbidity and mortality result from cardiac involvement known as rheumatic heart disease (RHD).

Despite causing a large burden of disease globally, the morbidity and mortality relating to ARF remain poorly understood. The most comprehensive longitudinal study addressing disease progression dates from 1965, almost half a century ago.3 In 2005, only 1 country in which RHD occurs at high rates (New Zealand) was thought to have reliable cause-specific mortality data relating to RHD.4 Similarly, little is known of the morbidity resulting from cardiac involvement or the time course of disease progression from ARF to RHD and heart failure. A large burden of disease exists in developing countries, where there is little scope for detailed epidemiological analysis.5 However, in some high-income countries, there are population groups that live in poverty and have high rates of ARF and RHD, including the Indigenous populations of northern and central Australia and New Zealand. Longitudinal studies in these populations will give insights into morbidity and mortality that may be extrapolated to low- and middle-income countries, albeit with appropriate adjustment for rates of disease and access to medical care.
The Aboriginal population living in the Northern Territory (NT) of Australia has the highest documented incidence rate of ARF in the world. Since the NT RHD Control Program established a computerized register in 1997, all known cases of ARF (including recurrent episodes) and RHD in the NT have been recorded. The register is used by RHD program coordinators to collect demographic data, to send reminders for secondary prophylaxis, and to facilitate specialist clinical care. This confidential password-protected database covers a population of >225,000 people scattered over an area of 1,346,000 km² ranging from coastal tropics in the north to desert in the south. Of this population, ≈64,000 (30%) are Indigenous (Aboriginal or Torres Strait Islander), the majority of whom live in small, very isolated remote communities characterized by poor-quality, overcrowded housing and widespread poverty.

There are currently ≈2500 people recorded on the register, and the RHD Control Program staff members consider that since 1997 the register has been almost complete (i.e., contains almost all people diagnosed with ARF or RHD) with incomplete data on cases for several years before that. These data have been used to date to report predominantly on the incidence of ARF and prevalence of RHD, not to look at longitudinal outcomes. The data collected offered an opportunity to explore the epidemiology, mortality, and morbidity of ARF and RHD in a population with very high rates of disease.

Methods

The NT RHD register includes data on patient demographics and diagnoses, clinical features of ARF episodes, reviews by doctors, and secondary prophylaxis administration. Deidentified data were extracted from the register in May 2011, assessed for data quality, and analyzed with STATA software (STATA Corp, College Station, TX). The study was approved by the Human Research Ethics Committee of the NT Department of Health and the Menzies School of Health Research. Access to register data was approved by the RHD Steering Committee and the register’s data custodian. No contact with registered patients was required.

Data Quality Assessment and Exclusions

People registered with a diagnosis of unconfirmed ARF or RHD and those with no diagnosis at all were excluded, as were people with missing demographic data such as sex and Indigenous status. Diagnosis and clinical review data were analyzed for inconsistencies (such as clinical reviews for RHD before the RHD diagnosis date); inconsistent data were resolved when possible, or the cases were excluded (see Results for details).

The study population was defined as NT residents who were registered with a confirmed first ARF episode or RHD diagnosis occurring between January 1, 1997, and December 31, 2010. In the NT, the diagnosis of ARF was based on the 1992 updated Jones criteria until the 2005 Australian guidelines became available. RHD was diagnosed by specialist physicians and confirmed by echocardiography. A first episode of ARF was defined as an ARF episode within the study period when there was no previous record of an ARF or RHD diagnosis. An ARF recurrence was defined as a second or subsequent ARF episode occurring in a person with a first ARF episode in the study period. Only recurrences in those who presented with RHD, presumed to have a missed first episode of ARF, were used (i.e., subsequent episodes of ARF in those who first presented with RHD, presumed to have a missed first episode of ARF, were not included) to allow measurement of time to recurrence. The date of diagnosis of RHD was defined as the date of diagnosis recorded on the register unless there were clinical reviews for RHD before the recorded diagnosis date, in which case the date of first review was used as a surrogate.

Statistical Analysis

Univariate and multivariate analyses of several outcome measures were performed, most stratified by sex, age at diagnosis, and year of diagnosis. The following outcome measures were analyzed:

1. Demographic characteristics of people diagnosed with ARF or RHD.
2. Clinical manifestations of ARF, restricted to first ARF episodes between October 2, 2007, and December 31, 2010, because recording of clinical manifestations was incomplete before 2007.
3. Age-specific and age-adjusted incidence rates for first ARF episode, total ARF episodes, and RHD diagnosis.
4. Negative binomial regression analysis of ARF and RHD incidence. Independent variables were Indigenous status, sex, age at diagnosis, and year of diagnosis. The model for RHD incidence also included an interaction term for Indigenous status by age at diagnosis because the effect of age was found to be different for Indigenous and non-Indigenous people. Negative binomial regression was used because incidence data were found to be overdispersed.
6. Rate of ARF recurrence after a first ARF episode in people diagnosed with their first ARF episode between January 1, 1997, and December 31, 2010, calculated as the number of second ARF episodes per 100 person-years.
7. Rate of progression from ARF to RHD. Proportional hazards regression analysis was performed of the incidence of RHD in people who had a first ARF episode between January 1, 1997, and December 31, 2010; independent variables were Indigenous status, sex, age at diagnosis, year of diagnosis, and presence of chorea at the first ARF episode.
8. Rate of progression from RHD to heart failure. Proportional hazards regression analysis was performed of the incidence of heart failure in people diagnosed with RHD between January 1, 2004, and December 31, 2010. Independent variables were Indigenous status, sex, age at diagnosis, and year of diagnosis.
9. Relative survival rate and standardized mortality ratio for people diagnosed with RHD in 1997 to 2010, which measure excess mortality resulting from RHD.

For measures 6 through 8, the follow-up time was censored at the earliest of the following: date of diagnosis (of second ARF episode, RHD, or heart failure, respectively), date of death, or December 31, 2010. Since 2004, the NT RHD Control Program has classified severity of carditis to guide appropriate medical follow-up. Patients are classified as priority 1 if they have established RHD with severe valve lesions; moderate to severe valve lesions with impaired left ventricular function; increased left ventricular size; shortness of breath, tiredness, edema, angina, or syncope; or any surgical intervention on their valves. We used the date of classification as priority 1 to indicate the date of diagnosis of heart failure. Analysis of progression to heart failure was restricted to the 645 cases of RHD diagnosed since the priority classification was introduced.

Relative survival analysis was used to estimate mortality caused by RHD because cause-of-death data were not available for cause-specific analysis and because a comparison cohort of people without RHD was not available for comparison of all-cause mortality in people with and without disease. Relative survival estimates mortality resulting from RHD by comparing the observed with the expected all-cause mortality rate for the RHD cohort; the expected rate is based on general population all-cause mortality rates matched by age, sex, year, and Indigenous status. Relative survival rates and standardized mortality ratios were calculated by the method described by Dickman et al using the “strs” commands in STATA.
Life tables for the total Australian population were used to calculate expected probability of death (by age, sex, and year) for non-Indigenous cases. Life tables for the total NT Indigenous population (by age, sex, and year) were calculated from NT Indigenous population mortality rates.

The number of non-Indigenous subjects was small (eg, only 15 of 615 first ARF episodes), so comparisons of Indigenous with non-Indigenous subjects were limited; for some outcome measures, multivariate analyses were restricted to Indigenous cases only. The estimated resident population of the NT by 5-year age group, sex, Indigenous status, and year as published by the Australian Bureau of Statistics was used as the denominator for calculation of population-based incidence rates.

Results

Data Quality Assessment and Exclusions

The register contained information on 2837 individuals with a total of 3920 diagnoses and 20890 clinical contacts. Eighty-four people were documented as having an RHD diagnosis date before the date of their first ARF episode. The first ARF diagnosis date was changed to the RHD diagnosis date if the difference was <30 days (29 subjects) and otherwise excluded from analysis of first ARF episode on the basis that this was unlikely to have been their first presentation (55 subjects).

In addition, 1170 diagnoses were excluded due to lack of identifying information (19), diagnosis not confirmed (443) or diagnoses made outside the study period (708). A further 673 individuals were excluded because they had no diagnosis details (528), lived interstate (141) or had missing data on Indigenous status (1) or gender (3), leaving 1465 individuals in the analysis data set (Figure 1).

The final data set included a total of 1465 subjects with 1149 diagnoses of RHD and 615 first diagnoses of ARF between January 1, 1997, and December 31, 2010.

Table 1. Demographic Characteristics of ARF and RHD Cases, NT, 1997 to 2010

<table>
<thead>
<tr>
<th></th>
<th>ARF</th>
<th>RHD</th>
<th></th>
<th>ARF</th>
<th>RHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indigenous</td>
<td>Non-Indigenous</td>
<td>Indigenous</td>
<td>Non-Indigenous</td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>600</td>
<td>15</td>
<td>1066</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>58.5</td>
<td>60.0</td>
<td>65.8</td>
<td>71.1</td>
<td></td>
</tr>
<tr>
<td>Age group at diagnosis, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 y</td>
<td>2.7</td>
<td>0.0</td>
<td>1.4</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>5–9 y</td>
<td>27.2</td>
<td>13.3</td>
<td>11.3</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>10–14 y</td>
<td>36.8</td>
<td>26.7</td>
<td>18.5</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>15–24 y</td>
<td>19.7</td>
<td>20.0</td>
<td>23.4</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>25–34 y</td>
<td>8.7</td>
<td>13.3</td>
<td>18.4</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>≥45 y</td>
<td>1.2</td>
<td>0.0</td>
<td>13.9</td>
<td>62.7</td>
<td></td>
</tr>
<tr>
<td>Median age at diagnosis, y</td>
<td>12</td>
<td>18</td>
<td>22</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Year of diagnosis, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997–2000</td>
<td>22.7</td>
<td>46.7</td>
<td>20.6</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>2001–2005</td>
<td>42.5</td>
<td>20.0</td>
<td>44.7</td>
<td>63.9</td>
<td></td>
</tr>
<tr>
<td>2006–2010</td>
<td>34.8</td>
<td>33.3</td>
<td>34.6</td>
<td>18.1</td>
<td></td>
</tr>
</tbody>
</table>

ARF indicates acute rheumatic fever; NT, Northern Territory; and RHD, rheumatic heart disease.

Acute Rheumatic Fever

Of the 615 people with a first episode of ARF between 1997 and 2010, 600 (97.6%) were Indigenous (Table 1). The proportion of female subjects was similar for Indigenous and non-Indigenous cases. The median age of first presentation was 12 years for Indigenous subjects regardless of sex. Non-Indigenous cases were older by 6 years for males (median age, 18 years) and 3 years for females (median age, 15 years). The incidence of first ARF episode was highest in the 5- to 14-year age group for both Indigenous and non-Indigenous people (Figure 2). The incidence rate in Indigenous people 5 to 14 years of age was 194 per 100 000 overall.
162 in males, and 228 in females. The incidence in non-Indigenous people was much lower in all age groups than for Indigenous people.

In multivariate analysis, the incidence of first ARF episode was 69 times higher for Indigenous than non-Indigenous people, adjusted for age, sex, and year of diagnosis (Table 2); however, this is not a precise estimate because of the low number of non-Indigenous cases (the lower bound of the confidence interval [CI] being a 40-fold increased risk).

In analysis restricted to Indigenous people only, ARF incidence was 49% higher in females than in males, and there was no evidence of a decrease in incidence between 1997 and 2010 (Table 2).

Clinical Manifestations at the First Diagnosis of ARF

One hundred forty-nine people were registered with their first episode of ARF between October 2, 2007 (when the register began uniform collection of data on clinical manifestations of ARF), and December 31, 2010. Of the major manifestations, joint involvement was the most common presenting feature, recorded in 77% of the total presentations (Table 3). Among those with joint involvement, 63.5% had polyarthritis, 7.0% had polyarthritis, and 29.6% had monoarthritis, the last 2 considered major manifestations in high-risk populations in Australia. Carditis was present in 27.5% and chorea in 19.5%. Because the rates of carditis were much lower than expected, a subgroup analysis was performed. Rates of carditis were found to be significantly lower (14.6%) in a subgroup in whom diagnosis was based on chorea or less stringent criteria for arthritis (ie, monoarthritis or arthralgia). In the subgroup with more classic features, carditis was present in a higher proportion (43.3%). The most common minor manifestation was a rise in inflammatory markers (74%). Fever was present in 53%.

Chorea

Twenty-nine of the 149 patients (19.5%) diagnosed after October 2, 2007, had chorea as a manifestation of their first ARF episode. Chorea was a more common manifestation of a first ARF episode in female (22 of 88, 25%) than male (7 of 61, 11%) patients and in those <20 years of age (28 of 123, 23%) than those ≥20 years of age (1 of 26, 4%). In multivariate logistic regression analysis (adjusted for diagnosis age [<20 or ≥20 years], sex, and diagnosis year), the associations with age (odds ratio, 0.90; 95% CI, 0.81–0.99) and sex (odds ratio, 3.21; 95% CI, 1.2–8.4) were significant.

Those with chorea were less likely to have concurrent arthritis (31% versus 88%), raised inflammatory markers (38% versus 83%), or fever (21% versus 29%). Rates of carditis in the initial episode were similar; of those with chorea, 49.5% were documented as developing RHD sometime during the study period compared with 51.5% of nonchorea patients. Evidence of the development of heart failure was less likely in chorea patients (3.7%) compared with nonchorea patients (26.4%).

Rheumatic Heart Disease

There were 1149 people registered as having been diagnosed with RHD between 1997 and 2010, 1066 of whom (92.8%) were Indigenous and 756 (65.8%) were female (Table 1). Male patients presented at a younger age than female patients, and Indigenous patients were much younger (male patients, 19 years; female patients, 23 years) at diagnosis than non-Indigenous patients (male patients, 46.5 years; female patients, 51 years).

Table 2. Multivariate Analysis of ARF Incidence, NT, 1997 to 2010

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>Indigenous Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>P Value</td>
</tr>
<tr>
<td>Indigenous status</td>
<td>68.82</td>
<td>0.000</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.50</td>
<td>0.004</td>
</tr>
<tr>
<td>Age</td>
<td>0.95</td>
<td>0.00</td>
</tr>
<tr>
<td>Year</td>
<td>0.98</td>
<td>0.497</td>
</tr>
</tbody>
</table>

ARF indicates acute rheumatic fever; CI, confidence interval; IRR, incidence rate ratio; NA, not applicable; and NT, Northern Territory.
Figure 3 shows an increasing prevalence of RHD among the Indigenous population with time. However, 71% of RHD cases recorded on the register were diagnosed after the register began (1997–2010), 25% of whom were ≥40 years of age when diagnosed. This indicates that although efforts were made to collect data on cases diagnosed before 1997, data collection was incomplete then. The lower prevalence in 2000 and 2005 is therefore due at least in part to the more recent diagnosis of long-standing RHD cases. In 2010, the peak prevalence was in the 45- to 64-year age group (3.1%).

For the NT Indigenous population, RHD incidence was highest in the 5- to 14-year age group for males and in the 15- to 24-year age group for females and was higher for females than males in all age groups except those ≥65 years of age (Figure 4). For the non-Indigenous population, the incidence rate was highest in the oldest age group and was much lower in all age groups than for Indigenous people.

In multivariate analysis, RHD incidence was 64 times higher for Indigenous than non-Indigenous people, adjusted for age, sex, and year of diagnosis (Table 4), with the lower bound of the CI being a 43-fold increased risk. The RHD incidence for female patients was almost twice that for male patients.

**Recurrences of ARF**

There were 846 total episodes of ARF registered in 1997 to 2010. This includes 94 recurrent episodes in 77 of the 615 people who had their first episode in that period. Sixteen of these 77 had ≥2 recurrences. The recurrence rate was highest in the first year after the first ARF episode and decreased to 0 by 10 years after the first episode (Figure 5). Among Indigenous people, the recurrence rate in the first year after diagnosis was 4.5% and the 5-year recurrence rate was 12.5%. In multivariate analysis, the recurrence rate decreased by 9%/y after the date of diagnosis of the first episode (Table 5). The recurrence rate also decreased with older age at initial presentation (by 7% per year of age). Although the point estimates suggested a possible association of female sex and Indigenous status with recurrence rate, the CIs for both of these associations included 1.0.

**Disease Progression**

**ARF to RHD**

In multivariate analysis, the only factor strongly associated with RHD incidence was age at first ARF episode (risk decreased by 2% per year of age; Table 6). There was a suggestion that the risk of developing RHD after an ARF diagnosis was higher for Indigenous than non-Indigenous people and for female than male patients, but the CIs for both hazard ratios included 1.0. Among Indigenous subjects, 35% developed RHD by 2 year after the first ARF episode and 61% by 10 years (Figure 6).

**RHD to Heart Failure**

Overall, 28% of those diagnosed with RHD developed heart failure at some stage between diagnosis and the end of the study period (December 31, 2010). Fourteen percent had heart failure at diagnosis. This increased to 21% at 1 year after diagnosis and 27% at 5 years after diagnosis (Figure 6). In multivariate analysis, there was little or no evidence of an

---

**Table 3. Clinical Manifestations at Initial Presentation of ARF, NT, 2007 to 2010**

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carditis</td>
<td>41</td>
<td>27.5</td>
</tr>
<tr>
<td>Chorea</td>
<td>29</td>
<td>19.5</td>
</tr>
<tr>
<td>Joint manifestations</td>
<td>115</td>
<td>77.2</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Monoarthritis</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Polyarthralgia</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised inflammatory markers (ESR/CRP)</td>
<td>110</td>
<td>73.8</td>
</tr>
<tr>
<td>Prolonged PR interval on ECG</td>
<td>41</td>
<td>27.5</td>
</tr>
<tr>
<td>Fever</td>
<td>79</td>
<td>53</td>
</tr>
<tr>
<td><strong>Total people, n</strong></td>
<td>149</td>
<td>100.0</td>
</tr>
</tbody>
</table>

ARF indicates acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; and NT, Northern Territory.
association between Indigenous status, sex, age at diagnosis, or year of diagnosis and risk of developing heart failure (Table 7).

**Mortality**

During 1997 to 2010, 79 individuals (6.9%) from the cohort diagnosed with RHD (1149 subjects) died: 3 non-Indigenous (3.6% of non-Indigenous cases) with a median age of 51 years and 76 Indigenous (7.1% of Indigenous cases) with a median age of 22 years.

There was no excess mortality from RHD among non-Indigenous cases relative to the general population of the NT of the same age and sex; relative survival was >100% at 5, 10, and 14 years after diagnosis.

Among the Indigenous cohort, the crude all-cause survival rate was 96.1% at 5 years after diagnosis and 88.4% at 10 years after diagnosis. The relative survival rate for Indigenous cases (ie, survival rate of Indigenous people with RHD compared with the total Indigenous population) was 98.9% at 5 years (95% CI, 97.4–100.1) but lower thereafter: 95.3% at 10 years (95% CI, 92.3–97.8) and 90.5% at 14 years (95% CI, 83.9–95.6). This indicates that Indigenous RHD patients suffer little if any excess mortality compared with the general NT Indigenous population in the first 5 years after their RHD diagnosis but suffer considerable excess mortality in subsequent years. This is consistent with the all-cause death rates of Indigenous RHD cases that increase with time after diagnosis, particularly >4 years after diagnosis (Figure 7).

Among Indigenous people diagnosed during or after 2004 (when the clinical priority classification was introduced), those with a first clinical assessment of severe disease had a 5-year relative survival rate of 89.7% (95% CI, 79.5–95.8), whereas those assessed as having moderate, mild, or inactive disease had a 5-year survival close to 100% (95% CI, 99.6–103.7).

The standardized mortality ratio among Indigenous cases was 1.56 (95% CI, 1.23–1.96), indicating that the number of deaths was 56% higher than expected compared with the NT Indigenous population, whereas for non-Indigenous cases, the standardized mortality ratio was 0.63 (95% CI, 0.13–1.85), which is consistent with their relative survival rates >100%.

**Discussion**

This is the first time that longitudinal data collected from an RHD registry have been used to evaluate disease burden and patterns of disease evolution in a high-incidence population. This audit demonstrates that the incidence rate and at-risk population for first episode of ARF have not changed significantly over the past 14 years. Those most at risk continue to be Indigenous children 5 to 14 years of age.

The incidence rates of first episodes of ARF reported here in Indigenous 5- to 14-year-olds (228 and 162 per 100 000 in girls and boys, respectively) are similar to previously documented rates of 250 to 300 per 100 000 in the same population.6,10 The slightly lower rates found in this audit are most likely attributable to the fact that we included only first episodes (whereas the previous study included all episodes) and to our strict inclusion criteria that resulted in the exclusion of a number of documented cases with insufficient diagnostic

---

**Table 4. Multivariate Analysis of RHD Incidence, NT, 1997 to 2010**

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th></th>
<th>Indigenous Only</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>P Value</td>
<td>95% CI</td>
<td>IRR</td>
</tr>
<tr>
<td>Indigenous status</td>
<td>63.65</td>
<td>&lt;0.01</td>
<td>43.0–94.2</td>
<td>NA</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.94</td>
<td>&lt;0.01</td>
<td>1.64–2.32</td>
<td>1.84</td>
</tr>
<tr>
<td>Age at diagnosis*</td>
<td>1.05</td>
<td>&lt;0.01</td>
<td>1.03–1.06</td>
<td>1.00</td>
</tr>
<tr>
<td>Year*</td>
<td>1.00</td>
<td>0.81</td>
<td>0.98–1.02</td>
<td>1.00</td>
</tr>
<tr>
<td>Indigenous by age</td>
<td>0.95</td>
<td>&lt;0.01</td>
<td>0.94–0.97</td>
<td>NA</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; IRR, incidence rate ratio; NA, not applicable; NT, Northern Territory; and RHD, rheumatic heart disease. *IRR for a 1-year increase.
information either recorded or present (the latter represents possible ARF).

It is unlikely that increased awareness and notification are responsible for the ongoing high rates of ARF in this population because the disease became notifiable in the NT in 1996 (before this study period) and campaigns to increase awareness have been present since World Health Organization recommendations in 1994. The more recent broadening of the definition of joint involvement, with the inclusion of polyarthralgia and monoarthritis in the diagnostic criteria and the inclusion of subclinical carditis, may account for increased numbers of diagnoses. However, it is likely that the rates remain high because of a failure to adequately address the socioeconomic determinants of health driving the high rates of infection in our remote Indigenous population. This therefore remains a significant public health concern worthy of further attention.

RHD has a demographic profile similar to that of ARF, with higher incidences occurring in the Indigenous population, females, and those living remotely. No decrease in incidence of RHD was demonstrated over the past 14 years. Because there was incomplete recording of cases before the register began in 1997, there has been a continual increase in prevalence as a result of the steady incidence of new cases combined with the long duration of incident cases. With the completeness of data collection over this period, the recent prevalence rates are likely to be nearing the true prevalence of disease in this population. Our reported prevalence rates, with a peak of 3.1% in the 45- to 64-year-old group, are consistent with previously reported rates in the NT. Because efforts to reduce recurrence rates of ARF appear to be having an effect and because the persistently high incidence of ARF may be explained partly by the recent inclusion of milder cases with a lower incidence of clinical carditis (as a result of the expansion of the diagnostic criteria to include subclinical carditis, monoarthritis, and polyarthralgia as major manifestations), the incidence of RHD can be expected to decline in coming years.

Females were 1.5 times more likely to present with ARF and significantly more likely to develop RHD. An increased risk of RHD in females has been found in almost all populations. Interestingly, females were less likely than males to have a recurrence, which may relate to willingness to receive medical care, including secondary prophylaxis. This suggests that sex susceptibility may be related to either an innate predilection for cardiac damage or a greater risk of exposure to group A streptococcus (because females tend to be more involved in child rearing) rather than limited access to prevention.

Although cases of ARF may be mild or even asymptomatic, ongoing presentations with RHD in the absence of a history of ARF suggest that detection, accurate diagnosis, and notification of ARF remain suboptimal. Contributing factors may include lack of training or awareness among health staff, transient health professional staffing in remote areas, poor access to medical services, and lack of health service use because of many factors, including inadequate cultural safety.

The most promising finding of this audit was the evidence of a reduction in the recurrence rate by 9%/y since 1997. This

---

Table 5. Recurrence of ARF: Multivariate Analysis of Recurrence Rate, NT, 1997 to 2010

<table>
<thead>
<tr>
<th>Hazard Ratio*</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous status</td>
<td>1.92</td>
<td>0.52</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.79</td>
<td>0.30</td>
</tr>
<tr>
<td>Age at first ARF episode†</td>
<td>0.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Year</td>
<td>0.91</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Proportional hazard regression.
†Per single year.

Table 6. Progression to RHD: Multivariate Analysis of Incidence of RHD After a First Episode of ARF, NT, 1997 to 2010

<table>
<thead>
<tr>
<th>Hazard Ratio*</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous status</td>
<td>1.54</td>
<td>0.34</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.19</td>
<td>0.13</td>
</tr>
<tr>
<td>Age at first ARF episode‡</td>
<td>0.98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Year</td>
<td>1.03</td>
<td>0.10</td>
</tr>
<tr>
<td>Chorea‡</td>
<td>0.85</td>
<td>0.29</td>
</tr>
</tbody>
</table>

ARF indicates acute rheumatic fever; CI, confidence interval; NT, Northern Territory; and RHD, rheumatic heart disease.

*Proportional hazard regression.
‡Presence of chorea as a clinical manifestation at the first ARF episode

---

Figure 5. Acute rheumatic fever (ARF) recurrence rate by time since the first episode. Rate is the number of recurrences per 100 person-years after a first ARF episode in 1997 to 2010 with 95% confidence interval.

Figure 6. Progression of acute rheumatic fever (ARF) to rheumatic heart disease (RHD) and cardiac failure among Indigenous subjects.
suggests that primary healthcare services in the NT, with support from the NT RHD Control Program, are having success in improving the delivery of secondary prophylaxis.

The true number of ARF recurrences is larger than measured in our study because only recurrences among those presenting with a first episode of ARF since 1997 were included (therefore missing recurrences in those diagnosed with ARF before 1997 or whose first presentation was RHD). This definition was required to analyze time between episode and recurrence but is likely to underestimate the total burden of recurrences.

World Health Organization recommendations on the duration of secondary prophylaxis are based on old studies, with no recent data on recurrence rates related to age or duration since the last ARF episode. Our finding of high rates of recurrence in the first year after diagnosis (4.5%) reducing to 0 by 10 years supports the current Australian guidelines for administering prophylaxis for a minimum duration of 10 years in those without severe carditis. Moreover, we demonstrated that recurrence rates are highest in the first 3 to 4 years after diagnosis, suggesting that secondary prophylaxis efforts should concentrate on this critical period. We also found that recurrences are more common in younger patients, supporting for now the Australian recommendation of continuing prophylaxis until a minimum of 21 years of age even in those diagnosed at a very young age. At present, our data are not strong enough to determine whether these young patients retain an elevated risk of recurrence after 10 years (eg, between 15 and 21 years of age in those whose first episode occurred at 5 years of age); ongoing data collection will allow us to re-evaluate this recommendation in coming years. Because compliance in adolescence is often problematic, this would be an important consideration.

World Health Organization recommendations on the duration of secondary prophylaxis are based on old studies, with no recent data on recurrence rates related to age or duration since the last ARF episode. Our finding of high rates of recurrence in the first year after diagnosis (4.5%) reducing to 0 by 10 years supports the current Australian guidelines for administering prophylaxis for a minimum duration of 10 years in those without severe carditis. Moreover, we demonstrated that recurrence rates are highest in the first 3 to 4 years after diagnosis, suggesting that secondary prophylaxis efforts should concentrate on this critical period. We also found that recurrences are more common in younger patients, supporting for now the Australian recommendation of continuing prophylaxis until a minimum of 21 years of age even in those diagnosed at a very young age. At present, our data are not strong enough to determine whether these young patients retain an elevated risk of recurrence after 10 years (eg, between 15 and 21 years of age in those whose first episode occurred at 5 years of age); ongoing data collection will allow us to re-evaluate this recommendation in coming years. Because compliance in adolescence is often problematic, this would be an important consideration.

The 2005 Australian guidelines were used for prioritization and follow-up. These guidelines and the 2012 updated version outline the importance of echocardiography in routine clinical care for RHD, particularly in Aboriginal people living in remote areas of Australia. Because history taking in this population is often impaired by cultural and language barriers, the use of echocardiography allows more accurate monitoring of the progression of valvular disease and the detection of severely affected patients to be targeted for intervention.

Of those with ARF, 35% developed RHD within 1 year and 61% developed RHD by 10 years. Although some of these cases with delayed development of RHD may represent natural evolution of initial mild or subclinical cardiac damage, most are likely attributable to ARF recurrences causing cumulative heart valve damage. The risk of developing RHD decreased with time since diagnosis and with older age at initial diagnosis. These data provide further evidence that secondary prophylaxis is critical and that, although important in all patients, enhanced efforts are needed to deliver secondary prophylaxis in younger patients and in the initial few years after diagnosis of ARF.

Heart failure developed in 28% of RHD cases, half of which was present at diagnosis, with almost all of the remaining cases presenting within 5 years. To the best of our knowledge, these are the only recent data on this most important clinical manifestation of ARF or RHD. Validating these data with ongoing surveillance and in other populations is essential because they are critical for informing estimates of disability caused by ARF and RHD. Reassuringly, compared with older natural history studies from the 1950s, when almost one third of children died in the 2 decades after diagnosis, morbidity and mortality appear to be much improved.

Patients were reviewed and offered medical and surgical treatment as required. Although the data analyzed for this report did not allow us to quantify access to or acceptance of medical care, others have found many barriers to Aboriginal people receiving optimal medical and surgical care for chronic diseases, related to healthcare systems, remoteness, and cultural factors. In the case of RHD, there is the added complication that cardiac surgery is not available in the NT, so surgical intervention involves travel to cities many thousands of kilometers away. If outcomes for RHD are to be improved in similar settings, healthcare services must improve the capacity of the health workforce, the availability of specialist care, the systems for delivering care to patients with complex, chronic diseases, and the mechanisms to address cultural impediments to uptake of Western medical care.

The burden of mortality is likely to be underestimated owing to the limitation of our study period (14 years). Among the Indigenous cohort, relative survival rate decreased with time since diagnosis. With longer follow-up, this may become even more pronounced. The excess mortality was calculated to be 56% higher among those with RHD compared with unaffected individuals of the same age and sex. These results confirm the large burden of mortality associated with RHD among Indigenous
NT residents and highlight the progressive nature of the disease. RHD is likely to play a significant causative role in this excess mortality, as demonstrated in other studies.24,25 Because mortality resulting from RHD should be preventable through secondary prophylaxis and better clinical care, these data reinforce the importance of treatment and prevention programs for RHD in this population. The non-Indigenous cohort, consisting predominantly of older individuals with most likely long-standing RHD, was too small to suggest any significant trends.

Although the clinical presentation of ARF in the NT has many similarities to classic descriptions over the past half-century,26–28 there are some striking differences. Joint manifestations were the most common manifestation (77% of cases, similar to reported rates of 65% to 85%),29 but we found that more than a third of these (23% of all cases) had monoarthritis. This has been reported previously in a retrospective case series in the NT,30 in other parts of Australia,31 and in the Pacific.32 Our data support the inclusion of monoarthritis as a major manifestation in ARF diagnostic criteria, as has been the case in Australia since 2006.32

We also found a remarkably low proportion of cases (28%) with documented carditis. This is substantially lower than previously reported in the NT30 and in other studies from different parts of the world, which uniformly report rates of 50% to 60%.33 This may potentially be explained by the inclusion of polyarthritis and monoarthritis in the diagnostic criteria, resulting in the detection of milder cases of ARF that are less likely to have cardiac involvement.

The proportion of cases with chorea (19.5%) is somewhat lower than the 28% previously found in NT Aboriginal people30 but still higher than the proportion found in most other populations.33 The reasons for particular ethnic or regional susceptibility to this manifestation of ARF are not clear. Given the striking presentation of chorea, it is unlikely that cases have gone undetected. More likely, the slight decrease in the proportion of cases presenting with chorea may be attributable to an increase in the detection of other presentations of ARF, particularly in patients with monoarthritis, related to increased awareness because of education campaigns. Although RHD was just as commonly diagnosed in chorea as in nonchorea cases, evidence of heart failure was less likely in chorea (3.7%) compared with nonchorea (26.4%) patients, supporting the hypothesis that chorea is associated with less severe carditis. Currently, the data are not strong enough to support lessening surveillance in this cohort. Because chorea is a late manifestation, the finding of a lack of acute inflammatory manifestations was expected.

This population had access to high-quality medical care, including active outreach services by specialist clinicians and echocardiography. This provides a higher level of care than is available in most developing countries where RHD exists in high numbers. We believe that the diagnoses and confirmation of severity of RHD are reliable because of easy access to echocardiography. Therefore, this study is unique in that it documents real-life outcomes of a whole population with high rates of RHD carefully followed up with specialist review and echocardiography.

To the best of our knowledge, the only high-quality population-based data on the health outcomes of RHD are from New Zealand and Australia. In the NT, we feel we have reached a point where we are identifying most presentations of RHD in the absence of routine screening. The same may not be true in developing countries that lack the capacity to establish registers on a large scale and to maintain high-quality surveillance of individual cases over the long term. In these countries, screening echocardiography may act as a tool both to understand disease burden and to identify cases that might otherwise not present for routine care.34

This analysis informs disease prevention and control efforts in the NT but also provides insights into pathogenesis and disease burden that also may be useful in other populations. We call for similar analyses of other RHD registers around the world and for the establishment of RHD registers where they do not already exist as part of control programs in developing countries where ARF and RHD are common.

Disclosures

None.

References

This is the first time that longitudinal data from a registry have been analyzed on the presentation and progression of acute rheumatic fever and rheumatic heart disease, conditions that continue to cause a large burden of morbidity and mortality in developing populations. This article analyzes data collected over a 13-year period in an area of high prevalence of acute rheumatic fever/rheumatic heart disease (the Northern Territory of Australia) and provides insights into trends in incidence, recurrence, and presentation over time. To the best of our knowledge, this is the only in-depth analysis in the last half-century in developing populations. This article analyzes data collected over a 13-year period in an area of high prevalence of acute rheumatic fever/rheumatic heart disease (the Northern Territory of Australia) and provides insights into trends in incidence, recurrence, and presentation over time. To the best of our knowledge, this is the only in-depth analysis in the last half-century in developing populations.

The findings inform disease prevention and control efforts in the Northern Territory but also provide insights into pathogenesis and disease burden that may be useful in other populations. This is of particular importance given that developing countries, where the main disease burden continues to lie, do not currently have the resources or capacity to establish registers on a large scale and to maintain quality surveillance of individual cases over the long term. The data presented in this article will be important references for international guidelines and controversies in diagnosis and public health policy.
Acute Rheumatic Fever and Rheumatic Heart Disease: Incidence and Progression in the Northern Territory of Australia, 1997 to 2010
Joanna G. Lawrence, Jonathan R. Carapetis, Kalinda Griffiths, Keith Edwards and John R. Condon

Circulation. 2013;128:492-501; originally published online June 21, 2013;
doi: 10.1161/CIRCULATIONAHA.113.001477
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/128/5/492

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.
Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints
Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/