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

Running title: Lawrence et al.; Rheumatic heart disease: Lessons from the register

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Abstract:

**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 (NT) 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 NT residents from 1997 to 2010. For Indigenous people, ARF incidence was highest in the 5-14 year age-group (males 162, 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 a first ARF diagnosis, 61% developed RHD within ten years. After RHD diagnosis, 27% developed heart failure within five years. For Indigenous RHD patients the relative survival rate was 88.4% ten years after diagnosis and the standardized mortality ratio was 1.56 (95% CI 1.23-1.96).

**Conclusions**—For Indigenous Australians in the NT, 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.

**Key words:** Acute Rheumatic Fever, Recurrence, Indigenous Australians, rheumatic heart disease, incidence
Background

Acute Rheumatic Fever (ARF) is an autoimmune phenomenon following infection with Group A streptococcus. Inflammation of the joints, heart and brain result in the common clinical manifestations of arthritis, carditis and chorea. Although now rare in developed countries, ARF maintains a note-worthy presence in economically disadvantaged populations driven by factors including household overcrowding and poor hygiene. The major morbidity and mortality result from cardiac involvement known as Rheumatic Heart Disease (RHD).

Compared with primary prevention or treatment of established carditis, secondary prophylaxis (in the form of two to four-weekly intramuscular benzathine penicillin G) has been proven to be the most cost-effective intervention in the management of ARF and RHD. Unfortunately, delivery of regular doses remains suboptimal in most countries, and many patients suffer repeat episodes of ARF and consequently develop potentially avoidable progressive heart damage.

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. In 2005, only one country in which RHD occurs at high rates (New Zealand) was felt to have reliable cause-specific mortality data relating to RHD. Similarly, little is known of the morbidity due to 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. 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 of Australia (NT) has the highest documented incidence rate of ARF in the world. Since the NT Rheumatic Heart Disease Control Program established a computerised 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, send reminders for secondary prophylaxis and facilitate specialist clinical care. This confidential password-protected database covers a population of over 225,000 people scattered over an area of 1,346,000 square kilometers ranging from coastal tropics in the north to desert in the south. Of this population, approximately 64,000 (30%) is 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 approximately 2,500 people recorded on the register and the Rheumatic Heart Disease Control Program staff consider that since 1997 the register is 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 incidence of ARF and prevalence of RHD, but 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. De-identified data were extracted from the register in May 2011, assessed for data quality and analysed using STATA software (STATA Corporation, College Station, Texas). 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, or 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 analysed for inconsistencies (such as clinical reviews for RHD before the RHD diagnosis date); inconsistent data were resolved where possible or cases 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 1st January 1997 and 31st December 2010. In the Northern Territory, the diagnosis of ARF was based on the 1992 updated Jones Criteria19 until the 2005 Australian guidelines became available.12 RHD was diagnosed by specialist physician and confirmed by echocardiography. A first episode of ARF was defined as an ARF episode within the study period, where 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 ARF were used (ie. subsequent episodes of ARF in those who first presented with RHD, presumed to have missed first episode of ARF, were not included) in order 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 prior to 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
analysed:

1. **demographic characteristics of people diagnosed with ARF and/or RHD**
2. **clinical manifestations of ARF: restricted to first ARF episodes between 2/10/2007 and 31/12/2010 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, gender, 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 than non-Indigenous people. Negative binomial regression was used because incidence data were found to be over-dispersed.**
5. **RHD prevalence on 31 December in 2000, 2005 and 2010**
6. **rate of ARF recurrence after a first ARF episode in people diagnosed with their first ARF episode between 1/1/1997 and 31/12/2010, calculated as the number of second ARF episodes per 100 person-years.**
7. **rate of progression from ARF to RHD: proportional hazards regression analysis of the incidence of RHD in people who had a first ARF episode between 1/1/1997 and 31/12/2010; independent variables were indigenous status, gender, age at diagnosis, year of diagnosis and the**
presence of chorea at the first ARF episode.

8. rate of progression from RHD to heart failure: proportional hazards regression analysis of the incidence of heart failure in people diagnosed with RHD between 1/1/2004 and 31/12/2010. Independent variables were Indigenous status, gender, age at diagnosis and year of diagnosis.

9. relative survival rate (RSR) and standardised mortality ratio (SMR) for people diagnosed with RHD in 1997-2010, which measure excess mortality due to RHD.

For measures 6, 7 and 8, the follow-up time was censored at the earliest of: date of diagnosis (of second ARF episode, or RHD, or heart failure, respectively); date of death; or 31/12/2010. 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 where left ventricular function is impaired; increased left ventricular size; shortness of breath, tiredness, oedema, angina or syncope; or had 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 due to RHD because: cause of death data was not available to for cause-specific analysis; and 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 due to RHD by comparing the observed with the expected all-causes 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 was 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 (e.g. only 15 of 615 first ARF episodes), so comparisons of Indigenous with non-Indigenous subjects was limited; for some outcome measures multivariate analyses were restricted to Indigenous cases only. The Estimated Resident Population of the NT by five-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 2,837 individuals, with a total of 3,920 diagnoses and 20,890 clinical contacts.

84 people were documented as having a RHD diagnosis date before the date of their first ARF episode. The first ARF diagnosis date was changed to the RHD diagnosis date if there was less than 30 days difference (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).

1,372 individuals were excluded from analysis because: they had no recorded diagnosis details (528 people, 222 of whom had died before 1997, 115 died between 1997 and 2010, 119 had an indication that they had an episode of unconfirmed ARF); they had been diagnosed with RHD before 1/1/1997 (495) or diagnosed with ARF before 1/1/1997 and had not been diagnosed with
RHD (197); or they were interstate residents (141). 1,469 individuals met the inclusion criteria for the study, four of whom were excluded from analysis because of missing data on Indigenous status (1) or gender (3), leaving 1,465 individuals in the analysis dataset (Figure 1).

The final dataset included a total of 1,465 subjects with 1,149 diagnoses of RHD and 615 first diagnoses of ARF between 1st January 1997 and 31st December 2010.

**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 females was similar for Indigenous and non-Indigenous cases. The median age of first presentation was 12 years old for Indigenous subjects regardless of gender. Non-Indigenous cases were older by 6 years for males (median age 18 years) and 3 years for females (median age 15 years). Incidence of first ARF episode was highest in the 5-14 year age-group for both Indigenous and non-Indigenous people (Figure 2). The incidence rate in Indigenous people aged 5-14 years was 194 per 100,000 overall, 162 in males and 228 in females. 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 being a 40-fold increased risk). In analysis restricted to Indigenous people only, ARF incidence was 49% higher in females than 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**

149 people were registered with their first episode of ARF between 2 October 2007 (when the
register commenced uniform collection of data on clinical manifestations of ARF) and 31 December 2010. Of the major manifestations, joint involvement was the most common presenting feature, recorded in 77% of total presentations (Table 3). Amongst those with joint involvement, 63.5% had polyarthritis, 7.0% had polyarthralgia and 29.6% had mono-arthritis, the latter two considered major manifestations in high risk populations in Australia. Carditis was present in 27.5% and chorea in 19.5%. As 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 where diagnosis was based on chorea or less stringent criteria for arthritis (ie. monoarthritis or arthralgia). In the subgroup with more classical 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 (19.5%) of the 149 patients diagnosed after 2/10/2007 had chorea as a manifestation of their first ARF episode. Chorea was a more common manifestation of a first ARF episode in females (22 of 88, 25%) than males (7 of 61, 11%) and in those aged <20 years (28 of 123, 23%) than those aged 20 and over (1 of 26, 4%). In multivariate logistic regression analysis (adjusted for diagnosis age (<20 or 20+), sex and diagnosis year, the associations with age (OR 0.90, CI 0.81-0.99) and sex (OR 3.21, CI 1.2-8.4) were significant.

Those with chorea were less likely to have concurrent arthritis (31% compared to 88%), raised inflammatory markers (38% compared to 83%) or fever (21% compared to 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 to 51.5% of non-chorea patients. Evidence of the development of heart failure was less likely in chorea (3.7%) compared to non-
chorea patients (26.4%).

**Rheumatic Heart Disease**

There were 1,149 people registered as having been diagnosed with RHD between 1997-2010, 1,066 (92.8%) of whom were Indigenous and 756 (65.8%) female (Table 1). Males presented at a younger age than females and Indigenous patients were much younger (males 19 years, females 23 years) at diagnosis than non-Indigenous patients (males 46.5yrs, females 51 years).

**Figure 3** shows an increasing prevalence of RHD amongst the Indigenous population with time. However, 71% of RHD cases recorded on the register were diagnosed after the register commenced (1997-2010), 25% of whom were aged 40 years and over when diagnosed. This indicates that although efforts were made to collect data on cases diagnosed prior to 1997, data collection was incomplete then. The lower prevalence in 2000 and 2005 is therefore at least in part because of more recent diagnosis of long-standing RHD cases. In 2010 the peak prevalence was in the 45-64 year age group (3.1%).

For the NT Indigenous population, RHD incidence was highest in the 5-14 age-group for males and in the 15-24 age-group for females, and was higher for females than males in all age-groups except 65+ (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 confidence interval being a 43-fold increased risk. RHD incidence for females was almost twice that for males.

**Recurrences of ARF**

There were 846 total episodes of ARF registered in 1997-2010. This includes 94 recurrent
episodes in 77 of the 615 people who had their first episode in that period. Sixteen of these 77 had two or more recurrences. The recurrence rate was highest in the first year after the first ARF episode and decreased to zero by ten years after the first episode (Figure 5).

Among Indigenous people, the recurrence rate in the first year after diagnosis was 4.5% and the five-year recurrence rate was 12.5%. In multivariate analysis, the recurrence rate decreased by 9% per year following 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 gender and Indigenous status with recurrence rate, the confidence intervals for both 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 females than males, but the confidence intervals for both hazard ratios included 1.0. Among Indigenous subjects, 35% developed RHD by one year after 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 (31 December 2010). Fourteen percent had heart failure at diagnosis. This increased to 21% at one year after diagnosis and 27% at five years after diagnosis (Figure 6). In multivariate analysis there was little or no evidence of an association between Indigenous status, gender, 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 greater than 100% at 5, 10 and 14 years after diagnosis.

Amongst the Indigenous cohort, the crude all-cause survival rate was 96.1% at five years after diagnosis and 88.4% at ten years after diagnosis. The relative survival rate for Indigenous cases (i.e. survival rate of Indigenous people with RHD compared to the total Indigenous population) was 98.9% at five years (95%CI 97.4-100.1), but lower thereafter: 95.3% at ten years (92.3-97.8) and 90.5% at 14 years (83.9-95.6). This indicates that Indigenous RHD patients suffer little if any excess mortality compared to the general NT Indigenous population in the first five years after their RHD diagnosis, but that they 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 more than four 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 five-year relative survival rate of 89.7% (95%CI 79.5-95.8), while those assessed as having moderate, mild or inactive disease had five-year survival close to 100% (99.6%-103.7%).

The Standardised Mortality Ratio (SMR) among Indigenous cases was 1.56 (95% CI 1.23-1.96) indicating the number of deaths was 56% higher than expected compared to the NT
Indigenous population, whereas for non-Indigenous cases the SMR was 0.63 (0.13-1.85), which is consistent with their relative survival rates greater than 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 has not changed significantly over the past 14 years. Those most at risk continue to be Indigenous children, aged 5-14 years.

The incidence rates of first episodes of ARF reported here in Indigenous 5-14 year olds (228 and 162 per 100,000 in females and males, respectively) are similar to previously documented rates of 250-300 per 100,000 in the same population.\(^6,10\) The slightly lower rates found in this audit are most likely due to the fact that we included only first episodes (whereas the previous study included all episodes), as well as our strict inclusion criteria resulting in the exclusion of a number of documented cases with insufficient diagnostic 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, as the disease became notifiable in the NT in 1996 (prior to this study period) and campaigns to increase awareness have been present since WHO recommendations in 1994.\(^15\) The more recent broadening of the definition of joint involvement, with the inclusion of polyarthritis and monoarthritis in the diagnostic criteria, as well as the inclusion of subclinical carditis\(^12\) may account for increased numbers of diagnoses. However, it is likely that the rates remain high due to a failure to adequately address the socio-economic
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 similar demographic profile to 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 prior to the register commencing in 1997, there has been a continual increase in prevalence due to 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 45-64 year old group are consistent with previously reported rates in the Northern Territory.\textsuperscript{6,10} As efforts to reduce recurrence rates of ARF appear to be having an effect, and the persistently high incidence of ARF may partly be explained by the recent inclusion of milder cases with a lower incidence of clinical carditis (as a result of expansion of diagnostic criteria to include subclinical carditis, monoarthritis and polyarthralgia as major manifestations\textsuperscript{12}), the incidence of RHD can be expected to reduce 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.\textsuperscript{5,16} 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 gender susceptibility may be related either to an innate predilection for cardiac damage or to a greater risk of exposure to Group A Streptococcus (as 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,\textsuperscript{17,18} ongoing presentations
with RHD in the absence of a history of ARF suggest that detection, accurate diagnosis and notification of ARF remains 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 utilization due to 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% per year since 1997. This suggests that primary health care 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 as only recurrences amongst 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 in order to analyse time between episode and recurrence but is likely to underestimate the total burden of recurrences.

World Health Organization recommendations regarding 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 following diagnosis (4.5%) reducing to zero by 10 years support the current Australian guidelines for administration of prophylaxis for a minimum duration of 10 years in those without severe carditis. Moreover, we demonstrated that recurrence rates are highest in the first three to four 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 even in those diagnosed at a very young age. At present, our data are not strong enough to determine if these young patients retain an elevated risk of recurrence after 10 years (e.g. between ages 15 and 21 years in those whose first episode occurred at age 5); ongoing data collection will allow us to re-evaluate this recommendation in coming years. As compliance in adolescence is often problematic, this would be an important consideration.

The 2005 Australian Guidelines were used for prioritisation and follow up. These guidelines, and the 2012 updated version20 outline the importance of echocardiography in routine clinical care for RHD, particularly in Aboriginal people living in remote areas of Australia. As history taking in this population is often impaired by cultural and language barriers, the use of echocardiography allows more accurate monitoring of progression of valvular disease, and detection of severely affected patients to be targeted for intervention.

Of those with ARF, 35% developed RHD within 1 year and 61% 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 to be due 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 five years. To our knowledge, these are the only recent data on this most important clinical manifestation of ARF or RHD. It is essential to validate these data with ongoing surveillance, and in other populations, because they are
critical for informing estimates of disability due to ARF and RHD. Reassuringly, when compared to older natural history studies from the 1950s, when almost a third of children died in the two decades following diagnosis, morbidity and mortality appear much improved.\textsuperscript{21}

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 health care systems and remoteness, as well as cultural factors.\textsuperscript{22,23} In the case of RHD, there is the added complication that cardiac surgery is not available in the Northern Territory, so surgical intervention involves travel to cities many thousands of kilometres away. If outcomes for RHD are to be improved in similar settings, health care services must improve the capacity of the health workforce, availability of specialist care, systems for delivering care to patients with complex, chronic diseases, and mechanisms to address cultural impediments to uptake of Western medical care.

The burden of mortality is likely to be under-estimated due to the limitation of our study period (14 years). Amongst the Indigenous cohort, relative survival rate decreased with time following diagnosis. With longer follow-up this may become even more pronounced. The excess mortality was calculated to be 56\% higher amongst those with RHD compared to non-affected individuals of the same age and gender. These results confirm the large burden of mortality associated with RHD among Indigenous Northern Territory residents and highlight the progressive nature of the disease. RHD is likely to play a significant causative role in this excess mortality, as is demonstrated in other studies.\textsuperscript{24,25} As mortality due to 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 infer any significant trends.

Although the clinical presentation of ARF in the Northern Territory has many similarities to classic descriptions over the past half-century, there are some striking differences. While joint manifestations were the most common manifestation (77% of cases, similar to reported rates of 65-85%), we found that more than a third of these (23% of all cases) had mono-arthritis. This has been reported previously in a retrospective case series in the NT, in other parts of Australia, and in the Pacific. Our data support the inclusion of monoarthritis as a major manifestation in ARF diagnostic criteria, as has been the case in Australia since 2006.

We also found a remarkably low proportion of cases (28%) with carditis documented. This is substantially lower than previously reported in the NT, as well as other studies from different parts of the world, which uniformly report rates of 50-60%. This may potentially be explained by the inclusion of polyarthralgia and monoarthritis in the diagnostic criteria resulting in the detection of milder cases of ARF, 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 people, but still higher than the proportion found in most other populations. 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 due to an increase in the detection of other presentations of ARF, particularly those with mono-arthritis, related to increased awareness because of education campaigns.

Although RHD was just as commonly diagnosed in chorea as non-chorea cases, evidence of heart failure was less likely in chorea (3.7%) compared to non-chorea patients (26.4%).
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. As 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 due to easy access to echocardiogram. Therefore, this study is unique in that it documents real-life outcomes of a whole population with high rates of RHD, carefully followed with specialist review and echocardiography.

To our knowledge the only high quality population based data on the health outcomes of RHD are from NZ and Australia. In the Northern Territory 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 maintain high quality surveillance of individual cases over the long term. In these countries, screening echocardiography may act as a tool to both understand disease burden but also 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 may be useful in other populations as well. We call for similar analyses of other RHD registers around the world, and for establishment of RHD registers where they don’t already exist, as part of control programs in developing countries where ARF and RHD are common.

Conflict of Interest Disclosures: None.
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**Table 1.** Demographic characteristic of ARF and RHD cases, NT 1997-2010.

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<th>ARF</th>
<th>RHD</th>
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<td>non-Indigenous</td>
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<td>600</td>
<td>15</td>
</tr>
<tr>
<td>Female (%)</td>
<td>58.5</td>
<td>60.0</td>
</tr>
<tr>
<td>Age-group at diagnosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 years</td>
<td>2.7</td>
<td>0.0</td>
</tr>
<tr>
<td>5-9</td>
<td>27.2</td>
<td>13.3</td>
</tr>
<tr>
<td>10-14</td>
<td>36.8</td>
<td>26.7</td>
</tr>
<tr>
<td>15-24</td>
<td>19.7</td>
<td>20.0</td>
</tr>
<tr>
<td>25-34</td>
<td>8.7</td>
<td>13.3</td>
</tr>
<tr>
<td>35-44</td>
<td>3.8</td>
<td>26.7</td>
</tr>
<tr>
<td>45+</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Median age at diagnosis (years)</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Year of diagnosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997-2000</td>
<td>22.7</td>
<td>46.7</td>
</tr>
<tr>
<td>2001-2005</td>
<td>42.5</td>
<td>20.0</td>
</tr>
<tr>
<td>2006-2010</td>
<td>34.8</td>
<td>33.3</td>
</tr>
</tbody>
</table>
Table 2. Multivariate analysis of ARF incidence, NT 1997-2010

<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 gender</td>
<td>1.50</td>
<td>0.004</td>
</tr>
<tr>
<td>Age (year)</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>

* incidence rate ratio.
† not applicable

Table 3. Clinical manifestations at initial presentation of ARF, NT 2007-2010

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Number</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</strong></td>
<td>149</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 4. Multivariate analysis of RHD Incidence, NT 1997-2010

<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>63.65</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at diagnosis†</td>
<td>1.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Year †</td>
<td>1.00</td>
<td>0.81</td>
</tr>
<tr>
<td>Indigenous by age</td>
<td>0.95</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* incidence rate ratio.
† IRR for a one year increase
‡ not applicable.
Table 5. Recurrence of ARF, multivariate analysis of recurrence rate, NT 1997-2010

<table>
<thead>
<tr>
<th></th>
<th>Hazards 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>
<td>0.27-13.9</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.79</td>
<td>0.30</td>
<td>0.50-1.23</td>
</tr>
<tr>
<td>Age at first ARF episode†</td>
<td>0.93</td>
<td>&lt;0.01</td>
<td>0.90-0.97</td>
</tr>
<tr>
<td>Year</td>
<td>0.91</td>
<td>0.01</td>
<td>0.84-0.97</td>
</tr>
</tbody>
</table>

* hazard ratio (proportional hazard regression).
† per single year.

Table 6. Progression to RHD, multivariate analysis of incidence of RHD after a first episode of ARF, NT 1997-2010

<table>
<thead>
<tr>
<th></th>
<th>Hazards 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>
<td>0.63-3.74</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.19</td>
<td>0.13</td>
<td>0.95-1.50</td>
</tr>
<tr>
<td>Age at first ARF episode†</td>
<td>0.98</td>
<td>&lt;0.01</td>
<td>0.96-0.99</td>
</tr>
<tr>
<td>Year</td>
<td>1.03</td>
<td>0.10</td>
<td>0.99-1.06</td>
</tr>
<tr>
<td>Chorea ‡</td>
<td>0.85</td>
<td>0.29</td>
<td>0.62-1.15</td>
</tr>
</tbody>
</table>

* hazard ratio (proportional hazard regression).
† per single year.
‡ presence of chorea as a clinical manifestation at the first ARF episode

Table 7. Progression to cardiac failure, multivariate analysis of incidence of heart failure after diagnosis of RHD, NT 2004-2010

<table>
<thead>
<tr>
<th></th>
<th>Hazards Ratio*</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous status</td>
<td>1.02</td>
<td>0.96</td>
<td>0.55-1.90</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.86</td>
<td>0.37</td>
<td>0.63-1.19</td>
</tr>
<tr>
<td>Age at RHD diagnosis†</td>
<td>1.01</td>
<td>0.25</td>
<td>1.00-1.02</td>
</tr>
<tr>
<td>Year</td>
<td>1.06</td>
<td>0.18</td>
<td>0.97-1.16</td>
</tr>
</tbody>
</table>

* hazard ratio (proportional hazard regression).
† per single year.

Figure Legends:

**Figure 1.** Application of Exclusion Criteria.

**Figure 2.** Age-specific incidence of first episodes of ARF 1997-2010.
Figure 3. RHD prevalence at three time points* by age-group, NT Indigenous only. *prevalence per 100 at 30 June in each year.

Figure 4. Age-specific incidence of RHD, NT 1997-2010.

Figure 5. ARF recurrence rate* by time since first episode. * number of recurrences per 100 person-years after a first ARF episode in 1997-2010, with 95% confidence interval.

Figure 6. Progression of ARF to RHD and cardiac failure among Indigenous subjects.

Figure 7. Death rate by 2 year period since diagnosis (Indigenous only).
3920 diagnoses in 2837 individuals

1. 2695 diagnoses in 2138 individuals
2. 1225 diagnoses excluded in 699 individuals
   - 19 no identification data
   - 443 ‘possible’ ARF or RHD
   - 708 outside study period
   - 55 ARF unlikely 1st presentation

3. 1764 diagnoses in 1465 individuals
4. 673 individuals excluded
   - 528 no diagnostic information
   - 141 interstate
   - 4 missing data
Figure 2
Figure 6
Figure 7

Death rate by two-year period since diagnosis

Indigenous only

Rate (per 10000)

Time since diagnosis in years
Acute Rheumatic Fever and Rheumatic Heart Disease: Incidence and Progression in the Northern Territory of Australia 1997-2010
Joanna G. Lawrence, Jonathan R. Carapetis, Kalinda Griffiths, Keith Edwards and John R. Condon

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