1   Outcomes of possible and probable rheumatic fever: a cohort study

2   using northern Australian register data, 2013-2019

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Abstract

Background: Outcomes after acute rheumatic fever (ARF) diagnosis are variable, ranging from recovery to development of severe rheumatic heart disease (RHD). There is no diagnostic test. Evaluation using the Australian clinical diagnostic criteria can result in a diagnosis of 'definite', 'probable' or 'possible' ARF. The 'possible' category was introduced in 2013 in Australia's Northern Territory (NT). Our aim was to compare longitudinal outcomes after a diagnosis of definite, probable or possible ARF.

Methods: We extracted data from the NT RHD register for Indigenous Australians with an initial diagnosis of ARF during the 5.5-year study period (01/01/2013 – 30/06/2019). Descriptive statistics were used to describe the demographic and clinical characteristics at initial ARF diagnosis. Kaplan-Meier curves were used to assess the probability of survival free of disease progression and the cumulative incidence risk at each year since initial diagnosis was calculated. Cox proportional hazards regression was used to determine whether time to disease progression differed according to ARF diagnosis and whether progression was associated with specific predictors at diagnosis. A multinomial logistic regression model was performed to assess whether ARF diagnosis was associated with RHD outcome and to assess associations between ARF diagnosis and clinical manifestations. A generalised linear mixed model (GLMM) was developed to assess any differences in the long-term antibiotic adherence between ARF diagnosis categories and to examine longitudinal trends in adherence.

Results: There were 913 initial ARF cases, 732 with normal baseline echocardiography. Of these, 92 (13%) experienced disease progression: definite ARF 61/348 (18%); probable ARF 20/181 (11%); possible ARF 11/203 (5%). The proportion of ARF diagnoses that were uncertain (i.e. possible or probable) increased over time, from 22/78 (28%) in 2013 to 98/193 (51%) in 2018. Cumulative incidence risk of any disease progression at 5.5 years was 33.6 (23.6–46.2) for definite ARF, 13.5 (8.8–20.6) for probable and 11.4% (95% CI 6.0–21.3) for possible ARF. The probability of disease-free survival was lowest for definite ARF and highest

41   for possible ARF (p=0.004). Cox proportional hazards regression indicated that disease

42   progression was 2.19 times more likely in those with definite ARF than those with possible

43   ARF (p=0.026). Progression to RHD was reported in 37/348 (11%) definite ARF, 10/181 (6%)

44   probable ARF, and 5/203 (2%) possible ARF. The multinomial logistic regression model

45   demonstrated a significantly higher risk of progression from no RHD to RHD if the initial

46   diagnosis was definite compared to possible ARF (p<0.001 for both mild and moderate-severe

47   RHD outcomes). The GLMM estimated that patients with definite ARF had a significantly

48   higher adherence to antibiotic prophylaxis compared with probable ARF (p=0.024).

49   Conclusion: These data indicate that the ARF diagnostic categories are being applied

50   appropriately, are capturing more uncertain cases over time, provide a useful way to stratify

51   risk and guide prognosis, and can help inform practice. Possible ARF is not entirely benign;

52   some cases progress to RHD.

Introduction

In Australia, high burdens of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) occur among Aboriginal and Torres Strait Islander peoples, particularly across northern and central Australia.(1) There is no diagnostic test for ARF. This impairs case detection and opportunities for early intervention with antibiotic secondary prophylaxis.(2) The Jones Criteria are syndromic criteria to diagnose ARF, dividing the clinical features into major and minor manifestations based on their prevalence and specificity.(3) The Jones Criteria have been regularly revised in response to evolving clinical knowledge and epidemiology, to reduce overdiagnosis in high-resource settings where ARF has become uncommon.(4-6) As a result, they became less sensitive for detection of cases in high-incidence populations. Different considerations were therefore added for high-risk groups (3, 5, 6), but to further avoid missed diagnoses in high-prevalence Aboriginal communities in Australia, additional diagnostic categories of 'possible' and 'probable' ARF were proposed.(7) This proposal was adopted and since 2013, diagnoses in Australia have been grouped as: possible ARF, probable ARF, definite ARF, and RHD. The distinction between probable and possible is subjective and requires thoughtful clinical decision making. These categories were further clarified in the revised 2020 Australian Guidelines (Box 1).(3) This is in contrast to international guidelines that only articulate two categories: definite and probable ARF.(6)

Box 1: Acute rheumatic fever diagnostic categories, 2020 Australian Guidelines (6)

> **Definite ARF:** acute presentation which fulfils the 2015 Revised Jones diagnostic criteria for ARF.
>
> **Probable ARF:** acute presentation which does not fulfil Jones diagnostic criteria for ARF, missing one major or one minor criterion or lacking evidence of preceding streptococcal infection, but ARF is still considered the most likely diagnosis.

> **Possible ARF:** acute presentation which does not fulfil Jones diagnostic criteria for ARF, missing one major or one minor criterion or lacking evidence of preceding streptococcal infection, and ARF is considered uncertain but cannot be ruled out.

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74 Previous research has described progression from ARF to RHD and other outcomes such as

75 morbidity and mortality rates.(8, 9) In Australia's Northern Territory (NT), the risk of

76 progression from definite ARF to RHD is high, with a cumulative incidence of progression of

77 27.1% at 1 year after diagnosis, 44.0% at 5 years and 51.9% at 10 years.(9) Adherence to

78 penicillin to prevent rheumatic fever recurrences reduces risk, with a dose-dependent

79 effect.(10) Previous studies routinely exclude possible ARF and often also exclude probable

80 ARF cases, so long-term outcomes of these diagnoses remain unknown.

81

82 To provide patients with better prognostic information, determine whether clinicians appear to

83 be applying diagnostic categories appropriately, and reflect on whether current management

84 guidelines (3) are appropriate, the aim of this study is to describe patient outcomes after a

85 diagnosis of possible or probable (collectively, 'uncertain') ARF, compared with definite ARF.

86 Further aims are to determine whether uncertain diagnoses differ from definite ARF in

87 demographic or clinical characteristics, severity of RHD if there is progression to RHD, and

88 penicillin adherence over time.

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Methods

90

Study design and data sources

91

92 We used a retrospective cohort design and Cox proportional hazards regression to analyse

93 the probability of disease progression after an initial diagnosis of ARF. Sub-analyses on initial

94 ARF diagnoses with RHD outcome and adherence to penicillin adherence were conducted

95   using multinomial logistic regression and generalised linear mixed-effects models (GLMM)

96   respectively. Data were extracted from the NT RHD Register (the Register) for a 5.5-year

97   period (01/01/2013 – 30/06/2019). The Register was established in 1997 as a tool to support

98   and coordinate care. Since then, all notified cases of ARF (including recurrent episodes) and

99   RHD in the NT have been recorded, capturing approximately 3,500 individuals at the time of

100   data extraction. The Register includes data on patient demographics, clinical features of ARF

101   and RHD, medical appointments and secondary penicillin prophylaxis, which is generally

102   required long-term after probable and definite ARF, and short term (12 months) after possible

103   ARF. Mortality data from the NT Births, Deaths and Marriages database are reviewed monthly

104   and integrated with the Register.

105

Study population and sample

107   The study population was defined as Indigenous Australians residing in the NT, which is

108   approximately 74,546 or 30% of the total NT population.(11, 12) The Register contained

109   information on 1,140 individuals with 1,567 diagnoses during the study period. Indigenous

110   Australians residing in the NT who were registered with an initial diagnosis of possible,

111   probable or definite ARF on the Register during the study period were included. Exclusions

112   comprised non-Indigenous people (11; 1%); cases whose first documented ARF episode was

113   labelled a recurrence (216; 19%); and concurrent ARF and RHD diagnoses (180; 16%). Those

114   whose first documented episode was labelled a recurrence were assumed to have had a

115   previous diagnosis of ARF before the study period began or in a different jurisdiction. One

116   case whose initial diagnosis date was on the final day of the study period was excluded from

117   the disease progression analyses due to a survival time of zero. Concurrent ARF and RHD

118   diagnoses (180 cases) were similarly excluded from disease progression analyses since they

119   had a disease-free survival time of zero. These cases represent severe ARF which has

120   already progressed to RHD at the time of first echocardiogram, or ARF occurring in someone

6

121   with previously unrecognised latent RHD, or documentation of rheumatic carditis in the register

122   as RHD (since distinguishing rheumatic carditis from established RHD is not always possible,

123   and misclassification may occur during clinical reporting or data entry). The exclusions mean

124   that the most severe form of ARF (definite ARF with carditis classified as RHD, or carditis

125   complicating RHD), were excluded from the Cox regressions but were still accounted for in

126   the multinomial model. The final sample size for the Cox regression was 732 cases and 913

127   cases for the multinomial model.

128

Outcomes

130   The main outcome of interest was time to disease progression. Disease progression was

131   defined as progression from possible to probable ARF, definite ARF or RHD; probable to

132   definite ARF or RHD; or definite ARF to definite ARF recurrence or RHD at any time during

133   the study period (Table 1). Individuals could progress and regress more than once during the

134   study period, however only the first progression was counted.

135

136   **Table 1. Definitions of disease progression**

Initial ARF diagnosis	Subsequent diagnosis
ARF possible	ARF probable, ARF definite or RHD
ARF probable	ARF definite or RHD
ARF definite	ARF definite recurrence or RHD

137

138   We also calculated the proportion of those without baseline carditis who progressed to RHD

139   and the risk to develop mild or moderate to severe RHD compared to no RHD based on initial

140   ARF diagnosis.

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142   Adherence to secondary prophylaxis with benzathine benzylpenicillin (BPG) was calculated

143   as the percentage of received doses / prescribed doses x100. BPG is usually required once

144   every 28 days for ARF secondary prophylaxis, i.e. 13 doses per year, but may be prescribed

145   every 21 days, i.e. 17 doses per year, in more severe or breakthrough cases. The number of

7

146 prescribed doses was estimated by dividing the number of days that BPG was prescribed (last

147 dose date minus first dose date) divided by 21 or 28 for 3-weekly and 4-weekly BPG

148 respectively. Adherence calculations were restricted to cases that had been prescribed at least

149 6 doses of BPG (equivalent to 168 days for a 4-weekly regimen). Adherence was considered

150 good if ≥80% of injections were received.

151

Predictors

153 Predictors used in the analyses included initial ARF diagnosis, sex, age group, clinical

154 manifestations, and adherence to secondary prophylaxis. Initial ARF diagnosis was defined

155 as the first diagnosis of possible, probable or definite ARF on the Register. Sex was classified

156 as per the NT RHD register (male, female, unknown). Age at initial diagnosis was grouped as

157 0-4, 5-14, 15-24, ≥25 years; these have different risk profiles for ARF and RHD.(3) Clinical

158 manifestations were grouped as major manifestations (carditis; arthritis or 'joint'; Sydenham's

159 Chorea; and subcutaneous nodules and erythema marginatum or 'skin'), minor manifestations

160 (fever; elevated ESR or CRP; prolonged P-R interval on ECG), and evidence of Group A

161 streptococcal infection (elevated serological titre or cultured from throat swab) as per the

162 RHDAustralia Clinical Guidelines.(3) The definition of adherence is described in the outcomes

163 section. Individuals who had missing data for adherence are excluded from analyses as these

164 data are unlikely to be missing at random and keeping these individuals in the analysis may

165 therefore introduce bias.

166

Statistical analysis

168 Descriptive statistics were used to describe the demographic and clinical characteristics at

169 initial ARF diagnosis (possible, probable, definite). Kaplan-Meier curves and log rank test were

170 used to assess the probability of survival free of disease progression and the cumulative

171 incidence risk at each year since initial diagnosis was calculated. Cox proportional hazards

172 regression was used to determine whether time to disease progression differed according to

173 ARF diagnosis category (definite, probable, possible), and whether it was predicted by age

174 group at diagnosis, sex, adherence to secondary prophylaxis or clinical manifestations (joint

175 manifestation-only and joint manifestation with carditis and/or chorea) at diagnosis. Hazard

176 ratios, 95% CI and p-values are reported.

177

178 A multinomial logistic regression model was performed to assess whether ARF diagnosis type

179 (definite, probable, possible) was associated with RHD outcome (no RHD, mild RHD

180 moderate-severe RHD). Moderate and severe RHD were combined to increase observations

181 per group level. Predictors included age group, sex, drug adherence and clinical

182 manifestations (carditis-only or joint manifestations-only. Chorea-only was excluded due to

183 the small number of observations). Multinomial logistic regression was also used to assess

184 associations between clinical manifestations (Jones major criteria) and ARF diagnosis.

185 Relative risk ratios, 95% confidence intervals (CI) and p-values were calculated for clinical

186 manifestations, age at diagnosis and sex, using definite ARF as the reference group.

187

188 A GLMM (beta regression family) was developed to assess any differences in the long-term

189 antibiotic adherence between ARF diagnosis categories and examine longitudinal trends in

190 adherence (glmmTMB package in R). This took into account the number of years receiving

191 BPG prophylaxis and a random intercept for patient identification. Model residuals were

192 checked for lack of patterns across fitted values and predictors (DHARMa package) and no

193 temporal autocorrelation.

194

195 Data were analysed using STATA version 15.1 (STATA Corp, College Station, TX), R (v4.1.3;

196 R Project for Statistical Computing, Vienna, Austria) and Microsoft Excel (2016).

197

Ethics approval

Study approval was granted by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (2019-3482). This approval was registered with the University of Melbourne's Medicine and Dentistry Human Ethics Sub-Committee (1955194). Access to register data was approved by the data custodian, Top End Health Service, NT Department of Health.

Results

Demographic and clinical characteristics

During the study period there were 913 initial diagnoses of ARF among eligible register participants: 509 (56%) definite, 196 (21%) probable and 208 (23%) possible ARF. All ARF types were more common among females than males and in those aged 5-14 years compared with other age groups (**Error! Reference source not found.**).

Table 2. Characteristics at initial acute rheumatic fever diagnosis among Indigenous Australians, NT, 2013-2019

Characteristic	ARF						Total	
	Possible		Probable		Definite			
	n	(%)	n	(%)	n	(%)	n	(%)
Cases	208	(100)	196	(100)	509	(100)	913	(100)
Sex								
Male	97	(47)	87	(44)	243	(48)	427	(47)
Female	111	(53)	109	(56)	266	(52)	486	(53)
Age group (years)								
0-4	25	(12)	11	(6)	27	(5)	63	(7)
5-14	113	(54)	92	(47)	298	(59)	503	(55)
15-24	37	(18)	53	(27)	107	(21)	197	(22)
≥25	33	(16)	40	(20)	77	(15)	150	(16)
Median, IQR	10	6-19	14	9-22	12	9-18	15	8-19
Year of diagnosis								
2013	9	(4)	13	(7)	56	(11)	78	(9)
2014	13	(6)	11	(6)	72	(14)	96	(11)
2015	18	(9)	28	(14)	77	(15)	123	(13)
2016	40	(19)	36	(18)	81	(16)	157	(17)

2017	38	(18)	52	(27)	87	(17)	177	(19)
2018	58	(28)	40	(20)	95	(19)	193	(21)
2019*	32	(15)	16	(8)	41	(8)	89	(10)
Adherence (%)								
<50	16	(7)	22	(11)	52	(10)	90	(10)
50-79	47	(23)	57	(29)	120	(24)	224	(24)
80-99	47	(23)	55	(28)	164	(32)	266	(29)
≥100	36	(17)	36	(19)	109	(21)	181	(20)
Unknown †	62	(30)	26	(13)	64	(13)	152	(17)
Clinical manifestation ‡								
Major								
Carditis	6	(3)	14	(7)	167	(33)	187	(20)
Joint	172	(83)	182	(93)	433	(85)	787	(86)
Sydenham chorea	3	(1)	0	(0)	62	(12)	65	(7)
Skin	2	(1)	1	(1)	7	(1)	10	(1)
Minor								
Fever	51	(24)	60	(31)	340	(67)	451	(49)
Elevated ESR or CRP	12	(14)	9	(6)	11	(2)	32	(5)
Prolonged P-R interval on ECG	10	(5)	19	(10)	196	(39)	225	(25)
Other								
Elevated GAS serological titre	183	(88)	168	(86)	480	(94)	831	(91)
GAS cultured from throat swab	5	(2)	7	(4)	18	(4)	30	(3)
Not recorded	6	(3)	1	(1)	0	(0)	7	(1)

214 ARF = acute rheumatic fever; GAS = group A beta haemolytic streptococcus; ESR =
215 erythrocyte sedimentation rate; CRP = C-reactive protein; ECG = electrocardiogram; CM =
216 clinical manifestation
217 * Note: only 6 months of data
218 † Note: includes those where prophylaxis data is not recorded and where prophylaxis was
219 prescribed for <6 months.
220 ‡ Note: cases may have more than one clinical manifestation, therefore the total does not
221 add up to 100%
222 ¥ Note: Elevated GAS serological titre or GAS cultured from throat swab only
223

224 Joint pain was the most common major Jones criterion for all ARF diagnostic categories.

225 Evidence of streptococcal infection (considered essential) was missing in 2% of cases

226 classified as definite ARF, and in approximately 10% of possible and probable ARF cases.

227 There were 2 deaths during the study period. The proportion of those adhering to penicillin

228 secondary prophylaxis was similar for possible and probable ARF but higher for definite ARF

229   (Table 2): the proportion receiving ≥80% of scheduled BPG injections was 37% and 46%

230   among possible and probable cases respectively, compared with 56% among definite ARF

231   cases. However, the proportion of possible ARF cases with unknown adherence was double

232   that among probable ARF and definite ARF cases (**Error! Reference source not found.**).

233   Each year, the number of ARF diagnoses increased (Fig 1).

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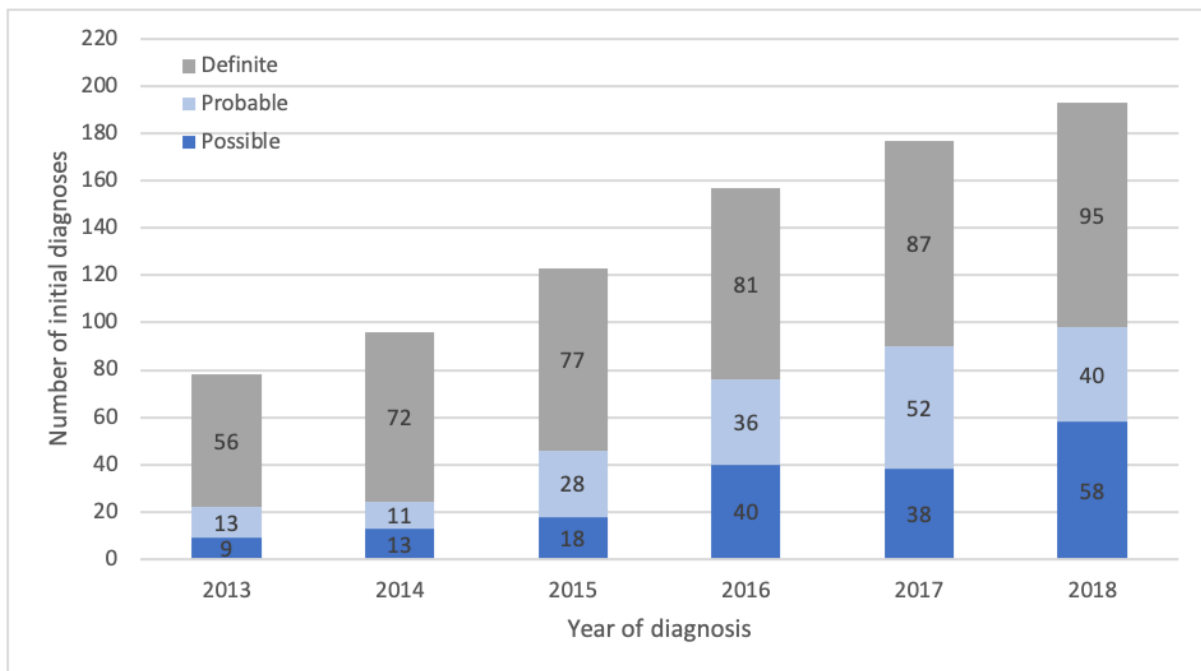
235   **Fig 1: Number of ARF diagnoses among Indigenous Australians, Northern Territory,**
236   **2013-2018. ARF indicates acute rheumatic fever.**
237

238   The proportion that was uncertain increased from 22/78 (28%) in 2013 when these diagnostic

239   categories started to be recorded, to 98/193 (51%) in 2018 (**Error! Reference source not**

240   **found.**).

241

Disease progression

243   After excluding cases with zero disease-free survival time, a total of 92 (13%) cases

244   experienced disease progression during the study period. Of those with an initial diagnosis of

245   definite ARF, 61/348 (18%) experienced disease progression, compared to 20/181 (11%) with

246   probable ARF and 11/203 (5%) with possible ARF. Of those who progressed, 37/61 (61%)

12

247   with definite ARF, 10/20 (50%) with probable ARF, and 5/11 (45%) with possible ARF (total of

248   52/92 or 57%) were diagnosed with RHD during the study period. Overall, progression to RHD

249   was reported in 37/348 (11%) definite ARF, 10/181 (6%) probable ARF, and 5/203 (2%)

250   possible ARF.

251

252   Possible ARF had the best probability of survival free of disease progression and definite ARF

253   had the worst survival probability (*p*=0.0043; log rank test; Fig 2).

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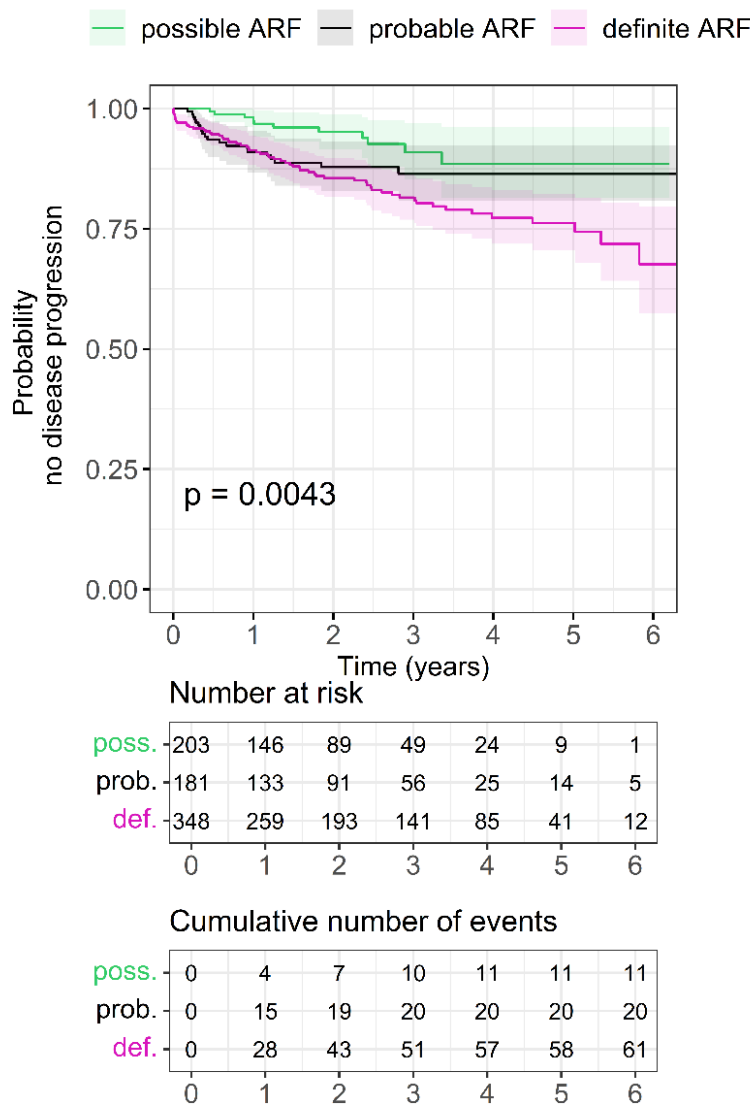
Fig 2: Kaplan-Meier progression-free survival estimates by initial ARF diagnosis among Indigenous Australians, Northern Territory, 2013-2019. ARF = acute rheumatic fever.

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258

259   For possible and probable ARF, the risk of disease progression continued to increase each

260   year up to 4 years and 3 years since initial diagnosis respectively. For definite ARF, the risk

261   of disease progression continued to increase each year of the follow-up period (Table 3).

262

263   **Table 3: Cumulative incidence risk of disease progression by year of follow-up among**
264   **Indigenous Australians, Northern Territory, 2013-2019**

Year	Possible ARF %, CI (95%)	Probable ARF %, CI (95%)	Definite ARF %, CI (95%)
1	2.46 (0.93 – 6.44)	9.03 (5.54 – 14.55)	8.66 (6.05 – 12.32)
2	4.85 (2.31 – 10.03)	12.13 (7.87 – 18.45)	14.43 (10.87 – 19.02)
3	9.05 (4.72 – 17.00)	13.54 (8.78 – 20.59)	17.98 (13.83 – 23.19)
4	11.44 (5.97 – 21.33)	13.54 (8.78 – 20.59)	22.19 (17.22 – 28.33)
5	11.44 (5.97 – 21.33)	13.54 (8.78 – 20.59)	23.26 (18.01 – 29.73)
5.5*	11.44 (5.97 – 21.33)	13.54 (8.78 – 20.59)	33.55 (23.61 – 46.21)

265   *Only six months of data are available for the final year
266

267   Cox proportional hazards regression indicated that disease progression was 2.19 times more

268   likely in those with definite ARF than those with possible ARF (p=0.026) (Table 4).

14

Table 4. Cox proportional hazards analysis of predictors associated with disease progression among Indigenous Australians, Northern Territory, 2013-2019

Variable	Hazard Ratio	Confidence Interval (95%)	P value
ARF Diagnosis			
Possible ARF	Ref		
Probable ARF	1.44	0.66 – 3.15	0.353
Definite ARF	2.19	1.10 – 4.34	0.026
Sex			
Male	Ref		
Female	1.06	0.67 – 1.67	0.811
Age group (years)			
0-4	0.73	0.26 – 2.06	0.552
5-14	Ref		
15-24	1.28	0.75 – 2.20	0.366
≥25	1.71	0.93 – 3.15	0.084
Adherence			
<50%	0.31	0.09 – 1.11	0.072
50-79%	1.48	0.66 – 3.29	0.337
80-99%	Ref		
≥100%	2.22	0.86 – 5.78	0.100
Clinical manifestations			
Carditis and/or chorea with or without joint manifestation	Ref		
Joint manifestation only (i.e. no carditis, no chorea)	0.48	0.24 – 0.95	0.035

ARF = acute rheumatic fever

Note:

1. Sample size for this analysis is 595 cases (137 cases missing drug adherence data and 181 cases with zero survival time were excluded)

2. Proportional hazard assumptions were not met for drug adherence nor joint manifestation and therefore, an interaction term with linear time was fitted for these 2 factors (likelihood ratio test Chi2(3) = 14.9; Chi2(1) = 7.4, P<0.01 for both). The time varying effect for joint manifestation was 1.7 (P=0.012) and 2.0 for prophylaxis adherence of <50% (P=0.010), both indicating a weakening protective effect with time.

277   The analysis also indicated that having joint manifestations only with no carditis nor chorea at

278   initial diagnosis of ARF was protective, with this group being 52% less likely to experience

279   disease progression compared with those who had other clinical manifestations including

280   carditis and/or chorea at initial diagnosis and with or without joint manifestation (p=0.035)

281   (Table 4). Disease progression was equally likely between sexes and age groups. In this

282   dataset, the association between penicillin adherence and progression was counterintuitive

283   and not statistically significant. People who had higher adherence were those who had disease

284   progression (Table 4).

285

286   ## Risk of developing rheumatic heart disease

287   The proportion of those who had no baseline carditis but still progressed to RHD is presented

288   by clinical manifestation (joint-only or chorea-only) in Table 5. Of those who progressed to

289   RHD with joint-only manifestations, 46% (17/37) progressed after one year. Of those who

290   progressed to RHD with chorea-only manifestations, only 3% (1/30) progressed after one year.

291   An additional case with neither chorea nor joint manifestations also progressed to RHD after

292   one year, bringing the total cases with progression to RHD after one year to be 19 cases.

293
294   **Table 5: Progression to RHD by clinical manifestation among Indigenous Australians,**
295   **Northern Territory, 2013-2019**

ARF diagnosis	Joint-only with no baseline echocardiographic pathology		Chorea-only with no baseline echocardiographic pathology	
	Total cases N	Progression to RHD n (%)	Total cases N	Progression to RHD n (%)
Possible ARF	167	4 (2%)	2	0 (0%)
Probable ARF	164	10 (6%)	0	-
Definite ARF	229	23 (10%)	28	3 (11%)
All ARF / total	560	37 (7%)	30	3 (10%)

296   ARF = acute rheumatic fever
297   Note: 181 cases with zero survival time were excluded from this analysis

298   The multinomial logistic regression model demonstrated a significantly higher risk of

299   progression from no RHD to RHD if the initial diagnosis was definite compared to possible

300   ARF (p<0.001 for both mild and moderate-severe RHD outcomes) (Table 6).

Table 6: Multinomial logistic regression of initial ARF diagnosis and development of RHD, by RHD severity, among Indigenous Australians, Northern Territory, 2013-2019

Multinomial model	Relative Risk Ratio	Confidence Interval (95%)	P value
Risk to develop mild RHD compared to no RHD after an initial ARF diagnosis			
ARF diagnosis			
ARF possible	Ref		
ARF probable	2.27	0.91-5.64	0.078
ARF definite	6.39	2.85-14.35	< 0.001 ***
Age group			
<= 4 yrs	0.29	0.07-1.26	0.098
5-14 yrs	Ref		
15-24 yrs	1.71	1.04-2.81	0.034 *
>=25 yrs	1.98	1.11-3.54	0.021 *
Clinical Manifestations			
Carditis only – Yes	0.95	0.27-3.32	0.939
Joint only – Yes	0.49	0.32-0.76	0.002 **
Adherence			
<50%	0.49	0.24-1.01	0.054
50-79%	0.77	0.47-1.26	0.294
80-99%	Ref		0.591
≥100%	0.86	0.50-1.48	
Gender – Female			0.084
Risk to develop moderate to severe RHD compared to no RHD after an initial ARF diagnosis			
ARF diagnosis			
ARF possible	Ref		
ARF probable	2.51	0.46-13.72	0.289
ARF definite	13.92	3.22-60.16	<0.001***
Age group			
<= 4 yrs	1.80	0.64-5.04	0.261
5-14 yrs	Ref		
15-24 yrs	1.88	0.98-3.61	0.059
>=25 yrs	2.11	0.94-4.72	0.071
Clinical Manifestations			

Carditis only – Yes	3.14	1.11-8.82	0.030*
Joint only – Yes	0.19	0.11-0.34	<0.001***
Drug adherence			
<50%	0.20	0.06-0.74	0.015*
50-79%	0.67	0.34-1.31	0.237
80-99%	Ref		
≥100%	1.41	0.75-2.66	0.281
Gender – Female	0.90	0.52-1.55	0.710

303 ARF = acute rheumatic fever; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ECG = electrocardiograph; GAS = Group A
304 Streptococcus; *** P<0.001; ** P<0.010; * P<0.050
305 Note: sample size for this analysis is 761 cases (151 cases missing drug adherence data were excluded)

306   There was a strong protective effect for those with joint manifestations only, with a 51%

307   reduced risk to progress to mild RHD and an 81% reduced risk to progress to moderate or

308   severe RHD from no RHD, with all other covariates held constant (p<0.001 for both; Table 6).

309   There was a three-fold increased risk of developing moderate-severe RHD compared to no

310   RHD for patients with carditis-only clinical manifestation (p=0.030).

311

312   ## Penicillin adherence

313   The GLMM estimated that patients with definite ARF had a significantly higher adherence to

314   antibiotic prophylaxis compared with probable ARF (p=0.024). Possible ARF, requiring only

315   12 months of treatment, was excluded from adherence comparisons. Time on prophylaxis was

316   also significantly inversely associated with adherence, with adherence being higher in the first

317   year after diagnosis and falling in years 2 to 6 after ARF diagnosis, for both definite and

318   probable ARF (p<0.001 for all) (Fig 3).

319

320
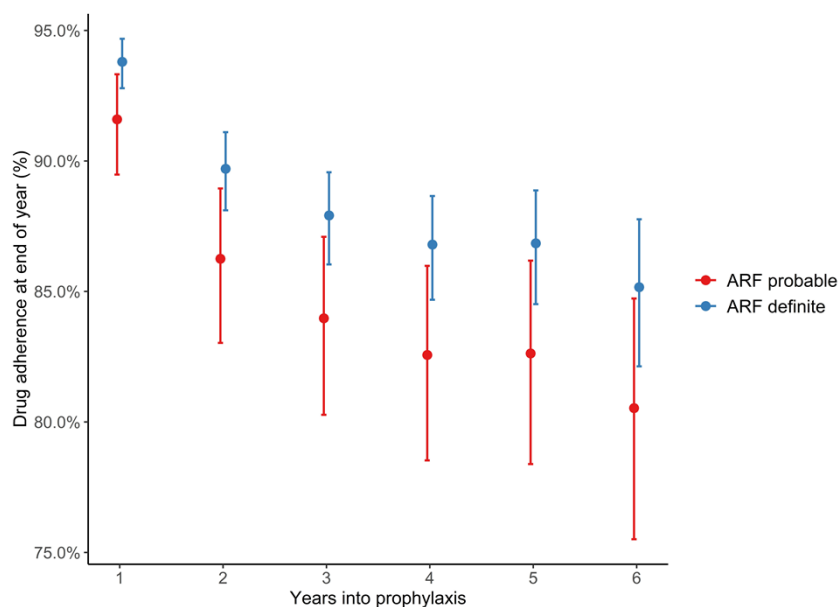
321   **Fig 3: Drug adherence by initial ARF diagnosis and year since diagnosis among**
322   **Indigenous Australians, Northern Territory, 2013-2019.**
323   ARF = acute rheumatic fever.

324

Discussion

To our knowledge, this is the first time that outcomes of possible and probable ARF have been determined. We show that since introduction of these diagnostic categories, they now make up over 40% of all initial ARF diagnoses in the Australian jurisdiction with the highest ARF burden. The diagnostic categories appear to be well applied by clinicians: the vast majority of children and young people diagnosed with possible ARF (95%) and probable ARF (89%) did not progress to definite ARF or RHD. These data are reassuring both for clinicians about the appropriate application of these diagnostic categories, and for patients and their families about the likelihood of a good outcome. However, the fact that some patients do progress emphasises that the Revised Jones criteria can still be inadequately sensitive in a high-burden environment, and the categories of 'possible' and 'probable' ARF add value by capturing some true cases who require institution of secondary prevention and appropriate clinical follow up.

Our findings highlight that definite, probable and possible ARF represent three distinct diagnostic categories with different prognoses. In a high-incidence setting, including the category of 'possible' ARF captures an important patient group who might otherwise receive an alternative generic diagnosis such as 'viral illness' or 'musculoskeletal pain'. International guidelines currently only articulate two categories: definite and probable ARF.(6) While many people labelled with possible ARF in our dataset may never have had true ARF, is not entirely benign; 4/200 (2%) with an initial diagnosis of possible ARF and a normal echocardiogram developed RHD; 3 within 12 months (1.5%), and 1 within 24 months (0.5%). The inability to predict which individuals are the ones most likely to progress highlights the need for biomarkers to diagnose and risk-stratify ARF. More research in this domain is needed.(13) Current Australian guidelines recommend 12 months of secondary prophylaxis after a diagnosis of possible ARF.(3) Our findings support this approach, since development of RHD more than 12 months after 'possible ARF' appears to be no more common than the

21

351   background population RHD risk, based on RHD population prevalence of 2% in 5-9 year old

352   children undergoing echocardiographic screening, and 6.8% in 10-15 year olds, in a high-

353   burden NT setting.(14)

354

355   Healthcare providers appear to be increasingly confident in accurately applying 'probable' and

356   'possible' ARF diagnoses since 2013 when these were defined and introduced into the NT

357   register. When total ARF diagnoses are captured, our data show that the increases over time

358   chiefly represent improving detection of uncertain cases from 22/78 (28%) in 2013 to 98/193

359   (51%) in 2018, with a smaller proportional increase in numbers of definite ARF (Fig 1). Efforts

360   to improve detection have included promotion of accessible clinical practice guidelines (2, 3,

361   15) and a diagnosis calculator available for smartphone use.(16)

362

363   The clinical manifestations of ARF we report are supported by previous NT data,(17) showing

364   arthritis to be most common major criterion followed by carditis then chorea, with almost all

365   additionally having fever.(18) Rheumatic carditis detected on echocardiogram is diagnostic of

366   definite ARF and should not be classified as possible or probable ARF. Possible and probable

367   cases noted to have echocardiographic valvar disease may have had known RHD and

368   presented with an acute illness not meeting criteria for definite ARF. When a child with RHD

369   presents with fever or elevated inflammatory markers, distinguishing ARF from other febrile

370   conditions with underlying RHD can be difficult and may result in a 'possible' or 'probable' ARF

371   diagnosis; the child is already prescribed penicillin prophylaxis but a new ARF diagnosis may

372   alter the duration of prophylaxis depending on their age. Sydenham chorea is synonymous

373   with ARF; once alternative causes of chorea have been excluded, a child with chorea

374   (especially if from a high-risk setting such as the NT) receives a diagnosis of definite ARF.

375   The possible and probable cases in this study noted to have chorea may, for instance, have

376   had a transient movement disorder not clearly evident as Sydenham chorea. Definite ARF

377   diagnoses require demonstration of recent streptococcal infection, except for when Sydenham

378   chorea is present, the onset of which might be very delayed.(3) The small number of definite

379   cases who lacked evidence of streptococcal infection on serology or throat swab may have

380   had chorea, may have had serological tests too early in disease without opportunity for

381   convalescent serology to be done, or the clinician may have chosen to override the

382   recommended diagnostic criteria.

383

384   The cumulative incidence risk of disease progression per year for those diagnosed with

385   possible ARF stopped increasing at 11%, 4 years from initial diagnosis, and for those

386   diagnosed with probable ARF at 14%, 3 years from initial diagnosis. In contrast, the cumulative

387   incidence risk of disease progression after definite ARF continued to increase each year since

388   initial diagnosis, from 9% at 1 year to 34% at 5.5 years from initial diagnosis (Table 3). While

389   the trend of increasing risk of disease progression from initial diagnosis largely concurs with

390   previous studies, the cumulative incidence risk of progression to RHD after definite ARF was

391   lower in our study. For example, a study of 1997-2013 Northern Territory data found that the

392   cumulative risk of progression from definite ARF to RHD increased from 27% at 1 year from

393   initial diagnosis to 52% at 10 years since initial diagnosis,(9) and another study of 1997-2010

394   data reported that the risk of progression from definite ARF to RHD was 35% at 1 year and

395   61% at 10 years.(19) The lower rate of disease progression in our study may reflect exclusion

396   of the most-severe ARF cases from cumulative incidence calculations, since they already had

397   the outcome of interest (RHD) at baseline. Other explanations may include improving delivery

398   of secondary prophylaxis which occurred during our study period(20), or greater clinical

399   detection over time of more subtle ARF cases which are less likely to progress, which the

400   increasing ARF detection rates reported here suggest.

401

402   Cox proportional hazards analysis demonstrated that those with more certain ARF were more

403   likely to experience disease progression (compared to those with possible ARF). The risk of

404   progression from no RHD to RHD was significantly higher if the initial diagnosis was definite

405   ARF compared to possible ARF (p<0.001 for both mild and moderate-severe RHD outcomes)

406   (Table 6). Those who had only joint manifestations at initial diagnosis of ARF were 52% less

407   likely to experience disease progression (compared to carditis and/or chorea). Joint-only

408   manifestations, which may only fulfill criteria for possible or probable ARF, may in other

409   settings be labelled as 'post streptococcal reactive arthritis', considered to be a separate entity

410   from ARF.(21, 22) However, since 6.6% (37/560) of people still developed RHD in our series

411   after initial joint-only presentations, we consider a diagnosis of ARF and provision of

412   secondary prophylaxis to be safer in our context.

413

414   In this dataset, people with ARF who had greater penicillin adherence were also those with a

415   higher risk of disease progression - but this association was not statistically significant (Table

416   4). Furthermore, of the cases that progressed (and had adherence data), less than half (40/86;

417   47%) were adherent to ≥80% of their BPG injections and adherence for both definite and

418   probable ARF cases was shown to decline over time from initial diagnosis (Figure 3). These

419   findings may be attributable to the association between disease severity and adherence.

420   Previous research using the same NT register, but an earlier time period, identified that those

421   with most severe disease (e.g. requiring surgery) were those who were subsequently most

422   adherent, potentially attributable to higher-level health system supports implemented for these

423   high-risk individuals, and greater patient understanding of the risks of non-adherence. (10)

424   The same paper showed a clear protective effect of adherence on ARF outcomes when

425   adherence prior to the event of interest was examined. Therefore, we conclude that adherence

426   reduces ARF recurrences or RDH progression, but in this dataset, we were unable to

427   demonstrate this relationship. Also, we used percent adherence which does not necessarily

428   factor in 'days at risk'(10); that is, the timing of dose administration (e.g. 13 BPG doses may

429   be given in a 12 month period, but if there are gaps of greater than 28 days, then the patient

430   will be at risk of ARF recurrence during those times).

431

24

432 Strengths of this study include that it is the first to include outcomes for possible and probable

433 ARF cases and that ARF is notifiable in the NT and therefore ARF diagnoses are well captured

434 and documented in the NT RHD Register. A limitation of this study is that a longer period of

435 follow-up time may have captured more events. For example, disease progression from ARF

436 to RHD is known to still occur at 10 years from initial diagnosis.(19) However, for possible and

437 probable ARF, the risk of disease progression appeared to stabilise approximately 4 years

438 from initial diagnosis (within the 5.5-year study timeframe). Another limitation is missed

439 diagnoses of ARF; up to 75% of newly diagnosed cases of RHD in northern Australia have

440 not been previously diagnosed with ARF.(3, 23) As noted, concurrent ARF and RHD

441 diagnoses were excluded since they had a disease-free survival time of zero so could not be

442 included in analysis of progression. Exclusion of these most severe ARF cases impacted

443 sample size and statistical rigour, follow-up time and the ability to calculate median survival

444 time, an important factor in the interpretation of survival data.(24)

445

Conclusion

447 This study provides much needed data about the likelihood of disease progression for children

448 and young people given a diagnosis of possible and probable ARF. Children and their families

449 can be reassured that possible ARF, probable ARF and ARF affecting the joints only, carry

450 relatively good prognoses. These diagnoses are more consistent with post-streptococcal

451 reactive arthritis than true ARF. However, secondary prophylaxis with penicillin is still of critical

452 importance given the morbidity of recurrences and the small but present risk of progression to

453 RHD. The data provide good news that clinicians appear to be detecting and reporting more

454 cases of uncertain ARF over time, a critical step in avoiding missed opportunities for

455 prevention.

456

Acknowledgements

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