

Adherence to secondary prevention of rheumatic fever and rheumatic heart disease in young people: an 11-year retrospective study

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Acute rheumatic fever (ARF) is an autoimmune response triggered by group A streptococcal infection that occurs mostly in children aged 5–14 years.¹ Rheumatic heart disease (RHD) is a chronic sequela that may result from one or recurrent ARF episodes and is characterised by scarring to valves of the heart. RHD has significant morbidity and causes premature mortality among disadvantaged populations; prevalence rates among Australian Aboriginal and Torres Strait Islander peoples are some of the highest reported in the world.²

Secondary prevention of RHD aims to prevent disease progression after diagnosis. This encompasses early diagnosis, regular monitoring and secondary prophylaxis.⁴ Secondary prophylaxis every 21–28 days with intramuscular benzathine penicillin G (BPG) is effective for preventing group A streptococcal infection and improving RHD severity over time.^{4,5} The recommended duration of secondary prophylaxis based on the Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease during this study was a minimum of five years (or until 21 years of age), whichever was longer.⁴

Rates of adherence to BPG remain low in Australia.⁶ Barriers to long-term uptake of BPG doses include pain with injections, under-resourcing of health care services, poor education, and low access to health services.^{7,8} A dedicated state-wide register is responsible for secondary prophylaxis

Abstract

Objectives: To evaluate the secondary prevention of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) in the Townsville region, Australia.

Methods: Adherence to benzathine benzylpenicillin G (BPG) was determined for 196 children and young adults aged under 22 years between January 2009 and December 2019, and factors associated with BPG adherence were analysed. Secondary outcomes included attendance at specialist reviews and echocardiograms.

Results: Adequate adherence (80%) to regular BPG injections was met by 51.1% of the cohort. Adequate BPG adherence more likely occurred for those that attended the Paediatric Outreach Clinic (OR4.15, 95%CI:2.13–8.05) or a school delivery program (OR1.87, 95%CI:1.11–3.45). People with moderate/severe RHD had greater BPG adherence (OR1.76, 95%CI:1.00–3.10). People in rural/remote areas were less likely to have adequate BPG adherence compared to urban counterparts (OR0.31, 95%CI:0.15–0.65). Adherence to echocardiography was 66% and specialist review attendance was 12.5–50%.

Conclusion: Half of the cohort in the Townsville region received adequate BPG prophylaxis to prevent ARF/RHD. Although rates were relatively higher than those reported in other Australian regions, health delivery goals should be close to 100%. Low attendance at specialist services was reported.

Implication for public health: Delivery models with dedicated services, case management and family support could improve BPG adherence in individuals with ARF/RHD. Further resources in rural and remote areas are needed.

Key words: adolescent, rheumatic fever, rheumatic heart disease, Penicillin G Benzathine, treatment adherence and compliance, medication adherence, antibiotic prophylaxis, secondary prevention

recall with monthly patient lists distributed to service providers to prompt action for injections.⁶ In Queensland, Australia, ARF and RHD are notifiable conditions, and the register regularly adds newly diagnosed or updated patient information. In addition, the register has a broader role in monitoring the effectiveness of the RHD control strategy.

Improved adherence to standardised secondary prophylaxis delivery and care models remains a priority for the Australian ARF/RHD Control Strategy.^{8,9}

This study aims to report adherence rates to secondary prevention of RHD⁴ and identify factors associated with adequate adherence in children and young adults in Townsville,

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The authors have stated the following conflicts of interest: Dr Andrew White is the director of Paediatrics at the Townsville University Hospital and a supervisor for this project.

He has been involved in the development and delivery of the Paediatric Outreach Clinic. Dr White was not directly involved in the data collection, filtering or data analysis processes. Joshua Liaw maintains responsibility for the integrity of the data and the accuracy of the data analysis.

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a major region of North Queensland with a high burden of RHD.

Methods

Setting

The Townsville region is a large geographical area (more than 148,000 km²) and includes 238,614 residents. In 2018, 7.8% identified as Aboriginal or Torres Strait Islander.¹⁰ The region includes one major urban centre (Townsville) and several regional, rural and remote communities.

Several delivery models for secondary prevention of RHD exist in the Townsville region. The Townsville University Hospital (TUH) runs a Paediatric Outreach Clinic for children under 16 living in the urban area. This nurse-led program administers BPG to children at TUH, at their school or homes depending on family preference. Other BPG providers in the Townsville region are school-based programs largely run at boarding schools by a school health nurse, primary health care providers (general practices and an Indigenous Medical Service), and Townsville Hospital and Health Service (THHS) centres at rural and remote sites. Classification of urban, regional, and remote sites in this study was determined by the Modified Monash Model (MMM),¹¹ which grades rurality based on population size and remoteness from capital cities. The scale ranges from MM1 (city) to MM7 (very remote – e.g. Palm Island).

Design

A retrospective cohort study was conducted from January 2009 to December 2019, with data provided by the Queensland RHD Register and TUH medical records. The register had been previously validated against TUH medical records and regularly undertakes internal processes to detect new or unregistered individuals with RHD in the region. For each case, database custodians provided the age, gender, ethnicity, RHD status, ARF recurrences, disease severity, dates and location of BPG injections, specialist and echocardiograms appointments. For each patient, the duration of follow-up was from the first injection of BPG in the Townsville region until either they left the region or they were 22 years of age, or until the end of the study period on 31 December 2019, whichever occurred first.

Ethics was granted by the THHS Human

Research Ethics Committee (HREC/2019/QTHS/56398). This study was endorsed by the Townsville University Hospital Aboriginal and Torres Strait Islander Health Leadership Advisory Council.

Eligibility criteria

All eligible patients were included in the analysis. Individuals aged 0–21 years who received at least three BPG doses (a period of 42–56 days based on the 3- or 4-weekly regimen) in Townsville districts were included. Those who received <3 BPG doses were excluded by the arbitrary cut-off, as they were determined to be non-permanent residents in Townsville. All specialist consultations and echocardiograms were included. A patient was no longer classified in the Townsville region if their 'primary provider' changed to one outside the Townsville region or a transfer date was listed; a 'primary provider' was defined as delivering >60% of BPG doses in any year.

Definitions of BPG adherence

Per cent adherence to BPG was calculated as the sum of BPG doses received divided by the total number required (either based on a 21- or 28-day schedule) from their first to their last BPG in the Townsville region. At a systems level, a recommended key performance indicator (KPI) for RHD Control Programs is the proportion of individuals receiving 80% of scheduled doses,^{4,6} so this was emphasised as our main outcome.

Days-at-risk (DAR) is the number of days a patient was not covered by secondary prophylaxis due to delays or missed BPG doses. In this study, the date a BPG dose was administered is 'day 1' and DAR starts on 'day 29' until another dose is administered. The inverse of DAR is proportion-of-days-covered (PDC) and was determined by the percentage of a year a patient was protected against GAS re-infection; $[(1 - \text{DAR}/\text{year}) \times 100\%]$.

For logistic regression, BPG adherence was dichotomized into a binary variable, defined as achieving or not achieving 80% adherence. This threshold was chosen in alignment with the current target for BPG adherence in Australia and is associated with a markedly reduced risk of ARF recurrence.⁴ It is also used as a cut-off for medication adherence in many other chronic conditions.^{1,22}

Clinical outcomes

BPG adherence was reported as the proportion achieving than 80% adherence,

median absolute per cent adherence, DAR and PDC. For patients who transferred out of the Townsville region to a new health district, DAR was used to measure the time interval until recommencing BPG at their new service provider.

Secondary outcomes measured were adherence to cardiology reviews, paediatrician reviews and routine echocardiograms. Adherence to these components was determined by using the local TUH guidelines, which stratify priority based on RHD severity (Supplementary File 1). Adherence was calculated as the percentage of the total number of attended appointments over the total number of scheduled appointments for the duration of follow-up. Paediatric services (paediatric cardiology and paediatricians) were accessed by those under 16 years of age, and those >16 years were transferred to adult cardiology for case management. Routine echocardiograms were performed by the radiology department.

Data analysis

Data analysis was performed using SPSS, version 27.0 (SPSS Inc, Chicago, IL, USA). Normality of data was determined by inspection of histograms. Adherence to BPG (per cent adherence, DAR, PDC) and specialist attendance (cardiology and paediatric reviews, echocardiograms) were reported as median (interquartile range), and categorical data were reported as frequency and percentage. Descriptive sub-analysis of individuals with paired paediatric data (<16 years) and adult (>16 years) data was also conducted.

Factors associated with adherence

The proportion of patients who received 80% BPG doses by age, RHD severity, gender, rurality, type of service provider, calendar year, number of providers, and location of initial ARF diagnosis were calculated. Statistical analysis was guided by a previous study⁵ and with the guidance of a statistician. Multivariate logistic regression with generalized estimating equations (GEE) model was used to identify factors associated with adherence. An autoregressive correlation structure was adopted. Factors were chosen a-priori. Stepwise backward selection ($P < 0.20$) was used for inclusion in the multivariate model. Odds ratios, 95% CI and p values, and a correlation matrix are reported.

Results

A total of 196 people in the Townsville region were included. Baseline characteristics of the cohort are displayed in Table 1A. The age of participants ranged from 4.5–20.8 years, with a median age of last follow up at 16.0 years.

Overall, 51.1% of the cohort received 80% of BPG injections during 2009–2019. The median (IQR) per cent adherence was 81.8% (66.7–94.8). Adherence calculated as PDC had a median of 75.9% (61.9–86.2). Attendance at recommended specialist services during the study period was relatively low (Table 1B), however higher adherence was reported for routine echocardiograms (66.67%, IQR 50–100).

The median duration of follow-up for patients in the Townsville region was short (2.8 years). The average age at first BPG dose was 12.0 years, and patient movement trends across age groups (Figure 1) found high rates of migration out of Townsville after 15 years.

Of those who transferred out of the Townsville region (n=80 people) to a new health district, an average delay of 21 (IQR 1–57) days at risk was observed before BPG recommencement.

Limited patients had attendance data across both paediatric and adult services during

their time in the Townsville district. Data are reported descriptively in Table 2. No change in BPG adherence was observed in individuals. However, a decline in median attendance at specialist services (adult cardiology) was observed in 27 children when patients transferred to adult services (adult cardiology).

There were 188 patients who contributed 568 annual estimates of adherence included in the multivariate analysis. Of those with complete data, 44% (252) were adherent (>80% adherent) to secondary prophylaxis (SP). See Table 3 for characteristics of the cohort.

Increased adherence was significantly associated with people receiving injections from the TUH Paediatric Outreach Program, and from school-based programs compared to primary health care providers (OR 4.15, 95%CI:2.13–8.05, $p<0.001$) and (OR 1.87, 95%CI:1.11–3.45, $p=0.045$), respectively. Adequate BPG adherence was significantly

associated with more severe disease; moderate/severe RHD (OR 1.76, 95%CI 1.00–3.10, $p=0.048$) and borderline/mild RHD (OR 1.66, 95%CI:1.10–2.72, $p=0.045$), compared to those with no RHD.

Living in small rural/remote (>MMM 5) areas was a predictor of lower adherence compared to urban and regional areas (OR 0.31, 95%CI: 0.15–0.65, $p=0.002$).

There was no significant difference in BPG adherence between calendar years. Those aged 16 had decreased BPG adherence but did not reach statistical significance. All OR and p-values are displayed in Table 3.

Discussion

Adherence to secondary prophylaxis for ARF/RHD in the Townsville region during this study is higher than previous reports of BPG adherence in Australia and regional Queensland ranging from 15–40% of cohorts

Figure 1: Sub-analyses of patient movement in the Townsville district by age group.

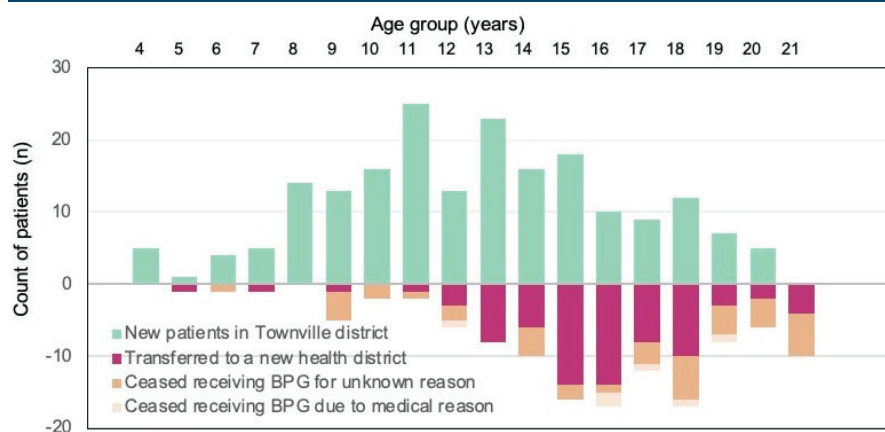


Table 1b: Overall median (IQR 25–75) adherence to secondary prevention of RHD.

Category	All (n) ^a	Median (IQR25–75)
Adherence to BPG		
Per cent Adherence	196	81.8 (66.7–94.8)
Proportion of Days covered		75.9 (61.9–86.2)
Days-At-Risk per year (days)		88 days (50.4–139.0)
Adherence to specialist components^b		
Echocardiogram (%)	159	66.7 (50.0–100.0)
Paediatrician review %	134	50.0 (0.0–100.0)
Paediatric cardiology %	25	33.3 (0.0–75.0)
Adult cardiology %	46	12.5 (0.0–100.0)
Transition out of Townsville District^c		
DAR during transition to a new health district	80	21.0 (1.0–57.0)

Notes:

IQR, interquartile range, BPG, Intramuscular Benzathine Penicillin G; RHD, Rheumatic Heart Disease; ARF, Acute Rheumatic Fever.

a: Total (n) is based on the number of patients with available data for each outcome.

b: Guidelines for recommended intervals of specialist components for ARF/RHD are outlined by priority classification and age (see Supplemental 1.0).

c: Data regarding Days-at-risk in transition out of Townsville catchment to a new health district was only available in 80 patients based on notifications to the RHD Register.

Table 1a: Characteristics of the cohort.

Category	All (n=196 patients)
Length of follow-up (years)	
Median (IQR 25–75)	2.2 (1.2–3.7)
Age at inclusion (years)	
Median (IQR 25–75)	13.09 (10.3–15.5)
Ethnicity	
Aboriginal and/or Torres Strait islander	187 (95.4%)
Other high risk (Maori, Pacific Islander)	5 (2.6%)
Caucasian	4 (2.0%)
RHD Severity	
No RHD	66 (33.7%)
Mild/borderline	93 (47.4%)
Moderate	24 (12.3%)
Severe	13 (6.6%)
Previous Valve Surgery	
No	187 (95.4%)
Yes	9 (4.6%)
ARF episode	
Confirmed	176 (89.8%)
Highly suspected	5 (2.5%)
Ruled out/Uncertain	10 (5.1%)
No history ARF episode	5 (2.6%)
Schedule of BPG injections	
28 days	189 (96.4%)
21 days	7 (3.6%)

receiving 80% adherence.^{5,6,8,13,14} BPG is the mainstay of effective secondary prevention for ARF and RHD.⁴ Adequate BPG adherence has been shown to reduce ARF recurrences, and in some cases reduce the severity of RHD over time.⁵

Median PDC was lower than the equivalent median per cent adherence of the cohort. This may be due to BPG doses administered early before their next prescribed date. Measurement with per cent adherence does not consider the overlap of BPG injections given early and may overestimate the true coverage of BPG.¹⁵ A recommended KPI for PDC should be considered for system-level monitoring as it is a more accurate measurement of the effective coverage of BPG in a cohort.

BPG adherence varied considerably between those under 16 years, classified as 'paediatrics', and those over 16 classed as 'adults' in Townsville Hospital and Health Services. Higher adherence to BPG in younger patients has been previously reported.⁵ This may be partially due to the greater influence of caregiver/s at this age. In addition, in this study, there was the effect of different service delivery models in Townsville regions for those under 16 years; predominantly the Paediatric Outreach Clinic and school-based delivery programs.

The strongest association with BPG adherence was the Pediatric Outreach Program at TUH. School-based programs were also strongly associated with secondary prophylaxis adherence, which is consistent with evidence from New Zealand.^{16,17} Both models are examples of 'outreach secondary prophylaxis' in Australia and are increasingly recognised as a priority in improving the secondary prophylaxis of RHD.^{7,17} This study cannot determine which aspects of these programs lead to better adherence; however, it is likely a combination of dedicated

resources with case management, active follow-up, consistency and accessibility of the service, and family self-selection. School-based providers similarly share many of these strengths, including ease of access, continuity of care and peer support among children with previous ARF or RHD.

Small rural and remote areas, defined by the Modified Monash Model as MMM5, had significantly lower adherence compared to the main urban centre (Townsville). This is consistent with findings in previous studies.^{5,13,18} Evidence suggests greater access to health clinics, such as being within walking distance or the availability of a community health bus service, can relatively improve BPG adherence in remote communities.¹⁵ Remote areas in this study such as Palm Island, which is situated approximately 70km offshore the mainland, could benefit from greater resource allocation for outreach health services for locals.

This study supports evidence for a larger role of system-level interventions on BPG adherence compared to individual factors. Increased availability and uptake of dedicated/outreach prophylaxis interventions may be beneficial to improving BPG delivery in Australia, particularly in remote areas. School-based and paediatric outreach programs are well placed to provide supportive clinical leadership alongside clinical information systems and recall systems.

Higher adherence to BPG in those with RHD compared to no RHD may be attributable to better awareness of a diagnosis, and more timely education, support and follow-up. Those with severe RHD may also be symptomatic.⁵ This study did not find an association of BPG adherence with gender or time since diagnosis. Conflicting literature on these factors,^{8,15,18} is likely to reflect varied patient demographics among cohorts.

BPG adherence appeared to increase in 2017–2019 compared to 2009–2012, but this was not statistically significant. While this may reflect improvement in the overall health service delivery in the region, many other factors such as population composition (i.e. percentage less than 16 years old), or geographic distribution variation across calendar years (i.e. net migration towards the urban centres) could be contributory. As such, the interpretation of calendar year-to-year trends in this study should be with caution.

Participants had a relatively short duration of secondary prophylaxis follow-up in the Townsville region during this study, despite many patients commencing prophylaxis at a young age. One possible explanation is the close proximity of other health service regions, with many families spread out across different health service catchments. When young patients move to different households they can move in and/or out of the Townsville health region. Another possible contributor to the short follow-up duration was the high

Table 2: Median (IQR) Adherence to components of secondary prevention of ARF and RHD before and after transition from paediatric to adult care.

Component	≤16 years	>16 years
Attendance at scheduled specialist review components ^a (n=27)	27.5 (54.2)	0.0 (100.0)
Percent adherence to BPG (n=29)	67.1 (21.4)	69.5 (39.9)

Note:
a: Recommended intervals for specialist components are based on local guidelines as detailed in Supplemental 1. These include Paediatrician and/or Paediatric Cardiology for those under 16 years, and Adult Cardiology for those over 16 years.

Table 3: Factors associated with adherence to secondary prophylaxis. Odds ratios from GEE logistic regression.

Factor	Category	Number (n) ^a	% (n) with ≥80% BPG adherence	Odds ratio (95% CI)	p value
Age (years)	≥16	219	33.8 (74)	0.68 (0.44–1.06)	0.091
	<16	349	51.0 (178)	Ref	
RHD grade	Moderate/Severe RHD	92	43.5 (40)	1.76 (1.00–3.10)	0.048*
	Borderline/Mild RHD	287	46.7(134)	1.66 (1.10–2.72)	0.045*
	No RHD	189	41.3 (78)	Ref	
Residence	Small rural and remote (MMM ≥5)	190	22.6 (43)	0.31 (0.15–0.65)	0.002*
	Regional THHS - MMM3/4	54	57.4 (31)	1.67 (0.77–3.59)	0.192
	Urban (TSV) - MMM1/2	324	54.9 (178)	Ref	
Service Provider	School-based program	121	43.8 (53)	1.87 (1.11–3.45)	0.045*
	Paediatric Outreach Program	148	72.3 (107)	4.15 (2.13–8.05)	<0.001**
	Other THHS Provider	175	26.3(46)	1.69 (0.74–3.87)	0.216
	Primary Health Centre	124	37.1 (46)	Ref	
Calendar Year	2017-2019	233	51.5 (120)	1.28 (0.77–2.14)	0.174
	2013-2016	229	38.9 (89)	0.73 (0.46–1.16)	0.373
	2009-2012	106	40.6 (43)	Ref	

Notes:
GEE, generalised estimating equations; BPG, Intramuscular Benzathine Benzylpenicillin G; Ref, reference; CI, confidence interval, MMM, Modified Monash Model; RHD, Rheumatic heart disease; THHS, Townsville Hospital Health Service.
a: (n) is the number of calendar year observations i.e. a patient with (x) years active in THHS will provide (x) number of calendar year observations.
*p<0.05 **p<0.001

transfers rates out of the Townsville region after age 15, which coincided with the end of secondary school.

Of those who transferred, delays were observed in patients recommencing BPG at their new provider. Patients accessing an unfamiliar service, a lack of planning and/or recall/reminder systems may contribute to these delays. Clear guidelines for referring clinics in notification and transfer processes should be readily available, and families should be encouraged to inform their health service when they move.

Some patients had unknown cessation of active care after 15 years. It is unknown what proportion were: a) transfers out of Townsville that were not notified to the register; b) never recommenced BPG after transfer; or c) lost to follow-up during step-down from paediatric outreach/school programs to community services in Townsville.^{6,19} Deterioration of health outcomes during the transition period from paediatric to adult services is seen in many chronic diseases.²⁰ Continuity of care in adolescents and young adults (15–24 years) is essential in RHD, as most morbidity and mortality from RHD occurs in adult life.^{21,22}

Further longitudinal insight is needed to accurately assess this 'vulnerable' period in RHD care, with greater importance on transfers between health districts. For adolescents who are stepped down from paediatric services after 16 years, a coordinated adolescent and young adult model with integrated pediatric and adult specialist services and involvement of primary health services is needed in Townsville.²⁰ State RHD registers and patient records must also ensure accurate case finding, linkage, monitoring and timely follow-up.

Sub-optimal adherence rates to recommended guidelines for specialist review were observed. Priority classifications based on RHD severity are used in national and local guidelines to assist specialist care plans,⁴ though uncertainty remains regarding the optimal level of specialist involvement in geographically challenging or resource-limited settings. Ensuring specialist attendance is essential for RHD management; however, low attendance may not always indicate poorer service or health outcomes. For example, in the Townsville region access to paediatric cardiology has been limited due to reliance on a visiting service, but those with moderate, severe or uncertain RHD were streamed into the cardiology service.

Improving accessibility of essential services is needed to ensure the best outcomes for children.

Strengths and limitations

ARF and RHD are notifiable conditions in Queensland and diagnosis is in general well documented. This study was able to show consistent trends in secondary prevention in the Townsville region during the 11-year study period, with major insights on care considerations that are applicable locally and in other health districts.

There are inherent limitations in the retrospective design and use of register data. The Queensland RHD register relies on the completeness of the database and may have recall bias by clinicians and underreporting.⁶ The inability to detect or track patients that are not receiving care is a long-standing issue of many state registers in Australia.¹⁹ TUH medical records were used to supplement register data, however, cross-validation of all providers was beyond the resources available for this study. Internal processes are routinely used by the register to detect unregistered individuals with RHD. Despite this, overall adherence to BPG may be overestimated in this study. Adherence to BPG is also influenced by a range of factors.⁵ Data on other potentially relevant factors such as access to health care, co-morbidities and patient attitudes was not available. Future studies could also document components of the Pediatric Outreach Program and school delivery programs that contribute to higher patient adherence in Australia. The inclusion of surrounding health districts in future studies could also allow for detailed analysis of the transition from paediatric to adult specialist care and patient tracking. Dental follow-up adherence was not measured in this study but remains an important component of secondary prevention for ARF/RHD.

Conclusion

Relatively higher overall adherence rates to BPG were identified in the Townsville region compared to previous Australian regions. However, further improvements are needed to improve rates of BPG adherence to an acceptable standard close to 100%. Adherence rates were significantly higher in school-based delivery programs and the Paediatric Outreach Clinic.

Targeted interventions for those living in rural and remote areas, and better services for adolescents and young adults may improve secondary prevention in the Townsville region. Improved availability of specialist services is also likely to be beneficial for patients with RHD. Better secondary prevention of RHD, with accurate monitoring systems by state registers, remains a priority in the continued public health efforts for Aboriginal and Torres Strait Islander Peoples and communities.

Data availability statement

The data received from the Queensland RHD Register cannot be shared publicly. Australian-based researchers can apply to the Townsville RHD Project team with a proposal to analyse a research question or part of this study, subject to internal and ethics approval of the investigator and their research plans.

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Ethics Approval Statement

Ethics was granted by the THHS Human Research Ethics Committee (HREC/2019/QTHS/56398). A waiver of consent was approved for this study.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary File 1: Guidelines for recommended intervals for specialist management of ARF/RHD in the Townsville region (unpublished).