# The evidence that rheumatic heart disease control programs in Australia are making an impact

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## Abstract

**Objective:** Rheumatic heart disease (RHD) comprises heart-valve damage caused by acute rheumatic fever (ARF). The Australian Government Rheumatic Fever Strategy funds RHD Control Programs to support detection and management of ARF and RHD. We assessed epidemiological changes during the years of RHD Control Program operation.

**Methods:** Linked RHD register, hospital and death data from four Australian jurisdictions were used to measure ARF/RHD outcomes between 2010 and 2017, including: 2-year progression to severe RHD/death; ARF recurrence; secondary prophylaxis delivery and earlier disease detection.

**Results:** Delivery of secondary prophylaxis improved from 53% median proportion of days covered (95%CI: 46-61%, 2010) to 70% (95%CI: 71-68%, 2017). Secondary prophylaxis adherence protected against progression to severe RHD/death (hazard ratio 0.2, 95% CI 0.1-0.8). Other measures of program effectiveness (ARF recurrences, progression to severe RHD/death) remained stable. ARF case numbers and concurrent ARF/RHD diagnoses increased.

**Conclusions:** RHD Control Programs have contributed to major success in the management of ARF/RHD through increased delivery of secondary prevention yet ARF case numbers, not impacted by secondary prophylaxis and sensitive to increased awareness/surveillance, increased.

**Implications for public health:** RHD Control Programs have a major role in delivering cost-effective RHD prevention. Sustained investment is needed but with greatly strengthened primordial and primary prevention.

**Keywords:** acute rheumatic fever, rheumatic heart disease, control programs, disease progression, cardiovascular epidemiology, indigenous health

## Introduction

Acute rheumatic fever (ARF) is an autoimmune reaction to an untreated skin or throat infection with Group A Streptococcus (GAS), usually occurring in children and young adults. Severe and/or repeated ARF can lead to permanent valvular heart damage, known as rheumatic heart disease (RHD), which is highly prevalent in northern Australia.[1] ARF and RHD occur where there is household

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crowding and inadequate hygiene and healthcare access. In Australia, Aboriginal and Torres Strait Islander people (hereafter respectfully Indigenous) and immigrants from low- and middle-income countries (ILIC) are greatly overrepresented.[1] Northern Territory (NT)-based longitudinal studies have estimated that in the first year after an initial ARF episode, 3–4% of people will experience ARF recurrence and 27–35% will progress to RHD.[2,3] RHD leads to adverse outcomes including heart failure and premature death, with a recent study reporting 23% of mild/moderate RHD cases <35 years progressed to cardiovascular complications or death within 8 years.[4]

The Australian Commonwealth-funded Rheumatic Fever Strategy (RFS) is the major government initiative to control RHD, with the long-term goal of reducing RHD-associated morbidity and mortality within Australia. Launched in 2009, the RFS focusses on RHD register establishment, operation, research, education, and data collection/surveillance.[5] Separate Control Programs established in the NT, Queensland (Qld), Western Australia (WA), and South Australia (SA) in conjunction with RHDAustralia have been supported by RFS funding over the last decade. New South Wales (NSW) also operates a Control Program, independently of RFS funding. The RFS-funded Control Programs promote early ARF/RHD diagnosis and encourage prompt enrolment of people diagnosed with ARF/RHD onto registers, facilitating primary care services to deliver secondary prophylaxis and specialist follow up as per National Guidelines for management of ARF and RHD (hereafter the "National Guidelines").[6] Since 2009, RHD Australia has actively promoted clinical excellence and best practice through development of the National Guidelines and educational resources for health professionals.[6]

The RHD Endgame Strategy, launched in 2020 and yet to receive implementation funding, has outlined the steps needed for elimination of ARF and RHD in Australia by 2031.[7] The five priority action areas identified by the Endgame Strategy target all stages of the GAS infection/ARF/RHD disease course. Also highlighted by the Endgame Strategy is the importance of Aboriginal and Torres Strait Islander leadership and need for addressing the root cause of RHD by improving access to healthy housing and built environments among those at risk. Addressing these social and environmental determinants of health that drive GAS infection will interrupt the cascade of events that ultimately leads to ARF and/or RHD.[8] Whilst the 2009 RFS targets ARF and RHD in their advanced stages by focussing on secondary and tertiary prevention, the 2020 Endgame Strategy expands this scope to include interventions at all stages of diseases.

Evaluation of the impacts of the existing RFS has been limited, with no person-based clinical outcomes reported for individuals with ARF/RHD.[9] The Australian Institute for Health and Welfare (AIHW) collates and publishes annual reports combining jurisdictional RHD register data, providing snapshots of surveillance indicators and patient characteristics based on the RHD register minimum data collection. However, longitudinal trends in disease control are hard to estimate due to methodological and reporting changes over time.[10–12] Additionally, AIHW reports are based on register-derived information only and do not incorporate information from other sources, such as hospitalisations. Pausing to reflect on the real-world impacts since the RFS is timely, given the current transition to RHD Endgame Strategy interventions that focus more heavily on early preventative measures.

The present clinically focussed study seeks to determine whether indicators of ARF/RHD diagnosis and management have changed over time using linked data from diverse sources collected between 2001 and 2017. The primary aim was to determine whether progression from first ARF or mild RHD to recurrent ARF or severe RHD/death, has changed since RHD Control Programs were established in Australia, and its association with secondary prophylaxis delivery. The secondary aims were (i) document changes over time in secondary prophylaxis delivery; (ii) report trends in ARF recurrence rates; (iii) determine whether there was a trend towards better ARF case detection. These aims will establish a baseline of ARF/RHD progression trends under the RFS, against which future impacts of the RHD Endgame Strategy can be measured.

## Methods

### Study Design

This is a retrospective longitudinal analysis of clinical outcomes of <35-year-old people who were notified to registers with confirmed ARF or mild RHD.

### Data sources and cohort selection

Data were obtained from linked ARF/RHD registers, hospitalisation and death records from NT, Qld, WA and SA, assembled by the ERASE project[13] (Australian New Zealand Clinical Trials Registry number ACTRN12620000981921). Deidentified patient data contained demographic and clinical information from January 2001 to December 2017, with benzathine benzylpenicillin (BPG) injection dates recorded since 2010. The period covered differed slightly for each analysis in order to incorporate the necessary follow-up times within the available data. Given earlier linkage of data in WA, this jurisdiction only had data available until mid-2017. In the NT, where ARF/RHD Control Programs and disease registers have been established since 1997, data since 2002 was extracted for inclusion in this analysis. Detailed data availability, cohort derivations and inclusions/exclusions are illustrated in Supplement 1.

People aged <35 years diagnosed with first-ever definite ARF (the 'ARF cohort') or mild RHD (the 'RHD cohort') between 2010 and 2017 were identified from RHD registers. Using register data for cohort derivation ensured that the inclusion criteria of initial ARF or mild RHD were reliable (these disease severity classifications are not captured by hospitalisation data), with good register coverage known to exist among young Australians.[14] Outcomes and follow-up were determined using all available ERASE data sources.[13]

### Baseline characteristics and covariates

Baseline demographic features for both cohorts included: age at diagnosis, calendar year of diagnosis, sex, population group (Indigenous, Immigrant from low-income country [ILIC, including Māori/Pasifika], other Australian), state of residence, geographical remoteness (ARIA) and area-level socioeconomic quintile (Index of Relative Socioeconomic Disadvantage, IRSD). Comorbid conditions were identified using any diagnosis field in hospitalisation records over all available lookback (up to 9 years) and included chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), diabetes, hypertension, prior infection-

related hospitalisation (dental, ear, skin or throat GAS) (see Supplement 2).

### Analysis framework and outcome indicators

Program logic models from the RFS Health Policy Analysis report[9] and indicators outlined by the RHD Endgame Strategy[15] provided the framework for the analysis of disease progression, BPG delivery, ARF recurrences and better ARF case detection. The outcomes were determined using the ERASE linked register, hospitalisation and death datasets.

1. Disease progression

Disease progression was defined in this study as (i) ARF recurrence or (ii) severe RHD or death from any cause within 2 years of diagnosis, for people in both the ARF cohort and the RHD cohort diagnosed January 1, 2010, to December 31, 2015. This ensured 2 years of data were available for each patient (Supplement 1).

2. BPG coverage

BPG coverage in the first year after diagnosis of ARF (ARF cohort) or RHD (RHD cohort) between January 1, 2010, and December 31, 2016, was measured by two methods: median proportion of days covered (PDC) and adjusted adherence. This time period was defined to ensure that one complete year of data coverage after diagnosis (at the individual level) was available for analysis (Supplement 1). PDC is a commonly used continuous measure of medication delivery.[16] Adjusted adherence is a pragmatic measure of BPG delivery[15]; this divides the number of administered injections by prescribed injections (excluding injections <14 days after a preceding dose[17]). The proportion of all people on prophylaxis who received 80–99% or 100% of their injections according to the adjusted adherence measure was calculated for each calendar year.

3. ARF recurrence rates

ARF episodes between January 1, 2010, and December 31, 2017, were categorised as "initial" or "recurrent" (from January 1, 2002 for NT data, Supplement 1). For register records, ARF status was provided for each ARF episode. For hospitalisation records, ARF status was defined as the first recorded ARF with no prior ARF record in ERASE data. Recurrent episodes were those occurring ≥90 days after the most recent ARF-related record (ICD-10AM codes I00-I02), consistent with previous ERASE definitions.[1,13] Person-year denominators were used for the calculation of ARF recurrence rates.

4. Better ARF case detection

Two indicators of better ARF case detection were used, assuming (i) that earlier detection of disease would be evident from increasing proportions of RHD with known prior ARF over time and (ii) the proportion of concurrent ARF/RHD diagnoses would decline over time if there was a trend towards earlier or less severe diagnoses.

The proportion of all new annual RHD registrations (first-ever diagnosis and otherwise) with any ARF episode occurring ≥90 days prior was calculated annually between January 1, 2010, and December 31, 2017 (from January 1, 2002 in NT). The proportion of concurrent initial ARF/RHD diagnoses (both ARF and RHD diagnoses occurring within 90 days) out of all new ARF or RHD registrations per year was also calculated.

### Statistical analyses

For 2-year progression trends over time, the proportion of people in the ARF cohort or RHD cohort who experienced (i) ARF recurrence and (ii) those who progressed to severe RHD/death by calendar year of first diagnosis for 2010–2015 was calculated, with 95% confidence intervals (CI), and temporal trends were assessed using a Cochran-Armitage trend test.

The associations between clinical/demographic predictors and 2-year progression were investigated using Cox proportional hazards regression and restricted cubic spline analysis. Univariate analyses were undertaken to select candidate variables for inclusion in the final multivariable results. Associations in the final model are reported as hazard ratios (HR) with 95% CI.

Annual ARF recurrence rates per 100 person-years were calculated for 2010–2017 (and 2002–2017 for NT). Individuals contributed time to the denominator from first-recorded ARF. Person-time calculations ceased at the end of available follow-up or death whichever occurred first. ARF recurrences were assigned to the numerator of the year of recurrence. Trends in recurrence rates by calendar year were estimated from Poisson log-linear regression models, using the exponential of the beta-coefficient for diagnosis year.

Cochran–Armitage trend tests were used to assess trends in secondary outcomes over time.

Analyses were undertaken using SAS v9.4 and R version 4.1.1.

## Results

Results are presented overall and stratified into NT (mature Control Program established 1997) and Qld/WA/SA (programs established in 2009/2010/2012 respectively).

The ARF cohort comprised 1,675 young people (n=876 NT register, n=849 Qld/WA/SA registers) and the RHD cohort identified 1,840 individuals (n=1,174 NT, n=734 Qld/WA/SA, Table 1). Approximately half of people diagnosed with ARF/RHD were females and aged 5–14 years. People with registered ARF or RHD were predominantly Indigenous Australians (≥90%), NT residents (50.7% ARF and 61.9% RHD), from remote or very remote areas (71.4% ARF and 73.8% RHD) and living in the lowest IRSD quintile areas (70.4% ARF and 72.2% RHD). Prior infection-related hospitalisations were recorded for 43.9% of people with ARF and 42.7% with RHD. Preexisting chronic comorbidities were recorded for 16.2% of the ARF cohort and 20.5% of the RHD cohort, most commonly non-RHD CVD and CKD.

The register subgroups had similar age/sex profiles (Table 1). A greater proportion of the NT registrants (84.3%) were from remote locations, than those from Qld/WA/SA (59%). Numbers of ARF and RHD cases increased over time (Table 1), most notably ARF in the NT (3-fold increase from 50 ARF cases in 2010 to 158 in 2017); NT RHD case numbers were 153 in 2010 and 162 in 2016. In Qld/WA/SA, ARF case numbers were 76 in 2010 and 134 in 2016; RHD 87 in 2010, 101 in 2016.

### ARF/RHD progression over time

*Initial ARF cohort*

Of 1050 people with initial ARF, 112 (10.7%) experienced an ARF recurrence and 88 (8.4%) progressed to severe RHD or death and within 2 years, with similar progression measured when stratified into NT and Qld/WA/SA subgroups (Supplement 3). ARF recurrence or

**Table 1: Demographic and clinical features of the ARF cohort and the RHD cohort.**

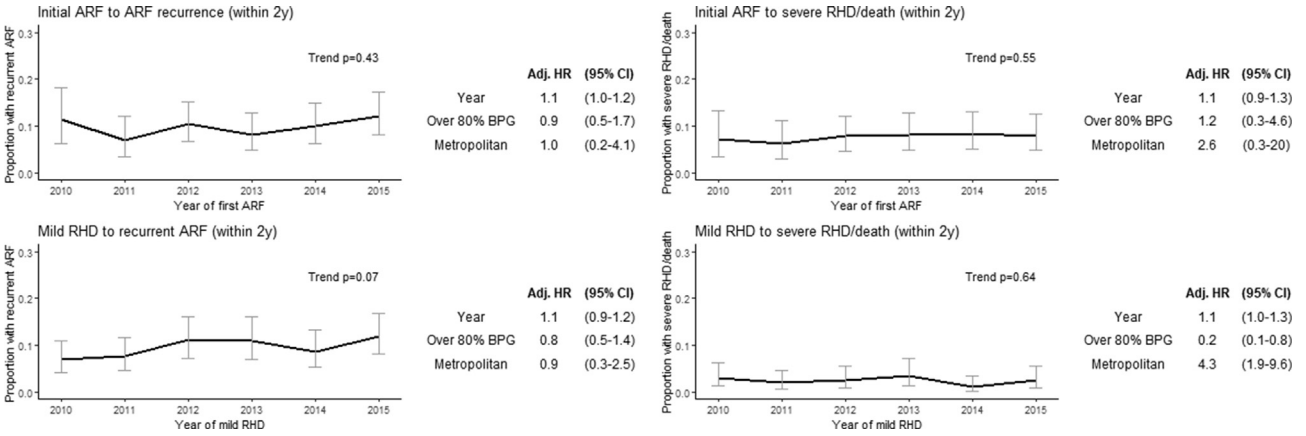
| | ARF cohort | | | RHD cohort | | |
|---|---|---|---|---|---|---|
| | NT/Qld/WA/SA Frequency (%) | NT Frequency (%) | Qld/WA/SA Frequency (%) | NT/Qld/WA/SA Frequency (%) | NT Frequency (%) | Qld/WA/SA Frequency (%) |
| | n = 1675 | n = 876[a] | n = 849[a] | n = 1840 | n = 1174[b] | n = 734[b] |
| Age category | | | | | | |
| 1–4 years | 49 (2.9) | 30 (3.4) | 20 (2.4) | 34 (1.8) | 27 (2.3) | 8 (1.1) |
| 5–14 years | 1064 (63.5) | 545 (62.2) | 538 (63.4) | 956 (52.0) | 620 (52.8) | 365 (49.7) |
| 15–24 years | 387 (23.1) | 209 (23.9) | 196 (23.1) | 564 (30.7) | 347 (29.6) | 234 (31.9) |
| 25–34 years | 175 (10.4) | 92 (10.5) | 95 (11.2) | 285 (15.5) | 179 (15.2) | 126 (17.2) |
| Sex | | | | | | |
| Male | 792 (47.3) | 421 (48.1) | 390 (45.9) | 828 (45.0) | 532 (45.3) | 318 (43.3) |
| Female | 882 (52.7) | 455 (51.9) | 458 (53.9) | 1011 (54.9) | 641 (54.6) | 415 (56.5) |
| Population group | | | | | | |
| Indigenous | 1575 (94.0) | 861 (98.3) | 764 (90.0) | 1755 (95.4) | 1150 (98.0) | 671 (91.4) |
| ILIC | 59 (3.5) | <5 (0.3) | 56 (6.6) | 43 (2.3) | <5 (0.3) | 40 (5.4) |
| Other Australian | 40 (2.4) | 12 (1.4) | 28 (3.3) | 40 (2.2) | 20 (1.7) | 21 (2.9) |
| State of residence | | | | | | |
| New South Wales/Victoria | <5 (0.1) | 0 | <5 (0.2) | <5 (0.2) | <5 (0.1) | <5 (0.1) |
| Queensland | 471 (28.1) | 10 (1.1) | 461 (54.3) | 481 (26.1) | 17 (1.4) | 464 (63.2) |
| South Australia | 40 (2.4) | 7 (0.8) | 39 (4.6) | 56 (3.0) | 12 (1.0) | 51 (6.9) |
| Western Australia | 313 (18.7) | 13 (1.5) | 300 (35.3) | 161 (8.8) | 13 (1.1) | 148 (20.2) |
| Northern Territory | 849 (50.7) | 846 (96.6) | 47 (5.5) | 1139 (61.9) | 1131 (96.3) | 69 (9.4) |
| Geographical remoteness | | | | | | |
| Major Cities of Australia | 79 (4.7) | <5 (0.1) | 78 (9.2) | 40 (2.2) | <5 (0.3) | 39 (5.3) |
| Inner Regional Australia | 16 (1.0) | | 16 (1.9) | 14 (0.8) | <5 (0.1) | 13 (1.8) |
| Outer Regional Australia | 236 (14.1) | 47 (5.4) | 192 (22.6) | 235 (12.8) | 66 (5.6) | 172 (23.4) |
| Remote Australia | 318 (19.0) | 153 (17.5) | 177 (20.8) | 344 (18.7) | 224 (19.1) | 138 (18.8) |
| Very Remote Australia | 878 (52.4) | 585 (66.8) | 327 (38.5) | 1014 (55.1) | 765 (65.2) | 293 (39.9) |
| Other | <5 (0.1) | | <5 (0.1) | <5 (0.1) | | <5 (0.1) |
| IRSD quintile | | | | | | |
| 1 (least disadvantaged) | 12 (0.7) | <5 (0.2) | 11 (1.3) | 10 (0.5) | <5 (0.3) | 7 (1.0) |
| 2 | 50 (3.0) | 8 (0.9) | 42 (4.9) | 37 (2.0) | 14 (1.2) | 23 (3.1) |
| 3 | 114 (6.8) | 43 (4.9) | 77 (9.1) | 102 (5.5) | 59 (5.0) | 52 (7.1) |
| 4 | 154 (9.2) | 26 (3.0) | 131 (15.4) | 140 (7.6) | 42 (3.6) | 101 (13.8) |
| 5 (most disadvantaged) | 1179 (70.4) | 707 (80.7) | 511 (60.2) | 1329 (72.2) | 940 (80.1) | 443 (60.4) |
| Pre-existing comorbidity | 272 (16.2) | 164 (18.7) | 126 (14.8) | 377 (20.5) | 239 (20.4) | 169 (23.0) |
| Non-RHD CVD | 130 (7.8) | 85 (9.7) | 56 (6.6) | 213 (11.6) | 140 (11.9) | 96 (13.1) |
| CKD | 85 (5.1) | 50 (5.7) | 37 (4.4) | 119 (6.5) | 80 (6.8) | 48 (6.5) |
| COPD | 79 (4.7) | 38 (4.3) | 44 (5.2) | 82 (4.5) | 49 (4.2) | 39 (5.3) |
| Diabetes | 30 (1.8) | 20 (2.3) | 15 (1.8) | 43 (2.3) | 27 (2.3) | 22 (3.0) |
| Hypertension | 29 (1.7) | 15 (1.7) | 18 (2.1) | 52 (2.8) | 26 (2.2) | 35 (4.8) |
| Prior documented infection | 736 (43.9) | 436 (49.8) | 328 (38.6) | 785 (42.7) | 553 (47.1) | 276 (37.6) |
| Dental infection | 200 (11.9) | 123 (14.0) | 82 (9.7) | 208 (11.3) | 143 (12.2) | 76 (10.4) |
| Ear infection | 314 (18.7) | 183 (20.9) | 143 (16.8) | 303 (16.5) | 219 (18.7) | 101 (13.8) |
| GAS infection | 7 (0.4) | <5 (0.3) | <5 (0.5) | 8 (0.4) | 5 (0.4) | <5 (0.4) |
| Skin infection | 464 (27.7) | 294 (33.6) | 190 (22.4) | 504 (27.4) | 365 (31.1) | 168 (22.9) |
| Throat infection | 75 (4.5) | 40 (4.6) | 37 (4.4) | 81 (4.4) | 49 (4.2) | 35 (4.8) |
| Year of incident diagnosis | | | | | | |
| 2010 | 123 (7.3) | 50 (5.7) | 76 (9.0) | 231 (12.6) | 153 (13.0) | 87 (11.9) |
| 2011 | 159 (9.5) | 68 (7.8) | 96 (11.3) | 251 (13.6) | 130 (11.1) | 130 (17.7) |
| 2012 | 231 (13.8) | 101 (11.5) | 134 (15.8) | 208 (11.3) | 125 (10.6) | 91 (12.4) |
| 2013 | 209 (12.5) | 94 (10.7) | 123 (14.5) | 200 (10.9) | 123 (10.5) | 84 (11.4) |
| 2014 | 202 (12.1) | 109 (12.4) | 103 (12.1) | 209 (11.4) | 122 (10.4) | 97 (13.2) |
| 2015 | 239 (14.3) | 130 (14.8) | 115 (13.5) | 247 (13.4) | 172 (14.7) | 82 (11.2) |
| 2016 | 282 (16.8) | 158 (18.0) | 134 (15.8) | 252 (13.7) | 162 (13.8) | 101 (13.8) |
| 2017 | 229 (13.7) | 166 (18.9) | 67 (7.9)[c] | 242 (13.2) | 187 (15.9) | 62 (8.4)[c] |

[a]due to interjurisdictional linkage between SA and NT only, 50 individuals appear in both SA and NT data collections and are represented in both stratified cohorts.

[b]due to interjurisdictional linkage between SA and NT only, 68 individuals appear in both SA and NT data collections and are represented in both stratified cohorts.

[c]smaller number in 2017 due to mid-2017 data linkage for WA.

**Figure 1: Proportion with initial ARF or mild RHD who experienced recurrent ARF or progressed to severe RHD/death within 2 years by calendar year of diagnosis and the adjusted Hazard Ratio (Adj. HR) and 95% confidence intervals from the multivariate model for each outcome.**




progression to severe RHD/death did not change during the study period (trend test p=0.43 and p=0.55, respectively) (**Figure 1**). Calendar year of first ARF diagnosis and receiving ≥80% BPG doses were not associated with 2-year progression to ARF recurrence or severe RHD/death in the multivariate analysis (Figure 1).

*Mild RHD cohort*

Of 1301 people with mild RHD, 126 (9.7%) experienced an ARF recurrence and 32 (2.5%) progressed to severe RHD or death and within 2 years, with similar progression measured when stratified into NT and Qld/WA/SA subgroups (Supplement 3). ARF recurrence or progression to severe RHD/death did not change during the study period (trend test p=0.07 and p=0.64, respectively, Figure 1). Calendar year of RHD diagnosis was not associated with 2-year ARF recurrence or progression to severe RHD/death in the multivariate analyses (Figure 1). Receiving ≥80% of BPG doses was not associated with ARF recurrence (HR 0.8, 95% CI 0.5-1.4) but was associated with lower 2-year progression from mild RHD to severe RHD/death (adj. HR 0.2, 95%CI 0.1-0.8, Figure 1).

### *BPG delivery, ARF recurrences and earlier diagnosis over time*

Median BPG delivery increased in the ARF cohort for all jurisdictions over time from 53% PDC (95%CI: 46-61%) to 70% PDC (95%CI: 71-68%) between 2010 and 2016 (**Figure 2**A). Similarly, there was an increase in patients with ≥80% PDC over time, increasing from 18.6% in 2010 (95%CI: 11.6-37.6) to 54.8% in 2016 (95%CI: 48.5-61.0, Figure 2A).

In the NT, ARF recurrence rates varied between 2002 and 2017; there was no average change in ARF recurrence rate (+2.2% annually, 95% CI: -0.5, +5.1). In Qld/WA/SA for 2010–2017, ARF recurrence rates decreased on average 7.5% annually (95% CI: -13.2, -1.4 Figure 2B).

RHD diagnosis with known prior ARF increased in the NT from 10.6% in 2010 to 16.1% in 2016 (trend p=0.41), but there was limited change in Qld/WA/SA, (24.7% in 2010, 22.2% in 2016, trend p=0.81, **Figure 3**B). Concurrent ARF/RHD diagnosis in the NT increased marginally between 2002 and 2016 (trend p=0.05), whereas in Qld/WA/SA, concurrent diagnoses increased more markedly over the study period (23.7% in 2010, 41.5% in 2016, trend p<0.001, Figure 3B).

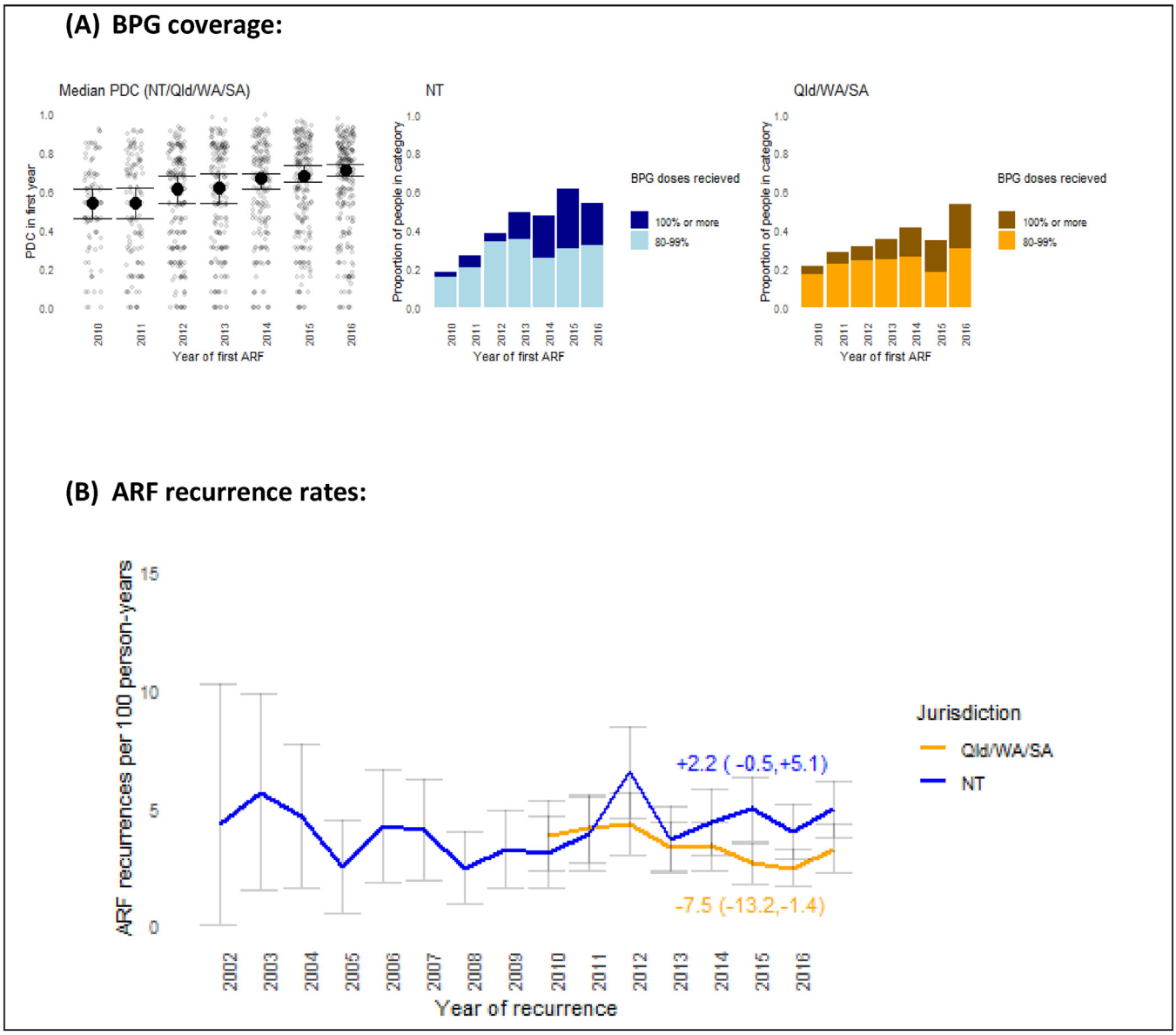
## Discussion

This study contributes evidence in support of ARF/RHD Control Program effectiveness in relation to delivery of secondary prophylaxis, based on real-world longitudinal data from multiple sources collected after RFS implementation. Disease progression remained unchanged over time. We found that BPG delivery significantly improved over time, and that receipt of ≥80% of BPG doses was associated with lower 2-year progression from mild RHD to severe RHD or death. We cannot directly attribute a causal relationship between RFS implementation and improvements in secondary prophylaxis, but secondary prophylaxis is the core function of ARF/RHD Control Programs with gains most likely being attributable to their activity. These jurisdictional-level data are congruent with clinic-level evidence that "systematic approach to follow up" is associated with higher levels of secondary prophylaxis delivery.[18] Despite these gains, the number of ARF and RHD notifications increased annually, and the proportion of people with subsequent ARF recurrence or progression to severe RHD/death within 2 years of ARF or mild RHD diagnosis was unchanged during the study period.

Reducing ARF cases numbers is largely beyond the reach of secondary prevention programs as currently designed. Increasing population size and improving case detection and notification may be playing a part in the rising case numbers we report, but the data clearly highlight the critical need for interventions that target primordial and primary prevention of ARF, which are beyond the scope of existing Australian RHD Control Programs.

Within 2 years of an initial ARF episode, we estimated 10.7% experienced ARF recurrence and 8.4% progressed to severe RHD or death; and within 2 years of mild RHD diagnosis, 9.7% experienced recurrent ARF and 2.5% progressed to severe RHD or death with no trends in these progression rates observed over time. While ARF recurrence rates reported by the present study are similar to those reported previously in the NT by Lawrence for 1997–2013 and He for 1997–2012, our progression rates from ARF to severe RHD/death are much lower by comparison (35% at 1 year, Lawrence, 27% at 1 year,

Figure 2: Trends in (A) BPG delivery and (B) ARF recurrence rate per 100 person-years in Australia. (A) Median BPG delivery in the first year after incident ARF diagnosis by calendar year for all jurisdictions combined (left) and proportion receiving 80 to 99% and 100% of doses for NT (middle) and Qld/WA/SA (right) subgroups. (B) ARF recurrence rate by calendar year for NT and Qld/WA/SA subgroups.

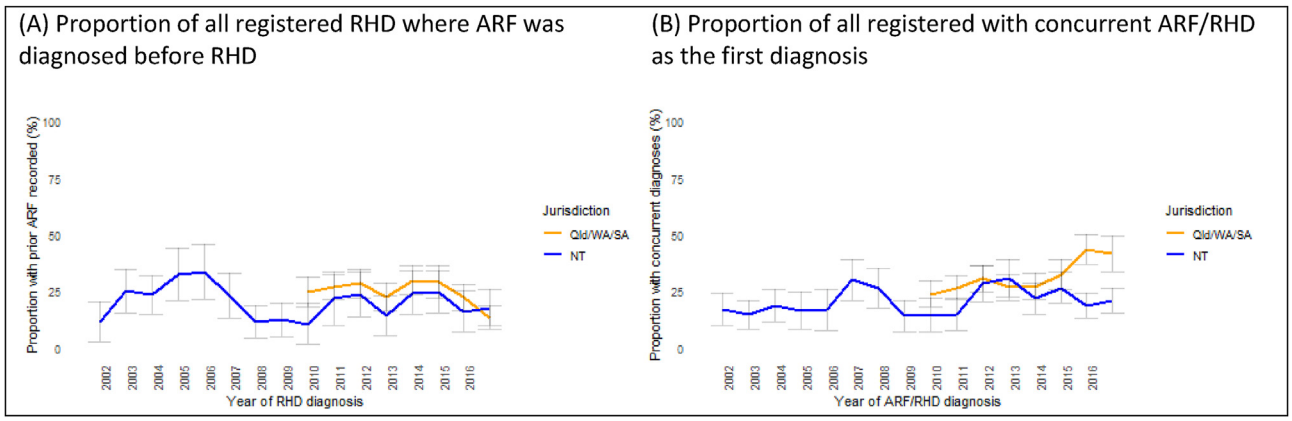



He). Differences between the estimates reported by each study can be explained by differences in study design (our cohort is younger, our outcome includes severe RHD/death) but might also be reflecting reduced disease progression over time.

The expectation is that increasing BPG delivery would translate into a decrease in ARF recurrences.[17] While this was seen in the pooled Qld, WA and SA data, ARF recurrences did not decrease in the NT in this dataset. This could reflect that ARF recurrences are being detected better over time. Better ARF detection has been strongly promoted during the study period through guidelines,[19,20] workshops and educational modules. This work continues through online tools,[21] smartphone applications[22] and community-based initiatives.[23–25] Our findings on recurrences are largely supported by AIHW reports but differ for BPG delivery: in 2016, the AIHW reported 36% of people received ≥80% of prescribed BPG doses, whereas here we report 55% for the same year.[11] Our cohort is restricted to <35 year olds with BPG records available, capturing doses received only during the first year after initial diagnosis, whereas the AIHW report data for all ages and all years after diagnosis, which likely explains higher BPG coverage reported by the present study.

Multivariable models identified that BPG coverage was significantly protective against progression from mild RHD to severe RHD/death only (and not ARF to recurrent ARF; ARF to severe RHD/death or RHD to severe RHD/death). Calendar year of diagnosis, which captured other systemic changes occurring over time, was not associated with any progression outcomes within the ARF cohort or RHD cohort. Our observations are possibly a consequence of low statistical power resulting from the limitations of using of real-world diagnosis and medication data to study outcomes within small populations. We also cannot rule out reverse causation, whereby people with mild RHD are

**Figure 3: Trends in disease detection over time by jurisdiction. Proportion of all people registered with RHD who were previously diagnosed with ARF (excluding concurrent diagnosis, A) and proportion of all people registered with ARF/RHD with a concurrent diagnosis (i.e. ARF and RHD within 90 days, B).**




more likely for various personal and clinical reasons to receive regular BPG injections than those with an initial diagnosis of ARF only; however, the relationship between increased BPG delivery and reduced RHD progression is generally accepted.[17,26]

RHD was diagnosed concurrently with initial ARF in an increasing proportion of cases over time in Qld/WA/SA but not NT (Figure 3), which may suggest improving access to echocardiography facilitating concurrent RHD diagnosis, or later diagnoses on average in Qld/WA/SA where Control Programs were established more recently. Changing RHD diagnosis and registration practises may also be implicated.

This study has minor limitations that are inherent to linked data, since the administrative records used were not collected specifically for this analysis. It is possible that BPG data are incomplete, potentially underestimating delivery particularly in the jurisdictions with newer registries, making the present findings a combination of improved data quality and increased BPG coverage over time, although we believe the impact of this to be low (NT studies have estimated <2.5% of BPG dose records are missing[28]). It is also possible that nonregistered ARF and RHD diagnoses have been excluded from this study, due to jurisdictional variation in notification requirements occurring over time[6]; however, register coverage among young people is known to be high making the impact of this minimal.[14] Additionally, the 2-year follow-up period constitutes only short-term clinical follow-up of individuals, a limitation imposed by data availability. Ideally, follow-up would be longer, particularly when examining death as an outcome. Finally, this study reports RFS impacts prior to the COVID-19 pandemic, which has substantially reduced BPG delivery in the NT (personal communication Anna Ralph).

The major limitation of the present study was that the social determinants of health that drive GAS infections that cause ARF and RHD were not captured by the register and associated ERASE linked data collection, so that any improvements or changes in these early indicators of disease risk have not been established.[8] Future analyses that evaluate the impacts of the RHD Endgame Strategy will ideally also examine trends occurring at earlier stages of the ARF and RHD disease course, for example, GAS skin and throat infections.[7] A recent WA Health Aboriginal Environmental health review has outlined the important role that primary healthcare data can have for measuring these kinds of environment-attributable health conditions.[8,27] Central to this is the availability of accessible primary healthcare data structures, Indigenous leadership and data sovereignty.[27]

This study provides the first longitudinal evidence using multiple real-world data sources that ARF/RHD Control Programs are likely to be contributing to improvements in ARF and RHD management. Despite an increasing annual volume of new ARF notifications and a constant annual increase in newly registered RHD patients, the coordinated delivery of BPG has increased and disease progression has remained low and stable for 2010–2017. ARF recurrence rates decreased significantly in Qld/WA/SA following the commencement of RFS funding in 2009 and were unchanged in the NT from 2002 to 2016, where RHD Control Programs have been active since 1997. With the launch of the RHD Endgame Strategy, the future focus of ARF and RHD control now also includes primordial and primary prevention strategies that reduce childhood GAS infections, with the goal of preventing these diseases entirely.[15] Control Programs that support primary care services to deliver secondary prevention measures remain critical infrastructure for those already living with ARF and RHD.

## Ethics

Human Research Ethics Committees of the Health Departments of NT (Menzies School of Health Research), Qld, WA and SA provided approval for the ERASE project. Aboriginal Ethics Committee approval was sought in jurisdictions where these were operational, with support letters received from peak bodies of the Aboriginal Community Controlled Health Services.

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The authors acknowledge that figures and other statistics represent the loss of health and human life with profound impact and sadness for people, families, community, and culture. These numbers also obscure the resilience and strengths of the people involved. We hope that the "numbers story" emanating from this project can augment the "lived stories" that reflect the voices of people with RHD and their families. The authors value the support/endorsement provided to the project by the following peak bodies representing the Aboriginal

Community Controlled Health sector: Aboriginal Medical Services Alliance Northern Territory, Kimberley Aboriginal Medical Service (the health service serving the high-burden region of WA), Aboriginal Health Council of South Australia, and Aboriginal Health and Medical Research Council (NSW). We also received support from the Aboriginal divisions of Queensland and WA Health Departments. We are committed to providing feedback to these organizations ensuring that the findings are accessible and provide the evidence needed for policy that can reduce the burden of ARF and RHD in Australia. The authors also thank the staff of the data linkage units of the State and Territory governments (WA, SA-NT, NSW, Queensland) for linkage of the ERASE project data. We thank the State and Territory Registries of Births, Deaths and Marriages, the State and Territory Coroners, and the National Coronial Information System and Victorian Department of Justice for enabling Cause of Death Unit Record File data to be used for this project. Further, we thank the data custodians and data managers for the provision of the following data. Inpatient hospital and Emergency Department data (5 States and Territories), RHD registers (5 States and Territories), The Australian and New Zealand Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database (single registry covering 5 States and Territories), Royal Melbourne Children's Hospital Paediatric Cardiac Surgery database (single data source for RHD pediatric patients from SA and NT receiving surgical intervention in Melbourne), Primary health care data from NT Department of Health. This work was supported by funding from the National Health and Medical Research Council (NHMRC) through project grant (#114652) and seed funds from the End -RHD Centre for Research Excellence and HeartKids. Ingrid Stacey is supported by an NHMRC Postgraduate Scholarship Grant (#2005398) and an Ad Hoc Postgraduate Scholarship from The University of Western Australia. Judith Katzenellenbogen and Lee Nedkoff are supported by National Heart Foundation of Australia Future Leader Fellowships (#102043, 105038).

## Conflicts of interest

The authors have no conflicts of interest to declare.

## References

1. Katzenellenbogen JM, Bond-Smith D, Seth RJ, Dempsey K, Cannon J, Stacey I, et al. Contemporary incidence and prevalence of rheumatic fever and rheumatic heart disease in Australia using linked data: the case for policy change. *J Am Heart Assoc* 2020;**9**(19):1–19.
2. He VY, Condon JR, Ralph AP, Zhao Y, Roberts K, de Dassel JL, et al. Long-term outcomes from acute rheumatic fever and rheumatic heart disease: a data-linkage and survival analysis approach. *Circulation* 2016;**134**(3):222–32.
3. Lawrence JG, Carapetis JR, Griffiths K, Edwards K, Condon JR. Acute rheumatic fever and rheumatic heart disease: incidence and progression in the Northern Territory of Australia, 1997 to 2010. *Circulation* 2013;**128**(5):492–501.
4. Stacey I, Hung J, Cannon J, Seth RJ, Remenyi B, Bond-Smith D, et al. Long-term outcomes following rheumatic heart disease diagnosis in Australia. *European Heart Journal Open* 2021;**1**(3).
5. Federal Financial Relations. In: CCo Australia, editor. *Rheumatic Fever Strategy: national partnership agreement on specified projects*. Canberra: Commonwealth of Australia; 2018.
6. RHDAustralia (ARF/RHD writing group), National Heart Foundation of Australia, Cardiac Society of Australia and New Zealand. The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (3rd ed.). 3 ed: RHDAustralia (ARF/RHD writing group); [https://www.rhdaustralia.org.au/Accessed 2020].
7. Wyber R, Noonan K, Halkon C, Enkel S, Ralph A, Bowen A, et al. *The RHD Endgame Strategy: the blueprint to eliminate rheumatic heart disease in Australia by 2031*. Available from: https://endrhd.telethonkids.org.au/siteassets/media-docs--end-rhd/end-rhd-cre--endgame-report.pdf; 2020.
8. Haynes E, Noonan S, Mitchell A, Stacey I, Martini A, Bessarab D, et al. *Investigating factors that impede and enable optimal implementation of regional rheumatic heart disease control in primary health care settings - strategies and interventions*. Perth: The University of Western Australia; 2022.
9. Health Policy Analysis. *Evaluation of the Commonwealth rheumatic fever Strategy – final report*. Canberra: Primary Healthcare Branch, Commonwealth Department of Health; 2017.
10. Australian Institute of Health and Welfare. *Acute rheumatic fever and rheumatic heart disease in Australia*. Canberra: AIHW; 2019. Available from: https://www.aihw.gov.au/reports/indigenous-australians/acute-rheumatic-fever-rheumatic-heart-disease.
11. Australian Institute of Health and Welfare. *Acute rheumatic fever and rheumatic heart disease in Australia, 2015–2019*. Canberra: AIHW.; 2021.
12. Australian Institute of Health and Welfare. *Rheumatic heart disease and acute rheumatic fever in Australia: 1996-2012*. Canberra: AIHW; 2013.
13. Katzenellenbogen JM, Bond-Smith D, Seth RJ, Dempsey K, Cannon J, Nedkoff L, et al., The End Rheumatic Heart Disease in Australia Study of Epidemiology (ERASE) Project: data sources, case ascertainment and cohort profile. *Clin Epidemiol* 2019;**11**:997–1010.
14. Agenson T, Katzenellenbogen JM, Seth R, Dempsey K, Anderson M, Wade V, et al. Case ascertainment on Australian registers for acute rheumatic fever and rheumatic heart disease. *Int J Environ Res Publ Health* 2020;**17**(15):1–21.
15. Wyber R, Noonan K, Halkon C, Enkel S, Cannon J, Haynes E, et al. Ending rheumatic heart disease in Australia: the evidence for a new approach. *Med J Aust* 2020;**213**(10):S3–31.
16. Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care* 2013;**51**(3):S11–21.
17. de Dassel JL, de Klerk N, Carapetis JR, Ralph AP. How many doses make a difference? An analysis of secondary prevention of rheumatic fever and rheumatic heart disease. *J Am Heart Assoc* 2018;**7**(24):e010223.
18. Quinn E, Girgis S, Van Buskirk J, Matthews V, Ward JE. Clinic factors associated with better delivery of secondary prophylaxis in acute rheumatic fever management. *Aust J Gen Pract* 2019;**48**(12):859–65.
19. National Heart Foundation of Australia(RF/RHD guideline development working group) and the Cardiac Society of Australia and New Zealand. In: *Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia – an evidence-based review*. Edition 1 2006.
20. RHDAustralia (ARF/RHD writing group) National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. The. In: *Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease*. 2nd ed. 2012.
21. RHD Australia. Online resources for ARF and RHD https://www.rhdaustralia.org.au/arf-rhd-guideline [accessed 2022] [Available from:: https://www.rhdaustralia.org.au/arf-rhd-guideline.
22. Fisher E, James C, Mosca D, Currie BJ, Ralph AP. Evaluation of an ARF diagnosis calculator: a survey and content analysis. *BMC Med Inf Decis Making* 2022;**22**(1):77.
23. Wyber R, Kelly A, Lee AM, Mungatopi V, Kerrigan V, Babui S, et al. Formative evaluation of a community-based approach to reduce the incidence of Strep A infections and acute rheumatic fever. *Aust N Z J Publ Health* 2021;**45**(5):449–54.
24. Kerrigan V, Kelly A, Lee AM, Mungatopi V, Mitchell AG, Wyber R, et al. A community-based program to reduce acute rheumatic fever and rheumatic heart disease in northern Australia. *BMC Health Serv Res* 2021;**21**(1):1127.
25. Haynes E, Marawili M, Marika BM, Mitchell AG, Phillips J, Bessarab D, et al. Community-based participatory action research on rheumatic heart disease in an Australian Aboriginal homeland: evaluation of the 'On track watch' project. *Eval Progr Plann* 2019;**74**:38–53.
26. Beaton A, Okello E, Rwebembera J, Grobler A, Engelman D, Alepere J, et al. Secondary antibiotic prophylaxis for latent rheumatic heart disease. *N Engl J Med* 2022;**386**:230–40.
27. Haynes E, Katzenellenbogen JM, Noonan S, Stacey I, Mitchell AG, Wade V, et al. Is the Australian primary healthcare system ready for the Rheumatic Heart Disease Endgame strategy? Data synthesis and recommendations. *Aust N Z J Publ Health* 2022;**46**(5):554–7.
28. de Dassel JL, Fittock MT, Wilks SC, Poole JE, Carapetis JR, Ralph AP. Adherence to secondary prophylaxis for rheumatic heart disease is underestimated by register data. *PLoS One* 2017;**12**(5):e0178264.

## Appendix A Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anzjph.2023.100071.