TITLE PAGE

Full title: Adherence to secondary antibiotic prophylaxis for patients with rheumatic heart disease diagnosed through screening in Fiji

Short title: RHD prophylaxis adherence following screening

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ABSTRACT

Objectives

Echocardiographic screening for rheumatic heart disease (RHD) can detect subclinical cases, however adequate adherence to secondary antibiotic prophylaxis (SAP) is required to alter disease outcomes. We aimed to investigate the adherence to SAP among young people with RHD diagnosed through echocardiographic screening in Fiji, and to investigate factors associated with adherence.

Methods

Patients diagnosed with RHD through echocardiographic screening in Fiji from 2006 – 2014 were included. Dates of benzathine penicillin G injections were collected from 76 health clinics nationally from December 2011 to December 2014. Adherence was measured using the proportion of days covered (PDC). Multivariate logistic regression analysis was used to identify characteristics associated with any adherence (≥ 1 injection received) and adequate adherence (PDC ≥ 0.80).

Results

Of 494 patients, 268 (54%) were female and the median age was 14 years. Overall, 203 (41%) had no injections recorded and just 33 (7%) had adequate adherence. Multivariate logistic regression showed increasing age (OR 0.93 per year, 95%CI 0.87-0.99), and time since diagnosis ≥1.5 years (OR 0.53, 95%CI 0.37–0.79) to be inversely associated with any adherence. Non-iTaukei ethnicity (OR 2.58, 95%CI 1.04-6.33) and urban residence (OR 3.36,

95%CI 1.54–7.36) were associated with adequate adherence, whereas time since diagnosis ≥1.5 years (OR 0.38, 95%CI 0.17–0.83) was inversely associated with adequate adherence.

Conclusions

Adherence to SAP following screening in Fiji is currently inadequate for individual patient protection or population disease control. Secondary prevention should be strengthened before further screening can be justified.

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KEY WORDS

Rheumatic heart disease; mass screening; medication adherence; antibiotic prophylaxis; secondary prevention; adolescent; Pacific Islands

INTRODUCTION

Rheumatic heart disease (RHD) is a major cause of global morbidity and mortality, affecting over 30 million people and causing over 345,000 deaths annually (1, 2). Secondary antibiotic prophylaxis (SAP) is a highly effective strategy that prevents further streptococcal infections and recurrence of acute rheumatic fever (ARF), and can lead to stabilisation and improvements in disease, particularly if commenced before RHD becomes severe (3). Screening, using echocardiography, is highly sensitive for identifying cases with early, mild RHD (4, 5). However, without adequate adherence to SAP, screening will not alter individual disease outcomes or reduce the population burden of RHD.

The World Health Organization (WHO) defines adherence as *"the extent to which ... taking medication… corresponds with agreed recommendations from a healthcare provider"* (6). Adherence, in contrast to compliance, implies the patient's agreement with health-care recommendations. Adherence to long-term medications for chronic diseases is a global problem, with approximately 50% adherence in developed countries, and far less in resource-limited settings (7).

Mirroring the experience of other chronic conditions, achieving adequate adherence to SAP for RHD is a major challenge for individuals and health systems, including in high-income countries (8-13). There have been few studies of adherence to SAP for RHD, and no studies of adherence of patients diagnosed with RHD through echocardiographic screening, which may be different to that of patients diagnosed clinically. Adherence has been variably defined and measured in these studies, including the mean or median percentage of injections of a population, the proportion missing one dose over a six-month period (14), and the proportion receiving a benchmark percentage of recommended injections. Eighty percent of

recommended injections has been the most frequent benchmark used to categorise adherent vs non- or poorly adherent (10, 15), although others have used 90% (16). Although there is no particular pathophysiological basis for any threshold, there is some empirical evidence for the 80% cut-off from other chronic diseases (17). WHO recommends utilising a register of RHD patients to facilitate secondary prevention activities, promote adherence and for epidemiological surveillance (18).

Understanding the profile and determinants of adherence is important before considering scale-up of screening services, such as is being considered in Fiji and many other settings (19). Therefore, we aimed to investigate the adherence to SAP among young people with RHD diagnosed through echocardiographic screening in Fiji, and to investigate factors associated with adherence.

METHODS

Design and Study setting

In this retrospective cohort study, we collected and collated information on SAP for young people diagnosed with RHD through echocardiographic screening in Fiji. Fiji is a South Pacific nation comprising 330 islands and a population of approximately 900,000. RHD is a leading cause of morbidity and mortality in children and younger adults (20). The Fiji RHD Control Program was established in 2005, based on a model developed by the WHO (18). Until 2014, the program was staffed by a single national coordinator, with oversight from the RHD Technical Advisory Committee within the Ministry of Health. Known cases were entered into a Microsoft Access register held on a desktop computer.

Echocardiographic screening for RHD has been conducted in Fiji since 2006. Four previous research projects have investigated approaches to screening using echocardiography, as described elsewhere (21-24). In addition, the Ministry of Health coordinated 14 outreach screening activities over the period 2008 – 2014, mainly to remote communities. Doctors and sonographers used focused echocardiography to screen school-aged children. Paediatricians with experience in cardiology and echocardiography made the diagnosis based on echocardiogram findings and clinical assessment in the field. Echocardiographic features were assessed according to various criteria, including those published by the National Institutes of Health (NIH) and WHO prior to 2012 (25), and the World Heart Federation (WHF) since 2012 (26). Counselling and education was provided to families of all children diagnosed with RHD, on the same or following day, by an experienced nurse or the screening paediatrician. Children were administered the first dose of intramuscular benzathine penicillin-G (BPG) and future doses were arranged with the local clinic nurse. Families were given a paper-based referral for further follow-up (including ECG and chest x-ray) at the

nearest hospital. The process of counselling and referral was consistent between the screening activities.

Guidelines for prophylaxis in Fiji over this period recommended SAP with BPG every 21 days for patients aged less than 15 years, and every 28 days for those aged 15 years and over. Oral prophylaxis is only recommended in cases of true penicillin allergy, and rarely used in practice. Injections of BPG are provided without cost at all government clinics (including divisional/subdivisional hospitals, health centres and nursing stations) and a small number of military and private facilities. Patients may attend multiple clinics for injections. Injection dates are recorded in a specific injection recording book distributed by the national RHD Control Program to each clinic. These books contain a template for recording injection dates on a separate page for each individual. Comments such as treatment dose and interval, cessation of treatment, patient migration or death can be added. It is not possible to purchase antibiotics without a medical prescription.

Study Cohort

All RHD cases diagnosed through echocardiographic screening were eligible. We created a database of all children screened for RHD by manually collating individual screening activity logbooks held by the RHD Control Program. We included definite RHD cases, possible and probable cases (as per NIH/WHO criteria) and borderline cases (as per WHF criteria). This resulted in a cohort of 831 cases of RHD from approximately 15,000 children screened. Cases were excluded from this study if they had been previously diagnosed with RHD before screening. Cases were also excluded if SAP was not recommended after family counselling.

Data Collection

We compiled a list of all clinics across the four administrative Divisions of Fiji (Central, East, West, and North). We collected itemised injection dates and recorded all comments from all patients in injection books at 76 clinics, covering the most populous geographic areas. Most clinics were visited in person; some remote clinics were contacted by phone. We assessed the availability and reliability of injection book data at each clinic. Only one clinic record, where injections were not recorded by individual patient, was considered unreliable. It was not possible to contact several clinics on very remote islands that did not have telephone access. Therefore, cases screened, attending or residing in the areas surrounding clinics that could not be contacted or the sole clinic with unreliable data were excluded from analysis.

Injection data were cross-referenced by name, date of birth and national hospital number against the database of individuals diagnosed through screening. Where a match was found, injection dates from all clinics were collated for that individual. Injections reported to have been administered at an interval of < 20 days were manually cross-checked for potential errors. Information regarding use of oral antibiotics was collected from comments in prophylaxis books, direct questioning of senior nursing staff at each clinic and local distributing pharmacies.

The period of observation was 1st December, 2011 – 31st December, 2014. Where injection dates were not available from any clinic for the entire period (for example, if reporting commenced in June 2013), the observation start date was adjusted for all cases with any injections at that clinic. The observation period was also adjusted for cases who commenced treatment after 1 December 2011; who were reported to have migrated or died; or who had prophylaxis ceased before or during the period of observation. Cases with an adjusted

observation period of less than 12 months were excluded, so that the range of observation was 12 – 37 months. Areas of residence were classified as rural or urban based on Fiji census definitions (27). Participant age was defined at 30 June 2013.

Measures of adherence:

We measured adherence using the proportion of days covered (PDC). PDC is a relatively recent, but now commonly used pharmacy quality measure for oral medications (28, 29), although proposed definitions vary (30). There are no other studies reporting PDC for a long-acting injectable medication such as BPG. Therefore, we defined the measure based on principles of ARF pathogenesis. We assumed that an injection of BPG would confer protection for 28 days, after which each subsequent day was considered a "day-at-risk" of developing a subsequent GAS infection and recurrence of ARF (31). We summed the days-at-risk between each injection, and added any days prior to the first injection and following the last injection. The PDC was then calculated by dividing the days-at-risk by the total days observed, and subtracting this ratio from 1. The threshold for adequate adherence was defined as PDC$\geq$ 0.80, consistent with definitions for other chronic conditions (32). We additionally calculated the percentage of injections received to allow comparison with previous ARF/RHD adherence studies. This was calculated by dividing the number of received injections by the number recommended. The dosing interval was taken from prescription records, or if no orders were found, by participant age (21-daily until 15 years age; 28-daily thereafter).

Statistical Analysis

The distribution of PDC was not symmetrical and therefore linear regression analysis of adherence was not performed. Logistic regression analysis was used to identify characteristics associated with any adherence (defined as $\geq$ 1 injection received) and adequate

adherence (defined as PDC ≥ 0.80). Characteristics measured on a continuous scale were inspected for symmetry, and those that were not symmetrical (i.e., time since diagnosis) were dichotomized. Characteristics with adequate data points were analysed with unadjusted bivariate logistic regression, and nominal variables with >2 categories were additionally analysed using Pearson's χ^2 test or Fisher's exact test; those with p-value < 0.10 were considered for inclusion in the multivariable regression. Collinearity was assessed using Pearson's correlation test. Where covariates were found to be strongly collinear ($r \geq 0.8$), only the more strongly associated variable was used in multivariable regression analysis. Stata version 13.1 (StataCorp, College Station, TX, USA) was used for analysis.

Ethical Approval

This study protocol was approved by the Fiji National Research Ethics Review Committee (2014.135) and the Royal Children's Hospital Human Research Ethics Committee, Australia (2015-02).

RESULTS

494 cases were included in the analysis. Primary reasons for exclusions were data unavailability (n=254); no record of commencing SAP (n=76); death (n=3); observation period < 12 months (n=3); and overseas migration (n=1). The median age was 14.2 years (range 6.3 – 21.0) and 54.3% were female (Table 1). The majority of cases (n=357, 72.3%) were observed for the entire 37-month period (median 1126 days, interquartile range [IQR] 974 – 1126). Of the cases with at least one injection, 240 (82.5%) attended one clinic for injections, 39 (13.4%) attended two; ten (3.4%) attended three and two cases (0.7%) attended four or more clinics. No cases were found to be receiving oral prophylaxis.

Adherence

Overall, 203 cases who had been commenced on SAP (41.1%) had no injections recorded. A further 171 cases (35.6%) had very low adherence (PDC: > 0 to 0.39) and only 33 cases (6.7%) had adequate adherence (PDC ≥ 0.80, Table 2). Thirty-one cases (6.3%) received ≥80% of recommended injections (Table 2).

Predictors of any adherence

Unadjusted bivariate logistic regression, comparing those with any adherence (≥1 injection) to those with no injections, identified age (OR 0.90 per year, $P < 0.01$) and time since diagnosis >1.5 years (OR 0.47, $P < 0.001$) as predictors of any adherence (Table 3). There was a difference in the proportion of cases with any adherence between screening activity location (range: 29.4% [2009-10 Central Division screening] to 88.9% [2012-13 National screening]; χ^2, $P < 0.001$) but numbers were insufficient to include in multivariate analysis. Additional checks, limiting to only screening activities with ≥20 adherent cases did not alter the results. There was no evidence of difference between Divisions (χ^2, $P = 0.12$).

Multivariable logistic regression showed increasing age (OR 0.93 per year, 95%CI 0.87-0.99, $P = 0.04$), and time since diagnosis ≥1.5 years (OR 0.53, 95%CI 0.37–0.79, $P < 0.01$) to be inversely associated with any adherence.

Predictors of adequate adherence

Unadjusted bivariate logistic regression, comparing those with adequate (PDC≥0.80) and inadequate adherence, identified ethnicity (OR 2.94, $P = 0.01$), place of residence (OR 3.27, $P < 0.01$), time since diagnosis ≥1.5 years (OR 0.46, $P < 0.05$) and screening activity type (OR 0.44, $P = 0.04$) as factors to advance to multivariate analysis (Table 4). There was a difference in the proportion of cases with adequate adherence between Divisions (range: 2.6% [North] to 17.3% [East]; Fisher's exact, $P = 0.001$) but numbers were insufficient to include in multivariate analysis. There were insufficient cases with adequate adherence to compare screening activity locations.

Multivariable logistic regression showed non-iTaukei ethnicity (OR 2.57, 95%CI 1.04-6.33, $P = 0.04$) and urban residence (OR 3.37, 95%CI 1.54–7.37, $P = 0.002$) were associated with adequate adherence. Time since diagnosis ≥1.5 years (OR 0.38, 95%CI 0.17–0.83, $P = 0.02$) was inversely associated with adequate adherence. A significant association was not found with screening activity type (Ministry of Health outreach, OR 0.66, 95%CI 0.26–1.66, $P = 0.38$).

DISCUSSION

The overall adherence to SAP for this cohort of young people diagnosed through echocardiographic screening was very low, with over 40% receiving no injections and only 6% receiving adequate injections to protect against ARF recurrence and progression of RHD. There are no previously published studies of cases diagnosed through screening for comparison, nor is there a suitable comparison group of clinical cases from Fiji. Two reports from Australia found 18% and 23% of patients received ≥80% of recommended injections (13, 33). Low adherence has been reported in many other settings, although comparison is limited by small sample sizes and variable methods. Publications from New Zealand (34) and Taiwan (35) reported high adherence after ARF diagnosis.

Adherence is driven by multiple factors, and best understood using a systems approach considering socioeconomic, healthcare, condition, therapy and patient-related factors (6). There are some reasons to suspect that adherence could be lower in those diagnosed through screening. In contrast to cases diagnosed with ARF or RHD that present to clinical services, cases diagnosed through screening are predominantly asymptomatic and well. Further, most clinically diagnosed cases are admitted to hospital, a memorable health event and healthcare interaction which may promote future adherence. Patient education and follow-up processes are also likely to be different for screened and clinically diagnosed cases due to health system structures and different opportunities for engagement with health professionals.

We found that increasing age and time since diagnosis were associated with worse adherence, whereas non-iTaukei ethnicity and urban residence were associated with better adherence. These results do not demonstrate or explain causation, but several factors may be relevant. Differences between the iTaukei population and Fijians of Indian descent have been observed

in a range of studies including the incidence of paediatric meningitis and pneumonia (36, 37), prevalence of scabies (38) and cervical cancer mortality (39), representing complex sociocultural and environmental factors. The association between increasing age and poor adherence may represent worse adherence amongst adolescents than younger children. Adolescence is known to be a vulnerable period for non-adherence (40, 41). Self-management of chronic health conditions requires neurodevelopmental maturity and executive skills that continue to develop into early adulthood (42). Adolescent-friendly health services are important to promote health seeking behaviours (43).

The association between increasing time since diagnosis may represent the challenge of chronic care, particularly in resource-limited settings. Families were provided some education at the time of diagnosis, but deficiencies in follow-up may have meant consolidation and reinforcement of health promotion messages appropriate for each stages of childhood did not occur. This is supported by reports of families deciding to discontinue treatment in some remote island communities, where access to clinical services is limited and specialists had not been able to visit for more than five years (Dr Joseph Kado, Fiji RHD Control Program, personal communication.) Further research into the appropriateness, timeliness and quality of patient management after diagnosis will inform health-system strengthening strategies. Cost may also be a driver of adherence in Fiji. Although injections and consultations are provided without charge, transport costs in rural and remote areas are high. Health beliefs about RHD, the need for regular SAP, and supply shortages of BPG may be additional contributing factors.

This study is the first to report adherence for RHD using the PDC measure. We believe the PDC, which can be thought of as a “protection index”, better incorporates current understanding of the causes and prevention of RHD than simply counting injections. This

measure builds upon the "days-at-risk" concept, where each day is counted after effective protection from prophylaxis ends (31). Days-at-risk may be a useful tool for improving patients' understanding of the importance of injection timeliness, rather than the absolute number of injections. For example, in our cohort we found many instances where injections had been given several days before the recommended interval, presumably to accommodate patient and healthcare circumstances. Early administration may lead to lengthier subsequent intervals, where an individual is not protected, but this risk is not captured by an injection count method. The PDC offers greater discrimination and analysis possibilities than an injection count, and therefore may be more useful for program monitoring and evaluation.

It should be noted that there is, as yet, no standard definition of the PDC (30). When used for estimating oral prescription coverage, the PDC is usually calculated from the date of the first prescription (44). In contrast, we defined PDC from the start of the observation period, in order to avoid over-estimation for cases who were non-adherent at the start of observation. Our definition of PDC would underestimate protection if an injection had been given in the days prior to the start of observation (e.g.: a late December injection, where PDC is defined from January 1st). However this underestimate would be minor over the period of observation, and would not change the overall impression of adherence. If an RHD control program were to incorporate a measure such as the PDC with real-time injection entry, it would be simple to incorporate prior injections into the definition of PDC.

The pathophysiological model underlying the PDC concept assumes protection from ARF recurrence is complete until day 28, and of increased and equal risk for each day thereafter. The 28-day cut-off point we used is somewhat arbitrary, but based on an estimated 14-21 days of therapeutic effect of BPG in preventing group A streptococcal infection (45), as well as protection from receiving penicillin within 9 days of acquiring a GAS infection (19), and is

consistent with common international dosing intervals (46). Further development of the PDC could incorporate more complex modelling of risk, including the pharmacology of BPG, non-linear protection after injection and seasonal variation in GAS infection, although we believe a simple measure is likely to be most useful for program monitoring and individual counselling. Although we defined PDC ≥ 0.8 as adequate adherence, the aim of secondary prophylaxis programs should be to receive all injections on time, where there are no days-at-risk, and the PDC approaches 1.0. Adherence to anti-retroviral treatments for HIV infection uses a PDC threshold of 0.9 (44), and a similar threshold may be appropriate for RHD.

Our study has some limitations. Data may not have been captured due to incomplete records at health clinics, patient migration and movement that was not recorded, or due to failure to link some records. It was not feasible to record data from all clinics, although those sites not visited are generally small and see very few RHD patients. These factors may have contributed to an underestimate of the true adherence. However, since adherence was inadequate at all locations, including those with robust documentation procedures, we do not believe this bias would have changed the conclusions of the study. It is possible that the apparent associations between adherence, age and years since screening were due to confounding, or that these associations were confounded by other factors which could not be assessed in the regression model due to the small cell sizes. However, that the OR did not change much between the bivariate and multivariate regression models suggests these associations are likely to represent the true result. We were unable to do the planned linear regression analysis of adherence due to the assymetry of the data, and this may have revealed different associations. The findings reported are only representative of adherence in Fiji, however the striking results may prompt other settings, particularly those that have commenced or are considering screening, to undertake similar evaluations. The strengths of

this study include the large sample size, robust data collection method, coverage of all administrative Divisions of Fiji and novel measurement using the PDC.

In summary, we report that adherence to SAP for patients with RHD diagnosed through screening in Fiji is low. At a national scale, adherence is inadequate to reduce the burden of RHD in the community using a screening strategy. Secondary prevention should be strengthened before further active case finding through screening can be justified. Such a program is currently underway in Fiji, with a broad, health systems strengthening project supporting the RHD Control Program. Project strategies include an enhanced web-based disease register, up-skilling of health workers, implementation of clinical guidelines, improving local penicillin quality and supply, and piloting of flexible and enhanced SAP recall and delivery systems (47).

Further research into RHD adherence is required. This should include an evaluation of adherence for patients diagnosed through screening in other settings, and in comparison to those diagnosed clinically. It would be useful to repeat the present analysis in Fiji after the current interventions, ideally through routine program data collection using the web-based register. Further qualitative investigation of the drivers of good and poor adherence will be valuable for targeting future adherence strategies (48). Advancements in therapy, such as a longer acting form of penicillin (49), could also improve adherence and disease control. Further development of the PDC, including studies linking to risk of ARF recurrence and outcomes, may enhance its utility as a tool for monitoring and promoting adherence to RHD prophylaxis.

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Competing Interests

None

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