Defining the Burden of Death and Disability Caused by Rheumatic Heart Disease in Fiji

1. Project Summary

Rheumatic heart disease (RHD) is considered a major public health problem in developing countries including Fiji but the risk of death and disability associated with the condition is poorly understood. At the request of the National Adviser for Non-Communicable Diseases, we have designed a two-component research study aimed at defining the risk associated with the condition in Fiji. The Medical Research Council UK and the Sir Halley Stewart Trust have funded the study.

The first component is a retrospective data-linkage cohort study covering the period 2008-2012. We will link records from the national patient information system ('PATIS'), death certificates submitted to the Ministry of Health, and the Disease Control Programme's register. We will estimate the number of RHD patients nationwide that died and/or were admitted to hospital with complications such as heart failure or stroke. We will compare the risk of death and complications to those in the general population.

The second component is a prospective cohort study. We will recruit approximately 500 patients with RHD in the Central Division and, over five years, record if they die and/or develop complications. Deaths will be ascertained from death registrations and by speaking to families and/or next of kin if the patient cannot be traced. We will obtain additional information from hospital records and at routine appointments in outpatients' clinics at the Colonial War Memorial Hospital. We will then use these data to calculate the risk of death, heart failure and other complications, and delineate the risk factors for these complications.

Our study will help meet the desperate need for information about the risk of death and disability associated with RHD. Initial estimates from the retrospective component will rapidly be made available to policy-makers followed by later more detailed information from the prospective component. Both will assist with public health and research strategy in Fiji and elsewhere.

2. General Information

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Defining the Burden of Death and Disability Caused by Rheumatic Heart Disease in Fiji

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3. Background and Rationale

3.1 Rheumatic heart disease

Rheumatic heart disease (RHD) is the chronic consequence of an aberrant immune response to infection by the bacterial pathogen *Streptococcus pyogenes* (Group A Streptococcus, GAS). The process begins with inflammation of the heart values during childhood, often accompanied by episodes of acute rheumatic fever (ARF), but over time progresses to the permanent scarring of the heart valves that is RHD during adolescence or early adulthood.(1) Clinically this may manifest as heart failure, arrhythmia, endocarditis, stroke and early death.(2) There is also a considerable risk to women during pregnancy.(3) In settings where the disease is endemic, the appearance of these complications amongst children and young adults presents a major public health challenge(4), with the disease widely considered the leading cause of cardiovascular morbidity and mortality amongst children and young adults in developing countries.(2,5)

Compounding this challenge is the limited availability of effective control strategies. The current mainstay of control is known as secondary prophylaxis, a form of secondary prevention, based on the long-term administration of three or four weekly benzathine penicillin G injection to patients with established disease aimed at limiting recurrences and progression.(6) However, this approach is reliant on early case detection, the optimal strategy for which remains unclear.(7) Further, there are considerable challenges to running an effective secondary prophylaxis programme in low resource settings and adherence to the therapy is often poor.(8) Beyond antibiotic prophylaxis, there are no specific preventative medical treatments for RHD and there is also no vaccine.(9) In those with symptomatic disease, percutaneous valve dilatation or cardiac surgery is usually recommended, both of which are extremely costly palliative measures that continue to absorb the greater part of health care funds spent on the disease.(2) Further, these interventions are often not available in endemic settings demanding funding for treatment overseas.(2)

3.2 Disease burden

Despite its apparent impact, the long-term consequences of the disease and the associated risk of death remain poorly defined, not least because the disease disproportionately affects those living in developing countries where surveillance is more challenging.(10) Nonetheless the World Heart Federation (WHF) considers this information a necessary basis for public health strategy, research, fundraising and advocacy(5), consistent with wider ongoing efforts to define the morbidity and mortality attributable to major human diseases.(11)

Estimates of prevalence provide a starting point for studies of disease burden.(12) At a minimum, there are probably 15 to 20 million people affected with the disease worldwide.(10) More recently, however, screening school children in developing countries by echocardiography has shown the global prevalence to be several-fold higher than previously realised.(13) Specifically, an influential study published in 2007 found that echocardiographic screening detected ten-fold more cases than clinical screening of school children, which, until that time, had been the mainstay of epidemiologic surveillance.(14) This result has since been replicated in a number of settings worldwide.(13)

The Global Burden of Disease Project estimated there were approximately 345,000 deaths due to RHD in 2010(11), consistent with the figure (230,000 to 300,000) estimated by a World Health Organisation (WHO) project in 2005.(10,15) Nonetheless, according to the WHF, “the current global figure for RHD mortality is speculative and likely to be a gross underestimate.”(5) The major problem with these estimates is that, despite systematic review of the literature(15), no current reliable estimates of mortality from developing countries are available.(10) Instead these global summary estimates were extrapolated from studies of mortality amongst patients with RHD during the early to mid-twentieth century, primarily in the UK, USA and Japan, with a consensus death rate of 1.5% per year applied to knowledge of prevalence.(15)

It is unlikely, however, that contemporary mortality rates for RHD in developing countries are comparable to those in industrialised countries from last century.(5,10) The only available data from developing countries originate from India(16), Ethiopia(17) and Nigeria(18), along with older reports from Indonesia and Taiwan.(19) A control programme register in India that included 257 children and adults totalling 1263 person-years follow-up reported annual mortality of 4.1%.(16) Studies conducted at other sites – none of which were considered reliable by the WHO review(15) – were small investigations of less than 100 patients that observed annual rates of between 0.5% in Thailand(19) and 12.5% in Ethiopia.(17)

In contrast to developing countries, RHD has been extensively studied amongst socially disadvantaged indigenous populations in Australia and New Zealand, who bear the highest prevalence worldwide.(20) Indeed the only longitudinal RHD study published in the last five years was an audit of patients enrolled in the control programme register in the Northern Territory (NT), Australia.(21) Indigenous RHD patients in the study had a relative survival rate of 88.4% ten years after diagnosis (equivalent annual cause-specific death rate 1.2%).(21) However, it is not clear how to extrapolate from indigenous populations in developed countries to patients in developing countries.(15)

4. Rationale

There is a clear need to determine the risk of death and disability amongst patients with RHD in developing countries(22,23) including Fiji. To meet this need we will use two complementary approaches. The first will be a retrospective record linkage cohort study(24) utilising routine clinical and administrative data that will rapidly produce initial estimates of risk and its broad determinants. The use of routine data for this purpose is not only an approach advocated by the World Heart Federation(5) but also consistent with the Ministry of Health's commitment to increase the use of health information as a basis for evidence-based policy making.(25) The second will be a traditional prospective cohort study that will refine these estimates and provide far greater detail on the determinants. The two-component approach not only guarantees policy-makers receive results of the study in a timely fashion but also allows us to validate our findings.

5. Aim and objectives

We aim to describe the burden of death and disability experienced by RHD patients in Fiji, where a high prevalence of the disease has been consistently reported.(26-28) Our specific objectives are:

i. To measure the risk of death and other complications including heart failure, arrhythmia, endocarditis and stroke experienced by patients with RHD

ii. To compare the risk of death and these other complications experienced by patients with RHD with that in the wider population

iii. To measure the risk of pregnancy and childbirth amongst patients with RHD, and compare that risk to mothers in general population

iv. To identify predictors of death and other complications amongst patients with RHD from factors including non-adherence to secondary prophylaxis and surgery

6. Design and methods

There are two components to this study but the analysis of both datasets will be similar:

6.1 Retrospective data-linkage cohort study

The first component is a retrospective data-linkage cohort study covering the period 2008-2012. We will link records from the national patient information system ('PATIS'), the national database of death certificates and the RHD control programme's register. The PATIS and death certificates data has been provided to investigators at the request of the National Adviser for Non-Communicable Diseases (Appendix 1) with permission of the Permanent Secretary of State for Health (Appendix 2). Information about each patient will be linked from across the databases using the national health number (NHN). Because of the potential for records to be provided with a missing or erroneous NHN, however, we will enhance this linking process by checking the validity of the NHN associated with each record and, where necessary, matching the record to PATIS to obtain the NHN.(29) In brief, we will, for each record, use statistical software to find the entry in PATIS that corresponds most closely in terms of a combination of identifiers (e.g. name, date of birth). The minority of records that cannot be reliably matched to PATIS, however, will be excluded. We will also identify and amalgamate duplicates (i.e. individuals with more than one NHN) by finding records that match each other. Patients will be eligible if they have received a clinical diagnosis of RHD at a health facility in Fiji, or have echocardiographic evidence of the disease.

6.2 Prospective cohort study

The second component is a prospective cohort study. We will focus on patients diagnosed by echocardiography(30), yet to undergo surgery, and living in the Central Division. They will comprise two groups: those with prevalent disease and those with incident disease. To ascertain the prevalent cases we will, at the outset, randomly select 500 of the approximately 2000 patients known to the national RHD control programme. Incident cases we will be all new diagnoses made at the Colonial War Memorial Hospital during the study period.

The study nurse will approach each patient either at routine outpatient appointments or in the community. At the first contact, the patient will be consented for the study with detailed contact information recorded including the contacts of at least one nominated next-of-kin. Using structured case report forms (CRFs) the nurse will also document baseline information on echocardiographic

features, symptoms of heart failure, previous complications, significant past medical history (e.g. type II diabetes mellitus), and socio-demographic information including age, sex, employment status, location of residence, and household income relative to the national poverty line. Over five years, the research nurse will review patients six monthly, typically at their routine clinic appointments, repeating the assessment of severity and symptoms of heart failure, and documenting new echocardiographic results as well as adherence to their prophylaxis regimen. Changes to the patient's socio-economic status will also be recorded. The research nurse will do twice weekly rounds of the inpatients wards and daily rounds of the emergency department and the maternity hospital searching both for those previously enrolled now presenting with complications and others presenting with complications of RHD not known to the study. Using further structured CRFs the nurse will document details of these complications and the outcome of the admission, as well as baseline information if the patient is new to the study. Non-governmental organisations visit Fiji once or twice a year to perform valve surgery and any surgery performed on patients in the cohort will be documented.

We recognise that many patients, even in the face of life-threatening complications, do not present to hospital but we nonetheless remain confident we can achieve high rates of follow-up. If the patient fails to present for review, the nurse will first contact the patient or their next-of-kin by telephone, and failing that the nurse will, with the assistance of local primary care nurses, visit the patient at home. Local experience suggests that if they are alive, few patients cannot be reached this way. At each review, the nurse will ask the patient or, if they are deceased or have moved away their nominated next-of-kin, a standardised series of questions to detect those complications that are most recognisable, namely stroke and heart failure. If the patient has not returned for review because they have died, the circumstances of the death will be documented. We will obtain further information by monthly reviews of PATIS, and at completion of the study we will review records of deaths held by the Ministry of Health.

6.3 Statistical analysis

The primary endpoint in both components of the study will be all-cause death and secondary endpoints will comprise: 1) cause-specific death; 2) recurrent ARF; 3) heart failure; 4) atrial fibrillation; 5) stroke; 6) infective endocarditis; 7) complications of pregnancy/delivery; 8) decline in socio-economic status. We will present survival data using Kaplan-Meier estimates for the endpoints. We will examine the association of these endpoints with severity of disease and presence of complications at presentation and the timing of surgery in those who undergo valve surgery during follow-up, presenting relative risks stratified for confounders using Mantel-Haenzel

methods and by deriving a multivariate Cox or Poisson regression model. We will compare risks with those in the general population by calculating standardised mortality ratios and relative survival.

7 Confidentiality and data management

The research team will inform the National RHD Control Programme of any new patients identified through either components of the study. Otherwise, participation will be strictly confidential.

Raw clinical and identifiable information used for the retrospective component will only be accessible to the research team, and, for monitoring purposes, responsible representatives at their respective universities. It will be stored on the encrypted hard-drive(s) of computers owned by the University of Oxford and erased after five years. Information used for analysis will be de-identified.

Raw clinical and identifiable information used for the prospective component will only be accessible to the research team in Fiji. The original study records will be stored in a locked repository in Fiji at the Fiji GrASP office.

Information used for analysis will be de-identified. The custodians of the data will be Drs Joseph Kado, Fiji Ministry of Health, and Andrew Steer, University of Melbourne.

8. Expected outcomes and dissemination

Our study will help meet the desperate need for information about the risk of death and disability associated with RHD. Initial estimates from the retrospective component will rapidly be made available to policy-makers followed by later more detailed information from the prospective component. Both will assist with public health and research strategy in Fiji and elsewhere.

9. Duration of the project

The retrospective component will cover the period 2008-2012. Analysis for this will be performed during 2013-2015. Recruitment will begin for the prospective component in November 2013 and the study will continue for a minimum of five years.

10. Ethical considerations

This study presents no risk to participants and raises little in the way of ethical considerations.

Routine clinical and administrative data – similar to those to be used in the retrospective component – are widely used in health care research, planning service provision, resource management, training and public health surveillance. Internationally, there is a consensus that, "Identifiable data can be used for medical research without consent, provided that such use is necessary and is proportionate with respect to privacy and public interest benefits."(31) Fiji's Health Information Policy outlines the need for research utilising existing routine data aimed at providing the country with high-quality evidence that can support public health policy.(25) Indeed, we previously demonstrated the value of such research to Fiji when, in 2008, by reviewing clinic notes in the Rewa subdivision, we found important evidence of under-diagnosis of ARF (FNRERC 2008-013)(32) a finding that had important ramifications for public health policy such that the study was awarded the Fiji Health Systems Research Prize in 2009. We have outlined above our strategy to safeguard the data and strictly maintain the privacy of those whose information is used for the retrospective component.

In the prospective cohort, we aim to observe the natural history of the disease in patients receiving standard of care as far as possible in accordance with the internationally recognised guidance published by the National Heart Foundation of Australia and New Zealand.(33) We recognise, however, that, where resources are limited, such recommendations will often not always be met and, while we stress this is not an interventional study, we believe it would be unethical to observe the natural history of disease while the patients receive substandard care. Thus, in an effort to assist local healthcare workers, the research nurse will at enrolment and each review briefly re-educate the patient on the importance of follow-up and adherence to their prophylaxis regimen, as well as provide the patient's clinical team with a summary of international recommendations for care. In addition, where we identify a patient is defaulting from clinic or from their secondary prophylaxis, we will, with the patient's consent, contact the clinical team to arrange review. Finally, the research nurse will provide a point-of-contact for clinical advice on management of RHD patients at the hospital.

11. Informed consent forms

There is an informed consent form for participation in the prospective component and an

information sheet. Children will be required to sign an assent form.

12. Budget and funding

Dr Parks' salary will be paid by his MRC Clinical Research Training Fellowship (G1100449/1) until August 2015 and afterwards by his NIHR Academic Clinical Fellowship (NTN OXF/CMT/032/A). This will be the only cost of the retrospective component.

The Sir Halley Stewart Trust will pay the cost additional costs of the prospective component:

	FJD	GBD
Salary Costs (£9000/year) for research nurse in Fiji	$80,730	£27,000
Local transport costs in Fiji (£1000/year)	$8,970	£3,000
Local administrative costs in Fiji	$5,980	£2,000
Return flights UK to Fiji for Principal Investigator	$5,980	£2,000
Total	$101,550	**£34,000**

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