Title Page

Informing the Prevention, Diagnosis and Management of

Acute Rheumatic Fever and Rheumatic Heart Disease in

Aboriginal Australian and Torres Strait Islander Populations

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Contribution of Others

This "thesis by publication" includes papers which the candidate co-authored with a number of colleagues. The nature and extent of the intellectual input of each author, including the candidate, for each of the included papers is outlined below.

The candidate was solely responsible for writing the introduction and discussion of this thesis with editorial input from his supervisors.

Chapter Number	**Details of Publication on which chapter is based**	**Nature and extent of the intellectual input of each author, including the candidate**
Ch. 2	**Rémond, M.G.W.**, and Maguire, G.P. (2012). Primordial and primary prevention of acute rheumatic fever and rheumatic heart disease in Australia. In, *The Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition)* (pp. 19-29). Darwin, Northern Territory: Menzies School of Health Research.	Rémond and Maguire developed the structure and themes of the review. Rémond performed a literature search and wrote the first draft of the paper in consultation with, and under the guidance of, Maguire. Maguire revised and edited the review and created the figures. Editorial input was provided by the lead authors and other members of the writing group of the guideline.
Ch. 2	**Rémond M.**, Maguire G. (2011). RHD: Women and Pregnancy. *O&G Magazine*. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), 47-50.	Maguire and Rémond developed the themes of the paper. Rémond undertook a literature review and wrote the first draft of the paper. Maguire provided editorial assistance to revise the paper. Rémond produced the figures and tables.

Chapter Number	**Details of Publication on which chapter is based**	**Nature and extent of the intellectual input of each author, including the candidate**
Ch. 2	**Rémond M.G.W.**, Coyle M.E., Mills J.E., and Maguire G.P. Approaches to improving adherence to secondary prophylaxis for rheumatic fever and rheumatic heart disease: a literature review with a global perspective. *Cardiology in Review (in press).*	Rémond and Maguire developed the concept and themes of the paper. Coyle undertook the primary literature search. Rémond prepared the first draft of the paper and undertook further literature searches. Rémond prepared figures. Maguire revised the paper and provided further intellectual input into the discussion. Mills and Coyle provided final editorial assistance.
Ch. 3	**Rémond MG**, Wark EK, and Maguire GP. (2013). Screening for rheumatic heart disease in Aboriginal and Torres Strait Islander children. *Journal Of Paediatrics And Child Health*. 49: 526-531.	Rémond, Wark and Maguire developed concepts and themes for the paper. Rémond and Wark conducted a literature search. Rémond prepared first draft of the paper. Maguire and Wark provided editorial assistance in revising the paper.

Chapter Number	Details of Publication on which chapter is based	Nature and extent of the intellectual input of each author, including the candidate
Ch. 3	**Rémond MG**, Atkinson D, White A, Hodder Y, Brown AD, Carapetis JR, and Maguire GP. Rheumatic Fever Follow-Up Study (RhFFUS) protocol: a cohort study investigating the significance of minor echocardiographic abnormalities in Aboriginal Australian and Torres Strait Islander children. BMC cardiovascular disorders. 2012;12:111.	All authors contributed to the development of the research question. Maguire created a funding proposal. Rémond wrote the first draft of the paper. Maguire created the map. Rémond created the hierarchy image. All authors edited and revised the paper to produce the final text.
Ch. 3	**Rémond MGW**, Atkinson DN, White A, Brown ADH, Carapetis JR, Remenyi B, Roberts K, and Maguire GP. Are minor echocardiographic changes associated with an increased risk of acute rheumatic fever or rheumatic heart disease? *Submitted to Circulation*.	The authors co-developed the research question. Rémond (with assistance from employed project staff) collected the data. Remenyi read all the echocardiograms collected during the study. Rémond and Remenyi entered all project data onto databases. Rémond cleaned the data and undertook data analysis with the assistance of Maguire. Rémond and Maguire drafted the paper. Rémond created the tables. All authors contributed to the revision and editing of the paper.

Chapter Number	**Details of Publication on which chapter is based**	**Nature and extent of the intellectual input of each author, including the candidate**
Ch. 4	**Rémond, M. G.**, Severin, K. L., Hodder, Y., Martin, J., Nelson, C., Atkinson, D., & Maguire, G. P. (2013). Variability in disease burden and management of rheumatic fever and rheumatic heart disease in two regions of tropical Australia. *Internal medicine journal*, *43*(4), 386-393.	All authors contributed to the development of the research question. Severin, Hodder and Rémond undertook data collection with the assistance of employed project staff. Rémond entered data into a database, cleaned the data and undertook data analysis. Rémond and Maguire wrote the first draft of the paper with Rémond developing the tables and Maguire developing the map. All authors contributed to the revision and editing of the final paper.
Ch. 4	Baskerville, C. A., Hanrahan, B. B., Burke, A. J., Holwell, A. J., **Rémond, M. G.**, & Maguire, G. P. (2012). Infective endocarditis and rheumatic heart disease in the north of Australia. *Heart, lung & circulation*, 21(1), 36-41.	All authors contributed to the development of the research question. Baskerville, Hanrahan, Burke, and Holwell collected the data. Rémond cleaned the data, undertook data analysis, and created the tables. Rémond and Maguire wrote the first draft of the paper. Maguire produced the map. All authors contributed to the revision and editing of the paper to produce a final manuscript.

Chapter Number	**Details of Publication on which chapter is based**	**Nature and extent of the intellectual input of each author, including the candidate**
Appendix 1	**Rémond, M. G.**, Wheaton, G. R., Walsh, W. F., Prior, D. L., & Maguire, G. P. (2012). Acute Rheumatic Fever and Rheumatic Heart Disease - Priorities in Prevention, Diagnosis and Management. A Report of the CSANZ Indigenous Cardiovascular Health Conference, Alice Springs 2011. *Heart Lung Circ*, 21(10), 632-638.	Wheaton, Walsh and Prior developed and delivered presentations at the CSANZ Indigenous Cardiovascular Health Conference on the major themes covered in this article. Rémond collated the information that was presented in these presentations, undertook further literature searches and, in conjunction with Maguire, further developed the themes and a framework for the paper. Rémond wrote the first draft of the paper. Maguire provided primary editing input. Wheaton, Walsh and Prior provided final editorial input.

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Abstract

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are auto-immune conditions associated with prior exposure to Group A streptococcus (GAS). ARF is an acute condition associated with fever and joint, brain, skin and heart inflammation. RHD is its chronic sequela and is characterised by permanent heart valve damage which can, in turn, lead to heart failure and an increased risk of endocarditis and stroke. To avoid such complications interventions may be required to repair or replace damaged valves.

ARF and RHD are preventable diseases rarely encountered in mainstream Australia. However, Aboriginal Australian and Torres Strait Islander peoples have amongst the highest reported rates of ARF/RHD in the world with significant morbidity and mortality.

This thesis comprises complementary projects and articles that can inform the community and health service response to prevention, diagnosis and management of ARF/RHD with a particular focus on Indigenous Australians.

Prevention: Three systematic reviews are presented that examine strategies to improve primary and secondary prevention of ARF/RHD. High quality studies are often lacking and much of the evidence informing strategies to prevent ARF/RHD is limited or absent. Available evidence indicates *primordial prevention* via improvements in social, economic and environmental conditions is key. While *primary prevention* may be achieved through improved diagnosis and early treatment of GAS pharyngitis, implementation can be difficult and research into the development of a GAS vaccine remains crucial.

Effective *secondary prevention* of ARF/RHD is possible with long-acting benzathine penicillin (LAB). Nonetheless, delivery of LAB is highly variable and frequently poor. Further work is needed to enhance health care systems to maximize uptake of LAB and to identify more effective formulations or delivery devices for administration.

Diagnosis: The utility of screening for RHD via echocardiography (heart ultrasound) to detect early disease is topical as this may facilitate early administration of secondary prophylaxis thereby limiting disease progression. A review of the feasibility of implementing RHD screening in Australia is presented and a number of limiting factors are

highlighted. These include a lack of an agreed case definition and a limited understanding of the significance, natural history and potential treatment of early and subclinical RHD. Further, the delivery of secondary prevention is often suboptimal and the impact of additional cases on health services, and the psychosocial health of patients and families, can be substantial.

The refinement of a screening-based case definition for RHD, and particularly the significance of minor heart valve abnormalities, was informed by the Rheumatic Fever Follow-up Study (RhFFUS). Children with prior Borderline RHD (defined under World Heart Federation (WHF) criteria) were up to nine times more likely to experience ARF compared with children with a normal echocardiogram. Their risk of having progressive valve damage was also significantly greater and 1 in 6 developed Definite RHD. In contrast, children with less severe valve abnormalities not satisfying criteria for Borderline RHD were at no greater risk of ARF or echocardiographic progression of valvular lesions.

These results provide cogent evidence that, in some children, valvular changes consistent with Borderline RHD detected on screening echocardiograms represent the earliest stage of Definite RHD. Such children may benefit from secondary prophylaxis or enhanced surveillance through regular echocardiographic monitoring to assess for progression of disease. Moreover, these results lend support to the validity of WHF criteria that distinguish Borderline RHD from other minor echocardiographic changes, as it is only in the former group that there is a greater risk of ARF and valvular lesion progression. Nonetheless, the fact that individuals with minor echocardiographic changes not satisfying criteria for Borderline RHD still had an increased risk of developing Definite RHD suggests that such individuals should be initially monitored with echocardiography to ensure they do not progress.

Management: The final component of this thesis comprises two papers that describe projects that were undertaken to inform potential improvements in the management of ARF/RHD. The first compared the quality of care provided to patients in the Kimberley and far north Queensland where differing models of care were operating. This highlighted more severe disease in the Kimberley and greater specialist follow-up and prescription and receipt of secondary prophylaxis in far north Queensland. This supported an association

between far north Queensland's single-provider model of care and centralised RHD control programme and improved patient care, potentially fewer cases of severe disease, and reduced need for surgical and other interventions. Since this study was completed, a centralized RHD control and management programme has been implemented in the Kimberley.

The second project related to the use of prophylactic antibiotics to prevent bacteremia, and potentially infective endocarditis (IE), in patients with RHD undergoing high-risk procedures. While this is recommended for Indigenous patients with RHD under Australian guidelines, American guidelines were recently amended to recommend prophylaxis only in people with prosthetic valves and not in those with "native-valve" RHD. A review of infective endocarditis cases in northern Australia was undertaken to determine whether native valve RHD was associated with an increased risk of IE. Results of this study showed that those with native valve RHD were at increased risk of IE (RR 58) compared to individuals without native valve RHD. Interestingly, the risk of IE in non-Indigenous patients with RHD was found to be 3.7 times higher than in Indigenous Australians with RHD. This study led to recommendations to broaden current Australian guidelines so as to offer prophylactic antibiotics to all persons with RHD undergoing procedures associated with a high risk of bacteraemia.

In conclusion, this thesis provides a number of new insights to address existing knowledge gaps regarding prevention, diagnosis and management of ARF/RHD. It is hoped that continued work on developing a GAS vaccine will eventually deliver an effective and safe method of primary prevention. In the interim the continued focus on early and accurate diagnosis of ARF/RHD and best-practice management (particularly improving uptake of secondary prophylaxis) should be pursued. Overarching these health initiatives must be a commitment to improving the socioeconomic and environmental status of Aboriginal Australian and Torres Strait Islander peoples living in remote communities as a means of effecting ARF/RHD primordial prevention.

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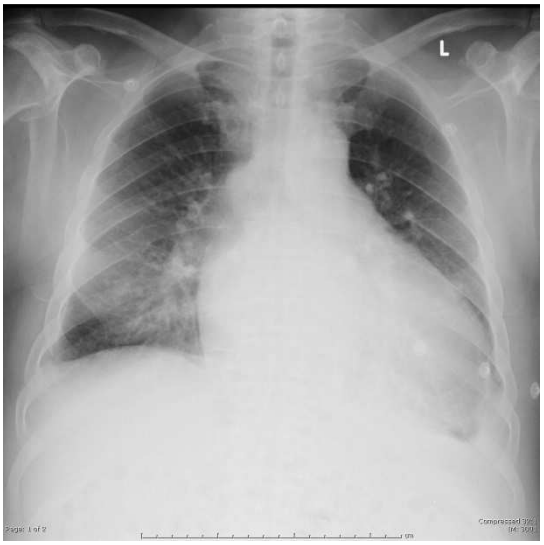
Chapter 1 – Introduction

A 21 year old Aboriginal man presents to hospital in Alice Springs, Central Australia complaining of breathlessness and fatigue. Three days later he dies from pulmonary oedema and heart failure (see Figure 1) as a result of severe mitral regurgitation and mitral stenosis secondary to rheumatic heart disease. This previously undetected damage to his mitral valve (see Figure 2) eventually resulted in irreparable damage to his heart. His family is left wondering how their seemingly fit and healthy son could have passed in such a fashion… and they have many questions: What is rheumatic heart disease? How did their son get it? Why weren't there any warning signs? What could have been done to save him?

Box 1. Introductory vignette.

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) remain significant issues for Aboriginal Australian and Torres Strait Islander peoples despite the fact that they are now rarely seen in the wider Australian population.[1] The story above (see Box 1), while fictitious, points to an all too common reality in the north of Australia. With some of the highest rates of ARF/RHD in the world, the morbidity and mortality associated with these diseases for Aboriginal and Torres Strait Islander populations remains unacceptably high.[2] Within this context, the broad aim of this project is to investigate means to inform the prevention, diagnosis and management of ARF and RHD in Aboriginal Australian and Torres Strait Islander populations.



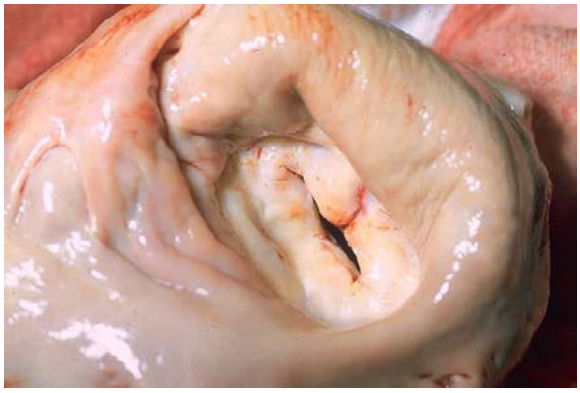


Figure 1. Chest X-Ray showing pulmonary oedema subsequent to heart failure.[i]

Figure 2. Image of stenosed mitral valve with thickened mitral valve leaflets resulting from RHD.[ii]

Synopsis

This thesis takes the format of a series of published and submitted papers that have been grouped together under three main themes: *prevention*, *diagnosis* and *management*. Of these three themes, prevention of ARF/RHD is key. Primary prevention remains the ultimate goal in ARF/RHD research and health service delivery. If successful, primary prevention obviates the need for diagnosis and management. However, as discussed later in this thesis, successful primary prevention of ARF/RHD remains elusive and hence secondary and tertiary prevention strategies are required. Secondary and tertiary prevention are inherent in both diagnosis and management of ARF/RHD. Accurate diagnosis and high quality management of ARF/RHD are pivotal in preventing progression of established disease, reducing symptoms and disability, and preventing premature death.

The section of this thesis devoted to *Prevention* comprises three review articles. The first explores potential mechanisms of primordial and primary prevention of ARF/RHD and

[i] Used with permission of Graeme Maguire
[ii] Image in public domain provided by Dr. Edwin P. Ewing, Jr. Accessed at http://phil.cdc.gov/PHIL_Images/02051999/00015/20G0015_lores.jpg on 5/2/14

discusses the benefits and challenges of implementing primary prevention strategies. The second paper examines the evidence surrounding secondary prevention programmes, the mainstay of ARF/RHD management practices, to prevent the development or worsening of RHD in people who have already had ARF. The third paper comprises a more specific review of the potential complications of RHD for pregnant women and describes the measures that are required to minimize the risks to mothers and their babies.

The section of this thesis focused on *Diagnosis* commences with a review paper that examines the feasibility of screening programmes for the early detection of subclinical RHD. Early detection enables timely implementation of secondary prevention treatment which can prevent worsening of disease thereby avoiding complications, morbidity and premature death. Two further papers are then presented that describe a research project that sought to determine whether minor but non-diagnostic changes to heart valve morphology and function in children living in regions with high ARF/RHD risk place these children at greater risk of a recurrence of ARF or progression of valvular damage to RHD. The importance of this study is that it provided clarity regarding the criteria used for echocardiographic diagnosis of RHD (i.e. whether subtle changes on echocardiography represent the earliest changes of RHD or mere variations of normal heart anatomy) and added to the debate regarding the feasibility and utility of screening programmes for such minor heart valve abnormalities.

The section of this thesis dedicated to *Management* comprises two research papers. The first compares and contrasts the management and epidemiology of ARF and RHD in two different regions of tropical northern Australia with a view to determining whether different jurisdictional approaches to management affect patient outcomes. The second paper examines the link between RHD and infective endocarditis in Australia with the aim of determining whether antibiotic prophylaxis is warranted for persons with RHD undergoing invasive procedures.

Background

The following background section provides a broad introduction to the problems of ARF and RHD. It aims to be accessible to a wide audience and is thus written for the reader who

may not have a detailed understanding of heart anatomy, ARF or RHD. It commences with a description of the conditions followed by a discussion of their causes, pathophysiology and epidemiology. Issues surrounding the diagnosis of ARF and RHD are also examined followed by a brief discussion of the prevention and management of these conditions. Having provided this background, a number of problems relating to the prevention, diagnosis and management of ARF and RHD will be described which provide a framework for the literature review and research components of this thesis.

Acute Rheumatic Fever and Rheumatic Heart Disease

ARF is an auto-immune condition resulting from prior infection with the bacterium Group-A streptococcus (GAS) or *Streptococcus pyogenes.* GAS is commonly found in the throat and on the skin.[2] Typically, ARF occurs a few weeks after a GAS throat infection (pharyngitis) although it has been suggested that skin infection with GAS may also cause ARF.[3, 4] The association between ARF and preceding symptomatic pharyngitis is not invariable as some studies indicate that only a third of ARF cases report an earlier sore throat.[5, 6]

Signs and symptoms of ARF result from localised and generalised auto-immune reactions and may include high fevers, painful swollen joints, skin rash, and inflammation of the heart (carditis) and brain (Sydenham's chorea - involuntary movements of the face, feet and hands). Patients often require hospitalisation during the acute phase of disease and whilst the course of ARF can be complicated it is typically self-limiting.[7] ARF is more common in children (5-14 years) although it may be diagnosed in susceptible adults.[2] People who have had one episode of ARF are at higher risk of developing a further episode (recurrent ARF) compared to people without such a history.[8]

Most effects of ARF are transitory in nature. However, carditis associated with ARF may lead to permanent damage of the heart valves. This condition is known as RHD and typically is associated with scarring and thickening of the mitral and/or aortic valves (see Figure 3). Whilst the incidence of ARF is highest in children and adolescents, RHD is most prevalent in people aged in their twenties and thirties.[1, 7] RHD results in significant and preventable morbidity and avoidable health care utilisation. Patients may experience

reduced quality of life and disability with RHD having the potential to cause premature death in seemingly healthy children and adults.

While a single episode of ARF can result in permanent damage to the heart valves, it is more common that RHD develops after recurrent episodes of ARF.[9, 10] Moreover, recurrent episodes of ARF in an individual who already has RHD are likely to cause further injury to already damaged heart valves thereby increasing severity of disease.[9, 10]

Damage to the heart valves associated with RHD typically results in detrimental changes in valve function. These changes include leaking (regurgitation) or blockage (stenosis) of blood as it moves between the chambers of the heart or into the aorta. Some of the more common signs of valvular dysfunction associated with RHD are outlined below:

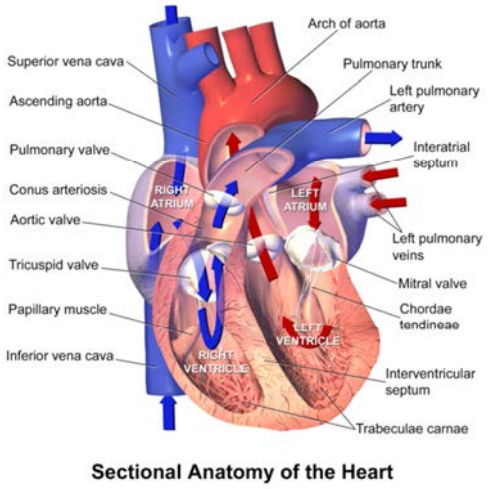


Figure 3. Sectional anatomy of the human heart - note particularly the mitral valve and aortic valve which are typically those affected by RHD.[iii]

Mitral Regurgitation (MR) is the most common functional valve lesion associated with RHD (see Figure 4). It occurs when the damaged mitral valve does not seal effectively during heart contraction (systole). This results in blood leaking back through the mitral valve from the left ventricle to the left atrium rather than being pumped across the aortic valve into the aorta. This means that the left ventricle does not eject its entire stroke volume

[iii] Image in public domain. By Blausen Medical Communications, Inc. http://commons.wikimedia.org/wiki/File%3ABlausen_0457_Heart_SectionalAnatomy.png. Donated via OTRS, CC-BY-3.0 (http://creativecommons.org/licenses/by/3.0), via Wikimedia Commons.

(SV) into the aorta with the regurgitant (wasted) SV passing back to the left atrium rather than into the arterial system.

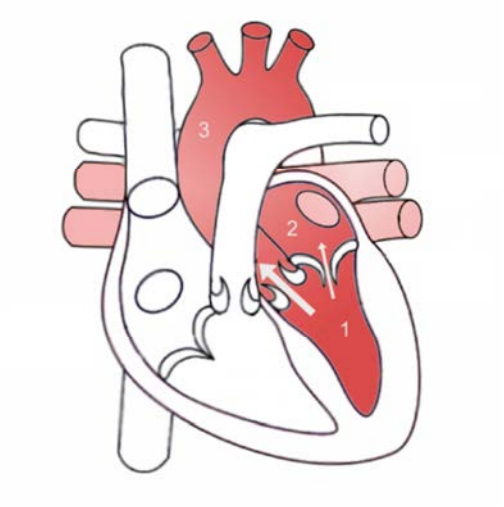


Figure 4. Mitral regurgitation. The mitral valve leaflets do not completely seal during systole allowing backflow of blood from the ventricle (1) into the atrium (2).[iv]

MR causes an haemodynamic overload on the heart as the left ventricle and atrium are required to deal with an increased volume of blood to achieve the same cardiac output. This volume overload can eventually lead to left ventricular compensatory adaptations and adjustments including dilation (enlargement) and a decline in systolic contractile function.[11] Carabello describes the pathophysiologic characteristics of MR as being progressive in nature and outlines three stages of MR which are discussed below.[12, 13]

In acute MR there is a sudden decrease in forward SV with a substantial part of the left ventricular SV being regurgitated into the left atrium. Left atrial hypertension results as this regurgitant volume is summed with the volume returning from the pulmonary veins leading to volume overload. Volume overload also occurs in the left ventricle resulting in stretching of sarcomeres in the left ventricular wall (increased preload) and increased left atrial pressure. This increase in sarcomere stretch allows for a modest increase in end-diastolic volume as well as enabling the ventricle to generate more work and eject a higher SV. Acute MR also results in a reduction of left ventricular afterload (end-systolic stress) as the

[iv] Image in public domain. http://upload.wikimedia.org/wikipedia/commons/5/54/Mitral_Regurgitation_scheme.png. Via Wikimedia Commons.

creation of a new pathway of ejection (through the unsealed mitral valve) reduces impedance to the emptying of the left ventricle thereby decreasing end-systolic volume. It should be noted that while these two effects on load act to increase the total SV, the forward SV is still reduced owing to the regurgitant fraction.

The second stage in the progression of MR is termed "chronic compensated MR".[12, 13] During this stage left ventricular dilation and eccentric hypertrophy develop. Together these result in a large increase in end-diastolic volume. Afterload (wall stress) returns to normal owing to the increased radius of the ventricle, preload remains elevated, and contractile function remains unchanged. This results in the ejection of a very large total SV which compensates for the regurgitant volume so that forward SV increases to near normal. In this stage the left atrium also enlarges thereby accommodating the regurgitant volume and reducing atrial pressure.

Carabello notes that a patient with chronic compensated MR may be asymptomatic and remain in this phase for long periods of time.[12] However, in cases of severe volume overload left ventricular contractile function decreases and the patient enters the third phase of "chronic decompensated MR". The reduced contractile function decreases ejection performance, total SV, and forward SV, while end-systolic volume increases. Additional left ventricular dilation may occur leading to increased afterload. During this phase congestive heart failure is likely to develop. Nonetheless, enhanced preload can maintain ejection fraction in the normal range even during this phase.

Mitral Stenosis (MS) occurs when the opening or orifice of the mitral valve narrows due to hardening/fibrosis and partial fusion of the two mitral valve leaflets (see Figure 5). In consequence, the valve does not fully open when the heart relaxes (diastole) resulting in a decrease in the volume of blood that flows from the left atrium to the left ventricle. This obstruction to left ventricular filling results in an increased pressure gradient across the valve – increased blood pressure in the left atrium is required to ensure adequate left ventricular filling. Over time an elevated pressure gradient can lead to enlargement or dilation of the left atrium, increased pressure in the blood vessels of the lung (pulmonary hypertension), and increased strain on, and potential failure of, the right ventricle.

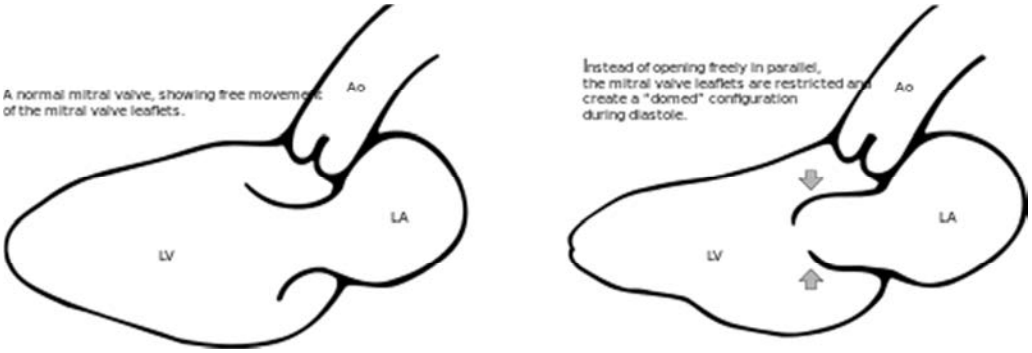


Figure 5. Mitral stenosis showing restricted opening of the mitral valve. (LA = left atrium, LV = left ventricle, Ao = Aorta).[v]

Aortic Regurgitation (AR) occurs when the damaged aortic valve does not fully close during diastole. This results in a backflow of blood from the aorta into the left ventricle (i.e. some of the blood ejected from the left ventricle during systole returns or regurgitates back from the aorta to the ventricle during diastole (see Figure 6)). Like MR, AR places a volume load on the left ventricle can lead to left ventricular dilation.

While both aortic and mitral regurgitation create a volume overload on the left ventricle, Carabello points out that the loading conditions they precipitate are very different.[13] In aortic regurgitation both the regurgitant volume and forward SV are ejected into the aorta in systole creating a wide pulse pressure and systolic hypertension. This systolic hypertension results in increased afterload. This may counteract the increased preload that results from regurgitation back into the ventricle during diastole.

[v] Image in public domain.
http://upload.wikimedia.org/wikipedia/commons/5/58/Heart_mitral_stenosis_lpla_view.svg.
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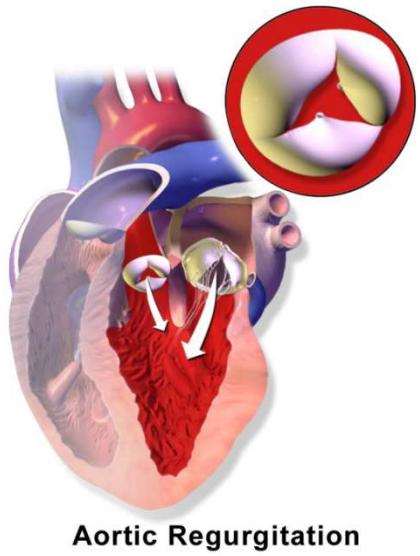


Figure 6. Aortic regurgitation. During diastole blood flows from the left atrium into the left ventricle but because the aortic valve is damaged blood also regurgitates from the aorta back into the left ventricle.[vi]

Aortic Stenosis (AS) results from narrowing of the aortic valve and thus increased resistance to blood flow. This requires the left ventricle to generate a greater pressure to eject the same volume of blood during systole. As described previously, to compensate for this the left ventricle may become thickened or enlarged and eventually fail.

Of the functional abnormalities discussed above, mitral regurgitation is the most common valvular lesion in RHD.[14, 15] In an Australian context, one study showed that 40% of Aboriginal patients with RHD in the Northern Territory had pure mitral regurgitation and that this proportion increased to 90% in children aged less than ten years.[16] The frequency of mitral stenosis in RHD patients seems to differ in different populations.[2] In developed countries mitral stenosis is thought to take decades to manifest after episodes of ARF while studies from developing countries report more rapid development of mitral stenosis.[17] Aortic regurgitation and stenosis are less common valvular lesions in RHD.[2] In an Indian study, isolated aortic regurgitation was reported in 4.5% of children and 2.8% of adults with RHD.[14] Isolated aortic stenosis is very uncommon in RHD.[2] Many individuals with

[vi] Image in public domain. BruceBlaus. Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010. ISSN 20018762. - Own work

RHD will exhibit combined and multiple valve lesions. For example, evidence from the Top End of the Northern Territory shows that 47% of RHD patients had damage to two or more valves with the mitral and aortic valves being the most commonly involved.[10] Furthermore, it is frequently observed that a single valve exhibits mixed lesions (stenosis and regurgitation).[2, 10]

RHD patients with more severe damage to their heart valves may experience a number of complications. These are associated with enlarged heart chambers (atria or ventricles), inability of the heart to pump a sufficient volume of blood to meet the needs of the body (heart failure) and increased pressure in the blood vessels in the lung (pulmonary hypertension). Symptoms can include tiredness and shortness of breath. All patients with RHD are at an increased risk of infection of the heart (endocarditis) and stroke as damaged valves and dilated heart chambers become a nidus for infection or blood clots. To avoid these complications, heart surgery and other interventions may be required. Damaged valves may be replaced with human/animal derived (bioprosthetic) or mechanical valves; the latter requires lifelong anticoagulation therapy (warfarin) to reduce the risk of valve clotting/thrombosis. In some cases it may be possible to repair a mitral valve at surgery without the need for replacement and suitable stenosed mitral valves may be opened at operation or by passing a balloon across the valve via a blood vessel (percutaneous balloon mitral valvuloplasty).

Pathophysiology

A detailed understanding of the exact pathway leading from GAS infection to ARF and RHD remains to be elucidated. However, it is clear that ARF and RHD result from an inappropriate immune response against specific parts or epitopes of the GAS bacterium in individuals susceptible to the disease.[7]

It has been postulated that only some strains of the GAS bacterium are “rheumatogenic” (i.e. able to cause ARF in a susceptible people).[18, 19] The major virulence factor of GAS bacteria is the M protein which is attached to the surface of the cell.[20] Over 130 types of GAS M protein have been identified[21] and strains lacking M protein are essentially nonpathogenic. While the relative “rheumatogenicity” of different strains of GAS has been

ascribed to certain M serotypes, there are believed to be other GAS cell surface factors important in the pathophysiology of ARF and debate continues around the concept of rheumatogenicity.[7]

Host susceptibility is also a factor in the development of ARF/RHD. Only 3-5% of people in any given population have an inherent susceptibility to ARF/RHD with a number of genetic markers being suggested as associated with the development of disease.[7, 22-24] Despite this, there remains no single genetic marker which accurately identifies those individuals who are at risk of ARF/RHD.

As to the mechanism for development of ARF/RHD, there is evidence available to suggest that molecular mimicry, the sharing of epitopes between GAS and susceptible people, is pivotal.[7, 18] Of particular interest in this context is the similarity between the M protein on the cell surface of GAS and a specific heart protein, cardiac myosin.[7, 21, 25, 26] Owing to this similarity it is postulated that ARF occurs when the human immune response against the GAS M protein "cross reacts" against cardiac myosin resulting in the heart tissue and valves being attacked by the patient's own immune system through the mediation of antibodies and T-cells.[24]

A second school of thought challenges the view that molecular mimicry is the sole driver behind rheumatic carditis and the development of RHD.[27] There is evidence to show that rheumatic carditis is associated not only with elevated levels of anti-cardiac-myosin but also anti-collagen.[28] Cunningham argues that both molecular mimicry of cardiac myosin and collagen-mediated autoimmunity may be involved in rheumatic carditis and the development of RHD.[29] Thus Cunningham proposes that initially mimicry of streptococcal and host antigens allows antibodies to attack the endothelial surface of the valve allowing T cells to infiltrate. In addition, oedema associated with this attack and stretching of the chordae tendinae (fibres attaching the valves to the papillary muscles of the heart) lead to the first stage of rheumatic carditis. Following this initial damage to the valve, antibodies against collagen, which had been released from the damaged valve or bound to the GAS bacterium, deposit on the valve and cause inflammation. This results in valve scarring and neovascularization of the valve which intensifies with each subsequent streptococcal infection. While pointing to the importance of cardiac myosin and collagen in the

development of rheumatic carditis and RHD, Cunningham also notes that the mechanisms of valve damage are not fully elucidated and that multiple autoantigens are likely to be involved in ARF/RHD.

Environmental and socioeconomic factors also play an important role in the pathogenesis of ARF and RHD. The distribution of ARF and RHD appears to be associated with communities characterized by lower socio-economic conditions, poor living conditions, overcrowding and poor access to health care.[21] In particular, studies from the 1940s onwards in the United States of America, United Kingdom and New Zealand have shown that ARF is associated with household income and overcrowding.[30-33] It is likely that overcrowded living conditions result in more frequent interpersonal contacts that can contribute to a more rapid spread of virulent GAS strains.[21] Further, there is evidence that dramatic falls in rates of ARF/RHD have occurred in populations undergoing improvements in socioeconomic and environmental conditions.[34-36] This has been seen in Australia, New Zealand and other high income countries over the last 50-150 years.[37-39] This pattern of reduced burden of ARF/RHD as socioeconomic and environmental conditions improve indicates that while individual immunological pre-disposition to ARF/RHD is important in the development of ARF/RHD, providing a healthy environment can ensure that these diseases remain rare even in susceptible individuals.

Epidemiology – the Australian context

It has been estimated that worldwide there are almost 500,000 cases of ARF each year and that 60% of these cases will develop RHD.[40] The prevalence of RHD has been estimated to be at least 15·6 million cases, with 282,000 new cases and 233,000 related deaths each year.[40]

While there has been a decrease in the incidence and prevalence of ARF and RHD in industrialized countries during the past 50-150 years, these diseases remain major public health concerns in developing countries.[21, 40] Children and young adults are particularly at risk in these regions with the result that RHD is the most common form of childhood heart disease in the world and the most common cause of death from heart disease in children and young adults.[2, 41]

Despite ARF and RHD now being relatively rare in developed countries, there are some population groups in such countries that remain at risk. This is the case within Australia where the acquisition of ARF and RHD is almost exclusively restricted to Aboriginal and Torres Strait Islander populations, particularly those living in rural and remote central and northern Australia.[1] In these populations, the burden of ARF and RHD is among the highest documented in the world.[42] The annual incidence of ARF in Aboriginal people in the Northern Territory has been reported as 250-350 per 100 000 per year in the 4-15 age group, and the prevalence of RHD 1.3-1.7 % (all ages).[1, 42] Similar levels of disease have been reported from northern Queensland and the Kimberley in the far north of Western Australia.[43, 44] By contrast, ARF in now rare in other Australian populations groups and the relatively small number of RHD cases seen in these groups occur mostly among the elderly.[2]

Diagnosis

ARF

Because of the rarity of ARF in mainstream Australia, and most of the developed world, it is common that many health practitioners have never seen a case during their working lives. This highlights the importance of education of health staff newly arrived in regional and remote Australia where ARF remains a concern. Misdiagnosis of ARF has serious implications; patients diagnosed with ARF are required to undertake a minimum of ten years of treatment (including secondary antibiotic prophylaxis in the form of monthly penicillin injections), primary health and specialist review, and investigations including, where necessary, echocardiography (heart ultrasound). Such protracted treatment and follow-up is inconvenient and costly and highlights the importance of not over-diagnosing ARF. In contrast, if an episode of ARF is missed then the patient may be placed at increased risk of recurrent attacks of ARF, development of RHD and disability or even death resulting from heart failure.

The diagnosis of ARF is difficult as there is no single diagnostic laboratory test to confirm its presence. A diagnosis is therefore based on clinical signs and symptoms as well as results of a number of investigations including electrocardiogram (ECG),

echocardiography, throat swab and blood tests assessing inflammation and exposure to GAS. The first major systematic approach to diagnosing ARF can be traced back to 1944 when the Jones criteria for the diagnosis of ARF were introduced.[45] These criteria developed by Thomas Duckett Jones divided clinical features of ARF into major and minor manifestations depending on how strongly they were associated with ARF. These criteria have been updated periodically and modified for an Australian context. They form the basis of the Australian guideline for the diagnosis of ARF outlined in Table 1.[2]

In response feedback from health providers, the candidate co-developed a flowchart based on the Australian criteria for the diagnosis of ARF. The aim of this flowchart was to provide a visual summary of the ARF diagnosis process so as to assist clinicians in making a determination about a diagnosis of ARF when assessing Aboriginal and Torres Strait Islander people in high-risk settings. This flowchart has been endorsed and branded by RHD Australia and is presented in

Figure 7.

The lack of a gold standard diagnostic test for ARF has led to a number of differences in the diagnostic criteria used in Australia compared to other settings. Notably, the Australian guideline for the diagnosis of ARF is presumptively more sensitive than others that have been developed by the American Heart Association (AHA) in the United States of America[46] and by World Health Organisation (WHO).[21] The driving force behind these changes were two studies from the Northern Territory that demonstrated that using the Jones criteria to diagnose ARF would result in a significant under-diagnosis of ARF in this high-incidence setting.[47, 48] The major difference in the Australian criteria are that subclincal carditis (evidenced by echocardiography in the absence of murmur detected by auscultation) is included as a major manifestation while not included in AHA or WHO guidelines. Furthermore, monoarthritis and polyarthralgia are included in the Australian guideline as major manifestations of ARF because in high-risk Aboriginal and Torres Strait Islander populations they are commonly associated with ARF and carditis.[2] In one retrospective study, monoarthritis was reported as occurring in 17% of confirmed cases of ARF without chorea.[48] In contrast, to improve specificity, neither the AHA nor the WHO

guidelines recognise monoarthritis and both only include polyarthritis as a minor manifestation.

The Australian guideline also includes a category of “probable ARF” to reflect recent Australian evidence from the Northern Territory that 31% of patients with suspected ARF did not fulfill the Jones Criteria.[47] This category was also incorporated in part as a response to the realities of providing health care in rural and remote Australian communities – in such contexts patients often delay their presentation and it is not always possible to undertake all recommended investigations that can assist in making a diagnosis of ARF.[2]

There are a number of other difficulties in the diagnosis of ARF that warrant consideration, Primarily, many of the clinical manifestations of ARF are non-specific and hence clinicians must be aware of potential differential diagnoses. Furthermore, whilst evidence of GAS infection via streptococcal antibody titres is crucial in the absence of a positive GAS culture, there is some debate surrounding what constitutes the upper limit of normal (ULN) in plasma ASO and the anti-DNase B titres.[49-51] The ULNs of these tests also vary with age and so it is preferable when considering a diagnosis of ARF to run sequential streptococcal antibody titres to determine whether there is a rise in titre over time rather than take a one off sample. However, this is not always practical.

	High-Risk Groups[*]	All Other Groups
Definite initial episode of ARF	2 major **or** 1 major and 2 minor manifestations **plus** evidence of a preceding GAS infection[†]	
Definite recurrent episode of ARF in a patient with known past ARF or RHD	2 major **or** 1 major and 2 minor **or** 3 minor manifestations **plus** evidence of a preceding GAS infection[†]	
Probable ARF (first episode or recurrence)	A clinical presentation that falls short by either 1 major or 1 minor manifestation, or the absence of streptococcal serology results, but one in which ARF is considered the most likely diagnosis. Such cases should be further categorised according to the level of confidence with which the diagnosis is made: • Highly-suspected ARF • Uncertain ARF	
Major manifestations	1. Carditis (*including* subclinical evidence of rheumatic valvulitis on echocardiogram) 2. Polyarthritis[‡] or aseptic monoarthritis or polyarthralgia 3. Chorea[¥] 4. Erythema marginatum[§] 5. Subcutaneous nodules	1. Carditis (*excluding* subclinical evidence of rheumatic valvulitis on echocardiogram) 2. Polyarthritis[‡] 3. Chorea[¥] 4. Erythema marginatum[§] 5. Subcutaneous nodules
Minor manifestations	1. Monoarthralgia 2. Fever[Ħ] 3. ESR ≥30mm/h or CRP≥30mg/L 4. Prolonged P-R interval on 5. ECG[Θ]	1. Fever[Ħ] 2. Polyarthralgia or aseptic monoarthritis 3. ESR ≥30mm/hr or CRP≥30mg/L 4. Prolonged P-R interval on ECG[Θ]

Table 1. Australian criteria for the diagnosis of ARF.[2]

CRP, C-reactive protein;

ECG, electrocardiogram;

ESR, erythrocyte sedimentation rate;

*High-risk groups are those living in communities with high rates of ARF (incidence >30 per 100,000 per year in 5–14 year-olds) or RHD (all-age prevalence >2 per 1,000). Aboriginal people and Torres Strait Islanders living in rural or remote settings are known to be at high risk. Data are not available for other populations, but Aboriginal people and Torres Strait Islanders living in urban settings, Maori and Pacific Islanders, and potentially immigrants from developing countries may also be at high risk.

†Elevated or rising anti-streptolysin O or other streptococcal antibody, or a positive throat culture or rapid antigen test for GAS.

‡A definite history of arthritis is sufficient to satisfy this manifestation. Other causes of arthritis/arthralgia should be carefully excluded, particularly in the case of mono-arthritis (e.g. septic arthritis, including disseminated gonococcal infection), infective or reactive arthritis (e.g. Ross River virus, Barmah Forest virus, influenza, rubella, Mycoplasma, cytomegalovirus, Epstein–Barr virus, parvovirus, hepatitis and Yersinia), and auto-immune arthropathy (e.g. juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis, sarcoidosis). Note that if polyarthritis is present as a major manifestation, polyarthralgia or aseptic mono-arthritis cannot be considered an additional minor manifestation in the same person.

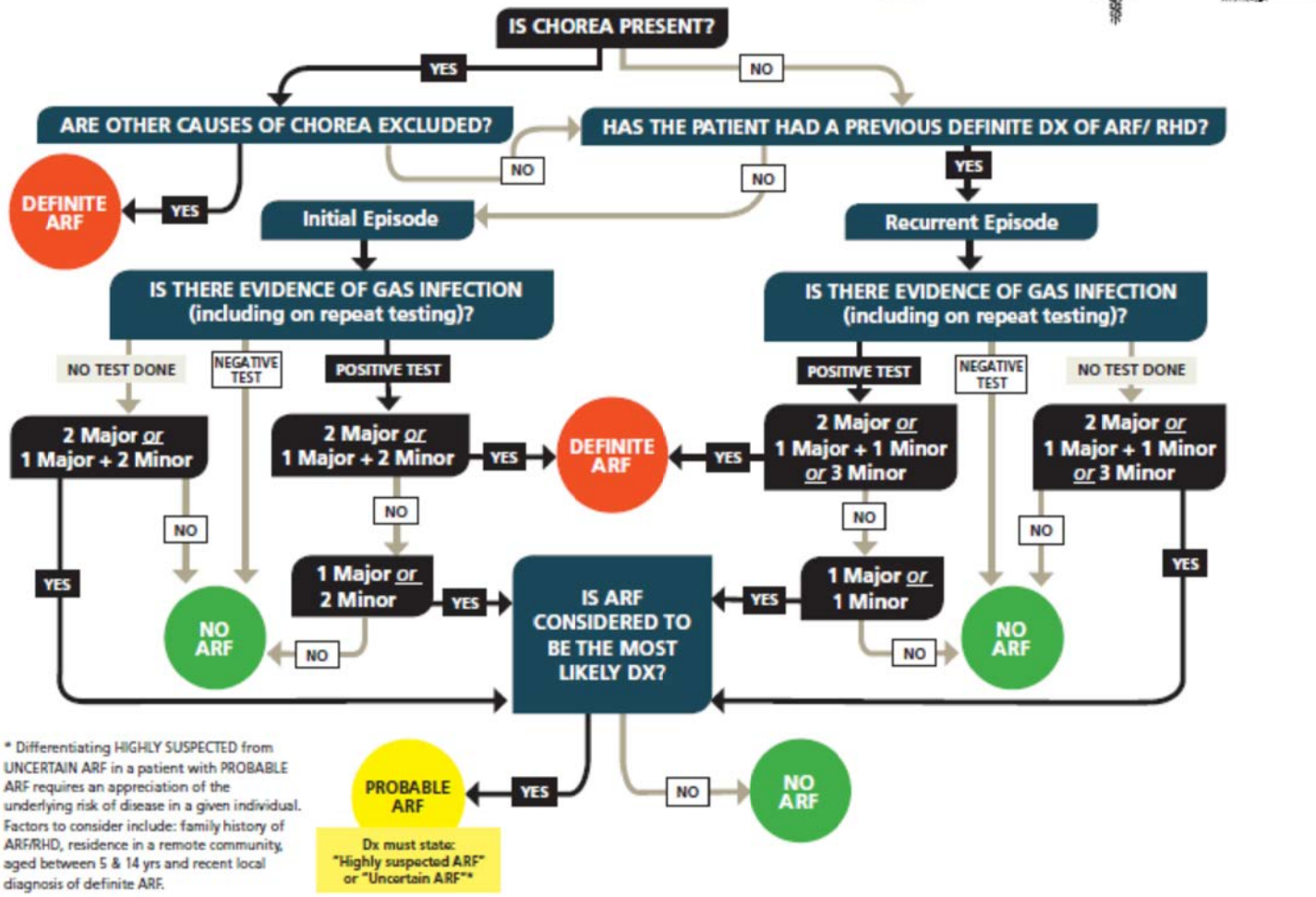
¥Chorea does not require other manifestations or evidence of preceding GAS infection, provided other causes of chorea are excluded.

§Care should be taken not to label other rashes, particularly non-specific viral exanthemas, as erythema marginatum.

ĦOral, tympanic or rectal temperature ≥38°C on admission, or a reliably reported fever documented during the current illness.

ΘIf carditis is present as a major manifestation, a prolonged P-R interval cannot be considered an additional minor manifestation.

ARF Diagnosis Flowchart *(based on the 2012 Australian ARF/RHD Guidelines)*



This flow chart was developed with the assistance of Marc Rémond (James Cook University), Rhona Dawson (KAMSC), Michael Dawson (KAMSC) & Graeme Maguire (Baker IDI). For suggestions or feedback, please email marc.remond@my.jcu.edu.au
Flowchart & tables based on: RHDAustralia (ARF/RHD writing group), National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition). 2012

	High-risk groups	All other groups
Definite initial episode of ARF	2 major OR 1 major AND 2 minor manifestations (Jones criteria) PLUS evidence of a preceding GAS infection* (ie. elevated anti-DNase or ASOT [repeat 10-14 days later if first test is not confirmatory] OR positive throat culture or RADT for GAS)	
Definite recurrent attack of ARF in a patient with known past ARF or RHD	2 major OR 1 major AND 1 minor OR 3 minor manifestations PLUS evidence of a preceding GAS infection*	
Probable ARF (first episode or recurrence)	A clinical presentation that falls short by either one major or one minor manifestation, or the absence of streptococcal serology results, but one in which ARF is considered the most likely diagnosis. Such cases should be further categorised according to the level of confidence with which the diagnosis is made: highly-suspected ARF uncertain ARF *(see national guidelines for more detail)*	
Major manifestations	• Carditis (clinical or echocardiographic evidence of pericarditis, pericardial effusion, myocarditis or heart failure, including evidence of subclinical carditis on echocardiogram) • Polyarthritis OR aseptic mono-arthritis OR polyarthralgia • Chorea[1] • Erythema marginatum • Subcutaneous nodules	• Carditis (as per high risk group but excluding evidence of subclinical carditis on echocardiogram) • Polyarthritis • Chorea[1] • Erythema marginatum • Subcutaneous nodules
Minor manifestations	• Mono-arthralgia • Fever ≥38°C • ESR ≥30 mm/h or CRP ≥30 mg/L • Prolonged P-R interval on ECG (if no carditis present)*	• Fever ≥38°C • Polyarthralgia or aseptic mono-arthritis • ESR ≥30 mm/h or CRP ≥30 mg/L • Prolonged P-R interval on ECG (if no carditis present)*

[1]Rheumatic (Sydenham's) chorea does not require other manifestations or evidence of preceding GAS infection provided other causes of chorea are excluded. Sydenham's chorea is characterised by jerky, uncoordinated movements, particularly affecting the hands, feet, face and tongue. The movements should disappear during sleep. The movements may only affect one side of the body (hemichorea).

***Definition of prolonged P-R interval**

Age group (years)	Sec
3–12	>0.16
12–16	>0.18
17+	>0.20

***Evidence of a preceding GAS infection**

- Positive throat culture for GAS, or
- Positive RADT for GAS, or
- Elevated or rising ASOT or other streptococcal antibody.

Age group (years)	ASOT	Anti-DNase B titre
1-4	>170	>366
5-14	>276	>499
15-24	>238	>473
25-34	>177	>390
35+	>127	>265

Figure 7. Flowchart developed the candidate and endorsed by RHD Australia to assist with the diagnosis of ARF. Based on criteria in the 2012 Australian ARF/RHD guideline.[2]

RHD

Traditionally RHD has been diagnosed on the detection of a heart murmur through auscultation in the setting of a previous episode of ARF. However, a number of studies have shown that screening for RHD by auscultation lacks both sensitivity and specificity.[52, 53] The evolution of more affordable and portable echocardiography as a medical imaging technique has resulted in this technology becoming the key component in making a diagnosis of RHD.[21, 41]

Echocardiography is safe and non-invasive (see Figure 8). With appropriately trained staff it is both sensitive and specific in regard to identifying valve lesions and functional heart valve abnormalities (regurgitation and stenosis) associated with established RHD.[54] Studies indicate that echocardiography results in up to ten times greater case detection than clinical examination alone[52, 53] although these studies have been limited by the earlier lack of validated criteria for the echocardiographic diagnosis of RHD. In addition, echocardiography can assist in differentiating RHD from non-rheumatic causes of valvular dysfunction (e.g. mitral valve prolapse, bicuspid aortic valve).[21] This leads to increased specificity in the diagnosis of RHD so that fewer patients are mislabeled as having RHD and subjected to unnecessary and prolonged medical management. However, expertise in interpreting echocardiographic images is crucial particularly so as to avoid the over-interpretation of trivial or physiological valvular regurgitation.[21]

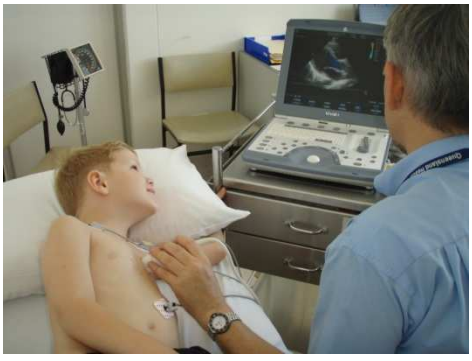


Figure 8. Echocardiography (heart ultrasound) is used to image the morphology and function of the heart valves and is a crucial tool in the diagnosis of RHD.[vii]

[vii] Photo used with permission of Graeme Maguire.

Echocardiography is also useful in the management of established RHD where it is utilized to assess the severity of RHD and to determine the size of the left ventricle and systolic function.[2] Over time, serial echocardiograms can indicate whether the damage to heart valves is progressive and whether heart surgery or other interventions are warranted in the management of RHD.

While echocardiography is a critical component in the diagnosis of RHD, until recently there have been no broadly accepted evidence-based criteria for diagnosing RHD. To address this issue, in 2012 the World Heart Federation (WHF) developed criteria for echocardiographic diagnosis of RHD.[55] These guidelines were designed to enable diagnosis of RHD in patients without a history of ARF. Indeed, the authors state that in individuals "with a history of definite ARF, *any* structural and functional abnormality of the valves must be considered to represent RHD until proven otherwise."[55] One further aim of these criteria was to address the concern that echocardiography might be overly sensitive leading to some children with normal variation in valvular structure and function being diagnosed with RHD. Hence a category of "borderline" RHD was introduced to cater for patients with minor echocardiographic lesions that do not meet criteria for definite RHD. The echocardiographic criteria for the diagnosis of RHD are outlined in Box 2.

Echocardiographic criteria for RHD in individuals aged ≤20 years

Definite RHD *(either A, B, C, or D):*

A) Pathological MR and at least two morphological features of RHD of the MV
B) MS mean gradient ≥4 mmHg
C) Pathological AR and at least two morphological features of RHD of the AV
D) Borderline disease of both the AV and MV

Borderline RHD *(either A, B, or C):*

A) At least two morphological features of RHD of the MV without pathological MR or MS
B) Pathological MR
C) Pathological AR

Normal echocardiographic findings *(all of A, B, C, and D):*

A) MR that does not meet all four Doppler echocardiographic criteria (physiological MR)
B) AR that does not meet all four Doppler echocardiographic criteria (physiological AR)
C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
D) Morphological feature of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation

Echocardiographic criteria for RHD in individuals aged >20 years

Definite RHD *(either A, B, C, or D):*

A) Pathological MR and at least two morphological features of RHD of the MV
B) MS mean gradient ≥4 mmHg
C) Pathological AR and at least two morphological features of RHD of the AV, only in individuals aged <35 years
D) Pathological AR and at least two morphological features of RHD of the MV

Echocardiographic criteria for pathological regurgitation

Pathological mitral regurgitation

- Seen in two views
- In at least one view, jet length ≥2 cm
- Velocity ≥3 m/s for one complete envelope
- Pan-systolic jet in at least one envelope

Pathological aortic regurgitation

- Seen in two views
- In at least one view, jet length ≥1 cm
- Velocity ≥3 m/s in early diastole
- Pan-diastolic jet in at least one envelope

Morphological features of RHD

Features in the MV

- AMVL thickening ≥3 mm (age-specific)
- Chordal thickening
- Restricted leaflet motion
- Excessive leaflet tip motion during systole

Features in the AV

- Irregular or focal thickening
- Coaptation defect
- Restricted leaflet motion
- Prolapse

Box 2. 2012 WHF criteria for the echocardiographic diagnosis of RHD. AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve.

Prevention

Prevention of ARF and RHD remains both the 'holy grail' to eradicate these conditions and the cornerstone of current management. To understand this statement first requires an appreciation of the different approaches to prevention. The prevention of any disease can be undertaken at a number of different levels. Primordial and primary prevention aim to stop a disease occurring in the first place, while secondary and tertiary prevention aim to limit the progression and reduce the consequences of established disease. The means by which these different levels of prevention are undertaken in relation to ARF/RHD are outlined below in Box 3.

PREVENTION IN THE CONTEXT OF ARF/RHD

Primordial prevention – broad social, economic and environmental initiatives to prevent or limit the impact of GAS infection in a population.

Primary prevention – initiatives undertaken to prevent the development of ARF in individuals.

Secondary prevention – early detection of disease and interventions in individuals with ARF or RHD to prevent progression of disease.

Tertiary prevention – intervention in individuals with RHD to reduce symptoms and disability and prevent premature death.

Box 3. Prevention in the context of ARF/RHD.

The majority of the research, knowledge and health initiatives associated with ARF/RHD prevention relate to secondary prevention focusing on limiting the more serious consequences of ARF/RHD through early diagnosis and treatment, and tertiary prevention targeted at reducing the impact and complications of established disease.[2] Nonetheless, initiatives to effect the primordial and primary prevention of ARF/RHD are key to the eradication of these diseases. Such initiatives include addressing environmental and social disadvantage associated with GAS infection and ARF,[56] developing a GAS vaccine,[57] and early treatment of GAS infection (pharyngitis) to lessen the post-infectious immune response that may lead to the development of ARF.[58-61]

Management

The development, and refinement, of national Australian guidelines for ARF and RHD diagnosis and management[2, 62] have facilitated the standardisation of ARF/RHD care across Australian state health departments. These national guidelines have been utilized to inform local management protocols.[63-65]

Management of an acute episode of ARF generally entails hospitalisation or outpatient treatment, medication for the relief of acute symptoms, and baseline investigations so that the diagnosis of ARF can be confirmed.[2] Echocardiography to assess for acute carditis or the pre-existence of RHD, review by a paediatrician or physician, and education are also recommended. During hospitalisation, treatment can be commenced including secondary antibiotic prophylaxis.

Management of RHD is aimed at preventing further attacks of ARF which can worsen the severity of RHD, preventing and managing complications such as infection of heart valves (endocarditis), stroke and heart failure, and assessing the need for, and timing of, surgery or other interventions for valve disease.[62] Follow-up includes regular echocardiography and cardiologist/physician/paediatrician review, dental check-ups, and treatment and secondary prophylaxis to prevent further episodes of ARF.

Management of ARF and RHD is complex and requires a multidisciplinary approach. Within an Australian context where ARF/RHD is most often seen in Aboriginal Australian and Torres Strait Islander people residing in regional and remote centres, the delivery of required health services is shared between visiting and local specialists, primary health care providers and tertiary referral centres. In order to better coordinate ARF/RHD care in Australia, register-based control programmes have been implemented in Northern Territory, Queensland and the Kimberley region of Western Australia. Such coordinated programmes are believed to be effective in improving uptake of secondary prophylaxis, increasing clinical follow-up (including specialist review and echocardiography) and coordinating care for those with ARF/RHD.[2]

Scope of this Thesis

The overall aim of this project is to inform the prevention, diagnosis and management of ARF and RHD in Aboriginal Australian and Torres Strait Islander populations. Prevention is the key theme throughout this thesis. Thus, while prevention in terms of eradicating ARF/RHD remains the ultimate goal in ARF/RHD research, prevention also remains a cornerstone of current diagnosis and management practices - early diagnosis of ARF/RHD and appropriate, timely management aim to halt disease progression and prevent complications associated with ARF/RHD.

The key issues explored within each these facets of ARF/RHD care are introduced below together with a brief review of how these issues are tackled within this project.

Section 1 – Informing the Prevention of ARF/RHD

The first section of this thesis focuses on the prevention of ARF/RHD. This section consists of three review articles that examine primary prevention, secondary prevention and prevention during pregnancy.

Primary Prevention

At its broadest definition, the prevention of disease refers not only to stopping a disease occurring but also to measures which aim to limit progression and reduce the consequences of disease once it is established. Currently, the major emphasis in ARF/RHD prevention, as evidenced by current management practices,[2] is secondary and tertiary prevention through secondary prophylaxis regimes, regular medical review and, where needed, surgical intervention . Such interventions aim to prevent the development, or progression, of RHD and to reduce symptoms and disability and prevent premature death. Nonetheless, ARF and RHD are entirely preventable diseases and the ultimate aim in ARF/RHD care must remain the eradication of these diseases. The question should not be whether this is possible but rather how this can be achieved.

The first review article in this thesis focuses on the evidence supporting initiatives which aim to stop ARF occurring and hence prevent the subsequent development of RHD. The

major concept that underlies these initiatives is primary prevention. The purpose of primary prevention is to limit the incidence of disease by controlling causes and risk factors.

This review of primary prevention of ARF/RHD was published as a chapter in the Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition).[2]

Secondary Prevention

Owing to the difficulties in implementing effective primary prevention strategies, current ARF/RHD management focuses on secondary prevention in the form of three to four-weekly long-acting intramuscular benzathine penicillin injections.[2, 66, 67] Secondary prevention aims to protect individuals who have previously had ARF, or already have RHD, against GAS infection and recurrent ARF so as to prevent the development or worsening of heart valve lesions. While the effectiveness of secondary prevention has been demonstrated[21], implementation is difficult.[68, 69] ARF/RHD patients not receiving adequate secondary prophylaxis are at risk of avoidable and progressive heart damage.

This review evaluates the evidence pertaining to improving uptake of ARF/RHD secondary antibiotic prophylaxis within the framework of the Chronic Care Model (CCM) developed by Ed Wagner and colleagues.[70] It has been accepted for publication in the journal Cardiology in Review.

Prevention during Pregnancy

Women are at higher risk of developing RHD than men despite similar rates of ARF.[71, 72] While the onset of RHD usually occurs in childhood and adolescence, it can often be first detected in women of child bearing age and can potentially complicate pregnancy and labour.[71] This is because the normal changes associated with pregnancy (increased blood volume and heart rate, reduced resistance of the arterial circulation, and an associated increase in cardiac output) tend to worsen pre-existing heart valve problems including those associated with RHD.

This review examines factors which are important in ensuring a good outcome for both mother and child where the mother has RHD. It was published in the O&G magazine, the

official publication of The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG).[71]

Section 2 – Informing the Diagnosis of ARF/RHD

The second section of this thesis explores issues relating to the diagnosis of RHD. Given that secondary antibiotic prophylaxis is an effective means of preventing the worsening of heart valve damage associated with RHD, it is vital that prompt and accurate diagnosis of RHD be made in order to commence treatment as early as possible. Such early intervention can reduce morbidity, mortality, and health care utilisation. However, this quest for early diagnosis and treatment must be balanced against the need to ensure that RHD is not over-diagnosed, particularly as management practices are long-term, inconvenient to patient and their families, and resource-intensive. This section of the thesis comprises a review article and a research project reported in two separate papers.

Screening for Rheumatic Heart Disease in Aboriginal and Torres Strait Islander Children

Many people with RHD in Australia first present with advanced valve disease.[73] One mechanism to prevent advanced RHD is to identify those with milder disease and offer them secondary antibiotic prophylaxis.[66] To this end, there has been increasing research regarding the utility of echocardiographic screening for the early detection of RHD in Australia and elsewhere as it may enable identification of those at-risk before symptoms develop.[52, 53, 74, 75] Concurrently there has been increased discussion in Australia regarding whether screening for RHD should become part of routine health care[62] for those at increased risk including Aboriginal and Torres Strait Island children.[1] Despite ongoing research, uncertainty remains regarding the potential benefits and risks of such a strategy.

This review article uses the framework of the Australian criteria for the assessment of population screening to examine the feasibility of echocardiographic screening for RHD.[76] It was published in the Journal of Paediatrics and Child Health.[77]

Rheumatic Fever Follow-Up Study (RhFFUS)

The major research component of this thesis is the rheumatic fever follow-up study (RhFFUS) which aimed to investigate the significance of minor non-diagnostic heart valve abnormalities in Aboriginal Australian and Torres Strait Islander children.

The increasing availability of more portable and affordable echocardiography to assess heart valve morphology and function has resulted in significant debate regarding the diagnosis of RHD on echocardiography alone. In an attempt to address this issue, in 2012 the World Heart Federation (WHF) released criteria for the diagnosis of RHD based on both morphological and functional findings on echocardiography.[55] The WHF criteria include a category of "Borderline" RHD, recognizing potential abnormalities on echocardiography that are of uncertain significance.

The importance of such minor abnormalities was highlighted by an Australian RHD prevalence and echocardiography validation study. The gECHO (getting Every Child's Heart Okay) Study undertook echocardiographic screening of 3978 high risk (Aboriginal Australian and/or Torres Strait Islander) and 1267 low risk (non-Indigenous Australian) children across northern and central Australia. Preliminary results revealed a number of children with mild potential abnormalities of doubtful significance (personal communication, Graeme Maguire). If these abnormalities are representative of the earliest changes of RHD then offering such children regular secondary prophylaxis may prevent disease progression.

RhFFUS aimed to clarify the significance of minor echocardiographic abnormalities detected in children and adolescents at high risk of ARF/RHD. More specifically, it aimed to clarify whether children with minor echocardiographic abnormalities were at increased risk of ARF or of progression of heart valve changes consistent with RHD. Answering this question would give clinicians a better understanding of whether such minor echocardiographic abnormalities merely represent a variation of normal or whether they may be the earliest signs of RHD. RhFFUS also aimed to inform the ongoing debate regarding the potential role of screening echocardiography in an Indigenous Australian setting.

This research was published in two separate papers. A "methods paper" was published in BMC Cardiovascular Disorders[78] while a "results paper" has been submitted to Circulation.

Section 3 – Informing the Management of ARF/RHD

One of the major foci in the management of ARF and RHD is secondary antibiotic prophylaxis to prevent further episodes of ARF which can in turn increase the likelihood of the development of RHD or worsen pre-existent RHD.[2] Management practices also include regular monitoring of patients for the development of symptoms and signs of heart failure and echocardiographic review to assess heart valve morphology and function to determine whether further intervention is required. Secondary and tertiary prevention are implicit in the management of ARF/RHD and this final section of the thesis describes two research projects aimed at improving the management of ARF/RHD so as to achieve better outcomes for patients.

Variability in Disease Burden and Management of ARF/RHD in Australia

Previous studies of ARF/RHD in the north of Australia have demonstrated suboptimal care: secondary prophylaxis coverage is inadequate, survival following heart valve surgery is low, and monitoring of anticoagulation following heart valve replacement is variable.[79-81] This earlier work, and the demonstrated high burden of disease, has provided a focus for local initiatives which aim to improve access to, and quality of, care. In order to explore optimal models of care for people with ARF/RHD living in the north of Australia, a project was undertaken to assess two differing systems: the first in the Kimberley region of Western Australia and the second in far north Queensland. The aim of this project was to assess the locally recognised burden of disease, audit the care received by patients, and benchmark care against local management guidelines.

Results from this study were published in the Internal Medicine Journal.[68]

Infective Endocarditis and Rheumatic Heart Disease in Australia

One of the complications that can result from RHD is the risk of developing infective endocarditis (IE) particularly during invasive procedures. In developed countries the

importance of RHD as a risk factor for IE is waning[82] but in many developing countries RHD remains the most frequent predisposing condition.[83] Current Australian guidelines[84] recommend providing prophylactic antibiotics to people viewed as being at an increased risk of IE prior to procedures which may cause bacteremia. This includes Indigenous Australians with RHD undergoing high-risk dental, respiratory, genitourinary and gastrointestinal procedures. However there has been debate over whether Australian recommendations should be amended to reflect the American Heart Association's guidelines[85] under which prophylaxis is recommended for patients with RHD only if they have prosthetic valves or prosthetic material in cardiac valve repairs. Patients with "native valve" RHD are not included. In addition, the American guidelines do not recommend providing prophylaxis for procedures involving the gastrointestinal and genitourinary tract.

In order to inform Australian recommendations for antibiotic prophylaxis to prevent IE in patients with RHD an audit of IE cases was undertaken to ascertain whether altering Australian recommendations to bring them in line with American Heart Association recommendations may expose Aboriginal and Torres Strait Islander people with RHD to an increased risk of IE.

This paper was published in the journal Heart, Lung and Circulation.[86]

Chapter 2 – Informing the Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease

2.1 Primordial and Primary prevention of ARF/RHD

Background

In 2012, a review was undertaken of the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand's guideline *Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia*.[62] Subsequent to this review, the organising committee decided to include a chapter on the primary prevention of ARF and RHD. In collaboration with Professor Graeme Maguire, the candidate completed a review of the evidence surrounding primordial and primary prevention of ARF/RHD. This review was incorporated into the updated 2nd edition of the *Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease*.[2] The guideline can be accessed at:

www.rhdaustralia.org.au/resources/arf-rhd-guideline

The importance of ARF/RHD prevention was highlighted by specialist clinicians, health service providers, researchers, and other stakeholders during a workshop at the 2011 CSANZ (The Cardiac Society of Australia and New Zealand) Indigenous Cardiovascular Health Conference held in Alice Springs, Northern Territory.[69] However, it was discussed that despite much anecdotal evidence about the potential benefits of successfully implemented primary prevention programmes, there was no evidence-based review available to more formally assess such programmes. Against this background, the following chapter was conceptualised and written.

Introduction

The prevention of disease may be undertaken at a number of different levels (see Box 4). Primordial and primary prevention aim to stop a disease occurring in the first place, while secondary and tertiary prevention aim to limit the progression and reduce the consequences of established disease. Most of the research, knowledge and health initiatives associated with ARF/RHD prevention relate to the latter: secondary prevention focusing on limiting the more serious consequences of ARF/RHD through early diagnosis and treatment, and tertiary prevention targeted at reducing the impact and complications of established disease.

PREVENTION IN THE CONTEXT OF ARF/RHD

Primordial prevention – broad social, economic and environmental initiatives undertaken to prevent or limit the impact of Group A streptococcus (GAS) infection in a population.

Primary prevention – reducing GAS transmission, acquisition, colonisation and carriage or treating GAS infection effectively to prevent the development of ARF in individuals.

Secondary prevention – administering regular prophylactic antibiotics to individuals who have already had an episode of ARF to prevent the development of RHD or who have established RHD in order to prevent progression of disease.

Tertiary prevention – intervention in individuals with RHD to reduce symptoms and disability and prevent premature death.

Box 4. Prevention in the context of acute rheumatic fever and rheumatic heart disease.

Because of the challenges and costs involved in implementing effective secondary and tertiary prevention programmes, the ultimate goal in ARF/RHD prevention must remain the elimination of disease. Changing disease patterns in many high income populations where ARF and RHD are now rarely seen attest that the near elimination of ARF and RHD outside rare and isolated outbreaks is possible.[35] The question is therefore not whether ARF/RHD elimination can be achieved but rather:

- What aspects of environment pre-dispose individuals and populations to an increased risk of ARF and RHD?
- What evidence is there that specific interventions can make a difference?
- Are such interventions an appropriate use of finite health and community resources?

This chapter will review the evidence supporting initiatives which aim to stop ARF occurring and hence prevent the subsequent development of RHD. The major concept that underlies such initiatives is primary prevention. The purpose of primary prevention is to limit the incidence of disease by controlling causes and risk factors. Primary prevention can either focus on an entire population (e.g. in the case of Australia this may be all Aboriginal Australians, Torres Strait Islanders, Pacific Islanders and perhaps immigrants from other regions with high rates of ARF/RHD) or can focus on individuals within that population who are at elevated risk (e.g. people with Group A streptococcal (GAS) infection).

An extension of the concept of primary prevention termed "primordial prevention" will also be examined here. This term was first proposed by Strasser who argued that the prevention of disease should go beyond primary prevention to include activities that prevent the penetration of risk factors into a population.[87]

In the context of ARF (a non-suppurative complication of GAS infection[88-90]) primordial and primary prevention would therefore involve:

1. Eliminating the risk factors associated with GAS infection – **primordial prevention**
2. Preventing infection, and perhaps colonisation, with GAS and the subsequent development of ARF – **primary prevention**

This chapter will examine both these concepts and conclude by providing suggested strategies for how available evidence may be utilised in conceptualising, advocating and implementing primordial and primary prevention initiatives for ARF/RHD in our region.

Primordial prevention

Primordial prevention aims to stop the development of risk factors for a disease in a population. In the case of ARF/RHD, primordial prevention means preventing the

acquisition of GAS infection through implementing "actions and measures that target environmental, economic, social and behavioural conditions, cultural patterns of living... that are known to increase the risk of [GAS infection]."[91]

Whilst socioeconomic and environmental disadvantage, in association to household overcrowding and limited access to infrastructure to maintain hygiene, are frequently posited as the predominant drivers of ARF/RHD, the evidence supporting this supposition remains limited.[92, 93] Nonetheless, studies from the 1940s onwards in the USA, United Kingdom and New Zealand have shown that ARF is associated with household income and overcrowding. [30-33] Further, there is evidence that dramatic falls in rates of ARF/RHD have occurred in populations undergoing improvements in socioeconomic and environmental conditions.[34-36] This has been seen in Australia, New Zealand and other high income countries over the last 50-150 years.[37-39] This reduction in disease burden now means that in most developed countries, ARF is no longer endemic and is restricted to rare, sporadic cases and defined outbreaks.[94] Such developments make a persuasive case that demographic, socioeconomic and environmental factors are important drivers of ARF/RHD.

Exactly what component of increasing affluence (housing quantity and quality, health care access and quality, education, economic advantage etc.) has played a role in the reduction of rates of ARF/RHD is unknown. However, Holmes and Rubbo in a review of ARF in Melbourne between 1938 and 1948 did find that the incidence of rheumatic fever was three times greater in low than in high rental districts.[37] Furthermore, in a systematic review identifying potential risk factors for ARF and possible interventions for its prevention, Kerdemelidis *et al.* found that overall evidence suggests that the incidence of ARF may be reduced by measures that alleviate poverty and crowding.[56] Alleviating household overcrowding has biological plausibility given the potential for increased risk of GAS transmission when living in close living conditions such as has been described in studies of outbreaks of GAS infection and ARF in the US military.[95] The association between crowding and transmission of GAS is not invariable with Danchin *et al.*'s prospective Australian study reporting no association between risk of GAS-positive sore throat and socioeconomic disadvantage or household crowding.[96] Nonetheless, this study did

demonstrate high levels of GAS transmission even in uncrowded households. Kerdemelidis *et al.* further argue that health knowledge, health literacy and access to healthcare are important aspects of primordial prevention for ARF.[56] Logically, as the authors state, "...if people do not consider sore throats important or have the knowledge that they can lead to permanent heart damage, they will not seek medical help, creating a barrier in RF prevention." The issue of access to healthcare was explored by Gordis in Baltimore (USA) in the 1960's when comprehensive primary care programmes were implemented in some parts of the city.[97] While not a randomised control trial, results did show a 60% reduction in ARF from 1960 to 1970 in those parts of the city where comprehensive primary care programmes were introduced compared with no improvement at other sites.[97]

Given the uncertainties regarding specific causes, advocating for the primordial prevention of ARF/RHD based on one or another specific environmental or social strategy cannot be supported by the available evidence. Nonetheless, consistent data demonstrating an association between overcrowding and ARF risk across multiple countries would indicate this particular factor is worthy of further study. The broader context of alleviation of poverty and social and environmental disadvantage, along with improved housing, education, health care access, and appropriate standards and quality of care, are likely to be key in addressing ARF/RHD as well as many other health issues in our region.

Despite the lack of evidence to support specific environmental or social interventions to address the acquisition of risk factors for ARF/RHD, this uncertainty should not dissuade action. The broader context of equity, poverty alleviation and justice in association with the empirical link observed between improved socioeconomic and environmental factors and reduced ARF incidence should be sufficient to drive advocacy and change. Such change, as Ursoniu notes, "...rests mainly on public education, the media, legislation and government policy, and is very dependent on the commitment and determination of individual governments."[91]

Primary prevention

Primary prevention assumes that the risk factor for ARF/RHD, namely the presence of GAS (particularly in the pharynx) is present in a given population. In reality this

assumption is borne out as GAS is present in all populations, both rich and poor, and those with and without high rates of ARF/RHD. Furthermore, GAS has been shown to be associated with up to 37% of sore throats infection[98] and 82% of skin infection.[4, 99] Whether other streptococci such as Group C (GCS) and Group G (GGS) Streptococci play a similar role in the pathogenesis of ARF/RHD is unclear.

Before further discussing the primary prevention of ARF/RHD it is necessary to have a clear and consistent definition of a number of terms (see Box 5):[100]

Colonisation – organisms are present but cause no host response. This implies associated transmission and acquisition.

Carriage – organisms remain in an individual after a clinical infection but cause no symptoms; an immunological response may remain.

Infection – the deposition and multiplication of organisms in tissue or on body surfaces which usually cause adverse effects; this is typically associated with an immunological response.

Pharyngitis – a clinical syndrome associated with infection/irritation of the pharynx and/or tonsils.

Box 5. Useful definitions in the context of discussing primary prevention.

Primary prevention of ARF/RHD through addressing GAS should prioritise identifiable populations at elevated risk of ARF/RHD. In Australia such populations include Aboriginal and Torres Strait Islander peoples, Pacific Islanders and perhaps immigrants from other countries with high rates of ARF/RHD.[1, 101, 102] However, this may also extend to other groups in the setting of a temporally-defined outbreak of ARF in a specific population which has previously had a low risk of ARF (e.g. as has been described in military recruits[94]).

The existing understanding of the pathophysiology of ARF/RHD highlights the importance of preceding GAS-associated pharyngitis 2-3 weeks prior to the development of ARF.[103] However, it is apparent that GAS infection without co-existent pharyngitis can precipitate

ARF. In a well-described outbreak of ARF in the intermountain area of the United States centred around Salt Lake City, Utah, a recent history of pharyngitis was frequently absent.[5, 6] One study reported that only 1/3 of patients had a clear-cut history of sore throat in the three months preceding the onset of ARF.[5] A follow-up study reported that over an 8 year period only 28% of children with confirmed ARF reported a history of a sore throat that parents considered serious enough to seek medical care. Only 17% sought medical attention and received antibiotic prescriptions.[6]

In some settings, particularly Australia, it has been suggested GAS-associated skin infection (impetigo) may play a similar role.[3] Whilst the evidence supporting such a link remains limited and contentious, it has provided an additional focus for primary prevention, particularly in Australia, and will be addressed here.

Primary prevention of GAS in the throat

There is a clear understanding regarding the primacy of pharyngeal GAS in the pathophysiology of ARF.[103] In a temporal sequence, an individual is exposed to GAS, the organism attaches to and colonises the pharyngeal mucosa, a process of infection incorporating an immune response is initiated, and, as part of this immune response, an episode of ARF occurs. This process is of course not inevitable. Exposure may not lead to colonisation, colonisation may not lead to infection, and the host immune response may not lead to ARF. Whilst it is not within the scope of this chapter to review the factors which may alter this process, such factors are likely to include the burden, type and diversity of GAS in a given population (see primordial prevention above), the inoculating dose, specific organism factors (e.g. the concept of rheumatogenic/ARF-causing strains of GAS[104]), host factors which may encourage colonisation and infection, and host factors which may predispose to ARF once GAS infection is established. A framework outlining potential targets for the primary prevention of ARF due to GAS and their relationship to primordial, secondary and tertiary prevention is outlined in Figure 9**Error! Reference source not found.**.

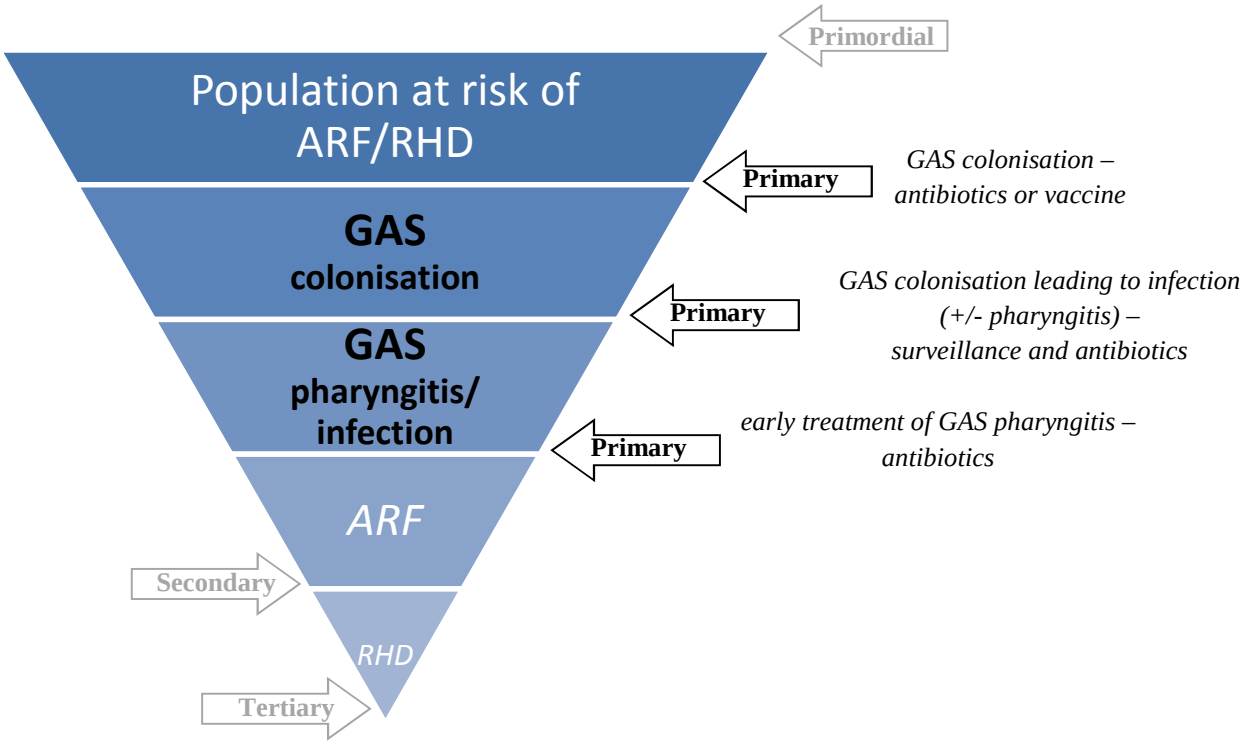


Figure 9. Outline of structure for preventive strategies for GAS pharyngeal colonisation and pharyngitis

Preventing GAS colonisation

There are at least two possible approaches which may be deployed to potentially pre-empt the acquisition of GAS in the pharynx: prophylactic antibiotics and vaccination. A third possibility, the use of probiotics in the primary prevention of GAS, has been raised but research in this area remains at the exploratory phase.[105, 106]

Prophylactic antibiotics to prevent the acquisition of GAS employ the same rationale that is used in the secondary prevention of ARF/RHD.[66, 107] The most compelling evidence for the effectiveness of this approach comes from the United States military where recruit camps have historically seen high rates of GAS and ARF infection.[108] After a significant rise in GAS infections and ARF during World War II, GAS prevention programmes based on intramuscular benzathine penicillin prophylaxis were implemented within United States Navy and Marine Corps recruit camps.[108, 109] Large scale mass prophylaxis campaigns in military training centres[110, 111] saw the incidence of ARF in the U.S. military falling

dramatically through the 1960s and 1970s.[108] However, in the 1980s when routine prophylaxis in some military centres was replaced by prevention programmes designed on the basis of local surveillance for GAS infection, further ARF outbreaks were reported.[112] To combat this "re-emergence" of ARF, prophylaxis with benzathine penicillin, given as a single dose at the beginning of each training cycle, was re-implemented in 1987 at naval recruit training centres and was in turn associated with a reduction in ARF.[107] In one study, Navy recruits were studied to determine the prevalence of GAS pharyngeal colonisation cultures before and two, four, and seven weeks after receiving benzathine penicillin prophylaxis.[107] The prevalence of GAS carriage fell by 75% at four weeks but by seven weeks had returned to pre-prophylaxis levels.

Whilst the evidence is restricted to cohort studies, antibiotic prophylaxis does appear to be effective in reducing GAS pharyngeal colonisation and associated ARF. Nonetheless the benefits of a single dose of benzathine penicillin are not sustained beyond four weeks. Furthermore, the use of regular prophylactic antibiotics to prevent GAS colonisation in otherwise healthy individuals is unlikely to be sustainable or cost-effective except in small, defined, static populations who are temporarily at elevated risk of ARF/RHD. Such a strategy would also entail risks for the individual receiving prophylaxis and the potential for antibiotic resistance.

Vaccination against GAS presents an ideal solution for the primary prevention of ARF/RHD. An effective vaccine would provide ongoing protection against GAS colonisation and infection as opposed to the four week protection afforded by a single dose of benzathine penicillin. Vaccines have been in development since early last century[113] but a number of scientific and regulatory obstacles have hindered the realisation of a GAS vaccine reaching market, including concerns regarding potentially cross-reactive epitopes.[57, 114, 115] Only one vaccine has entered clinical trials in the last 30 years. However, there has been increasing international interest in development of GAS vaccines in the past decade[116] including the World Health Organization.[117]

Modern vaccines can be categorized into two groups: those that focus on the M protein (the major GAS virulence determinant) and those that focus on non-M protein antigens. Although non-M protein vaccines such as streptococcal C5a peptidase, GAS carbohydrate,

and fibronectin binding proteins have progressed well in preclinical studies, none has progressed to clinical trials.

The most advanced vaccine candidate is a multivalent vaccine based on the amino terminus region of the M protein. It has undergone phase I and II clinical trials in adults, with good evidence of safety and immunogenicity.[118, 119] It is estimated that this 26-valent vaccine would provide protection against 80-90% of invasive GAS and pharyngitis isolates in North America.[120] However, there are many circulating types of GAS in developing countries and in northern Australia that would not be covered by this vaccine, as described in a recent review.[121] Reformulation of this vaccine into a 30-valent vaccine may circumvent these problems.[122] A second M protein vaccine (the "J8" vaccine), based on the conserved region of the M protein and developed in Queensland, Australia, may potentially provide protection against all GAS strains.[123, 124] Clinical trials of this candidate are currently in preparation.

Whilst the development of a safe and effective GAS vaccine to prevent ARF/RHD is yet to be realised it should remain a priority in ARF/RHD prevention.

Eradication of GAS colonisation

A number of health programmes have sought to identify and eradicate pharyngeal GAS colonisation in high risk populations to prevent ARF/RHD.[125] In the 1950s, as a prelude to mass antibiotic prophylaxis programmes in the US military, benzathine penicillin was administered to 624 asymptomatic recruits with positive throat cultures for GAS.[126] This single dose resulted in negative cultures for at least one month in 96% of these recruits. While there was no control group, ARF did not occur in any recruit who had received antibiotics. In Australia, one primary prevention programme in a remote Aboriginal community in far north Queensland involved tri-annual throat swabbing of 4-16 year olds and treatment for those with GAS carriage.[127] Whilst ARF surveillance suggested that this programme coincided with a reduction in the incidence of ARF, the lack of a control group rendered it difficult to determine the true efficacy of the intervention.

Another study investigated the impact of a three year streptococcal disease control programme among the Navajo Indians in north America.[128] In this programme, throat

specimens for culture were taken from school children at the beginning of the school year. Asymptomatic children were then swabbed periodically (usually monthly) while any child who presented to the school clinic with a sore throat was swabbed immediately. If GAS was identified, the child was treated with penicillin or erythromycin. A quasi-control group was included as schools in only five of the eight Indian Health Service Units that made up the Navajo reservation took part in the programme. In "covered" areas that participated in the surveillance programme, the rate of ARF was 39% lower during the programme (falling from 13.5 to 8.2 cases per 100,000 per year), while the rates in "uncovered" areas which did not participate in the programme showed little change. Nonetheless "covered" areas initially had substantially higher ARF rates compared with "uncovered" ones and the programme was adopted at different times with many sites participating only intermittently.

A recent prospective school-based study into the control of GAS upper respiratory tract infections in southern China has shown that asymptomatic children with positive throat cultures who are treated with penicillin/erythromycin therapy at school had significantly lower prevalence and incidence of GAS pharyngitis than children at the same school who sought medical care from their regular health providers.[129] While the incidence of ARF was not reported, this study does provide evidence that controlling GAS colonisation can reduce the incidence of GAS pharyngitis.

Whilst the presence of GAS in the nasopharynx indicates GAS load, there is debate over whether the presence of GAS without symptoms is associated with an elevated risk of ARF. The American Academy of Pediatrics' Red Book: Report of the Committee on Infectious Disease argues that carriage is not a risk to an individual or to spread in the population.[130] However, as Kaplan notes, the significance of the immunological difference between acute streptococcal upper respiratory tract infection and the relatively harmless streptococcal carrier state is not understood.[131]

Given the limited evidence it is difficult to advocate for the identification and eradication of GAS colonisation as a mechanism for reducing ARF incidence. Even if such an approach were effective in reducing ARF rates, the use of regular antibiotics to eradicate GAS colonisation in otherwise healthy individuals with no history of ARF/RHD poses issues associated with cost, client inconvenience and risk, and the development of antibiotic resistance.

Early Treatment of GAS pharyngitis

Given the limited evidence, and the level of resources that would be required, for preventing or eradicating GAS colonisation through the use of prophylactic antibiotics, and the current lack of an effective vaccine, the next possible focus in ARF primary prevention is the early identification and treatment of symptomatic GAS pharyngitis. In this case the aim is to identify symptomatic GAS pharyngitis in those individuals most at risk of ARF (typically children aged 5-14 years) and to eradicate the bacterium through the use of effective antibiotic treatment before it can precipitate the cascade of immune-mediated events which lead to the development of ARF. Studies have reported that GAS can be eliminated from the upper respiratory tract.[58, 132, 133] This, in turn, may prevent ARF if treatment is commenced within nine days of symptoms appearing.[38, 58, 134-136] Nonetheless, the question remains whether focused 'sore throat' programmes result in a reduction in the risk of ARF in high risk populations.

There are three possible approaches to the early treatment of GAS pharyngitis.

1. Standardised antibiotic treatment of sore throats.

The management of pharyngitis as a mechanism for preventing ARF/RHD is complicated by the fact that only a minority of sore throats are caused by GAS. Whilst it is possible to treat all cases of pharyngitis with antibiotics this would expose a significant proportion of patients to unnecessary treatment as only 20-40% of pharyngitis episodes are associated with GAS infection[134]; the remainder are caused by viruses or by bacteria for which antibiotic treatment is not recommended. Moreover, such an approach would require substantial resources and expose clients to unwarranted inconvenience and risk while increasing the possibility of antibiotic resistance. Nonetheless, some treatment guidelines

do suggest that people identified as being from populations at high risk of ARF, or who have established RHD but are not currently receiving secondary antibiotic prophylaxis, should be treated with antibiotics if they develop pharyngitis irrespective of other clinical features and before confirmatory testing for GAS is available.[137] Whilst empirically attractive there is no clear evidence such an approach is a safe or cost effective approach to reducing ARF incidence.

2. Antibiotic treatment of those with clinical features suggestive of GAS infection. Research from the 1950s involving the United States armed services indicated that antibiotic treatment of those with clinical features suggestive of GAS infection may be effective in preventing ARF in isolated, at-risk groups. In one seminal study, Denny *et al.* conducted a clinical trial of the effectiveness of crystalline procaine penicillin G in preventing ARF following GAS infection.[58] This trial involved 1602 serviceman admitted to hospital for respiratory tract disease who exhibited exudates on the tonsils or the pharyngeal wall. Penicillin treatment was provided to 798 patients while a control group of 804 patients received no treatment. Blinded follow-up was undertaken 3-4 weeks after the initial infection. In the treated group only 2 patients developed definite ARF and 2 patients developed probable ARF. In contrast, in the control group 17 patients (RR 8.4 times higher than treated group) developed definite ARF and 6 (RR 3.0) developed probable ARF. This represented a significant reduction in the attack rate of ARF in the treated group. The effect of penicillin treatment on the presence of GAS in throat cultures was also examined. In the treated group, the number of patients with a positive throat swab for GAS fell from 78.3% on admission to 18.1% at time of follow-up. The untreated group saw a reduction of 81.7% to 52.7%. Finally, results indicated the development of antistreptolysin O in the two groups was different with 51% of the treated group showing a rise in titre of 2 or more tubes, while 73% of the untreated group exhibited such a rise. In summary, this study showed that penicillin treatment of previous GAS pharyngitis significantly reduced the attack rate of ARF, eradicated GAS from most patients and decreased the antibody response to GAS.

In a later study it was shown that even when penicillin treatment was delayed until 9 days after the onset of illness, at a time when acute symptoms had subsided and when near maximal antibody response had occurred, it was still effective in preventing ARF.[132] In this

study rates of ARF were comparable in the control and treatment groups prior to treatment but then dropped significantly in the treatment group over the five weeks following delayed antibiotic treatment.

It should be noted that all these United States armed services studies involved very specific conditions and populations. The servicemen were housed in cramped living conditions and the GAS strains circulating appear to have been highly virulent and rheumatogenic. Whether the results seen in these studies are generalisable to broader populations is questionable. Nonetheless, the success of these interventions and the inclusion of control groups in each study provide strong evidence that such approaches may be successful in the primary prevention of ARF.

It has been argued that enhanced pharyngitis surveillance and treatment programmes may be effective in a broader context than the military situations described above. For example, Karthikeyan and Mayosi point to the reduced incidence and prevalence of ARF and RHD in Costa Rica[138] and Cuba[139] as evidence that primary prevention strategies are effective.[140] In Costa Rica a programme was introduced in the 1970s under which all people with clinical signs of GAS pharyngitis were treated with benzathine penicillin without the need for throat culture.[138] This was associated with a sharp decline in the incidence of ARF (70/100,000 in the early 1970s down to 1/100,000 in 1990). However, this dramatic fall in ARF incidence preceded an increased uptake in the use of benzathine penicillin suggesting other factors were responsible for this decline in ARF incidence. A substantial decline in the occurrence and severity of ARF and RHD was also reported from Cuba after a 10 year prevention strategy was introduced in the province of Pinar del Rio.[139] A similar multidimensional strategy in the French Caribbean islands of Martinique and Guadeloupe focused on the development of a registry and recall system for patients with ARF/RHD and enhanced education, detection and treatment of GAS-associated pharyngitis.[141] This was associated with a decline in ARF incidence of 74-78% over a ten year period. Whilst these findings are encouraging they shared a number of methodological limitations which should caution interpretation. These included the fact that these programmes involved elements in addition to primary prevention (e.g. secondary prevention of ARF/RHD, training of personnel, health education, dissemination of information, community involvement,

epidemiological surveillance, and the implementation of a national health care plan) and the lack of a comparable control group with outcomes being assessed using historic and surveillance data.[138]

3. Antibiotic treatment of those in whom testing confirms the presence of GAS.
Targeting only those people with confirmed GAS pharyngitis would be an effective means of limiting antibiotic use in primary prevention. If such an approach is taken then the rapid identification of GAS in people presenting with pharyngitis is necessary to allow institution of therapy within nine days of symptom onset. Such detection may rely on clinical features, antigen detection or the gold standard of bacterial culture.

A number of clinical scoring methods for predicting the presence of GAS, and thus the requirement for antibiotics, have been suggested. Typically, these methods stratify patients according to an algorithm whereby points are allocated based on factors such as patient demographics, season, and a number of specific signs and symptoms (e.g. elevated temperature, absence of cough, tender anterior cervical adenopathy, tonsillar swelling or exudate, absence of upper respiratory symptoms).[142-144] Patients with higher scores are classified as being at greater risk of GAS infection and are therefore recommended to have a throat swab culture and/or be treated with antibiotics. Validation studies of such scoring systems have demonstrated relatively low positive and negative predictive value for the subsequent isolation of GAS on throat swab.[144, 145] For example, in McIssac *et al.*'s study of the validation of the modified Centor score (which incorporates temperature, absence of cough, swollen/tender anterior cervical lymph nodes, tonsillar swelling or exudate, and age) the pre-test probability of GAS isolation in patients with a sore throat aged 3-17 years was 34%.[146] In this setting a positive clinical score prompted unnecessary treatment for GAS in 1/3 of children and a negative clinical score left 1/4 of children with GAS without treatment. Hence the utility of such clinical scoring systems in differentiating GAS and non-GAS pharyngitis in populations at higher risk of ARF, where the potential consequences of missed GAS infection are higher, would appear limited.

Given the difficulty in differentiating GAS from non-GAS pharyngitis on clinical features alone, microbiological laboratory testing to confirm the presence of GAS is recommended if feasible.[134] Bacterial culture from a throat swab is often viewed as the gold standard for

the diagnosis of GAS pharyngitis.[147] Unfortunately, this necessitates a time delay of 2-3 days. More rapid diagnostic tools including rapid antigen detection tests (RADTs) for GAS have shown promise but while most have a high specificity, their sensitivity can be variable.[147] The American Heart Association argues that there have been no definitive studies to determine the relative sensitivities of different RADTs and whether they are suitable for routine use in the diagnosis of children without confirming negative tests via throat culture.[147] Nonetheless, the evaluation of RADTs in low-resource settings which may be more analogous to remote Indigenous Australian communities have shown promise. In Rimoin *et al.*'s study of the utility of RADTs in detecting GAS pharyngitis in children aged 2-12 years presenting with a sore throat in a low-resource setting (Brazil, Egypt, Croatia and Latvia), they found a pre-test probability of GAS-culture positive pharyngitis of 29%.[148] In this setting a positive RADT (STREP A OIA MAX [Thermo Biostar/Inverness Medical Professional Diagnostics, Princeton, NJ, USA]) prompted unnecessary treatment for GAS in 1/5 children and a negative RADT missed only 8% of children with GAS pharyngitis.

A further complicating factor in the use of throat cultures and RADTs is that a positive result does not indicate whether an individual is truly infected with GAS (with an immunologic response to GAS) or is merely a carrier of GAS in the pharynx with a concomitant viral infection.[147] Whilst elevated or rising antistreptococcal antibody titres (e.g. antistreptolysin O and antideoxyribonuclease B) can provide evidence of recent GAS infection, such antibody responses are delayed, require the pain and inconvenience of venipuncture and provide little assistance in the immediate identification and treatment of GAS pharyngitis.[147]

It would appear therefore that in high risk populations, and particularly for Aboriginal and Torres Strait Islander people, the utility of either clinical scoring systems or RADTs to rapidly identify GAS as a cause of pharyngitis is uncertain. Whilst a combination of clinical scoring system, RADT and bacterial culture may be both sensitive and specific[146], it is unclear whether this provides any additional benefits to undertaking bacterial culture in all children with symptomatic pharyngitis. The validity and utility of clinical scoring systems, RADTs and other rapid diagnostic techniques in facilitating the rapid detection and

treatment of GAS pharyngitis in Aboriginal and Torres Strait Islander people as a mechanism for the primary prevention of ARF/RHD should be a priority for further study.

If pharyngitis is to be targeted in populations at high risk of ARF then only treating those with confirmed GAS on throat swab may be advocated. Two recent systematic reviews have suggested that a benefit may be gained from such interventions.[59, 60] However the studies included in these reviews were acknowledged by the authors to be variable and generally poor quality. More recently, a large, high quality study in New Zealand investigated the effectiveness of a targeted school-based sore throat programme.[61] Fifty-three schools (with approximately 22,000 students) were randomised into two groups: a control group that received routine general practice care and a treatment group that comprised a school-based sore throat clinic programme with nurse-observed oral penicillin treatment of those students with culture-confirmed GAS pharyngitis. While results revealed a 21-28% reduction in ARF episodes in schools assigned to the sore throat clinic programme, this finding was not statistically significant. The authors argued that this lack of statistically significant effect on ARF may have in part been related to a lack of household contact tracing and treatment. In this context it is worth considering the work of Gordis whose analyses of the impact of providing increased access to healthcare through publicly funded primary care clinics over a decade in Baltimore showed an associated reduction of 60% in cases of ARF in a high-risk US civilian community.[97] However, this was not a targeted sore throat programme and was not a randomised control study. Whilst the treatment of GAS pharyngitis may confer a small reduction in the duration of pharyngitis symptoms[147] there remains no convincing evidence that specific 'sore throat' programmes for GAS pharyngitis treatment outside of comprehensive primary health care can provide additional benefit in reducing ARF incidence even in high risk populations.

Overall there is currently no convincing argument or consistent evidence to suggest structured programmes focusing on the early treatment of GAS pharyngitis are likely to be effective in the primary prevention of ARF in high risk populations. Nonetheless, the lack of good evidence should not dissuade action in providing appropriate, accessible and high quality early management of pharyngitis as part of comprehensive primary health care. The impact of improved clinical scoring and rapid diagnostic tests in facilitating programmes

for the early treatment of GAS pharyngitis requires further study. As the Cuban, Costa Rican and French Caribbean experiences suggest, prioritising ARF/RHD as part of broader, multidimensional health service capacity building is likely to translate to improved outcomes. Nonetheless, even if primary antibiotic prophylaxis for the prevention of ARF and RHD is found to be effective in some settings, the expense and logistical difficulties in undertaking such initiatives must still be considered.[140]

In high risk populations where clinical follow-up may be difficult, the empiric management of pharyngitis with antibiotics in those at greatest risk of ARF (e.g. 5-14 years of age or pre-existing RHD) may be warranted. Where possible, confirmatory testing with throat swab culture should be undertaken and, if feasible, any decision to use antibiotic treatment should be based on culture results. The utility of clinical scoring systems, RADTs and other rapid diagnostic tests in predicting the presence of GAS versus non-GAS pharyngitis should be evaluated in Australia, particularly in Aboriginal and Torres Strait Islander communities. Focused programmes of early GAS pharyngitis diagnosis and management in populations at high risk of ARF have not yet been shown to translate to a significant reduction in ARF incidence.

Primary prevention of ARF through addressing GAS-associated skin infection

Whether GAS-associated skin infection plays a role in the development of ARF is unclear.[3, 20] It has been suggested that the low prevalence of GAS pharyngeal carriage and infection, high rates of pyoderma and rarity of rheumatogenic GAS M serotypes seen in some Aboriginal communities with high documented rates of ARF/RHD indicates that GAS-associated skin disease may be an important cause of ARF.[4] Similar patterns of disease, GAS carriage, M serotyping and ARF/RHD have been reported in Ethiopia, Jamaica and Fiji.[93, 149] It has also been noted that in some Aboriginal populations there is a greater association between confirmed ARF and elevated anti-DNase B titres (which correlate with both throat and skin infection[150]) rather than elevated ASO titres which are strongly associated with throat infection and less so with skin infection.[48]

McDonald *et al*., in the largest prospective study of skin and throat infections and carriage in three remote Aboriginal communities in the north of Australia where ARF rates are high, noted high rates of pyoderma and low rates of symptomatic pharyngitis.[4] In this study, 4.5% of all throat swabs isolated GAS and 19.5% of children had GAS isolated from their throats at least once during the two year study and 2 of the 9 people (22%) who complained of a sore throat during the study had GAS isolated. It is not clear if this amount of exposure to GAS in the throat may be sufficient to explain the extremely high rates of ARF in this population, regardless of the much higher levels of exposure to GAS skin infection. While 37.7% of children had pyoderma at least once during the study, only 29.2% of pyoderma swabs were positive for GAS, although it should be acknowledged that the methodology used in this study may have underestimated the association between GAS and pyoderma, given that other studies in the north of Australia have found GAS in 70-90% of skin swabs.[151, 152] The authors' conclusion that skin disease rather than pharyngitis is associated with ARF differed from their findings in a later, smaller study involving Aboriginal Australians living in the arid central region of the Northern Territory.[153] One other study demonstrated high rates of nasopharygeal carriage in an Aboriginal and Torres Strait Islander community.[49]

Although rheumatogenic GAS M protein serotypes appear to be rare in some Aboriginal populations with high rates of ARF, M non-typable (MNT) GAS serotypes with genetic similarities (*emm*-patterns) with classic rheumatogenic strains are often found.[154] This suggests that M protein serotyping may not identify all potentially rheumatogenic strains and that MNT GAS may play a significant role in ARF. Moreover there remains debate regarding the exact role of M protein subtypes of GAS in the pathogenesis of ARF (i.e. whether the concept of rheumatogenicity is sound).[155]

Despite the theoretical underpinnings of the possibility of a link between skin infection and ARF, there has only ever been one clearly documented case of this occurrence and that case was reported over 30 years ago.[156] Nonetheless, given the high prevalence of skin disease in many Aboriginal and Torres Strait Islander communities[157], it would be difficult to demonstrate such a causative link. Further research is needed to clarify the association between GAS pyoderma and ARF/RHD.

Whether early treatment of skin disease more generally may be an effective mechanism for preventing ARF remains to be seen. One study of a multidimensional community-based intervention to improve skin health in northern Australia was successful in reducing the prevalence of both pyoderma and scabies infections in Aboriginal children.[158] However, the impact of reducing skin disease on ARF and post-streptococcal glomerulonephritis could not be investigated. Another study provides limited evidence to suggest that the installation of swimming pools in remote Aboriginal communities may reduce the prevalence of both skin and throat infections.[159] Further work is required to validate these findings and monitor any association with ARF/ RHD.

There is currently insufficient evidence regarding the impact of skin health interventions on ARF and RHD to warrant recommending such programmes for the primary prevention for ARF/RHD.[56, 147] However, improved skin health is likely to have broader health impacts, and studies documenting the association of reduced rates of GAS skin infections with changes in ARF incidence will provide important information for future primary prevention programmes.

The role of non-Group A streptococci

Although GAS is the major factor associated with the pathogenesis of ARF there is debate around whether other strains of streptococcus can cause ARF. In particular, Group C and Group G beta-haemolytic streptococci (GCS and GGS) have been discussed in this context [3] as they, like GAS, may be associated with pharyngitis, polyarthritis, invasive disease and, in the case of GCS, acute poststreptococcal glomerulonephritis.[160-163] Haidan *et al.* have also shown that antibodies raised against GCS and GGS isolated from throat swabs can react with human cardiac myosin.[164] McDonald *et al.*[3] point out that carriage of GCS and GGS can be up to 20% higher than GAS in Aboriginal populations in the Northern Territory[164] and that similar results have been found in Trinidad, Saudi Arabia and Egypt.[163, 165, 166] Whether this association extends to a role for GCS and GGS in the pathogenesis of ARF remains unclear. However, given that infections with these organisms can be associated with raised ASO and antiDNase-B titres[167, 168] their potential role in the pathogenesis of ARF in patients where GAS is not isolated is worthy of further investigation.

Recommendations regarding primordial and primary prevention of ARF/RHD

Primordial Prevention:

Whilst there is only limited evidence to support the effectiveness of specific initiatives in the primordial prevention of ARF/RHD, ecologic data would suggest that the risk of ARF/RHD is linked to poverty and disadvantage. Housing and overcrowding would appear to be one important factor. However, given the uncertainties regarding specific causes, advocating for the primordial prevention of ARF/RHD based on one or another specific environmental or social strategy cannot be supported. The broader context of equity, poverty alleviation and justice, in association with the empirical link observed between improved socioeconomic and environmental factors and reduced ARF incidence, as well as many other health conditions, should be sufficient to drive advocacy and change.

Primary Prevention:

Primary prevention measures aimed at preventing ARF/RHD through the prevention or eradication of pharyngeal GAS colonisation or the early identification and treatment of GAS pharyngitis are of uncertain effectiveness. Whilst programmes aimed at preventing GAS colonisation through antibiotic use may be effective in the short term, any long-term implementation is likely to be unsustainable due to prohibitive costs, client inconvenience and the risk of antibiotic resistance. A GAS vaccine offers the possibility of a longer-term solution. Whilst significant hurdles remain in the development of a safe, effective and affordable vaccine that can be provided to populations at highest risk of ARF/RHD this should remain a priority.

Although some programmes aimed at the identification and treatment of GAS colonisation have shown promise, the evidence supporting such an approach remains poor. In line with preventing GAS colonisation such initiatives are also likely to be unsustainable due to cost, client inconvenience and the risk of antibiotic resistance. While the cost of managing established RHD is high, the number needed to treat to prevent RHD through such primary prevention programmes would be high.

While the early treatment of GAS pharyngitis in highly controlled environments (e.g. military camps) can prevent the subsequent development of ARF there is no evidence that community-based programmes which focus on the early treatment of GAS pharyngitis are effective in reducing the risk of ARF. The treatment of pharyngitis as part of comprehensive and accessible primary health care remains important. In this context, education of patients, carers, schools and communities is crucial to ensure that the detection of symptomatic pharyngitis prompts primary health care attendance.

The utility of clinical scoring systems or RADTs is variable in differentiating GAS and non-GAS pharyngitis. The development and validation of these and newer rapid diagnostic tests in the setting of Aboriginal and Torres Strait Islander populations at risk of ARF/RHD should be a priority. Empiric treatment of all cases of pharyngitis in those at high risk of ARF or throat swab-directed treatment should remain the priority in populations at high risk of ARF. The lack of a clear episode of symptomatic pharyngitis in all people presenting with ARF will mean there is an inherent failure rate in even the most comprehensive GAS pharyngitis treatment programmes.

The link between skin-related GAS infection and the pathogenesis of ARF/RHD remains contentious. The role of the treatment of GAS skin infection in the primary prevention of ARF/RHD remains unproven and is likely to be unsustainable without addressing the underlying drivers of skin disease (see primordial prevention above). Nonetheless, as with pharyngitis, the management of skin disease should remain a component of high quality, comprehensive and accessible primary health care for all populations irrespective of ARF/RHD risk.

Conclusion

Primordial and primary prevention of ARF/RHD through vaccination or the eradication or treatment of GAS remains elusive. Despite sound theoretical underpinnings for the effectiveness of such prevention measures, high quality evidence is lacking and successful health programmes are limited in number. To date the most effective measures in the control of ARF/RHD appear to be secondary prophylaxis to prevent recurrent episodes of ARF in persons previously affected by ARF or who have already developed RHD.

Nonetheless, given the decreasing incidence and prevalence of ARF and RHD in most developed counties, it is apparent that ARF/RHD can be prevented.

- Primordial prevention of ARF/RHD is likely to remain key. Despite uncertainties around which specific primordial factors impact on the incidence of ARF/RHD, ecologic data suggests overall improvements in social and environmental conditions will reduce disease prevalence.
- Ongoing research towards the development of a GAS vaccine should be a priority. Despite the technical and practical issues associated with vaccine development and delivery it is likely to be the most sustainable primary prevention strategy in the control of ARF/RHD.
- Evidence supporting primary prevention through the use of antibiotics to prevent or eradicate GAS colonisation or pharyngitis is limited and such initiatives are likely to be unsustainable. The development and validation of clinical scores and rapid diagnostic tests to rapidly identify those with GAS may enhance the efficacy and sustainability of such programmes in an Aboriginal and Torres Strait Islander setting.

Postscript - Limitations and Recent Developments

As this paper was conceived and developed to form part of the Australian guideline for prevention, diagnosis and management of ARF and RHD (2nd edition)[2] a focused and practical strategy, as opposed to a broad systematic review, was implemented to review the available literature relating to primordial and primary prevention of ARF/RHD. This strategy accorded with the broader search strategy adopted for the entire Guideline. While this approach may be perceived as limiting the academic rigour of the paper it was necessary given word limitations and the multiple areas of primordial and primary prevention that were required to be addressed.

Since the publication of this paper a number of recent papers relating to the primary prevention of ARF/RHD have been published that are of importance. Of particular interest is the work being undertaken by Irlam *et al.* in South Africa regarding the cost-effectiveness of primary prevention strategies.[169, 170] Working with children presenting to primary care clinics in a RHD study area in Cape Town, the researchers undertook a cost-

effectiveness analysis of a number of primary prevention strategies including: observation only ("Treat None"), empirical treatment with intramuscular penicillin ("Treat All"), treatment based on positive throat culture for GAS ("Culture All), and a number of treatment strategies based on a simple modified World Health Organization clinical decision rule (CDR). Results indicated that the most affordable and simple strategies were the Treat All and the CDR strategy with the CDR strategy being the most cost-effective. Culturing all children was the most costly strategy. These findings are promising and the authors argue that a strategy for primary prevention of ARF/RHD in urban South Africa should be adopted to complement primordial and secondary prevention programmes. Indeed, Mayosi nominates primary prevention of ARF, through syndromic treatment with penicillin of sore throat in children, as one of the 10 best buys in combatting heart disease in Africa.[171] These findings lend support for the view that local research is warranted to investigate whether empirical or CDR-based antibiotic treatment of sore throats in Indigenous Australian communities is feasible and cost-effective.

The review of the literature relating to primary prevention of ARF revealed a number of studies that reported significant reductions in ARF incidence rates due to prevention programmes. Nonetheless, it is argued that there is insufficient evidence to support the implementation of specific primary prevention initiatives in remote Indigenous Australian communities. More specifically, the reports of successful ARF reduction programmes from the French Caribbean[141], Costa Rica[138] and Cuba[139] suffered from methodological issues such that it was not possible to identify which components of multidimensional interventions were likely to be successful. Further, the studies involving the US military were in highly selected and controlled settings very dissimilar to the Aboriginal and Torres Strait Islander setting.[58, 136] It should also be noted that the most comprehensive randomised study of a community-based sore throat intervention undertaken in New Zealand failed to show a significant beneficial effect of active surveillance and treatment.[61] Despite these critiques, it must be stressed that these limitations in published evidence are not presented to support an argument that such interventions will not be effective (i.e. that a lack of evidence equates to a lack of effect). Rather, the thesis presented in this paper is that there simply is insufficient evidence of high quality to recommend specific primary prevention interventions in an Australian setting. It is suggested that a cautious approach needs to be

taken which may entail implementing action or translational research programmes with control groups and clear evaluation strategies. Such research activities should shed light on which previously reported primary prevention strategies are generalisable to Aboriginal and Torres Strait Islander settings.

It was argued above that programmes aimed at preventing or treating GAS colonisation or treating pharyngitis are likely to be unsustainable due to cost, client risk and inconvenience, and the risk of antibiotic resistance. The cost-effectiveness analysis by Irlam *et al*. discussed previously indicates that empiric treatment of sore throats or CDR-based management of purported GAS pharyngitis may be economically feasible.[169] Nonetheless, while Australia is a relatively wealthy country and hence would seem ideally placed to afford sore throat primary prevention programmes, it is important to remain cognisant of "opportunity costs" rather than solely focusing on the cost of LAB or oral antibiotics. That is, the use of resources in one area of health (in this case providing enhanced surveillance for sore throats and follow-up with administration of LAB) will necessarily entail the removal of resources from other health or government services, particularly in remote communities where such services are often over-stretched and under-staffed. Furthermore, with regard to the statement of risk associated with the use of LAB to treat all sore throats, it should be noted that the risks of anaphylaxis[172] and sciatic nerve injury[173] associated with intramuscular LAB injections are low but, given the potential consequences, important. Finally, with regard to the statement that widespread use of LAB may impact on drug resistance it is important to clarify that available evidence suggests that GAS remains universally susceptible to penicillin.[27] However, the indiscriminate use of LAB to treat sore throats in remote Aboriginal and Torres Strait Islander settings could be a catalyst for increased β-lactam resistance in other bacteria.[174] These factors must be weighed up against the potential benefit to be gained from universal treatment of sore throats with penicillin. And even if the risks of lost opportunity costs, adverse penicillin reactions, and potential increased drug resistance are found to be acceptable, it should not be forgotten that the lack of a clear episode of symptomatic pharyngitis in all people presenting with ARF will mean there is an inherent failure rate in even the most comprehensive GAS pharyngitis treatment programme.

2.2 Rheumatic heart disease: women and pregnancy

Background

Owing to the increased blood volume associated with pregnancy and the demand this places on the heart, pregnant women with RHD are at high risk of exacerbated complications resulting from the pre-existing damage to their heart valves. The following article was an invited review for the O&G Magazine published by the The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. In it the risks associated with RHD in pregnancy and the preventative measures that are recommended to ensure best outcomes for mother and child are discussed. The article has been edited to remove portions that are redundant in the context of this thesis.

Abstract

Rheumatic heart disease (RHD) is a consequence of earlier Group A streptococcal infection and associated acute rheumatic fever (ARF). In Australia RHD is particularly seen in Aboriginal and Torres Strait Islander peoples.[1] However, with immigration of people from countries with a higher risk of RHD (Africa, South America and Asia[40]) it can also be seen in young, non-Indigenous Australians. Generally the onset of RHD occurs in childhood and adolescence and it affects more women than men. It can often be first detected in women of child bearing age and can potentially complicate pregnancy and labour. While the presence of RHD rarely means women cannot become pregnant, there are a number of factors which are important in ensuring a good outcome for both mother and child (see Box 6).

1. **Detect EARLY and exclude RHD**
    a. In populations at high risk of RHD all women who have a heart murmur require an early echocardiogram.
    b. If there is a history of ARF the result of a recent echocardiogram should be reviewed.
2. **Assess and treat BEFORE pregnancy**
    a. Refer anyone with RHD for specialist physician/cardiologist review.
    b. Discuss fertility planning and contraception with women with RHD.
    c. Ensure fertility planning informs discussions regarding management in all women in whom surgery is planned.
3. **Ensure a COORDINATED AND MULTIDISCIPLINARY CARE TEAM** is in place early – pregnant women with RHD require a team approach linking primary health care, obstetric services, anaesthetics and specialist physicians/cardiologists.

Box 6. Important factors in the early detection and management of RHD in women who are planning to become pregnant or who are pregnant.

RHD and Women

Women are at higher risk of developing RHD compared with men despite similar rates of ARF. A prospective surveillance programme of ARF and RHD in Fiji between 2005 and 2007 revealed that the relative risk of admission for RHD for females compared with males was 2.5 (95% CI 1.6 – 3.8).[72] A recent audit of the management of ARF and RHD in the Kimberley region of WA and far north Queensland revealed a similar disparity in disease (see Figure 10). Of the 301 people with RHD 216 (71.8%, 95% CI 66.3 – 76.8) were women. Overall the odds of having RHD in women was 2.2 (95% CI 1.6 – 3.1) compared with men.

The reasons for this far greater risk of RHD in women remain poorly understood. While it may be explained by a greater exposure to GAS in women caring for children, this would fail to explain the lack of a similar gender disparity in ARF incidence in younger people. It

may also be, at least in part, attributable to women having a greater opportunity for diagnosis of RHD by accessing health care more frequently than men or a gender-related predisposition to autoimmune disease.[175]

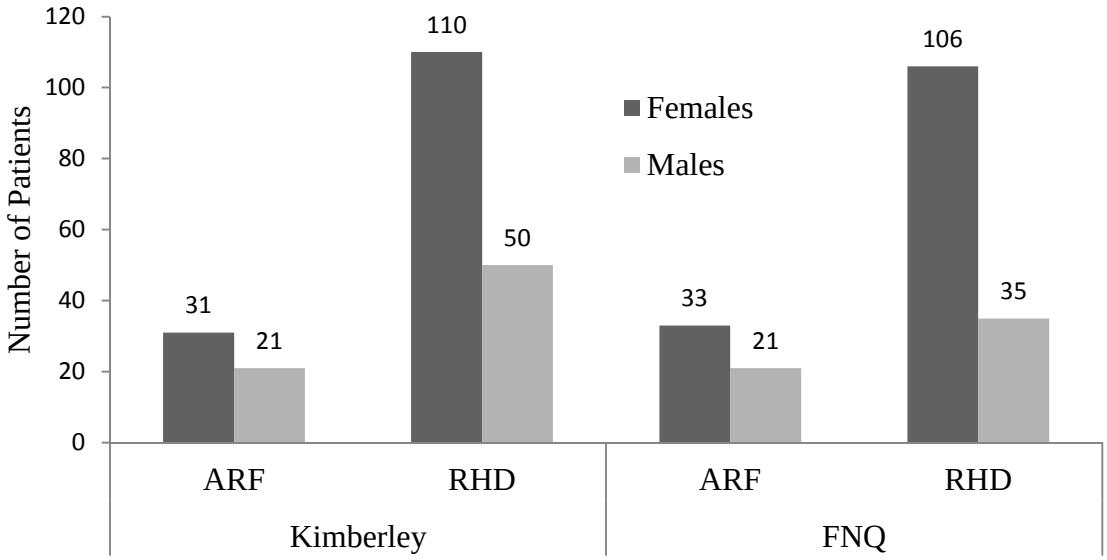


Figure 10. Over-representation of women with RHD in the Kimberley (Western Australia) and far north Queensland.

RHD in Pregnancy

Pregnancy places an increased demand on the heart even in otherwise well women. Changes associated with pregnancy include an increase in blood volume and heart rate, a reduction in the resistance of the arterial circulation and an associated increase in cardiac output. These normal changes tend to worsen pre-existing heart valve problems including those associated with RHD. For this reason it is not uncommon that RHD can sometime be first diagnosed in pregnancy through finding a heart murmur or the onset of heart failure. Unexplained shortness of breath in pregnancy and during and after delivery in patients at risk of RHD should always raise the suspicion of RHD and heart failure.

The National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand's *Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia: An evidence-based review*[62] highlights five maternal risk factors

associated with RHD during pregnancy. These are (1) reduced left ventricular function, (2) significant aortic or mitral stenosis, (3) moderate or severe pulmonary hypertension, (4) a history of heart failure, and (5) symptomatic valvular disease before pregnancy.

Health providers caring for pregnant women with RHD should refer to these guidelines for detailed advice. In general regurgitant valve lesions are much better tolerated in pregnancy compared with stenotic lesions. Mitral and aortic stenosis should therefore raise particular concern. The importance of identifying RHD in women before they become pregnant is reinforced by the high risk of foetal loss associated with valve surgery during pregnancy. The key to management of RHD in pregnancy remains early and regular monitoring by a multidisciplinary team. An outline of the management of specific valve lesions and prosthetic valves in pregnancy is outlined in Box 7. Management of labour and delivery in women with RHD and mechanical valves is complicated and is outlined in the review by Sartain.[176]

Mitral Regurgitation: Generally tolerated well during pregnancy. Heart failure may require diuretics and vasodilators (hydralazine, nitrates, dihydropyridine calcium channel blockers). Vaginal delivery is usually possible when heart failure is controlled.

Mitral Stenosis: If moderate or severe often causes heart failure. If symptoms are not severe, medical therapy with diuretics, digoxin and/or beta-blockers to slow heart rate is indicated. If symptoms remain there is significant risk to both mother and foetus and relief of mitral stenosis is usually required. Percutaneous balloon valvuloplasty is preferred given the high risk of foetal loss with surgery. Vaginal delivery is the usual approach although caesarean section should be considered in cases of severe disease with severe pulmonary hypertension.

Aortic Stenosis: If mild or moderate can usually be safely followed during pregnancy. Severe disease involves significant risk of adverse outcomes and percutaneous balloon aortic valvuloplasty may be required.

Prosthetic Heart Valves: Choice of valve prosthesis in the childbearing age group is complicated by the fact that while tissue valves have the advantage of not requiring anticoagulation most will require later replacement. Most patients with prosthetic valves and few symptoms tolerate pregnancy well.

Mechanical Prosthetic Valves and Anticoagulation: Mechanical valves are a high-risk group as all anticoagulation options pose maternal and/or foetal risks. Patients taking warfarin need early counselling and specialist advice before becoming pregnant. Women on warfarin who can become pregnant require reliable contraception.

Box 7. Specific recommendation for management of RHD and prosthetic heart valves in pregnancy (See Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia: An evidence-based review[62] for more details)

Conclusion

RHD has been “all but forgotten” in mainstream Australia. However, Aboriginal and Torres Strait Islander people, particularly those living in regional and remote Australia, have amongst the highest rates of ARF/RHD in the world. This burden is disproportionately borne by women. The normal cardiovascular changes associated with pregnancy exacerbate problems associated with pre-existing RHD and pregnant women with RHD must be managed according to the severity of their valve lesion and symptoms. Women with mechanical prosthetic valves who require anticoagulation are particularly at risk. The key to RHD management in pregnancy is detection and management before women become pregnant and early and regular multidisciplinary care in pregnancy including primary health care providers, obstetricians, anaesthetists and specialist physicians/cardiologists. If managed early and proactively most women with RHD can become pregnant with a positive outcome for mother and child.

2.3 Approaches to Improving Adherence to Secondary Prophylaxis for Rheumatic Fever and Rheumatic Heart Disease: a Literature Review with a Global Perspective

Background

While primordial and primary prevention of ARF/RHD are possible, as discussed previously, implementation of such prevention strategies has proved difficult and evidence regarding the success of such initiatives is yet to be adequately tested in an Australian Aboriginal and Torres Strait Islander setting. For this reason, secondary prophylaxis in the form of regular long-term intramuscular-injections of long-acting benzathine penicillin has become the mainstay of most ARF/RHD management strategies. Nonetheless evidence from a number of Australian studies indicates that many individuals living with ARF/RHD do not receive adequate secondary prophylaxis:

- Minchim *et al*. reported that in the Kimberley region of Western Australia less than one-fifth of patients having benzathine penicillin injections had a median injection interval of 3.5 – 4.5 weeks.[79]
- Eissa *et al*. reported that in an Aboriginal community with high ARF incidence only 42% of people receiving antibiotic prophylaxis had received 80% or more of the recommended doses in the previous year.[80]
- Stewart *et al*. investigated adherence with secondary preventative treatment in five Indigenous communities in the Katherine region of the Northern Territory and found that mean adherence with prophylaxis over a two year period was 56% of prescribed doses.[177]
- Harrington *et al*. conducted a quantitative and qualitative study of secondary prophylaxis use in a remote Aboriginal community in North East Arnhem Land and found that over a 21 month period only 59% of patients received >75% of prescribed injections.[178]
- Ralph *et al*. undertook an ARF/RHD CQI initiative in primary health clinics in regional and remote Aboriginal communities in the Top End and Centre of the Northern

Territory. At baseline, five of the seven sites included in the study had less than 30% of their ARF/RHD clients receiving ≥80% of scheduled benzathine penicillin injections. Despite subsequent interventions as part of the CQI initiative, there was no significant improvement in uptake over the two year duration of the study.[179]

- Rémond *et al*. audited the management 407 individuals with ARF or RHD living in the Kimberley (Western Australia) or far north Queensland. Of the 293 individuals prescribed benzathine penicillin only 17.7% had received ≥80% of scheduled doses in the preceding 12 months with the median number of doses being 6.[68]

The reasons for poor uptake of secondary antibiotic prophylaxis are complex and varied. It is not uncommon to hear anecdotal evidence of the success of new initiatives to solve this issue. However, high quality evidence around such initiatives is lacking. Within this context, the following review article was prepared with a view to examining the evidence around improving uptake of secondary prevention and providing recommendations for future initiatives and research.

This paper has been accepted for publication in the journal "Cardiology in Review".

Abstract

We used the Chronic Care Model as a framework to review initiatives to enhance the delivery of secondary antibiotic prophylaxis for acute rheumatic fever and rheumatic heart disease. The limited evidence available suggests the following elements may improve uptake of secondary antibiotic prophylaxis: registers and recall systems, strong staff-patient relationships, dedicated teams to deliver secondary prophylaxis, education, and community linkages (particularly between health services and schools).

The difficulty in translating an efficacious treatment, such as secondary antibiotic prophylaxis, into an effective programme that reduces the burden of acute rheumatic fever and rheumatic heart disease demonstrates the importance of on-going work in developing and evaluating research translation initiatives.

Introduction

The prevention of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) can be approached at a number of levels. On the broadest scale, primordial prevention involves addressing environmental and social disadvantage associated with Group A streptococcal (GAS) infection and ARF.[56] However, public health initiatives alone cannot readily address such broad issues. Research into the development of a GAS vaccine is ongoing[180] but has been hampered by the potential for cross-reactive epitopes and the risk that potential vaccines may stimulate the immune response that triggers ARF.[180] In the absence of an effective vaccine, primary prevention initiatives have focused on antibiotic treatment of GAS pharyngitis. In highly controlled populations, such as American military recruits, early treatment of GAS pharyngitis has been demonstrated to reduce ARF risk.[58] However, there is little convincing evidence that specific "sore throat" programmes in broader populations at high risk of ARF/RHD are effective.[59-61]

Owing to the difficulties in implementing effective primary prevention strategies, a core component of ARF/RHD management is secondary prevention of which one aspect is secondary antibiotic prophylaxis in the form of three to four-weekly long-acting intramuscular benzathine penicillin injections.[2, 66, 67] Secondary prevention aims to protect individuals who have previously had ARF, or already have RHD, against GAS, recurrent ARF, and development or progression of RHD.

While the effectiveness of secondary prevention has been demonstrated[21], implementation is difficult. ARF/RHD patients not receiving adequate secondary prophylaxis are at risk of avoidable and progressive heart damage. Even when prescribed, low uptake has been highlighted in numerous countries including Australia[68], Egypt[181], Taiwan[182], Brazil[183] and South Africa.[184] Reasons suggested for this include longevity (up to 10-20 years) and inconvenience of treatment, pain of injections, poor community engagement, inadequate patient education, cost, and distance from health centres.[69, 185]

Addressing this issue is an ongoing public health priority.[69] The aim of this review is to evaluate the evidence pertaining to improving uptake of ARF/RHD secondary prophylaxis within the framework of the Chronic Care Model (CCM) developed by Ed Wagner and

colleagues.[70] Given the longevity of secondary prophylaxis required for ARF/RHD patients, suboptimal uptake of treatment, and the reality that delivery of health care in this context is far broader than individual interactions between patients and clinicians, it is timely to examine ARF/RHD secondary prophylaxis within a CCM framework.

Chronic Care Model for ARF/RHD

There are a broad range of models of care that have been developed and utilised in chronic disease management.[186-188] Many of these focus on specific chronic diseases[189, 190], particular elements of treatment or the health care system[191], defined providers[192] or the client themselves.[190, 193] Others are based on Wagner's original CCM and encompass a broader, whole-of-system approach incorporating patient, provider and system-level interventions. The CCM has been utilised in this review as it provides a generic framework that is recognised and utilised internationally and for a broad range of communicable and non-communicable chronic diseases.[194-197]

The CCM is a whole-of-system framework developed for improving chronic disease care. It highlights that effective chronic disease care results from positive relationships between empowered patients and proactive care teams. Wagner argues that delivering effective chronic disease care is best achieved through redesigning delivery systems within the context of three core domains: community resources, health care organisation, and clinical practice (see Figure 11).

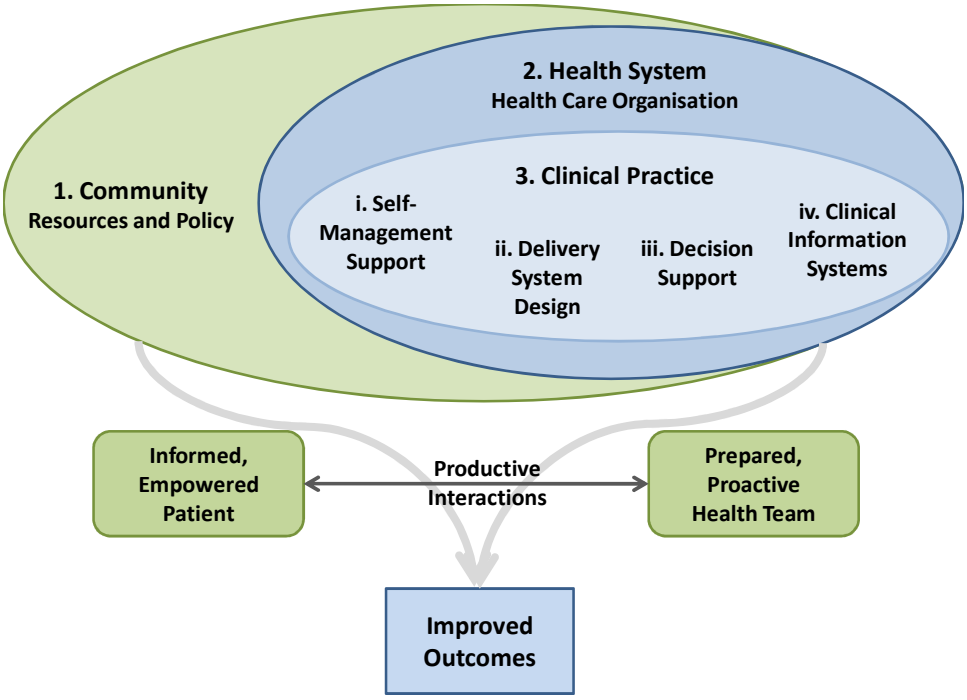


Figure 11. Diagrammatic representation of the Chronic Care Model.[70]

While the CCM has been associated with improvements in chronic disease care[70, 196, 197] it has not been utilised specifically in relation to ARF/RHD. Furthermore, the model has limitations including the fact that there are few data relating to its cost-effectiveness and the potential difficulties in applying a model of system redesign shown to be effective in well-resourced urban centres to regional and remote settings where many clients with ARF/RHD live. Nonetheless, given the broad nature of the CCM framework, this was considered the most suitable framework to use when examining potential strategies to improve the delivery of secondary antibiotic prophylaxis for ARF/RHD.

Search Strategy

A PubMed search of English language articles was undertaken to identify literature relating to activities undertaken to improve uptake of secondary antibiotic prophylaxis for ARF/RHD. Published conference abstracts were included. The reference lists of retrieved articles were also searched. The search strategy included a combination of the following search terms: “secondary prophylaxis OR antibiotic prophylaxis OR benzathine penicillin OR preventive therapy”, “rheumatic fever OR rheumatic heart disease”, and “adherence

OR compliance". A grey literature search was also undertaken examining the first ten pages of both Google and Google Scholar for the following search terms (used in combination) "secondary", "antibiotic", "prophylaxis", "penicillin", "rheumatic", "adherence", "compliance". The criteria for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were applied.

In total 104 articles were reviewed. Articles which did not report adherence data for secondary prophylaxis or which did not describe interventions to improve uptake were excluded. Sixteen articles satisfied all selection criteria and were included. Given this low number, other potential strategies for improving uptake of secondary prophylaxis were discussed based on evidence from studies in other areas of health care.

Review of Interventions to Improve Uptake of Secondary Antibiotic Prophylaxis within a CCM Framework

1. Community Resources

The CCM recognizes that while care takes place within a health care system, this system is embedded within the wider community. By mobilising "community resources" to meet the needs of patients, better outcomes may be expected.[70]

Mobilizing community resources to improve delivery of ARF/RHD secondary prophylaxis may involve such actions as increasing health access through community-control or clinical outreach, developing linkages between health services and community-based agencies (e.g. schools, sports bodies, stores, churches, and welfare agencies), and promoting secondary prophylaxis through community events and cultural activities. A thorough understanding of local community dynamics is likely to be integral to identifying potential community partners.

Within an Indigenous context, research focused on Canada's First Nations peoples has shown that community control of health services, self-governance, control of traditional lands, and community-controlled schooling can improve health outcomes.[198, 199] Nonetheless this research was specifically related to youth suicide and may not be generalisable to chronic disease care in general and ARF/RHD specifically.

Local events organised by identified partners, such as concerts and cultural gatherings, may provide a particularly useful forum for engaging young populations at particular risk of ARF who may not access structured health care. Whilst their role in encouraging the uptake of ARF/RHD prophylaxis is unknown, there is evidence that such support can influence health-related behaviour including reducing tobacco consumption.[200]

Developing linkages between health care and education systems can be particularly effective in improving uptake of secondary prophylaxis by children and adolescents. One secondary prophylaxis programme in Auckland, New Zealand, focused on delivering injections at schools by community nurses. This resulted in full compliance (percentage of clients receiving all scheduled injections over a 12 month period) ranging from 79.9% to 100% over nine different nursing offices.[201]

There is some evidence that a 'whole of community' response to ARF/RHD prevention can be effective.[138, 141, 202] Such an approach was undertaken in the Cuban province of Pinar del Rio between 1986 and 1996.[202] Five years later the occurrence of ARF and RHD had declined by up to 90%, and a progressive increase in uptake of secondary prophylaxis was reported. Community involvement and the utilisation of public media were key components of this programme. Similar success with 'whole of community' interventions has been reported in Costa Rica[138] and the Caribbean.[141] Unfortunately it is difficult to identify the exact elements which contribute to the success of such broad-scale programmes.

2. Health care organisation

The CCM highlights that to improve chronic disease care it is necessary to improve the quality and safety of the culture, systems and practices of health care organisations.[70] The role of clinician leadership and advocacy from service providers, patients, community leaders and clinical and consumer organisations would seem to be key to this process but the available evidence is limited to uncontrolled evaluations from Central America.[138, 141, 202]

One mechanism that is often used to facilitate the ongoing refinement of health systems, and which falls under the remit of "health care organisation" improvement, and particularly "delivery system design" (see figure 12), is continual quality improvement (CQI). CQI

refers to a structured organisational process to plan and implement a continuous suite of interventions to improve the quality of health care provided by an organisation.[203] It involves examining and reworking existing health care processes in light of best-practice, evidence-based knowledge and scientific methodologies.[203] While systematic reviews have demonstrated that CQI can be effective in improving other areas of health care, the evidence is limited.[204, 205] The effects are generally small to moderate with most positive results seen when baseline adherence to recommended practice is low and intensity of audit and feedback is high.[206] CQI programmes may be difficult to implement if they are complex, time-consuming and resource-intensive. These problems may be exacerbated in low resource, Indigenous, and remote settings[207] where ARF/RHD are most prevalent.

There are currently only limited published data reporting on the efficacy of CQI initiatives in ARF/RHD care. One study from the Northern Territory in Australia suggested that CQI activities did improve some aspects of ARF/RHD care but had no impact on the proportion of patients receiving $\geq$80% of their scheduled LAB injections.[179] Thus, it remains unclear whether formal CQI initiatives are superior to other organisational strategies including those that encourage reflective and responsive health care at an individual provider level.

Providing incentives to health care providers may be another potential mechanism to improve patient care. In the context of ARF/RHD secondary prophylaxis, providers could be rewarded for each dose delivered or when uptake targets are met. While there is no published literature in relation to such 'pay-for-performance' (P4P) strategies for secondary prophylaxis, there is evidence relating to other elements of health care. Unfortunately, systematic reviews have reported that the quality of research relating to P4P strategies in health care settings is poor and that the effects of such interventions are highly variable.[208-210] In these three systematic reviews the number of studies was limited, ranging from 5 to 9. In de Bruin[208] and Scott's[209] reviews, the authors found that there were small improvements in the quality of care but that most studies included significant methodological limitations and no assessment of cost effectiveness. Witters' review of interventions in low to middle income countries found little to support the use of P4P in such settings.[210] Furthermore, it has been argued that the complexity and design of P4P initiatives can make it difficult to generalise apparently successful initiatives to other settings.[211] Nonetheless, the success of

some P4P schemes suggests that well designed incentive systems with clear evaluation strategies are worthy of further investigation as a mechanism to enhance ARF/RHD secondary prevention.

3. Clinical Practice

3(i) Self-Management Support

The CCM recognises that a central component to improving chronic disease care is providing patients with the knowledge, skills, motivation and support to manage their own health.[70]

An uncontrolled evaluation of a secondary prophylaxis programme in Barbados demonstrated that supporting ARF/RHD patients to self-manage through the use of patient-carried cards to record injection dates may have improved uptake with adherence up to 97% of possible doses of therapy.[212, 213] The use of such cards was reported to have eased the administration of the ARF/RHD programme, involved the patient in the keeping of records of injections, and allowed for immediate assessment of adherence to prophylaxis.[212] However, the specific impact of such cards as opposed to the concurrent implementation of an ARF/RHD service and registration system meant that the individual impact of such cards could not be determined. In addition, there is a lack of information regarding the use and efficacy of hand-held records in other settings. Whilst such a system may be useful for patients who are mobile and access health care at various sites, there is little published evidence to support this.

Another mechanism that may support self-management is the use of mobile telephone-based short message service (SMS) reminders. One review of SMS reminders found that they substantially increased the likelihood of patients attending clinic appointments.[214] The increasing use of mobile telephones in low resource and remote settings means the use of SMS-based reminders may be a viable option to enhance ARF/RHD care across a broad range of settings.[215, 216] Nonetheless, at present there is no evidence to support this in ARF/RHD and their use is, therefore, best limited to settings where they can be associated with a clear evaluation strategy.

Whenever considering self-management it is important to be cognizant of the extent to which individuals and communities may wish to take on such a role. Evidence based on the experience of some Aboriginal Australians suggests self-management may not be a priority. In one ARF/RHD prophylaxis study in a remote Aboriginal community, a patient's sense of taking responsibility for their own health was not clearly related to uptake.[178] Rather, patients felt that the role of the health service was not only to provide medical care but also to perform a pastoral role in terms of home visits, engaging families, encouraging patients and caring for them emotionally. Another Australian study reported that the uptake of secondary prophylaxis was closely linked with positive patient – staff interactions.[217] These studies imply that in a remote Aboriginal context, self-management for ARF/RHD may play a secondary role to the quality of relationships between health staff and patients/families. Nonetheless, generalising these findings to other settings should be interpreted within a local cultural context.

A key component of chronic disease self-management is patient, family and community education. ARF/RHD education has been associated with an improvement in the uptake of secondary prophylaxis in Costa Rica[138] and the Caribbean.[141] Furthermore, an Egyptian study showed that inadequate education of parents regarding ARF/RHD and secondary prophylaxis was the main factor jeopardising quality of care for their children.[181] Nonetheless, the Costa Rican and Caribbean studies were uncontrolled, multi-dimensional interventions and so the isolated effects of education initiatives remain difficult to determine.

The use of patient/carer incentives to improve uptake of ARF/RHD secondary prophylaxis has been suggested.[69] Two recent Cochrane reviews of the effectiveness of incentives in limiting tobacco consumption[218, 219] and a systematic review investigating the use of financial incentives for the treatment for obesity[220] found that such schemes were not generally successful. Nonetheless, a review of eleven randomized controlled trials investigating the effect of financial incentives on compliance with medication, medical advice, or medical appointments did find a positive association.[221] As evidence of the effectiveness of patient incentives is unclear, and given there is no evidence relating to their

use in ARF/RHD prophylaxis, further research is required before recommendations can be made.

3(ii) Delivery System Design

Improvement in chronic disease outcomes requires the delivery of clinical care that is effective and efficient.[70]

It is often suggested that a key element in the successful delivery of secondary prophylaxis is having systems of patient registration and recall that are up-to-date, accessible and clear.[141] Such systems are particularly effective in ensuring appropriate response to follow-up, including missed injections.[2, 222] Nonetheless, the evidence supporting their effectiveness in enhancing secondary antibiotic prophylaxis is, at best, limited to uncontrolled audits whereby changes in prophylaxis uptake may have been influenced by other undefined factors.[21, 202, 223]

Successful delivery of secondary prophylaxis also requires clarity regarding roles and responsibilities of clinical and non-clinical health staff. For example, high uptake rates were reported for a New Zealand secondary prophylaxis programme that involved community-based nurses working with ethnically appropriate health workers who provided education, support and transport.[224] Other studies have confirmed that uptake of secondary prophylaxis improves where clear responsibility is placed upon a particular staff member to actively follow-up clients who miss injections.[217]

One study in central Australia investigated the novel concept of delivering secondary prophylaxis at times of the full moon.[225] While uptake increased significantly, the improved uptake did not occur at the time of the full moon. Such findings reinforce the need to critically evaluate claims that any specific initiative has enhanced ARF/RHD secondary prophylaxis uptake when often confounders and other uncontrolled factors may not have been adequately addressed or controlled for.

3(iii) Decision Support

The CCM recognises that clinical care provided to patients with chronic diseases must be based on current evidence while at the same time taking account of patient preferences.[70]

In respect of ARF/RHD care, evidence-based best-practice guidelines are available for a number of settings including South Africa, Asia, North America, New Zealand, Australia and globally, via the World Health Organisation.[2, 21, 147, 226-228] The CCM acknowledges the importance of incorporating these guidelines into existing care and register/recall systems. Nonetheless, we have highlighted above that the evidence in relation to secondary antibiotic prophylaxis implementation, and that is often cited to support guideline recommendations, is limited.

A number of specific issues are particularly pertinent in relation to decision-support regarding ARF/RHD secondary prophylaxis. First, there must be clarity and consistency in relation to timing of delivery and period of coverage required. Unfortunately, even in high income countries such as Australia, adherence to national guidelines is variable.[68] Second, support systems are required for local health providers to deal with more complicated management issues not adequately addressed by local guidelines. Such systems may include facilitating access to specialist or more experienced primary health care providers through telemedicine or outreach clinics. While there is no published evidence relating specifically to the use of telemedicine in secondary prophylaxis, one report noted that the use of telemedicine in the Pacific Islands enabled more efficient and effective evaluation and follow up of RHD patients requiring surgical intervention.[229] Third, as the severity of RHD dictates the frequency of health care review, and the longevity of prophylaxis required[2], routine review of patients and their medical records is required to ensure that decision support systems are correctly applied. Such review can ensure that secondary prophylaxis is ceased when appropriate thereby preventing unnecessary use of health resources and patient inconvenience.

3(iv) Clinical Information Systems

Effective clinical information systems provide easy access to up-to-date patient and population data thereby allowing health practitioners to make well-informed decisions about patient care. A preferred system for facilitating the uptake of ARF/RHD prophylaxis is one that integrates patient information, decision support and recall and follow-up.[2] The structure of any such system will be dependent upon available resources. In higher income settings this may include electronic patient medical records which interface with centralised

ARF/RHD register/recall systems and electronic decision support. In other settings these may be paper-based records, registers and protocols or hand held records. The role of such register/recall systems has been highlighted above.

Conclusion

The CCM provides a framework within to plan, implement and evaluate initiatives to improve chronic disease services. With evidence suggesting that the uptake of ARF/RHD secondary prophylaxis is often inadequate, we used the CCM framework to review interventions to improve service delivery.

There is limited published evidence pertinent to improving the delivery of ARF/RHD secondary prophylaxis. That which is available suggests that register/recall systems, dedicated teams for prophylaxis delivery, ARF/RHD education, linkages with the community (particularly schools), and staff-patient relationships may be important. However, it is difficult to generalise findings from individual studies to other settings, and high quality studies are lacking.

While the CCM concentrates on a broad based response to chronic disease care, the limited existing evidence relating to ARF/RHD recommendations has a particular focus on delivery system design and CQI (see 3.ii), decision support and guidelines (3.iii), and clinical information and recall systems (see 3.iv). Although evidence to inform self-management support (3.i) is lacking, initiatives in other settings would suggest a combination of patient reminders (e.g. SMS messaging), incentives, and self-managed medical records (whether electronic or hand held) are worthy of future investigation and evaluation.

The problem of uptake of ARF/RHD secondary prophylaxis remains vexed. The solution to preventing ARF/RHD is likely to lie in understanding and addressing the role of poverty, developing an effective GAS vaccine, and researching new systems of delivery of secondary prophylaxis that do not necessitate monthly injections over decades. In the interim the focus should be on evaluating initiatives that translate an efficacious treatment (secondary antibiotic prophylaxis) into effective programmes that reduce the burden of ARF/RHD. A current Australian multicentre community-based clinical trial evaluating a

multidimensional primary health care based intervention to enhance secondary prophylaxis delivery may inform this process.[230]

Key Points

1. Current management of ARF and RHD includes the use of secondary antibiotic prophylaxis but uptake of this in many settings remains low.

2. There is very limited high-quality evidence to inform initiatives to enhance the delivery of secondary prophylaxis

3. There is limited evidence to suggest that the following elements may improve uptake of secondary antibiotic prophylaxis: use of registers and recall systems, development of strong staff-patient relationships, creation of dedicated teams for the delivery of secondary prophylaxis, education programmes, and implementation of initiatives to improve community linkages (especially with schools).

4. The difficulty in translating an efficacious treatment, such as secondary antibiotic prophylaxis, into an effective programme that reduces the burden of ARF and RHD demonstrates the importance of on-going work in developing and evaluating research translation initiatives that reflect the practical realities of where people with ARF/RHD live.

Chapter 3 – Informing the Diagnosis of Rheumatic Heart Disease

3.1 Screening for Rheumatic Heart Disease in Aboriginal and Torres Strait Islander children

Background

The role of screening in the prevention and management of rheumatic heart disease (RHD) has become topical due to the increased availability of affordable and portable echocardiography machines. One of the first reported studies of echocardiographic screening was undertaken by Marijon and colleagues in Cambodia and Mozambique commencing in 2001.[52] Prior to this study, RHD screening programmes relied on clinical screening via auscultation followed by echocardiographic confirmation of diagnosis if a murmur suggestive of RHD was detected. However, the existence of subclinical valve disease raised debate as to whether such protocols significantly underestimated RHD prevalence.[231] The results obtained by Marijon and colleagues supported this notion in finding that systematic screening with portable echocardiography detected almost 10 times as many children with RHD compared with clinical screening.[52] Since this study, numerous further echocardiographic prevalence studies have been undertaken in a wide variety of countries including Australia[233], India[234], New Zealand[75], New Caledonia[235], Nicaragua[236], Senegal[237], and Uganda[238] and have been systematically reviewed by Rothenbuhler et al.[232]

The question of the role of screening in the prevention and management of rheumatic heart disease (RHD) has been highlighted as a priority for research in Australia.[69] Given the high rates of RHD already reported in Australian Indigenous populations it is arguable that screening should be undertaken in high risk settings so as to identify those with early disease, provide them with treatment, and prevent the worsening of damage to their heart valves. However, a number of significant questions around the feasibility of RHD screening programmes exist. The following review article explores these issues and, in

particular, provides a rationale for the research regarding echocardiographic diagnosis of RHD presented later in this chapter.

Abstract

RHD is preventable but causes significant morbidity and mortality in Aboriginal Australian and Torres Strait Islander populations. Screening echocardiography has the potential to detect early RHD thereby enabling timely commencement of treatment (secondary prophylaxis) to halt disease progression. However, a number of issues prevent echocardiographic screening for rheumatic heart disease satisfying the Australian criteria for acceptable screening programmes. Primarily, it is unclear what criteria should be used to define a positive screening result as questions remain regarding the significance, natural history and potential treatment of early and subclinical RHD. Further, at present the delivery of secondary prophylaxis in Australia remains suboptimal such that the potential benefits of screening would be limited. Finally, the impact of echocardiographic screening for RHD on local health services and the psychosocial health of patients and families are yet to be ascertained.

Introduction

Many people with RHD in Australia first present with advanced valve disease.[73] One mechanism to prevent advanced RHD is to identify those with milder disease and offer them secondary antibiotic prophylaxis.[66] To this end, there has been increasing research regarding the utility of echocardiographic screening for the early detection of RHD in Australia and elsewhere as it may enable identification of those at-risk before symptoms develop.[52, 53, 74, 75] Concurrently there has been increased discussion in Australia regarding whether screening for RHD should become part of routine health care[62] for those at increased risk including Aboriginal and Torres Strait Island children.[1] Despite ongoing research, uncertainty remains regarding the potential benefits and risks of such a strategy.

Before discussing the role of RHD screening in Australia it is necessary to define "health-related screening" and to provide a structured approach to assessing whether such screening is appropriate. Disease screening is the systematic application of rapidly applied tests or examinations to identify asymptomatic individuals at risk of a specific disorder. Its aim is

to identify disease early so that intervention and management can be established to reduce disease incidence, morbidity and mortality.[239]

While the benefits of detecting disease early are widely acknowledged, all screening tests have risks, costs and harms.[240] Any screening programme must achieve a balance between bringing effective treatment to those with previously undetected disease and avoiding harm to those not in need of treatment.[241] Due to the complexity in achieving this balance, a variety of thematic structures have been developed to assist decision makers when considering potential screening programmes.[76, 242, 243] In this review, we examine the suitability of echocardiographic RHD screening based on the Australian criteria for the assessment of population screening[76] (see Box 8) which closely follow those of the World Health Organisation and the Council of Europe.[242, 243]

The Condition *must be an important health problem, with a recognisable latent or early symptomatic stage, and the natural history of the disease must be adequately understood.*

The Test *must be highly sensitive and specific, validated and safe. It must have relatively high positive and negative predictive values and be acceptable to the target population. There must be established criteria for what constitutes positive and negative test results.*

Assessment *Systems should be in place for evidence–based follow–up assessment of all people with a positive screening test.*

Treatment and Management *The treatment must be effective, available, easily accessible and acceptable to all patients with the recognised disease or condition. There must be management protocols for those with the condition or at risk of developing the condition.*

The Screening Programme *must be evidence–based, be adequately resourced for screening and follow-up, have effective recall and management databases, be cost effective, and ensure that overall benefits of screening outweigh the harm.*

Box 8. Australian criteria for the assessment of population-based screening.

The Condition

The condition must be an important health problem, with a recognisable latent or early symptomatic stage, and the natural history of the disease must be adequately understood.

RHD is an important health problem, accounting for the highest percentage of adolescent cardiac disease in the world today.[21] Current global estimates indicate that more than 15.6 million people have RHD, with 470,000 new cases and 230,000 deaths each year.[7] The highest documented rates of acute rheumatic fever (ARF) and RHD in the world are found in Australian Aboriginal and Torres Strait Islander populations.[62] These groups have an 8-fold hospitalisation rate for ARF/RHD compared with non-Indigenous Australians and are 30-times more likely to die from complications.[244]

RHD causes significant cost to affected individuals, families, communities and society generally. The greatest impact is seen in young adults in their most socially and economically productive years.[245] This, coupled with excessive heath care costs and loss of social capital, contributes to an extensive national economic burden.[62] A study investigating 100 low-income patients affected by ARF/RHD over one year, identified 1,657 medical consultations, 22 hospital admissions, a 22% school failure rate, and that 22% of parents exhibited work absenteeism, 5% of whom lost their jobs.[246]

The natural history of RHD is well understood.[247] RHD usually develops after recurrent episodes of ARF. Once RHD is established further episodes of ARF are likely to cause additional valve damage thereby increasing disease severity. Although associated with ARF, a third of patients with established RHD do not have a history of ARF.[47] Typically, people with mild RHD exhibit no symptoms. Only with more severe disease do complications occur including heart failure, stroke and endocarditis.[62]

Whilst valve disease is classically associated with a heart murmur on auscultation this is not invariable. “Subclinical” RHD can exist whereby cardiac auscultation is normal but valve disease is evident on echocardiography.[9, 21, 62] Such subclinical RHD has been shown to persist[248] and progress to significant valvular disease over time.[9] Screening-based detection of subclinical RHD may allow the commencement of secondary prophylaxis at an earlier stage, thus preventing the development of more severe disease.

The Test

The test must be highly sensitive and specific, validated and safe. It must have relatively high positive and negative predictive values and be acceptable to the target population. There must be established criteria for what constitutes positive and negative test results.

Echocardiography is safe and non-invasive. It is both sensitive and specific in regards to identifying morphological and functional heart valve abnormalities associated with established clinical RHD.[54] However, there is substantial debate regarding criteria for a positive and negative result in any potential screening programme.

Traditionally, programmes to detect RHD in children have relied on auscultatory assessment followed by echocardiographic confirmation if a murmur was detected.[52] However, the existence of subclinical valve disease raises the possibility that such protocols may result in cases of RHD remaining undiagnosed.[231] Indeed, investigations of auscultation by highly trained clinicians concluded that the clinical diagnosis of murmurs is often inaccurate.[54] In contrast, echocardiography is a highly sensitive method for diagnosing and characterising valve lesions[53] and can result in a case detection rate for echocardiographically-defined RHD that is 10-fold that achieved by auscultation alone.[52]

With less expensive and more portable systems, echocardiography has been increasingly utilised for RHD screening in developing countries and remote regions.[52, 53, 236] A study by Marijon *et al*. of schoolchildren in Cambodia and Mozambique revealed that approximately 90% of echocardiographically-defined RHD cases were clinically silent leading the authors to suggest that echocardiographic screening may be an ideal means of optimising case identification.[249] A similar study conducted in Tonga concluded that 54% of the lesions determined to be definite RHD on echocardiography were either not discovered on auscultation, or were defined as 'innocent'.[53]

Nonetheless, there is a lack of evidence relating to the natural history of such subclinical RHD and whether its natural history and response to secondary prevention parallels classically diagnosed disease. If this were not the case then any RHD screening programme that assumes subclinical RHD is equivalent to RHD diagnosed in the setting of earlier ARF or a murmur could lead to inappropriate management. Conversely, if subclinical RHD does

represent true RHD then such screening criteria would potentially enable a significant proportion of RHD to be prevented through early intervention. There is therefore a clear need for further research to determine whether subclinical RHD has a natural history and response to secondary prevention that is equivalent to RHD diagnosed on the basis of a murmur or history of ARF. In addition, accepted and validated criteria for what constitutes a positive and negative RHD echocardiographic screening test are required to avoid potential over-diagnosis. Whilst international evidence-based criteria for the diagnosis of RHD in high-risk populations have been developed[55], the significance of minor abnormalities remains unclear.

Assessment

Systems should be in place for evidence based follow up assessment of all people with a positive screening test.

Until the uncertainties regarding echocardiographic screening criteria for RHD and the significance of subclinical RHD are clarified, it will not be possible to develop evidence-based systems for the follow up of a positive screening test. Nonetheless, where it has been assessed, the existing primary health care, specialist and echocardiographic follow-up of Australian patients with a history of ARF and RHD is suboptimal.[79, 80] A study in the Kimberley reported that of patients recommended visiting specialist or echocardiographic review, 78% and 64% attended respectively.[79] Similarly, in the Northern Territory only half the patients with moderate and mild RHD were adequately investigated and/or followed up.[80] It is unlikely existing systems for RHD clinical follow-up would be able to meet the increased workload associated with echocardiographic screening, including follow-up of people with positive screening tests, without additional investment and/or service realignment extending from primary to specialist health care.

Treatment and Management

The treatment must be effective, available, easily accessible and acceptable to all patients with the recognised disease or condition. There must be management protocols for those with the condition or at risk of developing the condition.

In Australia there are national guidelines for ARF and RHD diagnosis and management[62] which are utilized to inform local management guidelines for State and Territory jurisdictions.[64, 65] One key element in the management of RHD outlined in these guidelines is secondary prophylaxis through regular intramuscular injections with long-acting benzathine penicillin. This has been shown to prevent infection with Group A streptococcus (GAS)[107] and the development of recurrent attacks of ARF which can result in progressive RHD.[21] Successful secondary prophylaxis in people with mild RHD can retard progression and even reverse existing damage[250] with an attendant reduced need for surgery.[251] It is currently the only evidence-based and cost-effective strategy for the control of ARF/RHD.[7]

While secondary prophylaxis for ARF/RHD is available in Australia, its delivery remains suboptimal. A number of Australian studies have demonstrated that relatively few Aboriginal and Torres Strait Islander patients with ARF/RHD achieve adequate uptake[79, 80, 178] resulting in high rates of recurrent ARF.[178] The development of strategies to redress this is an ongoing public health issue.[178]

The unique cultural and demographic mix of high-risk areas for RHD in Australia (including the Northern Territory, and regional and remote Western Australia, South Australia and Queensland) coupled with geographic isolation and low population density has considerable implications for health care delivery, including the delivery of secondary prophylaxis. Further, numerous anecdotal factors are proffered to explain why existing systems for the delivery of secondary prophylaxis are inadequate (e.g. pain of injections, patient mobility, longevity and inconvenience of treatment, inadequate patient education). However, there remains no clear evidence regarding how best to respond to this service gap. Without such evidence, and the implementation of effective strategies to improve secondary prophylaxis uptake in high-risk Australian populations, delivery will remain poor and the potential benefits of screening will be limited.

The Screening Programme

The screening programme must be evidence-based, be adequately resourced for screening and follow-up, have effective recall and management databases, be cost effective, and ensure that overall benefits of screening outweigh the harm.

Currently there are ARF/RHD register and recall systems in Western Australia, the Northern Territory and Queensland. In these jurisdictions ARF is also a notifiable disease. Substantial evidence surrounds the importance of such centralised registers and organised recall systems for patients with ARF/RHD.[7] They improve case detection[223], increase adherence to secondary prophylaxis[245], and decrease hospitalisations.[245] Programmes that include active follow-up and recall beyond individual community boundaries and which are able to deal with patient mobility are most effective.[62]

Despite these systems, it remains to be seen how any echocardiography-based RHD screening programme in Australia may be delivered. Such a programme would, of necessity, involve Aboriginal and Torres Strait Islander children living in rural and remote settings. In such settings health service delivery is complicated by factors such as geographical isolation, seasonal weather patterns that impact on transportation, difficulty in staffing, and patient mobility. Given these issues, healthcare staff in remote Australian communities may have difficulty absorbing the additional workload associated with screening and/or follow-up of potentially abnormal findings, particularly as RHD requires complicated and intensive management.[62, 252] Any potential screening programme would therefore require additional funding and staffing to cover this additional activity.

The economic impact of screening considerably affects health services. Screening tests are expensive, and divert money from other healthcare areas. Nonetheless, there is evidence to show that secondary prophylaxis is cost-effective in the prevention of RHD. Michaud *et al.* estimated that secondary prophylaxis costs $142 for every disability-adjusted life year (DALY) gained and $5,520 for every death averted.[253] While our knowledge of the true economic impact of ARF/RHD remains limited[73], this is nonetheless extremely good value for money compared with other health interventions in this and other settings. For example, one study in the Northern Territory found that the average annual cost of providing dialysis and other treatment to Aborigines with end-stage kidney disease was at least $71,000.[254]

The ultimate benefit of screening programmes is to increase quality and longevity of life while avoiding medical and psychological costs associated with late-stage interventions.[255] These benefits are most apparent in populations with the highest disease risk/prevalence.[239] Given the high prevalence of RHD in Aboriginal Australians and Torres Strait Islanders

and its impact on affected individuals, their families and communities, a strong case may be made that the benefits of a successful programme would more than balance the costs, lengthening the productive life of the population at risk, and limiting tertiary health care expenditure.[243]

In regard to harm or risk, while echocardiography presents no physical risk to those being screened it does expose participants to the potential behavioural and psychosocial risks associated with false positive, false negative, and incidental findings.[256] Studies investigating the utility of mammography screening for breast cancer have demonstrated that for each screening-prevented death approximately 200 false-positive results are given.[257] Women who received false-positive results exhibited increased anxiety[258] with 5% describing their erroneous result as "the worst thing they had ever experienced".[259] Demonstrated effects on mood and behaviour do not immediately resolve, even if further investigations show no disease.[260] Thus, 18% of parents who had children with false-positive results on neonatal screening tests expressed great concerns after repeat tests revealed no abnormalities.[261] The economic costs of false-positive tests may also prove to be substantial.[256] It is estimated that receiving a false-positive result during prostate, lung or colorectal cancer screening, averages US$1,171 in additional medical costs, compared with having a negative screening test.[262] In contrast to false-positives, false-negative results may cause diagnostic delays (possibly increasing morbidity and/or mortality) and extensive, costly treatments associated with more advanced disease.[239] All these risks must be weighed against the potential positive outcomes that may be associated with the early detection of RHD through echocardiographic screening.[263]

Conclusion

RHD is a preventable disease that continues to cause significant morbidity and mortality in Aboriginal Australian and Torres Strait Islander populations. The ability to detect early RHD through screening echocardiography appears highly desirable as it would enable timely commencement of effective secondary prophylaxis to halt progression, or cause regression, of existing disease. However, a number of issues must be resolved before echocardiographic screening for RHD would satisfy criteria for an acceptable screening programme. While echocardiography is a sensitive and relatively specific tool for detecting

advanced valve disease, it is unclear what criteria should be used to define a positive screening result, particularly as questions remain regarding the significance, natural history and potential treatment of early and subclinical RHD. Further, while an effective "treatment" for RHD is available (secondary antibiotic prophylaxis), current delivery to Aboriginal and Torres Strait Islander peoples with a history of ARF/RHD is suboptimal. Finally, the impact that echocardiographic screening for RHD would have on local health services and the psychosocial health of patients and families is yet to be ascertained, while the cost-effectiveness and most appropriate age and frequency of screening also remains unclear. In light of these factors it is not yet time to advocate for echocardiographic screening for RHD for high risk populations including Aboriginal and Torres Strait Islander peoples living in regional and remote Australia.

Key Points

1. Aboriginal Australian and Torres Strait Islander populations have amongst the highest documented prevalence of rheumatic heart disease in the world resulting in significant morbidity and mortality.

2. Screening echocardiography has the potential to detect early rheumatic heart disease so that timely commencement of treatment (secondary prophylaxis) can be implemented to halt disease progression

3. It is premature to advocate for echocardiographic screening for rheumatic heart disease in Australia for a number of reasons: it is unclear what criteria should be used to define a positive screening result, delivery systems for secondary prophylaxis remain inadequate, and the potential impact of any such programme on local health services, patients and their families is unknown.

3.2 RhFFUS – Rheumatic Fever Follow-up Study

Background

One of the issues surrounding the feasibility of screening for early RHD is that, until recently, there have been no agreed criteria for the diagnosis of RHD based on echocardiographic findings alone. Many of the more recent RHD screening studies have used conflicting and/or unclear criteria for assessing whether the echocardiograms of study participants are normal or abnormal. In an attempt to address this problem and standardise RHD diagnosis, in 2012 the World Heart Federation published a guideline for the echocardiographic diagnosis of RHD.[55] This guideline provides clear diagnostic criteria based on the morphology and function of the mitral and aortic valves. Furthermore, it includes a category of "Borderline RHD" which encompasses those individuals with morphological or functional abnormalities of their heart valves that do not satisfy criteria for Definite RHD but which are of potential significance. The Rheumatic Fever Follow-up Study (RhFFUS) was, in part, undertaken to address this question of the significance of a diagnosis of Borderline RHD based on echocardiography. If clarity can be obtained about the significance of non-diagnostic heart valve lesions, that is whether such lesions are the earliest signs of Definite RHD, then one of the main issues regarding the feasibility of RHD screening programmes discussed above would be addressed (that is, what should constitute a positive or negative screening test). Furthermore, in the context of "prevention", clinicians presented with an echocardiogram report that describes minor heart valve abnormalities would have the evidence to decide whether or not to commence secondary antibiotic prophylaxis or undertake other clinical follow-up.

The following two papers report the RhFFUS project. The first paper outlines in detail the study methodology. The second paper examines whether individuals with non-diagnostic heart valve anomalies in a setting of high rates of ARF/RHD are at greater risk of ARF or progressive heart valve damage and development of Definite RHD.

3.2.1 Rheumatic Fever Follow-Up Study (RhFFUS) protocol: a cohort study investigating the significance of minor echocardiographic abnormalities in Aboriginal Australian and Torres Strait Islander children.

Abstract

Background: In Australia, rheumatic heart disease (RHD) is almost exclusively restricted to Aboriginal Australian and Torres Strait Islander people with children being at highest risk. International criteria for echocardiographic diagnosis of RHD have been developed but the significance of minor abnormalities which do not reach these criteria remains unclear. The Rheumatic Fever Follow-Up Study (RhFFUS) aims to clarify this question in children and adolescents at high risk of RHD.

Methods/Design: RhFFUS is a cohort study of Aboriginal and/or Torres Strait Islander children and adolescents aged 8-17 years residing in 32 remote Australian communities. Cases are people with non-specific heart valve abnormalities detected on prior screening echocardiography. Controls (two per case) are age, gender, community and ethnicity-matched to cases and had a prior normal screening echocardiogram. Participants will have echocardiography about 3 years after initial screening echocardiogram and enhanced surveillance for any history suggestive of acute rheumatic fever (ARF). It will then be determined if cases are at higher risk of (1) ARF or (2) developing progressive echocardiography-detected valve changes consistent with RHD.

The occurrence and timing of episodes of ARF will be assessed retrospectively for 5 years from the time of the RhFFUS echocardiogram. Episodes of ARF will be identified through regional surveillance and notification databases, carer/subject interviews, primary healthcare history reviews, and hospital separation diagnoses.

Progression of valvular abnormalities will be assessed prospectively using transthoracic echocardiography and standardised operating and reporting procedures. Progression of valve lesions will be determined by specialist cardiologist readers who will assess the initial

screening and subsequent RhFFUS screening echocardiogram for each participant. The readers will be blinded to the initial assessment and temporal order of the two echocardiograms.

Discussion: RhFFUS will determine if subtle changes on echocardiography represent the earliest changes of RHD or mere variations of normal heart anatomy. In turn it will inform criteria to be used in determining whether secondary antibiotic prophylaxis should be utilized in individuals with no clear history of ARF and minor abnormalities on echocardiography. RhFFUS will also inform the ongoing debate regarding the potential role of screening echocardiography for the detection of RHD in this setting.

Introduction

Whilst the long-term priority for addressing ARF and RHD remains identifying effective targets for primary prevention, to date these have proven elusive.[2, 264] Hence, the current emphasis remains the secondary prevention of Group A streptococcal (GAS) infection with prophylactic antibiotics in people with a history of ARF or known RHD.[2, 21, 107] This has been demonstrated to prevent recurrent ARF and progression of RHD.[66, 265-267]

Central to the delivery of ARF/RHD secondary prevention programmes is the diagnosis of ARF and RHD. A diagnosis of ARF is classically made in accordance with the Jones criteria based on a combination of major and minor symptoms, signs and investigation results.[2, 45, 251] Nonetheless given the variable manifestations of ARF, cases can be missed.[268] In high-risk populations in Australia, the Jones criteria have been modified with the aim of improving their sensitivity.[2]

Prior to the introduction of echocardiography (heart ultrasound), diagnosis of RHD required an experienced clinician with the requisite skill to identify and correctly interpret findings detected on auscultation of the heart. Nonetheless, it has been shown auscultation alone is neither sensitive[52] nor specific.[53] The increasing availability of more portable and affordable echocardiography to assess heart valve morphology and function (stenosis or regurgitation) has resulted in significant debate regarding the diagnosis of RHD on echocardiography alone. This particularly relates to the ability of echocardiography to confirm or refute a diagnosis of RHD. In an attempt to address this issue, the World Heart

Federation (WHF) recently released criteria[55] for the diagnosis of RHD based on both morphological and functional findings on echocardiography. The WHF criteria include a category of "Borderline" RHD, recognising potential abnormalities on echocardiography of uncertain significance.

The importance of such minor abnormalities was highlighted by a recent Australian RHD prevalence and echocardiography validation study. The gECHO (getting Every Child's Heart Okay) Study undertook echocardiographic screening of 3978 high risk (Aboriginal Australian and/or Torres Strait Islander) and 1267 low risk (non-Indigenous Australian) children across northern and central Australia. Preliminary results revealed a number of children with mild potential abnormalities of doubtful significance (personal communication, Graeme Maguire). If these abnormalities are representative of the earliest changes of RHD then offering such children regular secondary prophylaxis may prevent disease progression. This question has been identified as a priority for future investigation.[69, 269]

The Rheumatic Fever Follow-Up Study (RhFFUS) aims to clarify the significance of minor echocardiographic abnormalities in children and adolescents at high risk of ARF/RHD. More specifically, it aims to determine if Aboriginal and Torres Strait Islander children and adolescents aged 8-17 years with a previous potentially abnormal but non-diagnostic screening echocardiogram are at higher risk of (1) contracting ARF or (2) progressive echocardiography-detected changes consistent with RHD.

Hypothesis

Children from a population at increased risk of ARF and RHD who have minor and non-specific heart valve abnormalities on screening echocardiography are more likely to:

- have subsequent episodes of ARF and/or
- develop progressive echocardiographic changes consistent with RHD

than age, gender, ethnicity and community-matched children who had a previously normal echocardiogram.

Methods/Design

Study Design

RhFFUS is a cohort study of children with non-specific mitral and/or aortic valve abnormalities detected on prior screening echocardiography. Children will be assessed prospectively for the development of progressive valve abnormalities and retrospectively for the incidence of ARF. The comparator will be age, gender, community and ethnicity-matched controls who have previously had a normal screening echocardiogram (see Figure 12).

Study Populations

Participants in this study will comprise a subset of children who had an echocardiogram as part of the earlier gECHO screening study. These participants reside in 32 remote communities across northern and central Australia (see Figure 13).

Inclusion criteria

Children who participated in the gECHO study will be eligible for inclusion in RhFFUS if they identify as Aboriginal Australian and/or Torres Strait Islander and live in a remote location.

Exclusion criteria

Children who participated in the gECHO study will not be eligible for inclusion in RhFFUS if they identify as non-Indigenous Australians, live in urban locations, had a diagnosis of definite RHD based on gECHO screening, or had a diagnosis of congenital valvular heart disease that may generate morphologic or functional abnormalities similar to RHD (bicuspid aortic valve, dilated aortic root, mitral valve prolapse).

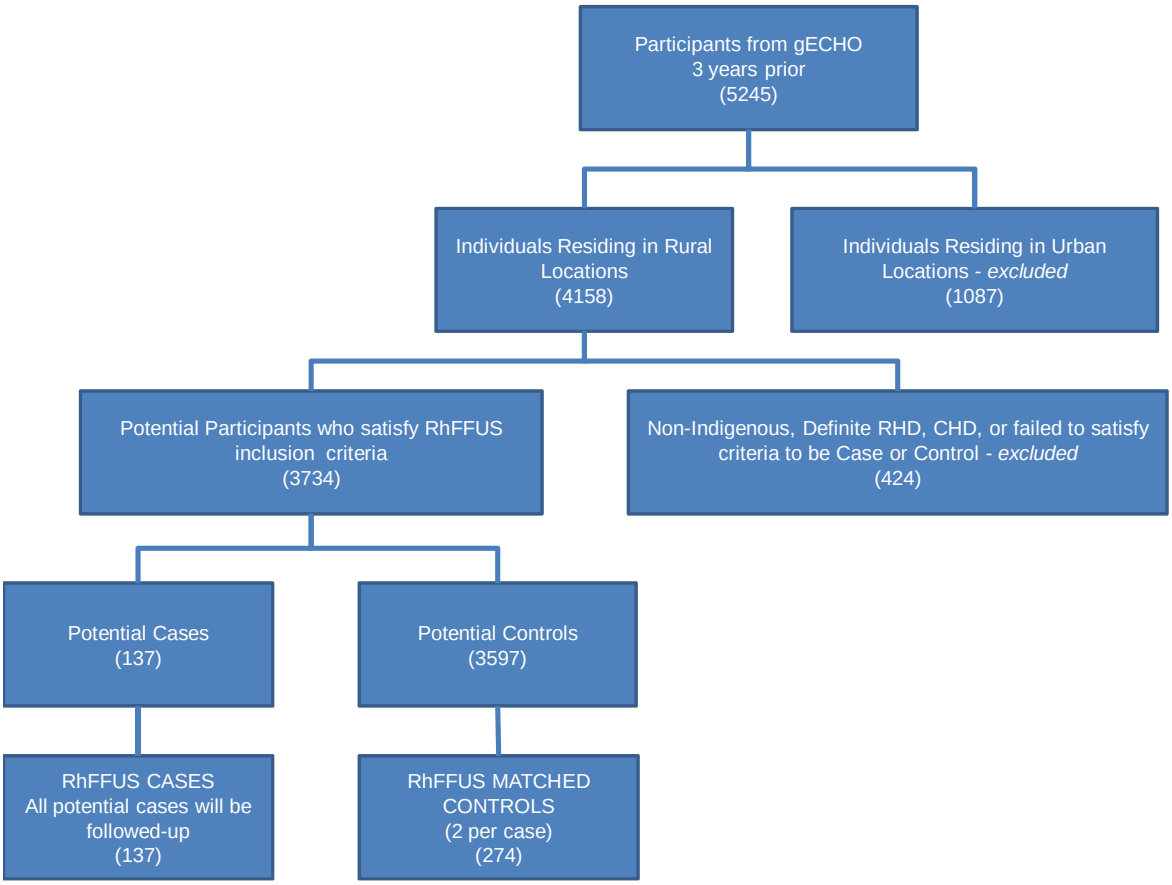


Figure 12. Protocol for selection of participants for RhFFUS. “Rural locations” comprise those communities involved in the gECHO that are outside of the cities of Cairns and Darwin. “Urban locations” comprise communities involved in the gECHO study that are within the cities of Cairns and Darwin. “RhFFUS inclusion criteria” are outlined in the text. “Non-Indigenous” refers to subjects enrolled in the gECHO project who self-reported as not being Aboriginal and/or Torres Strait Islander. “Definite RHD” as defined by WHF criteria.[23] “CHD” refers to a diagnosis of congenital valvular heart disease that may generate morphologic or functional abnormalities similar to RHD (bicuspid aortic valve, dilated aortic root, mitral valve prolapse). “Case or Control” criteria are defined in the text.

Figure 13. The 32 RhFFUS sites from Western Australia, the Northern Territory, and far north Queensland.

Case/control definition

Cases will be children with non-specific findings on their gECHO screening echocardiogram. More specifically, their screening echocardiogram from gECHO must not fulfill WHF echocardiography criteria for definite RHD[55] and must meet one of the echocardiographic criteria outlined in Box 1. Given the uncertainty of interpretation of minor echocardiographic abnormalities, criteria for cases are more sensitive than WHF criteria for borderline RHD[23]; 47 of the 137 cases included in RhFFUS satisfy the criteria for borderline RHD. Controls will be children who had a normal echocardiogram as defined in Box 9.

CASES:

1. One or more morphologic changes of mitral valve (MV)* and/or aortic valve (AV)* without pathologic mitral regurgitation (MR)* or aortic regurgitation (AR)*; or
2. Pathologic MR* with no or one morphologic feature of RHD* or pathologic AR* with no or one morphologic feature of RHD* (not both); or
3. Multiple MR jets and/or multiple AR jets (in at least two views) that do not fulfil criteria for pathologic MR* or AR*

CONTROLS:

1. No morphologic features of RHD of the AV or MV; and
2. MR < 1 cm; and
3. No AR; and
4. No other acquired or congenital valvular heart disease

Box 9. Echocardiographic case and control criteria for RhFFUS study. *Criteria for morphologic changes of MV and AV, and pathologic AR and MR as described by WHF criteria.[55]

It should be noted that the collection of echocardiograms during the gECHO study was completed before publication of the WHF criteria.[55] However, reading and reporting of these echocardiograms continued subsequent to the WHF criteria. The classification of participants in RhFFUS is based on the information contained in, and reporting of, gECHO echocardiograms at the time of the gECHO study. Even though gECHO baseline

echocardiograms will be reread during the RhFFUS study this will not be for the purposes of retrospectively reclassifying participants as cases or controls.

The matching process will involve stratifying all eligible gECHO participants by community, gender and age. For each identified case, the closest age-matched control from the same community and of the same gender will then be selected and assigned to the case. This process will be repeated so that two matched controls are assigned to each case.

Sample Size

Sample size estimations are based on projected rates of ARF based on the annual incidence of ARF in people with known RHD (2.5%) and the background annual incidence of ARF in 5 to 14 year old Aboriginal and Torres Strait Islander children in the Northern Territory (0.27%) (personal communication, Northern Territory ARF/RHD register) over a five year period. Based on an assumed alpha of 0.05 and beta of 0.1 (power of 90%) detecting a difference of one or more episodes of ARF in 12.5% of cases and 1.35% of controls over five years of follow-up, and using a ratio of cases to controls of 1:2, would require a sample size of 83 cases and 165 controls or a total number of 248 reviews. While it is apparent that carditis in the acute setting of ARF may resolve in up to half of cases[270] there are no clear data to inform the powering of progression of non-specific echocardiographic changes. Nonetheless, if it is assumed at most 5% of controls will develop morphologic and function valvular changes on echocardiography compared with 20% of those with pre-existing non-specific changes then it would require the follow-up of 77 cases and 154 controls to detect such a difference with the tolerances above, a number of enrolments well within the projected subject numbers.

Informed Consent

Parents, carers or guardians of all identified subjects will be informed regarding the study using local Indigenous research staff and local language translators as required. Written informed consent will be obtained. In addition written assent will be obtained from subjects who are 14 years and older. Subjects who are 16 years and older, who fulfill the criteria for mature minors[271] and who are not living with the people who would normally be identified as parents, carers or guardians will be able to provide their own consent.

Enrolling Participants

Potential participants will be approached with the assistance of local research assistants and the local primary health care centre. In addition, RhFFUS staff will visit the homes of potential participants in the company of a local health care staff member or a community-based Indigenous Australian research assistant in order to contact and enroll potential participants. If potential cases have moved to another location since the gECHO project, attempts will be made to ascertain their most recent address and, if feasible, to contact and follow them up there.

Data Collection and Outcomes

Outcome data for cases and controls will include ARF incidence and the development or progression of mitral and/or aortic valve abnormalities.

(a) ARF Incidence

The occurrence and timing of episodes of ARF will be assessed retrospectively for 5 years from the time of the RhFFUS screening echocardiography. Anecdotal evidence suggests that in the setting where RhFFUS is being conducted, episodes of ARF may be missed or not recorded owing to insufficient diagnostic information being collected at time of presentation to primary health care sites. Thus, in order to increase the power of RhFFUS to detect differences between case and controls, four categories of ARF will be used as outcome variables (see Table 2).

In order to gain a comprehensive overview of ARF episodes a number of sources of data will be examined. These comprise: regional surveillance and notification databases; carer/subject interviews; primary healthcare history reviews; and hospital separation diagnoses.

At time of enrolment an interview of the participants and/or their carers/family will be undertaken. Data collected will comprise: demographics, knowledge of ARF or RHD diagnoses, episodes suggestive of ARF (arthritis/arthralgia), whether the participant is receiving secondary prophylaxis, household crowding and socioeconomic data.

A primary health care and hospital history review will also be undertaken in a representative subset of participants. Data collected during this review will comprise information about potential episodes of ARF, arthritis/arthralgia, chorea and diagnoses of RHD. Clinical data regarding each potential episode of ARF, based on the Australian modified Jones criteria[2], will be collected. These data will be used to validate the accuracy of existing register-based ARF notifications.

Diagnosis	**Criteria**
Definite ARF	Australian modified Jones criteria for high risk populations (includes echocardiographic evidence of carditis and monoarthritis as major criteria)[2]
Probable ARF	• Arthritis/arthralgia; and • One or more of: temperature $\geq$ 38^{o}C, C-reactive protein $\geq$ 30 mg/L, erythrocyte sedimentation rate $\geq$ 30 mm/h, prolonged P-R interval on ECG*; and • GAS infection**; and • No other diagnosis[47]
Possible ARF	• Arthritis/arthralgia; and • GAS infection*; and • No other diagnosis
Potential ARF	• Arthritis/arthralgia; and • No other diagnosis

Table 2. Criteria for ARF – definite, probable, possible, potential. *Upper limits of normal of P-R interval are: 3-12 years, 0.16s; 12-16 years, 0.18s; 17+ years, 0.20s.[2] **GAS infection is defined as throat swab positive for GAS on culture or serology consistent with recent GAS infection including elevated antistreptolysin O titre and antideoxyribonuclease B antibodies as outlined in the Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition).[2]

(b) Progression of valvular abnormalities

Progression of valvular abnormalities will be assessed prospectively using transthoracic echocardiography and standardised operating and reporting procedures already developed and refined for the gECHO study. Briefly the echocardiogram will be undertaken using a Vivid i/e portable cardiac ultrasound machine (GE Healthcare) with a standardised machine setup as outlined in Box 10.

- Highest frequency transducer that gives adequate penetration,
- Colour gain set by gradually increasing until static background noise barely appears,
- No electrocardiography (ECG) for screening studies,
- ECG for comprehensive studies,
- At least 2 second video acquisition of each view with longer periods for detailed sweeping of potentially abnormal valves

Box 10. Standardised echocardiogram machine setup.

Studies will initially involve a screening echocardiogram which will proceed to a comprehensive study if there is one or more of: mitral regurgitation $\geq$ 10mm; any aortic regurgitation; any other abnormal mitral or aortic valve findings; or any other pathology present (e.g. abnormal morphology, thickening, multiple regurgitant jets etc.). Screening echocardiograms will incorporate the views and assessments outlined in Table 3.

Comprehensive echocardiograms, if required, will incorporate more detailed information based on the abnormalities detected on the screening study and will be undertaken using the views and assessments outlined in Table 4. All echocardiograms will be carried out by trained, accredited and practicing echocardiographers.

Echocardiographic view	Assessment
Parasternal long axis (PLAX) 2 dimensional (2D)	Mitral and aortic valves to assess the morphology of these valves Anterior mitral valve leaflet (AMVL) and posterior mitral valve leaflet (PMVL) thickness AMVL – ensure view is on axis and measure the thickest point of AMVL in late diastole when AMVL parallel with the IVS PMVL – ensure view is on axis and measure the thickest point of the PMVL mid diastole, exclude chordae from the measurements.
PLAX colour Doppler	Colour Doppler to view the mitral and aortic valves for evidence of regurgitation, include lateral and inferior sweeps
Parasternal short axis (PSAX) 2D	View of the mitral and aortic valves to assess morphology
PSAX colour Doppler	Colour Doppler to view the mitral and aortic valves for evidence of regurgitation, include lateral and inferior sweeps
Apical 2D	Apical 4/5 chamber view of mitral and aortic valves for morphology
Apical colour Doppler	Colour Doppler to view the mitral and aortic valves for evidence of regurgitation

Table 3. View and assessments required for RhFFUS screening echocardiogram.

Potential abnormality	View and Assessment
All comprehensive studies	PLAX 2D assessment of: - left ventricular chamber dimensions at the level of the mitral valve leaflet tips (interventricular septum thickness, left ventricular end-diastolic & systolic dimensions, left ventricular posterior wall thickness) - aorta and left atrium diameter at the aortic cusp level
Dependent on the presence of potential mitral or aortic valve disease	standardised additional studies including routine acquisition of colour, continuous and pulse wave Doppler measurements
Any other pathology	as per routine clinical protocols

Table 4. Requirement, view and assessments required for RhFFUS comprehensive echocardiogram.

Determination of progression of a valve lesion will be based on WHF criteria[55] and will be defined as one or more of:

1. development of any morphologic or function abnormality in a control subject
    - that is, development of pathologic AR or MR, or development of at least two morphologic features of RHD of the MV[55];
2. development of a new functional or morphologic abnormality in a case
    - that is, if case was previously classified as Borderline RHD because of the presence of pathologic regurgitation of one of the left-sided cardiac valves then development of pathologic regurgitation in the other left-sided cardiac valve; or
    - if case was previously classified as Borderline RHD due to the presence of 2 morphologic features of RHD of the MV then the development of pathologic MR or AR[55];
3. progression of severity of a functional valve lesion (regurgitation/stenosis) based on standard severity criteria of the American Society of Echocardiography Guidelines[272-274] (i.e. mild to moderate, or moderate to severe) or development of new mitral stenosis.

Progression of valve lesions will be determined by specialist cardiologist readers who will be provided with the initial gECHO screening and subsequent RhFFUS screening echocardiogram for each participant. Studies will be read and assessed individually and then in pairs. The readers will be blinded to the initial gECHO assessment and temporal order of the two echocardiograms. Reporting will use a standardised reporting template.

Blinding

In order to limit any potential for information bias in this study only the study coordinator at each site will know whether a participant is a case or control. Thus the sonographer carrying out the echocardiogram, the researchers involved in reviewing each participant's medical history and the cardiologist assessing the echocardiogram will be blinded to the participant's status as case or control.

Data Management

All data collected on paper-based forms (participant/carer/family interviews and medical history reviews) will be stored under numerical code in a locked filing cabinet in the RhFFUS study coordinator's office. Only research personnel will have access to these records.

Reports from the echocardiogram readers will be received in electronic format and will be saved in a password-protected folder on the study coordinator's computer.

Research staff will transfer the information from both paper forms and electronic echocardiogram reports to an Access database (Microsoft Office Access 2007, Microsoft Corporation, Redmond, Washington, USA) that will be password-protected. De-identified data will be analysed using STATA version 12 (StataCorp, College Station, Tex, USA).

Any information collected will be strictly confidential and no identifying information will be published or disseminated upon completion of the study. Data will be stored for at least 5 years as per Australian National Health and Medical Research Council guidelines.[275]

Statistical Analysis

The primary analysis will be based on univariate analysis comparing cases and matched controls. This will include a χ^2 analysis comparing the number of children with an episode of ARF (stratified by definite, probable, possible and potential (see Table 2)) during the period of follow-up and those who have demonstrated progression of a valve lesion (see above). More detailed analysis will include survival analysis comparing the timing of first episode of ARF to address potential loss of follow-up and Poisson regression for the rate of ARF to address the potential occurrence of more than one episode of ARF occurring in any one individual and a variable period of follow-up. Multivariate techniques (logistic regression and Cox proportional hazard) will be utilised if the matching of cases and controls is not successful and to address subsequently identified covariates including the possibility of concomitant prophylactic antibiotics.

Ethics

RhFFUS has been approved by human ethics research committees in each of the jurisdictions where it will be undertaken. Approval has been granted by the following committees: Darling Downs – West Moreton (Toowoomba and Darling Downs) Health Service District Human Research Ethics Committee (Queensland)(HREC/11/QTDD/10), James Cook University Human Research Ethics Committee (Queensland)(H4136), Central Australian Human Research Ethics Committee (Northern Territory)(HREC-12-35), the Human Research Ethics Committee of Northern Territory department of Health and Menzies School of Health Research (Northern Territory)(HREC-2011-1564), the WA Country Health Service Research Ethics Committee (Western Australia)(2011:31), the Western Australian Aboriginal Health Ethics Committee (Western Australia)(371-10/11), the University of Western Australia Human Research Ethics Committee (Western Australia)(RA/4/1/5313).

Funding

The RhFFUS project is funded by the Australian Government through a grant from the National Health and Medical Research Council (NHMRC Project Grant Application 1005951).

Discussion

The results of RhFFUS will be integral in informing the future response to ARF and RHD in Australia. In particular, RhFFUS will clarify the criteria to be used in determining whether secondary antibiotic prophylaxis should be prescribed in individuals with no clear history of ARF but minor potential abnormalities detected on echocardiography suggestive, but not diagnostic, of RHD. RhFFUS will also help inform the ongoing debate regarding the potential role of screening echocardiography in this setting. In particular, it will allow clinicians to understand the significance of subtle changes on echocardiography and to determine whether these represent the earliest changes of RHD or are merely variations of normal heart anatomy.

At present, minor non-diagnostic changes of heart morphology are the commonest silent findings when echocardiography is undertaken in otherwise well children. Whether such changes indicate a large burden of minor and undiagnosed RHD that would benefit from secondary prophylaxis or incidental normal variants will be essential in providing an evidence-based rationale for echocardiographic screening in populations at elevated risk of RHD.

Finally this project will continue to support the development of research capacity in northern and remote Australia and of Aboriginal and Torres Strait Islander people. It will enable us to ask and answer health-related questions which are relevant and a priority in informing the response to addressing the disparity in disease burden and health outcome between Indigenous and non-Indigenous Australians.

3.2.2 Are minor echocardiographic changes associated with an increased risk of acute rheumatic fever or progression to rheumatic heart disease?

Abstract

Background: Criteria for echocardiographic diagnosis of rheumatic heart disease (RHD) have been developed but the significance of minor heart valve abnormalities, including Borderline RHD, in predicting the risk of acute rheumatic fever (ARF) or RHD remains unclear.

Methods and Results: A prospective cohort study of Aboriginal and Torres Strait Islander children aged 8 to18 years in 32 remote Australian communities. Cases were children with Borderline RHD or other minor non-specific valvular abnormalities (NSVAs) detected on prior screening echocardiography. Controls were children with a prior normal screening echocardiogram. Participants underwent a follow-up echocardiogram to assess for progression of valvular changes and development of Definite RHD. Interval diagnoses of ARF were also ascertained.

442 individuals were enrolled. Borderline RHD Cases were at significantly greater risk of ARF (incidence rate ratio 8.8, 95% CI 1.4 – 53.8) and any echocardiographic progression of valve lesions (relative risk 8.2, 95% CI 2.4 – 27.5) than their matched Controls. Borderline RHD Cases were at increased risk of progression to Definite RHD (1 in 6 progressed) as were, to a lesser extent, NSVA Cases (1 in 10 progressed).

Conclusions: Children with Borderline RHD had an increased risk of ARF, progression of valvular lesions, and development of Definite RHD while children with NSVAs were at a lesser increased risk of progression to Definite RHD. These findings provide support for considering secondary antibiotic prophylaxis or ongoing surveillance echocardiography in high-risk children with Borderline RHD or NSVAs. Further work is needed to identify features of children with Borderline RHD or NSVAs who are at greatest risk.

Background

Prior to the introduction of echocardiography, diagnosis of RHD was primarily based on findings detected on auscultation. However, it has been shown that auscultation alone is neither sensitive[52] nor specific.[53, 276] The increasing availability of more portable, affordable and high-quality echocardiography to assess heart valve morphology and function has resulted in significant debate regarding the diagnosis of RHD on echocardiography alone. This debate has intensified owing to the publication of a number of RHD echocardiographic screening studies that have utilised differing diagnostic criteria.[52, 53, 74, 75] In an attempt to address this issue, in 2012 the World Heart Federation (WHF) published criteria for the diagnosis of RHD based on both morphological and functional findings on echocardiography in the absence of a previous diagnosis of ARF.[55] The WHF criteria include a category of "Borderline" RHD, recognising potential minor heart valve abnormalities on echocardiography that are of uncertain significance, but which may be early signs of developing RHD.

The importance of such minor heart valve abnormalities in a setting of high RHD risk was highlighted by a recent Australian RHD prevalence and echocardiography validation study. The gECHO (getting Every Child's Heart Okay) Study undertook echocardiographic screening of 3946 high risk (Aboriginal Australian and/or Torres Strait Islander) and 1053 low risk (non-Indigenous Australian) children across northern and central Australia.[233] Within the high-risk Aboriginal and/or Torres Strait Islander children, 34 (0.9%) met the WHF criteria for Definite RHD and 66 (1.7%) met criteria for Borderline RHD. In comparison, none of the low risk children met criteria for Definite RHD while 5 (0.5%) met criteria for Borderline RHD. Furthermore, in high risk children some degree of mitral regurgitation was detected in 22.1%, while 4.4% had aortic regurgitation. Morphological abnormalities of the mitral valve were reported in 2.9% of these children and abnormalities of the aortic valve in 0.9%.

The clinical significance of a diagnosis of Borderline RHD and/or other non-diagnostic valvular abnormalities in individuals without a known past history of ARF remains unclear. If these abnormalities represent the earliest changes of RHD then offering such children regular secondary prophylaxis may prevent disease progression. If, in contrast, they are

simply a variant of normal echocardiographic findings then a decision not to treat would avoid the pain, inconvenience and cost to the patient and health system of 10 or more years of 4-weekly intramuscular penicillin injections. The issue of the significance of Borderline RHD and non-diagnostic valvular abnormalities in high-risk ARF/RHD settings has thus been identified as a priority for future investigation.[69, 269]

The Rheumatic Fever Follow-Up Study (RhFFUS) aimed to clarify the significance of minor echocardiographic changes in children and adolescents at high risk of ARF/RHD. More specifically, it aimed to determine if Aboriginal and Torres Strait Islander children and adolescents aged 8 to18 years with a previous potentially abnormal but non-diagnostic screening echocardiogram were at higher risk of ARF and/or progressive heart damage consistent with the development of Definite RHD than those with a prior normal echocardiogram.

Methods

The methodology of the RhFFUS study has been described elsewhere.[78] Briefly, RhFFUS was a prospective cohort study of Aboriginal and/or Torres Strait Islander children and adolescents aged 8 to18 years residing in 32 remote Australian communities across central and northern Australia. Participants constituted a subset of children who had an echocardiogram as part of the earlier gECHO echocardiographic screening study between September 2008 and November 2011.[233] They were enrolled in RhFFUS between 2.5 and 5 years after their initial gECHO echocardiogram.

Cases were those children with non-specific changes of the mitral and/or aortic valves detected on their gECHO screening echocardiogram. This included Cases with Borderline RHD on WHF criteria and additional Cases with minor non-specific valvular abnormalities (NSVAs) not meeting the Borderline RHD definition. It was decided to make the criteria for Cases more sensitive than WHF criteria for Borderline RHD as there remains uncertainty regarding the interpretation and significance of minor echocardiographic abnormalities (see Box 11). Children with Definite RHD or congenital valvular abnormalities detected on their gECHO echocardiogram were excluded from this study.

Controls (two per Case) were selected who were age, gender, community and ethnicity-matched to Cases and had a prior normal gECHO screening echocardiogram.

ARF Outcome

For each participant, the occurrence and timing of episodes of ARF were assessed between the initial gECHO screening study and the subsequent RhFFUS study. Any participants found to have had a diagnosed episode of ARF before their gECHO echocardiogram were excluded.

Data relating to ARF were sourced from jurisdictional ARF/RHD notification databases in Western Australia, Queensland and the Northern Territory. In each, notification of an episode of ARF is a legislated requirement. In Western Australia the notification database was not established until February 2010 and hence prior to this date other local ARF registration sources were also used. Note that in the initial study protocol we envisaged collecting data about episodes of ARF from other sources including from carer/subject interviews and medical history reviews. However, during data collection it became apparent that carer/subject interviews were not furnishing objective data about episodes of ARF. Furthermore, reviews of medical histories provided very little information relating to ARF episodes. Many medical records were very difficult to navigate, devoid of relevant data, and only providing recent rather than more long-term information (particularly where paper records had been incompletely uploaded to electronic health management systems or where electronic systems had been updated or replaced by different software). For these reasons, only ARF data obtained from notification databases was utilised.

As use of secondary antibiotic prophylaxis in the form of long-acting benzathine penicillin was a potential confounder of ARF risk, data relating to dates of injections for participants receiving such prophylaxis were obtained from regional ARF/RHD databases. Based on timing of these injections, and on the assumption that a single dose provides 28 days of protection from Group A streptococcal infection and possible ARF, we calculated the “days at risk of ARF” for each participant during the period between their initial gECHO and subsequent RhFFUS echocardiograms.

CASES:

Echocardiogram from the earlier gECHO study that did not fulfill WHF criteria for Definite RHD[55] but which met one of the following:

Borderline RHD under WHF criteria[55]

A. At least two morphological features of RHD of the mitral valve (MV)* without pathological mitral regurgitation* (MR) or mitral stenosis; or
B. Pathological MR with no or one morphological feature of RHD of the MV; or
C. Pathological aortic regurgitation* (AR) with no or one morphological feature of RHD of the AV*; or

Non-specific valvular abnormalities (NSVAs)

- One morphologic feature of RHD of the MV and/or one or more feature of RHD of the AV without pathological MR or AR; or
- Multiple MR jets and/or multiple AR jets (in at least two views) that do not fulfil WHF criteria for pathological MR or AR; or
- MR $\geq$ 2cm or AR $\geq$ 1cm (that does not fulfil WHF criteria for pathological regurgitation) with no morphological features of RHD of the MV or AV.

CONTROLS:

Normal screening echocardiogram from gECHO defined as:

- No morphological features of RHD of the AV or MV; and
- No MR $\geq$ 1cm; and
- No AR; and
- No other acquired or congenital valvular heart disease

Box 12. Criteria used to assess status of participants recruited to RhFFUS and WHF criteria for the diagnosis of Borderline RHD.[55] *Criteria for morphologic changes of MV and AV, and pathologic AR and MR as described by WHF criteria (see Box 2).[55]

Progression of Valve Lesions Outcome

Progression of valvular abnormalities was assessed prospectively using transthoracic echocardiography and standardised operating and reporting procedures. Briefly, participants had a follow-up echocardiogram between 2.5 and 5 years after their baseline echocardiogram. A Vivid *i/e* portable cardiac ultrasound machine (GE Healthcare, Freiburg, Germany) was used with a standardised machine setup.[78, 233] Studies involved an initial screening echocardiogram that incorporated pre-defined views and assessments. A more detailed comprehensive echocardiogram was undertaken if the screening study revealed a potential abnormality. All echocardiograms were performed by trained, accredited and practicing echocardiographers who were blinded to participant status as Case or Control.

Progression of valve lesions was determined by a single specialist paediatric cardiologist who reviewed the baseline gECHO and subsequent RhFFUS echocardiograms for each participant. Studies were read and assessed individually and then in pairs. The reader was blinded to the initial report for the baseline echocardiogram and to the status of participants as Cases or Controls. Reporting was based on a standardised reporting template. The assessment of differences between the two echocardiograms took into account limitations in the discriminatory ability/resolution of echocardiography to detect such potential differences.

"Progression of any valve lesion", was defined as the echocardiographically significant:

- development of any significant morphologic or functional abnormality[55] in a Control;
    - that is, development of pathologic AR or MR, or development of at least two morphologic features of RHD of the MV;
- development of a new functional or morphologic abnormality[55] in a Case;
    - that is, if case was previously classified as Borderline RHD because of the presence of pathologic regurgitation of one of the left-sided cardiac valves then development of pathologic regurgitation in the other left-sided cardiac valve; or

    - if case was previously classified as Borderline RHD due to the presence of 2 morphologic features of RHD of the MV then the development of pathologic MR or AR;

- progression of severity of a functional valve lesion (regurgitation/stenosis) based on standard severity criteria[272-274] (i.e. mild to moderate, or moderate to severe) or development of new mitral stenosis.

An additional outcome measure was a diagnosis of Definite RHD.[55]

Inter-observer variability could be assessed as each participant's baseline echocardiogram was read twice (once during the initial gECHO study and subsequently during the RhFFUS study). To control for any bias introduced by inter-observer variability, progression of valve lesions was assessed in relation to the initial classification of participants as Cases and Controls based on the initial gECHO evaluation and then based on the subsequent RhFFUS study assessment.

Statistical Analysis

Statistical analysis was performed using Stata™ statistical package version 12.1 (StataCorp, Texas, USA) and SPSS version 20 (IBM Corp., Armonk, NY). Efficacy of matching of Cases and Controls was determined using χ^2 analysis for categorical measures and Mann-Whitney U tests for non-parametric numerical measures. Analysis of outcome measures was based on bivariate analysis comparing Cases and Controls, and subgroup analysis of Borderline Cases with their Matched Controls and NSVA Cases and their Matched Controls. A p-value less than 0.05 was taken to indicate statistical significance and all tests were two-sided.

ARF incidence rates were calculated both for "total time" between baseline echocardiograms and follow-up RhFFUS echocardiograms and for the "days-at-risk" between these dates taking into account the protection against ARF afforded by use of secondary antibiotic prophylaxis. Incidence rates and incidence rate ratios (IRRs) were calculated for Cases and Controls. An IRR with a 95% confidence interval (CI) not including one was taken to be statistically significant.

Risk of progression of valve lesions and risk of progression leading to Definite RHD was calculated for all groups. When comparing matched groups, absolute difference in risk between groups and relative risk (RR) between groups was determined with 95% CIs. Where the 95% CI of a RR did not include one statistical significance was inferred.

Logistic regression models were developed to identify independent factors associated with progression of valve lesions and progression to Definite RHD. These were developed using all factors associated with a particular outcome using bivariate analysis with a p-value < 0.1. These comprised: age, gender, days between echocardiograms, being in receipt of secondary antibiotic prophylaxis, and status as Borderline RHD of the mitral valve (Borderline RHD category A or B[55]) or Borderline RHD of the aortic valve (Borderline RHD category C[55]) or NSVA.

Inter-rater reliability was assessed using the linearly weighted Kappa statistic to determine concordance between initial reporting of baseline gECHO echocardiograms and subsequent rereads of these baseline echocardiograms during RhFFUS analysis.

Ethics

RhFFUS was approved by human ethics research committees in each of the jurisdictions where it was undertaken[78] and written informed consent was obtained from all participants.

Results

The study enrolled 447 individuals. Five participants (2 Cases and 3 Controls) were subsequently excluded as examination of ARF notification registers revealed that they had had a notified episode of ARF prior to their initial gECHO screening study.

Of the 171 potential Cases identified from the gECHO study, 119 (70%) were successfully enrolled. There were no significant differences in the age, gender or ethnicity of enrolled and non-enrolled Cases. For non-enrolled Cases median age at time of gECHO echocardiogram was 10.4 yrs (95% CI 8.5 – 12.3) [compared to 10.0 yrs (95% CI 8.1 – 11.9) for enrolled Cases], 50.0% (95% CI 37.1 – 62.9) were female, 88.9% (95% CI 77.8 – 94.8) were Aboriginal, 5.6% (95% CI 1.9 – 15.1) were Torres Strait Islander, and 5.6% (95% CI 1.9 – 15.1) were both Aboriginal and Torres Strait Islander.

While the RhFFUS research methodology prescribed two Matched Controls per Case, there was an excess of Controls enrolled. This was due to the study team being unable to locate and enroll some Cases after their matched Controls had already been enrolled. These "unmatched" Controls were included in the analysis in order to increase the power of the study and because their inclusion did not lead to any significant differences in the demographics of the Case and Control groups (see Table 5).

	Cases	**Controls**	**P value**
Total Number	117	325	n/a
Age (median years, IQR*)	13.7 (11.9 – 15.7)	13.7 (11.8 – 15.5)	0.733
Gender (% female, 95% CI)	59.0 (49.5 – 67.0)	57.2 (51.6 – 62.7)	0.787
Ethnicity (%, 95% CI)			0.965
Aboriginal	83.8 (75.8 – 90.0)	84.3 (79.9 – 88.1)	
Torres Strait Islander	6.8 (3.0 – 13.0)	7.1 (4.5 – 10.4)	
Aboriginal and Torres Strait Islander	9.4 (4.8 – 16.2)	8.6 (5.8 – 12.2)	
Prescribed secondary prophylaxis (%, 95% CI)	18.8 (12.2 – 27.1)	2.5 (1.1 – 4.8)	<0.001
Time between gECHO echocardiogram and RhFFUS enrolment (median days, IQR)	1346 (1171 – 1478)	1310 (1170 – 1440)	0.455

Table 5 Demographic data, use of secondary prophylaxis, and time to follow-up for participants. *IQR = Interquartile range.

Based on the original reporting of baseline gECHO echocardiograms, 55 (47%) Cases met WHF criteria for Borderline RHD[55] and the remaining 62 (53%) had NSVAs. Of the 55 Borderline RHD Cases, 13 (24%) were subcategory A (morphological features of RHD of

the MV), 21 (38%) were subcategory B (pathological MR) and 21 (38%) were subcategory C (pathological AR).[55] The most common NSVA was isolated mitral or aortic regurgitation without morphologic changes of RHD (30/62, 46%). The remaining NSVAs (32, 54%) were morphologic features of RHD alone or multiple non-significant regurgitant jets. A comparison of Borderline and NSVA Cases did not show any significant differences in the factors listed in Table 5 apart from prescription of secondary antibiotic prophylaxis; Borderline RHD Cases were more likely to be prescribed regular antibiotic prophylaxis compared with NSVA Cases (34.6% (95% CI, 23.4-47.8%) vs. 4.8% (95% CI, 1.7-13.3%), $p<0.001$).

ARF Outcome

There were 9 reported episodes of ARF in the cohort during the observation period: 4 in Cases and 5 in Controls. All met the Australian criteria for Definite ARF.[2] The IR of ARF was higher in Cases (4/117, 9.2 episodes of ARF/1000 person-years (95% CI, 2.5 – 23.5)) than Controls (5/325, 4.2/1000 person-years (95%CI, 1.4 – 9.7)), although this difference was not statistically significant (IRR 2.2 (95% CI, 0.6 – 7.9)).

Given that a significantly greater proportion of Cases were receiving secondary antibiotic prophylaxis during the study period (see Table 5) and this may have affected their risk of ARF, we reanalyzed ARF outcome data in the context of "days at risk" of GAS infection and ARF. The IR of ARF (adjusting for days at risk) was unchanged in Controls but increased in Cases to 9.9 episodes of ARF/1000 person-years-at-risk (95% CI, 2.7 – 25.4). This corresponded to an IRR of 2.3 (95% CI, 0.7 – 8.4) and again was not statistically significant.

All four Cases with a notified episode of ARF had Borderline RHD. The incidence rate of ARF in Borderline RHD Cases was 19.6/1000 person-years (95% CI, 5.3 – 50.3) and rose to 22.9/1000 person-years-at-risk (95% CI, 6.3 – 58.7) when controlling for secondary antibiotic prophylaxis use. In comparison with their matched Controls, Borderline RHD Cases were at a statistically significant increased risk of ARF (unadjusted IRR = 7.5 (95% CI, 1.2 – 48.3), IRR adjusted for use of secondary antibiotic prophylaxis = 8.8 (95% CI, 1.4 – 53.8)).

Progression of Valvular Lesions Outcome

Forty-two (9.5%, 95% CI, 7.1 – 12.6%) participants exhibited echocardiographically significant progression of valvular lesions on the later RhFFUS echocardiogram compared to their earlier gECHO echocardiogram. The majority of participants with progression (25, 60%) exhibited isolated increases in severity of valvular regurgitation, while 13 (31%) exhibited concomitant worsening of valvular regurgitation and morphology, and 4 (9%) exhibited isolated changes in valve morphology.

An episode of ARF was more likely in those with echocardiographic progression (RR 5.2, 95% CI, 2.3 – 11.2), with four of the 42 participants with echocardiographic progression (9.5%, 95% CI, 2.7 – 22) having an episode of ARF compared with five episodes in the remaining 400 participants (1.3%, 95% CI, 0.4 – 2.9) who did not exhibit progression (p=0.006).

Cases were at significantly greater risk of echocardiographic progression than Controls and this was predominantly due to an increased risk in the subgroup of Borderline RHD Cases (see Table 6). Of the Borderline RHD Cases, 4/13 (31%, 95% CI, 9 – 61) of Subcategory A, 6/21 (29%, 95% CI, 11 – 52) of Subcategory B, and 3/21 (14%, 95% CI, 3 – 36) of Subcategory C progressed. NSVA Cases were not at increased risk of progression (see Table 6).

	All	All Cases	All Controls	Borderline RHD Cases	Matched Controls	NSVA Cases	Matched Controls
Number	442	117	325	55	104	62	122
Progression of valve abnormalities (n, %, 95% CI)	42 9.5% (7.1 – 12.6%)	23 19.7% (13.5 – 27.8%)	19 5.9% (3.8 – 9.0%)	13 23.6% (14.4 – 36.4%)	3 2.9% (1.0 – 8.1%)	10 16.1% (9.0 – 27.2%)	13 10.7% (6.3 – 17.4%)
Absolute risk difference (%, 95% CI)	n/a	13.8% (6.9 – 22.2%)		20.8% (10.1 – 33.6%)		5.5% (4.3 – 17.4%)	
Relative risk (95% CI)	n/a	3.36 (1.90 – 5.94%)		8.19 (2.43 – 27.53%)		1.51 (0.70 – 3.25%)	

Table 6 Progression of valvular lesions on follow-up echocardiography.

Seventeen (40.5%) of the 42 participants who had progression of valvular lesions were diagnosed with Definite RHD.[55] The majority of these diagnoses (13/17, 76%) had isolated MV disease (Definite RHD A, pathological MR and at least two morphological features of RHD of the MV[55]). Two (12%) involved MV and AV disease (Definite RHD D[55]) and two (12%) involved isolated AV disease (Definite RHD C[55]).

An episode of ARF was more likely in those who developed Definite RHD (RR 10.3, 95% CI, 3.6 – 29.7), with three of the 17 participants with progression to Definite RHD (17.7%, 95% CI, 3.6 – 29.7) having an episode of ARF compared with six episodes in the remaining 425 participants (1.4%, 95% CI, 0.7 – 3.0) who did not exhibit progression (p=0.004).

Of the 17 individuals who progressed to Definite RHD, 9 (53%) had been initially classified as Borderline RHD Cases, 6 (35%) as NSVA Cases and 2 (12%) as Controls based on their baseline gECHO echocardiogram reports. Of the Borderline RHD Cases, 2/13 (15%, 95% CI, 4 – 42) of Subcategory A, 5/21(24%, 95% CI, 11 – 45) of Subcategory B, and 2/21 (10%, 95% CI, 3 – 29) of Subcategory C progressed to Definite RHD.

Cases were at significantly greater risk of progression to Definite RHD than Controls as was the subgroup of NSVA Cases and their Matched Controls (see Table 7). Borderline RHD Cases had an increased risk of progression compared to their Matched Controls ($p<0.001$, Fisher's exact test) but a relative risk could not be determined as none of their Matched Controls progressed to Definite RHD.

	All	**All Cases**	**All Controls**	**Borderline RHD Cases**	**Matched Controls**	**NSVA Cases**	**Matched Controls**
Number	442	117	325	55	104	62	122
Progression to Definite RHD (n, %, 95% CI)	17 3.9% (2.4 – 6.1)	15 12.8% (7.9 – 20.1)	2 0.6% (0.2 – 2.2)	9 16.4% (8.9 – 28.3)	0 0%	6 9.7% (4.5 – 19.6)	2 1.6% (0.5 – 5.8)
Absolute risk difference (%, 95% CI)	n/a	12.2% (7.1 – 19.5)		16.4% (8.1 – 28.3)		8.1% (1.4 – 18.0)	
Relative risk (95% CI)	n/a	20.8 (4.8 – 89.7)		Could not be determined.		5.9 (1.2 – 28.4)	

Table 7 Progression to Definite RHD.[55]

Logistic regression modelling revealed three common factors that were independently associated with progression of valve lesions and development of Definite RHD (see Table 8). Both functional and morphologic changes of the mitral valve were independently associated with progression and Definite RHD (data not shown) and were therefore combined. In addition, Borderline RHD of the aortic valve was found to confer a significant increase in the chance of development of Definite RHD but this was less than that seen with Borderline RHD of the mitral valve.

	Progression of Valvular Lesions	**Progression to Definite RHD**
Borderline RHD of the Mitral Valve (OR*, 95% CI)	4.6 (1.8 – 12.1)	30.0 (5.4 – 167.3)
NSVA (OR, 95% CI)	3.0 (1.3 – 6.8)	16.0 (3.1 – 81.8)
In receipt of secondary antibiotic prophylaxis (OR, 95% CI)	4.2 (1.5 – 11.7)	4.0 (1.1 – 15.3)
Nagelkerke R^2	14.7%	29.8%

Table 8 Factors that were independently associated with progression of valvular lesions and progression to Definite RHD in logistic regression models. Note: "Borderline RHD of the Mitral Valve" encompasses Borderline RHD category A and B under WHF criteria.[55] *OR = odds ratio.

We stratified Cases into two subgroups based on the presence or absence of MR and compared these two groups in relation to progression outcome data. Cases with MR were not at a significantly increased risk of any progression of valvular lesions (RR 1.2, 95% CI, 0.6 - 2.5) or progression to definite RHD (RR 1.5, 95% CI, 0.5 – 4.1) compared to those Cases without MR.

Inter-Observer Variability

Data outlining the different classifications assigned to each participant based on the original gECHO report of participants' baseline echocardiogram and subsequent re-report of that same echocardiogram as part of the RhFFUS study is presented in Table 9.

		Classification based on original reading of baseline echocardiogram			
		Normal	NSVA	Borderline RHD	Total
Classification based upon subsequent reread of baseline echocardiogram	Normal	279 (85.8%)	18	2	299
	NSVA	41	33 (53.2%)	7	81
	Borderline RHD	4	8	39 (70.9%)	51
	Definite RHD	1	3	7	11
	Total	325	62	55	442

Table 9 Inter-Observer variability in reading of gECHO baseline echocardiograms.

The inter-rater reliability for reading of the baseline echocardiogram using linear weighted Kappa was 0.656 ($p<0.001$, 95% CI, 0.592 – 0.721) and consistent with substantial agreement.[277]

In order to control for potential bias due to discordant reporting of baseline echocardiograms (see Table 9), Cases or Controls were reclassified based on the subsequent rereading of baseline echocardiograms. Any participants reread as Definite RHD on their baseline echocardiogram (and their Matched Controls) were excluded from this analysis. Following this reclassification, Cases remained at a higher, but non-significant, risk of ARF compared with controls (IRR 3.9, 95% CI, 0.8 – 25.3). Furthermore, Cases remained at significantly greater risk of any progression of valvular

lesions (RR 3.17, 95% CI, 1.69 – 5.94) and progression to Definite RHD (RR 24.9, 95% CI, 3.2 – 190.7) than Controls.

Discussion

We have shown, for the first time, that a diagnosis of Borderline RHD identifies a child who is at increased risk of both an ARF recurrence and progression of cardiac valvular lesions, including the potential to progress to a diagnosis of Definite RHD by WHF criteria.[55] It is therefore clear that at least some children with Borderline RHD have true RHD and require secondary antibiotic prophylaxis. We have also provided some insights into the features that place a child with Borderline RHD at particularly high risk of progression of valve disease, namely an initial diagnosis based on abnormalities of the mitral, rather than aortic, valve.

As in most high-income countries, ARF is rarely diagnosed in Australia. Nonetheless, disadvantaged groups within Australia, specifically Aboriginal and Torres Strait Islander populations, continue to experience some of the highest reported incidence rates in the world.[1] Our reported incidence of ARF in Controls (4.2/1000 person-years) was comparable to existing data in Aboriginal Australians in this setting (2.5 – 3.5/1000 person-years).[1, 42] Against this already high background risk of ARF, the children with Borderline RHD had a significantly increased risk of ARF (19.6 – 22.9/1000 person-years).

While the rates of progression of valvular damage seen in this study were greater than those reported in previous studies, this may in part be explained by our longer period of follow-up. An Indian study that followed up 100 children with subclinical RHD found that 4% progressed over a mean follow-up time 1.3 years.[234] This is similar to, but lower than, the current study (16% over 3.6 years). However, the criteria used to define “subclinical RHD”, and the case definition, in that study were different to those used in the current study.[55] A second study from Uganda used the WHF criteria as the basis for assessing the outcome for children diagnosed with Borderline RHD two years from the time of their initial echocardiogram.[278] It found that of 43 children with an initial diagnosis of Borderline RHD, 4 (10%) progressed to Definite RHD. Given the shorter follow-up time period in that study this is again similar to the findings in the current study.

This study examines the utility of existing WHF criteria for the echocardiographic diagnosis of RHD in individuals without a known history of ARF.[55] The gECHO study showed that Borderline RHD is nearly twice as likely to be found on echocardiogram as Definite RHD during population-based RHD screening[233], however the relevance of the Borderline RHD criteria and the risk of subsequent ARF/RHD had not been determined. This was an important follow-up question highlighted in the WHF guidelines.[55] Results from this study lend support to the criteria used by the WHF for Borderline RHD by demonstrating an increased risk of ARF, progression of valvular damage, and progression to Definite RHD in individuals previously diagnosed with Borderline RHD. In addition, we have demonstrated that children with other NSVAs may also be at some increased risk of progression to RHD. These findings highlight that both functional and structural/morphologic changes on echocardiography form a continuum. While the current Borderline RHD category reflects an increased risk of ARF and echocardiographic progression, NSVA should also be viewed as part of this continuum as it confers a greater than background risk for progression to Definite RHD. Only with a larger cohort with longer-term follow-up will it be possible to determine exactly where, on this continuum, the cutoff between 'normal' and 'abnormal' should lie to more accurately inform health care management and follow-up.

The increased risk of ARF and progression to Definite RHD in children with Borderline RHD suggests there may be a role for secondary antibiotic prophylaxis in such children. However, caution should be exercised for at least two reasons. The first relates to how we may more accurately identify the subset of individuals at risk of ARF and progression. There were too few episodes of ARF recorded in this study to provide sufficient power to undertake a subgroup analysis of the risk of ARF in those with Borderline RHD subcategory A, B or C. However, the logistic regression analyses we performed in relation to echocardiographic progression did provide some limited insight. These models reveal that those individuals with Borderline disease of the mitral valve (Borderline RHD subcategories A and B under WHF criteria[55]) were at greatest risk of deterioration of valve lesions and progression to Definite RHD. Nonetheless, children with Borderline disease of the aortic valve (Borderline RHD subcategory C) still had an increased chance of development of Definite RHD. Furthermore, utilizing MR as a predictor of progression or

development of Definite RHD was not useful even though previously it has been suggested that MR alone may have potential utility as a screening tool for RHD in high-risk populations.[279] Overall, these results suggest that a combination of functional and/or morphologic features of the mitral valve is important in detecting those at greatest chance of progression but that aortic valve changes cannot be ignored.

The second issue regarding ongoing management of Borderline RHD and NSVAs relates to the efficacy of secondary preventive initiatives in the context of this study. Whilst it may be reasonable to alert patients and their families with this condition to the risk of ARF and valvular progression, we have previously shown any intervention in this setting may be associated with reduced quality of life.[280] It also remains to be seen if this variant of sub-clinical RHD is equally responsive to secondary antibiotic prophylaxis. Doubt remains whether RHD, or its variants, demonstrated on echocardiography without preceding ARF can be assumed to be equivalently responsive to secondary antibiotic prophylaxis as disease detected in association with ARF or when an incidental murmur is noted.

Our findings also contribute to the ongoing debate regarding the relevance and feasibility of echocardiographic screening for RHD in high-risk populations.[77] Based on results from the earlier gECHO study[233], the follow-up of Borderline RHD would triple the number of additional patients who would potentially require management by local primary health care and specialist services. Previously it has been shown that even limited RHD screening activities can have a significant adverse impact on local health services with suboptimal follow-up and reduced patient quality of life.[280] In addition we have previously shown that even in the relatively well resourced health care environment of Australia the uptake of secondary antibiotic prophylaxis for ARF/RHD is often poor.[68] Despite these issues, if managing Borderline RHD cases can be supported by local health services then the results of this study may provide an additional rationale for supporting on-going echocardiographic screening in this setting.

One in three Borderline RHD Cases included in this study were prescribed secondary antibiotic prophylaxis. This was at the discretion of treating clinical staff rather than dictated, or even recommended, by the earlier gECHO study. This was presumably due to clinicians interpreting the relatively non-specific earlier echocardiographic findings as

being commensurate with Definite RHD. It was likely that such secondary antibiotic prophylaxis had a confounding influence on the subsequent risk of ARF. Unsurprisingly, when we controlled for this potential confounder, the risk of ARF in those with Borderline RHD was increased. The influence of secondary antibiotic prophylaxis on echocardiographic progression was less clear. Logistic regression modelling suggested that the use of prophylaxis was associated with a greater risk of progression. It is unlikely that secondary antibiotic prophylaxis was conferring such an increased risk. Rather, it was more likely that this was an incidental finding resulting from the fact that, based on gECHO screening results, clinicians were identifying individuals at greatest risk of progression and prescribing prophylaxis to them.

Whilst researchers involved in this project were blinded to the results of the initial gECHO echocardiogram, this was not necessarily the case for local clinicians and other health service staff. Given this fact, it was possible that clinicians caring for patients with previous non-specific echocardiographic findings may have increased their surveillance of such individuals and had a lower index for diagnosing and notifying ARF. Nonetheless, the increase in ARF was restricted to cases who met WHF criteria for Borderline RHD while no episodes of ARF were notified in the remaining NSVA Cases. If such bias was present, we would also have expected to see an increased rate of ARF notification in the NSVA Cases.

A further potential source of bias was inter-observer variability in reading echocardiograms. We demonstrated substantial agreement between the original reading of baselines echocardiograms and subsequent re-reading of these echocardiograms as part of the RhFFUS study. Further, when we reclassified participants as Cases or Controls based on the subsequent re-reading of their baseline gECHO echocardiograms, this did not alter findings regarding the risk of ARF, progression of valvular lesions, or progression to Definite RHD.

In conclusion, the results of this study support the contention that in high-risk children some diagnoses of Borderline RHD based on WHF criteria and other non-specific valvular abnormalities appear to represent the earliest changes of RHD or, at least, indicate a group at increased risk of subsequent progression of valvular lesions and development of Definite

RHD. In either case, our findings provide a rationale for considering enhanced clinical follow-up of high-risk children with Borderline RHD and, to a lesser extent, other NSVAs. Whether this means patient, family and health provider education regarding the symptoms and signs of ARF, ongoing regular echocardiographic surveillance or the institution of secondary antibiotic prophylaxis will remain a clinical judgment that will be informed by available resources and the likelihood of successful follow-up. These results may also add to the ongoing debate regarding RHD echocardiographic screening in this setting and whether such screening is feasible and necessary in the overall health service response to preventing and managing ARF/RHD.

Key Points

1. Criteria for echocardiographic diagnosis RHD have been developed by the WHF but the significance of minor heart valve abnormalities, particularly Borderline RHD, in predicting the risk of ARF or RHD remained unclear.
2. Children with Borderline RHD were shown to have an increased risk of ARF, progression of valvular lesions, and development of Definite RHD. Children with less severe NSVAs were at a lower increased risk of progression to Definite RHD.
3. These findings show that at least some children with Borderline RHD have true RHD. These findings also provide support for considering secondary antibiotic prophylaxis or ongoing surveillance echocardiography in high-risk children with Borderline RHD or NSVAs. Further work is needed to identify features of children with Borderline RHD or NSVAs who are at greatest risk of ARF or progression to RHD.

3.2.3 Further discussion regarding the significance and limitations of the RhFFUS study

There were a number of limitations regarding the RhFFUS study that were highlighted in the previous paper. However, owing to word restrictions in the journal to which this paper was submitted these limitations were only briefly addressed and hence a more comprehensive discussion is provided here.

Participant numbers and analysis

There was a discrepancy between the number of projected participants outlined in the RhFFUS Methods paper[78] and the number of participants subsequently enrolled in the RhFFUS study as described in the RhFFUS Results paper. The reason for this was that at the time of writing and publishing the RhFFUS Methods paper researchers involved in the gECHO study (from which RhFFUS participants were drawn) were still undertaking data analysis. More specifically, some comprehensive echocardiograms for gECHO participants were still to be read by cardiologists. When these comprehensive echocardiograms were read this resulted in a number of changes in the classification of gECHO participants as potential Cases (Borderline RHD or NSVAs) or Controls for the RhFFUS study. In particular, the number of potential Cases identified from the gECHO study increased from 137 to 171 individuals following this cardiologist review of comprehensive echocardiograms.

The sample size calculation reported in the RhFFUS Methods paper indicated that only 77 Cases and 154 Controls were needed to detect any significant differences in outcome measures between the two groups. Nonetheless, in undertaking the RhFFUS study we aimed to enroll all 171 possible Cases and their 342 Matched Controls. The reasons for this were twofold. Primarily, the researcher team involved in the RhFFUS study judged that we were ethically enjoined to offer follow-up echocardiography to any individual identified with potential heart valve abnormalities during the gECHO screening study especially given the uncertainty surrounding the significance of such findings. Secondly, owing to the inherent uncertainty associated with the effect size utilised for power analysis it was decided to enroll more participants subject to time and resourcing constraints.

The subgroup analysis reported in the RhFFUS Results paper (i.e. Borderline RHD Cases vs. Matched Controls, and NSVAs vs. Matched Controls) was not explicitly mentioned in the RhFFUS Methodology paper. Rather, the Methodology paper simply explained that individuals with minor non-specific valvular changes on baseline echocardiography would be enrolled as Cases in addition to individuals identified with Borderline RHD from gECHO owing to uncertainties regarding where the cut-off point between "normal" and "abnormal" studies should be. Given this oversight the reader may be justified in interpreting the subgroup analysis as post hoc in nature. Nonetheless, the initial intention was to undertake such analysis and it was only once all participants had been enrolled and data collected that it became clear that there were sufficient numbers to undertake such subgroup analysis.

ARF outcome

Results from the RhFFUS study revealed that Borderline RHD Cases were at greater risk of ARF than their Matched Controls (IRR = 8.8, 95% CI 1.4 – 53.8). However, it is important to note that the number of events (episodes of ARF) in this context was small – 9 events in total, 4 in the Borderline RHD Case group – and that the confidence interval for the incidence rate ratio was broad. Hence caution needs to be exercised in interpreting this result and any attempts to generalise these findings to other contexts. Nonetheless, it should also be noted that this analysis was undertaken to test an a priori hypothesis regarding the risk of ARF in individuals with non-specific heart valve abnormalities detected on RHD screening echocardiogram and that, despite the small number of events, this finding was statistically significant.

A secondary issue regarding the ARF outcome data relates to the difficulty in diagnosis of ARF previously discussed in the Introduction to this thesis. The fact that there is no diagnostic laboratory test for ARF and that many of the criteria for making a diagnosis of ARF are non-specific may raise concerns about the accuracy of reported episodes of ARF included in this study. However, it is important to note that the episodes of ARF counted in this study only comprised those which were reported to regional ARF/RHD registers and which had documented evidence satisfying Australian criteria for the diagnosis of ARF.[2]

A further issue regarding ARF outcome data is that it is possible that participants did have episodes of ARF during the study that were never diagnosed or reported. Under-diagnosis is a well recognised issue in Australia with findings from the Northern Territory indicating that approximately 40% of newly-diagnosed cases of RHD do not have a previously reported diagnosis of ARF.[42] In an attempt to address this issue the medical records of approximately 50% of RhFFUS participants were reviewed to investigate whether they contained evidence of potential episodes of ARF that may have been overlooked. Unfortunately, reviews of medical histories provided very little information relating to ARF episodes as many were difficult to navigate, devoid of relevant data, and not up-to-date. For these reasons, only ARF data obtained from notification databases were utilised.

Inter-observer variability

The nature of echocardiography and the reading of studies utilizing WHF criteria are such that minor differences in operator settings and reader interpretation of images may affect the final diagnosis of an individual. As noted by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery, all quantitative evaluations based on echocardiography have potential limitations; they combine a number of measurements and are highly sensitive to errors of measurement, and are highly operator-dependent.[281]

The RhFFUS paper reports inter-observer variability analysis based on classification of participants whose baseline echocardiograms were read first during the gECHO study and subsequently during the RhFFUS study. Linear Kappa analysis revealed substantial agreement between these readings. Furthermore, sensitivity analysis revealed that any differences between these baseline readings did not have significant effects on outcome findings relating to risk of ARF, progression of valvular lesions, or progression to Definite RHD. Nonetheless, limitations still remain regarding the reading of echocardiograms obtained during the RhFFUS study. It would have been desirable to undertake inter-observer analysis in reference to determination of progression of valvular lesions (i.e. cardiologist interpretation of the difference between each individual's gECHO and RhFFUS echocardiogram) and progression to Definite RHD (i.e. WHF criteria diagnosis based on an individual's RhFFUS echocardiogram). Unfortunately there was insufficient time and financial resources to undertake such analysis. Nonetheless, it is important to note

that all echocardiography reading undertaken for the RhFFUS study was carried out by a highly experienced paediatric cardiologist who was a lead author for the WHF criteria for the echocardiographic diagnosis of RHD.[55] It should also be noted that during enrolment for the RhFFUS study participants were given the opportunity to consent to their echocardiograms being used in future research. Given that most participants did consent to this possibility it is hoped that in future an inter-observer variability study addressing the questions raised above may be undertaken using these echocardiograms.

RhFFUS and feasibility of echocardiographic screening for RHD

The primary rationale for undertaking the RhFFUS study was to investigate whether non-diagnostic valvular changes detected on RHD screening echocardiography are the earliest signs of RHD. This question has significance in the context of implementing any RHD screening programme. As outlined at the beginning of this chapter, for a screening test to feasible the test used must be highly sensitive and specific, validated and safe. While WHF criteria for the echocardiographic diagnosis of RHD had been published, there is no internationally accepted standardised definition of what constitutes a positive screening echocardiogram in the context of a potential RHD screening programme.

Results of the RhFFUS study indicate that one in six children previously diagnosed with Borderline RHD on screening echocardiogram, and one in ten children with less severe non-specific valvular abnormalities, progressed to WHF-defined Definite RHD within 2.5 to 5 years. While this is an important finding that indicates that a proportion of these children did have the early stages of RHD when first screened, the fact that 83% of children with Borderline RHD and 90% of children with NSVAs did not progress to Definite RHD is equally important. The limitation of these findings lies in the fact that since only a relatively small proportion of RhFFUS Cases developed RHD it remains unclear where the cutoff between a normal and abnormal echocardiographic screening study should lie. That is, the results of RhFFUS do little to resolve the issue of what degree of valvular abnormality should be classified as a positive test when undertaking echocardiographic screening for RHD. If results of this study had been more conclusive, for example if many

more children with Borderline RHD had progressed to Definite RHD while fewer children with NSVAs had progressed, then this would have provided stronger evidence around using the WHF-defined criteria of Borderline RHD as a cutoff point for positive studies. The reality is that results of the RhFFUS study are too equivocal and so, as argued above, further research is required to identify which particular valvular lesions place children at greatest risk of developing RHD. This will require greater participant numbers than were enrolled in RhFFUS as well as a longer follow-up period.

Chapter 4 – Informing the Management of Acute Rheumatic Fever and Rheumatic Heart Disease

Background

Given that ARF and RHD are preventable, it is vital that ARF/RHD research continues to focus, at least in part, on improvements in primordial and primary prevention rather than being restricted to early detection, diagnosis, and treatment. Nonetheless, as argued in the previous two sections of this thesis, there remain significant hurdles to the development and implementation of primary prevention and screening programmes. It is for this reason that the central components of current ARF/RHD care focus on disease management, particularly in the form of secondary antibiotic prophylaxis, regular primary health and specialist review to monitor any disease progression or development of complications, and, where necessary, surgical intervention to repair or replace damaged heart valves.

The final section of this thesis focuses on the management of ARF/RHD. In particular, it presents two research projects aimed at improving current management practices for those already living with these diseases; those for whom it is too late to contemplate primary prevention and for whom screening initiatives are redundant.

4.1 Variability in Disease Burden and Management of Rheumatic Fever and Rheumatic Heart Disease in Two Regions of Tropical Australia

Background

While Australian national guidelines for the diagnosis and management of ARF and RHD have been in place since 2006, the models of care used in different jurisdictions to manage patients living with ARF/RHD are variable. Anecdotal evidence suggested that many patients were not receiving the standard of care recommended in the Australian guidelines. With a view to clarifying this question and providing recommendations around improving ARF/RHD management in northern Australia, a quality improvement initiative was undertaken in the Kimberley (Western Australia) and far north Queensland. This study took the form of a clinical audit and enabled us to compare the relative strengths of different management strategies as well as examine differences in disease burden between jurisdictions.

Abstract

Background: Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) contribute to Aboriginal Australian and Torres Strait Islander health disadvantage. At the time of this study, specialist ARF/RHD care in the Kimberley region of Western Australia was delivered by a broad range of providers while in far north Queensland (FNQ) a single provider model was used as part of a coordinated RHD control programme.

Aims: To review ARF/RHD management in the Kimberley and FNQ to ascertain whether differing models of service delivery are associated with different disease burden and patient care.

Methods: An audit of ARF/RHD management in the Kimberley and FNQ from 2007 to 2009. Classification and clinical management data were abstracted from health records,

specialist letters, echocardiograms and local and regional registers and recall databases using a standardised data collection tool.

Results: 407 patients were identified with 99% being Aboriginal and/or Torres Strait Islanders. ARF without RHD was seen in 0.4% of Aboriginal and/or Torres Strait Islander residents and RHD in 1.1%. The prevalence of RHD was similar in both regions but with more severe disease in the Kimberley. More FNQ RHD patients had specialist review within recommended timeframes (67% versus 45%, χ^2, $p<0.001$). Of patients recommended benzathine penicillin secondary prophylaxis, only 17.7% received ≥80% of scheduled doses in the preceding 12 months. Prescription and delivery of secondary prophylaxis was greater in FNQ.

Conclusions: FNQ's single-provider model of specialist care and centralised RHD control programme were associated with improved patient care and may partly account for the fewer cases of severe disease and reduced surgical and other interventions observed in this region.

Introduction

The development of national Australian guidelines for ARF and RHD diagnosis and management[62] have facilitated the standardisation of ARF/RHD care between Australian state health departments and they have been utilized to inform local management guidelines.[63-65] Management of ARF and RHD encompasses secondary antibiotic prophylaxis in the form of 3-4 weekly long-acting benzathine penicillin (BP) injections to prevent GAS infection and recurrent ARF, regular local primary healthcare review, echocardiography, specialist review and education.[62] Management of RHD also involves preventing and managing complications such as endocarditis, cardioembolism and heart failure, and assessing the need for valve related surgical procedures.[62]

Previous studies of ARF/RHD in the north of Australia have demonstrated suboptimal care: secondary prophylaxis coverage is inadequate, survival following heart valve surgery is low, and monitoring of anticoagulation is variable.[79-81] This earlier work, and the

demonstrated high burden of disease, has provided a focus for local initiatives which aim to improve access to, and quality of, care.

The processes and models of local service delivery for comprehensive ARF/RHD care remain variable. This is in part due to historic models of service delivery, geography, and population and health workforce distribution. The Kimberley region of Western Australia (WA) and Cape York and Torres Strait regions of far north Queensland (FNQ) (see Figure 14) illustrate such variability, with significantly different models of service delivery.

At the time of this review, ARF/RHD care in the Kimberley was based on a "multi-provider model" centred on primary health care with support and follow-up provided by community-based and outreach specialist service providers. These services included local regional physicians and paediatricians who visited large and small communities, and visiting cardiologists (paediatric and adult) and echocardiographers in larger centres. This involved public and private service providers from a number of different organisations with any required surgery being undertaken in one of three Perth hospitals. Individual primary health care sites maintained a variety of paper-based and electronic registers and recall systems with no single regional system.

In FNQ, ARF/RHD care was similarly centred on primary health care but with support and follow-up provided by a "multi-skilled single-provider model". This consisted of a single specialist outreach service of physicians (who also performed echocardiography) and paediatricians, with adult or paediatric cardiology review generally only provided when surgery was planned at regional referral centres (Cairns or Townsville). Registration and recall of ARF/RHD patients was provided from a regional database supported and coordinated by a centralised ARF/RHD programme.

In order to explore optimal models of care for people with ARF/RHD living in the north of Australia we undertook an assessment of these two differing systems. This included an assessment of the locally recognised burden of disease, an audit of the care received by patients, and benchmarking care against local management guidelines. This process focused on the performance and coordination of care across each region rather than on individual providers.

Materials and Methods

We reviewed the management of ARF/RHD patients who had accessed primary and specialist health care services in the Kimberley region of northern WA and in the Cape York and Torres Strait regions of FNQ (see Figure 14). In the Kimberley, these services were provided by Aboriginal community-controlled health services and/or health department primary health care clinics and hospitals. In FNQ they were predominantly provided by health department primary health care clinics and hospitals.

Inclusion criteria were a clinician-recorded diagnosis of either (1) ARF and/or (2) RHD in patients considered by the local health service to be "regular" clients. A diagnosis of ARF required health record documentation of ARF (irrespective of time of diagnosis and whether ARF was actively managed at the time of audit) or the use of an ARF care plan and, where available, no evidence of RHD on the most recent echocardiogram report. A diagnosis of RHD required documentation of RHD by the local health service with an associated abnormal echocardiogram, or a history of prosthetic valve replacement/valve repair/valvuloplasty, or an echocardiogram report consistent with RHD. Consistent echocardiography findings included: mitral stenosis, mitral regurgitation with thickening and/or distortion of the valve leaflets, or mitral valve and aortic valve regurgitation or stenosis.

Eligible patients were identified at local health services through interrogation of health information management systems (i.e. searching for clients assigned to an ARF/RHD "care plan", or generating ARF/RHD "problem" lists), accessing benzathine penicillin recall lists, and through questioning of local health service staff. In FNQ the regional ARF/RHD register was also accessed to identify potential clients for inclusion. Finally, electronic copies of specialist letters and echocardiography reports were searched for terms that may indicate the client had ARF/RHD (e.g. rheumatic, mitral, aortic, valve, regurgitation, stenosis) and the health records of clients identified through these methods checked for diagnoses.

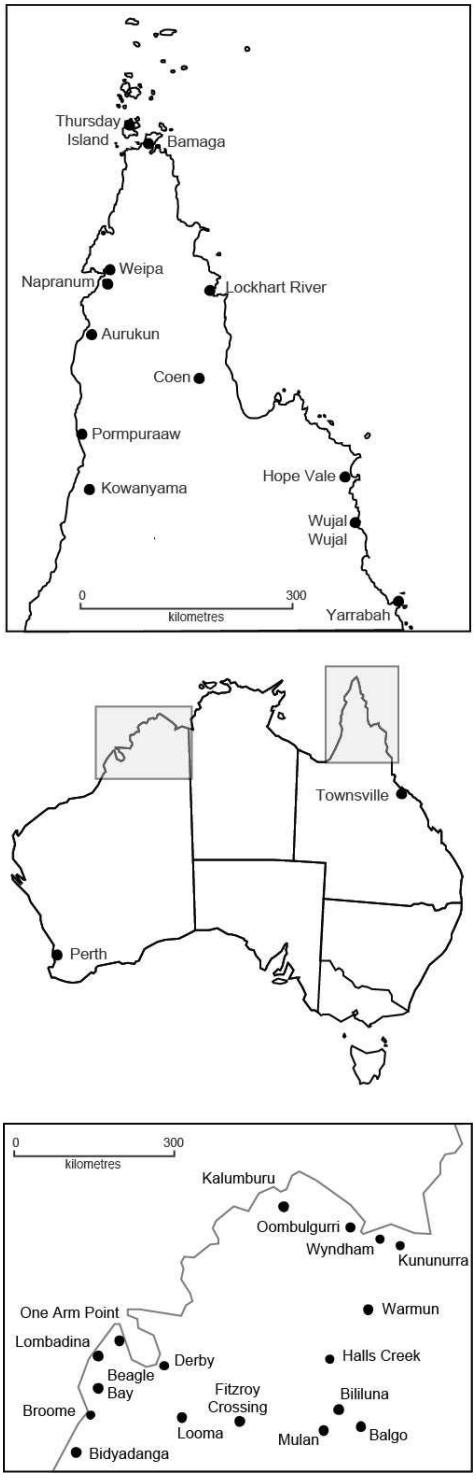


Figure 14 Study sites in the Kimberley (Western Australia) and far north Queensland.

Data were collected in the Kimberley between August and November 2007 at 17 primary health care sites and in FNQ between November 2008 and March 2009 at 12 sites (Figure 14). Data on clinical management were abstracted from local health records (paper-based and electronic), specialist letters, echocardiogram reports, and local and regional registers and recall databases. A standardised data collection tool was utilised with a manual providing standardised definitions for patient selection and service delivery.

Data collected and quality measures assessed included: patient demographics; echocardiogram timeliness and results; severity of ARF/RHD based on the classification system proposed by the national guidelines[62] (see Table 10); prescription and uptake of secondary prophylaxis in the 12 months prior to audit; timeliness of specialist review (cardiologist, physician, paediatrician); uptake of immunisations (influenza vaccination within past 12 months, pneumococcal vaccination within last 5 years); and appropriateness of anticoagulation. The delivery of health services was benchmarked against local standards of care as outlined in the Kimberley chronic disease protocols[64] and Queensland chronic disease guidelines[65] (see Table 11). For those clients receiving secondary prophylaxis, the proportion achieving >=80% of scheduled doses in the 12 months prior to audit was calculated and any episodes of recurrent ARF for that period recorded.

Classification	Criteria
Mild	ARF with no evidence of RHD; or trivial to mild valvular disease.
Moderate	Any moderate valve lesion in the absence of symptoms and with normal left ventricular function; or mechanical prosthetic valves.
Severe	Severe valvular disease; or moderate to severe valvular lesions with symptoms – shortness of breath, tiredness, oedema, angina or syncope; or tissue prosthetic valves and valve repairs.

Table 10 Protocol-based classification of severity of acute rheumatic fever and rheumatic heart disease.[62]

Priority	Low		Moderate		High	
	Kimb	**FNQ**	**Kimb**	**FNQ**	**Kimb**	**FNQ**
Specialist review	2 years	2 years	1 year	6 months	6 months	3 months
Echocardiography review	2 years	1 year	1 year	1 year	1 year	6 months
Dental review	2 years	1 year	1 year	1 year	1 year	1 year

Table 11 Recommended timeframe for delivery of health services to clients with ARF/RHD based on local standards of care as outlined in the Kimberley chronic disease protocols[64] and Queensland chronic disease guidelines.[65]

Population denominators were based on 2006 Australian Bureau of Statistics census data.[282] Disease prevalence in the Kimberley was based on the entire Aboriginal and Torres Strait Islander population of the region as clients from all possible health care sites were included. Disease prevalence in FNQ was based on population statistics for Local Government Areas associated with those sites audited. Data from Thursday Island were excluded, as accurate population denominator data were not available.

Data were analysed using SPSS (v15.0 for Windows, SPSS Inc., Chicago, IL, USA) and Intercooled Stata 12 (Stata Corporation, Texas, USA). All statistical tests were two-sided with a p-value < 0.05 taken to indicate statistical significance.

This project was approved as a clinical audit by the Western Australian Aboriginal Health Information and Ethics Committee (WAAHIEC), the Western Australia Country Health Service Board Research Ethics Committee, and the Human Research Ethics Committee of the Cairns and Hinterland Health Service District, Queensland Health.

Results

407 patients were included in the study. Patient demographics, disease prevalence and severity, and valve surgery/procedures are presented in Table 12. There were no significant differences in the demographics of Kimberley and FNQ patients. The prevalence of a previous diagnosis of ARF (with no progression to RHD) and RHD was similar in the two study areas but with more severe disease in the Kimberley. Significantly more RHD patients in the Kimberley had undergone valve surgery or associated procedures.

A history of ARF without associated RHD was seen in 24.5% (52/212) of Kimberley patients and 27.7% (54/195) of FNQ patients. Median age was 22.4 years (IQR 17.2 – 32.4) and women were overrepresented, accounting for 60.2% of patients. There was no significant difference in age or gender between Kimberley and FNQ ARF patients.

In people with a history of ARF it is recommended that an echocardiogram be performed at the time of diagnosis (to assess for carditis and pre-existent RHD) and prior to ceasing prophylaxis. FNQ ARF patients were more likely to have had any echocardiogram performed with 96% (52/54) having a record of an echocardiogram compared with 85% (44/52) of Kimberley patients (χ^2, $p < 0.05$).

Evidence of RHD was seen in 75.5% (160/212) of Kimberley and 72.3% (141/195) of FNQ participants. Median age was 30 years (IQR 20 – 43) and women were again overrepresented, accounting for 71.8% of patients.

Overall 55.1% (166/301) of RHD patients had had a specialist review by a paediatrician, physician or cardiologist in concordance with timeframes recommended in local management guidelines. Timely specialist review was more likely for FNQ RHD patients (66.7%, 94/141) compared with Kimberley patients (45.0%, 72/160) (χ^2, $p<0.001$).

	All patients (n = 407)	Kimberley (n = 212)	FNQ (n = 195)
Age, median years (IQR†)	29.1 (18.7 – 40.2)	29.4 (19.2 – 41.0)	27.4 (18.3 – 39.5)
Female, n (%)	280 (68.8%)	141 (66.5%)	139 (71.3%)
Aboriginal and/or Torres Strait Islander, n (%)	403 (99.0%)	211 (99.5%)	192 (98.5%)
Disease prevalence in Aboriginal and/or Torres Strait Islander population, %			
ARF (no progression to RHD)	0.36%	0.33%	0.41%
RHD	1.07%	1.02%	1.14%
Disease severity, n (%)			
ARF / Mild RHD	237 (58.2%)	101 (47.6%)	136 (69.7%)*
Moderate RHD	66 (16.2%)	38 (17.9%)	28 (14.4%)
Severe RHD	104 (25.6%)	73 (34.4%)	31 (15.9%)*
Valve surgery or procedures, n (% RHD patients)			
Any valve surgery/procedure	67 (22.3%)	44 (27.5%)	23 (16.3%)**
Mechanical valve	36 (12%)	24 (15%)	12 (8.5%)
Bioprosthetic valve	13 (4.3%)	9 (5.6%)	4 (2.8%)
Valvuloplasty/repair	18 (6%)	11 (6.9%)	7 (5.0%)

Table 12 Demographics, ARF/RHD severity and prevalence and type of valve surgery/procedure in patients included in this study. † Inter-quartile range, *χ^2, $p<0.0001$, **χ^2, $p<0.05$

Echocardiography was delivered to 60.5% (182/301) of RHD patients within recommended timeframes with no overall difference between regions. However, RHD patients in the Kimberley who had a history of valve surgery or other procedures were more likely to have received a timely echocardiogram than comparable patients in FNQ (31/44 (70.5%) versus 9/23 (39.1%), χ^2 p<0.001).

The delivery of secondary antibiotic prophylaxis to ARF/RHD patients is outlined in Table 13. Ten patients in FNQ and two in the Kimberley with a recommendation for benzathine penicillin prophylaxis had an episode of recurrent ARF in the 12 months prior to the study (Fisher's exact test, p<0.05). All of these cases were preventable with no patient receiving adequate secondary antibiotic prophylaxis in the 2 months prior to their episode of recurrent ARF.

	All patients (n = 407)	**Kimberley (n = 212)**	**FNQ (n = 195)**
Recommendation or prescription for BP† n (%)	293 (72.0%)	136 (64.2%)	157* (80.5%)
≥ 80% doses BP given n (% of those recommended BP)	52/293 (17.7%)	20/136 (14.7%)	32/157 (20.4%)
Number of doses of BP median (IQR†)	6 (2-8)	4 (1.5-8)	7** (4-9)
Recommendation for oral antibiotics n (%)	21/407 (5.2%)	0 (0%)	21/195*** (10.8%)

Table 13 Recommendation for, and delivery of, secondary antibiotic prophylaxis in the 12 months prior to review. *χ^2, p<0.001; **Wilcoxan Mann-Whittney test, p < 0.0001; *** Fisher's exact test, p<0.0001; †benzathine penicillin

One in five RHD patients was receiving warfarin anticoagulation (see Table 14). Based on a recommended frequency of international normalized ratio (INR) monitoring of six weekly[283], 36.7% of these had inadequate monitoring. Of all recorded INR results 65.1% were outside the recommended range.[62] No significant differences were observed between FNQ and the Kimberley.

	All (n=301)	**Kimberley (n=160)**	**FNQ (n=141)**
RHD patients on warfarin, n (%)	60/301 (19.9%)	37/160 (23.1%)	23/141(16.3%)
Primary indication for warfarin, n (%)			
Mechanical valve	35/60 (58.3%)	24/37 (64.9%)	11/23 (47.8%)
Atrial fibrillation	19/60 (31.7%)	10/37 (27.0%)	9/23 (39.1%)
Mitral valve disease	6/60 (10.0%)	3/37 (8.1%)	3/23 (13.1%)
Target INR, n (%)			
Documented in medical record?	49/60 (81.7%)	29/37 (78.4%)	20/23 (87.0%)
Concordant with national guidelines?[†]	19/49 (38.8%)	8/29 (27.6%)	11/20 (55.0%)
INR tests in previous 12 months			
Number, median (IQR)	11 (5 – 21.5)	15 (5 – 26)	9 (6.5 – 12)
Adequate testing[‡], n (%)	38/60 (63.3%)	23/37 (62.2%)	15/23 (65.2%)
Results above recommended range, n (%)	180/758 (23.7%)	129/517 (25.0%)	51/241 (21.2%)
Results below recommended range, n (%)	314/758 (41.4%)	232/517 (44.9%)	82/241 (34.0%)

Table 14 Anti-coagulation therapy and RHD in the Kimberley and FNQ. [†]National guideline INR recommendations[62]: atrial fibrillation without mechanical valve replacement 2 to 3; mechanical mitral valve 2.5 to 3.5; mechanical aortic valve 2 to 3. [‡]Based on a minimum recommended monitoring interval of 6 weeks.[283]

Influenza and pneumococcal vaccinations were recommended for all patients with ARF/RHD. Influenza and pneumococcal vaccination was more likely to be up-to-date in FNQ patients (influenza 54.4%, pneumococcal 47.7%) compared with Kimberley patients (38.6%, 37.3%) (χ^2, $p<0.01$ and $p<0.05$ respectively).

Discussion

This study is the first to highlight differences in the nature and burden of ARF/RHD, and the quality of care received by ARF/RHD patients in different northern Australian regions.

Results from this study confirm that in northern Australia ARF/RHD remains almost exclusively a disease of Aboriginal and Torres Strait Islander people with 99% of identified ARF/RHD patients being of Aboriginal and/or Torres Strait Islander ethnicity). The observed prevalence of RHD in Aboriginal and Torres Strait Islander people in the Kimberley (1.02%) and FNQ (1.14%) was comparable to earlier studies of Aboriginal Australian and low income country populations.[1, 42, 43, 284] This is in contrast to the waning burden of disease among other Australians (0.2% in the Top End of the Northern Territory and less than 0.1% in Central Australia)[1] and most other high income nations.[1, 7, 284]

The relatively young median age of RHD patients in this study is presumably related to premature mortality of people with RHD in this setting. This is supported by evidence from the Northern Territory where the mean age at death of Aboriginal people with RHD is 35.7 years compared to 67.3 years in non-Aboriginal RHD patients.[244]

The predominance of female patients has been noted previously.[1, 42] Whilst the cause of this remains unclear it has been suggested that a greater exposure to GAS associated with the care of children, enhanced diagnosis accompanying more frequent health care utilisation and a gender-related propensity to autoimmune disease may all contribute.[71]

While the overall prevalence of ARF/RHD was similar in both regions we demonstrated a greater proportion of severe RHD and higher levels of valve related procedures in the Kimberley. This difference may be explained by regional differences in the pattern of

ARF/RHD, differences in diagnosis and monitoring, and uptake of secondary antibiotic prophylaxis.

ARF/RHD is associated with economic and environmental disadvantage[92, 93] and incidence of infection with GAS[88]. The available data do not suggest differences in housing, employment, degree of remoteness or income between the Kimberley and FNQ[285] and there is no obvious reason to suspect that the natural history of ARF/RHD differs between the two regions.

It is possible that cases of ARF and/or mild RHD were not as readily identified in the Kimberley as in FNQ. In FNQ we observed a significantly greater proportion of ARF/mild RHD which may indicate that cases were being identified earlier here. Earlier identification would enable earlier intervention, including delivery of secondary prophylaxis to prevent the development or worsening of RHD, thereby ensuring that fewer patients progress to severe disease or require heart surgery. In Queensland there was a centralised RHD control programme and a regional ARF/RHD database in place at the time of this study. This programme incorporated an ARF notification system, a centralised coordination unit, regular reminders to health providers about individuals requiring BP prophylaxis and specialist follow-up, and ongoing training and support for health staff in relation to the management of ARF/RHD. In contrast, at the time there was no such programme or regional ARF/RHD database in the Kimberley. This difference in the coordination of care may be associated with the differences in observed service delivery and disease severity between the two regions. An ARF/RHD enhanced surveillance system similar to the one in place in FNQ has since been implemented in the Kimberley.

While we did demonstrate lower levels of echocardiography in ARF patients without RHD in the Kimberley, the use of echocardiography (and thus diagnosis and monitoring of severity) in those with RHD was comparable between regions. Differences in monitoring of disease severity alone do not explain the differences in disease severity observed.

More severe disease was associated with less delivery of secondary antibiotic prophylaxis and less specialist review in the Kimberley compared to FNQ. Even if the greater use of less effective oral antibiotic secondary prophylaxis[66] in FNQ was excluded, 16% more

patients were prescribed BP prophylaxis and the median number of BP doses delivered was 75% greater in FNQ. Greater delivery of secondary antibiotic prophylaxis in FNQ would be expected to have led to fewer episodes of recurrent ARF and hence less disease progression. The recorded rate of recurrent ARF was, however, significantly higher in FNQ. At the time, ARF was a notifiable disease in FNQ but not in the Kimberley suggesting that episodes of recurrent ARF were more likely to be reported in FNQ and that significant under-reporting and perhaps under-recognition was occurring in the Kimberley.

The delivery of specialist services observed in both the Kimberley and FNQ was less than optimal with only 55.1% of RHD patients being reviewed within recommended timeframes and 60.5% receiving a timely echocardiogram. An earlier study in the Kimberley reported that of those patients recommended visiting specialist or echocardiographic review, 78% and 64% attended respectively.[79] Similarly, in the Northern Territory, while RHD patients with severe disease were usually receiving follow-up, approximately half the people with moderate and mild disease had been inadequately investigated and/or had not received follow-up.[80]

RHD patients in FNQ were more likely to have been seen by a specialist within recommended timeframes. This was confined to patients with RHD who had not undergone heart valve surgery (data not shown). More frequent specialist review in FNQ may have enhanced the uptake of secondary antibiotic prophylaxis and thus impeded the progression of disease, but it is not possible to confirm this. Despite more frequent specialist review in FNQ, by a workforce who provided contemporaneous echocardiography, and a centralised recall system, there was no difference in the delivery of echocardiography services to RHD patients in the Kimberley and FNQ. Indeed Kimberley RHD patients with a history of valve surgery or other procedures were more likely to have received a timely echocardiogram compared with FNQ patients. Specialist-provided echocardiography in FNQ, while apparently more frequently available, may have been deferred in busy clinics with other clinical priorities. A dedicated echocardiography service such as that used in the Kimberley is not subject to similar distraction and appears to have ensured those with more advanced disease had echocardiography performed as scheduled.

Many patients with advanced RHD, in particular those who have a mechanical valve *in situ*, require anticoagulation. Delivery of anticoagulation therapy to RHD patients was suboptimal. The lack of concordance between INR targets recommended by national guidelines[62] and those recorded in patient notes is concerning, as is the finding that 1/3 of patients on warfarin did not receive adequate monitoring and that almost 2/3 of recorded INR results were outside recommended targets. A study in non-remote Australia found therapeutic anticoagulation in 57.6% of tests compared with 34.9% seen here.[286] It is vital that initiatives be developed to address this issue in these remote Australian settings. Newer oral anticoagulants which do not require INR monitoring have been developed, however evidence of their effectiveness in RHD, atrial fibrillation related to valvular disease, and mechanical valves is lacking.[287] Given the difficulties associated with anticoagulation and INR monitoring demonstrated here, balloon valvuloplasty, valve repair or bioprosthetic valve replacement are clearly preferable (where they are an option) for patients living in remote northern Australia.

While the differences in delivery of health services observed in this study, particularly the higher rates of BP prescription and delivery and the higher rates of timely specialist review observed in FNQ, may be associated with the differing models of service delivery in the two regions, it is important to note that data was collected in the Kimberley in 2007 while data was collected in FNQ in 2008-2009. The national Australian guidelines for ARF and RHD diagnosis and management[62] were published in 2006 and it is possible that one reason for improved concordance in FNQ was that the extra time between publication and audit in FNQ may have enabled the implementation of awareness programmes, education initiatives and system changes to align more closely with the guidelines.

Conclusion

This study has documented the nature, burden and management of ARF/RHD in two regions of northern Australia. We have demonstrated differences in disease severity that may, at least in part, be explained by differing levels of secondary prophylaxis uptake, differing specialist access and the presence or absence of a centralised ARF/RHD control programme. In both regions specialist and echocardiography services, secondary

prophylaxis and the management of anticoagulation have changed little over the last decade.[79, 80] Coordinated systems for ARF/RHD management supported by centralised database and recall systems and a consolidated specialist health care team were associated with improved patient care and may partly account for fewer cases of severe disease and a reduced number of surgical and other interventions observed in FNQ.

Key Points

1. Different models of service delivery for ARF/RHD care were operating in the Kimberley and FNQ. Specialist ARF/RHD care in the Kimberley was delivered by a broad range of providers while in FNQ a single provider model was used as part of a coordinated RHD control programme. This study aimed to review whether these different models were associated with different disease burden and patient care.
2. More severe disease was found in the Kimberley. More FNQ RHD patients had specialist review within recommended timeframes and prescription and delivery of secondary prophylaxis was greater in FNQ. However, only 1 in 5 patients recommended benzathine penicillin secondary prophylaxis received ≥80% of scheduled doses in the preceding 12 months.
3. FNQ's single-provider model of specialist care and centralised RHD control programme were associated with improved patient care and may partly account for the fewer cases of severe disease and reduced surgical and other interventions observed in this region.

4.2 Infective Endocarditis and Rheumatic Heart Disease in the North of Australia

Abstract

Background: To prevent infective endocarditis (IE), Australian guidelines recommend providing prophylactic antibiotics to Indigenous patients with rheumatic heart disease (RHD) prior to procedures which may cause bacteremia. In northern Australia RHD remains prevalent. We aimed to determine whether RHD is associated with an increased risk of IE, which risk factors are associated with IE, and the incidence and aetiology of IE.

Methods: A retrospective review of IE patients who fulfilled modified Duke criteria at two tertiary centres in northern Australia.

Results: 89 patients were reviewed. The rate of IE was 6.5/100 000 person-years. IE was more common in people with RHD (relative risk (RR) 58), Indigenous Australians (RR 2.0) and men (RR 1.7). RHD-associated IE was not confined to Indigenous Australians with 42% being non-Indigenous. The commonest risk factors for IE were intracardiac prosthetic material, injecting drug use and previous IE. One in five patients died.

Conclusions: In northern Australia the principle risk factor for IE is not RHD. While RHD increased the risk of IE it was not restricted to Indigenous Australians. Current Australian recommendations of providing prophylactic antibiotics to Indigenous patients with RHD prior to procedures which may cause bacteremia may need to be broadened to include non-Indigenous patients.

Introduction

While infective endocarditis (IE) is rare, its consequences can be significant including prolonged hospitalisation, valve replacement, stroke and death.[62] Incidence data for IE in Australia are limited. A recent review of adult IE in New South Wales reported an incidence of 4.7 per 100,000[229] and a study in regional Victoria a rate of 3.0 per 100,000.[288] This was comparable to rates in the USA and Western Europe (1.7 – 7.0 per 100,000).[289-291] IE incidence in developed countries is higher in particular risk groups including injecting

drug users (IDU) (150 – 2000 per 100,000)[292] and individuals with preexisting valve abnormalities, most notably mitral valve prolapse (100 per 100,000).[293] In developed countries the importance of rheumatic heart disease (RHD) as a risk factor for IE is waning[82] but in many developing countries RHD remains the most frequent predisposing condition.[83] The reducing importance of RHD is not universal in high income countries, especially where discrete populations remain at increased risk of RHD. This is the case in northern Australia where the prevalence of RHD in Aboriginal and Torres Strait Islander populations remains high (1.25%).[223] The incidence and nature of IE in this setting has not previously been described.

Current Australian guidelines[84] recommend providing prophylactic antibiotics to people viewed as being at an increased risk of IE prior to procedures which may cause bacteremia. This includes Indigenous Australians with RHD undergoing high-risk dental, respiratory, genitourinary and gastrointestinal procedures. It has been suggested that Australian recommendations be amended to reflect the American Heart Association's guidelines[85] under which prophylaxis is recommended for patients with RHD only if they have prosthetic valves or prosthetic material in cardiac valve repairs. Patients with "native valve" RHD are not included. In addition, the American guidelines do not recommend providing prophylaxis for procedures involving the gastrointestinal and genitourinary tract.

Despite the lack of evidence, there is concern that altering Australian recommendations to bring them in line with American Heart Association recommendations may expose Aboriginal and Torres Strait Islander people with RHD to an increased risk of IE.

In order to inform Australian recommendations for antibiotic prophylaxis to prevent IE in patients with RHD we undertook an audit of IE cases to ascertain:

1. whether RHD without a prosthetic valve or material is associated with an increased risk of IE;
2. which potential risk behaviours or procedures are temporally associated with IE in northern Australia; and
3. the local incidence and aetiology of IE.

Patients and Methods

A retrospective review of IE cases was undertaken at Cairns Base Hospital and Royal Darwin Hospital (see Figure 15). Medical records of individuals who fulfilled the selection criteria at each site were reviewed from December 2003 to December 2007 (4 yrs.) at Royal Darwin Hospital and from February 2002 to December 2007 (5.8yrs) at Cairns Base Hospital. Where an individual had multiple IE hospital separations only the most recent was included. Selection criteria for Cairns subjects included any individual (all ages) with a primary or secondary International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD 10) separation diagnosis of IE or other valve disorder[294] (ICD codes - I01.1; I02.0; I05.8-9; I06.8-9; I07.8; I08.0-3; I08.8-9; I09.1; I09.8; I33.0; I33.9; I34.8; I35.8; I36.8; I37.8; I38; I39.1; I39.3; I39.8; I42.3; I42.4; T82.6; Z95) AND who fulfilled modified Duke IE criteria for a definite or possible diagnosis.[295] If hospital separation was coded as IE (ICD I33.0) but modified Duke criteria were not met, then the subject was excluded. Potential subjects in Darwin were identified through the infectious diseases service database as ICD-10 separation data were deemed insufficiently specific and sensitive to identify possible IE patients. Similar inclusion criteria requiring a definite or possible diagnosis of IE based on the modified Duke criteria were used.

Figure 15 Geographic catchment of northern Australian centers included in this study - Cairns (Cairns Base Hospital) and Darwin (Royal Darwin Hospital).

Data collected included: demographics; IE diagnostic criteria; echocardiography, blood cultures and serology results; risk factors – both putative behavioural risk factors (e.g. IDU) and underlying heart disease; preceding medical and dental procedures; use of antibiotic prophylaxis; and outcome (length of stay, inter-hospital transfer, survival at the time of discharge from hospital, the need for cardiac surgery).

Data were collated with Microsoft Excel (2000) and analysis undertaken with SPSS (v17.0 for Windows; SPSS, Chicago, IL, USA) and Intercooled Stata 9.2 (Stata Corporation, College Station, TX, USA). Continuous data are presented as medians with interquartile range, proportions with binomial 95% confidence intervals (95% CI) and incidence as incidence density (person-years) with Poisson 95% CI. Australian Bureau of Statistics population estimates for 2004 and 2006 were used for population denominators for the total, Indigenous and non-Indigenous populations for the Cairns and Darwin hospital catchments.[296] Estimates of the prevalence of RHD were determined using data from existing registers maintained by the Northern Territory Department of Health.[223] Comparisons of continuous variables between groups used the Mann-Whitney U test and χ^2 for categorical variables. All reported P-values are two sided, and P-values less than 0.05 were considered to indicate statistical significance.

Approval to undertake this study was obtained from the Cairns and Hinterland Health Service District Human Research Ethics Committee and the Human Research Ethics Committee of the NT Department of Health and Families and Menzies School of Health Research.

Results

Of the 89 patients included in this audit 60 (67%, 95% CI, 57 – 76) satisfied criteria for a 'definite' diagnosis of IE.[295] Sixteen had pathologic criteria present, 33 had two major criteria, and 11 had one major and three minor criteria. The remaining 29 (33%, 95% CI, 24 – 43) patients fulfilled the definition of 'possible' IE: 26 had one major and one minor criterion, while 3 had three minor criteria.

Demographic and incidence data for IE patients are presented in Table 15. The rates of IE standardised to the 2004 Australian population for Darwin and Cairns were 6.5

cases/100,000 person-years for males, 3.9 for females and 5.2 overall. Darwin patients were more likely to be of Aboriginal and/or Torres Strait Islander origin. Men were more likely to have IE (RR 1.7, 95% CI, 1.1 – 2.6, χ^2 $p<0.05$). IE was rare in children; only 4/89 (4.5%, 95% CI, 1.8 – 11.0) cases occurred in patients younger than 18 years. Aboriginal and Torres Strait Islander adults were at greater risk of IE (RR 2.0, 95% CI, 1.3 – 3.1, χ^2 $p<0.01$). This was confined to the NT (RR 2.7, 95% CI, 1.4–5.1, χ^2 $p<0.01$) and was not seen in FNQ (RR 1.1, 95% CI, 0.4 – 2.4, χ^2 not significant). Twelve IE patients (14%, 95% CI, 8 – 22) had native valve RHD. The IE incidence in patients with native valve RHD was 290 (95% CI, 150 – 506) per 100,000 person-years. This corresponded to a relative risk of 58 (95% CI, 32 – 107, χ^2 $p<0.0001$) in comparison with individuals without native valve RHD. Further, in patients with native valve RHD, the risk of IE was greater in non-Indigenous Australians compared to Aboriginal and Torres Strait Islander Australians (RR 3.7, 95% CI, 1.2 – 11.5, χ^2 $p<0.05$).

The prevalence of risk factors associated with IE are presented in Table 16. Cairns patients were more likely to have congenital heart disease or a valve abnormality without prosthetic material *in situ* and to have had a previous episode of IE compared with Darwin patients.

A potential triggering event was identified in 24/89 (27%, 95% CI, 20 – 37) patients. Cairns patients were less likely to have an identified triggering event compared with Darwin patients (9/50, 18%, 95% CI, 9 – 31 versus 15/39, 38%, 95% CI, 23 – 55, χ^2 $p=0.03$). The commonest event was a recent intravascular device in 13/24 (54%, 95% CI, 33 – 74) patients. Recent dental procedures were noted in only two patients. In those with an identified triggering event, 6/24 (25%) had received prophylactic antibiotics, 12/24 (50%) had not, and the use of prophylactic antibiotics could not be determined in 6/24 (25%) cases. The use of prophylactic antibiotics was no different between sites (data not shown). A triggering event was noted in 2/12 (17%, 95% CI, 2 – 48) RHD patients and 22/77 (29%, 95% CI, 19 – 40) non-RHD patients (Fisher's exact test, not significant). Neither of these two RHD patients would have been recommended prophylactic antibiotics under existing Australian guidelines.[84] Similarly, the majority of all patients with a triggering event (21/24, 88%, 95% CI, 68 – 97) would not have been recommended antibiotic prophylaxis.

	All patients	Cairns	Darwin
Number	89	50	39
Incidence IE cases per 100,000 person-years (95% CI*)			
All patients	4.5 (3.6 – 5.5)	3.6 (2.7 – 4.8)	6.3 (4.5 – 8.6)
All adults (≥18yrs)	5.9 (4.7 – 7.3)	4.7 (3.4 – 6.2)	8.7 (6.1 – 11.9)
Non-Indigenous adults (≥18yrs)	4.9 (3.8 – 6.4)	4.6 (3.3 – 6.2)	5.9 (3.6 – 9.3)
Indigenous Australian adults (≥18yrs)	9.8 (6.5 – 14.3)	5.2 (2.2 – 10.1)	15.9 (9.6 – 24.9)
Age (median years)	45	52	42
(IQR†)	(36 – 61)	(36 – 68)	(36 – 50)
Gender (number female)	33	19	14
(% female, 95% CI)	37 (28 – 47)	38 (26 – 52)	36 (23 – 52)
Aboriginal and/or Torres Strait Islander (number)	29	9	20[a]
(%, 95% CI)	33 (24 – 43)	18 (10 – 31)	51 (36 – 66)

Table 15 Demographic and incidence data for Cairns and Darwin IE patients. *CI – confidence interval; †IQR – interquartile range; [a]χ^2, $p<0.01$

Number (% patients, 95% CI[*])	**All patients** **N = 89**	**Cairns** **N = 50**	**Darwin** **N = 39**
One or more risk factors	57 (64.0, 53.7 – 73.2)	35 (70.0, 56.2 – 80.9)	22 (56.4, 40.9 – 70.7)
RHD[†] (native)	12 (13.5, 7.9 – 22.1)	4 (8.0, 3.3 – 18.9)	8 (20.5, 10.8 – 35.6)
Prosthetic heart valve/material	17 (19.1, 12.3 – 22.1)	11 (22.0, 12.8 – 35.3)	6 (15.4, 7.3 – 29.8)
Congenital heart disease/valve abnormality (without prosthetic material *in situ*)	8 (9.0, 4.7 – 16.8)	8 (16.0, 8.4 – 28.6)	0[a] (0.0, 0.0 – 8.8)
Previous infective endocarditis	13 (14.6, 8.8 – 23.4)	11 (22.0, 12.8 – 35.3)	2[a] (5.1, 1.6 – 16.9)
Intravenous drug use	15 (16.9, 10.5 – 26.0)	9 (18.0, 9.8 – 30.9)	6 (15.4, 7.3 – 29.8)
Other[§]	7 (7.9, 3.9 – 15.4)	4 (8.0, 3.3 – 18.9)	3 (7.7, 2.8 – 20.4)

Table 16 The prevalence of risk factors associated with IE. [§]"Other" risk factors comprised: mitral valve prolapse, non-RHD mitral valve regurgitation, non-RHD aortic valve regurgitation and stenosis, left ventricular dilation. [*]CI – confidence interval. [†]RHD – rheumatic heart disease. [a]χ^2, $p<0.05$

A causative organism was identified in 82 patients (92%, 95% CI, 85 – 96) (Table 17). There were no significant differences in aetiology between the two sites, or between Indigenous and non-Indigenous patients, or patients with or without native RHD (data not shown). Patients with a history of IDU were more likely to have *Staphylococcus aureus* isolated (73% (11/15) versus 43% (39/89), χ^2 p=0.02).

The mitral valve was involved in 44 patients (49%, 95% CI, 39 – 60), the aortic valve in 25 patients (28%, 95% CI, 20 – 38), and the tricuspid valve in 16 patients (18%, 95% CI, 11–27). Seven patients (7.9%, 95% CI, 4.0 – 15) had more than one heart valve affected.

Outcome data are presented in Table 18. Cairns patients were less likely to undergo valve replacement or surgery than Darwin patients (odds ratio (OR) 0.31, 95% CI, 0.10 – 0.91). This persisted after controlling for patient demographics and risk factors (see Table 15 and Table 16). Additionally, the length of stay for Cairns patients and for those who were transferred was significantly shorter. Logistic regression modeling demonstrated that the only independent predictor of in-hospital mortality was age (surviving admission OR 0.95/year of age, 95% CI, 0.92 – 0.98) with 91% (20/22) of patients in the youngest age quartile (<36 years) surviving compared with 55% (12/22) of those in the oldest (>61 years) (Fisher's exact test, p<0.05).

The utility of specific endocarditis coding (ICD I33.0) or broader separation coding (see ICD codes above) to detect patients who met modified Duke criteria was explored in Cairns. Of the 75 episodes identified as endocarditis (ICD I33.0) only 41 (55%) met modified Duke criteria. Using broader separation coding increased the cases requiring review by 564 and resulted in the identification of an additional 9 IE cases that did not have an ICD I33.0 separation diagnosis. A separation diagnosis of endocarditis (ICD I33.0) had a sensitivity of 82% and specificity of 94% for identifying cases which met modified Duke criteria.

Number (% patients, 95% CI[*])	**All patients** (N=89)	**Cairns** (N=50**)**	**Darwin** (N=39)
Staphylococcus aureus	39 (43.8, 34.0 – 54.2)	24 (48.0, 34.8 – 61.5)	15 (38.5, 24.9 – 51.2)
Methicillin susceptible	32 (36.0, 26.8 – 46.3)	21 (42.0, 29.3 – 55.8)	11 (28.2, 16.6 – 43.9)
Methicillin resistant	7 (7.9, 3.9 – 15.4)	3 (6.0, 2.2 – 16.2)	4 (10.3, 4.2 – 23.7)
Streptococci and related species[†]	21 (23.6, 16.0 – 33.4)	11 (22.0, 12.8 – 35.3)	10 (25.6, 14.6 – 41.2)
Enterococcus faecalis	10 (11.2, 6.3 – 19.5)	5 (10.0, 4.4 – 21.4)	5 (12.8, 5.7 – 26.8)
Other gram positive bacteria[‡]	7 (7.9, 3.9 – 15.4)	2 (4.0, 1.2 – 13.5)	5 (12.8, 5.7 – 26.8)
Gram negative bacteria[§]	5 (5.6, 2.5 – 12.5)	3 (6.0, 2.2 – 16.2)	2 (5.1, 1.6 – 16.9)
No causative organism identified	7 (7.9, 3.9 – 15.4)	5 (10.0, 4.4 – 21.4)	2 (5.1, 1.6 – 16.9)

Table 17 Etiologic organisms identified in IE patients. [†]including Streptococcus agalacticae, bovis, gordonii, mitis, mutans, oralis, pasteurianus, pneumoniae, pyogenes, salivarius and Gemella morbillorum, Abiotrophic defective, Granulicatella spp .[‡] including Corynebacterium, Staphylococcus epidermidis, Propionobactermium acnes. [§] including Actinobacillus actinomycetemcomitans, Klebsiella pneumonia, Salmonella typhimurium, Bartonella henselae. [*]CI – confidence interval

	All patients (89)	Cairns (50)	Darwin (39)
Died during admission	18	11	7
(n, % patients, 95% CI)	(20.2, 13.2 – 29.8)	(22.0, 12.8 – 35.3)	(17.9, 9.1 – 32.8)
Transferred	34	15	19
(n, % patients, 95% CI)	(38.2, 28.8 – 48.6)	(30.0, 19.1 – 43.8)	(48.7, 33.8 – 63.9)
Valve Replacement/Surgery	18	6	12[a]
(n, % patients, 95% CI)	(20.2, 13.2 – 29.8)	(12.0, 5.7 – 23.0)	(30.8, 18.6 – 46.5)
LOS[*]	20	15	25[b]
(median days, IQR)	(10 – 32)	(9 – 31)	(15 – 34)

Table 18 IE patient outcomes. [*]LOS – length of stay, defined as time from admission to discharge, death or transfer. [a]χ^2, $p<0.05$. [b]Mann-Whitney U, $p<0.05$

Discussion

This is the first study to comprehensively describe IE in a northern Australian setting. The rate of IE was comparable to that seen in other Australian, American and European studies.[289, 297 288, 290, 291] Given that the risk of IE increases with age in other populations[82, 297], it is likely the younger age of patients in this study (median 45 years versus greater than 60 years in other studies[82, 297]) served to mask a greater risk of IE in northern Australia. This was reflected in the increased rate of IE seen in our northern Australian cohort when age standardised to the overall Australian population.

IE risk in our northern Australian population was greater in Aboriginal and Torres Strait Islander peoples (RR 2.0). Whilst it is possible this is related to the high prevalence of RHD in the Indigenous Australian population[298] only 7/12 (58%, 95% CI 28 – 85) of the RHD-associated IE cases occurred in Indigenous Australians suggesting that factors apart from RHD were involved. Why the greater risk of IE in Indigenous Australians was more

marked in the NT than in FNQ is unclear. It may in part be explained by the higher proportion of the Darwin catchment residing in remote and very remote communities (Darwin 20.7% compared with Cairns 10.7%).[296] Any such association between IE risk and remoteness may be attributable to the environmental and social disadvantage which characterises many remote Indigenous Australian communities.[299]

RHD was associated with a far greater risk of IE. This association between RHD and increased risk of IE is well documented in the developing world [83, 300, 301] but is no longer seen in many higher income countries.[82] In the latter context, RHD-associated IE has become less important as the prevalence of RHD has reduced[35] and rates of IDU have risen.[302]

The association between RHD and IE in this study was not limited to Indigenous Australians. Non-Indigenous Australians accounted for 5/12 (42%, 95% CI 15 – 72) cases of RHD-associated IE and non-Indigenous Australians with RHD were at greater risk of IE than Indigenous Australians with RHD (RR 3.7). Current Australian guidelines[84] recommend providing prophylactic antibiotics only to Indigenous Australians with RHD undergoing high-risk dental, respiratory, genitourinary and gastrointestinal procedures. Non-Indigenous Australians with RHD are not covered by this recommendation. Our findings suggest that restricting the use of antibiotic prophylaxis on the basis of ethnicity may place some non-Indigenous people with RHD at unwarranted risk.

Under the American Heart Association's guidelines[85], prophylaxis against IE is recommended for patients with RHD only if they have prosthetic valves or prosthetic material in cardiac valve repairs. Patients with "native valve" RHD are not included. The high prevalence of RHD in northern Australia and the increased risk of IE in people with native valve RHD demonstrated in this study suggest that it would be unwise to adopt the American guidelines in this setting. Altering Australian recommendations to reflect American standards may expose both Aboriginal and Torres Strait Islander people and non-Indigenous people with RHD to an increased risk of IE.

Men were at greater risk of IE. This is concordant with previous reviews of IE but reasons remain unclear.[291, 303] It may be in part explained by the greater prevalence of IDU in men

which in turn confers an increased risk of IE.[304] The association between IDU and males was reflected in our study with 10/15 (67%, 95% CI, 41 – 84) of IE patients with a recent history of IDU being men.

A temporally associated triggering event was noted in 27% of patients. The most common was recent healthcare-related intravenous access. Such nosocomial IE is a recognised significant contributor to IE cases, accounting for up to 30% of infections.[288, 297] Of note was the low number of triggering events seen in RHD-associated IE. It was not possible to ascertain whether this was due to the use of prophylactic antibiotics to prevent IE in RHD patients or the possibility that IE in patients with RHD tends to largely occur without a clear triggering event.

The microbiologic etiology of IE in our study was comparable to that seen in other Australian and international studies. [297, 302, 304, 305] In line with previous studies, IDU-associated IE was more likely to be caused by *Staphylococcus aureus*.[306]

The outcome for IE patients in northern Australia reflects the significant mortality and health care utilization associated with IE. One in five patients admitted to hospital with a definite or possible diagnosis of IE died. The association between advancing age and a greater risk of death from IE noted here has been seen elsewhere.[290] Despite the younger age of our cohort, the mortality seen in this series was comparable to that seen in earlier studies.[291, 297] Whilst Indigenous Australians are subject to well described health disadvantage[307], there was no increased risk of in-hospital mortality compared with non-Indigenous Australians. The shorter hospital length of stay compared with the previous Australian study (20 versus 30 days) [297] was in part explained by the significant proportion of IE patients who were transferred to other hospitals for ongoing management owing to the absence of local cardiothoracic surgical services.

Our investigation into the accuracy of ICD coding at Cairns raised a number of issues. Using IE separation coding (ICD I33.0) alone to identify cases as opposed to a broader search strategy (see ICD codes in Methods) would have missed nearly 20% of modified Duke criteria IE cases. Furthermore, 45% of patients with an ICD I33.0 coding did not satisfy modified Duke criteria for IE. Overall, IE separation coding (ICD I33.0)

underestimated the true prevalence of IE by 15%. This reflects Sy's earlier Australian study[297] where separation coding of IE in tertiary referral hospitals was accurate in 79% of cases. Whilst IE separation coding may be the easiest method for investigating IE we have shown it to be neither sensitive nor specific. Given the infrequent occurrence of IE and the substantial impact it has on health care and patients, alternate systems for correctly identifying cases of IE should be considered as part of ongoing surveillance.

Conclusion

This is the first study to assess IE in a northern Australian population. It has demonstrated parallels with IE in less remote Australian and other high income settings despite the remoteness of many patients and significant Aboriginal and Torres Strait Islander population. Even here the presence of prosthetic cardiac material, IDU and previous IE are the principle factors associated with IE. Whilst RHD markedly elevates the risk of IE, even in this northern Australian population it is not restricted to Indigenous Australians. Providing antibiotic prophylaxis to Indigenous Australians with RHD is thus unlikely to address the major drivers of IE and would exclude many non-Indigenous patients with RHD. For patients with RHD, current Australian recommendations of providing prophylactic antibiotics only if they are Indigenous may need to be broadened to include non-Indigenous RHD patients.

Key Points

1. To prevent infective endocarditis (IE) Australian guidelines recommend providing prophylactic antibiotics to Indigenous patients with rheumatic heart disease (RHD) prior to procedures which may cause bacteraemia. American guidelines were recently updated to recommend that prophylactic antibiotics be given to RHD patients prior to such procedures only if they have prosthetic valves or prosthetic material in cardiac valve repairs rather than "native valve" RHD. We aimed to determine whether RHD is associated with an increased risk of IE, which risk factors are associated with IE, and the incidence and aetiology of IE in northern Australia.

2. IE was more common in people with RHD (relative risk (RR) 58), Indigenous Australians (RR 2.0) and men (RR 1.7). RHD-associated IE was not confined to Indigenous Australians with 42% being non-Indigenous.
3. In northern Australia RHD increased the risk of IE but it was not restricted to Indigenous Australians. Current Australian recommendations of providing prophylactic antibiotics to Indigenous patients with RHD prior to procedures which may cause bacteraemia may need to be broadened to include non-Indigenous patients.

Chapter 5 – Discussion and Conclusions

The papers and projects that comprise this thesis provide a number of new insights into the prevention, diagnosis and management of ARF and RHD. Systematic reviews of existing evidence and new findings associated with a number of research projects are presented. These papers and projects will inform and complement existing research findings, policies and protocols whilst at the same time providing new insights to refine and expand the health service response to ARF and RHD.

The review papers included herein provide a synthesis of the current evidence pertaining to a number of areas relevant to the prevention of ARF and RHD whilst also providing a critique of deficits in the current state of knowledge. In addition, they suggest how future research to improve the response to ARF and RHD can be targeted to address gaps in existing knowledge with a particular focus on areas that are likely to have an early and substantial impact on disease prevention.

The research papers focus more specifically on mechanisms to improve the diagnosis and management of ARF and RHD through the critical evaluation of management practices in the north of Australia, quantification of the risk of endocarditis in people with RHD to inform a more rational use of prophylactic antibiotics, and clarification of diagnostic issues pertaining to the significance of non-specific changes in heart valve morphology and function detected by screening echocardiography.

Briefly the insights provided by this body of work are:

1. Primordial and primary prevention strategies, while desirable and seemingly successful in some contexts, have not yet been shown to be effective in an Australian Aboriginal and Torres Strait Islander context. Limitations of reported studies are outlined and it is argued that no specific programmes can be endorsed at this time. Translational research is required to investigate whether particular primary prevention strategies may prove effective in Australia.

2. There is a need to improve the uptake of secondary antibiotic prophylaxis for ARF/RHD in Australia. The review incorporated in this thesis demonstrates that there is little good

quality evidence to recommend implementation of any specific strategies to achieve this. Again, translational research is required.

3. Echocardiographic screening for RHD is desirable in that it offers the possibility of early detection and treatment. However, issues regarding what criteria should constitute a positive screening test, suboptimal delivery of secondary prophylaxis, and the potential impact of any such screening programme on local health services and communities are demonstrated and it is argued that further work is required before such a programme could be considered to be feasible in an Australian context.

4. The significance of minor heart valve abnormalities, including Borderline RHD, in predicting the risk of ARF and RHD was explored and partially clarified. Children with Borderline RHD are at an increased risk of ARF, progression of valvular lesions, and development of Definite RHD while children with NSVAs have a lesser increased risk of progression to Definite RHD. These findings provide support for considering secondary antibiotic prophylaxis or ongoing surveillance echocardiography in high-risk children with Borderline RHD or NSVAs. In addition, they highlight that the pool of children requiring ongoing follow-up in association with any RHD screening programme will be at least three times larger than if restricted to Definite RHD alone.

5. A single-provider model of delivery of ARF/RHD care was associated with improved patient care, fewer cases of severe disease, and reduced surgical and other interventions compared to a model of care incorporating a broad range of local and visiting specialists.

6. RHD is a significant risk factor for IE in northern Australia. Current Australian recommendations of providing prophylactic antibiotics to Indigenous patients with RHD prior to procedures which may cause bacteremia should be retained despite American guidelines no longer recommending prophylaxis in those with native RHD undergoing such procedures. Furthermore, Australian guidelines may need to be broadened to include non-Indigenous patients with RHD.

The following discussion explores these findings in more detail within the framework of the three major themes of this thesis: prevention, diagnosis and management.

Primordial, Primary and Secondary Prevention of ARF/RHD

Primordial and primary prevention aim to prevent disease occurring. In the publication "Primordial and Primary Prevention of ARF/RHD"[2] the candidate undertook a systematic review of the published evidence pertaining to programmes and strategies used to limit the transmission and burden of GAS or the development of ARF once GAS infection has occurred. The effectiveness of **primordial prevention** is perhaps best illustrated by the decreasing prevalence of ARF and RHD in "affluent" countries with higher socio-economic indices, access to uncrowded shelter, and easily accessible health care systems. Whilst the concept of 'affluence' or 'advantage' may be easily understood, it is nonetheless unclear exactly what components of such improved living standards are associated with the primordial prevention of ARF and RHD. However, this should not dissuade advocates, whether health care providers, politicians, community leaders or anyone advocating for social and health justice, from exploring mechanisms to alleviate poverty and social and environmental disadvantage, improve housing and education, and increase access to appropriate and effective health care. All these factors are likely to be crucial in addressing ARF/RHD, as well as many other health issues, in remote Australian communities. Given the lack of a defined target there should not be a limited focus on the primordial prevention of ARF/RHD within the health care system. Indeed, it is surely beyond the scope of any health care system to effect such change. Rather, primordial prevention should be encompassed in a broader emphasis on social justice and equity. The evidence pertaining to the primordial prevention of ARF/RHD highlights how the benefits of social and environmental policy may require a substantial and prolonged commitment, well beyond that of any short-term evaluation strategy.

The literature review of **primary prevention** strategies revealed a number of studies reporting significant reductions in incidence rates of ARF and RHD. However, there were limitations regarding these studies that suggest caution should be exercised in any attempt to generalise specific findings to an Australian context. More specifically, the studies from the French Caribbean[141], Costa Rica[138] and Cuba[139] reporting significant success in reducing ARF/RHD all suffered from methodological issues such that it was not possible to

identify which components of multidimensional interventions were likely to be successful. The tightly controlled studies involving the US military[58, 136] were more rigorous and yet were undertaken in highly selected and controlled settings very dissimilar to the Aboriginal and Torres Strait Islander setting. Finally, it is important to note that the most comprehensive RCT of a community-based sore throat intervention undertaken in New Zealand failed to show a significant beneficial effect of active surveillance.[61]

It is clear that the use of prophylactic antibiotics can reduce GAS colonisation of the pharynx and the associated risk of ARF. Indeed, such prophylaxis is one of the major foci of secondary prevention strategies for individuals with a previous diagnosis of ARF or RHD. Nonetheless, the widespread use of antibiotics as a primary prevention strategy in high-risk populations may require the diversion of substantial health resources from other areas of care and place otherwise healthy individuals at unnecessary risk while potentially increasing the likelihood of reduced antibiotic susceptibility in other bacteria. These factors are also relevant when deciding whether or not to treat individuals with sore throats prior to the identification of the causative organism. There is always a necessary balancing of the potential benefits of early treatment of those with GAS pharyngitis and unnecessary treatment of individuals with pharyngitis not related to GAS.

Despite there being insufficient high quality evidence to support specific primary prevention strategies in Australia it is important not to make the assumption that any such interventions will not work. That is, lack of evidence of effect does not equate to evidence of no effect. Indeed many of the primary prevention studies discussed in this thesis do provide evidence of effect. Nonetheless, it is important to exercise caution in generalising results from these studies to an Australian context involving Aboriginal Australians and Torres Strait Islanders living in remote communities.

The ideal solution to effect primary prevention of ARF/RHD is likely to remain the development of a GAS vaccine. While there are encouraging signs on this front with clinical trials underway, when a safe and effective vaccine may become available remains speculative. A particular hurdle in this instance is the underlying pathophysiology of ARF which involves cross-reactivity between GAS, and thus potentially vaccine, epitopes and cardiac tissue markers. Ensuring effective GAS vaccines reduce the risk of GAS infection

without also being associated with inadvertent autoimmune-mediated carditis will therefore be key. Further challenges include the great number of GAS strains that may be associated with ARF that would need to be covered by a vaccine and the limited commercial viability of any such vaccine.[27]

Whilst development of a GAS vaccine must remain a priority in the primary prevention of ARF/RHD prevention, in the interim it will be important for people comprising or working with high-risk populations to remain vigilant to the importance of seeking and providing appropriate health care when pharyngitis occurs. Further research into the utility of clinical scoring systems and rapid diagnostic tests in identifying GAS-associated pharyngitis should be evaluated in Australia, particularly in Aboriginal and Torres Strait Islander communities. Furthermore, in those at highest risk of ARF, and in situations where clinical follow-up of individuals may be difficult, empiric antibiotic management of pharyngitis, even when the aetiology has not been confirmed, is likely to remain necessary.

Secondary prevention relates to interventions that take place once a disease has been diagnosed. Secondary prevention aims to either cure or limit progression with the ultimate aim of ensuring a reduced impact in affected individuals. With respect to ARF/RHD, secondary prevention in the form of regular 3-4 weekly injections with long-acting benzathine penicillin is one of the mainstays of disease treatment. It has shown to be effective in preventing GAS infection and hence recurrent ARF and possibly development of, or worsening of, RHD. While it is an effective treatment, the implementation of effective secondary antibiotic prophylaxis programmes for ARF/RHD has proved difficult with many individuals not receiving adequate coverage against GAS.[68] Suggestions as to why delivery of secondary antibiotic prophylaxis is often suboptimal are numerous with many favouring factors such as longevity of treatment (minimum ten years), pain of injection, mobility of patients and culturally inappropriate health delivery systems. However, most evidence relating to improving the delivery of secondary prophylaxis appears to be anecdotal in nature.

In the review “Enhancing secondary prophylaxis for rheumatic fever and rheumatic heart disease” (submitted) the candidate undertook an evaluation of the published evidence pertaining to improving uptake of secondary antibiotic prophylaxis for ARF/RHD and

explored potential options for further research. This review highlighted the limited published evidence that is available to inform initiatives to enhance the delivery of secondary antibiotic prophylaxis. Nonetheless a number of elements where identified which are likely to be important in improving uptake: use of registers and recall systems; development of strong staff-patient relationships; creation of dedicated teams for the delivery of secondary prophylaxis; education programmes; and implementation of initiatives to improve community linkages (especially with schools). Despite these findings it may still be difficult to generalise findings from individual studies to other settings, and additional high quality studies in this field are still needed. Given these limitations a particular focus should be the evaluation of initiatives that translate what is an efficacious treatment (secondary antibiotic prophylaxis) into effective programmes that reduce the burden of ARF/RHD. Only by undertaking rigorous high-quality health services research will it be possible to obtain solid evidence, rather than what are currently often anecdotal views, regarding what can be done to better protect individuals with a prior history of ARF or RHD from disease progression. Alongside such research a longer-term aim should be to look beyond traditional forms of delivery of secondary antibiotic prophylaxis via regular intramuscular injections of benzathine penicillin to identify less painful and more convenient mechanisms of delivery.

Screening for RHD and Informing Echocardiographic Diagnosis.

The traditional pathway to a diagnosis of RHD relied on the detection of a heart murmur through auscultation, typically in the setting of a previous episode of ARF. More recently echocardiography has become the main focus of RHD diagnosis, enabling the non-invasive examination of both morphology and function of heart valves. As echocardiography equipment has become more affordable and portable it has been increasingly utilised for RHD screening in low and middle-income countries and in Indigenous population at increased risk of ARF/RHD in high-income countries (e.g. New Zealand and Australia).

Screening echocardiography has the potential to detect early RHD thereby enabling timely commencement of treatment (secondary antibiotic prophylaxis) to limit disease

progression. Despite its appeal and apparent simplicity, before deciding whether or not to implement an echocardiographically-based RHD screening programme it is necessary to examine the need for, potential feasibility and overall benefit of such screening. In the review article entitled "Screening for RHD in Aboriginal and Torres Strait Islander Children"[77] The candidate examined the feasibility of such programmes within the framework of the Australian criteria for the assessment of population-based screening.

This review concluded that a number of issues prevent potential initiatives for echocardiographic screening for RHD from satisfying the Australian criteria for acceptable screening programmes. Primarily, it is unclear what criteria should be used to define a positive screening result as questions remain regarding the significance, natural history and potential treatment of early and subclinical RHD (echocardiographic changes in the absence of a pathological murmur). Further, as discussed above, at present the delivery of secondary antibiotic prophylaxis in many areas of Australia remains suboptimal such that the potential benefits of screening in facilitating early treatment to impede or reverse disease progression would be limited. Finally, the impact of echocardiographic screening for RHD on local health services and the psychosocial health of patients and families are yet to be fully ascertained.

These findings suggest that unless and until these issues can be addressed, it is premature to suggest that routine screening for RHD should be undertaken in Aboriginal and Torres Strait Islander children. Such a screening programme would suffer from unclear diagnostic criteria, potential ineffective follow-up of, and delivery of secondary antibiotic prophylaxis to, those who screen positive, and potential negative impacts on local health providers, health service sustainability and the psychosocial health of patients and their families.

The debate over what constitutes a positive echocardiographic screening result for RHD has intensified over recent years owing to the publication of a number of RHD echocardiographic screening studies that have utilised differing diagnostic criteria. In order to address this issue, the World Heart Federation developed a set of diagnostic criteria for the echocardiographic diagnosis of RHD in the absence of a prior history of ARF. This set of criteria outlines three categories: Definite RHD, Borderline RHD, and Normal. The category of Borderline RHD recognises some people will demonstrate minor heart valve

abnormalities of uncertain significance on echocardiography. Whether Borderline RHD is an early variant of the Definite RHD category or the Normal category remains unclear and the clinical significance and natural history of Borderline RHD is therefore of particular importance if echocardiographic screening is to be considered.

RhFFUS (Rheumatic Fever Follow-Up Study) was designed to clarify the significance of minor heart valve findings on screening echocardiography.[78] Results from this study were the first to address the questions of whether individuals with Borderline RHD are at greater risk of ARF or progression of valvular lesions to Definite RHD. RhFFUS demonstrated that children with Borderline RHD on prior echocardiogram are at a seven to nine times greater risk of ARF than children with a prior normal echocardiogram. It also showed that they are at eight times higher risk of progression of valvular lesions, and significantly greater risk of progressing to Definite RHD (one in six progressed to Definite RHD). In contrast, children with less severe valve abnormalities that do not meet criteria for Borderline RHD (non-specific valvular abnormalities – NSVAs) were at no greater risk of ARF and a lesser risk of progression with one in ten developing Definite RHD.

These results, for the first time, provide cogent evidence that at least some children with Borderline RHD, and to a lesser extent other NSVAs, on screening echocardiogram actually have the earliest stages of definite RHD and may benefit from secondary prophylaxis and/or enhanced surveillance through regular echocardiographic monitoring to assess for progression of disease. Moreover, these results lend particular support to the criteria used by the WHF to distinguish Borderline RHD from other minor echocardiographic changes. It was the Borderline RHD subgroup that had an increased risk of ARF and greater risk of progression of valvular lesions and development of definite RHD. Nonetheless, the fact that individuals with minor echocardiographic changes that did not meet criteria for Borderline RHD still had an increased risk of progression, including to Definite RHD, suggests that the criteria for Borderline RHD may need to be broadened and that such individuals should also be monitored. General recommendations for treatment or follow-up are offered with caution, however, as an assessment of local risk of ARF and RHD and the ability to deliver secondary antibiotic prophylaxis and other clinical follow-up will influence any such decision. In reality, it is the clinician, working in partnership

with patients, families and communities, who must use their clinical judgment in determining how individuals with Borderline RHD or other non-specific changes identified on echocardiographic screening should be managed.

The findings from RhFFUS pose a number of questions that are likely to be important in informing policy and practice in this area.

- The period of follow-up for the study was on average 3.5 years. Whilst we demonstrated a significantly increased risk of ARF and echocardiographic progression in those with Borderline RHD, and to a lesser extent NSVAs, a longer period of follow-up period (e.g. to 10 years) would have provided a more detailed perspective of risk, and potentially provided a greater insight regarding which aspects of Borderline RHD and NSVAs conferred the greatest risk. Following up this cohort in another five years should therefore be considered.
- The numbers of Borderline RHD and NSVA individuals included in the study was limited thereby decreasing the power of the study. Presently there are a number of international screening studies being undertaken. A multi-national collaborative research project pooling data from these disparate projects will provide a far more powerful insight into the natural history of Borderline RHD and NSVAs and provide generalisability of our findings outside the Australian setting.
- Results of logistic regression analysis suggest that Borderline disease of the mitral valve (subcategories A and B) is associated with a particularly increased risk of progression, including to Definite RHD, in comparison to those with Borderline RHD involving the aortic valve (subcategory C). A combined study with greater participant numbers should enable confirmation and further refinement of this association.
- A number of individuals with Borderline RHD demonstrated improvement in their echocardiographic changes over the course of follow-up between the gECHO and RhFFUS studies. Future studies incorporating a longer follow-up period or a larger multi-national collaboration could provide insights into how to identify those most likely to spontaneously regress and who could thus be reassured and avoid further follow-up or intervention.

- The benefit of secondary antibiotic prophylaxis in people with Borderline RHD or NSVAs on progression of valve lesions and development of Definite RHD requires confirmation. Ideally, this question should be answered by a clinical trial whereby individuals with Borderline RHD or NSVAs are randomly assigned to regular four-weekly benzathine penicillin or a comparable placebo with up to ten years of follow-up. Any such study would face a number of ethical and feasibility issues. Nonetheless without this evidence there will remain ongoing doubt regarding the utility of secondary antibiotic prophylaxis in what might be viewed as the earliest stage of sub-clinical RHD.

RhFFUS provides valuable insights into the significance of minor echocardiographic abnormalities on screening echocardiography in populations at increased risk of RHD, and hence provides relevant information regarding what criteria should be used to determine a positive screening test if RHD screening is undertaken. Nonetheless, RhFFUS does not necessarily provide an irrefutable rationale for RHD screening as a component of regular health care delivery. Any such decision will require further knowledge as regards the longer term outcome of Borderline RHD and other non-specific valvular abnormalities and the benefits, sustainability and cost-effectiveness of enhanced surveillance and/or secondary antibiotic prophylaxis. If indeed screening is not pursued in Australia then, by extension, additional individuals with Borderline RHD will not be identified (except perhaps as an incidental finding when children are investigated for some unrelated cardiac condition). In this case the significance of Borderline RHD and NSVAs and the WHF criteria for screening-based diagnosis of RHD would become moot. Even if screening is pursued then any diagnosis of Definite or Borderline RHD will only be of use if there are effective, functional and sustainable systems for follow-up and secondary prevention in place. In light of these considerations the priorities in ARF/RHD care are likely, at this stage, to remain identification/diagnosis of ARF, effective delivery of secondary prophylaxis, and clinical follow-up and management of complicated valve disease.

Management

The final component of this thesis focused on elements pertinent to the management of ARF and established RHD. Management of these conditions includes secondary antibiotic prophylaxis to prevent GAS infection and recurrent ARF, regular local primary healthcare review, surveillance echocardiography, specialist medical and surgical review, education, and the prevention and management of complications resulting from heart valve damage and associated abnormal function.

In "Variability in Disease Burden and Management of Rheumatic Fever and Rheumatic Heart Disease in Two Regions of Tropical Australia"[68] the candidate investigated the quality of care provided to ARF and RHD patients in the Kimberley region of Western Australia and far north Queensland to ascertain whether differing models of service delivery were associated with differing disease burden and/or quality of patient care. In the Kimberley, specialist care was delivered by a broad range of visiting and local providers while in far north Queensland a single provider model was used as part of a coordinated RHD control programme that included a regional ARF/RHD register. Results indicated that there was more severe disease in the Kimberley and that patients in far north Queensland were more likely to receive specialist review, to be prescribed secondary prophylaxis, and to receive secondary prophylaxis than those in the Kimberley. These results indicated that far north Queensland's single-provider model of care and centralised ARF/RHD control programme were associated with improved patient care, potentially few cases of severe disease, and a reduced requirement for surgical and other interventions.

Studies such as this that can identify gaps in health service delivery are a crucial first step in any programme of continuous quality improvement and, where some aspects of care are clearly suboptimal, provide impetus for health system refinement and improvement. Interestingly, since the time of this study an ARF/RHD enhanced surveillance system and regional ARF/RHD database has been implemented in the Kimberley along similar lines to that seen in far north Queensland. A logical next step in any quality assurance initiative would be to repeat the study in the Kimberley at some future date to determine whether markers of service delivery, including delivery of secondary prophylaxis and specialist review, have changed since the model of care changed. It would be illuminating also to

assess disease severity to determine whether this change in the model of care has been associated with improved outcomes for ARF/RHD patients in the Kimberley.

Another aspect of the management of RHD is to provide prophylactic antibiotics to individuals with RHD prior to procedures that may cause bacteremia as a potential mechanism for preventing infection of damaged heart valves, a condition called infective endocarditis (IE). Australian guidelines recommend such treatment for Indigenous Australians with RHD undergoing high-risk dental, respiratory, genitourinary and gastrointestinal procedures. However, the American Heart Association guidelines have suggested such prophylaxis be limited to only RHD patients who have prosthetic valves or other cardiac prosthetic material *in situ* and not for those with "native valve" RHD. Given ongoing debate in Australian regarding whether a similar position should be adopted it was timely to undertake a review of IE cases in northern Australia to determine whether native valve RHD was associated with an increased risk of IE. The results of this study were published in "Infective Endocarditis and Rheumatic Heart Disease in the north of Australia".[86] Native valve RHD was shown to be associated with a far greater risk of IE (RR 58 compared to individuals without native valve RHD). Interestingly, however, this association was not limited to Indigenous Australians with the risk of IE in non-Indigenous patients with RHD being 3.7 times higher than Indigenous Australians with RHD.

These results suggested that it would be unwise, at this stage, to reflect the American Heart Association's recommendations to restrict prophylactic antibiotics in RHD patients to only those with prosthetic valves or other cardiac prosthetic material *in situ* in Australia. Furthermore, these findings highlighted that Australian guidelines may also need to be broadened as our findings suggest that restricting the use of antibiotic prophylaxis on the basis of ethnicity may place some non-Indigenous Australians with RHD at an increased and potentially preventable risk of IE.

Summary and Implications

While ARF and RHD are preventable conditions, Australia's Aboriginal and Torres Strait Islander peoples, particularly those living in remote communities, continue to experience some of the highest rates of these diseases in the world. In contrast, both ARF and RHD

have been relegated to the status of an anachronistic curiosity in non-Indigenous Australia where diagnoses have become so rare that health professionals are in danger of losing the knowledge and experience required to identify them. This disparity in disease burden necessitates a response; a response which acknowledges the difficulties of delivering health care in remote, isolated settings where sensitivity to cultural differences is paramount but which strives to overcome these barriers to ensure best possible outcomes for individuals at risk of, or already affected by, ARF and RHD. This thesis has presented a number of insights into the knowledge gaps regarding prevention, diagnosis and management of ARF/RHD and presented a number of recommendations to inform how health services might improve a number of aspects of care. The future and priority of ARF/RHD care should remain primordial and primary prevention. It is hoped that continued work on developing a GAS vaccine will eventually deliver an effective and safe primary prevention tool. In the interim, continued focus on early, accurate diagnosis of ARF/RHD and best-practice management (particularly improving uptake of secondary antibiotic prophylaxis and/or developing more effective delivery systems) should be pursued. Overarching these health initiatives must be a commitment to improving the socioeconomic, environmental and educational status of Aboriginal and Torres Strait Islanders living in remote communities as a means of effecting primordial prevention against ARF/RHD and many other health issues.

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Appendices

Appendix 1 – Priorities in the Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease.

In June 2011, an Indigenous Cardiovascular Health Conference organised by CSANZ (The Cardiac Society of Australia and New Zealand) was held in Alice Springs, Northern Territory. One of the workshops at the conference focused on ARF and RHD. Specialist clinicians, health service providers, researchers, and other stakeholders were given the opportunity to discuss their views regarding the priorities that should be pursued in addressing ARF/RHD in Australia and Oceania.

The candidate was a participant at this workshop and subsequently prepared a summary paper of the priorities identified during the meeting. These priorities provided a valuable background and rationale for much of the work contained in this thesis. In particular, the discussion regarding "echocardiography for screening and diagnosis", "secondary prophylaxis" and "primary prevention of Group A streptococcus" was integral in the development of the themes this thesis.

This paper is included as an appendix to this thesis not only to provide a context for this body of work but also to provide a stakeholder perspective on priorities for ARF/RHD in Australia and demonstrate some of the consultation work undertaken by the candidate during his PhD. This paper was published in the journal Heart, Lung and Circulation.[69]

Title Page

Title: Acute Rheumatic Fever and Rheumatic Heart Disease - *Priorities in Prevention, Diagnosis and Management. A report of the CSANZ Indigenous Cardiovascular Health Conference, Alice Springs 2011*

Short Title: Priorities in ARF/RHD

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Abstract

Three priority areas in the prevention, diagnosis and management of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) were identified and discussed in detail:

1. *Echocardiography and screening/diagnosis of RHD* - Given the existing uncertainty it remains premature to advocate for or to incorporate echocardiographic screening for RHD into Australian clinical practice. Further research is currently being undertaken to evaluate the potential for echocardiography screening.
2. *Secondary prophylaxis* – Secondary prophylaxis (long acting benzathine penicillin injections) must be seen as a priority. Systems-based approaches are necessary with a focus on the development and evaluation of primary health care-based or led strategies incorporating effective health information management systems. Better/novel systems of delivery of prophylactic medications should be investigated.
3. *Management of advanced RHD* - National centres of excellence for the diagnosis, assessment and surgical management of RHD are required. Early referral for surgical input is necessary with multidisciplinary care and team-based decision making that includes patient, family, local health providers. There is a need for a national RHD surgical register and research strategy for the assessment, intervention and long-term outcome of surgery and other interventions for RHD.

Keywords:

Rheumatic fever

Rheumatic heart disease

Australia

Indigenous population

Prevention and control

Text

Introduction

Any discussion of the prevention, diagnosis and management of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) will highlight the complexity inherent in providing an effective response to a condition that extends from acute through to chronic disease. Given the underlying association between ARF/RHD and socioeconomic disadvantage [1-3] such discussion must, by extension, involve multiple dimensions across all levels of health care and society more generally.

In Australia, these diseases are almost exclusively borne by Aboriginal and Torres Strait Islander peoples, particularly those living in remote locations.[4-7] Geographical isolation and socioeconomic disadvantage, along with the need to provide long-term monitoring and care for those living with ARF/RHD, pose a number of major challenges to many patients, families, communities and health services. Delivery of ARF/RHD care in this setting is often less than optimal. Within this context, the aim of this workshop, undertaken as part of the CSANZ Indigenous Cardiovascular Health Conference in Alice Springs in 2011, was to identify priorities and provide guidance to inform the future response to the prevention, diagnosis and management of ARF and RHD in Australia and Oceania.

Ten priority areas were identified through working with health service organisations and health care providers both before and during the workshop (see Box 1). Whilst time constraints meant only three were discussed in detail, they all provide a valuable insight into how stakeholders in health care can inform the future response to prevention and disease management. The discussions involved over fifty stakeholders in Australian and New Zealand health care who outlined the current understanding of these issues, identified gaps in knowledge and current practice, and provided recommendations and guidance to CSANZ and Australian jurisdictions regarding how these gaps may be addressed to improve outcomes for people living with ARF and RHD in our region. The overview of these discussions detailed below provides a valuable local and clinical perspective on ARF/RHD prevention and management that will be important in informing the future Australian response to these conditions.

1. Is there a role for echocardiography in the screening of high-risk populations and better diagnosis of RHD?
2. Coordinating long-term care for people with RHD.
3. Better and more appropriate management of advanced RHD.
4. An appropriate and sustainable workforce.
5. Getting secondary prophylaxis to work.
6. Health determinants and the primordial prevention of ARF/RHD.
7. Primary prevention and Group A Streptococcus
8. Health promotion –communicating to patients, families, communities and health care.
9. Getting ARF/RHD on the national health agenda - why did it take so long to be recognized as a priority and how can we ensure that it remains on the national health agenda?
10. What are the systems issues that fail people living with ARF/RHD such that they do not receive the best practice care that they need?

Box 1 - Priorities for addressing ARF/RHD in Australia

Workshop Discussions and Recommendations

The three priority areas addressed in detail were:

1. Is there a role for echocardiography in screening and better diagnosis?
2. Getting secondary prophylaxis to work.
3. Better and more appropriate management of advanced RHD.

For each of these issues a brief background was provided, gaps in current systems identified and potential solutions for addressing these gaps highlighted.

1. Is there a role for echocardiography in screening and better diagnosis?

Background

Echocardiography is a crucial tool in diagnosing and assessing the severity of RHD.[8,9] With the availability of portable and relatively affordable echocardiography machines it is now possible to provide this to small and very remote communities as part of specialist outreach services. Nonetheless, there is ongoing debate regarding the details of valvular

morphologic change and the degree of functional impairment (regurgitation or stenosis) that are necessary to make a definitive diagnosis of RHD.[10] In particular, the question of whether potentially minor abnormalities of heart valve appearance or function represent the earliest signs of RHD remains unclear. Given this limitation the possible role of echocardiography in screening for early RHD cannot yet be fully addressed.

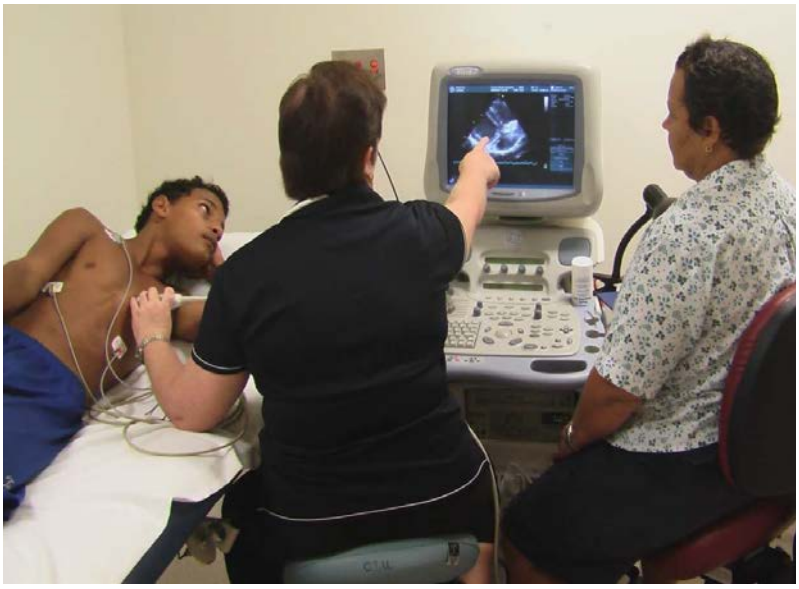


Figure 1 – Screening echocardiography – portable and non-invasive but is it effective?

Gaps

In discussing the use of echocardiography in screening for, and the better diagnosis of, RHD a number of gaps in knowledge were identified including:

- Based on existing uncertainty regarding **interpretation**, what should be done when echocardiography reveals minor changes in valve morphology? What are appropriate clinical algorithms for management of such minor abnormalities?
- **Valve (and particularly mitral valve) thickness** as a morphologic feature of RHD – measures of valve thickness are dependent on machine settings (gain, focus, transducer frequency) which are difficult to standardise. It seems unlikely that it will be possible to identify early disease through an objective echocardiographic measure of leaflet thickness.
- **Are lower cost and more portable echocardiography machines comparable to those that are more expensive in the diagnosis and assessment of RHD?** Anecdotal

evidence suggests lower cost portable machines may overstate the severity of valve lesions, especially for early disease. This is particularly important if the deployment of echocardiography-based screening programmes for RHD were considered with an attendant focus on early disease.

- **How could an echocardiography-based RHD screening programme be funded?** Could it be resourced within existing service frameworks?
- **Can an echocardiography screening programme fulfil the criteria** for "screening" if delivery of secondary prophylaxis remains poor?
- What would be an **appropriate service/workforce model of care if a screening programme were implemented**. Options could include an expanded scope of practice for primary health care staff to undertake screening echocardiography, delivery by specialist-led teams or outreach echocardiographers, and/or telemedicine for review of acquired echocardiography studies and discussion of management.

Solutions

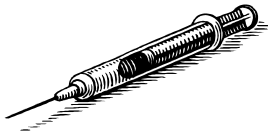
The response to some of the issues highlighted above is already underway. An extensive Australian screening study, the **gECHO** (getting Every Child's Heart Okay) study, is nearing completion. This project (a collaboration between Baker IDI (Alice Springs), James Cook University (Cairns), Menzies School of Health Research (Darwin) and the University of Western Australia (Broome) supported by the Australian Department of Health and Ageing) undertook screening echocardiograms in 4000 Aboriginal and Torres Strait Islander children and 1000 non-Indigenous Australian children across northern Western Australia and Queensland, and the northern Top End and Centre of the Northern Territory. Preliminary results of gECHO identified a significant proportion of children with mild morphologic abnormalities, particularly of the mitral valve, of doubtful significance. In order to clarify the significance of these results, a follow up study is being undertaken.

RhFFUS (Rheumatic Fever Follow-Up Study) is a prospective cohort study of children with non-specific mitral and/or aortic valve abnormalities that will examine whether such children are more likely to have an episode of ARF or develop RHD than children with normal heart valves. Supported by the National Health and Medical Research Council

(NHMRC), the findings of RhFFUS will provide clarity regarding the echocardiographic diagnosis of early RHD, help clinicians to better understand the significance of subtle changes on echocardiography, and inform the health service response for children with minor valve abnormalities. If such children are shown to have an increased risk of ARF and/or progression to RHD, then a case may be made for identifying high risk children earlier through screening echocardiography and offering them regular secondary prophylaxis to prevent progression to more severe RHD.

Given the existing uncertainty it remains premature to advocate for, or incorporate, echocardiographic screening for RHD into Australian clinical practice. If results of gECHO and RhFFUS indicate that screening may be viable then the next step will be to undertake a detailed scoping and impact study focusing on how such a programme would be delivered and sustained, its cost and comparative cost-benefit, and how it would impact on the existing primary and specialist workforce. If a case cannot be made, or support obtained, for a national RHD screening programme, there may remain a rationale for screening on a quasi *ad hoc* basis within high risk communities and areas.

2. Getting secondary prophylaxis to work



Background

Repeated episodes of ARF increase the likelihood that a person will develop RHD or will cause progression of RHD in those with minor disease.[11]If such repeated episodes of ARF can be prevented then the possibility of the development of severe RHD, with the attendant requirement for surgery to repair or replace damaged heart valves or other interventions, is reduced. For this reason, secondary prophylaxis in the form of four-weekly long-acting benzathine (LAB) penicillin injections is recommended for those who have had an episode of ARF or who have RHD.[9] The rationale for this treatment is the prevention of further GAS infections that may in turn lead to recurrent ARF. It should be noted that while there is good evidence that secondary prophylaxis for ARF/RHD is effective, oral antibiotics are inferior to intramuscular LAB in preventing recurrent ARF. The use of oral antibiotics is therefore only encouraged in patients with clear hypersensitivity to penicillin.[12]

While the effectiveness of secondary prevention is proven, achieving effective delivery and uptake of this has often been difficult. There is no agreed benchmark for the uptake of secondary prophylaxis, and indeed anything less than 100% of doses is suboptimal. However, a generally utilised target for adequate uptake utilised in Australia is 80% of recommended LAB injections over a 12-month period. Unfortunately, data shows that relatively few Aboriginal and Torres Strait Islander individuals living with ARF/RHD achieve this level of secondary prophylaxis uptake.[13,14] While there is much anecdote regarding why the system is failing, there remains no clear evidence regarding how best to respond to this clear service gap. It is likely that one particular issue with secondary prophylaxis for ARF/RHD is the longevity and inconvenience of treatment. Clients accessing secondary prevention treatment usually have to undergo 10-20 years of painful four-weekly injections that may be perceived as having little benefit. The consequences of ARF/RHD are, like hypertension or kidney disease, only apparent once the disease is advanced at which time secondary prevention is often futile.

Gaps

Potential issues and service gaps influencing the uptake of effective secondary prevention for ARF/RHD were identified including:

- While **oral penicillin is not recommended**, too many health professionals prescribe it in place of LAB injections. The protection provided by the variable use of oral antibiotics is not sufficient.[12]
- **Centralised RHD register and recall programmes** are important in coordinating care. Nonetheless the Northern Territory experience would indicate that such systems alone cannot achieve the required levels of secondary prophylaxis uptake.
- There are great **disparities in the uptake of secondary prophylaxis** in different communities. Successes should inform programme development.
- In a primary health care environment faced with acute health care needs, secondary prophylaxis, like chronic disease management, is sometimes not seen as a priority.
- **Mobility** of some Aboriginal and Torres Strait Islander patients can make it difficult for the health system to effectively deliver regular prophylaxis.

Solutions

- Develop a sense of **urgency and priority** for the delivery of secondary prophylaxis in primary health care. Whilst primary care providers are faced with a broad range of health issues, all placing demands on finite time and resources, it is necessary to prioritise the delivery of secondary prophylaxis. Potential strategies include:
  - marketing (patient, family, community, health providers - “we're talking about children/the future”).
  - education (including utilising ‘clinical champions’/opinion leaders such as cardiologists and cardiac surgeons; introducing health provider training and professional development for all relevant primary health care providers and specialists).
- **Systems based approaches** are required to ensure ARF/RHD fits within established chronic disease frameworks and systems. Active recall and follow-up is vital with effective health information management systems that allow the sharing of health data so that patients can access care at different health care centres and care items received are notified to a central database that can be widely accessed. There needs to be integration between central ARF/RHD registers and primary health care health information management systems.
- Development and evaluation of primary health care-based or led strategies for delivery of secondary prophylaxis including:
  - **Whose job is it?** Is it important to have a dedicated person within the team who is responsible for ensuring prophylaxis is delivered? Does opportunistic delivery work when provided by all members of the primary health care team? The most effective and appropriate model for primary health care-based delivery of secondary prophylaxis should be a priority for future research.
  - **Work flow** - fast-tracking individuals presenting for their injection at clinics.
  - Basing **timing** of secondary prophylaxis on patient/community concepts of time – e.g. seasonal or community events (e.g. injections due on the full moon).
  - **Communication and recall** – what are patient, family, community needs and preferences? Is the concept of self-management appropriate in this setting?

- **Continuous quality improvement** initiatives to ensure better delivery of services. Focus on what the health service is doing rather than on what the patient is not doing.
- **Patient control and information ownership** - Hand-held records for patients so that they can access secondary prophylaxis at any primary health care site. Participation in Australian national shared electronic health record (eHealth) initiative.
- **Incentives** – Is there are role for reward system to encourage clients to achieve high levels of secondary prevention uptake?
- **Community-based delivery** – alternate modes of delivery including the New Zealand model of secondary prophylaxis delivery by community-based public health nurses in schools and homes.
- **Smart recall systems** – explore innovate methods for supporting clients and families and providing reminders through schools or workplace, or by using technology including SMS messaging, email and other internet based platforms.

- **Better methods of delivery** - it is arguable that the delivery of secondary prophylaxis by 4-weekly LAB injections is a failed treatment model. A paradigm shift in the mechanism for delivery or a means of improving the delivery of intramuscular long-acting penicillin is required. Investment in the development of innovative delivery systems for secondary antibiotic prophylaxis of ARF/RHD which are more convenient, less painful and longer-acting should be a priority. Given the small potential market, relying on commercial imperatives alone is unlikely to achieve this and strategic relationships with device and drug development organisations with a cost and risk-sharing model will most likely be required.

3. Better and more appropriate management of advanced RHD

Background

When the heart is no longer able to compensate for the abnormal functioning of damaged valves, heart failure results. This is most common in young adults, but is also sometimes seen in children.[4] Once valve damage is severe there are a broad range of options available dependent

both on patient circumstances and the degree and type of valve damage. Some options will not require the patient to be on lifelong anticoagulation (warfarin), a desirable outcome given the risks of bleeding and inconvenience of regular blood test monitoring. Other options will require warfarin therapy with its inherent inconvenience and complications including bleeding, valve thrombosis and embolisation. Furthermore, some surgical interventions rarely require repeat intervention (mechanical valves) while others may eventually require later operations (bioprosthetic valves, valve repair, balloon valvuloplasty). The choice and timing of intervention therefore needs to carefully balanced taking into account patient preferences, the safety of anticoagulation and the risk of later reoperation before proceeding with any particular course of action.

In Australia, patients with RHD who require surgery are routinely transferred to one of approximately thirty city-based cardiothoracic surgical units. Given the number of units involved it is hardly surprising that the surgical management of RHD varies widely. For example, patients with mitral regurgitation, the most common valve damage seen in RHD, may undergo valve repair or a valve replacement with a mechanical or bioprosthetic valve; which occurs is often more dependent on where the operation is undertaken rather than on the application of consistent and objective criteria. This is perhaps why, once the patient returns to their usual health care providers, questions may arise regarding whether the intervention undertaken was the most appropriate option.

A similar situation exists for mitral stenosis. While percutaneous balloon valvuloplasty is an effective and comparatively safe treatment for mitral stenosis, particularly in younger and pregnant patients, there are few centres in Australia that undertake this in large numbers. If patients with mitral stenosis are referred to cardiothoracic surgeons anecdotal reports would indicate there can be a tendency to operate and replace the valve rather than to undertake balloon valvuloplasty.

The problem of inconsistency in surgical and other interventions (e.g. percutaneous balloon valvuloplasty) for the management of advanced RHD is further exacerbated by the fact that most patients undergo surgery in major city centres far removed from the realities of the

remote communities or regional centres where they usually live. This often entails a disconnection between the decisions being made by tertiary hospital-based specialists and surgeons, local primary and specialist health care providers, and the practical aspects of life and health service access in regional and remote Australia.

Gaps

- **Mitral valve repair** – The use of mitral valve repair versus mitral valve replacement for RHD varies greatly between different cardiothoracic surgical centres in Australia. Overall in Australia there is a general lack of experience with surgical repair as opposed to valve replacement.
- **Delay in presentation** - patients with RHD can first present for primary and specialist health care with symptomatic and advanced disease that requires early and occasionally urgent surgical intervention. This has particular implications for the suitability for mitral valve repair as late referral often means valve damage is extensive and mitral valve repair is not possible.
- **Consistency and leadership in the surgical management of RHD** – the diversity of the management of advanced RHD across Australia has been noted. There are no national centres of excellence for specialist RHD diagnosis, severity assessment and management.
- **Multidisciplinary team management of advanced RHD** – decisions regarding the details of management of advanced RHD are frequently undertaken by cardiothoracic surgical teams. This can often occur without broader input from the patient/family and other health care providers (including local primary health care providers and regional and visiting specialists) particularly with regard to the implications for local follow-up, the need for anticoagulation, future pregnancy, re-operation and infective endocarditis risk.

Solutions

- **Improved understanding of health care access and uptake of secondary prophylaxis** - issues pertaining to secondary prophylaxis for ARF/RHD are discussed above. A greater understanding is also required in relation to why patients are lost to

follow-up, how to identify RHD in women before they may become pregnant and how to encourage the early presentation and appropriate investigation of patients with unexplained shortness of breath.

- **National centres of excellence** for the diagnosis, assessment and surgical management of RHD are required. Health staff, particularly those at primary health care sites where most health care for people with ARF/RHD occurs, should be able to easily contact clinical experts who can provide consistent evidence-based advice that reflects the realities of regional and remote Australian life and clinical practice.
- **Multidisciplinary care and team-based decision making** for the planning of intervention for RHD. Decision-making needs to involve those who will be faced with the aftermath of intervention/surgery (i.e. patients, families and local primary and specialist health care providers).
- **Early referral for surgical input** would allow a broader range of options for intervention to be considered. Multidisciplinary and team-based decision making would encourage this particularly if such input could be provided locally either by telemedicine or through cardiothoracic surgical outreach to regional centres.
- **National RHD surgical register and research strategy** for the assessment, intervention and long-term outcome of surgery and other interventions for RHD. A priority is the development of a surgical management and outcome register that incorporates details regarding a standardised baseline assessment, documents the rationale for the intervention chosen, and allows short and long-term follow-up which includes re-operation, readmission, morbidity (including stroke and endocarditis) and survival. Where possible, additional measures incorporating objective assessments of function (six minute walk test) and quality of life should be included. This will enable the development of evidence-based recommendations for surgical and other interventions in the management of advanced RHD in Australia and have significant implications for international practice.
- **Improving the use of warfarin** – warfarin is likely to remain a reality of RHD management. Research to enhance the understanding of how patients and primary health care providers perceive long-term anticoagulation and how monitoring and regular use of warfarin can be enhanced should be a priority.

Additional issues pertaining to ARF/RHD care discussed in less detail

Whilst there were at least seven other areas that were not discussed in any detail the primordial and primary prevention of ARF/RHD was a recurring theme.

Primary prevention and Group A Streptococcus – where to from here?

Whilst not all patients presenting with ARF have a history of pharyngitis[15], the early treatment of Group A Streptococcus (GAS) associated pharyngitis provides an effective opportunity to prevent the development of ARF.[16,17] New Zealand experience would indicate that there is limited awareness of the importance of the early management of pharyngitis in high-risk (Māori and Pacific Islander) populations both in community members and health care providers. Research investigating the understanding of how communities at high risk of ARF/RHD and local primary health services perceive and respond to pharyngitis (including seeking health care review) is required. This should inform community and health provider education initiatives to ensure pharyngitis prompts primary health care review and that primary health care providers have clear and consistent protocols for confirming a diagnosis of GAS-associated pharyngitis or treatment protocols for empiric management.

Conclusion

The Cardiac Society of Australia and New Zealand's Alice Springs 2011 Indigenous Cardiovascular Health Conference provided a unique and valuable opportunity for experts with 'on the ground experience' in primary and specialist health care delivery and planning to gather and identify shared priorities in the Australian response to ARF/RHD (see Box 2). Although time was limited this group provided clear recommendations to inform the local, jurisdictional and national response to ARF/RHD. There remains much to be done and many unanswered questions. Nonetheless, it is hoped this document helps chart a course for addressing what is a complicated health issue in regional and remote Australia and for Aboriginal and Torres Strait Islander peoples.

As one participant noted:

'I work in the primary health area. I've been in Aboriginal health for a long time. To think that rheumatic fever has been around for a very long time, and is only just got on the agenda, and it's making me think, yeah, I've... got relatives and family who's got rheumatic fever. We talk about diabetes, we talk about HIV / AIDS... but to me this has just come on the agenda.'

It is imperative that ARF/RHD now remains on the national and international health agenda. With the support and advocacy of CSANZ and the ongoing advice and commitment from patients, communities and health providers, ARF/RHD can be largely eradicated as it has been for non-Indigenous Australians.

1. **Echocardiography and Screening/Diagnosis of RHD** - Given the existing uncertainty it remains premature to advocate for or to incorporate echocardiographic screening for RHD into Australian clinical practice. Further research is currently being undertaken to evaluate the potential for echocardiography screening.
2. **Secondary Prophylaxis** – Secondary prophylaxis (LAB injections) must be seen as a priority. Systems-based approaches are necessary with a focus on the development and evaluation of primary health care-based or led strategies incorporating effective health information management systems. Better/novel systems of delivery of prophylactic medications should be investigated.
3. **Management of Advanced RHD** - National centres of excellence for the diagnosis, assessment and surgical management of RHD are required. Early referral for surgical input is necessary with multidisciplinary care and team-based decision making that includes patient, family, local health providers. There is a need for a national RHD surgical register and research strategy for the assessment, intervention and long-term outcome of surgery and other interventions for RHD.

Box 2. Summary of recommendations from the CSANZ Indigenous Cardiovascular Health Conference 2011 – ARF/RHD workshop.

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