ECHOCARDIOGRAPHIC SCREENING FOR RHEUMATIC HEART DISEASE IN NORTHERN AUSTRALIAN CHILDREN

A thesis submitted for the degree of Doctor of Philosophy

by

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November 2015

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Declaration

I declare that the work presented in this thesis is my own, and all references to the ideas and work of other researchers have been specifically acknowledged. It contains no material which has been previously submitted for a degree at this or any other university.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, and online via the University’s Open Access repository, eSpace.

Kathryn Roberts

November 2015
Abstract

Rheumatic heart disease (RHD) remains a significant cause of morbidity and mortality in Indigenous Australians. Echocardiographic screening in children potentially provides the opportunity to detect RHD in its mildest form, and instigation and regular delivery of secondary prophylaxis for detected cases should result in the majority avoiding severe RHD. Screening would also permit collection of accurate prevalence data, and quantify the burden of undiagnosed disease. However, evidence is needed for appropriate policy recommendations to be made.

This thesis aims to provide that evidence and is divided into three parts. The first describes RHD burden in Indigenous Australians and examines whether RHD fulfils standard public health screening criteria; the second presents the results of a large prospective echocardiographic screening survey of nearly 5000 children living in four regions of northern Australia; and the third is a cost-effectiveness analysis of a proposed model of echocardiographic screening for RHD in Indigenous children in the Northern Territory.

The principal findings are:

- The prevalence of Definite RHD in 3946 remote Indigenous children was 8.6 per 1000, compared with no cases detected in 1053 non-Indigenous children.

- Half of the Definite RHD cases were previously undiagnosed, suggesting that the true burden of RHD is higher than surveillance data reports.

- The prevalence of Definite RHD in Indigenous children from the Top End of the Northern Territory was 17 per 1000; more than double the prevalence in the other three study regions.
• Cardiac auscultation is not a useful method of screening for RHD.

• A proposed model of echocardiographic screening for RHD in Indigenous children is potentially cost-effective, but sensitive to a number of assumptions.

Echocardiographic screening for RHD in Indigenous Australian children is feasible and will detect new disease. However, if it is to be beneficial, it must be coupled with measures to improve the delivery of secondary prophylaxis.
Acknowledgements

I would most like to thank my principal supervisor, Professor Jonathan Carapetis, whose own PhD studies resulted in the establishment of Australia’s first RHD control program. He convinced me to diverge from my preferred role as a clinician, and supported me as I ventured into the world of research, teaching me many things along the way. His availability and responsiveness to his PhD students is remarkable, particularly considering his many commitments. A master of efficiency who is always looking at the big picture—thank you!

Thanks also to my associate supervisors Graeme Maguire and Josh Davis, particularly for proof-reading this thesis in recent weeks, and to the other gECHO investigators, David Atkinson and Alex Brown. The extensive clinical and research experience of this group in the field of Indigenous Health is humbling.

The gECHO study would never have eventuated without its amazing project team or without the support of so many schools and communities. Thank you so much to all staff, students and families who took part, and to all gECHO project coordinators—Lorraine Kelpie and Vijaya Joshi in the NT, Yvonne Hodder in Queensland and Rhona Dawson in the Kimberley—for all of your hard work. Particular thanks to Colette Davis who managed the project during its final phase, and who had the unenviable task of ‘burning’, archiving and distributing over 6000 echoes for reading; without her meticulous attention to detail, data analysis would not have been possible. Thanks also to Colette for many laughs, photo opportunities in green T-shirts, and an epic drive from Darwin to Lajamanu.
Thank you to all echo techs who travelled far from home to help with this study, and particularly to Cabrini Health for their support. I would also like to acknowledge all reporting cardiologists, particularly KK and his colleagues in India for their huge contribution to echo-reading for this study, despite such heavy clinical loads. Particular thanks also to Gavin Wheaton in Adelaide for his availability to discuss many aspects of this study at different stages.

To my good friend and colleague, Bo Remenyi, thank you for your expertise, for reading so many echoes, and for your indefatigable passion for echo screening and RHD in general. Most of all, thank you for your very high entertainment value and your many highly-unlikely-but-true stories!

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The last two years of my PhD voyage have been consumed by the momentous and elusive cost-effectiveness analysis. I am eternally grateful to health economist Jeff Cannon for bringing it to fruition, thanks to his expertise with mathematical modelling and the many
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To my family and friends, in Darwin and Melbourne, thank you for sticking by me through this rather protracted process. To my parents, Janet and Andrew Roberts, for their unending faith in me, my brother Stephen for always making me laugh, my children Anna and Oliver for the chaos and joy they bring to my life, and to my partner Hichem, ditto! Merci pour tout.

I dedicate this work to the many Indigenous Australian children and their families who continue to suffer the devastating effects of rheumatic heart disease. It is my hope that RHD burden in Indigenous and non-Indigenous people will be equally low one day, and that there will be no role for screening for this disease in Australia.
Publications arising from this work

**PUBLISHED MANUSCRIPTS**


**MANUSCRIPTS SUBMITTED TO PEER-REVIEWED JOURNALS, UNDER REVIEW**


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<th>Description</th>
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<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>AR</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute rheumatic fever</td>
</tr>
<tr>
<td>AV</td>
<td>Aortic valve</td>
</tr>
<tr>
<td>BPG</td>
<td>Benzathine penicillin G</td>
</tr>
<tr>
<td>CA</td>
<td>Central Australia</td>
</tr>
<tr>
<td>CHD</td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability Adjusted Life Year</td>
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<tr>
<td>DRG</td>
<td>Diagnostic Related Group</td>
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<tr>
<td>FNQ</td>
<td>Far North Queensland</td>
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<tr>
<td>GAS</td>
<td>Group A streptococcus</td>
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<td>GDP</td>
<td>Gross domestic product</td>
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<tr>
<td>gECHO</td>
<td>Getting Every Child’s Heart OK</td>
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<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<td>ICSEA</td>
<td>Index of Community Socio-Educational Advantage</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<td>IRSD</td>
<td>Index of Relative Socio-economic Disadvantage</td>
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<tr>
<td>MR</td>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>MSM</td>
<td>Multi-state model</td>
</tr>
<tr>
<td>MV</td>
<td>Mitral valve</td>
</tr>
<tr>
<td>NHF</td>
<td>National Heart Foundation of Australia</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>NT</td>
<td>Northern Territory</td>
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<tr>
<td>PLAX</td>
<td>Parasternal long axis</td>
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<td>PPV</td>
<td>Positive predictive value</td>
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<td>PSA</td>
<td>Probabilistic sensitivity analysis</td>
</tr>
<tr>
<td>PSAX</td>
<td>Parasternal short axis</td>
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<tr>
<td>RDH</td>
<td>Royal Darwin Hospital</td>
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<tr>
<td>RHD</td>
<td>Rheumatic heart disease</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SEIFA</td>
<td>Socio-Economic Indexes for Areas</td>
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<tr>
<td>WA</td>
<td>Western Australia</td>
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<td>WHF</td>
<td>World Heart Federation</td>
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Chapter 1:

Background and Aims of the Thesis
CHAPTER 1. BACKGROUND AND AIMS OF THE THESIS

1.1 Thesis overview

This thesis comprises a series of published and submitted papers that fall into three main sections. The background to the thesis is presented in the first two chapters. Chapter 1 introduces the disease and reviews the Australian literature regarding the magnitude of the problem in Indigenous Australians, and the current approaches to rheumatic heart disease (RHD) control in the Northern Territory of Australia. Some of the information in this background chapter is repeated in the introduction to the publications that make up subsequent chapters. Chapter 2 examines whether RHD fulfils standard criteria for a disease suitable for screening, by reviewing the literature about the global burden of disease and the emergence of echocardiographic screening for RHD on a global scale.

The second part of the thesis concerns the gECHO study (‘getting Every Child's Heart OK’), a large, prospective echocardiographic screening study of more than 5000 northern Australian children. Chapter 3 describes the methodology of this study in detail, results are presented in Chapters 4 to 6, and the study is summarised in Chapter 7.

The third part of the thesis is a cost-effectiveness analysis of echocardiographic screening for RHD in Australia. Chapter 8 presents an audit of the Northern Territory (NT) RHD register, which describes RHD severity and progression in a cohort of young Indigenous Australians. These data are used to derive a multi-state model of RHD evolution, which is required for the final cost-effectiveness analysis (Chapter 9). Chapter 10 concludes the thesis with a discussion about the potential role of screening as part of the national strategy to reduce the RHD burden in Australian Indigenous children.
1.2 What is rheumatic heart disease?

Rheumatic Heart Disease (RHD) is the only long-term sequel of Acute Rheumatic Fever (ARF), an immune-mediated, multisystem inflammatory disease that follows Group A streptococcal (GAS) infection. GAS, or *Streptococcus pyogenes*, is commonly found in the pharynx and on the skin, and it is estimated that approximately 3%-5% of people with GAS pharyngitis will go on to develop ARF,\(^1\) usually a few weeks after the initial infection. ARF has typical clinical characteristics which most commonly include fever, arthritis, carditis, and chorea.\(^2\)-\(^4\) While the acute illness is self-limiting, inflammation of the cardiac valves during single or repeated episodes of ARF can lead to scarring and chronic valvular dysfunction.

It is estimated that 50%-60% of patients develop RHD following the first episode of ARF.\(^1,5,6\) The left-sided heart valves are affected; mitral regurgitation is the most commonly observed lesion in patients with RHD, but mitral stenosis and aortic regurgitation are also characteristic. RHD prevalence peaks in young adulthood and is associated with substantial morbidity (including cardiac failure, atrial fibrillation, stroke, infective endocarditis and pregnancy complications) and premature death. The long-term prognosis of RHD depends on the severity of carditis at presentation and the number of ARF recurrences.\(^2,7\)-\(^11\)

Secondary prophylaxis with regular long-acting benzathine penicillin G (BPG) for all patients with ARF or RHD prevents ARF recurrences and remains the only proven intervention that can potentially prevent the development and progression of RHD.\(^12\)

1.2.1 Who gets RHD?

ARF and its resultant RHD are diseases of poverty. Over the past century, ARF has become rare in the industrialised world in parallel with improvements in socioeconomic conditions and access to antibiotics and medical care.\(^13\) Yet high rates persist in developing countries,
and in Indigenous populations of industrialised countries such as Australia and New Zealand. These disadvantaged groups continue to experience overcrowding and poor hygiene which facilitates transmission of GAS. Such living conditions, coupled with limited access to appropriate medical care, result in these populations bearing almost the entire burden of ARF and RHD today.

ARF is a disease of childhood, with its peak incidence occurring in 5 to 14 year olds. The emergence of RHD lags slightly behind the first episode of ARF, and RHD prevalence reaches its peak in the 25 to 44 year old age group.

1.2.2 How is RHD diagnosed?

Prior to the widespread availability of echocardiography, the diagnosis of RHD was made by cardiac auscultation, which aimed to detect characteristic murmurs in patients who had a past history of ARF. It is now widely accepted that auscultation is neither sensitive nor specific for the detection of RHD, and in settings with access to echocardiography, this is now the accepted gold standard for RHD diagnosis.

Mitral regurgitation (MR) is the most common valvular lesion seen in RHD, particularly in the early stages of disease. Mild to moderate MR can remain asymptomatic for many years, with compensatory left atrial and ventricular dilatation, until chronic volume overload eventually results in systolic dysfunction and/or pulmonary hypertension. Morphological changes of the mitral valve that frequently accompany MR can include leaflet thickening, thickening and shortening of the chordae tendineae, and restricted or excessive leaflet motion.

Frank mitral stenosis usually develops later in the disease process, and is thought to be a result of persistent or recurrent valvular inflammation resulting in partial fusion of the
mitral valve leaflets. Complications of left atrial enlargement include atrial fibrillation and its associated risk of thromboembolism, pulmonary hypertension and right ventricular failure.

Aortic regurgitation is uncommon in isolation; it is usually associated with some degree of MR. The aortic valve may have thickened cusps and rolled edges, but aortic stenosis is rare and most commonly present only in advanced disease. Tricuspid valve disease is uncommon, and is almost always associated with mitral valve disease. Tricuspid regurgitation is most often secondary to pressure disturbances caused by left-sided valve disease, and tends to be progressive.

In Australia, RHD is most commonly diagnosed following an episode of ARF, either at the time of hospitalisation with ARF, or during medical follow-up months or years afterwards. In developing countries with limited access to cardiology services, or where RHD surveillance programs do not exist, the first presentation with RHD is almost always due to heart failure, representing late disease.

1.2.3 How is RHD managed?

Once RHD is established, the primary aim is to prevent further episodes of ARF which almost invariably result in worsening of valvular lesions. Secondary prophylaxis with 3-4 weekly BPG prevents GAS infection and ARF recurrences, and is the mainstay of RHD control around the world. Mild RHD, in the absence of recurrent episodes of inflammation, has a very good prognosis and the majority of patients have no detectable disease after 10 years. Conversely, severe valve dysfunction rarely regresses and almost all of these patients will require surgery in time. Where surgery is not available, or is delayed, interim medical management of cardiac failure, with or without anti-arrhythmic
agents and anticoagulation, may be required. Ultimately however, cardiac valve surgery is the only treatment option that may improve the long-term prognosis of established, severe RHD.

The choice of procedure and timing of RHD surgery are critical. The need for surgery is generally dictated by a patient’s symptoms and deteriorating cardiac function, and there are standardised guidelines defining surgical indications for each valve lesion. It is well recognised that early surgical intervention results in better patient outcome.

The most common indication for surgery is severe mitral regurgitation, and mitral valve repair is now the first-line operation of choice in both adults and children when the valve is suitable and where the surgical expertise exists. If a valve is unable to be repaired, valve replacement is required. Bioprosthetic valves are associated with fewer thromboembolic complications, but have higher rates of valve failure, re-operation and valve-related mortality. Mechanical valves offer the greatest longevity and are generally preferred if replacement is required at a young age. However, the requirement for anticoagulation adds significant risks and may not be suitable for some patients (for example, women of child-bearing age). The first-line procedure for pure mitral stenosis is percutaneous balloon mitral valvuloplasty, and valve replacement can be avoided in most cases.
1.2.4 Opportunities for prevention

The prevention of ARF and RHD may be undertaken at a number of different levels (Box 1.1).

Box 1.1: Prevention strategies for ARF and RHD

<table>
<thead>
<tr>
<th>Prevention type</th>
<th>Aim</th>
<th>Examples of intervention</th>
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<tbody>
<tr>
<td>Primordial</td>
<td>Reduce transmission of GAS</td>
<td>Broad social and environmental change, improved housing, GAS vaccine</td>
</tr>
<tr>
<td>Primary</td>
<td>Prevent development of ARF</td>
<td>Appropriate antibiotic treatment of GAS pharyngitis</td>
</tr>
<tr>
<td>Secondary</td>
<td>Prevent recurrences of ARF, thereby preventing RHD establishment/progression</td>
<td>Continuous antibiotic prophylaxis</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Reduce disability and prevent premature death from RHD</td>
<td>Medical and surgical management of RHD</td>
</tr>
</tbody>
</table>

GAS- Group A streptococcus; ARF- acute rheumatic fever; RHD- rheumatic heart disease

Primordial prevention aims to reduce infection with GAS and includes broad strategies to address the social determinants of health (including poverty, housing and hygiene), as well as specific strategies to eradicate the organism such as a GAS vaccine. Vaccine development has been under way for some time, and one of the World Heart Federation’s current targets for RHD control is for Phase III GAS vaccine trials to be under way in RHD-endemic countries before 2025.

Prompt treatment of sore throats with appropriate antibiotics eradicates GAS and reduces the likelihood of ARF developing. However, the challenge of identifying individuals with GAS pharyngitis remains, particularly in resource-poor settings without access to laboratory services. Furthermore, not all ARF is preceded by a sore throat. Much work has been done on primary prevention programs, which focus on mass surveillance and treatment of
GAS pharyngitis. However, such programs are resource intensive and have so far failed to demonstrate a significant treatment effect. As a result, there is no proven strategy for primary prevention that is effective, or cost-effective, at a population level.

Secondary antibiotic prophylaxis delivered to patients with a history of ARF or RHD prevents GAS infection, thereby preventing ARF recurrences. It remains the only proven, cost-effective approach to controlling RHD at present. Secondary prophylaxis is most effectively delivered via a register-based control program, which is an essential part of any secondary prevention strategy. These programs aim to identify and register new cases of ARF and RHD, maximise adherence to antibiotic prophylaxis and deliver good clinical care. Screening for RHD may be considered part of secondary prevention, as it aims to detect cases earlier and prevent disease progression by the prompt instigation of secondary prophylaxis.

Tertiary prevention is a misnomer; medical and surgical management of advanced RHD may be life-saving or life-prolonging in the short term, but will not reduce the incidence of new cases that will continue to require this expensive care. Providing medical therapy, including adequate monitoring of anti-coagulation, is particularly challenging in resource-poor settings, and cardiac surgery, if available, is often prohibitively expensive. It is regrettable that the vast majority of resources for RHD in all countries are spent on tertiary care, when most countries do not have effective primary or secondary prevention strategies in place.

1.3 The role of RHD screening

It is estimated that up to 40% of people with established RHD have never had a recognised episode of ARF. Consequently, the only way this group will be detected is by: a) presentation with cardiac symptoms representing advanced disease; or b) a positive
screening test during the asymptomatic phase of disease. In recognition of this, and given the high disease burden in many countries, RHD has long been a target for public health screening.\(^{[46]}\)

Prior to the advent of echocardiography, screening was performed by auscultation, thus only detecting RHD with clinically appreciable signs (i.e. a cardiac murmur). More recently however, a number of studies have demonstrated that echocardiographic screening will detect many more children with ‘subclinical’ RHD (echocardiographic changes in the absence of a cardiac murmur).\(^{[16,18,47-52]}\) Although there is no clear agreement internationally on how subclinical RHD cases should be categorised or managed, there is an increasing body of evidence suggesting that subclinical carditis is part of the spectrum of RHD, which therefore may represent an appropriate target for RHD screening.

Chapter 2 discusses the evolution of echocardiographic screening for RHD in detail.

### 1.4 The Epidemiology of ARF and RHD in Australia

#### 1.4.1 The Australian context

The work presented in this thesis focuses on four regions of northern Australia: the ‘Top End’ and Central Australia in the Northern Territory, Far North Queensland (including the Torres Strait) and the Kimberley region of Western Australia (Figure 1.1). The Top End and Far North Queensland have tropical climates, whereas the Kimberley and Central Australia are desert regions. All four regions are characterised by their vast area (>2 million km\(^2\) in total), low population density (0.2-1 person per km\(^2\)) and high proportion of Indigenous residents, many of whom live in small, remote communities.
There are important differences between the Indigenous and non-Indigenous populations of Australia, related primarily to disadvantage. A 2014 Australian Government report confirms that “on average, Aboriginal and Torres Strait Islander Australians experience poorer outcomes than non-Indigenous people wherever they live”, and the level of disadvantage tends to increase with remoteness. This is particularly striking when considering household crowding, a measure that is highly relevant to ARF. In 2011, 64.1% of Indigenous Australians in very remote areas lived in overcrowded housing, compared with 25.4% nationally and 6.1% in the non-Indigenous population.
The Indigenous population is much younger than the non-Indigenous population, with 35.9% of Indigenous Australians less than 15 years of age, compared with 18.4% of the non-Indigenous population. Under-five mortality in Indigenous children is 165 per 100,000, nearly double that of non-Indigenous children, and life expectancy at birth for Indigenous Australians is 10 years younger than for non-Indigenous Australians (69.1 years for males and 73.7 years for females).

1.4.2 Sources of data about ARF and RHD in Australia

The quality of data about ARF and RHD burden in Australia varies between jurisdictions, primarily because surveillance is at various levels of establishment. In 1997, Australia’s first RHD control program was established in the Top End of the Northern Territory (NT), which included a register of all patients with a history of ARF or RHD. This program was extended to Central Australia in 2000, and now provides rich data about ARF and RHD patients in a central database. Many of the figures cited about the burden of disease in Australia are based on these NT data.

The first Australian Rheumatic Fever strategy was announced by the Australian Government in 2009, and funding was provided for the establishment of state-based RHD control programs and patient registers in jurisdictions with high rates of ARF and RHD. Queensland established its program in 2006 and Western Australia followed in 2009. Data from these programs only began to become available in 2012, and it has been recognised that case ascertainment to date has been incomplete, resulting in an underestimation of true disease burden.

By the end of 2015, it is hoped that these databases will be linked at a national level by the national coordination unit, RHD Australia (http://www.rhdaustralia.org.au/about-arf-
In addition, it has also recently been recommended that ARF and RHD become notifiable diseases in every Australian state and territory in order to improve disease surveillance on a national level.\(^{[63]}\)

While surveillance data are clearly valuable, they are based on clinical information, collected at the time of an individual’s contact with health services. This is likely to underestimate the true burden of disease as it relies on patients presenting for medical care, the diagnosis of ARF and/or RHD being appreciated by the clinician, and notification of the disease to the RHD register. No prospective, population-based survey has previously been undertaken to determine the prevalence of RHD in Australia.

### 1.4.3 ARF and RHD burden in Indigenous Australians

In Australia, ARF and RHD disproportionately affect the Indigenous population, and rates are among the highest in the world. There are currently just over 2600 individuals on the NT RHD register (unpublished data, NT RHD Control Program, 7/2/15), of whom 95% are Indigenous. A recent audit of ARF and RHD in the Kimberley region of Western Australia (WA) and Far North Queensland (FNQ) similarly found that 99% of patients identified were Aboriginal and/or Torres Strait Islander people.\(^{[61]}\)

The Australian ARF/RHD guidelines define a high-risk population as having an annual ARF incidence >30/100,000 5-14 year olds, or an all-age RHD prevalence >2/1000.\(^{[30]}\) The American Heart Association, in its recently revised Jones criteria, suggests that populations with ARF incidence >2/100,000 in school-aged children, or all-age RHD prevalence >1/1000 are at moderate to high risk of ARF.\(^{[64]}\) Table 1.1 demonstrates that disease burden in Indigenous Australians far exceeds any of these definitions.
# Table 1.1: Estimated rates of ARF and RHD in school-aged* Indigenous Australian children

<table>
<thead>
<tr>
<th>Region</th>
<th>Year(s)</th>
<th>ARF incidence (per 100,000 children*)</th>
<th>RHD prevalence (per 1000 children*)</th>
<th>RHD prevalence (per 1000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Territory</td>
<td>1997-2010</td>
<td>194</td>
<td>8</td>
<td>NR</td>
</tr>
<tr>
<td>Northern Territory</td>
<td>2005-2010</td>
<td>NR</td>
<td>NR</td>
<td>24.7</td>
</tr>
<tr>
<td>Northern Territory</td>
<td>2008</td>
<td>182.2</td>
<td>8.5</td>
<td>19.4</td>
</tr>
<tr>
<td>Northern Territory</td>
<td>2013</td>
<td>320</td>
<td>5.3</td>
<td>23.4</td>
</tr>
<tr>
<td>Top End</td>
<td>2006</td>
<td>NR</td>
<td>NR</td>
<td>24.8</td>
</tr>
<tr>
<td>Top End</td>
<td>1989-1993</td>
<td>254</td>
<td>5.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Top End</td>
<td>1999</td>
<td>191</td>
<td>5.5</td>
<td>13.3</td>
</tr>
<tr>
<td>Top End</td>
<td>2002</td>
<td>346</td>
<td>5.8</td>
<td>16.6</td>
</tr>
<tr>
<td>Central Australia</td>
<td>2002</td>
<td>365</td>
<td>7.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Central Australia</td>
<td>2006</td>
<td>NR</td>
<td>NR</td>
<td>18.1</td>
</tr>
<tr>
<td>Far North Queensland</td>
<td>1999-2004</td>
<td>162</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Far North Queensland</td>
<td>2001-2006</td>
<td>250 (Aboriginal) 450 (TSI)</td>
<td>2.8 (Aboriginal) 6 (TSI)</td>
<td>NR</td>
</tr>
<tr>
<td>Far North Queensland</td>
<td>2008-2009</td>
<td>NR</td>
<td>NR</td>
<td>11.4</td>
</tr>
<tr>
<td>Kimberley</td>
<td>1975-1979</td>
<td>227-353</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kimberley</td>
<td>1988-1992</td>
<td>375</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kimberley</td>
<td>2007</td>
<td>NR</td>
<td>NR</td>
<td>10.2</td>
</tr>
</tbody>
</table>

TSI-Torres Strait Islander people; NR- not reported in this study.

*School-aged" refers most commonly to 5-14 year olds, but exact age range varies in some studies.
ARF incidence

Estimates of annual ARF incidence in Indigenous children in the NT have varied from 150 per 100,000\(^{15}\) to 815 per 100,000 in one Central Australian community.\(^{75}\) Prior to the establishment of the NT RHD register, the most comprehensive epidemiological study of ARF and RHD in the Top End revealed an ARF incidence of 254 per 100,000 5-14 year olds (1989-1993)\(^{67}\) and figures have not significantly changed since that time. Of particular concern is the recent release of figures from the Australian Institute of Health and Welfare indicating that ARF incidence was 320 per 100,000 children in 2013.\(^{65}\)

Similar incidence rates have been documented in the Kimberley region of WA (375 per 100,000 Indigenous children between 1988 and 1992)\(^{74}\) and FNQ (162 per 100,000 Indigenous children between 1999 and 2004, although incidence was as high as 349 per 100,000 children in the Torres Strait).\(^{71}\) There are no recent data on ARF incidence in these regions.

RHD prevalence

In most reports of serial NT register data, RHD prevalence figures have increased over time, which is likely to be a reflection of improved case ascertainment, rather than a true increase in disease prevalence. The most recent estimates from the NT RHD register suggest that the all-age prevalence of RHD in the Indigenous population of the NT is around 2%, with rates of around 8 per 1000 in the 5-14 year old age group.\(^{6,59,65}\) Prevalence peaks in the 25-44 year older age groups (with over 3% of the population affected), and females consistently have higher rates than males across all age groups.\(^{6,15,65}\) The most marked difference between Indigenous and non-Indigenous Australians in the prevalence of RHD is seen in those aged under 35 years, where Indigenous Australians have a 122-fold greater
prevalence than non-Indigenous Australians.\(^{(59)}\) Lawrence et al also calculated that RHD incidence was 64 times higher for Indigenous than non-Indigenous people.\(^{(6)}\)

There are fewer data available about the prevalence of RHD in the Kimberley and FNQ, however two reports suggest an all-age prevalence of around 1\%.\(^{(61)}\) State-based data about Queensland and WA presented in national reports are difficult to interpret, as the population of the whole state is used as the denominator, rather than the populations of these two regions with high RHD burden.

**ARF recurrence**

A key indicator of the effectiveness of an RHD control program is the percentage of ARF episodes that are recurrences. In Carapetis’ initial study of ARF between 1985 and 1995, 45% of ARF episodes were recurrences.\(^{(67)}\) Similar rates were described in the late 1990s in the Kimberley (39\%)\(^{(74)}\) and FNQ (37\%).\(^{(71)}\) Following the introduction of the RHD control programs in the NT, recurrence rates dropped to around 25\%,\(^{(60)}\) however recent data would suggest that there have been no significant reductions in recurrences since the early 2000s.\(^{(15,59)}\) The most recent data from the Australian Institute of Health and Welfare (2010-2013) reports that 34\% of ARF episodes in Indigenous patients in the NT are recurrences, and noted that the proportion of recurrences increased with age (18\% for those under 15 years, compared with 55\% in those over 25 years).\(^{(63)}\)

**Adherence to secondary prophylaxis**

ARF recurrence rates are a reflection of adherence to secondary antibiotic prophylaxis following an initial ARF episode. The challenges of delivering secondary prophylaxis are well recognised, and seeking new approaches to improve BPG delivery remains on the international research agenda.\(^{(26,76)}\)
Adherence to BPG is known to be sub-optimal in many Indigenous patients. Data from the Kimberley (1982-1996) showed that an estimated 67% of prescribed doses were received, but that less than half were administered in a timely manner.\textsuperscript{(77)} A more recent audit of 407 ARF/RHD patients revealed that 14.7% of patients in the Kimberley and 20.4% of patients in FNQ had received >80% of their BPG in the previous 12 months.\textsuperscript{(61)}

Data from the NT are similar. In a small audit of communities in the Katherine region, mean adherence in 59 patients over 24 months was 56%.\textsuperscript{(78)} In larger series from the NT register, some improvements can be seen between 2005 and 2010, with the proportion of patients receiving >80% of required BPG doses increasing from 22.7% to 28.1%,\textsuperscript{(59)} and further to 33% in 2013.\textsuperscript{(63)} Unfortunately, however, this level of adherence is clearly insufficient to protect against ARF recurrences in the majority of patients.

1.4.4 Severity and prognosis of RHD in Indigenous Australians
The morbidity and mortality associated with RHD are significant, and affect Indigenous children and young adults in the most productive years of their life.

\textit{Disease severity and hospitalisation}

The Australian ARF/RHD guidelines\textsuperscript{(30)} define three levels of RHD severity: mild, moderate and severe, where the ‘severe’ category includes patients with symptomatic heart failure, patients requiring valve surgery and patients who have had valve surgery. In the NT, approximately one-quarter of those on the register currently have severe disease (unpublished data, NT RHD Control Program, 7/2/15.) In the 1997-2010 audit of the NT register, Lawrence et al found that 14% had severe disease at diagnosis, increasing to 21% after one year and 27% after five years.\textsuperscript{(6)} In another recent audit, 34.4% were registered with severe RHD in the Kimberley, compared with 15.9% in FNQ.\textsuperscript{(61)}
The same audit found that approximately 20% of all RHD patients were on warfarin. While adequate INR testing was documented in just over 60% of patients, INRs were only in the recommended range in 25% of those tested, putting these individuals at high risk for haemorrhagic or thromboembolic events.

At a national level, the hospitalisation rate for ARF or RHD between 2007 and 2010 was 67 per 100,000 Indigenous Australians compared with 10 per 100,000 non-Indigenous Australians. The majority of hospitalisations were in the 65+ age group in non-Indigenous patients (rate 49.0 per 100,000) whereas hospitalisations peaked in the 10-14 year old group in the Indigenous population (rate 123.4 per 100,000). There has been no change in the hospitalisation rate for ARF/RHD between 1999 and 2009.

**RHD surgery**

The implications of valve surgery in this population are particularly significant. Among Indigenous people receiving heart valve surgery for ARF or RHD, nearly 45% are under 25 years of age. The young age at surgery means that most of these patients will need multiple operations over their life, and the preponderance of the disease in females mean that many women of childbearing age will be affected. While mechanical valves offer the greatest longevity, the requirement for anticoagulation adds substantial risk, and complication rates are high in remote settings.

The proportion of RHD patients requiring cardiac surgery remains significant. Remond et al found that 27.5% of patients in the Kimberley and 16.3% in FNQ had undergone at least one surgical procedure. Of these, 27% underwent valve repair (which is similar to NT data from 2001-2002).
Outcomes of RHD surgery in Australian adults have recently been reported, based on an analysis of data from the national Cardiac Surgery Database (2001-2012).\textsuperscript{(79,80)} The cohort included 174 Indigenous patients and 1210 non-Indigenous patients, and Indigenous patients were noted to be significantly younger (median age at surgery 37.4 years versus 65.1 years), and more likely to live in a remote area (54.1% versus 1.6%) than non-Indigenous Australians.\textsuperscript{(79)} Mortality after any RHD valve surgery at 30 days, 5 years and 10 years was 3.1%, 15.3% and 25.0% respectively.\textsuperscript{(80)} There were no significant differences in the mortality of Indigenous versus non-Indigenous patients.

These data suggest better surgical outcomes than previous reports. Carapetis et al reviewed outcomes of 80 patients from the NT who underwent surgery for RHD between 1984 and 1996.\textsuperscript{(81)} Survival at 1, 5 and 10 years was 91%, 79% and 68% respectively. However, if event-free survival was considered, these figures were considerably lower, with 41% of living patients having had a significant complication (bleeding, thromboembolic event, infective endocarditis or valve dysfunction) by 5 years. Similar survival rates were described in a smaller series of surgical patients from the Cape York Peninsula and the Torres Strait Islands between 1992 and 2004.\textsuperscript{(82)} In a large series of 171 Indigenous patients from the NT undergoing valve replacement for RHD in Adelaide between 1993 and 2008, there were 32 deaths, and the hazard ratio for long-term all-cause mortality was 1.74 compared with non-Indigenous patients, although this was not statistically significant.\textsuperscript{(83)}

Each of these studies emphasised the importance of early surgical referral, prior to the development of pulmonary hypertension or reduced left ventricular ejection fraction, which are associated with poorer surgical outcomes.
Only one case series has specifically looked at the outcomes of RHD surgery in the paediatric age group in Australia.\(^{(84)}\) Rohde et al identified 112 Indigenous children who underwent cardiac surgery in their Brisbane hospital between 2002 and 2009. Twenty-three of these had RHD, of whom one died during the operation (giving a peri-operative mortality of 4.4%). The most concerning finding from this study was the inadequacy of follow-up after cardiac surgery; of the entire cohort (RHD and non-RHD surgery), 33% had medical follow-up within 8 weeks, 29% had follow-up after 8 weeks, and 38% never had documented follow-up by a cardiac surgeon, cardiologist or local medical officer.

**Mortality**

The first detailed review of mortality due to ARF or RHD in the NT between 1979 and 1996 revealed an age-standardised death rate of 30.2 per 100,000 person-years in Indigenous Australians compared with 1.1 per 100,000 in non-Indigenous people.\(^{(85)}\) A recent analysis of Australian mortality data showed slight improvement, with RHD mortality in NT Indigenous patients dropping to 25.3 per 100,000 in the period 1997-2005.\(^{(86)}\) Indigenous Australians with RHD are still over 20 times more likely to die than non-Indigenous Australians,\(^{66,69,86}\) with the death rate ratio (DRR) increasing to 54.8 if only Indigenous patients from the NT are considered.\(^{(86)}\)

Females consistently have higher death rates than males in all age groups, and the mean age of death remains between 35 and 40 years.\(^{15,85,87}\) The greatest disparity in death rates in the NT is seen in the 25 to 44 year old age group, where the DRR for Indigenous versus non-Indigenous patients is 187.6. When NT Indigenous data are compared with national, non-Indigenous data, the DRR peaks at 336.8 in the 5-24 year old age group.\(^{(86)}\)
1.5 The current approach to RHD control in the Northern Territory

1.5.1 RHD control program

A coordinated control program is the most effective approach to mitigating the burden of RHD in high-prevalence areas. A key element of such programs is the establishment of a patient register, which enables disease surveillance and coordination of clinical care. Register-based programs have been shown to improve case detection, increase adherence to secondary prophylaxis, reduce ARF recurrences and decrease hospitalisations. The first RHD control program in Australia was established in the Top End of the NT in 1997. Central Australia followed in 2000, and the two programs have since amalgamated to form a state-wide program.

1.5.2 School screening using cardiac auscultation

The Northern Territory is the only jurisdiction in Australia that has a formalised screening program for RHD. In 1996, routine screening for RHD was instigated in school-aged Aboriginal children in the Top End and the same program was adopted by Central Australia in 2000. In its initial form, the recommendation was that all 10 and 15 year old children in remote Aboriginal communities undergo cardiac auscultation by primary care doctors. Children with murmurs were referred to paediatricians who then determined the need for referral for echocardiography.

In 2007, the NT protocol was revised and became part of the Healthy School-Aged Kids (HSAK) school screening program. In its current form, RHD screening consists of cardiac auscultation of 10 and 15 year old children by a general practitioner who then directly refers any child with a new murmur or abnormal heart sounds for an echocardiogram. While doctors previously travelled routinely with the screening team, this is no longer the
case, and whether a child undergoes auscultation at all depends on the availability of a primary care doctor in the community clinic.

Evaluation data on auscultatory screening of children in the NT are scarce. While some data are available internally about the number of murmurs heard and referrals made, no data are available about the proportion of children who have actually had a follow-up echocardiogram, nor the number of RHD diagnoses that have been made. It is difficult to evaluate a public health intervention without this information, and there have been calls to review the utility of current practice.⁹⁰

1.6 Rationale for study

RHD clearly remains a significant cause of morbidity and mortality in Indigenous Australians and a major public health concern. It is likely that there is undiagnosed RHD among Indigenous children living in regions of high RHD prevalence, particularly remote communities in northern Australia which are known to be areas of high disadvantage. Screening for RHD provides the opportunity to quantify the burden of undiagnosed disease, as well as to provide accurate prevalence data for this age group in different regions of Australia. More importantly, if RHD is detected in its mildest form there is the opportunity to provide secondary prophylaxis which, if successfully delivered, should result in the majority these children avoiding severe RHD.
1.7 Thesis aims

The aims of this thesis, therefore, are:

1. To examine whether RHD meets the criteria for a disease suitable for screening;
2. To determine the prevalence of RHD detected by echocardiographic screening in northern Australian children;
3. To describe the echocardiographic findings of an urban population of children, at low risk for RHD;
4. To evaluate current consensus echocardiographic definitions of RHD;
5. To determine the sensitivity and specificity of cardiac auscultation, compared with echocardiography, for the detection of RHD;
6. To undertake an economic analysis of a potential echocardiographic screening program for RHD in the Northern Territory; and
7. To use this information to make recommendations about screening for RHD in school-aged Indigenous children living in rural and remote parts of Australia.
1.8 References


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Chapter 2:

Is Rheumatic Heart Disease a disease suitable for screening?
CHAPTER 2. IS RHEUMATIC HEART DISEASE A DISEASE SUITABLE FOR SCREENING?

2.1 Chapter Overview

This chapter is a literature review, published in *Nature Reviews Cardiology* in 2013, which extends beyond the Australian context presented in Chapter 1. The first part of the paper examines the critical question of whether rheumatic heart disease fulfils the public health requirements of a disease suitable for screening, and is structured around the four criteria defined by the Council of Europe in 1994 (Box 2 in this paper). In addressing each criterion, the literature is reviewed, providing current estimates of disease burden and prognosis, as well as outlining approaches to RHD diagnosis and management globally.

The second part of the paper reviews the history of RHD screening and describes the evolution of echocardiographic screening for RHD in detail. It concludes with a discussion about current controversies surrounding echocardiographic screening, as well as highlighting the importance of economic considerations when contemplating the implementation of any screening activity.

2.2 Statement of contribution to jointly authored work

I designed the structure of this article. The initial literature review was conducted with Samantha Colquhoun, and all authors contributed to the discussion of content. I prepared the manuscript, which was reviewed and edited by all authors prior to submission.

2.3 Journal article: *Screening for rheumatic heart disease: current approaches and controversies*
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Chapter 3:

The gECHO study- Methods
CHAPTER 3. THE gECHO STUDY- METHODS.

3.1 Chapter overview

This chapter describes the methodology for the gECHO study (‘getting Every Child’s Heart OK’), an echocardiographic screening study for RHD in high-risk and low-risk Australian children. The following three chapters comprise publications resulting from the gECHO study, and while an abridged version of the methods is included in each, this chapter describes the processes behind the study in more detail.

3.2 Study design and setting

The gECHO study was an observational cross-sectional survey of school-aged children in northern Australia, conducted between 2008 and 2010. The study was undertaken in four jurisdictions spanning three states in Northern Australia: the Kimberley region of Western Australia, the Top End of the Northern Territory, Central Australia in the Northern Territory and Far North Queensland, including the Torres Strait Islands (see Figure 1.1, Chapter 1 for geography and population estimates). Each jurisdiction has more than 100 remote Indigenous communities.

3.3 Study population

3.3.1 Community/school selection

We used a school-based approach to screening. Given that the peak incidence of ARF is in school-aged children, this has historically been the target age group for RHD screening. Using a school-based approach has the practical advantages of screening many children in one location, plus detection of disease in younger subjects has the greatest effect on outcome once preventative measures have been initiated.
Most remote Indigenous communities only have one school which may be divided into primary and secondary campuses, and our study sites were initially selected at a community level rather than a school level. For practical and historical reasons, communities were not selected at random. Rather, we aimed for a reasonable representation of small and large, remote and less-remote communities that were geographically dispersed across the regions. It is recognised that there may be biases introduced by community selection. However, truly representative sampling (i.e. random selection) would be logistically impossible in our context.

Community selection began with wide consultation with key stakeholders including local community leaders, councils, health advisory boards and education representatives. If support was indicated, a formal request for permission to proceed was sought from each local council and interested school. This process took from one to three months to complete for each community.

**Remote Indigenous cohort (high-risk for RHD)**

The high-risk cohort comprised Aboriginal and Torres Strait Islander children living in remote communities from the four regions. Following consultation with community stakeholders, 40 schools in 32 communities agreed to participate in the study (population range 150-3000 residents). Using standardised Australian measures of socioeconomic disadvantage incorporating data on income, education, employment and housing (Socio Economic Indexes for Areas\(^1\)), all participating communities had scores in the lowest decile, between 3 and 4 standard deviations below the Australian average. The average proportion of Indigenous students enrolled in participating remote schools was 94.5\%.\(^2\)
Urban non-Indigenous cohort (low-risk for RHD)

Our low-risk cohort comprised non-Indigenous children from the urban cities of Darwin and Cairns. Darwin is the capital of the Northern Territory, situated on the north coast of Australia. It has a population of around 120,000 of whom 11,000 (9.2%) are Indigenous. Cairns is a similar-sized town on the east coast of Northern Queensland with a population of 156,000 of whom 14,400 (9.2%) are Indigenous. Both are regional centres which lie to the north of the Tropic of Capricorn and experience a tropical climate. The majority of the non-Indigenous population live in single dwellings and experience a quality of life similar to other cities in Australia.

Given that the aim of including the urban cohort was to describe echocardiographic findings in healthy children at low risk for RHD, we intentionally selected schools in relatively affluent suburbs of Darwin and Cairns, predominantly attended by Caucasian children. The five selected schools all had standardised measures of socioeconomic advantage above the Australian average, and students of participating schools had median family incomes greater than the national median. More than 90% of students in the selected urban schools were non-Indigenous.

3.3.2 Individual participant selection

All children between the ages of 5 and 14 years (inclusive) were eligible to participate in the study, including children with a known history of ARF/RHD or congenital heart disease, which was noted. There were no exclusion criteria.

Children were identified by the enrolment record of participating schools. Following consultation with each school, including educational presentations to staff and students, study information (plain language statement) and consent forms were distributed to all
families of eligible children. In remote communities this was facilitated by community workers who spoke the local language, as well as school staff and sometimes health staff. Parental consent forms were largely completed prior to the screening visit.

In remote communities, some children were identified who were not on the school enrolment record. If their date of birth was able to be confirmed and parental consent obtained, these children were also screened.

### 3.3.3 Sample size calculation

Sample size was calculated based on Northern Territory register estimates that the point prevalence of rheumatic heart disease in those aged 5-14 years was 7.6 per 1000 in Indigenous (high-risk) children, and 0.2 per 1000 in non-Indigenous (low-risk) children.\(^{(3)}\) A sample size of 4000 high-risk children gave a 95% confidence interval (CI) of 5.1-10.7 per 1000 around the point prevalence of 7.6 per 1000, which was considered sufficiently precise. Using this sample, plus a comparison group of 1000 low-risk children, was adequate to detect a difference in prevalence between the two groups at the 0.05 significance level with a power of 80%.

Of the high-risk group, we aimed to screen 1000 children from each of the Top End and Central Australia, 1200 from Far North Queensland and 800 from the Kimberley; these numbers gave acceptable confidence intervals around the estimated point prevalence and were deemed feasible for individual regions. For the auscultation component of the study, we chose to examine NT children only (for staffing reasons), and aimed to screen 1000 children with both an echocardiogram and auscultation.
3.4 Ethical considerations

3.4.1 Consent
Written informed consent for RHD screening was obtained from the parents/guardians of children prior to enrolment. In addition, written assent was sought from children 13 years and older after explanation using flip-charts and culturally appropriate educational material.

3.4.2 Confidentiality
All participating children were registered into the study enrolment log by study number, name and date of birth. The study enrolment log was maintained exclusively by the study coordinator for each region, and all paperwork with identifiable details was stored in a separate, locked facility. All further data collected and analysed then used the de-identified study number only.

3.4.3 Access to medical record and RHD register
If a child was found to have an abnormality on his or her echocardiogram, the medical record and RHD register were accessed to confirm whether this was a new finding. Both records were also checked intermittently throughout the study to ensure that children who had been referred for specialist review or repeat echocardiogram had completed the necessary follow-up, and had been placed on the RHD register if appropriate.

3.4.4 Ethical clearance
Ethical clearance was obtained by the relevant committees in each jurisdiction:

- Cairns Base Hospital Ethics Committee (EC00157)
- Central Australian Human Research Ethics Committee (EC00155)
- Human Research Ethics Committee of Northern Territory Department of Health and Community Services (EC00153)
3.5 Screening procedure

3.5.1 Staffing, travel and site preparation

Each of the four regions had its own project manager who coordinated the screening visits, assisted by at least one other study staff member as well as local staff recruited at each site. Different approaches were used between jurisdictions to appoint cardiac sonographers; in the Kimberley, one technician performed 90% of the echocardiograms, whereas in the NT, a pool of technicians rotated from a cardiac service in Melbourne. Only certain trips in the NT were accompanied by a doctor (including a paediatrician, general practitioners, a cardiologist, and resident medical officers) who undertook cardiac auscultation.

Organising screening visits required consideration of a number of factors: community location, distance from the study coordination site (Darwin, Alice Springs, Broome or Cairns), the availability of commercial or government flights, road and weather conditions, and preferred timing of the individual communities involved. Means of travel included road (with the longest road trip taking 13 hours), commercial flights and chartered flights (in the NT only). Equipment frequently had to be transported separately by barge to coastal or island communities.

Screening took place in the community school, often in communal areas (for example in the school library or gym). Establishing a suitable space for screening was challenging at times
as it required the creation of two dark private areas for echocardiography, as well as a quiet area for auscultation in NT sites.

3.5.2 Collection of demographic details

Children who had returned completed consent forms and were present on the screening day were enrolled in the study. Age, date of birth, gender, address and ethnicity (self-reported by parent/guardian) were recorded for each participant. Dates of birth were cross-checked with school enrolment records or, of not available, with national health system (Medicare) records. Height and weight were measured on the day of screening by study staff. All demographic data were entered by hand onto paper forms identified by study identification number.

3.5.3 Echocardiography

All enrolled children had a screening echocardiogram. Transthoracic echocardiography was performed by cardiac sonographers using a portable cardiac ultrasound machine. The majority (>90%) of echocardiograms were performed using Vivid e™ or Vivid i™ (GE Healthcare, Freiburg, Germany) machines, and a small number were performed on an Acuson™ Cypress machine at the beginning of the study. A pool of 19 predominantly adult-trained sonographers was used, and all received detailed written instructions regarding the technical requirements of the study.

Screening echocardiograms were performed according to an abbreviated protocol previously used successfully in Tonga and Fiji. The limited views focused on the mitral and aortic valves, but also allowed detection of significant congenital lesions. Standard views included: parasternal long axis, parasternal short axis and apical four- and five-chamber views, noting valve morphology on cross-sectional two-dimensional imaging, and
the presence and extent of mitral or aortic regurgitation using colour flow Doppler. Pulse-wave and continuous-wave Doppler interrogation of regurgitant jets was subsequently undertaken to assess velocity, spectral envelope and duration through the cardiac cycle. Views were not routinely taken of the tricuspid and pulmonary valves unless the sonographer had particular concerns.

Gain settings were optimised by the sonographers as the large variation in body size precluded the use of standardised settings. A probe with a variable range from 2.5 to 5.0 megahertz was used for all studies.

The presence of any of the features listed in Box 3.1 prompted a more detailed, ‘comprehensive’ echocardiogram, involving additional views and Doppler interrogation of valves. Comprehensive studies, if required, were undertaken at the time of screening.

**Box 3.1: Indications for a comprehensive echocardiogram**

- A mitral regurgitant jet > 1cm
- Any aortic regurgitation
- Anterior mitral valve leaflet thickness > 2.5mm
- Posterior mitral valve leaflet thickness > 3mm
- Any other suspected pathology

All echocardiograms were recorded to DVD for off-site reporting. Additional copies were made for back-up and archive files. Echocardiograms were only identifiable to study staff using the enrolment identification number.

On average, screening echocardiograms took between 5 and 10 minutes to perform, and comprehensive echocardiograms took between 10 and 15 minutes. In a typical day of
screening, approximately 15 children (some of whom required both a screening and a comprehensive echocardiogram) would be screened by one sonographer.

3.5.4 Cardiac auscultation

In addition to their echocardiogram, a subset of remote NT children underwent cardiac auscultation by a doctor and a nurse. Different doctors and nurses with varying levels of experience performed auscultation during the course of the study. Auscultators were blinded to each other’s findings, the echocardiographic findings, and the clinical history of the child (which was unknown in most cases). Auscultation was performed with the child supine and sitting up, in a quiet room where possible. The diaphragm and bell of the stethoscope were used at the apex and axilla, lower left sternal edge, upper left sternal edge and upper right sternal edge. Findings were recorded on paper forms.

3.6 Reporting of echocardiograms

3.6.1 Reporting of echocardiograms for clinical purposes

At the end of each screening trip, all comprehensive echocardiograms were copied to DVD and sent to a pre-identified regional cardiologist for reporting. This was separate to the research process and aimed to provide a timely clinical management plan (see section 3.8 ‘Feedback to communities’). Reporting cardiologists were asked to provide a written report summarising the echocardiographic findings and their recommendations for follow-up. Screening echocardiograms were not reviewed, as the criteria for a comprehensive echocardiogram were designed to be sufficiently sensitive to ensure that pathology would not be missed.
3.6.2 Reporting of echocardiograms for research purposes

Separate to the clinical reporting of comprehensive echocardiograms, all screening echocardiograms were reported by a study cardiologist. A pool of 14 cardiologists was used, 9 of whom were paediatric cardiologists and who reported 87% of the studies. All reporting cardiologists had experience in the diagnosis and management of RHD.

Batches of 50 de-identified screening echocardiograms of high-risk and low-risk children were interspersed on the same DVD, and posted to cardiologists in Australia and overseas. Reporters were blinded as to whether the child came from the high- or low-risk cohort. Echocardiograms were reported according to our own standardised electronic protocol, and data were entered directly into a Microsoft Access™ database by the reporting cardiologist. Once complete, data was extracted and sent electronically to the research team.

Our reporting protocol was developed over a number of months in 2008/2009 (prior to the publication of the WHF echocardiographic criteria), in consultation with RHD experts in Australia and New Zealand. It required data to be entered according to the views captured by echocardiographers as described above (Section 3.5.3). A minimum of 15 fields required completion by reporting cardiologists if the screening echocardiogram was completely normal, increasing to a maximum of 100 fields if structural or functional abnormalities of the cardiac valves were reported.

All screening echocardiograms were reported at least once. A random selection of 10% of the screening echocardiograms was also reported a second time by a different cardiologist to assess inter-observer agreement. Comprehensive echocardiograms were read once by a single expert paediatric cardiologist who was also blinded to the risk status of the child.
Where there was a discrepancy in the final diagnosis between the screening and comprehensive echocardiograms, the result from the comprehensive study was accepted.

**Echocardiographic definitions**

1. **Subjective assessment of pathology**
   After viewing all echocardiography frames, cardiologists were asked to state whether they considered there to be pathology or not. If they indicated pathology, they were asked to specify whether they thought it was RHD (definite, probable or possible, with suggested definitions provided for each) or congenital pathology.

2. **2012 World Heart Federation criteria for RHD**
   During the course of the study, the World Heart Federation (WHF) developed and published criteria for the echocardiographic diagnosis of RHD in individuals without a history of ARF (Table 1, Chapter 4). In the final analysis, these criteria were used to classify children as having pathological valvular regurgitation or morphological abnormalities, and Definite or Borderline RHD. This was done post-hoc by extracting each individual echocardiographic feature, as objectively measured and recorded by reporting cardiologists, and combining features to determine whether WHF definitions were met.

   Auscultatory findings were not taken into consideration in the allocation of diagnosis.

3.7 **Data management and statistical analysis**
   All data from paper forms (demographic details plus auscultatory findings where relevant) were entered manually into a Microsoft Access database version 11.5 (Microsoft, Washington, USA); each state had its own copy of the database. Missing or inaccurate demographic fields were checked during this process. A formal data check was performed
on 10% of participants across all sites by comparing the paper files with the data entered into the database to ensure that data entry had been satisfactory. Once this had been established, the three databases were merged electronically.

Reporting cardiologists entered echocardiographic data directly into their own version of the database, which was subsequently imported into the central database. Cleaning of cardiology data and preparation of the whole dataset for analysis was undertaken using Stata statistical package version 12.1 (StataCorp, Texas, USA)

Details of specific statistical tests used for each component of the study are described in the relevant publication (Chapters 4-6).

3.8 Feedback to communities

3.8.1 Communication of individual results

All children were issued with certificates of participation stating that their echocardiogram would be reviewed, and that families would be notified if a possible abnormality was detected. Where follow-up was needed for an abnormal result, this was generally communicated in person by clinic staff in remote communities, and over the phone by research staff for urban children.

For remote children, cardiology reports of comprehensive echocardiograms were forwarded to the local primary health care clinic. In a minority of cases, cardiologists made immediate treatment recommendations regarding commencing secondary prophylaxis for RHD. In most cases, however, a follow-up echocardiogram or consultation was recommended. Paediatric review was generally able to be carried out by visiting specialists to remote communities. However, as most remote communities do not have visiting
paediatric cardiology services, children requiring repeat echocardiograms or cardiology review generally needed to be transferred to regional centres.

For urban children, parents were contacted by phone by study staff, and a written referral was made to the appropriate clinical service.

Children deemed to have RHD after clinical assessment and repeat echocardiogram by a cardiologist were commenced on secondary prophylaxis and referred to the regional RHD program. If clinical review was not able to be arranged quickly, and the reporting cardiologist had significant concerns about the comprehensive echocardiogram, some children were commenced on secondary prophylaxis while awaiting clinical review. At the time that this study took place, the WHF criteria had not been published, so the diagnosis and decision regarding secondary prophylaxis were at the discretion of the treating cardiologist, independent of the study team.

3.8.2 Dissemination of study results

At the completion of the study, a summary letter was sent to each participating school and major stakeholders outlining the major findings of the study. In addition, more specific information was sent to each remote site about how many children had been screened in their community, how many were found to have RHD, and how this compared to the overall results of the remote and urban cohorts. This was communicated in plain language posters and fliers that were distributed to schools and health clinics.
3.9 References


Chapter 4

Comparing echocardiographic findings in high and low risk Australian children
CHAPTER 4. COMPARING ECHOCARDIOGRAPHIC FINDINGS IN HIGH AND LOW RISK AUSTRALIAN CHILDREN

4.1 Chapter Overview

This chapter presents the main findings of the gECHO study and was published in Circulation in 2014. It describes the echocardiographic findings in 3946 remote Indigenous children at high risk for RHD and 1053 non-Indigenous urban children at low risk for RHD. Using the WHF criteria for the diagnosis of RHD (Table 1 in this paper), the prevalence of Definite RHD in high-risk children was 8.6 per 1000, compared with no cases in the low-risk cohort. Borderline RHD was detected in both groups, but was more common in high-risk children than low-risk children (16.7 per 1000 compared with 0.5 per 1000). This was the first screening survey to apply the WHF criteria, and by comparing findings between high-risk and low-risk children, served to validate the specificity and utility of these criteria in a screening context.

4.2 Statement of contribution to jointly authored work

This study was designed by Jonathan Carapetis, Graeme Maguire, Alex Brown and David Atkinson. The study was carried out by project teams in the four study regions over two years, and I was part of the field team for NT screening trips. In this role, I refined the study design and oversaw the scientific aspects of the protocol development and implementation. I developed the data collection form for reporting cardiologists and collated, cleaned and analysed all data. Assistance with statistical analysis was provided by Jiunn-Yi Su. I prepared all drafts of the manuscript. All co-authors contributed to revisions of the manuscript and approved the final version for publication.
4.3 Journal article: *Echocardiographic screening for rheumatic heart disease in high and low risk Australian children*
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Chapter 5

Prevalence of RHD in Indigenous children from four regions of northern Australia
CHAPTER 5. PREVALENCE OF RHD IN INDIGENOUS CHILDREN FROM FOUR REGIONS OF NORTHERN AUSTRALIA

5.1 Chapter Overview

This paper presents the results of the gECHO study in more detail, and was published in the Medical Journal of Australia in 2015. It focuses only on the high-risk Indigenous cohort, and examines differences in RHD prevalence between the four study regions, as well as discussing some of the challenges presented by the screening process in remote Australia. The major finding was that the prevalence of Definite RHD in children in the Top End of the NT (17.0 per 1000) was greater than in the other three regions (odds ratio 2.3), and nearly double previous estimates of the prevalence of RHD in NT Indigenous children. An evaluation of socioeconomic data is presented and suggests that the Top End group was the most disadvantaged of our cohort, which may provide an explanation for this finding.

5.2 Statement of contribution to jointly authored work

The contribution of authors to the overall study was described in Chapter 4. In addition, this paper required preparation of a dataset incorporating publically available socioeconomic data, and subsequent statistical analysis, both of which were done by myself. I prepared all drafts of the manuscript. All co-authors contributed to revisions of the manuscript and approved the final version for publication.

5.3 Journal article: Rheumatic heart disease in Indigenous children in northern Australia: differences in prevalence and the challenges of screening.
Rheumatic heart disease in Indigenous children in northern Australia: differences in prevalence and the challenges of screening

Rates of acute rheumatic fever (ARF) and its sequel, rheumatic heart disease (RHD), are high in Indigenous Australians (Aboriginal Australians or Torres Strait Islander peoples). Estimates of RHD prevalence have relied on register data collected for clinical purposes or on intermittent enhanced surveillance projects, and have suggested that 1%–2% of Indigenous Australians living in northern and central Australia have RHD.

Screening for RHD provides an opportunity to accurately define the current disease burden, as well as to identify children with undiagnosed disease who may benefit from early treatment. A number of studies have shown that cardiac auscultation lacks the sensitivity and specificity required for screening for RHD and should no longer be used for this purpose. Portable echocardiography has emerged as a more valuable tool, and its usefulness was enhanced by the publication of the World Heart Federation (WHF) criteria for the echocardiographic diagnosis of RHD in 2012 (Box 1).

We recently published the results of an echocardiographic screening study of more than 3000 school-aged children, including nearly 4000 Indigenous children living in four regions of northern and central Australia. We used the WHF criteria to compare the echocardiographic findings of children at high and low risk of RHD (as defined by the RHD Australia guidelines). We found that the overall prevalence of definite RHD in high-risk Indigenous children (8.6 per 1000) was comparable with previous register-based estimates from the Northern Territory. Definite RHD was not identified in any low-risk non-Indigenous children.

This study is methodologically the most rigorous exploration of echocardiographic screening yet conducted, and the first cross-sectional survey of the prevalence of RHD in Australia. However, we did not report the data in sufficient detail to maximise its relevance for local RHD control in Australia. In this article, we describe the prevalence of definite and borderline RHD in Indigenous children from the Top End of the NT, Central Australia, Far North Queensland (FNQ), including the Torres Strait, and the Kimberley region of Western Australia. By comparing the findings in different regions and describing some of the challenges of the screening process, we aim to inform decision making about the potential impact and usefulness of echocardiographic screening for RHD in different Australian regions.

Abstract

Objectives: To compare regional differences in the prevalence of rheumatic heart disease (RHD) detected by echocardiographic screening in high-risk Indigenous Australian children, and to describe the logistical and other practical challenges of RHD screening.


Setting: Thirty-two remote communities in four regions of northern and central Australia.

Participants: 3946 Aboriginal or Torres Strait Islander children aged 5–15 years.

Intervention: Portable echocardiography was performed by cardiac sonographers. Echocardiograms were recorded and reported offsite by a pool of cardiologists.

Main outcome measures: RHD was diagnosed according to 2012 World Heart Federation criteria.

Results: The prevalence of definite RHD differed between regions, from 4.7/1000 in Far North Queensland to 15.0/1000 in the Top End of the Northern Territory. The prevalence of definite RHD was greater in the Top End than in other regions (odds ratio, 2.3; 95% CI, 1.2–4.6, P = 0.01). Fifty-three per cent of detected cases of definite RHD were new cases; the prevalence of new cases of definite RHD was 4.6/1000 for the entire sample and 7.0/1000 in the Top End. Evaluation of socioeconomic data suggests that the Top End group was the most disadvantaged in our study population.

Conclusions: The prevalence of definite RHD in remote Indigenous Australian children is significant, with a substantial level of undetected disease. Important differences were noted between regions, with the Top End having the highest prevalence of definite RHD, perhaps explained by socioeconomic factors. Regional differences must be considered when evaluating the potential benefit of widespread echocardiographic screening in Australia.

Methods

Design, setting and participants

The study design and population and the sample size calculation have been described previously. Briefly, we performed screening echocardiograms on 3946 Indigenous children aged 5–15 years living in remote communities in northern Australia. Thirty-two communities were selected from four geographical regions (Box 2). Children were identified by the enrolment records of

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221.1
participating schools and were recruited at school or by approaching their families. Written informed consent was obtained from parents or guardians, and written consent was also obtained from children who were at least 13 years old.

The study was conducted from September 2008 to November 2010. Ethics approval was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Community Services, the Central Australian Human Research Ethics Committee, the Cairns and Hinterland Health Service District Human Research Ethics Committee, the James Cook University Human Ethics Committee, the University of Western Australia Human Research Ethics Committee, and the Western Australian Aboriginal Health Information and Ethics Committee.

Echocardiography protocol, reporting and definitions
Screening echocardiograms were performed by cardiac sonographers according to an abbreviated protocol that focused on the mitral and aortic valves. Sonographers were provided with a list of features that prompted a more detailed, comprehensive echocardiogram, also performed at the time of screening, if required. Screening echocardiograms were recorded to DVD and reported offsite by a pool of 14 cardiologists according to our standardised electronic protocol. These data were used post hoc to determine whether children met the WHF definitions of definite or borderline RHD.

Clinical follow-up
Separate to reporting for research purposes, all comprehensive echocardiograms were sent to a local cardiologist to guide clinical management of the participant. The cardiologist provided a written report that included the echocardiographic findings and recommendations for follow-up, including secondary prophylaxis. Reports were sent to the primary health care team, who used existing clinical services to coordinate the necessary referrals.

1. Echocardiographic criteria for rheumatic heart disease (RHD) in individuals aged ≤ 20 years

Definite RHD (one of the following features):
- Pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve;
- Mitral stenosis mean gradient ≥ 4 mm Hg;
- Pathological aortic regurgitation and at least two morphological features of RHD of the aortic valve;
- Borderline disease of both the aortic valve and mitral valve.

Borderline RHD (one of the following features):
- At least two morphological features of RHD of the mitral valve without pathological mitral regurgitation or mitral stenosis;
- Pathological mitral regurgitation;
- Pathological aortic regurgitation.

2. Northern Australian sites where echocardiographic screening for rheumatic heart disease was undertaken for this study

Socioeconomic comparisons
We explored whether differences in RHD prevalence between regions could be attributed to socioeconomic or demographic factors. No information about socioeconomic characteristics of the participating schools and communities. Information about school attendance and the Indigenous status of enrolled students, as well as Index of Community Socio-Educational Advantage (ICSEA) scores were obtained for each participating school from the Australian Government's MySchool website. The ICSEA is a measure of the educational advantage of the students enrolled at a particular school, based on information about each student’s family background (including parental occupation and level of education). The median value of the scale is 1000 with an SD of 100.
for Areas (SEIFA12) scores were obtained for each participating community from the Australian Bureau of Statistics 2011 census data. Two SEIFA scores were analysed: the Index of Relative Social Disadvantage (IRSD) and the Index of Relative Social Advantage and Disadvantage (IRSAD). These indices summarise socioeconomic information about the people and households in a geographical area, and scales are standardised with a mean value of 1000 and an SD of 100.

ICSEA, IRSD and IRSAD scores were assigned to individuals according to their school or community and to calculate aggregate scores for each of the four study regions.

Statistical analysis
Statistical analysis was performed with the Stata statistical package (version 12.1; StataCorp). Descriptive data are presented as medians and interquartile range (IQR) for non-normally distributed variables. Medians were compared with the Mann–Whitney U test (for two groups) or the Kruskal–Wallis test (for more than two groups). Categorical variables were compared with the χ² test. RHD prevalence (with 95% CIs) was calculated for the entire study sample and for each of the four regions. Multivariate logistic regression was used to compare the proportion of children with RHD in each region. Socioeconomic variables were compared by means of ANOVA (IRSD, IRSD and ICSEA) or Kruskal–Wallis and Mann–Whitney U tests (household crowding).

Results
The demographic characteristics of the 3946 remote Indigenous children who had a screening echocardiogram are presented in Box 3. Forty-one per cent of the FNQ participants were identified as Torres Strait Islanders or Aboriginal and Torres Strait Islanders, whereas more than 99% of the other groups were identified as Aboriginal only.

Despite the similar age and sex distribution of all four groups, children from the Top End of the NT had a significantly lower median body weight and body mass index than children from the other three regions (compared with Central Australia and FNQ, *P* < 0.001; with the Kimberley, *P* = 0.004; Box 3). Of the 569 comprehensive echocardiograms performed (13.3% of children screened), significantly more were undertaken in FNQ (17.2%) than in other jurisdictions (*P* < 0.001 compared with the Kimberley, *P* < 0.001; with Central Australia, *P* = 0.002; with the Top End, *P* = 0.26; Box 3). In the FNQ group, more Torres Strait Islander children (20.4%) required a comprehensive echocardiogram than did non-Torres Strait Islander children (14.9%, *P* < 0.001).

Prevalence of RHD based on the WHF criteria
The prevalence of definite and borderline RHD in each region is presented in Box 4. The prevalence of definite RHD was higher in Top End children than in children from the three other jurisdictions combined (odds ratio [OR], 2.3; 95% CI, 1.2–4.6, *P* = 0.01). This difference was not observed in the borderline RHD category. We have previously reported that 18 of the 34 children (52.9%) who met the criteria for definite RHD were new cases (no previous history of ARF or RHD); the majority (93.9%) of children meeting the criteria for borderline RHD were also new cases. The prevalence of previously undiagnosed definite RHD detected in the entire study sample by screening was 4.6 per 1000 (95% CI, 2.7–7.2); for the Top End, the prevalence of new cases of definite RHD was 7.0 per 1000 (95% CI, 2.8–14.4).

| Characteristic                  | Top End (n = 1000) | Central Australia (n = 895) | Far North Queensland (n = 1265) | Kimberley (n = 786) | *P*
|--------------------------------|-------------------|-----------------------------|---------------------------|-------------------|------
| Sex, n (%)                     |                   |                             |                           |                   |      |
| Male                           | 497 (49.7%)       | 479 (53.5%)                 | 641 (50.7%)               | 389 (49.5%)       | 0.30*|
| Female                         | 503 (50.3%)       | 416 (46.5%)                 | 624 (49.3%)               | 397 (50.5%)       |      |
| Ethnicity, n (%)               |                   |                             |                           |                   |      |
| Aboriginal                     | 998 (99.8%)       | 892 (99.7%)                 | 746 (59.0%)               | 786 (100.0%)      |      |
| Torres Strait Islander         | 2 (0.2%)          | 2 (0.2%)                    | 303 (24.0%)               | 0                 | < 0.001*|
| Aboriginal and Torres Strait Islander | 0 (0.1%) | 1 (0.1%) | 216 (17.1%) | 0 |      |
| Comprehensive echocardiogram performed, n (%) | 153 (15.3%) | 111 (12.4%) | 217 (17.2%) | 88 (11.2%) | < 0.001*|
| Age (years), median (IQR)     | 9.4 (7.4–11.6)    | 9.3 (7.3–11.3)              | 9.2 (7.2–11.2)            | 9.3 (7.3–11.5)    | 0.15*|
| Weight (kg), median (IQR)     | 26.5 (21.1–35.5)  | 29.8 (22.9–40.8)            | 28.5 (21.8–39.5)          | 27.4 (21.7–39.0)  | < 0.001*|
| Height (cm), median (IQR)     | 133.0 (121.9–147.0) | 135.0 (123.0–149.0)   | 133.4 (120.1–145.8)       | 133.0 (121.4–148.2) | 0.01*|
| BMI (kg/m²), median (IQR)     | 15.1 (14.0–16.6)  | 16.2 (14.9–18.9)            | 16.2 (14.7–19.0)          | 15.7 (14.4–17.9)  | < 0.001*|

BMI = body mass index; IQR = interquartile range; *χ² test; † Kruskal–Wallis test.
Comparison of the socioeconomic profiles of the four regions

Thirty-eight schools from 32 communities participated in the screening study. Mean and median ICSEA, IRSD and IRSAD scores for each region are presented in Box 5. The Top End communities had significantly lower mean ICSEA, IRSD and IRSAD scores (ANOVA), and significantly higher levels of household crowding (Kruskal–Wallis, Mann–Whitney U tests) than the other regions (P < 0.05 for all comparisons; Top End versus other regions combined or individually). Top End schools also had significantly lower median ICSEA scores than the other regions combined and each of Central Australia and FNQ (for each comparison, P < 0.001), but not when compared with Kimberley schools (P = 0.43).

Discussion

This is the first prospective screening survey for RHD in Indigenous Australian children, and the first study to provide reliable information about the epidemiology of RHD in children from FNQ and the Kimberley region of Western Australia. Our previous report confirmed that the prevalence of RHD is high in Indigenous children, and that the overall prevalence of definite RHD in school-aged children (8.6 per 1000) is comparable with figures from developing countries.14–18 Although this figure is similar to previous estimates of the prevalence of RHD in the NT,1,2,19 there are important differences between the four regions when examined individually.

The most striking difference is the higher prevalence of definite RHD in children from the Top End of the NT. The prevalence of 15.0 per 1000 is two to three times higher than in other regions, and nearly triple the previously published estimates of RHD prevalence in Top End children (5.8 per 100020). Two more recent audits of the NT register have been undertaken, but only the combined data from the Top End and Central Australia have been published.1,19 Reporting an RHD prevalence of 8.5 per 1000 in Indigenous children aged 5–14 years in the NT. Our study suggests that this significantly underestimates the burden of disease in the Top End, and that disease epidemiology may be different in the Top End and Central Australia.

This difference has not previously been reported, and reasons for a higher disease burden in the Top End are not clear. However, some features of our study sample may be relevant. We noted that the growth parameters of Top End children were significantly lower than those of children in the other regions, and that the participating Top End communities had the highest number of people per household, a mean of 6.3 persons, compared with the Australian average of 2.6 persons per household.15 In addition, the ICSEA, IRSD and IRSAD scores were also lowest in our Top End sample, between three and five SDs below the Australian average. It was striking how far below the Australian mean these scores were in all regions, highlighting the extreme disadvantage experienced in remote Aboriginal communities. We attempted to quantify the relationship between definite RHD and the four socioeconomic measures by logistic regression, but the small number of cases of definite RHD prevented this.

These observations suggest that the participating communities from the Top End were the most disadvantaged of the remote Indigenous communities we surveyed. Given that poverty-related factors, such as overcrowded housing, are known to be significant risk factors for ARF and RHD,71–23 extreme disadvantage would provide a plausible explanation for the higher prevalence of RHD in the Top End. Other possibilities include inherent differences in host susceptibility or in circulating strains of group A Streptococcus (GAS), but data are not available for the four sampled regions to explore these hypotheses. One NT study that investigated the diversity of GAS strains in the NT did not find

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“NT-endemic” strains, and the authors concluded that the high burden of GAS disease was more probably related to poor living conditions than to bacterial factors. Selection bias may also contribute to the observed differences in RHD prevalence. Given the logistical challenges of surveying a large number of Indigenous children in remote areas, we were unable to select communities at random. We instead carefully selected communities of different sizes and from different areas in the same geographic region to provide as broad a sample as possible (Box 2).

Only about 50% of school-enrolled children were screened in our study (although the percentages in Box 3 are slight underestimates, because the school enrolment record includes children of all ages, some of whom were not eligible for our study). Given that the average daily attendance in participating schools was 69%, this result is understandable, and indicates our efforts to maximise recruitment. Whether the children we screened were representative of all children in the participating communities is an important question. We were unable to collect information about children who had not consented to the study, but Box 3 shows that there were no differences in the sex or age distributions of the samples from each region. It is probable that these figures (equal sex and normal age distributions) are representative of the communities as a whole, and that selection bias is unlikely to explain the observed differences in RHD prevalence.

However, selection bias may have resulted in an overall underestimation of RHD prevalence. A school-based approach to screening is practical, but potentially excludes those most at risk of disease, such as children who are too sick to attend school, or who live in the most marginalised families. This may have resulted in underestimation of the full burden of RHD in remote Indigenous communities.

The number of new cases detected is a crucial element in evaluating the usefulness of any screening program. More than half of the children meeting the criteria for definite RHD were new cases (Box 4), with an overall prevalence of 4.6 new cases per 1000 children screened. This figure was substantially higher in the Top End cohort, and our results suggest that for every 1000 Top End children screened, 7 new cases of definite RHD would be detected, equivalent to about 50 new cases in this population. This information is
critical for evaluating the cost-effectiveness of screening, and we are currently analysing the data.

We encountered a number of practical difficulties that have implications for future echocardiographic screening in remote Australia. The logistical challenges of travel to remote communities are clear; travel by road is slow and sometimes impossible, and travel by plane is expensive, requiring chartered flights to isolated areas not served by commercial flights. After staff had arrived in the communities, the biggest challenge was finding and obtaining consent from the children to be screened, as school attendance was poor. We tried to include absentees by extending our screening activities beyond the school grounds, which was time-consuming and inefficient.

The most significant challenges faced by this study related to clinical follow-up and communication with families and health care providers. A total of 569 children (14.4%, Box 3) had comprehensive echocardiograms that required timely review by an offsite cardiologist to guide clinical management. This considerably increased the workload of local cardiologists, and it frequently took weeks to months for reports to be completed. Once available, the reports themselves often generated confusion and frustration for health care providers, as illustrated by a qualitative survey of health care providers, as reported by this study related to clinical follow-up. In addition, the reporting occurred within a much shorter time period, and clinical follow-up was performed by clinicians who were directly involved in the research process. In addition, the WHF criteria had been published before the study commenced, reducing diagnostic uncertainty regarding the significance of minor echocardiographic abnormalities and facilitating appropriate clinical follow-up.

In summary, our study identified a previously unrecognised difference in the prevalence of RHD in four remote regions of northern Australia. The prevalence of definite RHD in Top End children was nearly twice as high as that in the other three regions, and this may be related to socioeconomic factors. We estimate that 4–8 per 1000 Indigenous children in remote communities have undetected RHD that could be identified by echocardiographic screening. Whether such screening should be recommended will require further and careful consideration of its cost-effectiveness, feasibility, sustainability and impact on primary and specialist health care services. We are currently preparing a cost-effectiveness analysis that will allow us to make informed recommendations regarding RHD screening to national policymakers.

Acknowledgements: We gratefully acknowledge the work of study staff Loraine Kelpe, Vijaya Joshi, Collette Davis, Phena Dawson and Yvonne Holdes. We also thank Josh Sher and the other echocardiographers, Cabrini Health, and cardiologist Krishna Kumar; this work would not have been possible without their generous support. We also thank the staff and students at the participating schools and health clinics. This study was supported by the Office of Aboriginal and Torres Strait Islander Health of the Australian Government. Additional funding was received from the Children First Foundation, Kiwanis International, and Cabrini Health. Kathryn Roberts received an Australian Postgraduate Award Scholarship from the Charles Darwin University. Graeme Maguire is supported by an NHMRC Practitioner Fellowship and the Margaret Ross Chair in Indigenous Health.

Competing Interests: No relevant disclosures.

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Chapter 6

Is auscultatory screening for RHD useful?
CHAPTER 6. IS AUSCULTATORY SCREENING FOR RHD USEFUL?

6.1 Chapter Overview

This chapter evaluates the utility of auscultatory screening (the current approach to RHD screening in the Northern Territory) compared with echocardiography in 1015 NT children. It was published in the *Medical Journal of Australia* in 2013. It compares three methods: nurse only auscultation to detect any cardiac murmur, doctor only auscultation to detect significant cardiac murmurs and two-stage auscultation (by nurse to detect any murmur, followed by doctor to select significant murmurs). Nurses and doctors with varying levels of experience were used.

We found that cardiac murmurs were heard in approximately 25% of children by nurses and doctors, but that murmurs were only heard by both in about half of these cases. Sensitivity for detecting any cardiac abnormality by auscultation was less than 50% and the positive predictive value was less than 10%, regardless of the expertise of the examiner. This confirms that cardiac auscultation is not a useful screening test for RHD and we recommend that auscultation no longer be used to screen for RHD in Indigenous children in the NT.

6.2 Statement of contribution to jointly authored work

The contribution of authors to the overall study was described in Chapter 4. I performed the statistical analysis and wrote the manuscript. All co-authors contributed to revisions of the manuscript and approved the final version for publication.
6.3 Journal article: Utility of auscultatory screening for detecting rheumatic heart disease in high-risk children in Australia’s Northern Territory
Utility of auscultatory screening for detecting rheumatic heart disease in high-risk children in Australia’s Northern Territory

Rheumatic heart disease (RHD), the long-term sequel of acute rheumatic fever, is a leading cause of heart disease in children in low- and middle-income countries. Poverty and overcrowding are known risk factors for RHD, and with improvements in socioeconomic conditions, the disease has essentially disappeared from industrialised countries, with the exceptions of the Indigenous populations of Australia and New Zealand. Indigenous Australians continue to experience among the highest rates in the world, with an acute rheumatic fever incidence of up to 380 per 100,000 children aged 5–14 years, and an estimated RHD prevalence of 8.5 per 1000 children in this age group. A recent government report shows that young Indigenous Australians (<35 years) in the Northern Territory have a 122-fold greater prevalence of RHD than non-Indigenous Australians.

In populations with high prevalence, RHD satisfies many of the criteria for a disease to be deemed suitable for screening, and RHD has long been a target of public health screening internationally. Cardiac auscultation was the traditional approach, but with the evolution of portable echocardiography there has been increasing interest in echocardiographic screening for RHD. In the echocardiographic era, a new category of RHD has been recognised: “subclinical RHD”, defined as structural or functional changes consistent with RHD evident on an echocardiogram in the absence of a pathological cardiac murmur. By definition, it is not possible to identify children who have subclinical RHD using auscultatory screening alone, and published data consistently show that auscultation is considerably less sensitive than echocardiography, missing up to 90% of cases of RHD in some studies. Also of concern is the high false-positive rate associated with auscultation, resulting in many children undergoing further unnecessary diagnostic evaluation.

As part of a large echocardiographic screening study undertaken in northern Australia, we performed cardiac auscultation on a subset of schoolchildren in remote Indigenous communities in the NT and compared clinical findings with echocardiographic findings. We aimed to establish whether cardiac auscultation is an appropriate tool for RHD screening to identify children who should be referred for echocardiography.

Methods

Setting and participants
Our study was conducted in 12 rural and remote communities in Central Australia and the Top End of the NT between September 2008 and June 2010. Children aged 5–15 years, identified by school enrolment rolls, were eligible to participate. These children were a subset of a larger population of schoolchildren who received an auscultatory screening by medical students and local medical practitioners.

Participants
1015 predominantly Indigenous schoolchildren aged 5–15 years were screened between September 2008 and June 2010.

Design
Cross-sectional screening survey.

Intervention
All children underwent transthoracic echocardiography, using a portable cardiovascular ultrasound machine, and cardiac auscultation by a doctor and a nurse. Sonographers and auscultators were blinded to each others’ findings and the clinical history of the children. Echocardiograms were reported offsite, using a standardised protocol, by cardiologists who were also blinded to the clinical findings.

Main outcome measures
Presence of a cardiac murmur as identified by nurses (any murmur) and doctors (any murmur, and “suspicious” or “pathological” murmurs), compared with echocardiogram findings. RHD was defined according to the 2012 World Heart Federation criteria for echocardiographic diagnosis of RHD.

Results
Of the 1015 children screened, 34 (3.3%) had abnormalities identified on their echocardiogram; 24 met echocardiographic criteria for definite or borderline RHD, and 10 had isolated congenital anomalies. Detection of any murmur by a nurse had a sensitivity of 47.1%, specificity of 74.8% and positive predictive value (PPV) of 6.1%. Doctor identification of any murmur had 34.2% sensitivity, 75.1% specificity and 5.1% PPV, and the corresponding values for doctor detection of suspicious or pathological murmurs were 20.6%, 92.2%, and 8.3%. For all auscultation approaches, negative predictive value was more than 97%, but the majority of participants with cardiac abnormalities were not identified. The results were not different when only definite RHD and congenital abnormalities were considered as true cases.

Conclusions
Sensitivity and positive predictive value of cardiac auscultation compared with echocardiography is poor, regardless of the expertise of the auscultator. Although negative predictive value is high, most cases of heart disease were missed by auscultation, suggesting that cardiac auscultation should no longer be used to screen for RHD in high-risk schoolchildren in Australia.
group of children, from 17 communities in Northern Australia, who had echocardiography performed for a larger study. Nurse and doctor auscultators were present during visits to the 12 communities, and all the children in these communities who were participating in the larger study were eligible to participate in the auscultation component.

Written informed consent was obtained from parents and guardians, and written assent was obtained from children aged ≥13 years before they took part. Ethics approval was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Community Services, and the Central Australian Human Research Ethics Committee.

Echocardiography

All children had a screening echocardiogram performed by an experienced cardiac sonographer using a Vivid e (GE Healthcare) portable cardiovascular ultrasound machine. Sonographers were blinded to the auscultators’ findings and to the clinical history of the children. Screening echocardiograms were performed according to an abbreviated protocol, previously used in Tonga and Fiji, that focused on the mitral and aortic valves, but would also enable detection of significant congenital lesions. If a potential abnormality was detected, a complete echocardiogram was performed.

Echocardiograms were recorded to DVD and reported offline by a pool of 14 cardiologists who were blinded to the clinical findings. Detailed data about the mitral and aortic valves were entered into an electronic database.

Children were classified as having definite or borderline rheumatic heart disease and congenital abnormalities detected on echocardiogram; there was no difference in the findings when only definite rheumatic heart disease and congenital abnormalities were considered true cases (data not shown). AUC is a measure of overall test accuracy; 0.5 indicates zero discrimination, and values approaching 1.0 indicate high sensitivity and specificity.

Any murmur

<table>
<thead>
<tr>
<th>Auscultation approach</th>
<th>No. of children with abnormalities* (n = 34)</th>
<th>No. of children without abnormalities (n = 981)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>AUC† (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>One stage, by nurse</td>
<td>Any murmur 16 247 47.1% (29.8%–64.9%) 74.8% (72.0%–77.5%) 6.1% (3.5%–9.7%) 0.76% (96.2%–98.6%) 0.61 (0.52–0.70)</td>
<td>No murmur 18 734</td>
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<tr>
<td>One stage, by doctor</td>
<td>Any murmur 131 244 38.2% (22.2%–56.4%) 75.1% (72.3%–77.8%) 5.1% (2.7%–8.5%) 97.2% (95.8%–98.3%) 0.57 (0.48–0.66)</td>
<td>No murmur 211 737</td>
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<tr>
<td>One stage, by doctor</td>
<td>Significant murmur§ 7 77 20.6% (8.7%–37.9%) 92.2% (90.3%–93.8%) 8.3% (3.4%–16.4%) 97.1% (95.8%–98.1%) 0.56 (0.49–0.63)</td>
<td>No significant murmur 27 904</td>
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<tr>
<td>Two stage**</td>
<td>Significant murmur 6 51 17.6% (6.8%–34.5%) 94.8% (93.2%–96.1%) 10.5% (4.0%–21.5%) 97.1% (95.8%–98.1%) 0.56 (0.50–0.63)</td>
<td>No significant murmur 28 930</td>
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</table>

PPV = positive predictive value. NPV = negative predictive value. AUC = area under the receiver operating characteristic curve. * Definite or borderline rheumatic heart disease and congenital abnormalities detected on echocardiogram; there was no difference in the findings when only definite rheumatic heart disease and congenital abnormalities were considered true cases (data not shown). † AUC is a measure of overall test accuracy; 0.5 indicates zero discrimination, and values approaching 1.0 indicate high sensitivity and specificity. ‡ Includes 8 children with rheumatic heart disease (5 definite, 3 borderline) and 5 with congenital heart disease. § Includes 16 children with rheumatic heart disease (10 definite, 6 borderline) and 5 with congenital heart disease. * Definite or borderline rheumatic heart disease and congenital abnormalities detected on echocardiogram; there was no difference in the findings when only definite rheumatic heart disease and congenital abnormalities were considered true cases (data not shown). ** By a nurse to identify any murmur, then by a doctor to identify significant murmur.

Paediatricians and cardiologists. It was completed with children supine and sitting, in a quiet room where possible. The diaphragm and bell of the stethoscope were used at the apex and axilla, lower left sternal edge, upper left sternal edge and upper right sternal edge. The nurses and doctors who performed auscultation were asked to comment on the presence or absence of a murmur. The doctors were further asked to specify whether a murmur was “innocent”, “suspicious” or “pathological”. Suspicious and pathological murmurs were classified as “significant” murmurs. This enabled assessment of three screening approaches: one-stage auscultation by a nurse to detect any murmur; one-stage auscultation by a doctor to detect any significant murmur; and two-stage auscultation, with the first stage to detect any significant murmur by a nurse and the second stage to detect which of these was significant by a doctor.

Analysis

Statistical analysis was performed using Stata statistical package version 12.1 (StataCorp). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each screening approach.

Results

A total of 1986 NT children had a screening echocardiogram as part of the larger study, of whom 1015 had auscultation performed by a doctor.
and a nurse; 960 (94.6%) were Indigenous and 498 were girls (49.1%). The mean age was 9.3 years (SD, 2.5 years), and the median body mass index was 15.6 kg/m² (interquartile range, 14.4–17.8 kg/m²). Children who had an echocardiogram but did not undergo auscultation were slightly older (mean age, 9.7 years), but were otherwise comparable based on sex and body mass index.

Echocardiographic findings
Thirty-four children (3.3%) had abnormalities identified on their echocardiogram. Fifteen (1.5%) of them had definite RHD, 9 (0.9%) had borderline RHD (including two who also had small atrial septal defects), and 10 (1.0%) had isolated congenital anomalies: ventricular septal defect (two), atrial septal defect (one), mitral valve prolapse (two), patent ductus arteriosus (two), dilated aortic root (two) and complex congenital heart disease (one). Of the 24 children with RHD, 14 had pathological mitral regurgitation, six had pathological aortic regurgitation, and one child had both.

Clinical findings

One-stage auscultation
A cardiac murmur (significant or not) was heard by nurses in 263 children (25.9%), by doctors in 257 children (25.3%), and by a doctor and a nurse in 137 children (13.5%). Compared with echocardiogram, one-stage auscultation to detect any murmur by a doctor or a nurse had a sensitivity of less than 50%, a specificity of about 75%, and a positive predictive value (PPV) of less than 10% (Box 1). Asking doctors to decide which murmurs were pathological or suspicious increased the specificity from 75.1% to 92.2%, but further dropped the sensitivity to 20.6%. The breakdown of medical specialists and their auscultation findings are presented in Box 2.

Two-stage auscultation
Only 52% (137/263) of the murmurs heard by nurses were also heard by doctors. Of these, 57 were considered pathological or suspicious. Using two-stage auscultation, 28 children with abnormalities were missed (sensitivity, 17.6%), and six children with abnormalities were correctly identified (PPV, 10.5%). This approach had a specificity of 94.8%.

Discussion
Our study confirms that cardiac auscultation has poor sensitivity, despite moderately high specificity, for detecting RHD and other cardiac abnormalities evident on echocardiograms, regardless of the experience of the examiner. More than 50% of children with abnormal echocardiography results did not have a murmur detected, and more than 90% of murmurs heard were false positives. The observed high NPVs and low PPVs are expected in a low-prevalence disease such as RHD, and are consistent with the results of previous studies (Box 3). Our findings highlight the paramount importance of sensitivity in determining the utility of auscultation as a screening test for RHD.

The current approach to screening for RHD in the NT is one-stage doctor auscultation by a GP, with referral of any child with a murmur for an echocardiogram. Program reports suggest that cardiac murmurs are
heard in about 10% of those screened,21 but few data regarding follow-up and clinical outcomes for these children are available. In a detailed report on RHD screening in Central Australia during 2009, 67 of 1095 children who were screened (6.1%) had a murmur and were referred for echocardiography. One year later, only 38 of them had had their echocardiogram, of whom four had abnormalities (two with RHD, two non-RHD abnormalities).19 This prevalence of RHD (2 per 1000 children) is considerably lower than expected in the Central Australian population and suggests that some disease went undetected. In addition, the fact that nearly half of referred children had not had their echocardiogram 12 months later also highlights difficulties with the current approach.

According to the current NT screening model (one-stage doctor auscultation), 257 children in our study would have been referred for echocardiogram, with only 13 of them having abnormalities (eight with RHD, five non-RHD abnormalities).19 This prevalence of RHD (2 per 1000 children) is considerably lower than expected in the Central Australian population and suggests that some disease went undetected. In addition, the fact that nearly half of referred children had not had their echocardiogram 12 months later also highlights difficulties with the current approach.

The prognosis of RHD is best if secondary prophylaxis with long-acting intramuscular penicillin is commenced when the disease is mild; continuous adherence to treatment with penicillin can result in valve damage being halted or reversed.22-25 It is therefore imperative that the test used to screen for RHD is highly sensitive, so that children with the earliest stage of disease, who stand to gain the most from the only currently available preventive treatment, are identified.

It is widely accepted that echocardiography is more sensitive than auscultation. While there has been much discussion about echocardiographic definitions of RHD, including concerns about specificity, it is hoped that the publication of the WHF diagnostic criteria will minimise false-positive results. Whether echocardiographic screening for RHD is appropriate, feasible and cost-effective will vary between settings, and remains a topic of vigorous debate.6,23-25 A cost-effectiveness analysis of our data is underway and will contribute to our ultimate recommendations about the future of echocardiographic screening in Indigenous Australian children who are at high risk of RHD.

A limitation of this study is that auscultation was carried out by several different doctors and nurses, potentially leading to high interobserver variation. Similarly, the screening environment varied between communities, and the conditions under which auscultation was performed (eg, in a quiet room) were not the same for all participants. However, we believe that these limitations reflect the day-to-day reality of health care service provision in the participating communities, allowing valid extrapolation of our results to the current school screening procedure in the NT and many other settings.

We conclude that cardiac auscultation is not an effective method of RHD screening, regardless of the expertise of the auscultator. The risk of missing more than 50% of children with RHD, and the risk of overburdening cardiologists with false positives, preclude recommendation of one-stage or two-stage auscultation as a rational approach to RHD screening. We recommend that cardiac auscultation no longer be used to screen for RHD in high-risk schoolchildren in Australia.

Acknowledgments: We gratefully acknowledge the assistance of the study coordinators (Catherine Oakes, Lorraine Kepple and Waya Alick), echocardiographers and cardiologists who worked on this study. The study was funded by the Australian government, Children First Foundation, Khwaris Centre of Australia and Canberra Health. Kathryn Roberts was supported by an Australian Postgraduate Award from Charles Darwin University. Graeme Maguire is supported by a National Health and Medical Research Council Practitioner Fellowship and the Margaret Ross Chair of Indigenous Health.

Competing interests: No relevant disclosures.

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Chapter 7

Summary of the gECHO study
CHAPTER 7. SUMMARY OF THE gECHO STUDY

The gECHO study was one of the largest echocardiographic screening surveys conducted internationally, undertaken at a time when the World Heart Federation (WHF) diagnostic criteria\(^{(1)}\) were still under development. The inclusion of urban Australian children at low risk for RHD permitted detailed evaluation of echocardiographic findings in a large healthy cohort, which contributed to the understanding of ‘normal’ and ‘abnormal’ findings that were subsequently incorporated into the WHF criteria.

This study was the first to employ the WHF criteria to estimate the burden of RHD in our population. At the time of reporting, study cardiologists were not familiar with these criteria and we noted a significant discrepancy between cardiologist-identified RHD (subjective opinion based on experience) and criteria-identified RHD (cases which met WHF criteria when individual echocardiographic features were examined); cardiologists identified more than twice as many cases of RHD than the WHF criteria in both high- and low-risk groups.

A high rate of false positive results has important implications for screening programs, and we emphasise the importance of a standardised approach to performing and analysing screening echocardiograms. As experience with the WHF criteria increases, we expect that diagnostic precision will improve. Other international prevalence studies are now successfully using these criteria, and this standardised approach permits meaningful comparisons of RHD prevalence between regions around the world.

We confirm that the prevalence of Definite RHD in northern Australian Indigenous children remains unacceptably high, at 8.6 per 1000. If Borderline RHD is included, this increases to 25.3 per 1000 for the whole cohort, and 36.8 per 1000 if only 10-14 year olds are
considered. While the significance of Borderline RHD remains unclear, there is increasing evidence that a proportion of children with these findings are at increased risk of ARF,\(^{(2)}\) and of progression of valvular changes.\(^{(2-4)}\) If even a subset of Borderline cases are added to those meeting criteria Definite RHD, then the overall burden of disease in Indigenous Australian children is considerably higher than has been appreciated previously.

We found a previously unrecognised difference in the prevalence of Definite RHD between remote regions; prevalence was highest in children in the Top End of the NT (17.0 per 1000). Evaluation of socioeconomic data suggests that the Top End cohort was the most disadvantaged in our sample, which could provide a reasonable explanation for this finding. However, given that our sampling was not random, selection bias may also be a contributing factor. This regional difference in prevalence warrants further investigation.

More than half of the children found to have Definite RHD had previously undiagnosed disease, and we estimate that screening would detect a minimum of 4 new cases of RHD for every 1000 children screened. In the Top End of the NT, the number of new cases detected increased to 7 per 1000, suggesting that there may be as many as 50 children with undiagnosed RHD in the Top End today. This information is used in the cost-effectiveness analysis presented in Chapter 9.

In keeping with other international studies, we found that auscultatory screening for RHD is not useful. The sensitivity and positive predictive value of cardiac auscultation compared with echocardiography was poor; over half of the children with abnormal echocardiograms had no murmur detected, and over 90% of those with murmurs detected were false positives. We recommend that auscultation no longer be used to screen for RHD in Indigenous children in the NT.
Undertaking mass screening of over 5000 children in four jurisdictions of northern Australia presented a number of challenges that have implications for future echocardiographic screening in Australia. The geographical context means that vast distances have to be covered; travel was slow and expensive. The low population numbers in remote Indigenous communities, combined with high absenteeism from school, meant that considerable resources were required to screen relatively few children per site.

Follow-up of positive screening echocardiograms also proved challenging and created considerable extra workload for primary health care teams, as well as the already-stretched regional cardiology services. The importance of appropriate communication with families and health care staff was highlighted in a qualitative study that explored the experiences of a number of gECHO participants.\(^{(5)}\)

The practical challenges faced while conducting the gECHO study, as well as the study’s principal research findings, are important elements to take into consideration when designing a potential program of echocardiographic screening for RHD in Indigenous children. The next part of this thesis presents a cost-effectiveness analysis of a proposed RHD screening program in Australia.
7.1 References


Chapter 8

A multi-state model for RHD progression
CHAPTER 8. A MULTI-STATE MODEL FOR RHD PROGRESSION

8.1 Chapter Overview

In order to undertake a cost-effectiveness analysis, a model of disease progression is required. No such model currently exists for RHD, and much of our understanding of RHD progression is based on historical cohort studies conducted more than 50 years ago. This chapter describes the development of a multi-state model for RHD progression using data from a contemporary Australian cohort of RHD patients. Serial patient data from the NT RHD register were analysed, and an audit of patient progress over time is presented.

This chapter has been written as a manuscript which has been submitted to the European Heart Journal as a paired piece with the manuscript presented in Chapter 9. Important supplementary material was submitted with each manuscript - this is included as an appendix at the end of each chapter.

8.2 Statement of contribution to jointly authored work

This paper is co-first-authored with Jeffrey Cannon, a health economist. The data from the NT RHD register was extracted by register staff member Cath Milne, and the dataset was cleaned and prepared for analysis by myself. Jeff Cannon used this data to develop the mathematical model of disease progression, and he created all graphics. I prepared the manuscript, and co-authors contributed to revisions and approved the final version for submission.
8.3 Abstract

Background

Rheumatic heart disease (RHD) remains a disease of international importance, yet little has been published about disease progression in a contemporary patient cohort. Multi-state models (MSM) provide a well-established method of estimating rates of transition between disease states, and can be used to evaluate the cost-effectiveness of potential interventions. We aimed to create a MSM for RHD progression using serial clinical data from a cohort of Australian patients.

Methods and Results

The Northern Territory (NT) RHD register was used to identify all Indigenous NT residents diagnosed with RHD between the ages of 5 and 24 years in the period 1999-2012. Disease severity over time, surgeries and deaths were evaluated for 591 patients. A total of 131 surgeries were performed in 97 patients, and there were 18 deaths during the study period. 96 (16.2%) patients had severe RHD at diagnosis, and this proportion did not vary significantly by age. Of those diagnosed with severe disease, 50% had proceeded to surgery by 2 years, and 10% were dead within 6 years of diagnosis. Of those diagnosed with moderate RHD, there was a similar chance of disease regression or progression over time. The ‘mild RHD’ category was the most stable; after 10 years, 64% remained mild. Nonetheless, 11.4% progressed to severe RHD, with half of these requiring surgery.

Conclusions

The prognosis of young Indigenous Australians diagnosed with severe RHD is bleak; interventions must focus on earlier detection and treatment if the observed natural history is to be improved. This multi-state model can be used to predict the effect of different interventions on disease progression and the associated costs.
8.4 Introduction

Rheumatic heart disease (RHD) remains a disease of international importance, yet little has been published about disease progression in a contemporary cohort. Much of our understanding of the natural history of the disease stems from seminal studies conducted more than 50 years ago.\(^1\) While disease pathophysiology may have changed little since that time, the introduction of benzathine penicillin G (BPG) prophylaxis, as well as the availability of cardiac valve surgery in some settings, has changed the prognosis of established RHD considerably. An understanding of the current trajectory of RHD is important so that the potential impact of new interventions can be realistically estimated.

RHD is a disease of poverty, and the associations with over-crowding and lower socioeconomic status are well documented.\(^4\)\(^,\)\(^5\) While it is now predominantly a disease of developing countries, the Indigenous population of Australia continues to experience rates of acute rheumatic fever (ARF) and RHD that are among the highest in the world.\(^6\) In the Northern Territory (NT) of Australia there is an active RHD control program, and a computerised register was established in 1997. This register includes clinical information about individual patients’ diagnosis, treatment and clinical course, and provides the opportunity to evaluate local disease epidemiology in some detail. A number of audits have been undertaken using NT register data,\(^6\)\(^,\)\(^7\)\(^,\)\(^8\) but none to date have analysed the progression of RHD from diagnosis to the occurrence of several important clinical events, including heart failure, surgical intervention, death or disease remission.

In order to evaluate the potential health and economic impact of new interventions, a model of disease progression is required. As RHD is a chronic disease which can progress or regress over time, a multi-state model is well suited to this process (as opposed to a simple decision tree). The progression from diagnosis to heart failure, and the need for costly
surgery, is of primary interest for economic modelling. Quantifying the probability of progression over time through standard Kaplan-Meier estimates (used in survival analysis) will be inaccurate due to the competing risk of death,\(^{(9)}\) which is higher in RHD patients compared to the general Indigenous population.\(^{(8)}\)

We therefore aimed to create a multi-state model for RHD progression using serial clinical data from a real cohort of Australian RHD patients. This model can then be used to evaluate the cost-effectiveness of a proposed school-based echocardiographic screening program in the contemporary Australian context.

8.5 Methods

8.5.1 Model type

Multi state models (MSM) provide a flexible framework that allows us to model a disease process by defining several health states of interest and describing the probability of transitioning from one state to another over time.\(^{(10-12)}\) If transition out of a health state is possible, the state is said to be transient. If transition is not possible, that state is said to be absorbing (for example, death). A MSM is a particularly good model for RHD, a chronic process where patients may transition back and forth between different clinical states over time.

Our model is subject to the Markovian assumption that the transition process is ‘memoryless’, meaning that the probability of transitioning from one state to another is not affected by previous health states. This is somewhat artificial, given that prior history often affects future prognosis. Despite this limitation, we chose a MSM because it permits a more
useful and valid analysis of RHD progression than a simple survival analysis, which can only evaluate one event (e.g. time to surgery, or time to death) and does not take into consideration competing risks where one event precludes the event of interest occurring (e.g. death preventing surgery).\textsuperscript{[9,10]}

8.5.2 Data source

The NT RHD register includes data about patient demographics, clinical details and investigations of all individuals diagnosed with ARF or RHD in the NT. Data are entered by register staff at diagnosis, and at each subsequent clinical review, based on clinician notes and/or laboratory or echocardiography reports. Hospital and primary care databases are regularly searched by register staff to ensure clinical information is as complete as possible. De-identified data were extracted from the RHD register and assessed for inconsistencies and completeness. The study was approved by the Human Research Ethics Committee of the Menzies School of Health Research.

8.5.3 Study cohort

Our study was based on a cohort of Indigenous persons identified from the NT RHD register. We selected NT residents aged 5-24 years diagnosed with RHD between 1 January 1999 and 31 December 2012 (the date at which data were censored). We did not extract information about patients who had a diagnosis of ARF without RHD.
8.5.4 Health states

Patients on the NT RHD register are categorised as having mild, moderate or severe RHD (Priority level 3, 2 and 1 respectively), as outlined in the Australian ARF/RHD guidelines.[13] We used this classification to describe disease severity (Box 8.1).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
<th>Health state type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority 1 (Severe)</td>
<td>Severe valvular disease or moderate-severe valvular lesion with symptoms of cardiac failure</td>
<td>Transient</td>
</tr>
<tr>
<td>Priority 1a (Severe-surgery)*</td>
<td>Mechanical or tissue prosthetic valves replacements, valve repairs (including balloon valvuloplasty)</td>
<td>Transient</td>
</tr>
<tr>
<td>Priority 2 (Moderate)</td>
<td>Any moderate valve lesion in the absence of symptoms, and with normal left ventricular function</td>
<td>Transient</td>
</tr>
<tr>
<td>Priority 3 (Mild)</td>
<td>Trivial to mild valvular disease</td>
<td>Transient</td>
</tr>
<tr>
<td>Priority 4 (Inactive)</td>
<td>Ceased prophylaxis</td>
<td>Transient</td>
</tr>
<tr>
<td>Priority 5</td>
<td>Deceased (any cause)</td>
<td>Absorbing</td>
</tr>
</tbody>
</table>

*This is not a separate health state in the Australian ARF/RHD guidelines.

Patients’ priority levels are allocated by physicians, and are updated with each clinical encounter. It was assumed that patients remained in the same priority level each month between clinical encounters. Patients who require surgery are automatically assigned a ‘Severe’ priority level (Priority 1) in the register, however we modelled surgery as an explicit health state (Priority 1a). In cases where surgery was required at diagnosis, we modelled the assignment of the ‘Severe’ priority level followed by a delay of less than one week before transition to the ‘Severe-Surgery’ state. This change was required only at diagnosis to limit the initial states of RHD to mild, moderate and severe.
According to the Australian RHD guidelines, a patient may transition to the ‘Inactive’ state if he or she has completed a minimum of 10 years antibiotic prophylaxis after the most recent episode of ARF, and if there are minimal valvular changes on echocardiogram at the time of final review.

Possible transitions between RHD states are illustrated in Figure 8.1.

**Figure 8.1: Potential health state transitions of patients on the NT RHD register**

![Diagram of health state transitions](image)

Our analysis did not include two factors that could potentially affect the course of disease. Secondary prophylaxis data have only been entered into the register since 2007, and were therefore considered too incomplete to be useful. Recurrences of ARF were also difficult to capture, as they relied on a previous diagnosis of ARF, and some of our cohort had never had a previously recorded episode of ARF.
8.5.5 Data quality assessment and exclusions

The date of RHD diagnosis was defined as the date of diagnosis recorded on the register unless there were clinical reviews before the recorded diagnosis date, in which case the date of first review was used as a surrogate. If a priority level had not been assigned within one year of a recorded RHD diagnosis, individual clinical records were reviewed and, where possible, a priority level was allocated based on available clinical information (including clinician notes and echocardiogram reports) contained in the register. Cases were excluded if there was insufficient clinical information to permit allocation of a priority level at diagnosis.

8.5.6 Statistical Methods

All data analysis was performed in R (version 3.1.0). Age at diagnosis was categorised into four groups (5-9, 10-14, 15-19 and 20-24 years) for comparison with existing studies, and all data were summarised as frequency distributions. Chi-square tests were performed to assess differences in RHD severity at diagnosis, valve surgery and mortality between gender, and the age at diagnosis. Additionally, RHD severity at diagnosis was compared between genders within two subgroups; children (5-14 years) and young adults (15-24 years).

The probabilities of being in a particular RHD health state at the end of each month following diagnosis were obtained from the Aalen-Johansen transition estimates calculated by the ‘msSurv’ package, with corresponding 95% confidence intervals (CI) calculated from 200 bootstrap samples. Plots were constructed using the ‘ggplot2’ package.
8.6 Results

8.6.1 Dataset

Information about 618 Indigenous persons aged 5-24 years inclusive, diagnosed with RHD between January 1999 and December 2012, was extracted from the NT RHD register (Figure 8.2).

Detailed review of 272 records (44.0%) was required due to incomplete or inconsistent data. A priority level had not been allocated within one year of RHD diagnosis for 164 patients. Of these, sufficient clinical information was available to allow priority level allocation in 144 cases, but 20 were excluded due to inadequate information, including three deaths, which was the only data entry point for these patients.

Ninety-five patients had clinical reviews recorded more than one year before their RHD diagnosis date; seven of these were excluded due to an actual diagnosis date before 1999,
and the remainder had their diagnosis date revised to correspond with the date of first clinical review. Other reasons for review included surgery date before diagnosis date (n=2), interstate residence (n=3), and inconsistent sequences of records (for example, multiple priority transitions in less than six months; n=8). After exclusions, 591 records were available for analysis with a median follow-up time of 7.5 years post diagnosis (IQR 4.3-10.3).

8.6.2 Clinical information obtained from NT register

RHD incidence and severity

Clinical information regarding 591 cases of RHD is presented in Table 8.1. There were more females than males, which was consistent within each age category (data not shown), and the highest number of RHD cases was reported in 10-14 year olds.

Table 8.1: Clinical information about patients aged 5-24 years diagnosed with RHD between 1999 and 2012

<table>
<thead>
<tr>
<th>Clinical indicator</th>
<th>Gender</th>
<th>Age category</th>
<th>All-age Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male n (%)</td>
<td>Female n (%)</td>
<td>5-9yo n (%)</td>
</tr>
<tr>
<td>Number of RHD diagnoses</td>
<td>226 (13.7)</td>
<td>365 (17.8)</td>
<td>140 (15.0)</td>
</tr>
<tr>
<td>RHD severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Severe</td>
<td>31 (13.7)</td>
<td>65 (17.8)</td>
<td>21 (15.0)</td>
</tr>
<tr>
<td>2. Moderate</td>
<td>59 (26.1)</td>
<td>102 (27.9)</td>
<td>42 (30.0)</td>
</tr>
<tr>
<td>3. Mild</td>
<td>136 (60.2)</td>
<td>198 (54.2)</td>
<td>77 (55.0)</td>
</tr>
<tr>
<td>Number of patients having ≥1 surgeries</td>
<td>44 (19.5)</td>
<td>53 (14.5)</td>
<td>25 (17.9)</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>8 (3.5)</td>
<td>10 (2.7)</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>
At diagnosis, 96 (16.2%) patients had severe RHD, and over the 14-year study period 176 patients (29.8%) were diagnosed with severe RHD. The proportion with severe RHD at diagnosis did not vary significantly between gender (p=0.29) or age group (p=0.33; Table 8.1). However, within the subgroup of 5-14 year old children, a greater proportion of girls than boys presented with severe disease (p=0.03; Figure 8.3).

**Figure 8.3:** Number and severity at diagnosis of cases of RHD diagnosed between 1999 and 2012, by age and gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>0-14yo</th>
<th>15-24yo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>61 (20.5%)</td>
<td>41 (25.9%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>35 (16.9%)</td>
<td>30 (19.0%)</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (0.2%)</td>
<td>22 (29.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>111 (53.6%)</td>
<td>87 (55.1%)</td>
</tr>
</tbody>
</table>

**Surgery**

A total of 131 surgical procedures were performed in 97 patients; 73 patients had a single procedure, 18 had two procedures and 6 had ≥3 procedures. The number of patients requiring at least one operation did not statistically differ between age groups (p=0.32) or
gender (p=0.11). The median time to surgery for children diagnosed with severe RHD was two years. The age at first surgery is presented in the Appendix to this chapter (Figure A1).

Death

There were 18 deaths during the study period. Of these, 10 had severe RHD at the time of diagnosis, and 16 had severe RHD at the time of death. Eleven had undergone surgery. There was no statistical difference in the number of deaths by age group at diagnosis (p=0.12) or gender (p=0.58). The age at death is presented in the Appendix (Figure A2) and included two deaths in children less than 15 years of age.

8.6.3 Disease progression over time: a multi-state model for RHD

Transition probabilities between all RHD health states were calculated for each month over the 14-year study period. The probabilities that a patient will be in a given health state 1, 5 and 10 years after RHD diagnosis are presented in Table 8.2. For example, of the patients diagnosed with mild RHD, 93.9% remained mild one year after diagnosis while 4.7%, 1.1% and 0.3% progressed to moderate, severe, and severe with surgery respectively. Probabilities for age groups 5-14 and 15-24 years are presented separately in the Appendix to this chapter (Tables A1 and A2).
Disease progression over time, based on RHD severity at diagnosis, is graphically represented in Figures 8.4 and 8.5. Figure 8.4 represents the health states ‘Severe’ and ‘Severe with surgery’ as two mutually exclusive states, whereas Figure 8.5 follows the progression of all ‘Severe’ patients, and shows surgical patients as a subset within this category. Progression curves for age groups 5-14 and 15-24 years are presented separately in the Appendix (Figures A3-A6).
Figure 8.4: RHD prognosis over 14 years; probability that an individual will be in a particular health state over time, based on RHD severity at diagnosis

Young people who had severe RHD at the time of diagnosis had rapid disease progression and a poor prognosis; 50% of this group had surgery within two years, and 10% were dead within six years of their diagnosis. Patients diagnosed with moderate RHD had a mixed prognosis; 10 years after diagnosis, roughly one-third had progressed to severe RHD (with...
or without surgery), one-third remained moderate, and one-third had regressed to mild RHD. Those who had mild RHD at diagnosis had the most favourable prognosis, with more than 60% remaining mild after 10 years, and 10% being inactive by the end of the 14-year study period. Nonetheless, nearly 30% of this group demonstrated disease progression (18.3% moderate, 11.4% severe, half of whom had surgery) by 10 years.

**8.7 Discussion**

This is the first time a multi-state model for RHD progression has been developed using real patient data. The NT register contains the best available data on a contemporary cohort of RHD patients in the world, and we believe that our analysis provides an accurate picture of the trajectory of RHD for Indigenous Australians today. Furthermore, we believe that our model may be informative for other populations in RHD-endemic settings who face similar socioeconomic disadvantage, poor adherence to BPG and high rates of ARF recurrence.

Overall, 16.2% of our cohort had severe disease at diagnosis (Table 8.1). We were surprised that this proportion didn’t vary significantly between age groups, and that 15% of 5-9 year olds presented with severe disease. This suggests either that the first episode of ARF is occurring very early (and is being missed), or that there is a group of children who have a fulminant presentation with ARF carditis which quickly progresses to severe RHD. This notion could be supported by a number of earlier studies describing presentations with congestive cardiac failure and/or cardiomegaly in 10-20% of first ARF episodes. In all of these studies, severe carditis at presentation universally correlated with the poorest prognosis. Unfortunately, in this group of children screening is unlikely to make a difference to their disease trajectory, although mortality should be reduced by the availability of cardiac surgery in the Australian setting.
Over the 13 year study period, 176 patients (29.8%) were diagnosed with severe RHD, which is comparable to the 28% reported in Lawrence’s audit of NT data,\(^{(8)}\) despite our younger cohort. It should be noted that the majority of children with severe RHD in the Australian context would be considered New York Heart Association (NYHA) Functional Class I or II, as opposed to NYHA Functional Class III or IV, as was the case in the recently published REMEDY study\(^{(5)}\) (a multi-centre hospital-based registry of RHD patients in low and middle-income countries).

The prognosis of patients diagnosed with severe RHD is bleak. Figures 8.4 and 8.5 show the rapid progression to surgery, with 41.6% having surgery within 12 months of their diagnosis (Table 8.2). The proportion proceeding to surgery starts to plateau at about 60% by four years post-diagnosis, at which stage mortality starts to increase. This is particularly marked in the 15-24 year old age group (Appendix Table A2), which had 13.7% mortality by 5 years (95% CI 3.4-24.0) and 22.0% by 10 years (95% CI 9.0-35.0). By 10 years post-diagnosis with severe RHD, less than one-quarter of 15-24 year olds had not progressed to surgery or death (Appendix Figure A5).

The natural history of patients diagnosed with moderate RHD is the most dynamic, with roughly equal proportions likely to progress, regress or remain moderate at 10 years. We have previously undertaken a large echocardiographic screening survey of Indigenous children in the NT,\(^{(20)}\) and of the 18 new cases of Definite RHD detected, seven (39%) were considered to be moderate by the reporting cardiologist. Given that this group is asymptomatic, yet has established RHD on echocardiogram, these children may stand to benefit most from screening. Here, our data confirms that this group is capable of regressing or remaining static in the moderate state, and it would be hoped that early
detection and instigation of regular secondary prophylaxis would further reduce the proportion progressing to severe disease.

Over half of all new RHD diagnoses in this cohort were categorised as mild. It is perhaps most pertinent to look at the prognosis of this group, as these are the children who are most likely to be detected by screening. The mild group was the most stable in terms of disease evolution, with the majority remaining mild over time (73.7% and 63.9% at 5 and 10 years respectively, Table 8.2.) However, the fact that more than 10% had progressed to severe disease after 10 years, including 5.1% who underwent surgery, represents unacceptable morbidity in this group, which should have a benign prognosis.

Two Markov models looking at RHD progression have recently been published, but both rely on probability estimates derived from the literature, rather than data from an actual patient cohort. Manji et al. [21] compared three different strategies for RHD prevention, one of which was detection of early RHD using echocardiography, followed by lifelong secondary prophylaxis. Their model is limited by the fact that it only describes two states following diagnosis with RHD: RHD and death. There is no distinction made between mild and severe disease despite the significantly different clinical trajectories and associated costs of these two states.

The model published by Zachariah et al. earlier this year [22] aimed to evaluate the cost-effectiveness of RHD screening in the Northern Territory of Australia, and it is interesting to compare their theoretical work with ours. Following a diagnosis of RHD, they describe six clinical states, similar to ours. Definitions of severe disease were equivalent, however their surgical state only considered valve replacement surgery not valve repair, which is the preferred intervention for young Indigenous patients in Australia. Zachariah’s assumptions
around the progression of severe disease do not appear to be appropriate for the current Australian context. They required that a patient be in the ‘RHD Congestive Heart Failure’ state for at least one year prior to undergoing surgery. As previously outlined, our data suggest that disease progression is considerably more rapid than this.

Our study provides a reliable picture of RHD evolution in a contemporary cohort of Indigenous Australians. However, there are some limitations to our data. Firstly, patient severity levels, our outcomes of interest, are assigned by clinicians and are open to a degree of subjectivity. While definitions of RHD severity are provided in national guidelines (Table 8.1), they themselves are broad and potentially open to interpretation. It was noted in the data analysis process that there was some overlap between patients labelled as Priority 3 (Mild RHD) and Priority 2 (Moderate RHD) despite similar clinical and echocardiographic reports. It is not possible to further analyse the potential impact of this suspected inter-observer variability, however it is reassuring that the patterns of disease progression we observed were what we expected intuitively, and from the literature. From a service delivery point of view, quality control is essential, and it would be helpful to ensure that all clinicians managing RHD patients were consistently categorising disease severity as per the national guidelines.

Detailed mortality information is another limitation of our data. Death in this age group remains a rare outcome, so complete ascertainment is important, yet we had to exclude three deaths due to incomplete information. We are therefore unable to make any comment about absolute survival rates, or about cause of death (i.e. RHD- or non-RHD-related) as this was not consistently specified on the register. Similarly, we are unable to comment on other clinically significant outcomes such as infective endocarditis, atrial fibrillation or stroke, as this information is presently not systematically recorded in the NT.
register. While these are of paramount importance in the adult RHD population, it is unlikely that the incidence of these outcomes would have been high enough in our young cohort to meaningfully incorporate into our model.

Our model has not explicitly taken into consideration adherence to secondary antibiotic prophylaxis or ARF recurrences, both of which obviously affect disease progression. However, these figures are available from previous reports based on the NT register, and we believe that it is reasonable to assume similar rates for our cohort. Effective BPG delivery remains a significant challenge in our setting, and while adherence has improved since 2005, in 2010 only 28.1% of patients on the NT RHD register were receiving >80% of prescribed BPG doses.\(^6\) Consequently, ARF recurrence rates remain high, consistently representing between one-quarter and one-third of ARF notifications over the last 10 years.\(^6,7\) The disease trajectory that we have described, therefore, is more likely to reflect natural disease progression than disease modified by prophylaxis, supporting the notion that our model may be applicable to other disadvantaged populations.

It is highly likely that the trajectory of mild and moderate RHD would be improved with improved BPG adherence, and this is a parameter that will be varied in the sensitivity analysis as part of our proposed cost-effectiveness analysis. Clearly, improvement in BPG delivery must be a priority if RHD screening is to be implemented. Indeed if RHD screening is to fulfil the international criteria for a disease suitable for screening, the delivery of successful treatment which improves the natural history of disease is a pre-requisite.\(^23\)

**8.8 Conclusion**

We have developed a robust multi-state model for RHD using data from a contemporary cohort of Indigenous Australian RHD patients. Our data highlight the bleak prognosis for
young Indigenous Australians diagnosed with severe RHD, and reinforce the need to detect and treat the disease prior to this stage. Echocardiographic screening provides an opportunity for earlier detection, and our model of disease progression can be used to evaluate the cost-effectiveness of different screening strategies.
References


8.10 Appendix to Chapter 8

Figure A1: Age of RHD patient at time of first cardiac surgery

Figure A2: Age of RHD patient at time of death
Table A1: Estimated severity of RHD patients (aged 5-14 years at diagnosis) 1, 5 and 10 years after diagnosis

<table>
<thead>
<tr>
<th>Severity at diagnosis</th>
<th>Severity after x years</th>
<th>Time (x years) since RHD diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 year</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td><strong>Mild (n=212)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>92.4 (87.9-96.8)</td>
<td>71.2 (61.6-80.8)</td>
<td>60.6 (45.2-76.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5.9 (2.9-8.9)</td>
<td>17.0 (12.1-21.9)</td>
<td>17.2 (10.6-23.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>1.4 (0.1-2.6)</td>
<td>4.9 (2.5-7.2)</td>
<td>7.7 (3.6-11.8)</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.3 (0.0-0.7)</td>
<td>3.8 (1.9-5.8)</td>
<td>7.4 (4.0-10.8)</td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
<td>0.5 (0.0-1.5)</td>
<td>0.8 (0.0-1.9)</td>
</tr>
<tr>
<td>Inactive</td>
<td>-</td>
<td>2.6 (0.3-4.8)</td>
<td>6.3 (1.7-11.0)</td>
</tr>
<tr>
<td><strong>Moderate (n=98)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10.1 (4.4-15.8)</td>
<td>26.4 (18.8-33.9)</td>
<td>31.8 (21.8-41.9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>80.9 (72.4-89.3)</td>
<td>45.6 (35.9-55.3)</td>
<td>28.0 (18.2-37.8)</td>
</tr>
<tr>
<td>Severe</td>
<td>7.1 (2.7-11.4)</td>
<td>13.3 (7.6-19.0)</td>
<td>14.0 (7.1-20.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>1.9 (0.3-3.6)</td>
<td>13.9 (8.1-19.6)</td>
<td>21.1 (13.0-29.3)</td>
</tr>
<tr>
<td>Death</td>
<td>0.0 (0.0-0.1)</td>
<td>0.3 (0.0-0.7)</td>
<td>1.1 (0.0-2.8)</td>
</tr>
<tr>
<td>Inactive</td>
<td>-</td>
<td>0.6 (0.0-1.2)</td>
<td>3.9 (0.4-7.4)</td>
</tr>
<tr>
<td><strong>Severe (n=49)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1.2 (0.1-2.2)</td>
<td>5.1 (2.1-8.2)</td>
<td>7.2 (3.1-11.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>11.5 (3.5-19.6)</td>
<td>12.5 (6.3-18.7)</td>
<td>8.3 (3.7-12.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>47.9 (33.5-62.3)</td>
<td>16.8 (8.1-25.5)</td>
<td>10.6 (4.3-16.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>37.4 (24.3-50.5)</td>
<td>61.9 (47.5-76.2)</td>
<td>66.8 (47.3-86.3)</td>
</tr>
<tr>
<td>Death</td>
<td>2.0 (0.0-5.9)</td>
<td>3.6 (0.0-8.6)</td>
<td>6.2 (0.0-13.1)</td>
</tr>
<tr>
<td>Inactive</td>
<td>-</td>
<td>0.1 (0.0-0.2)</td>
<td>1.0 (0.0-2.0)</td>
</tr>
</tbody>
</table>
Figure A3: RHD prognosis over 14 years; probability that an individual (age 5-14 years at diagnosis) will be in a particular health state over time, based on RHD severity at diagnosis.

Figure A4: RHD prognosis (5-14 year olds) over 14 years showing surgery as a subset of patients with Severe RHD.
Table A2: Estimated severity of RHD patients (aged 15-24 years at diagnosis) 1, 5 and 10 years after diagnosis

<table>
<thead>
<tr>
<th>Severity at diagnosis</th>
<th>Severity after x years</th>
<th>Time (x years) since RHD diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 year % (95% CI)</td>
</tr>
<tr>
<td><strong>Mild</strong> (n=122)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>96.8 (92.6-100)</td>
<td>77.9 (68.5-87.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.4 (0.0-5.0)</td>
<td>17.0 (10.8-23.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>0.6 (0.0-1.7)</td>
<td>3.3 (0.9-5.7)</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.2 (0.0-0.7)</td>
<td>0.9 (0.0-1.8)</td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
<td>0.2 (0.0-0.6)</td>
</tr>
<tr>
<td>Inactive</td>
<td>-</td>
<td>0.8 (0.0-2.3)</td>
</tr>
<tr>
<td><strong>Moderate</strong> (n=63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>4.7 (0.0-9.9)</td>
<td>25.3 (15.6-35.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>93.7 (86.0-100)</td>
<td>58.5 (45.3-71.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>1.6 (0.0-4.6)</td>
<td>12.1 (5.1-19.1)</td>
</tr>
<tr>
<td>Surgery</td>
<td>-</td>
<td>3.0 (0.3-5.8)</td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
<td>0.9 (0.0-2.1)</td>
</tr>
<tr>
<td>Inactive</td>
<td>-</td>
<td>0.2 (0.0-0.6)</td>
</tr>
<tr>
<td><strong>Severe</strong> (n=47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0.1 (0.0-0.2)</td>
<td>1.8 (0.0-3.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.0 (0.0-5.8)</td>
<td>6.3 (0.8-11.8)</td>
</tr>
<tr>
<td>Severe</td>
<td>51.8 (37.2-66.4)</td>
<td>23.9 (11.5-36.3)</td>
</tr>
<tr>
<td>Surgery</td>
<td>46.2 (32.0-60.3)</td>
<td>54.2 (37.9-70.6)</td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
<td>13.7 (3.4-24.0)</td>
</tr>
<tr>
<td>Inactive</td>
<td>-</td>
<td>0.0 (0.0-0.04)</td>
</tr>
</tbody>
</table>
Figure A5: RHD prognosis over 14 years; probability that an individual (age 15-24 years at diagnosis) will be in a particular health state over time, based on RHD severity at diagnosis.

Figure A6: RHD prognosis (15-24 year olds) over 14 years showing surgery as a subset of patients with Severe RHD.
Chapter 9

Cost-utility analysis of echocardiographic screening for RHD in Indigenous Australian children
CHAPTER 9. COST-UTILITY ANALYSIS OF ECHOCARDIOGRAPHIC SCREENING FOR RHD IN INDIGENOUS AUSTRALIAN CHILDREN

9.1 Chapter Overview

Using the disease transition probabilities derived from the multi-state model presented in Chapter 8, this chapter presents a cost-utility analysis of echocardiographic screening for RHD in Indigenous Australian children. It has been submitted with the manuscript presented in Chapter 8 to the *European Heart Journal*. The analysis is set in the Northern Territory and two different screening strategies are evaluated. Given that it is unknown how much earlier screening may detect RHD, three scenarios were modelled: that RHD could be detected 1, 2 and 3 years earlier by screening. We compared clinical outcomes and cost per disability adjusted life year (DALY) averted. Using an incremental cost-effectiveness ratio (ICER) threshold of AU$50,000 per DALY averted, we found that one of the screening strategies was cost-effective if it is assumed that screening detects RHD at least two years earlier than clinical presentation.

9.2 Statement of contribution to jointly authored work

This paper is also co-first-authored with Jeffrey Cannon. I designed the proposed screening program and assumptions, with input from Graeme Maguire, David Atkinson, Alex Brown, Gavin Wheaton, Bo Remenyi and Jonathan Carapetis. I sourced all cost data and hospital admission data. Jeff did all of the modelling, performed the sensitivity analyses and created all graphics. Assistance with some economic aspects was provided by Liz Geelhoed. I prepared the manuscript, and co-authors contributed to revisions and approved the final version for submission.
9.3 Abstract

Background

Rheumatic heart disease (RHD) remains a leading cause of cardiovascular morbidity and mortality in children and young adults in disadvantaged populations. The emergence of echocardiographic screening provides the opportunity for early disease detection and intervention. Using our own multi-state model of RHD progression derived from Australian RHD register data, we perform a cost-utility analysis of echocardiographic screening in Indigenous Australian children, with the dual aims of informing policy decisions in Australia and providing a model that could be adapted in other countries.

Methods and results

We simulated the outcomes of two screening strategies, assuming that RHD could be detected 1, 2 or 3 years earlier by screening. Outcomes included reductions in heart failure, surgery, mortality, disability adjusted life years (DALYs) and corresponding costs. Only a strategy of screening all Indigenous 5-12 year olds in half of their communities in alternate years was found to be cost-effective (ICER <AU$50,000 per DALY averted), assuming that RHD can be detected at least 2 years earlier by screening, however this result was sensitive to a number of assumptions. Additional modelling of improved adherence to secondary prophylaxis alone resulted in dramatic reductions in heart failure, surgery and death; these outcomes improved even further when combined with screening.

Conclusions

Echocardiographic screening for RHD in Indigenous Australian children is cost-effective in our context if we assume that RHD can be detected two or more years earlier by screening. Our model can be adapted to any other setting, but will require local data or acceptable assumptions for model parameters.
9.4 Introduction

Rheumatic Heart Disease (RHD) has long been a target of public health screening, and the World Health Organisation (WHO) continues to recommend screening as a component of RHD control in high prevalence areas.\(^1\) Over the past decade, many groups around the world have undertaken population-based screening for RHD using portable echocardiography, demonstrating its feasibility in different contexts.\(^2\) To date, the role of screening has primarily been to define disease burden, and enthusiasm for scaling up screening programs has been tempered by concerns about potential costs, as well as about the unclear significance of subclinical echocardiographic abnormalities.\(^3,4\) The publication of the World Heart Federation (WHF) criteria for the echocardiographic diagnosis of RHD in 2012\(^5\) has provided standardisation and improved specificity, and the utility of these criteria in the screening context is now widely recognised by the cardiology community.\(^2\)

In this light, RHD moves closer to fulfilling the criteria for a disease suitable for screening.\(^4\) It has previously been accepted that in high prevalence regions there is an obvious disease burden, there is treatment available (four-weekly benzathine penicillin G (BPG)), and treatment at an early stage of disease improves outcome (BPG prevents recurrences of acute rheumatic fever which are known to worsen RHD). There is also a ‘latent’ stage which can be detected (by echocardiography using WHF criteria), and while conjecture remains about the natural history of WHF’s ‘Borderline’ category,\(^6\) there is an evolving consensus that screen-detected Definite RHD represents true disease and is an indication for BPG prophylaxis.\(^2\)

Economic evaluations provide important information about proposed public health interventions. Given that a systematic, large-scale echocardiographic screening program for RHD has not yet been instigated, mathematical modelling is required to evaluate the possible economic and health outcomes. Two previous groups have published cost-utility
analyses of RHD screening in a hypothetical cohort of children.\(^{(7,8)}\) Zachariah et al set their analysis in the Northern Territory of Australia, but there were a number of questionable assumptions about health care delivery in remote Australia, as well as potential inaccuracies in the proposed costs. Both analyses were limited by the lack of an accepted model of RHD progression. To date, there has not been a comprehensive economic evaluation of RHD echocardiographic screening based on an accepted model of RHD progression and real-life screening data.

We have recently prepared a multi-state model for RHD progression in Indigenous Australians, based on serial clinical data from a contemporary cohort of 591 indigenous patients, aged 5-24 years (Chapter 8). Our analysis demonstrated a bleak prognosis for young people diagnosed with severe RHD, and highlighted the need for earlier detection and treatment - an opportunity which is afforded by echocardiographic screening. We believe that our model can accurately predict the trajectory of RHD in our population, and here we use this model, together with data from our screening study in Indigenous Australian children,\(^{(9)}\) to estimate the cost-effectiveness of a proposed echocardiographic screening program compared with current practice. Our aims were to inform health policy in Australia, to identify the major drivers of cost for RHD screening programs, and to provide a model that could be relatively easily adapted to other settings, including low-resource settings.
9.5 Methods

9.5.1 Population, setting and current practice

Geographic context

This economic evaluation is set in the Northern Territory (NT) of Australia, a vast area of 1.35 million square kilometres, with a population density of 0.2 people per square kilometre. The estimated Indigenous population is 69,000 (representing nearly 30% of the NT population), of whom approximately 80% live in rural or remote locations.\(^{10}\) While most remote communities have a primary care clinic, providing health care to a small population dispersed over a large remote area poses challenges, including limited availability of general practitioners, minimal access to medical specialists and high travel costs to access these services at a regional centre.

The NT Department of Health identifies approximately 80 remote communities in which it currently conducts health screening activities among children\(^{11}\). The all-age population of each ranges between 100-3000, and over 95% of residents are Indigenous. Using 2010 data from the NT Department of Health Gains Planning, it is estimated that there are approximately 10,000 Indigenous children aged 5-14 years who live in rural or remote communities of the NT.

Target population

The peak incidence of acute rheumatic fever (ARF) is in school-aged children (aged 5-14 years), and this group has been targeted in most international echocardiographic screening surveys to date. In our own echocardiographic screening study, the mean age of children detected with Definite RHD (as defined by the WHF\(^{5}\)) was 10.4 years (SD 2.5 years) and the peak prevalence was 23.5 per 1000 in 12 year olds.\(^{9}\) While some groups have identified a role for screening in older age groups,\(^{12}\) poor high school attendance would make this...
virtually impossible in our context. Furthermore, it is hoped that if there was an effective school screening program, children would be identified before late adolescence.

A recent audit of the NT RHD register confirmed that RHD incidence was nearly as high as ARF incidence in 5-14 year old children (194 per 100,000),\(^\text{(13)}\) highlighting that RHD onset is also observed in childhood. Reviewing the data used for our own disease progression model (Appendix to this chapter, Figure A1), we determined that there was an average of 27.6 new cases of RHD per year in Indigenous 5-15 year old children in the NT (we included 15 year olds for reasons outlined below, see 9.5.4 *Modelling approach*).

**Current practice: Clinical diagnosis of RHD**

Children with RHD in the NT are currently identified in two ways. Most commonly, they present symptomatically with ARF (or occasionally RHD) to their local primary care clinic. Consistent with recommendations in the Australian ARF/RHD guidelines,\(^\text{(14)}\) most suspected cases (we estimate 90%, based on our experience) are transferred to one of two NT referral hospitals, and have a full assessment including echocardiography to confirm acute carditis or chronic RHD. Alternatively, a cardiac murmur is opportunistically detected by auscultation during routine physical examination or school screening (which currently continues, although we have recently reported that this is not a useful approach\(^\text{(15)}\)) and children are referred for an outpatient diagnostic echocardiogram.

**9.5.2 Proposal: Echocardiographic screening for RHD**

In this study, we evaluate two echocardiographic screening strategies (Box 9.1), which were the product of consultation with local stakeholders and experts, and which incorporated data and insights gained from undertaking our own screening study in the NT.\(^\text{(16)}\) The first (‘Echo A’) is to visit all 80 remote NT communities on an annual basis and to screen only 8 and 12 year olds (an estimated 2000 children per year). The second (‘Echo B’) reduces
annual travel by visiting half of the communities in alternate years, and screens all children aged 5 to 12 years inclusive (an estimated 4000 children per year). We estimate that both strategies would require the staffing equivalent of one full-time echocardiographer, one full-time nurse, and a paediatric cardiologist for four hours per week.

While we resourced Echo A and Echo B to screen the estimated number of age-eligible children, we have assumed a baseline screening attendance of 75%, which approximates the average school attendance of Indigenous children in the NT.\(^{(17)}\)

We evaluated a number of alternative approaches based around these strategies, such as increasing the number of children screened (e.g. including screening 8, 10 and 12 year olds every year in every community). However, these alternatives did not alter our main conclusions and we found the above two strategies were the most feasible.

Box 9.1: Definitions used in this paper

<table>
<thead>
<tr>
<th>Activity/Hypothesis</th>
<th>Label</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Strategy</td>
<td>Echo A</td>
<td>Screen all 8 and 12 year old Indigenous children living in 80 rural/remote communities of the NT annually</td>
</tr>
<tr>
<td></td>
<td>Echo B</td>
<td>Screen all 5-12 year old Indigenous children in approximately half (40) of the rural/remote NT communities in alternate years.</td>
</tr>
<tr>
<td>Screening Effectiveness Hypothesis</td>
<td>Scenario 1</td>
<td>Assumes that screening diagnoses RHD 1 year earlier than current practice</td>
</tr>
<tr>
<td></td>
<td>Scenario 2</td>
<td>Assumes that screening diagnoses RHD 2 years earlier than current practice</td>
</tr>
<tr>
<td></td>
<td>Scenario 3</td>
<td>Assumes that screening diagnoses RHD 3 years earlier than current practice</td>
</tr>
</tbody>
</table>

*NT- Northern Territory; RHD- rheumatic heart disease*

In both strategies, a screening echocardiogram would be performed by a cardiac sonographer on a portable machine (Vivid I™ GE, or equivalent) in the community. A screen
would be considered positive if there were pre-determined structural and/or functional changes of the left-sided heart valves that may meet the WHF criteria for RHD. (While it is anticipated that a number of congenital anomalies would also be detected by screening, evaluating the costs and benefits of earlier detection of this group is beyond the scope of this analysis.)

Positive screens would be reviewed, off-site, by the program’s paediatric cardiologist who would determine whether a cardiology consultation and a more detailed diagnostic echocardiogram were required. This follow-up may be possible during routine cardiology outreach clinics to certain communities, but more commonly would require the child to travel to a regional hospital. Due to the uncertainty about the significance of Borderline RHD, only children diagnosed with Definite RHD would be commenced on four-weekly BPG prophylaxis.\(^2\)

Our previous echo screening study had a high proportion of positive screens (14.4%), largely because screening was commenced before the publication of the WHF criteria, and our criteria were deliberately over-inclusive to avoid missing cases in the context of a research study.\(^{16}\) Other groups have demonstrated much lower positive screen rates.\(^{18}\) We believe that with appropriate training of sonographers, and consistent application of the WHF criteria, the proportion of positive screens could be reduced to around 5%. We also estimate that detailed review of high-quality images by a cardiologist could further reduce the number of children requiring clinical follow-up (to confirm a diagnosis) to around 2.5%.\(^{19}\)
9.5.3 Hypothesised effects of RHD screening

**Earlier diagnosis of disease**

There are no empiric data to inform how much earlier RHD may be detected via screening compared with current practice, so three hypothetical scenarios were modelled: where RHD was diagnosed one, two and three years earlier for screened children (Screening Effectiveness Scenario 1, 2 and 3; Box 9.1). Children who are not screened are assumed to present symptomatically and are diagnosed as per current practice.

**Milder disease at the time of diagnosis**

It is also unknown how RHD severity might be altered for children diagnosed by screening versus clinical presentation, however it is expected that disease would be detected at an earlier (less severe) stage. In our previous analysis (Chapter 8), we described the distribution of RHD severity at diagnosis, which provides an accurate picture of the severity of RHD when diagnosed according to current practice. In the 5-15 year old age group (n=387), we found that 59.5%, 27.1% and 13.4% had mild, moderate and severe RHD respectively at diagnosis.

In the screening context, we would expect a higher proportion of mild disease and lower proportion of severe disease; in our own echocardiographic screening study in Australia, only one (5.6%) of the 18 new cases of RHD detected was classified as ‘severe’. (9)

Therefore, we propose a severity distribution of 80% mild, 15% moderate and 5% severe when RHD is diagnosed by screening. Given the uncertainty around this assumption, the severity distribution was varied in the sensitivity analysis.
9.5.4 Modelling approach

**Multi-state model**

Our multi-state model for RHD progression incorporates six health states: inactive (past history of ARF or RHD), mild, moderate, severe without surgery, severe with surgery, and death (an absorbing state). Disease severity is defined according to the Australian RHD guidelines.\(^{(14)}\) Possible transitions between health states are illustrated in Figure 9.1, and example transition probabilities for the first year after RHD diagnosis are included.

**Figure 9.1:** Transition probabilities between health states in the first year of RHD diagnosis

```

Disease progression was modelled using individual patient-level simulation. Each simulated patient was assigned an age at diagnosis between 5 and 15 years inclusive, based on the age distribution observed under current practice (Appendix, Figure A1). We chose 15 years as the upper age limit so that we could compare the outcomes with a patient who is diagnosed up to three years earlier at the screening age of 12 years. For the no-screen
cohort, RHD severity at diagnosis was allocated according to current observations (Appendix, Figure A1).

The same patients were simulated under each of the two screening strategies. In screened children, the earlier age of diagnosis was assigned according to the scenario of screening effectiveness (diagnosing RHD 1, 2 or 3 years earlier) and screening strategy (Echo A or B).

**Time horizons**

We modelled a cohort of children screened over a five year period. Following diagnosis, RHD progression was modelled using monthly cycles until the minimum age of follow-up recommended in the Australian ARF/RHD guidelines (21, 35 and 40 years for mild, moderate and severe RHD respectively). Monthly-specific transition probabilities were used to simulate the rate of RHD progression during the first 10 years, as presented in our disease progression model (Chapter 8). The average rate of progression over this 10-year period was then used to extrapolate progression until the minimum age of follow-up.

**Software**

The model was implemented in TreeAge Pro 2015 (Williamstown, MA). Transition probabilities were obtained from the Aalen-Johansen transition estimates calculated by the ‘msSurv’ package in R (version 3.1.0), as described in Chapter 8, along with plots using the ‘ggplot2’ package.

**9.5.5 Health outcomes**

To capture the morbidity of RHD in a composite measure, each health state was mapped to a disability weight based on the closest matching health category from the 2010 Global Burden of Disease (Box 9.2). Disability weights were aggregated on a yearly basis to calculate the patient’s Disability Adjusted Life Year (DALY). The average DALY for all patients
simulated under each screening strategy was subtracted from the average DALY for non-screened patients to report the average DALYs averted by echo screening. A disability weighting of one was assigned in the event of death during the follow-up period. DALYs were discounted at a rate of 5\% per annum, as recommended by the Australian Pharmaceutical Benefits Advisory Council,\cite{23} and started from the age of potential diagnosis.

Box 9.2: RHD health states and matched disability weights from the 2010 Global Burden of Disease\cite{22}

<table>
<thead>
<tr>
<th>RHD Health state</th>
<th>Global Burden of Disease category</th>
<th>Disability weight (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Generic uncomplicated disease: worry and daily medication</td>
<td>0.031 (0.017-0.050)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Heart failure: mild</td>
<td>0.037 (0.021-0.058)</td>
</tr>
<tr>
<td>Severe – after surgery</td>
<td>Heart failure: moderate</td>
<td>0.070 (0.044-0.102)</td>
</tr>
<tr>
<td>Severe – before surgery</td>
<td>Heart failure: severe</td>
<td>0.186 (0.128-0.261)</td>
</tr>
</tbody>
</table>

*RHD*-rheumatic heart disease; CI- confidence interval

9.5.6 Resources and Costs

Resources and costs were taken from the government healthcare perspective, which is useful for public policy decisions but likely underestimates the true economic value of screening as other costs to the patient, family and society at large are excluded. All health resources were costed in Australian dollars (AU$) at 2013 price levels and future costs were discounted at a rate of 5\% per annum, as recommended in Australia.\cite{23} Costs were aggregated over the entire time horizon for each diagnosed patient. Summarised costs are presented in Table 9.1, and detailed breakdowns are presented in Appendix Tables A1-5.
## Table 9.1: Costs and parameter estimates for sensitivity analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Min-Max</th>
<th>Distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost – RHD management</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Per episode costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARF/RHD outpatient diagnosis</td>
<td>$1,428</td>
<td>$428-$4,564</td>
<td>Triangular</td>
<td>Table A1</td>
</tr>
<tr>
<td>ARF/RHD hospital admission</td>
<td>$11,471</td>
<td>$8,661-$30,200</td>
<td>Dirichlet(^b)</td>
<td>Table A2</td>
</tr>
<tr>
<td>RHD Surgery</td>
<td>$88,126</td>
<td>$46,503-$138,749</td>
<td>Triangular</td>
<td>Table A3</td>
</tr>
<tr>
<td><strong>Annual costs (outpatient management)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>$198</td>
<td>$164-$231</td>
<td>Triangular</td>
<td>Table A4</td>
</tr>
<tr>
<td>Mild RHD</td>
<td>$2,567</td>
<td>$1,676-$4,233</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Moderate RHD</td>
<td>$3,267</td>
<td>$1,843-$6,353</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Severe RHD</td>
<td>$4,732</td>
<td>$3,368-$11,976</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Severe-surgery RHD</td>
<td>$4,732</td>
<td>$3,368-$13,809</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td><strong>Cost – RHD screening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Annual costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment(^a)</td>
<td>$37,045</td>
<td>Not varied</td>
<td>-</td>
<td>Table A5</td>
</tr>
<tr>
<td>Admin and consumables</td>
<td>$5,500</td>
<td>$4,500-$6,500</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Staff salaries</td>
<td>$259,000</td>
<td>$216,100-$297,000</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Travel (Echo A)</td>
<td>$221,270</td>
<td>$156,524-$270,782</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Travel (Echo B)</td>
<td>$136,399</td>
<td>$89,274-$206,115</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td><strong>Per episode costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiology follow-up (per child)</td>
<td>$1,260</td>
<td>$260-$2,324</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td><strong>Other parameter estimates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discount factor</td>
<td>5%</td>
<td>3%-7%</td>
<td>Uniform</td>
<td>PBAC, 2013</td>
</tr>
<tr>
<td>Incidence of RHD (cases per year)</td>
<td>27.6</td>
<td>22.1-33.2</td>
<td>Uniform</td>
<td>Figure A1</td>
</tr>
<tr>
<td>Health state transition probabilities</td>
<td></td>
<td></td>
<td>Bootstrap</td>
<td>Chapter 8</td>
</tr>
<tr>
<td>Mild</td>
<td>0.031</td>
<td>0.017-0.050</td>
<td>Triangular</td>
<td>Box 9.2</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.037</td>
<td>0.021-0.058</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Severe (no surgery)</td>
<td>0.186</td>
<td>0.128-0.261</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Severe after surgery</td>
<td>0.070</td>
<td>0.044-0.102</td>
<td>Triangular</td>
<td></td>
</tr>
<tr>
<td>Screening parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% screened</td>
<td>75%</td>
<td>50%-100%</td>
<td>Uniform</td>
<td>Assumed</td>
</tr>
<tr>
<td>Sensitivity of echo</td>
<td>100%</td>
<td>95%-100%</td>
<td>Uniform</td>
<td>Assumed</td>
</tr>
<tr>
<td>% diagnosed mild</td>
<td>80%</td>
<td>65%-95%</td>
<td>Dirichlet(^c)</td>
<td>Assumed</td>
</tr>
<tr>
<td>% diagnosed moderate</td>
<td>15%</td>
<td>5%-25%</td>
<td>Dirichlet(^c)</td>
<td>Assumed</td>
</tr>
<tr>
<td>% diagnosed severe</td>
<td>5%</td>
<td>0%-10%</td>
<td>Dirichlet(^c)</td>
<td>Assumed</td>
</tr>
<tr>
<td>% cardiology follow-up</td>
<td>2.5%</td>
<td>2%-5%</td>
<td>Uniform</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

ARF- acute rheumatic fever; RHD- rheumatic heart disease; PBAC- Pharmaceutical Benefits Advisory Council.
All costs are presented in AU$ at 2013 price levels. \(^a\) Annuity in advance over five years calculated as the upfront cost ($182,720) minus discounted re-sale price of 10% purchase price. \(^b\) A dirichlet distribution was used to sample the proportion of mild, moderate and severe cases with parameters n=10,7,1 (based on severity of new cases in our screening study(9)). \(^c\) A dirichlet distribution was used to sample the proportion of cases admitted with AR-DRG F69A, F69B, F75A, F75B, F75C, I66A, I66B with parameters n= 12, 47, 4, 33, 113, 10, 140 (derived from Royal Darwin Hospital admission data 2008-2013).
RHD management costs

Both inpatient and outpatient costs were incurred for each child with RHD. Hospital admission was required for initial RHD diagnosis in 90% of cases (10% were diagnosed as outpatients), and also for ARF recurrence (estimated recurrence rate of 4.5 per 100 patient-years,\(^{(13)}\) regardless of RHD severity.) Inpatient costs (Appendix Table A2) were allocated according to the relevant Australian Refined Diagnosis Related Groups (AR-DRG) defined by the Federal Australian health system.\(^{(24)}\) We used Royal Darwin Hospital (RDH) admission data from 2008-2013 to inform the proportion of children in each DRG, and hospital pricing data from 2012-2013 which calculates the average cost per DRG for that hospital (submitted to the National Hospital Cost Data Collection, Round 17).

Additional inpatient costs were required in the event of cardiac surgery (including pre-operative medical and dental management, post-operative intensive care and interstate travel to the centre which performs the surgery; Appendix Table A3). Pricing for cardiac surgery was obtained from the referral hospital, based on surgeries performed on NT Indigenous children in 2014. All hospital admissions required return travel for the child plus caregiver from their community.

Annual outpatient costs (Appendix Table A4) in the community included four-weekly administration of BPG by a nurse, plus 1-4 reviews by the general practitioner. Additional consultations that could occur in or out of the community included paediatrician, cardiologist, echocardiogram and dentist. The frequency of these consultations ranged from six monthly to two yearly, depending on the severity of RHD, as described by the Australian guidelines.\(^{(25)}\)

We did not apply the full outpatient cost to each patient, given that disease transition probabilities were derived from a population in which adherence to secondary prophylaxis
is known to be sub-optimal (between 2005 and 2010, an estimated 37.8% and 24.3% patients on the NT RHD register received <50% and >80% of the required BPG doses respectively.) In our analysis we therefore assumed a baseline adherence to follow-up of 50% in both the screened and unscreened cohorts.

**RHD screening costs (Appendix Table A5)**

We estimated that two sets of screening equipment, including two portable echo machines (Vivid i, GE Healthcare), would be required to enable screening out of the two major cities in the NT. Equipment costs were amortised over five years with the total cost calculated as the upfront costs minus a discounted re-sale value in the fifth year set at 10% of the purchase price. Staff costs comprised salaries for one full-time equivalent (FTE) echocardiographer, one FTE nurse and a cardiologist at four hours per week (for staff training, quality control, review of positive screens and referral as necessary.) Travel costs were for two staff and included transport (commercial flights, chartered aircraft or road), accommodation and travel allowance.

Children requiring a face-to-face cardiology consultation and repeat echocardiogram would be referred to existing services (not included in the screening cardiologist’s time). Costs for this follow-up included the consultations plus travel.

**9.5.7 Analytical Methods**

*Cost-utility analysis of RHD screening*

We compared the outcomes of each screening strategy with current practice using a cost-utility analysis, where the incremental cost-effectiveness ratio (ICER) was calculated as the difference in the mean aggregated cost of RHD for each strategy divided by the DALYs prevented. The ICER represents the additional cost of preventing one DALY and we adopted a standard threshold value of $50,000 per DALY prevented to determine if the screening
strategy was cost-effective.\textsuperscript{(27)} We also looked at the effect of increasing this threshold to $70,000, which would meet the World Health Organisation (WHO) definition of ‘very cost-effective’ (when cost per DALY averted is less than the per capita gross domestic product\textsuperscript{(28)}).

\textbf{Assumptions and Sensitivity analysis}

For the purpose of this analysis, we have made a number of assumptions, summarised below, which we subsequently evaluate in the sensitivity analysis:

1. The incidence of RHD is 27.6 new diagnoses per year in the target age group;
2. 75\% of age-eligible children are screened in each community;
3. Screening echocardiogram is 100\% sensitive for Definite RHD;
4. The proportion of screening echocardiograms requiring further clinical evaluation for RHD by a cardiologist was estimated to be 2.5\%;
5. RHD severity distribution when diagnosed by screening: 80\% mild, 15\% moderate, 5\% severe;
6. Where an RHD diagnosis is made by screening, a hospital admission for diagnosis will be avoided;
7. Adherence to prophylaxis and clinical follow-up was assumed to be 50\% in both screened and unscreened cohorts; and
8. Transition probabilities between RHD health states are the same in screened and unscreened children.

One-way sensitivity analysis was performed on individual parameters listed in Table 9.1, and a multi-way sensitivity analysis was performed on the proportions of children detected with Mild, Moderate and Severe RHD. Probabilistic sensitivity analysis (PSA) was performed by simultaneously varying all of the model’s parameter estimates. Parameters were sampled from appropriate probability distributions (Table 9.1) 100 times and, for each sample, 1000 individual patients were simulated for each screening year.
Cost-utility analysis of improving adherence to secondary prophylaxis

A separate analysis was done looking at the potential health effects and economic outcomes of improved adherence to secondary prophylaxis. For modelling purposes, we analysed the potential effect of increasing adherence to 100%, which, by reducing ARF recurrences, we hypothesised may result in the following improvements in disease progression:

- Mild RHD: remains mild (does not progress to moderate or severe disease)
- Moderate RHD:
  - A 50% reduction in progression from moderate to severe disease or surgery (in our current practice model, approximately 29% currently progress over 10 years since diagnosis (Chapter 8), so our improved prophylaxis model allowed 15% to progress, with the other 14% remaining moderate)
  - Other transitions from the moderate state remain the same
- Severe RHD: No change to observed disease progression

In addition to comparing outcomes of improved adherence in the screened cohort with current outcomes in the non-screened cohort, we looked at the effect of improving prophylaxis alone, without screening. Note that for these models, we did not attempt to incorporate costs associated with improving adherence rates, but calculated the potential spend that would be available to improve adherence while still remaining cost-effective.
9.6 Results

9.6.1 Simulated costs and health burden of RHD using current practice

The mean present-day cost of RHD (any severity) for patients diagnosed in the first study year was AU$54,511 per case over an average of 16.7 years, while the total treatment cost for a cohort of 138 incident cases diagnosed over a five-year period was AU$6.9 million (Table 9.2). Although only 13.4% had severe RHD at diagnosis, these cases contributed to almost one-third of the total cost. Similarly, 37.7% of children were diagnosed with, or progressed to, heart failure but contributed to almost three-quarters of the total cost.

The health burden in children diagnosed with RHD was an average 1.33 DALYs lost due to disease over 16.7 years. Children diagnosed with severe RHD lost 3.37 DALYs.

Table 9.2: Economic and health utility outcomes after completion of the minimum recommended duration of secondary prophylaxis

<table>
<thead>
<tr>
<th>RHD severity at diagnosis</th>
<th>Average proportion of simulated patients in each RHD health state</th>
<th>Total treatment cost all patients(^a) (AU$'000)</th>
<th>DALYs lost per person</th>
<th>Mean treatment cost per person(^b) (AU$'000)</th>
<th>Mean duration prophylaxis per person (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>59.5%</td>
<td>2,695</td>
<td>0.80</td>
<td>36.0</td>
<td>14.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>27.1%</td>
<td>1,961</td>
<td>1.48</td>
<td>52.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Severe</td>
<td>13.4%</td>
<td>2,202</td>
<td>3.37</td>
<td>118.5</td>
<td>22.6</td>
</tr>
<tr>
<td>Heart failure(any time)(^c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>62.3%</td>
<td>1,816</td>
<td>0.36</td>
<td>23.2</td>
<td>12.1</td>
</tr>
<tr>
<td>Yes</td>
<td>37.7%</td>
<td>5,042</td>
<td>2.94</td>
<td>106.2</td>
<td>24.3</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>68.9%</td>
<td>2,068</td>
<td>0.51</td>
<td>23.9</td>
<td>12.6</td>
</tr>
<tr>
<td>Yes</td>
<td>31.1%</td>
<td>4,789</td>
<td>3.15</td>
<td>122.4</td>
<td>25.9</td>
</tr>
<tr>
<td>Any RHD</td>
<td>100%</td>
<td>6,858</td>
<td>1.33</td>
<td>54.5</td>
<td>16.7</td>
</tr>
</tbody>
</table>

RHD- rheumatic heart disease; DALY- disability adjusted life year. Costs and DALYs were discounted at 5% per annum. \(^a\)Includes all new RHD diagnoses in the five-year study period (n=138) \(^b\)Assumes diagnosis was made in the first year of the five-year study period (n=27.6), and assumes 50% adherence to BPG and outpatient management. If 100% adherence is assumed, mean treatment cost per person is AU$73,454. \(^c\)Heart failure includes all cases diagnosed with 'severe RHD' at some time during the follow-up period.
9.6.2 Cost-utility analysis of echocardiographic screening for RHD

The predicted annual cost of screening up to 2000 children under Echo A was $585,815 (range $427,184-$727,547) and the annual cost of screening up to 4000 children under Echo B was $563,944 (range $422,949-$779,100; Appendix Table A5).

Echo B detected more RHD cases than Echo A over the first five years of the screening program (Table 9.3). Under both screening strategies, the number of RHD diagnoses increased as the hypothesised number of years of earlier diagnosis increased (Scenarios 1, 2 and 3 of screening effectiveness). Earlier diagnosis resulted in reduced RHD management costs for both screening strategies compared to current practice, as well as a reduction in mean DALYs. Once screening costs were added, Echo B was cost-effective under the assumption that RHD can be diagnosed two years earlier by echocardiographic screening (Scenario 2), with an ICER of $47,546 per DALY averted. Echo A was not cost-effective under any of the three scenarios tested (ICER>$50,000).

Clinical outcomes of screened versus unscreened children are also presented in Table 9.3. Screening resulted in improved clinical outcomes, including fewer deaths, surgeries and episodes of heart failure. Outcomes from screening were best using Echo B, and improved further as the hypothesised number of years of earlier diagnosis increased.

The total cost of Echo B over five years was $2.4 million, which equates to $161 per child screened, or $14,760 per case detected when our baseline assumptions are applied.
Table 9.3: Clinical outcomes and cost-utility analysis of two RHD screening strategies, assuming that RHD can be diagnosed 1, 2 or 3 years earlier by screening (Scenarios 1, 2 and 3)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No screen</td>
<td>Echo A</td>
<td>Echo B</td>
<td>Echo A</td>
</tr>
<tr>
<td><strong>Clinical Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHD severity at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (%)</td>
<td>59.5</td>
<td>61.5</td>
<td>63.9</td>
<td>62.6</td>
</tr>
<tr>
<td>Moderate (%)</td>
<td>27.1</td>
<td>26.3</td>
<td>25.8</td>
<td>26.3</td>
</tr>
<tr>
<td>Severe (%)</td>
<td>13.4</td>
<td>12.2</td>
<td>10.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Heart failure at any time (%)</td>
<td>37.7</td>
<td>36.7</td>
<td>35.2</td>
<td>35.9</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>31.1</td>
<td>30.2</td>
<td>29.0</td>
<td>29.6</td>
</tr>
<tr>
<td>Death (%)</td>
<td>11.3</td>
<td>10.9</td>
<td>10.4</td>
<td>10.7</td>
</tr>
<tr>
<td><strong>Cost-Utility Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of diagnoses</td>
<td>138</td>
<td>143</td>
<td>146</td>
<td>151</td>
</tr>
<tr>
<td>Mean cost per diagnosis ($,000)</td>
<td>49.6</td>
<td>65.4</td>
<td>61.0</td>
<td>62.5</td>
</tr>
<tr>
<td>RHD Screening cost</td>
<td>-</td>
<td>18.2</td>
<td>16.5</td>
<td>17.2</td>
</tr>
<tr>
<td>RHD Management cost</td>
<td>49.6</td>
<td>47.2</td>
<td>44.5</td>
<td>45.3</td>
</tr>
<tr>
<td>Mean utility per diagnosis (DALY)</td>
<td>1.33</td>
<td>1.30</td>
<td>1.25</td>
<td>1.28</td>
</tr>
<tr>
<td>ICER (AUS/DALY saved)</td>
<td>-</td>
<td><strong>489,016</strong></td>
<td><strong>147,170</strong></td>
<td><strong>253,994</strong></td>
</tr>
</tbody>
</table>


*Cost-effective strategy (ICER< $50,000 AUD/DALY saved)

9.6.3 Sensitivity analysis

Given that Echo B was the dominant screening strategy (less costly and more effective at improving clinical outcomes than Echo A), sensitivity analysis is only performed for Echo B. This was further limited to Scenario 2 (RHD diagnosed two years earlier by screening), because Scenario 3 was clearly cost-effective (ICER $24,985), and Scenario 1 was not (ICER $144,216). This is demonstrated by Tornado plots of each scenario, presented in the Appendix (Figure A2). Only the sensitivity analysis of Echo B, Scenario 2 is presented here.
One-way sensitivity analysis

One-way sensitivity analysis was conducted on a number of parameters as listed in Table 9.1. A tornado plot is presented in Figure 9.2, and demonstrates that the ICER of screening is sensitive to most parameters if a threshold of $50,000 per DALY averted is used. If a higher threshold is adopted ($70,000; equivalent to the Australian per capita GDP\textsuperscript{[29]}, the results are more robust, although remain sensitive to screening attendance, RHD incidence (the underlying number of cases expected to occur in Indigenous children, currently estimated at 27.6 cases per year) and the proportion of children detected with severe disease.

Figure 9.2: Tornado plot showing the effect of varying individual parameter estimates on the ICER of echocardiographic screening for RHD (Echo B, Scenario 2)

ICER - incremental cost-effectiveness ratio; RHD - rheumatic heart disease; DALY - disability adjusted life-year. The solid line in each bar represents the baseline assumption. The dashed line represents an ICER threshold of $50,000 per DALY averted. The dotted line represents an ICER threshold of $70,000 (which approximates Australia’s per capita GDP\textsuperscript{[29]} per DALY averted). *At a maximum admission cost of AUS$30,200, screening was cost-saving (ICER<0 per DALY averted).
**Multi-way sensitivity analysis**

Multi-way sensitivity analysis was performed on the proportions of children detected with Mild, Moderate and Severe RHD. Screening was cost-effective when the proportion detected with Moderate RHD ranged between 5% and 25%, provided the proportion detected with Severe RHD was less than 5%. If the proportion of children detected with severe disease increased to 10%, screening was only cost-effective if the proportion with Moderate RHD was below 10%.

**Probabilistic sensitivity analysis (PSA)**

In PSA using 100 random draws from the parameters’ distributions outlined in Table 9.1, screening was cost-saving in 6% of iterations. It was cost-effective in 41% of iterations with an ICER threshold of less than AU$50,000 per DALY averted, and increased to 63% of the iterations with an ICER of less than AU$70,000 per DALY averted. More than 90% of all iterations resulted in an ICER of less than AU$130,000 per DALY averted. Figure 9.3 shows the probability that Echo B is cost-effective for different ICER threshold values.

**Figure 9.3: Cost-effectiveness acceptability curve for Echo B, Scenario 2**
9.6.4 Cost-Utility analysis of improving adherence to secondary prophylaxis

Our baseline model assumed that only 50% of children in both screened and unscreened cohorts would be adherent to the recommended follow-up (and therefore 50% of costs were applied), and that disease progression, once diagnosed, would be the same in both groups. We also modelled the hypothetical effects of improving adherence to 100% (as described on page 149), with or without screening. Table 9.4 shows that improving adherence alone could result in dramatic reductions in heart failure, surgery and death, and that predicted outcomes improved even further if improved adherence was combined with screening.

We calculated that an additional AU$22,068 per diagnosis could be spent on a program to improve prophylaxis delivery over that patient’s life of prophylaxis (which reduced to an average of 13.8 years with improved disease progression) and it would remain a cost-effective intervention (ICER<$50,000 per DALY averted). Based on an average of 27.6 new diagnoses per year, this equates to an additional $44,000 ($1600 per diagnosis) per year.
Table 9.4: Clinical outcomes and cost utility analysis of improving BPG adherence with and without screening

<table>
<thead>
<tr>
<th></th>
<th>NO-SCREEN</th>
<th></th>
<th>SCREEN(^a)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current</td>
<td>Improved</td>
<td>Current</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>progression</td>
<td>progression(^b)</td>
<td>progression</td>
<td>progression(^b)</td>
</tr>
<tr>
<td>RHD severity at diagnosis</td>
<td>(50% BPG)</td>
<td>(100% BPG)</td>
<td>(50% BPG)</td>
<td>(100% BPG)</td>
</tr>
<tr>
<td>Mild (%)</td>
<td>59.5</td>
<td>59.5</td>
<td>67.2</td>
<td>67.2</td>
</tr>
<tr>
<td>Moderate (%)</td>
<td>27.1</td>
<td>27.1</td>
<td>25.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Severe (%)</td>
<td>13.4</td>
<td>13.4</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Heart failure at any time (%)</td>
<td>37.7</td>
<td>18.9</td>
<td>33.5</td>
<td>12.9</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>31.1</td>
<td>15.2</td>
<td>27.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Death (%)</td>
<td>11.3</td>
<td>6.5</td>
<td>9.9</td>
<td>4.6</td>
</tr>
</tbody>
</table>

**Cost-utility analysis**

- Number of diagnoses: 138 (NO-SCREEN) vs. 138 (SCREEN\(^a\)) vs. 164 (NO-SCREEN) vs. 164 (SCREEN\(^a\))
- Mean cost per diagnosis (AUS,000): 49.6 (NO-SCREEN) vs. 51.3 (SCREEN\(^a\)) vs. 55.5 (NO-SCREEN) vs. 55.6 (SCREEN\(^a\))
- RHD Screening cost: 
  - NO-SCREEN: -
  - SCREEN\(^a\): -
- RHD Management cost: 49.6 (NO-SCREEN) vs. 51.3 (SCREEN\(^a\)) vs. 40.7 (NO-SCREEN) vs. 40.8 (SCREEN\(^a\))
- Mean utility per diagnosis (DALY): 1.33 (NO-SCREEN) vs. 0.86 (SCREEN\(^a\)) vs. 1.21 (NO-SCREEN) vs. 0.69 (SCREEN\(^a\))
- ICER (AUS/DALY saved)*: 
  - NO-SCREEN: -
  - SCREEN\(^a\): 3,463* vs. 47,546* vs. 9,329*

*compared with current progression in no-screen cohort

**BPG-** benzathine penicillin G; **RHD-** rheumatic heart disease; **DALY-** disability adjusted life-year; **ICER-** incremental cost-effectiveness ratio. \(^a\)Echo B, Scenario 2
\(^b\)Improved progression assumes:
- Mild disease does not progress
- Half of the moderate disease that currently progresses to severe will not progress
- All other transitions remain the same

**9.7 Discussion**

This is the most comprehensive analysis of the potential cost-effectiveness of echocardiographic screening for RHD to date. We found that echocardiographic screening alone resulted in modest improvements in clinical outcomes, and under our most plausible set of assumptions, including that RHD can be diagnosed at least two years earlier by screening, screening all remote Indigenous children aged 5-12 every second year is a potentially cost-effective strategy for RHD detection in the Northern Territory of Australia (ICER $47,546 per DALY saved, Table 9.3). If, in addition to screening, adherence to secondary prophylaxis was improved, our model predicts that clinical outcomes would be
dramatically better, with a corresponding improvement in the ICER. While the costs and logistics of our proposed screening program are context-specific, the model we present could be adapted to any other setting, provided that reasonable local data or assumptions are available for the model parameters.

A strength of our study is that we were able to use disease transition probabilities that were derived from our own contemporary population, rather than relying on historical data as previous analyses have done.\textsuperscript{(7,8)} As such, we believe that the RHD transition probabilities we have used are the best available. However, our model did not estimate the risk of certain RHD complications including stroke or endocarditis which incur significant expense, morbidity and mortality. Given this, the cost of undetected disease is likely to be higher than our estimate, potentially resulting in improved cost-effectiveness of screening.

Modelling invariably requires a number of assumptions, and in our analysis we have made assumptions about the disease itself, as well as about parameters related to the proposed screening process. Given that there are no data to inform how much earlier RHD may be detected using echocardiographic screening, we modelled three scenarios of screening effectiveness, and found that health and economic outcomes were best if RHD was detected three years earlier by screening (ICER $25,387 per DALY saved; Table 9.3). Even if we assume that RHD could only be detected two years earlier, screening remains a cost-effective proposition.

Another major assumption about screened cases of RHD was disease severity at diagnosis. We assumed that disease would be less severe if detected early, and assigned screened cases according to the distribution of 80% mild, 15% moderate and 5% severe. One-way and multi-way sensitivity analyses revealed that the ICER was not sensitive to an increase in the proportion of moderate cases up to 25%, provided the proportion of severe cases was
≤5%. We would hope that screening would reduce the proportion of children detected with severe RHD to this level, but note that the ICER was sensitive to this assumption. The model was also sensitive to RHD incidence. It is, however, highly unlikely that the incidence of RHD is lower than our baseline assumption (which was based on 14 years of patient data). A higher incidence is possible, and would favour the cost-effectiveness of screening.

One-way sensitivity analysis revealed that our model was particularly sensitive to two parameters relating to the screening process itself: screening attendance (ie, number of children screened) and the proportion of screened children requiring cardiology follow-up. We have assumed a baseline screening attendance of 75%. This is slightly higher than the average school attendance of Indigenous children in the NT, meaning that a screening program would need to maximise efforts to recruit all school attendees, as well as potentially using strategies to capture non-attendees. The fact that Echo B can screen twice as many children per year as Echo A is the principal reason that is the more cost-effective option.

The sensitivity and specificity of a screening test compared with a diagnostic test are key determinants of its utility. Evaluating the performance of any proposed screening test for RHD is difficult given that there is no ‘gold standard’ diagnostic test. However, there is an evolving consensus that the 2012 WHF criteria should be used for the echocardiographic diagnosis of RHD, thus providing a new gold standard against which a screening test can be compared. Our baseline assumption that only 2.5% of screened children would require face-to-face cardiology follow-up is based on the premise that screening sonographers need to be well trained and familiar with the WHF criteria.

Two recent studies would suggest that this is feasible. Beaton et al screened 4869 children in Uganda using portable echocardiography performed by an expert operator. Only
2.7% had an abnormal screening echocardiogram, and following further evaluation, nearly half of these were considered to have physiological regurgitation. In New Zealand, Cramp et al.\(^\text{(19)}\) screened 685 children and classified 8.2% of echocardiograms as abnormal, of whom 1.6% met the equivalent of the WHF criteria for Definite RHD. Of note is that only 11 echocardiograms (1.6%) needed to be repeated on a hospital machine; screening image quality was sufficient to make a diagnosis in the remainder. In our model, it is anticipated that more than 2.5% of screens would need to be reviewed by the program cardiologist, but the considerable additional follow-up costs would only be incurred if a consultation is required. One-way sensitivity analysis reveals that even a small increase in the proportion of children needing review (e.g., to 3%) would increase the ICER above the $50,000 threshold.

The potential expense of echocardiographic screening in resource-poor settings has been identified as a potential barrier.\(^\text{(30)}\) To counter this, an emerging area of interest is screening using a hand-held ultrasound by local health staff with basic training, which would avoid the need for highly skilled technicians to travel to screening sites.\(^\text{(31,32)}\) While this technology certainly holds promise in some settings, it is not likely to be a cost-saving alternative in remote Australia because the positive screen rate for an unskilled operator is likely to be higher, resulting in more referrals for costly cardiology review.

One of the major drivers of cost in our model is travel, a cost which is incurred both in current practice and in a proposed screening program. The geographic context in which we have set our analysis is unique and is likely to render the potential cost of screening more expensive than in some other parts of Australia and the world. Not only are the distances vast, but community populations are small, meaning that considerable resources are required to reach relatively few children. Cost-effectiveness would be markedly improved if travel costs were reduced and/or the number of children available to be screened was greater. Screening Indigenous Australian children in urban settings, for example, is likely to
be highly cost-effective, as the RHD risk is still high, and screening costs would be nearly halved. Screening in densely populated developing countries is also likely to be more cost-effective than our model, provided the appropriate resources are available.

Perhaps the most important principle of screening is that treatment is available to improve outcome if disease is detected earlier. While secondary prophylaxis with BPG is known to be effective in preventing ARF recurrences and is readily available in Australia, it is recognised that adherence rates in the Indigenous population of the NT are sub-optimal. Given that the transition probabilities for disease progression were derived from this population in which we estimated adherence to be 50%, we modelled the hypothetical effect of improving adherence to 100%, independently of screening. Table 9.4 demonstrates the dramatic improvement in clinical outcomes that may result from this intervention alone: a 50% reduction in heart failure, surgery and death over the 10-35 years following RHD diagnosis. Outcomes would improve even further if screening was combined with an improvement in BPG adherence. The ICERs for the 100% adherence scenarios are an underestimate, as no costs to achieve this have been included, but we calculate that $44,000 per year could be spent on improving prophylaxis delivery for new diagnoses and it would remain a cost-effective intervention in its own right. Improving adherence to secondary prophylaxis must remain a priority in RHD control.

Whether an ICER of $50,000 AUD per DALY averted is appropriate for the Indigenous population in Australia could be debated; this figure is a widely-used, but arbitrary threshold. A major Australian study looking at the cost-effectiveness of numerous preventative strategies on health outcomes (ACE-Prevention) discussed this, and included an additional cost-effectiveness category ($50,000–150,000 per DALY prevented) for Indigenous populations. Alternatively, the WHO defines an intervention as very cost-effective if the cost per DALY averted is less than the gross domestic product (GDP) per
capita ($68,503 in Australia in 2014\textsuperscript{(29)}, and cost-effective if the cost per DALY averted is between one and three times per capita GDP.\textsuperscript{(28)} The cost-effectiveness acceptability curve (Figure 9.3) shows that our screening model would have a 63\% probability of being cost-effective if the threshold was set at $70,000 compared with 41\% at $50,000. Equity concerns about Indigenous health in Australia may be expressed as a greater willingness to pay for the same health gain.

Economic analyses are not the only considerations in determining whether to implement a new health strategy. There may be important social and ethical reasons to tackle RHD even at great expense, given that it selectively affects the most disadvantaged and the young, and has largely been eliminated from affluent populations. On the other hand, there are considerations regarding the logistics required to organise mass screening programs and the opportunity costs of devoting time and dollars to this at the expense of other health interventions.

\textbf{9.8 Conclusions}

We have demonstrated that echocardiographic screening for RHD is cost-effective in our context if we assume that RHD can be detected two or more years earlier by screening. Our model is sensitive to a number of assumptions, and particular emphasis would need to be placed on screening attendance, as well as maximising the specificity of the screening echocardiogram. We have also demonstrated the dramatic improvements in clinical and economic outcomes that could result if adherence to secondary prophylaxis was improved, and emphasise that this remains the cornerstone of RHD control.
9.9 References


9.10 Appendix to Chapter 9

Figure A1: Number and severity of RHD cases diagnosed between 1999 and 2012 in Indigenous children of the Northern Territory, Australia (n=387*)

*Average annual incidence of RHD: 27.6 new cases per year in children aged 5-15 years.
Figure A2: One-way sensitivity analysis of Echo B, Scenarios 1, 2 and 3

Scenario 1

Scenario 2

Scenario 3
### Table A1: Cost (AU$, 2013) of outpatient diagnosis of RHD

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (min-max)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Blood Examination</td>
<td>14</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>C Reactive Protein</td>
<td>15</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>Erythrocyte Sedimentation Rate</td>
<td>14</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>Streptococcal serology</td>
<td>13</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>Throat swab- culture</td>
<td>19</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>Blood culture</td>
<td>26</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>Xray-joint/chest</td>
<td>40</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>ECG</td>
<td>27</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>196</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>Paediatric cardiologist consult</td>
<td>64</td>
<td>MBS, 2013</td>
</tr>
<tr>
<td>Return travel to cardiology appointment*</td>
<td>1,000 (0-4,072)</td>
<td>RDH, 2011/12</td>
</tr>
</tbody>
</table>

**Total cost (per episode)**: 1,428 (428-4,564)


### Table A2: Cost (AU$, 2013) of ARF/RHD admission to Royal Darwin Hospital (RDH)

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (min-max)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient admission with average length of stay*</td>
<td>7,057 (4,247-25,786)</td>
<td>NHCDC (2012/13) (RDH)</td>
</tr>
<tr>
<td>Return travel to RDH</td>
<td>2,036</td>
<td>NHCDC (2011/12) (RDH)</td>
</tr>
<tr>
<td>Boarder costs (travel + accommodation)</td>
<td>2,378</td>
<td>NHCDC (2011/12) (RDH)</td>
</tr>
</tbody>
</table>

**Total cost (per episode)**: 11,471 (8,661-30.200)

*ARF*- acute rheumatic fever; *RHD*- rheumatic heart disease; *NHCDC*- National Hospital Cost Data Collection; *RDH*- Royal Darwin Hospital. *Inpatient cost based on a weighted average of the following Diagnosis Related Groups: F69A, F69B, F75A, F75B, F75C, I66A and I66B. Weights were based on the frequency of ARF/RHD admissions to RDH of 5-14 year olds, between 2008 and 2013. Costs per DRG were obtained from the Royal Darwin Hospital pricing data submitted to the NHCDC.
Table A3: Cost (AU$, 2013) of cardiac valve surgery including transfer from the Royal Darwin Hospital (RDH) to the Royal Children’s Hospital (RCH) in Melbourne, Victoria, where surgery is performed

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (min-max)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental procedure pre-surgery (RDH)</td>
<td>3,431</td>
<td>NHCDC (2012/13) (RDH)</td>
</tr>
<tr>
<td>Medical stabilisation pre-surgery (RDH)</td>
<td>25,246 (0-25,246)</td>
<td>NHCDC (2012/13) (RDH)</td>
</tr>
<tr>
<td>Cardiac surgery (RCH)</td>
<td>64,000 (35,000-102,000)</td>
<td>RCH, 2014&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Return travel to RDH (2 people)</td>
<td>4,072</td>
<td>NHCDC (2011/12) (RDH)</td>
</tr>
<tr>
<td>Return travel to RCH (2 people)</td>
<td>4,000</td>
<td>Patient Travel, RDH</td>
</tr>
<tr>
<td><strong>Total cost (per episode)</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td><strong>88,126 (46,503-138,749)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Average lifetime cost of surgery</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td><strong>124,495 (65,695-196,010)</strong></td>
<td></td>
</tr>
</tbody>
</table>

NHCDC, National Hospital Cost Data Collection; DRG, Diagnosis Related Group.
<sup>a</sup>DRG D40Z. <sup>b</sup>DRG F69A. <sup>c</sup>Costs provided by the RCH, Victoria, from a sample of NT RHD patients aged 5-14 during the year 2014 (n=6) who had RHD surgery with a mean cost of $64,000 each (range $35,000 - $102,000.)<sup>d</sup>Total cost reflects an estimated 50% probability of admission for medical stabilisation at some point prior to surgery (max cost reflects all cases are admitted for medical stabilisation prior to surgery). If a patient has heart failure and requires surgery, only the date of first surgery is simulated but the cost is multiplied by the probability of requiring future surgeries and discounted to reflect the delayed cost.<sup>e</sup>Average lifetime cost represents the possibility of multiple surgeries and was derived from the observed data where 63 children aged 5 to 15 years had 89 surgeries (RHD register 1999-2012).
Table A4: Cost (AU$ 2013) of outpatient RHD care – annual cost per patient, depending on RHD severity

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit cost (min-max)</th>
<th>Source</th>
<th>Annual frequency (min-max) of cost, by RHD severity&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inactive Mild Mod Severe</td>
</tr>
<tr>
<td>GP consult (in community)</td>
<td>70 (36-103)</td>
<td>MBS 2013</td>
<td>1 1 2 4</td>
</tr>
<tr>
<td>Paediatrician consult (in community)</td>
<td>64 (64-128)</td>
<td>MBS 2013</td>
<td>1 1 2</td>
</tr>
<tr>
<td>Dental consult (in community)</td>
<td>128</td>
<td>PHIAC 2013</td>
<td>1 2 (1-2) 2 (1-2) 2 (2-2)</td>
</tr>
<tr>
<td>Cardiology consult (in hospital)</td>
<td>64</td>
<td>MBS 2013</td>
<td>0.5 (0.5-1) 1 (1-2) 2 (2-4)</td>
</tr>
<tr>
<td>Echocardiogram (in hospital)</td>
<td>196</td>
<td>MBS 2013</td>
<td>0.5 1 2 (2-4)</td>
</tr>
<tr>
<td>Return travel for cardiology consult&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1000 (0-2036)</td>
<td>RDH 2011-12</td>
<td>0.5 (0-1) 1 (0-2) 2 (1-4)</td>
</tr>
<tr>
<td>BPG Prophylaxis</td>
<td>29</td>
<td>MBS 2013</td>
<td>13 13 13 (13-17)</td>
</tr>
<tr>
<td>Prophylaxis nurse</td>
<td>50</td>
<td>NTPS EA 2011-14</td>
<td>13 13 13 (13-17)</td>
</tr>
<tr>
<td>ARF recurrence admission&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11,471</td>
<td>Table A1</td>
<td>0.045 (0.025-0.045) 0.045 (0.025-0.045) 0.045 (0.025-0.045)</td>
</tr>
<tr>
<td>Total cost per patient per year (min-max)</td>
<td></td>
<td></td>
<td>198 (164-231) 2567 (1,676-4,233) 3267 (1,843-6,353) 4732 (3,368-13,809)</td>
</tr>
</tbody>
</table>

*RHD- rheumatic heart disease; GP-general practitioner; MBS-Medicare Benefits Schedule; PHIAC, Private Health Insurance Administration Council; RDH-Royal Darwin Hospital Patient Travel; BPG, Benzathine penicillin G; NTPS EA- Northern Territory Public Sector Enterprise Agreement; ARF acute rheumatic rever. <sup>a</sup>As recommended by the Australian guidelines. <sup>b</sup>Includes travel for patient and escort. <sup>c</sup>Annual probability of ARF recurrence =4.5% (min 2.5%); sourced from Lawrence et al, (ref 13)
<table>
<thead>
<tr>
<th>Item</th>
<th>Unit cost (AU$)</th>
<th>Echo A (screen 2000 children/year in 80 sites)</th>
<th>Echo B (screen 4000 children/year in 40 sites)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Freq.</td>
<td>Total cost (min-max)</td>
<td>Freq.</td>
</tr>
<tr>
<td>Fixed costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment (lasts 5 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vivid I portable echo machine</td>
<td>90,000</td>
<td>2</td>
<td>180,000</td>
<td>2</td>
</tr>
<tr>
<td>Patient bed</td>
<td>360</td>
<td>2</td>
<td>720</td>
<td>2</td>
</tr>
<tr>
<td>Laptop (mid-range)</td>
<td>1,000</td>
<td>2</td>
<td>2,000</td>
<td>2</td>
</tr>
<tr>
<td>Sub-total (5 years)</td>
<td></td>
<td></td>
<td>182,720</td>
<td></td>
</tr>
<tr>
<td>Sub-total (annual)</td>
<td></td>
<td></td>
<td>37,045</td>
<td></td>
</tr>
<tr>
<td>Source</td>
<td></td>
<td></td>
<td>Estimate</td>
<td></td>
</tr>
<tr>
<td>Fixed costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staff (annual FTE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo technician</td>
<td>117,000</td>
<td>1</td>
<td>117,000 (100,100-130,000)</td>
<td>1</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>250,000</td>
<td>0.1</td>
<td>25,000 (25,000-50,000)</td>
<td>0.1</td>
</tr>
<tr>
<td>Sub-total</td>
<td></td>
<td></td>
<td>259,000 (216,100-297,000)</td>
<td></td>
</tr>
<tr>
<td>Travel (annual- for 2 staff)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial plane (2 people, return)</td>
<td>1,500</td>
<td>10</td>
<td>15,000</td>
<td>10</td>
</tr>
<tr>
<td>Charter plane-day trip</td>
<td>5,000</td>
<td>10</td>
<td>50,000</td>
<td>5x2</td>
</tr>
<tr>
<td>Charter plane-overnight trip</td>
<td>8,000</td>
<td>10</td>
<td>80,000</td>
<td>-</td>
</tr>
<tr>
<td>Four-wheel drive (per week)</td>
<td>470</td>
<td>50</td>
<td>23,500</td>
<td>25</td>
</tr>
<tr>
<td>Fuel (per round trip)</td>
<td>105</td>
<td>50</td>
<td>5,250</td>
<td>25</td>
</tr>
<tr>
<td>Accommodation (2 people per night)</td>
<td>300</td>
<td>50x2</td>
<td>30,000</td>
<td>40x3</td>
</tr>
<tr>
<td>Travel allowance (2 people per night)</td>
<td>175</td>
<td>50x2</td>
<td>17,520</td>
<td>40x3</td>
</tr>
<tr>
<td>Sub-total</td>
<td></td>
<td></td>
<td>221,270 (156,524-270,782)</td>
<td></td>
</tr>
<tr>
<td>Total fixed (annual)</td>
<td></td>
<td></td>
<td>522,815 (414,169-611,327)</td>
<td></td>
</tr>
<tr>
<td>Variable costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive screen (follow-up)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic echocardiogram</td>
<td>196</td>
<td>1</td>
<td>196</td>
<td>1</td>
</tr>
<tr>
<td>Cardiology consult</td>
<td>64</td>
<td>1</td>
<td>64 (64-128)</td>
<td>1</td>
</tr>
<tr>
<td>Travel (patient + escort)</td>
<td>1000</td>
<td>1</td>
<td>1,000 (0-2,000)</td>
<td>1</td>
</tr>
<tr>
<td>Sub-total (per child)</td>
<td></td>
<td></td>
<td>1,260 (260-2,324)</td>
<td></td>
</tr>
<tr>
<td>Total variable (2.5% positive cases)</td>
<td>n=50</td>
<td></td>
<td>63,000 (13,015-116,220)</td>
<td>n=100</td>
</tr>
<tr>
<td>Total screening costs (AU per year)</td>
<td></td>
<td></td>
<td>585,815 (427,184-727,547)</td>
<td></td>
</tr>
</tbody>
</table>
Notes regarding Table A5

RHD- rheumatic heart disease; FTE- full-time equivalent. NTPS - Northern Territory Public Sector; SONT - Specialist Outreach Northern Territory; MBS- Medicare Benefits Schedule; RDH- Royal Darwin Hospital.

a Cost includes service and insurance over the recommended 5-year life span.

b Annuity in advance over five years calculated as the upfront cost minus discounted re-sale price of 10% purchase price ($168,403).

c Based on pump price of $1.40 per litre and fuel efficiency of 10L/100km, average travel distance 750km round trip.

d Minimum cost based on 10 commercial plane trips (day trip) + 10 charter plane trips (day trip) + 60 road trips (four-wheel drive hire and fuel, accommodation and travel allowance);

maximum cost based on 10 commercial plane trips (overnight trip including accommodation and travel allowance) + 20 charter plane trips (overnight trip including accommodation and travel allowance) + 50 road trips (four-wheel drive hire and fuel, accommodation and travel allowance).

e Minimum cost based on 10 commercial plane trips (overnight trip including accommodation and travel allowance) + 30 road trips (four-wheel drive hire and fuel, accommodation and travel allowance);

maximum cost based on 5 commercial plane trips (overnight trip including accommodation and travel allowance) + 10 charter plane trips (overnight trip including accommodation and travel) + 25 road trips (four-wheel drive hire and fuel, accommodation and travel allowance).
Chapter 10

Conclusions and future directions
CHAPTER 10. CONCLUSIONS & FUTURE DIRECTIONS

10.1 Summary of main findings

Echocardiographic screening for rheumatic heart disease is a field which has evolved during the course of my candidature. A number of countries have now undertaken large population-based screening surveys, different echocardiographic definitions of RHD have been explored and debated, and the evidence-based World Heart Federation (WHF) criteria for the echocardiographic diagnosis of RHD were developed and published in 2012. The gECHO study contributes to the international literature on this subject as well as providing insights specific to the Australian context. The aims of this thesis presented in Chapter 1 have been addressed and are discussed below.

1. Does RHD meet the criteria for a disease suitable for screening?

Expanding on the review of the Australian literature in Chapter 1, Chapter 2 examines whether RHD fulfils standard criteria for a disease suitable for screening. It confirms that some, but not all, of the criteria are met. 1) There is an obvious burden of disease in disadvantaged populations globally, including Indigenous Australians. 2) Echocardiographic screening permits the identification of a latent stage of disease, but the long-term outcome of children with subclinical RHD has not been established; this is now the subject of a number of follow-up studies. Regarding the test itself, echocardiography is non-invasive and highly sensitive for RHD. As experience with the WHF criteria increases, it would appear that specificity is also acceptable, particularly for the Definite RHD category. 3) Adequate treatment in the form of four-weekly benzathine penicillin G (BPG) prophylaxis is available in many settings, and is known to prevent recurrences of ARF, which worsen RHD. 4) Echocardiographic screening aims to detect mild cases of RHD. If secondary prophylaxis is
instigated at this early stage of disease, recurrent valvulitis is prevented and prognosis is improved.

Some outstanding questions about public health aspects of RHD screening remain, including how to evaluate the performance of the WHF criteria in the absence of a ‘gold standard’ test for RHD, as well as determining the natural history of a child diagnosed with subclinical RHD by echocardiographic screening. These questions are discussed in the ‘Future directions for research’ section below.

2. What is the prevalence of RHD detected by echocardiographic screening in northern Australian children?

The prevalence of RHD detected by screening 3946 high-risk Indigenous children and 1053 low-risk non-Indigenous children is presented in Chapter 4. The overall prevalence of Definite and Borderline RHD in high-risk children was 8.6 per 1000 and 16.7 per 1000 respectively, similar to rates observed in developing countries. Half of those found to have Definite RHD were new cases, suggesting that there is a higher disease burden than previously appreciated, and that screening remote Indigenous children would identify around 4 per 1000 with undiagnosed Definite RHD.

In low-risk children, no Definite RHD was detected, and the prevalence of Borderline RHD was 0.5 per 1000. Following clinical evaluation of these cases, it was deemed that these were most likely to be false positive results, representing the upper range of normal findings.

Chapter 5 examines the prevalence of RHD in the four participating regions individually, and found that the prevalence of Definite RHD in Indigenous children from the Top End of the Northern Territory (NT) was more than twice as high as that found in other regions (17.0
per 1000). Evaluation of socioeconomic factors suggests that participating Top End communities were the most disadvantaged of the gECHO cohort, which may provide an explanation for the higher prevalence of RHD in this group. However, given that our sampling method was not random, selection bias would provide an alternative explanation, and this finding warrants further investigation.

3. What are the echocardiographic findings in an urban population of children, at low risk for RHD?

Chapter 4 includes a summary of the echocardiographic findings of children at low risk for RHD. It was observed that some degree of mitral regurgitation (MR) was common, seen in 18.6% of low-risk children. While individual abnormalities of mitral or aortic valve structure or function were observed in this group, very few had the required number of features to meet WHF definitions of pathology, suggesting that the criteria are appropriately specific. Consistent with other reports in the literature, the prevalence of congenital cardiac anomalies was 2.5%; most were minor.

4. Evaluation of current consensus echocardiographic definitions of RHD

By recording echocardiographic data in detail, it had been the intention of the gECHO study to evaluate existing echocardiographic definitions of RHD at the time and, potentially, to propose alternatives. This objective changed with the commencement of the WHF criteria project, and data from gECHO’s low-risk cohort (shared prior to publication) contributed to the formulation of these criteria, by providing information about the spectrum of normal findings.

Once the criteria were published, the detailed data collected by the gECHO study enabled a post-hoc evaluation of their performance in high-risk and low-risk groups. Chapter 4 concludes that the criteria are appropriately specific, with no low-risk children meeting the
definition of Definite RHD. In addition, the performance of a simplified screening protocol was evaluated, finding that, for Definite RHD, the sensitivity and specificity of a single mitral regurgitant jet ≥2cm in length were 91.2% and 98.5% respectively. There is potential for minimally trained staff to use such criteria in settings where skilled technicians are not available.

5. **What is the sensitivity and specificity of cardiac auscultation, compared with echocardiography, for the detection of RHD?**

Chapter 5 compares the results of 1015 children who underwent cardiac auscultation by a doctor and a nurse, with findings on echocardiography. The sensitivity of finding any murmur on auscultation compared with an abnormal echocardiogram was <50%, specificity was around 75% and the positive predictive value of hearing any murmur was less than 10% for both groups of auscultators. Sensitivity decreased and specificity increased if doctors were asked to identify ‘significant’ murmurs. Chapter 5 concludes that cardiac auscultation is not a useful method of screening for RHD, and should be discontinued in the NT.

6. **Results of an economic analysis of a potential echocardiographic screening program for RHD in the Northern Territory**

A model of disease progression was created for use in the economic analysis. Chapter 8 describes the development of this model, using 14 years of data from the NT RHD register, concerning 618 Indigenous patients aged 5-24 at diagnosis. The most striking finding was the poor prognosis of Indigenous children and young adults diagnosed with severe RHD; 50% had proceeded to surgery by two years, and 10% were dead within six years of their diagnosis. The majority of patients diagnosed with mild RHD remained mild after 10 years, suggesting that this patient group, the group most likely to be detected by screening, has a good prognosis if treatment is instigated early.
Using this model of RHD progression, a cost-utility analysis of two proposed echocardiographic screening programs in the NT is presented in Chapter 9. Applying an incremental cost-effectiveness ratio (ICER) threshold of AU$50,000 per disability adjusted life year (DALY) saved, a model of screening all 5-12 year olds in 40 NT communities every second year was found to be cost-effective if it is assumed that screening will detect RHD at least two years earlier than current practice. Given the high costs associated with travel and healthcare in remote NT, it is likely that screening would be more cost-effective in urban settings and larger Indigenous communities in Australia.

A separate cost-utility analysis of improved adherence to secondary prophylaxis suggested that dramatic improvements to clinical outcomes could result from this intervention alone. While achieving 100% adherence to secondary prophylaxis is unrealistic, the trends observed concur with existing literature that secondary prophylaxis is a cost-effective intervention for RHD control in its own right.

7. Recommendations about RHD screening in Indigenous Australian children

It is clear that cardiac auscultation is not a useful method of screening for RHD in children, and should be discontinued. Whether to recommend echocardiographic screening for RHD in Indigenous Australian children, however, remains a vexed question. This thesis demonstrates that echocardiographic screening of school-aged children will detect new cases, is feasible, and is potentially cost-effective, under a stated set of assumptions.

A major dilemma when considering mass screening is the fact that delivery of secondary prophylaxis to individuals already known to have RHD is so poor. It could be argued that resources would be better invested in improving BPG adherence than in detecting
additional cases by screening, many of whom may not benefit from early detection due to the sub-optimal adherence currently observed in our setting.

This must be weighed against the possibility that perhaps the very act of screening has intangible benefits which outweigh these concerns. Screening, coupled with appropriate education about RHD, raises awareness of the disease and its consequences for patients, families and communities; this alone may improve adherence to secondary prophylaxis. Screening on a mass level would also highlight the extent of the burden of RHD in Australia, potentially galvanising policy-makers to address the social determinants of this disease of poverty.

One possible model for screening would be to start with a targeted implementation, conducted over a defined period of time (for example, five years). In this scenario, all children in selected high-prevalence communities would be screened. Two models that could be considered would be: 1) a regional approach such as screening in all communities of the Top End of the NT, where we have demonstrated the highest RHD prevalence, or 2) selecting large Indigenous communities throughout northern Australia, as this is where the highest number of cases is likely to be detected, and the economic analysis showed that the biggest driver of cost-effectiveness was the number of children able to be screened in one location.

A targeted approach would provide the opportunity to validate the assumptions made in the cost-effectiveness analysis about the severity and progression of screen-detected RHD, and to refine feasibility aspects of the program before implementation on a larger scale. Screening high-risk Indigenous children in urban settings (for example residents of town camps) or boarding schools (attended by remote Indigenous children) is another approach
to consider. Each of these approaches, however, raises questions of equity, as they involve the selection of only a subset of the at-risk population.

Ultimately, the decision about whether to invest in a screening program needs to take into consideration not only the disease and program in question, but also the competing pressures on the public health dollar. Other factors that may also influence decision-making include political pressures, palatability for the electorate, and questions of equity, to name just a few. With parallel investment into improving secondary prophylaxis adherence, echocardiographic screening for RHD has the potential to dramatically improve outcomes of this disease in Indigenous Australian children.

10.2 Future directions for research

Internationally, there is significant interest in echocardiographic screening for RHD, both as a means of more accurately defining disease burden in different contexts, as well as identifying many individuals with undetected disease who will benefit from early treatment. This is particularly pertinent in resource-poor settings where disease surveillance systems are not well established. As more screening studies are conducted, some questions continue to come to the fore, and others have evolved.

10.2.1 Evaluation of the WHF criteria

The absence of a ‘gold standard’ diagnostic test for RHD makes the evaluation of a screening test difficult. However, if the evidence-based WHF criteria themselves are considered as the gold standard, it is important to confirm that their application will result in consistent and reproducible differentiation of normal echocardiographic findings from mild RHD. This is in the process of being investigated by one of the co-authors of the gECHO
10.2.2 Understanding clinical outcomes of children with subclinical RHD

Since the WHF criteria were published, there has been an evolving consensus that children meeting definitions of Definite RHD should be considered to have true disease, requiring secondary prophylaxis. While the natural history of this group has not been formally evaluated, it would now seem unethical not to offer treatment to these children.

What approach to take with children meeting criteria for Borderline RHD, on the other hand, is much less clear. Data regarding the short-term follow-up of this group are becoming available, and it appears that at least a subset demonstrates progression of valve lesions, and/or is at increased risk of ARF. Determining whether there are any features which can prospectively identify those at risk of disease progression is important, but long-term follow-up of a large number of children will be required.

The variable use of BPG in this group is likely to confound the results of observational studies, and a randomised control trial (RCT) of BPG versus no treatment in children detected with Borderline RHD is being considered. However, questions regarding the practicality of conducting such a study in settings with poor health service availability, as well as ethical concerns among some clinicians who would choose to offer prophylaxis to this group, make an RCT unlikely. An alternative approach has been proposed: a prospective global register of borderline and otherwise asymptomatic, screen-detected RHD cases, in which clinical progress as well as BPG adherence data will be documented.
10.2.3 Increasing feasibility of RHD screening in resource-poor settings

As echocardiographic screening for RHD has become more widespread, a need for a simplified process has been recognised in settings where skilled staff and expensive equipment are not readily available. Different approaches using inexpensive handheld devices operated by staff with minimal training have been explored and successfully implemented in different settings. Simplified screening protocols have been used, which have excellent sensitivity but only moderate specificity; the ideal simplified criteria are the subject of ongoing research. The success of such an approach is largely dependent on local capacity to follow up positive screens with a formal diagnostic evaluation; the improved feasibility is not beneficial if there is nobody with cardiac sonography skills available, or if the cost is prohibitive.

10.3 Conclusions in summary

The burden of rheumatic heart disease in Indigenous Australian children remains unacceptably high. Echocardiographic screening for RHD is feasible in Australia and will detect previously undiagnosed disease. However, in order to respect the public health principles of screening, an effective treatment that improves outcome for those diagnosed with early disease must be available. While secondary prophylaxis with BPG theoretically fulfils this requirement, its reliable delivery to patients already known to have RHD remains elusive in our population. If echocardiographic screening is to be incorporated into the national RHD control strategy, it must be coupled with measures to improve the delivery of secondary prophylaxis. Perhaps more importantly, however, the focus should be on primordial prevention and addressing the social determinants of the health, which would benefit many more aspects of the health and well-being of Indigenous Australians.