Global Epidemiology, Prevention and Control of Rheumatic Heart Disease with a Focus on the Pacific Islands Region

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Abstract

Rheumatic heart disease (RHD) is a leading cause of cardiac disease among children in developing nations and Indigenous populations in some industrialised countries. In 1990, there were 29,172,383 prevalent cases of RHD globally, which increased to 34,232,795 in 2010, with 8,593,116 deaths during this entire period. Mortality due to RHD in Australia disproportionately affects young Indigenous people, with deaths due to RHD 43.1 times more common among young Indigenous people than the general population.

Despite this, accurate documentation of the burden of RHD, particularly mortality, is lacking in many high-risk countries, and regional and global estimates of the disease require updating. In response, four studies were undertaken with the following aims:

1. to determine the prevalence of RHD in Fiji using echocardiography
2. to investigate the training of nurses in basic echocardiography to detect RHD
3. to estimate the global burden of RHD
4. to determine the mortality of RHD among Indigenous Australians.

The prevalence of RHD in 1,666 school-aged children in Fiji was measured using echocardiography. It was found to be high when using World Health Organization criteria (7.2 cases per 1,000), and higher when using the new World Heart Federation criteria (8.4 per 1,000). Two nurses trained in basic RHD echocardiography in Fiji had high sensitivity to detect RHD (83% and 100%).
The Global Burden of Disease Study estimates of RHD outlined in this thesis suggest a higher burden than previously reported, and support the contention that morbidity and mortality due to RHD have been underestimated globally. However, more robust epidemiologic data, such as those from Fiji and Indigenous Australia, are required to better inform these estimates. Novel approaches, such as the training of nurses in echocardiography, may enhance data collection in resource-poor settings. Better data will enhance advocacy to bring RHD control to those most in need.
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<th>Description</th>
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<tbody>
<tr>
<td>2-D</td>
<td>two-dimensional</td>
</tr>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>ACT</td>
<td>Australian Capital Territory</td>
</tr>
<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>ARIA</td>
<td>Accessibility/Remoteness Index of Australia</td>
</tr>
<tr>
<td>ARF</td>
<td>acute rheumatic fever</td>
</tr>
<tr>
<td>ASGC</td>
<td>Australian Standard Geographical Classification</td>
</tr>
<tr>
<td>BPG</td>
<td>benzathine penicillin G</td>
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<tr>
<td>CHD</td>
<td>congenital heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>COAG</td>
<td>Council of Australian Governments</td>
</tr>
<tr>
<td>CODEm</td>
<td>Cause of Death Ensemble Model</td>
</tr>
<tr>
<td>CWM</td>
<td>Colonial War Memorial</td>
</tr>
<tr>
<td>DALY</td>
<td>disability adjusted life years</td>
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<tr>
<td>DRR</td>
<td>Death rate ratio</td>
</tr>
<tr>
<td>GAS</td>
<td>group A streptococcal</td>
</tr>
<tr>
<td>GBD</td>
<td>Global Burden of Disease (Study)</td>
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<tr>
<td>GrASP</td>
<td>Group A Streptococcal Project</td>
</tr>
<tr>
<td>GRIM</td>
<td>General Record of Incidence of Mortality</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IHME</td>
<td>Institute for Health Metrics and Evaluation</td>
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<tr>
<td>IQ</td>
<td>interquartile</td>
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<td>NCD</td>
<td>non-communicable disease</td>
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<td>National Institutes of Health</td>
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<td>NSW</td>
<td>New South Wales</td>
</tr>
<tr>
<td>NT</td>
<td>Northern Territory</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PhD</td>
<td>Doctor of Philosophy</td>
</tr>
<tr>
<td>PLAX</td>
<td>parasternal long axis</td>
</tr>
<tr>
<td>PSAX</td>
<td>parasternal short axis view</td>
</tr>
<tr>
<td>RHD</td>
<td>rheumatic heart disease</td>
</tr>
<tr>
<td>QIMR</td>
<td>Queensland Institute of Medical Research</td>
</tr>
<tr>
<td>QLD</td>
<td>Queensland</td>
</tr>
<tr>
<td>SA</td>
<td>South Australia</td>
</tr>
<tr>
<td>SMR</td>
<td>standard mortality rate</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>WA</td>
<td>Western Australia</td>
</tr>
<tr>
<td>WHF</td>
<td>World Heart Federation</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>YLD</td>
<td>years lived with disability</td>
</tr>
<tr>
<td>YLL</td>
<td>years of life lost</td>
</tr>
</tbody>
</table>
Declaration

I hereby declare that the work herein, now submitted as a thesis for the degree of Doctor of Philosophy of the Charles Darwin University, is the result of my own investigations, and all references to the ideas and work of other researchers have been specifically acknowledged. I hereby certify that the work embodied in this thesis has not already been accepted in substance for any degree, and is not currently being submitted in candidature for any other degree.

09 January 2014

Samantha M Colquhoun
Acknowledgements

This work is dedicated to the children and families of the Fiji Islands; to the Fiji GrASP team members; and to the Fijian nurses, teachers and doctors who work to improve the health of children and families, with the goal of improving wellbeing and quality of life in order to minimise the effect of poverty and inequity in Fiji and the Pacific Islands region.

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My supervisors have been endlessly supportive in providing guidance and intellectual oversight throughout the research and analysis that forms the work of this thesis. Enormous thanks to Jonathan Carapetis for allowing me to be creative and autonomous in my approach to my work and writing, and for his support, friendship, advice, leadership flexibility and ‘can do’ approach. Andrew Steer has been wonderfully encouraging and supportive, and has provided me with day-to-day advice, guidance and assistance both in Fiji, from Canada, and back in Melbourne. I will be forever grateful for his support and belief in me. John Condon has helped me to gradually become confident and competent with the complexities of mortality analysis; his constant patience and friendly, kind manner have been invaluable to me, and are very much appreciated. Thank you also to Stephen Lambert for advice and encouragement along the way and for reading and commenting on the final draft of this thesis.
Fiji

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Internationally

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Huge gratitude also to my esteemed colleague and friend, Tom Parks, from the University of Oxford, for his support, his interest in my work and many long brainstorming teleconference calls to discuss new ideas and innovative future projects.
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Thank you to our funding organisations, without whom none of this research work would have taken place: the National Institutes of Health (NIH), Department of Microbiology and Infectious Diseases (DMID), World Heart Federation, Cure Kids New Zealand & Fiji (plus Accor group), Fiji Water Foundation and the Fiji Ministry of Health. In addition, the Menzies School of Health Research supported this work with the award of a PhD scholarship (2009 to 2011), and provided research seed money to undertake the scoping work that led to the nurse-led echocardiography project described in Chapter 5.

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My family and friends have been enormously loyal, helpful and encouraging, and I hope that, post-submission, there will be more time for socialising, rowing, art and music. I thank them greatly for keeping me to the task when I had had enough and was ready to give up and spend the next 10 years sitting under a coconut tree. Thank you particularly to Vanessa Johnson, Kathryn and Matthew Bright, Kelly and Vladimir Pacheco, Mandy O’Brien, Jan Taylor, Julie Stout, Martin Stone, Sally Murray, Sally McCredie, Tash Rabbidge, Joseph Sherman, Liz Kennedy, Andy
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Chapter 3 was written jointly with Kathryn Roberts, and the final version was published in *Nature Reviews in Cardiology* in 2013. The Royal Children’s Hospital
Melbourne senior librarian, Poh Chua, assisted me with literature searches and formatting the references in the final version of this thesis.

Unless stated above, I conducted the work presented in this thesis, including managing the project team in Fiji; writing the protocols for the studies completed in Chapters 4, 5 and 7; and submitting all ethics proposals to various Ethics Committees, along with their annual progress reports. I completed the writing and design of the databases, the bulk of the data cleaning (assisted by Laisiana Matatolu in Chapters 4 and 5) and the data analysis, unless otherwise stated. Most of the work in this thesis has been either accepted or submitted for publication in peer-reviewed journals. I was the primary author on these manuscripts and the work is my own, unless otherwise stated above.
Publications in Support of this Thesis

Peer-reviewed publications arising directly from this work:


Colquhoun SM, Kado JH, Reményi B, Wilson N, Carapetis JR, Steer AC. Echocardiography screening in a resource poor setting: borderline rheumatic heart disease could be a normal variant. (Submitted to Int J Cardiology 2013). (Arises from Chapter 4)


Christopher JL Murray, Theo Vos, Rafael Lozano, Mohsen Naghavi, Abraham D. Flaxman, Catherine Michaud, Majid Ezzati, Kenji Shibuya, Joshua Salomon, Safa

Samantha Colquhoun, PhD thesis, 2015


**Peer-reviewed publications related to, but not arising directly from, this work:**


**Other peer-reviewed articles published during candidature:**


Presentations and Abstracts

Invited speaker at international meetings:

WHO Pacific Regional NCD Forum, Auckland, New Zealand (Sept 2013).

Presentation: RHD the most neglected NCD in the Pacific region: why RHD should be included in the NCD Package of Essential Interventions strategy. World Congress of Paediatric Cardiology and Cardiac surgery (WPCCS), Capetown, South Africa (Feb 2013).

Presentation 1: Programmes and perspectives: The Pacific Islands: a sustainable RHD programme

Presentation 2: Prevention and control of rheumatic fever and rheumatic heart disease: lessons from autonomous programmes

NZ and Polynesian Rheumatic Fever meeting, University of Auckland (2010).
Presentation: World Heart Federation Pacific Rheumatic Heart Disease Control Programme.

NZ inaugural ARF/RHD meeting 2009, Middlemore Hospital, Counties Maunikau, New Zealand.
Presentation: Technical and programme assistance to RHD programmes in the Pacific region.
Bangkok WHF RHD echocardiography standardisation meeting 2011: attended as an observer and presented *Fiji Nurse led echo study preliminary results*.

**International meetings posters and abstracts:**

WPCCS Cape Town (Feb 2013).

Poster co-author: *Rheumatic heart disease health worker training and system strengthening in four Pacific Island nations.*

Poster co-author: *Nurse led echocardiographic screening for rheumatic heart disease in Fiji: design of a training syllabus.*

Poster first author: *Nurse led echocardiographic screening for rheumatic heart disease in Fiji: results from a pilot study.*

Poster co-author: *School based screening for rheumatic heart disease in Nauru.*

Poster co-author: *School based screening for rheumatic heart disease in Tuvalu.*

Poster first author: *Rheumatic heart disease in the Fiji Islands: echocardiography confirmed prevalence and screening approaches.* World Congress of Cardiology, Dubai, April 2012.


Poster first author: The global burden of rheumatic heart disease. World Congress of Cardiology, Beijing, June 2009.

National meetings:

Invited speaker: RHD control and prevention activities in the Pacific region

Invited speaker: Pacific RHD programme and RHD global burden of disease epidemiology.

Australian Rhematic Fever and RHD meeting, Alice Springs, July 2008.
Presentation: RHD in the Pacific region.
Chapter 1: Introduction
1.1 Introduction

Acute rheumatic fever (ARF) is an autoimmune disease that follows group A streptococcal (GAS) infection. It is the long-term cardiac sequelae that are of greatest concern because, with a severe first episode or with multiple episodes of ARF, an individual is at increased risk of developing chronic rheumatic heart disease (RHD).(1)

RHD is the result of valvular damage that can follow ARF. Rheumatic valvular damage is most likely to occur when the first attack of ARF is severe, and when there are recurrent attacks of ARF.(2, 3) RHD most commonly involves damage to the mitral valve, leading to valvular incompetence—predominantly in young people—and potentially leading to mitral stenosis in adolescence or adulthood as a result of scarring and retraction of valve leaflets and chordae.(4-6) The aortic valve can also be affected, while damage to the tricuspid valve can also occur due to increased pressures from mitral or aortic valvular disease, or as a result of rheumatic inflammation.(7)

ARF has all but disappeared from industrialised countries; however, the available data suggest that the disease has remained a major problem in developing countries during the past century.(8, 9) Two global regions, Africa and the Pacific, have been identified as ‘hot spots’ for ARF/RHD.(8,9) RHD is common in the Pacific region and causes considerable health and economic effects. The adequate control of RHD in the Pacific faces many barriers, including competing disease priorities, difficult
access to small populations in remote areas, migration of skilled healthcare workers and chronic programme under-funding.

Based on work undertaken in the 1980s by the World Health Organization (WHO), guidelines for ARF/RHD prevention and control were published that have been available internationally since that time. These guidelines make a number of recommendations for RHD control and prevention. Two key recommendations are:

1. the need for register-based secondary prevention programmes
2. early detection of RHD through screening.

In resource-poor countries, a register-based secondary prevention programme is recommended as the central pillar of disease control; however, to date, most countries do not have a prevention programme in place. Very few countries in the Pacific currently have coordinated prevention and control programmes.

Sustainable and affordable RHD screening methodologies are required for early case detection. Recent advances in technology have seen the development of high quality, increasingly affordable, portable echocardiography machines that can be used to screen for RHD in a field setting. Early detection of RHD and an increased focus on prevention and control strategies could considerably reduce the need for expensive surgical intervention, and could encourage more cost-effective use of limited health funding, by both local governments and regional non-government organisations. Further evidence is required for the widespread implementation of echocardiographic screening of children in developing countries, particularly because echocardiography can detect mild abnormalities on echocardiogram and the significance of these findings is currently uncertain.
1.2 Context and Rationale

A major challenge to RHD control is how to identify people with RHD earlier so that preventative measures (secondary prophylaxis) can be commenced with the greatest effect. Secondary prophylaxis delivered to people with mild RHD leads to the majority of these patients having no detectable disease five to 10 years later. Most new patients entered onto ARF/RHD registers have already developed significant rheumatic valvular lesions. Therefore, there is a need to identify these patients earlier. Screening is an important way to identify RHD patients when they are asymptomatic; however, there are a number of issues that require exploration if RHD screening is to be considered at a public health level.

The first section of this thesis explores RHD screening in a high-risk region, and examines potentially feasible screening methodologies within an RHD register-based prevention and control programme.

1.2.1 World Heart Federation Pacific RHD Prevention Programme and Fiji GrASP Project

With support from the World Heart Federation (WHF), the Pacific Rheumatic Heart Disease Prevention Programme was commenced in 2005 with an initial focus on two Pacific Island countries as demonstration sites: Fiji and Samoa. Prior to this time, there was no coordinated programme for registering or managing RHD and ARF in
Fiji, while, in Samoa, RHD prevention and surveillance activities had previously been undertaken, but were no longer operational.

In conjunction with the commencement of the WHF Pacific RHD programme, the Fiji Group A Streptococcal Project (GrASP) commenced. This project formed Dr Andrew Steer’s Doctor of Philosophy (PhD) work, supervised by Jonathan Carapetis as Principal Investigator and Dr Joe Kado in the field. Fiji GrASP was funded by the National Institutes of Health (NIH) in the United States (US) to undertake a series of epidemiological studies to determine the baseline burden of GAS disease, including ARF and RHD, in Fiji. Fiji GrASP was commenced as a collaborative partnership between the Queensland Institute of Medical Research (QIMR), the University of Melbourne, the Fiji School of Medicine (now the Fiji National University) and the Fiji Ministry of Health. The aim of this partnership was twofold. First, it sought to progress a GAS vaccine candidate through preclinical stages to a clinical trial at the QIMR. Second, it sought to establish a field site for future GAS vaccine trials in a less developed country by undertaking detailed epidemiological research into GAS disease in Fiji.

The work undertaken through this funding mechanism formed the body of the work for Dr Steer’s PhD thesis, and has been published in peer-reviewed journals.(12-17) The work undertaken in Chapter 4 of this thesis follows on from Dr Steer’s work, and was funded by an additional grant through NIH (DMID Funding Mechanism: U01AI60579). Since 2008, Fiji GrASP has continued as the research arm of the Fiji National RHD programme. Further studies examining the RHD burden in Fiji and investigating screening methodologies have been undertaken within this partnership,
funded by multiple bodies, including the Menzies School of Health Research, Cure Kids New Zealand and the Fiji Water Foundation. The epidemiological research conducted in Fiji under the auspices of the Fiji GrASP under my leadership forms Section 1 of this thesis.

1.2.2 Research Priorities for RHD

Carapetis and Zühlke recently published an article outlining the global research challenges for ARF/RHD that stated four main challenges that need to be addressed during the next decade to advance the control and prevention of RHD (Box 1.1).(18) They hypothesise that, to reduce the burden of both ARF and RHD, a global approach is required that will permit countries to learn from each other’s experiences, to increasingly place RHD control on the international agenda, and to progress GAS vaccines to clinical trials.

Box 1.1: Global Challenges to RHD Control (18)

| Challenge 1: How to translate what we already know into practical RHD control. |
| Challenge 2: How to identify people with RHD earlier, so that preventative measures have a higher chance of success. |
| Challenge 3: How to attain better understanding of disease pathogenesis, with a view to improved diagnosis and treatment of ARF and RHD. |
| Challenge 4: How to find an effective approach to primary prevention. |

1.3 Structure and Aims of this Thesis

The broad aims of this thesis are to address two main areas of research that are encompassed in challenges one and two outlined in Box 1.1. The thesis is presented
in two sections, each of which addresses a significant overall theme relevant to challenges one and two.

Section 1 is entitled ‘RHD in the Pacific Islands’. The aims of this section are to:

1. review the current RHD epidemiology in the Pacific Islands region
2. review methods of RHD screening in the public health setting
3. determine the echocardiography confirmed prevalence of RHD in Fijian primary school-aged children
4. examine methods of RHD screening in Fiji.

Section 1 provides a review of the Pacific regional epidemiology and existing RHD activities (Chapter 2), plus an examination of screening for RHD as a public health intervention (Chapter 3). This is followed by a description of the echocardiography confirmed prevalence of RHD in primary school–aged children in Fiji (Chapter 4) and an exploration of an innovative approach to undertaking RHD echocardiography field screening (Chapter 5).

Section 2 is entitled ‘The Global Burden of RHD’. This section focuses on updating the global epidemiology of RHD, and examines mortality from RHD in a high-risk Indigenous population. This is undertaken because solid evidence-based population data are required for both high-risk regions and first-nation populations in high-income countries in order to implement prevention programmes, direct policy and funding, and increase advocacy for RHD as a neglected non-communicable disease that affects the poorest of the world’s poor. The aims of Section 2 are to:
1. provide an update of the global epidemiology of RHD, including prevalence, incidence, mortality, years of life lost (YLL), years of life lived with disease and disability-adjusted life years (DALY)

2. examine RHD mortality time trends and rates in a high-prevalence population.

The thesis concludes with a discussion of the implications of the research described (Chapter 8).
Section 1: RHD in the Pacific Islands
Chapter 2: Review of RHD and its Control in the Pacific Islands Region
2.1 The Pacific Region

There are 24 countries or territories in the Pacific region, including Australia and New Zealand, with diverse geographies, cultures, economies and politics. The Pacific is divided into four main regions: Melanesia to the west, Polynesia to the southeast, Micronesia to the north and Australasia to the southwest (Figure 2.1). While the region is vast (more than 30 million square kilometres), more than 95% of the area is ocean. The total population (approximately 32 million people) is relatively small, given the size of the region.(19) Population size varies considerably between nations; the largest populations are in Australia (21 million) and Papua New Guinea (six million), while the smallest is in Tokelau (1,100).(20) Aside from Australia, New Zealand and the French and American Territories, the majority of countries in the region have gross national incomes below US$4,000 per capita.(20) Geopolitically, the region is very diverse and includes independent nations, as well as countries with varying levels of political association with larger nations outside the region. All these factors affect the delivery of acute and preventative healthcare.
2.2 Burden of RHD in the Pacific

2.2.1 Epidemiologic Studies

RHD has been identified as an important health issue in the Pacific for some time by clinicians.\(^{(21, 22)}\) Table 2.1 summarises the available RHD data from specifically-conducted epidemiologic studies since 1985. A pooled estimate of the data from studies conducted from 1985 to 2005 suggests that the prevalence of RHD in the Pacific in school-aged children is approximately 3.5 per 1,000—second only to Sub-Saharan Africa (5.7 per 1,000), and tenfold higher than that in established market economy countries (0.3 per 1,000).\(^{(9, 23)}\) More recently, two studies conducted among primary school children in Fiji and Tonga using echocardiography found much higher prevalence than previously reported from these countries.\(^{(16, 24)}\)
Tongan study found the highest published prevalence of echocardiographically confirmed RHD ever reported (33.2 per 1,000; 95% confidence interval [CI] 30.1–40.3). However, it should be noted that echocardiograms were performed on all children with a heart murmur, whether clinically significant or innocent; thus, the results of this study are not comparable with the others in Table 2.1. The prevalence found in the Fijian study (8.4 per 1,000) may be more representative of the true prevalence of ‘clinical’ RHD in Pacific school-aged children.
Table 2.1: Published Burden of RHD Data from the Pacific Region

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Year</th>
<th>Prevalence per 1,000</th>
<th>Comments</th>
<th>Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiji</td>
<td>2006</td>
<td>8.4</td>
<td>Cross-sectional survey of school children aged 5–14 years; auscultation screening followed by echocardiographic confirmation</td>
<td>5–14 years</td>
</tr>
<tr>
<td>New Caledonia</td>
<td>2006</td>
<td>26.8</td>
<td>Cross-sectional school echocardiography survey of primary school children</td>
<td>6–14 years</td>
</tr>
<tr>
<td>Tonga</td>
<td>2003</td>
<td>33.2</td>
<td>Cross-sectional survey of school children; echocardiographic screening of children with any heart murmur (innocent or pathological)</td>
<td>4–12 years</td>
</tr>
<tr>
<td>Samoa</td>
<td>1997</td>
<td>77.8</td>
<td>Cross-sectional survey of school children using auscultation without echocardiographic confirmation</td>
<td>5–17 years</td>
</tr>
<tr>
<td>Tonga (Tongatatapu)</td>
<td>1986</td>
<td>0.7</td>
<td>School surveys</td>
<td>5–15 years</td>
</tr>
<tr>
<td>French Polynesia</td>
<td>1985</td>
<td>8.0</td>
<td>Community survey</td>
<td>All ages</td>
</tr>
<tr>
<td>Tonga (Eua Island)</td>
<td>1985</td>
<td>0.4</td>
<td>Hospital survey—auscultation only</td>
<td>5–12 years</td>
</tr>
<tr>
<td>Federated States of Micronesia (29)</td>
<td>1988</td>
<td>0.4</td>
<td>Hospital survey</td>
<td>All ages</td>
</tr>
<tr>
<td>Australia (Northern Territory Top End) (30)</td>
<td>2002</td>
<td>17 (Indigenous) &lt; 2 (Non-Indigenous)</td>
<td>Compiled from register data</td>
<td>All ages</td>
</tr>
<tr>
<td>Australia (Central) (30)</td>
<td>2002</td>
<td>13 (Indigenous) &lt; 1 (Non-Indigenous)</td>
<td>Compiled from register data</td>
<td>All ages</td>
</tr>
<tr>
<td>Australia Indigenous (Top End) (5)</td>
<td>1996</td>
<td>9.6</td>
<td>Hospital and community survey</td>
<td>5–14 years</td>
</tr>
<tr>
<td>Australia (North Queensland) (31)</td>
<td>1991</td>
<td>13.9</td>
<td>Community survey</td>
<td>5–18 years</td>
</tr>
<tr>
<td>Australia (Central) (32)</td>
<td>1990</td>
<td>7.9–12.3</td>
<td>Clinic record review</td>
<td>&gt; 5 years</td>
</tr>
</tbody>
</table>
The data on ARF incidence from the Pacific are less reliable than those on RHD prevalence because of a paucity of studies and inadequacy of surveillance in most countries. Rates of hospitalised ARF in Fiji, consistent with the high prevalence of RHD, have not been found. This may be because the diagnosis of ARF can easily be missed in these settings. In the Northern Territory (NT) of Australia, nearly half of all patients diagnosed with RHD have no prior history of ARF. In most cases, earlier episodes of ARF are misdiagnosed, possibly because of reduced awareness by health professionals of the disease, or because some cases of ARF are mild and thus may not present for medical care. This scenario appears to be similar in the Pacific Islands, with children commonly presenting with RHD at first clinical presentation with no recorded or reported prior episodes of ARF. A recent review undertaken in Fijian primary care clinics found an incidence of ARF twice that based on hospital presentations. It also found a substantial number of additional cases of possible ARF presenting to primary care, but in whom there was insufficient testing or clinical documentation to allow for a definite diagnosis.

The ARF burden in New Zealand is almost exclusively found in the Maori and Pacific Islander populations, and the proportion of notifications in these populations has increased in recent years, comprising 83% in 2003 and 91% in 2005 of all ARF notifications. From 1996 to 2005, the New Zealand rates for non-Maori, non-Pacific Islander populations decreased from 1.2 per 100,000 to 0.4 per 100,000. These observations highlight the vast and diverging disparity among disease rates when calculated by ethnicity. Similar disparity in prevalence rates by ethnicity between Pacific Islander and other non-Indigenous populations have been highlighted by studies in Fiji and Hawaii.
2.2.2 Informal Data and Economic Cost

The screening research projects conducted in Fiji and Tonga used well-defined population denominators, allowing for the accurate calculation of RHD prevalence. There are additional data available from other sources throughout the Pacific region that add to understandings of the disease burden, and in some cases suggest that the disease burden may be much higher than previously calculated in individual countries. For example, in American Samoa, a retrospective chart audit found that 95 children were diagnosed with ARF between 2000 and 2006 in a paediatric population of slightly more than 21,000, equating to a minimum annual incidence of 65 per 100,000 children aged three to 16 per year.\(^{(37)}\) The authors indicated that there were limitations to their retrospective data; however, the incidence of newly diagnosed ARF in American Samoa is comparable to that in Samoan populations resident in Hawaii.\(^{(36, 37)}\) A recent school-based clinical survey undertaken in western Fiji using rapid echocardiography as the primary screening tool suggested that the RHD prevalence may be as high as 70 per 1,000, although this study did not use standardised methods or diagnostic criteria as did the Tongan and other Fijian studies.\(^{(38)}\)

RHD causes considerable strain on the public purse in many Pacific Island countries because of the high cost of cardiac surgical procedures for patients with severe disease. Samoa and Tonga spend up to 15% of their health budgets referring cases overseas for surgery \(^{(39)}\) (personal verbal communication, Dr T Fakakovikaetau, Tonga Ministry of Health, Oct 2011). Some countries receive visiting cardiac
surgical teams from Australia and New Zealand. A cardiac surgical team from Australia has visited Fiji annually for the past 25 years, and 80% of the cases operated on at any one visit are patients with RHD (Fiji RHD National Register data 2009). The cost of sending one patient case overseas for valvular surgery is equivalent to the annual running cost for a national RHD prevention programme in a Pacific Island country with a small population (such as Tuvalu or Nauru). The cost of two to three surgical cases is equivalent to the cost of running a prevention programme in a country with a larger population (such as Fiji or Vanuatu), yet most countries in the region do not have coordinated prevention programmes.

The annual cost of running a secondary prevention programme in a country such as Fiji or Samoa is approximately US$25,000, which includes funding for a dedicated national nurse coordinator, maintenance of a national RHD register, training workshops for health professionals, health promotion, case finding and provision and delivery of benzathine penicillin G (BPG). To send a single RHD case overseas for valve repair or replacement surgery varies depending on the country providing the service, with a range between US$25,000 to 45,000 per case (Data presented at WHO & WHF Pacific Regional RHD workshop, Nadi 2006).

2.3 Prevention and Control of RHD

There are two recognised methods of control of ARF and RHD—primary and secondary prophylaxis. Primary prophylaxis refers to the timely and appropriate treatment of GAS pharyngitis, which has been clearly shown to be effective in preventing ARF.(40-42) Secondary prophylaxis involves regular administration of
antibiotics (usually three- or four-weekly BPG) to prevent recurrent ARF, which has been shown to lead to regression of existing heart valve lesions and to reduce RHD mortality.(43, 44)

Primary prevention is effective at the individual level,(41) and there are observational data to support community-based primary prevention programmes.(45-47) However, the only randomised controlled trial of community (school)–based primary prevention failed to show a statistically significant effect on the incidence of ARF (relative risk 0.81, 95% CI 0.47–1.39).(48) This was a very high quality and well-designed study that included over 85,000 person years of observation. Primary prophylaxis is also less cost-effective than other approaches.(47) There are other barriers to easy implementation of these programmes in developing countries, including the lack of appropriate and easily accessible microbiologic facilities that are required for the timely confirmation of GAS pharyngitis.(49)

Secondary prevention is both effective and cost-effective.(50) Delivery of BPG is inexpensive, and large numbers of patients can be managed by a relatively small number of staff at the primary health level.(37) Achieving satisfactory levels of adherence can be difficult; thus, delivering secondary prevention within a centralised register-based programme, which also includes a focus on health education and support of families and health staff, is an important factor.(51) With these factors in mind, the focus of efforts to control RHD in many Pacific countries has been on secondary prevention. Although primary and secondary prophylaxis-based control strategies are the cornerstone of RHD control, primordial prevention—including reduction in overcrowding and the alleviation of poverty—are most likely to have the
greatest long-term effect in curbing RHD. In Denmark, the incidence of ARF fell by half prior to the introduction of penicillin, which was almost certainly due to a concomitant rise in the standard of living.(52)

A primary prevention strategy for the future will be the use of a vaccine. There are a number of GAS vaccines in preclinical development; however, only one has reached clinical trials during the last 30 years.(53, 54) A widely available, effective and inexpensive vaccine is thus a number of years away.(53, 54) A vaccine that successfully prevents ARF may need to prevent both GAS pharyngitis and GAS impetigo. It has been hypothesised in Australian Indigenous communities—in which rates of pharyngitis are very low, but impetigo rates are very high—that GAS skin infection may play a role in the pathogenesis of ARF and RHD; however, this link is yet unproven and controversial.(55, 56)

2.4 RHD Control Programmes

The WHO first established register-based, secondary prevention projects for the control of ARF and RHD in the 1970s in seven countries in Africa, the Americas and Asia. An additional seven countries in Latin America were added in a study coordinated by the Pan American Health Organization. Both these projects demonstrated that, in developing countries, public health campaigns to control RHD were feasible and cost-effective.(27, 57-59) In 1984, the Cardiovascular Unit of the WHO, in collaboration with the International Society and Federation of Cardiology (which subsequently became the WHF), launched a Global Programme for Control of ARF/RHD in 16 participating countries (including one country in the Pacific—
As part of this programme, almost 1.5 million school-aged children were screened, and over 3,000 cases of RHD or prior ARF were detected.(61)

A review of the programme highlighted its successes, including improved compliance with secondary prophylaxis, even in the face of financial constraints.(62) Despite this, only a few countries expanded their programmes beyond the pilot phase, and funding for the WHO Global Programme ceased in 2001. Some countries have experienced individual success in RHD control. A register-based control programme aimed at reducing ARF reoccurrences, with an emphasis on education of health professionals, in Martinique and Guadeloupe in the French Caribbean Islands, demonstrated a rapid decline in ARF incidence over 10 years from 1981. Overall, there was a 78% reduction in the frequency of ARF in Martinique and a 74% reduction in Guadeloupe.(63)

2.5 RHD Control in the Pacific

New Zealand has led the way with register-based prevention programmes in the Pacific region. A series of disease registers were established in the 1970s, predominantly in regions with high rheumatic fever rates.(64) In New Zealand, ARF is a notifiable disease, with statistics collated by the Ministry of Health. A recent study showed that rates of ARF in Maori and Pacific Islander people were 10.0 and 20.7 times higher, respectively, than that in New Zealand European and other resident populations.(35) The NT of Australia established the first register-based RHD control programme in Australia in 1997. In 2007, the Australian government allocated more than AU$11 million for a national RHD strategy, RHDAustralia,(65)
which included the establishment of a national coordination unit to address the overwhelming burden of RHD and ARF in Indigenous Australians.(66)

In 2003, a programme to support Pacific Island nations to establish RHD control programmes was established with support from the WHF. Vanuatu was the first country to benefit, with the establishment of a register-based prevention programme. In 2004, the programme expanded to include Fiji and Samoa. The emphasis of this project was on strengthening the capacity of local health services to create integrated and sustainable control programmes in line with WHO recommendations for RHD prevention (see Table 2.2).(1)

Table 2.2: WHO Core Recommendations for a Register-based RHD Control Programme (1)

- A centralised ARF/RHD register, linked to local registers, established within existing healthcare networks
- Commitment from government, national, regional and local services to ensure long-term funding
- Activities guided by locally relevant, evidence-based guidelines
- A dedicated, centrally-based coordinator for each control programme
- An effective advisory committee
- Prioritisation of secondary prophylaxis
- A stable supply of BPG
- Procedures to find new cases of ARF and RHD and to monitor the burden of disease
- Education for health practitioners

Fiji and Samoa were established as demonstration sites, with the addition of Tonga in 2006. National RHD registers have been developed in these three demonstration sites, and have resulted in a marked increase in the number of cases registered since the commencement of the demonstration programmes in 2005 (see Table 2.3).
In 2011, funding was secured to assist four additional Pacific Island countries (Tuvalu, Kiribati, Nauru and the Solomon Islands) to establish RHD prevention programmes within the countries’ Ministry of Health non-communicable disease (NCD) structure. This work has drawn on the experiences, modules and resources developed in Fiji, Tonga and Samoa, and aims to expand capacity for RHD prevention and control in each of these countries as part of an initial three-year programme. Baseline echocardiography confirmed RHD prevalence data has been defined for the first time in these countries (see Table 2.4).
Table 2.4: Echocardiography Confirmed Prevalence of RHD in Four Pacific Island Countries in Children Aged 5–14 Years

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence per 1,000</th>
<th>Criteria</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuvalu</td>
<td>35.6</td>
<td>WHF</td>
<td>2012/2013</td>
</tr>
<tr>
<td>Nauru</td>
<td>36.6</td>
<td>WHF</td>
<td>2012/2013</td>
</tr>
<tr>
<td>Kiribati</td>
<td>20.6</td>
<td>WHF</td>
<td>2012</td>
</tr>
<tr>
<td>Solomon Islands*</td>
<td>24.0</td>
<td>WHF</td>
<td>2013</td>
</tr>
</tbody>
</table>

Note: * 4–16 years

The majority of patients presenting to hospitals and clinics with ARF in the Pacific region are presenting as recurrent cases. Therefore, a focus on education at the primary health level to enhance early diagnosis has been a central part of the programme in the demonstration sites.(12) In addition, screening activities have aimed to improve early detection of RHD in school children. The effectiveness of the programme has not yet been formally assessed.

Two regional training meetings were also held for health officials from 18 Pacific Island countries. Delegates at both meetings issued a ‘Call to Action’ document highlighting the magnitude of the burden of RHD in the Pacific, and calling on governments and international aid organisations to establish and maintain RHD control programmes.(67)

New Caledonia has a well-coordinated RHD prevention programme run through the Department of Health, with activities focused on primary and secondary prevention and health promotion, as well as yearly echocardiography screening of school-aged children. The echocardiography confirmed prevalence of RHD in school-aged children in New Caledonia was recently estimated at 13.5 per 1,000 population.(68) Clinical and health promotion resources are available in French through the New
2.6 Screening for RHD

The WHO recommends school-based screening for RHD to identify previously undiagnosed patients in high-prevalence regions and populations. The rationale for screening is to recognise patients with mild disease that stand to benefit the most from secondary prophylaxis. Studies in five countries—Mozambique, Cambodia, Tonga, Uganda and Nicaragua—have shown that echocardiography as a primary screening tool for RHD is extremely sensitive—up to 13 times more sensitive than auscultation. However, there is debate regarding whether echocardiography is overly sensitive.

Part of this debate centres around specific technical issues in the interpretation of echocardiograms of otherwise normal children, including determining normal values for regurgitation at the mitral valve as measured by Doppler, and determining normal values for mitral valve thickness as measured on two-dimensional (2-D) imaging. Fortunately, large studies are currently underway to establish validated criteria for the diagnosis of RHD on echocardiogram, and to determine the sensitivity and specificity of echocardiography as a screening tool. The issues surrounding screening for RHD will be further explored in Chapter 3 of this thesis.

The Fijian screening study mentioned above included a first stage of auscultation to detect clinically significant heart murmurs, followed by echocardiographic
confirmation. In contrast, the Tongan study included a number of cases without clinically significant murmurs—so-called ‘subclinical’ RHD. There remains a lack of understanding of the natural history of cases identified through the screening process with subclinical RHD. These children have no murmur detectable on auscultation and usually have only subtle changes on echocardiogram. In high-prevalence settings, many clinicians are often unwilling to risk the development of RHD; thus, they place most—if not all—of these children on antibiotic prophylaxis. There are some preliminary data available from Tonga that provide part of an answer to this issue: two- to three-year follow-ups of children found to have ‘borderline’ subclinical RHD on screening indicated that approximately 30% of the cases subsequently developed further valvular disease (personal verbal communication, Dr Toakase Fakakovikaetau, Tonga Ministry of Health, Oct 2011).

Screening entails the clinical and ethical responsibility to provide appropriate management of children identified as having RHD. Therefore, screening should not be conducted until the infrastructure is in place to ensure the reliable delivery of secondary prophylaxis through a register-based system.

2.7 Conclusion

The gaps in the disease burden data in Pacific Island countries need to be addressed to allow all countries within the region to determine whether RHD is a local disease control priority. An epidemiological tool similar to the rapid assessment tool developed for Haemophilus influenzae type b infections by the Centers for Disease
Control in the US may allow rapid assessment of the ARF/RHD disease burden in the countries where these gaps exist. (78)

An increased focus on the prevention and control of RHD by strengthening the existing register-based programmes (or developing such programmes where they are absent) that improve primary care and increase awareness of ARF and RHD in countries with high disease burdens is fundamental. In addition, the high prevalence of RHD throughout the region and the relatively small populations of many Pacific Island countries mean that a regional collaborative approach may be appropriate. A regional coordinating centre could provide technical assistance and support for echocardiographic RHD screening programmes.

Securing funding to develop and expand RHD prevention and control activities is fundamental. To date, small-scale funding has been secured by individual nations and on a regional level through a number of international non-government organisations. Governments, as well as clinicians, must prioritise RHD control in order to secure ongoing funding and recognition from large regional organisations.

Further research is required to define models of echocardiographic screening that are practical, affordable and widely applicable. The research described in Chapter 5 of this thesis examines pilot nurse-led echocardiography screening using relatively inexpensive and portable echocardiography machines.

In the next five years, it is hoped that reliable and well-run register-based programmes will be established in all Pacific countries where RHD is an important
health problem. In addition, echocardiography-based screening programmes and even primary prophylaxis programmes may also be established in some high-incidence countries. However, none of this will occur without the commitment of and dedicated funding from Pacific country governments and external funding agencies.
Chapter 3: Review of Screening for RHD—Current Approaches and Controversies
3.1 Background

RHD is a leading cause of cardiac disease among children in developing nations and in the Indigenous populations of some industrialised countries. In endemic areas, RHD has long been a target of screening programmes that have historically relied on cardiac auscultation. The evolution of portable echocardiographic equipment has changed screening for RHD during the past five years, with greatly improved sensitivity. However, concerns have been raised about the specificity of echocardiography, and the interpretation of minor abnormalities poses new challenges. The natural history of RHD in children with subclinical abnormalities detected by echocardiographic screening remains unknown, and long-term follow-up studies are needed in order to evaluate the significance of detecting these changes at an early stage. Notably, the validity of screening programmes for RHD has not been irrefutably proven. For a disease to be deemed suitable for screening from a public health perspective, it needs to fulfil a number of criteria. RHD meets some, but not all, of these criteria. If screening programmes are to identify additional cases of RHD, parallel improvements in the systems that deliver secondary prophylaxis are essential.

3.2 Introduction

RHD is the leading cause of cardiac disease among children in developing countries. The cost associated with RHD to the healthcare system and the community is enormous. Given this substantial burden of disease, which primarily
affects young people in the most productive years of their life, RHD has long been a target for public health screening and control programmes.(79)

RHD screening has traditionally consisted of cardiac auscultation performed by health professionals with varying levels of expertise. Over the past decade, the results of population-based surveys performed in various settings have suggested that the prevalence of RHD is significantly underestimated when cardiac auscultation is used for screening.(24, 70-72, 80-82) Therefore, with the evolution of portable echocardiographic equipment, interest in echocardiographic screening for RHD has increased. Consensus exists that echocardiography is a more sensitive tool for the detecting of RHD than auscultation. However, concern remains about its specificity and the interpretation of subclinical findings, particularly those detected in the context of screening.(83-85) The recently published WHF criteria for echocardiographic diagnosis of RHD provide precise definitions, and are likely to improve the specificity of echocardiography as a screening tool.(86)

This chapter examines whether RHD fulfils the criteria for a disease suitable for screening, and appraises the literature on current approaches to screening for this condition. It also highlights areas of controversy and issues that require further research in order to make rational recommendations about screening for RHD.

3.2.1 Rational for RHD Screening

The aim of screening is to identify a disease or pre-disease condition in apparently healthy individuals.(87) Various guidelines for screening exist; however, the
principles of early disease detection through screening are consistent. In this review, RHD will be considered in light of the 1994 Council of Europe criteria for selecting diseases suitable for screening (see Box 3.1).(88) In a research context, screening can also provide useful data on the epidemiology of a disease that can be used to guide the setting of health priorities, or can be used as an advocacy tool. This review does not consider these uses of screening further, but focuses on screening as it is usually practised in the context of public health.

**Box 3.1: Criteria for Selecting Diseases Suitable for Screening (88)**

<table>
<thead>
<tr>
<th>The disease should be an obvious burden for the individual and/or community in terms of death, suffering, economic or social costs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The natural course of the disease should be well known, and the disease should go through an initial latent stage, or be determined by risk factors that can be detected by appropriate tests.</td>
</tr>
<tr>
<td>An appropriate test is highly sensitive and specific for the disease, as well as being acceptable to the person screened.</td>
</tr>
<tr>
<td>Adequate treatment or other intervention possibilities are indispensable. Adequacy is determined both by proven medical effect and ethical and legal acceptability.</td>
</tr>
<tr>
<td>Screening followed by diagnosis and intervention in an early stage of the disease should provide a better prognosis than intervention after spontaneously sought treatment.</td>
</tr>
</tbody>
</table>

### 3.2.2 Burden of Disease: Morbidity, Mortality and Cost

Disease burden encompasses both prevalence and severity. In the 2005 review of the global burden of GAS diseases, Carapetis et al. estimated that >2.4 million children aged five to 14 years have RHD.(1) The estimated worldwide, all age prevalence of 2.5 to 3.2 cases of RHD per 1,000 of the population (15.6 to 19.6 million people) (9) is likely to be an underestimate, owing to the paucity of data from many developing countries, where the disease burden is highest. The global figures were updated in the
Regional variation exists in the prevalence of RHD, with the highest estimates in 2005 reported for Sub-Saharan Africa, the Pacific Islands, and Indigenous populations in Australia and New Zealand. The prevalence of clinically detectable RHD—defined as a pathological murmur, plus echocardiographic changes—in school-aged children from these populations ranges from 8.5 per 1,000 (89) to 14.0 per 1,000. As an increasing number of community surveys are undertaken and published, the previously unrecognised burden of disease is becoming clear, and high rates of RHD in Central America, South Central Asia (91, 92) and the Middle East (93) are now being reported. The highest prevalence of paediatric RHD reported to date was in an echocardiographic screening survey of Indigenous Maori and Pacific Islander children residing in high deprivation indexed zones of Auckland, New Zealand (56.5 per 1,000 children aged 10 to 13 years). Whereas most reviews of RHD prevalence published in the past decade have required echocardiographic confirmation of RHD, estimates vary substantially depending on exact case definitions and particularly on whether subclinical disease is included.

RHD is associated with substantial morbidity and mortality. Prior to the introduction of secondary penicillin prophylaxis in the 1950s, 20-year mortality from ARF and RHD in the US was as high as 30 to 80%, with the most affected individuals dying before the age of 30. Similar figures continue to be observed in developing countries, with death rates of 3.0 to 12.5% per year. In some studies, the mean age at
death was < 25 years. (98-100) In contrast, mortality from RHD in industrialised
countries has fallen dramatically as living conditions and access to medical care have
improved. (101-103) An exception to this trend is Indigenous populations in Australia
and New Zealand. Indigenous Australians are > 20 times more likely to die of RHD
than non-Indigenous Australians, and Maori or Pacific Islander people are up to 10
times more likely to die of RHD than other New Zealanders. (104-107) Mortality
from RHD in the Australian Indigenous population is examined in detail in Chapter 7
of this thesis.

Morbidity from RHD is also highly prevalent and severe, with an estimated 10.1
million DALYs lost to RHD each year globally. (108) Patients with RHD are at
increased risk of infective endocarditis and stroke, while pregnant women with RHD
experience high complication rates. (9, 109-111) Between 44 and 80% of children
with untreated ARF and RHD progress to severe cardiac failure, requiring medical or
surgical treatment within 20 years of diagnosis. (96, 97) Patient outcomes after valve
surgery in developing countries are poor and relate to the severity of disease at
presentation; cardiac surgical expertise, which is often limited; and the need for
repeated procedures following valve repair or bioprosthetic valve replacement at a
young age. (85) Although mechanical valves potentially offer greater longevity, the
ensuing complications of inadequately monitored anticoagulation can be
catastrophic. (112, 113) The burden and implications of such severe disease in young
adults are clear, in terms of both the health services required and the loss of
productivity, to say nothing of the effect it has on individuals and their families.
3.2.3 Risk Factors and Natural History

The natural history of ARF has been well documented.(44, 96, 114) Acute carditis (predominantly valvulitis) affects 30 to 80% of patients during their first episode of ARF, and is the only feature of the acute disease that causes permanent damage. Carapetis et al. estimated that up to 60% of patients develop chronic RHD following the first episode of ARF.(9)

The long-term prognosis of RHD depends on the severity of carditis at presentation, and the number of ARF recurrences.(2, 44, 96, 114, 115) Patients with mild or no carditis at presentation, who maintain regular secondary antibiotic prophylaxis, have an extremely good prognosis, with the majority having no detectable disease after 10 years.(3, 11, 44, 114) Conversely, patients who have severe valvular dysfunction rarely regress, and most will require valve surgery in their lifetime. Regardless of the initial degree of carditis, recurrent episodes of ARF worsen all grades of RHD. Recurrence rates are highest in the first five years after the initial episode, and can occur in up to 75% of patients who do not receive regular secondary prophylaxis.(3)

An estimated 40% of people with established RHD have never had a recognised episode of ARF.(116, 117) Consequently, RHD is only detected when the individual presents with cardiac symptoms, representing late disease, or when a screening test is positive during the ‘latent’ phase of disease. This latent phase is when rheumatic valvular damage can be detected through auscultation or echocardiography, but before symptoms are evident. The natural history of RHD in this latter group of
patients is unknown, and remains a key issue in evaluating whether screening for RHD is justifiable and beneficial.

### 3.2.4 Sensitivity and Specificity of Screening

No single diagnostic test for ARF exists; however, the clinical criteria initially described by Jones in 1944 (118) and revised by other groups (119, 120) enable a confident clinical diagnosis of ARF to be made in most acute settings. The diagnosis of RHD in an individual without a clear history of ARF, such as with patients detected through screening, is often uncertain.

Screening for RHD can be performed by cardiac auscultation, transthoracic echocardiography, or a combination of both. Auscultation is the traditional approach, and has the advantages of being cheap, quick and potentially able to be performed by various health professionals. Echocardiography is a more sensitive test, but is expensive; necessitates logistical considerations, such as transport of equipment and a reliable source of electricity; and requires an operator with technical expertise. Both tests are non-invasive and acceptable to the population being screened. The sensitivity and specificity of auscultation and echocardiography for RHD screening are difficult to ascertain in the absence of a ‘gold standard’ diagnostic test. This is discussed further in Section 3.3.
3.2.5 Diagnosis and Treatment of RHD

If screening is to be undertaken for RHD, facilities for confirmatory diagnosis, followed by appropriate treatment, must be available. An abnormal screening test for RHD necessitates confirmation of the diagnosis, ideally involving clinical examination by a specialist (such as a paediatric cardiologist) and detailed, high-quality echocardiographic assessment. Although this course of action is feasible in well-resourced settings, it poses potential difficulties in resource-poor countries and, indeed, in some remote parts of Australia where RHD prevalence is highest. Paediatric cardiology services might not be available in such settings. If they do exist, the numbers of such highly trained clinicians is likely to be low, which limits their availability to review large numbers of possible cases, many of which would be normal. Such a diagnostic strategy has the potential to overwhelm already-stretched services, and to detract from providing essential care to those with established cardiac disease. Thus, the cost-effectiveness and feasibility of this process needs to be evaluated in individual settings.

All patients with established RHD require secondary antibiotic chemoprophylaxis. In addition, those with severe disease require clinical management, and the availability of medical—and potentially surgical—treatment of cardiac failure is an important consideration. Secondary prophylaxis consists of three- to four-weekly administration of antibiotics (most commonly intramuscular injection of BPG, unless allergy prevents this, in which case oral Erythromycin in generally administered on a twice-daily basis) to patients with a history of ARF or RHD, in order to prevent recurrent infection and ARF. The efficacy of secondary prophylaxis in preventing
ARF recurrence was established in the 1960s, and has been part of the WHO RHD prevention strategy since 1972.(43, 121-123) In addition to preventing ARF recurrence, continuous adherence to secondary prophylaxis is associated with decreased mortality and with reduced RHD severity, including complete regression of mild RHD in many cases.(2, 3, 124, 125)

In the absence of confirmed severe allergy, penicillin is the antibiotic of choice. Regional variations exist in the route, dosage, frequency and duration of secondary prophylaxis.(110) However, a Cochrane review published in 2002 confirmed that intramuscular BPG is superior to oral penicillin, and that administration once every three weeks is superior to four-weekly intervals, when feasible.(126) Current WHO guidelines recommend that patients be given three- to four-weekly BPG for a duration of five years, or until they are have reached the age of 18 (whichever is longer), after the first episode of ARF without carditis.(1) For patients with mild or resolved carditis, the recommended duration of therapy is longer (10 years, or until the age of 25—whichever is longer). For patients with moderate or severe carditis, or who have undergone valve surgery, lifelong therapy is recommended.

BPG has the advantages of being widely available and inexpensive. However, the injection is painful and needs to be administered frequently over many years. These factors could reduce its acceptability to patients. Concerns have also been raised by healthcare providers, particularly in developing countries, about serious allergic reactions to long-term BPG administration.(127-129) However, in a large prospective multicentre study of 1,790 patients receiving secondary prophylaxis for RHD, anaphylaxis was rare, with an estimated incidence of 1.2 per 10,000 injections,
including one death.(130) Importantly, medical staff delivering secondary prophylaxis should be trained in the management of anaphylaxis.

Although the efficacy of secondary prophylaxis has long been established, its effectiveness in preventing ARF recurrence is dependent on continuous adherence. The issue of ensuring adequate administration of secondary prophylaxis is the major global challenge in ARF and RHD management, and non-adherence rates continue to be high.(18, 110, 131) The WHO deems that secondary prophylaxis can most effectively be delivered using a register-based control programme,(1) yet few such programmes exist in developing countries. Even with a well-resourced, register-based control programme, such as that used in the NT of Australia, consistent BPG delivery remains challenging. Some primary care services struggle to deliver more than 50% of prescribed doses.(89, 132) If a screening programme is to increase identification of RHD, parallel improvement in the systems that deliver secondary prophylaxis is essential.

3.2.6 Effect of Screening on Prognosis

Secondary prophylaxis in patients with a clinically apparent episode of ARF, or in those with clinically detectable RHD (that is, with a ‘significant’ cardiac murmur), is of proven benefit. Whether this knowledge can be extrapolated to asymptomatic individuals with subclinical echocardiographic abnormalities identified in a screening context is not known. The prognosis of RHD is best in those with mild disease who receive regular secondary prophylaxis. Therefore, intuitively, asymptomatic children stand to gain the most from a screening process because they
would be otherwise unlikely to come to clinical attention until their disease progressed. However, in the absence of long-term follow-up studies with standard echocardiographic definitions of ‘subclinical RHD’, the benefit of secondary prophylaxis in this group remains unknown.

3.3 Approaches to Screening

3.3.1 Auscultation Alone

The WHO recognised the importance of early RHD detection in the 1970s, and initiated their first mass-screening programme for RHD in 1984. Over 1.4 million school children in 16 developing countries were screened with cardiac auscultation, which detected over 3,000 children with previously undiagnosed RHD (overall prevalence 2.2 per 1,000; range 0.7 to 4.7 per 1,000).(133) However, because auscultation has poor sensitivity and specificity for the diagnosis of RHD, even with experienced practitioners, relying solely on the clinical diagnosis of RHD in settings where echocardiography is now available is no longer acceptable.

3.3.2 Auscultation Plus Selective Echocardiography

With the evolution of echocardiography, the next phase of RHD screening moved to identify children with a ‘significant’ murmur on auscultation, followed by referral for further clinical assessment and echocardiography. A number of large studies have now documented that the sensitivity and specificity of cardiac auscultation for the assessment of RHD is generally poor compared with echocardiography, regardless of the experience of the examiner.(16, 24, 38, 70, 81)
In their study of > 5,000 children in Cambodia and Mozambique, Marijon et al. strikingly demonstrated that auscultation by experienced physicians was poorly sensitive, missing up to 90% of children with abnormal echocardiograms (Table 3.1).(70)

Table 3.1: Follow-up Studies of Children with Subclinical RHD Detected with Echocardiogram

<table>
<thead>
<tr>
<th></th>
<th>Nicaragua (72)</th>
<th>Harayana, India (82)</th>
<th>Bikaner, India (80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication year</td>
<td>2010</td>
<td>2011</td>
<td>2011</td>
</tr>
<tr>
<td>Number of school children screened</td>
<td>3,150</td>
<td>6,270</td>
<td>1,059</td>
</tr>
<tr>
<td>Diagnostic criteria used</td>
<td>NIH criteria*</td>
<td>Modified WHO criteria*</td>
<td>WHO criteria*</td>
</tr>
<tr>
<td>Number (%) with subclinical RHD</td>
<td>137 (4.3%)</td>
<td>128 (2.0%)</td>
<td>54 (5.1%)</td>
</tr>
<tr>
<td>Number (% of cases) of subclinical cases followed up</td>
<td>126 (92.0%)</td>
<td>100 (78.1%)</td>
<td>54 (100%)</td>
</tr>
<tr>
<td>Secondary prophylaxis commenced</td>
<td>Yes</td>
<td>No (unless moderate MR)</td>
<td>Yes</td>
</tr>
<tr>
<td>Follow-up duration (months)</td>
<td>4–12 (median 5.7)</td>
<td>3–27 (mean 15.4)</td>
<td>24</td>
</tr>
<tr>
<td>Subclinical lesion unchanged</td>
<td>73 (57.9%)</td>
<td>68 (68.0%)</td>
<td>36 (66.7%)</td>
</tr>
<tr>
<td>Subclinical lesion improved/resolved</td>
<td>41 (32.5%)</td>
<td>28 (28.0%)</td>
<td>18 (33.3%)</td>
</tr>
<tr>
<td>Subclinical lesion worsened</td>
<td>12 (9.5%)</td>
<td>4 (4.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Clinical ARF episodes during follow-up</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: *See Table 3.3; NR = not reported; MR = mitral regurgitation

In a study conducted in Tonga, 980 children underwent auscultation by a medical student to identify any murmur, then by a paediatrician to identify ‘significant’ murmurs, followed by an echocardiogram.(24) Detection of a murmur by a medical student had a sensitivity of 96.4%, but a specificity of only 1.3%, compared with echocardiography. The paediatrician was more specific (65.1%), but less sensitive (46.4%), and was unable to detect a pathological murmur in over half of the children with pathology demonstrable on echocardiography.(24) Further, of the 358 murmurs deemed pathological by the paediatrician, only 65 had an abnormal echocardiogram,
which suggests a functional origin (and hence a false positive rate) of over 80%.(24) In a study based in Fiji, 3,462 children underwent auscultatory screening by an experienced paediatrician, which revealed similar results.(16) A ‘significant’ murmur (defined by authors as ‘pathological’ or ‘suspicious’) was detected in 331 of these children who then underwent echocardiography, which revealed RHD pathology in just 41. Thus, almost 90% of ‘significant’ murmurs were false positives.(16)

In reporting the sensitivity and specificity of auscultation, the assumption is that echocardiography is the gold standard for RHD diagnosis, and that subclinical disease (that is, echocardiographically diagnosed RHD without a pathological murmur) is important. In the absence of a true gold standard test for RHD, this assumption seems reasonable, but necessitates robust echocardiographic definitions of RHD, which have not been consistent across studies to date. Further, in order to validate echocardiography as the gold standard for RHD diagnosis, longitudinal studies would need to demonstrate that subclinical echocardiographic changes progress to clinically apparent disease in the absence of treatment. Such a process is difficult because of the time required to test this assumption, as well as ethical concerns about withholding prophylaxis. This issue is further discussed in Section 3.4.

3.3.3 Echocardiography Alone

We have now entered an era in which large-scale screening using portable echocardiography is feasible, and this approach is already becoming widespread in some areas of high RHD prevalence. A number of studies have been undertaken
internationally in school-aged children (generally aged five to 15 years), and the striking and consistent finding is that the prevalence of RHD detected by echocardiogram alone is significantly higher than that detected by clinical assessment alone (Table 3.2). However, notably, the methodologies (including personnel and equipment used) and the echocardiographic definitions of RHD vary substantially between studies, thus making direct comparisons of prevalence difficult. In studies with less well-defined echocardiographic criteria (for example either valvular regurgitation or morphological valvular changes, but not both) and those in which ‘possible RHD’ is included as a definition, a much higher prevalence is reported. This finding is more likely to be a reflection of the different definitions of RHD, as was demonstrated by Marijon et al. when they retrospectively re-analysed their Mozambique data using different echocardiographic criteria, and produced strikingly different results.(134) The observation that minor changes in echocardiographic definitions have such a strong effect on the apparent disease prevalence highlights the importance of adopting standardised echocardiographic diagnostic criteria and timeliness of the publication of internationally accepted WHF echocardiographic diagnostic criteria.(86)
Table 3.2: Prevalence of Clinical and Subclinical RHD Detected by Echocardiographic Screening in School-aged Children

<table>
<thead>
<tr>
<th>Country (publication year)</th>
<th>Sample size</th>
<th>Definite RHD prevalence (clinical examination plus echocardiography)*</th>
<th>Definite RHD prevalence (echocardiography only)*</th>
<th>Definite/possible RHD prevalence (echocardiography only)‡</th>
<th>Echocardiographic criteria: Valvular regurgitation§</th>
<th>Echocardiographic criteria: Morphological MV changes§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia (2007) (70)</td>
<td>3,677</td>
<td>2.2 per 1,000</td>
<td>NR</td>
<td>21.5 per 1,000</td>
<td>Any regurgitation in two planes</td>
<td>+ two morphological changes</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Mozambique (2007) (70, 135)</td>
<td>2,170</td>
<td>2.3 per 1,000</td>
<td>NR</td>
<td>30.4 per 1,000</td>
<td>Any regurgitation in two planes</td>
<td>+ two morphological changes</td>
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<tr>
<td>Tonga (2008) (24)</td>
<td>4,794</td>
<td>NR</td>
<td>33.2 per 1,000</td>
<td>38.4 per 1,000</td>
<td>WHO criteria</td>
<td>+ one morphological change</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>India (2010) (80)</td>
<td>1,059</td>
<td>0.9 per 1,000</td>
<td>14.0 per 1,000</td>
<td>51.0 per 1,000</td>
<td>WHO criteria</td>
<td>+ thick MV (measured)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicaragua (2010) (72)</td>
<td>3,150</td>
<td>2.0 per 1,000</td>
<td>2.0 per 1,000</td>
<td>48.0 per 1,000</td>
<td>NIH criteria</td>
<td>+ thick MV ± deformity</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand (2011) (136)</td>
<td>1,142</td>
<td>7.6 per 1,000</td>
<td>26.0 per 1,000</td>
<td>56.5 per 1,000</td>
<td>NIH criteria</td>
<td>+ one morphological change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (2011) (82)</td>
<td>6,270</td>
<td>0.8 per 1,000</td>
<td>1.8 per 1,000</td>
<td>20.4 per 1,000</td>
<td>WHO criteria</td>
<td>+ one morphological change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda (2012) (71)</td>
<td>4,869</td>
<td>4.9 per 1,000</td>
<td>5.1 per 1,000</td>
<td>14.8 per 1,000</td>
<td>NIH criteria</td>
<td>+ one morphological change</td>
</tr>
</tbody>
</table>

Note: *Definite RHD requires both ‘significant’ valvular regurgitation and morphological abnormalities of the valve/s evident on an echocardiogram. Children in these categories were given BPG. ‡Possible RHD includes children with either ‘significant’ valvular regurgitation or minor morphological abnormalities, which may represent RHD, but are not considered definite RHD. In some studies, children in this category were given BPG. MV = mitral valve; NR = not reported
Echocardiography is known to be extremely sensitive for the detection of valve abnormalities; thus, unsurprisingly, more cases of RHD are detected with this technology than with auscultation alone. However, concerns have been raised about the specificity of echocardiography in the context of screening, as the consequences of a high false positive rate are important. In terms of public health, the major concern is the possible increase in the number of referrals to tertiary care services for further evaluation, and the risk of swamping already-stretched paediatric cardiology services. In terms of individual patients, a false positive result generates anxiety and can result in a healthy child being prescribed unnecessary long-term secondary prophylaxis. The potential harms of false positive results are important considerations in any screening programme, and must be balanced against the benefits of early disease detection in the small group of individuals that truly has the disease.(137, 138)

3.4 Controversies and Future Research

3.4.1 The Definition of ‘Subclinical RHD’

The appropriate echocardiographic criteria for the diagnosis of RHD, in the absence of a clinically ‘significant’ murmur on auscultation, have been much discussed in the international cardiology community. In 2001, a WHO expert committee published echocardiographic criteria for subclinical ‘indolent carditis’. (1) These criteria focus on valvular regurgitation only, and are considered by some to be over-inclusive of potentially physiological mitral regurgitation (83, 84) and by others to exclude patients with potentially pathological valve changes. (73) In 2006, a combined NIH/WHO working group released more stringent criteria, (139) in which a greater
degree of valvular regurgitation was specified, as well as the requirement for morphological abnormalities of the mitral valve. These criteria are summarised in Table 3.3.

In 2012, long-term consultation between international experts and a detailed review of the available evidence culminated in the publication of the WHF criteria for echocardiographic diagnosis of RHD.(86) These criteria consider both morphological and functional changes of the left heart valves, and are designed to improve the accuracy of RHD diagnosis, independently of cardiac auscultation, in high-prevalence areas. The hope is that adoption of these criteria will result in consistency in the definition of subclinical RHD, particularly among physicians undertaking screening programmes. Such uniformity will enable the prevalence of RHD to be compared between regions, and will facilitate recruitment of similar patients to long-term follow-up studies.

However, there is concern that the WHF criteria may be too complex for immediate application in the field, particularly in remote school-based or community-based surveys where skilled practitioners are likely to be scarce.(134) This concern has generated great interest in developing and evaluating simplified screening protocols to allow echocardiographic detection of RHD by technicians with a basic level of training. One such protocol was tested by Mirabel et al. when they retrospectively applied a single echocardiographic criterion (a Mitral regurgitant jet > 2 cm seen in one plane) to their Mozambique data.(73) When compared to their ‘reference criteria’ (comprising morphological and functional changes of the mitral valve), the simplified criteria had a positive predictive value of 92%, but a sensitivity of only
73%. While there is practical appeal to such an approach, over-simplification to this extent risks breaching the principle that a screening test needs to be appropriately sensitive and specific. If a simplified protocol is to be devised, further careful, prospective evaluation is required.

3.4.2 The Natural History of Subclinical RHD

The detection of mild valvular changes is only beneficial if they indeed represent early disease amenable to intervention. Therefore, documenting the natural history of subclinical valvular regurgitation and morphological changes is important. Do these changes progress to clinical RHD with time, and are children with these findings at increased risk of ARF? An affirmative answer to at least one of these questions is required in order to reasonably justify secondary prophylaxis.

Children with subclinical RHD detected incidentally by screening echocardiography have been assessed in three published studies (Table 3.2. (72, 80, 82). Each group of researchers found that over half of subclinical lesions remained unchanged, and about one third of lesions improved or resolved during the follow-up period (of three to 27 months). Notably, in groups studied in Nicaragua (72) and Haryana (India) (82) respectively, 9% and 4% of subclinical lesions progressed to clinically detectable disease. In the Nicaraguan study, penicillin prophylaxis was offered, but no information was provided about compliance, although the authors suggest that compliance in their setting was ‘very low’. In the study from Haryana, prophylaxis was only offered to children with moderate mitral regurgitation (11 out of 128 cases initially diagnosed with subclinical RHD), but it is not stated whether these 11 were
included in the cohort of 100 that were subsequently followed up. In Haryana, penicillin was provided to all subjects via a register-based programme, and no disease progression was noted.\(^{(82)}\)

Despite the low numbers of patients studied, the short durations of follow-up, and the lack of precise information about secondary prophylaxis, these studies demonstrate the potential of incidental subclinical lesions to progress to clinically evident disease, but also show that many subclinical lesions resolve completely. These observations highlight the dilemma of how to manage these children, as well as highlighting the need for more rigorous long-term longitudinal studies. Understanding the natural history of subclinical RHD, and whether treatment of this group in this setting improves patient outcomes, is critical to assess the potential benefits or drawbacks of RHD screening programmes.

### Table 3.3: Definitions of ‘Significant’ Valvular Regurgitation and Morphological Abnormalities of the Mitral Valve

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Significant’ mitral regurgitation</td>
<td>Jet length &gt; 1 cm in two planes</td>
<td>Jet length ≥ 2 cm in two planes</td>
</tr>
<tr>
<td></td>
<td>Peak velocity &gt; 2.5 m/s</td>
<td>High velocity (mosaic pattern)</td>
</tr>
<tr>
<td></td>
<td>Pansystolic</td>
<td>Pansystolic</td>
</tr>
<tr>
<td>‘Significant’ aortic regurgitation</td>
<td>Jet length &gt; 1 cm in two planes</td>
<td>Jet length ≥ 1 cm in two planes</td>
</tr>
<tr>
<td></td>
<td>Peak velocity &gt; 2.5 m/s</td>
<td>High velocity (mosaic pattern)</td>
</tr>
<tr>
<td></td>
<td>Pandiastolic</td>
<td>Pandiastolic</td>
</tr>
<tr>
<td>Morphological MV changes</td>
<td>Not required</td>
<td>Thickened MV leaflets, ‘elbow’ or ‘dog-leg’ deformity of AMVL, or both</td>
</tr>
</tbody>
</table>

Note: AMVL = anterior mitral valve leaflet; AR = aortic regurgitation; MV = mitral valve

### 3.4.3 Secondary Prophylaxis for Subclinical RHD

The question of whether individuals with subclinical RHD should receive secondary prophylaxis cannot rationally be answered until the definition and natural history of

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subclinical RHD have been determined. However, in the meantime, screening studies continue, and decisions must be made about the management of individuals with abnormalities thought to indicate subclinical disease. An agreed approach on whom to treat remains an important ethical principle when undertaking screening,(87) and decisions must be made on a case-by-case basis in the absence of definitive evidence.

In a 2001 report on ARF and RHD,(1) the WHO recommended that secondary prophylaxis should be given to any individual with ‘significant’ valvular regurgitation (after excluding non-rheumatic causes), in areas in which ARF and RHD are endemic. These guidelines appear to have been followed in most studies undertaken in developing countries, and many children have received BPG injections as a result. Whether all of these children would have developed RHD is unknown. However, in endemic areas, the clinician preference seems to be to give secondary prophylaxis to some children who might not need it, rather than risk ARF recurrence and progression of RHD if secondary prophylaxis is withheld.

Only one small, randomised control trial (62 patients in Kenya) of prophylaxis versus no prophylaxis for subclinical RHD has been commenced to date.(140) In the text of the article, the authors describe how they detected 62 children with trivial mitral regurgitation and randomised 31 to BPG injections and 31 to no treatment. They stated that the children would be followed up with six-monthly echocardiograms, but never published the results. Opinions about the ethics of such a trial differ. Some argue that withholding secondary prophylaxis in children with subclinical RHD is unethical. Others emphasise that no evidence exists to confirm the benefit of secondary prophylaxis in patients with subclinical RHD who have not had an
identified episode of ARF. As such, equipoise seems to exist within the medical community, thus ethically permitting a randomised control trial to be conducted. However, in the absence of such a randomised control trial, it is necessary to rely on prospective studies that document the clinical outcomes of these patients, including adherence to secondary prophylaxis as one of numerous potential confounders in the analysis. One such prospective study is currently being undertaken in Australia, in which the clinical and echocardiographic outcomes of children with subclinical abnormalities identified during screening echocardiography will be compared with healthy controls three to four years after the original screening study.

### 3.5 Economic Considerations

A final, important consideration when contemplating whether to screen for RHD is that of cost-effectiveness. In any country, screening programmes are expensive, resources for medical care and prevention are limited, and screening policy decisions need to be made in the context of competing priorities. Resources spent on screening for RHD can diminish those available for the acute care of patients with established RHD or other diseases of high priority in the community. This tension is particularly important in developing countries where the burden of RHD is highest, but where the prevalence of other diseases—such as human immunodeficiency virus (HIV), malaria and tuberculosis—can be even greater.

Secondary prophylaxis for patients with RHD is known to be cost-effective, yet, currently, almost all funds spent on RHD are allocated to the medical
and surgical treatment of advanced disease, which is clearly the least cost-effective intervention. (110) Cardiac surgery is not available in most developing countries; however, some countries have the option of transferring small numbers of patients overseas at exorbitant expense. Surgery may be paid for by charitable organisations, but otherwise it places enormous strain on limited local health budgets. In Samoa and Tonga, it has been estimated that up to 15% of the national health budget is consumed by sending 20 to 30 RHD patients annually to New Zealand for cardiac surgery. (144) Further, the cost of mitral valve repair or replacement in one patient (estimated at US$25,000 to 45,000) is the equivalent of the annual running cost of a secondary prevention programme in a small Pacific Island nation. (144)

Data regarding cost estimates of screening for RHD are scarce. In a study conducted in Fiji, the cost of echocardiographic screening with one echocardiographic machine, one operator and one nurse was estimated to be US$37.55 per case of definite RHD detected, rising to US$59.00 when the additional costs of diagnostic confirmation were included. (38) These estimates are very approximate and specific to the context, particularly whether RHD screening experience and established pathways for diagnosis and management exist. In reality, more staff and equipment than used in the Fijian study would be required to run an effective large-scale screening programme for a substantial population, which would quickly increase costs. In addition, the costs associated with a continuous screening programme for RHD— including maintenance of equipment; administration, such as database management; and expansion of the programme to provide secondary prophylaxis and coordination of clinical care—would need to be included in cost-effectiveness calculations. A
The potential exists to increase the feasibility and reduce the cost of echocardiographic screening for RHD, particularly in developing countries. Rather than relying on highly trained medical practitioners or cardiac sonographers, the possibility of training nurses or health workers to perform screening echocardiography is currently being explored in the Pacific region (described in Chapter 5 of this thesis). The prohibitively high cost of top-quality portable machines is another potential barrier that could be overcome by industry-commissioned cheaper machines. Development of cheaper machines—which would be of lesser quality, but adequate for screening purposes—and advances in handheld echocardiographic technology could make screening more affordable. Cost and feasibility will vary substantially in different settings, and a comprehensive economic analysis is an important component in any model for a sustainable screening programme.

### 3.6 Conclusion

Although RHD fulfils some of the Council of Europe criteria for a disease suitable for screening, several concerns need to be addressed before echocardiographic screening can be advocated on a global scale. Controversy persists about the suitability of echocardiography as a screening tool, owing to uncertain specificity in the absence of a gold standard test. However, clarity should be provided by the publication and adoption of the 2012 WHF criteria for the echocardiographic
diagnosis of RHD.(86) Longitudinal follow-ups of children detected with minor valvular abnormalities are crucial to determine the natural history of subclinical disease, and subsequently to determine whether early treatment with secondary prophylaxis improves patient outcomes. Perhaps most importantly, existing evidence-based practices that are known to improve outcomes—such as register-based control programmes and effective delivery of secondary prophylaxis—must be strengthened before routine RHD screening can be considered.
Chapter 4: Echocardiography Confirmed Prevalence of
RHD in Fiji
4.1 Introduction

This study is an extension of the first of five studies in Fiji aimed at evaluating the epidemiology of infections caused by the GAS. This larger project is the Fiji GrASP. The Fiji GrASP epidemiologic studies are important precursors to vaccine clinical trials because they will help gain a clear picture of the burden of GAS disease, develop ongoing surveillance and clinical endpoints for vaccine trials, collect isolates of GAS in Fiji, investigate immune correlates of vaccine protection, and prepare the existing clinical trial site for vaccine trials.

Research published since the 2006 study to determine RHD prevalence in Fiji, undertaken by Fiji GrASP, supports the contention that substantially more cases of RHD are found on echocardiogram than on auscultation, suggesting that auscultation is less sensitive than echocardiography in diagnosing RHD. (70, 72, 75, 80, 81) The highest prevalence of paediatric RHD reported to date was in an echocardiographic screening survey of Indigenous Maori and Pacific Islander children residing in high deprivation indexed zones of Auckland, New Zealand (56.5 per 1,000 children aged 10 to 13). (81) As discussed in Chapter 3, most reviews of RHD prevalence published in the past decade have required echocardiographic confirmation of RHD, and prevalence estimates vary substantially depending on exact case definitions and particularly on whether subclinical disease is included. (71, 82, 83)

The previous RHD screening study undertaken in Fiji in 2005 was a two-step study in which only cases that had suspicious murmurs detected on auscultation were investigated using echocardiogram. The study described in this chapter was
undertaken to investigate the prevalence of RHD on echocardiography in all children enrolled in the study cohort, and to compare the results of this with the results from using the two-step approach.

4.2 The Epidemiology of RHD in Fiji and the Pacific Region

As discussed in Chapter 2, Pacific Island countries have among the highest prevalence in the world of RHD, and have documented high incidences of ARF.(23, 26, 36, 146) The Global Burden of Disease Study (Chapter 6 of this thesis) estimated that RHD caused 4,126 deaths in 2010 in the Oceania and Australasia region, with 37,789 DALY lost. The true figures are likely be higher, as death reporting in many Pacific countries is poor, and autopsies to confirm cause of death diagnosis are not commonly performed. Since 2005, Fiji has had an RHD control and prevention programme, run though the Ministry of Health and supported by the WHF and Menzies School of Health Research Pacific Rheumatic Heart Disease Control Programme. The prevention and control programme is based on WHO recommendations for secondary prevention.(1)

Study one of the Fiji GrASP project screened 3,462 primary school children aged five to 15 years for RHD in 2006. Overall, 889 children (25.7%) had a murmur detected by auscultation and 530 children (15.3%) of the total were thought, by the auscultating paediatrician, to have an innocent murmur. The remaining 359 children (10.4%) of the total were found to have a suspicious murmur (murmurs thought to be pathological, or where pathology could not be excluded). Screening echocardiograms were performed on 331 of these 359 children. There were 31 cases of definite or
probable RHD (19 definite, 12 probable) detected in this study, which used the NIH and WHO criteria. These results demonstrated an overall prevalence (definite plus probable RHD) of 8.4 cases per 1,000 (95% CI 5.6–12), and a prevalence of definite RHD of 4.1 per 1,000 (95% CI 2.2–6.8). Of the 12 children with definite congenital heart disease (CHD), there were six children with ventricular septal defect, four children with atrial septal defect and two children with bicuspid aortic valves. This represents a prevalence of CHD of 3.5 per 1,000 (95% CI 1.8–6).

A second RHD screening study undertaken in Fiji (not part of GrASP) and published in 2011 also used a two-step algorithm of auscultation plus echocardiography of children who were found to have a murmur. This study used an earlier unpublished version of the NIH/WHO definitions for definite, probable and possible RHD. Possible RHD was defined as for probable, except without a cardiac murmur. A combined prevalence of definite, probable and possible RHD of 55.2 cases per 1,000 in a primary school–aged population was reported. These data support the contention that there are high rates of undiagnosed RHD in school children in Fiji; however, the limitation of the two-step process of screening—in which only those children found to have a suspicious murmur undergo echocardiography—may have led to an underestimation of the true disease burden. The study described in this chapter was undertaken to determine the echocardiography confirmed prevalence of RHD using the published NIH/WHO definitions in a large cohort, and to include a comparison between auscultation and echocardiography results. In addition, it aimed to undertake basic auscultation training for nurses to explore this as a screening methodology.
4.2.1 Fiji Demographics

Fiji is an independent republic of approximately 330 islands located in the Western Pacific, north of the Tropic of Capricorn (Figure 4.1). Fiji is ranked 96 out of 187 nations on the United Nations Development Programme Human Development Index. It has a gross domestic product per capita of US$4,087, and an infant mortality rate of 17 per 1,000. The overall crude mortality rate in Fiji is 6.1 per 1,000, and life expectancy at birth is 69.4 years.(147)

![Figure 4.1: Map of the Fiji Islands](image)
The population figures for Fiji used in this study are from the 2007 national census (Fiji Bureau of Statistics, 2007). The population of Fiji at that time was estimated as 837,271 people. The population of children aged five to 14 years living in Fiji in 2007 was estimated at 160,403. The infant mortality rate in Fiji in 2007, according to United Nations figures, was 18.1 per 1,000, and under-five mortality was 18 per 1,000.(148)

Geographically, there are two main islands—Viti Levu, where the capital, Suva, is located, and Vanua Levu—and over 300 other islands. The Ministry of Health divides the country into three medical divisions to direct services: Northern Division, Western Division and Centre-East Division. In 2007, 87% of the population lived in the Central and Western Divisions, both of which are located on Viti Levu. The population of the Central Division is 430,237, with 80,071 of this population aged between five to years. Forty-nine per cent of the entire population of children aged five to fourteen years in Fiji live in the Central Division, which is predominantly the eastern side of the larger island, Viti Levu. The population of Suva (city and peri-urban) is 186,216. Of the 837,271 people in Fiji, in 2007, 49.3% lived in rural areas. However, this proportion varies by division:

- in the Central Division, 27% of the population lives in rural areas
- in the Western Division, 58% of the population lives in rural areas
- in the Northern Division, 74% of the population lives in rural areas
- in the Eastern Division, 88% of the population lives in rural areas.

Fiji Bureau of Statistics figures from the 2007 census indicate that 56.8% of the population is Indigenous Fijian, 37.5% of the population is Indo-Fijian and the other
5.7% of the population are predominantly other Pacific Islanders, Europeans and Chinese.(149)

4.3 Study Objectives

4.3.1 Primary Objective

The primary objective of this study was to estimate the prevalence of RHD in primary school–aged school children in Fiji, diagnosed by echocardiography.

4.3.2 Secondary Objectives

The secondary objectives were as follows:

- to describe the echocardiographic features of RHD and CHD in primary school–aged school children in Fiji
- to compare the RHD auscultation findings by a paediatrician and nurse with the echocardiography gold standard
- to compare auscultation by nurses trained in basic auscultation for RHD with that of the paediatrician.

4.4 Study Design

This was an observational cross-sectional study of school children aged five to 14 years in Fiji. Each child enrolled had a screening echocardiogram for RHD, as well as auscultation performed by a paediatrician and a nurse. A group of school health team nurses received brief training to undertake screening auscultation, and their
auscultation results were compared to the paediatrician’s results to determine whether the nurses receiving auscultation training could identify children with suspicious murmurs and requiring referral, with high sensitivity and specificity.

During the first visit, all children had a heart auscultation examination using a stethoscope by both a nurse from the Fiji Ministry of Health school health team and a paediatrician. During the second visit, all children—with or without the presence of a murmur—had a screening echocardiogram performed, unless they were not able to be located for follow-up. Children thought to have abnormal cardiac pathology following the screening echocardiogram had an extended screening echocardiogram performed by the echocardiography technician during the second visit in order to provide more comprehensive echocardiography views for the cardiologists to review.

All children diagnosed with definite or probable RHD were referred to a paediatrician for ongoing management and monitoring of their disease status, as well as to ensure that follow-up occurred. They were also added to the Fiji RHD register and flagged for a six- to 12-monthly follow-up. All children with RHD and their families were provided with educational materials on RHD and information by the Fiji RHD team staff.

4.4.1 Sampling

In Fiji, there is a very high rate of school enrolment (98%); however, school attendance diminishes throughout primary school, particularly in rural areas, where it is estimated that 15% of children do not complete primary school due to poverty.
Primary school extends from grade one (approximately age five) to grade eight (approximately age 14), and thus captures the target population well. High school attendance is lower and decreases steadily, with less than 25% of children estimated to reach the final year of school—grade 13.(150)

To gain a representative sample of the population, primary schools were chosen as the primary sampling unit. Primary school attendance is high; thus, it is reasonable to assume a representative sample of the entire population aged five to 14 could be attained by using primary schools as the sampling unit. However, a disadvantage of this method is that it may underestimate the prevalence of RHD because those children who do not attend school are more likely to be of lower socioeconomic status—a known association with RHD.

The Korovou and Nausori subdivisions were chosen by the Fiji Ministry of Health as appropriate sites for this study because both areas had school nurse teams who were nominated by the Ministry of Health to attend the auscultation workshop and take part in the auscultation component of the study. Nausori is a town adjacent to the capital Suva, and is surrounded by rural areas and small villages. Korovou is a small rural town that close to the coast and surrounded by dairy farms and forest; it is 30 minutes’ drive north of Nausori and its population is predominantly rural and comprised of subsistence farmers.

Random sampling of primary schools is ideal in terms of scientific technique, and provides an overall representative sample. However, it may not provide sufficient information about smaller subgroups within the sample. There are known differences
within the Fijian population, including location (Central, Western, Northern and Eastern Divisions), environmental (rural versus urban) and ethnicity (Indo-Fijian versus Indigenous Fijian). Therefore, stratified sampling was employed, taking into account the distribution of the population by division and by rural/urban location. This study attempted to include both Indigenous Fijian and Indo-Fijian Schools within the urban and rural areas. Census data from 2007 indicate that the percentage of Indo-Fijians in Fiji is approximately 37.5%, and Indigenous Fijians is 56.8%.(151) This study aimed to achieve as close to these percentages as possible.

The Central Medical Division of Fiji was used as the sampling region. The percentage of population that lives in the rural areas in the Central Division was 28%; however, in order to extrapolate the results to the Fijian population, the sampling was based on a figure of 53.6% (the total rural population of Fiji). Within the Central Division, there are five subdivisions: Rewa, Serua, Tailevu, Naitasiri and Namosi. The Rewa (Nausori) and Tailevu (Korovou) subdivisions were the study sites. The Ministry of Health identified these subdivisions as the most appropriate to undertake the auscultation component of the study because both provinces have dedicated school nurse teams and can be accessed relatively easily from Suva on a daily basis. School nurse teams are employed throughout Fiji by the Ministry of Health, and their role includes undertaking basic routine annual health checks on all primary school–aged children in their allocated areas. The teams are based at health centres in Korovou and Nausori.
4.4.2 Selection of the Study Population

Ten schools were selected to participate in the study, with a total of 2,297 students enrolled in 2008. The subdivisions where the schools were located are indicated in Figure 4.2. All schools had classes from grade one to grade eight (age range approximately five to 15 years). These schools are within the urban and peri-urban area of Nausori and in the rural areas surrounding the towns of Nausori and Korovou. All children between the ages of five to 14 within the schools identified were considered eligible to participate in the study (Figure 4.2).

![Study site](image)

Figure 4.2: Map of the Fiji Islands Showing Government Divisions and Study Site

The estimated prevalence of RHD from previous studies in Fiji was used to estimate that a sample size of 1,900 children was required for the echocardiography component of the study. This allowed detection of a prevalence of RHD of 1%, with a 95% CI of 0.6 to 1.5%, with a 95% CI of ± 5%. A sample size of 1,900 children for
the auscultation part of the study was calculated based on a minimum acceptable sensitivity estimate of 80% for nurses to detect the presence of a significant murmur in 13% of primary school–aged children. This calculation was based on previous research (undertaken by the Fiji GrASP team in 2006) that found that 23.3% of all Fijian primary school–aged children had a murmur, and 13% of children examined had a significant murmur that required expert examination and echocardiography.

Seven of the schools were in rural areas, and three were in urban areas. The urban schools tended to be larger than most of the rural schools, as some children from rural areas travel to attend urban schools. Although Indo-Fijian children do attend Fijian schools, the population of the six ‘Fijian’ schools was predominately Indigenous Fijian. Many Indigenous Fijian children attend Indo-Fijian schools. Children were allocated to urban or rural status, depending on the location of the school they attended, rather than according to their place of residence, because this was much more difficult to ascertain accurately in this setting.

School-aged children were enrolled after written informed consent was obtained. In addition, written assent was obtained for all children aged more than 10 years of age. All children enrolled were recorded into the study enrolment log by study number and initials. All study visits were planned with the school principals and teachers to ensure minimal disruption to the daily teaching routine.

All children were offered an echocardiogram and auscultation by a nurse and paediatrician. In addition, all children had height and weight measurements recorded using standardised and daily calibrated instruments. During the auscultation and
echocardiography procedures, screens were used to maintain the children’s privacy, and a chaperone was present. The Fiji Ministry of Health and Fiji Ministry of Education approved this arrangement.

4.4.3 Echocardiography

All children were booked to have a screening echocardiogram to assess their mitral and aortic valves for evidence of RHD. Echocardiographic criteria for RHD were based on those previously published by the NIH and WHO,(139) modified following recent RHD screening studies in Tonga (24) and Fiji (16). These were subsequently referred to as ‘NIH/WHO criteria’ (Table 4.1).
Table 4.1: Definition of RHD on Echocardiogram from the WHO and NIH

**RHD Working Party Guidelines, with Modifications from Studies in Fiji and Tonga (16, 24, 139)**

<table>
<thead>
<tr>
<th><strong>Definite RHD</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite mitral regurgitation due to RHD</td>
<td>Significant mitral regurgitation on echocardiography(^a) plus morphological changes of the mitral valve on echocardiography(^b).</td>
</tr>
<tr>
<td>Definite aortic regurgitation due to RHD</td>
<td>Significant aortic regurgitation on echocardiography(^c) plus morphological changes of the mitral valve on echocardiography without another evident aetiology for aortic insufficiency, such as bicuspid valve or annuloaortic ectasia.</td>
</tr>
<tr>
<td>Definite mitral stenosis due to RHD</td>
<td>Significant mitral stenosis on echocardiography(^d). Additional echocardiographic changes that may be present include thickening of the mitral valve leaflets, ‘elbow’ or ‘dog-leg’ deformity of the anterior mitral valve leaflet, fixed or markedly restricted motion of the posterior mitral leaflet, calcification and commissural thickening.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Probable RHD</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable mitral regurgitation due to RHD</td>
<td>Significant mitral regurgitation on echocardiography without morphological changes of the mitral valve on echocardiography.</td>
</tr>
<tr>
<td>Probable aortic regurgitation due to RHD</td>
<td>Significant aortic regurgitation on without morphological changes of the mitral valve on echocardiography.</td>
</tr>
<tr>
<td>Probable mitral valvular pathology due to RHD</td>
<td>Morphological changes of the mitral valve on echocardiography without significant mitral stenosis, mitral regurgitation or aortic regurgitation on echocardiography.</td>
</tr>
</tbody>
</table>

Note:  
\(^a\) Significant mitral regurgitation on echocardiography is defined as a mitral regurgitant jet at least 2 cm from the coaptation point of the valve leaflets, seen in two planes, with a high velocity mosaic pattern and persisting throughout systole.  
\(^b\) Morphological changes of the mitral valve on echocardiography are defined as thickened mitral valve leaflets and/or elbow or dog-leg deformity of the anterior mitral valve leaflet.  
\(^c\) Significant aortic regurgitation on echocardiography is defined as an aortic regurgitant jet at least 1 cm from the coaptation point of the valve leaflets, with a high velocity mosaic pattern and seen in two planes.  
\(^d\) Significant mitral stenosis on echocardiography is defined as evidence of flow acceleration across the mitral valve with a mean pressure gradient greater than 4 mmHg.

Echocardiography was performed by an echocardiography technician using a Siemens Cypress Accuson portable echocardiography machine with either a 7-3 or 3-2 MHz phased array transducer, as appropriate for the patient. The probe frequency was 6 Hz, with a frame rate 20-30 frames per second with three beats per loop. The screening echocardiogram used a specially designed, abbreviated 15- to 30-minute protocol (Table 4.2). Each echocardiogram was labelled with the individual’s study number, date of the exam and subject’s date of birth, but not the subject’s name.
The screening protocol was a seven-step algorithm to assess the morphology of the mitral and aortic valves using 2-D mode in three views, and an assessment of regurgitant flow by colour Doppler across the mitral and aortic valves in three views. These views also enabled a screening examination for common congenital abnormalities, including ventricular septal defect and atrial septal defect. If there was no evidence of abnormality, no further assessment was required. If there was evidence of any abnormality, the echocardiography technician was asked to complete an extended echocardiogram.

**Table 4.2: Seven-step Algorithm for Screening Echocardiography**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Parasternal long axis view of the mitral and aortic valves. 2-D mode to view morphology of these valves.</td>
</tr>
<tr>
<td>Step 2</td>
<td>Parasternal long axis view of the mitral and aortic valves. Colour Doppler to view the mitral and aortic valves for evidence of regurgitation (a regurgitant jet more than 1 cm for the mitral valve was considered reason for a full echocardiogram, and any regurgitation of the aortic valve was considered reason for a full echocardiogram).</td>
</tr>
<tr>
<td>Step 3</td>
<td>Parasternal short axis view of the mitral and aortic valves. 2-D mode to view morphology of these valves.</td>
</tr>
<tr>
<td>Step 4</td>
<td>Parasternal short axis view of the mitral and aortic valves. Colour Doppler to view the mitral and aortic valves for evidence of regurgitation.</td>
</tr>
<tr>
<td>Step 5</td>
<td>Apical four and five chamber view of the mitral and aortic valves. 2-D mode to view morphology of these valves.</td>
</tr>
<tr>
<td>Step 6</td>
<td>Apical four and five chamber view of the mitral and aortic valves. To view the mitral and aortic valves for evidence of regurgitation (a regurgitant jet more than 1 cm for the mitral valve was considered reason for a full echocardiogram, and any regurgitation of the aortic valve was considered reason for a full echocardiogram).</td>
</tr>
<tr>
<td>Step 7</td>
<td>Note any other abnormalities.</td>
</tr>
</tbody>
</table>

The criteria for extending the echocardiogram to a full echocardiogram were:

- the presence of mitral regurgitation of greater than 1 cm
- the presence of any aortic regurgitation
- any abnormal mitral or aortic valve morphology
- the presence of any other pathology, such as ventricular septal defect or atrial septal defect, bicuspid aortic valve or other abnormalities.
The extended echocardiographic protocol included more detailed morphologic assessment of the mitral and aortic valves, and colour wave Doppler assessment of the regurgitant jets of the mitral and aortic valves in four and five apical chamber views.

4.4.4 Review and Clinical Referral

All echocardiograms were subsequently reviewed by a cardiologist not involved with the initial screening. If the cardiologist viewed a screening echocardiogram and there was uncertainty, a second cardiologist was asked to review the echocardiogram. The second cardiologist was blinded to the review of the first cardiologist. Where there was a difference of opinion or any uncertainty, the opinion of a third cardiologist as a tiebreaker was sought. If the cardiologist viewed any screening echocardiograms that he or she thought were abnormal, the study team were notified, the family of the child was contacted, and an off-study appointment was made. Children with symptoms suggestive of ARF, as judged by the paediatrician assessing the participant, were managed accordingly and re-evaluated for the presence of RHD once active rheumatic inflammation had subsided after two months.

4.4.5 Case Definitions of RHD

RHD cases were categorised as definite or probable (Table 4.3). If an echocardiogram was performed and diagnosis was inconsistent with the clinical findings, the echocardiographic findings took precedence. For example, a person with clinical findings consistent with significant mitral regurgitation, but with an
echocardiogram that was normal or only showed trivial mitral regurgitation, was categorised as not having RHD.

4.5 RHD Echocardiography Diagnosis with NIH/WHO Guidelines Versus WHF Definitions

New standardised guidelines for echocardiographic diagnosis of RHD were published in 2012, which was after the commencement of this study. These guidelines were produced by an international panel of RHD experts and cardiologists in response to an increasing number of international studies for RHD echocardiographic screening revealing a higher RHD burden than previously determined. The WHF standardised RHD echocardiography guidelines intend to provide clearer definitions for RHD diagnosis for future studies to evaluate the role of echocardiographic screening in RHD control.

Although this study was not designed for the new 2012 WHF criteria, the results are presented in this chapter using these criteria as a comparison to the NIH/WHO criteria. It is recognised that some of the features required on echocardiography for the WHF criteria may not have been captured adequately to make a valid comparison, so these results should be interpreted with some caution. The differences and similarities between the NIH/WHO criteria used in this study protocol and the newer WHF criteria for RHD echocardiography diagnosis are outlined in Table 4.3.

In terms of morphologic criteria, the only area in which inadequate data was collected in this study in comparison to the WHF criteria requirements was for the
measurement of valve thickness. The NIH/WHO criteria have no requirement to measure and record thickness in millimetres; instead, a subjective measurement was recorded as ‘thick’—that is, an assumption was made that the valve was ≥ 3 mm. The multiple morphological variables collected for this study were combined to categorise data for analysis using WHF criteria. These were thickening of anterior or posterior mitral valve leaflets, presence of elbow deformity, tethering of mitral valve chordae (restricted leaflet motion) and elongation of anterior mitral valve chordae (excessive leaflet tip motion). Doppler measurement variables were also adapted for analysis using the WHF criteria. Specifically in cases where velocity specific measurement was not recorded, subjective assessment of high velocity was inferred from Doppler colour recording—that is, an assumption was made that these cases had velocity > 3 m/sec when the cardiologist noted a ‘high velocity Doppler jet’.
### Table 4.3: NIH/WHO versus WHF Echocardiography Criteria for RHD

<table>
<thead>
<tr>
<th>Regurgitation</th>
<th>NIH/WHO criteria</th>
<th>WHF criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitrail regurgitation</strong></td>
<td>All of: 1) MR jet &gt; 2 cm in 2 views; 2) with high velocity and mosaic pattern; 3) through systole</td>
<td>All of: 1) MR jet seen in 2 views; 2) with at least one view &gt; 2 cm; 3) with high velocity (&gt; 3 m/s); 4) pan systolic jet in at least one envelope</td>
</tr>
<tr>
<td><strong>Aortic regurgitation</strong></td>
<td>All of: 1) AR jet &gt; 1 cm in 2 views; 2) with high velocity and mosaic pattern</td>
<td>All of: 1) AR jet seen in 2 views; 2) with at least one view &gt; 1 cm; 3) with high velocity (&gt; 3 m/s) in early diastole; 4) pandiastolic jet in at least one envelope</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve morphology</td>
<td>Any of: 1) thickened MV leaflets; 2) elbow/dog-leg deformity of anterior MV leaflet*</td>
<td>Two or more of: 1) AMVL thickening &gt; /= 3 mm; 2) chordal thickening; 3) restricted leaflet motion; 4) excessive leaflet tip motion during systole</td>
</tr>
<tr>
<td>Aortic valve morphology</td>
<td>No definition; not included as criteria</td>
<td>Two or more of: 1) irregular or focal thickening of aortic valve; 2) coaptation defect; 3) restricted leaflet motion; 4) prolapse</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>MS with a mean gradient of &gt; 4 mmHg</td>
<td>MS with a mean gradient of &gt; 4 mmHg with congenital abnormalities excluded</td>
</tr>
<tr>
<td><strong>Overall criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Definite</strong></td>
<td>Definite A: Definite mitral regurgitation—significant MR plus morphological changes of the mitral valve</td>
<td>Definite A: Pathological MR plus morphological changes of MV (i.e. two or more)</td>
</tr>
<tr>
<td></td>
<td>Definite B: Definite mitral stenosis—significant MS</td>
<td>Definite B: Mitral stenosis</td>
</tr>
<tr>
<td></td>
<td>Definite C: Definite aortic regurgitation—significant AR plus morphological changes of the mitral valve (when other causes of AR are excluded)</td>
<td>Definite C: Pathological AR plus morphological changes AV (i.e. two or more)</td>
</tr>
<tr>
<td></td>
<td>Definite D: Borderline disease of both MV and AV</td>
<td></td>
</tr>
<tr>
<td><strong>Probable/borderline</strong></td>
<td>Probable A: Probable mitral valve pathology—morphologic changes of the MV without MS, MR, AR</td>
<td>Borderline A: Morphological features of the MV (i.e. at least two) without pathological MR or MS</td>
</tr>
<tr>
<td></td>
<td>Probable B: Probable aortic regurgitation—significant AR without morphologic changes of the mitral valve</td>
<td>Borderline B: Pathological MR</td>
</tr>
<tr>
<td></td>
<td>Probable C: Probable mitral regurgitation—significant MR without morphologic changes of mitral valve</td>
<td>Borderline C: Pathological AR</td>
</tr>
</tbody>
</table>

Note: *Elbow/dog-leg deformity represents AMVL thickening plus AMVL restricted motion; ** Borderline criteria refers to WHF criteria; AMVL = anterior mitral valve leaflet; AR = aortic regurgitation; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve
4.5.1 Auscultation

The children had a cardiac auscultation examination by one of 19 school nurses who had received training in basic RHD auscultation at a week-long workshop undertaken in February 2008 at the Colonial War Memorial (CWM) Hospital (see Appendix 1) and also by one of the three paediatricians assisting with the study.

The nurse used a stethoscope to auscultate the child’s heart, with the child sitting upright at a 45-degree angle with the chest exposed. The nurse then listened to the heart in five places: apex (for mitral valve), axilla (for mitral valve), left lower sternal edge (for tricuspid valve/ventricular septal defect), left upper sternal edge (for pulmonary valve) and right upper sternal edge (for aortic valve). The nurses were instructed to identify the S1 and S2 sounds, and time the cardiac cycle. They were also asked to identify any extra sounds and categorise them as soft, intermediate or loud (Figure 4.3). Each participant was auscultated by only one of the nurses, and the nurses’ results were pooled for analysis.
Listen to the heart in 5 places with child sitting at 45°

Identify S1 and S2

Added sounds

Loud, intermediate or soft

Is it loudest at the apex?

Innocent murmur—

EXIT

Loud or intermediate

REFER

Yes or unsure

REFER

EXIT

Figure 4.3: Fiji Nurse RHD Auscultation Module
Auscultation was performed by one of three paediatrician auscultators who were experienced in auscultation. The children were examined sitting at 45 degrees in a quiet room, using the diaphragm and bell of the stethoscope at the apex, axilla, left lower sternal edge, left upper sternal edge, right upper sternal edge and back. The praecordium was palpated for thrills and heaves, and dynamic manoeuvres were conducted as necessary. The paediatrician was asked to categorise the nature of the murmur, if present, as ‘systolic’, ‘diastolic’, ‘thril’ or ‘other’, and provide a diagnosis of ‘pathological’ or ‘suspicious’. It the murmur was termed ‘pathological’, the paediatrician was asked to record whether it was ‘mitral regurgitation’, ‘mitral stenosis’, ‘aortic regurgitation’ ‘atrial septal defect’, ‘ventricular septal defect’ or ‘other’.

The nurses and paediatricians auscultated each child independently, and completed a data collection form with their diagnosis, which was returned to the study coordinator. They were blinded to each other’s interpretation in the field.

4.5.2 Analysis

The primary outcome measure was expressed as a prevalence figure. RHD prevalence is routinely expressed per 1,000 in the population of interest. The prevalence figures were calculated with binomial 95% CIs. Categories of regurgitant jet lengths were calculated (< 1 cm; 1 cm–< 1.5 cm; 1.5 cm–< 2 cm; ≥ 2 cm for mitral valve regurgitation, and < 1 cm or ≥ 1 cm for aortic valve regurgitation). The other echocardiography data were presented descriptively. Odds ratios (ORs) were calculated when analysing demographic associations with RHD. Univariate and
multivariate regression analyses were undertaken to determine risk associations comparing gender, ethnicity, school location and age. Sensitivity and specificity were calculated for the nurse auscultation component of the study when compared with echocardiography, and kappa values were calculated when comparing the auscultation results between the paediatrician and the nurses. All data were entered into Epidata version 3.1 (Denmark) electronic databases, and exported into STATA 12 (STATA Corp, Texas, US 2012) for analysis.

4.5.3 Ethical Approval

This study was approved by the Fiji Human Research Ethics Review Committee, the Fiji National Health Research Committee, the QIMR Human Ethics Review Committee, and the Human Research Ethics Committee of the NT Department of Health and Community Services and Menzies School of Health Research. Approval to undertake the fieldwork in primary schools was granted by the Fiji Ministry of Education.

4.6 Results

4.6.1 Enrolment

A total of 1,834 children consented to participate, and were subsequently enrolled in this study. Of these, 1,666 had an echocardiography examination completed, while 168 cases were not available for follow-up after enrolment and had no study procedure recorded. The study team attempted to follow-up these children; however,
this was not possible in the majority of cases. Of these 1,666 children, 1,525 had an auscultation examination by both a nurse and a paediatrician (Table 4.4).

Table 4.4: Total Number of Children Screened by School

<table>
<thead>
<tr>
<th>School location</th>
<th>Eligible at each school</th>
<th>Enrolled (% of eligible)</th>
<th>Screened by echocardiography (% of enrolled)</th>
<th>Auscultation by nurse and paediatrician, plus echocardiography (% of screened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban A</td>
<td>326</td>
<td>242</td>
<td>239</td>
<td>236</td>
</tr>
<tr>
<td>B</td>
<td>440</td>
<td>355</td>
<td>323</td>
<td>323</td>
</tr>
<tr>
<td>C</td>
<td>210</td>
<td>183</td>
<td>165</td>
<td>163</td>
</tr>
<tr>
<td>Total urban</td>
<td>976</td>
<td>780</td>
<td>727</td>
<td>722</td>
</tr>
<tr>
<td>Rural D</td>
<td>273</td>
<td>217</td>
<td>211</td>
<td>133</td>
</tr>
<tr>
<td>E</td>
<td>279</td>
<td>218</td>
<td>206</td>
<td>202</td>
</tr>
<tr>
<td>F</td>
<td>182</td>
<td>137</td>
<td>124</td>
<td>119</td>
</tr>
<tr>
<td>G</td>
<td>210</td>
<td>175</td>
<td>105</td>
<td>103</td>
</tr>
<tr>
<td>H</td>
<td>152</td>
<td>135</td>
<td>133</td>
<td>96</td>
</tr>
<tr>
<td>I</td>
<td>60</td>
<td>46</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>J</td>
<td>165</td>
<td>126</td>
<td>118</td>
<td>113</td>
</tr>
<tr>
<td>Total rural</td>
<td>1,321</td>
<td>1,054</td>
<td>939</td>
<td>803</td>
</tr>
<tr>
<td>Total</td>
<td>2,297</td>
<td>1,834 (80%)</td>
<td>1,666 (91%)</td>
<td>1,525 (91%)</td>
</tr>
</tbody>
</table>

4.6.2 Demographic Details of Echocardiography Cohort

Table 4.5 presents the demographic breakdown of the cohort. Of note is that Indigenous Fijian children comprised 66.5% of the cohort (compared to the intended 58.6%), and 56.4% attended a school in a rural setting (compared to the intended 37.5%). The median age of the sample was 9.9 years (interquartile [IQ] range 7.9 to 12.2 years).
Table 4.5: Demographic Details of Cohort

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>841 (50.5)</td>
</tr>
<tr>
<td>Female</td>
<td>825 (49.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous Fijian</td>
<td>1,108 (66.5)</td>
</tr>
<tr>
<td>Indo-Fijian</td>
<td>543 (32.6)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (0.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>939 (56.4)</td>
</tr>
<tr>
<td>Urban</td>
<td>727 (43.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–8</td>
<td>433 (26.0)</td>
</tr>
<tr>
<td>9–11</td>
<td>622 (37.3)</td>
</tr>
<tr>
<td>12–15</td>
<td>611 (36.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Range</th>
<th>Weight (kg)</th>
<th>33.5 (IQ range: 11.0–91.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>138.5</td>
<td>99.8–179.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>16.3</td>
<td>8.7–31.6</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index

4.6.3 Prevalence of RHD on Echocardiogram

There were 12 cases of definite RHD identified on echocardiogram, giving a prevalence of 7.2 cases per 1,000 (95% CI 3.7–12.5). An additional 47 cases of probable RHD were identified, giving a prevalence of 28.2 cases per 1,000 (95% CI 20.8–37.3). The overall prevalence (definite plus probable RHD) was 35.4 per 1,000 (95% CI 27.1–45.4). The median age of children with definite RHD was 9.9 years (IQ range 7.5–12.1 years), the median age of probable cases was 9.8 years (IQ range 7.9–11.9 years), and 54.2% were female. All cases identified with definite RHD were of Fijian ethnicity, as were 59.5% of the probable RHD cases.

Table 4.6 presents the echocardiographic features of children identified with definite RHD. One of the definite cases was a known case of RHD (case number three in Table 4.6). Of the 47 probable cases, 44 cases had morphological changes of the
mitral valve, but no significant mitral regurgitation, and three had significant aortic regurgitation, but no morphological changes of the mitral valve.
## Table 4.6: Echocardiographic Features of Cases of Definite RHD Identified with NIH/WHO Criteria

<table>
<thead>
<tr>
<th>Case number</th>
<th>Morphological change of mitral valve</th>
<th>Mitral valve regurgitation</th>
<th>Mitral stenosis</th>
<th>Aortic valve regurgitation</th>
<th>Diagnostic features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PLAX</td>
<td>Apical Velocity (m/second)</td>
<td>PLAX</td>
<td>Apical Velocity (m/second)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jet length (cm)</td>
<td>length (cm)</td>
<td>Mean pressure (mmHg)</td>
<td>Jet length (cm)</td>
</tr>
<tr>
<td>1</td>
<td>Thickened AMVL, elbow deformity of AMVL</td>
<td>3.06</td>
<td>3.56</td>
<td>4.5</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Thickened AMVL, elbow deformity of AMVL</td>
<td>2.13</td>
<td>3.26</td>
<td>3.79</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Thickened AMVL, elbow deformity of AMVL, Thickened PMVL</td>
<td>3.62</td>
<td>4.71</td>
<td>3.99</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Tethered and thickened PMVL</td>
<td>0.94</td>
<td>-</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Thickened AMVL, elbow deformity of AMVL, tethered AMVL</td>
<td>2.84</td>
<td>2.54</td>
<td>3.37</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Elbow deformity of AMVL, tethered PMVL</td>
<td>2.8</td>
<td>2.4</td>
<td>4.6</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Thickened AMVL, elbow deformity of AMVL</td>
<td>2.22</td>
<td>2.08</td>
<td>4.64</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Thickened AMVL, elbow deformity of AMVL</td>
<td>2.64</td>
<td>3.19</td>
<td>4.42</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Thickened AMVL, shortening of chordae</td>
<td>2.04</td>
<td>2.01</td>
<td>3.83</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Thickened AMVL, PMVL prolapse</td>
<td>2.35</td>
<td>4.6</td>
<td></td>
<td>2 high velocity</td>
</tr>
<tr>
<td>11</td>
<td>Elbow deformity of AMVL, tethered PMVL</td>
<td>3.02</td>
<td>3.11</td>
<td></td>
<td>high velocity</td>
</tr>
<tr>
<td>12</td>
<td>Thickened AMVL/prolapse AMVL</td>
<td>2.56</td>
<td>2.7</td>
<td></td>
<td>high velocity</td>
</tr>
</tbody>
</table>

Note: a reported as severe mitral stenosis by cardiologist; b reported as moderate mitral stenosis by cardiologist; c reported by cardiologist as high velocity, pansystolic jet; MR = mitral regurgitation; AR = aortic regurgitation; MS = mitral stenosis; PLAX = parasternal long axis; AMVL = anterior mitral valve leaflet; PMVL = posterior mitral valve leaflet; m/second = metres per second
4.6.4 Factors Associated with RHD

Table 4.7 presents the demographic data and tests of association of gender, ethnicity and location of school with definite and probable RHD. Definite RHD was more common in females than males (OR 5.1, 95% CI 1.1–48.3), in Indigenous Fijian children (all cases identified with definite RHD were of Indigenous Fijian ethnicity) and in children who attended a school in a rural location (OR 2.3, 95% CI 0.6–13.50). These differences in distribution were not observed for cases of probable RHD. Notably, there were more males than females identified as probable cases, although the OR was not statistically significant, while probable RHD was associated with urban, rather than rural, school attendance (OR 0.5, 95% CI 0.2–0.9).

A multivariate analysis using a logistic regression model that included all four covariates (ethnicity, gender, age and school location) found a similarly strong association of definite RHD with female gender, but no association could be tested with ethnicity, as all cases were found in Indigenous Fijians (Table 4.8). For definite RHD, the distribution of cases was almost equal (OR 1.1, 95% CI 0.3–4.1) between rural and urban locations when only Indigenous Fijians were analysed.
Table 4.7: Univariate Associations with RHD Cases Identified with NIH/WHO Criteria

<table>
<thead>
<tr>
<th>Factor</th>
<th>RHD cases</th>
<th>Total number</th>
<th>Prevalence of cases per 1,000 (95% CI)</th>
<th>Odd ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite RHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>825</td>
<td>12.1 per 1,000 (5.8–22.2)</td>
<td>5.1 (1.1–48.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>841</td>
<td>2.4 per 1,000 (2.9–8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fijian</td>
<td>12</td>
<td>1,110</td>
<td>10.8 per 1,000 (5.6–18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indo-Fijian/other</td>
<td>0</td>
<td>556</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>9</td>
<td>939</td>
<td>9.6 per 1,000 (4.4–18.1)</td>
<td>2.3 (0.6–13.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Urban</td>
<td>3</td>
<td>727</td>
<td>4.1 per 1,000 (0.9–12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9 years</td>
<td>6</td>
<td>838</td>
<td>7.1 per 1,000 (2.6–15.5)</td>
<td>1.0 (0.3–3.8)</td>
<td>0.98</td>
</tr>
<tr>
<td>≥10–15 years</td>
<td>6</td>
<td>828</td>
<td>7.2 per 1,000 (2.7–15.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Probable RHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>826</td>
<td>26.6 per 1,000 (16.7–40)</td>
<td>0.9 (0.5–1.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>840</td>
<td>29.8 per 1,000 (19.4–43.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fijian</td>
<td>29</td>
<td>1,110</td>
<td>26.1 per 1,000 (18.2–35.3)</td>
<td>0.7 (0.4–1.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Indo-Fijian/other</td>
<td>18</td>
<td>556</td>
<td>32.5 per 1,000 (19.3–50.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>18</td>
<td>939</td>
<td>19.2 per 1,000 (11.4–30.1)</td>
<td>0.5 (0.2–0.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urban</td>
<td>29</td>
<td>727</td>
<td>39.9 per 1,000 (26.9–56.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9 years</td>
<td>23</td>
<td>838</td>
<td>27.5 per 1,000 (17.5–40.9)</td>
<td>1.0 (0.5–1.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>≥10–15 years</td>
<td>24</td>
<td>828</td>
<td>30 per 1,000 (18.7–42.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Definite plus probable RHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>825</td>
<td>38.8 per 1,000 (26.7–54.3)</td>
<td>1.2 (0.7–2.1)</td>
<td>0.47</td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>841</td>
<td>32.1 per 1,000 (21.3–46.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fijian</td>
<td>40</td>
<td>1,110</td>
<td>36 per 1,000 (25.9–48.8)</td>
<td>1.1 (0.6–2.0)</td>
<td>0.85</td>
</tr>
<tr>
<td>Indo-Fijian/other</td>
<td>19</td>
<td>556</td>
<td>34.2 per 1,000 (20.7–52.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>32</td>
<td>939</td>
<td>34.1 per 1,000 (23.4–47.8)</td>
<td>1.2 (0.7–2.1)</td>
<td>0.47</td>
</tr>
<tr>
<td>Urban</td>
<td>27</td>
<td>727</td>
<td>37.1 per 1,000 (24.6–53.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9 years</td>
<td>31</td>
<td>838</td>
<td>37.0 per 1,000 (25.3–52.1)</td>
<td>0.9 (0.5–1.6)</td>
<td>0.73</td>
</tr>
<tr>
<td>≥10–15 years</td>
<td>28</td>
<td>828</td>
<td>33.8 per 1,000 (22.6–48.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.8: Multivariable Analysis for Risk Factors of RHD (NIH/WHO)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odd ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite RHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female: Male)</td>
<td>4.8 (1.5–22.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ethnicity (Fijian: Indo-Fijian)</td>
<td>na*</td>
<td>na</td>
</tr>
<tr>
<td>Location of school (Rural: Urban)</td>
<td>1.1 (0.3–4.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>Age (5–&lt; 9 years: 9–&lt; 15 years)</td>
<td>1 (0.3–3.2)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Probable RHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female: Male)</td>
<td>0.9 (0.5–1.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>Ethnicity (Fijian: Indo-Fijian)</td>
<td>1.1 (0.5–2.0)</td>
<td>0.88</td>
</tr>
<tr>
<td>Location of school (Rural: Urban)</td>
<td>0.5 (0.2–0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (5–&lt; 9 years: 9–&lt; 15 years)</td>
<td>0.9 (0.5–1.6)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Definite + probable RHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female: Male)</td>
<td>1.2 (0.7–2.1)</td>
<td>0.46</td>
</tr>
<tr>
<td>Ethnicity (Fijian: Indo-Fijian)</td>
<td>1.4 (0.7–2.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>Location of school (Rural: Urban)</td>
<td>0.6 (0.3–0.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Age (5–&lt; 9 years, 9–&lt; 15 years)</td>
<td>0.9 (0.5–1.6)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Note: *all definite cases identified were of Indigenous Fijian ethnicity

4.6.5 Examination of RHD Echocardiography Results Using Inferred WHF Criteria

By applying the inferred WHF RHD echocardiography criteria, 14 cases of definite RHD and 18 cases of borderline RHD were identified, giving a prevalence of definite RHD of 8.4 cases per 1,000 (95% CI 4.6–14.1) and a prevalence of borderline RHD of 10.8 cases per 1,000 (95% CI 6.4–17.0). The combined prevalence of definite and borderline cases using the inferred WHF criteria was 18.6 cases per 1,000 (95% CI 6.0–16.3), with 62.5% of all cases identified as female. Of the definite cases, 71% were female and 85.7% were of Fijian ethnicity. Of the borderline cases, 55.4% were female and 47.1% were of Fijian ethnicity. The median age of children with definite RHD was 9.4 years (IQ range 7.9–11.7 years) and the median age of borderline cases was 9.8 years (IQ range 8.2–11.6 years).
All 12 cases of definite RHD using the NIH/WHO criteria were also identified as definite RHD using the inferred WHF criteria. An additional two cases identified as probable RHD using the NIH/WHO criteria were identified as definite RHD cases using the inferred WHF criteria (Table 4.9). These cases had pathological changes to the mitral valve and mitral regurgitation of high velocity and greater than 2 cm in one view.

### Table 4.9: Echocardiographic Features of Additional Cases of Definite RHD Identified using Inferred WHF Criteria

<table>
<thead>
<tr>
<th>Case number</th>
<th>Morphological change of mitral valve</th>
<th>Mitral valve regurgitation</th>
<th>Aortic valve regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PLAX Jet length (cm)</td>
<td>Apical Jet length (cm)</td>
</tr>
<tr>
<td>Case 1</td>
<td>Elongation of AMVL chordae, excessive motion, tethered PMVL</td>
<td>1.94 cm</td>
<td>2.05 cm</td>
</tr>
<tr>
<td>Case 2</td>
<td>Thickened AMVL, tethered PMVL</td>
<td>2.10 cm</td>
<td>1.50 cm</td>
</tr>
</tbody>
</table>

Note: \* high velocity, pan systolic jet reported by cardiologist; PLAX = parasternal long axis, AMVL = anterior mitral valve leaflet; PMVL = posterior mitral valve leaflet; m/second = metres per second

There were 18 cases classified as borderline RHD using the inferred WHF criteria, and all these cases were included as probable RHD cases by the NIH/WHO criteria, meaning that the NIH/WHO criteria identified an additional 27 cases. The WHF borderline cases were classified as Borderline A (n = 16) and Borderline C (n = 2) (refer to Table 4.3 for classification definitions). Table 4.10 presents the demographic data and risk associations for the definite and borderline cases identified using the inferred WHF criteria. Using univariate analysis, the female children identified had a higher risk of having definite RHD than did the male children (OR 2.6, 95% CI 0.7–11.2). Similar to the findings using the NIH/WHO
criteria, Indigenous Fijian children identified using the inferred WHF criteria had a higher risk than did the Indo-Fijian children (OR 3.1, 95% CI 0.7–27.9). The association with female gender, rural school location and Indigenous Fijian ethnicity were similar using the inferred WHF criteria to those found when using the NIH/WHO criteria (Tables 4.7 and 4.10). A multivariate analysis was undertaken using a logistic regression module that included all four covariates; however, the results showed similar findings to the univariate analysis (Table 4.11).
### Table 4.10: Univariate Associations with RHD Cases Identified using WHF Criteria

#### Definite RHD

<table>
<thead>
<tr>
<th>Factor</th>
<th>RHD cases</th>
<th>Total number</th>
<th>Prevalence of cases per 1,000 (95% CI)</th>
<th>Odd ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>825</td>
<td>12.1 (5.8–22.2)</td>
<td>2.6 (0.7-11.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td>841</td>
<td>4.8 (1.3–12.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Ethnicity       |           |              |                                        |                   |        |
| Fijian          | 12        | 1,110        | 10.8 (5.6–18.8)                        | 3.1 (0.7 - 27.9)  | 0.13   |
| Indo-Fijian/other | 2       | 556          | 3.6 (0.4–12.9)                         |                   |        |

| Location of school |          |              |                                        |                   |        |
| Rural            | 10        | 939          | 10.6 (5.2–19.5)                        | 1.9 (0.6-8.5)     | 0.25   |
| Urban            | 4         | 727          | 5.5 (1.5–14)                           |                   |        |

| Age              |          |              |                                        |                   |        |
| 5–9 years        | 8         | 838          | 9.5 (4.1–18.7)                         | 0.8 (0.2–2.5)     | 0.61   |
| ≥ 10–15 years    | 6         | 828          | 7.2 (2.7–15.7)                         |                   |        |

#### Borderline RHD

| Gender          |          |              |                                        |                   |        |
| Female          | 10        | 826          | 12.1 (5.8–22.2)                        | 1.3 (0.5–3.7)     | 0.61   |
| Male            | 8         | 840          | 9.5 (4.1–18.7)                         |                   |        |

| Ethnicity       |          |              |                                        |                   |        |
| Fijian          | 8         | 1,110        | 9.7 (3.1–14.2)                         | 0.4 (0.1-1.1)     | 0.04   |
| Indo-Fijian/other | 10      | 556          | 17.9 (8.7–32.8)                        |                   |        |

| Location of school |          |              |                                        |                   |        |
| Rural            | 4         | 939          | 4.3 (1.2–10.9)                         | 0.3 (0.1–0.7)     | 0.01   |
| Urban            | 14        | 727          | 19.3 (10.6–32.1)                       |                   |        |

| Age              |          |              |                                        |                   |        |
| 5–9 years        | 11        | 838          | 13.1 (6.6–23.4)                        | 0.6 (0.2–0.8)     | 0.36   |
| ≥ 10–15 years    | 7         | 828          | 8.4 (3.4–17.3)                         |                   |        |

#### Definite + borderline RHD

| Gender          |          |              |                                        |                   |        |
| Female          | 20        | 826          | 24.2 (14.9–37.1)                       | 1.7 (0.8–3.9)     | 0.13   |
| Male            | 12        | 840          | 14.3 (7.4–24.8)                        |                   |        |

| Ethnicity       |          |              |                                        |                   |        |
| Fijian          | 20        | 1,110        | 18.0 (11–27.7)                         | 0.8 (0.4–1.8)     | 0.62   |
| Indo-Fijian/other | 12      | 556          | 21.6 (11.2–37.4)                       |                   |        |

| Location of school |          |              |                                        |                   |        |
| Rural            | 14        | 939          | 4.3 (8.2–24.9)                         | 0.6 (0.3–1.3)     | 0.15   |
| Urban            | 18        | 727          | 24.8 (14.7–38.8)                       |                   |        |

| Age              |          |              |                                        |                   |        |
| 5–9 years        | 13        | 838          | 15.5 (8.3–26.4)                        | 0.7 (0.3–1.5)     | 0.3    |
| ≥ 10–15 years    | 19        | 828          | 22.9 (13.9–35.6)                       |                   |        |
Table 4.11: Multivariate Association of Risk Factors for RHD (Inferred WHF Criteria)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odd ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite RHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female: Male)</td>
<td>2.4 (0.8–7.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Ethnicity (Fijian: Indo-Fijian)</td>
<td>2.5 (0.5–12.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Location of school (Rural: Urban)</td>
<td>1.4 (0.4–4.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Age (5–&lt; 9 years: 9–&lt; 15 years)</td>
<td>0.8 (0.3–2.2)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Borderline RHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female: Male)</td>
<td>1.5 (0.6–4.0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Ethnicity (Fijian: Indo-Fijian)</td>
<td>0.8 (0.3–2.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Location of school (Rural: Urban)</td>
<td>0.3 (0.1–0.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Age (5–&lt; 9 years: 9–&lt; 15 years)</td>
<td>0.6 (0.1–0.9)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Definite + borderline RHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female: Male)</td>
<td>1.9 (0.9–3.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Ethnicity (Fijian: Indo-Fijian)</td>
<td>1.1 (0.5–2.6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Location of school (Rural: Urban)</td>
<td>0.6 (0.3–1.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Age (5–&lt; 9 years: 9–&lt; 15 years)</td>
<td>0.7 (0.3–1.4)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

4.6.6 CHD

There were 31 confirmed cases of CHD, most of them not serious (Table 4.12). The prevalence of all CHD was 18.6 per 1,000 (95% CI 12.7–27.3) for all cases detected, and 6.6 per 1,000 (95% CI 3.3–11.8) for more severe cases (atrial septal defect, ventricular septal defect, atrioventricular canal defect, cleft anterior mitral valve, patent ductus arteriosus, left ventricular outflow tract obstruction and atrial tumour). Two of the children detected on screening with CHD were previously known to have disease.
Table 4.12: Total Number of Cases Diagnosed with CHD

<table>
<thead>
<tr>
<th>Congenital defect</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve prolapse</td>
<td>7</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>5</td>
</tr>
<tr>
<td>Dilated coronary sinus</td>
<td>4</td>
</tr>
<tr>
<td>Atrioventricular canal defect</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Dilated aortic root</td>
<td>2</td>
</tr>
<tr>
<td>Cleft anterior mitral valve</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal mitral valve chordal attachment</td>
<td>2</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1</td>
</tr>
<tr>
<td>Atrial tumour plus sub-aortic membrane and distillation of non-coronary cusp</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular outflow tract obstruction secondary to fibro muscular shelf</td>
<td>1</td>
</tr>
<tr>
<td>Total CHD</td>
<td>31</td>
</tr>
</tbody>
</table>

4.6.7 All Echocardiographic Findings

The most common finding detected was mitral regurgitation, with 37% of all participants having some degree of mitral regurgitation in at least one view.

However, only 4.3% and 2.0% had a jet measurement greater than or equal to 1.5 cm and 2 cm, respectively, in one view (Table 4.13).

Table 4.13: Mitral Regurgitation

<table>
<thead>
<tr>
<th>Jet length</th>
<th>PLAX</th>
<th>APICAL</th>
<th>Two views</th>
<th>One view only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivial (≤ 0.99 cm)</td>
<td>141 (8.5)</td>
<td>143 (8.6)</td>
<td>47 (2.8)</td>
<td>237 (14.2)</td>
</tr>
<tr>
<td>≥ 1 cm–≤ 1.49 cm</td>
<td>98 (5.9)</td>
<td>101 (6.1)</td>
<td>24 (1.5)</td>
<td>175 (10.5)</td>
</tr>
<tr>
<td>≥ 1.5 cm–≤ 1.99 cm</td>
<td>36 (2.2)</td>
<td>48 (2.9)</td>
<td>12 (0.7)</td>
<td>72 (4.3)</td>
</tr>
<tr>
<td>≥ 2 cm</td>
<td>30 (1.8)</td>
<td>22 (1.3)</td>
<td>18 (1.1)</td>
<td>34 (2.0)</td>
</tr>
<tr>
<td>≥ 2 cm plus full envelope</td>
<td>11 (0.7)</td>
<td>11 (0.7)</td>
<td>11 (0.7)</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>

Note: PLAX = parasternal long axis

There were 65 cases in which morphological changes of the mitral valve were seen. Of these, 25 children (0.3%) had more than one abnormality of the mitral valve recorded (Table 4.14).
Table 4.14: Morphological Changes of Mitral Valve

<table>
<thead>
<tr>
<th>Morphological change</th>
<th>Any view</th>
<th>PLAX</th>
<th>PSAX</th>
<th>APICAL</th>
<th>Two views</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any view</td>
<td>52 (3.1)</td>
<td>46 (2.7)</td>
<td>10 (0.6)</td>
<td>15 (0.9)</td>
<td>16 (1.0)</td>
</tr>
<tr>
<td>Thickening anterior mitral valve leaflet</td>
<td>11 (0.7)</td>
<td>9 (0.5)</td>
<td>5 (0.3)</td>
<td>4 (0.2)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Thickening posterior mitral valve leaflet</td>
<td>11 (0.7)</td>
<td>9 (0.5)</td>
<td>5 (0.3)</td>
<td>4 (0.2)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Elbow deformity anterior mitral valve leaflet</td>
<td>14 (0.9)</td>
<td>10 (0.6)</td>
<td>na</td>
<td>8 (0.5)</td>
<td>14 (0.9)</td>
</tr>
<tr>
<td>Tethering posterior mitral valve leaflet</td>
<td>18 (1.1)</td>
<td>14 (0.9)</td>
<td>6 (0.4)</td>
<td>6 (0.4)</td>
<td>6 (0.4)</td>
</tr>
<tr>
<td>Elongation of the chordae tendinae</td>
<td>11 (0.7)</td>
<td>2 (0.1)</td>
<td>na</td>
<td>11 (0.7)</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>

Note: PLAX = parasternal long axis view; PSAX = parasternal short axis view

Nine percent of the cohort had an aortic regurgitant jet seen in at least one view, and 2.7% had a jet that measured greater than or equal to 1 cm; however, only three children had aortic regurgitation greater than or equal to 1 cm and a full envelope seen. Of note, five of the cases with aortic regurgitation were found to have bicuspid aortic valves, and three had minor congenital defects (Tables 4.12 and 4.15).

Table 4.15: Aortic Regurgitation

<table>
<thead>
<tr>
<th>Jet length</th>
<th>PLAX</th>
<th>APICAL</th>
<th>Two views</th>
<th>Any view</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.5 cm and full envelope</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>≥ 1 cm and full envelope</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>≥ 1 cm</td>
<td>35 (2.1)</td>
<td>20 (1.2)</td>
<td>45 (2.7)</td>
<td></td>
</tr>
<tr>
<td>≥ 0.5–≤ 0.99 cm</td>
<td>18 (1.1)</td>
<td>8 (0.5)</td>
<td>87 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Trivial (≤ 0.49 cm)</td>
<td>4 (0.2)</td>
<td>2 (0.1)</td>
<td>17 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

Note: PLAX = parasternal long axis

4.6.8 Findings on Auscultation

Of the 1,525 children auscultated, 435 (28.5%) were found to have a murmur heard by a paediatrician. Of these, 42 (2.8%) were considered pathological, and five (0.3%) had pathology on echocardiography (three RHD and two congenital defects). Of the
136 (25.9%) suspicious murmurs diagnosed by a paediatrician, 10 (2.9%) had pathology on echocardiography (four RHD and six congenital defects) (Table 4.16).

### Table 4.16: Auscultation Findings by a Paediatrician

<table>
<thead>
<tr>
<th>Type of murmur</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No murmur</td>
<td>1,090 (71.5)</td>
</tr>
<tr>
<td>Any murmur</td>
<td>435 (28.5)</td>
</tr>
<tr>
<td>Pathological murmur</td>
<td>42 (2.8)</td>
</tr>
<tr>
<td>Suspicious murmur</td>
<td>136 (25.9)</td>
</tr>
<tr>
<td>Murmur identified as RHD</td>
<td>21 (1.4)</td>
</tr>
<tr>
<td>Murmur identified as CHD</td>
<td>21 (1.4)</td>
</tr>
</tbody>
</table>

The cohort of 1,525 children who had both echocardiography examination and auscultation by a paediatrician contained 56 of the 59 ‘definite’ and ‘probable’ RHD cases identified using the NIH/WHO criteria in the echocardiography cohort, 10 of the cases identified as definite RHD, and 46 of the cases identified as probable RHD using the NIH/WHO criteria. Sensitivity and specificity by murmur classification compared to echocardiography diagnosis is presented in Table 4.17.
Table 4.17: Correlation between Paediatrician Auscultation and Echocardiography

<table>
<thead>
<tr>
<th>Any murmur detected by a paediatrician</th>
<th>Definite and probable RHD</th>
<th>Not RHD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>17</td>
<td>418</td>
<td>435</td>
</tr>
<tr>
<td>Negative</td>
<td>39</td>
<td>1,051</td>
<td>1,090</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>1,469</td>
<td>1,525</td>
</tr>
</tbody>
</table>

% 95% CI

Sensitivity 30.4 18.8–44.1
Specificity 71.5 69.2–78.3

Echocardiography screening

<table>
<thead>
<tr>
<th>Suspicious or pathological murmur detected by paediatrician</th>
<th>Definite and probable RHD</th>
<th>Not RHD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>7</td>
<td>169</td>
<td>176</td>
</tr>
<tr>
<td>Negative</td>
<td>49</td>
<td>1,300</td>
<td>1,349</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>1,469</td>
<td>1,525</td>
</tr>
</tbody>
</table>

% 95% CI

Sensitivity 12.5 5.2–24.1
Specificity 88.5 86.8–90.1

Echocardiography screening

<table>
<thead>
<tr>
<th>Pathological murmur detected by paediatrician</th>
<th>Definite and probable RHD</th>
<th>Not RHD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>3</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>1,476</td>
<td>1,483</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>1,515</td>
<td>1,525</td>
</tr>
</tbody>
</table>

% 95% CI

Sensitivity 30 6.7–65.2 6.7–65.2
Specificity 97.4 96.5–98.2 96.5–98.2

4.6.9 Nurse Auscultation Results

A total of 19 nurses attended and completed the week-long auscultation training workshop. The median number of children auscultated per nurse was 90 (range 32 to 146 children auscultated). The nurses’ results were pooled for analysis. The nurses identified 254 (16.7%) children with a murmur; of these, they determined that 215 were suspicious and 39 were innocent. When a comparison was made of the nurses’ auscultation results for the presence of any murmur with the echocardiography
results, sensitivity was 30.4% and specificity was 83.8%, which was comparable to the paediatrician auscultation for any murmur. Comparison of suspicious murmur showed similar sensitivity and specificity to the results for any murmur (Table 4.18). Inter-rater correlation between paediatrician and nurse auscultation was poor for both the detection of any murmur and of a suspicious and/or pathological murmur (Table 4.19).

Table 4.18: Sensitivity and Specificity of all RHD Diagnosed by Echocardiography and Nurse Auscultation

<table>
<thead>
<tr>
<th>Any murmur detected by nurse</th>
<th>Echocardiography screening</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any murmur detected by nurse</td>
<td>Echocardiography screening</td>
<td>RHD</td>
<td>Not RHD</td>
<td>Total</td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
<td>237</td>
<td>254</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>39</td>
<td>1,232</td>
<td>1,271</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>1,469</td>
<td>1,525</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>30.4%</td>
<td>18.8–44.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>83.8%</td>
<td>81.8–85.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suspicious murmur detected by nurse</th>
<th>Echocardiography screening</th>
<th>RHD</th>
<th>Not RHD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>15</td>
<td>200</td>
<td>215</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>41</td>
<td>1,269</td>
<td>1,310</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>1,469</td>
<td>1,525</td>
<td></td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>26.8%</td>
<td>15.8–40.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>86.4%</td>
<td>84.5–88.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.19: Agreement between Nurse and Paediatrician Auscultation

<table>
<thead>
<tr>
<th>Any murmur detected by nurse</th>
<th>Any murmur detected by paediatrician</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Murmur</td>
<td>No murmur</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any murmur detected by nurse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>Negative</td>
<td>308</td>
<td>963</td>
</tr>
<tr>
<td>Total</td>
<td>435</td>
<td>1,090</td>
</tr>
<tr>
<td>Agreement</td>
<td>74%</td>
<td>Kappa</td>
</tr>
<tr>
<td></td>
<td>0.2009</td>
<td>0.0242</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suspicious murmur detected by nurse</th>
<th>Murmur</th>
<th>No murmur</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>56</td>
<td>159</td>
<td>215</td>
</tr>
<tr>
<td>Negative</td>
<td>121</td>
<td>1,189</td>
<td>1,310</td>
</tr>
<tr>
<td>Total</td>
<td>177</td>
<td>1,348</td>
<td>1,525</td>
</tr>
<tr>
<td>Agreement</td>
<td>35%</td>
<td>Kappa</td>
<td>SE</td>
</tr>
<tr>
<td></td>
<td>0.0275</td>
<td>0.030</td>
<td></td>
</tr>
</tbody>
</table>

Note: SE = standard error

4.7 Discussion

4.7.1 RHD Prevalence

This study found a higher prevalence of RHD in Fijian school children when using echocardiography as the diagnostic tool, compared to the researchers’ previous study in which only children with suspicious heart murmurs underwent echocardiography.

This study found 35.4 cases per 1,000 (95% CI 27.1–45.4) of definite plus probable RHD, compared to a prevalence of 8.4 cases per 1,000 (95% CI 5.6–12) in the 2006 Fiji GrASP study.(16) Both studies used the NIH/WHO criteria for echocardiographic confirmation of RHD. The prevalence of definite RHD in this study, using the same criteria, was higher than found in the 2006 study (7.6 and 4.1 per 1,000, respectively). However, there was a considerable increase in the prevalence of probable RHD detected in this study: 28.2 cases per 1,000 (95% CI 20.8–37.3), compared to 4.3 cases per 1,000 (95% CI 2.4–7.1) in the earlier study.
Another previous study in Fiji found a much higher prevalence; however, this study used different criteria and also included possible RHD. (38)

When using both the NIH/WHO and WHF criteria, there was a characteristic distribution of definite RHD in Indigenous female children and in children attending school in a rural location. This is consistent with previous published data. (16, 38) In contrast, there was a difference in the characteristics of the probable RHD cases identified, showing more males, more children of Indo-Fijian ethnicity and a predominance of children attending school in an urban location. It is unclear why there was a difference in the distribution of probable cases identified in this study, compared to previously seen trends. This may have been due to an issue with the diagnostic criteria used in this study.

The NIH/WHO criteria may be too sensitive and thus may have included cases that do not have true RHD pathology. If the 27 cases identified as probable by the NIH/WHO criteria are excluded, the 18 cases identified by both criteria as probable or borderline RHD showed slightly more males (10) than females (8). However, the distribution of cases showed a similar pattern to the definite RHD cases for other characteristics, with a predominance of children of Fijian ethnicity who attended school in a rural location. This suggests that the additional probable cases may not have RHD, as they were not identified as RHD cases by the inferred WHF criteria. Although the number of borderline cases identified using the inferred WHF criteria was significantly less than the number of probable cases identified using the NIH/WHO criteria, the WHF criteria may still potentially include some cases that are
normal in the borderline group, given the weaker risk associations than the definite cases.

The significance of morphological changes seen in the probable and borderline classifications is not fully understood. In a recent study undertaken in New Zealand, there was an increase in the number of probable and possible RHD cases reported in a high-risk population compared to a low-risk population. There were no definite or probable cases seen in a low-risk population cohort of 396 children screened, compared with eight and 19 cases of definite and probable RHD, respectively, in a population of 1,142 screened in a high-risk population. There were two cases of possible RHD in the low-risk group, giving a prevalence of 5.1 per 1,000 (95% CI 1.4–18.2) compared to 46 cases defined as probable or possible in the high-risk group (40.3 per 1,000; 95% CI 3.0–5.3), giving a risk ratio of 8.0 (95% CI 1.9–32.7).(152)

These data suggest that probable RHD may be part of the spectrum of true RHD; however, studies in other populations are needed to investigate this. Of the 47 probable RHD cases, 28 (96.6%) were categorised as ‘probable mitral valvular pathology due to RHD’ and exhibited one feature of abnormal morphology, plus or minus mitral regurgitation of less than 2 cm. One case (3.4%) had aortic valve regurgitation without evidence of morphological abnormality of the mitral valve. There has been much recent discussion in the published literature regarding the significance of subclinical disease and potential for over-diagnosis.(73, 77, 81, 153)
The NIH/WHO criteria used case definitions for echocardiography diagnosis that were based on consensus opinion by experts. However, in 2005, there were less available published data and less experience with the range of normal findings of echocardiography undertaken in children from high-prevalence RHD regions. Although this study was not designed for use with the 2012 WHF criteria, when it was attempted to apply these criteria, a discrepancy was found in the number of probable compared with borderline cases identified, suggesting a lack of specificity of the NIH/WHO probable case definition. The WHF criteria are less sensitive and more specific than the NIH/WHO criteria in identifying abnormal morphology (they require at least two features of abnormal mitral valve morphology). The majority of the additional probable cases identified by the NIH/WHO criteria did not exhibit these features and were identified as ‘Probable A’ cases (see Table 4.3) and were thus excluded as cases when the inferred WHF criteria was applied.

This study commenced in 2008 and strictly followed the NIH/WHO guidelines, and the data were reported in line with these criteria. It was considered that an additional exercise that might provide an interesting comparison was to analyse the reported data using the recently published WHF RHD echocardiography standardisation criteria. This additional analysis created questions about the discrepancy in the increased number of probable compared to borderline cases detected. However, the analysis relied on the data that were collected and reported according to the original study protocol, which did not focus with as much detail on some aspects of recording of pathology and morphology. This throws some doubt on the true validity of the results using the WHF criteria.
Although the sample size calculated to detect the presence of RHD on echocardiography was 1,900 children, only 1,666 children were included to have an echocardiography examination. Despite this, the data showed overwhelmingly that the echocardiography confirmed diagnosis of RHD was higher than previously estimated by studies that relied on a two-step process of auscultation plus echocardiography.

4.7.2 CHD

This study found a higher prevalence of CHD than previously identified in Fiji. All CHD identified on echocardiography was included, which resulted in a higher prevalence being detected in this study. The findings of 6.6 per 1,000 for CHD and 35.4 cases per 1,000 for definite and probable RHD correlate with results seen elsewhere, and substantiate the evidence that RHD is the most common cause of heart disease diagnosed in Fijian school-aged children.

The global incidence of CHD at birth is estimated to be between six cases per 1,000 to 75 cases per 1,000, based on whether only moderate to severe forms or all forms (including bicuspid aortic valves, tiny muscular ventricular septal defects and atrial septal defects) are included.(154) A number of recent studies have reported on findings of CHD in populations screened for RHD. Paar et al. found a prevalence of CHD of 13 per 1,000 in Nicaragua (1.3%), the majority of which were aortic valve abnormalities.(72) In a recent New Zealand RHD screening study, 26 cases per 1,000 of children (2.6%) were found to have non-rheumatic cardiac abnormalities, of which 0.96% of the total cohort had minor mitral valve abnormalities.(81)
A large echocardiography screening recently published from Uganda found a prevalence of 9.8 per 1,000 of CHD cases.(71) Screening undertaken in resource-poor settings for RHD frequently detects some previously undiagnosed, generally minor congenital lesions; however, the majority of more severe and symptomatic lesions will present at an earlier age if treatment and intervention is required. There is insufficient evidence to recommend screening for CHD.

4.7.3 Auscultation

The comparison between paediatrician auscultation and confirmed RHD cases on echocardiography showed a poor sensitivity. This may be due to the subjective nature of auscultation examination or because of poor auscultatory training and experience over the past two decades, as sophisticated diagnostic tools have become more available. Echocardiography has been proven to be more sensitive and specific than auscultation.(70-73, 75, 80, 81) Few echocardiographically confirmed cases in this study would have been detected by using auscultation alone, as paediatrician auscultation had a sensitivity of only 30%. Basic auscultation training was provided to nurses in this study, and the nurses’ results showed poor agreement with the paediatricians’ auscultation results, and poor sensitivity when compared to the echocardiography findings.

Although the sample size calculated to detect the presence of a pathological or suspicious murmur on auscultation was 1,900 children, only 1,525 children were included to have an auscultation examination performed by both a nurse and a
paediatrician. Despite this, the data showed overwhelmingly that auscultation performed poorly compared to echocardiographic diagnosis. Together with the body of published evidence now in existence, these data confirm that auscultation should now be considered obsolete as a screening tool for RHD. (16, 24, 38, 70, 81, 82)

4.7.4 Study Limitations

This study focused on a cohort of children attending primary schools. Undertaking school-based screening is the easiest way to screen a representative sample of children; however, it may have missed some of the sickest children who were unable to attend school due to illness or disability. Over the past decade, Fiji has experienced two coup d’états, overthrowing democratically led governments and affecting the standard of living and poverty ranking. Fiji has slipped from ninetieth to ninety-sixth position on the United Nations Development Index, while increasing poverty—particularly in rural areas—has been reported. (155, 156) Alongside this increasing poverty, recent reports show that school attendance has decreased and 15% of children do not complete primary school education. (150, 157) These children usually come from the poorest families, which potentially gives them an increased risk of RHD.

Another limitation of this study is that there was the potential for selection bias due to the loss of 168 participants who were enrolled, but did not have echocardiogram and auscultation completed, thereby excluding children who do not attend school. The above factors may have led to an underestimation of RHD prevalence in Fiji.
4.7.5 Management of Cases

Fiji has a RHD control and prevention programme, and all cases identified in this study have been referred for inclusion on the national RHD register and have had clinical review. Children that were identified as probable cases will undergo annual review to determine if their disease status has changed. To allow for this increased number of children requiring clinical review, additional RHD clinics must be organised, which places further pressure on the limited expert human resources and health system. In a resource-poor setting such as Fiji—which has an established high burden of disease and a national RHD control programme that has begun to develop capacity to undertake echocardiography screening—the importance of highly sensitive and highly specific RHD echocardiography diagnostic criteria has paramount importance. This is because of the clinical, human and resource implications that are involved in treating and managing large numbers of cases with uncertain diagnosis.

Extrapolation of the prevalence figure found using the NIH/WHO criteria to the national population aged five to 14 years in Fiji suggests that there may be approximately 543 children in this age group with definite RHD, and an additional 2,128 children with probable RHD. Using the prevalence figures calculated with the WHF criteria indicates that there may be approximately 619 children in this age group with definite RHD, and an additional 815 children with borderline RHD. The difference in extrapolated numbers, particularly of the probable compared to the borderline cases, further highlights the importance of having highly specific diagnostic criteria when diagnosing RHD in this population, with potential
identification of an additional 1,313 cases that would require clinical monitoring and management. The future use of the WHF criteria for diagnosis of RHD during echocardiography screening in Fiji may minimise the large numbers of probable/borderline cases identified that require monitoring; however, efforts to strengthen the Fiji RHD programme’s capacity to manage all RHD cases is required, particularly at the primary health level.

The Pacific region is a known to have high prevalence of RHD. A number of countries have developed RHD control programmes over the past five to seven years, and there is increasing interest from Ministries of Health to develop capacity within their public health programmes to undertake routine echocardiography screening of school children. The results of this study highlight the importance and need for highly sensitive and specific diagnostic criteria for echocardiography diagnosis of RHD in this region.

4.8 Conclusion

Echocardiography as a tool for diagnosis of and screening for RHD, in conjunction with standardised guidelines for diagnosis that allow high sensitivity and specificity, appear to have made auscultation obsolete. (71) However, many resource-poor countries in the Pacific region and elsewhere lack the funds and infrastructure to undertake echocardiographic screening. With the advances in portable echocardiography technology, and its increased affordability, echocardiography screening for RHD will become increasing feasible if a skilled workforce of echocardiography technicians can be developed.
This study’s results suggest that there are a significant number of children with previously undetected RHD in Fiji. It is potentially possible to undertake field screening in a resource-poor setting such as Fiji if highly sensitive and specific guidelines are accessible for clinicians to assist diagnosis. However, this must be undertaken within a dedicated control programme so that clinical management can be coordinated and so that a facility to review cases exists.
Chapter 5: Pilot Study of Nurse-led RHD

Echocardiography Screening in Fiji
5.1 Introduction

Identifying a feasible and appropriate model for conducting RHD screening as part of a public health programme in resource-poor areas is a challenge for health ministries in developing countries. Conducting routine screening to detect cases early in their disease process is recommended, but is difficult when the population may be located remotely from major centres, with limited resources and a lack of available skilled staff. In industrialised countries, echocardiographers undertake complex echocardiography scanning in hospitals on patients with complex heart problems. They have usually received advanced training over many years, often at university; are highly paid; and are based in private consulting rooms. In contrast, trained echocardiographers are a scarce resource in developing countries.

In Chapter 4, the results of an echocardiography-based prevalence study of RHD completed in Fiji were presented. In order to facilitate the fieldwork component, there was a need to build local echocardiography expertise and capacity, as the scarce number of Fijian medical staff with echocardiography skills could not be removed from their normal clinical duties in order to perform field screening. A Fijian sonographer was seconded from the radiology department at the CWM Hospital to receive six weeks of echocardiography field training, comprising a four-week attachment to the cardiology department at the Starship Children’s Hospital in New Zealand, and two weeks supervised field training in Fiji (provided by an expatriate Australian echocardiography technician) on her return. This brief RHD echocardiography training proved highly successful and the sonographer is now a skilled and competent RHD echocardiographer. However, she is the only non-
medically qualified person in Fiji with echocardiography skills; moreover, her skills are still required in the hospital radiography department. Therefore, there was a demonstrated need to train more RHD echocardiographers for RHD screening to be practical in Fiji.

Based on this previous successful experience, the researchers wondered whether it might be possible to train people with clinical skills, but without ultrasonography experience—primarily nurses—to enable them to conduct echocardiography at a level adequate for field screening for RHD. This chapter describes a pilot study of a training module for nurses in Fiji, conducted to determine whether they could perform RHD echocardiography at the level of performing basic 2-D and colour echocardiography scans. A similar model has been trialled in Mozambique, evidently with some success (results not published—verbal communication, Dr Daniel Sidi 2009). More recently, a project was undertaken to train medical students in American Samoa to undertake RHD echocardiography screening; however, details of the training and methodology were not presented.(158)

The pilot training was developed with the following guiding principles:

- the nurses would be trained only in basic RHD screening echocardiography
  (it was not the intention to train them to a level of a formally-qualified echocardiographer)
- the nurses would receive weeks to months of training, rather than years
- a feasible and affordable model could be developed using available local capacity
remuneration would be substantially less than for fully trained echocardiography technicians; thus, the cost of a local screening programme would be lower and more feasible in a resource-poor setting.

The aim would be for nurse echocardiographers to be able to identify a relatively small subset of children with possibly abnormal findings, who would then be referred for confirmatory echocardiography by a more highly trained echocardiographer.

If successful, this model could potentially address a key resource problem for echocardiography screening for RHD in high-risk populations worldwide, as the nursing graduate pool is large and a small team of semi-skilled nurse echocardiographers could routinely screen large numbers of school children in high-prevalence populations at affordable cost. This model requires a high sensitivity and relatively high specificity in order to minimise the number of missed cases, while not requiring too many children to have confirmatory echocardiography, which could overwhelm the clinical workforce.

5.2 Background

5.2.1 Control of RHD

The only proven, cost-effective approach to controlling RHD is delivering three- to four-weekly penicillin injections at the primary health level as part of a disease prevention and control programme.(1) A coordinated national RHD control and prevention programme has been running in Fiji since 2005. It is known that regular administration of three- to four-weekly penicillin injections to children with mild heart valve lesions results in the vast majority having no detectable disease five to 10
years later.(2, 3, 11, 43, 44, 96) However, in the absence of a screening programme, by the time most patients are identified, they often already have more severe rheumatic valvular lesions that result in symptomatic heart failure. The chance of these people having a normal life expectancy is suspected to be much lower than if the intervention started before they developed symptoms.

5.2.2 Detecting RHD by Screening

RHD follows ARF, which occurs primarily in children aged five to 15. The prevalence of RHD increases with age because it is a cumulative disease in which valve damage becomes more pronounced with each subsequent episode of ARF with carditis, and peaks in the third decade of life.(117, 159) However, screening for RHD is usually undertaken in children of school age, mostly because of ascertainment difficulties with the adult population, but also because screening younger subjects allows for detection of the disease at an earlier, milder stage, when intervention (secondary prophylaxis) is likely to have the greatest effect on the outcome of the disease.

Since epidemiological screening research to define the burden of RHD in Fiji commenced in 2006, in excess of 600 new previously undiagnosed cases have been identified in school-aged children, who have been referred to the RHD programme and commenced on secondary prophylaxis. Establishing an early screening module to detect asymptomatic RHD in school-aged children in Fiji is a consideration for the Ministry of Health to assist the control of RHD and to identify cases early in the disease process. Research completed in Fiji in 2006 by the Fiji GrASP project, led by

Samantha Colquhoun, PhD thesis, 2015
Dr Andrew Steer, used a two-step process of auscultation, followed by echocardiography of those children found to have a clinically significant heart murmur. This study found an RHD prevalence of 8.4 per 1,000 in children aged five to 14, based on the NIH and WHO working party guidelines for echocardiographic diagnosis of RHD. (16)

The results of the study described in Chapter 4 of this thesis, in which all children enrolled had two initial auscultation reviews—one by a paediatrician and one by a nurse—followed by echocardiography, showed that the echocardiography confirmed rate using the NIH/WHO criteria was 35.4 per 1,000 in children aged five to 14. This is higher than the prevalence shown in the preceding 2006 study, which is unsurprising given that there was an initial auscultation step in that study.

Additional field studies undertaken in 2008 in Lautoka in the Western Division of Fiji demonstrated that the approach of using a stethoscope to detect suspicious heart murmurs, followed up with confirmatory echocardiography, lacked sensitivity and missed the majority of RHD cases detected if all children underwent echocardiography examination. (38) This supports the findings of similar RHD echocardiography studies in Nicaragua, Tonga, India, New Zealand, Cambodia and Mozambique. (24, 70, 72, 80, 81)

These data support the contention that there are many cases of undiagnosed RHD in school children in Fiji. The data are supported by a growing body of international evidence that suggests that potentially up to 10 times as many cases of RHD are detected using echocardiography, compared to auscultation. (70, 72, 75) There
remains contention regarding the diagnostic criteria for mild or borderline RHD using echocardiography; however, consensus definitions for echocardiographic diagnosis of severe and moderate RHD have been developed and are well accepted. (70, 71, 73, 86) Recent work has been undertaken to develop consensus guidelines for RHD echocardiography, with the aim of providing guidance to assist screening diagnosis sensitivity and specificity. (86)

An important aspect when considering RHD prevention activities is to determine whether echocardiography screening could be practical and affordable in a low- to middle-income country with a high prevalence of RHD. Many of these countries, including in the Pacific, face challenges with training and then retaining highly skilled doctors, nurses and technicians. Even if they stay in the country, many are lost to the public health system because they increasingly choose to move to private practice, which targets the population at lowest risk of RHD in these countries. RHD is a disease of poverty that predominantly affects the most socially deprived and economically disadvantaged populations in developing countries and Indigenous populations. (160, 161) A number of skilled doctors with varying levels of cardiology training work in Fiji; however, they all have demanding clinical commitments and cannot be regularly called upon to undertake screening using echocardiography in settings that are often distant from the main hospitals.

In Australia and New Zealand, the majority of echocardiography technicians have nursing or science qualifications. It is the requirement of the Health Insurance Commission (HIC) that all echocardiography sonographers are registered with the
Australasian Sonographers Accreditation Registry (ASAR) and must hold an Australian Institute of Radiographers certificate for proficiency in ultrasound.

The Fiji Ministry of Health has previously indicated that the most feasible and sustainable means of developing a dedicated RHD screening programme is to train nurses already working with school or community health teams to undertake basic RHD echocardiography screening. School health nurses are employed by the Ministry of Health, and are located in all regions of Fiji. Their role consists primarily of undertaking routine annual health checks on all primary school–aged children. These checks include height, weight, basic vision tests and immunisations. In the previous project described in Chapter 4, a training workshop was undertaken to train school team nurses in basic auscultation to identify a suspicious murmur requiring referral for further investigation. The nurses were found to have poor sensitivity and specificity in identifying suspicious murmurs, as did the paediatricians involved in this study, and the current international evidence suggests that this approach will miss most cases of early RHD.

Instead, screening children for RHD using echocardiography may be the most accurate approach. This normally requires a highly trained echocardiography technician or a cardiology-trained doctor to undertake screening, where doctors are scarce and unavailable for such large-scale public health programmes. In Fiji, there is also a cadre of highly trained nurses, called nurse practitioners, who are trained to undertake a variety of advanced clinical and diagnostic procedures, including auscultation using stethoscopes. Their numbers are relatively few and they generally practice as sole clinicians in remote and very remote areas of Fiji. (162)
In 2008, to increase human capacity in this area, the Fiji GrASP project seconded a Ministry of Health sonographer who had no previous echocardiography experience to receive brief training in RHD echocardiography. The sonographer was selected because she was already experienced with the concept of sonography and techniques such as holding a probe steady in order to gain correct views. The sonographer undertook four weeks of field training in New Zealand under the supervision of Dr Nigel Wilson—a paediatric cardiologist. On her return to Fiji, she was supervised by Dr Joseph Kado—a senior Fijian paediatrician with considerable experience in cardiology and echocardiography—to undertake RHD echocardiography screening of the children enrolled in the RHD echocardiography prevalence study described in Chapter 4. Her skill level after receiving basic field training was high, and she has since become a competent echocardiographer able to undertake RHD echocardiography screening for early detection and referral of children who require clinical review.

5.3 Methods

5.3.1 Project Aim

The aim of this study was to complete a pilot project to train nurses who had no prior expertise or knowledge of echocardiography screening for RHD to undertake a screening echocardiogram and identify those children who required referral for clinical investigation for RHD. The eventual aim was to develop a training module that could potentially be used to train nurses across Fiji from the existing relatively large school health team workforce.
5.3.2 Hypothesis

It was hypothesised that nurses could be trained to gain basic RHD echocardiography skills using an introductory workshop, followed by hands-on field training. In Fiji, all primary school-aged children undergo an annual health check in schools. If a programme could eventually be developed for a brief RHD screening echocardiogram to be undertaken as part of these visits for children in some classes (such as grades two, six and eight), this could significantly add to the number of cases that are identified early, before the disease has progressed to a symptomatic level.

This pilot study had three main components. The first step was a training workshop for nurses in basic RHD echocardiography. In the second step, the nurses completed two weeks of supervised field screening training. The third step was a blinded comparison of the nurses’ ability to identify patients with RHD on echocardiography, compared to a paediatric cardiologist also using echocardiography (Figure 5.1).
Informed consent was obtained from the parents and guardians of all participating children prior to any study procedures. In addition, assent was obtained from all children who were over 10 years of age. After informed consent and assent was obtained, the demographics data collection form was completed to provide identifying information. All children enrolled were recorded into the study enrolment log by study number and initials.

5.3.3 Selection of Nurses

The selection of nurses was essentially made on practical and financial grounds. One nurse was employed by Fiji GrASP as the senior research nurse and was thus already...
on the payroll of the project, while the second nurse was the Fiji RHD national project officer and a highly skilled nurse practitioner. Both nurses were Suva based, and neither had any prior knowledge or experience in echocardiography.

The research staff were all local and spoke Fijian, English and some Hindustani. If interpretation was required, this was facilitated by using medical or nursing staff with local language fluency. Ethics approval to undertake this project was obtained from the Fiji National Research Ethics Committee and the Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research. The study was conducted in full conformity with the current revision of the Declaration of Helsinki, and with International Conference for Harmonisation of Good Clinical Practice (ICH-GCP) regulations and guidelines. In addition, approval and endorsement to undertake the study in primary schools was obtained from the Fiji Ministry of Education and principals at the selected participating schools.

5.4 Outline of Study Steps

5.4.1 Outline of Workshop Components

5.4.1.1 Step 1: Suva Workshop and Field Training/Experience Phase

A week-long training workshop was held at the CWM Hospital, Department of Paediatrics, Suva, Fiji, in March 2010. Two paediatricians with extensive experience in RHD echocardiography facilitated the training. The two nurses received training in basic RHD echocardiography, with an emphasis on obtaining views of the left side of the heart and identifying mitral valve regurgitation, and capturing images of the
mitral and aortic valve in three views (parasternal long axis [PLAX], parasternal short axis [PSAX] and apical). The primary emphasis was on identifying and measuring a regurgitant mitral and/or aortic jet using the colour Doppler function. In addition, the nurses were asked to comment on whether the mitral and aortic valves appeared normal or abnormal (see Appendix 1).

Paediatric medical registrars from the CWM Hospital were invited to attend the workshop; however, they did not take part in the field or testing components of the pilot project. The overall aim of the teaching module was for nurses with no previous echocardiography training to learn to perform very basic echocardiography of the left side of the heart, and identify regurgitation of the mitral valve following a basic 12-step RHD screening echocardiography algorithm (Table 5.1).

Table 5.1: Twelve-step Basic Algorithm for Nurse-led RHD Screening

<table>
<thead>
<tr>
<th>Step</th>
<th>View</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PLAX</td>
<td>2-D</td>
</tr>
<tr>
<td>2</td>
<td>PLAX</td>
<td>Colour Doppler mitral valve</td>
</tr>
<tr>
<td>3</td>
<td>PLAX</td>
<td>Colour Doppler aortic valve</td>
</tr>
<tr>
<td>4</td>
<td>PSAX at level of aortic valve</td>
<td>2-D</td>
</tr>
<tr>
<td>5</td>
<td>PSAX at level of aortic valve</td>
<td>Colour Doppler</td>
</tr>
<tr>
<td>6</td>
<td>PSAX at level of mitral valve</td>
<td>2-D</td>
</tr>
<tr>
<td>7</td>
<td>PSAX at level of mitral valve</td>
<td>Colour Doppler</td>
</tr>
<tr>
<td>8</td>
<td>Apical 4 chamber</td>
<td>2-D (also visualise the mitral valve)</td>
</tr>
<tr>
<td>9</td>
<td>Apical 4 chamber</td>
<td>Colour Doppler of the mitral valve</td>
</tr>
<tr>
<td>10</td>
<td>Apical 5 chamber</td>
<td>2-D (visualise the aortic valve well)</td>
</tr>
<tr>
<td>11</td>
<td>Apical 5 chamber</td>
<td>Colour Doppler of aortic valve</td>
</tr>
<tr>
<td>12</td>
<td>Record results on data collection form</td>
<td></td>
</tr>
</tbody>
</table>

5.4.1.2 Step 2: Supervised Field Training Component in Suva, Fiji

Two primary schools with large enrolment numbers located in close vicinity to the Fiji GrASP and RHD office in Suva were selected for Step 2 (the supervised field
component) of the study to allow easy access for supervising doctors to travel between the study site and the hospital on a rotational basis, thus minimising disruption to their routine clinical duties. The research team planned visits in liaison with the school principals and teachers to minimise disruption and effect on education and daily school routine.

5.4.2 Field Screening and Testing Phase Echocardiography Procedure

All children aged between five to 14 years attending the two identified primary schools were eligible for inclusion in the field experience phase of the study, if written informed consent was obtained. The screening echocardiograms on average took 15 to 30 minutes per child. During the echocardiography procedures, screens were used to maintain the child’s privacy, and a chaperone was present. A screening echocardiogram was performed on all participants by one of the nurses who had attended the training workshop. Each echocardiogram was labelled with the individual’s study number, date of the exam, and subject’s age, but not with his or her name. If the supervising staff felt that the echocardiography identified children thought to have possible acute rheumatic carditis, RHD or other abnormal cardiac findings, they were referred for further off-study investigation to the Paediatrics Department at CWM Hospital.

5.4.3 Off-study Review of Cases Requiring Referral

The aim was to give very clear guidance to the nurses about children who needed confirmatory echocardiography by a more highly trained person (need for referral)
and thus eliminate most children who had normal findings from this next step. The RHD echocardiography screening criteria were developed with a view to the nurses obtaining high sensitivity (ideally > 80%) and reasonably high specificity, with sensitivity being of primary importance. Children identified as having any one or more of the following criteria on echocardiogram, as identified by the nurse (and confirmed by the supervising expert during the field experience phase) were referred for off-study cardiac review at CWM Hospital:

- the presence of mitral regurgitation of greater than 1 cm from the coaptation point of the valve leaflets
- the presence of any aortic regurgitation
- any abnormal mitral or aortic valve morphology
- the presence of any other pathology, such as ventral septal defect or atrial septal defect.

Conservative measurements were chosen for the nurses to determine the need for referral (≥ 1 cm of mitral regurgitation) to limit the likelihood of false negatives.

It was intended that each nurse would undertake 60 to 80 echocardiograms under the supervision of an experienced echocardiographer over a two-week period following the workshop, in order to gain dexterity, experience and competence in identifying children who require cardiac referral. After further review, the children who proved to have confirmed RHD were placed on the RHD register. This is standard care in Fiji and follows established protocols for secondary prophylaxis, as established by WHO. (1) This standard of care includes regular follow-up with a physician experienced in the care of patients with RHD, interval echocardiography, three-weekly intramuscular BPG injections, and assessment for cardiac surgery. All
children with RHD and their families were given educational materials on RHD by the Fiji RHD team.

5.4.4 Definition of Echocardiography Confirmed RHD used in the Testing Phase

The definitions for definite and probable RHD used in this study were those used in previous screening studies in Fiji, modified from the NIH/WHO RHD working party echocardiography screening guidelines (Table 5.2).(139) The cardiologist acting as the ‘gold standard’ echocardiographer was asked to follow these guidelines when categorising RHD cases detected among the 50 children in the testing sample. The analysis used the data completed on the data collection sheets by the nurses and the cardiologist to compare variables and calculate the sensitivity and specificity of the nurses’ correlation with the data collected by the cardiologist, against the echocardiography definitions for the classification of RHD cases as definite and probable.
Table 5.2: Definition of RHD on Echocardiogram‡

<table>
<thead>
<tr>
<th>Definite RHD</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite mitral regurgitation due to RHD</td>
<td>Significant mitral regurgitation on echocardiography† plus morphological changes of the mitral valve on echocardiography.†</td>
</tr>
<tr>
<td>Definite aortic regurgitation due to RHD</td>
<td>Significant aortic regurgitation on echocardiography‡ plus morphological changes of the mitral valve on echocardiography without another evident aetiology for aortic insufficiency, such as bicuspid valve or annuloaortic ectasia.</td>
</tr>
<tr>
<td>Definite mitral stenosis due to RHD</td>
<td>Significant mitral stenosis on echocardiography.‡ Additional echocardiographic changes that may be present include thickening of the mitral valve leaflets, ‘elbow’ or ‘dog-leg’ deformity of the anterior mitral valve leaflet, fixed or markedly restricted motion of the posterior mitral leaflet, calcification and commissural thickening.</td>
</tr>
<tr>
<td><strong>Probable RHD</strong></td>
<td></td>
</tr>
<tr>
<td>Probable mitral regurgitation due to RHD</td>
<td>Significant mitral regurgitation on echocardiography without morphological changes of the mitral valve on echocardiography.</td>
</tr>
<tr>
<td>Probable aortic regurgitation due to RHD</td>
<td>Significant aortic regurgitation on without morphological changes of the mitral valve on echocardiography.</td>
</tr>
<tr>
<td>Probable mitral valvular pathology due to RHD</td>
<td>Morphological changes of the mitral valve on echocardiography without significant mitral stenosis, mitral regurgitation or aortic regurgitation on echocardiography.</td>
</tr>
</tbody>
</table>

Note: *Significant mitral regurgitation: a mitral regurgitant jet at least 2 cm from the coaptation point of the valve leaflets, seen in two planes, with a high velocity mosaic pattern and persisting throughout systole.
†Morphological changes of the mitral valve on echocardiography: thickened mitral valve leaflets and/or elbow or dog-leg deformity of the anterior mitral valve leaflet.
‡Significant aortic regurgitation on echocardiography: an aortic regurgitant jet at least 1 cm from the coaptation point of the valve leaflets, with a high velocity mosaic pattern and seen in two planes.
§Significant mitral stenosis on echocardiography: evidence of flow acceleration across the mitral valve with a mean pressure gradient greater than 4 mmHg.
‡From the WHO and NIH RHD working party guidelines.(139)

5.4.5 Selection of Testing Location and Cohort of Children

5.4.5.1 Testing Phase at Lautoka Hospital

In the week following the field experience in Suva, the nurses were required to test their skills on a blinded sample of 50 children. Children who had been screened using echocardiography in 2008 in Lautoka, whose cardiac diagnosis was known, were approached by the Lautoka RHD nurse and the Fiji GrASP study coordinator to participate in this phase of the study. The 50 selected children included 10 children...
with cardiac pathology diagnosed as RHD, and 40 with normal echocardiographic findings as diagnosed in 2008. (38)

5.4.6 Location of Testing Site

Lautoka is Fiji’s second largest city, and is located approximately four hours’ drive from the capital Suva (Figure 5.2). Lautoka Hospital is the second largest hospital in Fiji; a part-time Fiji Ministry of Health RHD nurse coordinates care of RHD cases at Lautoka Hospital. This location was chosen because none of the children selected for the testing cohort were known to the nurses involved in the training.

![Figure 5.2: Map of Fiji Showing Study Sites (Lautoka and Suva)](image)
5.4.7 Blinding of Nurses to Children’s Cardiac History

To reduce any potential bias in this phase of the study, only the senior medical officer, the Lautoka RHD nurse and the study coordinator knew the children’s cardiac diagnoses. The 50 children involved in this phase each had three echocardiograms undertaken—one by each of the two nurses being tested and the third by the cardiologist. The cardiologist completed all echocardiograms on the enrolled participants in a room isolated from the nurses undergoing the testing phase. The two nurses were in a large room separated by screens from each other. They were instructed prior to commencing the training phase that they would not be permitted to speak to each other during the echocardiography examinations. They were supervised at all times during the testing phase by either the study coordinator or the Lautoka RHD nurse.

At the time of enrolment of the 50 children for the testing phase, the nurse/study coordinator requested that the children and their parents not discuss their cardiac status with the nurses completing the echocardiography examination. They were given the opportunity to discuss or ask questions about their children’s health and the echocardiography with the Lautoka nurse in private, and with the cardiologist following the echocardiography examinations, but at no times with the nurses being tested. The nurses were supervised during the testing phase to ensure no discussion regarding the children’s health status occurred.
5.4.8 Echocardiography Protocol

The echocardiography examination undertaken by the two nurses throughout the study and the cardiologist testing phase followed the 12-step basic algorithm that the nurses had been trained to use in steps one and two of the study (Table 5.1).

5.4.9 Echocardiography Machines

All echocardiography examinations were performed using three portable Mindray machines (Mindray Diagnostic Ultrasound System Model M5). These relatively inexpensive machines allow 2-D, motion-mode (M-mode), colour Doppler mapping, and continuous wave and pulse wave Doppler imaging. All echocardiography was undertaken in a transthoracic mode using an appropriate ultrasound gel and with the aid of electrocardiography tracing. Echocardiogram studies were stored on the hard drive of the echocardiogram machine during the day. At the end of each day, these studies were downloaded to a laptop computer for storage and further review.

5.4.10 Data Analysis

5.4.10.1 Comparison of Nurses’ Results to Cardiologist’s Results

Data from the testing phase (step three only) were analysed to determine the nurses’ sensitivity and specificity in identifying the cases with RHD echocardiography features recorded by the cardiologist using the echocardiography definitions. The nurses and cardiologist were asked to complete a data form that contained detailed information about each view and measurement, as detailed in the algorithm in Table
5.1. The nurses were asked to obtain and record measurements of mitral valve regurgitation, and comment on the presence of any aortic valve regurgitation. The nurses also commented on the presence or absence of mitral valve morphology. The primary outcome measure was the nurses’ finding of a mitral regurgitant jet and/or any aortic regurgitation—so-called ‘screen-positive’—compared with the cardiologist assessment of definite RHD, as defined by the study criteria, for each nurse. Sensitivity and specificity with 95% CIs were calculated for all comparisons. In addition, other comparisons were made between the nurses’ and cardiologist’s assessments using Spearman’s correlation coefficient.

5.4.10.2 Mitral Valve Regurgitant Jet Length

Three categories were made to compare the nurses’ measurements of regurgitant mitral valve jet length in PLAX and apical views. These categories were the nurses’ identification of a regurgitant jet of $\geq 2$ cm, $\geq 1.5$ cm or $\geq 1$ cm. The categories included the presence or absence of valve morphology in line with the study echocardiography criteria. Each of these categories, for each nurse, was compared with the cardiologist’s measurement in PLAX and apical views of a regurgitant jet $\geq 1$ cm (cardiologist measurement of $\geq 1$ cm compared with nurses’ 2 cm, 1.5 cm, 1 cm or $< 1$ cm in PLAX and apical views, and analysed for sensitivity and specificity) (Figure 5.3).
5.4.10.3 Aortic Valve Regurgitant Jet Length

The cardiologist’s measurement of aortic regurgitation of $\geq 1$ cm was compared to the nurses’ answer ‘yes’ or ‘no’ to the presence of aortic regurgitation of $\geq 1$ cm in PLAX and apical views.

**Figure 5.3: Flowchart of Analysis of Nurses’ and Cardiologist’s Echocardiography Results**

5.4.10.4 Presence of Mitral Valve or Aortic Valve Abnormality

The data analysis involved comparisons of the nurses’ detection of abnormal valve morphology with the cardiologist’s results at the most basic level—that is, whether either of the valves were abnormal in appearance. The intention of this study was to focus on the nurses’ ability to undertake RHD echocardiography following an
algorithm, and identify and measure regurgitant jets at the mitral and aortic valves.

Understanding valve morphology and measuring valve thickness is a skill that cardiologists develop over many years of training. There remains a degree of subjectivity in interpreting valve morphology even among experienced cardiologists, and it was beyond the scope or aims of this study to provide training to the nurses in the identification and classification of abnormal valve morphology.

All data were entered by experienced staff into an electronic database created in software package Epidata 3.1 (Epidata Association, Denmark). Electronic data were exported into STATA version 10 (Statacorp, Texas, US) for cleaning and analysis.

5.4.11 Funding and Organisational Involvement

The research work was coordinated and undertaken by the Fiji GrASP and Fiji RHD teams under the supervision of Dr Joseph Kado and the Fiji RHD technical advisory group. The Fiji RHD and GrASP teams were partially funded by the WHF through a programme led by Menzies School of Health Research and the Centre for International Child Health, University of Melbourne. Additional funding for this study was obtained through Cure Kids New Zealand, the Fiji Water Foundation and Caritas Australia. All staff involved in this project were experienced local investigators who had received training in Good Clinical Practice.
5.5 Results

5.5.1 Workshop and Field Training Component

The nurses all completed the echocardiography training workshop component and attended two weeks of supervised field training in two Fijian primary schools in Suva. A total of 223 children were screened in the two primary schools during Step 1 (the field training component). Four previously undiagnosed cases of RHD and one case of CHD were detected during the field training. All new cases were found by the same nurse (Nurse B), and a Fijian cardiologist confirmed the diagnosis. These cases were referred to the RHD clinic at CWM Hospital for further off-study clinical investigation and management, and cases of RHD were recorded on the Fiji national RHD register.

5.5.2 Testing Phase

5.5.2.1 Description of Cohort of 50 Children Enrolled in Testing Phase

Fifty children were recruited for the testing cohort; of these, 10 were selected because they had RHD found on echocardiography in 2008. When echocardiography was undertaken by the cardiologist during the present study, one of these 10 children was found to have a bicuspid aortic valve, but not to have RHD. The nurses also correctly identified this case. This case was excluded from all analysis. In the cohort of the remaining nine children identified as RHD cases, six were found on repeat echocardiography to have definite RHD, and one had possible RHD, as defined by the study’s echocardiography definitions (Table 5.2). Two cases no longer fit the definitions to be included as RHD cases. Although these cases did not meet the
echocardiography criteria, they exhibited some features included in the criteria—
either significant regurgitation in at least one view or abnormal valve morphology
(these cases are shown as cases eight and nine in Table 5.3). The echocardiography
features of all the cases identified by the cardiologist are shown in Table 5.3.

Table 5.3: Characteristics of the Nine RHD Cases in the Sample, as Identified
by the Cardiologist*

<table>
<thead>
<tr>
<th>Case</th>
<th>Mitral valve</th>
<th>Aortic valve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morphology</td>
<td>MR PLAX (cm)</td>
</tr>
<tr>
<td>Case 1</td>
<td>Elbow deformity, thickened AMVL</td>
<td>2.4</td>
</tr>
<tr>
<td>Case 2</td>
<td>Thickened AMVL</td>
<td>2.6</td>
</tr>
<tr>
<td>Case 3</td>
<td>Elongated chordae, thickened AMVL, tethered PMVL</td>
<td>2.5</td>
</tr>
<tr>
<td>Case 4</td>
<td>Thickened AMVL</td>
<td>2.2</td>
</tr>
<tr>
<td>Case 5</td>
<td>Thickened AMVL</td>
<td>2.2</td>
</tr>
<tr>
<td>Case 6</td>
<td>Thickened AMVL</td>
<td>Nil</td>
</tr>
<tr>
<td>Case 7</td>
<td>Normal</td>
<td>1.4</td>
</tr>
<tr>
<td>Case 8</td>
<td>Thickened AMVL</td>
<td>1.93</td>
</tr>
<tr>
<td>Case 9</td>
<td>Thickened AMVL, thickened PMVL, tethered PMVL</td>
<td>1.46</td>
</tr>
</tbody>
</table>

Note: *Cases one to six fit the criteria for definite RHD and were used for primary data analysis, case seven fit probable RHD, and cases eight and nine did not fit the criteria, but were identified as being abnormal by the cardiologist; MR = mitral regurgitation; AMVL = anterior mitral valve leaflet; PMVL = posterior mitral valve leaflet

A further seven children were found to have a regurgitant mitral valve jet of between
1.5 to 1.99 cm, while eight children had a regurgitant mitral valve jet of between 1.0
to 1.49 cm. The remaining 28 children had either no mitral regurgitation or
regurgitation measuring less than 1 cm (Table 5.4). Of the 49 included children, three
were found to have an aortic valve jet greater than 1 cm, and the remaining 46 had no aortic valve regurgitation. The nurses did not measure the distance of aortic regurgitant jet, but instead were asked if there was regurgitation of > 1 cm present at the aortic valve. The nurses were not required to measure the length of the aortic regurgitant jets, thereby not allowing any further detailed analysis; however, it is likely that the majority of these children were identified as having \( \leq 1 \) cm of aortic regurgitation. When comparing the nurses’ measurement of the length of the mitral regurgitant jet directly against the cardiologist’s measurement, there was only fair agreement with a Spearman’s correlation coefficient of 0.46 and 0.39 for Nurse A and B, respectively (Figures 5.4 and 5.5).

**Table 5.4: Number of Cases and Cardiologist’s Measurement of Mitral and Aortic Regurgitation in any View**

<table>
<thead>
<tr>
<th>Mitral valve regurgitation</th>
<th>&gt; 2 cm</th>
<th>1.5–&lt; 2 cm</th>
<th>1–&lt; 1.5 cm</th>
<th>No regurgitation or &lt; 1 cm</th>
<th>Total number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>28</td>
<td>49</td>
</tr>
<tr>
<td>Aortic valve regurgitation</td>
<td>&gt; 1 cm</td>
<td>&lt; 1 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases</td>
<td>3</td>
<td>46</td>
<td></td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>
Figure 5.4: Correlation of Nurse A Measurement of Mitral Regurgitation Jet Length to that of the Cardiologist

Figure 5.5: Correlation of Nurse B Measurement of Mitral Regurgitation Jet Length to that of the Cardiologist
5.5.2.2 Sensitivity and Specificity of Nurses’ Results Compared to RHD Definitions

Comparing the nurses’ results in detecting > 1 cm and < 1.5 cm of mitral valve regurgitation showed a sensitivity of 100% for both nurses, with specificity of 41.9% and 76.7%. By varying the measurement to compare the nurses’ measurements of > 1.5 cm and < 2 cm of mitral regurgitation, Nurse A had a sensitivity of 100% and an improvement in specificity to 67.4%. Nurse B showed a sensitivity of 83% and no substantial improvement in specificity (79.1%). The nurses’ results at a measurement of > 2 cm of mitral regurgitation showed sensitivity of 66.7% and 83% and specificity of 74.4% and 93%, respectively—higher specificity than seen in the previous measurement categories, but with a corresponding decrease in sensitivity at this level (Table 5.5).

Table 5.5: Sensitivity and Specificity of Nurses’ in Identifying Cases of Definite RHD, as defined by Study Definitions (n = 6), when using Different MR Jet Length Cut-offs and the Presence of any AR as Screen Positive

<table>
<thead>
<tr>
<th>Cut-off used for mitral regurgitant jet</th>
<th>Cases of mitral regurgitation detected by nurse</th>
<th>Sensitivity 95% CI</th>
<th>Specificity 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 cm</td>
<td>31</td>
<td>100</td>
<td>54.1–100</td>
</tr>
<tr>
<td>1.5 cm</td>
<td>20</td>
<td>100</td>
<td>54.1–100</td>
</tr>
<tr>
<td>2 cm</td>
<td>15</td>
<td>66.7</td>
<td>22.3–95.7</td>
</tr>
<tr>
<td>Nurse B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 cm</td>
<td>16</td>
<td>100</td>
<td>54.1–100</td>
</tr>
<tr>
<td>1.5 cm</td>
<td>14</td>
<td>83</td>
<td>35.9–99.6</td>
</tr>
<tr>
<td>2 cm</td>
<td>8</td>
<td>83</td>
<td>35.9–99.6</td>
</tr>
</tbody>
</table>

Note: *Nurses were not asked specifically to identify cases of RHD, but to identify cases with significant mitral regurgitation using different cut-offs, to be referred for further assessment.*

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5.5.2.3 Sensitivity and Specificity of Nurses’ Results Compared to the Cases the Cardiologist Identified

The two nurses’ results for sensitivity and specificity were also compared with the entire nine cases the cardiologist identified (Table 5.6). These results showed a similar picture, with 100% sensitivity for both nurses at 1 cm level and specificity of 45% and 82.5%. At 1.5 cm, the results showed high sensitivity (88.9% for both nurses) with specificity of 70 and 85%. At the 2 cm cut-off, sensitivity decreased, with a corresponding increase in the specificity of both nurses’ results.

Table 5.6: Sensitivity and Specificity of Nurses in Identifying Cases of RHD that were also Identified by Cardiologist (n = 9)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of cases</th>
<th>Sensitivity 95% CI</th>
<th>Specificity 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse A</td>
<td>1 cm cut-off</td>
<td>31</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>1.5 cm cut-off</td>
<td>20</td>
<td>88.9</td>
</tr>
<tr>
<td></td>
<td>2 cm cut-off</td>
<td>15</td>
<td>66.7</td>
</tr>
<tr>
<td>Nurse B</td>
<td>1 cm cut-off</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>1.5 cm cut-off</td>
<td>14</td>
<td>88.9</td>
</tr>
<tr>
<td></td>
<td>2 cm cut-off</td>
<td>8</td>
<td>66.7</td>
</tr>
</tbody>
</table>

5.5.2.4 Mitral and Aortic Valve Morphology

The aim of the pilot project training was to focus on the nurses’ ability to detect mitral and/or aortic regurgitation and identify cases that require referral, with high sensitivity and specificity. However, they were asked to answer a ‘yes’ or ‘no’ question, given their very brief level of training, on whether they thought abnormal mitral valve morphology was present. The cardiologist identified a total of 17 out of 50 cases with some degree or abnormal or suspicious mitral valve morphology. Two of these cases also had an aortic valve abnormality recorded. There were no cases
identified with isolated aortic valve abnormality. The nurses’ results are compared to the cardiologist in Table 5.7. Sensitivity was low for both the nurses’ results; however, one nurse showed a specificity of 100% and the other of 65.6%.

### Table 5.7: Sensitivity and Specificity of Nurses’ in Identifying Cases of Abnormal Mitral Valve

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse A</td>
<td>20</td>
<td>52.9</td>
<td>27.8–77.0</td>
<td>65.6</td>
</tr>
<tr>
<td>Nurse B</td>
<td>5</td>
<td>29.4</td>
<td>10.3–56.0</td>
<td>100</td>
</tr>
</tbody>
</table>

### 5.6 Discussion

This pilot project has provided proof of the principle that nurses, given brief focused training and supervised field experience, can follow an algorithm to undertake RHD echocardiography in a developing country setting, with reasonable accuracy. The nurses involved in this study were asked to detect and measure mitral valve regurgitation of 1 cm or greater, and detect aortic valve regurgitation of 1 cm of greater. This conservative measure was used as a baseline for the nurses to ensure that there were not a large number of false negatives detected. The current guidelines for RHD describe a significant mitral regurgitation being a mitral regurgitant jet at least 2 cm from the coaptation point of the valve leaflets. This level of 2 cm of mitral regurgitation—as captured by the cardiologist’s echocardiography examination—was used to compare to the nurses’ results at the varied cut-off points.

Comparing the nurses’ results with the cardiologist’s results at the cut-off level of 1.5 cm showed good sensitivity and specificity of results, when compared to the cardiologist’s referral results (Table 5.6) and against the echocardiography
definitions used in this pilot (Table 5.2). Using a 1 cm cut-off for mitral valve regurgitation resulted in excellent sensitivity results, but poor specificity, suggesting that a 1.5 cm cut-off may be a more appropriate level to focus on in the next proposed phase of this project, assuming that mitral valve regurgitation < 1.5 cm continues to be considered irrelevant in diagnostic guidelines developed in future.

These results warrant further research with a view to developing a module to guide RHD echocardiographic screening by nurses within the existing public health infrastructure in high-prevalence, resource-poor regions. A key factor in determining an appropriate screening module is the accuracy of the screening tool to correctly identify children who require further clinical referral without missing cases (ensure high sensitivity) and the ability of the tool to exclude large numbers of children whose cardiac pathology is normal (high specificity). Poor sensitivity leads to potentially missed RHD cases who may go on to present with severe untreatable disease, yet unnecessary referral of large number of cases for clinical review will overwhelm the already burdened clinical services. An appropriate screening module will have high specificity and high specificity, therefore capturing children with established disease in its early form, but not resulting in referring large numbers of children who may have normal pathology. Borderline RHD cases identified by screening echocardiography should be followed, which may put an added burden on clinicians in resource poor regions.

This pilot study also highlighted inconsistency in the cardiologist’s diagnosis and the definitions provided in the protocol. Reviews of recent publications of echocardiography screening for RHD show an emerging consensus, particularly
relating to the classification of probable RHD, and that published studies often lack
detail in their stated methods regarding the criteria for RHD echocardiography
diagnosis. The echocardiography definitions for definite RHD cases are well defined;
however, there remains a high degree of subjectivity and interpretation consensus
among cardiology experts regarding the appropriateness of the criteria for diagnosis
of less severe forms of RHD by echocardiography, particularly in reference to the
inclusion of valve morphology.(24, 73, 77, 136, 164, 165)

A recent publication compared cases using the WHO guidelines with guidelines that
included a more detailed examination of abnormal valve morphology found that
significantly higher numbers of cases—up to three times as many—are diagnosed
with inclusion of examination of valve morphology; however, they had no means of
validating that the abnormal valve morphology actually was RHD.(73) This degree
of subjectivity has serious clinical implications when echocardiography screening is
undertaken in high-prevalence, resource-poor regions. This may result in clinicians
opting to put many additional children with less well-defined RHD pathology on
prophylaxis medication, particularly when there is not the facility or resources to
review suspect cases clinically and by echocardiography at regular and frequent
intervals.

The cardiologist who undertook the echocardiography examinations for this pilot
study during the testing phase found a large number of children with abnormal valve
morphology (34% of cases). It was not the intention of this study to train nurses to
focus interpreting valve morphology, and there was poor consensus in the nurses’
results compared with the cardiologist’s results. Further detail obtained from the
cardiologist’s examination may have eliminated many of the cases as abnormal. The poor performance of the nurses in this aspect may reflect more on the training and limitations of the pilot study, rather than their ability to be trained in this area. This pilot study focused on training the nurses to operate the echocardiography machine, obtain optimal images and measure regurgitant jets at the mitral and aortic valves. Provided diagnostic guidelines are clear (and this issue has international work related to it), the results from this pilot project support the view that nurses can be trained to recognise children who may have abnormalities based on those guidelines. When standardised protocols for screening echocardiography are developed, they need to be followed rigorously and consistently.

5.7 Conclusion

This pilot has shown that, given brief comprehensive training, nurses can operate sophisticated portable echocardiography machines with competence, and detect findings suggestive of RHD with high sensitivity and reasonable specificity. Additional training and experience will be required to increase specificity. Further development of a RHD training module for nurses in a high-prevalence, resource-poor setting would include increased supervised field experience and be undertaken using standardised RHD echocardiography guidelines and protocols, such as the recently published WHF RHD echocardiography screening criteria.(86)

There are currently no published studies that examine the cost-effectiveness of RHD echocardiography screening in resource-poor settings. Although there is good reason to think that early detection of RHD will lead to reduced healthcare costs and
increased lifetime productivity in individual patients, this has not been formally assessed. While portable echocardiography machines are becoming more affordable, undertaking disease screening at a public health level is labour intensive and may have considerable downstream workforce consequences. A cost-effectiveness study of RHD screening is underway in Fiji and New Caledonia.

This study provides a useful basis for the next phase of developing a training module. There is a need for more a comprehensive field-training component and exposure in the next phase to ensure that all nurses develop competency with experience. Since 2010, the nurses trained in this pilot have gone on to undertake supervised RHD echocardiography screening on multiple field trips to remote regions of Fiji and neighbouring Pacific Island countries. As echocardiography is a skill that increases with experience, the researchers aim to retest the nurses in the future to review their current level of expertise and determine whether they have improved with additional field experience and practice.

5.7.1 Future Research Directions

The data obtained from the pilot study enabled calculation of the sample size required for a future nurse-led screening study in Fiji. Previous echocardiography studies undertaken in Fiji using the gold standard test (full echocardiogram performed by a highly trained echocardiographer and read by at least one cardiologist) indicate that between nine to 16% of children have ‘disease’ (will need referral based on established data). For the purposes of sample size calculations, 15% was used as the point estimate for the planned future study to validate the training
module. In studies investigating screening, the sensitivity of the test is more critical than specificity. Therefore, the future study will aim for a sensitivity of 95% and a specificity of 75%, using the formula for binomial distribution of sensitivity (Sn) and specificity (Sp):

\[ Sn \pm Z \sqrt{Sn(1-Sn)/n1} \quad \text{and} \quad Sp \pm Z \sqrt{Sp(1-Sp)/n2} \]

where \( Z = 1.96 \), \( n1 = \) number with disease and \( n2 = \) number without disease.

A sample size of 2,000 (\( n1 = 300 \) and \( n2 = 1,700 \)) would provide a 95% CI of +/- 2.5% around an estimate of 95% sensitivity, and a 95% CI of +/- 2% around a specificity of 75%. A study is now underway in Fiji to train an additional seven nurses, with the aim of validating the RHD echocardiography screening module and increasing the Ministry of Health RHD screening capacity across the country, and potentially providing a echocardiography training model to be used in the future in Fiji and elsewhere in the Pacific region.

It is hoped that this information will assist with the development of a feasible national screening and training model for the Fiji Ministry of Health to incorporate within its RHD control and prevention programme. It will also contribute to international research to define a feasible methodology for RHD screening in resource-poor settings.
Section 2: The Global Burden of RHD

This section focuses on updating the global epidemiology of RHD and examining mortality from RHD in a high-risk Indigenous population. The aims of Section 2 are to:

1. provide an update of the global epidemiology of RHD, including prevalence, incidence, mortality, YLL, years of life lived with disease and DALY
2. examine RHD mortality time trends and rates in a high-prevalence population.
Chapter 6: Global Burden of RHD
6.1 Introduction

In 1990, the Global Burden of Disease (GBD) Study published global population-based data showing estimates of RHD prevalence, incidence and mortality. Since that time, a number of important RHD prevalence studies and two systematic reviews have been published.9, 94, 71,117 Although the number of new RHD screening studies is relatively few, most have used echocardiography as the primary diagnostic tool, resulting in much more accurate estimates of disease burden than previously published. However, many gaps in understanding the full burden of RHD remain because few studies are available to show incidence, morbidity and mortality from RHD. The researchers became involved in the GBD 2010 Study to assist with understanding and updating global RHD epidemiology.

6.1.1 Background to GBD Study

The first GBD study (the GBD 1990 Study) was commissioned by the World Bank in 1991 to provide a comprehensive assessment of the burden of 107 diseases and injuries, as well as 10 selected risk factors for the world, divided into eight major regions. In 2000, the WHO began publishing regular GBD updates for the world and 14 regions. New estimates for 2001 were published as part of the second revision of the Disease Control Priorities Project.

The new Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 Study) commenced in 2007. It was led by a consortium including Harvard University, the Institute for Health Metrics and Evaluation at the University of
Washington, Johns Hopkins University, The University of Queensland and the WHO. The GBD 2010 Study aimed to bring together a community of experts and leaders in epidemiology and other areas of public health research from around the world to measure current levels and recent trends in all major diseases, injuries and risk factors, and to produce new and comprehensive sets of estimates.

The deliverables of the 2010 Global Burden of Diseases, Injuries, and Risk Factors Study, as stated in the GBD manual,(166) included:

- Comprehensive estimates of the burden of diseases and injuries—by age, sex and region—for 1990, 2005 and 2010. The estimates include deaths, YLL, years lived with disability (YLD), incidence, prevalence and duration of cases, and disabling sequelae.
- Comprehensive estimates of mortality and burden of disease attributable to selected risk factors—by sex, age, and region—for 1990, 2005 and 2010.
- Analysis of trends between 1990 and 2010 for all diseases, injuries and risk factors.

The work outlined in this chapter highlights the effort undertaken by the RHD expert writing group for the GBD 2010 Study. The work was led by Professor Jonathan Carapetis and overseen by Professor George Mensah—the leader of the GBD cardiovascular group—with the RHD expert writing group members all contributing to the project. The RHD expert group members were Associate Professor Andrew Steer, Professor Ganesan Karthikeyan, Professor Bongani Mayosi, Associate Professor John Condon and PhD student Samantha Colquhoun.
Samantha Colquhoun was responsible for undertaking the literature search and acting as second reviewer on all publications and grey data. She coordinated and summarised the data from the systematic review, and liaised with the core GBD group at Harvard University and the University of Washington. She also wrote up the results in the form of this thesis chapter, and wrote an accompanying GBD paper specifically on RHD.

The first GBD summary results for all diseases were published in December 2010 in *The Lancet.* (137, 166, 167) These publications included estimations of prevalence, incidence, DALY, YLL and YLD by region and globally. However, the RHD expert writing group considers that these disease published estimates are likely to have significant errors. Therefore, the RHD expert writing group continues to work with the core GBD group in Seattle to remodel the data and finalise estimations. The data presented in this chapter focus on the systematic review undertaken by the GBD RHD writing group, and the process that has taken place to date to deliver the initial estimations.

### 6.2 Methods

#### 6.2.1 Aim

The project’s aim was to describe the epidemiology of RHD for a comprehensive reassessment of RHD burden in 21 regions of the world, for the period 1990 to 2010. The GBD 2010 Study operational components are shown in Figure 6.1, demonstrating the process of data review, analysis and modelling, and the interaction...
between the expert groups and core group to produce the estimates for incidence, prevalence, mortality, DALY, YLL and YLD.

Figure 6.1: GBD 2010 Operational Components

Source: (168)

6.2.2 GBD Regions

The GBD 2010 Study presented estimates for 187 countries and 21 geographical regions of the world. These regions were selected based on the following principles (168):

- all regions were based on broad geographic regions or continents
- all regions were comprised of no fewer than two countries
countries were grouped based on child and adult mortality levels, and the major causes of death in each country
despite the fact that income is clearly related to epidemiologic profiles, neither income nor national population affected the end result of regionalisation.
The regions are shown in Figure 6.2 and are listed by country in Table 6.1.
Table 6.1: Countries in Each GBD 2010 Region

<table>
<thead>
<tr>
<th>Asia Pacific, High Income</th>
<th>Asia, East</th>
<th>Asia, South</th>
<th>Australasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunei, Japan, Republic of Korea, Singapore</td>
<td>China, Democratic People’s Republic of Korea, Hong Kong, Taiwan</td>
<td>Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan</td>
<td>Australia, New Zealand</td>
</tr>
<tr>
<td>Asia, Central</td>
<td>Asia, South East</td>
<td>Caribbean</td>
<td>Europe, Central</td>
</tr>
<tr>
<td>Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan</td>
<td>Cambodia, Indonesia, Laos People’s Democratic Republic, Malaysia, Maldives, Mauritius, Mayotte, Myanmar, Philippines, Seychelles, Sri Lanka, Thailand, Timor Leste, Vietnam</td>
<td>Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Cayman Islands, Cuba, Dominica, Dominican Republic, French Guiana, Grenada, Guadeloupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, Netherlands Antilles, Saint Kitts and Nevis, St Lucia, St Vincent, Suriname, Trinidad and Tobago, Turks and Caicos Islands</td>
<td>Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia and Montenegro, Slovakia, Slovenia, The Former Yugoslav Republic of Macedonia</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>Europe, Western</td>
<td>Latin America, Andean</td>
<td>Latin America, Central</td>
</tr>
<tr>
<td>Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine</td>
<td>Andorra, Austria, Belgium, Channel Islands, Cyprus, Denmark, Faeroe Islands, Finland, Greece, Greenland, Holy See, Iceland, Ireland, Isle of Man, Israel, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, Saint Pierre et Miquelon, San Marino, Spain, Sweden, Switzerland, United Kingdom</td>
<td>Bolivia, Ecuador, Peru</td>
<td>Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela</td>
</tr>
<tr>
<td>Latin America, Southern</td>
<td>Latin America, Tropical</td>
<td>North Africa/Middle East</td>
<td>North America, High Income</td>
</tr>
<tr>
<td>Argentina, Chile, Falkland Islands (Malvinas), Uruguay</td>
<td>Brazil, Paraguay</td>
<td>Algeria, Bahrain, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Occupied Palestinian Territory, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, United Arab Emirates, Western Sahara, Yemen</td>
<td>Canada, the US</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Oceania</th>
<th>Sub-Saharan Africa, Central</th>
<th>Sub-Saharan Africa, East</th>
<th>Sub-Saharan Africa, Southern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Sao Tome and Principe, Senegal, Sierra Leone, Togo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.2.3 RHD Expert Writing Group

The RHD expert writing group was tasked with undertaking a systematic review to provide population-based RHD data to the GBD core group in Seattle. The data provided by the RHD expert group focused on RHD prevalence, incidence and mortality where population denominators could be provided. The data supplied by the RHD expert group, in combination with vital statistics data from all countries and regions of the world, were used by the core group to assist with the data estimations and modelling process.

6.2.4 Search Strategies for Systematic Review

A systematic review of RHD population-based data (published and grey data) was undertaken to identify data for RHD prevalence, incidence and mortality. The inclusion criteria were population-based data, where the denominator could be calculated and articles or reports for the year of study included as between 1990 to 2009. This timeframe was extended from the GBD guidelines (1990 to 2005 timeframe) to include recently published echocardiography-based studies. Only data on RHD incidence, prevalence and mortality were included. Data pertaining to ARF were not included in this project.

The exclusion criteria were journal articles or reports that were case studies; hospital series; related to diagnosis and treatment; focusing on the Jones Criteria, aetiology, surgical treatment, echocardiography and interventional cardiology, echocardiography (when dealing with techniques and discussing methods of
implementation), clinical profiles, and the outcomes of valve repair; or considering rheumatic fever data only.

6.2.5 Literature Review

The search for published and peer-reviewed data was undertaken with the assistance of a senior medical librarian using Medline & Embase (Ovid SP) and the Cochrane databases. The search terms for published data were ‘rheumatic fever’, rheumatic heart disease’, ‘incidence’, ‘prevalence’, ‘mortality’, ‘epidemiologic studies’, ‘cohort studies’, ‘cross-sectional studies’, ‘epidemiologic methods’ and ‘mass screening’. The search was limited to the years 1990 to 2009.

The search history was checked against a set of key RHD papers to ensure that no critical data were missed. Citations from key publications were also checked, and any additional papers that were not found in the search were included for expert review. Following initial review, papers and reports that did not fit the inclusion criteria were discarded, and the remaining data were sent to two expert reviewers from the RHD GBD writing group (Figure 6.1).

As the number of published population-based studies was limited, it was necessary to search for grey data. This was undertaken in three main ways. First, comprehensive information was requested from regional and national RHD registers in regions where they existed. Second, expert RHD leaders and cardiologists were contacted around the world for unpublished data and/or register data. Third, data sources were searched, including SIGLE, LILAC, university electronic thesis databases,
Lancefield International Symposium on Streptococcal Diseases (LISSD) proceedings and abstracts, Google Scholar, the WHO website and in-country reports, and international government reports and statistics. The search terms for the grey data were ‘rheumatic heart disease’, ‘rheumatic fever’, ‘prevalence/incidence’ and ‘mortality’. The search was limited to the years 1990 to 2009.

The published and grey data for RHD prevalence, incidence and mortality were reviewed by two expert reviewers. Following the correction of data-entering errors, the final dataset was sent to the GBD core team at Harvard University and the University of Washington (Institute for Health Metrics and Evaluation).
6.2.6 Synthesis of Data by Core GBD Group for Modelling Process

The key information required by the GBD group to model the RHD estimates were mortality (by cause of death), incidence, prevalence and duration of life lived with disease. The systematic review was undertaken by the RHD expert group to provide the information for all of these parameters in relation to RHD epidemiology.

However, very few population-based data were found, except for prevalence (where...
most of the studies were in school-aged children). Due to the lack of real data available for many of the parameters and geographical regions, the GBD core group had to use other methods to calculate these parameters.

Cause of death relied on modelling from a total cause of death model. Incidence calculations relied on two methods of modelling, depending on whether data for the region were available or not (see Section 6.2.9). Prevalence was calculated for older age groups, where data were lacking, by modelling in DisMod (personal communication, Mohammad H Forouzanfar, Institute for Health Metrics and Evaluation [IHME], October 2013). DisMod III is a meta-regression modelling tool that integrates results over all ages; thus, if data were available to inform estimations for the younger ages, distribution could be estimated for the older ages by the model (Box 6.1).

**Box 6.1: DisMod III**

DisMod III is a Bayesian meta-regression tool that produces prevalence, incidence, remission, and mortality estimates that are internally consistent. For example, all prevalence cases must have previously been incidence cases, and any decrease in prevalence cases must be accounted for in corresponding increases in remission or mortality. DisMod III uses datasets composed of estimates of a given disease’s prevalence, incidence, remission and mortality from published literature, survey data and cause-specific mortality modelling. It also has the capacity to use predictor variables as covariates (such as income per capita) and expert priors (such as specifying that disease prevalence is zero before a given age) to strengthen its predictive validity.

Source: (169)

### 6.2.7 DisMod Model Development

To ensure that the studies included in the analysis were comparable, the diagnostic method used and population studied were both evaluated. The included studies used echocardiographic confirmation of a clinical diagnosis as the gold standard.
Prevalence data obtained on an Aboriginal population in Australia were used to inform regions where there were sparse or absent data because of high quality of data across all age ranges in the Aboriginal population. The core GBD group used the logarithm of the age-standardised death rate at the country level to inform differentiation between countries, and to estimate for countries without data.

Key parameters selected for the DisMod III model for RHD were considered carefully as follows. First, it was assumed that maximum disease remission rate was 0.02 under the age of 40 years for RHD. This assumption was based on Bland’s longitudinal study published in 1951 that showed, by the end of 20 years of follow-up, the RHD had disappeared in 16% of patients. Second, if valvuloplasty or valve replacement was undertaken, the patient was still considered to have RHD. Third, because of limited data, five-year increments for ages under 30 were chosen to more accurately indicate the different levels of prevalence and incidence for younger ages. RHD does not occur in the early years of life; thus, it was agreed with the core GBD group that the age group of zero to one year would be excluded. However, the core GBD group chose to include data from children in the >1–4 years age group, despite RHD being very uncommon in this age group (Figure 6.4).

6.2.8 Cause of Death Analysis

Due to the paucity of global mortality data for RHD, the mortality estimates were not informed by actual data from high-prevalence countries and regions. Instead, the data were informed by a series of published studies undertaken in the US in the mid-
twentieth century (including Bland’s paper) that examined the long-term outcomes of patients with RHD.(96, 170)

6.2.9 Non-fatal Health Outcomes

The core GBD group generated estimates of disease prevalence, incidence, remission and mortality using DisMod III (Box 6.1).(171) Different epidemiological parameters were extracted, including prevalence of RHD, hospitalisation, cause-specific mortality, valvuloplasty and heart valve repair.

There were very few data to estimate incidence, with observations limited to Fiji, Samoa and Indigenous populations within Australia—all of whom have an established high prevalence of RHD. The data from Australia were not considered nationally representative and there were very scarce data from other countries; thus, the GBD core group calculated incidence data for region-specific models from the prevalence and mortality rates. In countries where prevalence data were sparse or absent, incidence data were derived entirely from Bayesian models, which adjusted for factors such as socioeconomic data, demographic data and all-cause mortality data. The models constructed for the countries where data were available were used
to derive these estimates; therefore, the derived patterns of incidence and prevalence were all similar. Due to global variations in the quality of care and access to advanced treatments for RHD, indicators of hospitalisation or heart valvuloplasty were not used to inform incidence or prevalence estimates.

Finally, the mortality rate of RHD produced during the cause of death estimation (see Section 6.2.7) was used as an input to the models in two ways. In the first method, the log of the age-standardised mortality rate of RHD as a country-level covariate was used during modelling. In the second method, the cause-specific mortality rate of RHD as input data at the regional level was independently used. Since patients with RHD have a higher risk of death due to related cardiovascular conditions, such as stroke, heart failure and endocarditis (all of which were separately estimated as part of the GBD study), the cause-specific mortality rate of RHD was input separately in the Bayesian model.

As the prevalence of RHD and the RHD mortality rate were used as the lower bound for prevalence multiplied by excess mortality, data were required on the survival of patients. Therefore, the literature was searched for the natural history and long-term survival of RHD. Only two studies were found, both from the US in the 1950s.(96, 170) These studies both followed the patients over a 20-year timespan. One study reported the mortality rate of patients in comparison to the general population (8.3 per 1,000 compared to 3.1 per 1,000).(170) The rate of the patients was divided by the population, and this value was used as standardised mortality ratio data and applied to all regions.
Data from Australia and New Zealand Indigenous and Maori populations were used to inform estimates for the Oceania countries of Papua New Guinea and Fiji. Age-standardised hospitalisation rate (diagnosis at discharge) due to RHD was added to the model for 25 countries (Austria, Belgium, Brazil, Canada, Chile, Cyprus, Czech Republic, Denmark, Ecuador, Spain, Finland, Great Britain, Hungary, Ireland, Israel, Italy, Lithuania, Latvia, Mexico, the Netherlands, Norway, Portugal, Slovakia, Sweden and the US). These countries had good quality vital statistics data on RHD (personal communication, Mohammad Forouzanfar, IHME, October 2013).

### 6.2.10 YLD, YLL and DALY

The DALY is a measure that was developed by Harvard University for the World Bank for the GBD 1990 Study. The WHO subsequently adopted the method in 2000. It is now widely used in public health to measure the effect of a disease at a population level. A DALY can be used to quantify loss of healthy years of life due to dying prematurely or due to living with the health consequences of diseases, injuries or risk factors. It is expressed as the number of years lost due to ill health, disability or early death. DALYs refer to the sum of potential YLL due to premature mortality, and productive YLL due to disability. Calculation of potential YLL is an estimate of the average years a person would have lived if he or she had not died prematurely. It is a measure of premature mortality that can be used as an alternative to death rates as it gives more weight to deaths that occur among younger people.(172) YLL does not consider the effect of YLD. DALYs are calculated by considering the sum of these two estimations (DALY = YLL + YLD). See Figure 6.5 for the interaction between DALY, YLD and YLL.
Figure 6.5: Interaction between DALY, YLD and YLL

Source:

6.2.11 Calculation of Disability Weights

The core GBD group calculated the disability weights for all diseases. A disability weight is a weight factor that reflects the severity of the disease on a scale from zero (perfect health) to one (equivalent to death). Years lost due to disability are calculated by multiplying the incident cases by the duration and disability weight for the condition. The studies use the same ‘ideal’ life expectancy for all population subgroups and exclude all non-health characteristics (such as race, socioeconomic status or occupation), apart from age and sex, when calculating lost years of healthy life. Most importantly, they use the same ‘disability weight’ for everyone living one year in a specified health state (168).

When calculating disability weighting, the GBD 2010 Study used the estimated prevalence of clinical RHD. Therefore, it was assumed that RHD patients without heart failure would have a sequel and the disability of having a chronic disease that needs frequent medication and care. For patients with heart failure, the average
disability was calculated by assessing the distribution of the severity of heart failure. The total number of heart failure cases included patients with severity of $\geq$ II based on the New York Heart Association classification of severity of heart failure; thus, two levels of disability were developed. The levels included mild/moderate, and severe heart failure (Box 6.2).

**Box 6.2: New York Heart Association Classification of Heart Failure Severity**

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea (shortness of breath).</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea.</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnoea.</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to undertake any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

**6.2.12 Calculation of Mortality Using Cause of Death Ensemble Model**

To maximise the validity of the Cause of Death Ensemble Model (CODEm), which relies on information other than cause of death data to estimate RHD mortality, five general principles were used in this study:

1. identify all the available data
2. maximise the comparability and quality of the dataset
3. develop a diverse set of plausible models
4. assess the predictive validity of each plausible individual model and the ensemble models
5. choose the model or ensemble model with the best performance in out-of-
sample predictive analysis.

CODEm explores a large variety of possible models to estimate trends in causes of death. Possible models were identified using covariate selection algorithms that yielded many plausible combinations of covariates—risk factors that are associated with RHD—that were then run through different model classes (personal email communication Feb 2013, Mohammad Forouzanfar, Christopher JL Murray, Mohsen Naghavi, GBD core group members).

The covariates chosen were considered plausible based on their relation to the probability of transmission and socioeconomic status. RHD incidence is known to be related to socioeconomic status. Health system access, access to improved water and sanitation, incidence and case fatality, education, and per capita income were included as indicators for socioeconomic status. High population density was included because this increases the transmission of GAS, which can lead to ARF. Malnutrition was selected for its relation to immune system incompetence.

The GBD core group selected a set of plausible covariates based on existing literature, and divided these covariates into three groups based on the strength of epidemiological evidence for their association with RHD:

1. Class 1 covariates had strong evidence and a biologically plausible pathway
2. Class 2 covariates had some evidence, but with a less direct causal pathway
3. Class 3 covariates had general correlation evidence for a relationship, as observed in previous time series or cross-sectional studies.
Each plausible covariate was assigned an expected direction, with a negative direction indicating that an increase in that covariate leads to a decrease in RHD, and a positive direction indicating the reverse.

The level of data available for cardiovascular disease varied by data source, with studies reporting all cardiovascular deaths as one aggregate category. In order to take advantage of all cardiovascular death data and produce a more accurate estimate of RHD deaths over time, RHD mortality was adjusted so that the sum of cause-specific mortality rates equalled the mortality rate from all cardiovascular causes. The GBD core group also corrected the all-cardiovascular mortality to sum with other causes to all-cause mortality using the same approach. From an estimation perspective, this is an important step because the data available to inform trends and levels in all cardiovascular and all-cause mortality are usually orders of magnitude larger than the data for cause-specific mortality (email communication with GBD core group: 2012, 2103).

Mortality envelopes were created comprising all deaths from RHD compiled from published data, vital statistics data and verbal autopsy. Comparable estimates of mortality envelopes were developed for all countries with populations estimated to be 250,000 or more in 2005 (countries with populations of less than 250,000 were generally treated in regional aggregates) and for smaller countries with non-problematic sources of data. The estimates were developed for the period from 1990, 2005 and 2010, by gender and for five-year age groups from age five to age 84 and an open-age interval of 85 years plus. Deaths were then cumulated across countries within each GBD study region and by GBD study age groups.
6.3 Results

6.3.1 Systematic Review

The Medline search of peer-reviewed publications found 473 articles. Of these, 126 included studies that met the inclusion criteria for review and, of these, 47 were considered appropriate for inclusion following review by the GBD RHD expert group. An additional eight articles were included following reference cross-checks and identification of key papers by the RHD expert group members. Requests to international colleagues and searches for grey data identified an additional 80 sources of potential data. Of these, 18 met the initial inclusion criteria and were sent to the GBD RHD expert group for review, and all 18 were deemed suitable for inclusion. A total of 76 articles and reports met the inclusion criteria (Figure 6.6).

6.3.2 Summary of Data Found

Regional data were obtained for 18 of the 21 regions included in the GBD study regions. No data were found for the regions of America Southern, Europe Western or Asia Central. Prevalence data from 76 studies covering 18 GDB regions are summarised in Appendix 2. The majority of data found came from the Asia, Africa, Australia, New Zealand and Pacific (Oceania) regions. A total of 84% of the published studies were conducted in school-aged children, assessing RHD prevalence only. A number of the most recent studies used echocardiography confirmed diagnosis, whereas earlier studies relied on clinical findings alone. Only five published studies describing RHD incidence were found. Studies providing
population-based mortality data were also lacking, with only four sources of population-based mortality data identified, from Australia, New Zealand and Ethiopia. The GBD core group independently collected vital statistics data from all global regions, which were used to inform modelling in conjunction with the systematic review data.

Figure 6.6: Flowchart of GBD RHD Expert Group Systematic Review Process

6.3.3 GBD Core Group Input Data from Systematic Review

There were three types of input data from the GBD RHD expert group’s systematic review that were included in the DisMod modelling: prevalence data, incidence data and mortality data. First, the GBD core group extracted prevalence data from the 76
studies. The definition of RHD differed between studies. Surveys primarily used diagnosis by a physician during physical examination; however, some studies reported cases assessed by echocardiography. Diagnosis by a physician with confirmation using echocardiography was used as the gold standard, and studies with other means of diagnosis were used as a covariate. Specific studies that reported prevalence that was higher than expected were reevaluated, and one study that included diagnoses by both echocardiography and clinical diagnoses was used to adjust for an implausibly higher prevalence in Central Latin America compared to other regions. Data included in the modelling from the systematic review informed prevalence and mortality in the DisMod modelling process (Table 6.2).

### Table 6.2: Data Records of Each Data Type Included in the Modelling

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
<th>Mortality</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia, South</td>
<td>49</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Asia, Southeast</td>
<td>30</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Australasia</td>
<td>24</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>North Africa/Middle East</td>
<td>23</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Sub-Saharan Africa, East</td>
<td>22</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Oceania</td>
<td>16</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Latin America, Central</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Central</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>North America, High Income</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Asia, East</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Caribbean</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Latin America, Andean</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Latin America, Southern</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Europe, Western</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Europe, Central</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asia, Central</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asia Pacific, High Income</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: One study may provide several lines of data by age, sex or years
6.3.4 RHD Prevalence Data by Region, Age and Sex

In 1990, the total number of prevalent cases of RHD estimated globally was 29,172,383. This increased to 33,468,203 in 1995 and to 34,232,795 in 2010 (Table 6.3). The number of cases was higher in females than males for all regions and all periods examined. In 2010, the regions with the highest number of cases were the populous regions of Asia South, Asia East and Asia South East, with Eastern Europe also having a high number of cases reported. The regions with the lowest number of cases were Australasia, Oceania and Latin American regions (Table 6.3). However, in 2010, the highest all age global prevalence per 1,000 population was seen in Oceania and Eastern Europe (both 9.8 per 1,000); Sub-Saharan Africa, West (7.6 per 1,000); Sub-Saharan Africa, East (7.2 per 1,000); Asia, South East (6.3 per 1,000); and Asia, Central (6.4 per 1,000). The lowest regional prevalence figures were seen in Australasia (1.1 per 1,000) and the Caribbean (1.8 per 1,000). See Table 6.4 for prevalence data from all regions for 2010.
### Table 6.3: Prevalence of RHD by Region and Gender

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>North America, High Income</td>
<td>373,185</td>
<td>732,236</td>
<td>1,105,421</td>
<td>424,531</td>
<td>636,429</td>
<td>1,060,960</td>
<td>436,101</td>
<td>645,954</td>
<td>1,082,055</td>
</tr>
<tr>
<td>Latin America, Southern</td>
<td>71,587</td>
<td>113,809</td>
<td>185,396</td>
<td>70,705</td>
<td>110,978</td>
<td>181,683</td>
<td>73,569</td>
<td>115,669</td>
<td>189,238</td>
</tr>
<tr>
<td>Europe, Western</td>
<td>597,643</td>
<td>970,904</td>
<td>1,568,547</td>
<td>564,227</td>
<td>915,063</td>
<td>1,479,290</td>
<td>550,786</td>
<td>904,295</td>
<td>1,455,081</td>
</tr>
<tr>
<td>Australasia</td>
<td>10,901</td>
<td>17,486</td>
<td>28,387</td>
<td>10,009</td>
<td>16,557</td>
<td>26,566</td>
<td>10,417</td>
<td>17,588</td>
<td>28,005</td>
</tr>
<tr>
<td>Asia Pacific, High Income</td>
<td>220,117</td>
<td>353,705</td>
<td>573,822</td>
<td>183,451</td>
<td>305,404</td>
<td>488,855</td>
<td>184,508</td>
<td>299,153</td>
<td>483,661</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>957,948</td>
<td>1,585,936</td>
<td>2,543,884</td>
<td>886,326</td>
<td>1,370,654</td>
<td>2,256,980</td>
<td>784,917</td>
<td>1,281,033</td>
<td>2,065,950</td>
</tr>
<tr>
<td>Europe, Central</td>
<td>278,849</td>
<td>422,737</td>
<td>701,586</td>
<td>249,078</td>
<td>319,620</td>
<td>568,698</td>
<td>242,003</td>
<td>305,447</td>
<td>547,450</td>
</tr>
<tr>
<td>Asia, Central</td>
<td>187,347</td>
<td>289,637</td>
<td>476,984</td>
<td>210,102</td>
<td>310,658</td>
<td>520,760</td>
<td>210,002</td>
<td>308,637</td>
<td>518,637</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>546,804</td>
<td>902,967</td>
<td>1,449,771</td>
<td>908,218</td>
<td>1,370,563</td>
<td>2,278,781</td>
<td>1,037,326</td>
<td>1,521,926</td>
<td>2,559,252</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>130,993</td>
<td>206,994</td>
<td>337,987</td>
<td>172,492</td>
<td>272,811</td>
<td>445,303</td>
<td>177,775</td>
<td>266,925</td>
<td>444,700</td>
</tr>
<tr>
<td>Sub-Saharan Africa, East</td>
<td>648,346</td>
<td>955,177</td>
<td>1,603,523</td>
<td>966,648</td>
<td>1,474,119</td>
<td>2,440,767</td>
<td>1,080,809</td>
<td>1,655,892</td>
<td>2,736,701</td>
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<td>Sub-Saharan Africa, Central</td>
<td>155,691</td>
<td>241,319</td>
<td>397,010</td>
<td>201,691</td>
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<td>496,000</td>
<td>234,722</td>
<td>350,058</td>
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<td>North Africa / Middle East</td>
<td>307,891</td>
<td>459,366</td>
<td>767,257</td>
<td>408,689</td>
<td>584,571</td>
<td>993,260</td>
<td>441,109</td>
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<td>Asia, South</td>
<td>1,965,424</td>
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<td>5,022,782</td>
<td>4,095,412</td>
<td>5,431,748</td>
<td>9,527,160</td>
<td>4,220,195</td>
<td>5,662,012</td>
<td>9,882,207</td>
</tr>
<tr>
<td>Oceania</td>
<td>24,300</td>
<td>33,110</td>
<td>57,410</td>
<td>35,809</td>
<td>48,516</td>
<td>84,325</td>
<td>38,978</td>
<td>52,469</td>
<td>91,447</td>
</tr>
<tr>
<td>Asia, Southeast</td>
<td>1,236,225</td>
<td>1,979,432</td>
<td>3,215,657</td>
<td>1,544,876</td>
<td>2,335,231</td>
<td>3,880,107</td>
<td>1,576,475</td>
<td>2,343,023</td>
<td>3,919,498</td>
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<tr>
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<td>3,344,926</td>
<td>5,093,119</td>
<td>8,438,045</td>
<td>2,371,637</td>
<td>3,590,599</td>
<td>5,962,236</td>
<td>2,326,592</td>
<td>3,446,920</td>
<td>5,773,512</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
<td>118,837</td>
<td>188,038</td>
<td>306,875</td>
<td>130,255</td>
<td>187,024</td>
<td>317,279</td>
<td>133,412</td>
<td>192,513</td>
<td>325,925</td>
</tr>
<tr>
<td>Latin America, Central</td>
<td>96,849</td>
<td>149,009</td>
<td>245,858</td>
<td>110,708</td>
<td>185,335</td>
<td>296,043</td>
<td>118,068</td>
<td>193,062</td>
<td>311,130</td>
</tr>
<tr>
<td>Latin America, Andean</td>
<td>32,409</td>
<td>50,948</td>
<td>83,357</td>
<td>36,094</td>
<td>58,574</td>
<td>94,668</td>
<td>37,959</td>
<td>60,507</td>
<td>98,466</td>
</tr>
<tr>
<td>Caribbean</td>
<td>24,384</td>
<td>38,437</td>
<td>62,821</td>
<td>27,477</td>
<td>41,008</td>
<td>68,485</td>
<td>27,661</td>
<td>42,427</td>
<td>70,088</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>11,330,658</td>
<td>17,841,725</td>
<td>29,172,383</td>
<td>13,608,433</td>
<td>19,859,770</td>
<td>33,468,203</td>
<td>13,943,383</td>
<td>20,289,412</td>
<td>34,232,795</td>
</tr>
</tbody>
</table>
Table 6.4: RHD Prevalence Rate per 1,000 Population, by Region, 2010

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence per 1,000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific, High Income</td>
<td>2.7</td>
<td>1.7–4.1</td>
</tr>
<tr>
<td>Asia, Central</td>
<td>6.4</td>
<td>4.8–8.3</td>
</tr>
<tr>
<td>Asia, East</td>
<td>4.1</td>
<td>2.7–5.8</td>
</tr>
<tr>
<td>Asia, South</td>
<td>5.9</td>
<td>4.6–7.4</td>
</tr>
<tr>
<td>Asia, Southeast</td>
<td>6.3</td>
<td>5.0–8.1</td>
</tr>
<tr>
<td>Australasia</td>
<td>1.1</td>
<td>0.7–1.5</td>
</tr>
<tr>
<td>Caribbean</td>
<td>1.8</td>
<td>1.3–2.5</td>
</tr>
<tr>
<td>Europe, Central</td>
<td>4.5</td>
<td>3.5–5.8</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>9.8</td>
<td>6.7–14.1</td>
</tr>
<tr>
<td>Europe, Western</td>
<td>3.4</td>
<td>2.9–4.0</td>
</tr>
<tr>
<td>Latin America, Andean</td>
<td>1.8</td>
<td>1.3–2.6</td>
</tr>
<tr>
<td>Latin America, Central</td>
<td>1.3</td>
<td>1.0–1.7</td>
</tr>
<tr>
<td>Latin America, Southern</td>
<td>3.1</td>
<td>2.1–4.7</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
<td>1.6</td>
<td>1.1–2.3</td>
</tr>
<tr>
<td>North Africa / Middle East</td>
<td>2.3</td>
<td>1.9–2.8</td>
</tr>
<tr>
<td>North America, High Income</td>
<td>3.1</td>
<td>2.5–3.9</td>
</tr>
<tr>
<td>Oceania</td>
<td>9.8</td>
<td>6.7–14.3</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Central</td>
<td>6.3</td>
<td>4.3–9.4</td>
</tr>
<tr>
<td>Sub-Saharan Africa, East</td>
<td>7.7</td>
<td>6.4–9.3</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>6.1</td>
<td>4.0–9.3</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>7.6</td>
<td>5.7–10.1</td>
</tr>
<tr>
<td>Global</td>
<td>5.0</td>
<td>4.5–5.5</td>
</tr>
</tbody>
</table>

The prevalence data for all time points showed a large number of cases in the younger age groups, commencing in the five to nine age group, and rising steadily across all regions until 20 to 24 years, followed by a progressive decline in the number of prevalent cases in the older age groups. The data showed a peak in the number of cases detected in the younger age groups (Figure 6.7).
The regional variation in prevalence showed Oceania and Eastern Europe with the highest prevalence for all age groups across all three time points. The data from 2010 are shown in Figure 6.8, with the Asian and Sub-Saharan African regions also showing high prevalence. Australasia, North America and Western Europe showed the lowest prevalence across all age groups.
The global number of incident RHD cases for 1990 and 2005 was reported as 2,146,273 and 1,542,454, respectively. In 2010, there were 1,775,145 incident cases, with females representing a total of 959,827 cases (54.1%) (Figure 6.9).
The age distribution of the total number of incident cases by age group showed high numbers of incidence cases in very young children aged five to nine years. It also showed a rapid decline through later childhood and adolescence, and a steady increase in the number of cases from 40 years of age, with the highest number of cases shown in the oldest age groups (Figure 6.10). The data by selected region for 2010 are shown in Figure 6.11. The data from 1990 and 2005 presented similar age distribution across regions (data not shown).
Figure 6.10: Global RHD Incidence per 100,000 by Age Group, 1990, 2005 and 2010

Figure 6.11: Global RHD Incidence (Per 100,000) 2010—Selected Regions
6.3.6 Deaths from RHD

The data modelled by the GBD core group presented a global total of 8,593,116 deaths from RHD for the period 1990 to 2010, collectively. There was a decline in the annual number of deaths estimated globally over this period, from 462,579 deaths in 1990 to an estimated 345,100 in 2010. The calculated number of deaths per year and by region is shown in Table 6.5.

Table 6.5: Estimated Number of Deaths from RHD by Region and Time Point

<table>
<thead>
<tr>
<th>Region</th>
<th>1990</th>
<th>2005</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America, High Income</td>
<td>11,492</td>
<td>7,496</td>
<td>7,712</td>
</tr>
<tr>
<td>Latin America, Southern</td>
<td>5,304</td>
<td>4,468</td>
<td>4,608</td>
</tr>
<tr>
<td>Europe, Western</td>
<td>36,917</td>
<td>25,697</td>
<td>25,402</td>
</tr>
<tr>
<td>Australasia</td>
<td>1,105</td>
<td>823</td>
<td>922</td>
</tr>
<tr>
<td>Asia Pacific, High Income</td>
<td>14,234</td>
<td>9,510</td>
<td>10,873</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>20,327</td>
<td>15,162</td>
<td>10,080</td>
</tr>
<tr>
<td>Europe, Central</td>
<td>10,717</td>
<td>7,901</td>
<td>7,505</td>
</tr>
<tr>
<td>Asia, Central</td>
<td>4,946</td>
<td>5,346</td>
<td>5,430</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>8,324</td>
<td>7,684</td>
<td>7,787</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>1,661</td>
<td>3,704</td>
<td>2,853</td>
</tr>
<tr>
<td>Sub-Saharan Africa, East</td>
<td>11,711</td>
<td>11,783</td>
<td>11,813</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Central</td>
<td>2,839</td>
<td>3,423</td>
<td>3,819</td>
</tr>
<tr>
<td>North Africa/Middle East</td>
<td>33,769</td>
<td>30,380</td>
<td>31,671</td>
</tr>
<tr>
<td>Asia, South</td>
<td>106,205</td>
<td>106,402</td>
<td>109,388</td>
</tr>
<tr>
<td>Oceania</td>
<td>522</td>
<td>654</td>
<td>655</td>
</tr>
<tr>
<td>Asia, Southeast</td>
<td>40,590</td>
<td>33,598</td>
<td>32,357</td>
</tr>
<tr>
<td>Asia, East</td>
<td>134,804</td>
<td>77,994</td>
<td>60,348</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
<td>8,380</td>
<td>5,612</td>
<td>5,892</td>
</tr>
<tr>
<td>Latin America, Central</td>
<td>5,531</td>
<td>3,440</td>
<td>3,477</td>
</tr>
<tr>
<td>Latin America, Andean</td>
<td>1,463</td>
<td>1,278</td>
<td>1,285</td>
</tr>
<tr>
<td>Caribbean</td>
<td>1,741</td>
<td>1,320</td>
<td>1,232</td>
</tr>
<tr>
<td>Global</td>
<td>462,579</td>
<td>363,864</td>
<td>345,110</td>
</tr>
</tbody>
</table>

Figure 6.12 shows the age-standardised global RHD mortality for the three time points for both sexes combined, demonstrating increasing mortality commencing from 40 years of age. The age-standardised mortality was higher in females for all three time points and for all ages. Male data and 1990 and 2005 data are not shown (Figure 6.13).
Figure 6.12: Global RHD Age-standardised Mortality (per 100,000), 1990, 2005 and 2010 (Both Sexes Combined)

Figure 6.13: RHD Age-standardised Mortality (per 100,000) by Selected Region, 2010 (Female Only)
6.3.7 YLL

The data provided by the core GBD group showed a decline in the numbers of YLL globally due to RHD over a 30-year period, from 13,800,000 in 1980 to 8,704,175 in 2010. The regions with the largest number of YLL were South East Asia, East Asia and South Asia; however, South East Asia and East Asia showed a decline in numbers over this 30-year period, whereas South Asia showed an increase. The data from North Africa/the Middle East showed a decline in YLL over the 30-year period; however, the numbers were very high compared to most other regions (Table 6.6).
Table 6.6: Summary of YLL (Five-year Intervals)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>North America, High Income</td>
<td>233,292</td>
<td>206,867</td>
<td>178,826</td>
<td>156,023</td>
<td>112,849</td>
<td>96,679</td>
<td>95,619</td>
</tr>
<tr>
<td>Latin America, Southern</td>
<td>92,482</td>
<td>98,919</td>
<td>102,454</td>
<td>88,361</td>
<td>68,664</td>
<td>61,451</td>
<td>60,381</td>
</tr>
<tr>
<td>Europe, Western</td>
<td>641,353</td>
<td>550,488</td>
<td>483,627</td>
<td>413,325</td>
<td>327,634</td>
<td>264,038</td>
<td>244,679</td>
</tr>
<tr>
<td>Australasia</td>
<td>19,097</td>
<td>17,518</td>
<td>15,851</td>
<td>13,871</td>
<td>11,007</td>
<td>10,050</td>
<td>10,323</td>
</tr>
<tr>
<td>Asia Pacific, High Income</td>
<td>237,865</td>
<td>228,195</td>
<td>214,476</td>
<td>135,663</td>
<td>97,836</td>
<td>94,334</td>
<td>95,466</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>756,250</td>
<td>700,774</td>
<td>595,869</td>
<td>727,069</td>
<td>520,781</td>
<td>429,102</td>
<td>264,324</td>
</tr>
<tr>
<td>Europe, Central</td>
<td>324,517</td>
<td>293,133</td>
<td>257,518</td>
<td>227,348</td>
<td>160,927</td>
<td>128,911</td>
<td>111,412</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>294,538</td>
<td>320,567</td>
<td>352,155</td>
<td>392,176</td>
<td>356,069</td>
<td>311,987</td>
<td>302,902</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>68,650</td>
<td>65,184</td>
<td>66,942</td>
<td>86,766</td>
<td>131,962</td>
<td>163,267</td>
<td>113,490</td>
</tr>
<tr>
<td>Sub-Saharan Africa, East</td>
<td>394,658</td>
<td>430,588</td>
<td>462,400</td>
<td>466,540</td>
<td>438,889</td>
<td>423,543</td>
<td>396,678</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Central</td>
<td>98,349</td>
<td>106,526</td>
<td>115,995</td>
<td>125,902</td>
<td>127,504</td>
<td>132,560</td>
<td>147,615</td>
</tr>
<tr>
<td>North Africa / Middle East</td>
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<td>1,123,817</td>
<td>1,120,854</td>
<td>1,060,506</td>
<td>888,115</td>
<td>817,669</td>
<td>828,959</td>
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<tr>
<td>Asia, South</td>
<td>2,907,818</td>
<td>2,992,602</td>
<td>3,344,002</td>
<td>3,686,517</td>
<td>3,718,625</td>
<td>3,262,740</td>
<td>3,229,197</td>
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<tr>
<td>Oceania</td>
<td>12,427</td>
<td>14,103</td>
<td>17,115</td>
<td>19,138</td>
<td>20,274</td>
<td>21,269</td>
<td>20,945</td>
</tr>
<tr>
<td>Asia, Southeast</td>
<td>1,133,103</td>
<td>1,176,333</td>
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<td>1,378,431</td>
<td>1,263,327</td>
<td>1,083,147</td>
<td>997,508</td>
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<tr>
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<td>4,341,728</td>
<td>3,929,722</td>
<td>3,225,940</td>
<td>2,641,705</td>
<td>1,868,130</td>
<td>1,334,049</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
<td>282,663</td>
<td>250,638</td>
<td>221,657</td>
<td>190,187</td>
<td>147,108</td>
<td>133,879</td>
<td>128,358</td>
</tr>
<tr>
<td>Latin America, Central</td>
<td>196,584</td>
<td>168,843</td>
<td>157,452</td>
<td>134,342</td>
<td>102,544</td>
<td>86,605</td>
<td>82,944</td>
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<tr>
<td>Latin America, Andean</td>
<td>47,544</td>
<td>50,204</td>
<td>47,650</td>
<td>44,842</td>
<td>36,380</td>
<td>34,559</td>
<td>31,299</td>
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<tr>
<td>Caribbean</td>
<td>61,182</td>
<td>59,975</td>
<td>51,647</td>
<td>45,205</td>
<td>38,410</td>
<td>32,661</td>
<td>28,080</td>
</tr>
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<td>13,800,000</td>
<td>13,400,000</td>
<td>13,200,000</td>
<td>12,900,000</td>
<td>11,400,000</td>
<td>9,650,691</td>
<td>8,704,175</td>
</tr>
</tbody>
</table>
6.3.8 YLD

Final YLD calculations were obtained by applying the disability weights to the final prevalence estimates. The highest burden was seen in Asian regions across all three time points, while Eastern Europe also showed a high burden with similar numbers to East and West Sub-Saharan Africa (Table 6.7).

Table 6.7: YLD by Region and Time Point

<table>
<thead>
<tr>
<th>GBD region</th>
<th>1990</th>
<th>2005</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America, High Income</td>
<td>40,153</td>
<td>42,594</td>
<td>44,595</td>
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<tr>
<td>Latin America, Southern</td>
<td>8,391</td>
<td>9,644</td>
<td>10,586</td>
</tr>
<tr>
<td>Europe, Western</td>
<td>76,168</td>
<td>84,077</td>
<td>86,833</td>
</tr>
<tr>
<td>Australasia</td>
<td>2,042</td>
<td>2,264</td>
<td>2,618</td>
</tr>
<tr>
<td>Asia Pacific, High Income</td>
<td>23,797</td>
<td>21,342</td>
<td>22,260</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>103,376</td>
<td>103,488</td>
<td>97,706</td>
</tr>
<tr>
<td>Europe, Central</td>
<td>29,553</td>
<td>27,721</td>
<td>27,992</td>
</tr>
<tr>
<td>Asia, Central</td>
<td>19,345</td>
<td>22,854</td>
<td>23,413</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>48,457</td>
<td>76,044</td>
<td>86,356</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>12,264</td>
<td>16,895</td>
<td>17,380</td>
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<tr>
<td>Sub-Saharan Africa, East</td>
<td>58,298</td>
<td>88,474</td>
<td>101,214</td>
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<td>Sub-Saharan Africa, Central</td>
<td>13,941</td>
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<td>North Africa / Middle East</td>
<td>36,868</td>
<td>48,236</td>
<td>53,218</td>
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<td>Asia, South</td>
<td>214,632</td>
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<td>410,273</td>
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<td>2,171</td>
<td>3,374</td>
<td>3,774</td>
</tr>
<tr>
<td>Asia, Southeast</td>
<td>123,538</td>
<td>142,184</td>
<td>146,215</td>
</tr>
<tr>
<td>Asia, East</td>
<td>300,427</td>
<td>227,971</td>
<td>225,499</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
<td>15,950</td>
<td>18,735</td>
<td>20,467</td>
</tr>
<tr>
<td>Latin America, Central</td>
<td>12,137</td>
<td>15,020</td>
<td>16,484</td>
</tr>
<tr>
<td>Latin America, Andean</td>
<td>3,299</td>
<td>4,084</td>
<td>4,356</td>
</tr>
<tr>
<td>Caribbean</td>
<td>3,052</td>
<td>3,722</td>
<td>3,948</td>
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<tr>
<td>Global</td>
<td>1,147,859</td>
<td>1,363,011</td>
<td>1,427,018</td>
</tr>
</tbody>
</table>

6.3.9 DALY

The DALYs calculated by the core GBD group are presented in Table 6.8. There was a decline in the number of global DALYs due to RHD over the period studied, with
an estimated 14,382,011 DALYs in 1990 declining to 10,131,193 in 2010. The highest DALY burden from RHD was shown in the regions of South East, South and East Asia; however, the data also presented a high number of DALYs from RHD in the North Africa/Middle East region, greatly in excess of the DALY burden seen in the high-prevalence Sub-Saharan African regions (Table 6.8).

Table 6.8: DALYs by Region and Time Point

<table>
<thead>
<tr>
<th>GBD region</th>
<th>1990</th>
<th>2005</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America, High Income</td>
<td>218,979</td>
<td>139,273</td>
<td>140,214</td>
</tr>
<tr>
<td>Latin America, Southern</td>
<td>110,845</td>
<td>71,095</td>
<td>70,967</td>
</tr>
<tr>
<td>Europe, Western</td>
<td>559,795</td>
<td>348,115</td>
<td>331,512</td>
</tr>
<tr>
<td>Australasia</td>
<td>17,893</td>
<td>12,314</td>
<td>12,941</td>
</tr>
<tr>
<td>Asia Pacific, High Income</td>
<td>238,273</td>
<td>115,676</td>
<td>117,726</td>
</tr>
<tr>
<td>Europe, Eastern</td>
<td>699,245</td>
<td>532,590</td>
<td>362,030</td>
</tr>
<tr>
<td>Europe, Central</td>
<td>287,071</td>
<td>156,632</td>
<td>139,404</td>
</tr>
<tr>
<td>Asia, Central</td>
<td>209,672</td>
<td>216,965</td>
<td>203,360</td>
</tr>
<tr>
<td>Sub-Saharan Africa, West</td>
<td>400,612</td>
<td>388,031</td>
<td>389,258</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Southern</td>
<td>79,206</td>
<td>180,162</td>
<td>130,870</td>
</tr>
<tr>
<td>Sub-Saharan Africa, East</td>
<td>520,698</td>
<td>512,017</td>
<td>497,892</td>
</tr>
<tr>
<td>Sub-Saharan Africa, Central</td>
<td>129,936</td>
<td>150,829</td>
<td>169,446</td>
</tr>
<tr>
<td>North Africa / Middle East</td>
<td>1,157,722</td>
<td>865,905</td>
<td>882,177</td>
</tr>
<tr>
<td>Asia, South</td>
<td>3,558,634</td>
<td>3,648,759</td>
<td>3,639,470</td>
</tr>
<tr>
<td>Oceania</td>
<td>19,286</td>
<td>24,643</td>
<td>24,719</td>
</tr>
<tr>
<td>Asia, Southeast</td>
<td>1,431,153</td>
<td>1,225,331</td>
<td>1,143,723</td>
</tr>
<tr>
<td>Asia, East</td>
<td>4,230,149</td>
<td>2,096,101</td>
<td>1,559,548</td>
</tr>
<tr>
<td>Latin America, Tropical</td>
<td>237,607</td>
<td>152,614</td>
<td>148,825</td>
</tr>
<tr>
<td>Latin America, Central</td>
<td>169,589</td>
<td>101,625</td>
<td>99,428</td>
</tr>
<tr>
<td>Latin America, Andean</td>
<td>50,949</td>
<td>38,643</td>
<td>35,655</td>
</tr>
<tr>
<td>Caribbean</td>
<td>54,699</td>
<td>36,383</td>
<td>32,028</td>
</tr>
<tr>
<td>Global</td>
<td>14,382,011</td>
<td>11,013,702</td>
<td>10,131,193</td>
</tr>
</tbody>
</table>

6.3.10 GBD 2010 Global RHD Data Summary

A summary of the global RHD data estimates produced by the core GBD group for the three time points (1995, 2005 and 2010) and published in 2012 as the initial estimates are shown in Table 6.9.(108, 137, 166)
Table 6.9: Summary GBD 2010 Study Global RHD Data for Three Time Points

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>2005</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>29,172,383</td>
<td>33,468,203</td>
<td>34,232,795</td>
</tr>
<tr>
<td>YLL</td>
<td>13,267,810</td>
<td>9,670,605</td>
<td>8,720,292</td>
</tr>
<tr>
<td>YLD</td>
<td>1,150,422</td>
<td>1,365,502</td>
<td>1,429,575</td>
</tr>
<tr>
<td>DALY</td>
<td>14,418,232</td>
<td>11,036,107</td>
<td>10,149,867</td>
</tr>
<tr>
<td>Deaths</td>
<td>462,579</td>
<td>363,864</td>
<td>345,110</td>
</tr>
</tbody>
</table>

6.4 Discussion

The data estimated by the GBD 2010 Study present a higher burden of RHD than previously reported, with a global prevalence of 34,232,795 RHD cases, 8,593,116 incident cases and 345,110 deaths globally in 2010. This compares to the 2005 estimation published by Carapetis et al. that showed a global prevalence of 15.6 million RHD cases (less than half the number reported in this new estimation), 282,000 incident cases and 233,000 deaths each year. The GBD 2010 Study calculated incident cases at 363,864 in 2005, which is closer to the 2005 published estimate.

6.4.1 Prevalence Data

The GBD 2010 data showed a decline in the number of prevalent cases over the period 1990 to 2010 globally and in most regions of the world. The distribution of prevalence by age seen in 2005 and 2010 had an unusual pattern, showing a peak in early childhood followed by a decline from teenage years onwards. The 1990 data appeared to present a more plausible and familiar distribution of prevalence by age group (Figure 6.7). Further examination of the data is required to determine if the distribution of prevalence from 2005 and 2010 are correct. While these data are
probably closer to the true burden than previous estimates, caution must be taken when interpreting and reporting the results. Many regions lack accurate data on which to base estimates, and the echocardiography screening data that are available are mainly from studies undertaken in school-aged children, without standard methodologies in place. New international consensus guidelines for RHD echocardiography diagnosis were published in 2012, and these will contribute to a more standardised approach in the screening methodology used in prevalence studies. This will allow the provision of better quality data as portable echocardiography becomes more accessible and available for use in field RHD screening.

The regions with the highest prevalence were Oceania and Eastern Europe (both 9.8 per 1,000 cases). There are good published and grey data available from Oceania from a number of screening studies and from RHD registers in the region, and the results presented here substantiate the evidence that there are very high rates of disease in this region. However, the figures reported from Eastern Europe have not previously been substantiated by published or grey data reports, and further examination of the data is required to explore this phenomenon. The Sub-Saharan African and Asian regions show a high prevalence of disease, with an increase in the number of prevalent cases reported over the period studied. This may be due to better quality data becoming available; however, there are still relatively few published RHD prevalence studies from the African region to influence the calculation of the total burden from RHD.
Prevalence was seen to decline in East Asia from 8.4 million cases in 1990 to 5.7 million cases in 2010, which may partly be due to the strengthening of the Chinese economy. However, the prevalence in East Asia at all three time points is still considerably higher than previously estimated. The GBD East Asia region includes middle to higher income countries, such as the Democratic People’s Republic of Korea, Hong Kong and Taiwan, as well as China. This regional allocation may mask subpopulations within China where there are people living in very poor circumstances alongside wealthier classes.

The allocation of countries to the 21 GBD regions does not allow examination of inequity between socioeconomic status both between and within countries. A key example of this problem is the very low overall prevalence seen in the Australasia region, despite the fact that Indigenous and Maori populations of Australia and New Zealand are demonstrated to have among the highest prevalence of RHD globally.

There are a number of situations in which there appear to be regional inconsistencies in the data. For example, the North Africa/Middle East region had a prevalence of 2.8 per 1,000—three times lower than Sub-Saharan Africa—but report three times the number of deaths (31,671 deaths in North Africa/the Middle East compared to 11,813 in Eastern Sub-Saharan Africa and 7,787 in Western Sub-Saharan Africa). This highlights an issue with the data available from the GBD core group, where deaths were provided to the RHD expert group as absolute numbers instead of rates. It may be that RHD mortality rate is actually lower in North Africa/the Middle East region than Sub-Saharan African regions; however, without the availability of
population denominators used by the core group for these regions, it was not possible to make this calculation.

The GBD RHD expert writing group did not have input into the grouping of countries in the region, and noted that some regions contained both low and high-income countries, such as North Africa/the Middle East. The regionalisation of countries did not allow for analysis of potentially at-risk subpopulations (such as the Indigenous populations of Australia, New Zealand, the US and Canada) or inequity in socioeconomic status within countries (such as populations in China, India and the Middle East/North Africa). The approach of clustering countries together to form 21 regions appears to be a shortcoming of the GBD process because it did not permit examination of the data by subpopulations and known high-prevalence countries within wider regions. In some cases, this regional allocation may be appropriate—such as in the Oceania region, where the burden of RHD is distributed fairly evenly across the nations. However, many other regions contain disparate populations and countries of different socioeconomic circumstances with inequitable distribution of wealth, which could not be explored using this methodology. Recently, the GBD core group released estimations by country on the IHME website; however, this study did not have access to these data.

6.4.2 Incidence Data

The incidence data estimates currently available are concerning for two main reasons. First, the data show the highest incidence in very young children and people aged above 70 years. This is at odds with the natural history of RHD, where the peak
incidence is known to be in young people aged in their early teenage years up until age 30 to 35, with a rapid decline in incident cases in people aged over 40. (173) Recent data from the NT, Australia, shows incidence distribution by age group. The distribution of incidence by age group has been shown to be similar in earlier studies (Figure 6.14) that are very different from the incidence distribution by age group shown by the GBD RHD data (see Figures 6.9, 6.10 and 6.11).

![Figure 6.14: Age-specific RHD Incidence in the NT, Australia, 1997–2010](image)

Source: Used with permission of J Lawrence (173)

Second, it is concerning that the core GBD group’s model shows that incidence has decreased considerably over the period examined. This apparent decrease was surmised to be an aberration that was potentially driven by the modelling process, where incidence was modelled from the remission data from publications of longitudinal studies undertaken in the 1950s, as well as cause-specific mortality data. The Bland and Jones series included patients with ARF (not RHD), and their assumption of ‘remission’ was based on ‘the regression and ultimate disappearance’ of apical murmurs. Thus, strictly speaking, this is the natural history of ARF (rather
than RHD) and perhaps not truly a remission of valve lesions (as the assessment was entirely clinical).(96)

It is unclear from the methodologies of these studies whether remission occurred in patients with ARF and mild valve changes (this was also prior to the echocardiography era, thus the data presented in these studies has little detail). In addition, the cohort in the US in the 1950s was highly monitored, received optimal prevention medication and was managed in a highly organised and efficient health system. None of these aspects are likely to exist in high-prevalence, resource-poor countries in the present day. The researchers are not aware of any countries or regions, other than suburban Auckland, New Zealand, that can demonstrate optimal levels of adherence to prevention medication that can guard against recurrence and potentially led to regression of pathological valve lesions.

A more accurate approach to estimate incidence may be to use the incidence and mortality data from Aboriginal Australians and New Zealand Maori populations to extrapolate to high-prevalence countries. The Australian Indigenous data are the most comprehensive data available globally, and were provided to the core GBD group with the intention that they could be used to assist with modelling in all high-prevalence regions where incidence data are lacking. These data were not nationally representative; thus, the core GBD group was reluctant to use them to influence modelling. However, these data are comprehensive in examining RHD mortality in Indigenous Australians compared to the non-Indigenous population, and are currently the only data available that examine patterns of disease evolution from a population basis.
These Indigenous data could potentially be used to inform modelling in low-income countries and regions because they are representative of the first-nation people of Australia, who have similar health determinants—although improved access to healthcare—to populations residing in resource-poor regions. However using these data to influence modelling would provide underestimates when applied to low resource countries, but may be more accurate than modelling influenced by historical cohort studies from the US in the 1950s. The non-Indigenous Australian mortality data could potentially be used to model mortality rates from populations in higher income and wealthier nations.

Globally, the most readily available data for RHD prevalence was in the five to 14 age group (84% of included studies of prevalence). RHD incidence data were generally not available, except for Australia and New Zealand. Therefore, it was hypothesised that incidence data need necessarily be imputed from prevalence data. In this study’s compilation of the data from the Indigenous population in the NT, Australia, and from the New Zealand Maori populations, it appears that the relationship of RHD prevalence to incidence—calculated by dividing incidence by prevalence figures in the few countries that good data exist—is relatively constant (around two to four times).

Since this study used RHD incidence, rather than ARF incidence, it was possible to ignore the effect of secondary prophylaxis and other health system issues that might affect the relationship between incident ARF and subsequent development of RHD. Therefore, extrapolation of the relationship of RHD incidence and prevalence
derived from the Australian and New Zealand data to other regions may be reasonable, irrespective of country income and socioeconomic status (Tables 6.10 and 6.11).

**Table 6.10: Relationship between ARF Incidence, RHD Incidence (Based on Hospital Admission and Other Data from Australia and New Zealand)**

<table>
<thead>
<tr>
<th>Age group</th>
<th>ARF incidence (per 100,000)</th>
<th>RHD incidence (per 100,000)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–24 years</td>
<td>10–12</td>
<td>3–5</td>
<td>2–3</td>
</tr>
<tr>
<td>5–15 years</td>
<td>10–40</td>
<td>5–10</td>
<td>2–4</td>
</tr>
</tbody>
</table>

**Table 6.11: Relationship between ARF Incidence, RHD Incidence by Ethnicity and Geographical Area (1–24 Years)**

<table>
<thead>
<tr>
<th>Age group</th>
<th>ARF incidence (per 100,000)</th>
<th>RHD incidence (per 100,000)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacific origin (resident in New Zealand)</td>
<td>60–70</td>
<td>15–35</td>
<td>2–4</td>
</tr>
<tr>
<td>Maori (New Zealand)</td>
<td>25–35</td>
<td>5–10</td>
<td>3–5</td>
</tr>
<tr>
<td>Counties Maunikau (New Zealand low socioeconomic status)</td>
<td>30–40</td>
<td>10–15</td>
<td>2–3</td>
</tr>
<tr>
<td>Australian Indigenous (NT)</td>
<td>150–170</td>
<td>175–180</td>
<td>1.1–1.2</td>
</tr>
</tbody>
</table>

The RHD prevalence at different age groups is usually a factor of the incidence of disease across these age groups. There is a well-established relationship between RHD incidence and the age of the population. It was hypothesised that, to obtain more accurate data, the ratio of RHD prevalence to RHD incidence from the data available from Australia and New Zealand could potentially be applied to other regions where prevalence data is available in the four to 15 and 16 to 24 age groups. This could be done to provide estimates for RHD incidence in populations where no data exists—that is, most regions of the world (other than Fiji and Papua New Guinea, as was done to influence the current modelling process for estimation of...
incidence). The relationship between RHD incidence and prevalence calculated from the Australian and New Zealand data is presented in Figure 6.15.

![Graph showing the relationship between RHD incidence and prevalence in Australia and New Zealand (Per 100,000 Population, Expressed on a Log Scale) across age groups (5–45 years).](image)

**Figure 6.15: Relationship between RHD Incidence and RHD Prevalence in Australia and New Zealand (Per 100,000 Population, Expressed on a Log Scale) Across Age Groups (5–45 Years)**

Indigenous Australians have a similar burden of disease to populations in developing countries; thus, this may be useful as a starting point. The New Zealand data for the Pacific Island and Maori populations could potentially be used to inform modelling for middle-income countries (Box 6.3) because New Zealand has largely solved the problem of ARF recurrence with a strong public health programme; however, it still has a high RHD burden in subpopulations.

Another alternative approach would be to model incidence using indicators of socioeconomic status, such as gross domestic product or Human Development Index.
data, to obtain differential estimates of disease burden within countries, as most studies within countries have not collected socioeconomic data.

**Box 6.3: Low- and Middle-income Countries**

<table>
<thead>
<tr>
<th>Low income/developing</th>
<th>Emerging/mixed/middle income</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia South, Asia South East, Asia Central, Oceania, Sub-Saharan Africa Central, Sub-Saharan Africa East, Sub-Saharan Africa Southern, Sub-Saharan Africa West</td>
<td>Asia East, Caribbean, Europe Central, Europe Eastern, Latin America, Andean, Latin America, Central, Latin America Southern, Latin America Tropical, North Africa/Middle East</td>
</tr>
</tbody>
</table>

**6.4.3 Mortality Data**

The mortality estimates calculated show a higher numbers of deaths globally than estimated in the two previous reviews. (9, 94) These new estimates may be more accurate than previous calculations because they used vital statistics data, as well as the limited number of population-based studies found in the systematic review, to make this estimate. The calculation of number of deaths from RHD globally, undertaken by Carapetis et al. used natural history studies that estimated the total proportion of RHD cases that will die each year. Studies of patients who do not receive secondary prophylaxis or contemporary medical care (the situation for most patients in developing countries) from the US, Asia and Australia suggest that approximately 1.5% of patients with RHD will die each year. If 1.5% of people with RHD die each year, using this proportion, the estimated number of deaths due to RHD ranges from 233,000 to 294,000 per year.

Additional calculations were based on New Zealand standard mortality rate (SMR) estimates of 2.0 and 9.6 for non-Indigenous and Indigenous groups, respectively, to represent reasonable middle-range estimates for RHD mortality in more developed
countries and less developed countries. This gave a global total of 492,042 deaths per year due to RHD (23,877 in more developed countries and 468,164 in less developed countries).(54) This method may underestimate global RHD mortality, as Maori and Pacific Island populations living in New Zealand have access to much higher quality medical care than most developing countries.

Research recently undertaken in Fiji to estimate the national mortality rate from RHD by linking multiple hospital, government and death reports found that the un-adjusted RHD death rate was 5.7% per year (CI 5.1–6.3).(174) Standardised by age, gender and ethnic group, patients with RHD were at nine-fold increased risk of death (SMR 8.8) compared to the general population—a similar rate to that seen in New Zealand Maori population. Indigenous Fijian patients were at greater risk than patients of Fijian-Indian descent (SMR 12.4 versus SMR 5.0) and young Indigenous Fijian men were at greatest risk (SMR 50.0).

The strongest risk factor for death was heart failure, with a far greater effect among young people (Relative Risk (RR) 39.5 in age 4–19 years, versus RR 6.16 ≥ 40 years, both p < 0.001). These data are the first available from a developing country, and could be applied to high-risk settings globally. The Indigenous Fijian SMR of 12.4 estimated from this project compares to a SMR of 6.2 per 100,000 calculated for Fiji by the GBD core group (IHME website accessed 02 Oct 2013). This suggests that mortality has been grossly underestimated, at least in Fiji, and arguably in other countries and regions.
6.4.4 Limitations

The two major limitations of this study were discussed in the previous section of this chapter. They pertained to the lack of good quality population-based data available for estimating incidence and mortality rates, and the allocation of geographic regions that prevented examination of the burden of RHD in subpopulations within individual countries.

A further limitation of this study was the omission of the examination of ARF incidence. This exercise was not included in the project due to the lack of population-based ARF incidence data. There is currently only one systematic review examining the incidence of ARF available.(175) The authors of this project were contacted; however, the methodology of this review did not fit with the GBD approach. Further research is required to examine the global burden of ARF.

The time restrictions of the GBD 2010 RHD review did not enable inclusion of data on known major complications from RHD that significantly affect deaths and disability from stroke, infective endocarditis and atrial fibrillation. In the 2005 systematic review undertaken by Carapetis et al., an exploration of these conditions was undertaken to attempt to define the proportion of deaths and disability that occurred from RHD.(9) It was estimated that between 3.5 to 7.0% of strokes globally could be attributed to RHD, with between 108,000 to 269,000 annual deaths due to RHD-related stroke. It was estimated that RHD-related infective endocarditis occurred in more than 33,700 patients each year in less developed countries,
resulting in over 8,400 deaths. These estimates were based on applying data from the limited number of studies available at the time.

The 2008 systematic review of RHD in Asia found a number of new studies that confirmed that infective endocarditis and stroke related to RHD cause much morbidity and mortality, with at least half of all infective endocarditis cases due to underlying RHD.(94) A recent prospective study of stroke in China found that RHD was responsible for 7.9% of cases of stroke, that stroke outcomes were significantly worse for RHD patients, and that the death risk for patients with RHD was 2.0 fold higher than for patients without RHD.(109) A 2007 publication from Iran, analysing data from a large stroke register, found that RHD caused 4.3 preventable strokes per 100,000 people per year in Iran.(111) Carapetis et al. estimated that if the incidence of stroke due to RHD in Iran was applied to the population of Asia (3.9 billion), it could be estimated that RHD causes 167,000 preventable strokes each year in Asia.(94)

These data from previous reviews and studies suggest that RHD-related stroke and infective endocarditis exact a large, but often unstated, morbidity and mortality burden. In subsequent research, the current researchers plan to liaise with other GBD expert groups who have undertaken examination of stroke, infective endocarditis and atrial fibrillation burden of disease as part of the GBD 2010 Study in order to explore their data to determine the proportion of cases that have RHD.
6.5 Conclusion

The GBD 2010 Study provided a unique opportunity to gain a greater understanding of the global epidemiology of RHD. This comprehensive exercise was complicated for RHD due to the gaps in the regional and global data available, and there remain issues with the current modelling that need to be remedied before final numbers can be confirmed. There is a need for better quality incidence and mortality data, potentially gained from new RHD registers as countries develop these as part of RHD control programmes.

The global, and some regional, prevalence and mortality calculations were found to be somewhat higher than previously estimated; however, further examination and modelling—using current data where they are available—is required to determine the accuracy of the figures and finalise the estimates.

The age distribution of the RHD incidence figures is clearly inaccurate. Thus, alternate approaches need to be examined and evaluated in order to remodel the data to reflect the natural progression of the disease and the relationship between the incidence and prevalence of RHD. It may be that the numbers are correct, but the distribution of current data by age is flawed. Both the lack of real data and current assumptions applied to the data continue to underestimate the true burden.

In the period between the 2005 systematic review and the GBD 2010 Study, there have been many additional studies completed that provide valuable insights to many regions of the world. However, they continue to focus on prevalence in school-aged
children, rather than RHD incidence, mortality or severity. The effect of RHD burden of disease in subregions, populations living in inequitable circumstances in countries where there is unequal distribution of wealth, and Indigenous populations known to be at high risk of RHD are masked by the method of regional allocation in this study. These populations include Australian Indigenous people, New Zealand Maoris and poor populations in countries with emerging economies, such as many Asian countries.

The researchers intend to publish a paper with the final GBD 2010 RHD estimates once the remodelling process has been completed. Data regarding morbidity and disability from RHD associated stroke, infective carditis and atrial fibrillation were not available for inclusion in this review. Further research and liaison with other GBD expert groups is required to attempt to quantify this burden.

6.5.1 Priority Issues

As the estimates of all diseases are published on the IHME website by the GBD core group, it is imperative that these current estimates are remodelled with input of solid available epidemiological data from the countries where it is available. It is imperative to work towards obtaining more accurate estimates for the GBD 2013 Study, based on the experience of undertaking the GBD 2010 Study. Over the coming year, the researchers will work with international collaborators from high-prevalence regions to obtain population-based mortality and incidence data and RHD data. They will also work with countries and regions that have RHD registries in place.
There is a need for increased global action and advocacy for RHD, and the burden of RHD needs to be put in context (Box 6.4). RHD is a neglected disease of poverty, with high levels in resource-poor countries. Data are often scarce where the problem is worst. Gaps in the global epidemiology of RHD need to be addressed to allow the direction of policy and input from global and regional health organisations to address the effect of RHD on vulnerable populations.

**Box 6.4: Key Points**

<table>
<thead>
<tr>
<th>The RHD burden needs to be put into context:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHD is predominantly a disease of the young</td>
</tr>
<tr>
<td>RHD is a disease of poverty and social injustice</td>
</tr>
<tr>
<td>There exists inequitable distribution of RHD—it affects the poorest of the poor, often in countries that lack the infrastructure to report accurately on disease statistics</td>
</tr>
<tr>
<td>Many incident cases and deaths are eminently preventable</td>
</tr>
<tr>
<td>Mortality is likely to be grossly underestimated</td>
</tr>
<tr>
<td>Data are lacking for most of the regions of the world most affected by the disease</td>
</tr>
<tr>
<td>Good population-based epidemiology data are urgently required for high-risk populations</td>
</tr>
</tbody>
</table>
Chapter 7: RHD Mortality in Indigenous Australians
7.1 Introduction

As described in the preceding chapters of this thesis, RHD remains the most common cardiovascular disease affecting children and young people globally. Up to 15 million people live with RHD, almost all in developing countries and in Indigenous populations in developed nations, such as Maori people in New Zealand and the Indigenous population in remote Australia.

RHD is a classic disease of social injustice and deprivation. Over the past 60 years, there have been impressive declines in the prevalence of RHD throughout Australia and the industrialised world, resulting mainly from improvements in living conditions, improved socioeconomic conditions, improved sanitation and medical care, and reduction in household crowding. These improvements are yet to be seen in many developing countries and in Indigenous populations defined by ethnicity or geographical location. Indigenous populations in developed countries frequently live in deprived settings, facing similar issues of lower living standards as populations in developing countries. Indigenous Australians have among the highest incidence of ARF and RHD in the world.

As demonstrated by the RHD systematic review undertaken as part of the GBD 2010 Study (described in Chapter 6), there is very little population-based mortality data available globally. The review undertaken to inform the modelling for the GBD 2010 Study found only three countries with recent data: Australia, New Zealand and Ethiopia.(99, 106, 176, 177) In a previous systematic review to quantify the global mortality burden from RHD, the authors had to resort to fairly crude methods to
estimate global mortality. This included inferring annual mortality from prospective studies undertaken in the US in the 1950s, and applying the proportion of cases found to die from RHD to the estimated global and regional prevalence estimates. Australia is one of the few settings with a high RHD incidence population that also has access to good cause-specific mortality data, which could assist with the global understanding of RHD mortality in the twenty-first century.

This chapter will focus on examining Indigenous versus non-Indigenous mortality from RHD in Australia, with a specific focus on the NT. There is existing evidence that RHD still has a strong influence on the health of Indigenous people; however, there are currently no detailed RHD mortality data for this population. Indigenous identification in the NT has been known to be accurate since 1977, and complete in several other states since 1997.(178) This study investigates RHD mortality in Indigenous people compared with non-Indigenous people in five states where complete Indigenous identification exists, between 1997 to 2005. In the NT, this study investigates time trends over a 29-year period.

7.1.1 Indigenous Australians

Indigenous Australians comprise approximately 2.5% of the Australian population. They predominantly live with lower social, economic and environmental conditions, and often have poorer health status than do non-Indigenous Australians.(179) Approximately 89% of the Australian Indigenous population live in five states of Australia: the NT, Queensland (QLD), South Australia (SA), Western Australia (WA) and New South Wales (NSW) (Table 7.1).(180) Indigenous Australians
comprise 30.4% of the NT population, the majority living in remote or very remote areas.(179) In all other states and territories, Indigenous Australians comprise less than 4% of the population.

Table 7.1: Estimated Resident Indigenous Australian Population, 30 June 2006

<table>
<thead>
<tr>
<th>State/territory</th>
<th>Indigenous No.</th>
<th>Indigenous %</th>
<th>Non-Indigenous No.</th>
<th>Non-Indigenous %</th>
<th>Total No.</th>
<th>Total %</th>
<th>Proportion of Indigenous %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSW</td>
<td>152,685</td>
<td>29.5</td>
<td>6,663,402</td>
<td>33.0</td>
<td>6,816,087</td>
<td>32.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Victoria</td>
<td>33,517</td>
<td>6.5</td>
<td>5,093,023</td>
<td>25.2</td>
<td>5,126,540</td>
<td>24.8</td>
<td>0.7</td>
</tr>
<tr>
<td>QLD</td>
<td>144,885</td>
<td>28</td>
<td>3,946,023</td>
<td>19.6</td>
<td>4,090,908</td>
<td>19.8</td>
<td>3.5</td>
</tr>
<tr>
<td>SA</td>
<td>28,055</td>
<td>5.4</td>
<td>1,539,833</td>
<td>7.6</td>
<td>1,567,888</td>
<td>7.6</td>
<td>1.8</td>
</tr>
<tr>
<td>WA</td>
<td>70,966</td>
<td>13.7</td>
<td>1,988,415</td>
<td>9.9</td>
<td>2,059,381</td>
<td>9.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Tasmania</td>
<td>18,415</td>
<td>3.6</td>
<td>471,536</td>
<td>2.3</td>
<td>489,951</td>
<td>2.4</td>
<td>3.8</td>
</tr>
<tr>
<td>NT</td>
<td>64,005</td>
<td>12.4</td>
<td>146,622</td>
<td>0.7</td>
<td>210,627</td>
<td>1.0</td>
<td>30.4</td>
</tr>
<tr>
<td>Australian Capital Territory</td>
<td>4,282</td>
<td>0.8</td>
<td>329,837</td>
<td>1.6</td>
<td>334,119</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Australia</td>
<td>517,043</td>
<td>100.0</td>
<td>20,180,837</td>
<td>100.0</td>
<td>20,697,880</td>
<td>100.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

7.1.2 Accuracy of Indigenous Identification in Australian Death Data

Almost all deaths in Australia are registered; however, Indigenous status is not always recorded, or recorded correctly. The incompleteness of Indigenous identification means that the number of deaths registered as Indigenous is an underestimate of the actual number of deaths that occur in the Aboriginal and Torres Strait Islander population. NT Indigenous death identification was consistent over the entire 29-year period studied. However, analysis was restricted to the period 1997 to 2005 for the remaining four states because previous data quality assessment indicated that completeness of Indigenous identification improved considerably for these
registries between 1991 and 1997, with the exception of NSW, which had incomplete reporting for 1997.

Table 7.2 shows the improvement and consistency in Indigenous identification in reporting deaths that occurred in NSW, QLD, SA and WA from 1997 onwards. Indigenous death identification remains poor in Victoria, the Australian Capital Territory (ACT) and Tasmania; thus, these states were excluded from the analysis. In the NT, identification of Indigenous deaths in death registrations is near complete because recording of Indigenous status was added to death notification forms in 1988. For deaths in the NT prior to 1988, a dataset of deaths with inferred Indigenous status, held by the Health Gains Planning Branch of the NT Department of Health, was used. In this dataset, Indigenous status was inferred from other information on the death registration (such as a name in an Indigenous language or other distinctively Indigenous or Torres Strait Islander names, parents’ names, place of birth, residence in a remote Indigenous community, place of burial and person who conducted the burial). The accuracy of inferred Indigenous status in this dataset has been validated and found to be reliable with a positive predictive value of 0.977 and a negative predictive value of 0.955 (corrected from original reference, personal email communication, Associate Professor John Condon 2011). The cause of death was unknown for a high proportion of NT Indigenous deaths before 1977; thus, investigation of NT RHD deaths was undertaken for the period 1977 to 2005.

RHD mortality rates were calculated for the combined Indigenous populations of the NT, QLD, SA, WA and NSW (referred to as the ‘five states’) to provide a semi-national estimate for Indigenous Australians that included 89% of the total
Indigenous Australian population and all jurisdictions with reliable data on Indigenous identification. The RHD mortality rate for the combined non-Indigenous population of the same five states was used as the Indigenous comparator in all analyses.

Table 7.2: Number of Registered Deaths Identified as Indigenous and Torres Strait Islander, by State/Territory, 1994–2010

<table>
<thead>
<tr>
<th>Year</th>
<th>NSW</th>
<th>Victoria</th>
<th>QLD</th>
<th>SA</th>
<th>WA</th>
<th>Tasmania</th>
<th>NT</th>
<th>ACT</th>
<th>Aust.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>207</td>
<td>50</td>
<td>np</td>
<td>123</td>
<td>377</td>
<td>np</td>
<td>380</td>
<td>10</td>
<td>1,153</td>
</tr>
<tr>
<td>1995</td>
<td>224</td>
<td>50</td>
<td>np</td>
<td>121</td>
<td>384</td>
<td>np</td>
<td>387</td>
<td>9</td>
<td>1,182</td>
</tr>
<tr>
<td>1996</td>
<td>177</td>
<td>49</td>
<td>258</td>
<td>118</td>
<td>370</td>
<td>np</td>
<td>328</td>
<td>np</td>
<td>1,306</td>
</tr>
<tr>
<td>1997</td>
<td>88</td>
<td>93</td>
<td>531</td>
<td>132</td>
<td>351</td>
<td>5</td>
<td>458</td>
<td>4</td>
<td>1,662</td>
</tr>
<tr>
<td>1998</td>
<td>462</td>
<td>123</td>
<td>593</td>
<td>127</td>
<td>378</td>
<td>13</td>
<td>415</td>
<td>3</td>
<td>2,114</td>
</tr>
<tr>
<td>1999</td>
<td>435</td>
<td>130</td>
<td>529</td>
<td>116</td>
<td>350</td>
<td>11</td>
<td>399</td>
<td>6</td>
<td>1,976</td>
</tr>
<tr>
<td>2000</td>
<td>473</td>
<td>108</td>
<td>535</td>
<td>144</td>
<td>407</td>
<td>np</td>
<td>450</td>
<td>np</td>
<td>2,127</td>
</tr>
<tr>
<td>2001</td>
<td>481</td>
<td>93</td>
<td>565</td>
<td>125</td>
<td>345</td>
<td>np</td>
<td>429</td>
<td>np</td>
<td>2,072</td>
</tr>
<tr>
<td>2002</td>
<td>516</td>
<td>64</td>
<td>590</td>
<td>107</td>
<td>371</td>
<td>20</td>
<td>462</td>
<td>4</td>
<td>2,136</td>
</tr>
<tr>
<td>2003</td>
<td>485</td>
<td>82</td>
<td>569</td>
<td>137</td>
<td>338</td>
<td>23</td>
<td>435</td>
<td>9</td>
<td>2,079</td>
</tr>
<tr>
<td>2004</td>
<td>490</td>
<td>54</td>
<td>579</td>
<td>131</td>
<td>400</td>
<td>20</td>
<td>449</td>
<td>10</td>
<td>2,136</td>
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<tr>
<td>2005</td>
<td>507</td>
<td>71</td>
<td>519</td>
<td>142</td>
<td>406</td>
<td>28</td>
<td>454</td>
<td>11</td>
<td>2,141</td>
</tr>
<tr>
<td>2006</td>
<td>530</td>
<td>111</td>
<td>584</td>
<td>124</td>
<td>443</td>
<td>20</td>
<td>452</td>
<td>14</td>
<td>2,279</td>
</tr>
<tr>
<td>2007</td>
<td>601</td>
<td>95</td>
<td>594</td>
<td>138</td>
<td>502</td>
<td>24</td>
<td>461</td>
<td>6</td>
<td>2,421</td>
</tr>
<tr>
<td>2008</td>
<td>559</td>
<td>97</td>
<td>562</td>
<td>141</td>
<td>605</td>
<td>24</td>
<td>467</td>
<td>16</td>
<td>2,472</td>
</tr>
<tr>
<td>2009</td>
<td>591</td>
<td>106</td>
<td>632</td>
<td>160</td>
<td>444</td>
<td>30</td>
<td>431</td>
<td>10</td>
<td>2,405</td>
</tr>
<tr>
<td>2010</td>
<td>622</td>
<td>117</td>
<td>948</td>
<td>147</td>
<td>436</td>
<td>37</td>
<td>447</td>
<td>13</td>
<td>2,767</td>
</tr>
</tbody>
</table>

Notes: np = not available for publication, but included in totals where applicable, unless otherwise indicated
(a) From 2007 onwards, Indigenous status for deaths registered in Victoria, SA, WA, Tasmania, the NT and ACT was sourced from both the Death Registration Form and Medical Certificate of Cause of Death.
(b) State or territory of usual residence.
(c) Due to differing levels of recording Indigenous status by the states and territories and over time, care should be taken in interpreting change in numbers of deaths. As a result, data for Australia should not be analysed as a time series.
(d) QLD began to register Aboriginal and Torres Strait Islander deaths as such in 1996. Care should be taken when interpreting Aboriginal and Torres Strait Islander deaths data for QLD for 2010.
(e) The Australian Bureau of Statistics (ABS) are currently investigating the volatility of Aboriginal and Torres Strait Islander deaths in WA in recent years. Until this investigation is finalised, ABS advises caution when analysing Aboriginal and Torres Strait Islander deaths data for 2007, 2008 and 2009.
(f) Includes other territories.

Source: (183)
7.1.3 Indigenous People in the NT

In the NT, 92% of people with RHD are Indigenous, of whom 85% live in remote communities and towns. (184) NT Indigenous people continue to experience higher avoidable mortality than other Australians, and this disparity or ‘gap’ has increased over time. Living in remote communities is a contributing factor to this gap, as well as a major barrier for adequate follow-up and access to healthcare. (89) A number of initiatives have been undertaken both nationally and within the NT to address the disparity. One such initiative is the Council of Australian Governments (COAG) Close the Gap in Indigenous Disadvantage initiative (Box 7.1). (185) Some improvements in the reduction of Indigenous mortality have occurred in recent decades. For example, in the 20 years between 1985 and 2004, avoidable mortality rates for all causes fell by 18.9% in NT Indigenous people. However, the decline remains much greater in non-Indigenous Australians—avoidable mortality rates for the same period fell by 61.1% in NT non-Indigenous people and 59.5% in Australians overall. (186)

Indigenous people living in the NT exhibit the highest reported RHD incidence globally. (5, 159) This disparity in the distribution of the burden of disease contributes to the gap in life expectancy of Indigenous Northern Territorians. In recent years, a number of initiatives have been undertaken to try to address this. These include the establishment of the NT RHD register in 1996 and the commitment of the Australian government to a semi-national RHD programme: RHDAustralia. Control strategies are important to target vulnerable groups and develop strategies to address inequity within the health system.
Box 7.1: COAG Closing the Gap Initiative

The six targets for Closing the Gap are:

1. Close the gap in life expectancy within a generation.
2. Halve the gap in mortality rates for Indigenous children under five within a decade.
3. Ensure all Indigenous four year olds in remote communities have access to early childhood education within five years.
4. Halve the gap for Indigenous students in reading, writing and numeracy within a decade.
5. Halve the gap for Indigenous students in Grade 12 attainment of equivalence attainment rates by 2020.

7.1.4 Existing Australia RHD Mortality Reporting

The best available data on the influence of RHD are death data from government sources such as the ABS and Australian Institute of Health and Welfare (AIHW). Australia has a comprehensive system of recording mortality that covers the entire population and has produced accurate and detailed statistics on RHD mortality for several decades. The system is based on national reporting of death registrations to the ABS with national mortality data compiled at the ABS and AIHW. The AIHW regularly updates RHD mortality figures for Australia by state, gender and age of death in a series of publications known as the General Record of Incidence of Mortality (GRIM) books. (187) Disease-specific GRIM books are available for both RHD and ARF and cover the period 1968 to 2007, providing data on numbers, rates and time trends by state, gender and year, which demonstrate the decline in total Australian RHD death rates for the past four decades (Figure 7.1). Deaths are coded by International Classification of Diseases (ICD) codes.
There were two changes in ICD coding over the period studied; from ICD8 to ICD9 and from ICD9 to ICD10. The change in ICD coding from ICD8 to ICD9 occurred in 1978, and resulted in an artificial sharp reduction in the age-standardised death rates. Thus, death rates are presented separately in Figure 7.1 as pre- and post- the 1978 ICD coding change.(188) The change in coding from ICD9 to ICD10 did not appear to affect the reported death rates.

![Trends in Death Rates for Chronic RHD in Australia, 1965–2005](image)

**Figure 7.1: Trends in Death Rates for Chronic RHD in Australia, 1965–2005**

Source: (187)

The GRIM books provide mortality statistics for the total Australian population—they do not provide separate statistics for Indigenous Australians. Reporting RHD mortality statistics for the total Australian population only (Indigenous and non-Indigenous combined) disguises the excess mortality from RHD in Indigenous people. A summary report from the AIHW of cardiac risk factors in Indigenous people from 2002 to 2005 in QLD, WA, SA and the NT found RHD mortality 23 times higher for Indigenous than non-Indigenous people in the same states. RHD
mortality was 2.3 times higher for Indigenous females than males, and 8.0 times higher for females when compared with males in the 65+ age group. (189)

Several reports of RHD mortality in the NT indicate that deaths from RHD occur predominantly in young Indigenous Australians, with particularly high rates in Indigenous women (approximately 40 per 100,000 for women, compared with 30 for Indigenous men). (51, 106, 182) Although this disease has virtually disappeared in the Australian non-Indigenous population, RHD mortality in Indigenous Australians, particularly in the NT, remains at a rate comparable with total Australian rates in the 1930s to 1940s (Figure 7.2). (190)

Figure 7.2: Age-standardised Mortality Rate for RHD in Australia, 1930–1990

Source: (187)
7.1.5 Aims

This study was undertaken to provide a comprehensive examination of RHD mortality rates and trends in Indigenous Australians. This study aimed to:

1. investigate the number and proportion of deaths attributable to ARF and RHD in Indigenous people in the NT
2. investigate time trends in RHD mortality rates for the Indigenous and non-Indigenous populations of the NT for the period 1977 to 2005
3. compare RHD mortality of the NT Indigenous population with that of Indigenous and non-Indigenous Australians elsewhere in Australia for the period 1997 to 2005
4. compare RHD mortality rates for Indigenous people at the semi-national level for the period 1997 to 2005 by remoteness of residence (urban/regional/remote)
5. investigate the proportion of deaths attributed to RHD as the underlying cause of death and as an associated cause of death.

7.2 Methods

7.2.1 Deaths Data

This study used the national death registrations dataset compiled by the ABS from death registrations data supplied by the state and territory Registries of Births, Deaths and Marriages. Data from the four states were compared to the NT for the period 1997 to 2005.
7.2.2 Coding of Death Data

To ensure that all deaths associated with RHD were captured, all codes for ARF and chronic RHD were included because deaths from recurrent acute carditis may occur in patients with pre-existing RHD. Cause of death was coded by the ABS using the ICD. The ninth edition was used for deaths registered in 1977 to 1999 (three-digit codes 390 to 398), and the tenth edition was used for 1999 to 2005 (three-digit codes I02 to I09). The change in ICD coding from ICD9 to ICD10 occurred in July 1998 in NSW and NT, and July 1999 in WA, SA and QLD. To identify inconsistency between the ninth and tenth revisions, deaths for 1997 and 1998 were coded to both revisions by the ABS. As part of the analysis in this study, a regression analysis was performed to determine if there was a difference in the coding in RHD mortality for the time periods pre- and post-ICD coding change.

Medical certificates of cause of death may include more than one contributing cause. Prior to 1997, the ABS identified and coded only one underlying cause of death, which is the fundamental disease or injury that leads to death, rather than the immediate biological failure that was the direct cause of death. From 1997, the ABS also coded associated causes of death, which are other diseases or injuries that contributed to the death.
7.2.3 Study Populations

7.2.3.1 Indigenous Population of the NT

RHD mortality in the NT was investigated for the period 1977 to 2005, comparing Indigenous with non-Indigenous populations, with a particular focus on the time trends in RHD mortality over this 29-year period. These long-term data were able to be examined in the NT because deaths data with a consistently high level of accuracy were available (but not elsewhere) for this period.

7.2.3.2 Indigenous Populations Elsewhere in Australia

The Indigenous RHD mortality of the NT population was compared with that of the Indigenous population in four other states: NSW, QLD, SA and WA. The comparison of this period was limited to 1997 to 2005 because the accuracy of Indigenous identification was poor in these four states before 1997 (see Section 7.1.2). Time trends could not be investigated for Indigenous people elsewhere in Australia because of the data limitations described above.

7.2.3.3 Semi-national Indigenous Populations

The RHD mortality was also calculated for the Indigenous population of the five states/territories combined (referred to as the ‘five states’) for the period 1997 to 2005, in order to provide as close as possible to a national estimate of RHD mortality for Indigenous Australians. This ‘semi-national’ estimate covered 89% of the Indigenous population of Australia that lived in the five states.
7.2.3.4 Non-Indigenous Populations

For the analysis of RHD mortality in the NT for 1977 to 1995, the NT Indigenous population was compared to the NT non-Indigenous population. For all other analyses (covering the period 1997 to 2005), RHD mortality in Indigenous populations was compared to that in the non-Indigenous population of the five states combined. This provided the best available estimate for RHD mortality in the total non-Indigenous Australian population.

7.2.4 Population Denominator

The population data used as the denominator to calculate mortality rates were the estimated resident population (by Indigenous status, sex, five-year age group and calendar year) of each state/territory published by the ABS.(191)

7.2.5 Statistical Analysis

The following outcome measures were calculated:

- number of RHD deaths
- crude death rate
- age-specific death rate (in age groups zero to four, five to 24, 25 to 44, 45 to 64 and > 65 years)
- age-adjusted death rate.
The ratios of age-standardised death rates are not presented because very large differences in mortality rate ratios were found between age groups—that is, the mortality rate ratio was not homogeneous across age strata.

Most analyses only included deaths in which the *underlying* cause of death was RHD (including ARF). A separate analysis was undertaken to compare RHD as the *underlying* cause of death, with RHD as the *associated* cause of death, in order to investigate the extent to which RHD was contributing to deaths, but was not identified as the single *underlying* cause.

The age distribution of the 2001 Australian Estimated Resident Population was used as the standard weights for calculation of age-adjusted rates.

### 7.2.5.1 NT Analysis, 1977–2005

RHD death rates were compared for Indigenous and non-Indigenous populations by age group and sex. Time trends were examined by calculating mortality rates for three periods (1977 to 1986, 1987 to 1996 and 1997 to 2005). Death rate ratios (DRRs) were calculated using the age-specific mortality of the NT Indigenous population compared to the non-Indigenous population of the five states.

### 7.2.5.2 Regional Variation in the NT, 1977–2005

Deaths data were analysed by place of residence at the time of death, using the seven NT health districts classifications: Darwin Urban, Darwin Rural, Alice Springs...
Urban, Alice Springs Rural, East Arnhem, Barkly and Katherine. To compare RHD mortality in urban and remote areas, the Darwin Urban and Alice Springs Urban districts were combined into one ‘urban’ category and the remaining five districts into one ‘remote’ category (Figure 7.1). To examine the influence of introducing the NT RHD control programme in the Top End of the NT in 1996 and in Central Australia in 2000, RHD death rates for two periods (1987 to 1996 and 1997 to 2005) were compared separately for the Top End and Central Australia.

Multivariate (negative binomial regression) analysis was also used to analyse RHD mortality in the NT from 1977 to 2005. Negative binomial regression was used (rather than Poisson regression) because the deaths were found to be over-dispersed. The regression model included terms for Indigenous status (Indigenous compared with non-Indigenous population), age of death (per single year of age), sex (female compared with male), year of death (in single calendar years), and two interaction terms—Indigenous status by age at death and Indigenous status by year of death. The interaction terms were included because the effect of age at death and year of death were found to be different for Indigenous compared with non-Indigenous people.

A separate regression analysis examined RHD mortality in two periods in the Top End compared with Central Australia. This model included terms for age, sex, period (1987 to 1996 compared with 1997 to 2005) and region (Top End compared with Central Australia).
7.2.5.3 Four States, 1997–2005

For the four states, RHD mortality rates for the non-Indigenous population of the five states combined were used as the non-Indigenous comparator. Mortality rates were compared for Indigenous with non-Indigenous populations by age group and sex. DRRs were calculated using the age-specific mortality of the four states’ Indigenous populations compared to the non-Indigenous populations of the five states.

Multivariate (negative binomial) regression was also used to compare the NT Indigenous population with the other two population groups. Negative binomial regression was used (rather than Poisson regression) because the deaths data were found to be over-dispersed.

The regression model included terms for population group (NT Indigenous, Indigenous from the other four states, and non-Indigenous), age (in five-year age groups) and sex. Year of death was included in the model only for analysis of NT Indigenous RHD mortality for the longer period (1977 to 2005). Year of death was not included on other analyses because analysis of time trends was not feasible for the shorter period of only nine years. The regression model for analysis of RHD deaths in the NT population between 1977 and 2005 included terms for Indigenous status, sex, age at death as a single ordinal variable, and year of death.
Indigenous RHD mortality rates from the five states combined were compared to the non-Indigenous population of the same five states. Mortality rates were compared between Indigenous and non-Indigenous populations by age group and sex. A multivariate analysis was undertaken to examine the effect of Indigenous status, gender and age for the semi-national data. The regression model for the five-state analysis for the period 1997 to 2005 included terms for Indigenous status, age, base year and gender.

All data were analysed using STATA software (version 11; STATA Corp, College Station, Texas, US). All mortality rates were expressed as per 100,000 person years.

7.2.6 Ethical Approval

This was a collaborative project between the Menzies School of Health Research and the Health Gains Planning Branch, NT Department of Health. Ethics approval was granted by the Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research (including its Indigenous subcommittee).
7.3 Results

7.3.1 NT, 1977–2005

7.3.1.1 RHD Death Rates

In the NT for the period 1977 to 2005, there were 280 deaths from RHD as the underlying cause—253 (90%) were Indigenous people and 164 (59%) were females. For Indigenous people, RHD death rates increased with increasing age and were higher for females than males in all age groups. For non-Indigenous people, death rates were low for all age groups, except those aged over 65 years. Death rates were much higher for Indigenous than non-Indigenous people in all age groups, with the highest rates seen in the 25 to 44 age group. The highest DRR (206.2) was seen in Indigenous women aged 25 to 44 years (Table 7.3).
Table 7.3: NT Age-specific RHD Deaths* (Number, Rate and Rate Ratio)


<table>
<thead>
<tr>
<th>Age group</th>
<th>Indigenous</th>
<th>Non-Indigenous</th>
<th>Rate ratio**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate***</td>
<td>CI</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>1</td>
<td>1.0</td>
<td>0.2–7.3</td>
</tr>
<tr>
<td>5–24</td>
<td>34</td>
<td>10.7</td>
<td>7.6–14.9</td>
</tr>
<tr>
<td>25–44</td>
<td>42</td>
<td>22.8</td>
<td>16.9–30.9</td>
</tr>
<tr>
<td>45–64</td>
<td>20</td>
<td>30.1</td>
<td>19.4–46.7</td>
</tr>
<tr>
<td>65+</td>
<td>5</td>
<td>31.4</td>
<td>13.1–75.4</td>
</tr>
<tr>
<td>Female</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>2</td>
<td>2.1</td>
<td>0.5–8.4</td>
</tr>
<tr>
<td>5–24</td>
<td>26</td>
<td>8.2</td>
<td>5.6–12.0</td>
</tr>
<tr>
<td>25–44</td>
<td>64</td>
<td>33.6</td>
<td>26.3–42.9</td>
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<td>45–64</td>
<td>45</td>
<td>57.7</td>
<td>42.7–76.6</td>
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<td>14</td>
<td>67.4</td>
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<tr>
<td>0–4</td>
<td>3</td>
<td>1.6</td>
<td>0.5–4.8</td>
</tr>
<tr>
<td>5–24</td>
<td>60</td>
<td>9.4</td>
<td>7.3–12.1</td>
</tr>
<tr>
<td>25–44</td>
<td>106</td>
<td>28.3</td>
<td>23.4–34.2</td>
</tr>
<tr>
<td>45–64</td>
<td>65</td>
<td>44.8</td>
<td>35.1–57.1</td>
</tr>
<tr>
<td>65+</td>
<td>19</td>
<td>51.8</td>
<td>33.0–81.1</td>
</tr>
</tbody>
</table>

Note: * Underlying cause; ** Indigenous compared to non-Indigenous; *** per 100,000; RR = rate ratio

Over the 29-year period examined, a decline in the age-adjusted death rates was evident for both Indigenous and non-Indigenous people (Table 7.3). The Indigenous rate (males and females combined) decreased from 33.5 per 100,000 in 1977 to 1986 to 25.3 in 1997 to 2005 (Table 7.4). This decline is further investigated in the multivariate analysis for the NT time trends.
Figure 7.3: NT RHD Deaths (Age-adjusted Rate), 1977–2005

Table 7.4: NT RHD Deaths* (Number and Age-adjusted Rate), 1977–2005

<table>
<thead>
<tr>
<th>Period</th>
<th>No.</th>
<th>Rate**</th>
<th>CI</th>
<th>No.</th>
<th>Rate</th>
<th>CI</th>
<th>No.</th>
<th>Rate</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indigenous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1977–1986</td>
<td>32</td>
<td>23.2</td>
<td>13.7–32.8</td>
<td>49</td>
<td>43.5</td>
<td>27.6–59.5</td>
<td>81</td>
<td>33.5</td>
<td>24.2–42.8</td>
</tr>
<tr>
<td>1987–1996</td>
<td>40</td>
<td>25.5</td>
<td>15.4–35.6</td>
<td>49</td>
<td>31.2</td>
<td>21.8–40.6</td>
<td>89</td>
<td>28.2</td>
<td>21.5–35.0</td>
</tr>
<tr>
<td>1997–2005</td>
<td>30</td>
<td>14.8</td>
<td>0.80–21.6</td>
<td>53</td>
<td>33.1</td>
<td>22.3–44.0</td>
<td>83</td>
<td>25.3</td>
<td>18.3–32.2</td>
</tr>
<tr>
<td><strong>1977–2005</strong></td>
<td>89</td>
<td>20.5</td>
<td>15.6–25.4</td>
<td>132</td>
<td>35.2</td>
<td>28.4–42.1</td>
<td>253</td>
<td>28.4</td>
<td>24.1–32.7</td>
</tr>
<tr>
<td><strong>Non-Indigenous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1977–1986</td>
<td>6</td>
<td>2.9</td>
<td>0.0–5.8</td>
<td>6</td>
<td>10.6</td>
<td>0.1–21.0</td>
<td>12</td>
<td>6.9</td>
<td>1.3–12.6</td>
</tr>
<tr>
<td>1987–1996</td>
<td>7</td>
<td>2.1</td>
<td>0.5–3.8</td>
<td>2</td>
<td>1</td>
<td>0.0–2.4</td>
<td>9</td>
<td>1.6</td>
<td>0.5–2.8</td>
</tr>
<tr>
<td>1997–2005</td>
<td>1</td>
<td>0.1</td>
<td>0.0–0.4</td>
<td>5</td>
<td>2.5</td>
<td>0.2–4.9</td>
<td>6</td>
<td>1.3</td>
<td>0.1–2.6</td>
</tr>
<tr>
<td><strong>1977–2005</strong></td>
<td>14</td>
<td>1.3</td>
<td>0.6–2.1</td>
<td>13</td>
<td>3.1</td>
<td>1.2–4.9</td>
<td>27</td>
<td>2.3</td>
<td>1.3–2.4</td>
</tr>
</tbody>
</table>

Note: * Underlying cause; ** per 100,000

7.3.1.2 NT Remoteness and Region

There were 279 deaths (99.6%) in which RHD was the underlying cause with a place of residence recorded at the time of death that could be used to analyse remoteness and region. Age-standardised mortality rates for remote and urban categories are presented in Table 7.5. The rates for Indigenous people were higher in urban areas.
than in rural areas, for both sexes. Indigenous females had the highest rates in both urban and rural categories—approximately 10 times higher than non-Indigenous women.

Table 7.5: Age-standardised RHD Mortality* Rates by Remoteness, Gender and Indigenous Status, 1977–2005

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate*** CI</td>
<td>Rate CI</td>
<td>Rate CI</td>
</tr>
<tr>
<td>Indigenous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>13.8 6.4–21.3</td>
<td>20.7 9.7–31.8</td>
<td>17.6 10.7–24.4</td>
</tr>
<tr>
<td>Urban**</td>
<td>18.7 13.0–24.5</td>
<td>31.1 23.8–38.3</td>
<td>25.3 20.6–30.0</td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>1.4 0.5–2.3</td>
<td>2.0 0.5–3.5</td>
<td>1.8 0.9–2.7</td>
</tr>
<tr>
<td>Urban</td>
<td>0.8 0.0–2.4</td>
<td>3.8 0.0–11.3</td>
<td>2.3 0.0–5.9</td>
</tr>
</tbody>
</table>

Note: *Underlying cause; **urban is comprised of Darwin and Alice Springs and their immediate hinterland; *** per 100,000

RHD death rates were also compared for two periods (1985 to 1995 and 1997 to 2005) for the two service delivery regions within the NT:

- the Top End (northern) region with health and other services centred in Darwin
- the Central Australian (southern) region with services centred in Alice Springs.

This was undertaken to examine whether RHD mortality was lower in each region after the commencement of the RHD control programme in 1996 in the Top End, and 2000 in Central Australia.

In the Top End region, RHD death rates for Indigenous people were lower in 1997 to 2005 than in 1985 to 1996 for both males and females (although CIs overlapped). In the Central Australian region, the death rate in 1997 to 2005 was lower for males, yet
higher for females than in the earlier period (although CIs were wide and overlapped). Thus, there was little difference in death rates for males and females combined between the two periods (Table 7.6). RHD death rates were higher in Indigenous women in both periods and both regions (Figures 7.4 and 7.5). The results from the regression analysis to compare the rates between the Top End and Central Australia are shown in Table 7.7.

Table 7.6: NT Age-adjusted Mortality* Rate, Top End compared with Central Australia

<table>
<thead>
<tr>
<th>Period</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>CI</td>
<td>Rate</td>
</tr>
<tr>
<td><strong>Indigenous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top End</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1996</td>
<td>27</td>
<td>16.0–38.1</td>
<td>33</td>
</tr>
<tr>
<td>Central Aust.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1996</td>
<td>23</td>
<td>7.8–38.2</td>
<td>35.7</td>
</tr>
<tr>
<td>1997–2005</td>
<td>8.5</td>
<td>2.5–14.5</td>
<td>40.8</td>
</tr>
<tr>
<td><strong>Non-Indigenous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top End</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1996</td>
<td>2.5</td>
<td>0.7–4.3</td>
<td>1.0</td>
</tr>
<tr>
<td>1997–2005</td>
<td>0.2</td>
<td>0.0–0.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Central Aust.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1996</td>
<td>2.7</td>
<td>0.0–7.1</td>
<td>0.0</td>
</tr>
<tr>
<td>1997–2005</td>
<td>0.0</td>
<td>na</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Note: *Underlying cause; ** per 100,000
Table 7.7: Multivariate Analysis for Indigenous People from Top End

Compared with Central Australia for Two Periods*

<table>
<thead>
<tr>
<th>Variable</th>
<th>DRR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of age¹</td>
<td>1.04</td>
<td>1.03–1.05</td>
</tr>
<tr>
<td>Female²</td>
<td>1.31</td>
<td>0.98–1.76</td>
</tr>
<tr>
<td>Period 1997–2005³</td>
<td>0.79</td>
<td>0.55–1.00</td>
</tr>
<tr>
<td>Top End⁴</td>
<td>0.93</td>
<td>0.68–1.26</td>
</tr>
</tbody>
</table>

Note: ¹ = single year of age (age 50); ² = compared with male; ³ = compared with 1985 to 1996; ⁴ = compared with Central Australia; *1985 to 1996 and 1997 to 2005

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7.3.1.3 NT Multivariate Analysis

Multivariate (negative binomial regression) analysis was used to estimate the association of RHD death rates (the dependent variable) with Indigenous status, sex, age at death and year of death (the independent variables). The effect of age at death and year of death was found to be different for Indigenous than non-Indigenous people; thus, interaction terms for Indigenous status by age at death and Indigenous status by year of death were included in the final regression model. In regression analysis, the term for age at death was based at age 50 (the median death age) and year of death was based at 1991 (the mid-point of the study period).

The RHD death rate for females was 34% higher than for males (Table 7.8). For non-Indigenous people, RHD death rates increased by 10% per one-year increase in age, and decreased by 7% per year between 1977 and 2005. For Indigenous people, the increase in death rates with year of age was much less (4% per year of age) and there was minimal, if any, decrease in RHD death rates between 1977 and 2005 (DRR 0.98, 95% CI 0.97–1.00).

Table 7.8: Multivariate Analysis, RHD deaths, NT, 1977–2005

<table>
<thead>
<tr>
<th>Variable</th>
<th>DRR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous status</td>
<td>24.18</td>
<td>15.61–37.46</td>
</tr>
<tr>
<td>Female</td>
<td>1.34</td>
<td>1.06–1.71</td>
</tr>
<tr>
<td>Age</td>
<td>1.10</td>
<td>1.07–1.13</td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>1.04</td>
<td>1.03–1.04</td>
</tr>
<tr>
<td>Indigenous</td>
<td>0.98</td>
<td>0.97–1.00</td>
</tr>
</tbody>
</table>

Note: 1 = at age 50 in year 1991; 2 = compared with male; 3 = single year of age
7.3.1.4 Influence of Changes to ICD Coding in the NT

This study considered whether there might be an artificial reduction in RHD rates in the NT due to the changes in ICD coding during the 29-year period. The two major changes in Australia that may have affected the continuity of mortality statistics were:

1. the change from the ninth to the tenth revision of the ICD for classifying deaths registered from 1 January 1999
2. the introduction of the Automated Coding System for processing deaths registered from 1 January 1997.

To examine the effect these may have had on time trends in mortality rates, a model was completed to analyse the entire 29-year period (for the Indigenous population only). A term was included for pre-/post-1997. The DRR estimate for the pre-/post-1997 term was 0.92, \( p = 0.72 \). This indicated that the difference in mortality rates between the two periods was not statistically significant. The DRR for the ‘year’ term in the same model was 0.99, \( p = 0.25 \). This indicated that there might have been a small reduction over the 29 years (after considering any effect of the change of coding); however, the evidence for a reduction is far from convincing (Table 7.9). This is consistent with the analysis for the two periods separately (Table 7.6).
Table 7.9: Multivariate Analysis for Examining Changes due to Alteration of ICD Coding over 29-year Period in the NT

<table>
<thead>
<tr>
<th>Variable</th>
<th>DRR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age¹</td>
<td>1.04</td>
<td>1.03–1.04</td>
</tr>
<tr>
<td>Female²</td>
<td>1.36</td>
<td>1.05–1.75</td>
</tr>
<tr>
<td>Year³</td>
<td>0.99</td>
<td>0.96–1.01</td>
</tr>
<tr>
<td>ICD period⁴</td>
<td>0.92</td>
<td>0.59–1.43</td>
</tr>
</tbody>
</table>

Note: 1 = single year of age; 2 = compared with male; 3 = year of death, per single year; 4 = 1997 to 2005 (ICD10 coding period) compared to 1986 to 1996 (ICD9 coding period)

7.3.2 RHD Mortality in NT Indigenous Compared to Other Indigenous and Non-Indigenous Australians

7.3.2.1 RHD Death Rates

RHD mortality for Indigenous people in the NT was compared with other Australian Indigenous people and non-Indigenous Australians, for the period 1997 to 2005. From 1997 to 2005, there were almost as many RHD deaths in Indigenous people in the NT (n = 82) as in the four states combined (n = 104). RHD death rates were much higher for Indigenous people in the NT than in the four states combined (Figure 7.1, Table 7.1). Both were much higher than the non-Indigenous rates. Age-specific death rates were higher for Indigenous people in the NT than in the four states combined in all age groups and for both males and females, with the largest relative differences in the younger age groups (Table 7.10).
RHD death rates were much higher for Indigenous people in the NT and in other states than for non-Indigenous Australians, in 1997 to 2005 (Table 7.10). Within the Indigenous population, RHD death rates were considerably higher in the NT than elsewhere in Australia. Other than in the zero to four age group (in which there were only two deaths in total), RHD death rates were higher in all age groups for Indigenous than non-Indigenous Australians, with the greatest disparity in younger age groups. This reflects the larger number of non-Indigenous elderly Australians who die from RHD (Table 7.10).
Table 7.10: Age-specific RHD* Deaths (Number, Rate and DRR), 1997–2005, Indigenous in NT and Four States and Non-

Indigenous in Five States

<table>
<thead>
<tr>
<th>Sex</th>
<th>NT Indigenous</th>
<th>Four states Indigenous</th>
<th>Five states non-Indigenous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age group</td>
<td>No.</td>
<td>Rate</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0–4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5–24</td>
<td>7</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>25–44</td>
<td>17</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>5</td>
<td>18.1</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>1</td>
<td>18.1</td>
</tr>
<tr>
<td>Female</td>
<td>0–4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>5–24</td>
<td>7</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>25–44</td>
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<td>27.9</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>15</td>
<td>46.1</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>8</td>
<td>92.5</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>0–4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>5–24</td>
<td>14</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>25–44</td>
<td>39</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>20</td>
<td>33.2</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>9</td>
<td>63.4</td>
</tr>
</tbody>
</table>

Note: *Underlying cause only; ** per 100,000; ‡ NT Indigenous compared with five states non-Indigenous; † four states Indigenous compared with five states non-Indigenous
7.3.2.2 Multivariate Analysis

From 1997 to 2005, the RHD death rate (at age 50) was much higher for Indigenous people in both the NT (54 times higher) (Table 7.11) and in the four states combined (12 times higher) (Table 7.12) than for non-Indigenous Australians. The increase in death rates with age, and for females compared to males, was similar in both analyses.

Table 7.11: Multivariate Analysis, NT Indigenous Compared with Non-Indigenous, 1997–2005

<table>
<thead>
<tr>
<th>Variable</th>
<th>DRR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous status</td>
<td>54.80</td>
<td>41.58–72.24</td>
</tr>
<tr>
<td>Female</td>
<td>1.52</td>
<td>1.35–1.72</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>1.12</td>
<td>1.11–1.13</td>
</tr>
<tr>
<td>Indigenous</td>
<td>1.04</td>
<td>1.03–1.05</td>
</tr>
</tbody>
</table>

Note: 1 = base age 50; 2 = compared with male

Table 7.12: Multivariate Analysis, RHD Deaths of Indigenous in Four States Compared with Non-Indigenous in Five States

<table>
<thead>
<tr>
<th>Variable</th>
<th>DRR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous status</td>
<td>12.74</td>
<td>10.09–16.09</td>
</tr>
<tr>
<td>Female</td>
<td>1.52</td>
<td>1.34–1.71</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>1.12</td>
<td>1.11–1.13</td>
</tr>
<tr>
<td>Indigenous</td>
<td>1.05</td>
<td>1.04–1.06</td>
</tr>
</tbody>
</table>

Note: 1 = at age 50; 2 = compared with male; 3 = per single year of age

7.3.3 Semi-national Indigenous RHD Death Rates (Five States Combined), 1997–2005

RHD mortality was also examined for the NT, NSW, QLD, SA and WA combined in order to provide semi-national data on Indigenous RHD mortality covering 89% of
the Australian Indigenous population. From 1997 to 2005, there were 1,753 deaths with RHD as the underlying cause of death, of which 187 (10.7%) were Indigenous (69 males and 118 females) and 1,157 (66%) were females.

The age-specific rates were higher for Indigenous people in all age groups (Table 7.13). The DRR peaked in those aged five to 24 years, and remained dramatically elevated in those aged 25 to 44 years. The DRR remained elevated, although less so, in the older age groups. The five-state multivariate analysis showed that (at age 50 years) the RHD death rate for the Indigenous population of the five states combined was 18.85 times higher than that of non-Indigenous Australians (Table 7.14).

Table 7.13: Age-specific RHD* Deaths (Number and Rate) and DRR, Semi-national (NT, QLD, SA, WA and NSW), 1997–2005

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age group</th>
<th>Indigenous</th>
<th>Non-Indigenous</th>
<th>Rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. Rate CI</td>
<td>No. Rate CI</td>
<td>DRR CI</td>
</tr>
<tr>
<td>Male</td>
<td>0–4</td>
<td>0 0.0 na</td>
<td>1 0.0 0.0–0.2</td>
<td>na -</td>
</tr>
<tr>
<td></td>
<td>5–24</td>
<td>12 1.5 0.8–2.6</td>
<td>3 0.0 0.0–0.1</td>
<td>39.2 7.6–252.2</td>
</tr>
<tr>
<td></td>
<td>25–44</td>
<td>33 6.6 4.7–9.3</td>
<td>21 0.2 0.1–0.2</td>
<td>31.9 15.5–64.1</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>18 8.7 5.5–13.8</td>
<td>100 0.7 0.6–0.9</td>
<td>10.3 5.3–18.4</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>6 13.5 6.0–30.0</td>
<td>405 5.9 5.9–6.5</td>
<td>2.1 0.7–5.0</td>
</tr>
<tr>
<td>Female</td>
<td>0–4</td>
<td>1 0.9 0.1–2.8</td>
<td>0 0.0 na na</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5–24</td>
<td>13 1.6 1.0–2.8</td>
<td>3 0.02 0.0–0.1</td>
<td>46.9 10.0–289.7</td>
</tr>
<tr>
<td></td>
<td>25–44</td>
<td>47 8.9 6.7–11.8</td>
<td>30 0.17 0.1–0.2</td>
<td>33 18.6–58.1</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>34 15.1 10.8–21.1</td>
<td>138 0.98 0.8–1.2</td>
<td>10 5.8–16.2</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>23 38.4 25.5–57.9</td>
<td>865 10.13 9.5–10.8</td>
<td>2.9 1.6–4.8</td>
</tr>
<tr>
<td>All</td>
<td>0–4</td>
<td>1 0.19 0.0–1.4</td>
<td>1 0.0 na na</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5–24</td>
<td>25 1.55 1.0–2.3</td>
<td>6 0.0 na na</td>
<td>39.2 7.6–252.2</td>
</tr>
<tr>
<td></td>
<td>25–44</td>
<td>80 7.75 6.2–9.7</td>
<td>51 0.1 0.1–0.2</td>
<td>31.9 15.6–64.2</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>52 12.04 9.2–15.8</td>
<td>238 0.84 0.7–1.0</td>
<td>10.3 5.3–18.4</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>29 27.76 19.9–40.0</td>
<td>1,270 8.26 7.8–8.7</td>
<td>2.1 0.7–5.0</td>
</tr>
</tbody>
</table>

Note: *Underlying cause
Table 7.14: Multivariate Analysis, RHD Deaths Semi-national, 1997–2005

<table>
<thead>
<tr>
<th>Variable</th>
<th>DRR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous status¹</td>
<td>18.85</td>
<td>15.52–22.89</td>
</tr>
<tr>
<td>Female²</td>
<td>1.52</td>
<td>1.35–1.71</td>
</tr>
<tr>
<td>Age³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Indigenous</td>
<td>1.12</td>
<td>1.11–1.13</td>
</tr>
<tr>
<td>Indigenous</td>
<td>1.05</td>
<td>1.04–1.05</td>
</tr>
</tbody>
</table>

Note: 1 = at age 50 years; 2 = female compared with male; 3 = per single year of age

7.3.4 RHD Mortality by Underlying and Associated Cause in Five States, 1997–2005

Among Indigenous people who died from RHD, the majority had RHD recorded as the underlying cause of death (rather than the associated cause of death): 64% for Indigenous RHD deaths in the NT and 58% in the other four states. Only a small proportion of Indigenous RHD deaths were among people aged 65 and over. For non-Indigenous people, the majority of those who died from RHD had RHD recorded as their underlying cause of death (59%). However, unlike Indigenous people a majority (60%) of non-Indigenous RHD deaths among people aged 65 plus had RHD as an associated cause of death, rather than as the underlying cause (Table 7.15).
Table 7.15: Number of RHD Deaths in NT and Four other States, by Age Group and Underlying/Associated Cause, 1997–2005

<table>
<thead>
<tr>
<th>Age group</th>
<th>NT Indigenous</th>
<th>Other Indigenous (4 states)</th>
<th>Non-Indigenous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Underlying</td>
<td>Associated</td>
<td>Underlying</td>
</tr>
<tr>
<td>0–4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5–24</td>
<td>14</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>25–44</td>
<td>39</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>45–64</td>
<td>20</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>65+</td>
<td>9</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>83 (64%)</td>
<td>46 (36%)</td>
<td>104 (58%)</td>
</tr>
</tbody>
</table>

7.4 Discussion

Aim 1: To investigate the number and proportion of deaths attributable to rheumatic fever and RHD in Indigenous people in the NT.

From 1977 to 2005, there were 280 deaths from RHD as the underlying cause, 90% of which occurred in the Indigenous population and 59% of which were among females. RHD death rates increased with increasing age, and were higher for females than males in all age groups for the Indigenous population. Death rates were much higher for Indigenous than non-Indigenous people in all age groups across all time points, with the highest rate ratios seen in the five to 24 and 25 to 44 age groups. The DRRs for Indigenous NT people compared to the non-Indigenous population were 336.8 in the five to 24 age group, and 179.3 in the 25 to 44 year age group. This indicates the gross disparity in the mortality burden from RHD that occurs in young Indigenous Northern Territorians.

Deaths in non-Indigenous people occurred at high rates only in the 65 years plus population, suggesting that RHD is now a disease almost exclusively of the elderly in...
the non-Indigenous Australian population. This most likely reflects a historical burden of disease from a period up to the middle of the last century, when RHD was prevalent throughout Australia. Non-Indigenous Australians were also more likely to die from other causes, with RHD contributing as an associated, rather than primary, cause of death. This discrepancy may be due to gains in access to health service delivery benefiting non-Indigenous Australians at much greater levels than Indigenous Australians, and the poor housing and sanitation conditions to which many Indigenous people in the NT continue to be exposed. (192-195) This will only be improved by addressing social and environmental determinants, such as overcrowded housing, increasing access to health services, improved sanitation and nutrition, and directly targeting RHD as a neglected disease by strengthening initiatives such as the RHDAustralia programme to enhance the treatment, management and prevention of the disease.

7.4.1 RHD in the NT Indigenous Population

<table>
<thead>
<tr>
<th>Aim 2: To investigate time trends in RHD mortality rates for the Indigenous and non-Indigenous populations of the NT for the period 1977 to 2005.</th>
</tr>
</thead>
</table>

The time trend analysis showed a slight trend to reduced RHD mortality in Indigenous people over time (1.8% reduction per year); however, the corresponding decrease in RHD mortality for non-Indigenous people was four times greater (7.4% per year). This highlights how health indicators are improving much more slowly for Indigenous than non-Indigenous people in Australia, thus contributing to widening the gap in health outcomes, such as life expectancy.
The NT RHD control programme commenced in the Top End in late 1996, and, in 2000, it was extended to include people living in Central Australia. This may have affected the lower rates in the 1997 to 2005 period. A recent audit of the NT RHD register data found a reduction in the ARF recurrence rate by 9% per year since 1997. This suggests that primary health services in the NT supported by the NT RHD control programme are improving and preventing recurrence of RHD, which would support the contention that the NT RHD control programme has also had some effect on the lower mortality rates reported in this study for the 1997 to 2005 period. The audit of the NT register also found that, among Indigenous people, the relative survival rate decreased with time since diagnosis, with the excess mortality calculated to be 56% higher among those with RHD compared with unaffected individuals of the same age and sex. These new data, in conjunction with the study results, confirm the large burden of mortality associated with RHD among Indigenous Northern Territorians.

7.4.2 NT Indigenous Compared with Other Indigenous Australians

Aim 3: To compare RHD mortality for the NT Indigenous population with that for Indigenous and non-Indigenous Australians elsewhere in Australia for the period 1997 to 2005.

A comparison with RHD death rates for other states was completed for the nine-year period from 1997 to 2005. RHD mortality was higher for Indigenous people in the NT than for Indigenous people in the other four states examined. Indigenous people
aged 25 to 44 years in the NT had an age-specific death rate of 25.2 (95% CI 18.4–34.5), compared with 4.7 (95% CI 3.4–6.3) for Indigenous people of the same age group in the other four states.

7.4.2.1 Age-specific Mortality

The age-specific rate for Indigenous NT people aged 25 to 44 in this period was 25.2 (CI 18.5–34.5) compared to 4.7 (CI 3.4–6.3) for Indigenous people aged 25 to 44 in the other four states. This suggests that the gap in RHD mortality is far greater in Indigenous Northern Territorians than in Indigenous people residing outside the NT. The DRR (comparing Indigenous with non-Indigenous) for Indigenous people aged five to 24 years in the four states was 43.1, compared to a DRR of 336.8 in the same age group of Indigenous Northern Territorians. The DRR for Indigenous Northern Territorians was higher in all age groups compared to the Indigenous population in the other four states. Although the DRR was generally lower in the older age groups, the DRR for the 65 years plus age group was nearly three times higher in the NT Indigenous population than in the Indigenous populations in the other four states.

There was high mortality from RHD in the young Indigenous population, whereas mortality in non-Indigenous people was found to occur mainly in the elderly. This reflects a time more than 50 years ago when RHD incidence was high in non-Indigenous Australians, suggesting that non-Indigenous Australians have selectively benefited from reduced mortality from RHD over this time. This increased mortality from RHD in young people is seen elsewhere in high-prevalence, resource-poor countries, although limited population-based mortality is available to quantify this,
and further studies are required. (107, 117, 177) A recent examination of the Fiji RHD national register showed that patients with RHD have an 8.8 times increased risk of death, compared to the general population. This risk is greatest among young Indigenous men (DRR 50, CI 35.0–69.2,) compared to the non-Indigenous Fijian population. The mortality rate for patients with RHD was nearly 60 per 100,000 population. (174)

7.4.2.2 Reasons for Excess Indigenous Mortality in the NT

The disparity in mortality rates between Indigenous and non-Indigenous NorthernTerritorians may be partly due to the poorer living conditions and household overcrowding to which the NT Indigenous population are exposed, or due to the large proportion of this population living in remote areas. It is well documented that the poor quality of living conditions, household overcrowding and gap in life expectancy for Indigenous Northern Territorians is disparate to Indigenous people residing outside the NT, and the gap significantly widens when comparing these factors with non-Indigenous Australians.

7.4.2.3 Gender Difference

RHD mortality was approximately 50% higher for females than for males, for both Indigenous and non-Indigenous people. This increased mortality in females in this study is consistent with published evidence that RHD mortality rates are higher among females in other regions. (182, 183, 196). There were no data available to examine risk of death in pregnancy from RHD in this period.
Aim 4: To compare RHD mortality rates for Indigenous people at the semi-national level for the period 1997 to 2005 by remoteness of residence (urban/regional/remote).

7.4.2.4 Remoteness of Residence

There exists an inequity in the mortality from RHD in Indigenous Australia; however, routine data collected by government agencies is not readily available to highlight the disparity in mortality that has been shown in this analysis, or the potential effect of remoteness on mortality figures. Despite the collection of mortality data by the ABS via the Accessibility/Remoteness Index of Australia (ARIA) code, the ABS does not currently classify mortality data to link remoteness and cause of death for RHD.

The ABS has established the Australian Standard Geographical Classification (ASGC) as the national standard for classifying geographical locations in Australia. The ASGC has included a ‘remoteness’ structure since 2001, based on categories of the ARIA. The five remoteness categories are major city, inner regional, outer regional, remote and very remote. The place of residence in national death registrations data is coded according to the ASGC classification structures; however, unfortunately, it is not coded to the remoteness structure.

During an extended negotiation with the ABS, the researchers proposed several alternatives to use other ASGC classification structures to establish a ‘proxy’
classification of remoteness for deaths data, such as grouping statistical divisions into categories of ‘urban’, ‘rural’ and ‘remote’ so that mortality figures for Indigenous status and location of residence could be examined. Following extensive discussion and multiple requests, the researchers were informed that linking the mortality datasets with ARIA codes by census district was not possible, nor was the provision of RHD mortality data by Indigenous status, as this could potentially identify individuals and could be in breach of privacy legislation.

Instead, this study combined data by district and classified these as rural and urban for the NT. This enabled examination of the data for comparison, but not at the level of community that would have provided a more detailed picture of the relationship of location and RHD mortality. The ability to link these data in the future could provide valuable information regarding the mortality of Indigenous people in remote locations.

7.4.2.5 NT and Remoteness

The NT Indigenous populations is predominantly remote, and even the urban population often lives in similar conditions to remote communities—such as town camps in Alice Springs and the Bagot Community in Darwin. In other jurisdictions, a larger proportion of the Indigenous population live in large urban centres, and the extent of socioeconomic deprivation—while still significant—is not as great as in the NT. Thus, overall, there will be a diluting effect of less-deprived Indigenous people in other jurisdictions (given that RHD is a disease of poverty) than in the NT.
In the NT for the period studied, the accuracy of death certification is high due to previous projects linking datasets of census and mortality data.(178) There is an additional issue of the accuracy of death certification data for the four other states studied. In the NT, RHD awareness is greater than in other jurisdictions because of the high prevalence and the RHD control programme that has been in existence since the late 1990s. The NT RHD control programme has seen many cases of pre-existing, but undiagnosed, RHD identified and registered. This suggests that there may be many similar cases in WA, QLD, SA and NSW, as none of these states had registers or control programmes in place during the data analysis period. Thus, it is likely that there are people with RHD who have died, but whose RHD was either unknown or was not thought to have contributed to their death, and this proportion may be greater in the other states than in the NT.

7.4.2.6 Semi-national Data

The semi-national data presents the best estimates available to date to allow a comparison of RHD mortality for Indigenous and non-Indigenous people in Australia. There exists a disparity in the death rates of Indigenous people dying from RHD in Australia compared to the non-Indigenous population. However, the excess mortality is far greater in Northern Territorian Indigenous people, suggesting that further analysis is required with a more detailed examination of potential contributing factors, such as remoteness, access to services and poor living conditions.
7.4.3 Underlying or Associated Cause of Death

Aim 5: To investigate the proportion of deaths attributed to RHD as the *underlying* cause of death and as an *associated* cause of death.

Data available by *underlying* and *associated* cause was only available for the nine-year period from 1997 to 2005. Across both the NT and four states, non-Indigenous people were more likely to die in their elderly years of *associated* cause RHD mortality (59% of total non-Indigenous deaths); however, Indigenous people died in much larger proportions at a younger age and in greater proportions by *underlying* causes attributed to RHD (58% from *underlying* cause). These data suggest that non-Indigenous people are living longer with disease and die from associated factors, which may be due to better clinical management of disease, whereas Indigenous young people tend to die earlier with RHD as a direct cause. New data published from an examination of the NT RHD register has shown that excess mortality from RHD in NT Indigenous people was minimal in the first five years after their diagnosis; however, they suffered considerable excess mortality in subsequent years.(173)

7.5 Limitations of this Study

7.5.1 Restrictions on Data Access

The Department of Health, Health Gains Planning Branch, holds a copy of the national deaths dataset from 1967 to 2007. These are a composite of annual collections that are provided under government agreements that have varied over the
years. Two provisions were of particular relevance to this project. The first was that it is not permissible to make a copy of the dataset. As a result, analysis of the data was undertaken within the Health Gains Planning Branch, where the data are held on a secure server, with access restricted to named individuals.

The second restriction was that, while the data for the period up to and including the 2006 ABS deaths dataset are held by agreement with the NT government through the NT Department of Health, the 2007 deaths dataset was further constrained so that only those individuals approved by the registrars in each state are allowed access. For the NT data, a 29-year period consisting of 10 years (1977 to 1986), 10 years (1987 to 1996) and nine years (1997 to 2005) was used, and, for the other four states, a nine-year period (1997 to 2005) was possible for direct comparison of data.

7.5.2 Indigenous Identification

The accuracy of Indigenous certification is less reliable in the other four states than it is in the NT. The NT death data has been validated with a reported accuracy of 98.8% for Indigenous identification. Compared to the NT, the other states’ death data by Indigenous status may be underestimated by approximately 15%.(198) QLD has had consistent Indigenous identification since 1997; however, registration of data by Indigenous status did not commence there until 1996. Indigenous identification was also consistent in WA, SA and NSW throughout the period 1997 to 2005, with the exception of 1997 in NSW, where identification was incomplete. This may lead to a slight underestimate of the mortality rates in NSW for the nine-year period studied.(199)
7.5.3 ICD Coding

Another factor that may have influenced the accuracy of the data for the 29-year period in the NT were the two changes in ICD coding. In 1997, there was a change in ICD coding from ICD9 to ICD10, which resulted in some artefactual variation in disease coding. The comparability with ICD9 has been assessed by the ABS.(195, 197) Changes in coding may contribute to an underestimation of mortality rate and falsely suggest a decline. The effect of the change to ICD10 appears to be small and have affected ARF codes only. The change in ICD10 coding appears to have produced a step in the decline in mortality from 1997 to 1999; however, it was found that the effect of the change in coding was less than expected and did not appear to produce a statistically significant change.

7.6 Conclusion

Indigenous people are much more likely to die from RHD than are other Australians. Rates of death from RHD among Indigenous people in the NT exceed other states in Australia and those reported in many industrialised countries over a century ago. An Indigenous person living in the NT of Australia is 54.8 times more likely to die of RHD than is a non-Indigenous person. The majority of deaths among non-Indigenous Australians occur in people aged over 65 years, and reflect a time in the last century (pre-1960s) when ARF and RHD were more common among young Australians generally.
There is evidence of improvement over the past three decades; however, the mortality rate in non-Indigenous Australians has decreased at a faster rate than for Indigenous Australians. Significant achievements in the control of RHD and prevention of new cases are possible in the short to medium term, as has been witnessed with comprehensive approaches to control of ARF and RHD in the French Caribbean, New Zealand and elsewhere.(63, 200, 201)

A commitment to alleviating the underlying socioeconomic determinants of ARF and RHD is fundamental to prevent the mortality of Indigenous people from RHD and associated morbidities. Brown et al. state that ‘The most important of these determinants—overcrowded housing—is also the easiest to address, but requires a dramatically greater investment by governments than we are currently seeing’.(160) The incidence of many NCDs is increasing both in Indigenous and non-Indigenous people, including diabetes, tobacco-related disease, ischaemic heart disease and obesity. All these are so-called ‘lifestyle diseases’ that are difficult to prevent across the community, yet RHD incident cases are almost exclusively found in young Indigenous people.

Although in the NT Indigenous population, RHD mortality decreased by 25.4% from 1977 to 1986 and 1997 to 2005, the gap in mortality between Indigenous compared to non-Indigenous people has widened. RHD is highly preventable by addressing the social determinants that allow it to remain in Indigenous communities, and by delivering regular, inexpensive secondary prophylaxis to prevent recurrence in people known to have had ARF, as part of a comprehensive primary health programme.
The NT has had a register-based RHD control programme since 1996. This focus on RHD appears to have had some effect on reducing the recurrence of ARF. With good primary health management of known ARF/RHD cases, this will subsequently affect the mortality rates from RHD. Through the RHDAustralia programme, there is increased focus on prevention, management and control strategies for ARF/RHD in the NT and the other four states included in this study. However, a further difficulty for the management of RHD patients in the NT is the lack of cardiac specialist services in remote regions—outside Darwin and Alice Springs—and there is no surgical facility within the territory. This means that RHD patients requiring surgery have to travel to cities thousands of kilometres distant, dislocating them from their support systems and culture. This has significant implications both at a personal and financial level for RHD patients. To improve outcomes, special healthcare services must improve the capacity of the health workforce, increase the availability of specialist care, and improve the systems for delivering care to patients with complex, chronic diseases.

This mortality study has provided a comprehensive review of RHD mortality in Australia, with a focus on understanding the disparity in mortality between Indigenous and non-Indigenous populations. Similar research is required internationally to fully understand the epidemiology of RHD. As evidenced by the 2005 GAS Burden of Disease Study (9) and the recent update of the GBD (Chapter 6), there are very few RHD data available to define the true mortality estimates for RHD in both high- and low-prevalence regions. Current published global mortality estimates are largely based on estimations extrapolated from the expected numbers of
deaths of people living with RHD, rather than on vital statistics or register-based mortality data. Further research is required to determine the rates of RHD mortality both in first-nation populations in developed countries, and in developing countries with known high prevalence of RHD.
Chapter 8: Conclusions
8.1 Reasons for Undertaking These Studies

RHD is a neglected NCD disease of poverty that affects children and young people in large numbers, despite a relatively affordable and accessible treatment, compared to other NCDs. However the lack of good data globally, as well as for specific regions, such as the Pacific, prevents due attention being given to develop programmes to prevent and control the disease. In order to strengthen control strategies and gain the attention and prioritisation of governments, non-government organisations and other funding bodies, good epidemiological data are required to highlight the effect of RHD on populations.

The studies performed in Fiji will assist to further understand the effect of RHD, and aid in the adoption of strategies and policy at both a national and regional level. In addition, the data will assist Ministries of Health to further develop a feasible screening programme to target populations with a high burden of disease living in remote and resource-poor regions.

The GBD 2010 Study (Chapter 6) was designed to provide comprehensive and contemporary estimates of the burden of RHD globally analysed by region so that regional variation could be assessed. This provides an insight into the difficulty in obtaining good data to accurately estimate the burden that RHD still exacts on most lower- to middle-income countries. The majority of data available to assist modelling came from RHD prevalence studies undertaken in school-aged children, and data were absent from almost every global region to assist with incidence and mortality modelling calculations.
The Indigenous Australian mortality study (Chapter 7) aimed to fill part of the gap evident from the GBD modelling exercise, by providing mortality figures based on Indigenous and non-Indigenous status, both in the NT and at a semi-national level. These data have given some insight into the time trend of RHD mortality over 29 years in the NT, and highlighted the importance of examining RHD epidemiology by Indigenous status, as the majority of disease morbidity and mortality in Australia occur in the Indigenous population. These data will augment the few data available globally to understand the mortality burden of RHD by providing reliable population-based data that can be used to assist with modelling mortality estimates from high-prevalence, resource-poor regions. Similar studies are required from other high-risk RHD regions to understand the morbidity and mortality caused by RHD in vulnerable populations.

8.2 Findings of the Studies

8.2.1 Main Findings

8.2.1.1 High Echocardiographically Confirmed Burden of RHD in Fiji (Chapter 4)

The results of this study highlighted the use of highly sensitive and specific diagnostic criteria for echocardiography diagnosis of RHD, and confirmed there is a high burden of undiagnosed RHD in Fiji. The WHF RHD echocardiography criteria gave a prevalence of definite RHD of 8.4 cases per 1,000 (95% CI 4.6–14.1) and a prevalence of borderline RHD of 10.8 cases per 1,000 (95% CI 6.4–17.0). The prevalence of definite cases was similar using the NIH/WHO criteria; however, there were substantially fewer borderline (WHF criteria) cases identified compared to
NIH/WHO probable cases. This highlighted the need for sensitive and specific criteria to use in resource-poor settings where the implications of monitoring and treating large numbers of RHD cases can easily over-burden the healthcare system.

8.2.1.2 Nurses Given Training can Undertake Field RHD Echocardiography Screening Following an Algorithm for Referral (Chapter 5)

This pilot study showed that, given brief but comprehensive training, nurses can operate sophisticated portable echocardiography machines with competence. The nurses were able to detect findings suggestive of RHD with high sensitivity and reasonable specificity, which allowed the study to define regurgitant jet length cut-off as 1.5 cm to develop the protocol for a validation study. Additional training and experience will be required to increase specificity.

A study to evaluate and validate a RHD training module for nurses undertaking RHD echocardiography field screening is underway in Fiji, using the basic modules developed for this study and expanding the training and field experience. The results of this follow-on study will be published in 2014. There is much interest from colleagues globally in the development of this model for use in undertaking field RHD echocardiography screening in resource-poor settings. However, RHD screening may only be appropriate as a research tool or be undertaken at a population-based level in resource-poor countries that have a comprehensive RHD programme and strategy that can ensure adequate adherence rates to protect against disease.
8.2.1.3 High and Underappreciated Burden of RHD Globally (Chapter 6)

The estimated number of people living with RHD globally was found to be more than double the previous estimate of 34,232,795 in 2010, compared to the 2005 Lancet estimate of 15,600,000.(9) The highest all age global prevalence of RHD, based on the current estimates available from the GBD core group, was in the Pacific (Oceania) region (9.8 per 1,000), Sub-Saharan Africa (6.1–7.6 per 1,000 and South East Asia (6.3 per 1,000).

An examination of the epidemiology of RHD comorbidities such as atrial fibrillation, embolic stroke and infective endocarditis, could not be completed with the data available through the GBD study. These data are crucial to augment the figures estimated to date, and further studies are required to examine the effect of these RHD comorbidities in high-risk regions.

8.2.1.4 Indigenous Australians, Especially in the NT, have High RHD Mortality Rates Compared to Other Indigenous Australians and Non-Indigenous Australians (Chapter 7)

The mortality study has provided a comprehensive review of RHD mortality in Australia, with a focus on understanding the disparity in mortality between Indigenous and non-Indigenous populations. Indigenous people are much more likely to die from RHD than are other Australians, and at a younger age. There was an increased mortality risk found for Indigenous Northern Territorians compared to non-Indigenous Australians aged 25 to 44 years (DRR 179.3, CI 95% 115.0–277.4).
The ratio, although high compared to the non-Indigenous population, was not as pronounced for Indigenous Australians living outside the NT (DRR 33.1, CI 95% 21.4–51.0).

It was not possible to explore issues of remoteness in detail to assess this increased risk in the NT Indigenous population. Although there has been a decline in RHD mortality over the past 30 years in the NT, the rate of decline has been higher in non-Indigenous people (a decline of 7% per year for non-Indigenous people, compared with 2% per year for Indigenous people in the NT). Rates of death from RHD among Indigenous people in the NT exceed other states in Australia, as well as those reported in many industrialised countries over a century ago.

8.3 Limitations of the Studies

8.3.1 Fiji Echocardiography Prevalence Study (Chapter 4)

The study was undertaken on the main island of Viti Levu in the Tailevu and Rewa medical subdivisions. Although the researchers sought to enrol students to approximately match the ethnic and rural/urban distribution of the national population, extrapolation of the data to the rest of the country may not be accurate. This is due to the different environmental, socioeconomic and ethnic distribution of the population throughout the nation, where subgroups (such as urban squatter settlements) may live in reduced conditions that may not be reflected in the data presented. Further examination of the risk factors of RHD in these populations may be warranted.
With increasing poverty in Fiji, recent reports show that school attendance has decreased, and 15% of children do not complete primary school education. Children who do not attend school come from the poorest families, potentially giving them an increased risk of RHD. In addition, there was the potential for selection bias due to the loss of 168 participants who were enrolled, but did not have echocardiogram or auscultation completed, thereby excluding children who did not attend school. The above factors may have led to an underestimation of RHD prevalence in Fiji.

**8.3.2 WHF Borderline RHD Categorisation**

Despite the development of the new WHF RHD echocardiography consensus guidelines, for diagnosis of RHD, there remain a number of questions regarding the specificity of the guidelines to accurately identify borderline RHD. The Fiji echocardiography prevalence study (Chapter 4) found that risk associations for the cases identified as borderline did not follow the same pattern as the definite RHD cases, and previously demonstrated in other similar studies(16, 38), which suggests that many of the borderline cases identified may not be true RHD. Longitudinal cohort studies to follow the borderline cases to determine whether this pathology is true RHD are required.

In Fiji, patients that have a borderline RHD diagnosis, as well as their parents and guardians, are counselled by the paediatricians and given the option to commence BPG, as there is no clear evidence currently available to provide treatment guidelines for this group and understand the natural history of pathology that is determined as borderline RHD. A randomised control trial would assist in addressing this question.
(as discussed in Chapter 3). This may be possible to undertake in a country such as Fiji, where there is a situation of clinical equipoise in treatment and where BPG delivery is less than optimal for the vast majority of RHD patients.

There is a lack of understanding about the natural history of probable and borderline RHD. Studies in Nicaragua (72) and India (80) found that 9% and 4%, respectively, of subclinical lesions progressed to clinically detectable disease. Despite the limitations of these studies (discussed in Chapter 3), they demonstrate the potential of incidental subclinical lesions to progress to clinically evident disease, but also show that many subclinical lesions resolve completely. These data highlight the dilemma of how to manage these children, and the need for more rigorous long-term longitudinal studies. Understanding the natural history of subclinical RHD, and whether treatment of this group of probable/borderline cases improves patient outcomes, is critical to assess the potential benefits or dilemmas of programmes to screen for RHD in high-risk settings.

There remains a lack of understanding about what echocardiography findings of RHD mean. Echocardiography as a diagnostic tool for RHD is a relatively new concept, and longitudinal follow-up of children detected with minor valvular abnormalities is crucial to determine the natural history of subclinical and mild disease, and subsequently to determine whether early treatment with secondary prophylaxis improves patient outcomes. This study did not specifically collect data to compare probable (NIH/WHO criteria) with borderline (WHF inferred criteria) cases.
8.3.3 Nurse-led Echocardiography Pilot Study

Due to limited funding, it was only possible to train two nurses in the nurse-led echocardiography pilot study. If it had been possible to train an increased number of nurses, further correlation studies could have been undertaken, which may have led to more comprehensive data. However, the results were encouraging and led to a larger study being undertaken by this group that will be completed in 2014. This larger study is using the training modules from the pilot study that have been modified to be more comprehensive in their focus of measuring the regurgitant jet, and have included a much longer period of supervised experience following the initial workshop training.

8.3.4 GBD 2010 Study

At the time of writing this thesis, there were concerns regarding the accuracy of the available figures, particularly related to RHD incidence modelling and age distribution of cases. The data currently available, and the summaries published in the initial Lancet series of summary papers examining all disease burden, may not be accurate for RHD, particularly in terms of disease distribution by age group. There are few data available to examine the relationship between incidence and prevalence of RHD.

Data available from Australia and New Zealand (Chapter 6) show that there seems to be a ratio of 1: 2–3 in these settings. Further investigation is warranted to assess this relationship where data are available. Understanding this relationship could provide
estimations across all age groups for RHD incidence in high-risk settings, where only prevalence studies have been undertaken (the majority among young people) and where it is difficult to obtain solid incidence data, due to less than optimal data collection and reporting systems.

The researchers will continue to work to remedy this issue with the core GBD modelling group, using the available Australian and New Zealand incidence data and new RHD mortality data that has recently become available from Australia (173) (Chapter 7) and new mortality and incidence data from Fiji (Dr T Parks, MSc thesis [unpublished data], 2013).

8.3.5 Indigenous Mortality Study

Due to the lack of good Indigenous identification in the population and census data in some states of Australia, this study was limited to semi-national data from the one territory and four states that had good Indigenous identification for the period studied. Although the semi-national population studied encompassed the majority of the Indigenous population in Australia, it would have been interesting and valuable to be able to report national Indigenous compared with non-Indigenous mortality data at a national level. The study was also limited to examining the time trends for RHD mortality to the NT because this was the only region of Australia that had accurate validation of Indigenous status since the 1970s.

A further limitation was the inability to examine mortality at the community level. Due to restrictions from the ABS relating to privacy, this was not able to be
undertaken. Instead, only rural and urban NT populations were compared. Further examination of Indigenous mortality data relating to place of death may provide additional information that could assist with directing health policy and services to deprived communities or regions.

8.4 Public Health Implications

8.4.1 RHD Screening and Control

The capacity to undertake RHD screening in Fiji has been greatly expanded over the past eight years of the Fiji GrASP project. This began with training the Fijian sonographer in New Zealand to undertake the echocardiography study (described in Chapter 4) and with the informal echocardiography training of paediatric registrars by Dr Joseph Kado. Due to the success of this informal training in building echocardiography screening capacity, the pilot study to train nurses in basic RHD echocardiography was completed (described in Chapter 5). This pilot study has since led to a larger project to evaluate and validate an improved training module for nurses. Currently, the training of seven Ministry of Health nurses from three medical divisions of Fiji and online training modules for nurses are under development in a parallel project.

The Fiji RHD control programme now has the capacity to undertake RHD screening as part of Ministry of Health outreach visits that occur three to four times each year. However, this expansion of screening has not been matched by expansion of the capacity of the RHD control programme to monitor the delivery of BPG, or to review patient care. Screening identifies many new cases of RHD that require coordinated
care to ensure the disease status does not advance. Currently, there is little capacity within the RHD programme to monitor patient care and BPG compliance, and patients are frequently lost to follow-up. Thus, increased emphasis on improving primary health management and expansion and investment in the RHD programme is urgently required.

The Ministry of Health in Fiji is engaged and committed to improving RHD control; however, to date, the programme has only one official staff member and lacks the staff capacity to coordinate activities for the entire country. Further, RHD screening in the field delivers many cases into the system that require expert clinical review and diagnosis. This leads to increased pressure on the paediatric clinical services. For example, a facility for clinical review is currently available at the CWM Hospital in Suva at the weekly RHD echocardiography clinic; however, this is not adequate to manage an increased numbers of cases, and additional clinics must be organised to cope with the referrals from RHD screening across the country.

An increased emphasis on improving the capacity of the Fiji RHD programme and clinical services for review is fundamental to delivering coordinated health management. The expansion of RHD screening at a public health level should be equalled by further investment, expansion and integration of the Fiji RHD programme within the Ministry of Health NCD programme to improve the management of ARF/RHD cases and ensure optimal delivery and monitoring of BPG. A real opportunity has arisen to increase integration with primary health NCD services with the implementation and support of the WHO NCD Package of Essential Noncommunicable (PEN) Disease Interventions strategy in the Pacific
region. The WHO NCD PEN strategy is a global public health initiative focused on addressing the prevention and management of NCDs at the primary health level.

8.4.2 Global Epidemiology of RHD

The RHD component of the GBD 2010 Study provides an updated understanding of the global and regional burden of RHD; however, until remodelling has been completed, the final RHD figures cannot be reported with certainty. With the exception of RHD studies of prevalence in young people, there are very few data available to define the incidence, disability and mortality associated with RHD. RHD affects the poorest of the poor in the greatest numbers; however, data are largely lacking to define the epidemiology in the most at-risk communities and regions of Asia and Africa. Understanding the true burden of RHD is important to enable advocacy, prioritisation of resources and development of RHD strategies within public health infrastructure.

8.5 Future Research

These study results and reviews raise more questions that require answers. Future areas for research include the following. Improvements in the delivery and monitoring of BPG adherence rates are required in Fiji (and elsewhere in the region). Early diagnosis and delivery of secondary prophylaxis remains the mainstay of RHD prevention; however, most countries with high-risk populations struggle to deliver this at the primary health level. In Fiji and the wider Pacific, there has been much interest and engagement in building capacity in RHD echocardiography screening;
however, this expansion has not been equalled by improvements in delivery of BPG, even within countries with RHD strategies in place. Further research is required at both the health systems and community level to understand the barriers to adherence, and to examine novel alternatives and approaches. Ensuring that coordinated RHD programmes are in place and fully integrated into public health systems would help address issues of secondary prophylaxis delivery; however, very few countries have been able to demonstrate adequate delivery of BPG.

There is a need for longitudinal studies to follow RHD cases diagnosed as borderline in order to understand the natural history of disease. As RHD echocardiography screening capacity has increased in Fiji (and elsewhere in the Pacific), many children have been diagnosed with borderline RHD. This requires clinicians and Ministries of Health to decide whether to place these children on secondary prophylaxis, based on the availability and capacity of their clinical services, without solid evidence-based guidelines to assist them to make treatment decisions regarding these cases.

There is a need for an epidemiological tool to rapidly estimate disease burden due to RHD in Pacific Island countries and other high-prevalence, resource-poor regions, using either readily available data or data that can be easily obtained. The model for this could be the US Centers for Disease Control, *Haemophilus influenzae type b* (Hib) Rapid Assessment Tool (Hib RAT), which has been successfully used globally and within the Pacific region to estimate disease burden, and has been instrumental in leading to policy change, exemplified by the introduction of routine Hib vaccination in many countries. While global and regional estimates of the ARF/RHD disease burden may already be available, variations in the availability of and access
to health services, as well as the overall level of development in the community, may lead to major differences in disease burden between countries and populations in the same region. For this reason, health decision makers and policy makers prefer local data. Several options are available for collecting these local data, including population-based surveillance or other special studies of RHD disease burden (such as RHD screening, using hospitalisation data and so forth).

As the majority of the estimates presented in the GBD 2010 Study and earlier systematic reviews were calculated by extrapolating prevalence data mostly from children in school-based studies or modelled from historical cohort studies, a greater understanding of the incidence and mortality from RHD is urgently required from most regions of the world. Studies examining good quality register data (where they exist) in regions of India, Africa and the Pacific would allow for a greater understanding of the true estimates of RHD and the effect of the disease in high-risk regions.

All these future directions in research studies could promote interest in and raise awareness of RHD, and assist Ministries of Health and non-government organisations in terms of advocacy, policy decision making regarding the allocation of resources, funding requests, and introducing control programmes to lead to improved awareness and prevention of RHD.


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Appendix 1: Nurse-led Echocardiography Workshop

Training Aims
The achievement of the workshop aims required theoretical and practical knowledge, as follows.

1. **Anatomy and pathology**
   An understanding of cardiac anatomy and physiology (cardiac cycle). An understanding of the pathology and pathogenesis of RHD.

2. **Training aims, methods and procedures**
   An understanding of the aims, background, rationale and methods of the proposed study.

3. **Echocardiography basics**
   A basic understanding of the physical principles of ultrasound, including Doppler. A detailed and practical understanding of patient and transducer positioning, as they relate to cardiac orientation and position. A basic understanding of the modes of echocardiography. An understanding of the transducers used in echocardiography. A detailed and practical understanding of the following 2-D views: PLAX, PSAX, apical four chamber and apical five chamber. A basic understanding of the other commonly obtained echocardiographic views (subcostal and suprasternal).

4. **Echocardiography practical**
   A basic familiarity with the specifications of the Mindray portable echocardiogram machine, including safety and maintenance aspects. An advanced ability to set up the machine. An advanced ability to obtain good quality views in these four windows and to optimise these views in 2-D. An advanced ability to obtain good quality
colour Doppler images at the mitral valve in the PLAX and apical four-chamber view, and the ability to optimise these images. A basic ability to obtain good quality colour Doppler images at the aortic valve, and the ability to optimise these images. A basic understanding of continuous and pulse wave Doppler measurements.

5. Echocardiography of RHD

An understanding of the findings on echocardiography with RHD. An advanced ability to identify regurgitation at the mitral valve in the PLAX and apical four-chamber view. An advanced ability to measure jet length at the mitral valve in the PLAX and apical four-chamber view. A basic understanding of the findings of mitral stenosis. A basic understanding of aortic regurgitation.

6. Echocardiography of other childhood cardiac disease

A basic understanding of the findings on echocardiography of common congenital heart lesions.

7. Following study procedures

An ability to closely follow the screening echocardiogram protocol and follow the 11 steps outlined in Table 5.1.

The nurses were required to complete a series of quizzes for each topic covered, so that revision could be undertaken for areas of confusion or uncertainty during the workshop training, and prior to the commencement of the field experience.
### Auscultation Training Workshop Module for School Health Nurses

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<tr>
<th>Session</th>
<th>Day 1: Background</th>
<th>Day 2: Practical skills</th>
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| **8.30–10 am** | Welcome and introduction Lectures:  
- Background—What is RHD?  
- Overview of screening and rationale | Review of day one Lectures and interactive session:  
- Introduction to the diagnostic algorithm  
- The steps of the algorithm  
- Use of the data collection form |
| **10–10.15 am** | **Morning tea** | Practical session:  
- Auscultation of normal subjects  
- Auscultation of subjects with innocent murmurs  
- Auscultation of subjects with pathological murmurs |
| **10.15 am–12 pm** | Lectures:  
- Basic cardiac anatomy  
- Basic cardiac physiology  
Lecture and listening session:  
- Heart sounds and what makes a murmur | Practical session (continued) |
| **12–1 pm** | Lecture:  
- Cardiac examination  
Interactive session:  
- Using a stethoscope | Quiz 2:  
- Algorithm steps |
| **1–2 pm** | **Lunch** | Practical session (continued) |
| **2–3 pm** | Lecture and listening session:  
- All about innocent murmurs | Interactive session:  
- Murmur recognition  
- Review and questions |
| **3–4 pm** | Lecture and listening session:  
- Pathological murmurs (RHD and CHD) | Formal assessment:  
- Auscultation testing |
| **4–4.30 pm** | Interactive session:  
- Review and questions  
Quiz 1:  
- Anatomy, physiology and heart sounds | Feedback |
Appendix 2: Studies from Systematic Review—Published and Grey Data
Abdel-Moula AM, Sherif AA, Sallam SA, Mandil AM, Kassem AS, Zaher SR.
Prevalence of rheumatic heart disease among school children in Alexandria, Egypt: a
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<tr>
<th>Source</th>
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<th>Year</th>
<th>Reference</th>
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