The Active Surveillance of Children Diagnosed with Echocardiography-Detected Rheumatic Heart Disease

(2007-2012)

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Ethical Approval and Consultation

This study received ethical approval from the Ministry of Health Central Health and Disability Ethics Committee (reference #: 14/CEN/138). Consultation was also undertaken with the Ngai Tahu Research Consultation Committee.

In 2013, Auckland District Health Board and the University of Otago collaborated to develop a project investigating rheumatic heart disease screening, which was funded as part of the Rheumatic Fever Partnership Programme (administered by the Health Research Council). This report explores one component of this project, which focused on describing the follow-up practice and procedures used in echocardiography studies which took place between 2007-2012.

Summary

In this report, we present data relating to the follow-up care and active surveillance of children diagnosed with rheumatic heart disease (RHD) as part of a series of RHD screening studies conducted in six District Health Boards between 2007-2012, during which time 142 children were classified as having either definite, probable, possible or borderline RHD. We followed these patients up until the end of 2014. By the end of the follow-up period, all of those with definite RHD remained under medical follow up, whilst 26% of probable, 44% of possible and 36% of borderline RHD were medically discharged. All (100%) of those with definite RHD and most of those with probable (96%), possible (89%) and borderline (81%) RHD received at least one repeat echocardiography scan following the screening test. We observed some heterogeneity in receipt of care according to which of the two screening criteria ('modified' and 'WHF') was employed in a given region: for example, in those regions that utilised the 'modified' criteria, the median time between repeat scanning ranged from 86-138 days, compared with a median time of 413-727 days in those programmes utilising the WHF criteria. Such variation might be explained by study protocol evolution over the course of the pilot screening programme. Regarding antibiotic prophylaxis, all (100%) of those with definite and 96% of those with probable RHD promptly received antibiotic prophylaxis; while 21% of possible and 7% of borderline RHD went onto receive prophylaxis over the follow-up period.

Introduction

Rheumatic heart disease (RHD) is the cardiac consequence of acute rheumatic fever (ARF). Each year, more than 150 New Zealanders die of rheumatic heart disease (RHD);[1] and while RHD is most common during childhood,[2 3] mortality from this disease is most likely to occur in adulthood.[1] Māori and Pacific children are disproportionately impacted by ARF, placing them at greater risk of RHD.[4]

There is no specific treatment for RHD.[3] Short of surgical intervention and medical management of complications, the best that can be achieved once RHD is diagnosed is to prevent recurrent episodes of ARF via secondary prophylaxis with four-weekly intramuscular benzathine penicillin injections, which has been shown to improve long-term cardiac outcomes.[5] Where necessary due to severe symptomatic RHD, valve repair or replacement may be required however this may not be effective in all cases.[2]

It has been estimated globally that over 40% of patients who present with symptomatic RHD do not have a known history of ARF;[6 7] and for this reason, there is growing interest and debate regarding the utility of echocardiography screening as a tool for active case-finding in high risk populations.[3 8] The primary motivation for screening in this context is to identify patients with RHD before they become symptomatic, and then to intervene to prevent ARF reoccurrence via initiation of secondary prophylaxis – theoretically making these patients less likely to progress to a severe, symptomatic stage of RHD or to require costly and risk-filled cardiac interventions.[5]

A series of echocardiographic screening studies have taken place over the past several years in New Zealand in New Zealand, commencing in 2007 in South Auckland and extended to multiple other regions until 2012.[9 10] Echocardiography screening was offered to children through their schools in high deprivation areas (and one low-deprivation area, i.e. Auckland's North Shore) in six geographically-diverse regions. The aim was to identify undiagnosed rheumatic heart disease among largely Māori and Pacific 10-13 year olds.

Active surveillance of screened populations

It is the responsibility of public health to concern itself with the safety of screened populations.[11] The current study focuses on children who have no history of diagnosed or symptomatic RHD, many or most with minor echocardiographic changes where the natural history is currently unknown and the treatment pathway uncertain. For those identified with significant RHD active intervention supersedes active surveillance. For patients with minor changes, there is the possibility that mild

abnormalities observed during echocardiography may only represent normal or non-pathological variations of heart anatomy [12 13] – and thus any over-diagnosis, anxiety and possibly overtreatment of these patients may be harmful.

In the case of RHD screening, cardiac abnormalities detected by echocardiography are categorised by diagnostic criteria according to the likelihood that they are indicative of RHD. As there is no diagnostic 'gold standard' for RHD, these criteria have not been compared with a reference standard.[14 15] The early World Health Organisation-National Institute of Health (WHO-NIH) criteria [9] were revised following international expert consensus and review of available evidence, resulting in the publication of the 2012 World Heart Federation (WHF) criteria;[5] however the relevance and utility of these diagnostic criteria in the setting of population-based RHD screening programmes is yet to be determined.[3 8 14]

Two sets of criteria have been used for the RHD screening studies in NZ. The first, the modified NHI/WHO criteria, groups those with a positive screening test into definite, probable and possible RHD,[9] and the second, the WHF criteria, into definite and borderline.[5] Current international consensus is that those with definite or probable RHD should be referred for secondary antibiotic prophylaxis, while those with possible or borderline abnormalities undergo active surveillance.[16] The latter involves prospectively following the patient to monitor for disease progression. Active surveillance is recommended for these patients because the natural history and clinical significance of borderline RHD remains uncertain.[13 17]

For those with abnormalities that do not clearly indicate RHD, an active surveillance approach is appealing; follow-up echocardiography along with clinical re-evaluation at various intervals allows clinicians to monitor progression, potentially saving patients from 4-weekly intramuscular antibiotic injections. Such follow-up also provides opportunities for discussion and education regarding primary prevention of rheumatic fever by recognising and treating group A streptococcal infection. To date, actual practise in relation to the follow up of individuals with a positive RHD screen has not be described in detail in New Zealand.

Thus, the objective of this report was to summarise the follow up of children with a positive RHD screening test, including: a) active surveillance of asymptomatic patients with an abnormal echocardiogram following screening; b) ongoing receipt of repeat echocardiography scans; and c) initiation of antibiotic secondary prophylaxis. In addition, we have described active surveillance strategies employed in similar contexts internationally; and finally, we have combined this

information to make some recommendations regarding follow-up care for those classified as having sub-clinical or borderline RHD in New Zealand.

Methods

Participants

Those children who were screened as part of the multiple regional RHD screening studies (2007-2012), and who had an abnormal screening echocardiogram were included as participants for this study (n=144). Those diagnosed with acute rheumatic fever (ARF) at the time of screening were excluded from further analysis (n=2), leaving a final cohort of 142 (Figure 1).

Data sources

The primary data source for this report was records kept by organisers of the RHD screening studies, supplemented by clinical records where required (e.g. dates of repeat echocardiography scans within hospitals). The final dataset was provided to University of Otago researchers by Auckland District Health Board (ADHB) research staff, with identifiers removed and replaced by a unique study identifier. Final clinical data extraction was performed by ADHB staff in December 2014, with the final dataset provided to University of Otago researchers on 23/12/2014.

Follow-up protocol

The follow-up period for this study extended from the date screened until December 2014. Following participation in the programme, participants were reviewed at various intervals over the study period. Follow-up reviews consisted of a clinical assessment and repeat hospital-based echocardiogram. All echocardiograms were reviewed and reported by a cardiologist.

In two of the early regional screening studies – South Auckland and Auckland's North Shore – the study protocol required those participants deemed abnormal to have a repeat hospital-based echocardiogram following the initial portable echocardiogram, to assess the diagnostic accuracy of

portable echocardiography. For the studies in other regions, this was not a part of the protocol (Table 1).

Follow-up extended from the date screened until the end of follow-up, or when participants were medically discharged or lost to follow-up. Participants were only considered to be medically discharged if the date of discharge was recorded in the dataset. Loss to follow-up information was incompletely recorded. For the purposes of analysis, in the absence of a record, loss to follow occurred when a participant moved out of the study area, when follow-up did not occur due to inability to contact the participant or the participant had failed to present for review on multiple occasions. Follow-up was considered ongoing if the participant did not fall into these two categories (i.e. discharged or lost to follow up).

Variables

Age at the time of screening (in years) was defined by taking the difference between the date that the participant was screened and their date of birth. ***Sex*** was defined for each participant as either male or female. Self-identified ***ethnicity*** was defined using the prioritised ethnicity approach, whereby participants were categorised as either Māori or Pacific, with those identifying as neither of these groups categorised as non-Māori/non-Pacific. Despite allowing for recording of multiple ethnicities, there were no instances where a Māori participant identified as both Māori and Pacific (or vice-versa).

Screening result was the diagnostic classification of participants at screening, with participants classified as either 'definite', 'probable', 'possible' or 'borderline' RHD. There was a change in the ***diagnostic criteria*** used for screening over the course of the multiple screening studies (Table 1), whereby earlier studies had utilised a modified National Institutes of Health/World Health Organization (NIH/WHO) criteria (herein 'modified' criteria), whilst later studies used the World Heart Federation (WHF) criteria. A key difference between these two diagnostic criteria is that clinical examination is not needed for the diagnosis of RHD using the WHF criteria; i.e. the WHF criteria are exclusively based on echocardiographic findings.[5]

Table 1: Rheumatic heart disease diagnostic criteria, by study region.

Location	Diagnostic Criteria	Repeat scan in hospital for those deemed abnormal (i.e. two-step process)
South Auckland	Modified NIH/WHO	Yes
North Shore	Modified NIH/WHO	Yes
Tairawhiti	Modified NIH/WHO	No
Bay of Plenty	WHF	No
Kaitaia	WHF	No
Porirua	WHF	No

Repeat echocardiography scans. Based on data pertaining to the dates when participants received echocardiography re-scans following the date of screening (up to 20 scans), a binary variable regarding receipt of a follow-up scan (Yes/No) was created, and the total number of re-scans received by a given participant was categorised (0, 1, 2, 3, 4, 5+). For those from the South Auckland and North Shore studies who were sent for a hospital-based scan as a matter of routine, this scan was counted as their first re-scan for the main analysis.

Time to echocardiography re-scanning. Amongst those who went on to have a repeat echocardiography scan, the time from the date of screening to the first re-scan was determined and reported in days.

Antibiotic prophylaxis. Data pertaining to whether a given participant received antibiotic prophylaxis following the screening event was available as a binary variable (Yes/No), with an associated variable describing the date of prophylaxis commencement. Amongst those who received antibiotic prophylaxis, the time from the date of screening to prophylaxis commencement was determined and reported in days. In those cases where prophylaxis commencement data were either missing or unclear (e.g. 'mid-2009'), the given patient was not included in assessments of time to prophylaxis onset (n=11 patients; 19% of those who received antibiotic prophylaxis). The subsequent adherence over time with prophylaxis was not available as of 2014, but has been reported by others subsequently.[18]

Data Analysis

Crude descriptive analyses were completed for each variable, both for the total cohort and stratified by screening criteria. All analyses were performed in SAS v9.3 and Microsoft Excel.

Ethics and consultation

This study received ethical approval by the Ministry of Health's Health and Disability Ethics Committee (reference #: 14/CEN/138), and underwent consultation with the Ngai Tahu Research Consultation Committee.

Results

Patient demography and screening results. Table 1 shows the demographic characteristics of the cohort, as well as diagnoses made and screening criteria used. The mean age of the 142 patients with a positive RHD screening test was 12.3 years (SD 1.2 years). The number of males (51%) and females (49%) was approximately equivalent. The vast majority of the cohort was either Māori (47%) or Pacific (44%), with a minority of non-Māori/non-Pacific patients (9%). The greatest proportion of patients were identified in South Auckland (39%), followed by Tairawhiti (20%), Porirua (16%), Kaitaia (15%), Bay of Plenty (8%) and Auckland's North Shore (1%).

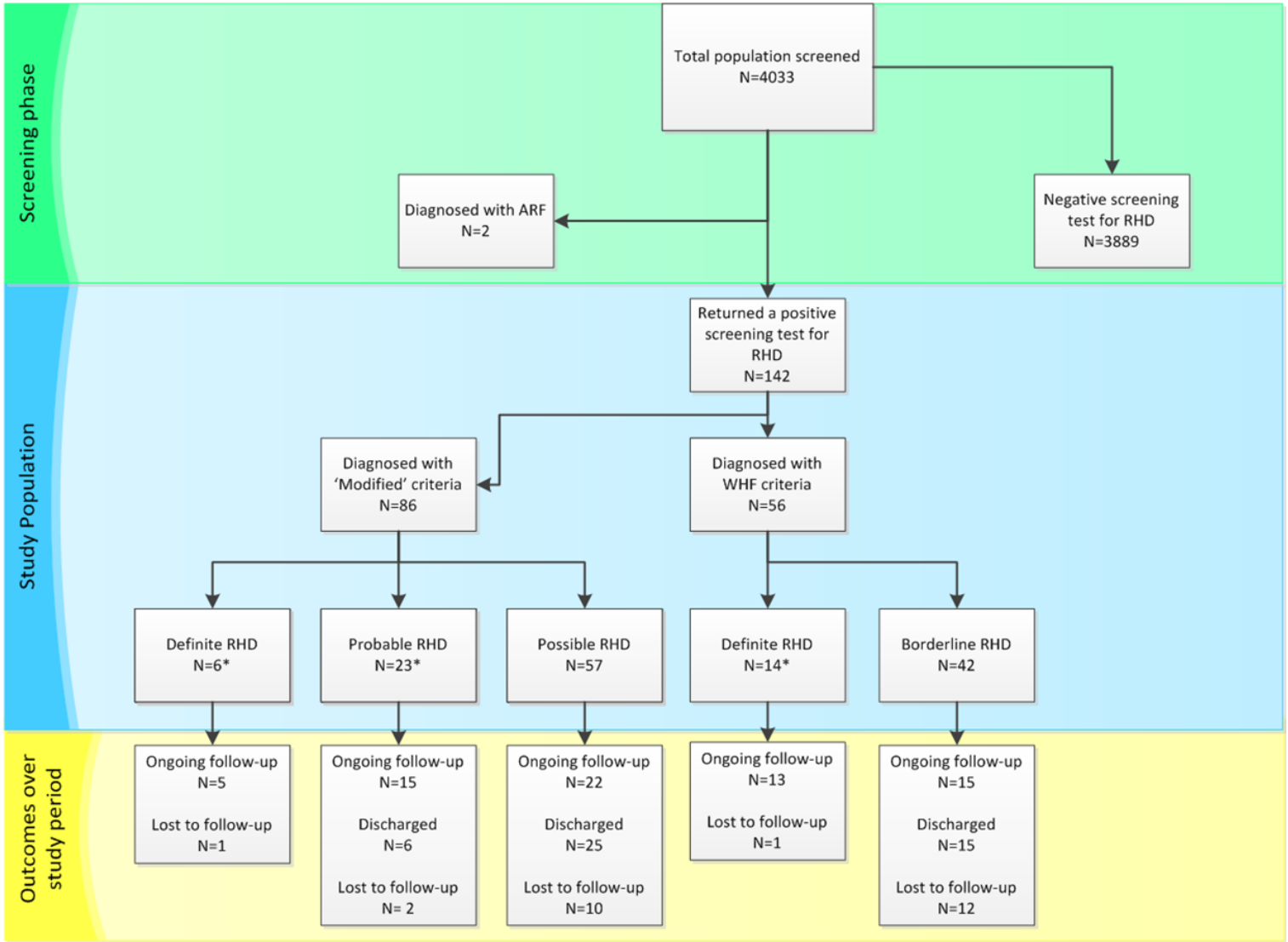
A majority of patients were classified using the 'modified' screening criteria (61%), with a minority classified using the WHF criteria (39%). Only a small minority of patients were diagnosed with definite RHD via echocardiography screening (14%), with the vast majority of the cohort classified as having either probable (16%), possible (40%) or borderline (30%) RHD. If we were to group across screening criteria, 30% of the overall cohort had either Definite RHD (WHO-NIH or WHF) or Probable RHD (WHO-NIH) and 70% of the overall cohort had Possible RHD (WHO-NIH) or Borderline RHD (WHF).

Table 1: Demographic characteristics of cohort, as well as screening result and criteria used.

	Total Cohort	
	n	%
Total	142	100%
Age (years)		
Mean (SD)	12.3	(1.2)
Ethnicity		
Māori	67	47%
Pacific	62	44%
Non-Māori/non-Pacific	13	9%
Gender		
Male	72	51%
Female	70	49%
Study region		
Bay of Plenty	12	8%
Kaitaia	21	15%
North Shore	2	1%
Porirua	23	16%
South Auckland	55	39%
Tairawhiti	29	20%
Screening result		
Definite RHD	20	14%
Probable RHD	23	16%
Possible RHD	57	40%
Borderline RHD	42	30%
Definite + Probable	43	30%
Possible + Borderline	99	70%
Diagnostic Criteria		
Modified NIH/WHO Criteria	86	61%
WHF Criteria	56	39%

Figure 1 shows the screening pathway, the number who returned a positive screening test, their diagnostic classifications and outcomes over the study period (i.e. ongoing follow-up, discharged, lost to follow-up). By the end of the study period, 83-93% of definite, 65% of probable, 39% of possible and 36% of borderline RHD were still receiving ongoing follow-up. None of those with definite RHD were discharged over the study, whilst 26% of probable, 44% of possible and 36% of borderline RHD were discharged. Loss to follow-up was greatest in those classified with borderline RHD (n=12 out of 42, 28%), followed by those with classified with definite RHD using the 'modified' criteria (n=1 out of 6, 17%) and possible RHD (n=10 out of 57, 18%).

Figure 1: Flow diagram showing screened population, subsequent diagnoses and disposition as at 2014.



* Denotes antibiotic prophylaxis routinely given

Repeat echocardiography scans. Our observations regarding receipt of repeat echocardiography scans are shown in Table 2 (total cohort) and Table 3 (stratified by screening criteria). All of those classified with definite RHD (100%) and most of those classified with probable (96%), possible (89%) and borderline (81%) disease received a repeat echocardiography scan. There was large heterogeneity in the time between screening and repeat echo scanning between classification groups, with this duration ranging from one day up to several years. The shortest median time between screening and repeat scans was found among those classified with either probable (median 130 days, inter-quartile range [IQR] 182 days) or possible (138 days, IQR 280 days) RHD. The longest median time was observed for patients classified with borderline RHD (727 days, IQR 672 days). Those classified with definite RHD had a median time between screen and repeat scan of 292 days.

In line with the findings for the total cohort, all of those classified with definite RHD using the 'modified' screening criteria (100%) and most of those classified with probable (96%) and possible (89%) disease received a repeat echocardiography scan. Similarly, all of those classified with definite RHD using the WHF criteria received a repeat scan, while nearly all (81%) of those classified with borderline RHD received a repeat scan. There was large heterogeneity in the time between screening and repeat echo scanning between classification groups for both screening criteria (Table 3).

The time between screening and re-scan was substantially shorter among those classified using the 'modified' criteria compared to those classified using the Modified WHF criteria (Table 3). This relates to the research protocol in South Auckland and North Shore where individuals were referred for a hospital echocardiogram and evaluation if found to have a positive portable screening echocardiogram (Table 1). By way of comparison, 100% of those participants from South Auckland who were classified with probable RHD received a re-scan, compared to 83% of participants outside this region, while 94% of those from South Auckland/North Shore who were classified as possible RHD received a re-scan compared to 81% of participants outside of these regions. The median time to a repeat scan among those classified with definite RHD in South Auckland/North Shore was 42 days, compared to 401 days outside these regions, 98 days compared to 832 days for participants classified with probable RHD, and 86 days compared to 855 days for possible RHD. We must caution that these stratified estimates are based on small numbers of participants, and thus their precision is limited.

Given the systematic manner in which participants from South Auckland/North Shore may have differed in terms of echocardiography re-scanning likelihood (and timing) to the rest of the cohort, we have repeated our analyses for these variables excluding the first re-scan following the screening test. These data are presented in the Appendices (Tables A1 and A2). As might be expected, by excluding the first re-scan we observed a drop in proportion of those classified as having definite, probable and

possible RHD who were observed to receive an echocardiography re-scan (definite: 90%, probable: 70%, possible: 84%). Additionally, we observed an elongation in the median time to re-scan for those classified as having definite (350 days, IQR 487 days), probable (1510 days, IQR 1724 days) and possible (496 days, IQR 543 days) RHD. The pros and cons of excluding this first scan are discussed further in the Discussion section of this report.

Table 2: Receipt of repeat echocardiography scans, including time to first repeat scan.

		Screening Result							
		Definite RHD		Probable RHD		Possible RHD		Borderline RHD	
		n	%	n	%	n	%	n	%
Received Repeat Echo Scan									
	Yes	20	100%	22	96%	51	89%	34	81%
	No	0	0%	1	4%	6	11%	8	19%
Number of Repeat Scans									
	0	0	0%	1	4%	6	11%	8	19%
	1	12	60%	9	39%	11	19%	24	57%
	2	2	10%	8	35%	23	40%	8	19%
	3	1	5%	4	17%	10	18%	2	5%
	4	1	5%	1	4%	6	11%	0	0%
	5+	4	20%	0	0%	1	2%	0	0%
Time to First Repeat Scan [1] (days)									
	Mean (SD)	431.8	(418.6)	280	(405.4)	337.9	(420.2)	611.6	(328.1)
	Median (IQR)	291.5	(488)	130	(182)	138	(280)	726.5	(672)
	Range (min/max)	1 - 1549		27 - 1700		13 - 1763		33 - 1219	

[1] Among those who received a repeat echo scan. IQR = Interquartile range.

Table 3: Receipt of repeat echocardiography scans, including time to first repeat scan, by screening criteria used: a) Modified NIH/WHF criteria; b) WHF criteria.

	a) Modified NIH/WHO Criteria					
	Definite RHD		Probable RHD		Possible RHD	
	n	%	n	%	n	%
Received Repeat Echo Scan						
Yes	6	100%	22	96%	51	89%
No	0	0%	1	4%	6	11%
Number of Repeat Scans						
0	0	0%	1	4%	6	11%
1	2	33%	9	39%	11	19%
2	0	0%	8	35%	23	40%
3	0	0%	4	17%	10	18%
4	1	17%	1	4%	6	11%
5+	3	50%	0	0%	1	2%
Time to First Repeat Scan [1] (days)						
Mean (SD)	100.7	(98.1)	280	(405.4)	337.9	(420.2)
Median (IQR)	85.5	(155)	130	(182)	138	(280)
Range (min/max)	1 - 259		27 - 1700		13 - 1763	

b) WHF Criteria

		Definite RHD		Borderline RHD	
		n	%	n	%
Received Repeat Echo Scan					
	Yes	14	100%	34	81%
	No	0	0%	8	19%
Number of Repeat Scans					
	0	0	0%	8	19%
	1	10	71%	24	57%
	2	2	14%	8	19%
	3	1	7%	2	5%
	4	0	0%	0	0%
	5+	1	7%	0	0%
Time to First Repeat Scan [1] (days)					
	Mean (SD)	573.6	(424.5)	611.6	(328.1)
	Median (IQR)	412.5	(734)	726.5	(672)
	Range (min/max)	67 - 1549		33 - 1219	

[1] Among those who received a repeat echo scan. IQR = Interquartile range.

Antibiotic prophylaxis. All of those classified with definite RHD (100%), most of those classified with probable RHD (96%) and some of those classified with possible (21%) or borderline (7%) RHD received antibiotic prophylaxis. Again, there was large heterogeneity in the time between screening and prophylaxis onset, with this duration ranging from one day up to several years. The shortest median time between screening and prophylaxis onset was found among those classified with definite RHD (median: 45 days, IQR: 46 days). The longest median time was observed for patients classified with possible RHD (352 days, IQR 402 days). We were unable to ascertain whether antibiotic prophylaxis was only started for those initially classified as having possible or borderline disease upon subsequent evidence of disease progression, which may account for the longer delay in this group.

In line with the findings for the total cohort, all of those classified with definite RHD using the 'modified' screening criteria (100%) and most of those classified with probable RHD (96%) disease received antibiotic prophylaxis. Few of those classified with possible RHD (21%) received antibiotic prophylaxis. Similarly, all (100%) of those classified with definite RHD using the WHF criteria received prophylaxis, while only a few (7%) of those with borderline RHD received prophylaxis. There was large heterogeneity in the time between screening and receipt of antibiotic prophylaxis between classification groups for both screening criteria (Table 3).

Table 4: Receipt of antibiotic prophylaxis, including time to prophylaxis onset.

	Screening Result							
	Definite RHD		Probable RHD		Possible RHD		Borderline RHD	
	n	%	n	%	n	%	n	%
Received Antibiotic Prophylaxis								
Yes	20	100%	22	96%	12	21%	3	7%
No	0	0%	1	4%	45	79%	39	93%
Time to Antibiotic Prophylaxis [1] (days)								
Mean (SD)	56.4	(43.1)	114.9	(71.3)	581.9	(503.5)	254.3	(270.8)
Median (IQR)	45	(46)	98	(120)	352	(402)	102	(473)
Range (min/max)	1 - 162		27 - 247		62 - 1734		94 - 567	

[1] Among those who received antibiotic prophylaxis. Missing date of onset data prevented calculation of time to prophylaxis for 11 patients (19% of those who received antibiotic prophylaxis).

Table 5: Receipt of antibiotic prophylaxis, including time to prophylaxis onset, by screening criteria.

a) Modified NIH/WHO Criteria

	Definite RHD		Probable RHD		Possible RHD	
	n	%	n	%	n	%
Received Antibiotic Prophylaxis						
Yes	6	100%	22	96%	12	21%
No	0	0%	1	4%	45	79%
Time to Antibiotic Prophylaxis [1] (days)						
Mean (SD)	25.3	(34.9)	114.9	(71.3)	581.9	(503.5)
Median (IQR)	11.5	(40.5)	98	(120)	352	(402)
Range (min/max)	1 - 77		27 - 247		62 - 1734	

b) WHF Criteria

	Definite RHD		Borderline RHD	
	n	%	N	%
Received Antibiotic Prophylaxis				
Yes	14	100%	3	7%
No	0	0%	39	93%
Time to Antibiotic Prophylaxis [1] (days)				
Mean (SD)	66	(41.8)	254.3	(270.8)
Median (IQR)	46	(54)	102	(473)
Range (min/max)	3 – 162		94 - 567	

[1] Among those who received antibiotic prophylaxis. Missing date of onset data prevented calculation of time to prophylaxis for 11 patients (19% of those who received antibiotic prophylaxis).

Discussion

This report has described the follow-up care and active surveillance experience of children who participated in multiple RHD screening studies across New Zealand. Of the total population screened (n=4,033), 142 mainly Māori and Pacific children screened positive for RHD. Screen-detected definite RHD was found in 14% of cases, with the addition of probable cases (diagnosed using the WHO-NIH criteria) taking this total to 30% definite or probable RHD. This correlates with similar findings in other studies, where asymptomatic definite RHD is detected in a small proportion of a screened population.[19-22]

Follow-up. It should be noted that the follow-up period for this report ceased in December 2014. We are aware that follow-up of many of these patients (including echocardiography re-scanning of all possible/borderline RHD cases) is ongoing. Over the study period, none of those with definite RHD were discharged, compared to 44% of possible RHD and 36% of borderline RHD. It was not clear from the data available which factors prompted discharge: they may have occurred because of a false positive diagnosis at screening, or if the screen-detected disease improved. The observation that possible and borderline RHD was more likely to be discharged is consistent with other research and suggests that possible/borderline RHD has a variable natural history.[19-22]

Approximately 1 in 5 participants over the study were lost to follow-up (at least based on the criteria used, as described under "Follow-up protocol"). Participants with non-definite RHD – i.e. those for whom active surveillance was the primary mode of follow-up care – were more likely to be lost to follow-up. Such a loss to follow-up mirrors the findings in other RHD screening studies [19-22] and raises two issues for any proposed screening programme: firstly, large losses to follow-up need to be minimised, otherwise they can undermine the efficacy of a screening programme;[23] and secondly, minimising the loss to follow-up can be resource intensive and costly.

Echocardiography re-scanning. When considering the particulars of active surveillance of this cohort, all of those with definite RHD and most of those with a probable (96%), possible (89%) and borderline (81%) RHD screening result received at least one repeat echocardiography scan. The number of repeat scans each participant received varied by diagnostic classification. For those with definite and borderline RHD, most participants (60% and 57%, respectively) had only one scan. However, those with probable and possible RHD were more likely to have had more than one repeat scan (Table 3). In those regions that

utilised the 'modified' NIH/WHO criteria, the median time between repeat scanning ranged from 86-138 days, compared with a median time of 413-727 days in those programmes utilising the WHF criteria.

Such variation can partially be explained by study protocol evolution over time: as discussed previously, early studies performed in South Auckland and the North Shore referred those participants with abnormal screening results for a re-scan as a matter of course. We conducted sensitivity analyses in which we removed the first re-scan for participants from those two regions, which predictably increased the median time to re-scan as well as reduced the proportion of participants who were observed to receive an echocardiography re-scan (Tables A1 and A2).

It is difficult to decide whether the inclusion or exclusion of these first re-scans provides a more accurate representation of the true echocardiography follow-up experienced by participants of the screening studies. On the one hand, we might consider that the sole intention of the first re-scan among those in the South Auckland/North Shore regions was to validate the result achieved with the portable echocardiography equipment – in which case this first re-scan could be considered an extension of the screening test itself, rather than a form of clinical follow-up. Following this assumption, it would be correct to exclude these first re-scans from our pooled analysis. On the other hand, removing these re-scans makes it falsely appear that a number of participants received no hospital re-scan whatsoever – since a number of participants (particularly those with a screening classification of probable RHD) did not receive any further scans beyond their first re-scan (see Tables A1 and A2). It is also important to note that the 'confirmatory' re-scans did not occur within days of the original screening test, but rather months (time to first re-scan: definite RHD 42 days, probably RHD 98 days, possible RHD 86 days).

We have decided for the purposes of this report that the exclusion of these first re-scans would result in a less-accurate picture of the receipt of echocardiography follow-up by participants in the South Auckland/North Shore regions – and thus the primary results (i.e. Tables 2 and 3) include all hospital re-scans, regardless of their *a priori* intention. However since arguments can be made in either direction, we have additionally presented these tables with those relevant re-scans removed (i.e. Tables A1 and A2).

Antibiotic prophylaxis. Regarding antibiotic prophylaxis use, all of those with definite and 96% of those with probable RHD at screening received antibiotic prophylaxis in accordance with treatment recommendations.[24] For non-definite RHD at screening, 21% of possible and 7% of borderline RHD went on to receive prophylaxis over the study period. It is possible that these observations suggest disease progression among those with non-definite disease; however, the dataset used for this study did not

systematically describe why participants were discharged or why they were started on antibiotics. In the absence of this information, it cannot be said whether changes in management over the follow-up period were actually due to disease progression or regression.

Contact with health services. In addition, the dataset used for this study did not allow us to systematically describe active surveillance in the form of contact with health services. While we are unable to quantify this contact for the entire study cohort, we are aware that many patients and their whānau received significant contact with health services, including nursing staff (particularly for those receiving antibiotic prophylaxis), specialists, community paediatricians and general practitioners. We have presented two case-studies by way of example in the paragraph below.

Firstly, the whanau of one boy with RHD diagnosed on screening had four clinic appointments to reach agreement on prophylaxis, which District Nursing Services provided at 28 day intervals. Following subsequent admission to hospital for a separate condition, he had a repeat echo which documented worsening mild- to moderate-mitral valve incompetence. After a period off prophylaxis out of his home region, he recommenced four-weekly antibiotics and will continue to be followed by cardiac specialists. Secondly, after discussions with clinicians the whānau of a girl diagnosed with mild mitral valve incompetence chose not to use regular prophylaxis, but rather chose to vigilantly respond to future sore throats. This girl also receives ongoing follow-up, including repeat echocardiogram over the six years since her initial scan.

Changes in screening criteria over time. Finally, it is important to reiterate that comparisons between screening criteria groups is limited by the fact that these two criteria were not mutually-exclusive; rather, one (the WHF criteria) was developed to replace the other (the 'modified' criteria). Thus, differences in some measures between these groups regarding factors such as elapsed time between the screening event and receipt of an echocardiography re-scan cannot reasonably be attributed to the screening criteria *per se*, but are more likely related to the fact that the screening studies evolved from 2007 to 2012.

International comparison

New Zealand is not the only country to undertake echocardiographic screening of children in order to detect undiagnosed RHD. In a screening study run in South Africa and Ethiopia, children classified as

having definite or borderline RHD were referred for 'consideration' for antibiotic prophylaxis – and also placed on a local registry to enable continued follow-up.[25] Similarly in Peru, children screened and classified with definite or borderline RHD were invited to receive antibiotic prophylaxis and ongoing clinical follow-up.[26] In an Australian study, screened patients were triaged by trained cardiologists, who made recommendations to primary care services regarding follow-up (including antibiotic prophylaxis).[27] New Caledonia has had an established echocardiography-based screening programme – one of the few Government-mandated programmes internationally – for RHD since 2008, targeting primary school aged children. Each year those aged between 9-10 are screened via echocardiography at school. Children with a positive screening test (either definite or borderline) for RHD are treated with antibiotics, and are routinely monitored and followed-up.[22] Thus, a key difference between the New Caledonian and other programmes is that all children in New Caledonia classified as having screen-detected RHD – be it definite or borderline – are initiated on prophylaxis.

One of the challenges arising from the international echocardiography screening literature is that there is no consistent approach to the follow-up and management of screen-detected RHD over time. As a consequence, it is difficult to describe international best-practice and benchmark New Zealand's screening experience against international comparators. This is a rapidly evolving area of research, and more information on natural history of echo-detected RHD is needed to inform standards for such care in the future.

Limitations

As mentioned above, it was our initial intention to describe the frequency of contact with health services and at what level it occurred (e.g. secondary care). However, as mentioned the data available for our analysis only allowed us to describe receipt of repeat echocardiography scan, antibiotic prophylaxis, and disposition (i.e. whether a patient was receiving active follow-up, had been lost to follow-up or had been discharged).

In addition, it was also our initial intention to describe receipt of follow-up care by geographic region, allowing crude descriptive comparisons between DHBs. However, it was decided that such comparisons would not be made for the following three reasons: a) a low number of cases in some regions (e.g. Bay of Plenty, North Shore); b) large heterogeneity in the chronological timing of screening between study regions (e.g. South Auckland 2007/2008, Porirua 2012), during which screening protocol standardisation was evolving; and c) heterogeneity in the screening criteria used between some regions (Table 1). In the case of the latter, as noted earlier it is likely that the rate and timing of echocardiography re-scanning in

the 'modified' criteria group was affected by the fact that those screened in South Auckland and North Shore were, as a matter of course, referred for a repeat scan if found to have a positive screening result.

Standard of care for screen-detected RHD

Over the period 2007-2012, the follow-up care received by patients classified with RHD as a result of screening largely adhered to national recommendations regarding their treatment (or non-treatment).[16] Almost all patients with abnormal findings received a follow-up scan after the initial screening event, and receipt of antibiotic prophylaxis was largely confined to those with either definite or probable RHD. This homogeneity – occurring, as it did, across a wide range of geographic regions – suggests a high-level of communication and integration of clinical procedures between those involved in providing care to these patients.

In addition to these factors, our observations made during this report lead us to provide the following three recommendations for optimising active surveillance for this population.

- Antibiotic prophylaxis. Given the uncertainty regarding the natural history of RHD, it is unclear what the threshold for management of those classified with sub-clinical disease should be. (It should be noted that patients who have had ARF with and without subclinical residual RHD have prophylaxis based on the understanding of the impact of ARF recurrence.) In the case of antibiotic prophylaxis, the vast majority of those study participants who were indicated to receive it did so – and in a relatively timely manner. What remains unclear within the literature is whether antibiotics for screen-detected disease provide a clinically relevant benefit (e.g. reduction in cardiac valve surgery or significant progression of valve disease). Given this, it is important that data are routinely recorded on reasons for both instigating and stopping antibiotic prophylaxis for those who have been identified through a screening programme, and on whether there is evidence of disease progression or regression. In the longer term, continued consideration is warranted regarding whether antibiotic prophylaxis improves outcomes for those with screen-detected RHD, although the data collected within the context of a screening programme are unlikely to be able to address this question in isolation.

- Echocardiography re-scanning. The vast majority of those who were classified with RHD as a result of screening were re-scanned during the follow-up period; however, in many cases the time between the screening event and subsequent re-scanning was several years. Further investigation and consideration is required regarding a) how frequently re-scanning should occur

in screen-detected disease, and b) how best to ensure that health care services are prepared to meet this demand. In the case of the latter, screening in the absence of available resources is clearly not desirable in terms of ensuring timely re-scanning.

- Data collection and ongoing management. High-quality patient surveillance requires high-quality data collection and management. Standardisation of data collection – in terms of both the variables collected and minimum standards regarding completeness of these variables – is critical to success in this area. For example, assessing the impact of RHD screening on subsequent clinical outcomes requires us to know whether antibiotic prophylaxis was prescribed to a given patient as a direct result of the screening event, or some other event that occurred after it: without information to this effect, we can only presume the link between the two based on date information. In addition, linking with regional rheumatic fever registers (if not already in place) should be considered for patients classified with RHD following screening.

  We have included a list of suggested core data fields for any ongoing RHD screening database in Appendix 2.

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Appendix 1: Additional tables

Table A1: Receipt of repeat echocardiography scans, including time to first repeat scan, **excluding the first re-scan received by participants from South Auckland and the North Shore.**

		Screening Result							
		Definite RHD		Probable RHD		Possible RHD		Borderline RHD	
		n	%	n	%	n	%	n	%
Received Repeat Echo Scan									
	Yes	18	90%	16	70%	48	84%	34	81%
	No	2	10%	7	30%	9	16%	8	19%
Number of Repeat Scans									
	0	2	10%	7	30%	9	16%	8	19%
	1	10	50%	9	39%	23	40%	24	57%
	2	2	10%	6	26%	17	30%	8	19%
	3	1	5%	1	4%	7	12%	2	5%
	4	3	15%	0	0%	1	2%	0	0%
	5+	2	10%	0	0%	0	0%	0	0%
Time to Repeat Scan [1] (days)									
	Mean (SD)	489.1	(406.2)	1551.1	(839.7)	608.8	(385.5)	611.6	(328.1)
	Median (IQR)	350	(487)	1510	(1724)	496	(542.5)	726.5	(672)
	Range (min/max)	67 - 1549		289 - 2645		152 - 1763		33 - 1219	

[1] Among those who received a repeat echo scan. IQR = Interquartile range.

Table A2: Receipt of repeat echocardiography scans, including time to first repeat scan, by screening criteria used: a) Modified NIH/WHF criteria; b) WHF criteria. **Excludes the first re-scan received by participants from South Auckland and the North Shore.**

	a) Modified NIH/WHF Criteria					
	Definite RHD		Probable RHD		Possible RHD	
	n	%	n	%	n	%
Received Repeat Echo Scan						
Yes	4	67%	16	70%	48	84%
No	2	33%	7	30%	9	16%
Number of Repeat Scans						
0	2	33%	7	30%	9	16%
1	0	0%	9	39%	23	40%
2	0	0%	6	26%	17	30%
3	0	0%	1	4%	7	12%
4	3	50%	0	0%	1	2%
5+	1	17%	0	0%	0	0%
Time to Repeat Scan [1] (days)						
Mean (SD)	193	(63.9)	1551.1	(839.7)	608.8	(385.5)
Median (IQR)	197.5	(104)	1510	(1724)	496	(542.5)
Range (min/max)	118 - 259		289 - 2645		152 - 1763	

b) WHF Criteria

		Definite RHD		Borderline RHD	
		n	%	n	%
Received Repeat Echo Scan					
	Yes	14	100%	34	81%
	No	0	0%	8	19%
Number of Repeat Scans					
	0	0	0%	8	19%
	1	10	71%	24	57%
	2	2	14%	8	19%
	3	1	7%	2	5%
	4	0	0%	0	0%
	5+	1	7%	0	0%
Time to Repeat Scan [1] (days)					
	Mean (SD)	573.6	(424.5)	611.6	(328.1)
	Median (IQR)	412.5	(734)	726.5	(672)
	Range (min/max)	67 - 1549		33 - 1219	

[1] Among those who received a repeat echo scan. IQR = Interquartile range.

Appendix 2: List of suggested core data fields for RHD screening database

Patient Characteristics and risk factors
NHI
DOB
Gender
Ethnicity 1
Ethnicity 2
Family history of ARF/RHD? (yes/no)
Household overcrowding? (yes/no)

Screening test information
Patient age at screening
Date of screening
Region of screening
Location of screening (school/hospital)
Echocardiographer

Screening Test
Abbreviated echo screening test result (normal/abnormal)
Complete echo screening test? (yes/no)
Complete echo screening test performed by?
WHF classification of repeat imaging
Other echo abnormalities detected? (details)
Incomplete scan? (details)
Requires repeat formal scanning?

Management - Initiation of Antibiotic Treatment
Antibiotic treatment started? (yes/no)
Date treatment commenced
Antibiotic commenced
Contraindication to penicillin? (yes/no)
Mode of antibiotic administration (oral or IM)
Linked to RF register? (yes/no)
Provider of on-going antibiotic treatment

Management - Active Surveillance
Date of repeat follow-up 1
Clinical examination? (yes/no)
Abnormal findings from examination?
Repeat echo imaging? (yes/no)
WHF classification
Change from screening echo? (details)
Other echo abnormalities detected? (details)
(Repeat above variables repeated for re-scans)

Management - Follow-up and outcomes
*ARF**
Developed ARF? (yes/no)
Date of diagnosis

Antibiotic prophylaxis initiated? (yes/no)
Linked to RF register? (yes/no)
Provider of on-going antibiotic treatment

*RHD outcomes**
Hospitalisation related to RHD? (yes/no)
Date of hospitalisation
Reason for hospitalisation
RHD-related valvular intervention? (yes/no)
Details of valvular intervention
Date of valvular intervention

Discharge
Date discharged from active follow-up
Reasons for discharge
Diagnosis on discharge

Loss to follow-up
Date patient lost to follow-up
Reasons for loss to follow-up

*Data for these factors may be obtained through routine data linkage with other available sources, such as hospitalisation data or rheumatic fever registers.

- End of Report -