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Household Contact Tracing for Acute Rheumatic Fever

A Review of the Literature and Case Series

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*A dissertation submitted in partial fulfilment of the requirements for the degree of Master of
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Abstract

Acute rheumatic fever (ARF) and its sequel rheumatic heart disease (RHD) are serious public health problems in New Zealand (NZ), with rates similar to those in developing countries, large ethnic inequalities and little progress in control over the past 30 years. Household contact tracing is a preventative intervention that has been recommended in NZ since the 1990s on the basis of studies demonstrating the infectiousness of Group A Streptococcus (GAS) within households, but is highly resource intensive. This dissertation involved a critical appraisal of the evidence for effectiveness, appropriateness and feasibility of ARF contact tracing in NZ with a view to determining whether it should be pursued. No published studies of ARF contact tracing could be found, neither was a standardised framework for evaluating contact tracing programmes available. Therefore a set of criteria for judging an “ideal” contact tracing programme were derived from the literature, with particular reference to screening programme criteria. When these were applied to ARF numerous evidence gaps were apparent. A study of ARF contact tracing at NZ’s largest public health unit (PHU) contributed valuable information, in particular demonstrating that GAS was present in the throats of 13% of household contacts, but evidence gaps still remained. According to these criteria therefore there is insufficient evidence to recommend ARF contact tracing. When other approaches to assessing the current recommendation were considered the same conclusion was reached. Urgent research is recommended to evaluate whether the benefits of the programme outweigh the costs and harms, with an initial goal of quantifying the natural secondary attack rate of ARF in household contacts. Concurrently, resources assigned to contact tracing should be diverted to other priority areas of ARF control: addressing upstream determinants, such as poverty, housing and access to healthcare, as well as optimising secondary prevention.

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Abbreviations

AAP	American Academy of Pediatrics
Anti-DNase B	Anti-deoxyribonuclease B
AR	Absolute risk
ARF	Acute rheumatic fever
ARPHS	Auckland Regional Public Health Service
ASIM	American Society of Internal Medicine
ASOT	Anti-streptolysin titre
BPG	Benzathine penicillin G
CDC	Centers for Disease Control
CFR	Case fatality rate
CI	Confidence interval
GAS	Group A streptococcus
GATE	Graphic Approach to Epidemiology
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
Hib	<i>Haemophilus influenzae</i> type b
IDSA	Infectious Diseases Society of America
iGAS	Invasive group A streptococcus
IM	Intramuscular
MB	Meshblock
MeSH	Medical Subject Headings
MoH	Ministry of Health
NHF	National Heart Foundation

NMDS	National minimum data set
NNT	Number needed to treat
NZ	New Zealand
NZDep2006	New Zealand Deprivation Index 2006
NZHIS	New Zealand Health Information System
PHN	Public health nurse
PPV	Positive predictive value
RHD	Rheumatic heart disease
RR	Relative risk
SARS	Severe acute respiratory syndrome
STI	Sexually transmitted infection
TB	Tuberculosis
WHO	World Health Organization

Chapter 1. Introduction

1.1. Introduction

This dissertation has as its focus the control of ARF and RHD through contact tracing. In this introductory chapter I provide a brief overview of these conditions, their control and treatment. I discuss the research question and rationale for the research, and outline the structure of the dissertation.

1.2. Acute rheumatic fever and rheumatic heart disease

Acute rheumatic fever (ARF) is a generalised inflammatory condition resulting from an autoimmune reaction to pharyngeal infection with a particular bacterium, Group A streptococcus (GAS).^{1,2}

The importance of ARF lies in the acute heart inflammation (carditis) that can occur following GAS infection. This may progress to chronic rheumatic heart disease (RHD) resulting in serious long-term morbidity and incapacity, and in some cases premature mortality. Because the condition typically affects children in the 5 to 15 year age group, the personal, societal and economic costs incurred are substantial.^{3,4}

ARF and RHD were once common in most countries, but have been virtually eradicated from the majority of industrialised countries following improvements in living conditions and access to medical care during the 20th century.² However, they remain significant problems in many developing countries and in certain sub-populations, principally indigenous or seriously socio-economically disadvantaged people groups of Australia and NZ.^{5,6} Māori and Pacific people in NZ suffer some of the highest rates in the world, highlighting dramatic and widening ethnic health inequity within NZ.⁵

Although ARF and RHD are considered largely preventable diseases there has been little discernable improvement in incidence rates over the past quarter of a century in NZ.^{1,2} This, together with the huge ethnic disparities in occurrence, indicates that more effective control measures are urgently needed.

1.3. Current strategies for disease control in NZ

Control of RHD is achieved by the prevention of initial and recurrent attacks of ARF. These attacks are preventable by preventing or treating pharyngeal GAS infections. Control measures can be categorised as primary, secondary or tertiary prevention. These will be discussed in more detail in the Background chapter. However, a brief description is appropriate at this point.

Primary prevention describes the measures taken to avoid an initial attack of ARF. This includes tackling upstream determinants of ARF (such as household crowding and poverty) to reduce the GAS burden. It

also includes the timely and effective treatment of GAS throat infections to prevent progression to ARF.^{2,7} If a GAS vaccine was available it would also fall into the category of primary prevention, but at this point in time no such vaccine is available.²

Secondary prevention refers to the prevention of recurrences of ARF in those who have had a previous episode, through the provision of long-term monthly prophylactic intramuscular (IM) benzathine penicillin G (BPG).²

Tertiary prevention involves the pharmacological and surgical treatment of patients with established RHD, in order to ameliorate symptoms and slow disease progression.

This dissertation focuses on a single control strategy, contact tracing, which combines aspects of both primary and secondary prevention.

1.4. Contact tracing for rheumatic fever

In the context of communicable disease control, a contact may be defined as

“a person that has been in such association with an infected person or animal or a contaminated environment as to have had opportunity to acquire the infection”.⁸

The purpose of contact tracing is that such people may be appropriately managed through testing, vaccination, treatment or quarantine to prevent further disease.⁹

In the context of ARF, contact tracing involves three steps: 1) finding people who shared the same household as the index case of ARF at the time leading up to their illness, 2) performing throat swabs and 3) treating those in whom GAS is isolated, regardless of any symptoms of illness they may have. The rationale of these steps is to attempt to reduce the burden of GAS in the household so as to reduce the risk of a case of ARF developing in the contact or contacts, and to reduce the risk of a recurrence of ARF (and hence of RHD) in the index case.

Contact tracing for ARF is not universally practiced. It has been recommended in NZ since 1998, but only formally implemented by most PHUs over the past few years. While it is recommended by various authorities in the USA, such as the American Academy of Pediatrics (AAP), it is not practiced in Australia (personal communication, Matthew Parnaby, Coordinator Northern Territories Rheumatic Heart Disease Program, Centre for Disease Control, Department of Health and Families, Northern Territory Government, 2010) and is not a standard practice in other countries.

In Auckland, NZ's largest city with more than 1.4 million residents, contact tracing for ARF is undertaken by the Auckland regional PHU and consumes a substantial amount of time and resources.¹⁰ In 2009 alone, it was conservatively estimated that contact tracing for ARF cost over \$NZ80,000 in staff time

alone, not including transport, medication and overheads.¹⁰ This should be no surprise: contact tracing is inherently resource intensive.¹¹⁻¹³ For this reason the decision to start contact tracing, or to maintain it where it is already part of a programme, should be weighed against the evidence that it is achieving its goals of containing or reducing the incidence of a transmissible disease and its sequelae. This leads to the aim of this dissertation.

1.5. Dissertation aim

This dissertation aims to review and critically appraise the evidence of household contact tracing for ARF as an effective preventative strategy and thereby to inform current policy and practice in NZ and elsewhere. Specifically, the main question this dissertation seeks to answer is:

What is the evidence to support contact tracing for ARF and should it be pursued as an ARF prevention strategy in NZ?

1.6. Dissertation outline

The dissertation has three main parts. In the first part I begin with a qualitative literature review that elaborates on important background information pertaining to ARF and the dissertation objectives. This includes a brief summary of the relevant background to the problem of ARF and its control in NZ and summarises the current guidelines and practices around contact tracing for ARF locally and globally. Next, the findings from a combined qualitative and systematic literature review to address the main dissertation research question are presented. This begins with a review of the literature to establish a set of criteria on which to base an ideal contact tracing programme, encompassing clinical effectiveness, feasibility and appropriateness. Then the literature on whether and to what extent these criteria are fulfilled for ARF contact tracing in NZ is outlined, including a review of direct evidence of its effectiveness at preventing ARF and other evidence supporting its rationale, with gaps in the evidence highlighted.

In the second part of the dissertation I outline an observational study of contact tracing that I have conducted over the course of my Master's in Public Health degree in my role as a Medical Officer at NZ's largest PHU, Auckland Regional Public Health Service (ARPHS). This is the first such a study of ARF contact tracing in NZ and thereby sheds light on processes and outcomes of the programme about which little was previously known. It facilitates my assessment of ARF contact tracing by providing valuable contributions towards the numerous evidence gaps exposed by the Literature Review. The dissertation concludes with a Discussion and Conclusions section in which I draw together the findings of the Literature Review and the ARPHS contact tracing study to make an overall appraisal of the value of ARF contact tracing programme as an ARF prevention strategy and its recommendation in the NZ context. Where evidence gaps exist I offer suggestions for additional research to further progress our knowledge of this important subject.

Chapter 2. **Background**

2.1. The burden of ARF and RHD

2.1.1. Introduction

ARF is a multisystem nonsuppurative inflammatory condition, caused by an autoimmune response to pharyngeal GAS infection, that classically involves the heart, joints, subcutaneous tissues and central nervous system.^{6, 14} Most importantly it may cause carditis and can progress to chronic RHD, which is characterised by heart valve lesions, heart failure and premature death.^{6, 14}

2.1.2. Historical aspects

It is likely that ARF has afflicted humans for centuries, but it was not recognised as a distinct clinical entity until the early 1800s when William Charles Wells drew the association between rheumatism and carditis.⁶ Around this time observations of a connection between sore throats and rheumatism were also beginning to emerge and a Lancet paper in 1880 by J. K. Fowler was one of the first published accounts of this.^{15, 16} The real breakthrough in understanding of this connection came in 1931 and is credited to Alvin Coburn¹⁷ and William Collis¹⁸ who independently hypothesised that haemolytic streptococcus was the aetiological agent in ARF.¹⁶ This paved the way for investigators of the 1930s to 1950s to establish the firm causal relationship between pharyngeal GAS and ARF through demonstrations that epidemics of GAS and ARF occurred in parallel, that ARF was accompanied by high streptococcal titres and that antibiotic treatment of GAS pharyngitis prevented ARF.⁶ Treatment and prevention programmes were initiated shortly thereafter in industrialised regions facilitated by this greater understanding of the disease and the antibiotic revolution of the latter part of the 19th century.⁶

2.1.3. Pathogenesis

Although GAS is known to be the inciting agent, the pathogenesis of ARF has not yet been fully elaborated.⁶ Evidence best supports the hypothesis that ARF occurs as an autoimmune reaction to GAS infection, in a phenomenon referred to as molecular mimicry.⁶ In this model, antibodies developing against GAS cross-react with host tissues such as the heart, resulting in inflammation.¹⁹

It should be noted that ARF only appears to occur as a sequel to GAS infections located in the throat,¹⁴ rather than the skin or elsewhere. It has been proposed that the site of infection may relate to lymphatic connections.¹⁴ The association is not invariable: throat infections with GAS do not inevitably lead to ARF in every case.²⁰ The reason for this is thought to lie in the interplay between infectious agent, environmental and host factors, known as the epidemiological triad.

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Considering first the infectious agent, there is a limited body of evidence to support the concept of some strains of GAS being “rheumatogenic” in the context of epidemic ARF (although no specific “rheumatogenic factor” has yet been isolated).^{6, 14, 21} These are strains of certain M serotypes or genotypes (*emm* types) from case clusters or outbreaks that show a strong epidemiological association with ARF, in contrast to other strains that fail to cause the disease even in highly susceptible individuals.⁶ This was well illustrated by the resurgence of ARF in the USA during the 1980s that was strongly associated with M18 serotype.²² The virulence of rheumatogenic strains is likely to be enhanced in settings that favour rapid person to person transmission, due to natural selection.²²

In terms of host factors, the risk of developing ARF has been related to the overall degree of the immune response against GAS infection.^{19, 23} Genetic susceptibility has long been suspected, based on the strong familial clustering noted during the late early 20th century²⁴ and the fact that circulating B lymphocytes of ARF patients have been shown to express a higher proportion of certain alloantigens than in controls.²⁵ Studies linking HLA antigens and ARF not have been conclusive, although there is some degree of association between class II alleles and ARF risk.²⁶ Inheritance is postulated to be autosomal recessive with limited penetrance, but despite much research no reliable ARF susceptibility marker has yet been identified.^{14, 19} In NZ it is thought that the over representation of Māori and Pacific people with ARF is accounted for more by environmental factors such as socio-economic status and crowding, than by genetic susceptibility.²

2.1.4. Clinical features and natural history

A latent period of an average of 19 days occurs between GAS infection and the onset of ARF (range 1 to 5 weeks),^{6, 27, 28} although in a recent small NZ case series (n=7) the average latent period was longer at 27 days (range 2 to 49 days).²⁹ In cases where chorea or indolent carditis is the first manifestation (see below) a significantly longer period occurs.²

The presentation of ARF is highly variable. Migratory polyarthritis occurs in up to 75% of initial ARF episodes,^{2, 6} carditis in 40-50%,⁶ chorea in 15%,⁶ subcutaneous nodules in less than 2% and erythema marginatum rarely.²

Diagnosis is based on the constellation of clinical manifestations in conjunction with evidence of a preceding GAS infection. The most commonly used diagnostic criteria are the Jones Criteria originally introduced in 1944 and updated most recently by the American Heart Association (AHA) in 1992 and the World Health Organization (WHO) in 2003. NZ uses a modified version of the 1992 update that incorporates echocardiographic findings (see Appendix 3).²

ARF is usually self-limiting over several weeks except for the cardiac pathology which targets the valves and may be permanent. Following an initial episode of ARF about 60-80% will have residual heart damage and go on to develop RHD.^{29, 30} Among those with RHD, 20% warrant surgical intervention such

Chapter 2. Background

as valve replacement.³¹ Mortality from ARF was once appreciable, but is rare today due to advances in tertiary care.³² RHD has a mortality rate of approximately 0.5% per year in developed countries and 1.5% in developing countries.³³

Importantly, patients who have had a previous episode of ARF are at a much higher risk of an ARF recurrence when they develop a subsequent GAS throat infection (25-75%).³⁴ Such recurrences are significantly more likely to affect the heart.

2.1.5. Management

Once ARF has begun no treatment has been shown to alter its outcome except for heart failure management where appropriate.² The mainstays of symptomatic treatment are bed rest, salicylates and non-steroidal anti-inflammatory medication.² It is recommended that penicillin should be started as soon as possible to ensure eradication of GAS from the upper respiratory tract, although it has not been shown to alter the course of valve lesions.²

2.1.6. Epidemiology

ARF is predominantly a disease of childhood. It is most frequent in children aged 5 to 15 years and virtually unheard of in those under 3 or over 45 years of age.^{2, 6} In NZ the 5 to 14 year age group accounts for 69% of cases, while a further 15% occur in the 15-24 year age group (1996-2005).¹ This is a reflection both of the epidemiology of GAS and the fact that very young children's immune systems are too immature to mount an adequate immune response to GAS to result in ARF.³⁵ Carditis predominates in children whereas in adults arthritis is a more common manifestation.³⁵ There is no gender preponderance.⁶ In temperate countries like NZ seasonal variation occurs with a higher incidence of ARF in the winter.⁶ RHD develops as a consequence of recurrent ARF with its prevalence peaking in the 30s and 40s.⁴

There is an association of ARF with several social determinants of health, including crowded living conditions, poor quality housing and poverty. The strongest of these associations is crowding.² This is biologically plausible as crowding promotes transmission of GAS which is spread by respiratory droplets and close contact.³⁶

At the turn of the 20th century ARF was rife in industrialised countries and was dubbed the "dread disease".¹⁶ Over the past century there has been a dramatic decline in the incidence and prevalence of ARF and RHD in most of these countries, despite the fact that rates of GAS pharyngitis have remained relatively constant.³⁷ While the reasons for this are not fully understood it is thought in part to be due to improvements in living conditions and sanitation, in keeping with the theories of public health pioneer Thomas McKeown who attributed the decline of TB and other infectious diseases in the UK in the 1800 and 1900s to such factors.³⁸ Other proposed reasons for the observed decline in ARF and RHD include

better access to healthcare, the antibiotic revolution and a change in GAS strain virulence.^{2, 37} Sadly, the diseases continue unabated in developing countries and within certain sub-populations in some industrialised countries. Of these Australian Aborigines and NZ Māori and NZ-based Pacific people are amongst the worst afflicted in the world, although rates in Australian Aborigines exceed those in NZ-based populations.^{5, 24, 39} Although surveillance is poor the burden of disease is also very high amongst Pacific people in their countries of origin.⁴⁰ As there is no known genetic link and the climate and living conditions are distinct in NZ and the Pacific Islands it is likely that common factors such as limited access to medical treatment, poverty or high living density is responsible for the high rates witnessed in both locations.

2.1.6.1. Global epidemiology

In industrialised countries ARF incidence has fallen from as high as 250/100,000 for children in Denmark in the 1800s²¹ to less than 1/100,000 in most countries today.⁴¹ However, the current global burden of disease remains significant. A 2005 report by the WHO estimates the global prevalence of RHD as 15.6 million cases, with annual deaths attributable to ARF or RHD of 233,000.³³ The prevalence of previous ARF (without carditis) requiring prophylaxis is 1.88 million.³³ There are 470,000 new ARF cases each year and about 60-80% of these progress to RHD.^{24, 29, 30, 33} RHD is the leading form of cardiac disease in children worldwide.⁴²

Most of the burden is attributable to developing countries in the Pacific region, the Indian subcontinent, Asia, sub-Saharan Africa, Latin American and Caribbean, where lack of infrastructure means penicillin prophylaxis and access to healthcare is limited and environmental conditions that promote ARF prevail.^{3, 30} In fact, 95% of ARF cases are thought to arise in developing countries.³⁰ In some developing countries the incidence of ARF in children is more than 50/100,000,²⁴ contrasting with an incidence 1/100,000 or less in most developed countries.⁴¹ RHD prevalence in school age children is as high as 2% to 3% in countries such as Cambodia and Mozambique,³ while it is 0.05% and falling in developed countries.³³

This pattern of declining disease in the industrialised world was upset by an unexpected resurgence of ARF in the Intermountain area of the USA during the mid-1980s that affected a largely middle class demographic group.⁴³ This reasons for this outbreak are not fully understood, but it is thought at least in part to relate to the circulation of virulent “rheumatogenic” strains of GAS that were found to be associated with the cases, particularly M18.⁶

2.1.6.2. Local epidemiology

NZ is a remarkable exception to the global pattern of disease reduction. In NZ, focal areas and population sub-groups have rates of ARF and RHD that exceed those seen most in developing countries.¹ Although now rare in NZ Europeans, ARF and RHD have not been nearly eradicated in NZ as they have been elsewhere. Persisting high rates occur in Māori and Pacific populations, predominantly in socio-

economically deprived areas of the North Island.² Auckland bears the largest burden of disease due to its large Māori and Pacific populations and Auckland hospitals receive 60% of national ARF admissions.⁴⁴

ARF incidence:

ARF has been notifiable in NZ since 1986. Incidence data are derived from a combination of hospital admissions and notifications. In the 1920s the incidence of ARF in Pakeha school children is reported as 65/100,000³² while between 1961 and 1970 in Wairoa, a region heavily populated by Māori, the incidence reached more than 1,000/100,000.⁴⁵ Subsequently there was a steady decline in overall ARF admission rates until the early 1980s when the downwards trend stalled with ARF incidence remaining static at 3.4/100,000 for the whole population (1996-2005)^{1, 5} and 17.2/100,000 for the 5 to 14 year age group (2000-2009) [personal communication Richard Milne, Managing Director Health Outcomes Associates Limited, 2010]. These rates are amongst the highest reported in a developed country¹ and obscure huge socio-economic and ethnic disparities. The incidence in children living in the two most deprived deciles between 2003 and 2007 was 30 times higher than in those from the two least deprived deciles⁴⁶ and the age specific incidence for Pacific children in the 1990s was 64.5/100,000, 31.9/100,000 for Māori and 1.7/100,000 for Europeans.⁴⁷ Figure 2-1 below demonstrates differences in ethnic rates.

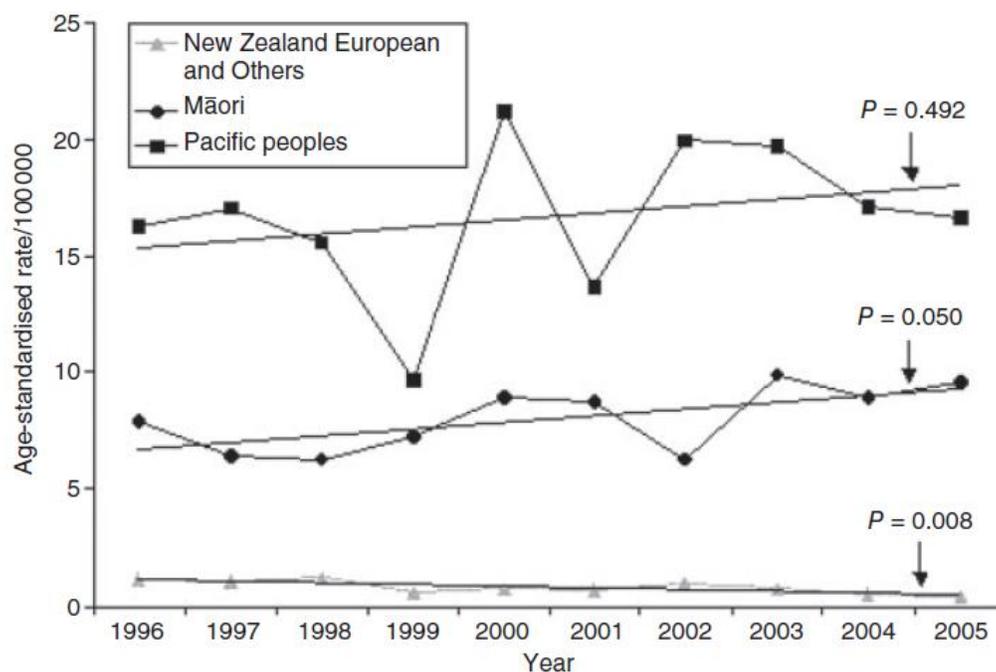


Figure 2-1. Age standardised annual rates of ARF first admissions by ethnicity, total population, NZ, 1996-2005

Source: Jaime et al, *Journal of Paediatrics and Child Health*, 2008¹

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Prevalence of RHD:

RHD is not a notifiable disease in NZ and is often subclinical until advanced disease occurs. Therefore the true rate is more difficult to estimate than for ARF. However, hospital data reveal a similar pattern to ARF: admission numbers have remained essentially unchanged since the early 1980s, although numbers have actually increased in the under 24 year age group over the past decade.⁴⁶ The total population admission rates were 25.2/100,000 for Māori and 5.5/100,000 for non-Māori from 2003 to 2005.⁴⁸ A landmark study performed in 2007 to 2008 in a high risk population of mainly Māori and Pacific 10-13 year olds in socio-economically deprived schools in South Auckland revealed a RHD prevalence of 24/1000, which is comparable to that found in developing countries such as Nicaragua and Mozambique.⁴⁹

RHD mortality

The number of annual deaths from RHD has also been relatively constant since 1980 at approximately 146 per year (2000-2004).⁴⁸ The overall mortality rate for the period 2000-2007 is 4.4/100,000 (personal communication Richard Milne, Managing Director Health Outcomes Associates Limited, 2010). The Māori mortality rate (6.0/100,000) for 2000-2004 is six times higher than the non-Māori rate and the Pacific rate is not known. The only other communicable disease that causes a higher rate of premature death in New Zealanders under 65 years is AIDS.⁵⁰ Another comparison of note is that RHD accounts for more than twice as many deaths per year in NZ as cervical cancer.⁵¹

Economic costs:

Aside from the considerable morbidity and mortality incurred by these diseases there is also a significant economic cost to NZ. This includes reduced productivity and financial costs generated by medical and surgical treatment.¹ While the costs of loss of productivity have not been measured, in 1993 an analysis of primary, secondary and tertiary costs for the Auckland Health Board found annual costs of approximately \$NZ3.6 million.⁵² RHD accounted for the majority of these costs.^{2, 4} Applying the 1993 model to the Auckland region for 2008-2009 shows that the current annual cost of ARF and RHD is of the order of \$NZ5.1 million (personal communication, Andy Roche, policy analyst, ARPHS, 2009).

In summary, in comparison with other diseases of public health importance, ARF and RHD place a significant burden of incidence, prevalence, morbidity, mortality and financial costs for NZ, largely on individuals and families who can least afford it given their socio-economic position and overall health status. The huge ethnic disparity in burden within NZ represents a major inequity,^{1, 5} that from any perspective, whether a Treaty of Waitangi, human rights or social justice perspective, should not be ignored. However, to address ARF and RHD the causal factors involved in their occurrence and persistence need to be better understood. A complex web of factors are involved, from upstream structural determinants of health such as social marginalisation and its downstream consequences

including overcrowded housing and poor health knowledge and limited access to primary care, through to under recognition and under or inadequate treatment of GAS pharyngitis in high risk populations.⁵³

2.2. Preventative interventions for ARF and RHD

ARF and RHD are considered by many to be preventable diseases, yet they persist in NZ despite a number of primary, secondary and tertiary prevention initiatives.⁴² Unfortunately there is no “magic bullet” or quick fix. While primary prevention is the ideal approach from a public health perspective, it has many practical limitations, as outlined below. Secondary and tertiary prevention merely mitigate the degree of morbidity arising from ARF rather than stemming the tide of new cases. The strengths and limitations of control strategies and their use in NZ are outlined in the sections below and in Table 2-1.

2.2.1. Primary prevention

The aim of primary prevention is prevent occurrence of disease and it is directed towards the stage of susceptibility. In the context of ARF it refers to measures that either reduce exposure to GAS or prevent GAS infection and its progression to ARF following exposure.

Reducing GAS exposure involves addressing social determinants such as housing and poverty so as to improve hygiene, reduce crowding and thereby the transmission of GAS. Such upstream issues are broad and systemic and not simply solved in NZ.

The prevention of ARF following established GAS pharyngitis by using antibiotic treatment is referred to as primary prophylaxis. In a recent meta-analysis penicillin was shown to reduce the risk of ARF by almost 70% (relative risk [RR] 0.32).⁵⁴ Penicillin must be given orally for 10 days or as IM BPG within 9 days of the onset of infection to be effective.^{28, 55} Other antibiotics such as amoxicillin and cephalosporins are also effective although there is less evidence to support their use. While it appears promising, barriers to this approach being fully effective in practice exist, such as difficulties in accessing primary healthcare, under-prescribing of antibiotics for GAS pharyngitis and subclinical episodes of infection that do not trigger a visit to a health professional (approximately one third of ARF episodes are not preceded by a sore throat).^{2, 5}

A safe and effective vaccine against GAS would be an ideal solution to the ARF problem. A 26-valent vaccine is currently undergoing human trials in North America, but even if effective it is unlikely to cover the strains of GAS commonly associated with ARF in NZ.⁵⁶

In NZ the traditional approach to primary prevention has been a reliance on appropriate treatment of sore throats in primary care. Unfortunately this approach has made no impact on the incidence of ARF. In recognition of this failing updated guidelines for ARF management in NZ include sore throat algorithms for

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use in primary care (see Appendix 7)⁷ and a call for school and community based sore throat clinic initiatives, though these latter initiatives are yet to gain widespread acceptance and implementation.²⁶

Table 2-1. Forms of ARF and RHD prevention in NZ

Method	Implementation in NZ	Results/Effectiveness	Limitations
Primary prevention			
Addressing social determinants	Healthy Housing programme.	27% reduction in hospital admission for infectious diseases, but no effect on ARF incidence demonstrated. ⁵⁷	Requires long-term approach.
Vaccination	Not available.	Currently under trial.	Unlikely to cover NZ <i>emm</i> types.
Improving access to healthcare, including awareness raising	Several locally initiated community and school-based surveillance and sore throat clinics. Primary sector reforms and Māori and Pacific providers. ⁵⁸ Local awareness raising initiatives. No nationally coordinated health promotion campaign.	Successful eradication of ARF in a Northland community through sore throat clinics. ⁵⁹ Auckland school based sore throat clinic trial showed non significant reduction in ARF, ²⁹ meta-analysis of community and school based sore throat interventions showed 60% reduction. ⁶⁰ Primary healthcare reforms and Māori and Pacific providers have not reduced ARF incidence. ⁵⁸	Sore throat clinics intensive and expensive.
Seasonal mass antibiotic prophylaxis	No.	Insufficient evidence to recommend. ²⁶	Insufficient evidence to recommend. ²⁶
Prompt treatment of symptomatic GAS pharyngitis ("primary prophylaxis" of ARF)	National guidelines for sore throat management published in 2008. ⁷ ARF household contact tracing, introduced formally from 2005.	Treatment of GAS pharyngitis associated with ARF risk reduction of 70-80%. ^{54 61} Unknown effect of contact tracing.	Barriers to access to healthcare. Practitioner compliance with guidelines in primary care. Risk of emergence of antibiotic resistance. Patient compliance with antibiotic treatment. Up to 2/3 of ARF not preceded by symptomatic infection. ⁴³ Resource intensiveness of contact tracing.
Secondary prevention			
Early detection of ARF	National guidelines for rheumatic fever diagnosis published in 2006. ² Contact tracing for early case finding.	Impact unknown.	Barriers to access to healthcare. Subclinical ARF. Resource intensiveness of contact tracing.
Penicillin prophylaxis	ARF is a notifiable disease. Public health community-based secondary prevention programmes with local and/or regional databases/registers to help manage treatment.	Successful at preventing recurrences (87-96% reduction). ^{44, 62} Cost effective. ⁶³	Does not prevent primary ARF.
Contact tracing to reduce GAS burden in home of ARF case	ARF household contact tracing, introduced formally from 2005.	Effect unknown.	Resource intensiveness.
Tertiary prevention			
Pharmacological and surgical treatment of RHD	Utilised extensively.	Ameliorates symptoms.	Does not prevent primary ARF. Expensive.
Echocardiogram screening for subclinical RHD	Research stage. ⁵³	In South Auckland school children RHD prevalence of 2.4% found on echocardiogram screening. ⁵	Does not fulfil criteria for screening programme implementation. ⁵³ How to manage possible or probable RHD unknown. ⁵³

2.2.2. Secondary prevention

The aim of secondary prevention is to prevent clinical disease or reduce its severity once it emerges. In the case of ARF and RHD the objective is to prevent the heart damage that results from recurrent episodes of ARF with carditis. Continuous prophylaxis with IM BPG every 28 days reduces the risk of recurrence by 87-96%.⁶² The duration of prophylaxis recommended in NZ is at least 10 years or until age 21 or 30 years depending on the severity of carditis.² Secondary penicillin prophylaxis programmes became common place in most industrialised countries by the 1960s. They were introduced in NZ from the mid-1970s to the early 1980s and ARF became a notifiable disease in 1986.⁴⁷ These programmes have been found to be cost effective and in NZ have contributed to a marked reduction in recurrence rates of ARF and therefore progression to RHD.^{2, 44, 47} This has been one of the few success stories of ARF prevention in NZ with 95-96% compliance rates according to an Auckland audit in 1998-2000 and a recurrence rate of 5% from 1993-1999.^{2, 44, 64} Less favourably though individuals moving between regions are commonly lost to follow up.⁵³ There have been calls to move to a web-based national register to address this, but this is yet to be implemented.^{5, 44}

However, a key limitation of secondary prevention is that it does nothing to address the new incident initial attacks of ARF that occur each year, nor does it alter the course of episodes of subclinical or undiagnosed ARF that present later in life as established RHD.

2.2.3. Tertiary prevention

Tertiary prevention aims to prevent progression of disease and its complications. For RHD this means pharmacological prevention and treatment of endocarditis and strokes with antibiotics and anticoagulants, treatment of heart failure pharmacologically and by surgical interventions such as cardiac valvotomy, valve repair or replacements. Costs associated with treatment of RHD account for approximately 70% of the total expense incurred by ARF and RHD combined⁵ and although it may prolong life it is viewed as essentially palliative.⁶³ Subclinical RHD can exist, and screening for this using mass echocardiography in high-risk population groups is promoted by some as a means of tertiary prevention.⁵ Currently echocardiography does not meet standard criteria for screening, particularly as the lower limit of certainty of the test and the natural history of those with borderline findings are unknown.⁵³ Research is ongoing to establish its true benefits, however even if these issues can be resolved it may risk diverting resources away from more upstream measures.

2.3. Contact tracing as a preventative intervention

2.3.1. Definitions

The definition of a contact was presented in the Introduction chapter. The type of contact may vary depending on the specific disease and nature of the exposure and can include such categories as sexual,

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household, close or casual. Contact tracing is the identification of these contacts so they may be managed appropriately, for example with counselling, testing, quarantine, prophylaxis, vaccination or treatment.^{9, 65} It is a key control measure applicable to a wide range of communicable diseases.¹² The main benefit is that it targets those most likely to be at risk of infection.⁶⁶

The earliest incarnation of contact tracing was quarantine, which was employed against plague in the 14th century.⁶⁷ With the advent of modern disease theory more sophisticated techniques for contact management evolved, first for sexually transmitted diseases (STIs) such as syphilis as early as 1917 and then for tuberculosis (TB) in the 1950s.⁶⁸ Contact tracing continues to be used for these diseases as well as for others such as viral hepatitis, enteric infections, a number of pathogens spread by the respiratory route including meningococcal disease, measles and *Haemophilus influenzae* type b (Hib), and for outbreaks of novel or re-emerging infections such as severe acute respiratory syndrome (SARS).⁶⁶

2.3.2. Purpose

Contact tracing may serve different purposes in different situations; however its core aim is to reduce the overall disease burden.⁶⁹ This is achieved primarily through case prevention which has four components: preventing transmission to others (isolation or restriction of activities), preventing development of disease if infected (chemo or immuno-prophylaxis), preventing subsequent infection (vaccination or chemoprophylaxis) and encouraging early presentation (education and counselling).^{13, 70} A further goal is active case finding in which those with the early stages of disease are detected and prompt treatment commenced.⁷⁰ In the context of outbreaks the chief objective is mitigation or containment, but contact tracing also provides invaluable information about the epidemiology of novel agents such as the most likely transmission networks.¹¹

2.3.3. Process

Contact tracing is a multi-stage and often iterative process that usually requires a large time and human resource investment.¹² The first stage is the diagnosis of the index case. The second stage is the contact assessment process whereby contacts are identified, tested, quarantined, treated or given prophylaxis as appropriate and provided with education. In the final stage any contacts subsequently found to be infected are reclassified as new cases and the process is repeated.¹²

2.3.4. Contact tracing for ARF

In the context of ARF contact tracing generally refers to identifying members of the household of patients recently diagnosed with ARF, or those who have slept in the same household over night for at least a night in the month leading up to the onset of their ARF symptoms, performing throat swabs and providing appropriate antibiotic treatment to those with positive GAS culture. This may also extend to providing

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education about sore throats and checking whether any household contacts are displaying features of ARF and managing appropriately.

2.3.4.1. Rationale

The rationale for contact tracing for ARF is that it offers the potential to eradicate GAS from those people in whose throats it is detected, thereby preventing the development of ARF in these individuals, and also preventing its transmission to others in the household, including especially any individuals at risk of secondary ARF. This includes the index case, who is particularly susceptible to a recurrence⁷¹ although such individuals are generally well protected by secondary prophylaxis which has a very low failure rate in NZ.⁴⁴

2.3.4.2. Recommendations and practices globally and locally

The recommendation for swabbing and treatment of GAS positive ARF household contacts originates from the USA. The AAP has been recommending it in its Report of the Committee on Infectious Diseases ("Red Book") since 1977,⁷² as has the AHA in its rheumatic fever prevention guidelines dating back to the same year.⁷³ It has also been endorsed by the Infectious Diseases Society of America (IDSA) in its group A streptococcal guidelines from at least as far back as 1997. The AAP recommendation is based on expert opinion (personal communication, Michael A. Gerber, M.D., Cincinnati Children's Hospital Medical Center, Division of Infectious Diseases, 2010) that stems from studies demonstrating the infectiousness of GAS within a household, rather than any direct evidence that it actually reduces the risk of ARF. In USA implementation of this recommendation appears most likely to be the domain of individual treating clinicians rather than public health departments and the degree to which it is actually practiced is not known (personal communication, Edward L. Kaplan, M.D., Department of Pediatrics, University of Minnesota Medical School, 2010).

Invasive GAS disease (iGAS) is a condition that, like ARF, arises as a serious complication of GAS infection. Consequently there are likely to be parallels in regards to transmission and risk to contacts within in a household. It is interesting therefore, that in contrast to the USA recommendations for ARF contact tracing the Centers for Disease Control (CDC) in the USA have concluded that the routine testing or treatment of household contacts of iGAS is not warranted.⁷⁴ Outside of the USA a comparable recommendation for ARF contact tracing elsewhere, other than NZ does not exist. It is not practised in Australia despite the scale of the ARF problem amongst its indigenous population being even worse than that seen in NZ (personal communication, Matthew Parnaby, Coordinator Northern Territories Rheumatic Heart Disease Program, Centre for Disease Control, Department of Health and Families, Northern Territory Government, 2010).

In NZ household contact tracing was being carried out sporadically led by paediatricians in Auckland from the early 1980s (personal communication, Professor Diana Lennon, Community Paediatrics, the

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University of Auckland, 2010). An official national recommendation was first made in 1998 by the Ministry of Health (MoH) in its Communicable Disease Control Manual.⁷⁰ However it was not formally implemented in most regions until the latter part of this decade following the publishing of the NZ Guidelines for Rheumatic Fever (Part 1) in 2006, which reinforced the recommendation.² As ARF is rare in the South Island contact tracing programmes are confined to the North Island.

Guidelines and practices in NZ have more operational detail than those from North America noted above. Within NZ, there are a number of operational variations between the NZ Guidelines for Rheumatic Fever, the MoH Communicable Disease Control guidelines and the contact tracing practices of different PHUs. These chiefly relate to the ages of the contact requiring follow up, the time period during which follow up is offered and the antibiotic treatment used. The NZ Guidelines for Rheumatic Fever advise that “all symptomatic and asymptomatic household contacts of the index case aged 3 years and older should have a throat swab if the contact was no longer than month before the onset of ARF in the index case.”² In contrast, the MoH guideline requires public health staff to “throat-swab all household contacts under the age of 20, and treat with penicillin if group A streptococci are isolated.”⁷⁰ Meanwhile some PHUs, such as ARPHS, restrict swabbing to those aged 3 to 45 years because this age group is at greatest risk of ARF. The NZ Guidelines for Rheumatic Fever suggest either oral penicillin, IM BPG or once daily oral amoxicillin can be used as treatment, with erythromycin for penicillin allergy⁷ and this approach has been adopted by some PHUs, whereas the 1998 MoH guideline recommends penicillin alone and other PHUs tend to follow this approach. A 2010 draft of the updated MoH Communicable Disease Control guidelines aligns with the NZ Guidelines for Rheumatic Fever in terms of ages of those to swab and the antibiotic choices, however it is yet to be finalised.

Neither of the guidelines defines at what point, if any, after the onset of ARF symptoms in the index case it would be too late to perform contact tracing. Some PHUs have adopted a pragmatic policy of not following up those notified a few months after symptoms started on the reasoning that to confer any benefit the GAS needs to be detected and treated soon after acquisition. Conversely other PHUs have no defined time limit, reasoning that the household remains at risk because GAS may circulate for some time. All PHUs define contacts as those with household contact with the index case during the one month prior to the onset of ARF symptoms in the index case. Table 2-3 below illustrates the regional differences in contact tracing programmes as elucidated by an email survey of key ARF informants in each PHU I performed from June to August 2010.

Table 2-2. Comparison of international guidelines for ARF contact tracing

Guideline body	Year recommendation first made	Definition of contacts to swab and treat	Timeframes for contact tracing	Antibiotic treatment specified in most recent update
AAP	1977	All household members	Not specified	Penicillin V 10 days first choice. Alternatives IM BPG, oral amoxicillin 10 days. Penicillin allergy: oral erythromycin or first generation cephalosporin. ³⁶
AHA	1977	All household members	Not specified	First choice penicillin V 10 days or BPG first choice. Alternative once daily amoxicillin 10 days. Penicillin allergy: oral erythromycin, narrow spectrum cephalosporin, clindamycin, azithromycin or clarithromycin. ⁷⁵
IDSA	1997	All household members	Not specified	Penicillin V 10 days first choice. Alternatives IM BPG, oral amoxicillin 10 days. Penicillin allergy: oral erythromycin or first generation cephalosporin. ⁷⁶
NZ MoH	1998	Household members aged <20 years exposed in the month prior to onset of ARF symptoms in case	Not specified	Penicillin ⁷⁰
National Heart Foundation of NZ (NHF)	2006	Household members aged 3 years and older exposed in the month prior to onset of ARF symptoms in case	Not specified	Oral penicillin 10 days as first choice. Alternatives: IM BPG or once daily oral amoxicillin 10 days. Penicillin allergy: oral erythromycin. ^{2,77}

Table 2-3. Comparison of ARF contact tracing practices in North Island PHUs in NZ

Region	Date started contact tracing	Household contact ages swabbed (years)	Contact tracing timeframes (from onset of ARF symptoms in case)	Antibiotics used	Average number of cases contact traced per year	Average number of contacts per case	Proportion of contacts with GAS positive swabs
Auckland	December 2008	3-45	No limit	Oral amoxicillin, IM BPG. Allergy: Oral erythromycin	63 (2009)	5-6	13% (see study in Chapter 4)
Bay of Plenty and Lakes	September 2009	3 and over	No limit	As per NHF guidelines	9 (2005-2009)	6	Unknown
Hawkes Bay	June 2008	Less than 20	Up to 3 months	Oral penicillin	5	Less than 5	Unknown
Mid Central	February 2007	Less than 20	1-2 months if all in household well	Oral penicillin. Allergy: oral erythromycin	2 (range 1-7)	2	0% to date
Northland	2005	3 and over	No limit	As per NHF guidelines	11.2 (2005-2009)	2-10	Unknown
Tairāwhiti	Intermittently over a number of years	No specific age limit (all children and young adults, and others who want it)	No limit	Oral penicillin	4	Approximately 5	Unknown
Taranaki	2006	3-45	1 month	Oral penicillin. Allergy: oral erythromycin	0.4	Unknown	Unknown
Waikato	March 2009	3-45	No limit	Oral penicillin, oral amoxicillin. Allergy: oral erythromycin	18 (2007-009)	4.5 range (2-10)	5%
Wellington	October 2006	3 and over	No limit	Referred to GP	12	4-5	Unknown
Whanganui	Not yet commenced						

2.4. Costs of contact tracing

The practice of infectious disease contact tracing is acknowledged as being resource intensive and expensive.^{11, 13} This has been borne out for ARF contact tracing at ARPHS. An estimate of resource utilisation performed for the year ending 2009 found that each case of ARF contact traced consumed approximately 12 hours of clinical and administrative time and cost in excess of NZ\$1,300.¹⁰ Multiple

phone calls and home visits were required to locate and swab all contacts. With over 60 cases notified per year in Auckland alone, and 100-150 nationally,^{1, 5} nationally, the cumulative economic cost incurred is not insignificant. Furthermore the associated opportunity cost of directing less effort into other aspects of ARF control or other important communicable diseases must be considered.

2.5. Summary

Given the importance of ARF and RHD as public health problems both globally and locally finding the right focus for control is crucial. Household contact tracing forms a component of the preventative armamentarium in NZ, but in few other locations. In view of the high resource consumption of this intervention together with discrepancies in international and national guidelines and regional processes, an evaluation of the ARF contact tracing programme and its effectiveness, appropriateness and feasibility in NZ is justified.

Chapter 3. Literature Review

3.1. Aim

The purpose of this literature review is two-fold: one, to ascertain what evidence there is to support household contact tracing for ARF as an effective control measure, in particular in reference to the NZ context, and two, to establish where gaps in the evidence exist. As stated in the Introduction chapter the main research question this dissertation seeks to answer is:

What is the evidence to support contact tracing for ARF and should it be pursued as an ARF prevention strategy in NZ?

3.2. Method

In this section the methods used to identify literature evaluating the effectiveness, appropriateness and feasibility of ARF household contact tracing are outlined.

The approach taken was an iterative one. This was necessitated by the paucity of material found that pertained directly to the research question. All searches were performed between February and September 2010 and automatic email alerts were set up to advise of any relevant newly published materials that became available between performing the initial search and completing the literature review in September 2010. The literature review process is divided into four steps as follows.

3.2.1. Step 1: Literature review for the research question “What is the evidence to support contact tracing for ARF and should it be pursued as an ARF prevention strategy in NZ?”

The original plan was to perform a systematic review of published studies addressing the effectiveness, appropriateness and feasibility of ARF contact tracing in NZ. However a comprehensive search of multiple databases of peer reviewed journals yielded no published studies directly dealing with the topic of ARF household contact tracing in NZ or even globally. Therefore a search of grey literature was undertaken and the advice of experts in the field was also sought. These processes are outlined below.

3.2.1.1. Search terms

The following terms were used both matched to MeSH (Medical Subject Headings) and as key words.

- Rheumatic fever
- Rheumatic heart disease
- Group A streptococcus/Streptococcus pyogenes

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And each was combined with each of the terms below:

- Household
- Family
- Contact tracing/Contact trace/Contact examination/Contact screening
- Contact
- Secondary case/Secondary transmission/Secondary attack rate
- Outbreak/Cluster/Epidemic

3.2.1.2. Sources searched

Databases

- Medline (1950 to present) and Medline in process
- Embase (combined file 1947 to present)
- Index New Zealand: INNZ (no time limits)
- Health and Medical Complete (no time limits)
- CINAHL Plus (no time limits)
- Scopus (no time limits)
- Cochrane central register of controlled trials (CENTRAL/CCTR) [no time limits]
- Cochrane database of systematic reviews (CDSR) [no time limits]
- Google scholar (no time limits)

Limits

English language

Books

- Agarwal's Rheumatic Fever and Rheumatic Heart Disease in Developing Countries⁷⁸
- American Health Association Control of Communicable Disease Manual⁷⁹
- AHA's The Epidemiology of Rheumatic Fever⁸⁰
- Blackwell Communicable Disease Control Handbook⁸¹
- Feigin and Cherry's Textbook of Pediatric Infectious Diseases¹⁴
- Markowitz and Gordis's Rheumatic Fever⁸²
- Mandell's Principles and Practice of Infectious Diseases^{6, 83}
- Red Book: 2006 Report of the Committee on Infectious Diseases³⁶
- Stollerman's Rheumatic Fever and Streptococcal Infection⁸⁴
- Wallace/Maxcy-Rosenau-Last Public Health and Preventative Medicine⁸⁵

Websites

National and International Ministries of Health, Health Department and PHU websites for guidelines for GAS, ARF and RHD

- WHO

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- NZ:
 - MoH⁷⁰
- United States:
 - CDC
 - Colorado
 - Massachusetts
 - New York
 - Ohio
 - Pennsylvania
 - Salt Lake City
 - Texas
 - Utah
- Canada:
 - Canadian Public Health Agency
 - Novia Scotia
- United Kingdom:
 - Health Protection Agency
- Australia:
 - Department of Health and Aging
 - Queensland Health
 - Northern Territory Public Health

Guideline websites for: GAS, ARF and RHD Guidelines

- AAP
- American College of Cardiology: clinical statements
- AHA
- CPG info base (Canadian Medical Association)
- EON project Stanford University
- Health Services Technology Assessment (USA)
- Infectious Diseases Society of America
- National Guideline Clearinghouse (UK)
- Medical matrix (healthtel corporation)
- Scottish Intercollegiate Guidelines Network

Australasian published guidelines for GAS, ARF and RHD

- NHF of Australia and the Cardiac Society of Australia and New Zealand's Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia⁸⁶
- NHF of New Zealand and the Cardiac Society of Australia and New Zealand's New Zealand Guidelines for Rheumatic Fever^{2, 7, 26}

Other sources

- Experts: two USA rheumatic fever experts were emailed, one directly and one through the Red Book online query engine to request citations to support the Red Book's recommendation for ARF contact tracing; the Red Book's archivist was also emailed to obtain information from early editions of the Red Book
- Wellington, Waikato and Bay of Plenty ARF contact tracing guidelines were obtained by email requests to PHUs in these regions
- Specific hand journal searches: scanning of bibliographies/references of literature retrieved

3.2.2. Step 2: Search and literature review of what constitutes an effective communicable disease control contact tracing programme

In step 1 it was established that no studies of ARF contact tracing in the NZ setting or even internationally had been published. The grey literature yielded several guidelines recommending ARF contact tracing and these have already been discussed at length in the Background chapter.

Given the lack of direct evidence to support ARF contact tracing I undertook to systematically research what constitutes a successful communicable disease control contact tracing programme so that this could be applied to ARF in the NZ context, as follows.

3.2.2.1. Search terms

The following terms were used both matched to MeSH and as key words.

- Contact tracing/Contact trace/Contact screening/Contact examination/Partner notification

The above terms were combined with each of

- Effectiveness/Effective
- Evidence

3.2.2.2. Sources searched

Databases

- Medline (1950 to present) and Medline in process
- Embase (combined file 1947 to present)
- Index New Zealand: INNZ (no time limits)
- Health and Medical Complete (no time limits)
- CINAHL Plus (no time limits)
- Scopus (no time limits)
- Cochrane central register of controlled trials (CENTRAL/CCTR) [no time limits]
- Cochrane database of systematic reviews (CDSR) [no time limits]
- Google scholar (no time limits)
- Google (no time limits)

Limits

English language

Books

- American Health Association Control of Communicable Disease Manual⁷⁹
- Blackwell Communicable Disease Control Handbook⁸¹
- Feigin and Cherry's Textbook of Pediatric Infectious Diseases¹⁴
- Gregg's Field Epidemiology⁸⁷
- Mandell's Principles and Practice of Infectious Diseases^{6, 83}
- Oxford Handbook of Public Health Practice⁸⁸
- Red Book: 2006 Report of the Committee on Infectious Diseases³⁶
- Wallace/Maxcy-Rosenau-Last Public Health and Preventative Medicine⁸⁵

Other sources

- NZ MoH Communicable Disease Control Manual⁷⁰
- Discussions with Public Health Physicians in Auckland

Finding no specific published standard criteria for what constitutes an effective contact tracing programme I devised a set of criteria based on the findings of my review and by adapting the standardised criteria used for screening programmes, because of the parallels between the two interventions.

3.2.3. Step 3: Search and literature review to apply criteria for an effective contact tracing programme to ARF household contact tracing in NZ

The final step was to apply these criteria to ARF. The style of review was a mixture of a systematic and narrative. The broad approach was systematic: each criterion was reframed as a research question, a comprehensive literature search was performed and a standardised appraisal system was used to judge whether sufficient evidence was amassed to fulfil each criterion or not. However, because of the limited volume and quality of available material and the broad and qualitative nature of some of the questions a more narrative style was taken in reviewing the literature accessed. A strict systematic approach would have proven very limited and narrow because much of the relevant published literature dates from the 1950s or earlier, before rigorous standards for conduct and analysis of research were well established. The bulk of studies were observational rather than the "gold standard" randomised controlled trials. Furthermore, for a number of the criteria the evidence answering the questions was accrued many decades ago and at the time of review was accepted medical fact. To revisit the evidence in a systematic manner in these instances seemed unnecessarily burdensome.

For critical appraisal of the studies reviewed I drew on the "Graphic Approach to Epidemiology" (GATE) frame that was developed by the EPIQ group at University of Auckland School of Population Health.⁸⁹ However because of the aforementioned nature of the material being reviewed individual appraisals of studies were limited to key studies and were primarily in the form of qualitative

comments incorporated into the text. For selected research questions comprehensive tables summarising all published studies and the associated quality of evidence have been compiled and can be found in the appendices. These were restricted to research questions where existing systematic reviews are lacking, but enough studies exist to make a tabulated comparison valuable. A table of all the studies of GAS transmission within households has been created, because it is a useful way of collating the evidence which forms the basis for the current recommendation of ARF household contact tracing.

The individual search terms for each criterion are described under each of the criteria headings in the following section. The sources searched were the same as those outlined in section 3.2.1.1 and to maintain search sensitivity the only limit applied was English language. For each criterion a decision was made in regards to whether there was sufficient evidence to accept or reject the criterion or insufficient evidence to do so. This was based on the GRADE approach to evaluating the quality of evidence, a system developed by the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) for evaluating the quality of evidence.⁹⁰ This system was chosen as it widely used in the health arena, including by more than 20 organisations including the WHO and the Cochrane Collaboration. The GRADE approach specifies four levels of quality, which can be downgraded or upgraded depending on the presence of several factors.⁹⁰ These levels of quality of evidence are shown below in Table 3-1. Further information regarding the assessment processes can be found in Appendix 4.

Table 3-1. Levels of quality of a body of evidence in the GRADE approach.Source: Cochrane Handbook for Systematic Reviews of Interventions, 2009.⁹⁰

Underlying methodology	Quality rating
Randomised trials; or double-upgraded observational studies.	High
Downgraded randomised trials; or upgraded observational studies.	Moderate
Double-downgraded randomised trials; or observational studies.	Low
Triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.	Very low

For the purposes of fulfilment of contact tracing programme criteria I decided that there needed to be at least “high” or “moderate” evidence according to the GRADE system for the criterion to be definitely met or not met. If there was insufficient evidence then it was graded as “insufficient evidence” and an evidence gap established. In such circumstances the degree of existing evidence and the direction in which it points is indicated.

3.3. Findings

3.3.1. Step 1

There were no published studies directly pertaining to the effectiveness, appropriateness or feasibility of household contact tracing for ARF incidence reduction. In terms of clinical effectiveness studies were confined to swabbing and antibiotic treatment in non-household ARF outbreak situations or to swabbing and antibiotic treatment in households, but without the context of recent ARF in a household member.⁹¹ A minority of studies that did look at swabbing of household members where ARF had occurred in a household member did not adequately evaluate the effectiveness of this as an ARF control method. There were no relevant NZ based studies. The later section (Step 3, Criterion 17) elaborates on these findings in greater detail. The grey literature was similarly unyielding.

Of all the sources searched contact tracing was only recommended by the bodies outlined in the Background chapter and in addition the Massachusetts Health Department and North Island PHUs (the latter basing their recommendations on the NZ Guidelines for Rheumatic Fever). However, none cite studies to directly support its effectiveness at reducing ARF. The NZ Guidelines for Rheumatic Fever do quote a series of four studies demonstrating the infectiousness of GAS within a household as support for their recommendation, which is graded as expert opinion.² The Red Book collaborators with whom I had email correspondence also indicated that the recommendation was based on expert opinion stemming from studies of GAS household transmission (personal communication, Michael A. Gerber, M.D., Cincinnati Children's Hospital Medical Center, Division of Infectious Diseases, 2010; personal communication, Edward L. Kaplan, M.D., Department of Pediatrics, University of Minnesota Medical School, 2010). They cited one study of GAS spread within Cleveland families performed

between 1948 and 1952.⁹² This study and the studies cited by the NZ Guidelines for Rheumatic Fever are elaborated on later in the Literature Review (Criterion 3) and in Appendix 10.

3.3.2. Step 2: Assessment of the value of contact tracing programmes

This search did not uncover any standardised criteria for determining what constitutes an effective contact tracing programme. I therefore adapted features of effective contact tracing programmes from the literature search, including those specifically focused on communicable disease chemoprophylaxis and combined these with the standardised approach for evaluating disease screening programmes developed from the well known work of Wilson and Jungner.⁹³

3.3.2.1. Evidence based criteria for an ideal contact tracing programme

As outlined in the Introduction and Background chapters contact tracing can be defined as the identification of those persons who have had such an association with an infected person, animal, or contaminated environment as to had the opportunity to acquire the infection, so they may be offered appropriate counselling, testing, quarantine or treatment.^{9, 65}

Much of the published literature around contact tracing either focuses on the effectiveness of an existing specific infectious disease contact tracing programme in a defined setting, or presents mathematical contact network modelling to evaluate the hypothetical effectiveness of contact tracing a given disease at various levels of prevalence or in various networks.⁹⁴ The diseases most commonly studied are TB, novel respiratory pathogens like SARS or avian influenza and STIs such as chlamydia. There are no studies involving ARF contact tracing. Mathematical modelling studies are valuable because they allow virtual experiments to be conducted that may not be practical or ethical in reality.⁹⁵ However the majority of the mathematical modelling studies examine contact tracing efficacy in the context of epidemics and therefore some of the findings may not be directly applicable to ARF, which in NZ is an endemic disease. They are also limited as they are based on assumptions that may be flawed in real life situations.

As alluded to in the Background chapter contact tracing is utilised in two main types of communicable disease setting. The first is the control of outbreaks of novel or re-emerging pathogens, or of diseases that are in the final stages of eradication.⁶⁶ The second is the control of endemic communicable disease.⁹⁴ As ARF is endemic in NZ I will focus mainly on the commonalities and the features specific to an endemic disease programme by looking at the disease, the contacts, the intervention and the programme.

The disease

Occurrence

There is wide consensus from both computational modelling and real life studies that contact tracing is most effective where the occurrence of the infectious disease in the general population is low.^{66, 94, 96-99} Depending on the type of disease, low occurrence may translate to low incidence, for example for acute infectious diseases of epidemic potential, like avian influenza, or to low prevalence for more

endemic chronic conditions like hepatitis B.⁹⁸ The reason is that above a certain occurrence threshold other forms of disease control, such as improved identification and management of symptomatic cases, screening or increased primary prevention, are considered comparatively more effective, both in terms of clinical and cost-effectiveness.^{66, 94, 98, 100} By way of illustration, contact tracing of TB cases is routine in countries such as NZ where there is a low overall prevalence. However, in countries where the prevalence is higher and resources far more limited, passive case finding is considered more useful.^{94, 100}

In an epidemic, once community wide transmission is sustained, contact tracing is unable to contain the spread of infection.^{66, 101} This was demonstrated during the first wave of the H1N1 pandemic in NZ in 2009. Rigorous contact tracing efforts with the use of prophylactic antivirals and quarantine were initially employed to try and prevent spread from the first overseas imported cases in the “stamp it out” phase. However, these efforts were subsequently abandoned once it became clear that local community transmission was occurring. Instead a “manage it” phase was initiated where resources were redirected into public awareness campaigns about infection control, managing institutional outbreaks and tertiary care of severe cases.¹⁰²

Therefore as prevalence or incidence alters so then may the indication for contact tracing, in lieu of another control method.

Understanding the natural history of infection

Contact tracing relies on case identification through development of case defining symptoms and self presentation.¹⁰³ If symptoms can be recognised then index case and secondary case finding are facilitated.¹² If there is a substantial degree of transmission prior to symptom onset then contact tracing will only be partially effective at achieving overall control and other measures that generally reduce the degree of contact between people, irrespective of whether they are known to be infected or not (such as hand washing and social distancing), may be more effective.¹⁰³ Therefore contact tracing is most effective if the time between infection and development of symptoms (and therefore seeking help, becoming an index case, receiving treatment and being contact traced) is short and the transmissibility (speed of transmission) is low, because there will be fewer asymptomatic infectious people in the population (a lower steady state prevalence of disease).⁹⁷

However, where there is a long asymptomatic infectious phase in which the infection is able to be rapidly identified and treated by contact tracing then contact tracing will prove very beneficial, as other than screening it is the only means by which this in this phase can be detected.^{11, 66, 94} In fact it may be essential for disease eradication under circumstances where each asymptomatic case gives rise to at least another asymptomatic case.⁶⁶

It was difficult to determine from the literature precisely how the infectivity, infectious period and interval between successive infections may influence the effectiveness of a contact tracing programme. On the one hand the additional benefit to overall control conferred by contact tracing a condition will be low if the infectivity is low due to a poor yield of secondary infection amongst the contacts. Conversely, if a disease is highly and rapidly infectious then contact tracing will only be a

useful intervention in the overall context of control if performed efficiently and rapidly enough to prevent sustained community spread. Thus in planning a contact tracing programme it is important to be cognisant of the natural history of the condition, in particular the incubation period and serial interval (the interval between successive cases),^{104, 105} as well as its prevalence or incidence in the general population. Understanding the former is critical for knowing when the most effective time for control measures like prophylaxis is.^{104, 105}

The contacts

Contact tracing is likely to be more efficient and effective when the disease is spread in clustered networks as this results in a higher occurrence of disease in the contacts than the general population.^{66, 106} This type of uneven distribution of disease is more common with airborne diseases than STIs and more likely to be seen when the overall prevalence is low.⁶⁶ For airborne diseases targeting contacts who are school aged children and young adults will generally be most effective.¹⁰⁷ The disease burden due to subsequent cases in contacts should be significant relative to that caused by sporadic cases in the general population both in absolute and relative terms.⁷⁴ Targeting those where the contact to case ratio is higher is considered potentially more effective.^{96, 108}

Other contact factors improving the effectiveness of contact tracing include acceptance and compliance with tracing^{99, 108} and the degree of sensitivity and positive predictive value (PPV) of tracing.^{109, 110} Sensitivity refers to the proportion of all contacts genuinely exposed to the index case who are identified and managed, while the PPV refers to the proportion of traced individuals who are actually infected.¹⁰⁹ In general, higher levels of these measures are associated with more effective contact tracing and therefore better control of the disease.

The intervention

A high level of case finding is a desirable characteristic of an effective contact tracing programme, although it may be a secondary goal to that of prevention of disease transmission.^{96, 108} It is imperative that the testing, treatment, quarantine or other intervention is carried out rapidly to prevent the onward spread of disease.^{12, 66, 109} Just how quickly this can occur depends on the type and degree of transmissibility of the disease – for example those diseases with respiratory spread require more rapid tracing.^{66, 107} This is of particular importance in contact tracing for epidemics (“the race to trace”).^{97, 111}

The test not only needs to be rapid, but also reliable, while the treatment must be effective.¹² In evaluating whether chemoprophylaxis for bacterial disease is warranted in contacts it has been suggested that it is indicated when the disease in question is severe, specific risk groups can be defined, and a safe, effective, and affordable prophylactic agent is available.¹¹² Chemoprophylaxis is not recommended unless all 3 of these criteria are met, otherwise it may be ineffective or unnecessary.¹¹² A Working Group on the Prevention of Invasive Group A Streptococcal Infections in organised by the US Centres of Disease Control in 1998 presented the following framework for deciding whether contact chemoprophylaxis is warranted:

- 1) The disease is severe;

- 2) There is an increased risk of severe illness or death with infection caused by a virulent strain;
- 3) Contact with a patient results in an increased risk of a severe disease; and
- 4) A safe and effective preventive regimen is available.¹¹³

The contact tracing programme

Due to the intensity of contact tracing required for it to function effectively there must be adequate resources, including facilities, data management capacity and trained, skilled staff.^{11, 99} Utilising standardised protocols is believed to improve the efficiency and effectiveness of a contact tracing programme.¹¹⁴ Cost effectiveness of the programme should be considered as well as the acceptability of the programme in the particular setting where it is being deployed.^{94, 97-99}

In terms of contact tracing capacity or the efforts and resources devoted to contact tracing it should be appreciated that the effectiveness of contact tracing has diminishing returns to scale: for each incremental increase in the resources (time, staff etc) devoted to the contact tracing process, the corresponding degree of overall disease reduction diminishes.⁹⁷

Chemoprophylaxis programmes for communicable diseases

As alluded to above in the contact tracing intervention section certain criteria for appraising whether a chemoprophylaxis programme for specific conditions should be initiated have been posited by some researchers. As chemoprophylaxis is a subset of the overall tracing and management of contacts it is useful to examine these suggestions further to assess whether they may be applicable to communicable disease contact tracing in general. Five reviews were found, four of which refer specifically to iGAS and one to bacterial disease in general in the context of a discussion of meningococcal disease.

The guidelines for chemoprophylaxis of iGAS have been performed by reputable three public health authorities, namely the CDC USA (in 1998 and revised in 2002),^{74, 113} the Health Protection Agency (2004)¹¹⁵ and the Public Health Agency of Canada (2006).¹¹⁶ The two proposed sets of criteria have been presented above. However, I have extracted elements from the body of the guidelines to arrive at 4 criteria common to all reviews as follows:

For chemoprophylaxis to be recommended all of the following appear to be deemed necessary:

- 1) Severity and burden of disease: the disease should be severe and of significant overall burden;
- 2) The risk of subsequent disease in a defined contact group: there should be a higher risk of disease in a defined group of contacts, as determined by the secondary attack rate in contacts versus the sporadic incidence, and the overall burden of disease due to secondary cases should be significant;
- 3) The effectiveness of chemoprophylaxis: chemoprophylaxis should provide significant reduction in RR and absolute risk (AR) and the number needed to treat (NNT) to prevent 1 case should be as low as possible;

- 4) The potential burden of chemoprophylaxis: chemoprophylaxis should be safe, affordable and logistically feasible.

These criteria could plausibly be generalised to include all types of contact tracing programmes. However I believe they are too narrow to suffice because they fail to encompass some of the other aspects described above that are also integral to effective contact tracing programmes. These include, in particular, whether the occurrence of the condition is such that contact tracing is likely to be the best preventative strategy, the role of case finding, the use of other interventions such as tests, which must be of adequate quality, or quarantine, and importantly the acceptability of the programme to the recipients and staff.

Screening programmes

Another population based communicable disease control intervention that shares some similarities with contact tracing is screening. Contact tracing is in fact a highly targeted form of screening and therefore established frameworks for evaluating screening programmes warrant review as we seek to understand how contact tracing programmes should be appraised.

Screening refers to the early detection of unrecognised disease through tests or examinations, or in more simple terms early case finding and is a form of secondary prevention.^{8, 117} In general, screening is applied to populations where there is a relatively low prevalence of the disease. However, to maximise effectiveness the prevalence is ideally higher than that seen in the total population when contact tracing occurs.^{85, 98} Screening can take several forms including mass (the whole population), selective (high risk groups, often large scale) and multi-phasic (applying two or more tests to a population).¹¹⁷ In a landmark WHO publication in 1968 Wilson and Jungner presented a set of classic screening criteria designed to guide the selection of diseases that were suitable for screening (Table 3-2), largely in an attempt to ensure optimal management for those in whom disease is detected while minimising harm.^{117, 118}

Table 3-2. Wilson and Jungner's principles of early disease detection¹¹⁷

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognised disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Since then screening has become widespread and although much more has been written on the topic Wilson and Jungner's criteria remain as a gold standard. More recently the UK National Screening Committee has developed a set of criteria for appraising the viability, effectiveness and appropriateness of a screening programme that are adapted from Wilson and Jungner's principles, but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the potential adverse effects of screening in the modern climate.¹¹⁹ They were first formulated in 1997 and revised in March 2009 (personal communication, Nick Warrell, Head of Communications, UK National Screening Committee). They are conveniently grouped into four categories: the condition, the test, the treatment and the programme, and focus on the following questions:

- Do we understand the natural history of the disease?
- Is there a good screening test?
- Is there an effective treatment?
- Is the programme acceptable to the population.^{119, 120}

The criteria are outlined in Appendix 5.

Evidence based criteria for an ideal contact tracing programme

In the absence of a comprehensive published framework for contact tracing, I incorporated the findings of the literature review on ideal contact tracing into the UK National Screening Committee criteria for a screening programme. This resulted in the following set of evidence-based criteria for an ideal contact tracing programme (Table 3-3). The criteria are grouped under four headings: the condition, the contacts, the intervention and the programme.

The criteria encompass three different aspects of an ideal contact tracing programme that are important in healthcare interventions: clinical effectiveness, appropriateness and feasibility.¹²¹

Effectiveness pertains to whether an intervention works as it is intended to, for example reducing the

incidence of ARF, and defines what the benefits and harms are and who will benefit.¹²¹

Appropriateness refers to the psychosocial aspects of the intervention such as its impact on people and whether it is acceptable to those being contact traced.¹²¹ Feasibility is concerned with the impact contact tracing would have on an organisation or provider, and the resources, including costs needed to ensure it can be implemented successfully. Some criteria align with a single one of these while others to a combination. All except for 3 pertain at least in part to effectiveness.

As with the UK National Screening Committee criteria it is intended that ideally all criteria should be fulfilled prior to the initiation of a contact tracing programme. While this may not be practical in reality, the idea is that they be viewed as a “gold standard”. It is envisaged that the criteria should be worked through in a stepwise fashion from 1 to 23, such that the appropriateness of the condition is first considered, followed by the suitability of targeting contacts, the effectiveness of intervention and then the programme as a whole. In doing so we are attempting to sequentially establish the following:

- 1) Condition: The existence of a disease that is a serious public health problem and is likely to be amenable to contact tracing because of its infectious nature and occurrence in the population;
- 2) Contacts: A higher risk gradient in contacts versus the rest of the population such that an intervention targeting contacts is warranted, and the feasibility of identifying and managing these contacts;
- 3) Intervention(s): The effectiveness of the intervention or combination of interventions in reducing the risk in contacts;
- 4) Programme: The benefits weighed against the harms and costs of the intervention, and the programme’s feasibility and acceptability.

The reasoning behind this sequence is that it should first be established that there exists significant risk and burden in contacts of a condition that is an important from a public health perspective, before attempting to set up a programme to modify this risk and burden. If the risk in contacts is not higher than the risk to the general population or if the total burden in contacts is very low there may be little point in investigating an intervention to address this.

A caveat to the use of these criteria is that they are likely to be impractical in the context of a rapidly developing infectious disease epidemic. In such situations there may be insufficient time for evidence to be gathered and appraised, and the risks of delaying intervention outweigh the benefits of intervening without full information. Thus they are designed primarily to be applied to endemic communicable diseases.

Table 3-3. Evidence based criteria for an ideal contact tracing programme

1. The condition:

- 1) The condition should be serious and of important public health importance^{93, 122}
- 2) The condition should be caused by an infectious agent that is communicable from person, vector or environment, to person
- 3) The natural history of the condition should be known from latent to declared disease.⁶⁶
Knowledge of the degree and duration of infectiousness, timing of infectious period in relation to onset of symptoms, incubation period and serial interval are important in terms of optimising the timing of contact tracing.
- 4) The proportion of cases with the condition that are not diagnosed promptly should be low. Contact tracing relies on prompt case identification through development of case defining symptoms and self presentation.¹⁰³
- 5) The occurrence of the condition should be low in the general population^{66, 94, 96-99}

2. The contacts:

- 6) There should be a high degree of sensitivity (a high proportion of contacts genuinely exposed to the case is identified, consent to and comply with management)
- 7) The contacts should be able to be identified, located and managed in a timely manner, ideally before onward infection transmission or secondary disease acquisition has occurred
- 8) There should be a high PPV (a high proportion of the traced contacts should be infected)
- 9) There should be a higher risk of infection and/or severe disease in contacts than in the general population (i.e. in the absence of contact tracing the occurrence of the infection and subsequent disease in contacts [secondary attack rate] should be higher than the occurrence in the general population), and the overall burden of secondary disease should be significant^{12, 66, 74}

3. The intervention: includes case finding, quarantine, isolation, screening test, clinical assessment (history, or examination), treatment or vaccination, education

Condition case finding

- 10) The rate of case detection should be greater than that expected to be found by screening or by presentations of individuals to healthcare on the basis of development of symptoms^{94, 98}
- 11) There should be an effective treatment /intervention for patients identified with the condition through contact tracing, with evidence that this early treatment/intervention leads to better disease outcomes and/or reduction in transmission than no or late treatment/intervention.^{93,}

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Secondary condition case prevention: Where utilising tests/clinical assessment

- 12) There should be a suitable (i.e. simple, safe, precise, valid and rapid) and acceptable test or clinical assessment (i.e. history or examination) available to detect the infection or infectious carriage or immunity to the infection, that, in the event of infection, ideally can be

administered *before* the person develops the condition

- 13) There should be an agreed policy on the further management options of individuals with a positive test/clinical assessment result

Secondary condition case prevention: Where utilising other interventions:

- 14) There should be an effective treatment or intervention (e.g. quarantine, vaccination, chemoprophylaxis) for contacts identified through testing or clinical assessment as having infection, or for contacts with no current clinical evidence of infection but deemed to be at significantly increased risk of infection because of their contact, and be evidence that early intervention/treatment leads to better outcomes and/or reduction in transmission than no or late treatment/intervention
- 15) There should be an agreed policy on the further management options of individuals with a positive test/clinical assessment result

4. The programme:

- 16) Evidence of disease reduction in this setting: There should be evidence from high-quality randomised controlled trials that the contact tracing programme is effective in reducing mortality or morbidity from the condition
- 17) There should be evidence that the complete contact tracing programme (test, diagnostic procedures, treatment/intervention) is clinically, socially, culturally and ethically acceptable to health professionals and the public
- 18) The benefit from the contact tracing programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures, treatment or other interventions)
- 19) The costs should be balanced against the benefits: The opportunity cost of the contact tracing programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to all other options for managing the condition, to ensure that no more cost-effective intervention could be introduced or current interventions increased within the available resources
- 20) There should be a plan for managing and monitoring the contact tracing programme and an agreed set of quality assurance standards
- 21) Adequate resources: Adequate staffing and facilities for testing, diagnosis, treatment, and programme management should be available prior to the commencement of the contact tracing programme
- 22) Evidence-based information, explaining the consequences of the contact tracing intervention (testing, treatment, other interventions) should be made available to contacts to assist them in making an informed choice
- 23) Public pressure for widening the eligibility criteria for contact tracing should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

3.3.3. Step 3: Search and literature review to apply criteria for an effective contact tracing programme to ARF household contact tracing in NZ

3.3.3.1. Criterion 1: The condition should be serious and an important public health problem

Research questions

This criterion is divided into two research questions as follows:

- 1) Is ARF a serious condition?
- 2) Is ARF an important public health problem?

Search terms

The following terms were used both matched to MeSH and as key words, with only information pertinent to NZ considered:

Rheumatic fever; Rheumatic heart disease; New Zealand; Serious; Morbidity; Mortality; Prevalence; Incidence; Cost.

Findings

Both questions have already been indirectly addressed in the Introduction and Background chapters, therefore further in-depth systematic review is not required and the following is mostly reiteration.

Findings for question 1

For the purposes of this criterion a serious condition is taken to refer to a disease with severe clinical outcomes for individuals. This is well documented for ARF. Although the case fatality rate in NZ is very low in NZ today (from 1971-1980 the mortality rate was 1.1 per 1,000,000 for males and 1.8 per 1,000,000 for females)¹²³ it causes significant acute morbidity as well as chronic sequelae.

Acute morbidity is described in the Background chapter and most commonly includes arthritis and carditis, with chorea and skin problems occurring less frequently.^{2, 6} While these features are self limiting, except potentially for carditis, the average duration of an episode without anti-inflammatory treatment is significant at 3 months.⁶ Subclinical disease aside, the majority of symptomatic cases will require hospitalisation for considerable periods to undergo investigation and management.² In Middlemore Hospital, South Auckland those with no or mild carditis are typically admitted under observation for approximately 2 weeks, while those with more severe carditis remain in hospital for 4 weeks or longer.⁵ A study of hospital admissions in Auckland in 1987 revealed an average stay of 47 days for ARF.⁴ Following an initial episode of ARF monthly penicillin injections are required for at least 10 years or for some up until the age 30 years.²

Chronic RHD is the outcome following approximately 60% of ARF first episodes³⁰ and the consequences include valvular lesions, heart failure, endocarditis and stroke together accounting for considerable morbidity and hospitalisation.⁶³ The average duration of non-surgical RHD admissions to Auckland hospitals in 1987 was 8 days.⁴ Surgical intervention (usually valve surgery) is required in 20% of RHD³¹ and premature death is common.³⁰

An estimate of disability adjusted life years (DALYs) lost for ARF and RHD has not been published for NZ in isolation, but for the Western Pacific region as a whole it was estimated at 105.5/100,000 in 2000 by the WHO.⁴¹

On these grounds it can be concluded that ARF is a serious public health problem.

Findings for question 2

The first principle of screening according to Wilson and Jungner is that “the condition sought should be an important health problem”.¹¹⁷ In ascertaining whether this is so they state that consideration should be given not only to how common the condition is, but also to the seriousness of its consequences for both the individual and their family, or for the community as a whole.¹¹⁷ In the section above I have already examined the seriousness of ARF’s consequences for the individual. Therefore I will now examine the condition from the point of view of its prevalence and incidence and their trends, along with impacts of morbidity, mortality and economic costs at a population level. A further important consideration is whether health inequities exist as these are viewed as having a negative overall impact on the health of a society.¹²⁴ As we are considering contact tracing in the NZ setting then I will examine each of these from a NZ perspective.

Incidence of ARF

During the 20th century the global burden of ARF has dramatically declined in industrialised countries due to an improvement in medical care and living standards, such that rates are generally less than 1/100,000 in these countries.¹²⁵ However, in NZ hospital admission data reveals that approximately 150-230 first cases of ARF continue to occur annually⁵ giving an overall rate of 3.4/ 100,000 (1996-2005)¹ or 17.2/100,000 for the 5-14 year age group (2000-2009) [personal communication Richard Milne, Managing Director Health Outcomes Associates Limited, 2010]. These rates have remained static since the 1980s and are some of the highest rates reported in a developed country.^{1, 5} In addition there are major ethnic disparities with an annual incidence in under 25 year olds of 29.2/100,000 for Māori, 61.9/100,000 for Pacific people and 1.3/100,000 each for European and Asian.¹²⁶ Māori and Pacific peoples have amongst the highest rates in the world.¹ This ethnic disparity is widening and represents a major inequity.^{1, 5}

Prevalence of RHD

As outlined in the Background chapter admission rates for RHD have not decreased over the past 30 years. The prevalence is disparate between different sectors of society with the highest prevalence in Māori and Pacific people.⁵ A landmark study performed in 2007 to 2008 in a high risk population of 10-13 year olds in socio-economically deprived schools in South Auckland revealed a prevalence of 24/1000, which is comparable to that found in developing countries such as Nicaragua and Mozambique.¹²⁷

Mortality from RHD and ARF

RHD accounted for 127 deaths per year from 1992 to 1997 (MoH 1997), with 175 in 2005 and 186 in 2006 (New Zealand Health Information Service [NZHIS]).⁵ The overall mortality rate for the period

2000-2007 is 4.4/100,000 (personal communication Richard Milne, Managing Director Health Outcomes Associates Limited, 2010). RHD accounts for more than twice as many deaths per year as cervical cancer⁵¹ and AIDS is the only communicable disease that causes a higher rate of premature death in New Zealanders under 65 years.⁵⁰

Non clinical costs to the community

ARF and RHD have negative effects on quality of life not only for the individual, but also their families and communities due to absence from education or work, physical disability and psychosocial impacts.²

National economic costs associated with ARF and RHD include reduced productivity and financial costs incurred through medical and surgical treatment.¹ While the cost of loss of productivity has not been measured, in 1993 an in depth analysis of primary, secondary and tertiary costs for the then Auckland Health Board was undertaken with annual costs amounting to approximately \$NZ3.6 million.⁵² Chronic RHD accounted for the majority of these costs.^{2, 4} Applying the 1993 breakdown to the Auckland region in patient analysis for 2008-2009 suggests that the current annual cost of ARF and RHD is of the order of \$NZ5.1 million (personal communication, Andy Roche, policy analyst, ARPHS, 2009).

It can thus be concluded that considering disease rates, trends and their impacts on society, together with comparisons with comparable OECD countries and other diseases of public health importance, ARF and its sequel RHD contribute significant incidence, prevalence, morbidity, mortality and financial costs to NZ. Furthermore they are an example of a massive ethnic health inequity. ARF is therefore an important public health problem.

Conclusion

Much of the observational data presented here is derived from national notifications, local rheumatic fever prophylaxis registers or from hospital admissions (sourced from the National Minimum Dataset [NMDS] held by the NZHIS). While under-notification or miscoding of admissions is possible these sources are generally considered relatively robust and large amounts of longitudinal data are available. In terms of disparities between NZ and other industrialised countries, and within NZ between Māori and Pacific and other ethnicities the magnitude of the difference is very large. Together these enable the observational studies to be rated as upgraded according to the GRADE approach. Therefore the quality of the evidence is moderate in respect to ARF being a serious condition and an important public health problem, which is sufficient to conclude that this criterion is met.

Criterion 1: <i>The condition is serious and an important public health problem</i>	
Criterion met:	Yes
GRADE evidence level:	Moderate
Evidence gap:	No

3.3.3.2. Criterion 2: The condition should be caused by an infectious agent that is communicable from person to person, vector to person or environment to person

Research questions

This criterion is divided into two research questions as follows:

- 1) Is ARF caused by an infectious agent?
- 2) Is this infectious agent communicable from person to person, vector to person or environment to person?

Search terms

The following terms were used both matched to MeSH and as key words:

Rheumatic fever; Group A streptococcus; Streptococcus pyogenes; Aetiology; Pathophysiology; Transmission; Spread.

Findings

From as early as the 1950s evidence of a recent GAS infection was deemed integral to confirming the diagnosis of ARF and it was thus included in all revisions of the diagnostic Jones Criteria from 1956 onwards.² As the research establishing GAS as the cause of ARF is extensive and it has long been firmly accepted by the medical community, a systematic review of the evidence is deemed unnecessary. However, some of the key research will be summarised below.

Similarly it has long been established as medical fact that this organism responsible for ARF is transmissible from person to person. Therefore a comparable approach will be taken for dealing with this question.

Infectious cause

Observations associating sore throats and “rheumatism” began in the early 1800s, although it took almost a century and a half to cement GAS tonsillo-pharyngitis as the cause of ARF.¹⁶ The key initial researchers noting this association included Haygarth (1805), Trousseau (1861) and Garrod (1874).¹⁶ The first to publish on it was J. Kingston Fowler in an 1880 paper in the Lancet.¹⁵ Triggered by his own episode of ARF a few years earlier following a bout of tonsillitis Fowler recorded a case series of 20 ARF patients whose attacks were preceded by sore throats.^{15, 16} Further observational evidence continued to accrue following this landmark publication, whilst in parallel the microbiological discovery of streptococci was taking place. Distinctions between different types of streptococci were developed during the early 20th century and in 1919 beta-haemolytic streptococci were first distinguished from other types of haemolytic streptococci by J.H. Brown.¹²⁸

In 1931 an American physician Alvin Coburn¹⁷ and an English physician William Collis¹⁸ both published reports positing that ARF was due to a haemolytic streptococcal infection of the throat.¹⁶ Coburn performed bacteriological studies which showed that in some cases of throat infection preceding ARF haemolytic streptococci could be isolated only at the time of throat symptoms and not at the time of ARF, explaining why the importance of this organism in relation to ARF may not have

been previously appreciated.¹⁷ Collis reported on an outbreak of tonsillitis and ARF recurrences occurring in convalescing rheumatic fever children in which haemolytic streptococcus was the predominant organism isolated from throats.¹⁸

In 1933 Rebecca Lancefield succeeded in developing the serogroup classification for beta-haemolytic streptococci that is in use today and group A beta-haemolytic streptococcus was at last recognised as a distinct organism.¹²⁸ This breakthrough, together with the discoveries of 1931, paved the way for investigators of the 1930s to 1950s to confirm the causal relationship between pharyngeal GAS and ARF. The supporting evidence relates to three main areas of research,^{19, 129, 130} namely demonstrations that epidemics of GAS and ARF occurred in parallel, that ARF was accompanied by high GAS titres and that antibiotic treatment of GAS pharyngitis prevented ARF.⁶ These bodies of research are now noted in turn.

The first studies showing that epidemics of GAS and ARF occurred in parallel were undertaken predominantly from the 1930s and 1940s in military training settings. They demonstrated that the development of ARF was epidemiologically linked to prior GAS infections.¹³¹⁻¹³³ The second body of research, also performed in the 1930s and 1940s, showed that ARF is accompanied by rises in antibody titres against GAS.^{19, 134-137} The third series of studies took place in the 1940s and 1950s and showed that antibiotic treatment of GAS pharyngitis reduces the incidence of GAS.^{55, 129, 130, 138} Rammelkamp, Wannamaker, and Denny in their pioneering work at Warren Air Force Base, Wyoming from 1949 to 1951 are credited with elucidating much of what we now know about the epidemiology of GAS infections in relation to ARF.¹³⁹

Importantly, all evidence points towards the throat as the site of the GAS infection that precedes ARF.^{2, 140} While there is speculation about whether GAS skin infections may be implicated in its pathogenesis their involvement remains unproven.²

I therefore conclude that ARF is caused by the infectious agent GAS, where the site of infection is the throat.

Transmission

While ARF is not considered infectious in itself, its antecedent GAS certainly is. The mode of transmission of GAS has been reviewed extensively in infectious disease and public health textbooks and is summarised below.⁸³

It is well established that transmission of GAS occurs chiefly via the direct route from infected or colonised people to new hosts.⁷⁹ The main sites of infection or colonisation from which transmission may occur include the pharynx, skin and sometimes the perineal region.⁸⁵ The two main forms of direct transmission involved are direct contact between skin or mucous membranes, such as touching or kissing and rarely sexual contact,¹⁴¹ and respiratory droplet spread (the projection of droplets from the mouth or nose of the infected person to another, for example, by coughing or sneezing).^{8, 79} Droplet spread requires close interpersonal distances as droplets will usually fall to the ground over a distance greater than 1 metre, and thus such spread is promoted in crowded conditions.^{6, 83, 85} Studies

that established respiratory droplet spread were chiefly observational studies performed in USA military barracks and hospitals from the 1940s to the 1960s and demonstrated high levels of GAS in saliva¹⁴², the expulsion of GAS droplets through sneezing, nose blowing and coughing^{142, 143} and a relationship between GAS acquisition rates and the distance between beds.¹⁴⁴

Indirect transmission occasionally has been reported via contaminated food, milk or water.¹⁴⁵ The role of indirect spread via fomites was systematically reviewed by the NHF in 2008 in the second part of New Zealand Guidelines for Rheumatic Fever and does not appear to occur to a clinically significant degree.⁷

There is thus a large body evidence to show that person to person transmission of GAS occurs with direct contact and droplet spread as the primary transmission route and there is a minor contribution from indirect spread via contaminated food or beverage spread. Fomite transmission appears to be insignificant.

Conclusion

I have not commented on the quality of individual studies, because of the volume of studies pertaining to this research question. However overall there is a large enough number of observational studies of satisfactory quality to classify the level of evidence according to GRADE as moderate with respect to ARF having an infectious cause that is transmissible from person to person. Therefore I conclude that this criterion is met.

Criterion 2: *The condition should be caused by an infectious agent that is communicable from person to person, vector to person or environment to person*

Criterion met:	Yes
GRADE evidence level:	Moderate
Evidence gap:	No

3.3.3.3. Criterion 3: The natural history of the condition should be known from latent to declared disease

Research questions

The key research question is:

What is the natural history of ARF from latent to declared disease?

This equates to the progression from exposure to and infection with GAS to the development of ARF and subsequent RHD. Important components are the timeframes involved and the risk of progression at each step. This criterion is divided into sub research questions as follows:

- 1) What are the host and environmental factors predisposing to pharyngeal GAS infection?
- 2) What are the infectious agent factors influencing infection?
- 3) How is infectious pharyngeal GAS within a household setting?
 - After exposure what is the risk of:
 - GAS acquisition overall?
 - Asymptomatic GAS colonisation (no symptoms, GAS isolated from throat culture, no serological evidence of infection)
 - Symptomatic GAS infection (respiratory symptoms, GAS isolated from throat culture, serological evidence of infection)
 - Asymptomatic true GAS infection (no symptoms, GAS isolated from throat culture, serological evidence of infection)
 - What percentage of acquisitions is symptomatic?
 - What percentage of acquisitions are true infections?
 - Is asymptomatic carriage/colonisation infectious?
 - What is the secondary attack rate in a household and who is most at risk?
 - What is the serial interval between pharyngeal GAS infections in a household?
- 4) What is the duration of infectiousness and when is the infectious period?
 - Untreated
 - Carrier
 - Treated
 - Are ARF patients infectious when they are diagnosed?
- 5) What is the incubation period of GAS pharyngitis?
- 6) What are the clinical features and their duration?
- 7) Virulence: What is the secondary attack rate of ARF following GAS pharyngitis?

Chapter 3. Literature Review

- Epidemic setting
- Endemic setting
- By *emm* type
- Previous ARF
- Can asymptomatic carriers progress to ARF?

8) What is the latency period between GAS infection and ARF onset?

9) What percentage of ARF cases are subclinical?

10) What is the risk of ARF progressing to RHD?

Search terms

The following terms were used both matched to MeSH and as key words.

Rheumatic fever; Group A streptococcus; *Streptococcus pyogenes*.

And each was combined with each or focused to the terms below:

Aetiology; Pathophysiology; Susceptibility; Immunity; Transmission/transmissibility; Contagious; Infectivity; Spread; Carrier/carriage; Incubation period; Latency/latent period; Reproductive number; Infectiousness/infectivity; Attack rate; Household; Family; Contact.

Findings

The natural history of ARF is important to appreciate so timing of contact tracing interventions can be optimised. A thorough understanding of GAS pharyngeal infection, the prerequisite to ARF and RHD (a necessary but insufficient cause) is essential. Pharyngeal infection with GAS, like infection with any organism depends on interactions between three factors: the host, the environment and the infectious agent.⁸⁵

1. Host and environmental factors predisposing to pharyngeal GAS infection

Host factors

Numerous studies have examined host risk factors for pharyngeal GAS acquisition and infection and the consistent finding is that it is most frequently seen in those aged 5 to 15 years with a peak during the first few school years.⁸³ Although it is possible that this age group has an enhanced susceptibility to infection once exposed, the more likely explanation is that this pattern is due to behavioural patterns whereby an increased number of close interactions with others in school age children facilitates exposure.⁷⁹ Infants appear to have relative protection from GAS infection by virtue of protection from persisting maternal type-specific antibodies.¹⁴⁶ Following infection with GAS M type specificity immunity ensues that may last for years, even if the infection was unapparent.⁷⁹ This does not necessarily prevent colonisation but inhibits type-specific illness¹⁴⁷ and may be interfered with by antibiotic treatment.⁷⁹ M types specify immunologically distinct M proteins found on the surface of GAS that resist phagocytosis and well over 100 have been identified.¹⁴⁸

Environmental factors

As discussed in the previous criterion (Criterion 2) GAS is spread from person to person by direct contact and droplets. A higher prevalence of GAS pharyngeal infection is associated with crowded living conditions due to an increased degree of person to person contact and winter peaks are probably a reflection of indoor congregation during the colder months.⁸⁵ Interestingly, crowding may also promote natural selection of GAS into a more virulent state.⁸³ Any differences in infection rates between ethnic groups are probably due to these environmental factors.

2. Infectious agent factors influencing infection

Infectious agent factors that universally influence the course of infections are infectivity, virulence and pathogenicity. Infectivity is the ability of the organism to enter and multiply in the host, virulence is the serious disease producing potential while pathogenicity is the extent to which symptomatic disease occurs in the infected population.⁸⁵ These will be discussed below.

3. Infectivity and pathogenicity of pharyngeal GAS within a household setting

The classical measure of the infectiousness and thus the epidemic potential of an organism is represented by its reproductive number. This is defined as *the number of secondary infections that arise from a typical primary case in a completely susceptible population.*¹⁴⁹ A reproductive number of 1 or higher indicates epidemic potential.

A multi-database search of the reproductive number for GAS returned no results.

Another measure is the secondary attack rate, which *is the probability the infection will occur in a susceptible person following exposure to an infected person.*⁸⁵ The literature search yielded various studies of GAS that examined secondary attack rates and other features of transmission in settings including schools, closed communities such as military bases, and households. As we are considering contact tracing in the household context the most pertinent information was derived from two groups of studies: those conducted before and those conducted after the antibiotic era. The early studies include those performed by Krause and Rammelkamp in the 1950s in the armed forces in the USA,^{139, 150} Kuttner in rheumatic fever hospitals,¹⁵¹ Cornfeld in schools¹⁵² and those performed in households in the 1950s and 1960s by researchers including James, Breese, Meyer, Matanoski, Zimmerman, Sheehe, Quinn.^{92, 153-157} More contemporary research on GAS epidemiology in households has been contributed by Poku, El Kholly, Falck and Danchin.^{91, 158-160}

Household secondary attack rate of pharyngeal GAS acquisition and infection after exposure

Pharyngeal GAS acquisition can be divided into the following categories:

- 1) Asymptomatic colonisation (carriage) where GAS can be cultured from the throat, but there are no associated respiratory symptoms and no streptococcal antibody titres rise observed.¹⁶¹ Note that titres may sometime still be raised if the carrier state was preceded by pharyngitis.¹⁶²
- 2) True infection, as evidenced by both positive GAS throat culture and streptococcal titre rise. This can be subdivided into:

- a. Asymptomatic infection
- b. Symptomatic infection, where respiratory symptoms occur.

A further category that may be confused with symptomatic true infection is chronic asymptomatic colonisation with an acute intercurrent viral pharyngitis.

I will examine the risk of acquiring secondary colonisation or infection, symptomatic or otherwise in the various studies. They vary considerably in terms of what is defined as “infection”, “acquisition” and “carrier” and unfortunately the vast majority do not combine serology with culture results and symptomology in their definitions (but tend to use combinations of only two of these). In general most of these studies are observational and of poor quality. Further details of these studies can be found in the summary Table A-3 in Appendix 10.

The secondary attack rate can be considered in terms of the risk of either pharyngeal GAS acquisition (which includes both carriage and true infection) or infection (which is a subset of acquisition), following exposure to an index case who themselves may be classified as having either have carriage or true infection. The studies vary considerably in terms of which actual secondary attack rate they measure and this is not always explicit. It is important to attempt to distinguish between carriage and true infection in reference to both the index and secondary cases as true infection is more infectious and carries the risk of non suppurative sequelae.

Historical studies

James et al. looked at the spread of GAS within 61 Cleveland families from 1948-52.^{92, 163, 164} The total pharyngeal GAS acquisition rate was 1.3/1,000 person days and was highest amongst young school children, who were also most likely to introduce GAS from outside the home. Following exposure to an asymptomatic carrier (defined by positive throat culture, no serology performed) the secondary attack rate of total pharyngeal GAS acquisitions (defined by positive throat culture of the same GAS strain) in households was 9% (26/291) over a period of 10 weeks, whereas following exposure to a symptomatic index case (positive throat swab, compatible illness, no serology performed) the secondary household acquisition risk was 25% (46/183). Highest secondary attack rates were seen in the 3 to 4 year age group (18% following exposure to an asymptomatic carrier and 54% after exposure to a symptomatic index case). Of those who acquired GAS in the study 41% (156/379) had symptoms consistent with GAS pharyngitis. Thus following exposure to a symptomatic index case resulted in a secondary attack rate of symptomatic GAS pharyngitis of approximately 10% in households (41% of 25).

Breese and Disney in their study of 363 families in New York in 1953 defined an index case as those with sore throats and GAS isolated on throat culture.¹⁵⁴ Index cases were treated with IM BPG. The secondary attack rate in siblings (of upper respiratory tract illnesses including those other than pharyngitis, together with positive throat swabs) over 3 weeks was 20.6% (134/650), or 19.4% (96/496) for pharyngitis alone. The attack rate in adults was 3.7% (29/791). The number attacked in a

household was roughly proportional to the household size. This study suffered from bias as not all siblings were swabbed and those that were swabbed were more likely to be unwell and younger.

Matanoski et al. conducted a series of case control studies from 1957 to 1959 on a group of families in Maryland, USA.¹⁵⁵ In a study examining household spread of pharyngeal GAS 103 families where a member had suffered ARF at some point were compared with 101 control families over a period of 9 months or more.¹⁶⁵ The rate of secondary GAS acquisition (defined by a positive GAS throat culture) within 8 to 10 weeks of exposure to an index case (an individual with the initial isolate of a new strain in the household) was 1.5% per person in ARF families and 2.9% in controls. This was a poor quality study due to design flaws including unclear selection criteria and matching and statistical analysis was not undertaken to ascertain whether there was a true difference between the results in cases and controls.

Utilising Greenwood's chain-bimodal model and the data collected by Matanoski et al. in the study above,^{155, 165, 166} Poku estimated the risk of siblings of acquiring GAS on throat culture following an introduction into the household.¹⁵⁸ The risk was calculated as 0.05-0.06 per person per month, which equates to 27.5% per month for a household with 5 susceptible people.⁷ Serology and symptomology were not evaluated. Limitations of this study include the use of data from a poor quality study and imperfect fit of the model.

A case control study of families residing at an air force base in Maine, USA from 1962-64 was conducted by Levine et al.¹⁶⁷ Over a 9 month period the secondary attack rate of total GAS acquisitions (defined by a positive throat swab) in families following exposure to an index (respiratory symptoms and a positive throat swab) was 21.3%. However only 72.4% were of the same GAS type, giving an overall secondary attack rate of 15.4%. The rate of GAS isolation from contacts of controls was 4.5%. There was a high risk of bias in this study as cases and control contacts were incompletely matched and cases received antibiotic treatment inconsistently.

El Kholly et al. in a controlled study of penicillin therapy on GAS acquisitions in Egyptian families from 1972-74 demonstrated a secondary attack rate of GAS acquisition (defined by positive throat culture alone) in rheumatic fever families of 8.7% and control families of 8.2% when the index case (defined by positive throat culture alone) was asymptomatic, increasing two to three-fold to 27.7% and 15.1% respectively when the index case was ill.⁹¹ The timeframes over which secondary acquisition occurred were not discussed and these results combined families treated and not treated with penicillin. Significant streptococcal antibody rises were associated with 9% of acquisitions. This would give an overall true infection secondary attack rate in a rheumatic fever household following exposure to someone ill with a positive throat culture of 2.5% (9% of 27.7%) however this is likely to be an underestimate as serology was only performed 6 monthly. Limitations of this study include risk of bias due to poor description of eligibility criteria and a high subject dropout rate. Precision measures were not calculated for the results discussed.

Contemporary studies

Falck et al. conducted a study of the intra-familial spread of GAS in 114 index cases and their families for 1 year from 1988-1989.¹⁵⁹ Index cases (defined as having typical symptoms of GAS pharyngitis in conjunction with a positive throat swab) were treated for 5 days with penicillin and family members were followed for 1 month. The secondary attack rate of GAS acquisition of the same type (positive throat swab) in family members over 1 month was 33% and the corresponding rate for symptomatic secondary acquisitions was 8%. The secondary acquisition rate of the same period was 26% where the index cases had only a positive throat swab, but double this at 52% if they also had a positive nasal swab. The researchers proposed that clinical treatment failure in index cases might be due to “ping-pong” infection from family members.

A more contemporary study of secondary attack rates within households was that by Danchin et al. conducted in Melbourne from 2001-2.¹⁶⁰ A primary case was defined as a symptomatic episode of pharyngitis that was either GAS culture positive or serologically confirmed. A secondary case was either the isolation of GAS on throat culture, or serological evidence of infection, irrespective of symptoms. The secondary attack rate in family members over a 2 week period was 13% overall, and 5% for symptomatic secondary cases. In families who had an index case 43% developed at least 1 secondary case. Overall this was a well conducted study, however a drawback is that it is unclear from the published account whether antibiotic treatment of all index cases was standardised.

Lindbaek et al. conducted a well designed study in primary care in Norway.¹⁶⁸ It involved 110 index patients with sore throat and GAS cultured on throat swab who were treated with oral penicillin for 10 days, and their households (290 individuals). The secondary attack rate (defined as a clinically compatible illness with a positive throat swab) in household members was 14% within 4 weeks, and 27% of households had 1 or more secondary cases over this period. A higher proportion of spread was seen in households with 4 or more people.

The most recently published study of relevance was a Japanese controlled trial study by Kikuta et al. involving 1,181 index cases and 1,440 siblings from 2005-2006.¹⁶⁹ They compared the secondary attack rate in siblings following exposure to an index case with symptomatic GAS pharyngitis (defined by clinical features and a positive pharyngeal rapid antigen test). Siblings were nonrandomised to receive nonstandardised courses of prophylactic antibiotics or no prophylaxis. Where the siblings were not given prophylactic antibiotics the secondary attack rate of symptomatic GAS pharyngitis (defined as per the index case) in siblings over a 7-88 day time period (mean 24.8 days) was 5.3%, which is half of that observed by James et al.⁹² This study had many methodological flaws including a lack of randomisation of contacts to antibiotic prophylaxis or control and failure to account for any antibiotic of treatment of contacts.

Despite the shortcomings of many of these studies there is general concurrence between them that GAS is moderately infectious within a household. If the index case is symptomatic, as opposed to being an asymptomatic carrier, the risk of secondary transmission increases by a factor of about three.^{91, 92} The secondary acquisition rate following exposure to a symptomatic case ranges from 13-

28% over a variable time period. The secondary illness attack rate (symptomatic GAS pharyngitis) following exposure to a symptomatic case ranges from 5-10%, although it tends to be consistently higher in children versus adults (20% rate in siblings versus 4% in adults in Breese et al.'s study).^{91, 92, 153, 154} The only study looking at the secondary acquisition rate following exposure to an index case, where the index cases include all those with positive throat cultures who are either symptomatic or asymptomatic, was that by Poku where the rate was found to be 0.05-0.06 per person per month in those up to 16 years of age.¹⁵⁸

Factors relating to household spread

The speed of spread within a household varies dramatically from study to study with some indicating significant spread occurs within 2 to 3 weeks^{156, 160} and others demonstrating that secondary cases may still occur months or even up to 120 weeks after the initial introduction.⁹²

Factors that increase the risk of onward transmission include the particular strain of GAS and the degree of infectiousness of transmitter, whereby those with acute untreated exudative pharyngitis who have the organism in both the nose and throat are most infectious and those with chronic asymptomatic pharyngeal carriage are least infectious.^{139, 162} Of intermediate infectiousness are asymptomatic carriers who have recently recovered from symptomatic pharyngitis (dubbed "dangerous carriers").¹⁷⁰ Interestingly the association of household crowding with facilitation of onward transmission has been inconsistent amongst the studies reviewed.¹⁵⁴

Studies consistently show that children are at higher risk of acquisition than adults, although the particular age group most at risk varies considerably depending on the study.^{91, 92, 154, 160} A particular risk factor is intimacy of contact with the index case, for example sleeping in the same room.¹⁵⁶

The index case or introducer is most often a school aged child¹⁷¹ although this was not borne out in all studies. Sheehe and Feldman and El Kholy and colleagues independently showed that approximately 62-63% of acquisitions originate from sources outside the home.^{91, 153}

Interrelationship between acquisitions, symptoms, true infection and carriage

It is important to know what percentage of pharyngeal acquisitions are symptomatic, what percentage of acquisitions represent true infection and finally what percentage of true infections are symptomatic as this influences how easily they may be detected and treated, as well as their risk of onward transmission and of secondary complications.

Carriage

Before addressing these questions one needs to first understand carriage and whether it is infectious, a subject of much controversy. Carriage, or colonisation, has already been defined above. It is thought to be a distinct state from infection and as such does not result in suppurative or non-suppurative sequelae like ARF. Carriage often may follow infection or may occur de novo without preceding infection. It does not cause symptoms, but intercurrent viral pharyngitis may mimic GAS pharyngitis resulting in diagnostic confusion. Evidence from studies of GAS spread, many of which have been presented above clearly demonstrate that onward transmission may occur from carriers.^{150,}

¹⁷⁰ Kuttner and Krumwiede demonstrated that a carrier lead to an outbreak of recurrent ARF in a rheumatic fever ward in 1937-38¹⁵¹ and numerous studies have noted carriers introducing infection into a households, although the risk of transmission is approximately three-fold lower than in cases of symptomatic infection.^{91, 92} The degree of infectiousness of carriage, as proposed by Pichichero and Casey, depends on the number of organisms in the nasopharynx (which tends to be higher earlier in carriage), the timing of the exposure in relation to the onset of carriage (more infectious earlier in carriage) and the nature of the strain carried.¹⁶²

Symptomatic acquisitions

The proportion of pharyngeal acquisitions that are symptomatic has been recorded in a number of studies. Cornfeld et al. found that 20% of acquisitions in school children were associated with clinical illness.¹⁵² In the household setting James et al.⁹² found that comparable level was 41%, while Meyer et al. reported 43%,¹⁴⁷ Zimmerman 25-51%,¹⁵⁶ Falck 29%¹⁵⁹ and Danchin 41%.¹⁵⁹ Thus the reported percentage ranges from approximately 20-50%. There is evidence that some strains, for example type 4 and 6 are more pathogenic than others.⁹²

Acquisitions that represent true infection

In respect to the proportion of acquisitions that represent true infection, as opposed to carriage, serology is required to distinguish between the two states and there are few published studies looking at this. I found three set in households, two set in the community and one in emergency departments. All have some design limitations and these are described in more detail in Appendix 8.

Meyer et al. in a 1960-61 study of susceptibility to GAS in families demonstrated that 29% of pharyngeal GAS acquisitions in households were associated with a two-fold rise in titre suggesting that 29% were true infections.¹⁴⁷ The comparable rate found by Matanoski et al. in households was 29.9-52.7%,¹⁶⁶ while El Kholy et al. demonstrated a rise in anti-DNase B antibodies in 30.7% and of ASOT in 9.0% of household acquisitions.⁹¹

Valkenburg et el. in a community study of 1,517 people in the Netherlands in the 1960s found streptococcal titre rises accompanied 33.5% of positive GAS throat cultures in those with sore throats who were not treated with antibiotics.¹⁷² In the same study, of all those over 6 years of age found on quasi-randomised community sampling to harbour pharyngeal GAS, only 5-12% had an associated ASOT rise. During the same era Kaplan et al. found that 43% of episodes of symptomatic pharyngitis in children less than 15 years presenting to USA emergency departments, where GAS was recovered from the throat were accompanied by a paired titre rise.¹⁷³ Ozturk et al. in a prospective study of Turkish school children aged 11-13 years published in 2004 found that single ASOTs were elevated in 37% of those who were both asymptomatic and had throat cultures positive for GAS.¹⁷⁴

Thus the reported percentage of GAS acquisitions that represent true pharyngeal infections ranges from about 30-50% and is likely to be higher when associated with a sore throat. Alternatively when performing cross sectional throat swabbing of a population the percentage of those harbouring pharyngeal GAS who have true infection seems to be lower, possibly because proportionately more

may have chronic carriage rather than recent GAS acquisitions. The studies by Ozturk and Valkenburg indicate it lies somewhere between 5% and 37%.

Subclinical infections

The final question is what percentage of true infections is symptomatic. The answer is not directly available but may be extrapolated from ARF case series as all ARF cases, by definition, arise from true infection. Up to two thirds of these give no history of sore throat preceding their illness.⁴³ The proportion varies depending on the series. Commonly quoted rates are 40-50%,^{172, 175} although in a recent NZ series it was only 28%.²⁹ Therefore it is possible that up to two thirds of true infections may be subclinical.

4. The duration of the infectious period for GAS pharyngitis?

Like the degree of infectiousness the duration is thought to relate to the volume of organisms present in the nose and throat, which tends to correlate with symptoms. The infectious period for pharyngeal GAS has been reported as unknown in a recent systematic review of critical periods for childhood infectious diseases.¹⁰⁴ However the AAP Red Book and several reputable communicable disease manuals state that untreated symptomatic but uncomplicated GAS pharyngitis is infectious for approximately 10 days to a few weeks, while those with purulent discharges may remain infectious for up to months.^{36, 79, 81} As discussed, asymptomatic carriage may also be infectious although considerably less so. Its duration is variable with a range of 3 to 123 weeks and a median of 3 months reported.^{104, 176-178} Once GAS pharyngitis is treated with appropriate antibiotics it is considered non-infectious after 24 hours,^{36, 79} although failure to eradicate the organism occurs in a small proportion of these cases resulting in ongoing carriage. It is not clear from the literature whether the onset of the infectious period precedes the onset of symptoms.¹⁰⁴

An important question in the context of contact tracing is whether ARF patients are infectious when they present with ARF symptoms. I could find no literature directly addressing this however it is likely to depend on whether GAS can still be isolated from their throat. Rates of this vary, with 50 to 60% reported by Catanzaro in the 1950s,¹⁷⁹ 25% reported by Markowitz and Gordis,⁸² and 57% in a recent NZ trial.²⁹ Because of the latent period (as discussed below) the acute most infectious phase will usually have passed so those who remain culture positive are probably of low infectiousness. Once penicillin is started this should cease.

5. The incubation period of GAS pharyngitis

The incubation period ranges from 12 hours to 5 days,¹⁰⁴ but is commonly 2 to 4 days.^{6, 85} Shorter periods are seen with food borne infections.¹⁸⁰

6. Clinical features of GAS pharyngitis and their duration

Clinical features alone are unreliable in the diagnosis of GAS pharyngitis. Typically there is a sudden onset of sore throat accompanied by headache and fever. Cough is usually absent. Examination findings include anterior cervical lymphadenopathy and inflamed tonsils sometimes with exudates.^{83, 85} The duration of symptoms in uncomplicated course is under 1 week, with fever lasting less than 3 or 4

days.^{83, 181} Clinical features are atypical in toddlers in whom a picture of rhinitis and fever predominates.³⁶ As discussed, infection may be subclinical, possibly in up to two thirds of cases.

7. Virulence: the attack rate of ARF following GAS pharyngitis

As has been discussed in the Background chapter only a small proportion of those with GAS pharyngitis develop ARF. The attack rate appears to be higher if the infection is associated with a higher magnitude immune response and if GAS persists for longer in the throat during convalescence.¹³⁹ Thus, asymptomatic carriers of GAS are not thought to be at risk of developing ARF. Higher secondary attack rates are observed in epidemic versus endemic settings¹⁴ and the rate may plausibly vary with the "rheumatogenic" potential of the strain of GAS although there is no direct evidence to support this. There is a significantly higher risk of developing ARF (25-75%) following a given GAS infection in the context of a background of previous ARF.^{55, 139}

The attack rates quoted in the various studies that have been conducted are dependent upon the definition of GAS pharyngitis used and tend to be lowest if the definition just includes a sore throat accompanied by the isolation of GAS on throat culture and highest if there is also a significant streptococcal titre rise and the pharyngitis is exudative. A titre rise and positive throat swabs irrespective of symptoms gives an intermediate attack rate. Most studies of attack rate were performed prior to the era of routine antibiotic administration for GAS pharyngitis and such studies would be difficult to ethically perform on at-risk populations today. The key studies and their limitations are summarised in Appendix 9.

Warren Air Force Base in Wyoming, USA in the 1940s and 1950s provided an ideal platform for Rammelkamp and colleagues to study GAS pharyngitis and ARF because of the relatively closed population living in close proximity.¹³⁹ Epidemics of exudative GAS pharyngitis were frequently observed and the attack rate of ARF following these epidemics (where typeable GAS was isolated on throat swab) was found consistently to be 3%, despite variations in the GAS strain, season and age.¹³⁹ These rates concur with those found in other epidemic settings, including following milk-borne GAS tonsillo-pharyngitis outbreaks and civilian-based epidemics.¹⁸²⁻¹⁸⁵

Various studies performed in endemic settings have shown invariably lower rates of less than 1%.³⁶ Siegel et al. (1956-59, Chicago) found a rate of 0.39% in 519 outpatient children aged 3-16 years with untreated GAS pharyngitis (defined as a sore throat in combination with GAS isolated on throat swab).¹⁸⁶ Valkenburg et al. estimated of the attack rate in a 73,500 person-years observational study of three villages in the Netherlands from 1959 to 1965.¹⁷² This involved 27 GP practices and an overall study population of 57,500. Both patients presenting with sore throats and a random sample of 15% of the population were studied. Symptoms, throat cultures and streptococcal titre rises were collated and associated rates of ARF calculated in those who did not receive antibiotics. Complete data was available on 1,065 subjects of whom just under half were treated with penicillin and the remainder (628) were untreated. The attack rate ranged from 0.17-0.80% and was dependent upon the definition of the initial GAS pharyngitis, with less sensitive definitions resulting in a lower attack

rate. The attack rate associated with our earlier definition of “true pharyngitis” (GAS isolated on throat swab and a two-fold or higher streptococcal titre rise) was 0.26% in this study.

No NZ based studies have directly looked at the attack rate ARF in those not treated with antibiotics. However a randomised group trial was conducted in South Auckland schools between 1998 and 2001 to examine the effectiveness of a school-based sore throat intervention.²⁹ This study included approximately 22,000 primary and secondary students of predominantly Māori and Pacific ethnicities from 53 schools located in low socio-economic regions of Auckland. Half the schools were randomised to the intervention group and half were controls receiving no intervention. The intervention comprised daily questioning of students about sore throats and all those responding positively had throat swabs taken. In addition monthly surveillance throat examinations were performed and those with inflamed pharynx or tonsils had swabs taken. All those with positive throat swabs received 10 days of observed oral penicillin. The primary outcome measure of the study was the incidence of ARF in the intervention schools compared with the control schools and a non statistically significant reduction of 28% was found in the intervention group. The non statistical significance of this result was attributed to underpowering.

A secondary outcome that was not reported in the original publication, but is reported elsewhere was a ARF attack rate following GAS pharyngitis of 0.2% in the intervention group (where GAS pharyngitis is defined as either a sore throat plus GAS isolated on swab, or inflamed pharynx/tonsil plus GAS isolated in swab).¹⁴ Although the comparable rate is not known for untreated pharyngitis it can be approximated from this data. As penicillin is deemed approximately 80% effective at preventing ARF⁵⁴ and compliance was reported as 75% in this study then hypothetically approximately 60% of potential cases of ARF may have been prevented by the intervention. Extrapolating, the expected attack rate in the absence of the intervention would be 0.33%. An alternative attack rate estimate can be calculated for the control group. If we assume that the rate of GAS pharyngitis was the same in the intervention and control groups we can work backwards from the ARF incidence difference in the two groups. The RR increase of ARF in the control group over the intervention group is 1.3, giving an attack rate following GAS pharyngitis in this group of approximately 0.26%. Therefore the attack rate of ARF following untreated GAS pharyngitis, as defined in this study, is approximately 0.3% (0.26-0.33%) in 5-18 year olds in population endemic for ARF.

8. The latency period between GAS infection and ARF onset

A delay between GAS infection and the onset of ARF is seen and it is presumed to be due to the time taken for the host to develop the immune response that results in tissue inflammation.¹⁹ Rammelkamp et al. found an average latent period of 19 days in airmen afflicted with ARF at Fort Warren Air Force Base from 1949-1953.²⁷ Further series have suggested common range of 1 to 5 weeks.⁸⁴ In the aforementioned NZ school based study the average latent period was 27 days with a range of 2 to 49 days.^{14, 29}

9. Subclinical ARF

Subclinical ARF may be defined as illness that is either asymptomatic or so mild that medical attention is not sought. The true rate of subclinical ARF is unknown. While there are many examples of a retrospective diagnosis of subclinical ARF being made, no quantification of the degree to which it occurs has been performed. The best evidence of the existence of subclinical ARF comes from echocardiogram population screening studies. In a study of 1,142 ten to thirteen year olds in a high risk demographic in South Auckland 27 (2.4%) were found to have echocardiogram changes consistent with previous ARF. None of these children reported a history of symptoms suggestive of ARF (personal communication, Rachel Webb, infectious diseases paediatrician Starship Hospital, Auckland, 2010). Dr Nigel Wilson, paediatric cardiologist at Starship Hospital in Auckland estimates that more than 100 “silent” ARF cases occur per year in NZ (personal communication, Dr Nigel Wilson, paediatric cardiologist, Starship Hospital, Auckland, 2010). This will be discussed further in the next criterion (Criterion 4).

Further support for the concept of subclinical carditis comes from studies of echocardiograms performed on known cases of ARF. The rate of subclinical carditis was estimated at 16.8% in a recent meta-analysis and half were thought to persist or worsen.¹⁸⁷

10. The risk of ARF progression to RHD

The overall rate of progression to RHD has already been covered in the Background chapter is approximately 60%-80%.^{29, 30}

Conclusion

In conclusion much of the natural history of ARF, from its antecedent GAS throat infection through to clinical ARF and finally RHD, is known. Numerous large observational studies of moderate quality contribute to our understanding of the progression of this condition. In several areas the evidence is weaker and further research to improve our understanding is recommended. This includes the duration of infectiousness and what proportion of true GAS pharyngitis, which its inherent potential to cause ARF, is asymptomatic or subclinical, and in turn what percentage of ARF itself is subclinical. These help to provide an idea of how much impact certain aspects of primary and secondary prevention that rely on symptomatic presentations of GAS infection and ARF respectively can make. They are also particularly relevant to contact tracing in terms of case identification and optimal timeframe

Criterion 3: *The natural history of ARF and RHD is known from latent to declared disease*

Criterion met: Yes*

GRADE evidence level: Moderate

Evidence gap: Partial*

*Gap in evidence regarding duration of pharyngeal GAS infectiousness, extent of subclinical GAS pharyngitis and ARF

3.3.3.4. Criterion 4: The proportion of cases with the condition that are not promptly diagnosed should be low

Research question

What proportion of ARF episodes is accurately diagnosed?

Search terms

The following terms were used both matched to MeSH and as key words and only information pertinent to NZ was considered:

Rheumatic fever; Rheumatic heart disease; Subclinical; Asymptomatic.

Findings

There are no published studies that address this question and indeed it would be a difficult question to directly answer. The information is needed to answer it includes the following:

- 1) What proportion of ARF is asymptomatic or subclinical?
- 2) What proportion of symptomatic ARF accesses healthcare?
- 3) Of this, what proportion is accurately diagnosed?

The first question has already been discussed in Criterion 3. To reiterate, while there are many examples of a retrospective diagnosis of subclinical ARF being made, no quantification of the degree to which it occurs has been performed. The best evidence of the existence of subclinical ARF comes from echocardiogram population screening studies. In a study of 1,142 ten to thirteen year olds in a high risk demographic in South Auckland 27 were found to have echocardiogram RHD changes consistent with previous ARF.¹²⁷ None of these reported a history of symptoms suggestive of ARF (personal communication, Rachel Webb, infectious diseases paediatrician Starship Hospital, Auckland, 2010). Other evidence comes from echocardiograms performed on those patients assessed during their first ever presentation for ARF that reveal changes consistent with previous episodes of ARF carditis and women presenting with rheumatic mitral stenosis in pregnancy who have no prior history of clinical ARF (personal communication, Dr Nigel Wilson, paediatric cardiologist, Starship Hospital, Auckland, 2010). Dr Nigel Wilson, paediatric cardiologist at Starship Hospital in Auckland estimates that more than 100 “silent” ARF cases occur per year in NZ. This is based on the ratio of annual RHD deaths to ARF episodes per year being higher than it should be considering the natural history of ARF with secondary prophylaxis and the relatively stable numbers of ARF and RHD in NZ over the past 30 years ARF (personal communication, Dr Nigel Wilson, paediatric cardiologist, Starship Hospital, Auckland, 2010).

The second question refers to access to healthcare. It is acknowledged that those at highest risk of ARF, that is Māori and Pacific people and low income New Zealanders, have difficulty accessing healthcare.^{48, 188, 189} Barriers include cost, transport, language difficulties and cultural issues.^{26, 48, 189} However it is not known to what extent these barriers prevent ARF patients from seeing a health professional.

There is no pathognomonic symptom, clinical sign or test for ARF so the diagnosis therefore relies on a combination of these features, as outlined by the Jones criteria.¹⁹⁰ As explained in the Background chapter the 1992 Jones criteria with NZ modifications and exceptions are used in NZ (see Appendix 3).² In summary diagnosis is often not easy. It requires a high index of suspicion combined with myriad investigations, often including serial specialist investigations such as echocardiograms.² It is likely that there is an under diagnosis of ARF in NZ although again this has not been measured.

Conclusion

There is insufficient evidence to answer this question and fulfil this criterion. However indirect evidence suggests that subclinical ARF may be significant, accessing healthcare is a problem for those most at risk of ARF and under diagnosis may occur even once health professional help is sought. An evidence gap is established.

Criterion 4: *The proportion of cases with the condition that are not promptly diagnosed is low*

Criterion met:	Insufficient evidence
GRADE evidence level:	Moderate, towards not meeting criterion
Evidence gap:	Yes

3.3.3.5. Criterion 5: The occurrence of condition should be low in the general population

Research questions

This criterion is divided into two research questions as follows:

- 1) What is the overall occurrence (incidence and prevalence) of ARF and RHD in NZ?
- 2) What is considered low occurrence?

Search terms

The following terms were used both matched to MeSH and as key words, and only information pertinent to NZ was considered:

Rheumatic fever; Rheumatic heart disease; New Zealand; Prevalence; Incidence.

Findings

The overall occurrence of ARF in NZ can be determined by considering both the incidence of acute episodes and the prevalence of its chronic sequel RHD.

Findings for question 1

Incidence of ARF

The incidence of a condition is the count of new cases occurring in a defined population over a specified time period.⁸⁸ The incidence of ARF in NZ has been reported already in the Background chapter. The most recent accurate total population rate is 3.4 per 100,000 per year.¹ This is derived from hospitalisation data from 1996 to 2005 and population data from the 1996 and 2001 censuses.¹

Prevalence of RHD

The prevalence of a condition is the number of existing cases of a disease in a given population at a point in time.⁸⁸ It is a measure of its burden on society and is dependent both on its incidence and duration.⁸⁸ The prevalence of ARF is not generally measured; because of its acute nature its occurrence tends to be expressed in terms of incidence. However the prevalence of its sequel RHD may be measured. RHD is not a notifiable disease in NZ and as much of it may be subclinical until advanced unfortunately true population prevalence is not known. A technical report by the WHO in 2005 on the burden of GAS diseases estimated the school age prevalence the Pacific and Indigenous Australia and NZ to be 3.5/1,000, although none of the studies used to derive this estimate were performed in NZ.³⁰ In 1983 a survey in Hamilton reported a prevalence of RHD in school age children of 6.5/1,000 for Māori and 0.9/100,000 for non Māori.¹⁹¹ The best recent estimate of prevalence in a high risk subpopulation in NZ was an echocardiogram screening study of 10 to 13 year olds in socio-economically deprived schools in South Auckland which revealed a prevalence of 24/1,000.^{5, 127} The overall prevalence in the general population would be expected to be much lower than these figures as it would include lower risk subgroups such as NZ Europeans.

Findings for question 2

In terms of preventable infectious diseases once the occurrence of the disease in the general population crosses a certain threshold, while contact tracing may be successful in detecting or preventing new disease, overall it will not be the most effective control strategy.^{66, 94} Other interventions such as population screening, increased primary prevention efforts or better identification and management of cases may be more appropriate and cost effective. This contact tracing threshold has not been precisely defined in the literature and may vary depending on the disease and the setting. Computational modelling has been developed by biomathematicians at Stanford University to estimate the disease prevalence above which screening is indicated over contact tracing, taking into account economic considerations. It has been applied to several infectious diseases including viral hepatitis, TB and STIs.^{94, 98} The estimated threshold prevalence for hepatitis B is 3%,⁹⁸ chlamydia is 2.6%,⁹⁷ HIV is 0.6%⁹⁴ and TB is 8%.⁹⁴

While the occurrence in a high risk subgroups in NZ might be considered relatively high in global terms, and on a par with some developing countries,⁴⁹ the incidence of ARF and prevalence of ARF are low in the overall population and certainly likely to be below the thresholds for the above diseases.

We can conclude that the overall occurrence of ARF and its sequel are low in the general NZ population. However, the caveat is that it is not possible to confidently state where the occurrence lies in relation to a threshold above whether other preventative strategies are warranted in favour of contact tracing. Determination of this threshold would require better knowledge about the cases expected to be prevented by ARF as function of contact tracing input, in relation to other control strategies followed by the application of mathematical modelling.

Conclusion

The incidence data presented here is derived from hospital admissions (sourced from the NMDS held by the NZHIS). While miscoding of admissions is possible these sources are generally considered relatively robust and large amounts of longitudinal data are available. The quality of prevalence data conversely is less robust due to the reasons outlined. Overall however there is a sufficient degree of quality observational research evidence to conclude that the occurrence of ARF is low in the general population of NZ. Therefore this criterion is met. However it must be noted that the threshold occurrence level above which contact tracing may not be indicated is not known and therefore it is unknown whether the noted occurrence level falls above or below this.

Criterion 5: <i>The occurrence of ARF is low in the general population</i>	
Criterion met:	Yes*
GRADE evidence level:	Moderate
Evidence gap:	No*
*Note that it is not known where this occurrence lies with respect to the contact tracing threshold for ARF	

3.3.3.6. Criterion 6: There should be a high degree of contact tracing sensitivity (a high proportion of contacts that are genuinely exposed to the case is identified, consent to and comply with management)

Research question

What proportion of contacts genuinely exposed to the case is identified, consent to and comply with management?

Findings

As I have already discussed my search found no published papers examining the process of ARF contact tracing *per se* and the grey literature is similarly unyielding. It is therefore not possible to answer this question.

The information needed to answer it includes the following:

- A clear definition of what constitutes a contact;
- The proportion of true contacts that are brought to the attention of contact tracing staff. Contacts are usually nominated by the case or their caregiver and this relies on their honesty, cooperation, memory and degree of acquaintance with the contacts;
- The proportion of those identified that are able to be located and then consent to and comply with the entire contact tracing process.

Conclusion

No information regarding this question is available. Therefore it can be concluded that there is insufficient evidence from the literature to fulfil this criterion and an evidence gap is established. Research in this area is desirable. The study outlined in chapter 4 attempts to address this gap.

Criterion 6: *There is a high degree of contact tracing sensitivity (a high proportion of true contacts are identified, consent to and comply with management)*

Criterion met: Insufficient evidence

GRADE evidence level: Nil

Evidence gap: Yes

3.3.3.7. Criterion 7: The contacts should be able to be identified, located and managed in a timely manner, ideally before onward infection transmission or secondary disease acquisition has occurred

Research questions

This criterion is divided into two research questions as follows:

- 1) What is the ideal timeframe within which ARF household contact tracing should be performed?
- 2) Is contact tracing performed within this timeframe in NZ?

Search terms

The search terms for this search were the same as those for Criterion 3.

Findings for question 1

Ideally, contact tracing should be able to be performed before onward GAS transmission has occurred, or if it already has then within such time that interventions can prevent the development of ARF. There are no specific studies examining this. While the question cannot be directly answered, drawing upon knowledge of the natural history of GAS infection and its progression to ARF, as has been discussed extensively in Criterion 3, enables some estimates to be made which are outlined below.

Onward transmission of pharyngeal GAS

Estimates of onward transmission of pharyngeal GAS within a household range between 13-28% following exposure to a symptomatic index case and possibly one third this rate if exposed to an asymptomatic index case over a variable period. A mathematical modelling study by Poku showed the risk after exposure to either an asymptomatic or symptomatic case was only 5-6% person per month.¹⁵⁸ This study has been discussed under Criterion 3 and appraised in Appendix 9. Despite the limitations of the study Poku's figure is the most useful available in the context of ARF contact tracing because one to two thirds of cases have asymptomatic GAS infection. Some studies showed that a significant degree of the spread occurred within 2 to 3 weeks,^{156, 160} whereas other demonstrated onward transmission was still possible many months later.⁹²

From the point of view of minimising the risk of onward transmission, contact tracing and management should ideally be carried out before a significant proportion of household contacts have been potentially infected. Using the model presented by Poku¹⁵⁸ in which the risk of onward transmission is assumed to be 5% per person per month then for a household containing 5 susceptible contacts then by 4 months all will have acquired GAS, each with a 30-50% chance of having true infection that in turn carries an approximate 0.3% risk of progression to ARF in an endemic setting. Assuming contact tracing is 100% effective, to prevent 75% of potential GAS acquisitions in a household of 5 susceptible contacts contact tracing would need to be completed within approximately 1 month after the initial acquisition in the index case, to avoid 50% within 2

months, 25% within 3 months and diminishing returns would occur after 4 months. Given an average latency period of 19 days the corresponding timeframe from the onset of ARF symptoms in the index case to prevent 75% of acquisitions is only 9 days. These timeframes would be different for different sized households.

It should be noted that a controlled study of GAS acquisitions in Egypt that has already been mentioned in Criterion 3 demonstrated that penicillin treatment within 8 days of recognition of persons who acquired GAS had a negligible effect on spread of the organism within the family.⁹¹

Completing contact management within 1 month or less is unlikely to be feasible for ARF contact tracing because of the latent period between GAS infection and ARF symptoms (1 to 5 weeks, average 19 days), along with the lag time associated in diagnosis, and it may still be difficult to complete within 2 to 3 months depending on the latent period and speed of diagnosis. On the other hand there may still be some value in contact tracing even weeks or months after the initial index case GAS infection because GAS may circulate for long periods. It is likely there will be diminishing returns however for late contact tracing, as the majority of spread may already have occurred and GAS tends to be less infectious when associated with chronic carriage. However, the possibility of “ping-pong” re-infections within households leading to prolonged presence of GAS within a household is also worth considering. This is a controversial concept that has been posited by some researchers¹⁵⁸ and discredited by others.¹⁹² It assumes inadequate immunity is acquired following initial acquisitions to prevent reacquisition.

Secondary ARF acquisition

The minimum time period between an index ARF case and a secondary case (following a secondary GAS infection) assumes exposure with immediate transmission and is therefore the minimum incubation period (1 day) plus the minimum latent period (approximately 1 week, although occasionally shorter periods can occur) equating to approximately 8 days. The maximum comparable period would be the maximum time from first exposure to acquisition plus the maximum incubation period (5 days) plus the maximum latent period (for indolent carditis or chorea this may be up to 6 months).¹⁴ In the absence of antibiotic treatment the longest time between first exposure to the index case and a contact acquiring secondary infection would be the duration of the infectious period which is approximately 3 weeks after the onset of the index case’s GAS infection (although possibly longer if carriage continues, but with less chance of transmission). Thus this total period equates to approximately 7 months (3 weeks plus 5 days plus 6 months).

However, to be of most benefit, contact tracing would need to occur in time to prevent the majority of secondary ARF cases. Antibiotic treatment within 9 days of the onset of the GAS infection has been demonstrated to be effective in preventing progression to ARF.¹⁷⁹ Thus, for the same household described above using Poku’s model¹⁵⁸ to prevent 75% of GAS acquisitions and their potential ARF progression then contact tracing would need to be completed within approximately 5 ½ weeks (1 month plus 9 days), to avoid 50% within 9 ½ weeks (2 months plus 9 days), 25% within 13 ½ weeks (3 months plus 9 days) and diminishing returns would occur after 4 months. Given an average latency

period of 19 days the corresponding timeframe from the onset of ARF symptoms in the index case to prevent 75% of acquisitions and their potential progression to ARF is just 18 days.

Findings for question 2

These are currently unknown as there are no published studies or relevant reports in the grey literature. The following chapter presenting findings from a contact tracing study in Auckland will aim to shed some light on this.

Conclusion

There is insufficient evidence to clearly define the optimal timeframes for ARF contact management. However, available evidence allows for some estimates to be made. In terms of preventing any onward transmission within a household ideally all the contacts would be managed within 1 month or less of the index case's initial GAS infection, which in most instances would be unrealistic given the time lag associated with the latent period and diagnosis. If onward transmission cannot be avoided then the next aim is to prevent secondary infections progressing to ARF. To prevent 75% of acquisitions with the potential for progression to ARF in a household of 5 susceptible contacts, contacts would need to be managed within 5 ½ weeks of the index case's initial GAS infection. There is no information about typical timeframes involved with ARF contact tracing in NZ. Thus an evidence gap is established.

Criterion 7: The contacts are able to be identified, located and managed in a timely manner, ideally before onward infection transmission or secondary disease acquisition has occurred

Criterion met: No

GRADE evidence level: Very low

Evidence gap: Yes

3.3.3.8. Criterion 8: There should be a high contact tracing positive predictive value

Research question

What is the positive predictive value of ARF contact tracing? (I.e. what proportion of ARF contacts has pharyngeal GAS infection?)

Search terms

The following terms were used both matched to MeSH and as key words:

Rheumatic fever; Group A streptococcus; Streptococcus pyogenes; Aetiology; Pathophysiology; Susceptibility; Immunity; Transmission/transmissibility; Contagious; Infectivity; Spread; Carrier/carriage; Incubation period; Latency/latent period; Reproductive number; Infectiousness/infectivity; Attack rate; Household; Family; Contact.

Findings

As I have already discussed there are no published papers looking specifically at the process of ARF contact tracing and the grey literature is similarly unyielding. It is therefore not possible to directly answer this question, particularly in respect to contact tracing the NZ context. However I have identified six studies specifically looking at the occurrence of pharyngeal GAS within ARF households which contribute valuable information towards this question. Unfortunately symptoms and streptococcal titres rises were not evaluated in the majority and thus the rate of true infections cannot be determined. The overall quality of the studies and applicability to the current context is poor. Further details can be found in Appendix 11. No relevant studies have been conducted in NZ.

A study in India in 1964 compared rates of pharyngeal GAS isolation in household contacts of recently diagnosed ARF patients with controls. The rate in contacts was 16% (10/62) and in controls was 24% (15/62).¹⁹³ Titres and symptoms were not measured. The overall quality of this study was poor due to a high risk of bias and random error.

A 1971 study of 21 ARF families demonstrated a pharyngeal GAS isolation rate of 19% in family contacts.¹⁹⁴ ASOTs were moderately increased in 16% of all the family contacts, while anti-DNase B titres were markedly elevated in 96%. The authors point out that recent skin infections may account for these findings. Symptoms were not evaluated.

In Chile from 1978 to 1982 throat swabs were performed on 98 cases of ARF and 360 family contacts (of 607) and the isolation rate in contacts was 7.8%, versus 4.1% in controls (no statistically significant difference).¹⁹⁵ Interestingly the rate in post streptococcal glomerulonephritis family contacts was higher at 13.9% ($p \leq 0.01$). The participation rate in ARF contacts was only 60% creating potential for bias. Again titres and symptoms were not assessed.

A 9 year prospective study of 294 children with ARF in Kuwait and 303 of their family contacts (1980-1989) found the rate of isolation of pharyngeal GAS in family contacts to be only 0.3%.¹⁹⁶ Streptococcal titres and symptoms were not assessed.

A study performed in Pennsylvania during the USA ARF resurgence between 1994 and 2003 identified 121 ARF cases.¹⁹⁷ Of the 147 family members tested pharyngeal GAS was isolated in 14%. Titres and symptoms were not assessed, but family contacts with positive swabs were offered antibiotic treatment.

An Egyptian study (1972-74) compared the isolation rate of pharyngeal GAS in families where there was a member with a history of previous ARF and those with no ARF members.⁹¹ The swabbing did not occur acutely after the index case was diagnosed. The prevalence in ARF families was 33.1% and in controls it was 19%. It is not known what proportion was symptomatic or had elevated titres.

Thus it appears that the rate of isolation of pharyngeal GAS from ARF household contacts ranges from 0.3% to 33.1%. What proportion of this represents carriage (which does not progress to ARF, although it may be mildly infectious to others) versus true infection is not certain. However if we extrapolate findings from Criterion 3 the true infection rate might be in the order of 30-50% of this, which translates to up to 0.1-16.5%. The true rate of infection is important to know as it correlates with the risk of developing ARF.

Conclusion

No direct information regarding this question is available. Therefore it can be concluded that there is insufficient evidence from the literature to fulfil this criterion and an evidence gap is established. Available evidence, relying on a degree of assumptions points towards an infection rate of up to 16.5%. Research in this area is desirable particularly in the NZ setting and ideally throat swabs should be used conjunction with serology to estimate true infection rates in contacts. The study that will be presented in chapter 4 will attempt to partially address this gap.

Criterion 8: *There is a high contact tracing positive predictive value*

Criterion met: Insufficient evidence

GRADE evidence level: Low, towards not meeting criterion

Evidence gap: Yes

3.3.3.9. Criterion 9: There should be a higher risk of infection and/or severe disease in contacts than in the general population (i.e. in the absence of contact tracing the occurrence of the infection and subsequent disease in contacts [secondary attack rate] should be higher than the occurrence in the general population) and the overall burden of secondary disease should be significant

Research questions

This criterion is divided into three research questions as follows:

- 1) Is the occurrence of pharyngeal GAS infection higher in ARF household contacts than in the general population?
- 2) Is the secondary attack rate of ARF higher in ARF household contacts than the incidence in the general population?
- 3) What is the overall burden of secondary disease?

Search terms

The following terms were used both matched to MeSH and as key words:

Rheumatic fever; Rheumatic heart disease; Streptococcus pyogenes; Group A streptococcus; Pharyngitis; Contact tracing; Contact; Contact examination; Contact screening; Household; Family; Secondary case; Secondary transmission; Secondary attack rate; Prevalence; Incidence; Occurrence; Acquisition.

Findings for question 1

As previously discussed occurrence can be represented by both prevalence and incidence. Where it refers to the incidence in contacts this is known as the secondary attack rate.

Occurrence of pharyngeal GAS in ARF household contacts compared with the general population

A smattering of studies were found that attempt to define the occurrence of pharyngeal GAS in ARF household contacts and some that also compare this with the occurrence in households without an individual with a history of ARF. Some of these have already been mentioned in Criterion 3.

Studies with no controls

Potter and colleagues compared the isolation rates of pharyngeal GAS in families of 21 patients with ARF with families of 44 patients with acute glomerulonephritis in Trinidad in 1971.¹⁹⁴ Family contacts of all ages had throat swabs performed within 2 to 3 weeks of the patient's admission to hospital. The isolation rate in ARF family members was 19%, while it was 25% for the glomerulonephritis group.

A similar study was performed by Majeed and colleagues in Kuwait over a 9 year period from 1980 to 1989.¹⁹⁶ Members of 62 ARF families and 56 acute glomerulonephritis families over the age of 2 years had throat swabs taken within 1 week of the index case's admission. Only 1 out of 303 ARF family contacts had a positive swab (0.3%). The isolation rate in glomerulonephritis contacts was 9.5%.

Martin and colleagues looked the rate of pharyngeal GAS isolation in family contact of those recently diagnosed with ARF from 1994 to 2003 in Pennsylvania.¹⁹⁷ Although the inclusion rate and ages of family members was not discussed 147 family members associated with 84 cases were swabbed and the GAS isolation rate was 14%.

Controlled studies

Quinn and Federspiel sought to compare the rates of pharyngeal GAS acquisitions over a 5 year period from 1958 to 1963 in 19 families in which there was a history of ARF or RHD, dubbed "rheumatic families", with 17 control families.¹⁵⁷ As it was not a requirement for the ARF episode in the rheumatic families to be recent the household members technically may not have qualified as contacts of an acute episode. Throat swabs were taken on all subjects 8 to 10 weekly and whenever a respiratory illness occurred in any family member. Streptococcal serology was also taken when a positive throat culture was observed or GAS pharyngitis was clinically suspected. Overall the rate of GAS isolation in rheumatic families was 6.1% versus 6.3% in control families. The incidence of GAS infection, as defined by either typical clinical features, a positive swab, a significant streptococcal titres rise or any combination of these, was 3.7 per 100 person months in rheumatic family contacts and 4.3 among controls. No statistical tests were applied to determine whether there was a difference between cases and controls, but the authors concluded that there was not. Thus GAS pharyngitis attack rates and GAS isolation rates were not demonstrated to be higher in rheumatic households.

Matanoski and colleagues also investigated the epidemiology of GAS infections in rheumatic and non-rheumatic families.^{155, 158, 165, 166} From 1957 to 1959 80 families were followed up within 6 weeks of a member developing ARF and compared with 84 families with a member with a more distant history of ARF and 179 control families. Throat cultures were routinely performed monthly and streptococcal titres 3 monthly (or monthly for 4 months in a family where a positive culture occurred) on those aged between 3 months and 16 years. GAS isolation rates were found to be similar in ARF families and controls, at 9.53 and 9.49 per 100 person-months respectively. Following the introduction of a new strain of GAS into a household secondary spread was assessed. The secondary attack rate within 8 to 10 weeks in the rheumatic fever families were 1.5 per 100-person exposures for positive throat swabs and 5.4 for two-fold titre rises. The comparable rates in control families were 2.9 and 5.3. Again no statistical tests were applied to determine whether there was a difference between cases and controls, but the authors concluded that there was not.

Collee and colleagues also compared 19 families were a member had a history of ARF with 10 control families in Baroda, India.¹⁹³ Their study was conducted from 1963 to 1964 and unlike Quinn and Federspiel they specified that the ARF episode be recent. Numbers were small, but 16% (10/62) of contacts in the rheumatic households had pharyngeal beta-haemolytic streptococci isolated versus 24% (15/62) in the control families. They also concurrently determined the prevalence of healthy school boys aged 9 to 19 years in 1964 and found a prevalence of 18%. They were not able to determine GAS rates but state that subsequent findings suggest almost all the beta-haemolytic streptococci were GAS. The findings of this study concur with those of Quinn and Federspiel.

Berrios and colleagues compared the pharyngeal GAS isolation rate in family contacts of ARF, acute glomerulonephritis and controls between 1978 and 1982 in Chile.¹⁹⁵ Throat swabs were taken as soon as the case was indentified presumably on family contacts of all ages. The rate in ARF family contacts was 7.8% versus 4.1% in controls, but this was not statistically significantly higher. The rate in glomerulonephritis contacts was 13.9%. Mean ASOTs were the same in ARF contacts and control contacts.

El Kholy and colleagues in 1980⁹¹ examined the prevalence and incidence of pharyngeal GAS in 43 suspected rheumatic and 108 non rheumatic households in a cluster randomised cross-over trial conducted over 2 years from 1972-74. Bimonthly swabs were taken for all subjects and the intervention household individuals were treated with IM BPG if positive for GAS. Rheumatic families were defined as those where a member was suspected of having RHD by a cardiologist, however a recent ARF episode was not a proviso. The prevalence of GAS isolation was 19% in untreated control families and similar in untreated rheumatic families. In each year of observation a similar percentage of members of untreated control and rheumatic families had GAS isolated at least once (73.4% versus 70.7%). Following the introduction of a new strain into a family the secondary attack rate in the untreated control families was 8.6% versus 11.4% in the suspected rheumatic families; the corresponding rate for rheumatic families where RHD was confirmed at a 5 year re-examination was 9.8%.

In general the quality of these studies was poor due to methodological flaws and lack of precision measures. The study by Berrios and colleagues was the only one to employ statistical tests to determine whether there was a difference in GAS occurrence between cases and controls and no difference was demonstrated in this study. The applicability of these studies to modern day NZ is likely to be poor.

NZ studies

Unfortunately there are no studies of pharyngeal GAS occurrence in ARF household contacts and controls, although this will be partially addressed by the study presented in the following chapter. A few studies have looked at background carriage rates in school children both in areas of low ARF endemicity (the South Island) and high endemicity (Wairoa, Waikato and South Auckland).

Lines and colleagues found a rate of 3.7% in 592 12 year old Auckland children in 1974.¹⁹⁸ A study of control programmes for Wairoa primary school children included 3 monthly throat culture survey of 944 children in 1976. The prevalence ranged from 7.4% in November to 16.1% in May.¹⁹⁹ A cross sectional survey of 789 Waikato school children aged 5 to 11 years attending five schools in 1977 revealed a comparatively high prevalence of pharyngeal GAS isolation of 35.5%,²⁰⁰ while a similar study in a secondary school in Wairoa in 1978 demonstrated a prevalence of 13.6%.²⁰¹

A longitudinal study of GAS acquisitions in 103 5 and 6 year olds at three Dunedin primary schools was performed over 27 months from 1987 to 1989.¹⁷⁸ They were swabbed on 9 occasions during this

period and overall 19.8% were positive for GAS. The prevalence at each testing period ranged from 9-27.1%. Fifty-eight per cent of subjects had GAS isolated on at least one occasion.

A follow up study was conducted in 1997 in which 290 Dunedin children from 10 primary schools had monthly throat swabs for 10 months.¹⁷⁶ During this period 41% had GAS isolated at least once and 28% were found to be chronic carriers (the same strain present over 2 months or more).

More recently in a 86,874 person-years Auckland primary and secondary school study running from 1998 to 2001 throat swabs were performed on all those presenting daily with sore throats or monthly on those with signs of pharyngitis on surveillance by clinical examination.²⁹ The overall GAS isolation rate was 7% and children had a 1 in 3 chance of it being detected per year. This rate is likely to exclude a proportion of those with asymptomatic carriage.

It is intriguing that the burden seems to be higher in Dunedin where ARF is rare, however this is likely to be attributable to strain differences with those of low “rheumatogenic” potential prevailing in Dunedin.¹⁷⁶

The conclusion for this question is that the occurrence of pharyngeal GAS is not higher in ARF household contacts than the background rate. This suggests that if a higher secondary attack rate is seen in these contacts it is due to increased individual susceptibility in the contacts, which may be genetic.

Findings for question 2

Secondary attack rate of ARF in ARF household contacts compared with the incidence in the general population

Secondary attack rate is defined as the number of cases of an infection that occur among contacts within the incubation period following exposure to a primary case in relation to the total number of exposed contacts.⁸

The secondary attack rate is defined as the number of cases attributable to an exposure to a primary case divided by the total number of exposed contacts.¹⁰⁵ The number of cases attributable to the primary case are those arising within one case onset serial interval from the primary case, where the serial interval is the time from clinical onset of ARF in the index case to clinical onset of ARF in the secondary case.¹⁰⁵ Therefore this is determined by when GAS transmission occurs in relation to onset of ARF symptoms in the index case, the incubation period of GAS infection in the secondary case and the latent period of ARF in the secondary case. The serial interval will have a minimum and a maximum and follow a frequency distribution between these extremes.¹⁰⁵ This was discussed in Criterion 7 in relation to the optimal timeframes in preventing onward transmission of GAS and the development of ARF.

The minimum serial interval would potentially be negative one, as if exposure and transmission of GAS occurred as soon as the index case became infectious and then the minimum incubation and latent periods prevailed in the secondary case, ARF could develop as early as just over a week after

initial exposure to GAS, which may in fact be before the index case develops ARF symptoms depending on the length of their own latent period. Conversely for the maximum serial interval we can make the assumption that transmission of GAS occurs towards the end of the maximal infectious period for GAS pharyngitis in the index case (approximately 3 weeks after infection, although lower risk transmission may occur beyond this), and that the index case develops their ARF symptoms after a minimal latent period of 1 week, and that this is followed by the maximum GAS pharyngitis incubation period of 5 days in the secondary case and then a prolonged latent period of 5 weeks, or 6 months if the secondary case presents first with chorea or indolent carditis. Thus the maximum serial interval is approximately 5 weeks (for classical ARF) or about 6 months for those presenting with isolated chorea or indolent carditis. In the latter cases it will be more difficult to directly attribute the ARF exposure to the index case as GAS exposure in the community could have occurred during this long interval. As pharyngeal GAS may potentially circulate in a household for some time (as discussed in Criterion 3) there also exists the risk of tertiary or quaternary ARF cases i.e. those who have caught GAS from another household member who had contracted GAS from the index case.

The sporadic incidence of ARF in the general population has been discussed in the Background chapter and in Criterion 1 and in NZ from 1996 to 2005 it is 3.4 per 100,000 per year.¹ If the maximum serial interval for ARF is assumed to be 6 months and thus the secondary attack rate in households is examined over a 6 month period then the background rate for comparison with the secondary household attack rate would be 1.7/100,000, although this may need to be adjusted for factors such as ethnicity and age.

Remarkably however a search reveals no recently published studies looking specifically for the secondary attack rate of ARF within households, and in particular there is no data pertaining to NZ. Hence it has been necessary to search published material from as far back as the 1920-40s to find any relevant articles. The articles found are observational studies, consisting of a mixture of cohort studies, cases series and case control trials from USA to investigate the familial occurrence of ARF/RHD. A table summarising these studies can be found in Appendix 12. The infectious nature of the aetiology was suspected at this time, but the causative organism not confirmed until the 1930s and Jones Criteria not established until 1944. Therefore the diagnostic criteria used in these studies are questionable by current standards. While they were performed almost a century ago in some ways this was an ideal period to study this aspect of ARF because its overall incidence was higher due to a combination of poorer environmental conditions and lack of use of penicillin for ARF and therefore familial patterns and attack rates were more readily observed. Unfortunately interpretation of these studies is limited though because of universal problems with non standardised diagnostic criteria for ARF/RHD, study design and reporting that is poor by today's standards and analysis that lacks precision. Additionally their generalisability to the present day context, whereby the incidence and prevalence is dramatically lower is somewhat questionable.

However these studies do consistently suggest clustering of ARF and RHD within families above that expected in unaffected families or controls or the background population, and that simultaneous episodes, or episodes occurring within several weeks of each other were frequently observed within a

household. In general during this study era which spanned about 1920-1940, there was a reasonable chance (ranging from 24-61%) that those families with child with a history of ARF or RHD also had multiple members similarly affected.

In 1922 St Lawrence published a prevalence study of 100 families comprising 480 family contacts of children with a cardiac condition.²⁰² ARF was found to occur in 10% of contacts and this was stated by the author to exceed the occurrence in the general population, however unfortunately he does not quantify it.

A case control study by Faulkner and White in 1924 demonstrated that families with a known member with a history of ARF, chorea or RHD had increased RR of 2.2 of having another member in the family similarly afflicted.²⁰³ Irvine-Jones in a case control study in 1933 echoed this with a the finding that the rate of secondary rheumatism in families where a member already had a history of rheumatism was almost twice as high as in families where no member had been previously diagnosed with rheumatism.²⁰⁴

In 1931 Paul and Salinger give a qualitative report of the relationship between the time of onset of cases of ARF in a household in a cohort study of 15 families.²⁰⁵ They conclude that primary or recurrent episodes of ARF are frequently accompanied by almost simultaneous or immediately subsequent episodes in other family members and that bouts tend to sweep through families in synchronous waves. In a prevalence study conducted from 1922 to 1932 Stroud and colleagues examined 148 families of children admitted with ARF and found that 34% had more than one member with RHD.²⁰⁶

A case control study by Read et al. in 1938 stated there was a relative increased in attack rate per person per year of 3.9 in siblings of families where at least one member had a history of ARF, versus those with no history of ARF, although the risk in the weeks or month following an acute episode was not evaluated.²⁰⁷ Rosenblum and Rosenblum in 1941 noted a RR increase of 2.5 for the incidence of RF cases in a family after contact with a family member with an acute episode of ARF compared with before, but again the time after the exposure for which the measurement was made was not stated.²⁰⁸

In respect to ARF episodes occurring within a family within quick succession (which would support a significant secondary attack rate), a number of the studies qualitatively make mention of its occurrence. Rosenblum and Rosenblum however quantify it further with 21% of the families they studied (only 19 in total however) having simultaneous attacks.²⁰⁸ In Irvine-Jone's case series of rheumatic families 34% of all rheumatic attacks in occurred within an 8 week period of following the index episode, giving a one third chance of attacks being clustered rather than sporadic.²⁰⁴

Anecdotally, there have been a number of clusters of ARF cases within one family reported to the Auckland Rheumatic Fever register since its inception (personal communication Professor Diana Lennon, Community Paediatrics, the University of Auckland, 2010).

While the findings of the historical studies above all lean towards an increased secondary attack rate for ARF in households during the weeks or months following an attack in an index case, in comparison with the background risk, none of the studies actually attempted to quantify this. This in combination with the design, methodology and precision problems already noted and the questionable generalisability of such historical findings to a modern day context means I conclude there is insufficient evidence to answer this research question.

Findings for question 3

The absolute number of secondary cases of ARF in household contacts is unknown; therefore the disease burden cannot be estimated.

Conclusion

There is good evidence that the risk of pharyngeal GAS infection is not higher in ARF household contacts than the background risk; however this has not been directly confirmed in the NZ setting. This observation does not necessarily preclude there being a higher secondary attack rate of ARF in these contacts than in the general population as there may be certain susceptibility factors at play. While a number of studies from the early 1900s suggest family members are at increased risk of ARF attacks these are of poor quality and not generalisable to the modern day NZ context. There is no available information on the numbers of secondary ARF cases in NZ. Therefore insufficient evidence exists to satisfy this criterion and an evidence gap is established. Research to determine the secondary attack rate in ARF households with and without contact tracing is suggested, as well as to determine the occurrence of GAS in ARF household contacts in comparison with controls in the NZ setting.

Criterion 9: *There is a higher risk of pharyngeal GAS infection and/or ARF in ARF household contacts than in the general population*

Criterion met:	Insufficient evidence
GRADE evidence level:	Nil-very low, towards not meeting criterion
Evidence gap:	Yes

3.3.3.10. Criterion 10: The rate of case detection should be greater than that achieved by expected by screening or presentations of individuals to healthcare, on the basis of development of symptoms

Research questions

This criterion is divided into two research questions as follows:

- 1) What is the ARF case finding rate with ARF household contact tracing?
- 2) What is the case finding rate through other methods including screening and patient self presentation to a health practitioner because of symptoms?

Findings for question 1

As discussed there are no studies of ARF contact tracing therefore the case detection rate amongst contacts is unknown. The study of contact tracing at Auckland presented in the following chapter will look at this.

Findings for question 2

Case finding by other methods refers to detection through self presentation of patients to a health practitioner because of symptoms (usually their GPs or emergency departments), or to detection via screening programmes.⁹⁴ Screening for the detection of subclinical RHD has been trialled in some areas of the North Island, however it remains in the research phase and its true case finding utility has yet to be defined.⁵ Therefore prior to the introduction of the contact tracing programme in NZ all case finding has relied on self presentation of patients to primary or secondary care. With this being the case then the reported incidence of ARF mainly reflects symptomatic presentations. Thus the rate of first episode of ARF case finding through symptomatic presentations to health practitioners in NZ is approximately 3.4 per 100,000 per year.¹ In Auckland the absolute number of cases diagnosed in this manner in 5 to 14 year olds alone is approximately 74 per year.²⁰⁹

Conclusion

It is not known what the rate of ARF case finding amongst contact traced individuals is in NZ, or internationally and how this relates to other methods of case detection. Therefore there is insufficient evidence to answer this question and an evidence gap is established. Theoretically because trained contact tracing staff should be on the alert for clinical features of ARF this could be expected to be a more sensitive method of detecting cases than waiting for those affected to self present to health practitioners. In reality this will be highly influenced by the risk of ARF amongst those contact traced versus the rest of the population, access to healthcare and the astuteness of health practitioners in making the diagnosis in both settings. It is not yet known whether screening, for example with echocardiograms, may have a role in case finding of those previously afflicted by ARF.

Criterion 10: The rate of case detection is greater than that expected to be found by screening or presentations of individuals to healthcare, on the basis of development of symptoms

Criterion met: Insufficient evidence

GRADE evidence level: Nil

Evidence gap: Yes

3.3.3.11. Criterion 11: There should be an effective treatment or intervention for contacts identified with the condition through contact tracing, with evidence that this early treatment or intervention leads to better disease outcomes and/or reduction in transmission than no or late treatment or intervention

Research question

Is there an effective treatment or intervention for ARF cases detected through contact tracing, with evidence that this leads to better disease outcomes and /or reduction in transmission of GAS than no or late intervention?

Search terms

The following terms were used both matched to MeSH and as key words.

Rheumatic fever; Rheumatic heart disease.

And each was combined with each of the terms below:

Recurrence; Prevention; Penicillin; Secondary prophylaxis.

Findings

While this question has not been specifically answered with respect to cases detected through contact tracing, there is a large body of evidence relating to the long-term management of those who have had an ARF episode. For cases detected through contact tracing the intervention includes the management of the acute episode itself and instigation of secondary penicillin prophylaxis to prevent recurrences.

The acute management entails hospitalisation, assessment of the extent of carditis, anti-inflammatories for arthritis and medical and/or surgical management of cardiac failure as indicated. Aside from cardiac failure interventions other treatment modalities have not been shown to alter outcomes, although they may provide symptomatic relief.^{14, 42} Theoretically early detection and treatment of those with ARF may reduce the chance of onward GAS transmission, however not all cases will still be infectious when diagnosed as a variable but significant proportion have negative throat swabs at presentation.²⁹ The potential reduction in transmission of GAS through contact tracing case finding has not been assessed.

The more important intervention is commencing secondary prophylaxis. This is defined as the continuous administration of antibiotics to prevent infection of the upper respiratory tract with GAS and the development of recurrent ARF.⁴² The rationale for this is that further episodes of GAS pharyngitis in these patients carry a high risk (25-75%) of an ARF recurrence and this recurrence is more likely to involve the heart than initial episodes, with the subsequent development of chronic RHD.^{6, 14} The efficacy of secondary prevention has been extensively reviewed, including in a Cochrane meta-analysis in 2002, by the New Zealand Guidelines for Rheumatic Fever in 2006 and in a WHO report on ARF control in 2005.^{2, 42, 63} Standard prophylaxis internationally and in NZ is with IM

BPG, usually given 4 weekly, although sometimes 3 weekly.⁴² In those with adequate adherence it has been demonstrated to reduce RHD severity and mortality.²¹⁰ It has in fact been associated with a regression of heart disease in 50-70% who adhere over a decade.²¹¹⁻²¹³ A Cochrane systematic review published in 2002 examined nine randomised and quasi-randomised studies and found that parenteral penicillin was associated with an 87-96% reduction in ARF recurrences and that IM penicillin was superior to oral preparations.⁶² In the NZ setting, a study of the failure rate of the secondary prophylaxis programme in Auckland (which covers 60% of NZ ARF registrations) is very low at 1.4 per 100 patient years, for which the actual penicillin failure rate is only 0.07 per 100 patient years.⁴⁴

Conclusion

There is robust evidence from systematic reviews of randomised trials that secondary penicillin prophylaxis administered to those diagnosed with ARF results in improved outcomes. It follows that any case detection occurring through contact tracing, that would otherwise not have occurred, will lead to interventions that result in better outcomes for that individual. There is insufficient evidence to ascertain whether a reduction in onward transmission of GAS would also be seen. Overall, there is sufficient evidence however to conclude that this criterion met.

Criterion 11: *There is be an effective treatment or intervention for contacts identified with the condition through contact tracing, with evidence that this early treatment or intervention leads to better disease outcomes and/or reduction in transmission than no or late treatment or intervention*

Criterion met: Yes*

GRADE evidence level: Moderate

Evidence gap: Partial*

*Insufficient evidence to ascertain whether reduction in GAS transmission

3.3.3.12. Criterion 12: There should be a suitable (i.e. simple, safe, precise, valid, and rapid) and acceptable test or clinical assessment (i.e. history or examination) available to detect the infection, infectious carriage, or immunity to the infection, that, in the event of infection, ideally can be administered *before* the person develops the condition

Research question

Is there a suitable and acceptable test or clinical assessment available to detect pharyngeal GAS infection or carriage, before the onset of ARF?

Search terms

The following terms were used both matched to MeSH and as key words and only information pertinent to NZ was considered:

Streptococcus pyogenes; Group A streptococcus Pharyngitis; Throat swab; Culture; Rapid antigen; Centor; Sensitivity; Specificity; Precision; Validity; Accuracy.

Findings

Tests or assessments available to detect pharyngeal GAS infection include clinical assessment with the use of an algorithm, bacterial throat swab culture, rapid antigen test and streptococcal serology. I will briefly discuss the availability and merits of each. However, as the test used for the contact tracing programme in NZ is bacterial throat swab, I will place more focus on this. Regarding the management of GAS sore throats, the NZ Guidelines for Rheumatic Fever conclude the throat swab culture is the optimal test for diagnosing GAS pharyngitis.⁷

Clinical assessment

Distinguishing GAS pharyngitis from the more commonly occurring viral pharyngitis is difficult because the signs and symptoms are similar.⁷⁶ For this reason, clinical prediction tools have been developed for evaluating whether a patient has GAS pharyngitis based on a combination of signs and symptoms. The most commonly used and most reliable of these is the modified Centor score (see Appendix 6).²¹⁴ The original Centor score, published in 1981, was designed for use in adults only.²¹⁵ Centor's criteria for predicting GAS pharyngitis included tonsillar exudates, tender anterior cervical lymphadenopathy or lymphadenitis, absence of cough and history of fever.²¹⁴ A revised version to use for both children and adults was developed by McIsaac and colleagues on behalf of the American Society of Internal Medicine (ASIM) in 2004 and is known as the modified Centor score and has been validated in clinical practice.²¹⁶ It incorporates the original Centor criteria as above with three age categories that are positively, neutrally or negatively scored according to risk. This system is employed in the NZ sore throat algorithm (see Appendix 7). However, while the modified Centor score may be applied rapidly, at best it has limited diagnostic value; the presence of 4 or more points has a PPV of just over 50% and in adults the specificity of a score of 3 or 4 points is only 43.8%.²¹⁶ Additionally, it was designed to diagnose acute GAS pharyngitis, not to identify those who may be infectious carriers.

Culture of bacterial throat swab

A cultured throat swab is the conventional method for diagnosing GAS pharyngitis in NZ⁷ and is also the preferred method for detecting pharyngeal GAS carriage. However, it cannot distinguish between acute infection and carriage.^{214, 217} Conventionally, a rayon-tipped swab is used to collect material from the tonsil and back of the throat. This is then placed in a tube of transport medium and sent to the laboratory, usually within 24 hours. Culture is performed on a 5% sheep blood agar plate and incubated for 24 to 48 hours.^{7, 76}

Throat swab cultures are simple, safe and relatively rapid (results are generally available within 48 to 72 hours after the swab is taken). As ARF can still be prevented if antibiotic treatment is administered within 9 days of the onset of GAS pharyngitis this test is considered to be sufficiently rapid.¹⁷⁹

Precision and validity must also be considered. Validity is the ability of a test to indicate which individuals have the disease and which do not and is expressed through the sensitivity, specificity and predictive values of a test.²¹⁸ Precision is synonymous with reproducibility and reliability and refers to the degree of similarity of results when a test is repeated on the same sample.²¹⁹ A single culture on sheep blood agar is considered 90-95% sensitive and 95-99% specific.²²⁰⁻²²² The PPV will depend on the prevalence in the population tested. The overall validity in this population therefore cannot be precisely determined as the prevalence is not known. Furthermore the validity of surface throat culture for determining infection as discussed is unlikely to be perfect as some from whom it is isolated may be carriers. A study of chronic tonsillitis found both the validity and precision of throat swabs to be low.²²³ However in chronic tonsillitis the surface organisms tend to be a poor reflection of the core organisms, as distinct from the acute situation. Reliability of throat cultures for acute GAS pharyngitis has been examined and the discordance rate for repeated culture is estimated to be less than 5% indicating high precision.²²⁰

Operator dependence must be borne in mind: if both tonsils and the pharynx are not touched by the swab or the tongue is touched this may invalidate the result.⁷

There are no published studies exploring the acceptability of throat swabs. While the test may be uncomfortable it is not generally painful and any adverse effects would be expected to be minimal. It is in common use in NZ.

Rapid antigen test

Rapid antigen tests detect GAS carbohydrate on a throat swab.⁷⁶ They are not currently available in NZ and are not considered to perform consistently enough to be recommended at this time.⁷

Depending on the setting and type of test sensitivities have ranged from 65-91% and specificities from 62-97%.²¹⁴ Like throat swab culture, they are unable to distinguish between infection and carriage.²¹⁷

Streptococcal serology

The most commonly used streptococcal antibody tests are ASOT and anti-deoxyribonuclease B (anti-DNase B) titre.²¹⁷ ASOT begins to rise 1 week after infection and peaks at 3 to 6 weeks, while anti-DNase B begins rising at 1 to 2 weeks and peaks after 6 to 8 weeks.²¹⁷ As they reflect past immunological

events serial tests may be required to assess for a rise and a delay of some weeks may be occur before an accurate result is available. Waiting this long is inappropriate in the context of contact tracing as onward transmission may occur, or ARF develop within this timeframe. Because levels may remain elevated for several months after infection and acute carriage often follows past infection they cannot always distinguish between the two.²¹⁷ However, they can be useful in distinguishing between acute infection and chronic carriage.²²⁴ Raised titres are not specific to the throat and may also be raised following skin infections.

Conclusion

Throat swab culture is a rapid and accurate test available for detecting the presence of pharyngeal GAS. Data on its acceptability and validity are not available although they are likely to be reasonably high. However, this test alone cannot distinguish between infection and carriage, with only the former carrying a risk of progression to ARF and the highest risk of onward transmission. Thus, the validity of the test alone (in the absence of clinical features) for infection will not be as high as it is for merely detecting of the presence of GAS. The gold standard test for infection would be culture of deep tonsillar or pharyngeal tissue but this is invasive and impractical. Although it may be useful in terms of quantifying risk of developing ARF in contacts to have a test that distinguishes between acute infection and chronic carriage, in the current contact tracing recommendations and programme, both states receive the same treatment so the distinction is not important. I conclude then that throat swab culture is a suitable test for contact tracing. However, its acceptability to contacts who may be asymptomatic is yet to be determined. The other tests or clinical prediction tools discussed are unsuitable because they lack validity or rapidity.

Criterion 12: *There is a suitable and acceptable test or clinical assessment to detect infection and/or infectious carriage of pharyngeal GAS condition that can be administered before the person develops ARF*

Criterion met: Insufficient evidence

GRADE evidence level: Moderate for rapidity, precision; nil/low for validity, acceptability (towards meeting criterion)

Evidence gap: Yes

3.3.3.13. Criterion 13: There should be an agreed policy on the further management options of individuals with a positive test/clinical assessment result

Research question

Is there an agreed policy on the further management options of individuals with positive GAS throat cultures?

Findings

Treatment options have already been discussed in the Background chapter. In NZ the two guidelines for contact tracing are found in the MoH Communicable Disease Control Manual 1998⁷⁰ and in the NHF New Zealand Guidelines for Rheumatic fever 2006.² Both documents recommend that those with positive throat swabs be treated with antibiotics.

The 1998 MoH Manual recommends simply treating with penicillin. However an unverified 2010 draft of the updated Communicable Disease Control Manual advises to refer to the NHF algorithm in the NHF Guidelines. These Guidelines state that individuals with positive throat cultures “should be offered antibiotic treatment” and elsewhere elaborates on the antibiotic treatment options. These can be found in Appendix 7 of this dissertation (the sore throat algorithm) and include 10 days of oral penicillin as first choice, or amoxicillin, stat IM BPG, or erythromycin for those allergic to penicillins.

Internationally US authorities that recommend contact management, including the AAP, IDSA and AHA, also recommend using oral penicillin for 10 days as first choice, and a variety of other drugs as second line options.

No mention is made of alternative management for those who decline antibiotics. Presumably they do not receive any increased surveillance for ARF.

Conclusion

There is good evidence that there is an agreed policy nationally on how to manage ARF household contacts with positive throat swabs. The unanimous recommendation is treatment with antibiotics, of which 10 days of oral penicillin is the first choice.

Criterion 13: *There should is an agreed policy on the management options of individuals with positive throat swab cultures*

Criterion met: Yes

GRADE evidence level: Moderate

Evidence gap: No

3.3.3.14. Criterion 14: There should be an effective treatment or intervention for contacts identified (through testing or clinical assessment) as having infection, or for contacts with no current clinical evidence of infection but deemed to be at significantly increased risk of infection because of their contact; and there should be with evidence that this early treatment or intervention leads to better outcomes and/or a reduction in transmission than no or late treatment or intervention

Research questions

This criterion is divided into three research questions as follows:

- 1) Does antibiotic treatment of those with pharyngeal GAS infection reduce the risk of ARF in comparison with no treatment?
- 2) Is there evidence that antibiotic treatment of contacts with GAS isolated on throat swabs is more effective at preventing ARF in those contacts than no antibiotic treatment?
- 3) Is there evidence that treatment of individuals with GAS isolated on throat swabs reduces transmission of GAS within a household?

Search terms

The following terms were used both matched to MeSH and as key words:

Rheumatic fever; Rheumatic heart disease; Antibiotics; Penicillin; Primary prevention; Sore throat; Group A streptococcus/streptococcus pyogenes; Transmission; Spread; Household; Family; Contact; Acquisition; Introduction.

Findings for question 1

There is good evidence from meta-analyses that antibiotic treatment of those with clinically suspected pharyngeal GAS infection significantly reduces the risk of ARF.

In 2005 Robertson and colleagues published a meta-analysis of the use of antibiotics for the primary prevention of ARF following a sore throat with or without confirmation by throat culture or rapid test.⁵⁴ They included two randomised and eight quasi-randomised controlled trials comparing the effectiveness of antibiotics versus no antibiotics for the prevention of ARF in patients presenting with a sore throat. In the quasi-randomised trials methods such as date of admission or military serial numbers were used for allocation. Allocation was not concealed in any of the studies. The trials were all conducted between 1950 and 1961 and in eight of them the subjects were young male adults living on US military bases. There were no studies conducted in NZ. The meta-analysis revealed a protective effect of all antibiotics of 68% (RR 0.32, 95% CI = 0.21-0.48) and an even more protective effect for the use of penicillin alone of 80% (RR 0.20, 95% CI = 0.11-0.36). The NNT to prevent one episode of ARF was 60 for penicillin.

These findings suggest antibiotic treatment can be effective for preventing ARF in a population with suspected GAS pharyngitis. However, one must be cautious in directly generalising these findings as these studies were performed during an era when guidelines for conducting trials were still evolving

and therefore by today's standards the methodological quality was generally poor. Furthermore they included only young adult males and were set in an environment where 70-90% of sore throats were due to GAS. The proportion of sore throats due to GAS and the secondary attack rate of ARF varies with the geographic location and age of subjects.⁵⁴

In 2006 Spinks and colleagues published a Cochrane systematic review of the use of antibiotics for sore throats. These researchers examined a range of outcomes including the incidence of nonsuppurative complications of GAS pharyngitis.⁶¹ Sixteen randomised or quasi-randomised placebo controlled trials that evaluated ARF as the outcome were included. As with Robertson et al.'s review, the majority of studies (n=10) were conducted from 1950 to 1961, and six were undertaken between 1996 and 2000. There were eight studies in common with Robertson et al.'s review. No studies were from NZ. Again not all the sore throats were confirmed as being caused by GAS. Overall, the use of antibiotics resulted in a 73% decrease in ARF (RR 0.27, 95% CI = 0.12 – 0.60). Most trials used penicillin. Confining the analysis to penicillin alone did not alter the result. None of the more recent group of studies showed an effect as no ARF cases occurred in either the antibiotic treated or control groups, a likely reflection of the relative rarity of ARF today compared with the 1950s.

The timing of antibiotic treatment is an important consideration. This was reviewed by Cantanzaro and colleagues in the 1950s.¹³⁰ They conducted a placebo controlled trial where young airmen admitted to hospital with exudative GAS pharyngitis were allocated to receiving IM penicillin on Day 9, 11 and 13 of the illness or sulfadiazine acutely or a control. Allocation methods were unclear but it presumably was not randomised. The attack rate of GAS after day 9 was lower in the penicillin treatment group, although prior to 9 days it was similar in all groups. However statistical significance was not calculated. They concluded that primary preventative treatment is effective even if started after a delay of up to 9 days after the onset of symptoms. As ARF rarely occurs within 9 days of the onset of pharyngitis the inference is that a delay in penicillin treatment of up to 9 days does not substantially increase the risk of developing ARF.⁷

Thus, two meta-analyses, independently performed, but with some content overlap, found comparable overwhelmingly positive results for the use of antibiotics in preventing ARF following sore throats. There is also weak evidence, based on one poorly designed study to suggest that this antibiotic treatment may be delayed by up to 9 days without forfeiting its protective effect. However as alluded to by Robertson et al. caution must be exercised in generalising these findings to the current context, for the reasons already outlined above.⁵⁴

Another factor to take into account is the comparable effectiveness of different types of antibiotics. IM long-acting penicillin is the only antibiotic that has been proven to prevent ARF in controlled studies.^{55, 225} However, because failure to eradicate GAS from the throat has been associated with failure to prevent ARF,²⁸ the surrogate microbiological endpoint of eradication of GAS from the throat has been used to assess oral antibiotic formulations.^{76, 226} Oral penicillin administered for 10 days has proven efficacy in this regard and once daily oral amoxicillin for 10 days has been shown to produce similar eradication rates.²²⁶ Oral treatment for 10 days is now regarded as the gold standard because shorter

courses of penicillin are less effective at eradicating GAS.^{227, 228} First generation cephalosporins and erythromycin are also effective and considered suitable for those intolerant of penicillins.⁷⁶ No instances of *in vitro* GAS resistance to penicillins have been reported, however bacteriological failure after treatment of acute infection occurs at a rate of approximately 10-25% for penicillin and 5-25% for orally administered erythromycin and cephalosporins.^{161, 229} A randomised controlled trial of 353 Auckland primary school children from 1996 to 1998 demonstrated a bacteriological failure rate of 12.7% and 11.9% for 10 day courses of once daily oral amoxycillin and twice daily oral penicillin V respectively at 12 to 16 days post treatment commencement.²²⁶ There was not a statistically significant difference between these.

Findings for question 2

As has been discussed there are no published studies of ARF household contact tracing, so this question has never been directly answered. It is tempting to assume that antibiotic treatment would be effective in light of the evidence from the two meta-analyses described above. However, there are a number of caveats to such an assumption. First, isolation of GAS on a throat swab may represent carriage in 50-70% of cases (as outlined in Criterion 3), not infection. As carriage alone is not associated with a risk of secondary nonsuppurative complications, treating those in this category is unnecessary in respect to this indication (although it may be effective in preventing transmission to others), and adverse effects also need to be considered. Determining true infection in a timely manner is not practical, however, and as possibly up to two thirds of GAS pharyngitis may be subclinical⁴³ a positive throat swab is probably a more sensitive test of GAS pharyngitis than the presence of a sore throat, although neither are highly specific. Secondly, the applicability of the findings of historical studies on very different populations to this setting is arguably limited.

Nonetheless, ARF household contacts in NZ generally fall into the high-risk demographic for developing ARF, and as a proportion of them with positive throat swabs will have true GAS infection a case could be made that treating these contacts with antibiotics should reduce their risk of ARF. However, the size of this effect and the NNT to prevent one episode of ARF is not known. It is important for decision making to know the size of the benefits of treatment versus the risk of adverse effects (such as allergy and antibiotic resistance, as discussed in Criterion 14).

Findings for question 3

In Criterion 3, studies examining household transmission of pharyngeal GAS were reviewed. Of these only two were identified that directly compared household spread with versus without the use of antibiotics. In a cluster randomised trial and a cross-over trial conducted over 2 years from 1972-74 using the same study population El Kholly and colleagues examined the prevalence, incidence and spread of pharyngeal GAS in households.⁹¹ One hundred and ten non "rheumatic" families and eight four suspected "rheumatic" families were drawn from Qalyub, Egypt, a semiurban town with a population of 30,000. Non-rheumatic families were those in which there were no children suspected of having RHD, while the rheumatic families had a child suspected of having RHD, although this was subsequently confirmed in only 30 of these 84 families. The rheumatic families in this study are not directly comparable with the ARF households in the contact tracing programme, as in the latter there

has been recent ARF and therefore GAS infection, whereas in the study families the ARF and its associated GAS infection may have been in the distant past. The selection criteria were not well described. In the cluster randomised trial 9 non rheumatic and 43 suspected rheumatic families were randomised to an intervention group (penicillin treatment) or a control group (no treatment) for 2 years. In the cross-over trial, 99 non rheumatic families were randomly assigned to 1 year in the penicillin treatment group or 1 year in the control group and then swapped over to the other condition for the second year.

Bimonthly swabs were taken for all subjects. Those individuals whose swabs grew GAS were treated with IM BPG if they were in the penicillin treatment group, regardless of symptoms, while those in control group received no treatment. The degree of potential contamination was unclear as it was not discussed whether the control group received penicillin for other intercurrent illnesses during study period.

BPG treatment appeared to result in a marked decrease in prevalence of pharyngeal GAS and a modest decrease in the number of GAS introductions into families. The prevalence of GAS in members of suspected rheumatic families where the index child had RHD confirmed at 5 year follow up was 33.1% in the untreated group and 9.0% in the treated group and the mean number of introductions in these families per year was 4.9 in the untreated group versus 3.5 in the treated group. Overall, combining non rheumatic and rheumatic families, penicillin treatment decreased the prevalence from 19.0% to 5.4% and the introductions into families from a mean 0.79 to 0.54 single introductions per person per year. This translated to a 23% reduction of single introductions in treated rheumatic families and 32% in treated non rheumatic families. While penicillin treatment did not reduce spread within non rheumatic families the secondary attack rate in all untreated suspected rheumatic families was 11.4% (9122 of 1,071) compared with 7.0% (55 of 784) in treated suspected rheumatic families. The comparable figures for rheumatic families where the index child was confirmed as having RHD at 5 year follow up were 9.8% (24 of 246) and 4.7% (14 of 295).

The statistical significance of these particular differences were not calculated and the numbers were much smaller than for the non rheumatic families where in fact the secondary attack rate was higher when treated (9.4%, 167 of 1,768) than untreated (8.6%, 206 of 2,396). Considering that the suspected rheumatic families are not directly comparable with ARF families as described above, it is not possible to draw a robust conclusion about whether penicillin treatment of those with pharyngeal GAS reliably reduces transmission within a household. As swabs and subsequent treatment were only performed bimonthly it is possible that more frequent intervention may have had a more positive effect on reducing household transmission.

The only other study identified in the literature review that examined the role of antibiotics in altering household spread of pharyngeal GAS was one conducted by Kikuta and colleagues. This was a prospective multicentre surveillance study carried out between 2005 and 2006 in Hokkaido, Japan.¹⁶⁹ In this study 1,241 children with GAS pharyngitis who attended private offices of paediatricians and hospitals were enrolled. Sixty were excluded due to non-compliance or incomplete follow up. GAS

pharyngitis was defined as the combination of clinically typical features and isolation of GAS on throat swabs. Index cases and their 1,440 siblings were non-randomly assigned the intervention group, where siblings received antibiotic prophylaxis and the control group where no prophylaxis was administered. This allocation was made arbitrarily by the treating doctor and there was no standardisation of the antibiotics used.

Approximately half of the 948 siblings in the intervention group received oral penicillin and the other half cephalosporins, mostly for a total of only 3 to 5 days. It was not clear whether there was a difference in treatment of the index case associated with the intervention and control siblings. The secondary attack rate of secondary GAS pharyngitis in siblings in the control group was 5.3% over 30 days, while in the antibiotic prophylaxis group it was 3.0% overall ($p = 0.04$). The incidence in siblings who received cephalosporins was 1.8% which was significantly less than the control group, but there was no significant difference in incidence in controls and the siblings who received penicillin (4.3%, $p = 0.5$). Furthermore the reduction in incidence associated with cephalosporins was only seen in those who received it for 5 days and the duration of this effect only lasted for 2 weeks; thereafter the secondary attack rate was similar in the control and prophylaxis groups.

It is difficult to generalise the findings of this study to ARF household contact tracing. First, it involved targeted treatment of GAS swab positive contacts rather than empirical prophylaxis. Second, it has a number of significant methodological flaws, such as not being-randomised, no concealment of intervention allocation, the use of non-standardised antibiotic prophylaxis and possible treatment of index cases in the control group. All are potential sources of bias and confounding. The preparations in standard use for contact tracing are longer courses of penicillin (10 days) and this was not studied. Given the low quality of the study and its poor generalisability to the current setting it is difficult to draw any meaningful conclusion from it about whether antibiotic prophylaxis has a benefit in reduction of spread.

Conclusion

There is evidence from meta-analyses of controlled trials that antibiotics for sore throats due to or presumed to be due to GAS are highly effective at preventing ARF. According to the GRADE approach these trials warrant “double downgrading” because of design limitations and the indirectness of the evidence to this population, but also receive “upgrading” because of the large magnitude of effect. Therefore overall the evidence they provide is moderate. In the context of ARF household contacts with GAS isolated on throat swab, antibiotic treatment is likely to have a protective effect against ARF for those with true GAS infection, although this has not been studied directly. Therefore, in considering whether there is an effective treatment likely to reduce the risk of progression to ARF in those infected with GAS there is sufficient evidence to satisfy this criterion. However, as the number of those with true infection and their absolute risk of developing ARF in this setting are not known, the size of this protective effect cannot be estimated. Further research is needed to quantify the number and proportion of contacts with GAS in NZ, and ideally to quantify the number and proportion with true infection, so potential benefits can be balanced against any potential adverse effects.

Whether treatment of contacts can reduce transmission of GAS to others at risk of ARF remains unproven in this setting and further research is recommended.⁶³

Criterion 14: *There is an effective treatment for contacts identified as having possible GAS pharyngitis and evidence that antibiotic treatment is more effective at preventing ARF or transmission of GAS than no antibiotic treatment*

Criterion met: Yes*

GRADE evidence level: Moderate

Evidence gap: Yes*

*Degree of benefit of ARF reduction has not been proven in this setting; reduction of GAS transmission has not been clearly demonstrated in this setting

3.3.3.15. Criterion 15: There should be agreed evidence based-policies covering which contacts should be offered treatment and the appropriate treatment to be offered

Research questions

This criterion is divided into two research questions as follows:

- 1) Are there evidence-based policies covering which contacts should be offered treatment?
- 2) Are there evidence-based policies on the appropriate treatment to offer?

Search terms

The following terms were used both matched to MeSH and as key words.

Rheumatic fever; Rheumatic heart disease.

And each was combined with each of the terms below:

Antibiotics; Penicillin; Primary prevention; Sore throat; Group A streptococcus/streptococcus pyogenes.

Findings

There are no published studies on ARF household contact tracing and therefore truly evidence based policies are not possible at this time. However, several guidelines recommend ARF household contact tracing (see Background chapter).

Findings question 1

The notable thing about the recommendations from several expert bodies in the USA and NZ is the variation in regard who to swab (and therefore who to treat). None of the North American guidelines place any age restrictions on which household contacts should be swabbed, whereas in NZ the MoH Guidelines recommend swabbing of all those under the age of 20 years and the NHF Guidelines swabbing of all those aged 3 years and over. All guidelines agree that swabs should be performed on both symptomatic and asymptomatic contacts falling within the particular age category and that antibiotic treatment should be given to all who have positive swabs.

While it is not explicitly stated within the guidelines it can be assumed that the age categories chosen are based on those having a higher risk of ARF. It is known that ARF rarely occurs below the age of 3 years or above the age of 45 years. In NZ 84% of case occur in those aged 5 to 24 years (1996-2005).¹ This is a reflection of the epidemiology of GAS, which peaks in incidence in the 5 to 15 year age group, although all age groups are susceptible.³⁵ However, treatment presumably has dual aims: that of preventing ARF in infected contacts and that of preventing transmission of pharyngeal GAS from one contact to another who may then be at risk of ARF. Therefore, a case could be made for restricting testing and treatment to those at highest risk of both GAS and ARF, such as those aged 5 to 15 years. Alternatively, it could be argued that treating all who are positive to eradicate GAS completely from the household and therefore protect those most at risk is equally sound. In

conclusion evidence-based policies on who to swab and treat are lacking because of an absence of relevant studies.

Findings question 2

As discussed in Criterion 14 there is evidence from two meta-analyses demonstrating the effectiveness of penicillin in preventing ARF following GAS pharyngitis. All the contact tracing guidelines discussed in the Background chapter recommend penicillin as the drug of choice and standard treatment is for 10 days duration. While the trials showing the protective effect against ARF were undertaken using IM long-acting penicillin, as outlined in Criterion 14, 10 days of oral penicillin or a number of other antibiotics including cephalosporins and macrolides are effective at eradication of GAS carriage, which is an outcome regarded as a proxy to ARF prevention. The guidelines all recommend drugs that have proven efficacy at eliminating GAS carriage. Therefore, there are evidence-based policies on the appropriate treatment to offer.

Conclusion

While policies on the appropriate treatment to use are evidence-based there is a lack of evidence around who should be tested and treated and therefore there is insufficient evidence to meet this criterion. An evidence gap exists around the latter point and therefore research is needed to define who should be treated in this context.

Criterion 15: *There are agreed evidence-based policies covering which contacts should be offered treatment and the appropriate treatment to be offered*

Criterion met:	Insufficient evidence*
GRADE evidence level:	Nil-low, towards meeting criterion
Evidence gap:	Yes*

*Evidence-based policies on appropriate treatment established, but insufficient evidence regarding who to treat

3.3.3.16. Criterion 16: There should be evidence of disease reduction in this setting; there should be evidence from high-quality randomised controlled trials that the contact tracing programme is effective in reducing mortality or morbidity from the condition

Research question

Is there evidence from high-quality randomised controlled trials that the contact tracing programme is effective in reducing mortality or morbidity from ARF and RHD?

Search terms:

The following terms were used both matched to MeSH and as key words:

Rheumatic fever ; Contact; Contact tracing; Contact examination; Contact screening; Household; Family; Secondary case; Secondary transmission; Secondary attack rate; Incidence.

Findings:

Studies of ARF household contact tracing

No randomised controlled trials examining the occurrence of or mortality from ARF/RHD for contact traced households versus non contact traced households were found.

In fact, there are no published studies at all exploring the effectiveness of ARF house contact tracing, let alone the effectiveness of household contact tracing on ARF/RHD occurrence. There are, however, two studies which investigate the effect on ARF rates (and GAS rates) of screening targeted populations such as families or communities for GAS and treating individuals with penicillin when positive.

Studies of the effect of swabbing and treating pharyngeal GAS in households on ARF incidence

EI Kholy and colleagues examined the prevalence and incidence of GAS in households in a cluster randomised cross-over trial of penicillin for GAS positive throat swabs conducted over 2 years from 1972-74 in Egypt.⁹¹ This has already been outlined in some detail in Criterion 15.⁹¹ To recapitulate 110 non rheumatic families and 84 suspected rheumatic families were randomised to the penicillin intervention group or control group. All had bimonthly throat swabs taken and all those in the intervention group were treated with IM penicillin if the throat swab grew GAS, whether symptomatic or not, while those in the control group received no treatment. The degree of potential contamination was unclear as it was not discussed whether the control group received antibiotics for other intercurrent illnesses during study period.

BPG treatment appeared to result in a decrease in prevalence of pharyngeal GAS and number of GAS introductions into families, but the researchers concluded that overall it did not decrease spread within families and there were no significant differences between rheumatic and non rheumatic families. No conclusion could be drawn regarding the effect of this intervention on the incidence of ARF as the study size was too small and only one case occurred (in a child in a non rheumatic family allocated to the control group).

Neilson and colleagues²³⁰ undertook an uncontrolled, non-randomised community intervention study in an isolated North Queensland Aboriginal community of 1250 people between 1985 and 1991. All 4-16 year olds had throat swabs three times a year. If positive for GAS they were treated with oral or IM penicillin or oral amoxicillin or erythromycin, and the family members also swabbed and treated if positive. The proportion of eligibles agreeing to participate in the intervention and the degree of compliance with it was not stated and intercurrent antibiotic treatment was not accounted for. ARF incidence was measured before and 6 years after the intervention (1985 and 1991). 89% of the whole population participated in 1985 survey however only 87% of children aged 4-16 years in 1991 survey potentially introducing bias. ARF incidence was reported to fall significantly from 4 per 1,000 per year pre-intervention to one case in the whole community over 6 years post-intervention (assuming the community population was stable at 1250 this equates to 0.13 per 1000 per year). However precision measures around the effect estimate were not reported and the reporting of the pre and post-intervention rates were not standardised for comparison.

The quality of both these studies was poor and in addition even if their findings were real it would be difficult to generalise them to the household contact tracing context. Both the interventions involved an ongoing programme of household swabbing and treatment at regular intervals, rather than the “one-off” swab and treat situation of current ARF household contact tracing programmes. In the Aboriginal community setting it is likely that the burden of GAS in the entire community would have been reduced as it was a whole of community trial. Conversely, when a household is contact traced in isolation the GAS burden may decrease in that household in the short term but GAS may readily be reintroduced from the outside the household in the community, for example from schools. Neither study examines the specific risk reduction of intervening in households with a recent case of ARF.

Conclusion

Thus there is insufficient published high-quality evidence showing that household ARF contact tracing reduces the occurrence of and mortality from ARF and RHD, and therefore an evidence gap is established. Further research is recommended to ascertain whether the secondary attack rate of ARF in contact traced households is significantly lower than in households where no contact tracing occurs. As ARF contact tracing is already recommended and well established in NZ it may be unethical to perform a study in NZ where some households are randomised to not receiving it. Therefore such research may need to come from countries where ARF is relatively common but contact tracing is not currently practiced. Another alternative is mathematical disease modelling which overcomes problems with ethics and the time, logistics and money involved in performing such a study, however relies on assumptions that may not be true in reality.

Criterion 16: *Evidence of disease reduction in this setting: There is evidence from high-quality randomised controlled trials that the contact tracing programme is effective in reducing mortality or morbidity from the ARF/RHD*

Criterion met: Insufficient evidence

GRADE evidence level: Nil

Evidence gap: Yes

3.3.3.17. Criterion 17: There should be evidence that the complete contact tracing programme (tests, treatment, interventions) is clinically, socially, culturally and ethically acceptable to health professionals and the public.

Research question

Is the contact tracing programme clinically, socially and ethically acceptable to health professionals and the public?

Findings

As I have already discussed there are no published papers looking at the process of ARF contact tracing *per se* and the grey literature is similarly unyielding. It is therefore not possible to answer this question.

The information needed to answer it includes the following:

Public:

- Is throat swabbing acceptable?
- Is antibiotic treatment acceptable?
- Are all other aspects of the contact tracing process and programme acceptable?

Health professionals:

- Is throat swabbing acceptable?
- Is antibiotic treatment acceptable?
- Are all other aspects of the contact tracing process and programme acceptable?

These questions would best be answered by surveys or qualitative studies (key informant interviews, focus groups etc) of previous contacts or general public selected from a population that contacts are likely to come from, and of health professionals involved or likely to be involved in the programme.

Anecdotally, PHNs in Auckland have observed poor acceptance of swabbing by contacts.

Conclusion

There is insufficient evidence to ascertain whether this criterion has is met or not and an evidence gap is established. Research is recommended.

Criterion 17: *There is evidence that the complete contact tracing programme is clinically, socially, culturally and ethically acceptable to health professionals and the public*

Criterion met: Insufficient evidence

GRADE evidence level: Nil

Evidence gap: Yes

3.3.3.18. Criterion 18: The benefit from the contact tracing programme should outweigh the physical and psychological harm (caused by tests, treatment, interventions)

Research question

Does the benefit from the contact tracing programme outweigh the physical and psychological harm?

Findings

As I have already discussed there are no published papers looking at the process of ARF contact tracing *per se* and the grey literature is similarly unyielding. It is therefore not possible to answer this question.

The information needed to answer it includes the following:

- 1) What benefits are derived from the programme?
 - Physical: Is there a reduction in the occurrence or burden of ARF/RHD?
 - Psychological: do cases, contacts and their families' psychological benefit from public health input and education?
- 2) What physical or psychological harm is associated with the programme?
 - Physical: what is the rate of adverse effects from antibiotic treatment?
 - Psychological: what is the psychological impact of phone calls and home visits by a PHN, having throat swabs taken and antibiotics administered (in some cases IM)?

The physical aspect of the first question can be answered as outlined for Criterion 16. Both psychological issues can be addressed by surveys or qualitative studies. Adverse effects of penicillins principally include allergic reactions, gastrointestinal upset and potential promotion of antibiotic resistance.^{231, 232} Internationally the rate of allergic reactions to IM BPG given for secondary prophylaxis is reported as 3.2% with a rate of 0.2% for anaphylaxis.^{233, 234} Erythromycin, which is used in lieu of penicillin when allergy exists, is also associated with gastrointestinal upset and has a large number of drug interactions. The rate of adverse effects from antibiotics in this context can be addressed by surveys/audits of contact tracing practice. The studyA case-contact study of ARF household contact tracing at Auckland Regional Public Health Service, 2008-2009presented in the following chapter will address this in part.

Conclusion

There is insufficient evidence to ascertain whether this criterion has is met or not and an evidence gap is established. Research is recommended.

Criterion 18: *The benefit from the ARF contact tracing programme outweighs the physical and psychological harm*

Criterion met: Insufficient evidence

GRADE evidence level: Nil

Evidence gap: Yes

3.3.3.19. Criterion 19: The costs of the contact tracing programme should be balanced against the benefits

Research question

Are the costs of the contact tracing programme outweighed by the benefits?

Findings

As I have already discussed there are no published papers looking at the process of ARF contact tracing, in particular in regard to costs and benefits and the grey literature is similarly unyielding. It is therefore not possible to answer this question.

The information needed to answer this question is that need to perform a cost benefit analysis and includes the following:

1) What is the opportunity cost of the contact tracing programme?

This includes money, time and resources expended on testing, treatment, administration, training and quality assurance. Although there are no published studies an internal audit of resource expenditure associated with ARF contact tracing during 2009 was carried out at ARPHS in 2010 by a public health registrar.¹⁰ It was designed as a rough analysis rather than a formal account of exact costs. The information was derived from key informant interviews that provided time estimates of work load. The staff time associated with contact tracing a “typical” case comprised over 12 hours of combined PHN, doctor and clerical time. The bulk of this was PHN time spent locating and managing contacts. Multiple visits to often more than one address were required. Given the number of cases seen annually (approximately 60) the total costs of staff time alone for 2009 amounted to over \$81,000 (\$1,360 per case). The set up costs associated with the programme were not assessed and the costs of resources such as throat swabs and antibiotics were excluded from this total. Throat swab processing was costed at \$12.45 per swab (a total of approximately \$4,000 for the entire period) while antibiotics were \$3 per course (amounting to a total of \$100). Factoring in these additional resources the total cost of running the established programme was approximately \$85,000. However a significant (up to 50%) under-notification rate is suspected in Auckland on the basis of hospital admission data. Measures are being taken to rectify this and therefore future costs of contact tracing could be expected to rise on the basis of volume. Subjective comments from PHNs were that ARF contact tracing was more intensive than most other communicable diseases and on a par with meningococcal disease.

2) What benefits are derived from the programme in monetary terms?

This question can be addressed first as outlined in Criterion 18 by defining the health benefits of the programme. This would then need to be converted into monetary terms. Therefore a quantification of the number of cases of ARF prevented per year by contact tracing would be useful so the costs associated with managing this number of cases could be calculated and compared with the costs of running the programme. An estimate of ARF and RHD hospital inpatient and outpatient related costs

was carried out in 1991.⁴ An uncomplicated case of ARF was projected to cost \$NZ19,226 in 1991 dollars, while a complicated case was conservatively estimated at \$NZ62,727. Updating these figures to today's context by accounting for inflation gives costs of \$NZ28,749 and \$NZ93,798 respectively.²³⁵

Conclusion

There is insufficient evidence to ascertain whether this criterion has is met or not and an evidence gap is established. Research is recommended to facilitate a cost benefit analysis being performed.

Criterion 19: *The benefit from the contact tracing programme is balanced against the costs*

Criterion met: Insufficient evidence

GRADE evidence level: Nil

Evidence gap: Yes

3.3.3.20. Criterion 20: There should be a plan for managing and monitoring the contact tracing programme and an agreed set of quality assurance standards

Research question

Is there a plan for managing and monitoring the ARF contact tracing programme in NZ and an agreed set of quality assurance standards?

Findings

As I have already discussed there are no published studies evaluating ARF contact tracing in NZ. Any national monitoring and quality assurance plans would be likely to be referenced in the NZ MoH Communicable Disease Control Manual⁷⁰ or the NHF NZ Guidelines for Rheumatic Fever.⁴² While the latter recommends monitoring the annualised rates of ARF in school aged children there is no specific mention in either of quality assurance and monitoring of contact tracing.²⁶ Monitoring and quality standards are important in terms of ensuring that many of the proposed ideal contact tracing programme criteria presented here are examined.

Factors that warrant managing and monitoring include:

- The occurrence (incidence and prevalence) of ARF and RHD, as if it rises above the contact tracing threshold then the indication for contact tracing would need reviewing^{66, 94, 96-99}
- The numbers of cases and contacts involved
- The under-notification rate of cases, which may be ascertained by comparing notifications to PHUs with hospital admission data or ARF secondary prophylaxis register data (a significant under-notification rate is likely to undermine contact tracing programme effectiveness)
- The proportion of contacts who are not followed up due to refusal or inability to locate them (the contact tracing sensitivity)^{109, 110}
- The proportion of contacts requiring treatment for positive throat swabs (the PPV)^{109, 110}
- Treatment consent and compliance rates and reported adverse effects^{99, 108}
- Timeframes involved with the process of contact tracing^{12, 66, 109}
- The secondary attack rate of ARF amongst contacts
- Contact tracing programme resource utilisation including costs.

Quality assurance standards should define the following:

- Ideal timeframes for completing the various stages of contact tracing
- Minimum acceptable contact tracing sensitivity
- Procedures for dealing with adverse treatment effects.

Conclusion

No plan for managing, monitoring, evaluation or provision of quality assurance exists in NZ for the contact tracing programme. Therefore this criterion is not fulfilled. It is recommended that there be national implementation of such measures.

Criterion 20: *There is a plan for managing and monitoring the ARF contact tracing programme and an agreed set of quality assurance standards*

Criterion met: No

GRADE evidence level: Not applicable

Evidence gap: No

3.3.3.21. Criterion 21: Adequate resources (staffing and facilities for testing, treatment and programme management) should be available prior to the commencement of the contact tracing programme

Research question

Are adequate resources available for ARF contact tracing in NZ?

Findings

This question has two components: the resources required to carry out the contact tracing programme and their availability.

No published papers were found that examine the process of ARF contact tracing. It is therefore not possible to answer this question based on published evidence.

To address the question I have referred to my experience with the implementation of the ARF contact tracing programme at ARPHS. When setting up the contact tracing programme in 2008 there was very little information available to guide resource needs and much has been learnt through experience. An internal audit of resource utilisation for the 2009 calendar year, which has been referred to several times already in this dissertation, provided an estimate of staff time involved, throat swabs used and antibiotic treatment courses administered.¹⁰ The conclusion from this audit was that resource requirements were high. Due to fiscal constraints no extra budget for staffing or other resources was able to be allocated at the time of programme implementation and thus an attempt was made to manage with existing resources. The impact 18 months later has been that nursing staff in particular have found it extremely difficult to absorb this into their existing workload. The most time consuming factor has been tracing contacts for swabbing. As a result, a further review of the programme was undertaken and limits were set on the time spent attempting to locate and swab contacts.

In short, in the Auckland region, staffing for such a high volume resource intensive programme is an issue.

As ARPHS follows up approximately 60% of NZ's initial ARF cases,⁴⁴ the workload is disproportionately higher so simply extrapolating these observations to other regions could be misleading. As can be seen from

Table 2-3 in the Background chapter most other regions have a far lower volume of cases annually and therefore resources are lower and may have been met.

The experience of ARPHS suggests that a resource gap exists in the Auckland region. Overall, it is not possible to conclude whether adequate resources are available to meet the needs of ARF contact tracing in other parts of NZ. Research is needed to scope the requirements and whether they are met.

Conclusion

There is insufficient evidence to ascertain whether this criterion has is met or not and an evidence gap is established. Research is recommended to facilitate a cost benefit analysis being performed. The study presented in the following chapter will provide an idea of the volumes of contacts to trace and the number requiring treatment in the Auckland region.

Criterion 21: *Adequate resources were available prior to the commencement of the ARF contact tracing programme*

Criterion met:	Insufficient evidence
GRADE evidence level:	Low, pointing towards criterion not being met
Evidence gap:	Yes

3.3.3.22. Criterion 22: Evidence-based information, explaining the consequences of the contact tracing interventions (testing, treatment or other intervention) should be made available to contacts to assist them in making an informed choice

Research question

Is evidence based information explaining the consequences of the contact tracing intervention available for contacts to assist them in making an informed choice?

Findings

As discussed there are no published studies on ARF contact tracing. I am aware however of the practices that occur at ARPHS where 60% of ARF cases occur because of my experience working there.⁴⁴ Contacts or their caregivers are provided with written material explaining the process and rationale for contact tracing. As has been outlined in the criteria visited thus far robust evidence to support all aspects of ARF contact tracing is lacking, however the information provided to contacts at ARPHS is based on the best evidence or expert recommendations available currently with informed choice as the goal. Verbal consent is gained before throat swabs are taken and written consent is obtained if parenteral penicillin is administered. When antibiotics are dispensed or administered verbal and written instructions for how and why to take them are provided. In addition general messages about sore throat management and ARF prevention are given in both verbal and written forms. It is likely that similar processes are observed at other PHUs as the provision of evidence based information and informed choice are considered standard public health practice in NZ.

Conclusion

Evidence informed material is provided to ARF household contacts in Auckland's largest PHU and it is likely that this also occurs in other PHUs involved in ARF contact tracing. This criterion is therefore met.

Criterion 22: Evidence-based information, explaining the consequences of ARF contact tracing interventions is made available to contacts to assist them in making an informed choice

Criterion met: Yes

GRADE evidence level: Moderate

Evidence gap: No

3.3.3.23. Criterion 23: Public pressure for widening the eligibility criteria for contact tracing should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

Research question

Are the eligibility parameters for ARF contact tracing evidence-based, where eligibility parameters refer to who qualifies as a contact and the timeframes involved?

Findings

As I have already discussed no published papers were identified that directly examine ARF contact tracing. However, a number of contact tracing guidelines exist (these are discussed in the Background chapter).

There are three American professional clinical bodies - the AHA, AAP and IDSA - that recommend ARF contact tracing, although they do not specifically refer to the term "contact tracing". The only stated eligibility parameter for swabbing and treatment given by all of them is that the person must be a household contact of an individual with ARF.²¹⁷ Such individuals qualify whether symptomatic or asymptomatic. No other parameters are specified, in particular with respect to timeframes or age restrictions. These recommendations are made on the basis of expert opinion which stems from studies demonstrating a high degree of GAS transmission within a household, with up to 25% of asymptomatic household members harbouring GAS (personal communications, Edward L. Kaplan, M.D., Department of Pediatrics, University of Minnesota Medical School, 2010; Michael A. Gerber, M.D., Cincinnati Children's Hospital Medical Center, Division of Infectious Diseases, 2010).¹⁶⁴

On the other hand, NZ guidelines provide more explicit eligibility parameters. However, there is a degree of inconsistency between them. While contacts are defined by both the MoH and NHF guidelines as those who had household contact with the ARF patient in the month leading up to the development of their ARF symptoms, the MoH specifies that all those under the age of 20 years qualify,⁷⁰ whereas the NZ Guidelines for Rheumatic Fever include all those over the age of 3 years.² Neither guideline provides a rationale for the age specification.

The various PHUs throughout the North Island of NZ each have their own protocols that align with either one or the other of these guidelines. In Auckland, people between the ages of 3 to 45 years are eligible. The rationale for this age range is that ARF is very rare outside of these age groups.²³⁶

With respect to contact tracing timeframes following the onset of ARF in the index case, neither the MoH nor NHF guidelines mention an outer limit. Operationally, PHUS are divided, with three ceasing to follow up after a delay of 1 to 3 months and the remainder having no cut off. Rationales for both are described in the Background chapter, but there is no clear evidence to support one over the other.

Thus, there is currently significant variability in eligibility parameters observed in different ARF household contact tracing guidelines and programmes in NZ. No robust scientific backing is available to specify exactly who should qualify for contact tracing and when.

Conclusion

There is insufficient evidence to justify eligibility parameters for ARF contact tracing at this time. Research is recommended to define which contacts are at highest risk and therefore to be targeted along with the optimal timeframes for contact tracing. The study presented in the following chapter aims to partially address this gap by examining risk factors for GAS acquisition in contacts.

Criterion 23: *The eligibility parameters for ARF contact tracing scientifically justifiable to the public*

Criterion met:	No
GRADE evidence level:	Not applicable
Evidence gap:	Yes

3.3.3.24. Summary of contact tracing programme criteria as applied to ARF in NZ

The Table 3-4 below summarises the findings from this part of the Literature Review. It can be seen that 7 of the criteria have been fulfilled according to the GRADE approach, while 2 are definitely not met and in the remaining majority (14) there is insufficient evidence available to appraise whether each criterion can be met or not. In summary there is insufficient evidence to currently conclude whether the NZ ARF contact tracing programme fulfils the criteria of an ideal contact tracing programme according to the methods I have described. The following chapter presenting a case-contact study of contact tracing in Auckland aims to contribute further evidence towards this. A reappraisal based on what this shows will be made in the Discussion and Conclusions chapter where I will weigh the findings against the limitations of the approach taken to draw an overall conclusion as to whether ARF contact tracing should be recommended in NZ.

Table 3-4. Summary of whether ideal contact tracing criteria are met for ARF on the basis of the literature review

	Meets criterion	If insufficient evidence to meet criterion, direction that evidence is leaning	GRADE evidence level	Evidence gap	If evidence gap, suggested research	Effectiveness or appropriateness or feasibility
Condition:						
1.Serious and of public health importance	Yes		Moderate	No		Appropriateness
2.Infectious cause, communicable from person, vector or environment to person	Yes		Moderate	No		Effectiveness
3.The natural history of the condition is known from latent to declared disease	Yes ^a		Moderate	Partial ^a	Quantify infectious period and subclinical GAS pharyngitis and ARF	Effectiveness
4. The proportion of cases with the condition that are not promptly diagnosed should be low	Insufficient evidence	Towards not meeting criterion	Low	Yes	Quantify subclinical disease, access to healthcare for those with ARF/RHD and clinician's recognition of ARF	Effectiveness
5.The occurrence of the condition is low in the general population	Yes ^b		Moderate ^b	No		Effectiveness
Contacts:						
6. There is a high degree of contact tracing sensitivity	Insufficient evidence	Unknown	Nil	Yes	Observational case series/audit of contact tracing in NZ	Effectiveness, appropriateness, feasibility
7.Contacts can be reached in a timely manner, before onward transmission, or disease development	Insufficient evidence	Towards not meeting criterion	Very low	Yes	Observational case series/audit of contact tracing practice in NZ. Better quantification of timeframes involved in onward spread of GAS within households	Effectiveness, appropriateness, feasibility
8.There should be a high PPV	Insufficient evidence	Towards not meeting criterion	Low	Yes	Research GAS pharyngitis rate in contacts in NZ	Effectiveness
9. There should be a higher risk of infection and/or severe disease in contacts than in the general population	Insufficient evidence	Towards not meeting criterion	Nil-very low	Yes	Determine secondary attack rate of GAS pharyngitis and ARF in ARF household contacts versus controls, and then ideally compare this with	Effectiveness

^a Gap in evidence regarding duration of pharyngeal GAS infectiousness, extent of subclinical GAS pharyngitis and ARF

^b It is not known where this occurrence lies with respect to the contact tracing threshold for ARF

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					and without contact tracing	
Intervention:						
Condition (ARF) case finding:						
10. The rate of case detection should be greater than that expected to be found by screening or by presentations of individuals to healthcare on the basis of development of symptoms	Insufficient evidence	Unknown	Nil	Yes	Study of case finding rate in contact tracing in NZ	Effectiveness
11. Intervention for cases found leads to better disease outcome for case and/or reduction in transmission	Yes ^c		Moderate	Partial ^e	Ascertain whether case finding makes an impact on GAS transmission	Effectiveness
Condition (ARF) case prevention: Test/clinical assessment:						
12. There should be a suitable (i.e. simple, safe, precise, accurate, valid, rapid) and acceptable test or clinical assessment (i.e. history or examination) available to detect the infection, infectious carriage or immunity to the infection that in the case of infection ideally can be administered <i>before</i> the person develops the condition	Insufficient evidence	Towards meeting criterion	Low	Yes	Study throat swab acceptability, precision, validity	Effectiveness, appropriateness, feasibility
13. There is an agreed policy on the further diagnostic investigation and treatment options of individuals with a positive test/clinical assessment result	Yes		Moderate	No		Effectiveness, appropriateness, feasibility
Condition (ARF) case prevention: Other interventions:						
14. Effective treatment or intervention for contacts identified through testing or clinical assessment as having infection (GAS), or for contacts with no current clinical evidence of infection but deemed to be at significantly increased risk of infection because of their contact; and there should be evidence that early intervention/treatment leads to better outcomes than no or late treatment/intervention	Yes ^d		High	Partial ^d	Quantify the number and proportion of contacts with GAS in NZ, and ideally to quantify the number and proportion with true infection, so potential benefits can be balanced against any potential adverse effects. Ascertain whether treatment of contacts reduces transmission of GAS.	Effectiveness

^c Insufficient evidence to ascertain whether reduction in GAS transmission

^d Degree of benefit of ARF reduction has not been proven in this setting; reduction of GAS transmission has not been clearly demonstrated in this setting

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15. Evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered	Insufficient evidence ^e	Towards meeting criterion	Nil-low	Partial ^e	Define who to test and treat	Effectiveness, appropriateness, feasibility
The programme:						
16. Evidence of disease (ARF/RHD) reduction: There should be evidence from high-quality randomised controlled trials that the contact tracing programme is effective in reducing mortality or morbidity from the condition	Insufficient evidence	Unknown	Nil	Yes	Controlled trial or mathematical disease modelling to determine secondary attack rate of ARF in contact traced versus not contact traced households	Effectiveness
17. The complete contact tracing programme (test, diagnostic procedures, treatment/intervention) is clinically, socially, culturally and ethically acceptable to health professionals and the public	Insufficient evidence	Unknown	Nil	Yes	Survey, qualitative: focus groups, key informant interviews	Appropriateness
18. The benefit from the contact tracing programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)	Insufficient evidence	Unknown	Nil	Yes	Surveys, audits, qualitative studies. ARF reduction outcome studies.	Effectiveness, appropriateness
19. The costs should be balanced against the benefits	Insufficient evidence	Unknown	Nil	Yes	Cost benefit analysis	Feasibility
20. There should be a plan for managing and monitoring the contact tracing programme and an agreed set of quality assurance standards	No		Not applicable	No		Effectiveness, appropriateness, feasibility,
21. Adequate staffing and facilities for testing, diagnosis, treatment, and programme management should be available prior to the commencement of the contact tracing programme	Insufficient evidence	Observation evidence in Auckland pointing towards criterion not being met	Low	Yes	Resource allocation audits	Feasibility
22. Evidence-based information, explaining the consequences of the contact tracing intervention should be made available to contacts to assist them in making an informed choice	Yes		Moderate	No		Effectiveness, appropriateness
23. Public pressure for widening the eligibility criteria for contact tracing should be anticipated. Decisions about these parameters should be scientifically justifiable to the public	No	Unknown	Not applicable	Yes	Research regarding who to target (those at highest risk) and optimal timeframes	Effectiveness, appropriateness

^e Evidence-based policies on appropriate treatment established, but insufficient evidence regarding who to treat

Chapter 4. A case-contact study of ARF household contact tracing at Auckland Regional Public Health Service, 2008-2009

4.1. Introduction

As has been noted, household contact tracing for ARF has been practised in the USA for more than 30 years and is also recommended in NZ. Following the publishing of the NZ Guidelines for Rheumatic Fever in 2006,² which reinforce earlier recommendations for contact tracing by the MoH⁷⁰ it has become standard practice in endemic regions in the North Island of NZ. In the Auckland region a formal contact tracing programme commenced in December 2008. In my role as a communicable diseases Medical Officer at ARPHS I was involved in designing a protocol for delivery, implementing the programme and providing ongoing clinical oversight to it.

Soon after its implementation it became evident that it was a highly resource intensive programme and this impression was confirmed by a recent internal audit that has already been outlined in the Literature Review chapter.¹⁰ In the resource constrained environment of public health this raised serious questions about the efficacy and cost-effectiveness of the programme and led me towards a review of the literature around ARF household contact tracing and ultimately this study.

The Literature Review, presented in chapter 3, revealed not only a dearth of published information directly relating to ARF household contract tracing and its efficacy, but also a lack of established criteria for evaluating communicable disease contact tracing programmes in general. However, the criteria for evaluating screening programmes provide a basis for this and can be applied to contact tracing.¹¹⁹ When these were applied to ARF a number of gaps in the evidence were identified.

In my role in managing the contact tracing programme at ARPHS I had established a database to record contact tracing data with the aid of Health Informatics Analyst/Developer Peter Grundy. In an effort to start addressing these evidence gaps I designed an observational study that would provide detailed descriptive information about the contacts and their outcomes through secondary analysis of this routinely collected data. I oversaw the data collection and performed the bulk of the data analysis myself. Assistance was provided by my supervisors Professor Diana Lennon, Community Paediatrics, the University of Auckland and Associate Professor Chris Bullen, Director of Clinical Trials Research Unit, School of Population Health, the University of Auckland, along with Dr Craig Thornley who is a Medical Officer of Health at ARPHS. Joanna Stewart, a statistician with the University of Auckland performed the more complex statistical analyses and Ron King Intelligence & Surveillance Specialist from ARPHS undertook the spatial analysis.

4.2. Aim

The aim of this study was to determine:

- 1) The epidemiology of pharyngeal GAS in household contacts (frequency, *emm* type and distribution of pharyngeal GAS in contacts and households);
- 2) The rate of secondary cases found in household contacts, including acute case finding and cases occurring after contact management;
- 3) Whether contact tracing was complied with (contact tracing sensitivity) and could be carried out in a timely fashion and
- 4) The reported adverse effects associated with contact management.

Determining the above will contribute to assessing the value of ARF household contact tracing by addressing some of the evidence gaps identified in the previous chapter. The 7 criteria described in the previous chapter with evidence gaps that this study hopes to help address are:

Criterion 6: Is there a high degree of contact tracing sensitivity (the proportion of contacts genuinely exposed to the case that is identified, consent to and comply with management)?

Criterion 7: Are contacts able to be reached in a timely manner, before onward disease transmission or disease development?

Criterion 8: Is there high PPV (the proportion of the contacts that are infected) for contact tracing?

Criterion 9: Is there a higher risk of infection and/or ARF in contacts than in the general population and a significant overall burden of secondary disease?

Criterion 10: Is the rate of case detection greater than that achieved by presentations of individuals to healthcare, on the basis of development of symptoms?

Criterion 14: What is the secondary attack rate of ARF in contacts who have undergone contact tracing versus those who have not?

Criterion 18: What are the adverse effects associated with contact tracing?

4.2.1. Hypotheses

The study tested the following hypotheses:

- 1) GAS epidemiology:
 - a. Pharyngeal GAS is found amongst a proportion of household contacts in Auckland at level at least comparable with or higher than that in the background population as indicated by the literature.
 - b. The risk of pharyngeal GAS is highest in those contacts with sore throats, aged 5-15 years, in households with many contacts, and in household primary residents (rather than overnight visitors).

- c. There is general concordance between GAS *emm* types of cases and contacts within the same household, suggesting household transmission.
- d. *Emm* types found in ARF households are associated with ARF in NZ, but differ from those found in the GAS vaccine under development in North America.

2) Secondary ARF in contacts:

- a. Case finding during contact tracing is low.
- b. The secondary attack rate in those contact traced is low.

3) Contact tracing sensitivity and timeframes:

- a. Contacts are not generally able to be followed up promptly or completely.

4) Adverse effects

- a. The adverse effects reported are low.

4.3. Methods

4.3.1. Setting and study population

This study was set in the greater Auckland region. Auckland is NZ's largest city with a population of 1.4 million that comprises one third of the national population.²³⁷ It is ethnically diverse and made up of 11.1% Māori, 14.4% Pacific peoples, 18.9% per cent Asian and 56.5% European.²³⁷

4.3.2. The ARPHS contact tracing programme

The study utilised the standard contact tracing procedures followed by ARPHS staff to source data. These are now described in detail.

Because ARF is a notifiable disease, clinicians are legally required to inform ARPHS by phone or fax on confirmation or strong clinical suspicion of the diagnosis. In NZ the diagnosis is made according to the NZ Guidelines for the Diagnosis of ARF, published in the NZ Guidelines for Rheumatic Fever, which are based on 1992 Jones Criteria with exceptions (see Appendix 3).²

Only those cases for which a hospital consultant deems a diagnosis of ARF to be at least likely are followed up by ARPHS. Households of the index case are visited by public health nurses (PHNs) who then identify contacts.

Contacts are defined as those aged between 3 and 45 years (inclusive) who, during the month prior to the onset of ARF symptoms, either

- a. Lived in the same household as the case or shared the same bedroom, dormitory room or hostel bunkroom with the case for at least 1 night, or

- b. Had intensive salivary exposure to the case, for example through intimate kissing.

Contacts or their caregivers are questioned by the PHN about ethnicity using the standard ethnicity question for the Health and Disability sector that mirrors the Statistics New Zealand 2001 Census ethnicity question.^{238, 239} They are also questioned specifically about the presence of a sore throat and of symptoms that might be suggestive of ARF, namely joint pains or swelling, fever, shortness of breath, skin rash or chorea. Those with the latter features are referred to their GP or local emergency department. PHNs are trained in throat swabbing technique to ensure that both tonsillar surfaces and the posterior pharynx are sampled and that the tongue is avoided. All those aged between 3 and 45 years who consent have throat swabs taken with Copan swabs which are transported in Amies agar gel. Swabs are delivered to the local hospital or community laboratory within 24 hours. Laboratory request forms for throat swabs are left behind for those contacts who were not present when the PHN visited, with instructions to go to the nearest community laboratory as soon as possible to have the swab taken.

Swabs are cultured on blood agar and beta-haemolytic colonies identified using standard microbiological techniques and those that are positive sent to the Environmental Science and Research Limited (ESR) Streptococcal Reference Laboratory for *emm* typing using established procedures. *Emm* typing is a system that determines the *emm* gene coding for the amino-acid terminal portion of the surface M virulence protein of GAS which is responsible for at least 100 known M serospecificities of the organism.^{79, 160, 240} Two highly conserved primers are used to amplify a large portion of the *emm* gene. The sequence encoding M serospecificity is adjacent to one of the amplifying primer sequences allowing it to be directly sequenced.²⁴⁰

Appropriate antibiotic treatment is administered or dispensed to those with positive swabs by the PHN under Standing Order: this is either a stat dose of IM BPG (1.2 mega units for those weighing 20kg or more and 0.6 mega units or those less than 20kg) or 10 days of oral amoxycillin (1.5gm once daily for those weighing 30 kg or more and 750mg once daily for those less than 30kg). Oral erythromycin in standard doses is used for those with penicillin hypersensitivity. All information collected by the PHN, along with swab results and antibiotic treatment and adverse reactions is recorded manually on a Contact Management Form and entered into a secure Microsoft Access Database which has been custom built for the routine contact tracing work. In addition, case data is entered in the national surveillance database EpiSurv 7.

4.3.3. Study methods and participants

The study period was determined to be from the date of the commencement of the contact tracing programme in Auckland (8 December 2008) until the end of the following year (31 December 2009), a period of 55 weeks. With an expected GAS positive rate of approximately 15% in contacts, as suggested by the literature,^{193, 194, 197} the width of the 99% confidence interval (CI) around the estimate of positive would be +/- 5% with a sample size of around 300 contacts. On the basis of preliminary

numbers of cases notified and their associated contacts (5 per case), it was estimated that this number of contacts would be followed up over the course of approximately one year.

All cases notified during the specified study period and subsequently confirmed as meeting the “definite” or “probable” case definition for ARF according to the NZ Guidelines for the Diagnosis of ARF, were included. Those who had been followed up by ARPHS on clinical suspicion of ARF in whom ARF had been later ruled out were excluded from the study.

Data from the included cases and their identified contacts was extracted from the contact management database onto a Microsoft Excel spreadsheet and the data de-identified. The de-identified data was analysed for relevant case and contact characteristics, including:

- 1) The frequency and distribution of pharyngeal GAS in ARF patients and their household contacts by age, gender, NZ Deprivation Index 2006 (NZDep2006), ethnicity, residence, relationship of contact to case and density of contacts per case;
- 2) The degree of clustering of pharyngeal GAS within households according to *emm* type;
- 3) The *emm* types observed in cases and contacts;
- 4) Secondary ARF cases in contacts detected at initial contact tracing before swabbing, and in the period up to 6 months after the onset of symptoms in the index cases;
- 5) The timeframes taken to carry out contact tracing;
- 6) The sensitivity of contact tracing;
- 7) The reported adverse effects associated with antibiotic treatment.

4.3.4. Statistical analysis

Simple descriptive statistics were used for numbers and proportions. Median values are reported because data were non-normally distributed.

Ninety five percent CIs of percentages were calculated around point estimates in SAS using PROC SURVEYFREQ to adjust the errors for the clustering around case, and formed using the approximation to a t distribution.

Analysis to determine whether there was a difference in demographic factors between contacts who were swabbed and those who were not, and to investigate risk factors for a contact having a throat swab positive for GAS was carried out using SAS version 9.2. Generalised mixed models were fitted which included a random effect of contact to allow for the correlation of contacts of a case. For the outcome of whether they were swabbed or not, explanatory variables included were age, sex and ethnicity of the contact and whether they resided with the case or were a genetic relative of the case. For the outcome of positive GAS swab the explanatory variables were age, sex and ethnicity of the contact, whether they resided with the case, were a genetic relative of the case, were a sibling or parent of the case, the NZDep2006 (an area-based measure of social deprivation) of the case, number of contacts per case, time from case symptoms to contact swab, season of swab and whether the contact had a sore throat. Odds ratios and 95% CIs were reported.

A spatial scan analysis was undertaken using SaTScan version 9.0 to assess geographic clustering of cases.²⁴¹ The methodology was purely spatial with the discrete Poisson model used to test for statistical significance. The method adjusts for location and density of general population at risk. The units of analysis were address weighted meshblock (MB) centroids. The case and denominator populations (usually resident population under 30 years from the NZ 2006 Census) within each MB were summed to this point with the spatial scan at this unified set of locations. An elliptical spatial scan was employed, constrained to 25% of the denominator population.

Ethnicity was reported using the prioritised ethnicity output²³⁹ rather than sole/combined and total methods because it is the standard output used by the Health and Disability sector in NZ.²³⁹ In prioritised output, each subject is allocated to a single ethnic group using the prioritisation system (Māori, Pacific peoples, Asian, other groups except NZ European; and NZ European). This system ensures that ethnic groups of policy importance, or of small size, are not swamped by the NZ European ethnic group.²³⁹ A disadvantage of this system is it may potentially undercount Pacific peoples if they indicate both Māori and Pacific ethnicities. Because ARF is an important problem for Pacific people I also ran this analysis using sole/combined and total outputs for comparison but the overall numbers did not vary much indicating that prioritised output represented Pacific people appropriately.

An estimate of the potential secondary attack rate in untreated contacts and the number of contacts that need to be completely contact traced in order to prevent one case of ARF and associated costs and timeframes was made using assumptions based on evidence presented in the Literature Review (see Criteria 3, 7, 14), as follows:

- 30-50% of those with GAS isolated on throat swab have true GAS pharyngitis^{91, 147, 166, 172-174}
- 0.3% (estimated attack rate of ARF in an endemic NZ setting)¹⁸⁶ to 3% (epidemic attack rate derived from literature)¹³⁹ of those with GAS pharyngitis risk progression to ARF if not treated with appropriate antibiotics
- secondary cases occur within 6 months of the onset of ARF symptoms in the index case
- ARF is preventable in 75% of those who commence antibiotic treatment within 18 days of the onset of the index case's ARF symptoms, assuming treatment is 100% effective^{27, 179}
- where compliance is 100%, antibiotic treatment is 70-80% effective at preventing ARF in these contacts^{54, 61}
- antibiotic compliance is 75% in an NZ setting²⁹
- the cost of contact tracing in NZ (human resources costs only) is approximately \$NZ1,360 per case¹⁰

4.3.5. Ethics approval

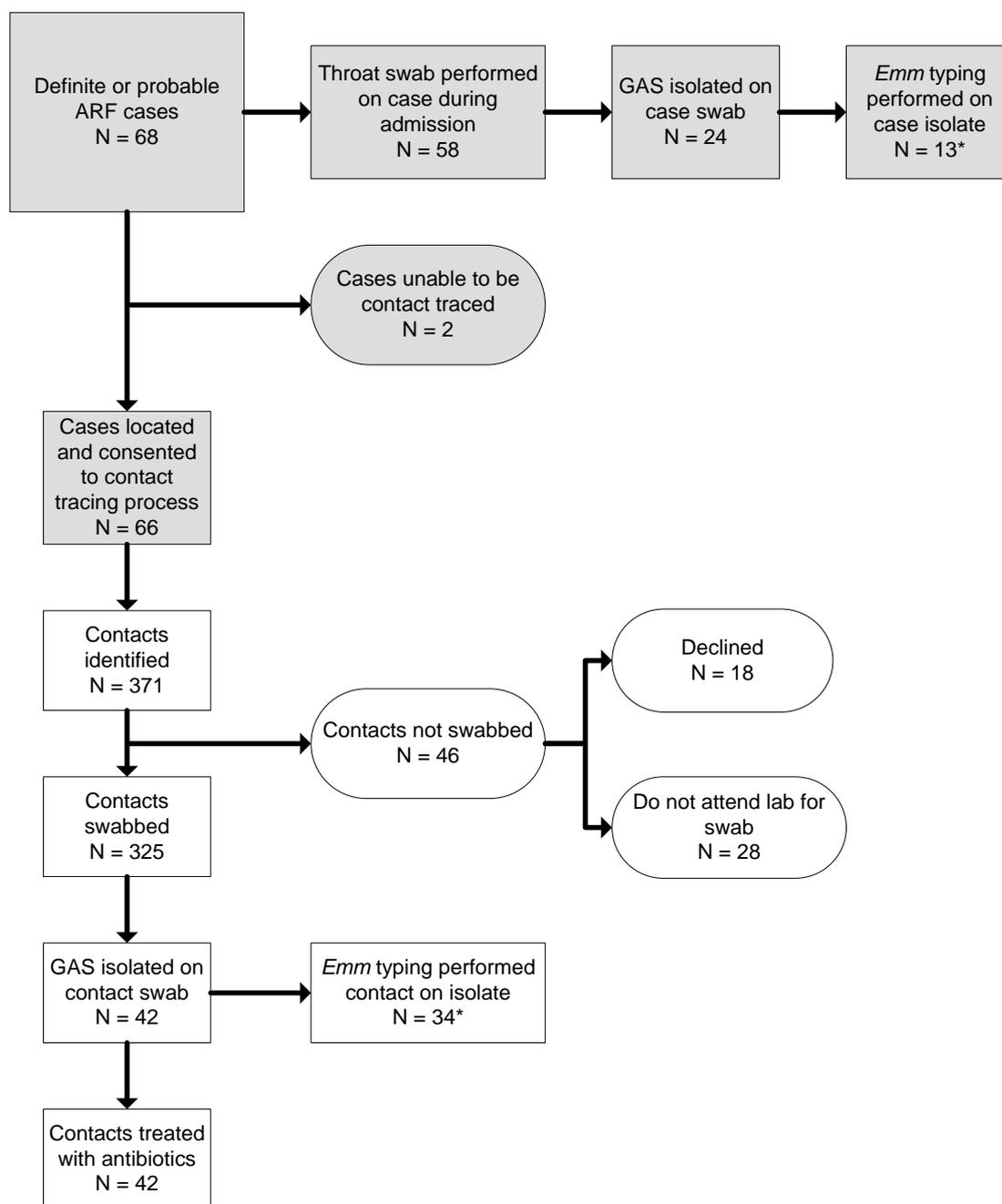
Ethics approval was gained from the Northern X Regional Ethics Committee on 19/03/10 (reference number NTX/10/EXP/038) and institutional approval granted by the Auckland District Health Board Research Office on 01/04/10 (research project A+4691).

4.4. Results

Figure 4-1 demonstrates the subjects included in the study and their interventions. Sixty-eight ARF cases meeting the inclusion criteria were notified during the study period, of which 60 (88%) were initial attacks and 8 (12%) recurrent attacks. One suspected case that had been contact traced by ARPHS and was subsequently found not to have had ARF was excluded from the analysis. Of the 68 who met the inclusion criteria 66 (97%) were followed up by PHNs. The remaining 2 were either not contactable (1 case) or declined follow up (1 case).

For the 66 cases that were able to be followed up a total of 371 household contacts were identified, of whom 325 (88%) were swabbed. Those who were not swabbed (n=46) either declined the swab (39%, 18/46) or could not be located (61%, 28/46). All in whom GAS was isolated (n=42) consented to antibiotic treatment.

The 2 cases that were not able to be followed up comprised one Pacific female aged 10 years and one Māori male aged 13 years. No differences could be demonstrated between the 46 contacts who were not swabbed and those who were swabbed in terms of age, gender, ethnicity, whether they usually resided with the case or whether they were a genetic relative of the case (see Table 4-1).



* Initial processing laboratory did not forward all specimens to reference laboratory for *emm* typing

Figure 4-1. Flow diagram showing study participants and their interventions

Table 4-1. Analysis of differences between variables of contacts who were not swabbed and contacts who were swabbed. Note: effects of continuous variables are assessed as one unit offsets from the mean

Variable	Odds ratio of contact not being swabbed	95% CI
Contact sex: (p= 0.42) Female: male	0.72	0.32-1.62
Contact age: (p = 0.20) Less than 5 years: over 25 years	1.21	0.20-7.45
5-15 years: over 25 years	0.34	0.12-0.98
16-25 years: over 25 years	0.67	0.23-1.86
Contact genetic relative of case: (p = 0.43) No: yes	2.58	0.83-8.02
Contact usually resides with case (p = 0.61) No: yes	0.73	0.22-2.43

4.4.1. Case results

4.4.1.1. Case demographics

Age and sex

Figure 4-2 shows that the 68 index cases were predominantly children with a median age of 11 years (inter-quartile range 9-14, range 4-32, mean 12.4). Recurrent cases had a median age of 16 years (range 6-23, mean 14.6). Excluding the 2 cases that could not be followed up the median age was 12 years. Sixty-two percent (42/68) of cases were male.

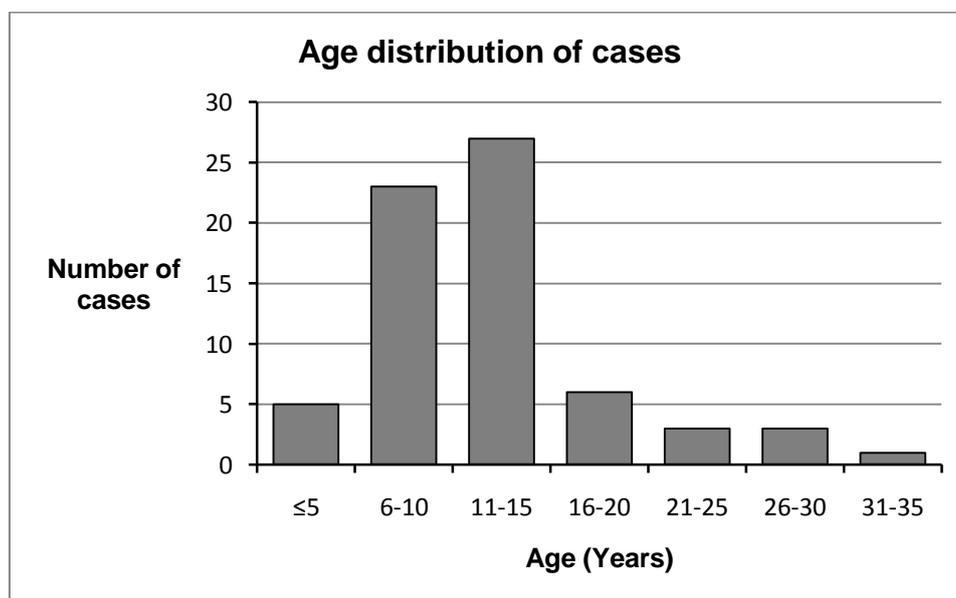


Figure 4-2. Age distribution of cases

Ethnicity

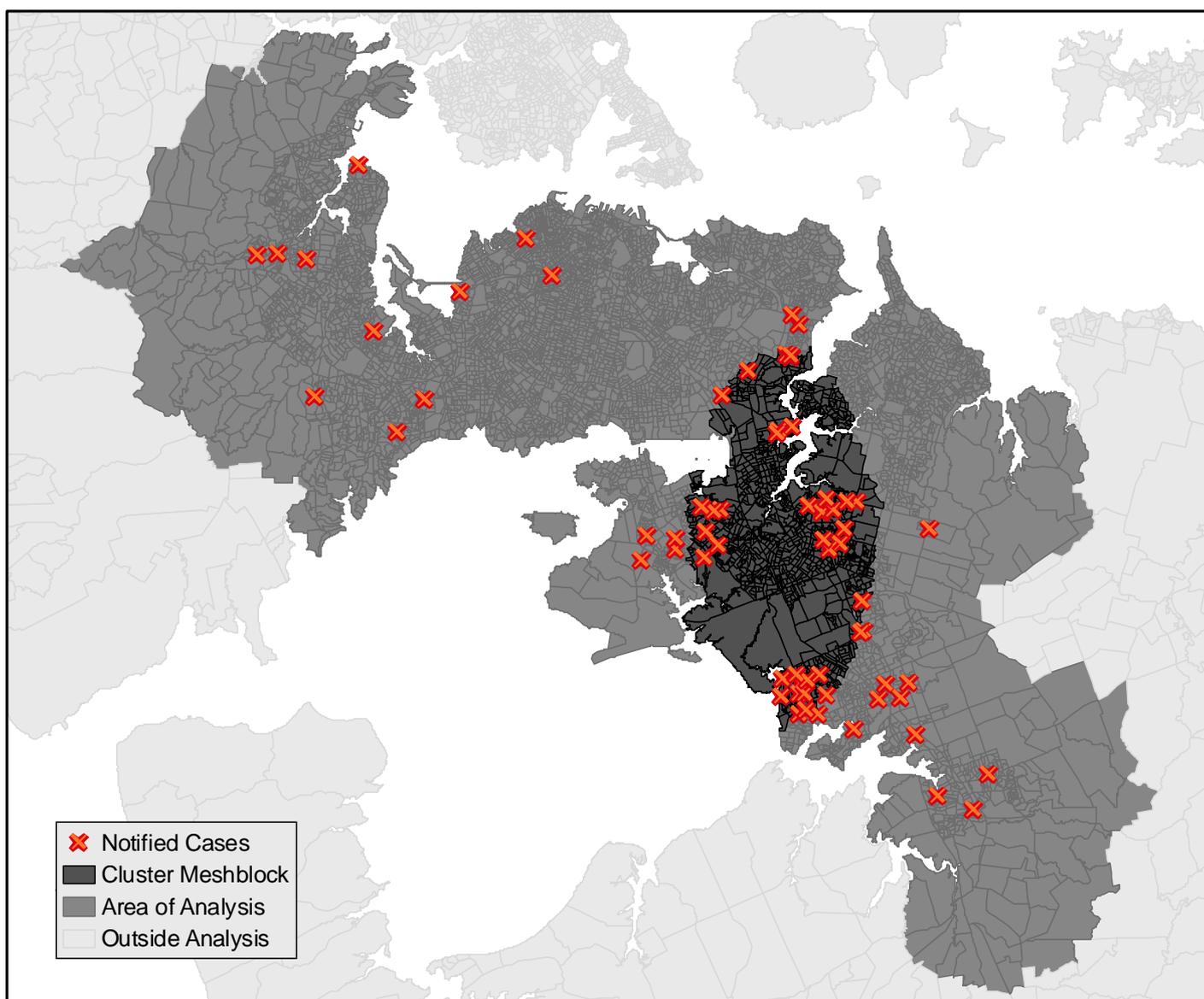
Using the prioritised ethnicity data output Pacific people comprised 63% (43/68) and Māori the remaining 37% (25/68).

Location

The spatial scan analysis of case's home addresses resulted in the identification of a statistically significant cluster on a North-South axis extending from Mt Wellington to Clendon (see Figure 4-3).

- Denominator Population: 88,094 (under 30 year resident population of Auckland)
- Observed cases: 36
- Rate: 37.7 per 100,000
- P-value: <0.001

Figure 4-3. ARF cluster analysis study area



Socio-economic position

The majority of cases (78%, 53/68) lived in locations with an NZDep2006 score of 9 or 10 (Figure 4-4).

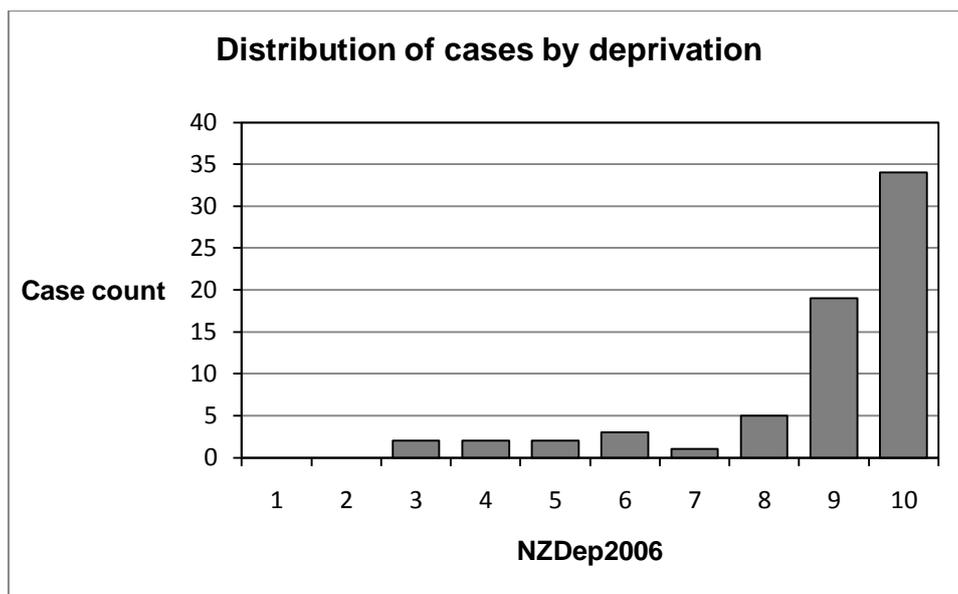


Figure 4-4. NZDep2006 distribution of cases

The cases in the cluster displayed a stronger association with more deprived MBs than did the non-clustered cases with 92% of clustered cases in deciles 9-10 compared with 65% of non clustered cases (Figure 4-5).

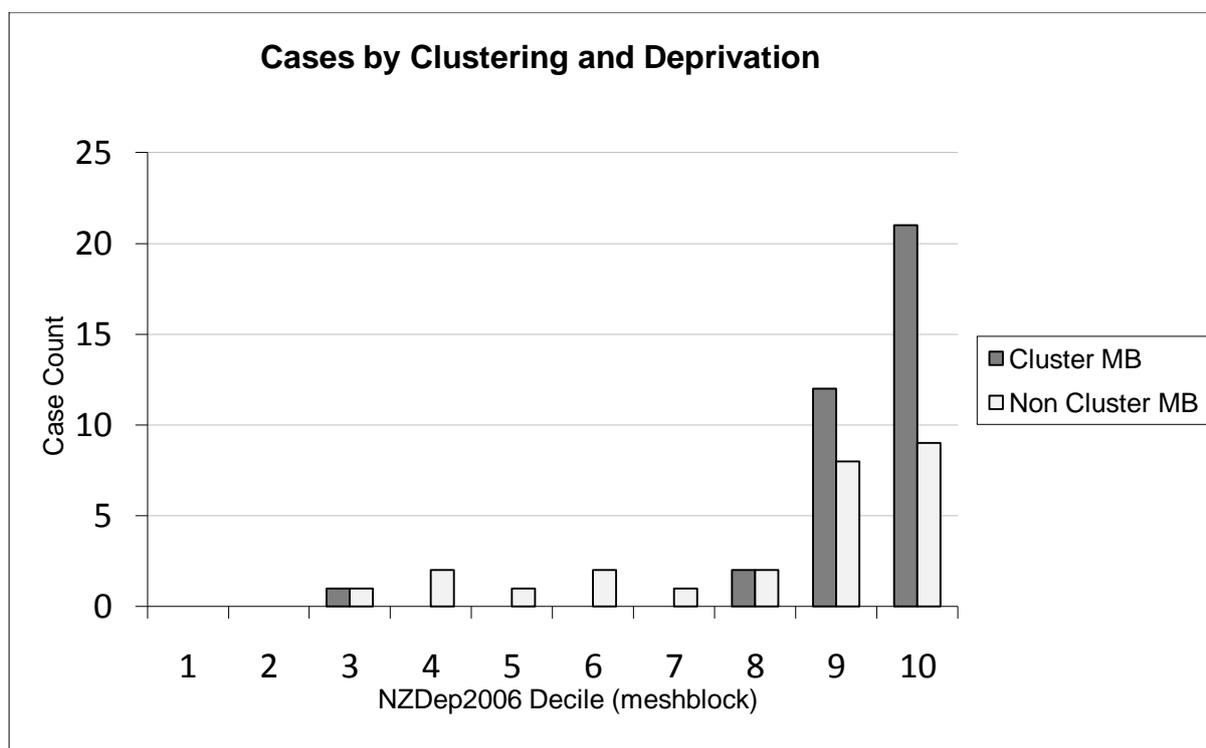


Figure 4-5. ARF case MB count by clustering and deprivation index

Comparing the cluster area in general with the region similarly shows the area to be more deprived than the region overall (non cluster MB in Figure 4-6). This is true of the total population, the under 30 year old population, and Māori and Pacific population.

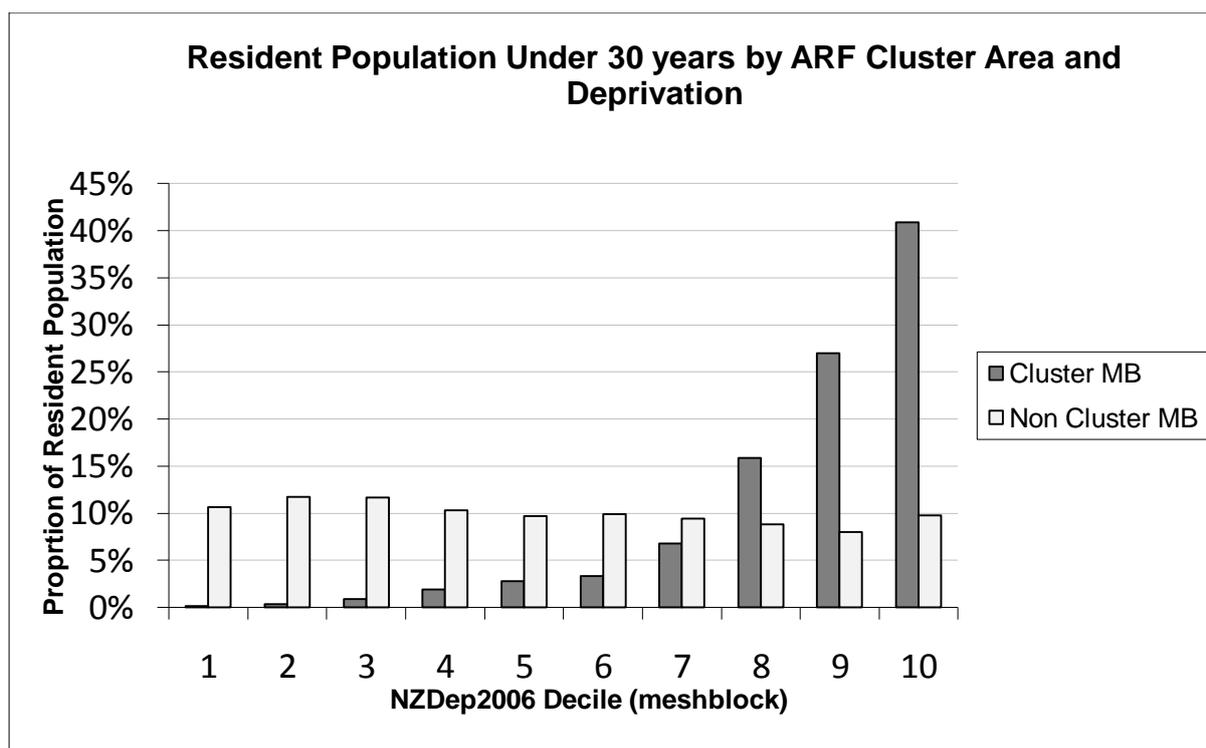


Figure 4-6. Resident 2006 Census Population by Rheumatic Fever Cluster Area and Deprivation

4.4.1.2. Case swab results

Of the 81% (55/68) of cases who had throat swabs taken during their hospital admissions, 44% (24/55) were positive for GAS, giving an overall swab positivity rate in all cases of 35% (24/68). *Emm* typing was arranged by hospital staff on 13 of the 24 positive cases (54%) and one each of the following *emm* types was isolated: 6, 12, 39, 49, 59, 74, 92, 93, 101, 106, 108, 61/44, 65/69.

4.4.2. Contact results

4.4.2.1. Contact demographics

Age and sex

The age distribution of contacts by year is shown in Figure 4-7 below. The median age was 17 years (inter-quartile range 9-30, range 3–45, mean 20.4). Approximately one third of the sample was in the 5-15 year age group (36%, 131/367) and another third in the 25-45 year age group (35%, 127/367), with one quarter aged 16-25 years (24%, 89/367) and a minority (5%, 4/367) under 5 years. For 4 contacts the age was unknown. Fifty three percent (197/371) of contacts were female and 46% (174/371) were male.

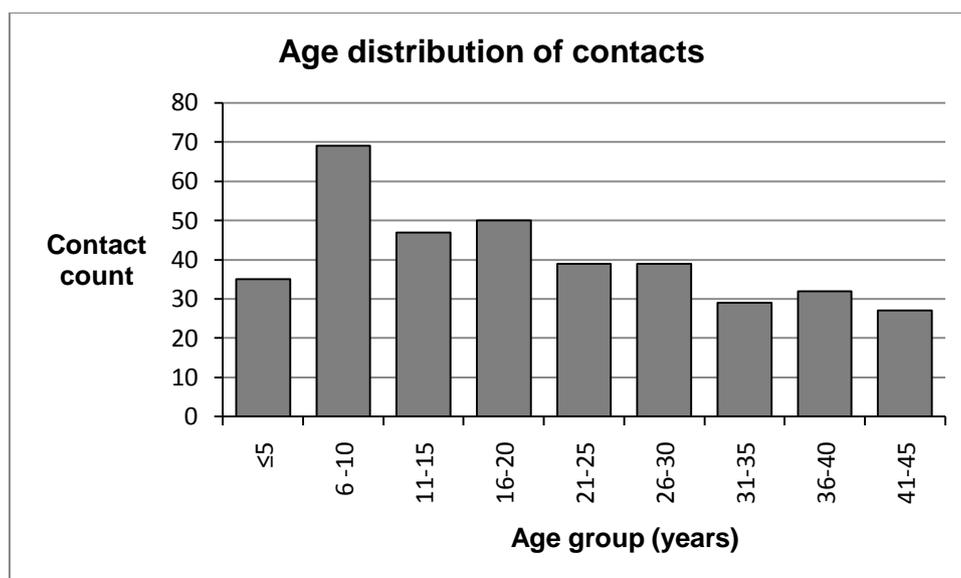


Figure 4-7. Age distribution of contacts by year

Ethnicity

The ethnicity of contacts was analysed according to prioritised output as described in the methods section. Results were similar to the pattern seen for cases, but with a small addition of Asians and Europeans together making up less than 5% of the total. Sixty-three percent (243/371) were Pacific people, 32% (117/371) Māori, 3.5% (13/371) NZ European, 1% (2/371) Asian and 0.3% (1/371) other European.

Contact relationship to case

More than two thirds of contacts (71%, 262/371) were usual residents of the index case's home and 81% (300/371) were genetic relatives with 59% (219/371) first degree relatives. Siblings made up 38% (141/371) of contacts and parents 19% (71/371).

Number of contacts per case

The median number of total contacts per case was 5 (interquartile range 4-6.5, range 2-19, mean 5.6). The median number of contacts who also were usual residents of the case's home, per case was 4 (interquartile range 2.5-5, range 1-11, mean 4.0).

4.4.2.2. Contact swab results

Thirteen percent (95% CI 10-17%) [42/325] of all contacts swabbed were positive for GAS. Of the cases followed up 38% (25/66) had at least 1 contact with a swab positive for GAS. Of these, the majority (88%, 22/25) had either 1 or 2 positive contacts (Figure 4-7). The mean number of contacts with positive swabs per case followed up was 0.64. In other words approximately 2 positive contacts were identified for every 3 cases followed up, or 1.5 cases needed to be followed up to detect 1 positive contact.

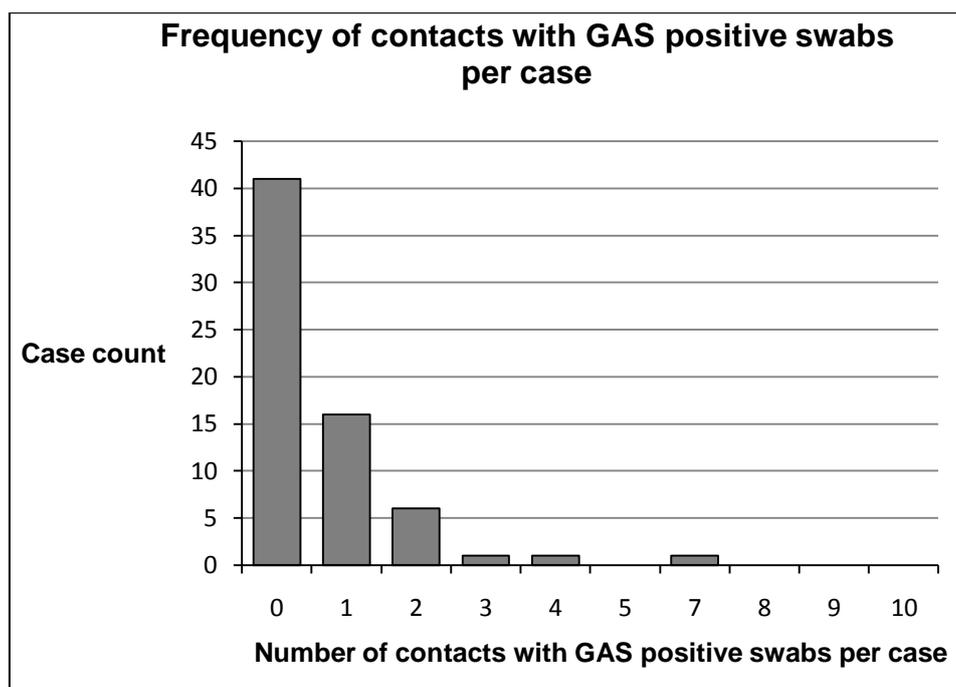


Figure 4-8. Frequency of contacts with throat swabs positive for GAS per case contact traced

Concordance of *emm* types between cases and contacts

Emm typing was performed on 34 of 42 (81%) contacts from whom GAS was isolated. The initial processing laboratory did not forward the remaining 8 specimens to ESR for *emm* typing. Only 3 sets of households had *emm* typing available for both the case and contacts. This comprised 3 cases and 6 contacts. In 2 of the 3 households there was 100% concordance between case and contact *emm* types within the household. In the household where case and contact's *emm* types were different only 1 contact had GAS isolated. In the remaining 2 households GAS was isolated in 2 and 3 contacts respectively (Table 4-2).

Emm typing was available for 23 of the 25 households where GAS was isolated in at least 1 contact. In 16 of the households within which *emm* typing was available, results were only available for 1 contact. Of the remaining 7 households with 2 or more contacts in whom GAS was isolated and *emm* typing available, there was complete concordance in 5 (accounting for 12 contacts in total), 71.4%. The remaining 2 households demonstrated a lack of concordance: in 1 household, 2 contacts had different *emm* types, and in the other there were 3 different *emm* types.

A formal statistical analysis of household clustering was not possible because of a lack of knowledge of the population distribution of different *emm* types in this specific community and time. However, there were 23 *emm* types observed amongst the 47 isolates (13 from cases, 34 from contacts) and therefore although an estimate of their relative probabilities is not available and the numbers are small it would be unlikely that this level of concordance was a chance occurrence. The most commonly isolated *emm* type was 6 (19%). Table A-7 in Appendix 14 details the *emm* types found and their frequency.

Table 4-2. Concordance of *emm* types between cases and contacts within the same household

Household	Case <i>emm</i> type	Contact <i>emm</i> type	Number of contacts with case's <i>emm</i> type	Total number in household with case's <i>emm</i> type (including case)
Household 1	49	63	1	1
Household 2	39	39	2	3
Household 3	6	6	3	4

Sore throats and results

Where possible, contacts were questioned about the presence of a sore throat at the time of swabbing. The results are shown in Table 4-3. Of the 92% (342/371) who responded, 5% (17/342) indicated they had a sore throat. Of these contacts with sore throats 27% (4/15) returned swabs positive for GAS. Amongst all contacts who had positive swabs for GAS, only 9.5% (4/42) complained of a sore throat. Of the contacts without sore throats 11.3% (34/300) yielded positive throat swabs. The combination of a sore throat and a swab positive for GAS constituted only 1.2% (4/325) of contacts swabbed.

Table 4-3. Presence of sore throat in contacts by swab result

Throat symptoms	Swab result		Total
	<i>Positive GAS swab</i>	<i>Negative GAS swab</i>	
<i>Sore throat</i>	4	11	15
<i>No sore throat</i>	34	266	300
<i>Unknown</i>	4	6	10
Total	42	283	325

4.4.2.3. Risk factors for positive swabs in contacts

The risk of a contact within various categories having a positive throat swab has been calculated as described in the methods section. A minority of contacts for whom age (1), ethnicity (3), presence of sore throat (28) or relationship with the case (1) were not available were excluded from this analysis.

There was strong evidence ($p = 0.005$) of an association of contact age, with the highest risk of GAS being isolated on throat swab in those in the 5-15 age group. Those in this age group versus those aged over 25 years had an odds ratio of having a positive swab of 3.59 (95% CI 1.43 to 9.07). The GAS positivity rate in 5-15 year olds was 22% (27/125, CI 13 – 30%), whereas for those outside this age group it was 8% (14/182, 95% CI 4 – 12%). Figure 4-9 displays the age distribution of contacts swabbed with the proportion in whom GAS is isolated for each age group. There was weak evidence of an association between sore throat and positive throat swab ($p = 0.06$) with an odds ratio of 0.28 (95% CI 0.07-1.06) for no sore throat versus a sore throat. Similarly there was weak evidence of an association between genetic relatives of the case and swab positivity with an odds ratio of 0.21 ($p = 0.07$, 95% CI = 0.04 to 1.10) for non relatives versus relatives, and longer time from onset of cases

symptoms to contact swab with an odds ratio of 1.01 ($p = 0.04$, 95% CI = 1.00 – 1.02). The results are displayed in the table below.

Table 4-4. Analysis of variables as risk factors for positive GAS throat swab in contacts. Note: effects of continuous variables are assessed as one unit offsets from the mean

Variable	Odds ratio of positive swab	95% CI
Contact sex: ($p = 0.17$) Female: male	1.73	0.79-3.80
Contact age: ($p = 0.005$) Less than 5 years: over 25 years	0.58	0.06-5.69
5-15 years: over 25 years	3.59	1.43-9.07
16-25 years: over 25 years	0.71	0.19-2.69
Contact genetic relative of case: ($p = 0.07$) No: yes	0.21	0.04-1.10
Contact sore throat: ($p = 0.06$) No: yes	0.28	0.07-1.06
Time from case illness onset to contact swab (in days) ($p = 0.04$)	1.01	1.00-1.02
Case NZDep2006 ($p = 0.07$)	0.82	0.66-1.02
Contact count per case ($p = 0.13$)	1.08	0.98-1.21

The proportion of sibling contacts with positive swabs was 15% (19/131, CI 7 – 29%) which is similar to the proportion in contacts overall. The comparable proportion for parents was 8% (5/63, CI 1-15%).

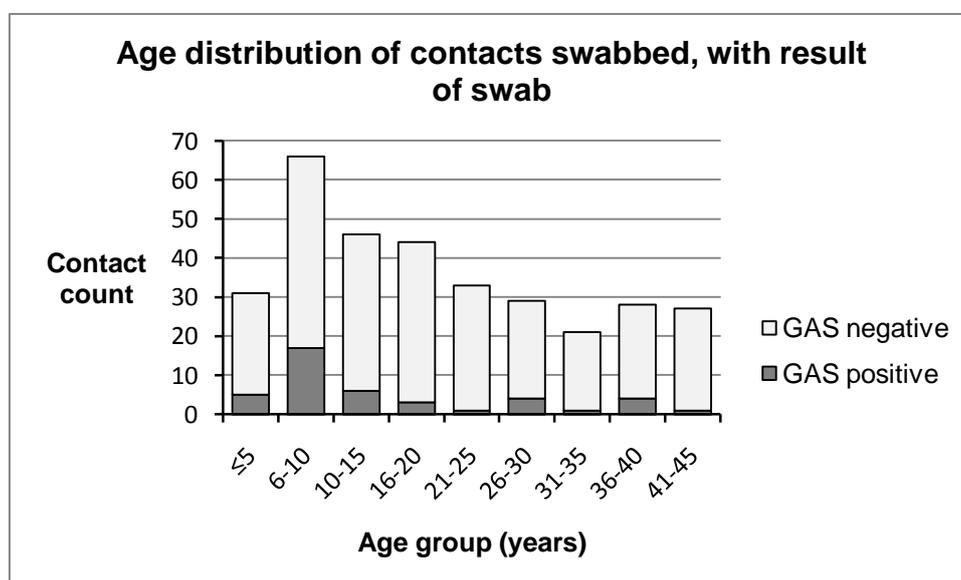


Figure 4-9. Age distribution of contacts who were swabbed illustrating the number and proportion in whom GAS was isolated

4.4.2.1. Secondary cases of ARF in contacts

A key component of contact tracing is active early detection of secondary cases or co-primary cases (case finding) and prevention of secondary cases. In this cohort all contacts were questioned about symptoms suggestive of ARF. One adult contact had some vague symptoms at the time of follow up

and was referred to the GP who ruled out ARF. Thus there was no active case finding during the study period.

None of the contacts identified during the study period, including both those swabbed and not swabbed was subsequently notified as a case of ARF in the 6 months following symptom onset in the index case. One subsequent episode of ARF occurred in 1 of the households that had been contact traced however it was 8 months after the index case became unwell. The index case was a young boy who had an initial episode in late 2008. During contact tracing his sister was found to have a positive swab for GAS and was treated with 10 days of oral amoxycillin. Eight months later the sister developed probable ARF. She and the others in the household all had negative swabs at this time. Due to the long timeframe involved this is considered to be a sporadic rather than a secondary case. Therefore no true secondary cases occurred in this cohort of household contacts.

4.4.2.2. Contact tracing timeframes

The median time period between the onset of ARF symptoms in the case and notification of the case to ARPHS was 19 days (interquartile range 7–32, range 0–253) [Figure 4-10 below]. The median time period between onset of ARF symptoms in the case and the date of swabbing of contacts who were able to be swabbed was 26 days (interquartile range 15-44, range 3-256) [Figure 4-11 below], while the median time from notification of the case to ARPHS and the swabbing of contacts was 5 days (interquartile range 4-7, range 0-227). Therefore the delay from case symptoms onset until contact swab was mainly accounted for by the time taken between case onset and notification. For those in whom GAS was isolated on swab the median time delay from swab being taken until administration of antibiotics was 5 days (interquartile range 4-7, range 0-12) and from onset of ARF symptoms in the case until administration of antibiotics was 33.5 days (interquartile range 21-57, range 8-261). Six contacts were excluded from this analysis because they had received antibiotics from their GPs rather than ARPHS. These timeframes are summarised in the table below.

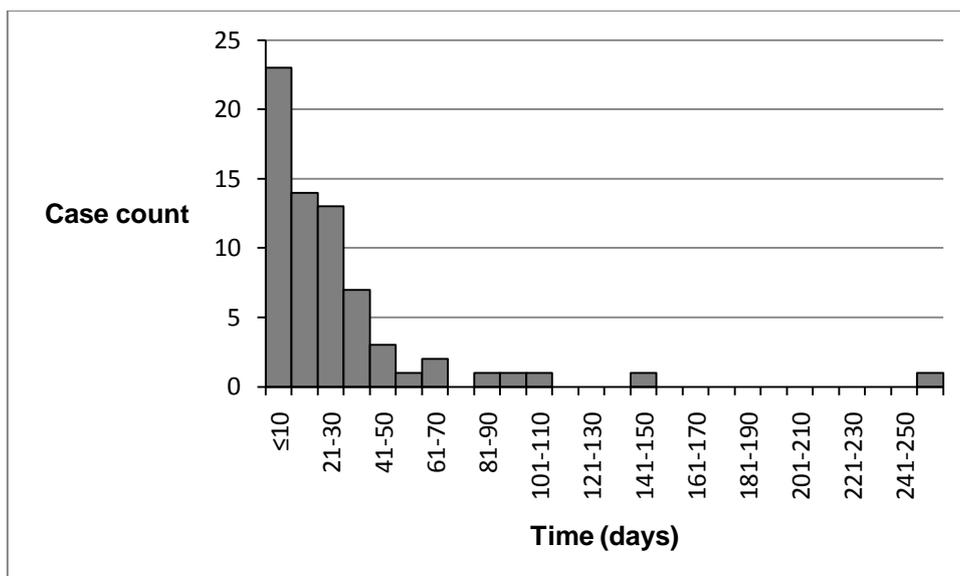


Figure 4-10. Time delay between onset of ARF symptoms in case and notification of case to ARPHS

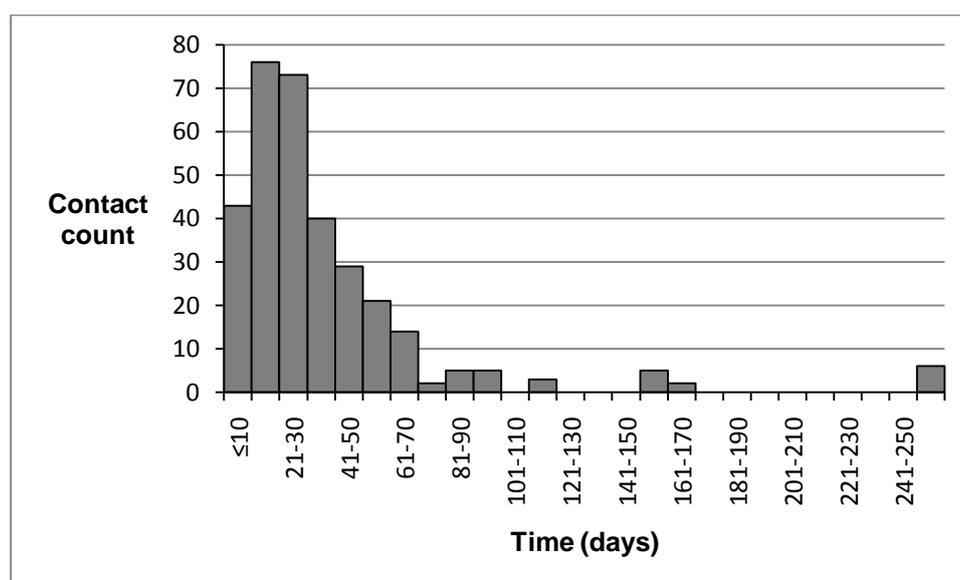


Figure 4-11. Time delay between onset of ARF symptoms in case and contact swabbed

Table 4-5. Important contact tracing timeframes

Period	Median duration (days)	Interquartile range
Onset of case ARF symptoms to notification to ARPHS	19	7-32
Onset of case ARF symptoms to contact swab	26	15-44
Notification to ARPHS to contact swab	5	4-7
Onset of case ARF symptoms to contact antibiotic administration	33.5	21-57
Contact swab to contact antibiotic administration	5	4-7

4.4.2.3. Adverse effects

Passive antibiotic adverse effects surveillance revealed no reports by contacts of adverse effects. The antibiotic most frequently used was oral amoxicillin (62%, 26/42). IM BPG which is generally reserved for those in whom compliance with oral antibiotics is deemed to be questionable was used in 19% (8/42) and oral penicillin prescribed by the contact's GPs in 10% (4/42). No erythromycin was dispensed. Four contacts with positive swabs were overnight visitors from Wellington and were tested by the local PHU and treated with unspecified antibiotics by their GPs. Compliance was not formally assessed.

4.5. Discussion

4.5.1. Principal findings

I will first discuss the principal findings in relation to the study hypotheses and existing published literature, outline its strengths and limitations and finally comment on how the findings have contributed to the evidence gaps established in the previous chapter's Literature Review.

4.5.1.1. Demographic characteristics of contacts

This study has described the characteristics of Auckland ARF household contacts and the epidemiology of GAS within these households. Although only those aged 3-45 years were included the age distribution of contacts was young in comparison with the Auckland population as a whole, with more than 40% aged 15 years or less and two thirds 25 years or less. This is a likely reflection of the large Pacific and Māori makeup of the cohort as these populations are relatively young compared with the other ethnicities found in Auckland (in 2006 almost one quarter of Auckland Māori was less than 10 years and 53% of NZ Māori was less than 25 years; the proportions of young people are even higher in Auckland Pacific people).^{48, 237}

Pacific people constituted just under two thirds of contacts, Māori one third, and Europeans or Asians a minority. These mirror the proportions of ethnicities observed in cases, although cases were exclusively either Pacific or Māori. This is vastly different to the Auckland parent population which comprises only 25.5% Pacific and Māori combined (Pacific people 14.4%, Māori 11.1%) and exemplifies the huge ethnic disparities associated with ARF in NZ.^{1, 237}

The majority (70-80%) of contacts were genetic relatives of the cases (59% first degree relatives) and usual residents of the case's home. Siblings made up over one third of the contacts (38%). The average occupancy of the households (including cases and contacts) was 6.6 if all contacts per case were included, or 5 if only usual residents were considered, with an upper range of 20. This contrasts with the average total household occupancy as defined by the 2006 census of 2.67 for NZ and 2.89 for Auckland.²⁴² Considering this cohort excluded those below 3 and over 45 years of age this finding suggests these households are at least twice as crowded as average. There is also a dramatic association between these households and high levels of socio-economic deprivation with almost

80% located in the two most deprived deciles according to NZDep2006. These two findings are in keeping with the established relationship between ARF and household overcrowding and poor socio-economic status.²

4.5.1.2. GAS epidemiology and risk factors

Isolation of pharyngeal GAS

The proportion of cases from whom GAS was isolated at ARF presentation was 35% (or 44% of those swabbed) which is comparable to proportions reported in the literature which range from 25%-60%.^{29, 82, 179, 197} Of all contacts swabbed 13% had GAS isolated, although this rose to 22% when only 5-15 year olds were considered. Only a handful of studies have also attempted to quantify the proportion of GAS positive swabs in ARF contacts, and none of them have been performed on NZ populations. They have been outlined in the Literature Review (Criterion 9), but I will briefly recapitulate, considering only studies where the proportion was ascertained following a recent episode of ARF in a household member. Like the current study none of these studies quantified the frequency of true pharyngeal GAS infection by examining paired streptococcal serology. Despite this and other methodological limitations there is reasonable concordance in frequencies between most of these studies and the current one. It should be noted though that most studies appear to include contacts of all ages, with the exception of that by Matanoski and colleagues³⁰ that was confined to those between 3 months and 16 years of age and that by Majeed and colleagues³⁴ that included those over 2 years of age. As the current study includes those aged between 3 and 45 years the proportions are not directly comparable.

The earliest work was a series of studies by Matanoski and colleagues conducted from 1957-59 in Baltimore, USA.¹⁵⁵ ARF family contacts were followed up with monthly throat swabs commencing within 6 weeks of the index case's episode of ARF. Eighty families and 394 contacts were included and the result was expressed as a rate of 9.53 positive GAS swabs per 100 person months.

A small study was performed in Baroda, India by Collee and colleagues from 1963-64 over two series.¹⁹³ In the first, involving 13 households where a member had recently had ARF, 82 household contacts were tested and pharyngeal GAS was isolated in 19.5%. In the second smaller series involving 62 contacts in 9 households, 16% of contacts had swabs positive for GAS.

Potter and colleagues studied the isolation rates of pharyngeal GAS in families of 21 patients with ARF in Trinidad in 1971.¹⁹⁴ Family contacts had throat swabs performed within 2 to 3 weeks of the patient's admission to hospital and the isolation rate in ARF family members was 19%.

Berrios and colleagues performed a similar study in Chile between 1978 and 1982.¹⁹⁵ Throat swabs were taken on 360 contacts as soon as the case was indentified, although only 59% of contacts were swabbed. The proportion of ARF family contacts with pharyngeal GAS was 7.8%.

Interestingly a comparable study performed by Majeed and colleagues in Kuwait over a 9 year period from 1980 to 1989 involving 62 ARF families revealed pharyngeal GAS in only 0.3% (1/303) of contacts.¹⁹⁶

The most recent study was conducted between 1995 and 2003 in Pennsylvania by Martin and colleagues.¹⁹⁷ Throat swabs were performed on 84 ARF patients in Pennsylvania and 147 of their family members. Non family household contacts were not mentioned and it is unclear what proportion of family members participated. In this cohort 14% of the family members swabbed had GAS isolated which is similar to the proportion found in this study. When researchers also looked at the proportions recovered in different family members the breakdown was highest in siblings at 25% (13/51), followed by parents at 8% (7/87) and none for the other category including aunts, babysitters, cousins and grandparents. The comparable proportions for siblings and parents in the current study were 14% (19/141) and 8% (5/71) respectively.

To assist in determining whether contacts are at higher risk of ARF than the background population (which would lend support to the rationale for ARF household contact tracing) it would be useful to be able to compare the occurrence of GAS pharyngitis in contacts with that of the general population. In the absence of the knowledge of true infection rates for either I will use isolation of GAS as a proxy. As discussed in the Literature Review (Criterion 3) approximately 30-50% of pharyngeal GAS acquisitions may be associated with streptococcal titre rises indicating true pharyngitis, while the comparable percentage for pharyngeal GAS detected on cross sectional sampling is approximately 5-37%.^{172, 174} If we assume that the ratio of carriage to true infection is the same in contacts and the background population, comparing overall proportions of those with GAS isolated may be an acceptable alternative to directly measuring the proportions of those with infection.

NZ pharyngeal GAS prevalence studies have been discussed in the Literature Review (Criterion 9) and findings range from 3.7% in Auckland 12 year olds in 1974,¹⁹⁸ to as high as 35.5% in Wairoa primary school children in 1977.²⁰⁰ Unfortunately the true contemporary prevalence in Auckland is unknown. However in an 86,874 person-years South Auckland primary and secondary school study running from 1998 to 2001 where throat swabs were performed on all those presenting daily with sore throats, or monthly on those with signs of pharyngitis on surveillance by clinical examination, the overall GAS isolation frequency was 7%.²⁹ This is likely to exclude a proportion of those with asymptomatic carriage as they may not have presented for throat swabbing, so the true isolation frequency would be expected to be higher than the observed 7%. The population in that study was probably most representative of the contacts in this study, although the age was restricted to only school children.

Therefore the first study hypothesis that the proportion of contacts in whom pharyngeal GAS is isolated is at least comparable with or higher than that in the background population is unable to be confirmed or refuted without further research to determine the background prevalence. It would be even more ideal to ascertain the rate of GAS pharyngitis in contacts over a time period after the index case becomes unwell and compare this with controls in the same population.

Risk factors for pharyngeal GAS isolation

Risk factors for recovery of GAS in contacts were examined in the current study and the only statistically significant risk factor of any magnitude was being aged between 5 and 15 years. GAS was isolated in 22% of contacts aged 5-15 years compared with 8% in those aged over 15 years. Although age was not looked at specifically in the studies of ARF contacts above, numerous prevalence studies support this as the highest risk age group for GAS carriage and infection.⁸³ Accordingly children of this age are most likely to acquire ARF.⁶ This hypothesis is therefore met.

Other hypothesised risk factors were sore throats, being a genetic relative of the case, inclusion in a household with many contacts, and sharing a primary residence with the case. A possible association with positive swabs was also found with the first two of these, however due to small numbers of contacts with positive swabs the results were not statistically significant. As transmission of GAS is believed to occur more readily in crowded environments⁸⁵ and the association between crowding and ARF is attributed to this²⁶ it is interesting that this study did not find evidence that a larger number of contacts associated with a household was associated with a higher risk of a positive swab. This could be attributable to the small study size. On the other hand in the Literature Review (Criterion 3) studies of pharyngeal GAS transmission were inconsistent in their demonstration of household crowding as a risk factor for pharyngeal GAS spread. In this study house size was not measured so a higher number of contacts is not necessarily a reflection of a more crowded environment. Further research is recommended to clarify the effect of crowding on GAS acquisition in the household.

An association between positive throat swabs and those who usually live in the same house, versus overnight visitors was hypothesised, as theoretically the former would have a greater degree of contact with the index case. That an association was not found may be a reflection of the study size being insufficient to demonstrate an effect, or alternatively that an overnight visit was sufficient exposure to acquire the organism.

Relationship of sore throat to swab results

The relationship of clinical symptoms to GAS pharyngitis is a complex one. The presence or absence of a sore throat cannot reliably predict whether an individual has pharyngeal GAS infection: "many sore throats are not streptococcal and many streptococcal throats are not sore".²⁴³ Typically only a minority (5-17%) of sore throats are due to GAS and the remainder are of viral origin.^{76, 244-247} Some of those with a sore throat and GAS isolated on swab are in fact GAS carriers with intercurrent viral pharyngitis, and streptococcal titres are required to make this distinction.²²⁹ GAS carriage is thought to be of low infectivity and unlikely to result in non suppurative sequelae in the host because of a lack of antibody production.^{162, 173, 229} Conversely pharyngeal GAS infection may occur asymptotically, as illustrated by the up to one third of ARF patients who give no history of an antecedent sore throat, yet have elevated streptococcal titres.¹⁴ It is also important to note that young children may not understand the concept or admit to a sore throat even if they have one.^{29, 248}

In this study very few contacts complained of a sore throat on direct questioning (5%); more than 90% of those from whom GAS was isolated denied having a sore throat. However GAS was recovered

from one quarter of those who admitted to a sore throat which was more than twice as high as in those without a sore throat. Throats were not examined in this study, but this also is not reliably predictive of GAS pharyngitis.¹⁸⁶ Anecdotally the public health message of a sore throat being a potential precursor to ARF does not yet seem to have gained traction in this target audience.

Emm types and concordance

Although the information was not available to draw a definitive conclusion there was a tendency towards concordance of the *emm* types found within a given household (2 of 3 households with both case and contact *emm* typing done and 5 of 7 households with *emm* typing done and more than 1 contact). This suggests that the hypothesis that transmission of GAS occurred from person to person within households may have some basis, and that the case may have infected the contacts or vice versa.

The *emm* types observed in this study were numerous and diverse, with 23 different types observed amongst 47 cases and contacts together, and 13 different types amongst 13 cases alone. The most commonly observed type both overall and in contacts alone was 6. This is classically associated with ARF both in NZ and in North America.¹⁴

The two studies that have determined the *emm* types connected with ARF in NZ are small and were both also conducted in Auckland in the 1980s and 1990s. The first study, conducted in 1983, included only a small number of isolates and suggested an association between ARF and M 53 and 58.²⁴⁹ The second study examined M types associated with 32 cases of ARF from 1984 to 1992. Those linked with ARF were M6, 53, 55, 66 and 89.⁵⁶ There is known concordance between M and *emm* types²⁵⁰ and thus the *emm* types known to be associated with ARF in NZ are 6, 53, 55, 66 and 89. Of these only 6 and 89 were observed in this study (the latter in 1 contact only) contrary to the study hypothesis. Thus this study builds on their findings, adding 21 potential new candidate ARF *emm* types if both contacts and cases are considered, or 12 if only cases are considered.

Other than type 6 the *emm* types found in this study are completely distinct from the *emm* types usually considered “rheumatogenic” in the Western Hemisphere (1, 3, 5, 6, 14, 18, 19 and 24).⁶ The 26-valent GAS vaccine under trial in North America covers types 1–3, 5–6, 11–14, 18, 19, 22, 24, 28, 29, 33, 43, 59, 75–77, 89, 92, 101, and 114.²⁵¹ This vaccine only cover 30% (7/23) of the strains seen in this series and 62% (8/13) of the ARF episodes would not have been prevented by it. This suggests that this vaccine would be unlikely to make an impact on the incidence of ARF in NZ as hypothesised. The *emm* types recovered in this study may be valuable in contributing towards local GAS vaccine development.

4.5.1.3. Secondary ARF in contacts

Case finding

An important aspect of any contact tracing programme is the early detection of new cases, referred to as case finding.^{96, 108} These cases are then able to receive treatment earlier than they otherwise would have and theoretically should have better outcomes and be then less likely to transmit the

disease, or its antecedent to others.^{96, 108} During the 55 week study period no early case detection occurred. This is consistent with the study hypothesis and is most likely to be a reflection of the overall low incidence of ARF.

Secondary attack rate of ARF in contacts

A comparison of the secondary attack rate of disease in contacts who are managed versus those who are not is a useful way of determining the effectiveness of contact management for that disease.²⁵²

For a contact tracing programme to be effective it would be expected that the secondary attack rate in the absence of contact tracing would be considerably higher than the sporadic rate in the general population, and that contact tracing could significantly reduce this secondary attack rate.^{112, 253}

Unfortunately the secondary attack rate in household contacts prior to the onset of contact tracing has not been evaluated in NZ. During the study period 1 subsequent case in a household previously contact traced occurred, but it was 8 months after the index case's illness onset. In the Literature Review (Criterion 9) the maximum period for a case to be considered secondary was discussed and concluded to be 6 months after the onset of the index case. This suggests that the subsequent episode observed in this study was due to the introduction of a new GAS infection and therefore was not a true secondary case. No true secondary cases occurred in either those contacts followed up completely (n=325) or those not followed up (n=46) so a difference in outcome could not be assessed for the two groups. Anecdotally there have been a number of clusters of ARF cases within one family reported to the Auckland Rheumatic Fever register outside this study period (personal communication Professor Diana Lennon, Community Paediatrics, the University of Auckland, 2010).

The case above that occurred 8 months following the initial case highlights a flaw in the approach of one-off contact tracing – it can, at best, only potentially prevent ARF due to GAS circulating at the time of follow up. Later infection of household members due to new GAS acquisitions from outside the household are commonplace according to the literature, with over 60% of pharyngeal GAS acquisitions originating from sources outside the home^{91, 153} and approximately 15% of school age children and up to 10% of adults suffering from a symptomatic bout of GAS pharyngitis yearly.³³ As numerous GAS strains exist and cross strain immunity is not conferred following infection⁸³ it appears contact tracing is unlikely to provide any medium or long-term protection.

4.5.1.4. Contact tracing sensitivity and timeframes

Important aspects of contact tracing programmes are the participation rates and the time delays taken to perform the contact tracing.^{12, 66, 99, 108-110} Low participation and long delays can detract from the performance of a programme.

Contact tracing sensitivity

Contact tracing sensitivity is defined as the proportion of all true contacts (those genuinely exposed to the index case) who are identified and managed.¹⁰⁹ In this study the participation rates were adequate with 97% of cases able to be followed up and 88% of contacts identified able to be swabbed and treated as appropriate. However this was at the expense of much effort and resource, often entailing

multiple phone calls, home visits and letters from PHNs. Thus the hypothesis that contact tracing was often incomplete is not borne out; however a reduction in the time invested in contact tracing would likely reduce completeness of contract tracing.

Timeframes

Substantial delays of an average of almost 3 weeks (median 19 days) were observed between the onset of ARF symptoms in the case and notification to ARPHS. This may be a partial reflection of the time lag in presenting to healthcare and in securing the diagnosis as some investigations may need to be repeated, for example streptococcal titres or echocardiograms. However clinicians may not have always notified promptly following diagnosis, an area that could potentially be improved. A further delay of a median of 5 days was seen between the notification to ARPHS and contact swabs being performed and this reflects the time taken to locate all contacts, or wait for them to attend the laboratory for testing. Overall the time delay between onset of symptoms of ARF in the case and contact swab was a median of 26 days. There was a large spread of numbers for these measures and they were skewed towards the mean. In those in whom GAS was isolated the time delay from swabbing to antibiotic administration was a median of 5 days and the total time from onset to treatment was a median of 33.5 days.

As discussed in the Literature Review (Criterion 7) the optimal timeframe for completing contact tracing, that is the time to administration of antibiotics in those in whom it is indicated, is unknown. However in order to minimise onward transmission of GAS within a household according to the available evidence it should aim to be completed within 1 month of the onset of GAS infection in the index case for a household of 5 susceptibles (the median number of contacts per case was 5).¹⁵⁸ With an average latent period of 19 days²⁷ this equates to administering antibiotics to GAS positive contacts within 9 days of the onset of the index case's ARF symptoms. Only 8% (3/36) of those who received antibiotics received them within this timeframe. In order to prevent 75% of potential GAS acquisitions (with their potential for progression to ARF) in a household of 5 susceptibles then antibiotics need to be administered to those with positive swabs within 5 ½ weeks of the index case's GAS infection translating to within 18 days of the onset of the index case's ARF symptoms. Only 17% (6/36) received antibiotics within this timeframe. Hence these cut offs are not met in this study in accordance with the study hypothesis (Figure 4-12).

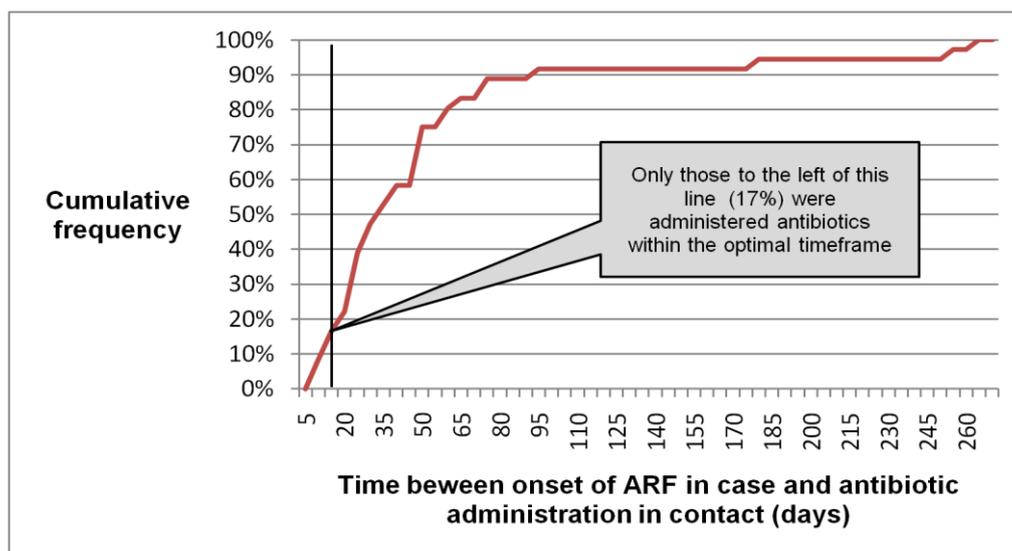


Figure 4-12. Proportion of contacts with positive throat swabs that were administered antibiotics within the optimal timeframe

4.5.1.5. Adverse effects

In line with predictions no adverse effects were passively reported. Specifically there were no reports of allergic reaction to antibiotics. However had a proactive approach to recording adverse effects been taken more may have been observed. Some adverse effects, such as the development of antibiotic resistance are not easily measurable and this study did not attempt to assess this variable.

4.5.2. Strengths

As far as can be ascertained, this is the first ever study that has ARF household contact tracing as its focus. As such it adds valuable understanding of the process and outcomes. Moreover it facilitates an appraisal of its utility, which has been identified as important for the reasons discussed in the Background chapter.

Auckland has the greatest proportion (60%) of NZ's ARF cases and therefore findings may be applicable to wider NZ.⁴⁴ They may also be generalisable to some degree to other countries where ARF occurs, in particular in the USA where contact tracing is also recommended.

Its strengths include satisfactory participation rates and efforts to account for potential bias by matching the demographic characteristics of those contacts swabbed and not swabbed. Precision measures were employed where appropriate and statistical significances were established.

4.5.3. Limitations

This study has a number of limitations. These pertain chiefly to study type, design and size. As a small observational case series performed over a relatively brief time period inferences from its results are necessarily circumspect. Although the sample of contacts was large, small numbers of positive contacts made true determination of risk factors for pharyngeal GAS difficult. The recruitment of

subjects relied on notification from clinicians when a suspected episode of ARF was diagnosed. A suspected significant under notification of ARF cases (as suggested by hospital discharge data from the same period)⁵ may mean that this sample is not truly representative of all incident ARF cases. Preliminary analysis of hospital data reveals that those not notified were more likely to be adults.

Because of the observational nature of the study no interventions additional to standard contact tracing procedure occurred. The major drawback associated with this study is that a positive throat swab alone is unable to distinguish between GAS carriage and true GAS pharyngitis.⁸³ This distinction would have required paired streptococcal titres to be performed, however interpretation would have been difficult as antibiotic treatment may interfere with antibody development.²⁵⁴ Therefore determining whether true infection had occurred would have necessitated delaying or withholding antibiotic treatment. This would have been difficult to justify ethically because it is not in line with standard contact tracing recommendations and carries a risk of progression to ARF for a genuinely infected contact. In addition the extended delays between the index case's illnesses and swabbing of the contacts in some instances may have lead to GAS isolation proportions that are not a true reflection of the acute situation, although an odds ratio for a positive swab with increasing delays of 1.01 (CI 1.00-1.02, $p = 0.04$) argues against this.

A further limitation of swabbing is that although considered highly sensitive and specific these values are not 100%. Incorrect swabbing technique may provide false negative results, however all PHNs were adequately trained in proper technique to minimise this.

It is not possible from this study to categorically know whether GAS recovered from contacts had been contracted from the index case (or vice versa) or whether it derived from outside the household. Similarly, the time of acquisition cannot be ascertained. Although the contact follow up rate was relatively high, *emm* typing was not complete limiting the assessment of household concordance. However where *emm* typing was available frequent concordance within households supports household transmission. In future a higher level of laboratory coordination should be ensured to improve the completeness of *emm* typing.

The study's primary focus was GAS epidemiology and as such it did not analyse adverse effects associated with contact tracing in-depth, nor did it address the costs or resources involved. The latter have already been estimated by way of an internal audit,¹⁰ but a more accurate examination of these would be useful. A further aspect of contact tracing that was not measured by this study was the potential impact of education in raising awareness of ARF and influencing future health seeking behaviour (encouragement to seek medical care in the event of a sore throat) and the psychological impacts, both positive and negative, of the contact tracing process on families. The potential positive effect of contact tracing on other GAS related morbidity such as impetigo and cellulitis was also not assessed in this study.

Some of the study's outcome variables ideally needed background values for comparison, however these were unavailable. These variables are the carriage rate of pharyngeal GAS in the general

population in Auckland and the secondary attack rate of ARF in households in the absence of contact tracing. The former could have been more accurately ascertained by instead performing a case control study to compare the epidemiology of GAS and ARF case finding in contacts and controls, however this would have been more costly and resource intensive. The latter could be assessed retrospectively by examining rheumatic fever registers. A prospective study that assesses the secondary attack rate in those not contact traced would not be ethically possible in this population while contact tracing remains the standard of care in NZ.

In a primary and secondary school based assessment of sore throat clinics to address ARF in a similar population (low socio-economic regions in South Auckland) 7% of those with sore throats had positive swabs for GAS versus 24% in this sample.²⁹ While this suggests a higher risk of GAS for ARF household contacts with sore throats than the background population, numbers in this study are probably too small to confidently draw such a conclusion. Unfortunately carriage rates were not assessed in that study.

4.5.4. Contribution to ideal contact tracing programme evidence gaps

A chief objective of this study was to address some of the evidence gaps in the effectiveness, appropriateness and feasibility of ARF contact tracing, as established in the Literature Review in the previous chapter. I will now discuss each of these.

4.5.4.1. Criterion 6: Is there a high degree of contact tracing sensitivity?

This refers to the proportion of true contacts that are identified, consent to and comply with management. The proportion of true contacts identified relies on information provided by the case or caregiver and would have been very difficult to verify in this study. However as the majority of household contacts were usual residents it is unlikely that lack knowledge of who the contacts were was a major issue. There is a possibility however that non NZ residents (illegal immigrants) were not identified for fear of eviction. The contacts associated with 2 cases were not able to be identified because of lack of cooperation in one instance and an inability to locate the case in another. For the 66 cases that were able to be followed up 88% were able to be swabbed and 100% of those with positive swabs consented to antibiotic treatment. Compliance with antibiotic treatment was not verified, except in the instances of IM BPG administration.

Overall a high degree of contact tracing sensitivity was observed which supports the effectiveness of the contact tracing programme, although it is noted that this was at the expense of high resource input.

4.5.4.2. Criterion 7: Are contacts able to be reached in a timely manner, before onward disease transmission or disease development?

As has been discussed the optimal timeframe for ARF household contact tracing completion is not known. However using best estimates from the literature, as outlined in the Literature Review, ideally

antibiotics would need to have been dispensed to those contacts harbouring GAS within 4- 5 ½ weeks of the index case's initial GAS illness, or, assuming a latent period of 19 days (which is the accepted average), within 9-18 days of the index case's ARF symptoms onset. This timeframe was exceeded in this study for the vast majority of contacts. Most of the time delay was from the onset of symptoms to the notification to public health. It is difficult to know whether the rate limiting factor here was delayed presentation to medical care, delayed clinician diagnosis, or delayed clinician notification to public health following diagnosis. If the latter then it could be improved by a drive to raise awareness amongst clinicians of the importance of prompt notification.

Although no secondary cases were detected the findings from this study suggest that at the moment contact tracing is not performed in an adequately timely manner in this setting to reliably prevent transmission of GAS and therefore potential secondary ARF.

4.5.4.3. Criterion 8: Is there high PPV (the proportion of the contacts infected) for contact tracing?

This study was able to determine that 13% of household contacts were harbouring pharyngeal GAS, the vast majority of who were asymptomatic. However as paired serology was not performed it was not possible to determine what proportion had true GAS pharyngitis. The literature suggests that 30-50% of acquisitions represent true infection. Using this assumption we can estimate that 4-7% may have been infected. For the 5-15 year age group, who are at highest risk of ARF this value is approximately 7-11%. Neither are high proportions. If we use an alternative definition of GAS pharyngitis (the one that was used in the study by Siegel et al.)¹⁸⁶ that is the combination of a sore throat and GAS isolated on throat swab then only 1.2% of this cohort had true infection. It is also worth noting that the time delays involved from the onset of GAS pharyngitis in the case to swabbing of contacts mean the results seen may not reflect true rates of secondary infection. The degree of PPV considered significant may vary depending on the condition and is unknown for ARF. This contributes to the evidence by adding NZ specific data, but it is insufficient to close the evidence gap.

4.5.4.4. Criterion 9: Is there a higher risk of GAS pharyngeal infection and/or ARF in contacts than in the general population and a significant overall burden of secondary disease?

As discussed above and in the discussion of the hypotheses the frequency of true GAS infection in contacts has not been determined by this study, but can be generously estimated to be 4-7% overall or 7-11% in 5-15 year olds. However the background frequency is unknown. Therefore while this study adds valuable and previously unknown information about the proportion of contacts with GAS in NZ, alone it does not provide sufficient evidence to close the identified evidence gap in respect to the risk of GAS infection in contacts versus the general population. No secondary cases of ARF (cases within 6 months of the index case's onset) occurred in the 46 contacts who were not able to be followed up. The total population background rate of ARF in NZ is approximately 1.7/100,000 per 6 months (a higher rate is seen if ethnicity, age and NZDep2006 are taken into account).¹ The number of contacts not followed up was likely too small to demonstrate the any difference in secondary attack rate in contacts versus the general population.

Estimating the secondary attack rate in contacts not managed by contact tracing

As the secondary attack rate of ARF in household contacts is pivotal in assessing the potential value of contact tracing it would be useful to be able estimate it with the available information, albeit imperfect. The critical variables needed to calculate it are:

- 1) The percentage of contacts with true GAS pharyngitis;
- 2) The attack rate of ARF following GAS pharyngitis in contacts.

Neither of these is known with certainty for this particular population; however they can be derived from a combination of findings from this study and the literature (subject to error because of assumptions made as outlined in the methods section). The frequency of pharyngeal GAS isolation is known (13% overall, 22% in 5-15 year olds) and the Literature Review (Criterion 3) suggests that between 30% and 50% of pharyngeal GAS acquisitions represent *bona fide* infection, although some studies have reported figures as low as 5%.

The attack rate of ARF following GAS pharyngitis has been studied and varies from under 1% in endemic populations¹⁸⁶ to consistent rates of 3% in epidemic settings.¹³⁹ Proposed prerequisites for epidemic ARF include a threshold GAS prevalence of at least 30% and one strain accounting for at least one third of the GAS isolated.²⁵⁵ As these are not met in this study population and no ARF epidemic was noted during the study period it can be assumed to be an endemic setting. The attack rate in Auckland school aged children who are from a similar ethnic and socio-economic background to contacts in this study was discussed in the Literature Review (Criterion 3).²⁹ Of those with GAS pharyngitis (diagnosed on the basis of compatible symptoms or signs together with a positive throat culture) who were treated with antibiotics, 0.2% went on to develop ARF.^{14, 29} The comparable attack rate in those not treated is estimated to be about 0.3%.

Estimate 1 (low/conservative)

If the variable in 1) is estimated as 50% and the variable in 2) as 0.3% then the secondary attack rate in contacts based on the GAS isolation proportion in this study is approximately 19.5/100,000. Extrapolating, even if contact management was 100% effective and timely, it would take 7 years and the tracing of over 5,000 contacts to prevent 1 case of ARF in NZ (assuming 150 cases of ARF per year and 5 contacts per case) at an approximate cost of \$NZ1.4 million (human resource costs only). This makes the case for contact tracing appear unfavourable. However when ethnicity is accounted for this calculated secondary attack rate is in fact lower than that in the background population. This is counter-intuitive and suggests an under-estimation of one or both variables and means the extrapolated figures are likely to be over-estimations and unreliable.

The logical step is to recalculate using higher values for 1) or 2). The variable that is going to alter the secondary attack rate most dramatically is the attack rate of ARF following GAS pharyngitis as it has a larger potential range. It is possible that the attack rate of ARF following GAS infection in contacts is higher than a normal endemic situation because the infection is with more virulent "rheumatogenic"

emm types. For contacts in an endemic setting it is very unlikely to exceed 3% though, as this is the maximum rate quoted in epidemic settings, independent of *emm* type.¹³⁹

Estimate 2 (mid-range)

Recalculating with variable 1) remaining as 50% and variable 2) increasing to 3%, the expected ARF secondary attack rate in contacts is ten-fold higher at 195/100,000. This translates into a more favourable scenario of 8 months and the tracing of 500 contacts to prevent 1 case (if contact management was 100% reliable) at a cost of \$NZ140,000.

Estimate 3 (high)

If instead we were to utilise the maximum possible projected values for 1) and 2) as 100% and 3% respectively then the secondary attack rate becomes 390/100,000. With 100% reliable contact tracing it would take 4 months and 250 contacts to prevent 1 case in NZ, an even more favourable scenario, approaching the values seen with meningococcal disease (see below). The cost of the contact tracing would be \$NZ70,000.

The caveat to the estimations around time period, number of contacts needed to trace and the associated costs to prevent 1 case is that 100% reliability of contact management is unrealistic and therefore these numbers will be higher than quoted. Generally antibiotic effectiveness for ARF prevention is 80% and compliance even with directly observed oral therapy is only 75% (most contacts in NZ receive oral antibiotics). Furthermore in this series only 17% of contacts received antibiotics in a timely fashion. Accounting for antibiotic effectiveness and compliance in the high secondary attack scenario (estimate 3) means it would take 7 months and the tracing of 400 contacts to prevent 1 case at a cost of \$NZ115,000. Also factoring the degree of timeliness observed in this study into this scenario means it would take over 3 years and the tracing of 2,500 contacts to prevent 1 case, at a cost of \$NZ680,000.

When these estimates are performed for the 5-15 year age group only under the high estimate conditions the secondary attack rate increases to 660/100,000. With 100% reliable contact tracing it would take 7 ½ months and 150 contacts to prevent 1 case, adjusting for antibiotic effectiveness and compliance, 1 year and 250 contacts and also adjusting for timeliness 6 years and 1,500 contacts.

By way of comparison with diseases for which contact tracing is well established the secondary attack rate for meningococcal disease and Hib in household contacts is 1/300 and 2.1-3.8% respectively. The number of contacts needed to treat to prevent 1 case of meningococcal disease is 200.

What these estimates reveal is that knowledge of the true GAS pharyngitis rate and attack rate of ARF following GAS pharyngitis in this population of contacts is essential for accurately deriving the expected secondary attack rate of ARF. Assumption based calculations made in the absence of this information produce high and low estimates with a twenty-fold difference between them proving too broad to draw a meaningful conclusion about the potential benefit of contact tracing. At the lower end

of the range the justification for contact tracing is questionable, whereas at the higher end of the range potential benefit exists provided the management can be delivered efficiently and completely. Therefore there is currently insufficient empirical information to deduce the secondary attack rate in contacts accurately and approximate associated contact tracing timeframes, numbers and costs.

An important point these estimates highlight is that if even the secondary attack rate is at the higher end of the spectrum it is likely that contact tracing would need to be performed significantly more quickly than in this series to actually make an impact and the degree of compliance will also have a critical influence.

4.5.4.5. Criterion 10: Is the rate of case detection greater than that achieved by presentations of individuals to healthcare, on the basis of development of symptoms?

The background rate of symptomatic presentations to healthcare in NZ approximates the incidence of ARF of 3.4/100,000 per year¹. According to NMDS data the mean number of ARF admissions to hospital per year in the wider Auckland region for 5-14 year olds per year is 74 (2004-2008).²⁰⁹ As this study was conducted in the wider Auckland region for a period of just over 1 year and included all age groups, a finding of no acute cases strongly suggests that contact tracing case finding does not exceed symptomatic presentations to healthcare in this setting.

4.5.4.6. Criterion 14: What is the secondary attack rate of ARF in contacts who have undergone contact tracing versus those who have not?

No secondary cases of ARF were observed in either identified contacts who were completely followed up or in those who were not able to be contact traced completely. The numbers are too small to ascertain whether there is a difference in outcome (development of ARF) for those contact traced versus those not contact traced. Therefore there is still a gap in evidence of whether treating GAS positive contacts reduces ARF in this setting and to what degree.

4.5.4.7. Criterion 18: What are the adverse effects associated with contact tracing?

This study looks at one aspect of adverse effects: reported side effects of antibiotics. None were reported, however while this is useful information other potential harm such as antibiotic resistance and psychological impacts of contact tracing remain unknown. Therefore the evidence gap remains.

4.6. Conclusion

This study has provided much needed information about the processes and outcomes of ARF household contact tracing in Auckland and these findings may be generalisable to other regions of NZ and abroad where contact tracing is practised.

In summary the important findings are:

- 1) Both cases and their contacts were almost exclusively of Pacific or Māori ethnicities;

- 2) Cases and their family contacts tended to live in houses with higher than average residencies in socio-economically deprived regions and one third of contacts were aged 5-15 years;
- 3) Pharyngeal GAS was isolated in 13% of overall contacts and 22% of those aged 5-15 years, the latter age group being a risk factor for having a positive swab result. Long delays between case's illnesses and contact's swabs in some instances may have produced spurious results. The proportion of contacts with true GAS pharyngitis was not measured;
- 4) There appears to be some degree of concordance between *emm* types within households suggesting household transmission; these *emm* types were numerous and largely distinct from those associated with ARF in North America and the 26-valent GAS vaccine under trial;
- 5) Although relatively high contact tracing sensitivity was possible and treatment appeared to be well tolerated, contact tracing was not completed in a timely enough fashion to optimise prevention of secondary ARF and did not contribute significant case finding. Timeliness appears to have an important influence on the potential utility of contact tracing.

By virtue of their ethnicity, NZDep2006 index and age many of the contacts fell into the high risk category for developing ARF in comparison with the background population. Over one fifth of the high-risk age group for ARF (5-15 year olds) harboured pharyngeal GAS, which represented true infection in an unknown proportion. Untreated this carries a risk of progression to ARF which is also unknown for this population. The rate of secondary ARF in household contacts is therefore yet to be quantified, with best estimates covering too broad a range to be useful. However, extrapolations from these estimates reinforce that the secondary attack rate of ARF in untreated contacts is a key factor in determining what contribution, at what cost and over what time household contact tracing can make to ARF control.

Research is needed to ascertain this secondary ARF attack rate so the potential benefit of contact tracing can be more accurately assessed. As elaborated in the Literature Review there are also a number of other criteria to weigh up in determining the overall utility of ARF household contact tracing. These will be discussed further in the following chapter and a final conclusion reached regarding the research question: whether ARF contact tracing should be pursued in NZ.

Chapter 5. Discussion and conclusions

In this chapter I draw together the findings of the Literature Review and the ARPHS contact tracing study, discuss the strengths and limitations of this work, and consider possible alternative approaches. I then discuss the implications of the conclusions reached and make recommendations for practice, policy and research.

As elucidated in the Background chapter and Literature Review ARF is an important public health problem in NZ, and a preventable cause of health inequality that warrants serious attention. To tackle this issue effectively and sustainably, resources should be prioritised towards the intervention or combination of interventions that will make the most impact on disease incidence. Understanding where household contact tracing sits in the preventative hierarchy is therefore critical to overall disease control.

5.1. Dissertation aim

The aim of this dissertation was to ascertain whether there was sufficient evidence that ARF household contact tracing was effective, appropriate and feasible, and whether the programme should be pursued in NZ. This question is important: contact tracing is very resource intensive, at least in Auckland, which bears the major national burden of disease. The corollary is there is a potentially a significant opportunity cost associated with the programme.

5.2. Approach to research question

Appraising the value of ARF contact tracing was not straightforward, owing to the lack of specific ARF contact tracing studies and the absence of a standardised framework for evaluating communicable disease contact tracing programmes. I therefore created a set of criteria against which contact tracing programmes may be evaluated prior to making a decision. According to this framework all criteria need to be met before proceeding with a contact tracing programme.

By reframing each criterion as a research question and performing a literature review specific to ARF for each, numerous gaps in the evidence were identified. These were summarised in Table 3-3 in the Literature Review. Next, I presented data from ARF contact tracing in Auckland, which provides previously unknown information about contacts and their outcomes. It adds valuable evidence towards several of the incomplete criteria, however, because it is a single observational study it does not have sufficient strength by itself to fulfil or refute them. Appendix 15 has a revised version of the table in the Literature Review that has been updated to reflect the contributions of this study.

5.2.1. Summary of outcome of application of ideal contact tracing programme criteria to ARF

Overall 7 criteria are met, 2 are not met and 14 have insufficient evidence available to decide whether they are met or not. Of the latter 3 have weak evidence leaning towards fulfilment of the criteria, while

5 have weak evidence pointing towards non-fulfilment of the criteria and the remainder have no or extremely little evidence associated with them. Therefore, according to this framework, ARF contact tracing should not be recommended in NZ unless further research is conducted that can demonstrate the 14 criteria with current evidence gaps are met and the 2 which are currently not met can be rectified.

As outlined in the Literature Review the criteria are generally designed to be worked through in a sequential manner such that the condition criteria are established before considering the contact criteria, followed by the intervention criteria and finally the programme criteria. While in reality they may occur in parallel the rationale for this sequencing is there is little point in administering a contact intervention programme if the communicable disease is not a public health problem and the risk and burden of disease in contacts absent any intervention is low. This concept can help guide where future research should first be focused for ARF contact tracing.

Examination of the condition criteria indicates that the majority are met (4 out of 5) with insufficient evidence relating to the proportion of cases with the condition that are promptly diagnosed. In an ideal world research should be directed towards establishing whether an adequate proportion of cases of ARF come to the attention of health professionals in a timely manner. However, this is unlikely to be easy in reality. Efforts may be better directed towards community and health professional education so clinical features can be recognised, and maximising access to healthcare for Māori and Pacific children.

Next the contact criteria can be considered. There is currently insufficient evidence to satisfy any of these. Three out of six of the intervention criteria are met, with insufficient evidence for the remainder. For the 8 programme criteria, 1 is met, 2 are not met and the remainder are characterised by insufficient evidence.

The conclusion is that efforts should be directed towards establishing the secondary attack rate and burden of ARF in contacts, before determining an intervention to potentially reduce this attack rate and burden, and creating a programme to support the intervention.

5.2.2. Critique of approach

The conclusion that there is insufficient evidence to support a recommendation of ARF contact tracing in NZ assumes the approach I have taken is valid. It is important to make an assessment of whether this is so and what alternative approaches could be considered.

Public health interventions can only be justified ethically on the basis that they are supported by evidence that they are effective.²⁵⁶ However, critics warn that the traditional biomedical definitions of evidence and effectiveness can be restrictive, placing too much emphasis on clinical endpoints derived from scientific trials and ignoring economic factors, patient preferences, social and cultural factors.^{256, 257} The strength of the framework I have created and applied is that it is based on a comprehensive review of the best available evidence and encompasses not only clinical effectiveness

outcomes, but also acknowledges the importance of feasibility (the impact on the provider and resources including costs) and appropriateness (psychosocial aspects of the intervention and stakeholder acceptability). However, a limitation of this framework is that it is not validated. Validating the criteria may be difficult as there is no current gold standard against which to compare them. Another limitation is that fulfilling of all 23 criteria may be overly rigorous and impractical in reality. A possible solution could be to apply them to a disease for which contact tracing is universally accepted and performed, for example Hib or meningococcal disease. However, this is beyond the scope of this dissertation.

A further limitation is that the study I conducted and presented in chapter 4 was not able to provide sufficient evidence to satisfy or refute the criteria that were incomplete after the Literature Review. This study had a number of other limitations that have already been outlined in the previous chapter and include the fact true pharyngitis rates in contacts were not able to be measured and long time delays may have produced spurious results with respect to GAS rates.

It is plausible that some criteria should be weighted more heavily than others and that the satisfaction of some should be considered a “bonus” rather than essential for a successful programme. An example of this is that case finding (Criterion 10) may not be important if the programme provides significant secondary cases prevention (Criterion 14), or the PPV need not be high (Criterion 8) provided the disease is severe enough and contact tracing prevents a significant proportion of secondary cases. The concept of differential weighting of criteria presents an area for future review.

5.2.3. Alternative approaches

It is useful to consider other ways of appraising the recommendation for ARF household contact tracing in NZ and compare the outcomes.

5.2.3.1. Applying a different framework

An alternative approach to the one I used could be to apply an adapted version of the criteria for undertaking chemoprophylaxis that were presented in the Literature Review. These criteria, adapted for contact tracing, are as follows.

For contact tracing to be recommended all of the following are necessary:

- 1) Severity and burden of disease: the disease should be severe and of significant overall burden (aligns with Criterion 1);
- 2) The risk of subsequent disease in a defined contact group: there should be a higher risk of disease in a defined group of contacts, as determined by the secondary attack rate in contacts versus the sporadic incidence, and the overall burden of disease due to secondary cases should be significant (aligns with Criterion 9);

- 3) The effectiveness of the contact tracing intervention: the intervention should provide significant reduction in RR and AR and the NNT to prevent 1 case should be as low as possible (aligns with Criterion 14);
- 4) The potential burden of contact tracing: the intervention should be safe, affordable and logistically feasible (aligns with Criterion 18, Criterion 19, Criterion 20).

As already discussed, the limitations of these criteria are that they do not consider other key components of contact tracing such as the prevalence or incidence of the condition in the population, the role of testing and case finding, nor the acceptability of the programme to its recipients. Nonetheless, it is interesting to observe that even if these limited 4 criteria are applied to ARF contact tracing there is still insufficient evidence to recommend the programme, as it would meet only 1 out of the 4 criteria. This is depicted in Table A-9. By way of comparison when applied to two other droplet spread diseases that are routinely contact traced (meningococcal disease and Hib) all 4 criteria are fulfilled.

5.2.3.2. Critiquing the basis for the original ARF household contact tracing recommendation

Another perspective to take in addressing the dissertation question is to critically evaluate the approach used to make the original recommendation for ARF contact tracing. As discussed in the Background chapter and Literature Review it arose from the USA in the 1970s and stems from studies demonstrating household transmission of GAS. The key study quoted is that by James and colleagues performed in the 1950s which found a 25% rate of secondary GAS acquisition in household contacts in the 10 weeks following exposure to symptomatic GAS positive index case.⁹² A systematic review of household transmission of GAS including this study and nine others was performed in Criterion 3 of the Literature Review with supplementary critical appraisal material in Table A-3 found in Appendix 10. Overall these studies were found to be of poor quality by today's rigorous epidemiological standards; however there is general concordance amongst them that GAS is moderately infectious within a household. That household ARF contacts may therefore be at risk of contracting potentially "rheumatogenic" GAS from the ARF index case and either transmitting to others in the household or going on to develop ARF themselves is a plausible, but unverified corollary. It is a large leap to actually recommend testing and treating these contacts without first quantifying the risk and evaluating whether the intervention is effective, feasible, acceptable or potentially harmful. There are numerous examples of health interventions that were initially thought to be beneficial and were widely used, but were subsequently found to be relatively ineffective or even harmful.²⁵⁸ Therefore, in my view, this is a less than prudent approach to making a recommendation about ARF contact tracing.

A secondary reason to examine the original recommendation is that it highlights an interesting discrepancy between the approach used for recommending ARF household contact tracing in the USA and that used to make recommendations about managing household contacts of iGAS disease in the USA. There are doubtless some parallels between the principles of contact tracing for these two conditions because of their common microbiological aetiology and presumably similar pattern of

spread amongst household contacts. They are also both arguably diseases of public health importance. It would therefore be reasonable to expect a similar approach to evaluating the role of contact tracing to be taken for both. However although more published data exists to support contact tracing for iGAS than for ARF, evidence to support the former is still considered insufficient by the CDC for it to be recommended routinely in the USA, while ARF contact tracing continues to be recommended in by the AAP, IDSA and AHA.

The difference may lie in the different focus of the groups involved and the eras in which the recommendations were initiated. The recommendation for ARF is historical and was made by professional bodies of infectious diseases and cardiology clinicians based on indirect evidence and expert opinion. The focus of clinicians is primarily on the health of individuals rather than on outcomes for populations. On the other hand, the recommendation for iGAS was made by the CDC, which has a strong population health ethos, and has occurred contemporaneously in a climate of evidence-based practise where more scientific rigour is demanded, and population health considerations are taken into account. The CDC based their recommendations on the chemoprophylaxis criteria described above and the only 1 that is unequivocally met is that it is serious and a significant burden. The CDC concluded that “although the risk of subsequent iGAS disease among household contacts of persons with iGAS infections is higher than the risk among the general population, subsequent iGAS infections are rare. Given the infrequency of these infections and the lack of a clearly effective chemoprophylactic regimen, the available data do not support a recommendation for routine testing for GAS colonisation or for routine administration of chemoprophylaxis to all household contacts of persons with iGAS disease.”⁷⁴

In NZ the NHF recommendation for ARF contact tracing appears to have been derived directly from the recommendations of the AAP in the USA, while the origins of the MoH recommendations are more obscure. As in the USA and UK contact treatment for iGAS is not routine in NZ and one could argue that consistency should be brought to the approaches to the two conditions here also.

5.2.3.3. Decision making when evidence is incomplete

The criteria based used in this dissertation involves a binary decision that is made on the basis of whether all the criteria are fulfilled or not: if they are met the programme is recommended, but if not, it is not recommended due to insufficient good quality evidence to support or refute it. However the reality of medicine and public health is that decision making commonly must occur in the absence of complete or perfect evidence.²⁵⁹ The National Institute for Health and Clinical Excellence (NICE), a professional group established to ensure equal access to medical treatments and high quality care in the UK²⁶⁰ advises that when evaluating whether to endorse a new healthcare intervention there are four possible outcomes:²⁶¹

- 1) Adopt the intervention on the basis existing evidence of net benefit;
- 2) Adopt the intervention but only in the context of research;
- 3) Reject the intervention on the basis of existing evidence of net harm;

- 4) Reject the intervention and demand further research.

To arrive at such decisions, according to NICE, all available evidence pertaining to clinical cost effectiveness should be weighed up, even if the evidence is incomplete, and factors such as equity, acceptability, preference and feasibility also considered.^{262, 263} If the net benefit (defined as mean benefit minus mean cost, including harms)²⁶² is positive with minimal uncertainty then option 1 applies. If the net benefit is positive according to available evidence, but some uncertainty exists and research is deemed to be of net value in resolving the uncertainty then option 2 applies.²⁶² If the available evidence points to net harm then option 3 applies. If there is no available evidence, or the available evidence points towards net harm, but with uncertainty then further research is warranted to resolve the uncertainty and option 4 applies.

Applying these to ARF contact tracing we must first weigh up the benefits and costs/harm. There is unfortunately a paucity of empirical evidence relating to either.

Benefits

Potential benefits include the primary clinical goal of the programme which is a reduction in morbidity and mortality from ARF and RHD, as well as possible indirect benefits such as reduced suppurative sequelae from GAS pharyngitis, reduction of overall GAS burden, improved health knowledge in families due to the education that accompanies contact tracing and less tangible psychosocial benefits from engagement with health staff. There is currently no evidence that contact tracing does or does not provide any of these. As has been outlined, a key initial step in determining the potential clinical benefit is to establish the secondary attack rate in untreated contacts. However, as demonstrated in the previous chapter's study, even modelling based on the best available information is not precise enough to provide a useful estimate of this.

Costs/harm

Costs and harms include direct financial costs, opportunity cost, and adverse physical and psychosocial outcomes. Although overall information is incomplete these have been better quantified than the benefits. The staffing costs associated with contact tracing 1 case according to the ARPHS audit presented in the Literature Review are approximately \$NZ1,360.¹⁰ We also know that the direct ongoing costs incurred to the health system by 1 case of ARF in NZ is estimated to be between \$NZ28,749 and \$NZ93,798 (analysis performed in 1991, inflation adjusted to 2010).⁴ In the absence of knowledge of the true secondary attack rate or the overall efficacy of treatment in this setting an estimate of the gross and net costs associated with preventing 1 case of ARF through contact tracing in NZ cannot be made. It can be concluded though that opportunity costs are potentially significant because of the large consumption of resources indicated by the audit.¹⁰

Adverse effects relating to antibiotics, including allergic reactions and the risk of resistance are important considerations and have not been actively measured in this setting. The risk of allergic reaction to BPG when given for secondary prophylaxis is reported to be 3.2%^{233, 234} and

gastrointestinal side effects from oral penicillins are generally common.^{231, 232} While no ill effects were found in the ARPHS study this information was not actively sought from contacts so under-reporting is likely.

Psychological impacts and stakeholder acceptability also have not been formally assessed. However, PHNs at ARPHS report that contacts are generally poorly receptive to the programme, displaying reluctance towards throat swabbing and taking antibiotics, particularly intramuscularly. This lack of community buy-in together with the large time commitment involved and the absence of evidence of effectiveness has led many staff to question whether the programme is worthwhile.

On balance the available evidence is insufficient to make an informed decision about whether the benefit outweighs the net costs and harm, although the costs/harms have been better evaluated than the benefits. Utilising the decision making model outlined option 4 applies – ARF contact tracing should not be pursued currently because of significant uncertainty, but research to clarify its role is warranted.

5.3. Conclusion, implications and recommendations

According to the framework I have developed, as well as considering the alternative approaches described above, there is insufficient direct evidence to support the ARF contact tracing programme. In fact, even in the absence of complete information definite risks and costs can be identified, while benefits although plausible remain theoretical. If consideration was being given to implementation of this programme I would recommend that it should not proceed unless subsequent research demonstrates a net benefit.

However, ARF contact tracing has already been implemented in most regions of NZ and is formally recommended by the MoH. Based on the logic presented above it should be discontinued and urgent research engaged in to define whether it has a role. However, the decision to withdraw a programme that has already diffused is more complicated than the decision to defer implementation of a proposed programme. Unintended negative consequences associated with ceasing it need to be carefully considered.

For decades ARF has been a largely neglected disease in NZ. The advent of ARF contact tracing by PHUs over the past several years may have helped raise the level of public health engagement with the disease. Some commentators have pointed out there is a risk that if the programme is discontinued PHUs may lose some of the momentum that has been gained. This is mitigated though by the fact that most PHUs also deliver secondary penicillin prophylaxis and therefore would have ongoing involvement with ARF control. Another issue to contemplate is whether inconsistencies in recommendations and practise over time could result in loss of credibility with stakeholders. An expectation of contact tracing may have been established amongst ARF communities and clinical staff, although anecdotally this is not the case in Auckland. If the programme was to be

disestablished, with the potential for later reinstatement should new supporting evidence emerge, a clear explanation would need to be communicated in a culturally sensitive manner to all affected.

While the focus of this dissertation is the role of ARF contact tracing as a subset of ARF control, in public health it is always important to consider the bigger picture. As we know ARF is a complication of GAS infection. However, GAS infection has a much wider impact than ARF alone. It is also responsible for a spectrum of morbidity that spans skin infections such as impetigo and cellulitis, respiratory tract infections such as otitis media and sinusitis, other non-suppurative sequelae such as glomerulonephritis and increasingly frequently iGAS. The burden of iGAS, like ARF is high in NZ compared with other developed countries.²⁶⁴ Traditionally the control of ARF and iGAS have been considered separately. However given their common aetiology and high burden in NZ it makes sense to pursue interventions that will address the overall burden of GAS infection. ARF contact tracing may temporarily reduce the GAS load in a given household, but is unlikely to make a sustained impact because of re-introductions from the community. Instead the focus should be on the socio-economic and environmental factors that perpetuate the stronghold this organism has within at risk communities.

5.3.1. Further research

The decision to undertake research should itself not be taken lightly as this too consumes resources and therefore carries an opportunity cost. While a randomised controlled trial provides the most powerful evidence it may not always be the most feasible type of study to administer. According to NICE, the value of information added by the research should outweigh the potential costs associated with it, including delaying the implementation of a potentially beneficial intervention.²⁶² In the context of ARF contact tracing it should be fit for purpose. This means only information that is sufficient to confirm or refute whether the benefit outweighs the net harm this should be sought, thereby minimising the amount of time and resources expended.

As outlined earlier in this chapter the current area of focus for research should be establishing the natural secondary attack rate of in household contacts and the burden of disease in contacts relative to sporadic cases. If neither is determined to be significantly high then further research is unnecessary because even an intervention that is 100% effective with no risk of harm will make little impact on overall disease control and therefore contact tracing is not indicated. The options for determining the secondary attack rate and burden include a retrospective analysis of rheumatic fever registers and hospital admission data performed on a nationwide basis, or a prospective study. The former is more feasible (most regions in NZ have ARF register data for the past 20-30 years) and will produce results more quickly, but would be subject to error, because only contacts who resided at the same address as the index case could easily be identified. Because of the low incidence of ARF a prospective study is not likely to deliver meaningful results for many years.

If the secondary attack rate and burden in contacts is found to be significant the next step is to prove that the contact tracing intervention significantly reduces this risk without harm. The ideal intervention

needs further clarification as it is unclear whether it may be more appropriate to treat all contacts with empirical chemoprophylaxis (as with meningococcal disease and Hib) or to treat only those with GAS isolated on throat swab. It is also unknown which antibiotic regimen is most effective, what the ideal timeframes are and who precisely should be targeted.

These could be investigated together in a study where contacts are randomised to being traced and treated or not, with various treatment arms, and the secondary attack rate of ARF compared, although large numbers would be required.

5.3.2. Future directions for ARF prevention

If ARF household contact tracing is to be no longer recommended, then efforts need to be refocused towards the priorities for GAS, ARF and RHD control. The time, effort and money currently devoted to ARF contact tracing could be diverted towards research as described above, as well as channelled towards strategies that are known to be effective in the prevention of ARF and RHD. This includes the optimisation of primary and secondary prevention. One area of research that could potentially deliver huge dividends is the development of a locally specific GAS vaccine, which covers *emm* types responsible for ARF and iGAS. The case-contact tracing study presented in chapter 4 has contributed valuable information about “rheumatogenic” *emm* types in NZ which could inform vaccine development. Such vaccine work has not yet been undertaken and poses many challenges however if successful it could make a huge impact on the growing burden of all GAS related diseases in NZ.

The study has also reinforced the dramatic association of ARF in NZ with Māori and Pacific ethnicities, high levels of socio-economic deprivation and overcrowding. Addressing upstream determinants such as poverty and inadequate housing, and improving access to healthcare for Māori and Pacific people are matters of social justice and human rights that governments have a responsibility to address through economic and social policy.

5.4. Summary

ARF is a serious public health problem in NZ. Household contact tracing has been practiced for some years as a preventative strategy however it consumes significant resources and the basis for its recommendation has never been critically examined. This dissertation sought to undertake a review of the evidence supporting it as a preventative intervention in NZ and ascertain whether it should continue to be practiced.

A literature review revealed no studies with ARF contact tracing as a focus so an evidence-based framework for assessing contact tracing programmes drawing on standardised criteria for screening programmes was constructed and applied to ARF, and an observational study of ARF contact tracing processes and outcomes conducted in Auckland. Many evidence gaps were apparent when parameters of effectiveness, appropriateness and feasibility were considered, translating into insufficient evidence to confidently recommend it in NZ. When critically examined the rationale behind the original recommendation has little backing by today's standards.

For these reasons it is recommended that ARF contact tracing is discontinued until research suggests otherwise, although consideration could be given to continuing to offer ARF prevention education to contacts in the interim. It is recommended that research is first conducted to ascertain the risk and burden of secondary ARF in contacts and then, if appropriate, the associated potential risk reduction with contact tracing. If the findings are positive then adverse effects, programme feasibility and acceptability should be assessed. Meanwhile efforts should also be refocused towards maximising ARF primary and secondary prevention initiatives.

Appendices

Appendices

Appendix 1: Ethics approval



Northern X Regional Ethics Committee

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Private Bag 92 522
Wellesley Street, Auckland
Phone (09) 580 9105
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19 March 2010

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Dear Brigid

Ethics ref: **NTX/10/EXP/038**
Study title: Epidemiology of pharyngeal group A streptococcus in acute rheumatic fever household contacts in Auckland, 2008-2009
Investigators: Dr Brigid O'Brien, Mr Chris Bullen, Dr Craig Thornley
Supervisor: Prof Diana Lennon
Localities: Auckland District Health Board

Thank you for your application received 17 March 2010. The above study has been given ethical approval by the Deputy Chairperson of the **Northern X Regional Ethics Committee** under delegated authority.

Approved Documents

- Protocol (undated, received 17/3/10) with the following appendices
Contact Management Form
Collection Personal Information

Accreditation

The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Final Report

The study is approved until **19 March 2011**. A final report is required at the end of the study and a form to assist with this is available at <http://www.ethicscommittees.health.govt.nz>. If the study will not be completed as advised, please forward a progress report and an application for extension of ethical approval one month before the above date.

Amendments

It is also a condition of approval that the Committee is advised if the study does not commence, or the study is altered in any way, including all documentation eg advertisements, letters to prospective participants.

Please quote the above ethics committee reference number in all correspondence.

Appendix 2: Institutional approval



1 April 2010

Dr Brigid O'Brien
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Website: www.adhb.govt.nz/ResearchOffice

Institutional Approval

Dear Dr O'Brien

RE: Research project A+4691 (Ethics # NTX/10/EXP/038) - Epidemiology of Pharyngeal Group A Streptococcus in Acute Rheumatic Fever Households in Auckland, 2008-2009

The Auckland DHB Research Review Committee (ADHB-RRC) would like to thank you for the opportunity to review your study and has given approval for your research project.

Your Institutional approval is dependant on the Research Office having up-to-date information and documentation relating to your research and being kept informed of any changes to your study. It is your responsibility to ensure you have kept Ethics and the Research Office up to date and have the appropriate approvals. ADHB approval may be withdrawn for your study if you do not keep the Research Office informed of the following:

- Any communication from Ethics Committees, including confirmation of annual ethics renewal
- Any amendment to study documentation
- Study completion, suspension or cancellation

More detailed information is included on the following page. If you have any questions please do not hesitate to contact the Research Office.

Yours sincerely

**On behalf of the Research Review Committee
Dr Samantha Jones
Manager, Research Office
Auckland DHB**

c.c. Richard Hoskins

..../continued next page

Appendix 3: NZ guidelines for the diagnosis of ARF

	DIAGNOSTIC REQUIREMENTS	CATEGORY
Initial episode of ARF	2 major or 1 major and 2 minor manifestations plus evidence of a preceding GAS infection*	Definite ARF
Initial episode of ARF	1 major and 2 minor with the inclusion of evidence of a preceding GAS infection* as a minor manifestation (Jones, 1956) ³⁹	Probable ARF
Initial episode of ARF	Strong clinical suspicion of ARF, but insufficient signs and symptoms to fulfil diagnosis of definite or probable ARF	Possible ARF
Recurrent attack of ARF in a case with known past ARF or RHD	2 major or 1 major and 2 minor or several** minor plus evidence of a preceding GAS infection* (Jones, 1992) ³⁷	
Major manifestations modified*** from Jones 1992 (see Table 3 for key points in identifying major manifestations)	Carditis (including evidence of subclinical rheumatic valve disease on echocardiogram) [#] Polyarthriti§ (or aseptic monoarthritis with history of NSAID use) Chorea (can be stand-alone for ARF diagnosis) Erythema marginatum Subcutaneous nodules	
Minor manifestations (see Table 4 for key points in identifying minor manifestations)	Fever Raised ESR or CRP Polyarthralgi§ Prolonged P-R interval on ECG.	

All categories assume that other more likely diagnoses have been excluded. Please see additional tables for details about specific manifestations. CRP = C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; GAS = group A streptococcus; RHD = rheumatic heart disease

- * Elevated or rising antistreptolysin O or other streptococcal antibody (Table 5), is sufficient for a diagnosis of definite ARF. A positive throat culture or rapid antigen test for GAS alone is less secure as 50% of those with a positive throat culture will be carriers only. Therefore, a positive culture alone demotes a case to probable or possible ARF
- ** Most cases of recurrence fulfil the Jones criteria. However in some cases (such as new carditis on previous RHD) it may not be clear. Therefore in order to avoid under-diagnosis, a presumptive diagnosis of rheumatic recurrence may be made where there are several minor manifestations and evidence of a preceding GAS infection in a person with a reliable history of previous ARF or established RHD. In addition, WHO (2004) recommendations state that where there is established RHD, a recurrent attack can be diagnosed by the presence of two minor manifestations plus evidence of a preceding group A streptococcal infection³⁸
- *** Acceptance of echocardiographic evidence of carditis as a major criterion is a modification to the Jones (1992) update
- # When carditis is present as a major manifestation (clinical and/or echocardiographic), a prolonged P-R interval cannot be considered an additional minor manifestation in the same person
- § Other causes of arthritis/arthralgia should be carefully excluded, particularly in the case of monoarthritis e.g. septic arthritis (including disseminated gonococcal infection), infective or reactive arthritis and auto-immune arthropathy (e.g. juvenile chronic arthritis, inflammatory bowel disease, systemic lupus erythematosus, systemic vasculitis and sarcoidosis. Note that if polyarthriti§ is present as a major manifestation, polyarthralgi cannot be considered an additional minor manifestation in the same person.

Special consideration should be given to high-risk population groups such as Māori and Pacific people, and those residing in poor socio-economic circumstances. In these cases, it may be important to err on the side of diagnosis and prophylaxis.

Source: NHF (2008). New Zealand Guidelines for Rheumatic Fever. 1. Diagnosis, Management and Secondary Prevention, page 15.²

Appendix 4: Factors that increase (“upgrade”) or decrease (“downgrade”) the quality of evidence according to the GRADE approach

Factors that may increase the quality level of a body of evidence (“upgrade”)²⁶⁵

1. Large magnitude of effect.
2. All plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect.
3. Dose-response gradient.

Factors that may decrease the quality level of a body of evidence (“downgrade”)²⁶⁵

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias.
2. Indirectness of evidence (indirect population, intervention, control, outcomes).
3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
4. Imprecision of results (wide CIs).
5. High probability of publication bias.

Appendix 5: UK National Screening Committee programme appraisal criteria

Criteria for appraising the viability, effectiveness and appropriateness of a screening programme^{119, 120}

Ideally all the following criteria should be met before screening for a condition is initiated:

The Condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

The Test

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

The Treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence based policies covering which individuals should be offered

treatment and the appropriate treatment to be offered.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

The Screening Programme

13. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (e.g. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these

Appendices

parameters should be scientifically justifiable to the public.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

Appendix 6: Modified Centor Criteria

SCORE (OUT OF 5)	RISK OF STREPTOCOCCAL INFECTION ^{44,45}	SUGGESTED MANAGEMENT
=<0	1-2.5%	No further testing or antibiotics
1	5-10%	No further testing or antibiotics
2	11-17%	Culture all, antibiotics for positive culture only
3	28-35%	Culture all, antibiotics for positive culture only
>=4	51-53%	Treat empirically with antibiotics and/or culture

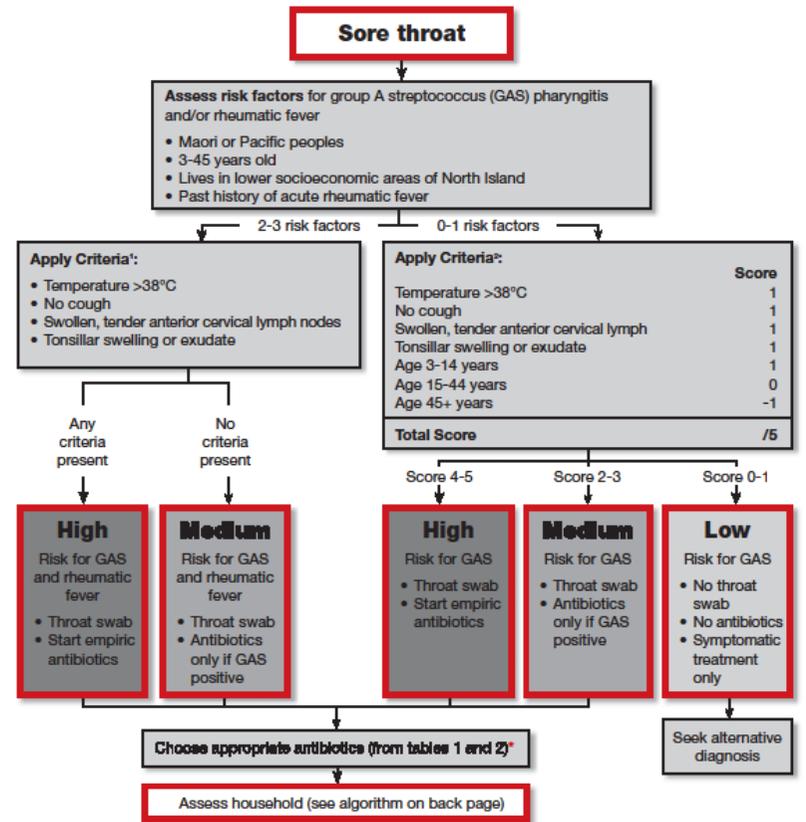
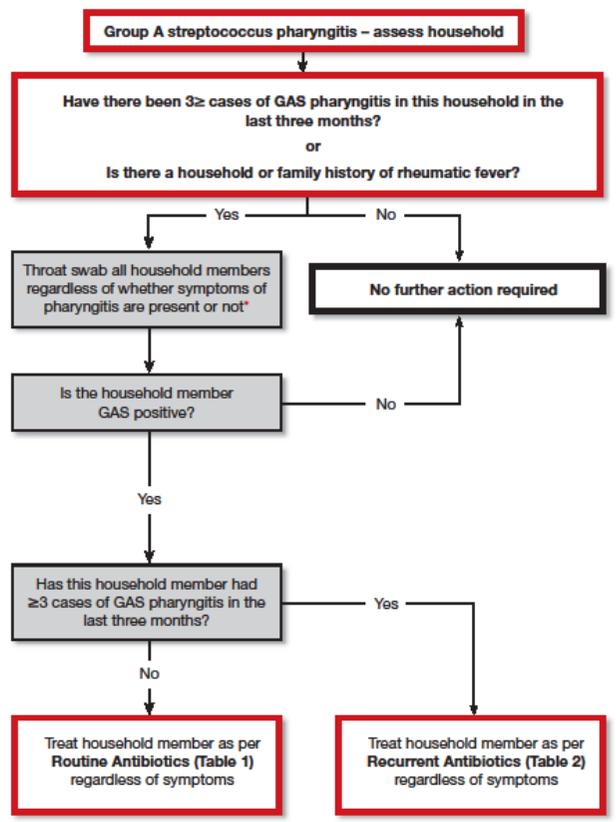
APPLY CRITERIA	POINTS
Temp > 38°C	1
No cough	1
Swollen, tender anterior cervical lymph nodes	1
Tonsillar swelling or exudate	1
Age 3-14 years	1
Age 15-44 years	0
Age 45+ years	-1
Total Score	/5

Source: Original source is Journal of the American Medical Association, 2004, 291(13): 1587-1596. Copyright © (2004) American Medical Association.²¹⁶ All rights reserved. Adapted with permission by the NHF (2008)⁷ who granted permission for reproduction in this dissertation.

Appendix 7: Algorithm for sore throat management in NZ

Source: NHF (2006).²⁶⁶ Available for download from
<http://www.heartfoundation.org.nz/files/Guide%20for%20Sore%20Throat%20Management.pdf>

[GUIDE] for household sore throat management **[GUIDE]** for sore throat management **ALGORITHM 4**



Abbreviations:
GAS = group A streptococcus
IM = intramuscular

* If impractical to swab, consider empiric antibiotic treatment

Algorithm based on the evidence-based, best practice New Zealand Guideline for Sore Throat Management (2006), produced by The National Heart Foundation of New Zealand and The Cardiac Society of Australia and New Zealand

Printed February 2007

- * If patient is on benzathine penicillin IM prophylaxis for acute rheumatic fever, and is GAS positive on throat swab, treat in the following way:
- If GAS positive in the first two weeks after IM penicillin injection has been given, treat with a ten day course of erythromycin (see table 1 and guideline)
- If GAS positive in the third and fourth weeks after IM penicillin injection, treat with a ten day course of oral penicillin (see table 1 and guideline).



Appendices

Table 1: Routine Antibiotics

Standard treatment of Group A Streptococcal positive pharyngitis for patient's first or second case of GAS pharyngitis in a three month period.

ANTIBIOTIC	ROUTE	REGIMEN	DURATION
Penicillin V Give as first choice Give on empty stomach	PO	Children: 20mg/kg/day in 2-3 divided doses Maximum 500mg 3 times daily (50mg 3 times daily for smaller children) Adults: 500mg twice daily	10 days
Erythromycin Ethyl Succinate (EES) Give if allergy to penicillin is reliably documented	PO	Children: 40mg/kg/day in 2-4 divided doses Maximum 1g/day Adults: 400mg twice daily	10 days
Benzathine Penicillin G (BPG) Give if compliance with 10 day regime likely to be a problem	IM	Children <20 kg: 600,000 U once only Adults and children >20 kg: 1,200,000 U once only	Single dose
Amoxicillin Useful alternative as can be given with food, may improve compliance	PO	Weight <30 kg: 750mg once daily Weight >30 kg: 1500mg once daily	10 days

Table 2: Recurrent Antibiotics

Recommendations for treatment of persons with multiple, recurrent, episodes of Group A Streptococcal pharyngitis proven by culture. Use if this is the patient's third (or more) case of GAS pharyngitis in a three month period.

ANTIBIOTIC	REGIMEN	DURATION	RATING [§]
Oral			
Clindamycin	Children: 20-30mg/kg/day in 3 divided doses Adults: 600mg/day in 2-4 divided doses*	10 days 10 days	B-II B-III
Amoxicillin; clavulanic acid	Children: 40mg/kg/day in 3 divided doses**,** Adults: 500mg twice daily	10 days 10 days	B-II B-III
Parenteral with or without oral			
Benzathine penicillin G	IM dose: See Table 1, or refer to IDSA guidelines [§]	1 dose	B-II
Benzathine penicillin G with Rifampicin	IM dose: See Table 1, or refer to IDSA guidelines [§] Rifampicin: 20mg/kg/day orally in 2 divided doses	4 days	

Source: Modified from Table five in the IDSA guidelines: Recommendations for treatment of symptomatic persons with multiple, recurrent, episodes of pharyngitis proven by culture or rapid antigen detection testing, Bisno A et al. 2002.³

Macrolides (e.g. erythromycin) and cephalosporins are not included in the table, because there is insufficient data to support their efficacy in this specific circumstance.

* Adult doses are extrapolated from data for children. Use of this drug for this indication has not been studied in adults. Clindamycin – further references available from: Tantz RR et al. 1991⁴, and Orling AA et al. 1994⁵

** Maximum dose, 750mg of amoxicillin per day

*** Refers to amoxicillin component. Note that clavulanic acid component may vary. Further reference from Kaplan EL et al. 1998⁶

§ Treatment with benzathine penicillin G is useful for patients in whom compliance with previous courses of oral antimicrobials is in question. Addition of rifampicin to benzathine penicillin G may be beneficial for eradication of streptococci from the pharynx.⁷ It has also been reported that addition of rifampicin (20mg/kg/day, once daily) during the final four days of a ten day course of oral penicillin V may achieve high rates of eradication.⁸ The maximum daily dose of rifampicin is 600mg; rifampicin is relatively contraindicated for pregnant women.

§ Infectious Diseases Society of America – United States Public Health Service grading system for rating recommendations in clinical guidelines⁹:

CATEGORY, GRADE	DEFINITION
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization, from cohort or case-controlled analytic studies (preferably from > 1 centre), from multiple time-series, or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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Appendix 8: Summary of studies looking at the proportion of pharyngeal GAS that represents true GAS pharyngitis

Table A-1. Summary of studies looking at the proportion of pharyngeal GAS that represents true pharyngitis

Study	Study design	Setting and subjects	Outcome	Quality	Generalisability to current NZ setting
Meyer and Haggerty (1962) ¹⁴⁷	Cohort	Massachusetts, USA, 1960-61 Households: 16 families with ≥2 children (100 individuals)	Percentage of pharyngeal GAS acquisitions in households associated with ≥2 fold rise in ASOT over 4 months (4 monthly samples) = 29%	Risk of bias as selection criteria not clear, participation rates unclear, potential contamination by penicillin treatment not accounted for, long interval between samples.	Poor. Historical and different population and setting.
Matanoski et al. (1968) ^{155, 165}	Case control	Maryland, USA, 1957-59 Households: Cases: 80 families (394 individuals) with a recent case of ARF and 84 families (408 individuals) with a distant case of ARF Controls: 179 non ARF families (1,017 individuals) Analysis performed on 103 ARF families and 101 controls able to be followed for ≥ 9 months	Percentage of pharyngeal GAS acquisitions in households associated with ≥2 fold rise in streptococcal titres (ASOT or antihyaluronidase, or both) over 8-10 weeks (monthly samples) = 29.9% in ARF families and 52.7% in controls	Poor. Risk of bias as selection criteria and participation rates unclear, statistical methods not used in matching. Risk of random error as no precision measures calculated, unclear whether statistically significant difference between cases and controls.	Poor. Historical and different population and setting.
El Kholy et al. (1980) ⁹¹	Cluster randomised controlled trial and cross-over study	Qalyub, Egypt, 1972-74 Households: 110 non ARF families and 84 suspected ARF families (with a child suspected of having RHD) Cluster randomised trial: 9 non RF and 43 suspected RF families randomised to penicillin treatment or control group for 2 years Cross-over trial: 99 non RF families randomly assigned to 1 year in the penicillin treatment group or 1 year in the control group, then changed for the 2nd year	Percentage of pharyngeal GAS acquisitions in households associated with ≥2 fold rise in streptococcal titres (monthly samples) = 9.0% for ASOT (7.6-10.5% in those not treated with antibiotics), 30.7% for anti-DNase B (30.3-37.3% for untreated), 9.3% for nicotinamide adenine dinucleotidase (6.1-8.7% in untreated)	Poor. Risk of bias as eligibility not well described, 43 families discontinued after 1 year. Risk of random error as no CIs and p values for the difference between the rates in ARF families and controls.	Poor. Historical and different population and setting.

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Valkenburg et al. (1971) ¹⁷²	Cohort	Netherlands, 1959-65 Eligible population from 27 GP practices 57,500; 1,517 patients with "pharyngitis" and 1,720 ≥ 6 years age sampled from Vourhoot and Southern Netherlands villages	56.2% (853/1,517) of those with pharyngitis (sore throat, red pharynx and no coryza or laryngitis or bronchitis) had GAS isolated on throat swab; 32.2% (489/853) of these not treated with antibiotics; 33.5% (164/489) of these with ≥2 fold rise in ASOT (3 weeks apart). In community sampling: 5% (11/234) to 12% (14/120) of those with GAS isolated in throat swab had ≥2 fold rise in ASOT (3 weeks apart)	Poor. Risk of bias as unclear difference between subjects who received antibiotic treatment and those who didn't, complete data only available on 70%.	Poor. Historical and different population and setting.
Kaplan et al. (1971) ¹⁷³	Prevalence, and case control	Emergency departments, Minnesota and Minneapolis, USA, 1964-67 624 children <15 years presenting with pharyngitis symptoms	GAS isolated on throat swab from 35% (218/624) of children presenting with pharyngitis symptoms; ≥2 fold rise in ASOT or anti-DNase B (3-6 weeks apart) in 43% of these (45% of those treated with antibiotics and 38% of those not treated with antibiotics)	Adequate. Risk of bias as participation rates not included and 80% received antibiotics which may have impaired titre rise.	Poor. Historical and different population and setting.
Ozturk et al. (2004) ¹⁷⁴	Prevalence	Duzce, Turkey, 2004 351 11-13 year old school children, with no symptoms of throat infection	GAS isolated on throat swab in 25.9% (91/351); single ASOT >200 IU/mL in 37% (34/91) of these; raised titres in 10.3% (27/260) of those with negative throat swabs (statistically significant difference, p< 0.05)	Poor. Risk of bias as participation rates not clear, unclear whether potential antibiotic treatment accounted for, single titre only may underestimate – paired titres more appropriate.	Poor. Different population and setting.

Appendix 9: Summary of studies of the attack rate of ARF following GAS pharyngitis

Table A-2. Summary of studies of the attack rate of ARF following GAS pharyngitis

Study	Study design	Setting and subjects	Variable of interest	Outcome	Quality	Generalisability to current NZ setting
Larsen (1933) in Madsen and Kalkak (1940) ¹⁸⁵	Outbreak investigation report	Kolding, Denmark, 1926-1927 2,500 inhabitants, 840 ill	Attack rate of ARF following milk-borne tonsillitis/pharyngitis in those requiring medical treatment	ARF attack rate in those with clinical tonsillitis and haemolytic streptococcus on throat swab (not sub-typed): 3.6% (30/840), 3 cases were recurrences	Poor. Risk of bias as case definition not stated, GAS not identified so attack rate probably over estimated. Risk of random error as no precision measures reported.	Poor. Historical and different population and setting.
Henningsen (1935) in Madsen and Kalkak (1940) ¹⁸⁵	Outbreak investigation report	Dragor, Copenhagen, 1935	Attack rate of ARF following milk-borne tonsillitis/pharyngitis in those requiring medical treatment	ARF attack rate in those with clinical tonsillitis and haemolytic streptococcus on throat swab (not sub-typed): 3.9%	Poor. Risk of bias as case definition not stated, GAS not identified so attack rate probably overestimated, unclear whether antibiotics given. Risk of random error as no precision measures reported.	Poor. Historical and different population and setting.
Henningsen and Ernst (1938) ¹⁸²	Outbreak investigation report	Morkov, Denmark, 1936 750 inhabitants, 100 ill	Attack rate of ARF following epidemic of milk-borne GAS tonsillitis/pharyngitis	ARF attack rate in those with clinical symptoms (sore throat): 2.2% (2/92)	Poor. Risk of bias as case definition not stated. Risk of random error as no precision measures reported.	Poor. Historical and different population and setting.
Dingle et al. (1945) ¹⁸³	Outbreak investigation report	North Carolina, USA, 1943 Fort Bragg infantry regiment; 228 exposed, 104 cases	Attack rate of ARF following epidemic of food-borne GAS tonsillitis in those admitted to hospital	ARF attack rate in those admitted to hospital with sore throat and GAS on throat swab: 3% (3/100). Some subjects received sulfadiazine for 5 days; attack rates in those treated and controls not reported.	Adequate	Poor. Historical and different population and setting.
Rammelkamp et al. (1952) ¹³⁹	Observational (unspecified)	Warren Air Force Base, Wyoming, USA, 1949-51 Young adult male military recruits, average age 20 years	Attack rate of ARF following exudative GAS pharyngitis (in which typeable GAS were isolated on throat swab) in those not treated with antibiotics	ARF attack rate: 3% (7/234)	Unclear from study report (not well described)	Poor. Historical and different population and setting.

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<p>Siegel et al. (1961)¹⁸⁶</p>	<p>Quasi – randomised controlled trial</p>	<p>Children’s Memorial Hospital Outpatient Department, Chicago, USA, 1956-59 2,545 children aged 3-16 years with clinical pharyngitis, those with GAS on throat swab (1,213) randomised to receive antibiotics (605), controls (608) treated symptomatically</p>	<p>Attack rate of ARF following GAS pharyngitis in controls</p>	<p>ARF attack rate varies according to definition of GAS pharyngitis: Sore throat: 0.15%; Sore throat and GAS on throat swab: 0.39%; Exudative pharyngitis and GAS on throat swab: 1.0%; Sore throat and GAS on throat swab and ≥ 2 fold rise in ASOT: 0.9%; Exudative pharyngitis and GAS on throat swab and ≥ 2 fold rise in ASOT: 2.1% No ARF in treatment group.</p>	<p>Poor. Risk of bias as unclear whether treatment and control groups well matched and whether different rates of participation (although 95% overall), no blinding. Risk of random error as no precision measures reported.</p>	<p>Poor. Historical and different population and setting.</p>
<p>Zimmerman et al. (1962)¹⁸⁴</p>	<p>Outbreak investigation report</p>	<p>Dickinson, North Dakota, USA, 1961 Population: isolated community of 10,000 (2,260 school children)</p>	<p>Attack rate of ARF following GAS pharyngitis</p>	<p>ARF attack rate of 3% (12/400) estimated in school children in whom GAS type 5 was isolated on throat culture</p>	<p>Poor. Risk of bias as case definition for GAS pharyngitis not stated, unclear whether subjects received antibiotics. Risk of random error as no precision measures reported.</p>	<p>Poor. Historical and different population and setting</p>
<p>Valkenburg et al. (1971)¹⁷²</p>	<p>Cohort</p>	<p>Netherlands, 1959-65 Eligible population from 27 GP practices 57,500; 1,517 patients with “pharyngitis” (sore throat, red pharynx and no rhinorrhoea, bronchitis or laryngitis) and 1,720 ≥ 6 years age sampled from Vourhoot and Southern Netherlands villages</p>	<p>Attack rate of ARF following GAS pharyngitis in those not treated with antibiotics</p>	<p>ARF attack rate varies according to definition of GAS pharyngitis: Patients with pharyngitis symptoms and GAS on throat swab and ≥ 2 fold rise in ASOT: 0.61%; Patients with pharyngitis symptoms and GAS on throat swab: 0.20%; Sampled individuals with sore throat and GAS on throat swab and ≥ 2 fold rise in ASOT: 0.80%; Sampled individuals with GAS on throat swab and ≥ 2 fold rise in ASOT: 0.26%; Sampled individuals</p>	<p>Poor. Risk of bias as unclear difference between subjects who received antibiotic treatment and those who didn’t, complete data only available on 70%.</p>	<p>Poor. Historical and different population and setting.</p>

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				with sore throat and GAS on throat swab: 0.17%		
Lennon et al. (2009) ²⁹	Group randomised controlled trial	South Auckland schools, NZ, 1998-2001 22,000 primary and secondary school students aged 5-18 years from 53 schools with ≥70% Māori or Pacific students, 27 schools randomised to intervention, 26 schools randomised to no intervention (control)	Intervention: school-based sore throat clinic with education, diagnosis and observed treatment of GAS pharyngitis (defined as sore throat with GAS on throat swab, or inflamed throat on examination with GAS on throat swab)	ARF incidence in intervention group (using NZ modified Jones Criteria) 59/100,000, incidence in control group 77/100,000 (RR 0.72, CI 0.40-1.30, p = 0.27). ARF attack rate following GAS pharyngitis in intervention group 0.2%. Compliance in intervention group 75%	Adequate. Risk of random error as underpowered.	Good. Similar population to contacts in Auckland (similar socio-economic status and ethnicities), although the study is limited to those 5-18 years whereas contacts may include a broader age group depending on particular contact tracing protocol used. Attack rate of ARF following pharyngitis in those not treated with antibiotics not directly measured so extrapolation required.

Appendix 10: Summary of studies of secondary attack rate of pharyngeal GAS acquisition and infection in households

Table A-3. Summary of studies of secondary attack rate of pharyngeal GAS acquisition and infection in households

Study	Study design	Setting and subjects	Variable of interest	Outcome	Quality	Generalisability to current NZ setting
James and Dingle et al. (1960) ^{92, 163, 164}	Cohort	Cleveland, USA, 1948-52 61 families, including adults and 170 children	Spread of pharyngeal GAS carriage and illness within households over 10 weeks	Rate of secondary GAS acquisition following exposure to asymptomatic carrier (positive GAS culture) = 9%. Rate of secondary GAS acquisition following exposure to symptomatic index case (positive GAS culture, compatible illness) = 25%. 41% of GAS acquisitions symptomatic, so rate of secondary symptomatic GAS following exposure to symptomatic index case = 10%	Poor. Risk of selection bias as selection was referral by doctor, reporting of illness reliant on subjects, no serological confirmation of infection. Risk of random error as no precision measures given.	Poor. Historical and different population and setting.
Breese and Disney (1956) ¹⁵⁴	Modified cohort	New York, USA, 1953 363 families, including 650 sibling contacts and 791 parent contacts of the index case.	Spread of pharyngeal GAS within households over 3 weeks	Secondary attack rate in siblings (of upper respiratory tract illnesses including those other than pharyngitis, together with positive throat swabs) = 20.6% and 19.4% for pharyngitis alone. Secondary attack rate in adults = 3.7%	Poor. Risk of bias as incomplete swabbing of siblings with younger and unwell siblings more likely to be swabbed, index cases given antibiotics at different stages of their illness, no serological confirmation of infection.	Poor. Historical and different population and setting.
Matanoski et al. (1968) ^{155, 165}	Case control	Maryland, USA, 1957-59 Cases: 80 families (394 individuals) with a recent case of ARF and 84 families (408 individuals) with a distant case of ARF Controls: 179 non ARF families (1,017 individuals) Analysis performed on 103 ARF families and 101 controls able to be followed for ≥ 9 months	Spread of pharyngeal GAS within households over 8-10 weeks	Rate of secondary GAS acquisition in 8-10 weeks (positive GAS culture) after exposure to an index case (first isolate in a household of a new strain) = 1.5% per person in ARF families and 2.9% in controls. Including negative cultures but streptococcal titres rise increased secondary attack rate to 5.4% and 5.3% per person for ARF and controls respectively.	Poor. Risk of bias as selection criteria and participation rates unclear, statistical methods not used in matching. Risk of random error as no precision measures calculated, unclear whether statistically significant difference between cases and controls.	Poor. Historical and different population and setting.

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Poku (1979) ¹⁵⁸	Mathematical modelling	Applied to selection of above population followed for 6 months, limited to those aged 0-16 years. ARF families; 102 Control families: 85	Spread of pharyngeal GAS within households over 1 month using Greenwood's binomial model	Average probability of GAS acquisition (positive throat culture) = 0.05-0.06 per person per month for both cases and controls.	Poor, because utilising results from a poorly designed study above, and because GAS does not fulfil one of the prerequisites for use of Greenwood's model (highly infective).	Poor. Historical and different population and setting.
Levine et al (1966) ¹⁶⁷	Case control	Loring Air force Base, Maine, USA, 1962-64 Cases and their contacts: 2,065 cases with positive GAS culture and compatible illness and 3,763 contacts Controls and their contacts: 709 controls with negative GAS culture and respiratory tract symptoms and 2,427 contacts	Spread of pharyngeal GAS within households over 9 months (over 2 seasons)	Rate of secondary acquisition of same type of GAS of 15.4% in case contacts. In control contacts overall GAS isolation rate was 4.5%.	Poor. Risk of bias as incomplete matching of cases and controls, some index cases treated with antibiotics and others not. Risk of random error as no precision measures used.	Poor. Historical and different population and setting.
El Kholy et al (1980) ⁹¹	Cluster randomised controlled trial and cross-over study	Qalyub, Egypt, 1972-74 110 non ARF families and 84 suspected ARF families (with a child suspected of having RHD)	Spread of pharyngeal GAS within households (treated and untreated results pooled) over undefined timeframe	Secondary attack rate of GAS acquisition (defined by positive throat culture alone) in ARF families of 8.7% in ARF families and 8.2% in non ARF families when the index case (defined by positive throat culture alone) was asymptomatic and rose to 27.7% and 15.1% respectively when the index case was ill with respiratory symptoms.	Risk of bias as eligibility not well described, 43 families discontinued after 1 year, unclear whether family size and ages were adjusted for in 2 groups. Risk of random error as no CIs and p values for the difference between the rates in ARF families and controls.	Poor. Historical and different population and setting.
Falck et al. (1997) ¹⁵⁹	Cohort	Primary care, Sweden, 1988-89 114 index cases and 110 families (263 family members)	Spread of pharyngeal GAS within households (over 1 month)	Secondary attack rate of GAS acquisition (positive throat culture) following exposure to index case (compatible illness and positive throat culture, treated with oral penicillin 5 days) of 33% and 8% for symptomatic acquisitions. Secondary attack rate doubles if index case has both positive throat and nasal swabs.	Adequate	Poor. Different population and setting.
Danchin et al. (2007) ¹⁶⁰	Cohort	Primary care, Melbourne, Australia 202 families (853 individuals)	Spread of pharyngeal GAS within households over 2 weeks	Secondary attack rate of GAS acquisition (positive throat culture or raised streptococcal serology) after exposure to an index case (compatible illness and positive throat culture or raised streptococcal serology) = 13%. Comparable rate for	Adequate. Unclear whether all index cases received antibiotics.	Poor. Different population and setting.

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				symptomatic acquisitions = 5%. 43% of families with an index cases developed ≥ 1 secondary case		
Lindbaek et al. (2004) ¹⁶⁸	Cohort	Primary care, Norway, 2000-2002 110 index cases and their household contacts (290 individuals)	Spread of pharyngeal GAS within households over 4 weeks	Secondary attack rate (clinically compatible illness with a positive throat swab, treated with 10 days oral penicillin) in household members = 14%. 27% of households with index case have ≥ 1 secondary case	Adequate	Poor. Different population and setting.
Kikuta et al. (2007) ¹⁶⁹	Non randomised controlled trial	Hokkaido, Japan, 2005-2006 1,181 index cases and 1,440 of their siblings (948 in prophylaxis group and 492 in control group)	Spread of pharyngeal GAS within households over 7-88 days in siblings not given antibiotic prophylaxis versus those given prophylaxis	Secondary attack rate in siblings who received no prophylaxis = 5.3%, in those with prophylaxis = 3.0%, only statistically significant for those given cephalosporins for 5 days	Poor. Non randomised, nonstandardised interventions, treatment of index case not accounted for, poor matching of those in intervention and control groups.	Poor. Different population and setting.

Appendix 11: Summary of studies comparing the occurrence of pharyngeal GAS in ARF household contacts with controls

Table A-4. Summary of studies comparing the occurrence of pharyngeal GAS in ARF household contacts with controls

Study	Study design	Setting and subjects	Comparison or intervention	Outcome	Quality	Generalisability to current NZ setting
Quinn and Federspiel (1966) ¹⁵⁷	Case control	Tennessee, USA, 1958-63 Cases: 19 ARF families (98 individuals) Control: 17 non ARF families (95 individuals)	Rate of pharyngeal GAS isolation, clinical pharyngitis and raised streptococcal titres	GAS isolated in 6.1% of ARF families and 6.3% of control families (presumed all ages). Incidence of GAS isolation and/or clinical pharyngitis and/or raised streptococcal serology 3.7 per 100 person months in ARF contacts and 4.3 in controls.	Poor. Risk of bias as selection criteria unclear, antibiotic treatment may have confounded, carriage and infection not distinguished. Risk of random error as no precision measures calculated, unclear whether statistically significant difference between cases and controls.	Poor. Historical and different population and setting. ARF episode not necessarily recent in ARF families, therefore may not meet definition for true contact.
Matanoski et al. (1968) ¹⁵⁵	Case control	Baltimore, USA, 1957-59 Cases: 80 families (394 individuals) with a recent case of ARF and 84 families (408 individuals) with a distant case of ARF Controls: 179 non ARF families (1,017 individuals)	Rate of pharyngeal GAS isolation	GAS isolation rates in recent ARF family members aged 3 months to 16 years: 9.53 per 100 person-months versus 9.49 in controls	Poor. Risk of bias as selection criteria and participation rates unclear, statistical methods not used in matching. Risk of random error as no precision measures calculated, unclear whether statistically significant difference between cases and controls.	Poor. Historical and different population and setting.
Collee et al. (1964) ¹⁹³	Case control (series 2)	Baroda, India 1963-64 Cases: 62 household members of 9 ARF patients Controls: 62 household members of 10 control patients	Rate of pharyngeal streptococcus on throat culture	Presumed GAS rate in contact (presumed all ages): 16% (10/62), Controls: 24% (15/62)	Poor. Risk of bias as participation rates not clear, poor matching of cases and controls, GAS not directly measured and risk of random error as small numbers, no precision measures, unclear whether statistically significant difference between cases and controls.	Poor. Historical and different population and setting.
Berrios et al. (1986) ¹⁹⁵	Case control	Santiago, Chile, 1978-82 ARF cases: 98 Family contacts: 360 Control individuals: 67 Control family contacts: 220	Rate of pharyngeal GAS on throat culture	GAS rate in family contacts (presumed all ages): 7.8%, controls 4.1%, no statistically significant difference (p=0.08)	Poor. Some risk of bias, because although high participation rate in cases and controls, cases and controls matched, only 60% participation rate in contacts. Random error accounted for with precision measures.	Poor. Historical and different population and setting.

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El Kholy et al. (1980) ⁹¹	Cluster randomised controlled trial and cross-over study	Qalyub, Egypt, 1972-74 110 non ARF families and 84 suspected ARF families (with a child suspected of having RHD)	Rate of pharyngeal GAS on throat culture in untreated families	GAS rate in family contacts (presumed all ages): ARF families: 33.1% Control families: 19%	Risk of bias as eligibility not well described, 43 families discontinued after 1 year, unclear whether family size and ages were adjusted for in 2 groups. Risk of random error as no CIs and p values for the difference between the rates in ARF families and controls.	Poor. Historical and different population and setting. ARF episode not necessarily recent in ARF families, therefore may not meet definition for true contact.
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Appendix 12: Summary of studies of secondary ARF in household/family members

Table A-5. Summary of studies of secondary ARF in household/family members

Study	Study design	Population and participants	Intervention or Comparison	Outcome	Results/Effect size	Quality	Generalisability to current NZ setting
Faulkner and White (1924) ²⁰³	Case control	Boston, USA, 1922-24 Cases: Families of 200 outpatients and ward cases of ARF, chorea and RHD at Massachusetts General Hospital (1,235 total subjects, 642 examined). Controls: Families of 75 people with no history ARF/chorea/RHD (474 total subjects, 366 examined).	Examination of 642 cases and 366 controls	Prevalence of ARF/chorea/RHD in families	35.5% of case families had >1 member with ARF/chorea/RHD while 16% control families had a members with this. Overall prevalence in cases sample of 8.79% and in control sample of 2.95%. Case families had increased RR of 2.2 of having another member in the family with ARF/chorea/RHD. 8.9% of 322 parents and 8.66% of the siblings of children with recent ARF also had evidence of a recent acute episode. Simultaneous infection frequently noted (not quantified). No comparison with control families.	Poor. Risk of bias as setting and selection process not well described, number of eligibles who participated not stated, controls and case not well matched, timeframes and method of information collection not well described or standardised, all important outcomes not assessed. Risk of random error as no precision measures.	Poor. The quoted secondary ARF attack rate of 8.9% in parents and 8.66% in siblings should be interpreted with caution. We do not know the timeframes involved or the corresponding background rate, and the diagnostic criteria used where dubious compared to today's standards.
St. Lawrence (1922) ²⁰²	Prevalence	New York, USA, ?1922 100 families (626 individuals) with at least 1 child aged 5-15 year with cardiac disease selected alphabetically from the Children's Cardiac Clinic of St Luke's Hospital. 63 families(580 individuals) studied completely; 480 "exposed persons" (family members of those with cardiac disease)	Questionnaire administered to parents in families	Rate of "rheumatic infection" (ARF, chorea or cardiac disease) and ARF in exposed persons and in families.	Rate of "rheumatic infection" in exposed persons of 14.8% (noted to be similar to the 14.6% of exposed family members reported to contract secondary TB in a study previously done on a similar population). 2 or more cases of "rheumatic infection" in 50% and ARF 24% respectively of families. ARF history in 10% of exposed persons, claimed to be much higher than background rate, although rate unknown. ARF history in 2 or more family members in 24%.	Poor. Risk of bias as unclear whether participants represent eligibles, timeframes not well described, unclear whether collection of data standardised, incidence measure used without stating timeframe involved. Risk of random error as no precision measures.	Poor. The rate of "rheumatic infection" in exposed family members while seemingly high should be interpreted with caution as it includes diagnoses that may not be ARF and the temporal relationship episodes between family members is not noted. The rate of ARF history in exposed people is stated to be higher than the background incidence but this is unknown.

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					Simultaneous attacks in 1 family.		
Stroud et al. (1933) ²⁰⁶	Prevalence	Philadelphia, USA, 1922-32 Eligible population: 458 children with ARF admitted to the Children's heart Hospital from 1922-32. From these 141 selected because more complete data was available in their case histories.	Hospital case history examination	Multiple epidemiological variables, including proportion of families in which there were more than 1 cases of RHD	34% (48/141) families with > 1 RHD member	Poor. Risk of bias as possible selection bias, diagnostic criteria not outlined, method of measurement unclear. Risk of random error as no precision measures.	Poor. Not useful in determining the secondary attack rate in households as the background rate is not stated and timeframes between ARF episodes within families not measured.
Paul and Salinger (1931) ²⁰⁵	Cohort	New Haven, USA, 1928 15 families from Children's Cardiac Clinic of the New Haven Dispensary and from the Cardiac Division of the Children's Community Center of New Haven in which 2 or more members had a history of ARF.	Survey	Relationship between time of onset of cases of ARF in a household	Qualitative only: primary or recurrent episodes of ARF frequently accompanied by almost simultaneous or immediately subsequent episodes in other family members and bouts tend to sweep through families in synchronous waves.	Poor. Risk of bias as selection not well described, unclear how many of eligibles declined, unclear whether measurement tool validated, recall bias likely, data incomplete for a large proportion, diagnosis of ARF unreliable. Risk of random error as very small sample size, outcomes not quantified and analysed.	Poor No quantification of secondary attack rate. No background prevalence or incidence of ARF/RHD given. Diagnostic unreliability. Poorly generalisable to the current context.
Irvine-Jones (1933) ²⁰⁴	Case control and case series	St Louis, USA and Toronto, Canada, 1933 Cases: 499 families with at least 1 "rheumatic member" from the Heart Clinic of the Hospital for Sick Children, Toronto, and 167 such families from the Children's Heart Clinic of Washington University and the St. Louis Children's Hospital. More in-depth	Mothers of children questioned, examination of family members, hospital records	Multiple epidemiological variables, including relative rate of rheumatism in case and control families, rate of rheumatism in unrelated household contacts, and the occurrence of simultaneous attacks of rheumatism in a family (within 8 weeks of initial case)	32-33% of case families had >1 member with "rheumatism". With index cases excluded the rate of secondary rheumatism in case families was 64 persons per 100 families in Toronto, 54 persons per 100 families in St. Louis and in control families was 31 persons per 100 families, an increase in RR in rheumatic families of almost 2. Rheumatism	Poor. Risk of bias as unclear what proportions of eligibles participated, potential for recall bias and diagnostic inconsistency, unclear whether cases and controls well matched, RR calculated per family but not standardised to size of family,	Poor. Unlike the studies listed above, this study supports familial clustering of ARF/RHD because a control is included to represent the background rate. However timeframes between onsets of ARF in various members of the same family are not given, so the secondary attack rate in the weeks or months following an episode of ARF cannot be determined. The finding of 1/3 of cases in

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		<p>case series study in 50 St. Louis and 166 Toronto families with > 1 member with rheumatism.</p> <p>Controls: 70 “non rheumatic” families from Toronto whose children attended heart clinic for non rheumatic persons, chest clinic or the holiday camp at Ontario.</p>			<p>occurred in 25% of unrelated borders and 65% of non first degree relatives living in close contact with rheumatic families (less than 20 total). 34% of all rheumatic attacks in the rheumatic families occurred “simultaneously” i.e. within an 8 week period of following the index episode, giving a 1/3 chance of attacks being clustered rather than sporadic.</p>	<p>incidence used without time periods. Risk of random error as no precision measures used.</p>	<p>families being “simultaneous” is interesting but the risk of another case occurring after an initial case is not stated.</p> <p>Rheumatism occurring in 25% of unrelated border and 65% of relatives suggests a relative increased risk for ARF household relatives of cases over non relatives; however the numbers are too small to be conclusive.</p>
Read et al. (1938) ²⁰⁷	Case control	<p>Baltimore, USA., 1935-36 Cases: 33 white children under 15 years, admitted to the Cardiac Clinic of Harriet Lane Home between 1935 and 1936. Controls: 33 white children, who had at least 1 child over 7 years in the family, admitted to the TB Clinic between 1935 and 1936</p>	<p>History and examination of all family members of cases and controls at baseline and twice more over 2 years</p>	<p>Family members with ARF or RHD</p>	<p>15.5% of siblings of cases had ARF/RHD history, compared with 4% of controls. Attack rate of ARF 14.1/1000/year in case's siblings and 4.1/1000/year in control's siblings, a RR increase in case's siblings of 3.9 (p =0.003) 20/33 (60.6%) of case's families had >1 ARF individual</p>	<p>Poor. Risk of bias as setting not well described, not clear what proportion of eligibles studied, unclear whether measurement standardised. Diagnostic criteria well outlined. Outcome measures relatively well described and precise.</p>	<p>Poor.</p> <p>Unlike some of the studies listed above, this study supports familial clustering of ARF/RHD because a control is included to represent the background rate. However timeframes between onsets of ARF in various members of the same family are not given, so the secondary attack rate in the weeks or months following an episode of ARF cannot be determined.</p>
Rosenblum and Rosenblum (1941) ²⁰⁸	Cross-sectional	<p>Chicago, USA, 1938 70 families with a child with a history of ARF attending the Christopher Public School</p>	<p>Survey/interviews performed with verification of answers from clinical records)</p>	<p>Multiple outcomes, the most relevant included: Prevalence of other family members with history of ARF Number of members of family with history of ARF per family. Incidence of ARF cases in a family before and after contact with a family member with an acute episode of ARF. Rate of simultaneous attack (up to several weeks apart) of ARF in more than one member of a family.</p>	<p>Prevalence of families with other ARF members with a history of ARF of 50%. Prevalence of a history of ARF amongst individuals of 9%. Number of people in family with history of ARF ranged from 1 -7, but 90% had either 1 or 2. Incidence of ARF cases in a family before contact with a family member with an acute episode of ARF of 4.55 cases per 1000 person years, and after of 10 per 1000 person years, a RR increase of 2.5, but the time after the exposure for which</p>	<p>Poor. Risk of bias as eligible population not well described, poor description of study period and data collection methods, unclear whether objective measurements e.g. validated questionnaire, risk of recall bias and misdiagnosis. Risk of random error as incidence used when should have been prevalence, no precision measures,</p>	<p>Poor.</p> <p>Suggests familial clustering of ARF; however background prevalence/incidence not stated so fails to demonstrate whether prevalence in families is higher than background prevalence. The 2.5 RR of having further cases of ARF in family after an index ARF case together with 21% of families having several members of the same family affected by ARF over a period of weeks does suggest a significant secondary attack rate in households for ARF, but these measurements are imprecise, do not state</p>

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				<p>Predisposing factors to ARF episode.</p>	<p>the measurement was made is not stated. Rate of simultaneous attack: occurred in 4 of 19 families (21%), but the attack rate per person and per unit time not given.</p>	<p>incidence not age standardised.</p>	<p>timeframes, involve small numbers and no background incidence or secondary attack rate in other settings such as schools is given for comparison. The overall rates during the 1930s were significantly higher than today and therefore it is difficult to generalise these figures to the current context.</p>
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Appendix 13: Summary of studies of the effect of swabbing and treating pharyngeal GAS in households on ARF incidence

Table A-6. Summary of studies of swabbing and treating pharyngeal GAS in households on ARF incidence

Study	Study design	Population and participants	Intervention or Comparison	Outcome	Results/Effect size	Quality	Generalisability to current NZ setting
El Kholy et al. (1980) ⁹¹	Cluster randomised controlled trial and cross-over study. Presumed no blinding or placebo used.	Qalyub, Egypt, 1972-74 110 non RF families (56 with a child previously determined to be a GAS carrier and 54 without a child GAS carrier) and 84 suspected RF families (with a child suspected of having RHD), of whom 30 families had a child with subsequently confirmed RHD Cluster randomised trial: 9 non RF and 43 suspected RF families randomised to penicillin treatment or control group for 2 years. Cross-over trial: 99 non RF families randomly assigned to 1 year in the penicillin treatment group or 1 year in the control group, then changed for the 2nd year.	Throat cultures were performed bimonthly on all subjects. Intervention: IM BPG treatment of individuals who had acquired pharyngeal GAS on throat culture, regardless of symptoms. Control: no treatment of those with pharyngeal GAS on throat culture.	Prevalence of GAS, number of introductions of GAS into families, spread of GAS within families, ARF incidence	Marked decrease in GAS prevalence in treatment group for both non ARF families (19.0 to 5.4%) and confirmed ARF families (33.1 to 9.0%). Modest decrease in GAS introductions into families (0.79-0.54 single introductions per person per year) in treatment group for both non RF (0.79 to 0.54 single introductions per person per year) and suspected RF families (from 0.66 to 0.50 single introductions per person per year). No decrease in spread within families in treatment group. 1 case of ARF only (in control group).	Poor. Risk of bias as eligibility and allocation not well described, not blinded, 43 families discontinued after 1 year, unclear whether in cross over or cluster randomised trial, unclear why. Compliance with throat swabs good (99.1%), but compliance with penicillin treatment not discussed. Contamination unclear: not discussed whether control group received penicillin for other intercurrent illnesses during study period. Unclear whether intervention and control group's family size and ages were adjusted for. Risk of random error as RR was only given for some outcomes and no precision mentioned (no p values or CIs), underpowered for ARF reduction.	Poor. Study too small to conclude whether treatment had an effect on the incidence of ARF, therefore a poor study for addressing the question of whether the intervention reduces ARF incidence. Also poorly generalisable to the situation of 1 off household swabbing and treatment as in this study households had bimonthly swabbing and treatment for 2 years.

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<p>Neilson et al. (1993)²³⁰</p>	<p>Uncontrolled, non-randomised community intervention</p>	<p>Yarrabah Aboriginal community in north Queensland, Australia, 1985-91.</p> <p>89% participated in 1985 survey and 87% of children aged 4-16 years in 1991 survey.</p> <p>All children aged 4-16 years eligible for intervention ?number of eligible and actual participants.</p>	<p>All subjects had throat swabs taken 3 times each year.</p> <p>Intervention: Those with swabs showing GAS were treated with antibiotics (oral penicillin, amoxicillin, erythromycin, or IM BPG); their contacts were also swabbed and treated if GAS were found.</p> <p>No control.</p>	<p>Incidence of ARF pre and post intervention</p>	<p>Incidence of ARF: Pre intervention: 4/1000/year.</p> <p>Post intervention: 1/community/6 years; assuming community population stable at 1250 = 0.1333/1000/year</p>	<p>Poor.</p> <p>Risk of bias as number/percentage of eligibles agreeing to participate in intervention not stated, compliance with intervention not stated, intercurrent antibiotic treatment not accounted for, small total number agreed to follow up at end of study potentially reducing chance of detecting new subclinical disease, no control group, the outcome measure (incidence post intervention was described but not converted into a standardized rate so comparison could be made with the pre intervention incidence). The RR reduction was not calculated.</p> <p>Risk of random error as no precision measures stated.</p>	<p>Poor.</p> <p>Poor generalisability from this context to the situation of one off household contact swabbing to reduce ARF incidence.</p> <p>This is because in this study those swabbed and treated were the entire community of children, not just household contacts of an ARF case, and they were swabbed and treated on an ongoing basis 3 times a year for 6 years, rather than as a 1 off occurrence. The reduction in incidence seen is probably as a result of total decreased GAS burden in the entire community.</p>
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Appendix 14: Frequency of *emm* types found in cases and contacts in ARPHS case-contact study

Table A-7. Frequency of *emm* types found in cases and contacts.

<i>Emm</i> type	Frequency	%	Frequency in cases	Frequency in contacts
6	8	19%	1	8
12	1	2%	1	0
39	3	6%	1	2
82	3	6%	0	3
101	3	6%	1	2
108	3	6%	1	2
49	2	4%	1	1
70	2	4%	0	2
74	2	4%	1	1
91	2	4%	0	2
99	2	4%	0	2
106	2	4%	1	1
61/44	2	4%	1	1
65/69	2	4%	1	1
58	1	2%	0	1
59	1	2%	1	0
63	1	2%	0	1
77	1	2%	0	1

Appendix 15: Summary of combined findings from literature review and ARPHS contact tracing study

Table A-8. Summary of combined findings from literature review and ARPHS contact tracing study, in respect to the evidence that the NZ ARF household contact tracing programme meets the criteria to be effective, appropriate and feasible

Condition	Meets criterion	If insufficient evidence to meet criterion, direction that evidence is leaning	GRADE evidence level	Evidence gap	If evidence gap, suggested research	Effectiveness or appropriateness or feasibility
Condition:						
1.Serious and of public health importance	Yes		Moderate			Appropriateness
2.Infectious cause, communicable from person, vector or environment to person	Yes		Moderate	No		Effectiveness
3.The natural history of the condition is known from latent to declared disease	Yes ^a		Moderate	Partial ^a	Quantify infectious period and degree of subclinical GAS pharyngitis and ARF	Effectiveness
4. The proportion of cases with the condition that are not promptly diagnosed should be low	Insufficient evidence	Towards not meeting criterion	Low	Yes	Quantify subclinical disease, access to healthcare for those with ARF/RHD and clinician's recognition of ARF	Effectiveness
5.The occurrence of the condition is low in the general population	Yes ^b		Moderate ^b	No		Effectiveness
Contacts:						
6. There is a high degree of contact tracing sensitivity	Insufficient evidence	Towards meeting criterion	Low	Yes	Further observational case series/audit of contact tracing in NZ	Effectiveness, appropriateness, feasibility
7.Contacts can be reached in a timely manner, before onward transmission, or disease development	Insufficient evidence	Towards not meeting criterion	Low	Yes	Further observational case series/audit of contact tracing practice in NZ. Better quantification of timeframes involved in onward spread of GAS within households	Effectiveness, appropriateness, feasibility
8.There should be a high PPV	Insufficient evidence	Towards not meeting criterion	Low	Yes	Research GAS pharyngitis rate in contacts in NZ	Effectiveness
9. There should be a higher risk of infection and/or severe disease in contacts than in the general population, and the overall burden of secondary disease should be significant	Insufficient evidence	Towards not meeting criterion	Nil-very low	Yes	Determine secondary attack rate of GAS pharyngitis and ARF in ARF household contacts versus controls, and then ideally compare this with and without contact tracing	Effectiveness
Intervention:						

^a Gap in evidence regarding duration of pharyngeal GAS infectiousness, extent of subclinical GAS pharyngitis and ARF

^b It is not known where this occurrence lies with respect to the contact tracing threshold for ARF

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Condition (ARF) case finding:						
10. The rate of case detection should be greater than that expected to be found by screening or by presentations of individuals to healthcare on the basis of development of symptoms	Insufficient evidence	Towards not meeting criterion	Low	Yes	Further studies of case finding rates in contact tracing in NZ	Effectiveness
11. Intervention for cases found leads to better disease outcome for case and/or reduction in transmission	Yes ^c		Moderate	Partial ^c	Ascertain whether case finding makes an impact on GAS transmission	Effectiveness
Condition (ARF) case prevention: Test/clinical assessment:						
12. There should be a suitable (i.e. simple, safe, precise, valid and rapid) and acceptable test or clinical assessment (i.e. history or examination) available to detect the infection, infectious carriage or immunity to the infection that in the case of infection ideally can be administered <i>before</i> the person develops the condition	Insufficient evidence	Towards meeting criterion	Moderate for rapidity, precision; nil-low for validity, acceptability	Yes	Study throat swab acceptability, validity	Effectiveness, appropriateness, feasibility
13. Agreed policy on the further diagnostic investigation and treatment options of individuals with a positive test/clinical assessment result.	Yes		Moderate	No		Effectiveness, appropriateness, feasibility
Condition (ARF) case prevention: Other interventions:						
14. Effective treatment or intervention for contacts identified through testing or clinical assessment as having infection (GAS), or for contacts with no current clinical evidence of infection but deemed to be at significantly increased risk of infection because of their contact; and there should be evidence that early intervention/treatment leads to better outcomes than no or late treatment/intervention	Yes ^d		Moderate	Partial ^d	Quantify the number and proportion of contacts with GAS in NZ, and ideally to quantify the number and proportion with true infection, so potential benefits can be balanced against any potential adverse effects. Ascertain whether treatment of contacts reduces transmission of GAS.	Effectiveness
15. Evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered	Insufficient evidence ^e	Towards meeting criterion	Nil-low	Partial ^e	Define who to test and treat	Effectiveness, appropriateness, feasibility
The programme:						
16. Evidence of disease (ARF/RHD) reduction: There should be evidence from high-quality randomised controlled trials that the contact tracing programme is effective in reducing mortality or morbidity from the condition.	Insufficient evidence	Unknown	Nil	Yes	Controlled trial or mathematical disease modelling to determine secondary attack rate of ARF in contact traced versus not contact traced households	Effectiveness
17. The complete contact tracing programme (test, diagnostic procedures, treatment/intervention) is clinically, socially, culturally and ethically acceptable to health professionals and the public	Insufficient evidence	Unknown	Nil	Yes	Survey, qualitative: focus groups, key informant interviews	Appropriateness

^c Insufficient evidence to ascertain whether reduction in GAS transmission

^d Degree of benefit of ARF reduction has not been proven in this setting; reduction of GAS transmission has not been clearly demonstrated in this setting

^e Evidence-based policies on appropriate treatment established, but insufficient evidence regarding who to treat

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18. The benefit from the contact tracing programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).	Insufficient evidence	Unknown	Very low	Yes	Surveys, audits, qualitative studies. ARF reduction outcome studies.	Effectiveness, appropriateness
19. The costs should be balanced against the benefits	Insufficient evidence	Unknown	Nil	Yes	Cost benefit analysis	Feasibility
20. There should be a plan for managing and monitoring the contact tracing programme and an agreed set of quality assurance standards	No		Not applicable	No		Effectiveness, appropriateness, feasibility,
21. Adequate staffing and facilities for testing, diagnosis, treatment, and programme management should be available prior to the commencement of the contact tracing programme	Insufficient evidence	Observation evidence in Auckland pointing towards criterion not being met	Low	Yes	Resource allocation audits	Feasibility
22. Evidence-based information, explaining the consequences of the contact tracing intervention should be made available to contacts to assist them in making an informed choice	Yes		Moderate	No		Effectiveness, appropriateness
23. Public pressure for widening the eligibility criteria for contact tracing should be anticipated. Decisions about these parameters should be scientifically justifiable to the public	No	Unknown	Not applicable	Yes	Research regarding who to target (those at highest risk) and optimal timeframes	Effectiveness, appropriateness

Appendix 16: Application of adapted chemoprophylaxis criteria to ARF and other communicable diseases

Table A-9. Application of adapted chemoprophylaxis criteria to ARF and other diseases

	Invasive meningococcal disease	Invasive Hib infection	iGAS infection	ARF
Severity and burden	Yes Incidence 2-6/100,000/year (UK), ²⁶⁷ 6.1/100,000/year (NZ 2005) ²⁶⁸ CFR 10-14%, 11-19% of survivors have long-term sequelae ²⁶⁹	Yes CFR 5% developed countries, 25% developing ²⁷⁰ Incidence 1.7/100,000 in <5 year olds (NZ 1999, post introduction of vaccination) ²⁷¹	Yes Incidence 3.1/100,000/year (USA 2000), 8.1/100,000/year (Auckland, 2005-06) ²⁶⁴ Deaths 0.4/100,000 Case fatality rate 12-13% ⁷⁴	Yes Incidence 3.4/100,000 (NZ 1996-2005) ¹ 60% of ARF leads to RHD; >120 RHD deaths per year (NZ 1992-97)
Increased risk of subsequent disease in household contacts and significant burden due to this: Increased RR AR	Yes ²⁷² 2-3% of all cases are secondary (USA, UK) ^{269, 272} RR 500-800 ²⁷³ AR 1/300 ²⁷³⁻²⁷⁶	Yes RR 585 ²⁷⁷ AR(in pre vaccine era): 0.3% all ages, ^{278, 279} 3.8% for <2 years, 2.1% for ≤5 years ²⁸⁰	Yes for increased risk, controversial for significance of burden. Increased risk in contacts in 2 studies, ^{281, 282} but AR low. RR: 19-200 ²⁸³ AR: 66-294/100,000 ⁷⁴	Unknown
Effectiveness of contact tracing intervention: NNT Risk reduction/number of cases prevented	Yes No controlled trials, 4 retrospective observational studies meta analysis ^{273, 275, 284-286} NNT: 200 ²⁸⁶ Risk reduction 89% ²⁸⁶	Yes Controlled trials: Rifampicin 92-97% effective at eradicating carriage ²⁸⁷⁻²⁹⁰ Controlled trials and observational studies: Rifampicin 100% efficacy at preventing disease ²⁹⁰ Estimated to prevent up to 180 cases per year in USA (1984) ²⁷⁹	Controversial No controlled trials ^{74, 115, 283} Lack of clearly effective chemoprophylactic regimen ^{74, 115} NNT: >2,000 (UK), ¹¹⁵ , 300 (Canada) ¹¹⁶ 8-64 cases prevented per year in US if 100% effective ⁷⁴	Unknown No controlled trials
Burden of contact tracing intervention: Safety Cost Feasibility	Yes Satisfactory safety, cost effectiveness and feasibility ^{112, 291}	Yes Satisfactory safety, cost effectiveness and feasibility ²⁷⁹	Controversial Safety questionable ¹¹⁵ Cost: \$Canadian 13,500 per case prevented – deemed cost effective in Canada ¹¹⁶ Feasibility questionable ¹¹⁵ 12,000-22,000 would require chemoprophylaxis yearly in US ⁷⁴	Unknown
Household contact tracing recommended or practised	Yes , widely for more than 50 years in Europe, North America, UK, Australasia. Chemoprophylaxis for all household contacts.	Yes , widely since 1990s in Europe, North America, UK, Australasia. UK: all household contacts of the index case with confirmed or probable invasive Hib disease should receive chemoprophylaxis if there is a vulnerable individual in the household (unimmunised child, or	Variable Canada: since 1995 chemoprophylaxis routinely recommended and practiced for contacts of severe cases only; advice to all. USA: routine chemoprophylaxis not recommended or practiced, advice to all and consider targeted	Variable USA: recommended and presumably practiced since 1970s. NZ: recommended and practiced variably since 1980 -1990s, more comprehensively in past 5 years. Australia: not recommended or practised. Elsewhere: no information on

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		<p>immunosuppressed or asplenic individual)²⁶⁰</p>	<p>prophylaxis for those at increased risk of sporadic disease. UK: chemoprophylaxis not routinely recommended except for neonate and mother, and those with symptoms of localised disease; advice to all. NZ: no national recommendation.</p>	<p>whether routinely recommended or practiced.</p>
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