



# New Zealand Guidelines for Rheumatic Fever

Group A Streptococcal Sore Throat Management  
Guideline: 2014 Update.



Evidence-based, best practice Guidelines on:

1. Diagnosis, Management and Secondary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease: 2014 Update.
- 2. Group A Streptococcal Sore Throat Management: 2014 Update.**
3. Proposed Rheumatic Fever Primary Prevention Programme

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# **Group A Streptococcal Sore Throat Management Guideline Update 2014**

He korokoro ora he manawa ora, mō tātou katoa

A healthy throat, a healthy heart for us all

*Lance O'Sullivan 2006*

**August 2014**

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## Preface

Acute rheumatic fever (ARF) is an auto-immune disease caused by untreated group A streptococcal (GAS) pharyngitis. It can cause significant ill health with lasting damage to the heart (rheumatic heart disease) and premature death. It “casts a long shadow” in terms of the health, social and economic costs to individuals, whānau and the broader community. As a serious sequela of one of a group of close contact infectious diseases, it is a marker of child and family poverty and ill-health which is closely related to poor quality housing and overcrowding. ARF has been almost eradicated in nearly all developed countries but high rates persist in New Zealand, almost exclusively in Māori and Pacific children. In recent years successful advocacy in New Zealand has resulted in increased public and political awareness of ARF. The current Government has targeted ARF and allocated funding for a national prevention programme. School sore throat clinics have been opened in high risk settings and more are planned. Funding has been allocated for community awareness campaigns and healthy housing initiatives. This national programme has now been underpinned by research investment in a number of projects across the causal pathway including vaccine development.

A concerted and sustained effort from the whole of the community and across Government will be required to control rheumatic fever. Effective primary and secondary prevention in high risk settings must be guided by evidence-based quality standards and closely linked to improvement in the “upstream” determinants for final success. The following guidelines are a revision of the initial Heart Foundation Guidelines (2008).<sup>1</sup> They are intended to provide best practice recommendations to underpin and inform the current substantial efforts being made in the community and through primary care to eradicate rheumatic fever.

Professor Norman Sharpe  
Medical Director (Retired), Heart Foundation

## Scope and Purpose of the Guideline Update

The purpose of this document is to update key aspects of the 2008 evidence-based guideline for *Group A Streptococcal Sore Throat Management*.<sup>1</sup>

This Guideline Update has been developed to inform current best practice for the management of group A streptococcal (GAS) pharyngitis and focuses on updating:

- Recommendations for antibiotic therapy in routine treatment and recurrent episodes of GAS pharyngitis
- Management of GAS spread
- GAS carriage
- Treatment of household contacts
- Role of tonsillectomy

Refer to [page 9](#) for Summary and Key Recommendations of this Guideline Update. **This Guideline Update supersedes the 2008 Guideline.** The clinical questions that have not been updated in this edition are clearly labelled in the text of this document.

Pharyngitis is a common medical condition which is usually viral and benign. In the New Zealand population, GAS pharyngitis is the most important bacterial throat infection encountered in primary care because of the morbidity and mortality associated with the sequelae of rheumatic fever. The underlying premise is that preventing and treating streptococcal pharyngitis will reduce the incidence of rheumatic fever.<sup>2</sup> The aim of this guideline update is to maximise diagnosis and management of pharyngitis in those who are at greatest risk of developing rheumatic fever, while minimising investigations and antibiotic use in those who are at the lowest risk. The clinical end point is rheumatic fever prevention.

This Guideline Update is intended for health professionals involved in the diagnosis and management of anyone who presents with pharyngitis in a community, public health, primary and secondary care settings including; general practitioners, public health nurses, practice nurses, other medical practitioners including paediatricians and physicians, nurses and doctors in emergency departments, nurses, community pharmacists and other community health workers.

## Outline of Grading Methodology Used

Levels of evidence and accompanying grades of recommendation ([Table 1](#)) are used in this guideline update. They were adapted and used in the 2008 Group A Streptococcal Sore Throat Management Guideline.<sup>1</sup>



**Table 1. Levels of Evidence for Clinical Interventions and Grades of Recommendation**

Level of Evidence	Study Design	Grade of Recommendation	
I	Evidence obtained from a systematic review of all relevant randomised controlled trials (RCT)	A	Rich body of high-quality randomised controlled trial (RCT) data
II	Evidence obtained from at least one properly designed randomised controlled trial	B	Limited body of RCT data or high-quality non-RCT data
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)	C	Limited evidence
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group	D	No evidence available – panel consensus judgement
III-3	Evidence obtained from comparative studies with historical control, 2 or more single-arm studies, or interrupted time series with a parallel control group		
IV	Evidence obtained from case series, either post-test or pre-test and post-test		

**Source:** The levels of evidence and grades of recommendations are adapted from the National Health and Medical Research Council levels of evidence for clinical interventions and the US National Institute of Health clinical guidelines. Details can be found at [www.nhlbi.nih.gov/guidelines/index.htm](http://www.nhlbi.nih.gov/guidelines/index.htm).

### Guideline Update Process

During 2012 to 2013 Dr Melissa Kerdelmidis was employed as a research fellow by the Department of Paediatrics at the University of Auckland and the Heart Foundation of New Zealand to update the Group A Streptococcal Sore Throat Management Guideline (search strategies in [Appendix 1](#)).<sup>1</sup> The Guideline Update was Co-Chaired by Professor Diana Lennon and Dr Briar Peat. Rachel Liddel was project manager. The Lead Authors identified the clinical questions that required updating and Dr Kerdelmidis undertook a review of the evidence. An Advisory Group consisting of experts from general practice, paediatrics, microbiology and nursing as well as the Ministry of Health met in August 2013 to consider the evidence and recommendations. The Advisory Group reviewed the guideline update before it was peer reviewed by national and international experts and endorsement sought by New Zealand and international organisations. Following peer review, the Advisory Group viewed the Guideline Update before it was published in August 2014.

### Disclaimer

The production of this document has been supported by the Heart Foundation of New Zealand and the Cardiac Society of Australia and New Zealand for the guidance of health professionals. The statements and recommendations it contains are, unless labelled as “expert opinion”, based on independent review of the available evidence. Interpretation of this document by those without appropriate health training is not recommended, other than at the request of, or in consultation with, a relevant health professional. The Heart Foundation does not accept any legal liability or responsibility for any loss, damages, costs or expenses incurred by the use of, or reliance on, or interpretation of, the information within this publication.

In addition, the recommendations in this Guideline Update are not intended to replace clinical judgement. Treatment of individuals should take into account co-morbidities, drug tolerance, lifestyle, living circumstances, cultural sensibilities and wishes. When prescribing medication, clinicians should observe usual contra-indications, be mindful of potential adverse drug interactions and allergies, monitor responses and ensure regular review. This guideline focuses on group A streptococcal pharyngitis and does not attempt to address other causes of sore throat including rarer bacterial pathogens which may need clinical treatment ([Appendix 2](#)).



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## **Endorsing Organisations**

This Guideline Update yet to be considered by professional organisations for endorsement.

## **Declaration**

No conflicts of interest were apparent in the development of this Guideline Update. Dr. Melissa Kerdelmelidis who researched the evidence for this guideline was funded primarily by the Heart Foundation of New Zealand and the University of Auckland and also by the Canterbury District Health Board. Dr. Melissa Kerdelmelidis co-ordinated the writing of the 2008 guideline and was funded at that time by The Rheumatic Fever Trust and the Heart Foundation and office space was funded by the New Zealand Guidelines Group.

## Summary and Key Recommendations

Both the sore throat management and household sore throat management algorithm have been updated.

- Acute rheumatic fever (ARF) can be prevented by the correct treatment of group A streptococcal (GAS) pharyngitis.
- In New Zealand, both populations at high risk for ARF, and populations at low risk for ARF, exist.
- The population at **High Risk for Rheumatic Fever** is defined as those individuals who have a personal, family or household history of rheumatic fever, or who have **two or more** of the following criteria; Māori or Pacific ethnicity, age 3-35 years or living in crowded circumstances or in lower socioeconomic areas of the North Island.
- The population at **Low Risk for Rheumatic Fever** is defined as those who are non-Māori and non-Pacific people, children under 3 years old and adults older than 35 years old, those not living in crowded circumstances or lower socioeconomic areas of North Island and with no personal, family or household history of acute rheumatic fever.
- In the population at high risk of ARF, the correct treatment of GAS pharyngitis will substantially reduce the occurrence of ARF.
- In the population at low risk of ARF, minimisation of throat swabbing and antibiotic treatment (and associated costs) should be the aim. There is no evidence that ARF rates have decreased due to pharyngitis management in this group. It is more likely to be an improvement in socio-economic circumstances including better housing.
- Throat swabbing remains the gold standard for diagnosing GAS pharyngitis.
- Rapid Antigen Diagnostic Tests are not currently recommended in high risk rheumatic fever settings. Further research is required to confirm their sensitivity and specificity in high risk settings so that they may reliably assist early diagnosis.
- Confirmed or suspected GAS pharyngitis in high risk populations, should be treated as soon as possible after diagnosis. To ensure ARF prevention, it is not safe to wait up to nine days as previously recommended.
- Antibiotic recommendations have been updated for the treatment of routine (first or second) and recurrent (third or more within a three month period) GAS pharyngitis.
  - Courses of oral antibiotics for GAS pharyngitis should be of 10 days duration. There is no evidence that shorter courses prevent the subsequent development of rheumatic fever.
  - Benzathine penicillin can be given with lignocaine to reduce injection site pain. Both can be used in pregnant and breast feeding women.
  - The smaller dose (450mg/0.6 mega units) of benzathine penicillin for smaller children is now recommended for all less 30kg.
  - For women on oral contraception, additional contraception (barrier or abstinence) is not required when taking antibiotics except for rifampicin where additional contraception is required during and 28 days after stopping rifampicin.
  - Non-steroidal anti-inflammatory drugs (NSAIDs) are useful for the symptomatic treatment of pharyngitis. If a diagnosis of rheumatic fever is being considered, NSAIDs should be avoided until a diagnosis is secure as NSAIDs can mask symptoms and test results.
- Patients on warfarin should have their international normalised ratio (INR) monitored at the time of antibiotic commencement, at day three or four and upon completion.
- Throat swabbing is recommended for symptomatic contacts of a patient with GAS pharyngitis. This is particularly so for school aged contacts. Contacts should be treated if they are found to be GAS positive.

- Antibiotic prophylaxis is not routinely recommended for GAS negative (uninfected) household contacts of patient with GAS pharyngitis.
- Consideration should be given to isolating a symptomatic GAS positive patient for 24 hours after starting antibiotics if he/she is:
  - A worker at risk of spreading GAS in their workplace (healthcare and residential care workers, food handlers, teachers and childcare workers)
  - Attending school or day care.
- End of antibiotic treatment throat swabbing is not recommended except in the following situations:
  - Those with a history of rheumatic fever
  - Where there is recurrent GAS pharyngitis within families
  - Those who develop GAS pharyngitis during outbreaks in a closed or partially closed community e.g. boarding schools, hostels, barracks, prisons
  - Those who develop GAS pharyngitis during outbreaks of acute rheumatic fever or post streptococcal glomerulonephritis.
- In high risk settings for rheumatic fever, the following current recommendations remain unchanged:
  - **Symptomatic** household members of a person with GAS pharyngitis should be throat swabbed and/or treated if GAS positive.<sup>1,3</sup> (see [Sore Throat Management Algorithm 2014](#))
  - Where there is a personal, family or household history of rheumatic fever, **all** household members of a person with GAS positive pharyngitis should be swabbed regardless of whether they are symptomatic or asymptomatic as both have the potential risk of spreading GAS.<sup>1</sup> This will also apply during an outbreak of rheumatic fever or acute post streptococcal glomerulonephritis.<sup>1</sup> See below.
  - Where **an individual** has had three or more episodes of GAS pharyngitis in the last three months, **all** household members should be swabbed to identify and treat any pharyngeal GAS regardless of whether they are symptomatic or asymptomatic as both have the potential risk of spreading GAS.<sup>1</sup>
  - Where there have been three or more cases in **a household** in the last three months all household members should be swabbed to identify and treat any GAS carriers who may be at potential risk of spreading GAS.<sup>1</sup>
  - **In an outbreak of GAS Pharyngitis in a closed or semi-closed community** e.g. a classroom or boarding school, **all** members should be swabbed to identify and treat any pharyngeal GAS regardless of whether they are symptomatic or asymptomatic as both those with incident pharyngitis and carriers have the potential risk of spreading GAS<sup>1</sup> **and management of all community** members with GAS is desirable in order to control an outbreak.
- In some circumstances, when a person presents with symptoms of pharyngitis, assessment of the risk of spreading GAS in the **workplace** is recommended. Throat swabbing is recommended for the following people:
  - Health and residential care workers<sup>4</sup> (and expert opinion)
  - Food handlers<sup>5,6</sup>
  - Teachers<sup>6</sup> (and expert opinion)
  - Childcare workers (expert opinion).

If an individual is GAS positive, throat swabbing and treating all GAS positive workplace contacts (symptomatic or not) may be necessary. This may include treating GAS carriers.

## Research Questions

Given the lack of clarity in the literature on certain aspects group A streptococcal (GAS) pharyngitis management including the definition, detection and management of GAS carriage, it is recommended that the following research is undertaken.

### 1. Quantify the disease burden of GAS in New Zealand.

This should include pharyngeal (carriage and symptomatic), outbreaks (including nosocomial), invasive GAS, post streptococcal glomerulonephritis (APSGN), rheumatic fever and skin infections. The research question might be: Is there a point where the amount of pharyngeal GAS (symptomatic GAS or carriage) in a group is associated with high(er) rates of serious GAS diseases (ARF, APSGN, invasive GAS)?

### 2. GAS sore throat signs and symptoms.

Research GAS sore throat signs and symptoms in different settings nationally. It is unknown if there are any signs and symptoms which are associated with GAS positive throat swabs in different settings around New Zealand. Collating information in different settings to determine (any) predictors of GAS pharyngitis (currently there is none within New Zealand). These settings should include rural, urban, North and South Island (different pre-test probabilities for GAS) high and low ARF settings and different skill set of staff as well as emergency departments, general practice, school settings and rapid response clinics. Other considerations are use of analgesia which may mask presenting symptoms, and clinical training as this may affect ability to detect clinical signs.

### 3. Identify the percentage of sore throats which are GAS positive.

In different settings nationally e.g. high and low ARF risk settings, general practice, school clinics, emergency departments, rapid response clinic in both North and South Islands.

### 4. Monitor the *emm* strains associated with serious GAS disease burden and a sample of isolates, including pharyngeal GAS carriage.

Do GAS strains vary in different geographical areas of New Zealand, and do they change over time? Is one or a few strains predominating in a region?

### 5. Study to determine the long-term natural history of GAS carriage.

*(Until this is undertaken, the exact risk of GAS carriage in developing rheumatic fever is unknown).*

This would require a large long-term study of individuals, requiring regular examinations, throat swabs, GAS serology (perhaps weekly), retrospective comparison of respiratory symptoms and ARF development. This would quantify the risk of GAS in the throat to the individual, in terms of risk of developing ARF. It would also help define possible 'carriage.'

### 6. Literature review on smoking and GAS. Is there an association?

If indicated, further research on whether cigarette smoking facilitates the entry of GAS into the naso- and oropharynx, and does it increase the rate of GAS sore throat or GAS throat carriage?

### 7. Study factors relating to spread in New Zealand of GAS pharyngitis/GAS positive throat swabs including nasal GAS.

Start with a literature review of nasal GAS.

### 8. Literature review on relationship between invasive GAS, varicella and broken skin/skin infections.

The literature related to this topic is outside the scope of this review. A consideration of this topic should include New Zealand data.

### 9. GAS spread within day care/kindergarten.

The literature related to this topic is outside the scope of this review. This research should include a study of presumed carriage. What is the rate of GAS positive throat swabs in children who go to day care or early childhood education compared to those who do not attend or who are part time? Within the New Zealand setting, what is the spread of GAS from an index child, in a day care? This could be assessed by swabbing all the children and workers in a day care with further consideration of swabbing the households of the index GAS case to identify the spread amongst siblings.

### 10. Reducing pharyngeal GAS burden.

Repeated episodes of GAS pharyngitis may be necessary to precipitate the development of ARF. To reduce this risk, exposure to GAS pharyngitis should be minimised. It is not clear whether GAS carriage poses an infection risk to others. This requires further research.

There is currently no recommendation for systematically searching and treating carriage in high risk population in New Zealand e.g. in a school to reduce the pharyngeal GAS burden. (NOTE: This is currently being actively researched in New Zealand.)

**12. Further testing of Rapid Antigen Diagnostic Tests' (RADTs) performance(s) in New Zealand settings.**

RADTs are currently being used in some areas of New Zealand. Further testing to ascertain RADTs sensitivity, specificity, positive predictive value and negative predictive value is required to determine which RADTs might be recommended and what their role might be in the New Zealand setting.

**13. Short course antibiotic therapy for GAS pharyngitis.**

Is six days treatment with amoxicillin or five days treatment with a cephalosporin not inferior to 10 days treatment with once daily amoxicillin?

**14. Role of tonsillectomy.**

In a high ARF risk population group, does tonsillectomy (1) reduce the amount of GAS in the throat (2) lead to lower rates of rheumatic fever?

# Algorithm: Guide for sore throat management

## Sore Throat

Aim: All GAS pharyngitis in high rheumatic fever risk patients are treated

Aim: Reduce unnecessary antibiotic use

### High Risk for Rheumatic Fever

High risk if personal, family or household history of rheumatic fever or have 2 or more criteria:

- Māori or Pacific
- Aged 3-35 years
- Living in crowded circumstances or lower socioeconomic area

If only 1 criterion see green box.

#### Primary Care or Emergency Departments

Throat swab if follow up possible

Start 10 days of empiric penicillin or amoxicillin or single dose of IM benzathine penicillin

#### School Sore Throat Clinics

Throat swab

Wait for result before starting antibiotics<sup>d</sup>

**If GAS positive:**

Start 10 days of antibiotics

### Low Risk for Rheumatic Fever

Assess severity of symptoms and occupational risk of spreading GAS.

1. Unwell patients have potential to develop local suppurative complications
2. Throat swabbing and/or antibiotic treatment\* may **not** be required for **mild** symptoms **unless** the patient is at increased risk of spreading GAS e.g. healthcare and residential care workers, food handlers, school and early childhood teachers and students. Instead consider analgesia.

\* 10 days of empiric penicillin or amoxicillin or single dose of IM benzathine penicillin

**If GAS positive:**

- Consider swabbing all symptomatic household members.<sup>a</sup>
- Consider isolating at home for 24 hours post starting 10 days of antibiotics.<sup>b</sup>
- Swab all household members (symptomatic or not), if:
  - ≥ 3 cases of GAS pharyngitis in household in the last 3 months, or
  - Personal, family or household history of rheumatic fever
 and promptly treat all GAS positive cases

See Household Sore Throat Management Algorithm.

**If GAS negative:**

- Stop antibiotics.<sup>c</sup>

### Reasons to Throat Swab in Those at High Risk of Rheumatic Fever

- To identify GAS pharyngitis in index case
- To discontinue antibiotics in GAS negative cases<sup>c</sup>
- To initiate antibiotic therapy (check and reinforce 10 day adherence) in following up GAS positive results
- To allow household contact tracing and initiate appropriate treatment
- To reduce unnecessary antibiotic prescribing
- To allow for surveillance of GAS pharyngitis resistant to antibiotics
- To provide education when following up throat swab results.

Consider not throat swabbing and instead start empiric antibiotics if follow-up may be problematic.

### Footnotes

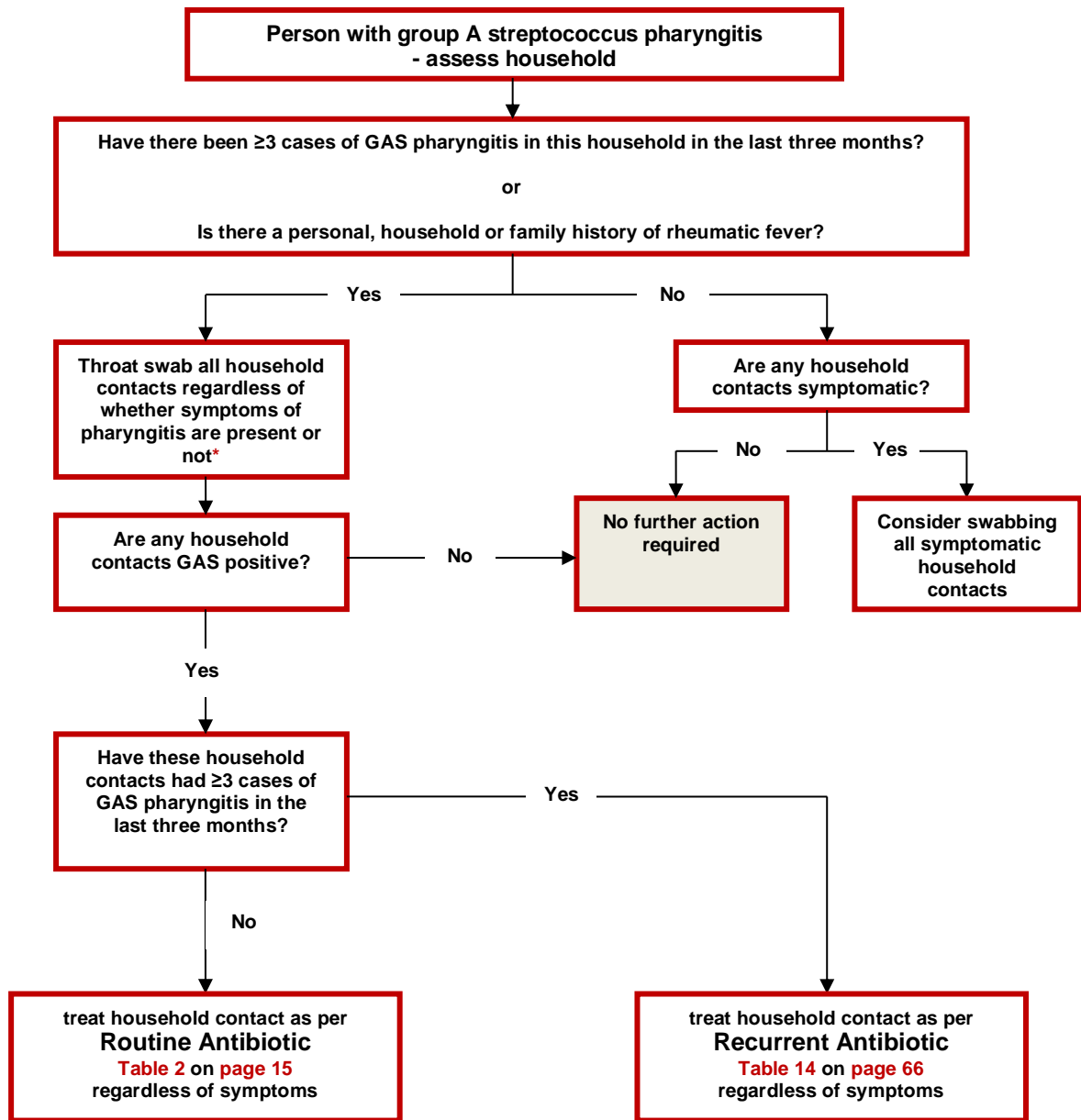
- In family households, more than half of secondary cases of serologically proven GAS pharyngitis were in 5-12 year old children. Risk of secondary GAS infection was 1.8 times greater than that of primary infection in the community.<sup>7</sup> Adults are at lesser risk of developing rheumatic fever but given their household contact status, they may spread GAS.
- The Writing Group recommends that for workers who are at increased risk of spreading GAS (healthcare workers, food handlers, teachers and childcare workers) isolation should be considered for 24 hours after starting antibiotics. Legislation allows Medical Officers of Health to enforce 7 days isolation for pupils, teachers and food handlers.<sup>6</sup>
- >70% of sore throats will be viral and do not need antibiotic treatment.<sup>8</sup>
- Start empiric antibiotics if results of throat swab are likely to be delayed.

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## Algorithm: Guide for Household Sore Throat Management



### Abbreviations:

GAS = group A streptococcus

\* If impractical to swab, consider empiric antibiotic treatment

## Algorithm Notes: Antibiotics for Routine Group A Streptococcal (GAS) Pharyngitis

Standard treatment for a patient's first or second case of confirmed GAS pharyngitis.

**Table 2. Standard treatment for a patient's first or second case of confirmed GAS pharyngitis**

Antibiotic	Route	Dose	Duration	IDSA GRADE 2012 <sup>*,9</sup>
<b>Penicillin V<sup>†</sup></b>	PO	<b>Children &lt;20kg:</b> 250mg two or three times daily <b>Adolescents &amp; Adults ≥20kg:</b> 500mg two or three times daily	10 days	Strong, high
<b>Amoxicillin<sup>†</sup></b>	PO	<b>Once daily:</b> 50mg/kg dose once daily <i>Max dose 1000mg per day</i> <b>Or:</b> Weight <30kg: 750mg once daily Weight ≥30kg: 1000mg once daily <b>Twice daily:</b> 25mg/kg dose twice daily <i>Max dose 1000mg per day</i>	10 days	Strong, high
<b>Benzathine penicillin<sup>‡</sup></b>	IM	<b>Children &lt;30kg:</b> 450mg (600,000 U) <b>Children &amp; Adults ≥30kg:</b> 900mg (1,200,000 U)	Single dose	Strong, high
<b>If concern about allergic (IgE mediated<sup>§</sup> or anaphylactic) response to beta lactams, use:</b>				
<b>Roxithromycin<sup>  </sup></b> <i>Pending Pharmac decision</i>	PO	<b>Children:</b> 2.5mg/kg dose twice daily <b>Adults:</b> 300mg once daily <b>Or:</b> 150mg twice daily	10 days	Unavailable in the USA
<b>Erythromycin ethyl succinate<sup>  , ¶</sup></b>	PO	<b>Children &amp; Adults:</b> 40mg/kg/day in 2-3 divided doses <i>Max adult daily dose 1000mg</i>	10 days	**
<b>For people on benzathine penicillin IM prophylaxis who are GAS positive:</b>				
Treat with a 10 day course of oral penicillin or amoxicillin. Check adherence to prophylaxis programme. Serum penicillin levels will be falling by week three and four post IM long acting benzathine penicillin injection. <sup>16</sup>				

**Source:** Modified from Table Two in Shulman ST et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2012; 55: 1279-1282<sup>9</sup> © by permission of Oxford University Press.

### Footnotes

- \* The Infectious Diseases Society of America (IDSA) used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (see [Appendix 3](#) for description)<sup>9</sup>
- † Amoxicillin can be taken with food whereas oral penicillin V is best absorbed on an empty stomach. Both are equally effective in eradicating GAS.<sup>10,11</sup> Lower frequency of antibiotic dosing has been shown to improve adherence.<sup>12,13</sup> Amoxicillin is relatively palatable.<sup>14</sup>
- ‡ Benzathine penicillin can be given with lignocaine to reduce injection site pain (see [page 33](#) and [Appendix 4](#)). It may be marginally more effective than oral penicillin or amoxicillin in eradicating GAS pharyngitis.<sup>15</sup>
- § IgE-mediated reactions include ANY bronchospasm, angioedema, hypotension, urticarial or pruritic rash.
- || Always check for drug interactions before prescribing. In particular, care should be taken when prescribing macrolides to patients taking warfarin and carbamazepine.
- ¶ The erythromycin currently funded by Pharmac is erythromycin ethyl succinate. There are other erythromycins available with different pharmacokinetic profiles.
- \*\* Erythromycin is not recommended in 2012 The Infectious Diseases Society of America (IDSA) Guideline.<sup>9</sup> In 2002 the IDSA recommended erythromycin based on a different grading system for clinical guideline recommendations ([Appendix 5](#))

### References

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## Introduction

In New Zealand, sore throats are among the top ten symptoms for which patients present to their general practitioner.<sup>17</sup> Based on their study of 10,506 visits to New Zealand general practitioners, Kljakovic and Crampton estimated the rate to be 3.6 visits per 100 to New Zealand general practitioners.<sup>17</sup> A similar consultation rate of 4.7 per 100 visits was found in the Waikato.<sup>18</sup>

Unlike many common infectious conditions presenting in primary care, the management of group A streptococcal (GAS) pharyngitis to prevent acute rheumatic fever (ARF) is well founded in evidence including randomised controlled trials (RCT) guiding antimicrobial choice and length of treatment.<sup>10,11,19-25</sup>

Despite many countries demonstrating a sharp decline in ARF,<sup>26</sup> the notification rate of ARF remains persistently high in New Zealand at 4.3 per 100,000 population for initial presentations, and 0.2 per 100,000 for recurrent cases with 194 notified new cases and 11 notified recurrent cases in 2013.<sup>27</sup> Pacific People had the highest rates of notification of initial attacks (32.9 per 100,000), followed by Māori (13.8 per 100,000), with the 10-14 years age group having the highest notification rate (33.3 per 100,000 population).<sup>27</sup> In 2013, there were 99 initial rheumatic fever and recurrent cases in Māori and 93 in Pacific people compared to six cases European and Other.<sup>27</sup> Notification data is an estimate only as it is not active surveillance and is not audited against a case definition. It is likely to be an under-estimate as it relies on physician notification (with no laboratory component as is the case with meningococcal disease). Hospitalisation data on the other hand is likely to be an over-estimate, with miscoding of rheumatic heart disease (RHD) as acute rheumatic fever accounting for most mis-classified cases in two studies.<sup>28,29</sup> Data from the Auckland Regional Rheumatic Fever Register (1998-2010) highlighted that approximately 88% of new ARF cases in the Auckland region are likely to be school-aged.<sup>30</sup> From hospitalisation data, Māori and Pacific children accounted for 95% of hospital admissions with first episodes of ARF in the 5-14 years age group from 2000 to 2009.<sup>31</sup>

The geographical distribution of initial hospitalisations 2009-2012 is summarised in the map found in [Appendix 6](#). The main areas of occurrence of ARF are in lower socioeconomic areas of the North Island, such as parts of Auckland, Waikato, Northland, Bay of Plenty, Rotorua, Gisborne, Hawke's Bay and Porirua. Hoke and Seckler 2011 have detailed studies of the incidence and prevalence of ARF and RHD around the world.<sup>32</sup>

Most sore throats are viral in origin, however 15–30% of sore throats in children and 10% in adults are estimated to be due to GAS.<sup>33-39</sup> Other rarer pathogens may be clinically significant (see [Appendix 2](#)). In approximately 0.3-3% of people, GAS pharyngitis may lead to ARF.<sup>40</sup>

Group A streptococci spread in crowded situations, such as army barracks and schools,<sup>41</sup> by droplet spread or from saliva or nasal secretions. Pharyngitis caused by GAS may present with or without fever, exudate and tender anterior cervical lymph nodes.<sup>42</sup> Some patients present with non-specific symptoms.

It is not yet possible to predict which patients will develop post-streptococcal sequelae. The process by which GAS pharyngitis leads to ARF is poorly understood, but has been postulated to have an autoimmune basis.<sup>43</sup> Appropriate treatment of GAS pharyngitis is the most effective means of preventing ARF.

Treating individuals with GAS positive throat swabs with appropriate antibiotics reduces the likelihood of subsequent development of ARF.<sup>19,21,44-46</sup> The reader is directed for more detail to the third New Zealand Guidelines for Rheumatic Fever: *Proposed Rheumatic Fever Primary Prevention Programme* (2009) which is a systematic review of primary prevention of ARF and the associated publication.<sup>47,48</sup> Shortly after the introduction of penicillin, epidemic ARF in the American armed forces was controlled using long acting injectable penicillin.<sup>19</sup> A meta-analysis demonstrated this effect in nine further studies, that also used injectable long acting penicillin, eight of which were in a military setting and one inconclusive study in a child population.<sup>2</sup> Subsequently, observational studies in Baltimore,<sup>44</sup> Cuba,<sup>49</sup> Costa Rica,<sup>45</sup> and the French Caribbean,<sup>46</sup> the latter three in low-resource environments, have shown ARF reduction. It is not clear in all of these community studies whether injectable penicillin was used or throat swabs taken. In Costa Rica, suspected GAS pharyngitis was diagnosed on clinical criteria alone; no throat swabs were performed. Patients were

treated with intramuscular (IM) benzathine penicillin.<sup>45</sup> In this observational study, new cases (first attacks) of ARF fell from 94 in 1970 to just four in 1991. It is likely there were no costs to the patients or families.

Inner-city comprehensive primary care programmes, free to the user, were set up in Baltimore, USA in the 1960s. The rate of ARF decreased by 60% in the programme areas between the two periods, 1960-1964 and 1968-1970, but was unchanged in the rest of the city.<sup>44</sup> ARF were 30/100,000 (5-14 year old age group) at the time of the Baltimore intervention programme compared to 60-80 per 100,000 in New Zealand Māori and Pacific people aged 5-18 years of age in the high risk area where the Auckland school-based randomised trial took place.<sup>50</sup> A ten year programme in the French Caribbean reduced the incidence of ARF by 78% in Martinique and 74% in Guadelupe.<sup>46</sup> The overall rate of ARF appears to have fallen largely due to secondary prevention, although primary prevention measures also contributed. Education of the community and healthcare providers was intensive in many areas reported in the studies quoted above.

In most countries in the developed world ARF has become extremely uncommon.<sup>51</sup> The example above in Baltimore, USA, a densely populated urban slum with modest rates of ARF, provides the most compelling evidence that appropriate medical intervention helps reduce the number of initial attacks of ARF. Important differences between this environment and the suburban or semi-rural environment in New Zealand where ARF is common could be access to transport, co-payments for drugs, community messages concerning the importance of GAS pharyngitis and the density of living circumstances influencing the household burden of GAS and the risk of re-infection.

In countries outside North America, where there was less emphasis on the evidence-based treatment of GAS pharyngitis, ARF has also virtually disappeared.<sup>32</sup> This appears likely to be due to improved socio-economic circumstances including, housing conditions and health care access, particularly following World War II. In the poorer countries of Europe where documented ARF persisted, factors such as unemployment and living circumstances appear to have been important factors.<sup>52</sup> Recently household crowding has been demonstrated as a likely contributing factor.<sup>53</sup>

The incidence of ARF has been demonstrated to be reduced by treating GAS sore throats with antibiotics. Rheumatic fever remains a problem in New Zealand. Local protocols are required to address the management of GAS pharyngitis.

These sore throat management guidelines provide guidance on the appropriate management of sore throats for the prevention of rheumatic fever in the New Zealand setting. This guideline updates and replaces the *2008 Group A Streptococcal Sore Throat Management Guideline*.

## Clinical Questions

The original 2008 Group A Streptococcal Sore Throat Management guideline included clinical questions on the diagnosis and management of group A streptococcal (GAS) pharyngitis.<sup>1</sup> This update uses a similar format organised into sections covering diagnosis, treatment and contact management.

A patient's risk of acute rheumatic fever (ARF) should be made at the start of the consultation according to the sore throat management algorithm (page 13). High risk patients are **overwhelmingly Māori or Pacific peoples who are aged three to 35 years**, and those with a past, family or household history of rheumatic fever. Living in a **lower socioeconomic area of the North Island** is also a risk factor (see Appendix 6). Households with more than three cases of GAS pharyngitis within a three month period should be managed according to the household sore throat management algorithm (page 14).

## DIAGNOSIS

### Question 1. Which test should be done to diagnose GAS pharyngitis?

Clinical presentation alone cannot reliably differentiate between GAS or viral.<sup>8,9</sup> Most sore throats are viral. This Guideline Update recommends that those at **high risk** of rheumatic fever are swabbed if follow up is possible (including those receiving empiric antibiotics) to ensure correct treatment of the patient and his/her household to prevent ARF and minimise inappropriate antimicrobial usage.

For those at **low risk** for rheumatic fever, the following factors should be considered before throat swabbing or treatment is undertaken:

1. ARF in New Zealanders who are non-Māori or non-Pacific has become extremely uncommon without specific emphasis on sore throat management
2. Unnecessary use of antibiotics should be avoided if at low risk of developing ARF
3. Antibiotics may have minimal effect on pharyngitis symptoms
4. Analgesia can be used for symptom relief
5. For some individuals there is a risk of spreading pharyngeal GAS e.g. healthcare or residential care worker, food handler, teachers or childcare worker which may be an important consideration
6. The potential risk of local suppurative complications e.g. peritonsillar abscess if the patient is unwell. Follow up may be appropriate if antimicrobial treatment is withheld.

### Use of Throat Swabbing

The current gold standard for the diagnosis of GAS pharyngitis is a rayon-tipped throat culture swab, taken by sampling the tonsils and back of the throat, carefully avoiding the tongue and other areas of the oral cavity to minimise contamination with oropharyngeal flora. The swab is then placed in a tube containing a transport medium, and sent to the laboratory. In cases of uncomplicated pharyngitis, it is then inoculated on to a 5% sheep blood agar plate. In certain other circumstances, laboratory staff may utilise other types of agar for throat swabs. Correct swabbing technique is summarised in Appendix 7.

In general, it is recommended that a throat swab be sent to the laboratory within two hours, but a delay of up to 24 hours before processing is acceptable.<sup>54</sup>

In a randomised controlled trial (RCT), Martin compared delayed and immediate transfer of throat swabs onto culture plates and the extraction of group A streptococci. Delayed plating was defined as 'after four days in the dark at room temperature' and immediate plating as 'within four hours of swabbing'. These results showed that delayed plating had a marginal superiority in GAS retrieval ( $p=0.0523$ ) over immediate plating. When plating was delayed, the result was not influenced significantly by the swab type (plain or serum coated swab) or whether there was silica gel present in the swab tube. A plain throat swab, with no silica gel in the tube, plated within four hours, was the least likely to lead to the isolation of GAS.<sup>55</sup>

McDonald et al found that in tropical conditions, optimal results were obtained from directly inoculating

culture media followed by cold-box transport (plating method) or sealing the swab in a bag with a silica gel desiccant and cold-box transport (desiccant method).<sup>56</sup> These two were superior to transporting swabs at ambient temperature and humidity, when paired throat swabs were compared.

### Benefits of Throat Swabbing

The Advisory Group considered the rationale and practical implications for culturing throat swabs for GAS. The following were identified as key benefits:

- **Precision of diagnosis** to correctly identify GAS pharyngitis in a patient presenting with a sore throat to ensure those **at high risk of ARF and their household contacts are correctly diagnosed and treated according to the accepted evidence.**
- Enabling practitioners **to discontinue antibiotic therapy in GAS negative cases** where empiric antibiotics were prescribed.
- The ability to follow evidence-based management of GAS pharyngitis using narrow spectrum antibiotic therapy for the required 10 day period and to reinforce adherence for pharyngeal GAS eradication which is the surrogate for ARF prevention.
- Triggering household contact tracing of patients with GAS pharyngitis and the appropriate treatment of pharyngeal GAS positive contacts to prevent new GAS cases in an ARF susceptible population.
- Reducing unnecessary antibiotic prescribing and thereby promoting antibiotic stewardship.
- Allowing for surveillance of antibiotic resistance to group A streptococcus with macrolides such as erythromycin as an example, and potentially allowing serotyping (*emm* typing) in particular situations.
- Providing an opportunity for education about sore throat management on follow-up of swab result especially to reinforce adherence to and the completion of prescribed oral antibiotic therapy.
- Costs per QALY for school programmes support this approach.<sup>57</sup>

Throat swabbing (and antimicrobial treatment) should be infrequent for patients at low risk of ARF presenting with a sore throat (see [page 13](#)).

The high cost of laboratory testing as the gold standard is acknowledged. However this approach is the recommended standard of care for the diagnosis of GAS pharyngitis and the prevention of ARF in a developed country setting.<sup>9</sup> Unnecessary throat swabbing and treatment in the population at very low risk of ARF should be given careful attention.<sup>58</sup> The current status of Rapid Antigen Diagnostic Tests (RADT) is discussed below.

See [page 21](#) for discussion on use of Prediction Rules.

### Throat Swabbing When Follow-up May be Problematic

The Advisory Group considered that it might not be appropriate to throat swab a patient if follow up is likely to be problematic.

Situations where follow-up may be problematic include patients who:

- Have no fixed abode
- Are not contactable by telephone
- Are not likely or able to return for a prescription if GAS positive
- Present at emergency departments and clinics where processes do not support follow up.

Where follow-up may be problematic, empiric antibiotics may be started without a throat swab.

<b>Recommendation:</b>	In New Zealand, throat swab and culture are recommended to confirm the diagnosis of GAS pharyngitis in most situations in the population at high risk of ARF. Where follow-up may be problematic, empiric antibiotics may be started without a throat swab.  Throat swabbing and antibiotic therapy in the population at low risk should be avoided in most situations.
<b>Recommendation grade:</b>	B
<b>Evidence level:</b>	II

### Use of Rapid Antigen Diagnostic Tests (RADTs)

Rapid group A streptococcal diagnostic tests (RADTs) are now commercially available in New Zealand. However, RADTs are not funded by the government and have not been sufficiently tested to determine their sensitivity and specificity in the New Zealand context. The Ministry of Health recommend that they be studied in settings where they might be used and a cost analysis undertaken before being considered in sore throat management.<sup>59</sup>

See [Appendix 8](#) for evidence on the use of RADTs in diagnosing GAS pharyngitis.

#### **RADT Use in Patients at High Risk for Rheumatic Fever**

Where patients are at high risk of developing ARF, RADTs are not currently recommended. Studies in New Zealand to date suggest that the sensitivity and specificity of the currently available tests mean that they may not be sufficiently reliable where high stakes decisions are being made (Upton, personal communication). Instead, a throat swab should be taken and sent for culture.

If an RADT is used and is negative, additional cost is then incurred as a follow up throat swab is required.

In the USA and Europe, it is recommended that negative RADTs are confirmed using a throat swab cultured on sheep blood agar.<sup>60</sup>

<b>Recommendation:</b>	RADTs should not be used to diagnose pharyngeal GAS infection or recurrence <b>in patients at high risk for rheumatic fever:</b> use throat swab and send for laboratory culture.
<b>Recommendation grade:</b>	Expert opinion

#### **RADT Use in Patients at Low Risk for Rheumatic Fever**

Treatment of GAS pharyngitis is primarily to prevent ARF which is now **extremely** uncommon in those at low risk in New Zealand.<sup>31</sup> Rheumatic fever has virtually disappeared in these populations without any specific public health message or focus on GAS pharyngitis management.

RADTs may be suitable for use in low ARF risk populations to diagnose GAS pharyngitis. Some children with a negative RADT, may not need a back-up throat swab sent for laboratory culture as the risk of ARF is extremely low. Follow up of the rare seriously unwell patient may be appropriate, watching for and managing the potential development of local suppurative sequelae such as peritonsillar abscess.

In family practices where these tests are used, further research is recommended to confirm their sensitivity and specificity in that setting. Ideally this testing should occur prior to their implementation.



<b>Recommendation:</b>	RADTs can be used to diagnose GAS in <b>low risk rheumatic fever settings</b> . For children with a negative RADT in a low risk setting, a back-up throat swab to diagnose GAS infection is <b>not</b> necessary as the risk of ARF in this population is very low.
<b>Recommendation grade:</b>	Expert opinion

## Use of Prediction Rules

A meta-analysis by Shaikh found it was not possible to reliably differentiate between the symptoms of bacterial and viral pharyngitis in children.<sup>8</sup> Internationally, a number of prediction rules for GAS pharyngitis have been developed. In 2008, the Heart Foundation of New Zealand developed a prediction rule based on expert opinion.<sup>1</sup> This utilised the Mclsaac revised Centor prediction criteria.<sup>42,61</sup> The Mclsaac prediction rule was originally included in the 2008 Guideline as it was the most validated and internationally successful prediction tool at that time.<sup>1</sup> It was hoped there would be subsequent studies to evaluate its sensitivity and specificity. However, in New Zealand there has been limited testing or validation of this or other prediction rules. Two instances are known, these are:

1. Jamiel, in a population at **high risk of rheumatic fever**, tested the Mclsaac revised Centor (1998)<sup>42,61,62</sup> rule in Auckland general practice patients (206 adults and children).<sup>63</sup> For 3-14 year olds, he found a sensitivity of 85.7% and specificity of 86.9%, for adults, a sensitivity of 81.8% and specificity of 89.6% was found when the rule was applied.

Jamiel found that with a Mclsaac revised Centor score of three, 12% of children (3-14 year olds) with sore throats were GAS positive, while 13% of children with a score of four were GAS. For adults 15 years and over, a score of three equated to 3% being GAS positive, and a score of four to a 31% likelihood of a GAS positive throat swab.<sup>63</sup>

2. Kerdemelidis on a dataset of 12,000 South Auckland **school sore throat clinic** examination and swab results, conducted in an area where rheumatic fever is endemic, found the Heart Foundation 2008, Mclsaac revised Centor<sup>61</sup> and two other international prediction rules (WALD rule 1998,<sup>64</sup> WHO rule1 1991<sup>65</sup>) performed too poorly to be recommended without culture backup in the school clinic setting.<sup>66</sup>

Reflecting this lack of validation, **it is recommended that prediction rules are not used** in the management of GAS pharyngitis in New Zealand either in the general practice or school clinic setting at this time.

For those at **high risk of rheumatic fever**, the motivation is not to miss any GAS throat infections. Hence a lower threshold is now recommended for throat swabbing and treatment i.e. personal, family or household history of ARF or two or more risk factors and a sore throat only (see Sore Throat Algorithm). This reflects current clinical practice; the authors recognise that there will be some over-treatment in the high rheumatic fever risk group but believe this is appropriate.

Clinical prediction rules are poorly supported by the evidence. However, in the population at **low risk of ARF** the risks and benefits of under and over diagnosis are different.<sup>29,67</sup> In addition, treatment inadequate to eradicate GAS from the pharynx has been found to be common.<sup>68</sup> Avoiding unnecessary treatment in this group may therefore be permissible based on symptomatology, if a viral cause is suspected. This reflects practice in the USA and in parts of Europe where ARF is now extremely uncommon and unnecessary treatment is actively avoided

Active follow up of the very unwell patient may be prudent to detect and manage the development of local sequelae such as peritonsillar abscess.

<b>Recommendation:</b>	Prediction rules tested in New Zealand lack the sensitivity and specificity to reliably rule in or rule out GAS pharyngitis in a high risk population and their use should be discouraged.
<b>Recommendation grade:</b>	C
<b>Evidence level:</b>	IV

## Question 2. Are two throat swabs more accurate than one?

*This Clinical Question has not been updated from the 2008 Guideline.*

There are no systematic reviews and only one randomised controlled trial found addressing this issue. Ezike studied 373 children with pharyngitis presenting to a paediatric emergency department. Children were randomised to have either one or two throat swabs taken. All swabs were cultured in addition to being tested using a rapid diagnostic test. Positive culture rates were approximately 42% and did not vary between one or two swabs.<sup>69</sup>

<b>Recommendation:</b>	Current recommendations in New Zealand and internationally are for a single throat swab to be taken and there is no evidence this should change.
<b>Recommendation grade:</b>	B
<b>Evidence level:</b>	II-I

# MANAGEMENT OF THE INDIVIDUAL WITH GAS PHARYNGITIS

## Question 3. How should patients in New Zealand have their pharyngitis managed?

Patients with pharyngitis are managed in a variety of healthcare settings including general practice, emergency departments and school sore throat clinics. Current factors affecting pharyngitis management include clinical presentation, the setting to which the patient presents, and their risk of developing ARF.

A targeted approach to pharyngitis management is recommended with emphasis on people known to be at high risk of developing ARF. This update also considers factors which impact on GAS pharyngitis control namely GAS spread (see [Question 13](#)) within pharyngitis management (see Sore Throat Algorithm, [page 13](#)). The scientific basis for the treatment of streptococcal pharyngitis to prevent ARF comes from early penicillin trials in population groups where there was a very high incidence of ARF. The rate was decreased from 2.8 to 0.2% with injectable long acting penicillin.<sup>19</sup> Ongoing work in a similar high risk population demonstrated that the risk of developing ARF persisted unless the group A streptococcus (GAS) was eliminated.<sup>21</sup> Hence GAS eradication (though this is never 100%) has become the surrogate endpoint instead of ARF against which new antimicrobials are judged. A 10 day course of oral penicillin treatment was found to be essential for this aim.<sup>20</sup> From these studies, penicillin, a bactericidal agent with activity against streptococci, became the drug of choice. To date, group A streptococci resistant to penicillin have never been documented.

Adherence to a 10 day course of twice a day oral penicillin is recognised as difficult, however a number of studies have shown that penicillin V is not as effective at GAS eradication when administered once daily or for less than 10 days.<sup>22-24,70</sup>

There is some evidence that medications once a day improve adherence.<sup>12,13</sup> Trials (under powered) in the 1990's were undertaken to compare twice a day penicillin to once a day amoxicillin.<sup>71,72</sup> Amoxicillin has a longer half-life and paediatric formulations are more palatable than penicillin. Two further high quality trials demonstrated once daily amoxicillin was non inferior to twice daily penicillin and it has now been incorporated into standard of care guidelines.<sup>9-11</sup> The New Zealand trial was conducted to streamline school clinic processes.

Shorter courses of six days of amoxicillin (administered twice a day) have been shown to be comparable to 10-day courses of penicillin V (administered thrice a day) in small poor quality studies.<sup>23,73,74</sup> Whether a similar effect could be gained with shorter courses of once-daily amoxicillin is yet to be determined. See [page 32](#) for further information on short course antibiotic treatment.

The need to differentiate between bacterial persistence and re-infection in GAS pharyngitis studies has led to the recommendation of serotyping (M typing) or genotyping (*emm* typing) of GAS isolates to accurately evaluate therapy.<sup>75</sup> Ideally, in addition, antibodies to GAS should be determined with acute and convalescent sera as true GAS infection, in contrast to pharyngeal carriage, is defined by the presence of the host's immunologic response to one or more of the organisms antigens.<sup>76</sup> Only patients with serologically confirmed infection are at risk for ARF. In addition, GAS eradication is more difficult to achieve in carriers<sup>77</sup> and more effectively done by cephalosporins.<sup>78</sup>

Published studies of incident pharyngitis in general practice and primary care settings, largely from areas of low ARF endemicity, report a GAS rate of 20-30% in children and 5-10% in adults.<sup>79,80</sup> New Zealand data is sparse: Kljakovic and Crampton reported 3.6 visits per 100 to general practitioners in New Zealand as being due to sore throats and McAvoy, 4.7 per 100 visits in the Waikato area.<sup>17,18</sup> Durham in a paper for the Ministry of Health, recommended that the general practice environment was not the ideal place to prevent ARF.<sup>81</sup> Data is accruing from resource poor areas with high ARF endemicity outside of New Zealand.<sup>82,83</sup> Both studies are from free walk-in clinics to which the parent would need to accompany the child.

In New Zealand, in a high risk area for ARF, a school based prevention programme was studied in a randomised controlled trial (RCT) where children reported their sore throat directly to a nurse or community health worker daily. This study found 7% of throat swabs positive in incident pharyngitis to be positive for GAS (age 5-17 years, year 1-13).<sup>50</sup> Current school programmes (year 1-8) in South Auckland and Porirua have incident GAS pharyngitis rates of approx. 9-22% (Light, personal

communications, 2014). Rates of GAS pharyngitis (and rheumatic fever) are lower in older adolescents.<sup>50</sup>

## **A. Management of Pharyngitis in Patients at High Risk of Rheumatic Fever**

Appropriate treatment of pharyngitis in high-risk populations will eradicate GAS in most cases, prevent individual cases of ARF and therefore subsequent chronic heart disease.<sup>19,44-46</sup>

In New Zealand, people with a personal, family or household history of ARF or with **two or more of the following** risk factors are at high risk for rheumatic fever:

- Māori and Pacific people
- Aged 3-35 years old
- Living in crowded circumstances or lower socioeconomic areas of North Island.

### **Crowded Circumstances**

The Canadian National Occupancy Standard is a comprehensive measure of household crowding used by Statistics New Zealand and included as part of the New Zealand Deprivation Index.<sup>84</sup> The Canadian Standard sets the bedroom requirements of a household according to the following composition criteria: there should be no more than two people per bedroom; parents or couples share a bedroom; children under five years, either of the same or the opposite sex, may reasonably share a bedroom; children under 18 years of the same sex may reasonably share a bedroom; a child aged five to 17 years should not share a bedroom with one under five of the opposite sex; single adults 18 years and over and any unpaired children require a separate bedroom.<sup>85</sup> Household crowding has found to be a contributing factor for the occurrence of ARF.<sup>53</sup>

### **Lower Socioeconomic Areas**

The geographical distribution of initial hospitalisations 2009-2012 is summarised in the map found in [Appendix 6](#). The main areas of occurrence of rheumatic fever are in lower socioeconomic areas of the North Island, such as parts of Auckland, Waikato, Northland, Bay of Plenty, Rotorua, Gisborne, Hawke's Bay and Porirua.

Between 1998 to 2010, 73% of first episodes of ARF presentation in the Greater Auckland area occurred in NZDep 9 and 10 (Auckland Regional Rheumatic Fever Register Data 2010).

### **Patients Under Three Years of Age**

There has been little research on the diagnosis and management of GAS pharyngitis in children under the age of three years internationally. The few studies available are inconclusive, hampered by the fact that the symptoms of streptococcal pharyngitis are difficult to assess in infants.<sup>61,86-96</sup> Rheumatic fever is rare in this age group in New Zealand.

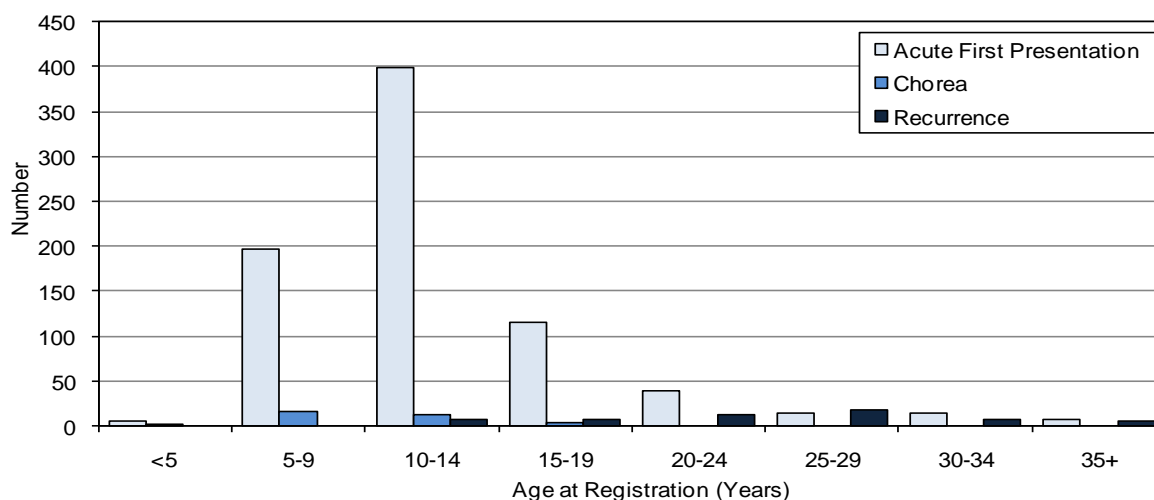
In the Auckland Region, between 1998 and 2013, the youngest patients with confirmed rheumatic fever were two patients who were three years old and five patients who were four year olds (Auckland Regional Rheumatic Fever Register 2014).

Throat swabbing may be performed in children under three years of age, although this may not be feasible as the child may not be compliant with opening their mouth. If compliance is possible, in some circumstances it may be appropriate to take a throat swab from an under three year old, such as in households or day care centres where there has been a case of ARF.

### **Upper Age for High Risk**

The upper age for people at high risk of rheumatic fever has been revised downwards from 45 years to 35 years (Auckland Regional Rheumatic Fever Register, 2010). [Figure 1](#) details the number of ARF registrations on the Auckland Rheumatic Fever Register (1998-2010). First episodes of ARF are rare above the age of 35 years.

**Figure 1. Acute Rheumatic Fever Registrations by Notification Type and Age Group, Auckland Rheumatic Fever Register 1998-2010.**



**Source:** Data obtained from the Auckland Rheumatic Fever Register, 2013.

**Recommendation:** Patients presenting in primary care or emergency departments with pharyngitis who are at **high risk for rheumatic fever** should have a throat swab taken. Consider commencing empiric antibiotics if follow up is problematic.

See sore throat management algorithm for pharyngitis management on [page 13](#) and [Clinical Question 5](#) on [page 28](#) for antibiotic choices.

**Recommendation grade:** D for the use of this algorithm in the NZ context as no trials held to date.

**Evidence level:** Expert opinion

### Children Attending a School Sore Throat Clinic

A meta-analysis by Shaikh found it was not possible to reliably differentiate between the symptoms of bacterial and viral pharyngitis in children.<sup>8</sup> In those areas of New Zealand where children have the highest risk for ARF,<sup>27</sup> investigations should be performed to diagnose GAS pharyngitis.<sup>3,9</sup> A meta-analysis of school and/or community based sore throat programmes showed a reduction in ARF.<sup>50</sup>

In many areas of New Zealand where there is a high incidence of ARF, children with symptomatic pharyngitis can attend a school-based sore throat clinic. These clinics focus on year 1-8 students (ages 5-13 years) from whom pharyngitis symptoms are actively sought. All consented children with symptomatic pharyngitis attending the school sore throat clinic have a throat swab taken and are then treated based on the throat swab result.

In high schools (year 9-13) where school clinics are available, students are encouraged to attend their school clinic if they have pharyngitis symptoms for a throat swab and treatment if GAS positive.

In these defined and accessible populations, overuse of antibiotics can be avoided using a throat swab to confirm diagnosis.

**Recommendation:** All consented children with symptomatic pharyngitis in high risk areas for rheumatic fever attending **school sore throat clinics** should have a throat swab and antibiotics commenced if GAS positive.

See sore throat management algorithm on [page 13](#) and [Clinical Question 5](#) on [page 28](#) for antibiotic choices.

**Recommendation grade:** B

**Evidence level:** I

## B. Management of Pharyngitis in Patients at Low Risk of Rheumatic Fever

Patients who are at low risk for rheumatic fever include:

- Non-Māori and non-Pacific people
- Children under 3 years old and adults older than 35 years old
- Not living in crowded circumstances or lower socioeconomic areas of North Island

If there is a **personal, family or household history** of acute rheumatic fever the person is automatically at high risk.

Most sore throats, in both children and adults, are viral in origin.<sup>17</sup> In the population at low risk of ARF, minimising throat swabbing, unnecessary antibiotic treatment and healthcare expenditure should be the aim. In these populations, it may be appropriate to consider associated symptoms such as rhinorrhoea and cough in order to avoid potentially unnecessary antibiotic prescribing, as the consequences of missing a true GAS pharyngitis are low. Significantly unwell patients however, require active diagnosis and management, particularly where symptoms are unilateral and the development of local suppurative complications such as peritonsillar abscess needs to be considered. (See Sore Throat Algorithm)

The utility of throat swabbing for wider community benefit should be taken into account. Adults presenting with symptomatic pharyngitis who have otherwise been assessed as being low risk for ARF, should be assessed (based on their employment) for their risk for spreading GAS in the workplace to those at high risk for ARF.

If they are assessed as being at increased risk of spreading GAS, it is recommended that a throat swab be taken for culture and if GAS positive, they should be treated with appropriate antibiotics. (See below and [Question 13](#) for further detail).

**Recommendation:** Treat patients at **low risk of ARF** as per sore throat management algorithm on [page 13](#).

**Recommendation grade:** D for the use of this algorithm in the New Zealand context as no trials held to date.

## C. Management of Pharyngitis in Patients at Increased Risk of Spreading GAS

Those at increased risk of spreading GAS include:

- Healthcare and residential care workers<sup>4</sup> (and expert opinion)
- Food handlers<sup>5,6</sup>
- Teachers<sup>6</sup> (and expert opinion)<sup>6</sup>
- Childcare workers (expert opinion).

When such workers present with a sore throat, consideration needs to be given to their risk of spreading GAS in their workplace and they should therefore be managed accordingly.

If GAS positive, further consideration should be given to isolation for 24 hours after starting antibiotics to prevent the risk of spreading GAS.

See [Question 13](#) and [21](#) for evidence of GAS spread in various settings.

<b>Recommendation:</b>	Consider throat swabbing and treating workers at increased risk of spreading GAS (healthcare and residential care workers, food handlers, teachers and childcare workers).  See sore throat management algorithm on <a href="#">page 13</a> and <a href="#">Clinical Question 5</a> on <a href="#">page 28</a> for antibiotic choices.
<b>Recommendation grade:</b>	C
<b>Evidence level:</b>	IV

### Aim of Reducing Unnecessary Antibiotic Use

Health practitioners should actively consider whether the patient presenting with an acute sore throat is at risk of developing ARF or not. In New Zealand, it is possible to differentiate populations which are at low or high risk for rheumatic fever.

In a patient at **low risk** of ARF the primary consideration should be the **avoidance** of antimicrobials or throat swabbing. A seriously unwell patient should be followed and/or treated if a suppurative complication e.g. peritonsillar abscess is a possibility.<sup>97</sup>

While in low risk populations, the aim should be to minimise the prescription of unnecessary antibiotics, in populations at **high risk** of ARF, the greatest benefit is obtained by having a lower threshold for prescribing appropriate antibiotics. In some circumstances this may mean empiric antimicrobial treatment, however the utility of throat swabbing (see Sore Throat Algorithm) should always be taken into account for the patient, whānau/family and wider community.

See [pages 16-17, 23, 28-29](#) for details on antibiotic rationalisation.

### Question 4. If prevention of ARF is the prime consideration, is it safe to wait for up to nine days, from the onset of GAS pharyngitis, before commencing antibiotics?

It is **not safe** to wait up to nine days, from GAS pharyngitis onset to commencing antibiotics. Early studies of the aetiology of ARF recommended that GAS sore throats be treated within nine days of onset of symptoms.<sup>98</sup> There is a latent period following GAS infection before the symptoms of ARF begin.<sup>98-100</sup> However one intervention study,<sup>98</sup> a randomised control trial (RCT)<sup>50</sup> and an observational study<sup>101</sup> documented cases of ARF developing within nine days of the first onset of GAS pharyngitis. The so-called “nine day rule” is quoted for the management of GAS pharyngitis in children in America where ARF is now uncommon.<sup>3</sup>

Timely treatment of streptococcal pharyngitis with penicillin is necessary to prevent the subsequent development of ARF.<sup>50,98,101</sup>

See [Appendix 9](#) for review of supporting evidence.

<b>Recommendation:</b>	Treat group A streptococcal pharyngitis as soon as possible.
<b>Recommendation grade:</b>	C
<b>Evidence level:</b>	IV



## Question 5. Which antibiotics should be used in treating GAS pharyngitis?

A recent Cochrane Review found that antibiotics shortened the duration of pain symptoms associated with GAS pharyngitis by an average of one day and reduced the incidence of ARF by more than two-thirds in communities where ARF is common.<sup>102</sup>

The antibiotic regimes included in the 2008 guideline have been updated for the treatment of GAS positive pharyngitis, for both routine and recurrent GAS pharyngitis.

For antibiotic regimes for routine (when first or second case of) GAS pharyngitis see [Table 4](#) on [page 30](#).

For antibiotic regimes for recurrent (third or more) GAS pharyngitis within a 3 month period or GAS carriage, see [Appendix 10](#).

### Group A Streptococci Susceptibility

Group A streptococci remain globally penicillin susceptible as shown in [Table 3](#). Up to date data on group A streptococcal sensitivities can be found on the Environmental Sciences and Research Ltd website: [http://www.surv.esr.cri.nz/antimicrobial/general\\_antimicrobial\\_susceptibility.php](http://www.surv.esr.cri.nz/antimicrobial/general_antimicrobial_susceptibility.php)

**Table 3. Group A Streptococcus Sensitivity, September 2013**

Antibiotic	Group A Streptococcus	
	% Resistant to Antibiotic	Numbers Tested
Penicillin	0%	5,126
Erythromycin*	3.9%	8,688

Source: Environmental Sciences and Research Ltd website: [www.esr.cri.nz/](http://www.esr.cri.nz/)

\* Applies to all of this class of antibiotics (macrolides) including roxithromycin, azithromycin, clarithromycin. The retrieval site of GAS isolates is not specified.

Since penicillin resistance has never been reported amongst *S. pyogenes*, it is common for penicillin susceptibility not to be routinely performed by clinical microbiology laboratories when *S. pyogenes* is isolated from samples such as throat swabs. For patients with beta-lactam allergies or in other situations when a non-beta-lactam regimen is recommended, testing of macrolide susceptibility may need to be specifically requested depending on local laboratory practice.

### Antibiotics for Routine GAS Pharyngitis

See [page 23](#) for background information on antibiotic treatment of GAS pharyngitis.

#### Reference to Intramuscular Penicillin in the 2014 Guideline Update

IM Benzathine Benzylpenicillin (New Zealand Formulary) is more commonly known as benzathine penicillin (trade name: Bicillin® LA), and also known as Penicillin G Benzathine or Benzathine Penicillin G (BPG). Within this guideline IM Benzathine Benzylpenicillin is referred to as 'Benzathine Penicillin', so as not to confuse with benzylpenicillin (which has different pharmacokinetic properties and is not recommended for the treatment of GAS pharyngitis or for secondary prophylaxis).

[Table 4](#) includes the recommended antibiotics for the standard treatment of GAS positive pharyngitis for a first or second episode of GAS pharyngitis in a three month period. Each antibiotic choice has its strengths and weaknesses.

The gold standard is injectable long acting benzathine penicillin as the original trials demonstrating ARF prevention used long acting injectable penicillin.<sup>19,21</sup> Acceptance may be limited by pain and

therefore patient tolerance which may deter a child from declaring further sore throats. In high risk communities in New Zealand, a child has a one in three chance each year of having a GAS pharyngitis.<sup>50</sup> In a longitudinal American study conducted when ARF was prevalent, a child up to the age of 13 years was found to have three (range one to eight) episodes of GAS pharyngitis.<sup>103</sup> Furthermore from New Zealand data, a child who lives in a region of high socioeconomic disadvantage (NZDep 2009 Decile 10) has about a one in 150 risk of being admitted to hospital for ARF by 15 years of age.<sup>31</sup> Injectable long acting benzathine penicillin is an acceptable option where adherence with oral antibiotic regimes may be in question. Pain associated with injections can be minimised by co-administration of lignocaine (see [page 33](#) and [Appendix 4](#))

As intramuscular injections may deter patients from presenting with future sore throats, the preference is to offer oral treatment as a first option, penicillin or amoxicillin. Both oral choices require 10 days of treatment with associated adherence issues. Adherence issues may be minimised by lower frequency of antibiotic dosing i.e. once or twice daily dosing.<sup>12,13</sup> A telephone call mid-way through an antibiotic regime may assist with adherence.<sup>104</sup>

For the penicillin allergic child in the community setting, careful questioning to ascertain if they have a true anaphylactic IgE mediated allergy (see [Table 4](#) footnote) should be undertaken. It is appreciated that a test dose approach may not be safe in the community setting. A macrolide is the usual alternative. There is considerable literature on older macrolides with erythromycin estolate being the preferred option.<sup>105</sup> This is no longer available in New Zealand. Erythromycin ethyl succinate is available as an elixir however the gastrointestinal side effects are well documented.<sup>106</sup>

Roxithromycin has fewer gastrointestinal side effects and is available in New Zealand for adult patients for this reason. A paediatric formulation is not yet available in New Zealand. The published literature is limited for GAS pharyngitis,<sup>107-113</sup> however it is unlikely to be different in its appropriateness for GAS pharyngitis compared to other similar macrolides e.g. clarithromycin where there is more information supporting this indication. A paediatric formulation of roxithromycin is available in Australia and is currently being requested from Pharmac in New Zealand.

In the interests of antibiotic stewardship, the Writing Group considered that both clarithromycin and azithromycin should be used sparingly and for specific indications. Although azithromycin has been made widely available by Pharmac as a paediatric formulation for this indication, widespread community use of azithromycin with its prolonged half-life,<sup>114</sup> may drive the emergence of macrolide resistance, which is currently modest in New Zealand.<sup>114</sup>

In New Zealand the commonly recommended regimens are in [Table 4](#). These differ from current recommendations in Australia, which are Benzathine penicillin G, phenoxymethylpenicillin and erythromycin ethyl succinate.<sup>115</sup>

**Table 4. Recommendations for Antibiotics Regimes for First or Second Case of Group A Streptococcal (GAS) Pharyngitis in a Three Month Period**

Antibiotic	Route	Dose	Duration	References	IDSA* GRADE 2012
<b>Penicillin V<sup>†</sup></b>	PO	<b>Children &lt;20kg:</b> 250mg two or three times daily <b>Children &gt;20kg &amp; Adults:</b> 500mg two or three times daily	10 days	Gerber 1985, <sup>116</sup> Bass 2000, <sup>117</sup> Shulman 2012, <sup>9</sup> Lennon 2009, <sup>50</sup> AAP 2012 <sup>3</sup>	Strong, high
<b>Amoxicillin<sup>†</sup></b>	PO	<b>Once daily:</b> 50mg/kg dose once daily <i>Max dose 1000mg per day</i> <b>Or</b> Weight <30kg: 750mg once daily Weight ≥30kg: 1000mg once daily <b>Twice daily:</b> 25mg/kg dose twice daily <i>Max dose 1000mg per day</i>	10 days	Clegg 2006, <sup>11</sup> Lennon 2008, <sup>10</sup> Feder 1999 <sup>72</sup>	Strong, high
<b>Benzathine penicillin<sup>‡</sup></b>	IM	<b>Children &lt;30kg:</b> 450mg (600,000 U) <b>Adults &amp; children ≥30kg:</b> 900mg (1,200,000 U)	Single dose	Wannamaker 1951, <sup>100</sup> Bass 2000 <sup>117</sup>	Strong, high
<b>If concern about allergic (IgE mediated<sup>§</sup> or anaphylactic) response to beta lactams, use:</b>					
<b>Roxithromycin<sup>  </sup></b> , Pending Pharmac decision	PO	<b>Children:</b> 2.5mg/kg dose twice daily <b>Adults:</b> 300mg once daily <b>Or</b> 150mg twice daily	10 days	Begue 1987 <sup>108</sup>	Unavailable in the USA
<b>Erythromycin ethyl succinate<sup>  , ¶</sup></b>	PO	<b>Children &amp; Adults:</b> 40mg/kg/day in 2-3 divided doses <i>Max adult daily dose 1000mg</i>	10 days	Bisno 1997 <sup>118</sup>	A-II <sup>**</sup>

**Source: Modified from Table two.** Shulman S et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2012.<sup>9</sup> ©by permission of Oxford University Press, 2014.

Choice of antibiotic therapy should be discussed with the patient. IM long acting benzathine penicillin is the gold standard with regards to proven efficacy for prevention of ARF. However injection pain (which can be reduced with co-administration of lignocaine) may deter future presentation of sore throats.

\* The IDSA used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (see Appendix 3 for description)

† Amoxicillin can be taken with food whereas oral penicillin V is best absorbed on an empty stomach. Both are equally effective in eradicating GAS.<sup>10,11</sup> Lower frequency of antibiotic dosing has been shown to improve adherence.<sup>12,13</sup> Amoxicillin is relatively palatable.<sup>14</sup>

‡ Benzathine penicillin can be given with lignocaine to reduce injection site pain (see page 33 and Appendix 4). It may be marginally more effective than oral penicillin or amoxicillin in eradicating GAS pharyngitis.<sup>15</sup>

§ IgE-mediated reactions include ANY bronchospasm, angioedema, hypotension, urticarial or pruritic rash.

|| Always check for drug interactions before prescribing. In particular, care should be taken when prescribing macrolides to patients taking warfarin and carbamazepine.

¶ The erythromycin currently funded by Pharmac is erythromycin ethyl succinate. There are other erythromycins available with different pharmacokinetic profiles.

\*\* Erythromycin is not recommended in 2012 The Infectious Diseases Society of America (IDSA) Guideline.<sup>9</sup> In 2002 the IDSA recommended erythromycin based on a different grading system for clinical guideline recommendations (see Appendix 5).<sup>119</sup>

## The Use of Once-Daily Amoxicillin

Four randomised controlled trials (RCTs) have assessed once-daily amoxicillin as an alternative to penicillin V (see [Appendix 11](#)).<sup>10,11,71,72</sup> Of the two studies which were sufficiently powered as non-inferiority trials to demonstrate that eradication of streptococci from the throat was sufficient in the study comparison group, Clegg comparing once (OD) to twice-daily (BD) amoxicillin, found the bacteriological failure rate was not inferior in the OD group as compared to the BD group.<sup>11</sup> Lennon found that there was no difference between penicillin and once-daily amoxicillin, with the latter being well tolerated. Its absorption is not affected by food.<sup>10</sup> The taste of amoxicillin suspension is relatively palatable.<sup>120</sup>

## Amoxicillin Maximum Daily Dosage

The maximum daily dosage recommended for amoxicillin is 1000mg, although up to 1500mg is acceptable and is well tolerated.<sup>10</sup> International guidelines and studies differ in the recommended maximum daily dose for amoxicillin:

1. 1000mg daily recommended in the IDSA Guideline<sup>9</sup>
2. 1200mg daily recommended in the Red Book<sup>3</sup>
3. 1500mg daily used in Lennon et al's randomised controlled trial (RCT) in treating and eradicating GAS in children with pharyngitis<sup>10</sup>
4. 750mg daily for under 40kg and 1000mg for those over 40kg.<sup>11</sup>

As GAS is exquisitely susceptible to penicillin, larger doses may not be necessary, even for heavier patients. Smaller maximum daily doses are likely to be better tolerated for children over 30kg.

## The Use of Amoxicillin in Pharyngitis

*This topic has not been updated from the 2008 Guideline.*

Amoxicillin should not be used if infectious mononucleosis (IMN) (Epstein-Barr Virus [EBV]) (see [Table 5](#) below) is considered a possible differential diagnosis, as a rash may occur.<sup>72,121,122</sup> With EBV infection, the rate of rash in reaction to amoxicillin may be 70-100%. In a small study of four IMN patients with amoxicillin-induced exanthema, Renn et al conducted skin tests and lymphocyte transformation testing (LTT), concluding that real sensitisation to amoxicillin could occur in this setting.<sup>123</sup> If a rash to amoxicillin is non-pruritic, maculopapular, and seen in a patient with IMN, then it is probable that subsequent penicillins are generally tolerated.<sup>124,125</sup> This type of rash is generally not immunoglobulin E (IgE) mediated. Although there may be a risk of recurrence of similar rash and there is likely some other underlying immunologic mechanism, there is not an increased risk of severe allergic reaction to subsequent courses.

If there was an urticarial rash or other features suggesting an IgE mediated mechanism then, even if a patient had IMN, evaluation for drug allergy should be undertaken prior to considering further courses of penicillin-based antibiotics.

**Table 5. Clinical Manifestations of Infectious Mononucleosis in Children and Adults**

Sign or Symptom	Frequency (%)		
	Age<4 yrs	Age 4+ yrs	Adults (range)
lymphadenopathy	94	95	93-100
fever	92	100	63-100
sore throat or tonsillopharyngitis	67	75	70-91
exudative tonsillopharyngitis	45	59	40-74
splenomegaly	82	53	32-51
hepatomegaly	63	30	6-24
cough or rhinitis	51	15	5-31
rash	34	17	0-15
abdominal pain or discomfort	17	0	2-14
eyelid oedema	14	14	5-34

Source: Feigin et al (eds) 2009<sup>126</sup> cited in Lennon D et al. 2011A.<sup>127</sup> Permission to publish copyright material pending.

## Amoxicillin and Penicillin

Once daily amoxicillin is not inferior to oral penicillin in the treatment of GAS pharyngitis.<sup>10,11</sup> Amoxicillin is acid stable and more reliably absorbed than penicillin when taken with food.<sup>128</sup>

<b>Recommendation:</b>	Amoxicillin is not inferior to oral penicillin in treating GAS pharyngitis.
<b>Recommendation grade:</b>	A
<b>Evidence level:</b>	I

## Duration of Antibiotic Treatment

**Courses of oral antibiotics with a duration of less than 10 days have not been demonstrated to reduce the incidence of ARF in high risk populations.**

In high rheumatic fever risk populations, the treatment of GAS pharyngitis is to prevent ARF. The risk of developing ARF persists unless GAS is eradicated.<sup>21</sup> These studies were undertaken using injectable long acting penicillins. Hence the surrogate endpoint against which new anti-microbial agents are judged is GAS eradication though this is never 100%.<sup>25,75</sup> In populations at high risk of ARF the quality of trials (particularly ensuring sufficient statistical power to support conclusions) of a new antibiotic, treatment doses or length of treatment are an important consideration. Critical aspects from trial publications include appropriate timing of follow up sampling, recording of symptoms and signs, adherence to medication and serotyping of GAS isolates.<sup>75</sup>

Compliance with oral antibiotics is more likely to be successful with shorter courses.<sup>73,129</sup> In terms of bacteriological eradication, five days of penicillin V is inferior to 10 days penicillin V.<sup>130</sup>

In low ARF risk populations, short courses (three to seven days, most commonly five days) of newer oral antibiotics have been widely studied. Many of these studies have been of low quality and results are inconsistent.<sup>25,131,132</sup> Differing study designs, study populations and antibiotics have been employed, making study comparisons difficult. The wide variety of antibiotics chosen means that the body of evidence behind any one antibiotic is small. Short course, low dose azithromycin is inferior to 10 days of penicillin V.<sup>133</sup> A meta-analysis comparing five days of macrolide therapy, excluding azithromycin, with 10 days penicillin V favoured neither treatment.<sup>24</sup> Two studies comparing six days amoxicillin with 10 days penicillin V also favoured neither treatment but were likewise small and underpowered.<sup>73,74</sup> Five days of one of a variety of second or third generation cephalosporins may not be inferior to penicillin V and may have improved bacterial eradication but results are inconsistent and the studies are of varying quality.<sup>24,131,132,134,135</sup> Short course treatment with either six days of amoxicillin or five days of a cephalosporin warrants further investigation.

The newer antibiotics which appear to perform better than penicillin are generally of broader spectrum and more expensive. The development of antibiotic resistance is favoured by low dose, longer term therapy and broad spectrum coverage.<sup>97</sup> Short course, high dose treatment may reduce the development of antibiotic resistance.<sup>136</sup>

Overall, short course antibiotics may be at least equivalent to standard 10 day treatment with oral antibiotics (penicillin V, amoxicillin) in terms of eradication of GAS bacteria after the completion of therapy. The vast majority of studies have, however, been conducted in low risk populations and only three studies had sufficiently long term follow up to study the prevalence of long term sequelae of GAS pharyngitis including ARF.

In low ARF risk populations, where most sore throats are viral and ARF is rare, antibiotic stewardship and minimising inappropriate prescribing, rather than shortening the duration of antibiotic therapy, should be the aim.

In high ARF risk populations, where ARF has a high prevalence, caution is advised.<sup>97</sup> It is not safe to recommend short course antibiotic therapy; the standard oral therapy remains 10 days of amoxicillin or penicillin V until further evidence is accumulated.

<b>Recommendation:</b>	Do not prescribe courses of oral antibiotics with a duration of less than 10 days to treat GAS pharyngitis in populations at high risk of ARF.
<b>Recommendation grade:</b>	B
<b>Evidence level:</b>	I

### Benzathine Penicillin Cut Off Weight

The following were considered when recommending an increase from 20kg to 30kg in cut off weight for Benzathine Penicillin:

- The Infectious Diseases Society of America (IDSA)<sup>9</sup> and the American Academy of Pediatrics<sup>3</sup> recommend a cut off weight of 27kg which equates to 60lb.
- Lower rates of prescribing errors are associated with round figures.
- This reduces the volume and the discomfort of the injection for children between 20-30kg which was emerging as an increasing problem (Ross Nicholson Paediatrician MMH Pers Comm).

<b>Recommendation:</b>	Children < 30kg: 600,000 U Adults and children ≥ 30kg: 1,200,000 U
<b>Recommendation grade:</b>	Expert opinion

### Lignocaine with Benzathine Penicillin Injection

Intramuscular benzathine penicillin injections can cause local pain and discomfort. This can lead to poor compliance in those requiring ongoing prophylaxis.<sup>137,138</sup> Amir et al demonstrated that pain can be significantly reduced when 1% lidocaine (lignocaine) was used to reconstitute benzathine penicillin for injection. This did not affect serum penicillin levels.<sup>137</sup>

A recent New Zealand study with ARF patients receiving monthly IM benzathine penicillin for prophylaxis has demonstrated a reduction in the subjective experience of pain when two analgesic interventions were offered with intramuscular delivery of benzathine penicillin; either 0.25ml of 2% lignocaine or 0.25ml of 2% lignocaine with a vibrating device and cold pack (Buzzy®). Both lignocaine and lignocaine and Buzzy® reduced the pain of the injection. Lignocaine and Buzzy® together resulted in a greater reduction in pain than lignocaine alone, but only in children aged 13 years or younger. In this age group, the fear of injection was also reduced.<sup>139</sup>

For the safe preparation and administration of lignocaine with benzathine penicillin refer to The KidzFirst Guideline on Analgesia for IM Penicillin injections (2011) in [Appendix 4](#). In many areas, the vibrating device recommended will not be available but the use of lignocaine should still be considered.

<b>Recommendation:</b>	Low dose lignocaine can safely be used with IM benzathine penicillin to reduce pain associated with administration (See <a href="#">Appendix 4</a> ).
<b>Recommendation grade:</b>	C
<b>Evidence level:</b>	III-2



## Lignocaine in Pregnancy

Low dose lignocaine is safe in pregnancy. A large number of pregnant women and women of child bearing age have been exposed to lignocaine.<sup>140,141</sup> Lignocaine crosses the placenta but there is no evidence of an association with fetal malformations, cardiac rhythm disturbances or other significant side effects in pregnant women or their babies.

<b>Recommendation:</b>	In pregnant women, low dose lignocaine may be co-administered with IM benzathine penicillin to reduce associated pain (See <a href="#">Appendix 4</a> ).
<b>Recommendation grade:</b>	C
<b>Evidence level:</b>	III-2

## Lignocaine in Breastfeeding

Lignocaine can be administered to breast feeding women. Lignocaine is excreted into breast milk in small amounts.<sup>140-144</sup> however the oral bioavailability of lignocaine is very low (35%).<sup>144</sup> Given the small amount of lignocaine used with benzathine penicillin the amount excreted into breast milk to which the infant is therefore exposed, is minimal. Lignocaine is unlikely to cause adverse effects in breast feeding infants.<sup>140-144</sup>

<b>Recommendation:</b>	In breast feeding women, lignocaine may be co-administered with IM benzathine penicillin to reduce associated pain (See <a href="#">Appendix 4</a> ).
<b>Recommendation grade:</b>	C
<b>Evidence level:</b>	IV

## Oral Contraception and Antibiotics

Additional contraceptive precautions are no longer recommended during or after courses of antibiotics that do not induce enzymes. With the exception of rifampicin, pharmacokinetic studies have failed to demonstrate changes in levels of ethinyl estradiol with concomitant use of antibiotics (including macrolides) and combined oral contraceptives.<sup>145,146</sup> Rifampicin is a potent inducer of the liver enzymes that metabolise oestrogen and/or progestogens. This leads to reduced bioavailability and reduces the effectiveness of oral contraceptives.

Women using combined oral contraceptives (COC) should be advised to use additional contraceptive precautions e.g. barrier methods such as condoms, while taking rifampicin and for 28 days after stopping rifampicin treatment. To minimise the risk of contraceptive failure as well as using additional contraception, an extended regimen (taking combined hormonal contraceptive continuously for  $\geq 3$  weeks until breakthrough bleeding occurs for three to four days) or tricycling (taking three pill packets consecutively without a break) and a shortened pill-free interval of four days is recommended. Only monophasic 21-day pill packs are suitable for extended use or tricycling and a minimum combined oral contraceptive strength of 30  $\mu\text{g}$  ethinyl estradiol is recommended.

Women using progestogen-only contraceptive pills (POP) or progesteron implants should be advised to use an additional alternative method of contraception. Alternatives include:

- One-off injection of depot medroxyprogesterone acetate.



- Continue POP pill and use additional contraceptive precautions e.g. barrier methods such as condoms, while taking rifampicin and for 28 days after stopping treatment.

Additional precautions are not required for women using progesterone only injectables (depot medroxyprogesterone acetate) or the levonorgestrel-releasing intrauterine system or copper-bearing intrauterine device.<sup>147</sup>

<b>Recommendation:</b>	For women on oral contraception, additional contraception (barrier or abstinence) is not required when taking antibiotics except for <b>rifampicin</b> where: <ul style="list-style-type: none"> <li>• Combined oral contraceptives (COCs) require additional contraception during and 28 days after stopping rifampicin as well as: <ul style="list-style-type: none"> <li>• Combined hormonal contraceptive continuously for <math>\geq 3</math> weeks until breakthrough bleeding occurs for 3-4 days, <b>or</b></li> <li>• Tricycling (taking three monophasic 21-day pill packs continuously without a break) and a shortened pill-free interval of 4 days</li> <li>• A minimum COC strength of 30<math>\mu</math>g ethinyl estradiol</li> </ul> </li> <li>• Progestogen-only pill (POP) or implant should be advised to use an alternative method of contraception.</li> </ul>
<b>Recommendation grade:</b>	D
<b>Evidence level:</b>	Expert opinion

### Warfarin and Antibiotics

Macrolides i.e. erythromycin, azithromycin, roxithromycin, clarithromycin, clindamycin, interact with many drugs by inhibiting an enzyme involved in metabolising approximately 50% of all prescribed drugs. Check for interactions **before** prescribing these agents ([www.medsafe.govt.nz](http://www.medsafe.govt.nz)).

Drug interactions with warfarin are of particular importance because they are potentially life threatening. Particular attention should be paid when considering starting warfarinised patients on macrolide antibiotics such as roxithromycin and erythromycin, with which increased symptomatic interactions have been reported.<sup>148</sup>

Beta-lactam antibiotics such as penicillin, amoxicillin and augmentin are good choices for patients on warfarin as they only occasionally elevate international normalised ratio (INR). INR monitoring is still required with these comparatively “safe” antibiotics. Specialist advice should be sought concerning patients requiring antibiotic therapy, who have anaphylactic reactions to beta lactam antibiotics and are taking warfarin.

Rifampicin will induce the metabolism of warfarin and will likely result in subtherapeutic INRs.

Patients taking warfarin should have their INR monitored at the time of treatment change. i.e. both when starting and stopping antibiotics and at day three or four.

<b>Recommendation:</b>	Care should be taken when prescribing antibiotics to patients on warfarin.  Warfarinised patients should have their INR monitored at time of antibiotic commencement, at day 3 or 4 and on completion.
<b>Recommendation grade:</b>	Expert opinion

## Antibiotics Not Recommended for the Treatment of GAS Pharyngitis

Antibiotics that are not recommended for treating GAS pharyngitis include; tetracyclines, sulfonamides and fluoroquinolones.<sup>3</sup> Sulfonamides (e.g. co-trimoxazole, TMP, trimethoprim-sulphamethoxazole) and tetracyclines should NOT be used in treating GAS pharyngitis. In a study in the Northern Territories, GAS has been demonstrated to be susceptible to co-trimoxazole in vitro.<sup>148</sup> There is however no clinical data on outcomes in GAS pharyngitis treated with trimethoprim-sulphamethoxazole.

**Table 6. Antibiotics Not Recommended in Management of GAS Pharyngitis**

Medication	Example	Reason not to Administer
Tetracyclines	Minocycline, doxycycline	10% are resistant to GAS <sup>149</sup>
Sulfonamides	Trimethoprim-sulphamethoxazole (co-trimoxazole)	Do not eradicate GAS <sup>149</sup>
Fluoroquinolone - old	Ciprofloxacin	Not effective <sup>149</sup>
Fluoroquinolone - new	Moxifloxacin	Unnecessarily broad spectrum <sup>9,150</sup> and expensive <sup>9</sup>

<b>Recommendation:</b>	Do not use tetracyclines, sulfonamides or fluoroquinolones antibiotics in the treatment of GAS pharyngitis.
<b>Recommendation grade:</b>	D, group consensus
<b>Evidence level:</b>	IV

## Adjunct Therapy Recommendations in the Treatment of GAS Pharyngitis

In addition to antibiotic treatment, symptomatic therapies may be useful in the treatment of GAS pharyngitis. Paracetamol should be considered for treating moderate to severe symptoms or for the control of high fever.<sup>9</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful for the symptomatic treatment of pharyngitis. If ARF is being considered as a diagnosis, NSAIDs should be avoided until a diagnosis is secure as NSAIDs can mask ARF symptoms and test results.<sup>47,115</sup>

NSAIDs are being used widely for symptomatic therapy in children. There has been no published data found to suggest that there is an association between NSAIDs and Reye Syndrome. Aspirin should be avoided in children under age of 16 years because of the risk of Reye syndrome.<sup>3</sup>

<b>Recommendation:</b>	Paracetamol and NSAIDs can be used in the symptom control of GAS pharyngitis. Aspirin should be avoided in children.
<b>Recommendation grade:</b>	Expert opinion

## Treatment of GAS Positive Pharyngitis in People Already on IM Benzathine Penicillin Prophylaxis

The recommendations for patients on IM benzathine penicillin prophylaxis for ARF and who are GAS positive on throat swab are as follows:

- If a throat swab is GAS positive treat with a 10 day course of oral penicillin or amoxicillin.
- Check adherence to prophylaxis programme. Serum penicillin levels will be falling by week three and four post IM long acting benzathine penicillin injection<sup>16</sup>

This recommendation has changed from the 2008 Guideline.<sup>1</sup>

**Recommendation:** For people already on IM benzathine penicillin prophylaxis:

If GAS positive treat with a 10 day course of oral penicillin or amoxicillin.

**Recommendation grade:** D

## Question 6. How should pharyngeal carriers of GAS be managed?

There is no accepted definition of carriage in the literature. The Infectious Diseases Society of America (IDSA) definition of chronic pharyngeal carriage is GAS present in the pharynx but no evidence of an active immunologic response to the organism, such as rising anti-streptococcal antibody titres.<sup>9,77,151</sup> However there is evidence to suggest that antibody responses can be moderated by such variables as age, sex, diabetes and prompt therapy.<sup>152,153,154</sup> Carriage has also been defined as the culture of GAS from throat or nasal swab without other evidence of acute infection.<sup>155</sup>

The preferred definition of GAS carriage is the isolation of GAS in the absence of clinical symptoms and signs and a lack of progression to disease. However, the long latent period of some GAS illnesses such as ARF means that true carriage can only be confirmed retrospectively.

Where tests for antistreptococcal antibodies are taken, changes in antibody titres take 10 to 14 days to occur. At the time of diagnosis, approximately half of patients with symptomatic, culture-positive GAS pharyngitis will not have a rise in anti-streptococcal antibodies.<sup>7,76,77,153</sup> This should not result in delays in treatment (see [Question 4](#)).

In the setting of an individual presenting with a symptomatic pharyngitis who may be a chronic carrier of pharyngeal GAS developing an acute upper respiratory viral infection and with a positive test for pharyngeal GAS (usually a throat swab) Gerber et al 2009 state :*"it is impossible... to distinguish between carriers from infected individuals" and "the individual should be treated"*.<sup>78</sup>

Gerber et al also state that chronic GAS carriers are not considered to be a risk to themselves or others for ARF development but quote a reference from 1980 when ARF was well under control in the USA and antimicrobial containment had become an issue.<sup>76</sup> This is relevant to the population at **low** risk of ARF in New Zealand only. Earlier USA publications when ARF was more prevalent support GAS carriers as being a risk to themselves and others for ARF, albeit less so. Hamburger et al found that GAS cross infections could occur on hospital wards when only one or two GAS carriers were present and that cross infections could be "subclinical".<sup>156</sup>

In areas of low ARF endemicity, the presence of symptoms more consistent with a viral pharyngitis such as associated cough or running nose may avoid repeated testing and repeated courses of antibiotic treatment.

### The Risk of GAS Throat Carriage to the Health of the Individual

The literature is equivocal as to whether carriers are at risk of suppurative or non-suppurative GAS complications e.g. rheumatic fever.<sup>157</sup> Currently the risk of ARF to the health of the individual cannot be determined in GAS carriers (see above). Further research is needed.

See [Appendix 12,13,14,15,16,17,18](#) for evidence on GAS carriage and [Appendix 10](#) for antibiotic choices.

**Recommendation:** There is insufficient data currently to determine the risk of rheumatic fever in individuals who are GAS carriers. Further research is needed.

## The Risk of GAS Throat Carriage to Others

People carrying GAS in the throat can spread GAS to others but are less likely to spread GAS than those with symptomatic pharyngitis.<sup>156,158,159</sup> This may be of significance where the risks of GAS related illnesses are high such as in settings with high rates of ARF.

See [Appendix 12,13,14,15,16,17,18](#) for evidence on GAS carriage and [Appendix 10](#) for antibiotic choices.

<b>Recommendation:</b>	GAS throat carriage can spread GAS to others. The recommendations are listed below.
<b>Recommendation grade:</b>	B
<b>Evidence level:</b>	IV

Where patients or contacts are at high risk of ARF, swabbing and treating pharyngeal GAS in an asymptomatic person (possible carriage) may be recommended (see below). In special circumstances this may be a necessary part of controlling the pharyngeal GAS burden and thus reducing the risk of ARF.<sup>160</sup>

In high risk settings\* for ARF, current recommendations (see Group A Streptococcal Sore Throat Guideline 2008)<sup>1</sup> remain unchanged:

1. Consider swabbing symptomatic household members of a person with GAS positive pharyngitis.<sup>3</sup> (See Sore throat management algorithm 2014 and [Clinical Question 18](#)).
2. Swab (and treat if positive for pharyngeal GAS) all household members (symptomatic or not) of a person with GAS positive pharyngitis where the index case has a personal, family or household history of rheumatic fever. This may identify and treat any GAS carriers who maybe at potential risk of spreading GAS.<sup>1</sup> See [Clinical Question 19](#).
3. Swab all household members where there has been three or more cases of GAS pharyngitis in the last three months. The purpose of this is to identify and treat any GAS carriers who may be at potential risk of spreading GAS.<sup>1</sup> See [Clinical Question 20](#).
4. Consider swabbing (and treat if positive for pharyngeal GAS) close contacts (symptomatic or not) in an outbreak (more than one case in close association particularly if associated with the same strain i.e. *emm* type) of ARF **or** acute post streptococcal glomerulonephritis.<sup>1</sup> A contact is someone who usually resides in the house with the ARF case or is an overnight visitor within two weeks of the ARF case presenting, is aged 3-45 years and has consented to be throat swabbed.
5. In addition, in school sore throat clinics, where an outbreak (three or more students with GAS pharyngitis) has been identified in a single classroom within a seven day period (sore throat declared by the student), it is recommended all consented children's throats are assessed and swabs performed on those with signs or symptoms of incident pharyngitis as per sore throat clinic RCT protocol.<sup>50</sup>

\* High risk for rheumatic fever if personal, family or household history of rheumatic fever or have 2 or more of following criteria:

- Māori or Pacific
- Aged 3-35 years
- Living in crowded circumstances or lower socioeconomic area.

In some circumstances when a person presents with pharyngitis symptoms, assessment of their risk of spreading GAS in the workplace is recommended. Throat swabbing is recommended for the following people:

- Healthcare workers including residential care workers<sup>4</sup> (and expert opinion)
- Food handlers<sup>2,6</sup>
- Teachers<sup>6</sup> (and expert opinion)
- Childcare workers (expert opinion).

If they are GAS positive, throat swabbing and treating all workplace contacts (symptomatic or not) might be necessary. This might include treating GAS carriers.

## Question 7. How should treatment failure and/or the recurrence of GAS pharyngitis be managed?

### Treatment Failure

Treatment failures i.e. failure to eradicate pharyngeal GAS in a symptomatic individual, occur more frequently in individuals treated with oral penicillin (or amoxicillin) in comparison with intramuscular benzathine penicillin.<sup>10,11,161</sup>

Treatment failure is strictly defined as the recurrence of symptomatic pharyngitis caused by the same serotype (*emm*) of GAS, accompanied by a corresponding rise in serial streptococcal serology.<sup>75</sup> While treatment failure can be carefully identified in the research setting, this is much more difficult in the primary care setting. Serotyping (*emm*-typing) is not readily available in everyday practice and while paired serology (acute and convalescent titres taken at least 14 days apart) are feasible, they are rarely performed even in antibiotic trials<sup>25,75</sup> and should not delay prompt treatment (see [Clinical Question 4](#)).

### Recurrence

Recurrences, defined as the patient's third or further episode of symptomatic and culture proven GAS pharyngitis in a three month period, can be treated using antibiotics in [Appendix 10](#). These are listed in order of preference. Important considerations are whether the infection is a result of poor adherence with treatment (relapse) or re-infection of the patient by the same or a new strain of GAS from a family, household or other contact. A second episode of pharyngitis by the original infecting strain of GAS is less common.<sup>162</sup>

Adherence to treatment may be improved by the use of once-daily oral amoxicillin. Where compliance is likely to be problematic, a single dose of IM benzathine penicillin should be given, see [Clinical Question 11](#).

Gerber et al considered the possibility that GAS may be isolated from the throats of chronic carriers actually suffering from viral upper respiratory tract infections. In New Zealand, the population at high risk of ARF also has high rates of respiratory illnesses, including poorly controlled asthma and bronchiectasis.<sup>163,164</sup> Determining a likely viral origin of a sore throat on the basis of accompanying symptoms may not be reliable in the high risk population. Until further research is performed on the New Zealand context, the Writing Group deems the risk/benefit of treating apparent recurrent episodes to favour treating, in the best interests of the patient. It is acknowledged that in some situations GAS pharyngeal carriage will be treated but it is considered that carriage itself poses some risk to both the patient and the household. See [Clinical Question 6](#) on GAS carriage.

Household contacts of patients experiencing recurrences should be assessed as per the Household Sore Throat Management Algorithm on [page 14](#). See [Clinical Question 19](#).

## Question 8. In patients with or without GAS pharyngitis, do antibiotics shorten symptoms of sore throat on day three and at one week (days six to eight)?

*This Clinical Question has not been updated from the 2008 Guideline.*

Data for this section comes from a Cochrane Review by Del Mar et al on antibiotics for sore throat.<sup>165</sup> A total of 27 studies were found which assessed antibiotics against controls in pharyngitis, 18 double-blinded and three single-blinded. Most of the studies were in adults.

Some of the studies were not placebo controlled and do not consider the possible placebo effect of treatment on throat pain (see [Appendix 19](#)).

### **Does Treating GAS Positive Pharyngitis with Antibiotics Make a Difference to Throat Pain at Day Three and Days Six to Eight?**

#### **At Day Three**

Del Mar et al found 11 studies which examined patients with pharyngitis who all had GAS positive throat swabs. Two studies did not use placebos. Giving antibiotics to patients with GAS positive pharyngitis reduced pain by 28% on day three (see [Appendix 19](#)).<sup>165</sup>

#### **At One Week (Six to Eight Days)**

In Del Mar et al's Cochrane analysis, there were six studies of GAS positive patients at one week. There were no placebos in two of the trials. Treatment with antibiotics, compared to no treatment, resulted in a 23% reduction in throat pain (see [Appendix 19](#)).<sup>165</sup>

### **Does Treating GAS Negative Pharyngitis with Antibiotics Make any Difference to Throat Pain at Day Three and Days Six to Eight?**

#### **At Day Three**

Del Mar et al found six studies which looked at throat pain on day three in patients with pharyngitis who all had GAS negative throat swabs. All used placebos. Reported throat pain was reduced by half in GAS negative patients treated with antibiotics, despite the negative throat swabs (see [Appendix 19](#)).<sup>165</sup>

#### **At Days Six to Eight**

In the Del Mar et al analysis, five studies were found which examined the symptom of sore throat at one week (six to eight days) in patients with pharyngitis who were GAS negative. The studies were all placebo-controlled. In negative GAS swab patients, antibiotic treatment did not make a significant difference to throat pain at one week (see [Appendix 19](#)).<sup>165</sup>

<b>Recommendation:</b>	There is insufficient data to draw conclusions about antibiotic limiting symptoms of pharyngitis in children. In adults, the symptom of throat pain in GAS positive pharyngitis is improved by antibiotics.
<b>Recommendation grade:</b>	A
<b>Evidence level:</b>	I

### **Question 9. Does treating pharyngitis with antibiotics reduce the suppurative complications of GAS pharyngitis (acute otitis media and quinsy)?**

*This Clinical Question has not been updated from the 2008 Guideline.*

Data for this section comes from a Cochrane Review on antibiotics for sore throat.<sup>165</sup> A total of 27 studies were found which assessed antibiotics against controls in pharyngitis (pharyngitis in general, not specifically GAS pharyngitis). Eighteen were double-blinded and three were single-blinded. Most of the studies were in adults (see [Appendix 19](#)).<sup>165</sup>

### **Does Treating Pharyngitis with Antibiotics Reduce the Incidence of Acute Otitis Media (by Clinical Diagnosis) Occurring within 14 Days?**

Del Mar et al found 11 RCTs which looked at this issue, nine were placebo-controlled. Overall, antibiotics reduced the rate of clinically suspected acute otitis media following pharyngitis by about 23% (see [Appendix 19](#)).<sup>165</sup>



## Does Treating Pharyngitis with Antibiotics Reduce the Incidence of Quinsy (by Clinical Diagnosis) Occurring within 2 Months?

Eight RCTs were found by Del Mar et al; in six the patients were given placebos. A potential benefit for antibiotic treatment (16% reduction) in preventing clinically suspected quinsy was demonstrated (see [Appendix 19](#)).<sup>165</sup>

<b>Recommendation:</b>	Treating pharyngitis with antibiotics reduces acute otitis media and quinsy.
<b>Recommendation grade:</b>	A
<b>Evidence level:</b>	I

## Question 10. Do antibiotics reduce the incidence of acute post streptococcal glomerulonephritis (APSGN) after GAS pharyngitis?

Data for this section comes from a Cochrane Review.<sup>165</sup> A total of 27 studies were found which assessed antibiotics against controls in pharyngitis. Eighteen were double-blinded and three were single-blinded. Most of the studies were in adults (see [Appendix 19](#)).<sup>165</sup>

## Does Treating Pharyngitis with Antibiotics Reduce the Incidence of Acute Post Streptococcal Glomerulonephritis (APSGN) Within One Month?

Del Mar et al reviewed ten RCTs, four were placebo-controlled. Only six studies looked at APSGN as an end point. Two cases of APSGN occurred, both in the control groups. Due to the small numbers involved, he concluded that there was insufficient data to find a benefit for antibiotics in sore throat management to reduce the incidence of APSGN (see [Appendix 19](#)).<sup>165</sup>

<b>Recommendation:</b>	While treating pharyngitis with antibiotics reduces the rate of ARF, there is insufficient evidence regarding acute post streptococcal glomerulonephritis.
<b>Recommendation grade:</b>	A
<b>Evidence level:</b>	I

## Question 11. Which measures improve adherence to antibiotic courses prescribed for GAS pharyngitis?

*This Clinical Question has not been updated from the 2008 Guideline.*

### Verbal/Written Interventions, Including Telephone Calls

A Cochrane review looked at interventions for enhancing medication adherence.<sup>166</sup> Three of the RCT studies are relevant to compliance with antibiotic treatment.<sup>167-169</sup> Overall, statistically significant improvements in medication adherence (31 of 67 studies) and treatment outcomes (22 of 67 studies) occurred no matter what the intervention.

An RCT in 2004 found that a telephone call four to five days into treatment increased antibiotic compliance from 54% to 78% among patients over 18 years old who attended a Spanish health clinic with pharyngitis.<sup>104</sup>

### Reducing the Number of Antibiotic Doses per Day

Pichichero estimated the failure rate of oral penicillin in eradicating GAS from the throat was ten to



25% and believed that at least some of this was due to poor compliance.<sup>129,170-178</sup> Simplifying medication regimes may increase compliance and the rate of eradication. Lan et al found twice-daily dosing of oral penicillin to be as effective as more frequent regimes and the cure rates with once-daily dosing only 12% lower than more frequent penicillin dosing.<sup>179</sup> There is evidence that once-daily dosage of amoxicillin is as effective as standard oral penicillin regimes.<sup>10,71,72</sup> Compliance with amoxicillin therapy may also be greater than with oral penicillin therapy, because amoxicillin preparations are more palatable and need not be taken on an empty stomach, simplifying regimes.

**Recommendations:** Ten days of oral penicillin twice daily is the gold standard for treating GAS pharyngitis. Once daily oral amoxicillin is a reasonable alternative, as is IM benzathine penicillin. Evidence for shorter regimes remains insufficient, nor is there sufficient evidence to make firm recommendations on clinical measures to increase compliance.

	Evidence level	Recommendation grade
Ten days twice-daily penicillin regimes	I	A
Ten days once-daily oral amoxicillin	III	B
Telephone support for compliance with antibiotics	III	B

## Question 12. How long should patients be excluded from daycare/school after starting antibiotics for GAS pharyngitis?

GAS throat infection is highly transmissible by droplet spread. Eradication of bacteria (i.e. throat swabs no longer culture group A streptococci) occurs after 24-48 hours of antibiotic treatment in the majority of patients.<sup>23,71,72,130,180-186</sup> See [Appendix 20](#) for evidence table.

The New Zealand Ministry of Health recommends that school and day care pupils should not attend school or early childhood services or have close contact with other children for a minimum of 24 hours from the first dose of appropriate antibiotics if possible.<sup>187,188</sup> This recommendation has remained through repeated revisions of the Health (Infectious and Notifiable) Diseases Regulation (1966 amended 2013).<sup>6</sup> It is rarely invoked.

The Advisory Group considered the evidence and current recommendations within the context of minimising school absenteeism and for those not commenced on empiric antibiotics; the delay in commencing treatment whilst waiting for the throat swab result. It is recommended that all symptomatic GAS positive school and day care children are isolated at home for 24 hours after starting antibiotics if possible.

Evidence for school and work exclusion in [Appendix 21](#) and evidence table in [Appendix 20](#).

See [Clinical Question 3C](#) for recommendations for workers at increased risk of spreading GAS in their workplace and [Clinical Question 13](#) for evidence of who is at risk of spreading GAS in their work environment.

**Recommendation:** Isolate at home, school and day care aged children with symptomatic GAS positive pharyngitis, for 24 hours after commencing antibiotics if possible.

**Recommendation grade:** Group consensus, national legislation

## Question 13. Who is at increased risk of spreading GAS?

Group A streptococcus is spread through droplets of saliva or nasal secretions,<sup>189</sup> as well as in water<sup>190</sup> and food preparation.<sup>191</sup> Nasal GAS infection has also been implicated by Hamburger et al (1945) and Jarrett et al (1950).<sup>156,192</sup>

GAS spread has been demonstrated to occur in a variety of settings, including households,<sup>7,193</sup> military barracks,<sup>189,192,194,195</sup> classrooms<sup>193,196</sup> day care,<sup>197,198</sup> hospitals<sup>156,199,200</sup> and residential care.<sup>201,202</sup> A GAS outbreak in Christchurch in 2014 in an aged care facility led to five deaths.

See [Appendix 22, 23, 24](#) for a review or representative evidence.

Those at increased risk of spreading GAS include:

- Healthcare and residential care workers (Pichichero & Casey 2007A,<sup>4</sup> expert opinion)
- Food handlers (Darrow 2002,<sup>5</sup> NZ Government 2013)<sup>6</sup>
- Teachers (expert opinion, NZ Government 2013)<sup>6</sup>
- Childcare workers (expert opinion).

Adults presenting with symptomatic pharyngitis who have otherwise been assessed as being low risk for ARF, should be assessed, based on their employment, for their risk for spreading GAS in the workplace to those at high risk for ARF. If they are assessed as being at increased risk of spreading GAS, it is recommended that a throat swab be taken for culture and if GAS positive, they should be treated with appropriate antibiotics. In addition, the Health (infectious and Notifiable Diseases) Regulations allow for seven days exclusion from work or school to be enforced for teachers and students with GAS pharyngitis.<sup>6</sup> As stated earlier, this legislation is rarely invoked.

See [Clinical Question 21](#) for which factors lead to the spread of GAS pharyngitis and [Clinical Question 6](#) on GAS carriage.

<b>Recommendation:</b>	Consider taking throat swabs for culture from people with pharyngitis who work in occupations where there is an increased risk of spreading GAS (healthcare and residential care workers, food handlers, childcare workers and teachers).  See Sore Throat Management Algorithm.
<b>Recommendation grade:</b>	D
<b>Evidence level:</b>	IV

#### **Question 14. Should throat swabs be repeated after antibiotic course has ceased?**

*This Clinical Question has not been updated from the 2008 Guideline.*

A follow-up throat swab following an adequate course of treatment for GAS pharyngitis is not usually recommended.<sup>119</sup>

End of treatment swabbing is recommended in the following specific circumstances where the risk of ARF is greatest and therefore treatment of possible re-infection or carriage (see [Question 6](#) above) either in the index case or contacts can be justified:

The IDSA<sup>119</sup> recommends the following patients in special situations be routinely swabbed after completing their antibiotic courses for GAS pharyngitis:

- Those with a history of ARF
- Those who develop GAS pharyngitis during outbreaks of ARF **or** post streptococcal glomerulonephritis (APSGN). Outbreaks of ARF are very unusual<sup>203,204</sup> but outbreaks of APSGN are more common.<sup>205,206</sup> They should be controlled if possible by controlling the spread of GAS. See [Clinical Question 6](#) and [12](#).
- Those who develop GAS pharyngitis during outbreaks in a closed or partially closed community e.g. boarding school, military barracks, prison
- Where there is recurrent GAS pharyngitis within families (IDSA evidence level B-III).<sup>119,207,208</sup>

The majority of asymptomatic patients who continue to have positive swabs post-antibiotic treatment are carriers.<sup>77,208</sup>

### Recommendation and recommendation grade:

Do NOT swab patients after they complete antibiotics for GAS pharyngitis (IDSA evidence level A-II), **unless:**

- The patient has a history of ARF and is not receiving prophylactic IM penicillin
- The patient develops GAS pharyngitis during an outbreak of ARF **or** post streptococcal glomerulonephritis
- The patient developed GAS pharyngitis during outbreaks in a closed or partially closed community
- There is recurrent GAS pharyngitis within the family/household (IDSA evidence level B-III)
- The patient remains symptomatic after completing their full course of antibiotics.

**Evidence level:** As above.

## Question 15. Does tonsillectomy have a role in reducing the number of sore throats from any cause?

### Children

For children with severe recurrent tonsillitis, tonsillectomy does offer benefit, by reducing the number of sore throats in the short term.

Four RCTs in a Cochrane Review<sup>209</sup> and a further RCT<sup>210</sup> have shown that tonsillectomy for severe recurrent tonsillitis in children reduces the number of sore throats in the short term. The Cochrane Review was limited to short term (12 months) follow-up. Severe recurrent tonsillitis was defined using Paradise's criteria:<sup>211</sup> seven or more sore throats per year for one year or five per year for two years or three per year for three years.<sup>209</sup>

For children with fewer sore throats than defined by Paradise, the risks of tonsillectomy may outweigh the benefits. In New Zealand, tonsillectomy is offered to treat severe recurrent tonsillopharyngitis causing significant disruption to schooling/employment and significant ill health. The Paediatrics and Child Health Division of the Royal Australasian College of Physicians and The Australian Society of Otolaryngology, Head and Neck Surgery in 2008 produced a Joint Position Statement on Tonsillectomy and Adenotonsillectomy in Children, which is consistent with the Cochrane meta-analysis, and endorses the Paradise 1984 severity criteria for tonsillectomy.<sup>212</sup> The Colleges recommend that:

*'Tonsillectomy/adenotonsillectomy is indicated for episodes of recurrent acute tonsillitis. As a guide, seven episodes in the preceding 12 months, or 5 in each year for 24 months, or 3 per year for 3 years; account should be taken of the clinical severity of the episodes and that this may result in as little as one less episode of sore throat with fever per year.'*

(The Paediatrics and Child Health Division of the Royal Australasian College of Physicians and The Australian Society of Otolaryngology, Head and Neck Surgery 2008)<sup>212</sup>

### Adults

It is unclear whether tonsillectomy reduces recurrent sore throats. Two small studies of 156 adults suggest a potential benefit of tonsillectomy in reducing throat infections, but numbers are too small to make definitive conclusions and long term data has not been collected.<sup>213,214</sup>

**Recommendation:**

**In children**, tonsillectomy for severe recurrent tonsillitis reduces the number of sore throats in the short term (12 months).

**For adults** there is insufficient data to allow the Advisory Group to make a recommendation.

	<b>Evidence level</b>	<b>Recommendation grade</b>
For children	I	B
For adults	II	B

**Question 16. Does tonsillectomy have a role in treating recurrent group A streptococcal sore throat infections?**

The focus of the RCTs referred to in Question 14, was on tonsillitis rather than pharyngitis and the analysis of the trials did not identify causal organisms.<sup>209,210</sup> These trials are not therefore able to provide conclusive evidence that tonsillectomy reduces recurrent GAS pharyngitis.

Only one of the papers covered by the Cochrane review looked at adults with recurrent pharyngitis due to GAS.<sup>213</sup> This paper only followed patients for 90 days but did show a statistically significant and clinically relevant reduction in sore throats over this period.

International guidelines such as the IDSA do not recommend tonsillectomy for reducing GAS pharyngitis, except for the '*rare patient whose symptomatic episodes do not diminish in frequency over time and for whom no alternative explanation for recurrent GAS pharyngitis is evident*'.<sup>9</sup>

Further research is needed to determine the role of tonsillectomy in treating GAS tonsillopharyngitis in those at high risk for ARF.

For evidence on role of tonsillectomy in treating GAS pharyngitis see [Appendix 25](#).

**Recommendation:**

There is insufficient data to allow the Advisory Group to make a definitive recommendation on the use of tonsillectomy in treating recurrent GAS pharyngitis.

# MANAGEMENT OF CONTACTS OF GAS PHARYNGITIS PATIENTS

## Question 17. Should GAS culture negative (uninfected) household contacts of a patient with GAS pharyngitis be prescribed preventive antibiotics?

Preventive antibiotics should not be routinely prescribed for GAS culture negative (uninfected) household members of a patient with GAS pharyngitis. See [Clinical Questions 18, 19 and 20](#) for recommendations on swabbing household contacts.

Two studies on the utility of chemoprophylaxis of uninfected household contacts of a patient who develops GAS pharyngitis<sup>215,216</sup> showed a benefit whilst a further two studies<sup>217,218</sup> did not.

The Infectious Diseases Society of America (IDSA) guideline does not recommend preventive antibiotic treatment for uninfected family contacts when a patient develops GAS pharyngitis.<sup>9</sup>

Evidence for managing uninfected household contacts is in [Appendix 26](#).

<b>Recommendation:</b>	Chemoprophylaxis should not be recommended for uninfected household contacts of patients(s) with GAS pharyngitis.
<b>Recommendation grade:</b>	D
<b>Evidence level:</b>	IV

## Question 18. How should symptomatic household contacts of GAS-culture positive pharyngitis patients be managed?

The likelihood of symptomatic householders, particularly school aged children, having GAS cultured positive pharyngitis is high. Within a household, the risk of secondary GAS infection was 1.8 times greater than that of a primary infection in the community.<sup>7</sup> In households, more than half of secondary cases of serologically proven GAS pharyngitis were in five to 12 year old children.<sup>7</sup> Danchin defined symptomatic as sore throat plus one of the Centor criteria: a history of fever, tender anterior cervical lymph nodes, pharyngeal exudate, or an absence of cough. Because these criteria were not developed for children, parents were encouraged to bring in their children with a broader set of symptoms, including headache, abdominal pain, vomiting, cough, coryza and hoarseness.

Falck et al followed 110 index GAS pharyngitis patients for a month and found at days six to ten, 20 out of 263 (8%) household contacts were symptomatic and cultured GAS, and 70 out of 263 (27%) were colonised (cultured GAS from their throats but were not symptomatic).<sup>219</sup>

See [Clinical Questions 13 and 21](#) on GAS spread and Household Sore Throat Management Algorithm on [page 14](#).

<b>Recommendation:</b>	Consider taking throat swabs for culture from all symptomatic household contacts of patients with GAS positive pharyngitis.  See Sore Throat Algorithm.
<b>Recommendation grade:</b>	B
<b>Evidence level:</b>	IV

### Question 19. How should asymptomatic household contacts of GAS-culture positive pharyngitis patients be managed?

It is not recommended that throat swabs for culture be taken from asymptomatic household contacts unless any household member, including the GAS positive index case has a personal, family or household history of ARF or unless there have been three or more cases of symptomatic GAS positive pharyngitis in the household in the last three months.

See Sore Throat Management Algorithm on [page 13](#) and Household Sore Throat Management Algorithm on [page 14](#).

<b>Recommendation:</b>	Consider swabbing all asymptomatic household members only if any household member (including the GAS positive index case) has a personal, family or household history of rheumatic fever.
<b>Recommendation grade:</b>	D
<b>Evidence level:</b>	IV

### Question 20. How should household contacts of recurrent GAS-culture positive pharyngitis patients be managed?

Recurrence is defined as the patient's third or more episode of GAS pharyngitis in a three month period.

If either an individual has had recurrent GAS pharyngitis or there have been three or more cases of GAS pharyngitis in a household in the last three months, it is recommended that all household members have throat swabs cultured, regardless of the presence or absence of symptoms. The purpose of this is to identify any GAS carriers who maybe acting as reservoirs of infection and be at potential risk of spreading GAS. This recommendation is unchanged from the 2008 Guideline.<sup>1</sup> If household members are GAS positive, they should be treated with appropriate antibiotics tables ([Table 4](#)).

<b>Recommendation:</b>	Swabbing all household contacts of recurrent GAS culture positive pharyngitis patients should be undertaken and all GAS positive patients treated appropriately.
<b>Recommendation grade:</b>	D
<b>Evidence level:</b>	IV

## FREQUENTLY ASKED QUESTIONS

### Question 21. Which factors lead to the spread of GAS pharyngitis?

Droplet spread, crowding and number of people in the home, fomites, hygiene measures, poverty and the presence of young children within the household have all been studied, however most studies are descriptive and not of high quality.<sup>53</sup>

#### Is GAS Droplet Spread?

Group A streptococcus is a respiratory pathogen and thought to spread through droplets of salivary or nasal secretions or occasionally through food preparation<sup>220</sup> or via water.<sup>190</sup>

#### Do Fomites (Dust/Clothing/Bedding) Have a Role in the Spread of GAS?

Although this area has not been extensively researched, current thinking is that GAS is not significantly spread through contaminated fomites such as dust, bedding and furnishings.<sup>190,221</sup> In two key experimental studies, Perry et al did not find any evidence that dust or GAS-contaminated blankets spread GAS pharyngitis.<sup>222,223</sup> Falck et al, in a case-control study also found that hygiene measures, such as changing toothbrushes and washing bedclothes, made no difference to the recurrence of GAS sore throat.<sup>198</sup> These studies are summarised in [Appendix 27](#).

#### Does Crowding/Number of People in the Household Affect the Spread of GAS Pharyngitis?

Most of this information comes from observational, retrospective studies looking at ARF. The crowding in the house and/or bed literature and its relationship to ARF incidence has been summarised by McNicholas.<sup>224</sup> McNicholas analysed nine key studies, including those in crowded military settings, a key Bristol study<sup>225</sup> and a study in a New Zealand setting.<sup>206</sup> A clear link was found between overcrowding and ARF incidence, independent of socioeconomic variables.

In a community outbreak of ARF in the United States in the late 1980s, cases were associated with larger families, but not lower socioeconomic status.<sup>226</sup>

A subsequent Indian study found a small increase in incidence of GAS pharyngitis per child-year when children lived in more crowded homes. They also found a peak during the rainy and winter seasons, when children tended to cluster indoors.<sup>227</sup>

Lindbaek et al, in a Norwegian study, found households with four or more members were more likely to have GAS spread.<sup>228</sup>

#### Does Having Young Children in the Household Influence the Spread of GAS Pharyngitis?

This is not well addressed in the literature. Lindbaek's study found the strongest predictor of GAS pharyngitis spread was having children less than 16 years of age in the household. All 30 of the households where the spread occurred had children under the age of 16 years. There was no spread of GAS pharyngitis where all members of the household were aged 16 years and over.<sup>228</sup> Powers and Boisvert have pointed out that children with streptococcal infections are important reservoirs of contagion, as they require close contact in their care.<sup>229</sup> However, Nandi et al in their household study of 536 children found the number of children in a family (one to five children) did not make a significant difference in the number of cases of GAS pharyngitis.<sup>227</sup>

#### What is the Chance of GAS Pharyngitis Spreading within a Household, and How Should Households with GAS Pharyngitis be Managed?

Four key studies were found which looked at this topic.

Breese found that a half to a quarter of sibling contacts developed a form of streptococcal infection during the study period although less than one in 20 parents did. Breese did not look solely at pharyngitis: pharyngitis, tonsillitis, scarlet fever, otitis media and cervical adenitis were all included. When analysing streptococcal pharyngitis and tonsillitis alone, the attack rate in siblings was 96 out of 496 (19.4%). Breese et al treated GAS pharyngitis with 600,000 units of IM benzathine



penicillin.<sup>230</sup>

Poku estimated the probability of one person aged up to 16 contracting GAS, positive on throat swab, in one month was 0.05-0.06, i.e. in a household with five susceptible people, the risk of one person becoming infected with GAS was  $1-0.94^{*5}$  (27%)<sup>231</sup>

Falck et al investigated 114 patients and their families, 305 possible exposed people and found 95 (31%) were infected with GAS pharyngitis within a month. Falck et al treated GAS pharyngitis with five days of phenoxymethylpenicillin. Falck et al proposed that most GAS treatment failures depended on ping-pong reinfection from family members with the same T and RFLP type as the index case and recommended further studies.<sup>219</sup>

Lindbaek et al found 30 out of 110 households (27%) had one or more new cases of GAS tonsillitis after an initial case (40 new infections). Lindbaek et al treated GAS pharyngitis with five days of penicillin.<sup>228</sup>

These studies suggest that the rate of spread seems to be about 30% per household, or five to six percent chance per at-risk person in the household per month, although the numbers are small. It is not possible to draw significant conclusions on the likelihood of spread to any particular age group, but adults seemed to be less susceptible.

No trials were found (with intervention and control groups, regardless of randomisation) where the treatment or not of households with GAS pharyngitis has been looked at.

The American Academy of Pediatrics (American Academy of Pediatrics 2012) does not recommend asymptomatic GAS carrier treatment except in certain situations, including where multiple episodes of documented symptomatic GAS pharyngitis continues within a family during a period of many weeks despite appropriate treatment.<sup>3</sup> See to **Clinical Question 6** for more detail.

Similarly, the IDSA guidelines recommend against routine culture of asymptomatic household contacts of patients with GAS pharyngitis, except in situations where there is increased risk of frequent infections.<sup>9</sup> See **Clinical Question 6** for more detail.

Although the literature is weak, if the true rate of symptomatic GAS pharyngitis cross infection within households is potentially between 19-50%, this is a problem in New Zealand because of the high rate 4.3 per 100,000 of initial cases of ARF.<sup>27</sup> Rheumatic fever is a notifiable condition in New Zealand.

### **Is Poverty a Factor in the Spread of GAS Pharyngitis?**

Research tends to focus on ARF and poverty rather than GAS pharyngitis. The studies tend to be observational and of poor quality. Najeeb, in a report for the World Health Organisation (WHO) on ARF in developing countries, argues that ARF is 'basically a socioeconomic disease'.<sup>232</sup> The report states that it has declined in developed countries, with the exception of pockets in city slums, due to medical and non-medical factors, including improvements in socioeconomic conditions. Furthermore, it is not the poverty per se, but the manifestation of poverty through overcrowding in substandard housing which is the cause of ARF.<sup>232</sup> Bhave et al in Bombay, India, found poorer children were more likely to have higher Antistreptolysin O (ASO) titres and were more likely to have rheumatic heart disease.<sup>233</sup>

Nandi did not detect a difference in socioeconomic status in the incidence of GAS pharyngitis in households, although the study was conducted in a slum community where there was 'no major difference in socioeconomic status between households'.<sup>227</sup>

<b>Recommendation:</b>	Addressing the socioeconomic factors which may contribute to the spread of GAS in the community, such as household crowding, is likely to reduce the incidence of ARF. However appropriate management of GAS pharyngitis reduces the occurrence of ARF even where socioeconomic conditions are poor.  Where three or more cases of confirmed GAS pharyngitis occur in a household, the household be screened and all those GAS positive on throat swab be treated with antibiotics regardless of whether symptoms are present or absent.
<b>Recommendation grade:</b>	D, expert opinion for the second recommendation
<b>Evidence level:</b>	Expert opinion

### Question 22. Can GAS be spread through sharing toothbrushes?

Toothbrush sharing in households is not recommended because of the risk of spreading respiratory pathogens. Toothbrush replacement after GAS pharyngitis treatment to reduce personal re-infection with GAS is not routinely recommended.<sup>3,234</sup>

<b>Recommendation:</b>	Do not share toothbrushes. There is no evidence that GAS is spread through sharing toothbrushes.
<b>Recommendation grade:</b>	Expert opinion

### Question 23. Should Group C and/or G streptococcal sore throats be treated with antibiotics?

Both group C and G streptococci can cause self-limiting pharyngitis. The clinical presentation can resemble group A streptococcal pharyngitis.<sup>235,236</sup> Neither group C or G streptococcal pharyngitis have been associated with subsequent ARF.<sup>9,237</sup> There have however been published reports of outbreaks of pharyngitis traced to food handlers.<sup>238,239,240</sup>

The decision to treat group C or G pharyngitis should be based on the severity of symptoms or if the patient is a food handler (see [Clinical Questions 3C](#) and [13](#)).

<b>Recommendation:</b>	Treatment of group C and/or G streptococcal pharyngitis should be based on clinical judgement, taking into account: <ul style="list-style-type: none"> <li>- The severity of symptoms</li> <li>- Co-morbidities</li> <li>- If working as a food handler</li> </ul>
<b>Recommendation grade:</b>	Expert opinion
<b>Evidence level:</b>	D

### Question 24. Do recurrent sore throats increase the risk of a patient progressing to ARF?

*This Clinical Question has not been updated from the 2008 Guideline.*

There is insufficient published data to answer this question with any degree of certainty. See [Appendix 28](#) for studies listing sore throat episodes and ARF.<sup>52,241</sup>

**Recommendation:** The 2008 writing group consensus is that recurrent GAS sore throats may increase the likelihood of developing ARF. Attempt to eradicate GAS recommended in high-rheumatic fever risk groups.

**Recommendation grade:** D, writing group consensus

**Evidence level:** Insufficient evidence

### Question 25. Is seasonal prophylaxis for recurrent streptococcal pharyngitis useful?

*This Clinical Question has not been updated from the 2008 Guideline.*

There is limited evidence from two RCTs that this may be effective in a circumscribed community.<sup>242,243</sup> These studies are summarised below.

**Table 7. Studies on Seasonal Prophylaxis for Pharyngitis**

Study	Patients	Intervention	Outcomes in Controls	Outcomes in Treatment Group
Aksit S et al. 1998 <sup>242</sup>	160 children aged 4-11 years, in Turkey, who had 2+ episodes of GAS pharyngitis during 4 month period in 1995	RCT. <b>Treatment group:</b> 80 patients given IM benzathine penicillin G every 3 weeks. <b>Control group:</b> 80 controls not given any medication. 4 month observation period for results	244 episodes of GAS pharyngitis. 5 control patients excluded for poor compliance	16 episodes of GAS pharyngitis. 2 patients excluded for poor compliance
Mora R et al. 2003 <sup>243</sup>	180 children aged 4-14 years, who had 3+ episodes of tonsillitis in the previous year	RCT. <b>Treatment group:</b> 90 patients given cefpodoxime 100mg po bd for 6 days a month for 6 months. <b>Control group:</b> 90 control patients given placebo medication at the same dosage and duration. Patients followed for 12 months	At 12 months: 86.4 episodes of tonsillopharyngitis, and 86.4 episodes of non-complete eradication or re-infection with GAS (on pharyngeal swab)	At 12 months: 11.6 episodes of tonsillopharyngitis, and 20 episodes of non-complete eradication or re-infection with GAS (on pharyngeal swab)

**Recommendation:** No recommendation is possible regarding seasonal prophylaxis.

**Recommendation grade:** D, insufficient evidence to make a judgment

**Evidence level:** Insufficient evidence to make a judgment

### Question 26. Does having a smoker in the house make GAS throat infection more likely?

*This Clinical Question has not been updated from the 2008 Guideline.*

There is insufficient published evidence to answer this question. A single Indian study found a link between the presence of a tobacco smoker in the household and the incidence of GAS pharyngitis in the children.<sup>227</sup> Evidence exists that the incidence of other respiratory illnesses, including meningococcal disease, is increased by the presence of smokers.<sup>244,245</sup>

<b>Recommendation:</b>	The 2008 writing group consensus is that streptococcal pharyngitis, like other respiratory illnesses, is likely to be exacerbated by smoking within the household and recommends cessation of smoking or smoking outdoors.
<b>Recommendation grade:</b>	D, writing group consensus
<b>Evidence level:</b>	Insufficient evidence

### Question 27. Is there a vaccine available for the control of GAS disease?

No GAS streptococcal vaccine has been marketed to date. Clinical trials continue.<sup>246-248</sup>

<b>Recommendation:</b>	No recommendations are available to be made, as possible vaccines are still under development
<b>Recommendation grade:</b>	D
<b>Evidence level:</b>	Insufficient evidence

## Implementation Plan

The purpose of this Guideline Update is to inform current best practice management for group A streptococcal pharyngitis to prevent rheumatic fever. A multi-faceted approach is recommended as outlined below:

### Peer Review and Endorsement

This Guideline Update has undergone international peer review. Endorsement by relevant New Zealand organisations will follow. These organisations will be asked to promote this Guideline Update to their members.

### Further resources

Future resources include the development of online, printable documents on:

- Key changes in recommendations in the Guideline Update
- Updated sore throat algorithm

It is strongly recommended that financial support is secured to print these resources and distribute to primary and secondary care facilities.

### Leadership

Strong leadership is required to ensure effective implementation. The Government has allocated funding for rheumatic fever prevention and it is recommended that the Ministry of Health in partnership with the Royal New Zealand College of General Practitioners (RNZCGP) take a leadership role in this guideline update implementation.

### Role of the Heart Foundation

The Heart Foundation will promote the Guideline Update on its website along with the *Diagnosis, Management and Secondary Prevention* Guideline Update and the original suite of rheumatic fever guidelines and resources.

Organisations will be encouraged to link to the Heart Foundation website for the latest Guideline Updates for rheumatic fever. [www.heartfoundation.org.nz](http://www.heartfoundation.org.nz)

All sore throat/rheumatic fever resources will be updated.

The Heart Foundation will continue to advocate for rheumatic fever eradication. In the *Stop the Heartbreak 2014*<sup>249</sup> campaign the Heart Foundation is calling on political parties to:

- Ensure the current national rheumatic fever prevention programme and research programme are sustained until rheumatic fever is eradicated.
- Implement a whole of government approach to address the upstream determinants of rheumatic fever.

### Decision Support

Decision support resources and tools are used across healthcare in the management of sore throats. The following will need revising and/or their development informed:

- Healthcare pathways (online and paper) being developed by District Health Boards (DHBs) and Primary Health Organisations (PHOs).
- Similar hospital resources (Blue Book)
- The *Primary Care Handbook 2012*<sup>59</sup> currently being updated.
- All Ministry of Health resources

Non-Government health information organisations such as Health Navigator need to include the Guideline Updates in their resource libraries.

### Audit and Research

It is recommended that audit of current treatment according to the guideline/guideline update is implemented. This should include audit of throat swabbing technique as a quality control measure.<sup>50</sup> In the school-based programme to prevent rheumatic fever, throat swabs with a scanty growth of any throat flora led to the student being re-swabbed. If this persisted, retraining by the worker was undertaken.<sup>50</sup>

Research questions that have arisen out of the guideline update are listed on [page X](#)

### Targeted Health Professional Education

The Ministry of Health are developing a health professional e-learning tool on rheumatic fever which includes a module on sore throat management.

The Guideline Update recommendations will be submitted for consideration to health professional journals (*New Zealand Medical Journal, Kai Tiaki*) and publications such as *NZ Doctor, Logic, Nursing Review and BPAC Journal*.

Education on sore throat management should be formally incorporated into health professional development. To achieve this will require strong leadership and identifying champions in these professional groups. The following groups and strategies are suggested. This is not an exhaustive list.

**Table 8. Suggested Strategies for Guideline Implementation**

<b>Group</b>	<b>Suggested strategies</b>
General Practitioners	Pharmac series, CME, conferences, NZMA newsletters, Map of Medicine, Ready Reckoners for GPs.
Practice Nurses	PHO cell group meetings, Kai Tiaki
Medical Officers of Health	MOH led Medical Officers of Health training days
Emergency Doctors	Association of Accident and Medical Doctors
Emergency Nurses	NZNO groups
School based clinic workers	
Paediatricians	Paediatric Society website
Public Health Physicians	NZCPHM newsletter, Public Health newsletter, Population Health congress
Public Health Nurses	Public Health newsletter and journal
Well Child Nurses	
Whānau Ora workers	
Pharmacists	Pharmacy Guild, Pharmacy Department of Otago and Auckland University

## Appendices

### Appendix 1: Search Strategies for Guideline Update

The following search strategies were undertaken by Dr. Melissa Kerdemelidis for the following clinical question. Where evidence reviews have been included in the appendices, the search strategies for these are included under the relevant appendices.

#### Antibiotics

Ovid Technologies, Inc. Email Service.

Databases searched: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to present.

Search date: 26 November 2012

#	Searches	Results
1	Streptococcus pyogenes/	10,910
2	Pharyngitis/	6,421
3	Anti-Bacterial Agents/	220,528
4	1 and 2 and 3	372
5	<a href="#">effectiveness.mp.</a>	241,216
6	Disease Eradication/	159
7	4 and 5	12

#### Group C and G Streptococcus

Databases searched: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), 1946 to present.

Search date: 14<sup>th</sup> November 2012

#	Searches	Results
1	Streptococcus/	19,574
2	Group C Streptococc\$.tw.	397
3	Group G Streptococc\$.tw.	443
4	2 and 3	812
5	pharyngitis.mp. or Pharyngitis/	8125
6	sore throat.mp.	3049
7	5 or 6	10006
8	4 and 7	67
9	Limit 8 to English language	61

Up to Date searched under: (1) group C and group G streptococcal infection (searched 19<sup>th</sup> Nov 2012); and (2) Treatment and prevention of streptococcal pharyngitis (searched 15<sup>th</sup> Nov 2012).

Red Book searched 22<sup>nd</sup> Nov 2012 under streptococcus.

References of found articles searched.

Previous articles held by author and their references searched.



## Appendix 2: Microbial Causes of Acute Pharyngitis

**Table 9. Microbial Causes of Acute Pharyngitis**

Pathogen	Syndrome / Disease	Estimated Percentage of Cases of Pharyngitis, in All Age Groups
<b>Viral</b>		%
Rhinovirus (100 types and 1 subtype)	Common cold	20
Coronavirus (3 or more types)	Common cold, SARS	>=5
Adenovirus (types 3, 4, 7, 14, 21)	Pharyngoconjunctival fever, ARD	5
Herpes simplex virus (types 1 and 2)	Gingivitis, stomatitis, pharyngitis	4
Parainfluenza virus (types 1-4)	Common cold, croup	2
Influenza virus (types A and B)	Influenza	2
Cocksackievirus A (types 2, 4-6, 8, 10)	Herpangina	<1
Epstein-Barr virus	Infectious mononucleosis	<1
Cytomegalovirus	Infectious mononucleosis	<1
HIV-1	Primary HIV infection	<1
<b>Bacterial</b>		
Streptococcus pyogenes (group A beta haemolytic streptococci)	Pharyngitis/tonsillitis, scarlet fever	15-30
Group C and G beta haemolytic streptococci	Pharyngitis/tonsillitis	5-10
Mixed aerobic/anaerobic infection	Gingivitis (Vincent's angina)	<1
	Peritonsillitis/peritonsillar abscess (quinsy)	<1
Neisseria gonorrhoeae	Pharyngitis	<1
Corynebacterium diphtheriae	Diphtheria	>=1
Corynebacterium ulcerans	Pharyngitis, diphtheria	<1
Arcanobacterium haemolyticum (Corynebacterium haemolyticum)	Pharyngitis, scarlatiniform rash	<1
Yersinia enterocolitica	Pharyngitis, enterocolitis	<1
Treponema pallidum	Secondary syphilis	<1
Francisella tularensis	Oropharyngeal tularemia	<1
<b>Chlamydial</b>		
Chlamydia pneumoniae	Pneumonia/bronchitis/pharyngitis	Unknown
<b>Mycoplasma</b>		
Mycoplasma pneumoniae	Pneumonia/bronchitis/pharyngitis	<1
Mycoplasma hominis (type 1)	Pharyngitis in volunteers	Unknown
<b>Unknown</b>		30

**Source:** Modified from table 51-1. This table was published in: Bisno A. Pharyngitis. In: Mandell GL Bennett JE, Dolin R (Eds), Mandell, Douglas & Bennett's Principles and Practice of Infectious Diseases, 6<sup>th</sup> ed, 2004A. Philadelphia, USA: Elsevier Churchill Livingstone. 2004; 1: 752-758.<sup>39</sup> Copyright Elsevier (2007).

## Appendix 3: Infectious Diseases Society of America Strength of Recommendations and Quality of the Evidence (GRADE), 2012

This table is used in the Infectious Diseases Society of America's 2012 Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis.

**Table 10. Strength of Recommendations and Quality of Evidence; IDSA 2012**

Strength of Recommendation and Quality of Evidence	Clarity of Balance Between Desirable and Undesirable Effects	Methodological Quality of Supporting Evidence (Examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation, very-low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available. Any estimate of effect for at least 1 critical outcome is very uncertain.
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low-quality evidence	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation, very-low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain.

Information is based on GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria [2-8]

Abbreviation: RCT, randomized controlled trial.

**Source:** Shulman ST et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2012; 55: 1279-1282. © by permission of Oxford University Press.

## Appendix 4: KidzFirst Guideline: Analgesia for IM Penicillin Injection, 2011

### Guideline Summary

Kidzfirst is committed to reducing pain during IM Penicillin injections for Rheumatic Fever. The use of BUZZY®\* prior to AND during this painful uncomfortable procedure as well as the utilization of behavioural techniques will be initiated as indicated. \*Buzzy® is a vibrating device which incorporates a cold pack, which should be frozen. The cold pack is inserted under the elastic band behind the Buzzy®.

2% Lignocaine 0.25ml will be mixed in with the Penicillin prior to the injection being given. The dose of Penicillin given will be based on the weight of the child, see below.

Advice on the use of paracetamol can be given to families if the injection site is causing pain later that day and/or the next day.

### Procedure

#### 1. Preparation of Benzathine & Lignocaine 2%

To prepare the injection immediately prior to administration.

1. Draw the correct dose (as charted) of Penicillin from the premixed syringe into a 3ml syringe.

Weight	Dose
< 30 kg	(1.15ml)
30 +kg	(2.3ml)

2. With a needle draw 0.25ml of 2% Lignocaine (as charted) into a 1ml syringe.
3. Add Lignocaine from 1ml syringe to Penicillin filled syringe
4. Mix with gentle inverting of syringe
5. Push plunger up so there is no air in the syringe
6. Attach IM needle to syringe

#### 2. Administering the IM injection

If it is the patient's first time with the BUZZY® let them feel it vibrating on their hand and explain that it will take some of the sting out of the injection.

- Obtain BUZZY®, frozen cold pack and necessary equipment for procedure.
- Warm injection in your hands
- Insert frozen cold pack into Buzzy®
- Locate site on upper outer quadrant of the gluteus
- Press Buzzy® directly on site where you will give the injection and activate vibration. This can be done by the nurse/caregiver or the child/young person themselves.
- Leave the Buzzy® in place for **1 minute +** before administering the injection
- When ready to administer injection slide Buzzy® 2 -5 cm proximal to site (pressing on boney area directly above injection site) with wider end of Buzzy® closer to site. The patient or caregiver can hold this in place.
- Use distraction while administering the injection (non-procedural talk/eye spy/breathing)
- Clean site with alcohol wipe
- Insert needle and inject the Penicillin slowly
- Leave BUZZY® vibrating and in place until the needle is removed
- Ask for a pain rating on faces scale 0-10
- Document on patient record the use of BUZZY® and pain score
- Clean BUZZY®, strap and cold pack with sani wipe.

Give advice (to caregiver or adolescent) on the use of paracetamol at home if the child or young person is experiencing pain later that day or the following day. If they do not have paracetamol at home then please arrange a prescription.

**Source:** KidzFirst Guideline: Analgesia for IM Penicillin Injection 2011 adapted with permission from Middlemore Hospital 2013.<sup>250</sup>

## Appendix 5: Infectious Diseases Society of America Strength of Recommendations and Quality of the Evidence, 2002

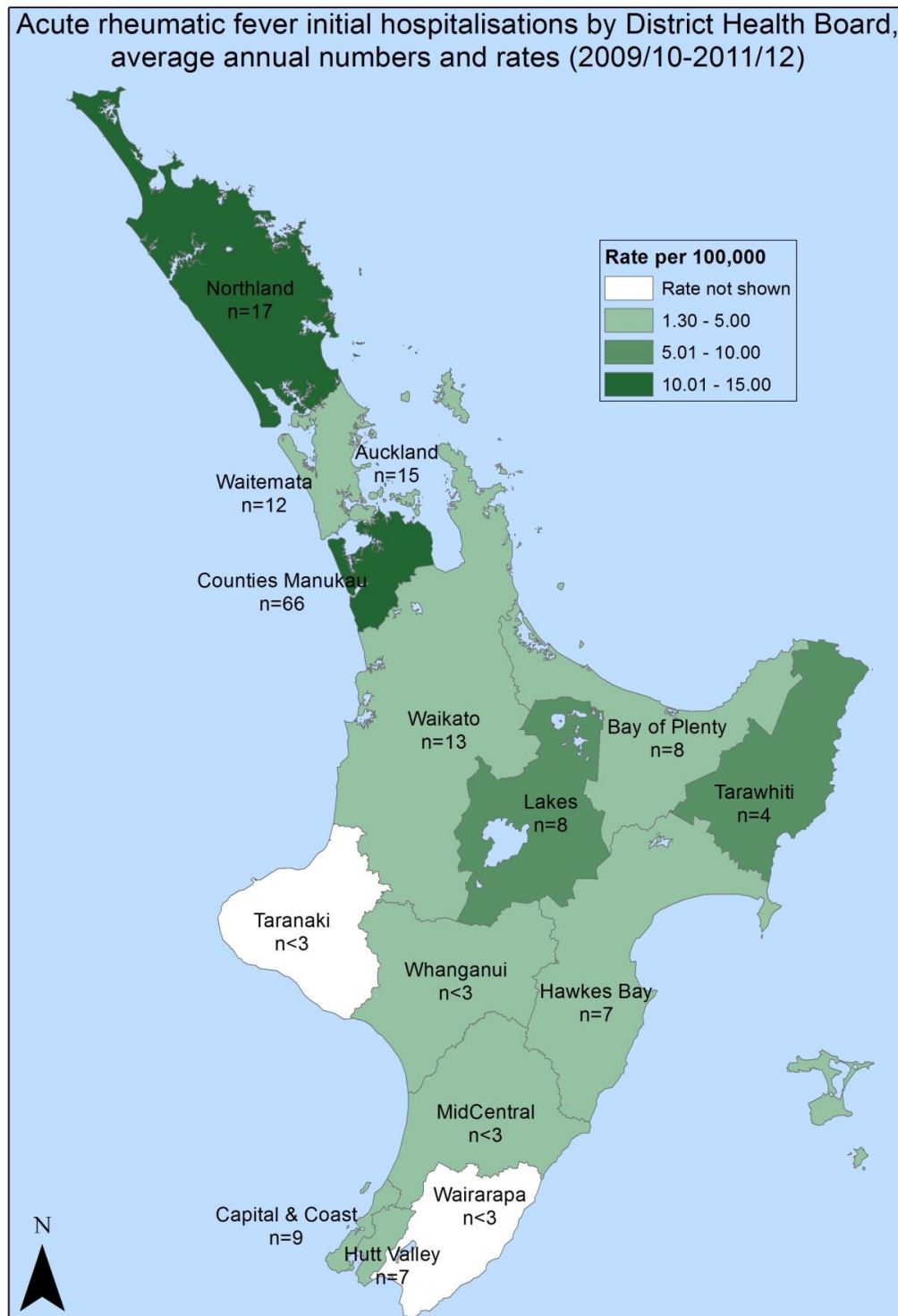
This table was used in the Infectious Diseases Society of America's 2002 Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis.

**Table 11. Strength of Recommendations and Quality of Evidence; IDSA 2002**

Category, grade	Definition
<b>Strength of recommendation</b>	
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
<b>Quality of evidence</b>	
I	Evidence from $\geq 1$ properly randomized, controlled trial
II	Evidence from $\geq 1$ well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from $>1$ center); 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

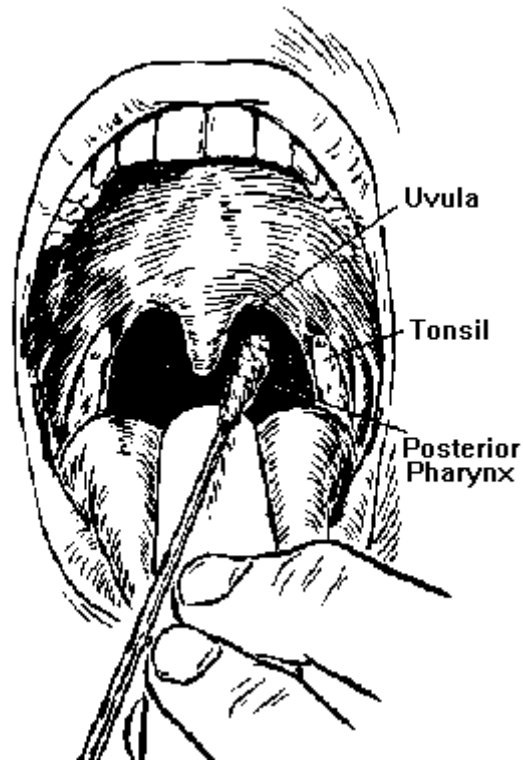
**Source:** Bisno AL et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America. Clin Infect Dis. 2002; 35: 113-125.<sup>119</sup> Permission to publish Copyright material pending.

## Appendix 6: Geographical Distribution of Rheumatic Fever Hospitalisations in the North Island of New Zealand



Source: New Zealand Ministry of Health National Minimum Dataset, 2013.

## Appendix 7: Throat Swab Technique



### Technique

Ask the culturee to open the mouth widely and say a long "ah". The tongue should be gently depressed with a sterile tongue blade. The swab is then gently passed over the tongue and into the posterior pharynx. The mucosa behind the uvula and between the tonsils should then be gently swabbed with a back-and-forth motion.<sup>251</sup>

The tongue should be depressed and the throat adequately exposed and illuminated. Routinely the swab should be rubbed over each tonsillar area and the posterior pharynx. Any area exhibiting exudate should also be touched. Care should be taken to avoid contaminating the swab by touching the tongue and lips.<sup>252</sup>

**Source:** Diagram and related text reprinted with permission from Johnson 2007.(Johnston)  
<http://web.indstate.edu/thcme/micro/samp-lab.html><sup>251</sup>

## Appendix 8: Use of Rapid Antigen Diagnostic Testing (RADTs) in Diagnosing Group A Streptococcal Pharyngitis

Culturing of throat swabs remains the gold standard for the diagnosis of group A streptococcal pharyngitis.<sup>1,79</sup> Rapid group A streptococcal diagnostic tests (RADTs) are now commercially available in New Zealand, however the accuracy of results may be affected by variables such as the pre-test probability of GAS infection, operator experience and the interpretation of test results.<sup>253</sup>

Internationally, RADTs have been tested and validated in different populations, with varying results depending on the population being tested and the choice of rapid test.<sup>254</sup> The Infectious Diseases Society of America (IDSA) considers RADTs highly specific, with few false positives.<sup>9</sup> It does however recommend that children and adolescents with a negative RADT be followed up with a throat swab sent for culture. The IDSA does not recommend follow up throat swabs in adults who have a negative RADT test in 'usual circumstances' (which the authors have interpreted as meaning in areas of low risk for rheumatic fever).<sup>9</sup>

In New Zealand, RADTs are not funded by the government but are used in clinical practice. RADTs have not been sufficiently tested in New Zealand to determine their sensitivity and specificity in the New Zealand context. The Ministry of Health recommend that they be piloted in settings where they might be used and a cost analysis undertaken before being considered in sore throat management.<sup>59</sup> The Advisory Group are not aware of any published New Zealand-based studies comparing rapid detection tests with cultured throat swabs. One Auckland study attempted to assess an RADT against cultured throat swabs but was terminated early due to poor sensitivity and specificity (Upton A, accepted NZMJ).

According to the IDSA guidelines, a positive RADT does not require further testing i.e. no need to send a swab for culture, as a positive result is sufficient to prove GAS infection. However, the Auckland study did not support this; positive RADTs not always being associated with positive culture (Upton, accepted NZMJ).



## Appendix 9: Evidence Review for Waiting Nine Days from GAS Onset to Commencing Antibiotics

The following evidence review is adapted from the Discussion Document the Advisory Group used in considering recommendations on this topic.

### Clinical Question

**Is it safe to wait for up to nine days, from the onset of GAS sore throat, before commencing antibiotics (without risking rheumatic fever)?**

### Introduction

Waiting for the throat swab results (before commencing treatment) can take up to nine days. The 2008 *Management of Group A Streptococcal Sore Throat* guideline<sup>1</sup> recommends:

*'Treatment of streptococcal pharyngitis can be delayed until culture results are available as rheumatic fever is unlikely to occur up to nine days after the first symptoms of pharyngitis'*.

### Evidence Level

Evidence is from one intervention study (Catanzaro et al 1954) and one RCT (Lennon et al 2009).<sup>50,98</sup>

### Issues

1. Literature reviewed is North American where there are different ARF risk populations
2. Old literature suggests suppression of body's immune response if antibiotics are started too early but generally the end points were recurrent pharyngitis (not ARF) and an assumption that antibiotic titre is important in fighting off disease
3. If antibiotics are started before throat swabs results are known and the result is negative. (Anecdotally GPs/nurses call patients, tell result and advise to stop). Should they continue with their antibiotic regime?
4. 2013 recommendation of commencing antibiotics as soon as possible – 'medium risk' in algorithm no longer necessary/needs amending? See suggested low/risk sore throat algorithm in Sore Throat Management Discussion Document.
5. Unable to locate article:

Morris AJ, Catanzaro FJ, Chamovitz R, Stetson CA and Rammelkamp CH. The relative importance of antigen and antibody in the pathogenesis of rheumatic fever. *Clin. Research Proc.* 1954; 2: 75.

### Search Strategy

Google search for '9 day rule' 21 Oct 2012.

Previous articles held by author (Dr. Melissa Kerdelmelidis).

Pubmed search (inconclusive) 21 Oct 2012.

Lennon et al 2009 article.

Summary notes held by Joanna Stewart (biostatistician) from the South Auckland rheumatic fever cases diagnosed by Lennon et al 2009.

Cochrane Library searched for 'pharyngitis' and 'streptococcus' 21 Oct 2012

### Discussion

In 1954, Catanzaro et al studied 1,177 patients with GAS sore throat. There were four groups of patients. Two groups were not treated with penicillin until day nine of their sore throat, the third group was a control and received no treatment and the fourth group was treated with five days of sulfadiazine from the start of their sore throat.<sup>98</sup>

Attempts were made to delay therapy so as not to affect the antibody response. The majority of patients who developed ARF, did so between days 10-45 (n=22; 20 of the control group and those treated with sulfadiazine, and two of the penicillin-treated patients). Importantly ten patients developed ARF in **under 9 days** from the onset of sore throat (10/1,777 = 0.85%). (See **Table 12**).

**Table 12. Tables I and V from Catanzaro et al's Study, 1954**

TABLE I  
DISTRIBUTION OF PATIENTS ACCORDING TO TYPE OF THERAPY\*

Treatment Group	No. of Patients	Therapy
First half of study: Control . . . . .	288	No specific therapy 900,000 units of depot penicillin administered on the ninth, eleventh and thirteenth days after the onset of illness
Penicillin—9 day . . . . .	301	
Second half of study: Sulfadiazine . . . . .	291	Two gm. administered at time of admission to study followed by 1.0 gm. every six hours for five days
Penicillin—9 day . . . . .	297	900,000 units of depot penicillin administered on the ninth, eleventh and thirteenth days after the onset of illness

\* Selection of patients for the various forms of therapy was determined by the Air Force serial number.

TABLE V  
DISTRIBUTION OF CASES OF RHEUMATIC FEVER ACCORDING TO THE INTERVAL FROM ONSET OF PHARYNGITIS TO ONSET OF RHEUMATIC FEVER

Interval in Days	Number developing rheumatic fever			
	Control (220)	Penicillin 9-day (219)	Sulfadiazine (230)	Penicillin 9-day (201)
0-4	1	1	1	2
5-9	2	2	1	0
10-14	3	0	4	0
15-19	1	1	3	1
20-24	1	0	1	0
25-29	1	0	1	1
30-35	0	0	3	0
36-45	2	0	0	0
>45	1	3	0	1

**Source:** Catanzaro et al (1954)<sup>98</sup> Reprinted from: Catanzaro FJ et al. The role of the streptococcus in the pathogenesis of rheumatic fever. Am J Med. 1954; 17: 749-756. © Copyright (2014), with permission from Elsevier.

The authors concluded that the delayed therapy had '*significantly reduced the attack rate of rheumatic fever*', eradicated GAS from the nasopharynx and throat, and hadn't adversely impacted on the patients' antibody responses.<sup>98</sup>

Lennon et al (2009) had noted a possible case of rheumatic fever prior to nine days in their randomised controlled trial of South Auckland school sore throat clinics. In this RCT, children either presented with sore throats or were screened and found to have a red throat, both of which were considered as pharyngitis and resulted in a throat swab being taken. If GAS positive they were then treated with antibiotics.<sup>50</sup>

Further review of the Lennon et al summary data found that among patients diagnosed with ARF, there were treatment delays between sore or red throats and commencement of antibiotics for several patients:

**Table 13. Delay Between GAS Positive Throat Swab and Commencement of Antibiotics**

RF case number	Did patient complain of sore throat or was the throat considered red on screening?	Days of delay, between GAS positive throat swab and commencement of antibiotics
14	Throat red on screening	2
16	Throat red on screening	8
17	Sore throat	4, followed 6 weeks later by another episode of GAS sore throat with a 5 day delay
19	Sore throat	6
24	Sore throat	4

Limitations in analysing the Lennon et al data include; two patients did not complain of sore throat (they were screened). It was possible that those patients who did have sore throats, may have had these for days before the throat swabs were taken and this is not taken into account. It is also possible that there were overlapping episodes of GAS sore throat i.e. a patient's ARF may have resulted from a prior GAS sore throat that was not treated.

Stollerman (1955) considered that for ARF prevention, '*Optimum results are obtained when treatment is initiated within forty-eight hours of symptoms of sore throat*' but he did note the study by Morris et al (1954)\* that '*treatment instituted even as late as nine days after the onset of symptoms may still exert some favorable prophylactic effect upon the incidence of rheumatic sequelae*'.<sup>255</sup>

\* Unable to locate article.

There may have been a case in August 2013 in Tauranga of recent ARF within nine days of sore throat.

Rammelkamp and Stolzer (1961) reviewed the records of all airmen admitted to Warren Air Force Base with symptoms of ARF between 1949-1953. Out of 127 airmen with ARF, 11 had developed ARF less than eight days after the onset of new respiratory illness symptoms. Rammelkamp estimated that 98% of ARF would have been prevented with prompt treatment on day zero of the respiratory illness. However Rammelkamp identifies that it is impossible to state whether the presenting GAS infection caused ARF or whether a previous sub clinical illness was the cause.<sup>101</sup>

Breese and Disney (1956) found a greater spread of GAS in households if the primary case was not treated within two days.<sup>230</sup>

### **Original GAS Sore Throat Management Guideline (2008) Recommendation(s)**

Page 32: Q14. Does delay in the availability of the throat culture result (up to nine days) increase the risk of the development of rheumatic fever?

#### **2008 Recommendation**

Treatment of streptococcal pharyngitis can be delayed until culture results are available as rheumatic fever is unlikely to occur up to nine days after the first symptoms of pharyngitis.

## Appendix 10: Recommendations for Antibiotics Regimes for Third or More Episode of GAS Pharyngitis in a Three Month Period and GAS Carriage

**Table 14. Recommendations for Antibiotics Regimes for Third or More Episode of GAS Pharyngitis in a Three Month Period and GAS Carriage**

Antibiotic	Route	Dose	Duration	References	IDSA Evidence Rating 2012
<b>Benzathine penicillin</b> <sup>†,‡</sup>	IM	<b>Children &lt;30kg:</b> 450mg (600,000 U) <b>Adults &amp; children ≥30kg:</b> 900mg (1,200,000 U)	One dose	Stollerman 1955 <sup>255</sup>	§
<b>Antibiotic options requiring Specialist Approval<sup>  </sup>:</b>					
<b>Benzathine penicillin</b> <sup>†,‡</sup> and <b>rifampicin</b> <sup>  ,¶</sup>	PO and IM	<b>Benzathine penicillin:</b> <b>Children &lt;30kg:</b> 450mg (600,000 U) <b>Adults &amp; children ≥30kg:</b> 900mg (1,200,000 U) <b>Plus</b> <b>Rifampicin</b> starting day of benzathine penicillin injection for 4 days:  20mg/kg/day orally in two divided doses <i>Max dose 600mg daily</i>	One dose  4 days	Tanz 1985 <sup>256</sup>	Strong, high
<b>Clindamycin</b> <sup>  , **</sup>	PO	150mg three times a day <i>Max dose 450mg a day</i>	10 days	Tanz 1991, <sup>257</sup> Shulman 2012 <sup>9</sup>	Strong, high
<b>Penicillin V</b> <sup>†</sup> and <b>rifampicin</b> <sup>  , ¶</sup>	PO	<b>Penicillin:</b> 50mg/kg/day in 4 divided doses for 10 days <i>Max dose 2000mg daily</i> <b>Plus</b> <b>Rifampicin</b> for last 4 days (days 7-10): 20mg/kg/day in one single dose daily <i>Max dose 600mg daily</i>	10 days	Chaudhary 1985, <sup>258</sup> Shulman 2012 <sup>9</sup>	Strong, high
<b>Amoxicillin</b> <sup>†,††</sup> with <b>rifampicin</b> <sup>  , ¶</sup>	PO	<b>Amoxicillin</b> for 10 days: <b>Once daily:</b> 50mg/kg once daily <b>Or</b> Weight < 30kg: 750mg once daily Weight ≥ 30kg: 1000-1500mg once daily <b>Twice daily:</b> 25mg/kg twice daily <i>Max dose 1000-1500mg daily</i> <b>Plus</b> <b>Rifampicin</b> for last 4 days (days 7-10): 20mg/kg/day in one single dose daily <i>Max dose 600mg daily</i>	10 days	##	\$\$
<b>Antibiotic options not requiring Specialist Approval:</b>					
<b>Cephalexin</b> <sup>†,§§</sup>	PO	<b>Children:</b> 20mg/kg/dose twice daily <i>Max dose 500mg twice daily</i> <b>Adults:</b> 500mg twice daily	10 days	##	§
<b>Amoxicillin,</b> <sup>†, ††,   </sup> <b>clavulanic acid</b>	PO	40mg/kg/day of amoxicillin divided into 3 doses daily <i>Max 2000mg of amoxicillin daily</i>	10 days	Kaplan 1988 <sup>259</sup>	Strong, moderate
<b>Ask about adherence to antibiotic regime, recommend family/household screening and consider end of treatment swab.</b>					

**Source:** Modified from Table Two in Shulman ST et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2012; 55: 1279-1282<sup>9</sup> © by permission of Oxford University Press.

- \* The IDSA used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (see [Appendix 3](#) for description)
- † **Do not** give beta lactam antibiotics if patient has suspected immediate or type 1 hypersensitivity (anaphylaxis) to penicillin, amoxicillin or cephalexin. Up to 5% of patients who are allergic to penicillin or amoxicillin will also be allergic to 1<sup>st</sup> generation cephalosporins.<sup>259</sup> Clindamycin may be offered as alternative, as tabled.<sup>260</sup>
- ‡ Benzathine penicillin can be given with lignocaine to reduce injection site pain. (see [page 33](#) and [Appendix 4](#))
- § The IDSA recommendation is not available for this indication
- || For rifampicin, Specialist Approval by: internal medicine physician, clinical microbiologist, dermatologist, paediatrician or public health physician.  
For clindamycin, Specialist Approval by: Infectious diseases or clinical microbiologist (or by protocol) in the hospital or any vocationally registered medical practitioner in the community.
- ¶ Rifampicin relatively contraindicated in pregnancy. Rifampicin interacts with many drugs and should be checked before being prescribed, in particular care with prescribing in combination with oral contraceptives, anti-convulsants and warfarin.
- \*\* No elixir available in New Zealand.
- †† Amoxicillin can be given with food.
- ‡‡ Once daily amoxicillin has been shown to be non-inferior to oral penicillin but has not been trialled specifically with rifampicin
- §§ Cephalexin is recommended by Advisory Group if compliance with other antibiotics is a concern.<sup>9,261-264</sup> Superiority of cephalosporins over penicillin V is questionable as the trials are of poor quality.<sup>265</sup>
- ||| Maximum dose in amoxicillin with clavulanic acid is 2000mg of amoxicillin per day.<sup>9</sup>

## Appendix 11: Once-Daily Amoxicillin Studies

Table 15. Once-Daily Amoxicillin Studies

Name	Study Type	Patients	Intervention	End Points	Sero-Typing
Shvartzman P et al. 1993 <sup>71</sup>	RCT	5 family practices, 393 patients with sore throat, 157 patients aged over 3 yrs. Positive GAS throat swab (blood agar)	82 patients in <b>penicillin arm</b> : 250mg po 3-4 x day for 10 days  75 patients in <b>amoxicillin arm</b> : (3 transferred to penicillin arm). 50mg/kg po daily for children, adults 750mg for 10 days  Compliance assessed by telephone interview and follow-up visits (it is unclear how compliance was assessed)	<b>Eradication:</b> <b>Amoxicillin:</b> 0/75 had positive throat cultures on day 14  <b>Penicillin:</b> 5/82 had positive throat cultures on day 14  <b>Symptoms:</b> pre and post treatment to day 10 were recorded; there was no significant difference between the two groups in terms of clinical response (fever, headache, malaise, sore throat)	No M subtyping. No serology to identify streptococcal carriers
Feder Jr, et al. 1999 <sup>72</sup>	RCT	152 children aged 4-18 years presenting to private practice with GAS pharyngitis	73 children in <b>penicillin V arm</b> : 250mg po tds for 10 days  79 in <b>amoxicillin arm</b> : 750mg po daily for 10 days  Compliance assessed by having parents perform dipstick on patient's urine on day 7 and mailed in the strip	<b>Eradication</b> at day 14-21 by throat culture: <b>Amoxicillin:</b> 4/79 (5%) had treatment failure (same M type), 9 (11%) had new M type of GAS.  <b>Penicillin:</b> 8/73 (11%) had same M type GAS (treatment failure), 7 (10%) had new M type.  <b>Symptoms:</b> no significant difference between two groups in signs and symptoms (fever, tonsillar exudate, cervical lymphadenitis, throat pain) at 18-24 hour follow up after treatment began	M typing done. No serology to identify streptococcal carriers
Lennon D et al 2008 <sup>10</sup>	RCT	254 children aged 5-12 years, diagnosed at a school clinic as positive for GAS on throat culture	176 children in <b>penicillin V arm</b> : 500mg po bd, or 250mg if weight $\leq$ 20 kg for 10 days  178 children in <b>amoxicillin arm</b> : 1500mg po daily or 750mg po daily if weight $\leq$ 30kg for 10 days  Compliance assessed by directly observed therapy on week days at school, and a diary to be filled in on the weekends	<b>Symptoms &amp; eradication:</b> <b>Eradication</b> at day 12-16 by throat culture: <b>Penicillin:</b> 7/159 (4.4%) had same M type, 12 (7.6%) had clinical relapse and 3 (1.9%) had new M type GAS.  <b>Amoxicillin:</b> 8/158 (5.1%) had same M type, 12 (7.6%) had clinical relapse and 2 (1.3%) had new M type GAS.  <b>Symptoms</b> at visit 2 (after 3-6 days of treatment), sore throat, tonsillar exudate, and tender lymph nodes were assessed. There was no difference between the two groups	M typing done. No serology to identify streptococcal carriers

<p>Clegg HW et al 2006<sup>11</sup></p>	<p>RCT</p>	<p>Children 3-18 years, with signs and symptoms of GAS pharyngitis, and positive rapid test for GAS. In 2001-03, of 2,139 potential patients, 652 enrolled, 326 into each arm. Both groups comparable with respect to demographic and clinical characteristics, except that the under 40kg children in both groups were more likely to have a rash on initial presentation, 33/326 (10%) in total, (p=0.015 for od group, p=0.074 for bd group). Investigators blinded</p>	<p>Randomised into once-daily or twice-daily amoxicillin, for 10 days.</p> <p><b>Once daily amoxicillin:</b> 750mg po od for &lt;40kg patients, 1000mg po od for patients &gt;40 kg</p> <p><b>Twice daily amoxicillin:</b> 375mg po bd for &lt;40kg patients, or 500mg po bd for &gt;40kg patients</p> <p>Failure rates determined by positive GAS rapid test at visit 2 (day 14-21 after treatment begun) and visit 3 (day 28-35). Compliance: medication inspected and daily medication log books (filled in by parents) inspected on visit 2</p>	<p><b>Bacteriological treatment failure:</b></p> <p><b>Amoxicillin od:</b> 59/294 who came to visit 2 had same M type, (20.1%). Intention to treat analysis: 108/326 (33%)</p> <p><b>Amoxicillin bd:</b> 46/296 who returned for visit 2 had same M type, (15.5%). Intention to treat analysis: 109/326 (33%)</p> <p>EFFECT SIZE: Difference: 4.53%, (90% CI, 0.6-9.7)</p> <p><b>Clinical recurrence:</b> Symptomatic patients with positive GAS rapid tests:</p> <p><b>Amoxicillin od:</b> 29/294 (10%)</p> <p><b>Amoxicillin bd:</b> 23/296 (8%)</p> <p><b>Side effects:</b> with any adverse event after day 3 (returning with log at visit 2):</p> <p><b>Amoxicillin od:</b> 45/271 (17%)</p> <p><b>Amoxicillin bd:</b> 39/270 (14%)</p> <p>(broken down into categories, abdominal pain most common followed by diarrhoea, same % in both od and bd groups)</p> <p>Physician-diagnosed allergic reactions seen in 0.9% of patients (6/635), each had diffuse urticaria or erythema multiforme on days 2-10, mean 7 days. 5 patients were in bd group and 1 in od group</p>	<p>M typing done. No serology to identify streptococcal carriers</p>
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## Appendix 12: Evidence Review for GAS Carriage

The following evidence review is adapted from the Discussion Document the Advisory Group used in considering recommendations on this topic.

### Table of Contents for GAS Carriage

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## Clinical Questions

### What is GAS carriage?

There is no accepted definition of carriage within the literature. Some have defined carriage as when GAS can be cultured on throat or nasal swab but there is no other evidence of acute infection.<sup>9,155</sup> Others have defined carriage as having an antibody response to rule GAS in or out, however antibody response can be moderated.<sup>152-154</sup>

The preferred definition of GAS carriage is the presence of GAS on the body with the absence of clinical signs and symptoms and a lack of progression to disease. However this diagnosis can only be confirmed retrospectively due to the long latent period of some GAS illnesses such as ARF.

#### 1. Is GAS throat carriage a risk to the health of the individual?

Carriage is a complex concept. There is no agreement on the exact definition or its significance. The literature is equivocal as to whether carriers are at risk of suppurative or non suppurative GAS complications e.g. rheumatic fever. Currently we cannot determine the risk of ARF in carriers. Further research is needed.

#### 2. Is GAS throat carriage a risk to others?

Yes, GAS throat carriage can spread GAS to others but they are less likely to spread GAS than those with symptomatic GAS. Symptomatic GAS is more likely to spread. This may be an issue where there are known risks of GAS related illnesses such as in settings with high rates of ARF.

## The 2014 Update Recommendations are:

The internationally agreed standard of care for treatment of symptomatic culture-positive GAS pharyngitis at the time of the microbiologic culture result will result in treatment of approximately 50% of patients without streptococcal antibody rise i.e. carriers.<sup>7,76,77,153</sup> (see definition below) This is unavoidable because antibody rise will not occur for more than 10 days. Treatment should be commenced as soon as possible. (see [Clinical Question 4](#) and [Appendix 9](#) on Nine Day Rule).

In some situations where the patient or contacts are at high risk of ARF, swabbing and treating pharyngeal GAS in an asymptomatic patient i.e. carriage, may be recommended. In special circumstances (army ref) this may be a necessary part of controlling the pharyngeal GAS burden and thus reducing the risk of ARF.

Thus there is no recommendation to throat swab individuals at the end of antibiotic treatment of culture positive GAS pharyngitis as it is likely that those who remain GAS positive are carriers. However end of treatment swabbing is recommended in the following specific circumstances where the rheumatic fever risk is greater and therefore treatment of possible carriage either in the index case or contacts can be justified:

- Those with a history of rheumatic fever
- Those who develop GAS pharyngitis during outbreaks of acute rheumatic fever or post streptococcal glomerulonephritis
- Those who develop GAS pharyngitis during outbreaks in a closed or partially closed community
- Where there is recurrent GAS pharyngitis within families (three or more cases of GAS pharyngitis in the last three months)

(See 2008 Guideline for details: [Clinical Question 18, page 33](#) and reproduced at end of this document)

In high risk settings\* for rheumatic fever current recommendations<sup>1</sup> remain unchanged:

1. Consider swabbing symptomatic household members of a person with GAS positive pharyngitis.<sup>3</sup> (See Sore throat management algorithm 2014)
2. Swab (and treat if positive for pharyngeal GAS) all household members (symptomatic or not) of a person with GAS positive pharyngitis where the index case has a personal, family or household history of rheumatic fever. This may identify and treat any GAS carriers who maybe at potential risk of spreading GAS.<sup>1</sup>
3. Swab all household members where there has been three or more cases of GAS pharyngitis in the last three months. This may identify and treat any GAS carriers who maybe at potential risk of spreading GAS.<sup>1</sup>
4. Consider swabbing (and treat if positive for pharyngeal GAS) close contacts (symptomatic or not) in an outbreak of rheumatic fever or acute post streptococcal glomerulonephritis.<sup>1</sup>

\* High risk for rheumatic fever if personal, family or household history of rheumatic fever or have 2 or more of following criteria:

- Māori or Pacific
- Aged 3-35 years
- Living in crowded circumstances or lower socioeconomic area

In some circumstances when a person presents with pharyngitis symptoms, assessment of their risk of spreading GAS in the workplace is recommended. Throat swabbing is recommended for the following people:

- Healthcare workers (Pichichero & Casey 2007A)<sup>4</sup>
- Food handlers (Darrow 2002,<sup>5</sup> NZ Government 1966 amended 2013)<sup>6</sup>
- Teachers (expert opinion, NZ Government 1966 amended 2013)<sup>6</sup>
- Childcare workers (expert opinion)

If they are GAS positive, throat swabbing and treating all GAS positive workplace contacts (symptomatic or not) might be necessary. This might include treating GAS carriers.

Depending on the circumstances there may be a need to use alternative antibiotics, see 'Antibiotics for recurrent GAS pharyngitis and GAS carriage' table in algorithm and 2014 Guideline Update.

## Summary

1. Carriage of pharyngeal group A streptococci (GAS) is a very complex topic. It relates to acute rheumatic fever (ARF) pathogenesis, antigenic response and antibody formation, epithelial cell action and the likelihood of GAS spread. The exact inter-relationships of these are currently unknown.
2. Although rheumatic fever pathogenesis is not well understood, there is an established association of ARF with a preceding positive GAS throat culture.<sup>2</sup> Usually patients recall having a sore throat or signs of respiratory illness, but not always.<sup>101</sup> There is also an established relationship with raised streptococcal antibodies.<sup>266,267</sup>
3. Given the lack of clarity on the risk for and development of ARF, reassurance cannot be given that symptomatic pharyngeal carriage of GAS in the throat in a person with or without symptoms and/or signs, is not associated with risk of ARF.
4. GAS in the throat of asymptomatic individuals can be transmitted from the throat and infect others, although it is less infectious than symptomatic GAS sore throats.<sup>158,159</sup> (See [Appendix 16, 17, 18](#)).
5. There is no accepted definition of 'GAS carriage' within the literature, partially due to rheumatic fever pathogenesis not being well understood. Some have defined carriage using antibody response to rule carriage in or out i.e. no antibody response in a person with a GAS positive throat swab with no clinical signs and symptoms. However there are factors which can moderate antibody response e.g. age, diabetes and the effect of prompt treatment.<sup>152-154,268</sup> Also the time lag between initial infection and antibody rise<sup>269</sup> means that in the acute clinical setting measuring antibody titres is unlikely to be clinically useful. Serological tests for antibodies may not be definitive.<sup>151</sup>
6. It is likely that there is a spectrum of risk for individuals for developing ARF that is not clearly understood, possibly due in part to genetics and prior GAS throat infections. However the role of GAS carriage (if any) in this is not clear. Confusing information on this topic includes:
  - Fewer symptoms with a repeat of a throat infection with the same serotype of GAS pharyngitis<sup>270</sup>
  - GAS throat carriers (i.e. no symptoms or signs of throat infection) can have antibody rises<sup>77</sup>
  - Some patients with sore throats and positive GAS throat swab but no antibody rise improved symptomatically following antibiotic treatment<sup>269</sup>
  - Numerous studies showing not all patients with ARF recalled having a preceding sore throat.
7. There is not always consistency between what individuals report and clinicians find on examination or agreement between clinician findings.<sup>271</sup>
8. There have been very few studies on the nature of carriage and long term follow up of patients to assess their risk of developing ARF.<sup>272</sup> To ascertain this risk, a definition of GAS carriage would have to be agreed and a large, long-term study would be needed. This would need to include regular throat swabs, anti-streptococcal titres and physical examinations of the patients. This would then allow definitive assessment of the risk of ARF development, correlating this with the number of sore throats, GAS positive sore throats and antibody responses. One small US household study.<sup>157</sup> did find a slightly raised risk of developing ARF among carriers (compared to non-carriers). Some studies of families and in military settings have occurred. However consistent follow up was a problem in many studies.
9. The GAS invasive strains tend to reflect the circulating pharyngeal strains and are not necessarily more virulent but just more abundant.
10. In New Zealand the rate of GAS throat carriage is not well studied and information on the *emm* types of GAS diseases such as ARF, invasive GAS and circulating pharyngeal GAS is incomplete.

Rates of ARF are high in some population groups in New Zealand such as Māori and Pacific children in the North Island.<sup>27</sup>

11. There is the notion of a tipping point of volume of pharyngeal GAS carried in a community before serious GAS diseases take hold.<sup>273</sup> The safe or unsafe percentage of GAS has not been established. Some have argued that repeated GAS infections may prime the immune system and this could be related to the amount of GAS infections in a community; however a tipping point has not been established. Populations of children at high risk of ARF have high streptococcal antibodies compared to low risk populations,<sup>274</sup> suggesting repeated exposure is a risk factor.
12. GAS throat carriage has been treated in some settings. Martin et al (2004) noted high ARF and high GAS pharyngeal carriage rates in an American elementary school (children with a mean age of 9.6 years) and recommended treatment on that basis.<sup>272</sup> Military studies and closed communities have treated carriage to reduce ARF risk in their populations. Treatment for GAS carriage in health care workers has been recommended by some experts.<sup>5,131</sup>

## In Conclusion

New Zealand has high rates of ARF in some settings. Onward transmission of GAS is well documented.<sup>158,159,275</sup> (see [Appendix 23](#)).

However the exact pathogenesis for developing GAS pharyngitis from carriage and the ensuing risk for developing ARF is unclear. Therefore, no reassurances can be given for a society with high rates of ARF (such as New Zealand has) that exposure to GAS from throat carriage is safe or that in many situations pharyngeal GAS carriers themselves may need to be treated.

## Search Strategy

1 .Hand search of MK's files for relevant articles including Brigid O'Brien's MPH thesis (University of Auckland, 2010)<sup>246</sup> and relevant international guidelines (IDSA Shulman 2012, also Red Book online 2014).<sup>9,3</sup>

2. Medline search conducted: CDSR, ACP Journal Club, DARE, CCTR, CLCMR, CLHTA, CLEED, Embase, Ovid MEDLINE(R), Ovid OLDMEDLINE(R).

Limit 6 to human (Limit not valid in CDSR, ACP Journal Club, DARE, CCTR, CLCMR).

Records obtained.

Search date: 15 January 2014:

Search strategy:

#	Searches	Results
1	streptococcus/	51234
2	Group A Streptococc\$.tw.	13606
3	1 or 2	62724
4	carriage.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]	22297
5	3 and 4	363
6	limit 5 to English language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	340
7	limit 6 to human [Limit not valid in CDSR,ACP Journal Club, DARE, CCTR, CLCMR; records were retained]	283

## What is GAS carriage?

### I. Definition of 'carriage' of GAS in the throat

There is no clear consensus on the definition of 'carriage' of group A streptococcus (GAS).

Much of the older literature (including most of the military studies) did not differentiate between GAS carriage and symptomatic GAS pharyngitis.<sup>156,192</sup>

In contrast most modern studies and guidelines try to distinguish between 'true' GAS infections of the throat and 'carriage' of GAS but the differentiation is not straightforward.

True GAS pharyngitis, if left untreated, is considered a definite risk for rheumatic fever so it is important to make this differentiation.

#### **(a) Definitions involving antibody response**

Recent attempts have been made to define symptomatic group A streptococcal throat infections as 'true' infections where there is *'the recovery of the organism plus a subsequent rise in titer of antibody'*,<sup>153</sup> with paired sera showing an antibody rise.

However antibody responses may not be sufficient for differentiating between carriage and true infection. There is a lack of clarity around the significance of serology in carriage and infection.

Anti-streptococcal serology is normally taken in pairs, using antistreptolysin O (ASO) or anti DNase B.

Requiring streptococcal antibodies for proof of infection has been suggested for some time. The Commission on Acute Respiratory Diseases, after perusing the cases of streptococcal disease in a military setting concluded that when streptococci was found in the throat, without streptococci antibody rise, they were not the likely cause of the throat exudate.<sup>276</sup>

However there are issues with reliability as anti-streptococcal antibody responses may be affected by age, sex, season and other variables.<sup>152-154</sup> Rantz et al (1944) found great variation in GAS antibody response in a US army camp after haemolytic pharyngitis, tonsillitis or scarlet fever illness in a group of 118 men who entered hospital in one 24 hour period.<sup>268</sup> Rantz et al (1951) found very young children were less likely to mount an antibody response, yet it appeared that children with repeated GAS infections began to mount higher antibody responses, suggesting that this was *'the result of conditioning of the antibody-forming mechanism by repeated infection with hemolytic streptococci'*.<sup>152</sup>

Wannamaker & Ayoub (1960) wrote that ASO antibody responses vary with previous exposure to GAS and with patient age. Factors that may have a role include the number of previous GAS infections, time since last infection and *'the height of the residual antibody level at the time of reinfection'*.<sup>154</sup>

In a comparison study of US children with US military service personnel, Siegel et al (1961) found that children had comparatively fewer rises in GAS serology (45% compared to 85%) and were less likely than the air force staff to be febrile (30% compared to 80%).<sup>277</sup>

Antibodies may be mounted to GAS infections at other non-pharyngeal sites thereby confusing the issue. ASO antibody rises have been found in patients presenting with bronchitis, otitis media and rhinitis.<sup>278</sup>

In some studies, initial streptococcal antibody serology seems to be higher in suspected GAS carriers. Gastanaduy et al (1980) took streptococcal serology from patients with GAS sore throats before treatment was commenced. They then compared the serology in 10 of the patients in whom treatment failed with 60 successfully treated patients. The mean ASO titres among treatment failure patients were 389 and 233 for successfully treated patients; and 229 and 186, respectively, for anti-DNase B.<sup>279</sup>

There were similar findings in a US study by Kaplan (1971), with higher initial titres in a group of patients which did not then increase on analysis of the second set of serology titres.<sup>153</sup>

*'Among pharyngitis patients with group A streptococci who did not show a rise, initial antibody titers were significantly higher than those in clinically and bacteriologically similar patients who did show a rise and were also higher than titers in control children...in the relatively large proportion of patients who failed to show an antibody response, the group A streptococci isolated reflected previous rather than current infection'*

El Kholy in a study of Egyptian school children found children who they determined were GAS throat carriers had a higher initial ASO (134 Todd Units) than those judged as non-carriers (76 units).<sup>280</sup>

Wannamaker<sup>281</sup> concluded:

*'It would seem reasonable that these patients who fail to show a rise are often not suffering from current streptococcal infection. Their high acute-phase titers and positive throat cultures are compatible with previous streptococcal infection.'*

Stetson (1954), in a summary of the literature to that date on the antibody response to GAS, found different GAS types seemed to yield a different average antibody rise and different attack rate for rheumatic fever. He did not find the initial ASO titre linked to the development of ARF in data from 1954 patients. However, he did find a link between the magnitude of the rise in ASO and developing ARF; those with a higher rise in ASO units were more likely to have ARF. When ASO titres for initial and convalescent titres were compared in 1898 patients with uncomplicated streptococcal pharyngitis and 56 patients with ARF, the rheumatic fever patients had an average rise of 339 and the uncomplicated streptococcal pharyngitis patients had an average rise of 228 units.<sup>282</sup>

Gerber et al (1988) in a review also found patients with GAS sore throats but no significant rise in streptococcal antibody titres still had a dramatic clinical response to antibiotics.<sup>269</sup>

Asymptomatic GAS with a rise in antibody titres have been reported in some instances.<sup>278,280,283</sup> Otzurk et al (2004) conducted a study of 351 asymptomatic school children in Turkey using throat swabs and ASO titres, and found significantly elevated ASO titres among 34 out of 91 (25.9%) identified 'carriers' compared to 27 out of 260 (10.4%) of non-carrier children.<sup>283</sup>

Gerber<sup>269</sup> highlighted:

*'As serologic responses to GABHS may take several weeks to develop, antibody titers can be used only retrospectively to distinguish between carriers and those who are truly infected.'*

Kilbourne and Loge (1948) *'showed that early and intensive penicillin therapy against streptococcal disease suppressed the production of anti streptolysin O'*.<sup>284</sup>

Groups C and G Streptococci can also lead to rises in ASO (summarized by Miller et al 1958).<sup>278</sup>

McCarty (1954) assessed the literature on GAS antibodies, and noted it was possible to have a rise in an antibody against one or two streptococcal antigens yet not others. Under two year olds did not always mount significant antibody rises to GAS infections, yet small children could mount higher antibody responses if they had frequent GAS infections.<sup>285</sup>

Gerber et al (1988) re-assessed the literature on GAS streptococcal carriage and concluded that antibody responses could not be correlated with acute phase reactants and clinical presentation as *'there is no accurate way to make this distinction at the time of the initial presentation'*.<sup>269</sup>

The IDSA recommend that to differentiate whether recurrent streptococcal sore throats are really throat carriage with overlying viral infection, information should be collected around:<sup>9</sup>

*'the precise nature of the presenting signs and symptoms...the clinical response to antibiotic therapy, and the presence or absence of GAS pharyngitis in cultures of throat swabs obtained during asymptomatic intervals...'* and serotyping or genotyping are useful (as carriers would have *'persistence of the same strain of GAS over time.'*

## **(b) Where does carriage and infection begin and end?**

This dilemma has been summarized by Kaplan:<sup>76</sup>

*'When does the infective state cease to exist (no further immune response) and carriage begin? More importantly from a pathogenic point of view...what factors change? At the present time, because of remaining significant gaps in our knowledge, all we can conclude is that bona fide infection with an accompanying immune response seems to be a requirement for the development of nonsuppurative sequelae'*

Taking into account this uncertainty, perhaps the best definition of 'carriage' in the literature comes from Pichichero & Casey,<sup>155</sup> who see GAS carriage as occurring when:

*'group A streptococci colonize the nasopharynx or oropharynx and can be cultured, but the patient has no other evidence of acute infection, then the patient is said to be a carrier'*

Their proposed definition of GAS carriage is:

*'a patient who does not have symptoms of GAS sore throat after adequate antibiotic therapy but does have a positive throat culture for GAS'*

However using self-reported symptoms in differentiating GAS pharyngeal carriage from 'true' throat infection is problematic as it is subjective



It is difficult differentiating carriage from true infection when one of the bases of this is whether the patients report symptoms of sore throat. Some patients may be stoic and deny symptoms which others would report. Xu et al studied 200 patients in Michigan and found that adult patients with sore throat tended to report more clinical signs than clinicians could reliably find.<sup>271</sup> These 200 patients were also independently assessed by two clinicians who were blinded to each other's assessment and to the rapid streptococcal test result. Study investigators found that there was 'moderate' agreement on history and examination findings.<sup>286</sup>

## II. Rheumatic fever pathogenesis

**There is an established association for rheumatic fever with a preceding GAS throat culture, a sore throat or signs of respiratory illness, and raised streptococcal antibodies (Summary point 2)**

However the role of carriage in pathogenesis needs to be considered. One difficulty with assessing GAS carriage's risk to the individual patient is that the causal pathway of developing carriage has not been well understood to date.<sup>237</sup>

### (a) How GAS enters the body

Group A streptococcus has a number of virulence factors which facilitate its movement into cells and avoidance of phagocytosis. These mechanisms are summarised in various analyses including those by Schlievert et al (1996),<sup>287</sup> Cunningham (2000)<sup>288</sup> and Kaplan & Gerber (2014).<sup>289</sup> Mechanisms utilized by GAS include its capsular M protein (binds factor H and fibrinogen) and its C5a peptidase (disarms complement). Saliva, mucus and epithelial exfoliation may prevent attachment of the GAS and conversely an area of damaged tissue may allow GAS to enter.<sup>288</sup>

Breaches of the patient's defenses allow entry of GAS. In review articles, factors including varicella, dermatitis and burns were shown to predispose to invasive GAS disease.<sup>287,288</sup> Hormonal changes during pregnancy may also influence immunity at a systemic or local (mucosal) level and allow GAS invasive disease.<sup>287</sup> In a Canadian study, once varicella vaccination was placed on the routine schedule for 12 month old children, the rate of invasive GAS disease fell significantly. In Quebec, 26 out of 85 (30.6%) invasive GAS infections were associated with varicella, and after the immunization, varicella associated invasive GAS infections fell to 3 out of 63 (4.6%).<sup>290</sup> A North Carolina study also found varicella was a predisposing factor in 13 out of 96 cases of invasive GAS disease.<sup>291</sup> A varicella outbreak was associated with invasive GAS in a daycare in America.<sup>292</sup> (New Zealand does not currently have varicella vaccination on the routine childhood immunization schedule).

It has been theorized that a preceding viral illness could allow communicability of GAS. Coburn & Pauli speculated that '*in the virus-infected host, the capacity to suppress liability may be temporarily in abeyance*';<sup>293</sup> however this causative link has not been proven.

It may be that GAS has a different effect or profile in children for reasons that are not known. Coburn & Pauli also speculated whether in '*the infant host the capacity to suppress liability may still be poorly developed*'.<sup>293</sup> GAS throat infection has been classically associated with fever and no cough in adults in some North American studies.<sup>42,61,62</sup> The older literature suggests young children with GAS were often sub-acutely ill with symptoms such as a runny nose, so called 'streptococcosis'.<sup>89</sup>

Wannamaker suggested that the higher number of GAS infections among school aged children, was perhaps not due to 'increased susceptibility' but may have been due instead to 'increased exposure' to GAS.<sup>41</sup>

It is notable that GAS can cause a spectrum of infections including toxic shock syndrome, invasive infections, bacteremia, scarlet fever, non-invasive infections (cutaneous and mucous membranes) and non-suppurative sequelae such as rheumatic fever and acute glomerulonephritis.<sup>287</sup>

Given the lack of clarity around rheumatic fever pathogenesis it is difficult to say with any certainty whether the presence of GAS in the throat is ever safe without sufficient long term studies.

### (b) GAS persistence in tissues and ongoing carriage

Pichichero & Casey (2007A) surveyed the evidence around explanations for recurrent streptococcal pharyngitis:<sup>4</sup>

**Table 16. Explanations for Recurrent Streptococcal Pharyngitis**



**Table 1**  
**Explanations for recurrent streptococcal pharyngitis**

Explanation	Number of studies with evidence type				
	I	II	III	In vitro	Animal studies
Carrier state; no disease <sup>4-12</sup>	1 <sup>10</sup>	3 <sup>5,9,12</sup>	8 <sup>4,5-8</sup>	0	0
Poor patient compliance	0	4	0	0	0
Recurrent exposures	0	3	1	0	0
Copathogenicity <sup>13-36</sup>	1 <sup>33</sup>	7 <sup>14,16,21,22,27,28,35</sup>	11 <sup>13,17,20,21,24,25,30-34</sup>	3 <sup>15,18,26</sup>	2 <sup>29,37</sup>
Coaggregation <sup>37</sup>	0	0	0	1 <sup>37</sup>	0
Poor tonsillar penetration <sup>37-43</sup>	0	0	1 <sup>39</sup>	5 <sup>38,40-43</sup>	0
Eradication of protective nonpathogenic pharyngeal flora <sup>14,26,29-36,44-52</sup>	3 <sup>58,59,62</sup>	3 <sup>45,47,51</sup>	1 <sup>14</sup>	3 <sup>26,44,46</sup>	3 <sup>29,36,50</sup>
Early antibiotic treatment <sup>53-55</sup>	3 <sup>63-65</sup>	0	0	0	0
Intracellular localization of GAS <sup>56-58</sup>	0	2 <sup>59,65</sup>	0	7 <sup>56-58,60-64</sup>	0
Penicillin tolerance <sup>66-72</sup>	0	2 <sup>69,70</sup>	1 <sup>71</sup>	3 <sup>66-68</sup>	0
Toothbrush or orthodontic appliance contamination <sup>73-74</sup>	0	0	0	2 <sup>73-74</sup>	0
Family pets as source of reinfection <sup>75-78</sup>	0	1 <sup>75</sup>	2 <sup>76,77</sup>	0	1 <sup>78</sup>

GAS, Group A streptococcal.

Grading system used by Pichichero & Casey 2007:<sup>4</sup>

I-III indicate quality of the supporting evidence:

I - Randomized, clinical trial

II - Epidemiological study without randomization

III - Case study or a review of the literature

In vitro - The manuscript was of in vitro studies of patient samples (such as throat culture specimens)

Animal studies - The manuscript involved an animal model to evaluate a hypothesis to examine a possible explanation for recurrent streptococcal pharyngitis.

**Source:** Pichichero ME, Casey JR. Systematic review of factors contributing to penicillin treatment failure in Streptococcus pyogenes pharyngitis. Otolaryngol Head Neck. 2007A; 137: 851-857. Copyright © 2014. Reprinted by permission of SAGE Publications.

It may be that GAS enters epithelial cells to evade host defenses (and carriage results) or '*internalization of group A streptococci by host epithelial cells represents successful containment of the pathogen by the host*'.<sup>288</sup>

Schlievert et al (1996) noted that '*GAS remain exquisitely sensitive to penicillin*'.<sup>287</sup> However, once inside a mammalian cell they are able to avoid this antibiotic. Laboratory testing by Kaplan et al showed that penicillin did not enter GAS-containing human epithelial cells very successfully as live bacteria were still seen in the epithelial cells six hours after exposure to penicillin in the surrounding media.<sup>284</sup>

Sela et al studied 42 GAS strains (13 from patients who had failed eradication and were now asymptomatic carriers, and 29 from patients who had eradicated GAS). They found that the average 'internalisation efficiency' of the GAS carriers' strains was 13.4% compared with 4.4% for the GAS strains of the control group. They concluded that '*in a significant number of cases, streptococcal internalisation might contribute to eradication failure and persistent throat carriage*'.<sup>295</sup>

Pichichero & Casey have theorised that GAS nasopharyngeal carriage may develop in two ways:<sup>4</sup>

*'some children who become colonized in their nasopharynx or oropharynx with GAS, do not show evidence of illness, and do not demonstrate an immune response to the acquisition of the bacteria. These children would be classified as carriers. A second common mechanism whereby a child becomes a carrier is after antibiotic treatment of an acute GAS pharyngitis episode'*

Bloomfield & Felty stated that usually a carrier '*under ordinary conditions*' would have previously had clinical tonsillitis<sup>296</sup> and that '*a very high degree of intimate contact*' was required for spread from a carrier.<sup>297</sup>

In 2011 The New Zealand Guidelines Group reviewed the literature and attempted to compare the rate of GAS carriage in a country or community with the rate of ARF. However most studies did not coincide in place or time and so they were unable to provide clear guidance. On the evidence

reviewed, they concluded 'it is not possible to draw any inference between asymptomatic GAS infection prevalence and rheumatic fever incidence'.<sup>254</sup> (See [Appendix 16](#)).

Dingle et al (1964) and James et al (1960) conducted a large study in Cleveland USA, of 443 individuals (86 families) followed for 977,036 person days (2,692 person years). The carrier state was discussed in terms of spread but there were no data published on the long term outcomes of carriage.<sup>158,159</sup>

Boisvert et al considered GAS carriage a latent condition which might activate and cause danger to the patient or others.<sup>89</sup>

*'The carrier state with respect to streptococci is perhaps the most important aspect of the subject – important alike for diagnosis in the individual case and for epidemiology. A positive result of culture without manifest streptococcal disease may represent in some cases a situation analogous to that of a typhoid carrier, who harbors the organism and although not ill himself is dangerous to other persons. In other cases the situation seems analogous to that of a patient with latent tuberculosis, in whom also the organisms are harbored but a change in whose resistance may lead to active disease although he was until that time of little danger to his contacts. At the present time we are obliged to continue to speak in terms of "latent: and "active" streptococcosis and of "sick" and "healthy" carriers of streptococci, with not too clear a conception of the clinical connotations of the words.'*

Coburn and Pauli summarized an outbreak of GAS in a New York hospital children's ward (October 1939 to January 1940) involving 38 people (13 children, 22 nurses, two doctors and one visitor). The index patient had bronchitis; and subsequent GAS infections which developed in the others included pharyngitis, cellulitis/impetigo, otitis media and mastoiditis. They found that children were not usually febrile and did not have particularly high rises in antistreptolysin antibodies, in contrast adults were febrile and developed high rates of antibodies.<sup>293</sup>

Coburn and Pauli<sup>293</sup> concluded:

*'Carriers of this organism usually do not communicate disease and they may usually be considered harmless. This applies to most carriers through-out most of the year. Under at least three conditions, however, the carrier may communicate disease and must then be considered dangerous. These three conditions are: (a) a seasonal increase in general activity of hemolytic streptococcus, probably due to some climatic effect; (b) increased infectivity of the organism associated with virus infection of the host; and (c) increased infectivity of organisms established in the tissues of infants and children. The dangerous carrier usually becomes a harmless carrier within 2 months; however, he may again acquire the capacity to spread disease under one of the three conditions just mentioned.'*

### **III. Levels of GAS pharyngeal carriage in the community**

**If carriage exists; Is there a level of GAS pharyngeal carriage in the population which does not cause problems such as rheumatic fever, and a level of carriage which does (i.e. a 'safe' amount of carriage)? (Summary point 11)**

*The rates of carriage in international and New Zealand studies are discussed in a later section of this document.*

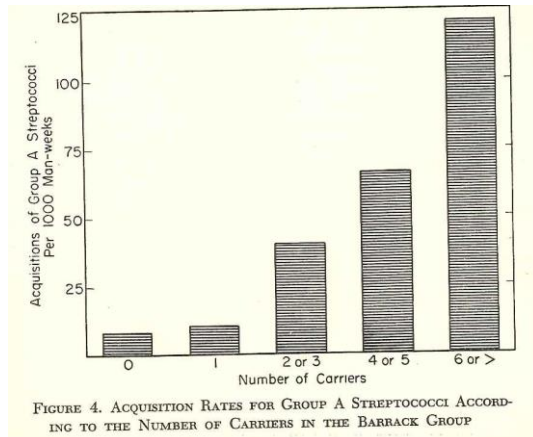
The New Zealand Guidelines Group (2011) tried to map the rate of rheumatic fever and the amount of reported GAS pharyngitis ([Appendix 16](#)), but no trend was found.<sup>253</sup> One limitation was that the studies were not always conducted in the same place and time.

The carrier rate of GAS was thought to rise during epidemics of streptococci according to Blake (as cited in Bloomfield & Felty 1923A):<sup>296</sup>

*'..In the recorded studies of epidemics, certain fairly definite alterations in the distribution of the causal bacteria among the general population have been observed; the carrier rate both among healthy contacts and healthy noncontacts almost invariably rises. During epidemics of meningitis, for example, the carrier rate may rise to 80 per cent, among the contacts in contrast to the average rate of about 2 per cent. in nonepidemic times and under average conditions. A similar phenomenon has been noted with the diphtheria bacillus, the fixed type pneumococci and streptococci'*

Wannamaker, found a linear relationship between the number of GAS carriers and the GAS acquisition rates in a barrack group.

**Figure 2. Acquisition Rates for Group A Streptococci According to the Number of Carriers in the Barrack Group**



**Source:** Wannamaker L. The epidemiology of streptococcal infections. In: McCarty M. (Ed). Streptococcal infections. Columbia University Press: New York. 1954; 157-175.<sup>41</sup> Permission to publish copyright material pending.

Schwentker compared four US Army stations and concluded that as GAS carriage increased so did the rate of Scarlet Fever. Carriage of GAS was 19% in the station with the highest rate of Scarlet Fever.<sup>298</sup>

Glover proposed, but doesn't prove, that when the carrier rate reaches a 'certain height (namely, 20 to 30 per cent.) clinical cases may occur'. Glover's observations in the British Medical Journal on naso pharyngeal epidemics in public schools are detailed below:<sup>273</sup>

*'It seemed possible at the school where the dropping cases of scarlet fever occurred that we were seeing a phenomenon ("the warning rise") rather similar to that seen in cerebro-spinal fever (and possibly in diphtheria)- that is to say that when the carrier rate (that is, the carrier epidemic) reaches a certain height (namely, 20 to 30 per cent.) clinical cases may occur. The observations were, however, too fragmentary for this to be anything but a surmise.....In the school thorough "spacing out" of beds was carried out, together with improvement of the ventilation of the dormitories, and since then no more cases have occurred, six months having now elapsed.'*

Green, in contrast, thought the matter was not clear cut, stating there was no obvious relationship between GAS carriage rates and clinical disease rates. He considered herd immunity to be the 'varying factor which complicates the issue'.<sup>299</sup>

Rubenstein agreed there was no proven link. Rubenstein noted that Schwenker<sup>298</sup> thought an increased carrier rate led to GAS, but he also noted that there wasn't an increase in the carrier rate prior to GAS pharyngitis outbreaks noted by Bloomfield & Felty,<sup>297</sup> and Kuttner & Krumwiede<sup>300</sup> did not consider that major outbreaks were caused by carriers.<sup>193</sup>

While Kuttner & Krumwiede (1941)<sup>275</sup> did find spread from some carriers, Glover<sup>301</sup> thought a level of 30 -50% of a single GAS carried in the community was dangerous. He reviewed the literature of the interwar years 1919-1939 around epidemics of rheumatic fever in schools and military barracks, concluding these epidemics occur with:

*'a regular cycle: overcrowding, a precursor epidemic of acute tonsillitis, an interval (representing the latent period in the individual) and then the occurrence of cases of rheumatic fever, usually numbering less than one tenth of the cases of tonsillitis. A high carrier-rate (say 30 to 50%) of a single type of Strep. Pyogenes is present, and the same type will be found in swabs from the tonsillitis patients'*

Since it is not clear whether there is a safe limit of GAS carriage in the community this could be an area of further research, correlating the level of GAS symptomatic and carriage with the spectrum of

GAS diseases such as rheumatic fever, glomerulonephritis, invasive GAS disease etc. There is some guidance as to when to intervene from the US military outbreak literature.

Since 1966, the US Army (within a closed population) has conducted routine surveillance of acute respiratory illnesses (ARDs), including GAS related illnesses (ARF, acute glomerulonephritis, streptococcal toxic shock, pneumonia and peritonsillar abscess).<sup>160</sup> In the Army, trainees are hospitalized if they present with fever. An ARD was defined as '*a trainee hospitalized with fever and at least one sign or symptom of respiratory tract disease*'.<sup>160</sup>

An ARD epidemic in the US army is defined as above,<sup>160</sup> this gives the limit at which the risk of GAS related illnesses requires action would be taken.

El Kholy et al (1980) found the risk of GAS spread increased as carriage continued (i.e. the longer the carriage the higher the risk).<sup>218</sup>

Erdem et al (2009) found ethnic differences in GAS throat carriage in a Pacific study of 1,061 asymptomatic students in Hawaii and American Samoa. The asymptomatic colonization rate in American Samoa was 13%, and in Hawaii was 3.4% overall. When Hawaii was looked at in more detail the Pacific Island children there had higher colonization rates (5.7%) than children in other ethnic groups (who had a rate of 1.2% GAS carriage).<sup>302</sup>

#### **IV. How common is carriage of GAS in the throat?**

Summary point 10.

##### **International Studies**

The amount of throat carriage of GAS in international populations varies depending on the study and setting.

The rate of asymptomatic carriage in an international meta-analysis by Shaikh et al (2010) found the prevalence of GAS carriage among well children with no signs or symptoms of pharyngitis was 12%.<sup>8</sup> However the majority of these studies did not have serology to confirm this finding and were in rheumatic fever low endemicity areas. Furthermore, without a longer follow up of these patients, it is unclear whether these patients were actually in the early stages of developing GAS pharyngitis.

##### **New Zealand Studies**

In New Zealand two studies have assessed GAS throat carriage in Dunedin primary school children. Dierksen et al found 28% of tested children carried GAS asymptotically for more than two months.<sup>303</sup>

Tagg and Ragland noted that 59 out of 103 school children had GAS positive throat swabs during their 27 month study, yet only 7 of the 59 GAS positive children had symptomatic sore throats.<sup>304</sup>

##### **Duration of carriage**

A four year study of carriage in a North American school involving 48 to 100 children per year found half of the recurrent episodes of GAS pharyngitis were associated with the same *emm* type. In their opinion, Martin et al (2004).<sup>272</sup>

*'a single infection with a specific emm type may not be sufficient to induce type-specific immunity or that early treatment may abort the development of type-specific immunity'*

Children who were carriers tended to remain carriers, even if they developed other *emm* types of GAS. Ten out of 11 carriers in the first year of the study remained carriers. GAS throat carriage of a single *emm* type lasted three to 123 weeks.

##### **Difficulty in treatment of GAS carriage**

Gastanaduy et al (1980) found during an outbreak it was harder to treat GAS pharyngitis than they expected with 19% of patients still GAS positive after a course of treatment. This led the authors to

raise the possibility that a percentage patients may have been GAS carriers and more difficult to treat.<sup>279</sup>

## V. Recommendations from international guidelines for GAS throat carriage

International guidelines have recommended that GAS throat carriage is **not** treated in most circumstances.

The Infectious Diseases Society of America (IDSA) state:<sup>9</sup>

*'We recommend that GAS carriers do not ordinarily justify efforts to identify them nor do they generally require antimicrobial therapy because GAS carriers are unlikely to spread GAS pharyngitis to their close contacts and are at little or no risk for developing suppurative or nonsuppurative complications (e.g., acute rheumatic fever....'*

*'Antimicrobial therapy is not indicated for the large majority of chronic streptococcal carriers. However, there are special situations in which eradication of carriage may be desirable, including the following:*

- (1) during a community outbreak of acute rheumatic fever, acute poststreptococcal glomerulonephritis, or invasive GAS infection;*
- (2) during an outbreak of GAS pharyngitis in a closed or partially closed community;*
- (3) in the presence of a family or personal history of acute rheumatic fever;*
- (4) in a family with excessive anxiety about GAS infections; or*
- (5) when tonsillectomy is being considered only because of carriage....'*

*'If a physician suspects that "ping-pong" spread of infections is the explanation for multiple recurrent episodes of infections within a family, it may be helpful to obtain throat swabs from all family contacts simultaneously and to treat those for whom culture or RADT results are positive.'*

The American Academy of Pediatrics recommend in the 2012 Red Book:<sup>3</sup>

**'Pharyngeal Carriers.** *Antimicrobial therapy is not indicated for most GAS pharyngeal carriers. The few specific situations in which eradication of carriage may be indicated include the following:*

- (1) a local outbreak of ARF or poststreptococcal glomerulonephritis;*
- (2) an outbreak of GAS pharyngitis in a closed or semi closed community;*
- (3) a family history of ARF; or*
- (4) multiple ("ping-pong") episodes of documented symptomatic GAS pharyngitis occurring within a family for many weeks despite appropriate therapy....'*

**'Testing Contacts for GAS Infection.** *Indications for testing contacts for GAS infection vary according to circumstances. Testing asymptomatic household contacts for GAS is not recommended except when contacts are at increased risk of developing sequelae of GAS infection, ARF, or acute glomerulonephritis; if test results are positive, contacts should be treated ...*

*'Asymptomatic acquisition of group A streptococci may pose some risk of nonsuppurative complications; studies indicate that as many as one third of patients with ARF had no history of recent streptococcal infection and another third had minor respiratory tract symptoms that were not brought to medical attention. However, routine laboratory evaluation of asymptomatic household contacts usually is not indicated except during outbreaks or when contacts are at increased risk of developing sequelae of infection (see Indications for GAS Testing, p 672). In rare circumstances, such as a large family with documented, repeated, intrafamilial transmission resulting in frequent episodes of GAS pharyngitis during a prolonged period, physicians may elect to treat all family members identified by laboratory tests as harboring GAS organisms.'*

The Red Book<sup>3</sup> and IDSA<sup>9</sup> agree that where there is a high risk of ARF or a local outbreak, or where there is 'ping ponging' of infections, carriage should be sought and treated, but they do not give any definite time frame or parameters around what constitutes an outbreak.



Pichichero and Casey<sup>4</sup> in an analysis of GAS throat carriage recommended more specific circumstances for treating GAS carriage:

**Table 17. When to Treat Group A Streptococcal GAS Carriers**

When to Treat Group A Streptococcal (GAS) Carriers	
<b>Definitely</b>	<ul style="list-style-type: none"> <li>• With a history of ARF</li> <li>• Carriers living with a person who has ARF</li> <li>• Carriers working in hospitals, nursing homes, chronic care facilities</li> <li>• Carriers in communities experiencing an ARF outbreak</li> </ul>
<b>Possibly</b>	<ul style="list-style-type: none"> <li>• Carriers in families exhibiting “ping-pong” spread of GAS</li> <li>• Carriers with particularly anxious family members regarding GAS infection</li> <li>• Recently established carriers (within 1 month of onset)</li> </ul>

**Source:** Pichichero ME, Casey JR. Systematic review of factors contributing to penicillin treatment failure in *Streptococcus pyogenes* pharyngitis. *Otolaryngol Head Neck*. 2007A; 137: 851-857.<sup>4</sup>

Sepdham et al<sup>305</sup> recommend considering treating GAS carriers under the following circumstances, with evidence grade C, expert opinion:

1. recurrent pharyngitis without cough or congestion
2. acute rheumatic fever or post streptococcal glomerulonephritis outbreaks
3. GAS pharyngitis outbreaks in a closed community
4. family history of acute rheumatic fever
5. multiple documented GAS pharyngitis episodes within a family over several weeks despite therapy
6. excessive patient/family anxiety about GAS
7. all treatment options, except tonsillectomy, have been exhausted'

Tanz et al wrote that treating GAS carriage 'may simplify management of subsequent episode of pharyngitis', 'alleviate physician and family anxiety', and treatment may be 'indicated for carriers among staff or long-term residents of hospitals or chronic care facilities or in closed populations with high rates of streptococcal disease'.<sup>256</sup>

It can be seen from some of the above recommendations that the risks from carriage take into account the risk of GAS spreading to others.

The US military, since the 1950s, has routinely treated new recruits with one or more doses of antibiotics to reduce the risk of GAS disease. One facility, the Marine Corps Recruit Depot and Naval Training Centers in San Diego, California, historically gave two doses of Benzathine penicillin G during the 13 week training (one on entry and a second dose between days 28-35. Oral erythromycin 250mg bd for 30 days was given in those allergic to penicillin).<sup>306</sup>

From the 2008 *Group A Streptococcal Sore Throat Management Guideline* (NHF 2008):<sup>1</sup>

**Question 8. How should asymptomatic pharyngeal carriers of GAS be managed?**

Treatment is **not** recommended for asymptomatic GAS carriers **except** in certain specific situations, as defined by the American Academy of Pediatrics 2006.<sup>307</sup>

- an outbreak of rheumatic fever or post streptococcal glomerulonephritis
- an outbreak of GAS in a closed or semi-closed community
- where a family history of ARF exists
- when multiple episodes of documented symptomatic GAS pharyngitis continue to occur within a family during a period of many weeks despite appropriate treatment (see **Question 7**)
- when a family is anxious about GAS infection
- when tonsillectomy is being considered only because of chronic GAS carriage.

Similarly the Infectious Diseases Society of America (IDSA) guidelines recommend against the

routine culture of throat swab specimens from, or treatment of, asymptomatic household contacts of patients with GAS pharyngitis, except in situations where there is increased risk of frequent infections or of non-suppurative streptococcal sequelae (IDSA level of evidence B-III, see [Table 2](#)).<sup>119</sup> (Bisno 2002)

**Recommendations:** Do not treat asymptomatic GAS carriers unless they meet one or more of the criteria listed above. If treatment is required, treat as per [Table 3](#), usual or routine antibiotics, unless this is the patients' third or more cases of GAS pharyngitis within three months, in which case use [Table 4](#)

**Recommendation grade:** D, for when to treat GAS carriers

**Evidence level:** Insufficient evidence for when to treat GAS carriers

(Heart Foundation 2008)<sup>1</sup>

The Health (Infectious and Notifiable Diseases) Regulations 1996 amended 2013<sup>6</sup> issued by the New Zealand Government recommend for:

**'13 Certain contacts and carriers not to engage in certain occupations**

(2) No carrier of ..... streptococcal sore throat (including scarlet fever) shall engage in the preparation, manufacture, or handling of any food for sale, nor shall he engage himself or be employed in any capacity in which in the opinion of the Medical Officer of Health he may cause or spread any such disease.'

**For further consideration in this Discussion Document, the carriage issue has been divided into two questions:**

1. Is group A streptococcal throat carriage a danger to the individual (who is a carrier)?
2. Is GAS carriage a danger to others?

### **Is GAS throat carriage a danger a risk to the health of the individual?**

**Short answer:** With respect to pharyngeal GAS carriage and the subsequent risk of the patient themselves developing ARF and invasive GAS disease it is not currently possible to answer this with any certainty.

The process of developing GAS throat carriage and the natural history of GAS carriage is still not well understood. There have been very few studies. There is no clear consensus as to whether the finding of GAS in the throat (with no obvious signs and symptoms and perhaps without a rise in serology) is an innocent self-limiting situation or whether carriage is actually the mild end of a true infection or early start of a true infection. Further research with *emm* typing and long term follow up of patients to determine the rate of GAS related illnesses would be required. GAS skin carriage is associated with invasive GAS disease.

## **Discussion**

### **I. GAS throat carriage could be in the continuum of GAS infections and may represent a mild infection as recurrent GAS throat infections may result in less signs and symptoms**

As evidence of preceding GAS infection (GAS positive throat swab and/or rise in serology) is required for a diagnosis of ARF, then the presence of GAS in the throat could potentially be a risk for future development of ARF. Studies have documented that some patients with ARF have GAS on throat culture but do not recall a sore throat.<sup>50,270,308,309</sup>

In Slater and Rosenbaum (1959), from 81 rheumatic fever patients, 55 had a recent sore throat (in prior 35 days), and 12 had GAS on throat swab.<sup>308</sup> In Rammelkamp & Stolzer (1961) 48% of rheumatic fever patients had been hospitalised with a recent previous respiratory illness.<sup>101</sup>

Miller found three studies in which patients with ARF had an antibody response but no bacteriological evidence of GAS infection.<sup>278</sup>



Lee et al (2000) found patients who had an episode of GAS pharyngitis of the same serotype as the immediately preceding GAS infection (confirmed by *emm* typing, and infection confirmed by 0.2 or greater rise in serology) were less likely to have clinically apparent signs and symptoms such as fever or sore throat. The study was small with 19 out of 295 patients (6%) having a repeat infection of the same serotype.<sup>270</sup> Pichichero & Casey concluded that if after treatment:<sup>4</sup>

*'there is a recurrence of GAS tonsillopharyngitis and the infection involves the same serotype, then patients may display milder symptoms', these patients 'are contagious to others in their environment and are, themselves, susceptible to rheumatic fever'*

This may be linked to the finding in the Yugoslavian studies of a link between 'frequent' sore throats and ARF.<sup>52,241,310</sup>

A military hospital study by Rantz (1945) of 1500 patients admitted with respiratory illnesses between 1 Jan–15 Apr 1944, found GAS infections in 410 individuals during the course of the study (which included 15 cases of ARF).<sup>311</sup> Rantz concluded that it was likely repeated GAS infections 'closely spaced' together that may predispose to 'late suppurative complications' of GAS.

Schlesinger believed repeated infections may have an important role in the pathogenesis of ARF.<sup>99</sup> From review of the records of approximately 500 children at West Wickham Hospital for children with rheumatic diseases from 1927-1929, he concluded that repeated GAS throat infections may have a role in sensitizing the immune system; resulting in ARF:

*'There is ample opportunity in childhood for sensitization of the tissues by repeated small invasions of streptococci from the tonsils. This invasion may not at first produce any definite signs of disease beyond a possible deterioration in general health. Nevertheless a process of sensitization has supervened, and when another attack of tonsillitis occurs, manifestations of rheumatism may appear as a result of the acquired bacterial allergy'*

Subclinical infection with GAS may be difficult to separate from carriage. Rammelkamp & Stolzer<sup>101</sup> reviewed the records of 565 airmen admitted with ARF to Warren Air Force Base 1949 to 1953, and made the case that:

*'a few patients exhibiting a very short latent period may have actually acquired a clinically inapparent-infection some weeks prior to the observed respiratory illness, and the observed illness actually represented the recurrence of sore throat which some patients with acute rheumatic fever experience. In favor of this interpretation is the high titer of antistreptolysin in the acute phase serum of some patients showing a short latent period. In addition, it appeared reasonable to assume that the majority of patients who exhibited a latent period of over 35 days probably had experienced a second, clinically inapparent streptococcal infection which was not detected by the techniques employed'*

Rantz et al studied a group of 1,500 American military patients with respiratory illnesses (previously mentioned). During 1944, 15 new cases of ARF developed. Of those 6 had one serotype of GAS isolated from the nasopharynx with an illness and then the same strain present at the time of diagnosis of ARF; however the other nine new ARF patients had different GAS serotype on their swabs with a respiratory illness than compared to when they presented with ARF. The conclusion was that reinfection with a new strain of GAS was responsible for the presenting ARF.<sup>311</sup>

A later US military study by Rammelkamp was not consistent with this finding of different GAS strains causing ARF. However he did advocate swabbing and treating carriage in household contacts of patients with streptococcal infections (although type of streptococcal infection was not detailed in article). He recommended that all contacts have oropharyngeal cultures *'since some infections will produce no symptoms and such individuals should receive the benefit of specific therapy'*.<sup>101</sup>

Wannamaker surveyed the GAS pharyngitis literature to date and concluded it was the antibody response which put a patient at risk of non suppurative complications of GAS such as ARF. Subclinical GAS infections were thought by Wannamaker to still have the potential to cause non suppurative complications. The literature shows approximately half of GAS infections with antibody rise *'never come to the attention of the physician'*.<sup>281</sup>

## **2. Not all patients with rheumatic fever recall a sore throat**

It is possible that patients have no apparent clinical signs or history of pharyngitis or symptoms of respiratory illness, and yet have a rise in antibodies and still develop ARF; patients do not always

recall a preceding illness. In a Maryland study 34% of patients with ARF did not recall a preceding respiratory illness.<sup>309</sup>

A 1950s study of British military recruits found 55 out of 81 rheumatic fever patients (68%) recalled a preceding sore throat but in 18 it was such a mild illness they did not report sick. Twelve other rheumatic fever patients did not recall a preceding sore throat yet they had GAS cultured from their throats.<sup>308</sup> Self-reporting of symptoms is not a reliable or consistent measure.

In an analysis of 169 GAS acquisitions among rheumatic families, Miller et al found 55% (93/169) of GAS acquisitions were asymptomatic. Of the symptomatic acquisitions 48 (64%) were tonsillopharyngitis, 11 were classified as fever of undetermined origin (FUO) (14%), and 17 (23%) were classified as miscellaneous. Streptococcal infection was diagnosed by throat culture or rise in ASO titer (even when throat culture was negative) and further classified as 'symptomatic' or 'asymptomatic'.<sup>278</sup>

### 3. Long-term health of GAS throat carriers

A longitudinal study of GAS carriers showed the incidence of rheumatic fever among carriers to be 0.2%, 0.2% for ARF recurrences, and 0.2% for glomerulonephritis.<sup>157</sup> Carriers were defined as:

*'a person on whom at least one positive culture for hemolytic streptococcus was found during the base period in time of health' (i.e. cultures were positive on a routine monthly visit during the initial 2 year period)*

However this was a small study and results weren't clearly articulated e.g. no rate per person years of carriage given or how long after GAS carriage complications occurred.

The study included 200 families, between 1952 and 1972 in Massachusetts, USA. Patients were in the study for varying lengths of time. Fifteen families (90 people) were still in the area available for follow-up analysis at the 20 year completion date.

The following two tables from Dunlap & Bergin (1973)<sup>157</sup> are derived from data on 706 people from 121 families in the study:

**Table 18. Long Term Health of GAS Carriers**

TABLE V. Subsequent health after carrier and noncarrier condition

Status	Total Patients	Deaths* Ill	Deaths* Acc.	Sequelae			Living Normal Lives
				First Attack	Rheumatic Fever Recurrence	Glomerulonephritis	
<b>Carriers</b>							
Before Jan. 1, 1960							
Adults	26	0	0	0	0	0	26
Children	119	0	0	0	1	1	119
After Jan. 1, 1960							
Group A							
Adults	33	0	2	0	0	0	31
Children	258	0	2	1	0	0	256
Group C or G							
Adults	8	0	0	0	0	0	8
Children	16	0	0	0	0	0	16
<b>Noncarriers</b>							
+ when ill							
Adults	35	0	0	0	0	0	35
Children	71	0	0	0	0	0	71
<b>Never +</b>							
Adults	218	3	1	0	0	0	214
Children	94	0	0	0	0	1	94

\* Ill means death from illness; acc. means death from accidental cause.

TABLE VI. Late suppurative streptococcal illness as related to past streptococcal experience (706 persons, 121 families)

Past Experience	Persons	Late Streptococcal Illness		Late Illness (Per Cent)
		Present	Absent	
<b>Adults</b>				
Carriers				
Noncarriers	55	2	53	3.7
Strep. when ill				
No strep. found	40	4	36	10.0
Children				
Carriers				
Noncarriers	308	120	188	38.9
Strep. when ill				
No strep. found	84	25	59	29.8
<b>TOTALS</b>				
Per cent	706	175	531	...
	...	25	75	...

**Source:** Dunlap MA, Bergin JW. Subsequent health of former carriers of hemolytic streptococci, NY State J Med. 1973; 73: 1875-1880. Permission to publish copyright material pending.

### 4. Carrier switch of emm types and risk for developing rheumatic fever

In a four year study of Pittsburgh children (48 to 100 children per year studied), Martin et al noted that carriers tended to switch emm types.<sup>272</sup> It was theorized that although carriage is thought not to be a risk for ARF, arguably children switching GAS carriage emm types may be at risk of ARF. It was concluded:<sup>272</sup>

*'On the basis of these observations and because we practice in an area of the country with a high rate of acute rheumatic fever, we now routinely treat all infections associated with a*

*GAS-positive throat culture among children with typical symptoms (sore throat and absence of cough and nasal congestion), even if the child is known to be a carrier of GAS. Practitioners in other areas of the country with similarly high rates of acute rheumatic fever should consider this approach'*

## **GAS throat carriage a danger to others?**

**Short answer:** Yes, GAS throat carriage can spread GAS but it is not as likely to spread GAS as symptomatic GAS. This may be an issue in areas where there are known risks of GAS related illnesses such as high rates of ARF.

### **Discussion**

#### **1. Guidelines have generally portrayed carriage of pharyngitis in the throat as harmless to others**

Guidelines and texts generally suggest that GAS throat carriage is not a danger to others. The Guidelines cited (see previous section) include the Infectious Diseases Society of America (IDSA 2012) and American Academy of Paediatrics (AAP 2012).<sup>3,9</sup> These were developed for the USA in times of low rheumatic fever incidence and not for areas with high rates of ARF.

Bloomfield and Felty in a study of 51 pairs of US nurses who were roommates, did not find having a GAS carrier as a roommate led to greater spread under ordinary circumstances.<sup>296</sup>

Kaplan & Gerber<sup>237</sup> state:

*'Data in the literature suggest that group A upper respiratory tract carriers are less dangerous to others because carriers only rarely spread the organism to close contacts. In addition, the risk of developing nonsuppurative sequelae, such as rheumatic fever, seems to be significantly reduced in carrier'*

The American Academy of Pediatrics (2012)<sup>3</sup> Red Book advises that GAS carriage can persist for months, but the risk of transmission to others is low.

The IDSA Guideline<sup>9</sup> recommends that:

*'GAS carriers do not ordinarily justify efforts to identify them nor do they generally require antimicrobial therapy because GAS carriers are unlikely to spread GAS pharyngitis to their close contacts and are at little or no risk for developing suppurative or nonsuppurative complications (e.g., acute rheumatic fever)'*

**It should be remembered that these North American guidelines are designed for low rheumatic fever settings and not intended for areas with high rates of rheumatic fever.**

The US military literature tends to take a different view. A review of the rheumatic fever literature by Hare in 1942 (in the pre-antibiotic era) suggested *'Every effort should be made to identify throat carriers and to segregate them from their fellows'*. He went on to recommend that GAS *'carriers should then be placed in a separate barrack room or hut where they sleep'*.<sup>312</sup> At this time rheumatic fever rates in military populations were up to 1000/100000 men.

Writing in the pre penicillin era, Kuttner & Krumwiede pointed out that GAS carriers were excluded from some institutions (sanatoria and convalescent homes) due to their risk of spreading GAS to others and causing GAS outbreaks and rheumatic fever recurrences.<sup>275</sup>

Darrow (2002)<sup>5</sup> recommends treatment in the following situations:

- Carriers in families with a history of rheumatic fever
- Carriers with a history of acute glomerulonephritis
- Carriers in families experiencing 'ping-pong' spread of disease
- Carriers in schools experiencing GAS epidemics
- Carriers who are food handlers
- Carriers who are hospital workers'

## 2. Additional factors influencing spread from carriage

Saliva can contain GAS in large numbers.<sup>313</sup> Nasal GAS carriage has been associated with increased spread of GAS.<sup>219</sup> Hamburger et al (1945) implicated nasal GAS as a source of spread to others on military hospital wards.<sup>156</sup> They concluded that carriers with strongly positive nose cultures (for hemolytic streptococci) were more dangerous than those who only had positive throat culture.

Falck et al (1997) found GAS in the nose gave rise to more cases of GAS than if it was only cultured from the throat.<sup>219</sup> Within one month the rate of GAS spread doubled from 26%, if the index cases had only a positive throat swab, to 52% chance of infection in household contacts, if both nose and throat were GAS culture positive.

Wannamaker (1954) also found a link between nasal GAS and spread; GAS in the nose and throat increased infectivity in the military barrack setting.<sup>41</sup> He found nasal and throat GAS together were more infectious than the presence of GAS in the nose alone or throat alone. Wannamaker also correlated GAS acquisitions in the barracks with the number of organisms of GAS isolated from the nearest carrier's nose or throat. The greater the number of streptococci cultured the greater the amount of spread (new acquisitions of GAS) in the barracks.

However El Kholly et al (1980) in a study of Egyptian families did not find nasal GAS increased GAS infection spread.<sup>218</sup> Altogether, these studies suggest that both close contact and bacterial load are important.

Crowding has been associated with spread from pharyngeal GAS.<sup>301</sup> (See Question 17: Does reducing crowded living conditions help reduce the incidence of rheumatic fever? in the Proposed Rheumatic Fever Primary Prevention Programme Guideline 2009).

Meyer and Haggerty (1962) followed 16 lower-middle class US families (100 persons) for one year with serial ASO and throat cultures. They found acute life stress or chronic family disorganization made family members more susceptible to acquiring GAS infections. In addition ASO titres following the acquisition of infections rose with increasing stress levels.<sup>314</sup>

Nandi (2001) found an association with GAS sore throat and the presence of tobacco smoking in the house.<sup>227</sup>

Since the early epidemiological studies of GAS (which were by and large from institutions such as hospitals, and military facilities), daycare may potentially have a role in allowing child-to-child spread of infections. Danchin et al (2007) found 20% of children under 5 developed a secondary case of GAS pharyngitis (i.e. were infected by the index patient).<sup>7</sup> They concluded '*higher rates of GAS pharyngitis are becoming increasingly common in younger children, presumably since the advent of child care.*' This is further supported by daycare/GAS pharyngitis literature from Scandinavia.<sup>197,315</sup>

Wannamaker (1954), considered that GAS carriage was dependent on factors including the age of the carrier, the existence of secondary complications or intercurrent non streptococcal infection and the duration of the carrier state. Wannamaker also noted that GAS carriage was less infectious after 2 weeks and more infectious earlier.<sup>54</sup>

Pichichero and Casey (2007)<sup>4</sup> state that three factors largely determine the threat a carrier has to a contact, namely:

- *The number of microorganisms found in the nasopharynx, which is highest early in the course of carriage*
- *The timing of exposure to the carrier, again with greater risk earlier in the course of carriage*
- *The nature of the strain carried.*

## 3. Onward infection is proven from pharyngeal GAS carriage

Onward infection in other individuals i.e. infection from the index patient to other people, has been proven from GAS pharyngeal carriage.

In France, Nguyen et al (1997) found healthy carriers in the home were implicated as a source of re-infection of 52 patients with GAS pharyngotonsillitis who had been treated with antibiotics. They considered this finding had implications as to whether recurrence of GAS pharyngitis was due to treatment failure or re-infection.<sup>316</sup>

James et al (1960) showed that in a 10 week period, there was a 9% risk of asymptomatic carriers transmitting GAS to their family members. However this study did not assess the type of infection the

family developed due to the relatively small numbers.<sup>158</sup> Among index GAS pharyngitis patients who had 'a streptococcal illness', the rate of transmitting GAS to family was 25% in 10.

- **The same invasive GAS disease strains may be common to the circulating pharyngitis GAS strains. Carriage may have a role in fuelling the burden of GAS diseases**

Pichichero (1999)<sup>317</sup> assessed the literature and wrote that the:

*'widely held notion that GABHS carriers are harmless to themselves and to others is not accurate'. The same GAS strains 'responsible for invasive, toxic shock and necrotising fasciitis infections may be prevalent among carriers and patients with symptomatic pharyngitis in a community'*

In 1994-95, North Carolina had high rates of invasive GAS diseases (96 patients with 11 fatalities). Kiska et al (1997) found that serotypes M1 and M3 accounted for 50% of recent invasive isolates and 58% of pharyngeal isolates.<sup>291</sup> This led the authors to conclude that *'pharyngeal infections may have served as a reservoir for virulent GAS clones'*. *emm* serotyping undertaken between October and December 1993 showed that 58% were M1 and M3, the same types that were responsible for most of the invasive infections occurring in January 1994.

Viglione et al (1997) documented a nine week outbreak of invasive GAS in 1987. This included nine postpartum infections (five with bacteremia, three with endometritis without bacteremia and one infected episiotomy). An obstetrician was later found to be an anal carrier of the GAS, which led to the nosocomial outbreak of GAS. Nose, throat, perineum and anus cultures were taken from staff. All the nine patients and the obstetrician's anal swab cultured the same M & T typed strain of GAS. The obstetrician was treated with antibiotic and had a small haemorrhoid removed. The outbreak ceased, but after 14 months, four new cases of GAS infection occurred and the obstetrician was again found to be 'heavily colonised' on anal swab with the same GAS.<sup>318</sup>

Ichihama et al (1997) investigated 21 family members of four invasive GAS patients. In household '1', four family members cultured the same strain of GAS, 3 cultured this from their throats and had mild to severe pharyngitis. In household '2', five family members had the same GAS, all in their throats, one had mild pharyngitis and the rest were carriers. In household '3', the patient and stillborn child had GAS in their blood, and the 3 family members all carried the same strain in their throats. In household '4' there were 4 family members with mild pharyngitis, two were not cultured, two carried the same strain in their throats.<sup>319</sup>

Following seven cases (four fatalities) of the same strain of invasive GAS in a Minnesota community, screening of school children was initiated.<sup>320</sup> 59 out of 187 (32%) children in this community had positive GAS cultures and 46 out of the 59 cultured the same clone as the invasive disease patients. This was comparatively higher than three control schools where the rate of GAS cultured from throats was 12, 16, and 23%, with 4 out of 151 of the GAS cultured belonging to the invasive clone strain. Carriers were treated with antibiotics.

Cockerill<sup>320</sup> theorized:

*'clusters of invasive streptococcal disease may occur when:*

*(1) a virulent clone is circulating in the general population,*

*(2) the clone becomes prevalent among asymptomatic carriers (particularly children) and persons with pharyngitis, and*

*(3) persons at high risk of invasive disease (ie, those who are elderly or those with underlying risk factors) are exposed to those in the community who are carriers of the organism.'*

This is consistent with Rogers et al's 2007 study of 220 GAS isolates from Victoria Australia (2002-3). Of these GAS isolates, 78 were invasive GAS, 34 were GAS pharyngitis, and 108 were GAS carriage. Serology was taken to confirm GAS infection and isolates were characterized using *emm* typing, random amplification of polymorphic DNA (RAPD) profiling, and superantigen genotyping.<sup>321</sup> They concluded:

*'the emergence of GAS strains with increased virulence is not the main factor responsible for the surge in GAS-related infections. The prevalence of particular emm types, RAPD profiles,*

*or superantigen genes in invasive disease may simply indicate widespread transmission of these strains in the population, rather than a particular ability to cause disease.'*

In a 240 bed nursing home, Georgia USA, Dooling et al (2013) found the same *emm* type of GAS in 19 residents with a total of 24 GAS infections: 15 with invasive GAS disease (three with recurrent), nine with non-invasive GAS disease (two with recurrent), and seven residents who were carriers of GAS. A carrier was defined as a patient with cultured GAS '*in the absence of clinical infection*'. Oropharynx swabs were taken, any wounds present were swabbed, and any indwelling lines were cultured. Ultimately 98% of residents and employees were treated with antibiotics.<sup>322</sup>

Martin et al (2004) argued that GAS '*invasive strains generally reflect the predominant pharyngeal strains*'.<sup>272</sup>

GAS has also been implicated in a household cluster of pneumonia.<sup>323</sup> From a US household of 12 individuals, there were five patients with pneumonia (four children and a mother), hospitalised with the same GAS. Three of these patients also had concurrent pharyngitis. At home a further two people also had GAS pharyngitis of the same type.

Schwentker (1943)<sup>298</sup> in a US Army study concluded it was the predominance of a single strain among carriers which was the problem:

*'During an epidemic of scarlet fever, most of the cases are caused by a single type of streptococcus. This type also represents a high percentage of the strains recovered from normal carriers. In contrast, during endemic periods no single strain is outstanding among those causing scarlet fever. Instead a number of types are involved. These types are also found in normal carriers but do not predominate over the other non- scarlatinal strains.'*

There is a definite relationship between the streptococcus carrier rates in a community and the incidence of scarlet fever. The logarithm of the morbidity varies directly with the carrier rate.<sup>298</sup>

## Appendix 13: Articles Showing Spread from Asymptomatic GAS Carriers to Others

This is not a definite list of all studies but examples of various settings where GAS spread from asymptomatic GAS carriers to others.

**Table 19. Articles Showing Spread from Asymptomatic GAS Carriers to Others**

Study	Setting/Description	Time-frame	Causation of Symptomatic GAS Pharyngitis GAS Disease in Contacts (%)	Causation of Asymptomatic GAS in Contacts (%) i.e. Spread of Carriage	Causation of Other GAS Diseases in Contacts (%)	Serology Taken? Yes or No.
Dingle et al 1964 <sup>158</sup> & James et al 1960 <sup>158</sup>	<p>Cleveland USA.</p> <p>443 individuals (86 families) followed for 977,036 person days (2692 person years).</p> <p>'The person involved was designated as the index carrier whether or not there was an associated illness'... 'Family contacts who acquired the type of streptococcus introduced into the family by the index person were considered to be secondary carriers'. Serological tests not done in most instances &amp; not required for diagnosis. Pharyngitis/tonsillitis diagnosis required presence of clinical findings 'commonly considered to be characteristic of these infections' (1 or more of the following symptoms: sore or injected throat, exudate, enlarged and tender anterior cervical lymph nodes, or nodes showing a definite enlargement since a recent observation) and bacteriological evidence of recently acquired GAS. Did not attempt to differentiate between pharyngitis &amp; tonsillitis.</p> <p>James et al 1960: 1 Jan 1948-1 July 1952 data (same results as Dingle tables here) 379 acquisitions occurring more than 30 days from another acquisition. Symptom diary kept, nurse took throat swab weekly from all patients. Secondary carrier defined as a member of the family who acquired the same type within 10 weeks of introduction. Illnesses occurring among secondary carriers were not analysed.</p>	10 years. 1 Jan 1948 – 31 May 1957.	<p>From an index carrier who did not have streptococcal illness, 9% of family members became secondary carriers of GAS within 10 weeks of identifying the initial case. [i.e. 26 out of 291 family members had GAS positive throat swabs]</p> <p>NOTE: Not documented whether family members developed symptoms, only that they had same serotype of GAS.</p> <p>Highest rate of acquisition of GAS from carriage occurred in 3-4 year olds (3/34=18% became GAS positive after exposure to an asymptomatic carrier).</p> <p>Comparison: when the index patient was symptomatic of GAS illness and had GAS positive throat swab; 25% of family members became secondary carriers (46/183 people in 10 weeks)</p> <p>James et al 1960 stated 43% of all GAS acquisitions were accompanied by illnesses considered to be streptococcal in nature.</p>	Approx 60% [James stated 43% of all GAS acquisitions were accompanied by illnesses considered to be streptococcal in nature].		Not in most cases (not required for diagnosis).
Holmstrom 1990 <sup>197</sup>	<p>7 Swedish daycare centres.</p> <p>Outbreak of Erythromycin resistant Group A Strep (ERGAS). 294 isolates of ERGAS, 277 were same serotype of GAS. 112/230 children, 7/93 staff, 37/163 parents and 22/61 siblings had positive throat swabs for ERGAS.</p> <p>Among the children who cultured ERGAS at the daycares, 30 were symptomatic and 82 were asymptomatic [presumed carriers]. Symptoms were mostly tonsillitis &amp; rhinopharyngitis with variable temperature</p>	1984 -85	<p>8.5*/42 (20%) of relatives developed symptomatic ERGAS infection from their child</p> <p>Comparison: 30 symptomatic ERGAS children spread symptomatic ERGAS to 16/56.5 (28%) of their relatives</p> <p>* The 0.5 is from 1 parent with 1</p>	By MK calculation then 42- 8.5=33.5. 33.5/ 42=80% of family members must have contracted asymptomatic ERGAS from		No



			symptomatic and with 1 asymptomatic child	their child		
				Comparison: 30 symptomatic ERGAS children caused asymptomatic ERGAS to spread to 7.5/16 (47%) of their relatives		
Allison 1938 <sup>324</sup>	Measles ward. Patients were swabbed weekly over 7 weeks. 43 patients total. 18 had GAS isolated on admission, 22 cross infected (51.2%). During the admission 22/35 patients showed clinical manifestations of GAS. 13 pts developed complications due to cross infection with GAS	7 weeks	Of the 13 patients who were cross infected on the ward with GAS, 4 patients developed rise in temperature, mild sore throat and malaise		Of the 13 patients cross infected on the ward with GAS: 4 developed otitis media, 1 developed Scarlet fever with otitis media and 1 developed rhinitis	No
Bloomfield A, Felty A, 1923b <sup>297</sup>	Nursing students at Johns Hopkins Hospital Training School. 1 Sep 1922 to 1 April 1923. Approx 40/200 women became ill with tonsillitis. There were 25 pairs of roommates where one was a carrier and the other was free of GAS.	6 months	Over the winter 7/28 (25%) of the roommates of the carriers developed tonsillitis (compared to tonsillitis incidence of 20% in the entire group of 200 nurses - this did not seem significant)			
Hamburger M Jr et al 1945 <sup>156</sup>	US Army wards. A "dangerous carrier". Though no streptococcal illness had come from Barracks A, the 67 men in this barracks had nose and throat swabs taken. One man with no signs or symptoms of respiratory infection had strongly positive nose and throat cultures for GAS type 46 (taken on 9 Mar). Two men had a few colonies of the same GAS type 46 in their nasal cultures but their throats were negative. Three other men had untypable GAS in their throats. Between 13-31 Mar, ten men from the barracks were hospitalised with tonsillitis or pharyngitis of the same type GAS 46.	Published 1945	10/67 = 15% [MK calculation]			
Hamburger M 1944 <sup>313</sup>	US army hospital wards, mostly 28–32 bedded wards. Daily throat cultures undertaken of all ward patients and of as many staff as possible. In a measles ward, four patients each cultured a different GAS type during routine culturing. Five days later an outbreak of GAS cross infections began, one (type 18) infected 12/14 persons, type 17 caused two cross	2 wks (varied)	(Not clear if symptomatic or asymptomatic acquisitions)			No

	<p>infections. At the end of two weeks only eight men did not become cross infected.</p> <p>However in two other respiratory wards with 55.8% and 45.6% carriers of GAS present, over 10 -13 days only one cross infection was detected. Wards fluctuated with admissions and discharges. For the first period sheets were hung between beds to see if infection spread was reduced)</p>				
El Kholly et al 1980 <sup>218</sup>	<p>Egypt. A study from Feb 1972 through to Jan 1974 of 110 apparently normal families and 84 families with a child suspected of having rheumatic heart disease. However two non-rheumatic families and 41 suspected-rheumatic families were enrolled for one year only.</p> <p>Posterior oropharyngeal swabbings for throat culture were taken initially and semi-monthly thereafter from all available family members, and serum specimens initially and every six months thereafter from available family members older than three years of age.</p> <p>For one year (treated year), each time a family member was found to have GAS in the throat, they were given 1.2 mU of benzathine penicillin G IM. There was a delay of six to eight days between obtaining and processing throat cultures to administering penicillin.</p> <p>For the other year (untreated year), penicillin was not given following the identification of GAS in the throat in routine cultures. Families enrolled in the cross-over study were arbitrarily assigned to begin either with the treated or the untreated year.</p> <p>Episodes were considered to have ended if the infecting strain was not found in any family member for eight consecutive semi-monthly (four months) culturing.</p> <p>Spread within families was most intense in those episodes in which the household contacts were two to 14 years of age, the introducer had sought medical care, or the introducer ultimately carried the streptococcal strain for three or more months.</p>	2 yr study	<p>Secondary attack rate of GAS acquisition (defined by positive throat culture alone) in ARF 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.</p> <p>Carriage (GAS positive throat swab and no illness) led to attack rate of 8.2% (305 of 3,714) in non-rheumatic families and 8.7% (154 of 1,772) in rheumatic families. When introducer was symptomatic the rate of spread was twice as high, 15.1%( 68 of 450) in non-rheumatic families and in rheumatic families 27.7%( 23 of 83)</p> <p>(treated and un-treated years combined and excluding those receiving continuous prophylaxis). No consistent differences were found in secondary attack rate according to the type of clinical illness (pharyngitis, otitis media, other respiratory infection, other).</p> <p>No difference in secondary attack rate between episodes in which the introducer was documented to have a &gt;0.2-log increase in ASO titer and those in which no such increase. For all episodes in which paired sera were available from introducers, the rates were 8.8% (329 of 3,783) without ASO rises and 8.6% (29 of 338) with ASO rises.</p> <p>The secondary attack rate in untreated families increased progressively with increasing total duration of carriage by the introducer, i.e.it was higher for introducers who harbored the strain for a longer time. With combination of suspected-rheumatic and non-rheumatic families, the respective secondary attack rates, by number of weeks from the first to last culture of the episode strain in the single introducer, were zero</p>		<p>Yes but only 6 monthly so may under estimate. Although the collection of sera at six-month intervals may have precluded the possibility of demonstrating a rise in antibody titer in many instances.</p>

			weeks, 5.3% (103 of 1,926); two weeks, 8.4% (38 of 454); four weeks, 11.7% (32 of 274); six weeks, 14.5% (32 of 220); eight weeks, 13.4% (26 of 194); > 10 weeks, 17.1% (102 of 597)			
Kuttner & Krumwiede 1941 <sup>275</sup>	<p>New York, 1937-1940.</p> <p>Sanatorium for rheumatic children; 108 children over 3 yrs (66 girls 42 boys). Children who had had one or more attacks of polyarthritis or carditis without marked cardiac damage were selected. The children lived and went to school in the same building. They had no contact with other children and each child was permitted only two adult visitors every six weeks. Rectal temperatures and pulse rates were taken three times daily. Leukocyte counts, haemoglobin estimations, and erythrocyte sedimentation rates were done routinely every three or four weeks, or more often when necessary.</p> <p>Children who had symptoms of upper respiratory infections were put to bed and isolated in cubicles, or when possible, in separate rooms. Leukocyte counts were taken on the first or second day of illness.</p> <p>Bacteriological procedures:</p> <p>Throat cultures to determine the presence of group A beta hemolytic streptococci were taken routinely once a week on every child throughout the year. Additional cultures were taken on two successive days on children who developed symptoms of any kind.</p> <p>Children in whom the appearance of streptococci in their routine throat cultures was not accompanied by symptoms, or by a rise in their white blood counts or in ASO titer, were considered to have become carriers, either temporary or chronic.</p>	3 yrs	<p>The epidemic strain of this year, streptococcus C51, was introduced by a carrier admitted in May 1937 and who was later discharged in October 1937.</p> <p>12 cases of pharyngitis developed in the other children (this also led to ARF recurrences in six of the 12 patients, 9-18 days later).</p> <p>[NB: detailed study, showed that most carriers did not spread disease to others]</p>	During the summer and fall of 1937, five other children became carriers of this strain		Yes. ASO titers (6) were determined every three to six weeks, and more often following upper respiratory infections or during rheumatic activity.
Nguyen et al 1997 <sup>316</sup>	<p>France.</p> <p>52 patients treated with either 10 days of penicillin 10<sup>6</sup> IU po or josamycin po (1g bd), diagnosed on rapid strep test, aged 12-65 years. They were monitored by family doctors for 3- 4 months. Samples were also collected from 92 'healthy carriers' living in close contact with 39 of the 52 patients; and from 25 adult patients with acute tonsillopharyngitis. Patients were swabbed pre antibiotics, day 30, and between days 90-120. Strains were M and T typed.</p>		<p>8/39 patients negative at day 0 were GAS positive when swabbed between days 90-120.</p> <p>4/20 patients who had a different strain of GAS at day 0, developed a new type strain of GAS which was the same type as that of a family contact carrier also at days 90-120.</p> <p>Note: It is not clear whether the newly infected patients were symptomatic of pharyngitis or asymptomatic and became GAS carriers.</p>			
CDC 1999 <sup>325</sup>	<p>Maryland.</p> <p>Nine post op patients, seven had endometritis (two with sepsis), one required ICU, one developed post caesarean wound infection, one developed UTI. 198 health care workers had swabs taken, one had a rectal isolate which matched.</p> <p>California.</p>					

	Three surgical patients developed streptococcal toxic shock, one surgeon had been in contact with all of them. He began taking antibiotics before swabs were completed but was suspected as source.					
Coburn & Pauli 1941 <sup>293</sup>	New York Hospital. An outbreak of GAS in children's wards occurred between Oct 1939 and Jan 1940 involving 38 people. The children 'showed little febrile reaction, developed many septic complications, showed few or no type 12 organisms in their throat or nose at a time when the epidemiological investigation indicated they spread contagion'.		Not quantified	Not quantified		Yes
Campbell et al 1996 <sup>326</sup>	Two babies developed GAS septicaemia in a NICU, two others had GAS cultured asymptotically from their throats, 5/103 NICU staff also cultured GAS (four throat and one anal). One child died. A staff member (respiratory therapist) colonized with the epidemic strain was thought to be the source					
Greene et al 2005 <sup>327</sup>	Georgia long-term care facility. The CDC investigated a cluster of GAS deaths in the facility. Eight invasive GAS cases were found (median age: 79 years); six patients died. GAS carriage in residents was 10% and 9% among staff. All isolates among residents and 63% among staff were type <i>emm</i> 77. Risk factors for GAS disease or carriage included having a GAS- infected or GAS-colonised roommate (RR = 2.0, 95%CI = 1.10-5.0).	(Retrospective)				
Falck et al 1997 <sup>219</sup> (see chart below)	Sweden. 110 index GAS pharyngitis cases and 263 family members, although at end of study only 114 patients & family members remained. Patients were treated with penicillin for five days and followed for a month. GAS of the same T-type as that of the isolate from the index case were found in other family members in 33% of the families. 40 patients had recurrent GAS pharyngitis (27 were defined as clinical recurrences with symptoms). 28 recurrences occurred within 10 days after the end of treatment. Of 20 T-typed patients with early clinical treatment failures, infected family members were detected in 16 families ( $p < 0.001$ ). Recurrence of same T type was classified as treatment failure. An 'extensive intrafamilial streptococcal spread' occurred. They concluded 'Most recurrences of GAS pharyngotonsillitis after penicillin treatment are probably due to "ping pong" infection from family members'	1 month	At the second visit, on days 6-10: Of the 305 household members exposed, 263 were investigated.  20 were ill (n= 8%)	At the second visit, on days 6-10: Of the 305 household members exposed, 263 were investigated.  70 (27%) were colonized (GAS cultured but patient asymptomatic)		
Strus et al 2000 <sup>328</sup>	Hospital in Poland. Four patients from the gynaecology department and two patients from the surgery department presented with clinical signs of GAS infection. Two general surgical patients developed local ulceration, four patients post caesarean developed symptoms including fever, tachycardia and local necrosis. Hospital operating theatre aid was identified as a GAS carrier, four confirmed and two probable cases were found among the patients. They cultured the same GAS from 2/4 Caesarean patients' surgical sites					

	(two had been given antibiotics promptly and cultures were negative), and two surgical patients' wounds, and the throat of the staff member.					
Kolmos et al 1997 <sup>329</sup>	Hvidovre Hospital, Denmark. Three orthopaedic surgery patients developed postoperative wound infection and septicaemia, caused by <i>S. pyogenes</i> over a three-and-a-half month period. One surgeon was common to all three patients; GAS and group G Strep were cultured from his tonsils. The three patients and surgeon all cultured the same T type of GAS. Two of the three patients died.	1990-1, approx. 3.5 months				

## Appendix 14: Reported Outbreaks of *S.pyogenes* Postoperative Wound Infections Originating from Carriers Among Surgical Staff

The following table by Kolmos et al (1997) shows examples of nosocomial GAS spread, from surgical staff. The sites of colonization or infection in the index patients included pharyngeal and non-pharyngeal sites.<sup>329</sup>

It was beyond the scope of this review to conduct a review of all instances of carriage spreading to other individuals and resulting in infections but this could be an area for further research/literature review by others in future.

**Table 20. Reported Outbreaks of *S.pyogenes* Postoperative Wound Infections Originating from Carriers Among the Surgical Staff**

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Table II. *Reported outbreaks of S. pyogenes postoperative wound infections originating from carriers among the surgical staff*

Reference	No. of cases	Source of outbreak	Site of carriage	<i>S. pyogenes</i> type
2	5	Surgeon	Throat	Inconclusive
4	2	Surgeon	Throat	T 22
3+5	11	Gyn/obstetrician	Anus	T 9
5	12	Anaesthesiologist	Skin	T 28
6	9	Anaesthesiologist	Anus	Not performed
7	13	Anaesthesiologist	Anus	T 12
8	6	Anaesthesiologist	Anus	T 28
9	4	Surgeon	Anus	T 28
10	18	Circulating nurse	Vagina	T 11
11	4	Attendant	Anus	T 12
12	10 (+2)	Circulating nurse	Anus + vagina	T 4 (+T 12)
13	20	Technician	Skin	T 28
14	4	Anaesthesiologist	Throat	T 28
15	9 (+4)	Obstetrician	Anus	T 28
This study	3	Surgeon	Throat	T 28

**Source:** Kolmos HJ et al. The surgical team as a source of postoperative wound infections caused by *Streptococcus pyogenes*. *J Hosp Infect.* 1997; 35: 207-214<sup>329</sup> Permission to publish copyright material pending.

## Appendix 15: Colonisation of Household Contacts Following Exposure to GAS Pharyngitis

Among household contacts exposed to an index GAS pharyngitis patient, 8% became ill (poorly) and 27% were colonized (turned into carriers) during the follow up period. T typing was undertaken.

**Table 21. Colonized and Ill Family Members at the Second Visit**

**Table 1. Colonized and ill family members at the second visit**

	Exposed <i>n</i>	Investigated		
		Total <i>n</i>	Colonized <i>n</i> (%)	Ill <i>n</i> (%)
Fathers	84	67	10 (15)	5
Mothers	63	57	8 (14)	4
Brothers	67	60	23 (38)	2
Sisters	80	69	27 (39)	8
Children				
Age (years)				
0–6	66	53	26 (49)	5
7–12	53	48	17 (35)	1
13–18	28	28	7 (25)	4
Lodgers	5	5	1	1
Families without children	6	5	1	
<b>Total</b>	<b>305</b>	<b>263</b>	<b>70 (27)</b>	<b>20 (8)</b>

**Source:** Falck G et al. The role of household contacts in the transmission of group A streptococci. Scand J Infect Dis. 1997; 29: 239-244.<sup>219</sup> Permission to publish copyright material pending.



## Appendix 16: Relationship Between GAS Throat Infection Rate and Rheumatic Fever by Country; New Zealand Guidelines Group, 2011

The following table details the rates of rheumatic fever and reported GAS carriage and levels of GAS pharyngeal carriage in the community. No trends were found.

**Table 22. Relationship Between GAS Throat Infection Rate and Rheumatic Fever by Country**

See [page 99](#) for references of studies included in this table.

Country	Reference	Year data relates to	Age range	GAS throat infection rate	Reference	Year data relates to	Age range	Rheumatic fever rate
	GAS throat infection				Rheumatic fever			
Oahu, Hawaii	Erdem et al <sup>98</sup>	2003		3.4%	Jackson et al <sup>108</sup>	2003 and 2006	5 to 15 years	Pacific Islander
American Samoa		2006		13%				9.5 to 12.4/100,000
Micronesia	Kohler et al <sup>99</sup>	2009	5 to 15 years	12.4%	Kohler et al <sup>99</sup>	2009	5 to 15 years	50 to 134/100,000
India	Dhakal et al <sup>94</sup>	2007	>0 to 12 years	4.5%	Jackson et al <sup>108</sup>	2003 and 2006	5 to 15 years	54/100,000
	Kumar et al <sup>100</sup>	2000 to 2002	5 to 15 years	1.3%	Tibazarwa et al <sup>18</sup>	1988 to 1991	5 to 18 years	51/100,000
	Lloyd et al <sup>101</sup>	2004		8.4%				
	Bramhachari et al <sup>92</sup>	2006 to 2008	5 to 17 years	1.5%				
			5 to 15 years					
Fiji	Steer et al <sup>107</sup>	2006	5 to 14 years	6.0%	Parks et al <sup>102</sup>	2003 to 2008	4 to 20 years	24.9/100,000
					Cuboni et al <sup>109</sup>	1996 to 2000	All ages	2.3/100,000
					Steer et al <sup>107</sup>	2005 to 2007	5 to 14 years	9.8/100,000
							5 to 15 years	15.2/100,000
Nepal	Rajal et al <sup>103</sup>	2008	5 to 16 years	9.2%	Limbu and Maskey <sup>110</sup>	Not stated	School children (ages not specified)	1.2 to 1.3/1000
	Dunre et al <sup>95</sup>	2007	5 to 15 years	10.9%				
Ethiopia	Abdissa et al <sup>91</sup>	2004 to 2005	6 to 14 years	8.7%	Abdissa et al <sup>91</sup>	2004 to 2005	Children (age not specified)	4.6 to 7.1/1000

**Source:** New Zealand Guidelines Group. Management of group A streptococcal sore throat for the prevention of acute rheumatic fever. Wellington: New Zealand Guidelines Group. 2011.<sup>254</sup> Copyright 2014 New Zealand Ministry of Health.

## References relating to **Table 22** on **page 98**:

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## Appendix 17: Examples of When GAS Carriage Has Been Treated in Various Settings

This is not a definite list of all studies but examples of various settings where GAS pharyngeal carriage has been treated.

**Table 23. Selected Studies of GAS Carriage Being Treated in Various Settings**

Study	Setting	
<b>Juvenile Detention Centres</b>		
Colling et al 1980 <sup>330</sup>	Juvenile detention centre in England in 1970s	In 1972 at a juvenile detention facility for 15-17 year old boys, there were a large number of admissions for tonsillitis. A survey of 100 boys showed 30% cultured GAS from their throats over the time of their two month stay (most boys stayed in the institution for 6-8 weeks). Initially attempts were made to treat symptomatic GAS pharyngitis and GAS carriage with antibiotics but this did not reduce GAS diseases, only initiating prophylaxis of 250 mg qid po for 10 days to all new entrants (from Dec 1974 onwards) reduced GAS infections. Comparing the six month period Oct 1972 to Mar 1973, with the six month period Oct 1975 to Mar 1976, the rate of tonsillitis fell from 20.6% to 4.7%, and GAS throat carriage fell from 31.0% of boys to 7.4%. The rate of reported sore throats fell from 57.3% in the six months (Oct 1972 to Mar 1973) to 3.2% (Jan 1977 to Jun 1977). During the 4 year survey 648 (18%) of the 3,582 of boys who passed through the institution had tonsillitis, and four developed ARF (0.16%).
Colling et al 1980 <sup>330</sup>	A juvenile detention centre in the UK	From Dec 1974, penicillin prophylaxis was initiated. Penicillin PO was given to all boys on entry to the centre, before the throat swab results were known. The rate of tonsillitis fell gradually, reduced to 4.7% in Jan-June 1977. Boys complaining of sore throats fell from 67% to 3.2% during the two years of prophylaxis. 3,582 boys passed through the detention centre during the 5 years of the survey, 18% (648) had tonsillitis, and four (0.6%) had ARF (diagnosed by revised Jones criteria 1965). (Colling et al 1980).
<b>Military Studies</b>		
Schneider et al 1964 <sup>331</sup> (See diagram below)	Loring air force base, Maine, USA	Population 15,625 consisting of: 2,600 children aged up to 5 yrs, 2,100 children elementary school age 6-11 years, 400 children junior high age 12-14 yrs, 325 high school age (15-17 yrs), 3,300 married airmen, 3,300 wives of airmen and 600 bachelor airmen. In 1962 it was noted that a number of patients were presenting with GAS pharyngitis, with one single type of GAS predominating (type 12). Between Jan to Apr 1962, 79 officers, 282 airmen, and 1077 dependents (family members) presented with clinical signs and symptoms of respiratory tract disease and with a culture of GAS. In addition 2,299 GAS positive throat cultures were obtained from contacts or from patients who did not have clinical information provided on the laboratory slip. Carrier surveys were undertaken in the third weeks of October 1962 and January 1963 and the first week of March 1963. The carrier rate had been found to be increasing from 15 to 20%. Initially all GAS positive throat cultures led to everyone at home or in the barrack room being throat swabbed and all GAS positive cultures treated, regardless of symptoms. However this did not control GAS. The dependent population was thought to be the greatest reservoir of infection. A voluntary prophylaxis regime was instituted for children aged 2-11 years and for bachelor air personnel. Children under 5 years received 600,000 IU of benzathine penicillin IM and persons aged over 5 years received 1.2 mega units IU of benzathine penicillin IM. Erythromycin was given to those allergic to penicillin; 40 mg/per kg per day. Altogether 2,200 (55%) of children aged 2-11 were treated and 2,106 (81 %) of the bachelor air personnel. There were two cases of ARF on the base in 1963 (one wife, one child) and one case of glomerulonephritis in 1962 (one child). After the mass antibiotic treatment there was a 'tenfold decrease' in the 'attack rates of streptococcal pharyngitis in military and dependent personnel'
Centre for Disease Control 1988 <sup>332</sup>	Naval Training Centre in San Diego	Prophylactic treatment of all naval recruits. Mass penicillin prophylaxis of all new recruits occurred for about 15 years but was discontinued due to perceived lack of need. In seven months (Dec 1986-Jul 1987), there were ten cases of ARF, the first since the mid-1960s. The attack rate for ARF was 0.75 per 100,000 recruits from Jan 1 1982 to December 1 1986. In 1986 it was 80 per 100,000. Prophylaxis was reinstated.
Heggie et al 1992 <sup>333</sup>		US navy recruits were treated with benzathine penicillin prophylaxis. Penicillin-allergic Navy and Marine Corp patients were given erythromycin. Throat cultures were taken from approximately 230 men before training and at two, four and seven weeks after prophylaxis and from men with pharyngitis diagnosed. The GAS pharyngitis rate was three to four times lower after prophylaxis. There were no cases of ARF diagnosed.

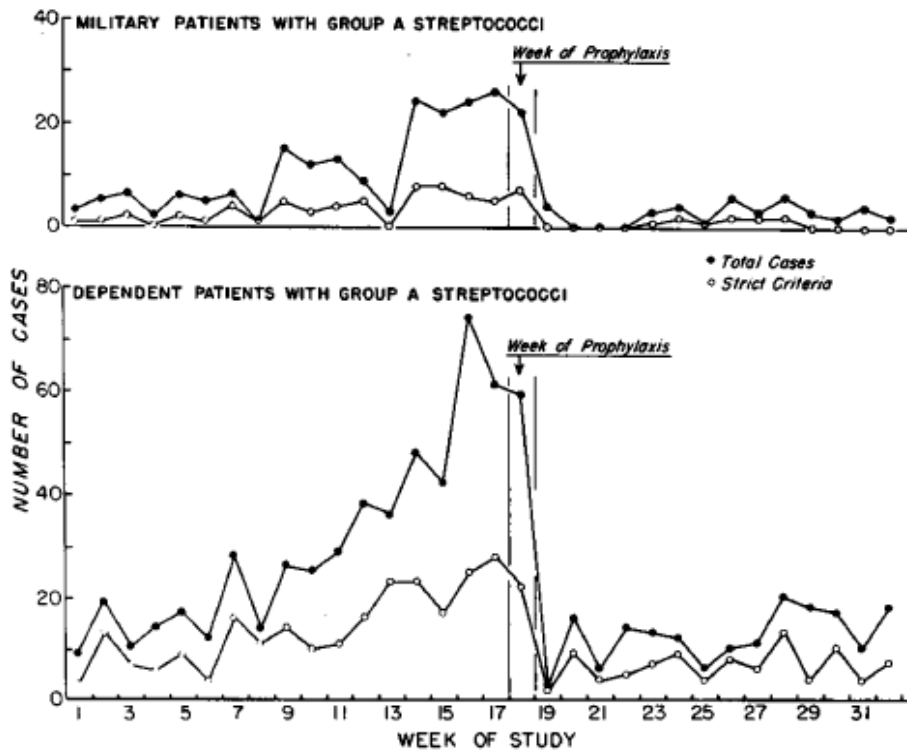
Gray et al 1991 <sup>334</sup>		US marine recruits (93%) received prophylaxis with two IM injections of 1.2 MU of penicillin G benzathine (administered 30-39 days apart) and 42% had GAS infection (defined as a two dilution rise in ASO titre). 7% of recruits were allergic to penicillin and received no prophylaxis; they were more likely to be colonised with GAS. After the study was completed, the penicillin-allergic recruits were given courses of erythromycin 250mg bd for 60 days, and the average weekly rate of clinically evident GAS pharyngitis fell by more than 75%. They also found that penicillin allergic recruits should be treated in this setting as they could be disease reservoir.
Gunzenhauser et al 1995 <sup>195</sup>	US Army basic training installations	Between 1989 to 1991, rapid recurrence of GAS infections occurred after penicillin prophylaxis was discontinued. Mass prophylaxis and tandem treatment of illnesses with benzathine penicillin G were reinstated: Annual admissions for ARF decreased from 1,927 to 690 (-64.2%) after benzathine penicillin G prophylaxis was begun and admissions with throat cultures positive for <i>Streptococcus pyogenes</i> fell from 595 to 63 (-89.4%).
Crum et al 2005 <sup>306</sup>		A total of 162 of 4,500 US Marine Corps personnel were hospitalized for respiratory symptoms between 1 Nov and 20 Dec 2002, with 127 (78%) having radiographically confirmed pneumonia. 34/127 (27%) with pneumonitis had definite or probable GAS pneumonia; 22/127 (17.3%) were coinfecting with GAS and another pathogen. Recruits and staff were screened (4,500 persons), pharyngeal GAS carriage rate of 17% among camp personnel. The GAS isolates were the same <i>emm</i> type. Antibiotic prophylaxis with a single dose of IM benzathine penicillin (1.2 million U) or azithromycin (1 g orally) was given. The outbreak of pneumonia ended on 20 Dec 2002. One week later, the rate of pharyngeal carriage of GAS was 2.2%, compared with the rate of 16% noted on 15 Dec. The BPG dosing schedule (for prophylactic injections given to new recruits) was subsequently switched to every 21 days (for a total of 3 injections) instead of two injections at days 0 and 28–35 of training.
<b>US Indian Reservation</b>		
Atha et al 1982 <sup>335</sup>	Indian reservation school clinics in Arizona	8 Indian reservation schools had monthly surveillance, and all positive GAS throat culture patients were screened again after the initial culture. A drop in ARF was found. Before the trial, in 1970-71 there were 9.5 per 10,000 new cases of ARF. After the study began, 1980-81 was the third consecutive year without a new case of ARF.
Coulehan et al 1982 <sup>336</sup>	Navajo reservation US	A Navajo reservation setting where screening for red throats took place. In the intervention schools GAS positive throat swabs were treated, resulting in a reduction of ARF in clinic schools
Reinstein 1955 <sup>337</sup>	US Indian community, Red Lake Minnesota USA	Mass antibiotic prophylaxis of a community was undertaken to reduce GAS, after a glomerulonephritis outbreak. This was also a remote US Indian community. Benzathine penicillin IM was administered to children under 15 years (600,000 units) and 1.2 mU to children and adults over 15 years. Over 70 per cent of the population of 1997 people agreed to the antibiotics, and of those nearly 500 people had nose and throat cultures taken. GAS was cultured from 10.8% of the 500 samples. One month later 381 people (of the 500) had repeat nose and throat cultures taken, 0.3% of the 381 cultured GAS
<b>Alaskan Villages</b>		
Bender et al 1972 <sup>338</sup>	Eskimo villages, Alaska	2 remote Eskimo villages, in Jan-May 1971, Nunapitchuk had 332 persons (129 school aged children); while the other village, Stebbins, had 239 persons (61 elementary school aged children). In the intervention Village (Nuna-Pitchuk): All patients positive for GAS were treated with either long acting penicillin or erythromycin. There were no cases of ARF in either village. One case of glomerulonephritis was found in Nunapitchuk. The authors postulate that if ARF frequency is assumed to be 3% for a streptococcal epidemic, then treating the GAS positives, together with the mass prophylaxis campaign, may have prevented several cases of ARF.
Brandt et al 1986 <sup>339</sup>	Alaska	Alaskan villages: 2,500 people in intervention villages. 2,350 in control villages. In intervention villages: cultures for sore throats were taken. Screening took place also (in the high intensity arms of study). GAS positives received IM penicillin. Some 0/2,500 cases of ARF between 1972-76. Control villages: 4/2,350 cases of ARF between 1972-76. Small numbers of cases of ARF and participants
<b>Schools &amp; Children's Homes</b>		
Jackson 1976 <sup>340</sup>		In Colorado there was some reduction in GAS with certain school sore throat protocols. The intervention had four protocols and four different school programmes: 1) Swabs taken daily from children with sore throats 2) Each week, all children inspected and throat cultures taken from those with signs of pharyngitis 3) Specimens from all students were cultured once per month 4) Specimens from all students were cultured once per month, but the students with GAS positive cultures were excluded from school until they began antibiotics.

		He found that schools using protocol (1) and (4) had a substantial reduction in streptococcal prevalence ( $p < 0.01$ ).
Wehrle et al 1957 <sup>341</sup>	Children's home, Syracuse New York	Outbreak of GAS diseases including scarlet fever. Cultures of 144 children and carers. Overall 34% (49/144 cultured GAS) 5-9 year olds, 31/56 (55%) cultured GAS, for 10 -14 year olds 16/73 (22%) cultured GAS, 15 – 19 none of 4 cultured GAS, 11 persons aged 20 + had 2/11 (18%) culture GAS. A prophylactic regime of penicillin IM and po (V and G) was instituted.
Jordan et al 2007 <sup>342</sup>	Long-term care facilities	Literature review of GAS infection outbreaks in long term care facilities. There were instances where all residents were treated with antibiotics in 5 investigations and 2 outbreaks. In 12 studies which tested staff nine studies found staff were carriers. GAS transmission was curtailed but the authors concluded 'Mass antibiotic prophylaxis may decrease carriage of the outbreak strain and interrupt transmission but is costly, and potential adverse reactions to antibiotics are a concern.'

## Appendix 18: Mass Antibiotic Prophylaxis (Including Carriers) Leading to Reduced GAS Illnesses

The arrow on the diagram indicates when prophylaxis with antibiotics was commenced. The rate of GAS illnesses decreased immediately and dramatically.

**Figure 3. Number of Military and Dependent Patients per Week from Whom Group A Hemolytic Streptococci Were Isolated**



**Source:** From Schneider WF et al. Prevention of streptococcal pharyngitis among military personnel and their civilian dependents by mass prophylaxis. *N Engl J Med.* 1964; 270: 1205-1212.<sup>331</sup> Copyright © 2014 Massachusetts Medical Society, Reprinted with permission from Massachusetts Medical Society.

## Appendix 19: Statistics for Clinical Questions No. 8, 9 and 10

Del Mar et al Cochrane review: 27 studies which compared antibiotics against controls in pharyngitis, 18 double-blinded, 3-single blinded. Most of the studies were in adults. Further details on quality of studies can be found in the review.<sup>165</sup>

**Table 24. Statistics for Clinical Questions (No. 8, 9 and 10) Treatment and Symptoms of Pharyngitis, Treatment and Suppurative and Non-suppurative Sequelae**

Outcome	Intervention	No. of RCTs	No. of Pts in Treatment Arm	No. of Pts in Control Arm	Outcome in Treatment Arm	Outcome in Control Arm	OR	p Value	95% CI
Symptom of sore throat pain on day 3 in patients with pharyngitis and GAS positive throat swabs	<b>Treatment arm:</b> given antibiotics. <b>Control arm:</b> not given antibiotics. 9 RCTs gave placebos	11	1,073	766	471/1,073	544/766	0.28	p <0.00001	0.23-0.34
Symptom of sore throat pain at one week (day 6-8) in patients with pharyngitis and GAS positive throat swabs	<b>Treatment arm:</b> given antibiotics. <b>Control arm:</b> not given antibiotics, 5 RCTs gave placebos	6	650	467	22/650	57/467	0.23	p <0.00001	0.14-0.37
Symptom of sore throat pain at day 3, in patients with pharyngitis and GAS negative throat swabs	<b>Treatment arm:</b> given antibiotics. <b>Control arm:</b> not given antibiotics, all given placebos	6	458	278	262/458	202/278	0.48	p <0.0001	0.35-0.67
Symptom of sore throat pain at one week (6-8) in patients with pharyngitis and GAS negative throat swabs	<b>Treatment arm:</b> given antibiotics. <b>Control arm:</b> not given antibiotics, all given placebos	5	315	226	42/315	43/226	0.67	p=0.12	0.40-1.11
Treatment of pharyngitis with antibiotics and outcome of acute otitis media (by clinical diagnosis) within 14 days	<b>Treatment arm:</b> given antibiotics. <b>Control arm:</b> not given antibiotics, 9 trials used placebos	11	2,325	1,435	11/2,325	28/1,435	0.23	p <0.0001	0.12-0.44



Treatment of pharyngitis with antibiotics and outcome of quinsy (by clinical diagnosis) within 2 months	<b>Treatment arm:</b> given antibiotics <b>Control arm:</b> not given antibiotics, 6 trials gave placebos	8	1,438	995	2/1,438	23/995	0.16	p<0.0001	0.07-0.35
Treatment of pharyngitis with antibiotics and outcome of acute post streptococcal glomerulonephritis within 1 month	<b>Treatment arm:</b> given antibiotics. <b>Control arm:</b> not given antibiotics, 5 studies used placebos	10	2,927	2,220	0/2,927	2/2,220	0.07	p=0.08	0.00-1.32
Treatment of pharyngitis with antibiotics and outcome of acute rheumatic fever within 2 months	<b>Treatment arm:</b> given antibiotics. <b>Control arm:</b> not given antibiotics, 8 trials used placebos, 6 trials had no placebos	14	4,332	3,843	22/4,332	84/3,843	0.27	p <0.00001	0.18-0.41

**Source:** Data adapted from Del Mar Cochrane review. Del Mar CB et al. Antibiotics for sore throat. (Systematic Review). Cochrane Database Syst Rev. 2006; 1-43<sup>165</sup>

## Appendix 20: Studies on Duration of Positive GAS Throat Cultures at 1-2 Days Post Commencement of Antibiotics

This table includes studies which had varying lengths of antibiotics regimens. All proven to have GAS on culture and sore throat/evidence of pharyngitis

**Table 25. Duration of Positive GAS Throat Cultures at 1-2 Days Post Commencement of Antibiotics (includes All Studies of Varying Antibiotic Regimens)**

Study	Setting	No. of Pts	Medication Given	% GAS Positive at 18-24 Hours Post AB Commencement	% GAS Positive at Approx. 2 Days Post AB Commencement	Evidence of Adherence to Antibiotics
Brink W et al. 1951 <sup>180</sup>	Military recruits, Army base hospital. RCT includes 198 control pts who did not receive antibiotics	80	Aureomycin 1g stat, 0.5g four hourly for 24 hours, then 0.25g four hourly for next 3 days.	-	At 48 hours: 70% (56/80)	Hospital inpatients
Brink W et al. 1951 <sup>180</sup>	Military recruits, Army base hospital. RCT includes 198 control pts who did not receive antibiotics	197	Procaine penicillin G 300,000 U IM on admission, 300,000 U IM at 48 hours and 600,000 U IM at 96 hours	14.2% (28/197)	At 48 hours: 3.1% (6/197)	Hospital inpatients
Edmond E et al. 1966 <sup>181</sup>	Children admitted to children's home in North Carolina, USA. Ages 7-18, average 12.4 yrs. RCT - pts chosen for antibiotic regime alternately	37	Phenoxymethylpenicillin 375mg PO -125mg given 3x a day for 7 days	At 18-24 hours: 22% (8/37)	At 42-48 hours: 0% (0/37)	No
Edmond E et al. 1966 <sup>181</sup>	Children admitted to children's home in North Carolina, USA. Ages 7-18, average 12.4 yrs. RCT - pts chosen for antibiotic regime alternately	40	Penicillin G 375mg PO -125mg given 3x a day	At 18-24 hours: 20% (8/40)	At 42-48 hours: 8% (3/40)	No
Randolph M et al. 1985 <sup>182</sup>	Pts seen in private paediatric clinic in Connecticut, USA. RCT.	68	Penicillin V 250mg/5ml PO for 3 doses	At 18-24 hours: 3% (2/68)		Urine, history, unused medicines checked.
Randolph M et al. 1985 <sup>182</sup>	Pts seen in private paediatric clinic in Connecticut, USA. RCT.	70	Cefadroxil 250mg/ 5ml PO for 3 doses	At 18-24 hours: 3% (2/70)	-	Urine, history, unused medicines checked.
Randolph M et al. 1985 <sup>182</sup>	Pts seen in private paediatric clinic in Connecticut, USA. RCT.	56	Placebo syrup PO	At 18-24 hours: 100% (56/56)	-	-
Krober M et al. 1985 <sup>183</sup>	26 pts from Hawaii & Washington who presented to paediatric practices. RCT.	11	Penicillin V 250mg PO for 3 doses	At 24 hours: 0% (0/11)	At 48 hours: 0% (0/11)	Urine.
Krober M et al. 1985 <sup>183</sup>	26 pts from Hawaii & Washington who presented to paediatric practices. RCT.	15	Placebo syrup PO	'nearly all' still GAS positive at 24, hrs post AB commencement	'nearly all' still GAS positive at 48 hrs (& 72 hrs)	-
Gerber M et al. 1986 <sup>184</sup>	195 children presenting to private paediatric practice in Connecticut, USA. RCT.	96	Cefadroxil 30mg/kg PO od	0% (0/96)	-	urine
Gerber M et al. 1986 <sup>184</sup>	195 children presenting to private paediatric practice in Connecticut, USA. RCT.	99	Penicillin V 250mg PO tds	2% (2/99)	-	urine

Gerber M, Randolph M. 1987 <sup>130</sup>	Pts presenting to private paediatric practice in Connecticut, USA. No randomisation.	188	Penicillin V PO (dose not specified)	At 18-24 hours: 9/155 GAS + on throat culture or rapid test. Intention to treat: 4.8% (9/188)(2 on both, 4 on culture alone, 9 on rapid test alone)	-	no
Gerber M et al. 1989 <sup>23</sup>	Pts with GAS pharyngitis presenting to private paediatric practice, Connecticut, USA. RCT.	76	Penicillin V 250mg PO tds	5.3% (4/76)	-	Urine
Gerber M et al. 1989 <sup>23</sup>	Pts with GAS pharyngitis presenting to private paediatric practice, Connecticut, USA. RCT.	74	Penicillin V 750mg PO od	At 18-24 hours: 5.4% (4/74) (these 4 pts then removed and rx with tds penicillin)	-	Urine
Snellman L et al. 1993 <sup>185</sup>	Pts at paediatric outpatient clinic, Minnesota, USA. RCT.	17	Penicillin V 250mg PO tds	Next morning: 29.4% (5/17) [22.2% if Abs began before 1pm on day one]	-	Directly observed therapy for first dose (given in the office) & 3 times in next 24 hrs (nurse visit) for most pts.
Snellman L et al. 1993 <sup>185</sup>	Pts at paediatric outpatient clinic, Minnesota, USA. RCT.	15	Erythromycin estolate 250mg PO tds	Next morning: 53.3% (8/15) [55.6% if Abs began before 1 pm on day one]	-	Directly observed therapy for first dose (given in the office) & 3 times in next 24 hrs (nurse visit) for most pts
Snellman L et al. 1993 <sup>185</sup>	Pts at paediatric outpatient clinic, Minnesota USA. RCT.	15	Benzathine penicillin G IM (6000,000 U if under 60 pounds weight, 1.2 mU if over 60 pounds)	Next morning: 26.7% (4/15) [22.2% if Abs began before 1 pm on day one]	-	N/A
Shvartzman P et al. 1993 <sup>71</sup>	5 family medical practices. Drs in Israel. Adults & children. RCT.	82	Phenoxymethylpenicillin 250mg PO tds or qid	-	At 24-48 hours: 7.3% (6/82)	Telephone interview & 'during the follow up visits'.
Shvartzman P et al. 1993 <sup>71</sup>	5 family medical practices. Drs in Israel. Adults & children. RCT.	75	Amoxicillin PO od (children 50mg/kg and adults 750mg for 10 days)	-	At 24-48 hours: 4% (3/75)	Telephone interview & 'during the follow up visits'.
Feder J et al. 1999 <sup>72</sup>	Pts presenting to private paediatric clinic, Connecticut, USA. RCT.	79	Amoxicillin 750mg PO od	0% (0/79)	-	Urine
Feder J et al. 1999 <sup>72</sup>	Pts presenting to private paediatric clinic, Connecticut, USA. RCT.	73	Penicillin V 250mg PO tds	1.4% (1/73)	-	Urine
Brook I. 2009 <sup>186</sup>	50 children in an acute care clinic, Washington DC, USA.	25	Amoxicillin (40mg/kg od) or 250mg PO tds	80% (20/25)	After 2 days: 56% (14/25)	Check off dosage card & inspection of medicine bottles.
Brook I. 2009 <sup>186</sup>	50 children in an acute care clinic, Washington DC, USA.	25	Cefdinir (14mg/kg or 600mg PO od)	64% (16/25)	After 2 days: 32% (8/25)	Check off dosage card & inspection of medicine bottles.
Total of antibiotic pts positive [excluding placebo syrup pts]				At 18-24 hours: 10.04% (121/1205)	At 24-48 hours: 16.8% (96/572)	

## Appendix 21: Evidence Review for School and Work Exclusion

The following evidence review is adapted from the Discussion Document the Advisory Group used in considering recommendations on this topic.

### Clinical Question

**How long should patients be excluded from education (daycare/school) or work after starting antibiotics for group A streptococcal throat infections?**

### Introduction

The current guideline (2008) recommends isolating children from school/daycare for 24 hours after antibiotics have begun.

### Evidence Level

RCTs & experimental trials.

### Issues

1. How long should we recommend exclusion from food handling if GAS positive?
2. Mel to feedback on recent advice from Stan Shulman (IDSA guidelines).
3. Unable to locate key article by Lampe (1985).

### Search Strategy

References obtained from Professor Diana Lennon's records including unpublished Eurosurveillance article peer-reviewed by Professor Lennon.

References from within articles were followed up.

The end point of a throat swab taken at 24-48 hours after commencing antibiotics was sought, to assess bacterial eradication. Only studies which mentioned a throat swab taken at up to 48 hours were included in the analysis. Time constraints did not allow all studies relating to GAS and antibiotics, to be searched for and reviewed for 24-48 hour throat swabs, so data used in this analysis may be incomplete.

Cochrane reviews relating to 'sore throat' were assessed, 3 relevant titles (van Driel et al 2013, Spinks et al 2006, Altamimi et al 2012) were found and reviewed for descriptions of studies which may be relevant.<sup>97,343,344</sup> One study by Lampe (1985) was not able to be located.

Medline search conducted. Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R): 1946 to present.

Search date: 26 November 2012

#	Searches	Results
1	Streptococcus pyogenes	10,910
2	Pharyngitis	6,421
3	Anti-Bacterial Agents	220,528
4	1 and 2 and 3	372
5	<a href="#">effectiveness.mp.</a>	241,216
6	Disease Eradication	159
7	4 and 5	12

### Discussion

For patients with group A streptococcus cultured on throat swab, after antibiotics were commenced, Brink (1951) found that throat cultures became negative after two days of penicillin treatment and five days for patients who did not take antibiotics.<sup>180</sup>

Assessing all antibiotic studies with throat swabs taken at 24-48 hours post antibiotics, 11 studies were found. When all antibiotics results were combined, at 24 hours, the majority of throat cultures were negative (90%), and at 24-48 hours, 83% were negative (Table 25). In contrast, in two studies

which assessed patients taking placebo medications, most of those patients were reported to still have GAS cultured/still have positive throat cultures at 24-48 hours after commencing placebos.

#### **For oral medications**

At 24 hours after commencing oral amoxicillin (a variety of regimes were taken), 80% of throat cultures became negative for GAS, and at 24-48 hours, 85% of patient's throat cultures were negative.

For penicillin V, 94% of throat cultures were negative 24 hours after starting antibiotics, and at 24-48 hours, 91% of throat cultures were negative for GAS. In one study involving erythromycin, just under half (7/15 patients) had negative throat cultures for GAS at 24 hours, but the study numbers were very small.

#### **For intramuscular medications**

For injected penicillin, 84% of throat cultures were negative for GAS at 24 hours and at 24-48 hours, 97% of throat cultures were negative.

#### **Limitations**

Limitations of this analysis include: some studies may not have been located, the study numbers are small (particularly for erythromycin), not all studies assessed antibiotic compliance and varying treatment regimens were combined which may not be a meaningful.

#### **New Zealand legislation**

Legislation requires school pupils and teachers with streptococcal sore throat to be isolated for 7 days from the onset of the disease, '*or for such lesser period as the Medical Officer of Health shall determine*' (Health (Infectious and Notifiable Diseases) Regulations 1966).<sup>6</sup>

#### **Contacts and carriers of infectious diseases including streptococcal sore throat:**

Contacts of GAS sore throat are not to '*engage in the manufacture, preparation, handling, or sale of any food (including milk, cream, or ice cream) until he has been proved by microbiological examination, in the case of a disease other than hepatitis A, hepatitis B, or hepatitis non A or B, to be free of infection or has been permitted to do so by the Medical Officer of Health.*'

No carrier of GAS sore throat '*shall engage in the preparation, manufacture, or handling of any food for sale, nor shall he engage himself or be employed in any capacity in which in the opinion of the Medical officer of health he may cause or spread any such disease.*' (Health (Infectious and Notifiable Diseases) Regulations 1966)<sup>6</sup>

## Appendix 22: Evidence Review for GAS Spread

The following evidence review is adapted from the Discussion Document the Advisory Group used in considering recommendations on this topic.

### Clinical Question

#### Who is at risk of spreading group A streptococcal sore throat?

### Introduction

Group A streptococcus is spread through droplets<sup>189</sup> of saliva or nasal secretions, as well as in water<sup>190</sup> and food preparation.<sup>191</sup>

Nasal GAS infection has also been implicated by Hamburger et al (1945), Jarrett et al (1950).<sup>156,192</sup>

### Evidence

Evidence for consideration by the Scientific Advisory Group:

1. This document which includes a literature review, the Health (Infectious and Notifiable) Diseases Regulation 1966<sup>6</sup> and excerpts from the American Academy of Pediatrics 'Red Book'<sup>3</sup>
2. Question 4. 'Which factors lead to the spread of GAS pharyngitis?' In 2008 Sore Throat Management Guideline<sup>1</sup> (included at end of this document)
3. GAS Spread (household) literature review from Brigid O'Brien's MPH dissertation<sup>246</sup>

### Issues

When considering GAS pharyngitis, studies have not all looked at the same start or end points. i.e. whether the index case was a symptomatic GAS pharyngitis or an asymptomatic carrier of GAS in the throat and whether the infected persons became symptomatic of GAS pharyngitis or asymptomatic carriers.

GAS spread can cause other conditions such as invasive disease pneumonia, carriage etc. which is reflected in the vast number of articles and studies on this topic.

Time constraints do not allow for this topic to be fully reviewed with a Medline search. For the purposes of considering recommendations on GAS spread management, studies on several different types of GAS spread were considered and reviewed as follows.

### Discussion

GAS spread has been demonstrated to occur in a variety of settings, including households, military barracks, classrooms, day care, hospitals and residential care.

Nasal spread has been implicated in studies by Jarrett et al (1950).<sup>192</sup>

### Households

Further to the evidence documented in [Question 20](#) in the 2008 Group A Streptococcal Sore Throat Management Guideline (NHF 2008), Danchin et al (2007) studied 202 families and found of those who had a primary case of GAS pharyngitis, 43% had at least one secondary case (18 of 42).<sup>1,7</sup> Where emm typing was able to be performed, 25 out of 26 were the same emm type as the index case of GAS. In family households, more than half of the secondary cases of serologically proven GAS pharyngitis were in 5-12 year old children. Within households, the risk of secondary GAS infection was 1.8 times greater than that of primary infection in the community.<sup>7</sup>

In a schoolroom outbreak of scarlet fever, in 1943-44, 43 out of 78 (55%) of family contacts cultured GAS of the same serotypes as the index case in their nose or mouth.<sup>193</sup>

Brigid O'Brien reviewed household spread in her dissertation; *Household Contact Tracing for Acute Rheumatic Fever: A review of the literature and case series*.<sup>246</sup> See [Appendix 14](#). She concluded from the literature 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.<sup>153,218</sup> 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).<sup>22,153,218,345</sup>

Breese & Disney (1956) found a greater spread of GAS in households if the primary case was not treated within two days.<sup>230</sup>

See [Appendix 14](#) for summary of studies of secondary attack rate of pharyngeal GAS acquisition and infection in households.

### Military Barracks

Historically the crowding of troops has led to high rates of GAS pharyngitis and ARF. In the pre penicillin era, rates were particularly high.<sup>189</sup> Comparative rates of ARF in military campaigns, from the mid-1800s to World War I, were documented by Glover (1930):

**Table 26. Acute Rheumatism in Modern Campaigns, 1930**

	Average annual incidence per 1,000 strength	Acute rheumatism admissions as a percentage of all non-battle admissions	Death-rate per 1,000 strength	Case mortality %
Crimea—				
(British), 1854–6 ..	24.5	3.2	1.16	4.7
American Civil, 1861–4—				
Union Army (Whites) ..	65.3*	4.7	0.20	0.44
Confederate .. ..	90*	3.6	—	4.0†
South African—				
(British), 1899–1902 ..	44	6.05	0.04	0.1
B E.F. France, 1915 ..	35	3.9	0.03	0.1
Dardanelles—				
(British), 1915 .. ..	56	4.5	0.15	0.26
Italy, 1918				
(British) Forward Area	0.27	0.07	—	—
Troops in U.K., 1914–18	2.42	0.84	—	—
British Army—				
All areas, 1917–19 ..	—	0.32	—	—
U.S. Army in U.S. and France, 1917–19 ..	2.14	—	0.01	0.18

\* Much inflated with cases of muscular rheumatism, etc.

† Based on 1,984 cases in Richmond (Van.) (Chimborazo Hospital).

**Source:** Reprinted from the Lancet: Glover J. Lecture 1. The incidence of acute rheumatism. Lancet. 1930; 215: 499-505.<sup>189</sup> Copyright 2014 with permission from Elsevier.

In the South African War (1899-1900) almost as many people were admitted to hospital with ARF (24,460) as were killed or wounded (27,273 people).<sup>189</sup> In 1918, during World War 1, the US Navy noted amongst its troops, 1,214 cases of scarlet fever and 772 cases of ARF, mostly among recruits;<sup>346</sup> while the Army in 1917-19 had rates of ARF 2.14 per 1000 soldiers.<sup>189</sup>

The rate of spread of GAS disease within barracks was also documented by Glover (1930).<sup>189</sup> Between Feb-Dec 1928 in an air force barrack containing 3,530 trainees, there were 427 cases of tonsillitis (175 per 1000), and 41 cases of acute rheumatism. In one year in a US Naval training facility with an average population of 43,000, there were 4,973 cases of scarlet fever, 50,000 cases of tonsillitis or pharyngitis and 1,375 cases of rheumatic fever.<sup>347</sup>

In the US army a known GAS carrier (positive nose and throat specimens) was placed in his first barracks. Within four weeks, nine men from this barrack had developed respiratory disease with GAS positive throat swabs and 13 had become GAS carriers (in the throat). All of the same serotype GAS. The carrier was transferred to his second barracks, and in the first two weeks there, another four people developed GAS positive sore throats and 9 became asymptomatic carriers.<sup>194</sup>

Jarrett et al (1950) documented the spread of GAS in two US naval regiments over two months in the winter of 1947-48. The same serotype of GAS spread in two Companies. Company A (117 men), had six GAS sore throats on admission (two on carrier survey), and the following month there were an additional 11 cases of GAS pharyngitis (eight of these men had positive nose cultures also) and 28 GAS throat carriers. In the second barracks (Company B) three weeks after they all entered the barracks, there were 15 cases of GAS pharyngitis (10 the same serotype as Company A's) and 30 men were noted to be throat carriers of the same serotype GAS.<sup>192</sup>

When penicillin became available, many military facilities developed regimes of prophylactic antibiotics for new entrants. Since the 1950s, many US military training facilities have had a policy in



place of prophylactic antibiotics for the Navy and Marine Corps Recruit Camps, summarized by Thomas.<sup>346</sup> The US army has had a surveillance programme for respiratory diseases including GAS since the 1960s, and some but not all facilities have had prophylactic antibiotics for new entrants.<sup>160</sup> When prophylactic antibiotic regimes have been lifted for new recruits, GAS illnesses have quickly recurred -within two months in a study by Gunzenhauser (1995).<sup>195</sup> Fort Leonard Wood in the USA, had routine benzathine penicillin G prophylaxis for recruits following a case of ARF.<sup>195</sup> In July 1989, after two trouble free years the decision was made to discontinue the prophylactic antibiotics, a GAS outbreak occurred two months later. By early Jan 1990 there were 'high' rates of GAS pharyngitis, four cases of peritonsillar abscess, two cases of sinusitis and two cases of ARF at Fort Leonard Wood.<sup>195</sup>

Whilst GAS pharyngitis and ARF have not been documented in the military setting in New Zealand, this evidence is still likely to be relevant in hostel type accommodation e.g. boarding schools and university.

### **Bed Distances**

Glover (1928) thought sleeping was important in terms of risk for catching droplet spread diseases because people sometimes have their mouths open when sleeping, allowing diseases in.<sup>273</sup> Clinicians in the early 1930s debated whether they should encourage people to sleep under a sheet to reduce the risk of developing a droplet spread infection.<sup>348</sup>

Sleeping in the same bed was thought to be a causative factor for ARF by Glover (1930).<sup>189</sup> In an epidemiological study, close bed distances in military barracks were associated with higher rates of ARF, and spacing beds apart by 2.5 feet reduced the rate of ARF.<sup>189</sup> Hare (1943) considered that 'The use of double tiered bunk beds is unsound', as he was concerned about bedding potentially transmitting GAS and 'the more men there are to each room the greater chance there is that one will be a carrier and so transmit infection to his room mates'.<sup>312</sup>

### **Classrooms**

Clusters of classroom GAS pharyngitis are well documented in South Auckland sore throat clinic initiatives.<sup>50</sup> Recently, related to a new case of ARF, four children in the same classroom as the rheumatic fever case were GAS positive (on throat swab). (personal comms, Liddel 2013).

A streptococcal scarlet fever outbreak occurred in six USA school rooms in 1943-44. This included 53 cases of scarlet fever and four sore throats, among the 225 children.<sup>193</sup> In four classrooms one single type of GAS was cultured, in the other two rooms there were two types of GAS cultured. Family contacts of the 53 were swabbed, 53 out of 78 also had the same serotype of GAS as the strain causing the illness in the classroom, there were also 19 secondary scarlet fever cases among the families.

Over 32 terms at the Royal Naval School at Greenwich, Dudley's study found 423 cases of scarlet fever in 1000 boarders at the Royal Naval School at Greenwich, but no cases in the 100 day attending boys.<sup>312</sup>

Four consecutive GAS pharyngitis outbreaks of different M types occurred in an English boy's school over a seven month period (1983-84).<sup>196</sup> Of 95 students, 37 developed GAS pharyngitis (39%). Boarders were again more affected (18 out of 38; 47%) than day attending boys (4 out of 25; 16%). Two asymptomatic carriers were found when the whole school was swabbed.<sup>196</sup>

### **Daycare**

Several studies have documented the spread of GAS pharyngitis and carriage in the daycare setting, these are summarised by Falck (1992).<sup>315</sup>

In a Swedish daycare centre, two weeks after an index case of GAS pharyngitis, all children were examined and throat cultures taken. Out of 31 children (two classes), five children had verified GAS and were already taking antibiotics, 14 children had the same GAS serotype as the index case and two teachers had sore throats and the same GAS type. A temporary kitchen hand reported having had a sore throat the week before, and was also found to be GAS positive. Subsequently, 20-30% of the children remained streptococcal carriers.<sup>315</sup>

Over 18 months (1984-1985) Holmstrom (1990) documented outbreaks in seven day cares in a region of Sweden, of Erythromycin-resistant group A streptococci (ERGAS).<sup>197</sup> Of the 294 isolates of ERGAS found during the outbreaks; 277 were the same serotype of GAS. 112 out of 230 (49%) children had positive throat cultures for ERGAS. The number of infected children in each daycare

varied between 37-88% (as per table below):

Among the infected children, 30 out of 112 were symptomatic (27%). Symptoms were mostly 'tonsillitis/rhinopharyngitis with variable temperature'. Twenty-one children also had GAS which was sensitive to erythromycin. All the daycare staff were throat swabbed and 7 out of 93 (8%) cultured ERGAS, with only one of the seven being symptomatic. Families of the ERGAS cases were swabbed and 23% (37 out of 163) of parents and 36% (22 out of 61) of siblings also cultured ERGAS.<sup>197</sup>

Holmstrom also documented the spread of symptomatic ERGAS from the outbreak (Table 27)

**Table 27. Correlation of Erythromycin-Resistant Group A Streptococci (ERGAS) Infected Day Care Centre (DCC) Children With or Without Symptoms and the Number of Infected Family Members, Total and With Symptoms**

Table III. Correlation of erythromycin-resistant group A streptococci (ERGAS) infected day care centre (DCC) children with and without symptoms and the number of infected family members, total and with symptoms

DCC children with ERGAS	No. of children	ERGAS-infected relatives <sup>a</sup> /exposed (%)	Symptomatic infections <sup>a</sup> /infected relatives (%)
Symptomatic	30	16/56.5 (28)	7.5/16 (47)
Asymptomatic	82	42/167.5 (25)	8.5/42 (20)
Total	112	58/224 (26)	16/58 (28)

<sup>a</sup> 1 parent with 1 symptomatic and 1 asymptomatic DCC child.

**Source:** Holmström L et al. Outbreaks of infections with erythromycin-resistant Group A streptococci in child day care centres. Scand J Infect Dis. 1990; 22: 179-185.<sup>197</sup> Permission to publish copyright material pending.

This showed a forward transmission from symptomatic children, to 16 relatives (28%). Of the relatives, seven went on to be symptomatic (47%). From asymptomatic carriers of ERGAS, 42 relatives were infected (25%), eight with symptomatic infection (20%).

## Food

### Group A Streptococcus:

Levy (2003) has summarized the key studies.<sup>191</sup> See Appendix 24 for key studies.

Attack rates of GAS illness transmitted by food were estimated by Levy at between 10–85%.<sup>191</sup> In the case studies, some of the food handlers who were suspected of spreading GAS, were asymptomatic but had GAS positive throat cultures. Items involving 'significant hand contact during preparation' such as eggs, sandwiches, salads, were implicated in 15 out of 21 studies where a food was pinpointed.<sup>191</sup> Skin lesions were implicated in two studies. Levy considered 'contamination of the hands with respiratory secretions is an important means of infecting the food'.<sup>191</sup> Items involving 'significant hand contact during preparation' (such as eggs, sandwiches, salads) were implicated in 15/21 where a food was pinpointed.<sup>191</sup>

In a case study in Australia, GAS pharyngitis spread in curried egg sandwiches prepared by a prison food handler with infected hand wounds.<sup>191</sup> Over a one month period GAS throat infections occurred in five of 57 inmates with primary cases and four of 15 inmates with secondary cases.

### Group C & G Streptococcus:

Groups C and G have been occasionally cultured from patients throat swabs at the time of the diagnosis of ARF but have not been definitively proven to cause ARF. A number of studies have implicated C and G streptococci spread through infected food or food handlers:

- Group C outbreaks spread in milk causing glomerulonephritis.<sup>349,350</sup>
- Group G pharyngitis outbreaks spread by food handlers.<sup>234,239</sup> In both studies spread was thought to be via egg salad and in another study; via chicken salad.<sup>240</sup>

## Hospital

Hamburger (1945) implicated seven hospital cross infections to patients with GAS cultured from their nose (of the same type). Furthermore a food handler with a runny nose and positive throat, hand and nose GAS cultures who was thought to have infected more than 100 patients with GAS through food handling.<sup>156</sup>

Hamburger also found that GAS cross infections could occur on hospital wards when only one or two GAS carriers were present and that cross infections could be "subclinical".<sup>156</sup>

Ramage (1996) describes a GAS outbreak in a 24-bedded Canadian medical ward, where over eight days three patients developed fatal GAS infections. Among nurses looking after the patients, three subsequently developed GAS pharyngitis, and three others were treated with antibiotics for pharyngitis but did not undergo throat cultures.<sup>199</sup>

Kakis et al (2002) documented the spread of GAS from an index patient to 24 hospital workers, who developed GAS positive throat swabs less than four days after contact. DNA typing showed the same serotype of GAS for 23 out of 24 throat cultures. The index patient had a history of upper respiratory tract illness but minimal posterior pharyngeal infection, and an area of skin blistering which was necrotising dermatitis on biopsy.<sup>200</sup> Four ICU nurses became ill with fever and sore throat on the fourth day of the patient's admission.

## Residential care

Schwartz & Ussery (1992) reviewed the literature and summarised five invasive and five non-invasive GAS infections in USA long term care facilities. Non-invasive disease included upper respiratory tract and skin infections. In three of the non-invasive GAS outbreaks, staff members were implicated but not proven as the sources of infection.<sup>201</sup>

In 2003, an outbreak of GAS pharyngitis and impetigo occurred in a facility for 251 intellectually disabled people in America.<sup>202</sup> Over five months, 52 definite cases of GAS pharyngitis and 15 probable suspected cases were reported. Measures to stop the outbreak included isolating suspected patients while throat cultures were pending, isolating patients with confirmed GAS pharyngitis for 24 hours post starting antibiotics, environmental cleaning and an increased emphasis on hand washing.

## The Health (Infectious and Notifiable Diseases) Regulations 1996, Amended 2013<sup>6</sup>

The Health (Infectious and Notifiable Diseases) Regulations 1996 recommend for streptococcal sore throat a 7 day period of isolation i.e. they should not:

*'...wilfully go outside the limits of the premises in which he resides, except with the permission of the Medical Officer of Health...*

*.... For 7 days from the date of the onset of the disease and until all symptoms have subsided, all abnormal discharges have ceased, and all open lesions have healed'*

This includes school exclusion for streptococcal sore throat for pupils and school teachers:

*'Every child and every school teacher who is suffering from, or is suspected to be suffering from, an infectious disease specified in Schedule 2 shall be excluded from school for the period of isolation shown (See above)'*

For GAS contact and carriers they recommend:

*'No contact of .....streptococcal sore throat (including scarlet fever) shall engage in the manufacture, preparation, handling, or sale of any food (including milk, cream, or ice cream) until he has been proved by microbiological examination, in the case of a disease other than hepatitis A, hepatitis B, or hepatitis non A or B, to be free of infection or has been permitted to do so by the Medical Officer of Health.*

*(2) No carrier of .....streptococcal sore throat (including scarlet fever) shall engage in the preparation, manufacture, or handling of any food for sale, nor shall he engage himself or be employed in any capacity in which in the opinion of the Medical Officer of Health he may cause or spread any such disease'*

Ref: <http://www.legislation.govt.nz/regulation/public/1966/0087/latest/whole.html#DLM24238>

## The American Academy of Pediatric's Red Book 2012<sup>3</sup>

Excerpt from the Red Book:

#### **'ISOLATION OF THE HOSPITALIZED PATIENT**

*In addition to standard precautions, droplet precautions are recommended for children with GAS pharyngitis or pneumonia until 24 hours after initiation of appropriate antimicrobial therapy. For burns with secondary GAS infection and extensive or draining cutaneous infections that cannot be covered or contained adequately by dressings, contact precautions should be used for at least 24 hours after initiation of appropriate therapy.*

#### **CONTROL MEASURES**

*The most important means of controlling GAS disease and its sequelae is prompt identification and treatment of infections.*

**School and Child Care.** *Children with **streptococcal** pharyngitis or skin infections should not return to school or child care until at least 24 hours after beginning appropriate antimicrobial therapy. Close contact with other children during this time should be avoided.*

**Care of Exposed People.** *Contacts of documented cases of GAS infection who have recent or current clinical evidence of a GAS infection should undergo appropriate laboratory tests and should be treated if test results are positive. Rates of GAS carriage are higher among sibling contacts of children with GAS pharyngitis than among parent contacts in nonepidemic settings; rates as high as 50% for sibling contacts and 20% for parent contacts have been reported during epidemics. More than half of contacts who acquire GAS infection become ill. Asymptomatic acquisition of group A streptococci may pose some risk of nonsuppurative complications; studies indicate that as many as one third of patients with ARF had no history of recent **streptococcal** infection and another third had minor respiratory tract symptoms that were not brought to medical attention. However, routine laboratory evaluation of asymptomatic household contacts usually is not indicated except during outbreaks or when contacts are at increased risk of developing sequelae of infection (see Indications for GAS Testing, p 672). In rare circumstances, such as a large family with documented, repeated, intrafamilial transmission resulting in frequent episodes of GAS pharyngitis during a prolonged period, physicians may elect to treat all family members identified by laboratory tests as harboring GAS organisms.'*

## Appendix 23: Summary of Studies of Secondary Attack Rate of Pharyngeal GAS Acquisition and Infection in Households

**Table 28. 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
James et al. (1960) <sup>158</sup>	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%
Breese and Disney (1956) <sup>230</sup>	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%
Matanoski et al. (1968A and 1968B) <sup>351,352</sup>	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 $\geq 9$ 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.
Poku (1979) <sup>231</sup>	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.
Levine et al (1966) <sup>353</sup>	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%.
El Kholly et al (1980) <sup>218</sup>	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.

Falck et al. (1997) <sup>219</sup>	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.
Danchin et al. (2007) <sup>7</sup>	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 symptomatic acquisitions = 5%. 43% of families with an index cases developed ≥ 1 secondary case
Lindbaek et al. (2004) <sup>228</sup>	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
Kikuta et al. (2007) <sup>216</sup>	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

**Source:** O'Brien 2010. Household contact tracing for acute rheumatic fever: A review of the literature and case series. Masters of Public Health Dissertation. 2010. University of Auckland.<sup>246</sup>  
Permission granted.

## Appendix 24: Studies on Foodborne Outbreaks of GAS as Summarised by Levy, 2003

Table 29. Previous Reports of Foodborne Outbreaks of Group A Streptococcal Infection

Reference	Date of outbreak	Location	Setting	No. of cases	Food that was the presumed cause of the outbreak	Status of food handlers	Typing of Streptococcus isolates
[1]	Jul 1941	Massachusetts, US	Church lunch	102	Ham	One of 2 cooks had an early stage of scarlet fever	Griffith 2
[2]	Jun 1942	Western US	Army base	~300	Not identified	—	Griffith 15
[3]	Nov 1942	United Kingdom	Air Force base	89	Tinned milk	Cook in charge of preparation of tinned milk was infected with streptococci	Type 9
[4]	Nov 1943	North Carolina, US	Army base	125	Creamed eggs	No findings despite thorough investigation	M5
[5]	Sep 1951	Northern Germany	Army base	265	Not identified	Thirty cooks; no specific findings	—
[6]	Mar 1952	Cambridge, United Kingdom	Army camp	43	Custard (the "skin")	One of the food handlers had a cough at the time of custard preparation; a throat swab specimen obtained 2 days later had a positive result	Type 9
[7]	Feb 1957	Maryland, US	Charity lunch	500–600	Egg salad	Food handlers had positive results of testing done 6 days after food preparation	Type 25
[8]	Sep 1965	Buffalo, US	University cafeteria	—	Shrimp salad	Three food handlers who prepared the shrimp salad had negative throat swab specimens	Not typed (coinfection with <i>S. flexneri</i> )
[9]	Apr 1968	Colorado, US	Air Force Academy	~1200	Tuna salad that contained boiled eggs	Thirty persons present at the salad preparation; 1 of 6 of those involved in egg preparation was throat swab positive	M-nontypeable, T12
[10]	Jul 1973	Arizona, US	Community picnic—Indian Reservation	255	Potato salad (included sliced eggs) <sup>a</sup>	Four food handlers, 1 of whom had a son with pharyngitis	T3/13/B3264
[11]	Aug 1974	Florida, US	Prison	290	Egg salad sandwich	One of 5 inmates who peeled the eggs had a fever and a sore throat; a throat swab specimen was positive for the outbreak strain	M9, T9
[12]	Apr 1975	Perm, Russia	—	185	Sour cream	—	—
[13]	1976	Ashdod, Israel	Factory	447	Egg salad	—	M-nontypeable, T12
[14]	May 1980	Israel	Military base	41	Boiled egg salad	One of the kitchen workers had tonsillitis 3 days before the outbreak; he and 5 other kitchen workers were positive for the outbreak strain	M3
[15]	May 1981	Oregon, US	Microbiology conference	~300	No specific food identified	Four of 10 food handlers had positive throat swabs, and 3 had skin lesion swabs positive for group A streptococcus	M-nontypeable, T9, SOR <sup>a</sup>
[16]	Jul 1982	New Hampshire, US	Private party	34	—	A food handler, who was asymptomatic, had a positive throat swab; a household contact had acute pharyngitis shortly before the party	M-nontypeable, T12, SOR <sup>a</sup>
[17]	Nov 1983	Tennessee, US	Charity luncheon	20	Rice dressing	Person who had prepared the implicated dish had had pharyngitis 3 weeks earlier and was culture positive at the time of the outbreak	M-nontypeable, T8/25, SOR <sup>a</sup>
[18]	1983	Japan	—	—	—	—	—
[19]	Mar 1984	Missouri, US	Conference luncheon	60	Mousse (most probably) and macaroni salad (less likely)	One food handler reported a sore throat; 5 food handlers had negative throat swabs and no visible hand lesions (8 days later)	—



[20]	Aug 1984	Puerto Rico	Private party	23	Conch salad	Four food handlers had negative throat swab specimens and were asymptomatic	M-nontypeable, T12, SOR <sup>a</sup>
[21]	Jul 1986	Venice, Italy	5 Banquets in the same restaurant	179	Prawn cocktail in banquet 1, squills and custard cake in banquets 2-4, and no identified food in banquet 5 <sup>b</sup>	Six of 18 staff members (5 of whom were from the manager's family) and 3 other children of the manager were positive for epidemic strain	M28, T28
[22]	1988	Turkey	—	58	Bean salad with boiled egg	—	M11, T3/13/B3264
[23]	Jun 1988	Israel	Military bases with a central kitchen	439	No specific food identified	Two of 12 asymptomatic food handlers had throat swab specimens positive for group A streptococcus (not typed)	Probable M29 variant, Tnontypeable
[24]	1989	Russia	—	—	—	—	—
[25]	Apr 1990	Israel	Military base	61	Boiled egg salad, cabbage salad, and probably egg salad	Two of 19 food handlers were symptomatic; both had throat swab specimens positive for the epidemic strain	M-nontypeable, T12
[26]	May 1990	Sweden	Church party	122, including 1 death	Sandwiches, including egg	Six of 7 food handlers had positive throat swab specimens; 5 of these 6 attended the party and ate the food. The one who did not attend the party had nasal symptoms 2 days before the party and peeled eggs the day before the party; a second food handler was symptomatic on the day of the party.	Fifty-one of 58 were T28; 5 of 58 were T28/4; 2 of 58 were autoagglutinin. The strain from the deceased and 4 random specimens were positive for erythrogenic toxins B and C.
[27]	1990	Sweden	—	—	—	—	—
[28]	Feb 1991	Israel	Military base	75	Cabbage salad	Three soldiers were symptomatic before the implicated meal; one was the cook who was throat swab positive for the outbreak strain	M56, T28
[29]	May 1991	Louisiana, US	School banquet	71	Macaroni with cheese sauce	Food handlers had negative throat swab specimens; 1 food handler had a positive result of culture of a hand lesion	M9, T5/9
[30]	1991	Djibouti	Military base	—	—	—	M-nontypeable, T11
[31]	Apr 1992	Israel	Air Force base	197	White cheese	Food handler was asymptomatic but was throat swab positive; he did not taste the cheese and was absent at the time of the outbreak	M-nontypeable, T 8/25/Imp19
[32]	May 1993	—	Military unit	162	Butter	—	T11
[33]	May 1996	Aichi Prefecture, Japan	Sports meeting	244	Boiled eggs, boiled fish paste, fried chicken, and wakame-gohan <sup>c</sup>	—	T1 (PFGE identical)
[34]	1997	Fukuoko Prefecture, Japan	—	—	—	—	—
[35]	1997	Ibaragi Prefecture, Japan	—	—	—	—	—

**NOTE.** *S. flexneri*, *Shigella flexneri*; SOR<sup>a</sup>, serum opacity factor positive; US, United States.

<sup>a</sup> Culture positive for epidemic strain.

<sup>b</sup> A chopping board was also found to be culture positive.

<sup>c</sup> All culture positive.

**Source:** Levy M et al. Tonsillopharyngitis caused by foodborne group A streptococcus: a prison-based outbreak. Clin Infect Dis. 2003; 36: 175-182.<sup>191</sup> By permission of Oxford University Press, 2014.

## Appendix 25: Evidence Review for Role of Tonsillectomy in GAS Sore Throat

The following evidence review is adapted from the Discussion Document the Advisory Group used in considering recommendations on this topic.

### Recommendations:

#### 1. Does tonsillectomy reduce the number of sore throats (from any cause) in patients?

**Children:** For children with severe recurrent tonsillitis, tonsillectomy does offer benefit, by reducing the number of sore throats in the short term.

'Severely affected' children are defined using the Paradise et al (1984) criteria of sore throat frequency: seven or more sore throats per year for one year or five per year for two years or three per year for three years.<sup>209</sup>

For children with fewer sore throats than this, the risks of tonsillectomy may outweigh the benefits. In New Zealand, tonsillectomy is offered to treat severe recurrent tonsillopharyngitis causing significant disruption to schooling/employment and significant ill health. The Paediatrics and Child Health Division of the Royal Australasian College of Physicians and The Australian Society of Otolaryngology, Head and Neck Surgery in 2008 produced a Joint Position Statement on Tonsillectomy and Adenotonsillectomy in Children, which is consistent with the Cochrane meta-analysis, and endorses the Paradise 1984 severity criteria for tonsillectomy.<sup>212</sup> The Colleges recommend that:

*'Tonsillectomy/adenotonsillectomy is indicated for episodes of recurrent acute tonsillitis. As a guide, seven episodes in the preceding 12 months, or 5 in each year for 24 months, or 3 per year for 3 years; account should be taken of the clinical severity of the episodes and that this may result in as little as one less episode of sore throat with fever per year.'*

**Evidence:** Five small RCTs. Four in a Cochrane meta-analysis;<sup>209</sup> and one subsequently published RCT.<sup>210</sup> The Cochrane Review was limited to short term (12 months) follow-up.

**Adults:** It is unclear whether tonsillectomy reduces recurrent sore throats. Two small studies of 156 adults suggest a potential benefit of tonsillectomy in reducing throat infections, but numbers are too small to make definitive conclusions.<sup>213,214</sup>

**Evidence:** Two small RCTs<sup>213,214</sup>

#### Issues

Tonsillectomy risks include post-operative pain and bleeding.

There are very few quality randomised controlled trials which have been published to date.

Long term data has not been collected for adults or children.

#### 2. Does tonsillectomy reduce the number of specifically group A streptococcal sore throats in patients?

There is a lack of high quality studies that prove tonsillectomy reduces GAS sore throats from occurring. Some observational studies showed reduced GAS sore throats but there are insufficient studies with serological evidence to prove that this is the case.

**Evidence:** observational studies.

#### Issues

Serology was not taken in most of the studies.

It may be that without tonsils, there is less surface area to swab, so infections are missed, and there may be fewer signs of inflammation/infection to observe, so there may be under diagnosis of GAS throat infections.

## Search Strategy

The Cochrane Library was searched for 'Tonsillectomy'.

Two Medline searches were conducted. Databases searched: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), 1946 to present.

- 1) Search date: 14 July 2013.  
Search Strategy:

#	Searches	Results
1	*Tonsillectomy/	5144
2	*Randomized Controlled Trials as Topic/	13928
3	1 and 2	6

- 2) Search date: 8 July 2013.  
Search Strategy:

#	Searches	Results
1	tonsillectomy.mp. or *Tonsillectomy/	9077
2	Streptococcus pyogenes/ and Pharyngitis/	1525
3	1 and 2	24

Personal search of files and footnotes of articles (MK).

## Discussion

Group A streptococcal throat infections may lead to ARF if they are not treated. Some GAS throat infections may manifest as sore throats (pharyngitis) while others may involve inflammation of the tonsils (tonsillitis).

### 1. Does tonsillectomy reduce the number of sore throats (from any cause) in patients?

Tonsils are lymphoid tissue, the term 'tonsils' usually refers to the palatine tonsils.<sup>354</sup> Tonsillectomy (removal of the tonsils surgically) may be performed for a number of indications.

Summarising the literature for Up to Date, Paradise (2013) argues that in the USA there may be fewer tonsillectomies performed for 'infective indications' and more performed for 'obstructive indications' of the upper airways.<sup>355</sup>

A Cochrane meta-analysis has been published on tonsillectomy.<sup>209</sup> This review included five randomised controlled trial studies, four in children (n=719) and one in adults (n=70).

'Severely affected' children in the Cochrane review were defined according to Paradise et al (1984)<sup>211</sup> criteria of sore throat frequency: seven or more sore throats per year for one year or five per year for two years or three per year for three years.<sup>209</sup>

The Paediatrics and Child Health Division of the Royal Australasian College of Physicians and The Australian Society of Otolaryngology, Head and Neck Surgery in 2008 produced a Joint Position Statement on Tonsillectomy and Adenotonsillectomy in Children, which is consistent with the Cochrane meta-analysis, and endorses the Paradise 1984 severity criteria for tonsillectomy.<sup>212</sup> The Colleges recommend that:

*'Tonsillectomy/adenotonsillectomy is indicated for episodes of recurrent acute tonsillitis. As a guide, seven episodes in the preceding 12 months, or 5 in each year for 24 months, or 3 per year for 3 years; account should be taken of the clinical severity of the episodes and that this may result in as little as one less episode of sore throat with fever per year.'*

## In Children

For children 'severely affected by tonsillitis' the Cochrane review found a benefit, in avoiding 'three unpredictable episodes of any type of sore throat, including one episode of moderate or severe sore throat in the next year'.

For children 'less severely affected' by tonsillitis there was not a clear benefit from tonsillectomy, as they 'may never have had another severe sore throat anyway and the chance of them so doing is modestly reduced by adeno-/tonsillectomy'. For this group the surgery could 'mean having an average of two rather than three unpredictable episodes of any type of sore throat'.

The review considered that for children, any benefits must be weighed against the costs of post-operative pain and surgical risks including primary and secondary haemorrhage.<sup>209</sup>

The Cochrane Review limitations:

- There was insufficient data to comment on the effectiveness of tonsillectomy for adults, due to the small numbers of patients (n=70).
- The review was not able to differentiate between outcomes for tonsillectomy and adeno-tonsillectomy.
- Numbers of patients in the studies were small and long term follow up beyond one year was not a feature of the majority.

Since this Cochrane another RCT of children's tonsillectomies has been performed in the United Kingdom, (the North of England and Scotland Study of Tonsillectomy and Adeno-tonsillectomy in Children (NESSTAC). This data was assessed by Wilson et al (2012) in an intention to treat analysis. A total of 461 children were enrolled in the cohort arm or trial arm (268 children).<sup>210</sup> The authors concluded that tonsillectomy:

*'saved 3.5 sore throats, whereas the as-treated model suggested an average reduction of more than 8 sore throats in 2 years for surgery within 10 weeks of consultation, falling to only 3.5 twelve months later due to the spontaneous improvement in the medical therapy group'*

## In Adults

One study by Alho et al (2007) was identified by the Cochrane review for adult tonsillectomy.<sup>213</sup> This randomised 36 adults to tonsillectomy and 34 to control group. At 90 days, GAS pharyngitis had recurred in eight (24%) of the control group and one (3%) of the tonsillectomy patients. At 5-6 months there was an overall reduction in sore throats (including those caused by GAS) in the tonsillectomy group.

Our search identified one further RCT on adult tonsillectomy published since the Cochrane; Koskenkorva et al (2013).<sup>214</sup>

Koskenkorva showed some benefit in tonsillectomy for adults but numbers studied were small. This study in Finland randomized 40 adults to a control group and 46 to a tonsillectomy group. Their primary outcomes were severe symptoms and C-reactive protein level >40 mg/L over the following 5 months. Secondary analysis included number of days of pharyngitis and number of episodes of pharyngitis.<sup>214</sup>

Over the following 5 months, among controls 32 (82%) had an episode of pharyngitis (self-reported) compared to 18 (39%) in the tonsillectomy group, a difference of 41%, (95% CI, 22-60%). One control patient and none in the tonsillectomy group had an episode of severe tonsillitis in the following 5 month period (difference 3%, 95% CI, 2-7%).

However patient numbers studied were small and the follow up period was shorter in the Koskenkora et al study (2013) than those in the Cochrane meta-analysis.<sup>209,214</sup>

## 2. Does tonsillectomy specifically reduce group A streptococcal sore throats, or rheumatic fever, in patients?

The evidence for preceding GAS throat infections and causation of rheumatic fever was summarised in the Heart Foundation's Guideline 3: Primary Prevention of Rheumatic Fever (Clinical Question 1,

page 16, and Appendices 5 and 6).<sup>47</sup> As untreated GAS sore throats and tonsil infections may lead to rheumatic fever it is worth considering whether tonsillectomy has a protective role against GAS.

The significance of tonsils has long been considered. Bach et al (1939) found an association between the presence of an attack of tonsillitis prior to developing ARF and permanent cardiac damage. There was definite tonsillitis in 53/1000 admissions for ARF and permanent cardiac damage in 70% of the 53.<sup>356</sup> Collis (1939) autopsied 17 children who died from ARF and in 14 patients he was able to culture haemolytic streptococci from the tonsils.<sup>357</sup>

Removal of the tonsils and/or adenoids surgically has been shown to alter oro- and naso- pharyngeal flora in a general way, in a few small scale studies. Such surgery (adenotonsillectomy,<sup>358</sup> tonsillectomy,<sup>359</sup> tonsillectomy and adenoidectomy<sup>360</sup>) resulted in a reduction in the amount of GAS cultured from the oropharynx, and in the flora of the nasopharynx (adenoidectomy<sup>361</sup>, tonsillectomy and adenoidectomy<sup>360</sup>). Mixed results were found in institutional and military studies (a selection in the [Table 30](#)).

The reason for this alteration in swab results could be due to two factors: fewer infections are occurring or they are occurring at the same rate but are harder to detect. Chamovitz et al. put forward the second explanation (1960).<sup>362</sup> There is no way to know more definitively without further studies which take streptococcal serology.

International guidelines such as the IDSA do not recommend tonsillectomy for reducing GAS pharyngitis, except for the 'rare patient whose symptomatic episodes do not diminish in frequency over time and for whom no alternative explanation for recurrent GAS pharyngitis is evident'.<sup>9</sup>

**Table 30: A Selection of Studies Relating to Tonsillectomy and GAS**

*Due to time and resource limits, this is not a definitive/exhaustive list.*

Study	Setting	Key findings
Le et al 2007 <sup>358</sup>	300 children in the Netherlands with 3-6 throat infections per year, or obstructive symptoms	Reduced GAS cultured from oropharynx after adenotonsillectomy (ATY). In the ATY group, prevalence of GABHS decreased. 13% had GAS cultured at baseline, but no GAS cultured (0%) at 3 months and 12 months. In the watchful waiting group, prevalence of H influenzae, GABHS, and S aureus did not change substantially
Orvidas et al 2006 <sup>359</sup>	290 children 4 to <16 years who experienced three or more episodes of group A beta-hemolytic streptococcal pharyngitis at least 1 month apart in 12 months. Retrospective cohort study	Reduced GAS cultured from oropharynx after tonsillectomy. Children without tonsillectomy were 3.1 times (95% confidence interval, 1.9-4.9; p <0.001) more likely to develop a subsequent group A beta-hemolytic streptococcal pharyngitis infection during follow up than children who underwent tonsillectomy after adjusting for the number of group A beta-hemolytic streptococcal pharyngitis infections per patient within the previous year and the presence of preexisting conditions
Manolis et al 1994 <sup>360</sup>	40 children with chronically hypertrophied and infected tonsils or adenoids were studied. Twenty of the children were treated by tonsillectomy and 20 by adenoidectomy. Greece	Reduced GAS cultured from oropharynx and nasopharynx after adenoidectomy and tonsillectomy
Talaat et al 1989 <sup>361</sup>	50 patients with chronically infected and hypertrophied adenoids, and 20 controls, in Egypt	Reduced GAS cultured from nasopharynx after adenoidectomy
Chamovitz et al 1960 <sup>362</sup>	Airmen at a military base in Wyoming, who reported sick between 1949–1954, with respiratory symptoms and who exhibited fever of at least 37.8 C or exudative tonsillitis or pharyngitis were hospitalized.  6,974 airmen at Warren Air Force Base in 1950	8.6% of tonsillectomy and 12.6% of non- tonsillectomy patients were diagnosed with strep throat. Less likely to see exudate in patients with little or no tonsillar tissue  They concluded: Tonsillectomy didn't alter susceptibility /risk of GAS throat infection but altered amount of exudative lesions seen in oropharynx and made it harder to diagnose Among 6,974 recruits passing through the air force base, 441 developed acute rheumatic fever (ARF) over 5 yrs. Tonsillectomies were 0.7% more common in the ARF patients than general recruits.  Chamovitz et al also summarised the literature to date on tonsillectomy and concluded that the rates of streptococcal



		infections were found to be the same in patients with tonsillectomy
Begovac et al 1993 <sup>363</sup>	1976 adults and children in Croatia	Tonsillectomy patients had less GAS cultured than those with intact tonsils
Bach et al 1939 <sup>356</sup>	Rheumatic fever children in London (city wide study), and sub analysis of 1,500 children in London aged under 16	Tonsillectomy did not affect whether they developed rheumatic fever or not. Unhealthy tonsillar or naso pharyngeal tissue 'by no means a necessary factor' for rheumatic fever Children who did not have tonsillectomy showed an increase of 8.7% in incidence of severe cardiac involvement, compared to those who had a tonsillectomy.
Keough et al 1939 <sup>364</sup>	530 girls in Australian orphanage	Tonsillectomy did not make any difference to susceptibility to GAS throat infections. They did find that GAS were recoverable for 1-2 weeks from patients with tonsillectomies, and 4-5 weeks for those with intact tonsils (without tonsillectomies)
Matanoski 1972 <sup>365</sup>	101 children with tonsillectomies matched to their control siblings who had tonsils. Johns Hopkins Hospital USA	Tonsillectomy patients were less likely to culture GAS on nasopharyngeal or throat culture, also less likely to have rises in antistreptolysin O titres than sibling controls
Finland et al 1933 <sup>366</sup>	654 patients with rheumatic polyarthritis in Boston	A similar course of illness in hospital (joint symptoms, fever, duration of hospitalisation) for patients with and without tonsillectomy, and similar relapse rates

Bach et al (1939) reviewed rheumatic fever in children in London. They noted statistical estimates that approximately 1/3 of London school children of 'elementary school age' had their tonsils removed, and half of tonsillectomies in the region were performed on children aged 5-7 years old inclusive, yet rates of institutional care for rheumatic fever had continued to rise in London throughout the 1930s.<sup>356</sup>

Bach et al also found an association with intact tonsils and more severe cardiac rheumatic disease (Table 31)

**Table 31. Comparison of Cardiac Complications in Children with Rheumatic Fever who Have Had Their Tonsils Removed with Those That Have Not**

**TABLE VII.—COMPARISON OF THE INCIDENCE OF THE MORE SEVERE AND PROGRESSIVE CARDIAC COMPLICATIONS IN RHEUMATIC CHILDREN WHOSE TONSILS HAVE BEEN REMOVED WITH THE INCIDENCE IN CHILDREN WHOSE TONSILS WERE IN SITU AT THE TIME OF THE FIRST ATTACK OF RHEUMATISM**

*(Figures from case records of children treated at Queen Mary's Hospital, Carshalton.)*

<i>Condition of Tonsillar Region.</i>	<i>Total Number.</i>	<i>Cardiac Condition.</i>			
		<i>Normal and Indefinite "Murmurs."</i>		<i>Mitral Stenosis, Mitral and/or Aortic Disease.</i>	
		<i>Number.</i>	<i>Per-centage.</i>	<i>Number.</i>	<i>Per-centage.</i>
<b>Tonsils not removed before onset ..</b>	<b>716</b>	<b>492</b>	<b>68.6</b>	<b>224</b>	<b>31.4</b>
<b>Tonsils satisfactorily removed before onset ..</b>	<b>159</b>	<b>123</b>	<b>77.3</b>	<b>36</b>	<b>22.7</b>

Source: Reproduced from: Bach F et al. Juvenile rheumatism in London. Ann Rheum Dis. 1939; 1; 210-241.<sup>356</sup> Copyright © 1939, with permission from BMJ Publishing Group Ltd.

### For rheumatic fever relapses

Historically, tonsillectomy has been debated in terms of whether it should be part of the treatment of ARF. However it does not seem to provide a protective effect.

This debate and articles for and against were summarised by Perry (1947).<sup>367</sup>

Sheldon (1931) in a small study comparing 19 rheumatic fever children who had relapsed with 89 rheumatic fever children who hadn't relapsed found the rate of tonsillectomy was essentially the same in both groups (6 of the 19 relapses had tonsillectomies, 31%; compared to 30 of the 89, 33%). He concluded 'the evidence seems to indicate that previous tonsillectomy is of no value as a safeguard against rheumatic relapses.'<sup>368</sup>

Feinstein and Levitt (1970) in a USA study of 532 children with ARF, found that in children with good adherence to antibiotic prophylaxis, the size of tonsils did not make any difference to the number of streptococcal infections or ARF relapses. However, for patients with poor prophylaxis, increasing tonsil size was associated with increasing numbers of streptococcal throat infections and ARF relapses. They used a tonsil grading chart.<sup>369</sup>

Ash (1941) reported that tonsillectomy was 'no longer been part of the routine treatment of the rheumatic child' at the Children's Hospital in Philadelphia USA.<sup>370</sup>



## Appendix 26: Evidence Review for Management of Uninfected Household Contacts

The following evidence review is adapted from the Discussion Document the Advisory Group used in considering recommendations on this topic.

### Clinical Questions

**Should uninfected household contacts of a patient with GAS pharyngitis be prescribed preventive antibiotics?**

**Is there evidence for household/familial chemoprophylaxis in this circumstance?**

### Introduction

Prophylactic antibiotics are currently not prescribed in New Zealand for household contacts of GAS pharyngitis.

### Evidence Level

Expert opinion is from one international guideline and several small scale interventional/ experimental studies.

### Issues

1. Limited quality research on household chemoprophylaxis.
2. By recommending 'routinely', are there 'non-routine' situations where antibiotics are currently being prescribed?

### Search Strategy

www.pubmed.gov search for pharyngitis, chemoprophylaxis.

Limit to English (4 useful articles found out of a total of 25).

Selected overseas guidelines reviewed.

### Discussion

The Infectious Diseases Society of America (IDSA) guideline does not recommend preventive antibiotic treatment for family contacts when a patient develops GAS pharyngitis.<sup>9</sup>

However in the intervention studies detailed below, opinion is divided as to whether chemoprophylaxis is beneficial.

### Studies Showing a Benefit

Two studies showed **a benefit** in treating household members to reduce further GAS pharyngitis.

1. **Kikuta et al 2007.**<sup>216</sup> This study showed a reduction in the secondary spread of GAS within 30 days, when 3-5 days of cephalosporins were given to siblings. The index patients were those who presented to private paediatricians in Japan. However, no benefit was shown when penicillins were given for 3-5 days (as opposed to cephalosporins). The study contained 507 cephalosporin patients, 441 penicillin patients and 492 controls who did not receive any antibiotic treatment. However there was no serotyping (Emm/M) of strains to prove whether the GAS has spread or if it was a new infection. There was no uniformity in the antibiotic prescribed (up to the paediatrician to decide), leading to a variety of cephalosporins and penicillins (including benzathine IM) being used. This makes it difficult to generalise from. In addition the preventive treatment was less than the recommended whole-10 day treatment course of antibiotics for GAS.<sup>216</sup>

2. **Johnson et al 1964.**<sup>215</sup> A benefit for antibiotic treatment of contacts was also found in Johnson et al 1964. Clinically ill patients with GAS (type of illness not specified) had household members followed up for three months in a penicillin treatment RCT. Throat cultures were taken and IM benzathine was given (600,000U to children 11 and under and 1.2 Mega U for adults). If after three

visits the nurse was not able to locate all household members, the family was excluded from the study. There were 2,908 in the penicillin group; 2,428 had throat cultures taken, of those, 668 (27.5%) were GAS positive. There were 2,649 controls; 2,193 had throat swabs taken and 650 (29.6%) were GAS positive. One month later throat swabs were retaken showing 3.5% of the penicillin group cultured GAS, compared to 5.6% of the control group. There were 12 streptococcal infections (type not specified) in the penicillin group and 35 in the control group, within the first month. In the second and third months of the study combined, there were 49 streptococcal illnesses in the penicillin group and 73 in the control group (?short term benefit). Johnson concluded that following a streptococcal infection, prophylactic penicillin was 'quite justifiable' for the 'entire family'.<sup>215</sup>

### **Studies that Did Not Show a Benefit**

Antibiotics were **not** recommended for treating household members to prevent GAS spread in the following two articles.

1. **Hass 1963.**<sup>217</sup> Antibiotic prophylaxis was trialed in the home medical service of Massachusetts USA hospitals. Family contacts (n=79) of 20 GAS pharyngitis index cases were treated with three days of penicillin V 400mg tds PO or erythromycin PO if allergic to penicillin. They were followed up for five months at the end of which, 13 had developed GAS pharyngitis. However when typing was performed, most of the time a result was not yielded with only 2 having the same serotype of GAS as the initial index case in their household. This study is limited by the typing methods and accuracy of the times.<sup>217</sup>

2. **El Kholly et al 1980.**<sup>218</sup> A cross over study (where two groups swapped treatment regimes) was conducted in Egypt over two years. This started with 110 'non-rheumatic' families and 84 'rheumatic' families (with children initially suspected of having rheumatic heart disease). Household groups underwent regular throat swabs. For one year they were either treated with benzathine penicillin IM if GAS positive or they received no treatment if GAS positive on throat swab. The following year the two groups swapped treatment regimes. Emm typing was performed and if the same serotype was found in the household it was assumed to have come from the index case. Penicillin reduced the amount of GAS positive throat cultures when families were in the treatment arm but did not significantly affect spread of GAS within the household. In non-rheumatic families GAS throat culture rate was 19.0% during non-treatment years and 5.4% during treatment years. For rheumatic families, GAS throat culture rate was 33.0% in non-treatment years and 9.0% in treatment years. The changes in treatment may have led to greater awareness of GAS pharyngitis and subsequently affected outcomes even in the non-treatment year. The authors concluded that '*the schedule of penicillin treatment used had a minimal effect on streptococcal spread and is unlikely to be an effective control tool.*'<sup>218</sup>

## Appendix 27: Studies involving fomites in the spread of GAS

**Table 32. Studies Involving Fomites in the Spread of GAS**

Study	Patients	Intervention	Result
Perry WD et al. 1957A <sup>222</sup>	37 airmen, 8 volunteers (laboratory staff and jail inmates), all involved in the intervention. Wyoming, USA	Experimental study. 2 volunteers (staff) repeatedly exposed to dust contaminated with GAS in confined space. 6 volunteers (staff and jail inmates) directly inoculated by sprinkling dust on posterior oropharynx or forcibly blowing the sample into the posterior nasopharynx. 37 airmen lived in GAS dust-contaminated barracks. Nasal and oropharyngeal cultures were taken regularly, for up to 10 days. M typing was done	No infections resulted
Perry WD et al. 1957B <sup>223</sup>	85 airmen (intervention group), 177 airmen as controls. Wyoming, USA	Experimental case-control study. <b>Intervention group:</b> 85 airmen given blankets 'naturally contaminated' with during the winter of 1952. <b>Control group:</b> 177 airmen. Oropharyngeal and nasal cultures were taken, and a record of respiratory symptoms was kept. They were observed for 17-23 days. M typing was done	<b>Intervention group:</b> 6 GAS oropharyngeal infections (in 8,688 days exposed). 4 of those were of a different serotype than the GAS on the blankets, 2 were the same. <b>Control group:</b> 16 GAS oropharyngeal infections (in 16,021 days exposed). 14 of those were a different serotype than the GAS on the blankets, 2 were the same
Falck G et al. 1998 <sup>198</sup>	114 patients with GAS pharyngitis and 289 family members	Experimental case-control. 54 patients and their families were instructed to change their toothbrush, bed linen and wash children's toys. At 6-10 days, household members had nose throat swabs taken and samples were taken from pillowcases, floors, toothbrushes, children's dummies and toys. T typing was done. Followed for 28-35 days	Recurrence with the same T type was designated treatment failure, and assessed after 35 days. <b>Intervention group:</b> 17/46=37% had treatment failure. <b>Control group:</b> 10/39=26% had treatment failure

## Appendix 28: Studies Listing Sore Throat Episodes and Rheumatic Fever

**Table 33. Studies Listing Sore Throat Episodes and Rheumatic Fever**

Study	Place	Study Group	Number of Sore Throats	Results	RR of Rheumatic Fever With The Frequent Sore Throats	P Value	CI
Adanja B et al. 1988 <sup>52</sup>	Yugoslavia	Case-control. 148 patients with first attack of rheumatic fever compared to 444 controls from the same neighbourhood	'Frequent' sore throat (not defined)	52.0% of rheumatic fever patients had a history of frequent sore throat, compared to 34.2% of controls	2.01	p= 0.00018	1.41-2.89 (% CI unstated)
Lennon D et al 2009 <sup>50</sup>	South Auckland, New Zealand	RCT. 24,000 school-children, half in treatment schools (with GAS pharyngitis clinics), half controls (no school clinics), followed for 4 years	In 1998, 50 throat swabs in children with pharyngitis were positive for GAS per 100 children per school year (in 24 schools). In children diagnosed with rheumatic fever, rate of sore throats was 1.13 per year. In children without rheumatic fever, rate of sore throats was 1.43 per year	Incidence of ARF: 60 per 100,000 in control group (without school clinics)			
Vlajinac H et al. 1991 <sup>241</sup>	Yugoslavia	Case-control. 148 cases with a first attack of rheumatic fever satisfying Jones criteria, which were home at time of survey. Three healthy controls matched for each rheumatic fever patient	2 or more sore throats per year	Patients with 2 or more sore throats per year were 2.26 times more likely to get rheumatic fever than patients who had one or less	2.26	p= 0.000	95% CI, 1.49-3.39

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## Key Definitions

**Case control study:** A study which involves identifying with the outcome of interest (cases) and control patients who do not have the same outcome and looking back to see if they had an exposure of interest.<sup>371</sup>

**Confidence interval (CI):** Quantifies uncertainty in measurement, usually uses 95% or 99%. A 95% CI is the range of values within which one can be 95% certain that the true value for the whole population lies.<sup>371</sup>

**Group A streptococcus (GAS):** Also known as *Streptococcus pyogenes*. Gram positive cocci producing beta haemolysis on blood agar.

**High Risk for Rheumatic Fever:** In New Zealand, people with **two or more of the following** risk factors are at high risk for rheumatic fever:

- Māori and Pacific people
- Aged 3-35 years old
- Living in crowded circumstances or lower socioeconomic areas of North Island
- Personal, family or household history of acute rheumatic fever

**Low Risk for Rheumatic Fever:** Patients who are at low risk for rheumatic fever include:

- Non-Māori and non-Pacific people
- Children under 3 years old and adults older than 35 years old
- Not living in crowded circumstances or lower socioeconomic areas of North Island

If there is a **personal, family or household history** of acute rheumatic fever the person is automatically at high risk.

**Meta-analysis:** A systematic review that uses quantitative methods to synthesize and summarise the results.<sup>371</sup>

**Odds ratio (OR):** The odds of having the target disorder in the experimental group, compared to the odds in favour of having the target disorder in the control group (in cohort studies or systematic reviews). Or the odds in favour of being exposed in participants with the target disorder divided by the odds in favour of being exposed in control participants (without the target disorder).<sup>371</sup>

**P value:** The probability a result could have occurred by chance. It is usually set at 0.05 by convention, which means there is a 5% probability that the effect occurred by chance. A p value of  $p > 0.05$  means the effect may have been due to chance, a p value of  $p < 0.05$  means the association between the exposure and the disease is considered statistically significant.<sup>372</sup>

**Penicillin (oral):** Oral penicillin is known by its ingredient name; phenoxymethylpenicillin, but is more commonly called 'Penicillin V'.

**Penicillin (intramuscular):** IM Benzathine Benzylpenicillin (New Zealand Formulary) is more commonly known as benzathine penicillin (trade name: Bicillin® LA), and also known as Penicillin G Benzathine or Benzathine Penicillin G (BPG). Within this guideline IM Benzathine Benzylpenicillin is referred to as 'Benzathine Penicillin', so as not to confuse with benzylpenicillin (which has different pharmacokinetic properties and is not recommended for the treatment of GAS pharyngitis or for secondary prophylaxis).

**Pharyngitis:** Acute pharyngitis is an inflammatory syndrome of the pharynx caused by a variety of micro organisms. Most cases are of viral aetiology and occur as part of common colds and influenzal syndromes. The most important cause of bacterial pharyngitis is that due to group A beta haemolytic streptococci (*Streptococcus pyogenes*).<sup>39</sup>

**Acute post streptococcal glomerulonephritis (APSGN):** An acute inflammatory disorder of the renal glomerulus characterised clinically by haematuria, oedema, hypertension and proteinuria, with evidence of an antecedent (usually group A) streptococcal infection of the pharynx or skin.

**Quinsy:** Peritonsillar abscess.

**Randomised controlled trial (RCT):** Clinical trial in which participants are randomly allocated into an experimental or into a control group and followed over time for the outcomes of interest.<sup>371</sup>

**Rheumatic fever:** Acute rheumatic fever (ARF) is a disease characterised by non-suppurative inflammatory lesions involving primarily the heart, joints, central nervous system, the skin and subcutaneous tissues. Permanent sequelae may result from cardiac involvement. Current opinion holds that all cases of ARF follow a group A streptococcal (GAS) upper respiratory tract infection, although the exact mechanism is unclear. ARF is diagnosed using the Jones Criteria<sup>373</sup> and adapted in New Zealand (and Australia) to permit echocardiography as a diagnostic criteria (see New Zealand Guidelines for Rheumatic Fever: 1. Diagnosis, Management and Secondary Prevention, available from: <http://www.heartfoundation.org.nz> ).

**Risk ratio (RR):** The ratio of risk in the treated group compared to the risk in the control group.<sup>371</sup>

**Sensitivity:** The proportion of people with the target disorder who have a positive test result.<sup>371</sup>

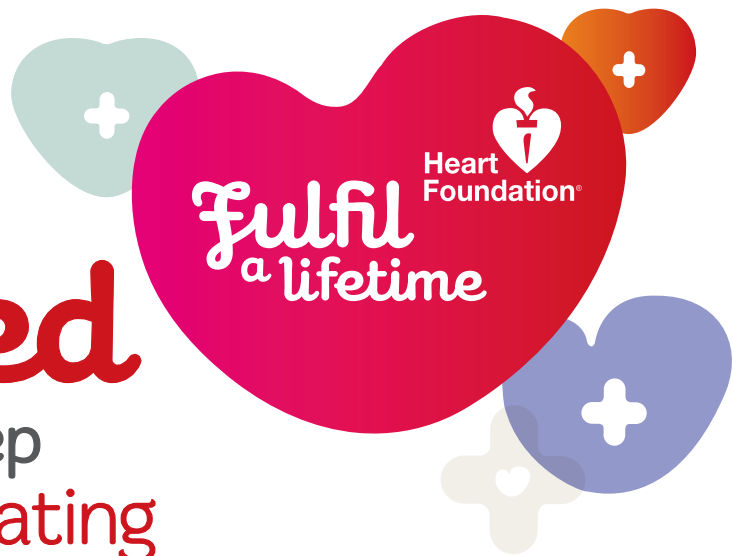
**Specificity:** The proportion of people without the target disorder who have a negative test result.<sup>371</sup>

**Systematic review:** A summary of medical literature that uses explicit methods to perform a comprehensive literature search and critical appraisal of individual studies and that uses appropriate statistical techniques to combine the valid studies.<sup>371</sup>

## Glossary

<b>APSGN</b> .....	acute post streptococcal glomerulonephritis
<b>ARF</b> .....	acute rheumatic fever
<b>ASO</b> .....	antistreptolysin O
<b>BD</b> .....	twice a day
<b>BPG</b> .....	benzathine penicillin G
<b>CDC</b> .....	Centers for Disease Control and Prevention
<b>COC</b> .....	combined oral contraceptive
<b>DHB</b> .....	district health boards
<b>DNA</b> .....	deoxyribonucleic acid
<b>EES</b> .....	erythromycin ethyl succinate
<b>EBV</b> .....	Epstein-Barr Virus
<b>ERGAS</b> .....	erythromycin-resistant group A streptococci
<b>ESBL</b> .....	extended spectrum beta lactamases
<b>GAS</b> .....	group A streptococcal
<b>ICU</b> .....	intensive care unit
<b>IDSA</b> .....	Infectious Diseases Society of America
<b>IgE</b> .....	immunoglobulin E
<b>IMN</b> .....	infectious mononucleosis
<b>IM</b> .....	intramuscular
<b>INR</b> .....	international normalised ratio
<b>LTT</b> .....	lymphocyte transformation testing
<b>NICU</b> .....	neonatal intensive care unit
<b>NSAIDs</b> .....	non-steroidal anti-inflammatory drugs
<b>OD</b> .....	once a day
<b>PO</b> .....	orally
<b>POP</b> .....	progesteron-only contraceptive
<b>QID</b> .....	four times a day
<b>RCT</b> .....	randomised control trial
<b>RR</b> .....	relative risk
<b>TDS</b> .....	three times a day
<b>UTI</b> .....	urinary tract infection

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