

# **Antibiotic use for the Prevention and Treatment of Rheumatic Fever and Rheumatic Heart Disease in Children**

Report for the 2<sup>nd</sup> Meeting of World Health Organization's  
subcommittee of the Expert Committee of the Selection and Use  
of Essential Medicines

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## Summary

Rheumatic heart disease (RHD) is the most significant sequela of Rheumatic Fever (RF). Although the exact causal pathway is unknown it seems that some strains of group A streptococcus (GAS) are “rheumatogenic” and that a small proportion of people in any population (3-5%) have an inherent susceptibility to acute rheumatic fever (ARF).<sup>1</sup> ARF is predominantly a disease of children aged 5-14 years.<sup>1,2</sup> However, people can have recurrent episodes well into their forties.<sup>1</sup>

In 2005, it was estimated that over 2.4 million children aged 5-14 years are affected with RHD and 79% of all RHD cases come from less developed countries<sup>3</sup>. Further, the annual number of new ARF cases in children aged 5-14 years was more than 336,000. Similar to RHD, 95% of cases come from less developed countries.<sup>3</sup>

The current antibiotics on the WHO EMLc for RF/RHD are benzathine benzylpenicillin, Phenoxymethylpenicillin and erythromycin. A search was undertaken, using the WHO website, Pub Med and Cochrane Library search engines from the year 2000 to present.

Primary prophylaxis is a proven method of prevention, however has not to date been proven to be cost-effective, resulting in secondary prophylaxis remaining the mainstay of RF/RHD management, as do IM benzathine benzylpenicillin, oral phenoxymethylpenicillin and oral erythromycin. There are currently no additions or alterations to the EMLc required.

It is however widely recognised that trials on the best antibiotic therapy, dose and regimen are sparse. Those that have been undertaken largely occurred 40 or more years ago and were poorly designed.

Currently, there is still debate in a number of key areas. Firstly whether IM benzathine benzylpenicillin (considered first line for secondary prophylaxis) should be administered every four weeks, versus every two or three weeks. It is suggested that rigorous clinical trials are required to identify the best regimen available, with consideration of factors such as newer preparations of penicillin, patient acceptance and local variation of the disease progression, are necessary. However, current evidence and discussion suggests that the four-weekly regimen be recommended, reserving the two- or three-weekly regimen for patients at higher risk of recurrence.

The internationally accepted dose for the secondary prevention of ARF in adults is 1.2 million IU.<sup>1,4-7</sup> However, there is some variance in opinion about a cut-off weight, below which a child should receive a lower dose. There is little discussion in the literature regarding this issue. Again, rigorous clinical trials are required to identify the best regimen available. Current pharmacokinetic evidence suggests 600,000 IU be given to patients weighing less than 20kg, and 1.2 million IU be given to all other patients.

## Introduction

The subcommittee of the Expert Committee on the Selection and Use of Essential Medicines identified Rheumatic heart disease as an area that more information was required to inform their decision for future meetings. The aim of this review was to address the following questions that came out of the initial meeting.

1. What are the preferred antibiotic(s) for prevention and treatment of rheumatic heart disease in children under 12 years?
2. Are these already on the EML in an appropriate dosage form and strength?
3. If not, what needs to be added?

Accordingly this review focuses on the antibiotic treatment and prevention of Rheumatic Disease and does not address the issues of the acute management of Acute Rheumatic Fever. In order to address the above questions, a literature search and review of existing guidelines was undertaken as outlined in appendix 1.

## **Background and Disease Burden of Rheumatic Heart Disease**

Rheumatic heart disease (RHD) is the most significant sequela of Rheumatic Fever (RF). Although the exact causal pathway is unknown it seems that some strains of group A streptococcus (GAS) are “rheumatogenic” and that a small proportion of people in any population (3-5%) have an inherent susceptibility to acute rheumatic fever (ARF).<sup>1</sup> Acute rheumatic fever (ARF) is an autoimmune consequence of infection with group A streptococci (GAS). It causes an acute generalised inflammatory response and an illness that selectively affects the heart, joints, brain and skin. Despite the dramatic nature of an acute episode, ARF leaves no lasting damage to the brain, joints or skin. However, damage to the heart valves, particularly the mitral and aortic valves, may persist after an acute episode has resolved. This involvement of the cardiac valves is known as rheumatic heart disease (RHD). People who have had ARF previously are much more likely to have subsequent episodes, and these recurrences may cause further damage to the cardiac valves. Thus RHD steadily worsens in people who have multiple episodes of ARF.<sup>8</sup>

ARF is predominantly a disease of children aged 5-14 years and generally does not affect children less than 3 years old or adults.<sup>1, 2</sup> However, people can have recurrent episodes well into their forties.<sup>1</sup> The prevalence of RHD peaks in the third and fourth decades.<sup>1</sup>

The World Health Organization (WHO) commissioned an Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease, and this WHO Technical Report, as well as a significant amount of recent literature,<sup>1, 3, 6, 7, 9-14</sup> outline the important part socioeconomic and environmental factors play in contributing to the magnitude and severity of RF and RHD, and although it is a disease rarely seen now in most developed populations, it is still a cause of major concern in many of the world’s developing nations and selected populations of some developed countries. In the 2004 WHO Technical Report<sup>9</sup> it was estimated that worldwide, there were 5.5 deaths per 100,000 population in 2000.

In 2005, Carapetis et al<sup>3</sup> published a summary of the major findings of an in depth review performed for WHO of the global burden of group A streptococcal diseases. From this review, they estimated that over 2.4 million children aged 5-14 years are affected with RHD.<sup>3</sup> In addition, 79% of all RHD cases came from less developed countries. Further, they estimated the annual number of ARF cases in children aged 5-14 years was more than 336,000. This was extrapolated out to an estimate of 471,000 ARF cases in all age groups. Similar to RHD, they found that 95% of cases came from less developed countries.<sup>3</sup>

From there, they estimated that of all cases of ARF, 60% would go on to develop RHD each year. They also estimated that, in addition, there are 1.88 million people (ten times the remaining 40% of new ARF cases each year) with a history of ARF but no carditis presently requiring secondary prophylaxis.<sup>3</sup> Finally, they estimated that there were over 492,000 deaths per year due to RHD, with approximately 468,000 of these occurring in less developed countries.<sup>3</sup>

This paper has since been cited frequently in a number of articles focused on contemporary issues and management related to RF and RHD.<sup>1, 6, 11, 13, 15, 16</sup> No more recent in-depth investigations into the current world wide burden of disease for RF and RHD, could be found.

More recently however, investigations have been made into using echocardiographic (ECG) screening to detect the true prevalence of RHD. Historically, screening for RHD has been based on clinical screening with ECG confirmation of suspected cases.<sup>13</sup> In 2007, Marijon et al<sup>13</sup> published a

study of ECG screening in over five and a half thousand school-aged children in Cambodia and Mozambique. Their findings suggested that this form of screening may detect approximately 10 times as many cases of RHD than clinical screening in this age group in Southeast Asia and sub-Saharan Africa.<sup>13</sup>

## Current Guidelines

There are a number of documents citing guidelines for the management of acute rheumatic fever and rheumatic heart disease. The majority are based on the 2004 WHO Guidelines.<sup>17</sup> In 2006, the National Heart Foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ) released an evidence-based review of the diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia.<sup>1</sup> Similarly, the National Heart Foundation of New Zealand (NHFNZ) collaborated with the CSANZ to produce the New Zealand Guidelines for Rheumatic Fever.<sup>5</sup> Table 1 compares these Guidelines.

The WHO Essential Medicines List for Children (EMLc), first written in 2007, and the WHO Model Formulary, latest edition released in 2008, have the following medications and dose regimens listed for the management of rheumatic fever (RF) and/or rheumatic heart disease (RHD):

### *Benzathine benzylpenicillin*

**Powder for injection: 900mg (=1.2 million IU) in 5-ml vial**  
**1.44 g (= 2.4 million IU) in 5-ml vial.**

Streptococcal pharyngitis; primary prophylaxis of rheumatic fever, *by deep intramuscular injection*, **ADULT** and **CHILD** over 30 kg, 900 mg as a single dose; **CHILD** under 30 kg, 450–675 mg as a single dose

Secondary prophylaxis of rheumatic fever, *by deep intramuscular injection*, **ADULT** and **CHILD** over 30 kg, 900 mg once every 3–4 weeks; **CHILD** under 30 kg, 450 mg once every 3–4 weeks

### *Phenoxyethylpenicillin*

**Powder for oral liquid: 250mg (as potassium salt)/5mL**  
**Tablet: 250mg (as potassium salt)**

For secondary prophylaxis of rheumatic fever, by mouth, 1-5 years: 125mg twice daily; 6-12 years: 250mg twice daily

### *Erythromycin*

**Capsule or tablet: 250mg (as stearate or ethyl succinate)**  
**Powder for oral liquid: 125mg (as stearate or ethyl succinate)**

No specific dose in Model Formulary

**Table 1: Current WHO, Australian and New Zealand Guidelines:**

	<b>WHO RF and RHD Technical Report Guidelines 2004<sup>9</sup></b>	<b>New Zealand Guidelines for RF 2006<sup>5</sup></b>	<b>NHFA/CSANZ RF and RHD in Australia – Review 2006<sup>1</sup></b>
<b>Acute Rheumatic Fever</b>			
Benzathine penicillin – <i>single dose IM</i>	-	< 20kg: 600,000 IU ≥ 20kg: 1.2 million IU <i>(As first dose of secondary prophylaxis, to be given in hospital)</i>	< 20kg: 600,000 IU ≥ 20kg: 1.2 million IU
Phenoxyethylpenicillin – <i>oral course if IM not acceptable/possible</i>	-	250mg twice daily for 10 days <i>(In this case, given initially and ceased once first dose of above given)</i>	10mg/kg up to 500mg twice daily for 10 days
Erythromycin – <i>oral course for patients hypersensitive to penicillin</i>	-	-	10mg/kg up 500mg twice daily for 10 days
Erythromycin ethyl succinate – <i>alternative oral course for patients allergic to penicillin</i>	-	40mg/kg/day in 2-4 divided doses, maximum of 1g/day in children	-
<b>Secondary Prophylaxis</b>			
Benzathine penicillin – <i>regular single dose IM</i>	< 30kg: 600,000 IU ≥ 30kg: 1.2 million IU	< 20kg: 600,000 IU ≥ 20kg: 1.2 million IU every 4 weeks <i>(3 weekly for those with confirmed recurrent ARF, despite full adherence to the four weekly regimen)</i>	< 20kg: 600,000 IU ≥ 20kg: 1.2 million IU every 4 weeks* *3 weekly for ‘high risk’ only
Phenoxyethylpenicillin – <i>oral course if IM not acceptable/possible</i>	250mg q12h	250mg twice daily	250mg twice daily
Erythromycin – <i>oral course for patients hypersensitive to penicillin</i>	250mg q12h	-	250mg twice daily
Erythromycin ethyl succinate – <i>alternative oral course for patients with documented allergy to penicillin</i>	-	400mg twice daily for children, in 2-4 divided doses. Maximum of 1g/day	400mg twice daily
Sulphonamide – <i>alternative oral course for patients with documented allergy to penicillin</i>	< 30kg: 500mg daily ≥ 30kg: 1g daily	-	-
Duration of prophylaxis	- For 5 years after the last attack of AEF or until 18 years of age	- Minimum of 10 years after last episode of ARF or until age 21	- Minimum of 10 years after last episode of ARF or until age 21

	<b>WHO RF and RHD Technical Report Guidelines 2004<sup>9</sup></b>	<b>New Zealand Guidelines for RF 2006<sup>5</sup></b>	<b>NHFA/CSANZ RF and RHD in Australia – Review 2006<sup>1</sup></b>
	(whichever is longer) - If carditis present, for 10 years after last attack, or at least until 25 (whichever is longer) - If more severe valvular disease or after valve surgery, lifelong	(whichever longer) - If moderate carditis exists, minimum of 10 years after last episode of ARF or until age 30 (whichever longer) - If severe carditis, minimum of 10 years after last episode of ARF or until age 30 (whichever longer) and then specialist review for consideration of possible lifelong prophylaxis	(whichever longer) - If residual heart disease (of more than mild severity) exists at that time, continue until age 35 - If severe heart disease or valve surgery involved continue until 40 or for life

## Discussion

### Primordial and Primary Prevention

Primordial prevention generally requires significant improvements in the social determinants of health such as improvement in housing, hygiene infrastructure and access to health care.<sup>8</sup> A discussion on this is beyond the scope of this review.

Primary Prevention is defined as the adequate antibiotic therapy of group A streptococcal upper respiratory tract infection.<sup>4</sup> Primary prevention is administered only when there is group A streptococcal URT infection. There is extensive discussion in the literature about the importance of primary prevention of RF,<sup>6, 18-21</sup> and the need for a vaccine to be developed.<sup>6, 11, 14, 22, 23</sup> Primary prevention has been shown to be effective in reducing the frequency of subsequent cases of RF,<sup>19</sup> however as outlined in a WHO discussion paper from 2005, systematic screening and treatment of sore throats has not been shown to be cost effective.<sup>21</sup>

### Antibiotic Treatment of Acute Rheumatic Fever

There is general consistency in the literature that the acute RF should be treated with intramuscular benzathine benzylpenicillin. However there is some debate about at what weight the dose should increase from 600,000 IU to the adult dose of 900,000 IU.<sup>1, 4-6, 8</sup> With the accepted oral alternative being phenoxymethylpenicillin (see table 1 for doses) or erythromycin if the patient has a penicillin allergy.

### Secondary Prophylaxis (Prevention)

Secondary prevention of rheumatic fever (RF) is defined as the continuous administration of specific antibiotics to patients with a previous attack of RF, or a well-documented rheumatic heart disease (RHD). The purpose is to prevent colonization or infection of the upper respiratory tract (URT) with group A beta-haemolytic streptococci and the development of recurrent attacks of RF.<sup>9</sup>

The WHO discussion paper from 2005 outlines that of the available control strategies, secondary prophylaxis is the only one that has been shown to be both effective and cost-effective at the community/population level and therefore, in populations with high prevalence of RHD, delivery of secondary prophylaxis should be the major priority for control of GAS diseases.<sup>21</sup> Since this discussion paper was released, there has been no substantial international studies or findings to suggest this notion has changed.<sup>1, 5, 6, 11, 14, 24</sup>

In the 2004 WHO Technical Report on RF and RHD,<sup>9</sup> IM injection of benzathine benzylpenicillin every three weeks (every four weeks in low-risk areas or low-risk patients) is outlined as the most effective strategy for prevention of recurrent attacks of RF.<sup>9</sup> They cite oral penicillin as a possible alternative, but raise the concern of non-compliance to a daily routine over many years.<sup>9</sup> For those allergic to penicillin, oral sulfadiazine or oral sulfasoxazole were considered optimal second choices. Oral erythromycin was reserved for those patients allergic to both penicillin and sulfa drugs.<sup>9</sup> See details below in table 2.

**Table 2: Antibiotics used in secondary prophylaxis of RF from WHO Technical Report on RF and RHD 2004<sup>9</sup>**

<b>Antibiotic</b>	<b>Mode of administration</b>	<b>Dose</b>
Benzathine benzylpenicillin	Single IM injection every 3-4 weeks	≥30kg: 1.2 million units <30kg: 600,000 units
Penicillin V	Oral	250 mg twice daily
Sulfonamide (e.g. sulfadiazine, sulfasoxazole)	Oral	≥30kg: 1 gram daily <30kg: 500mg daily
Erythromycin	Oral	250mg twice daily

Since this report was commissioned, several publications have been released supporting similar regimens. A recent Cochrane Review by Manyemba and Mayosi<sup>7</sup> searched the literature from 1980 to June 2007. They identified nine studies for inclusion in their review, of which all were cited to be methodologically poor. The following three points were the main conclusions from the review:

1. Three studies were found to compare penicillin to placebo. All three showed a decreased recurrence of RF, however only one was found to be statistically significant. IM penicillin appeared to be more effective than oral.
2. Four studies compared IM to oral penicillin. It appeared that IM penicillin was more effective in preventing RF recurrence, with all four studies showing a reduction in the risk of RF recurrence with IM penicillin, compared to oral.
3. Two-weekly or three-weekly injections appeared to be more effective than four-weekly injections of penicillin. The authors noted that the trials surrounding this finding were of poor quality. However, the evidence appeared to be quite strong and the authors suggested it was reasonable to promote current guidelines based on this until further evidence becomes available.<sup>7</sup> In addition, there are supporting pharmacokinetic studies that have demonstrated that penicillin injections given IM every two or three weeks ensure serum penicillin levels remain above the minimum inhibitory concentration.<sup>7</sup>

As outlined previously, the current guidelines (released in 2006) in Australia<sup>17</sup> and New Zealand<sup>5</sup> for secondary prophylaxis of RF are:

**Table 3: Antibiotics used in secondary prophylaxis of RF from NHF/CSANZ Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia: An evidence-based review<sup>1</sup>.**

Antibiotic	Mode of administration	Dose
Benzathine benzylpenicillin	Single IM injection every 4 weeks	≥20kg: 1.2 million units <20kg: 600,000 units
Penicillin V	Oral	250 mg twice daily
Erythromycin <i>OR</i> Erythromycin Ethyl Succinate	Oral Oral	250mg twice daily 400mg twice daily

These are similar to the 2001 WHO guidelines; however, the sulphonamide option is omitted without comment and the weight at which you increase the benzathine benzylpenicillin dose is lower.

### Recent publications supporting this regimen

Cilliers published a clinical review of RF and its management in December 2006.<sup>6</sup> In this she supports the WHO guidelines, outlined previously, for secondary prevention of RF, however omits the sulphonamide option without comment. She recognises the poor quality of the trials that many of the RF and RHD treatment measures are based on, including citing the above mentioned Cochrane review of penicillin use.

Mayosi published protocols for antibiotic use in primary and secondary prevention of RF in the South African Medical Journal in March 2006.<sup>18</sup> In this, he cited the above mentioned 2001 WHO technical report guidelines as new recommendations for the secondary prevention of RF. Again, the sulphonamide option was omitted without comment.

Carapetis et al similarly cited the WHO technical report guidelines as the recommendations of choice for secondary prevention of RF in their publication on Acute Rheumatic Fever, in the Lancet in July 2005.<sup>14</sup> Again, the option of an oral sulphonamide was omitted without comment.

The duration of secondary prophylaxis is discussed in the 2001 WHO technical report.<sup>9</sup> It is recognised as being difficult to provide a ‘blanket’ guideline as so many factors depend on it, such as age of patient, medical history and socioeconomic factors.<sup>9</sup> The WHO report continues on to suggest treatment for a patient without proven carditis for five years after the last attack or until 18 years of age (whichever longer). For a patient with carditis, ten years after the last attack or until 26 years of age (whichever longer). For those with more severe valvular disease or who have had valve surgery, prophylaxis should be lifelong.<sup>9</sup> These guidelines, or similar versions of this have been supported in contemporary publications.<sup>1, 5, 6, 14, 18</sup>

### Unanswered Questions

#### *2- or 3-weekly IM injections versus 4-weekly IM injections?*

There is still debate regarding the dose interval for benzathine benzylpenicillin IM injections for secondary prophylaxis of RF. The above mentioned Cochrane review concluded that on the basis of poor studies that 2 or 3 weekly injections were more effective than 4 weekly.<sup>7</sup> There are some pharmacokinetic studies which support the 3 weekly as being better than 4 weekly,<sup>25</sup> however once again they are small and of poor quality. In their article on acute rheumatic fever in the Lancet in 2005,<sup>14</sup> Carapetis et al promote the 4-weekly regimen. They and others raise the concern of patient acceptance of twice-weekly IM injections versus four-weekly, and thus the issue of adherence.<sup>24</sup> They went on to cite the experience from New Zealand, where recurrence rates were low when the four-weekly regimen was strictly adhered to.<sup>26</sup>

The New Zealand Guidelines for Rheumatic Fever<sup>5</sup> discuss this New Zealand experience further, acknowledging that serum penicillin levels may be low or undetectable 28 days following a dose of BPG and that some findings do suggest the three-weekly regimen results in fewer streptococcal infections and ARF recurrences.<sup>5</sup> However, the above mentioned prospective data from New Zealand suggests that recurrence rates for patients fully adherent to the four-weekly regimen compare favourably with those documented for the three-weekly regimen and go on to recommend the three-weekly regimen be reserved for patients with proven recurrent ARF, despite full adherence to the four-weekly regimen.<sup>5</sup>

Considering the Cochrane review findings<sup>7</sup> discussed and reflected in the above outlined debate,<sup>24, 27</sup> it is suggested that rigorous clinical trials are required to identify the best regimen available. Particularly considering the recognised poor quality of the original trials and the time that has passed since they were performed, consideration of other factors such as newer preparations of penicillin, patient acceptance and local variation of the disease progression, are necessary. However, current evidence and discussion suggests that the four-weekly regimen be recommended, reserving the three- or two-weekly regimen for patients at higher risk of recurrence.

#### *Exact dosing of IM benzathine benzylpenicillin secondary prophylaxis regimen – at what weight should a child receive the adult dose?*

The internationally accepted dose for the secondary prevention of ARF in adults is 1.2 million IU.<sup>1, 4-7</sup> However, there is some variance in opinion about a cut-off weight, below which a child should receive a lower dose. There is little discussion in the literature regarding this issue. As cited previously, the 2004 WHO Technical Report on RF and RHD<sup>4</sup> suggest for children below 30kg, a dose of 600,000 IU should be given. Alternatively, the 2006 Australian and New Zealand Guidelines<sup>1, 5</sup> suggest 600,000 IU should be given to children weighing less than 20kg. A pharmacokinetic study of BPG in children suggests higher per kg doses are required to achieve sustained penicillin concentrations in serum and urine, and that 600,000 IU is even insufficient for most children weighing less than 27kg.<sup>25</sup> In New Zealand, it has been found that the 600,000 IU dose being used in children weighing less than 20kg results in ARF recurrence rate in this group of only 0.6 per 100 patient-years.<sup>26</sup>

Again, rigorous clinical trials are required to identify the best regimen available. However, current evidence suggests 600,000 IU be given to patients weighing less than 20kg, and 1.2 million IU be given to all other patients.

## **Conclusion**

Antibiotic treatment of RF is established, as outlined above. Primary prophylaxis is a proven method of prevention, however has not to date been proven to be cost-effective, resulting in secondary prophylaxis remaining the mainstay of RF/RHD management.

The mainstay antibiotic is IM benzathine benzylpenicillin. Oral phenoxymethylpenicillin and erythromycin are also used as alternatives. These three antibiotics, in the required dosage forms are on the current EMLc. No additional antibiotic agents have been identified to date.

However, debate still remains regarding frequency of administration of IM benzathine benzylpenicillin and at what weight a child should receive a reduced dose. Based on evidence to date and considering the importance of patient acceptance in maintaining adherence to the long-term regimen, it is suggested that IM benzathine benzylpenicillin injections be given every 4 weeks as routine. Two or three weekly regimens should be reserved for those at high risk or who are still having recurrences of RF, despite full adherence to the four-week regimen.

The scarce pharmacokinetic data suggests that children  $\leq 20$ kg should be given a dose of 600,000 IU of benzathine benzylpenicillin and those above 20kg should receive the adult dose of 1.2 million IU.

It should be noted however that these antibiotic regimens are based on studies of questionable quality and higher quality studies, accounting for contemporary issues, are recommended.

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## Appendix 1: Search Strategy

### Initial Search:

- Reviewed current EMLc
- Reviewed current Australian Therapeutic Guidelines – Rheumatology<sup>2</sup>
- Reviewed Australian National Heart Foundation (NHf)/Cardiac Society of Australia and New Zealand (CSANZ) *Diagnosis and management of acute rheumatic fever and rheumatic heart disease in Australia: An evidence based review*<sup>1</sup>
- Searched WHO website for information and current documents regarding rheumatic fever and rheumatic heart disease
- Google search for rheumatic fever/rheumatic heart disease and burden of disease

### PubMed Database Search:

- Rheumatic Fever (in title) AND prevention (in title); review; no other limits – 17 items found
- Rheumatic Fever; 2000-2008; no other limits - 316 items found
- Rheumatic Fever (in title) AND treatment (in title); review; no other limits – 5 items found
- Rheumatic Fever (in title) AND antibiotics (any field); 2005-2008; no other limits – 19 items found
- Rheumatic Fever (in title) AND secondary prevention (in title); review; no other limits – 3 items found
- Rheumatic Fever (in title) AND secondary prevention (any field); 2000-2008; 24 items found
- Rheumatic Fever (in title) AND burden of disease (any field); no other limits – 0 items found
- Rheumatic Fever (in title) AND burden (any field); 2005-2008 – 2 items found
- Rheumatic Fever (in title) AND prevalence (any field); 2005-2008; no other limits – 2 items found
- Rheumatic Fever (in title) AND impact (any field); 2005-2008 – 1 item found
- Rheumatic Heart Disease (in title) AND prevention (in title); review; no other limits – 7 items found
- Rheumatic Heart Disease (in title); 2000-2008; no other limits – 191 items found
- Rheumatic Heart Disease (in title) AND treatment (in title); review; no other limits – 2 items found
- Rheumatic Heart Disease (in title) AND antibiotics (any field); 2005-2008; no other limits – 0 items found
- Rheumatic Heart Disease (in title) AND secondary prevention (in title); review; no other limits - 6 items found
- Rheumatic Heart Disease (in title) AND secondary prevention (any field); 2000-2008; no other limits - 11 items found
- Rheumatic Heart Disease (in title) AND burden of disease (any field); no other limits – 0 items found
- Rheumatic Heart Disease (in title) AND burden (any field); 2005-2008 – 4 items found
- Rheumatic Heart Disease (in title) AND prevalence (any field); 2005-2008; no other limits – 1 items found
- Rheumatic Heart Disease (in title) AND impact (any field); 2005-2008 – 3 item found
- Carapetis, JR; 2006-2006; no other limits – 34 items found (a recognised lead author in the field)

**Cochrane Library:**

Rheumatic Fever; no other limits – 5 items found

Rheumatic heart disease; no other limits – 3 items found

**BMJ Clinical Evidence ([www.clinicalevidence.bmj.com](http://www.clinicalevidence.bmj.com)):**

Rheumatic Fever; No other limits – 7 items found

Rheumatic heart disease; no other limits – 9 items found

Items were not relevant.

**National Guideline Clearinghouse ([www.ngc.gov](http://www.ngc.gov)):**

Rheumatic Fever; No other limits – 15 items found

Rheumatic heart disease; no other limits – 9 items found

Items were not relevant.