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MODELING ACUTE RHEUMATIC FEVER

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Acute rheumatic fever (ARF) is a major cause of heart disease, rare in developed countries, but of concern in New Zealand, where a unique feature is the prevalence of ARF among Maori and Pacific Island peoples. The incidence and prevalence of ARF in a population are modeled for the New Zealand case, where risks of contracting Group A Streptococcus or developing ARF are allowed to vary according to ethnicity, age, and ARF history. The critical parameter \( R_0 \) determines whether a disease will become epidemic or not. A proportional treatment protocol is the most effective at reducing ARF.

Keywords: acute rheumatic fever; critical parameter; effective treatment; heart disease; Maori; mathematical model; Pacific Island people

1. INTRODUCTION

Acute rheumatic fever (ARF) is an autoimmune response to an infection by Group A Streptococcus (GAS). In response to the infection, the immune system creates antibodies that attack the infecting bacteria and damage certain body tissues. Cardiac tissue, joints, skin, and the central nervous system may be affected (Cilliers, 2006). A severe complication of ARF is chronic rheumatic heart disease, characterized by progressive damage to heart valves (Jaine et al., 2008).

ARF is rare in developed countries (Stollerman, 2001) but is prevalent in developing countries (Cilliers, 2006). The rate of ARF in New Zealand is 14 times the Organisation for Economic Co-operation and Development average and the rate is 25 to 44 times greater for Maori and Pacific children (Craig et al., 2007). The rates for Maori and Pacific Islanders, particularly those aged between five and 45, are similar to those in many developing countries (Jaine et al., 2008).

We present a mathematical model that can be used to simulate the extent of ARF in a population. We first present a basic model in which population heterogeneity is ignored, and then we alter the model to allow for variation in susceptibility between different age and ethnic groups. We use data on births and deaths, together with GAS and ARF rates, to simulate the total number of ARF cases in New Zealand. We assess the accuracy of our model by comparing the simulated ARF numbers to...
numbers of reported cases. In sections 2 and 3 we summarize the main epidemiological characteristics of ARF and of GAS. In section 4 we present New Zealand statistics for GAS and ARF. In sections 5 and 6 we present deterministic and stochastic models for ARF incidence, and in section 7 we present a New Zealand specific model. We review available data in section 8 and adjust the NZ model to match data in section 9. In section 10 we determine the most effective ARF prevention protocol through treatment of strep throat.

2. ACUTE RHEUMATIC FEVER

ARF is an autoimmune response following an infection by GAS bacteria (Jaine et al., 2008). ARF may result from infection of the pharynx with GAS, though there is a hypothesis that a skin infection by GAS may be responsible for ARF in some communities (McDonald et al., 2004).

If a GAS infection is not properly treated, ARF may develop after two to three weeks (Stollerman, 2001). After apparent recovery from GAS infection, the individual experiences an inappropriate immune response. This response is thought to be due to molecular similarity between products of GAS degradation and certain human tissues. This similarity occurs in the heart, the joints, and the central nervous system. ARF is very rare among young children under the age of three (Olivier, 2000). The highest risk coincides with maturation of the immune system at around 10 years of age (Stollerman, 2001). First time infections of ARF commonly occur in children aged between five and 17 years (Cilliers, 2006), with 92% of cases occurring in children under the age of 18 (Olivier, 2000).

2.1. Diagnosis of ARF

ARF is diagnosed using clinical criteria (Olivier, 2000) because there is currently no definitive laboratory diagnostic test (Jaine et al., 2008). Updated versions of Jones criteria (Jones, 1944) are used in New Zealand and other countries to diagnose ARF. In the Jones criteria, the clinical features of ARF are divided into major and minor manifestations (National Heart Foundation, NZ and Cardiac Society of Australia and New Zealand, 2006). Examples of major manifestations are arthritis and carditis, while minor manifestations include fever and joint pain. A suspected case is placed into one of three categories: “Definitive ARF,” “Probable ARF,” or “Possible ARF,” based on the combination of major and minor manifestations seen. The pretest probability of placement into a category varies by location and ethnicity. For example, in a region with high incidence of ARF (such as the Northern half of the North Island), a person with fever and arthritis is more likely to have ARF than one in a low incidence region (such as the South Island) (National Heart Foundation, NZ and Cardiac Society of Australia and New Zealand, 2006).

2.2. Susceptibility and Prevention

Not all individuals infected with GAS will develop ARF if untreated. In a general population, 0.3% to 3.0% of people will develop ARF following a GAS infection (Ayoub and Ahmed, 1997; Cilliers, 2006). The incidence is much higher among individuals who have had previous attacks of ARF, with about 30% to
80% having a recurrence of ARF following a GAS infection (Ayoub and Ahmed, 1997). Individuals with a family history of ARF are nearly five times more likely to develop the disease (Bryant et al., 2009). This suggests a genetic susceptibility to ARF (Ayoub and Ahmed, 1997; Cilliers, 2006). Genetic predisposition is consistent with the results of twin studies where mono-zygotic twins were more similar in their susceptibility than dizygotic twins. However, a lower than expected level of similarity in susceptibility between twins suggests a complex pattern of inheritance (Bryant et al., 2009). It also suggests there is a role played by environmental factors in determining susceptibility. There is a long held belief that individuals who are susceptible to ARF also show a hyper-reactive immune response to GAS antigens (Ayoub and Ahmed, 1997). However, the degree to which host risk factors are inherited or acquired is unclear (Stollerman, 2001).

A recommendation for the prevention of ARF is treatment of GAS sore throats with antibiotics (World Health Organization, 2001; National Heart Foundation, NZ and Cardiac Society of Australia and New Zealand, 2009), although Lennon et al. (2009) found no significant benefit from a focused sore throat swab program. ARF can be prevented if antibiotic therapy for GAS is started within nine days from onset of symptoms (World Health Organization, 2001). Secondary prophylaxis in the form of regular administration of antibiotics to prevent infection with GAS and recurrent ARF is recommended for all people with a history of ARF or rheumatic heart disease (World Health Organization, 2001). The recommended duration of secondary prophylaxis is at least 10 years and is dependent on age, presence and severity of carditis, likelihood of continued exposure to GAS, and time elapsed since the last ARF episode (National Heart Foundation, NZ and Cardiac Society of Australia and New Zealand, 2006). Susceptibility to recurrence of ARF decreases with age (Stollerman, 2001). In a New Zealand study, ARF recurrences occurred more frequently within the first five years: 72% of recurrent cases occurred within five years and 12% within five to 10 years (Spinetto et al., 2011).

### 2.3. Treatment and Recovery

The treatment received by a patient with ARF is purely symptomatic, aside from treatment for heart failure if necessary (Kasper et al., 2005). Treatments include carbamazepine for chorea (Harel et al., 2000) and steroids for ARF-related myocarditis (Cilliers et al., 2003), although data are limited and results have been interpreted with caution. The main aim of treatment is to eliminate any remaining GAS from the original infection and suppress the inflammation caused by the ARF (Chin et al., 2010). Following such treatment, ARF attacks usually cease within two months of the initial GAS infection. Any relapse after this period is likely to be due to a new infection (Stollerman et al., 1956).

### 3. GROUP A STREPTOCOCCUS

Acute pharyngitis is one of the most common illnesses seen by pediatricians and other primary care physicians (Bisno et al., 2002). *Streptococcus pyogenes* strains, commonly referred to as Group A Streptococci (Ayoub and Ahmed, 1997) are the most frequent bacterial cause (Cunningham, 2000). GAS is primarily a
childhood disease occurring mostly in children aged between five and 15 (Cunningham, 2000).

Group A Streptococcus is spread through inhalation or contact with secretions from infectious individuals (Somro and Rehman, 2011). In temperate climates it usually appears in winter and early spring. At these times, up to 20% of asymptomatic children may be streptococcus carriers, but are unlikely to spread the organism to their close contacts and are at low risk of complications such as ARF. Because of the lack of immunity retained upon recovery from a GAS infection, the disease may “bounce around” within a family of household groups, unless everyone receives treatment.

Most asymptomatic patients who are still infected with GAS in the upper respiratory tract after a course of antibiotics are streptococcal carriers. While this may mean persistence of the infection in that individual, the circumstances that lead to such asymptomatic carriage usually mean the infection has relatively low virulence. This means asymptomatic carriage has negligible influence in infection models (Cunningham, 2000).

3.1. Symptoms and Diagnosis

Symptoms of GAS infection usually develop after an incubation period of 24 to 72 hours (Somro and Rehman, 2011). There is a large overlap between streptococcal and viral pharyngitis in terms of symptoms. Less than half of patients with acute pharyngitis are actually infected with GAS. Symptoms include sudden onset of a sore throat, pain on swallowing, and fever. Headache, nausea, vomiting, and abdominal pain may also be present, especially in children. None of these symptoms however are specific to GAS. The absence of fever or the presence of symptoms such as conjunctivitis, a cough, or diarrhea suggests viral rather than bacterial infection. Because of the overlap in symptoms with viral infections, unless GAS can be confidently excluded, a laboratory test is needed to determine if it is present or not (Bisno et al., 1997). The most reliable method for detecting the presence of GAS in the throat is by culturing a throat swab (Cunningham, 2000). Streptococcal pharyngitis is also a self-limiting disease with symptoms disappearing spontaneously within three to four days. Rapid identification and treatment of streptococcal pharyngitis is considered vital in reducing the risk of spread as well as ARF and other complications associated with the disease (Bisno et al., 1997).

3.2. Treatment and Recovery

Treatment of a GAS infection with penicillin reduces the risk of ARF by about 90%. In about 10% of cases, GAS will remain present in the throat even after a full course (Olivier, 2000). Treatment will also reduce the duration of symptoms by one or two days (Somro and Rehman, 2011). Erythromycin is a suitable substitute in the case of patients who are allergic to penicillin (Bisno et al., 1997).

Antimicrobial therapy has no benefit however in treating pharyngitis that is not caused by GAS. Its use in such situations unnecessarily exposes patients to expense and hazards as well as possibly contributing to the emergence of antibiotic-resistant bacteria. Therapy can be postponed for up to nine days after symptoms first appear and still reliably prevent the onset of ARF (Bisno et al.,
An untreated GAS infection will last for seven to 10 days (Somro and Rehman, 2011). Throat cultures should be performed regularly for patients with a sore throat and history of ARF (Bisno et al., 1997), with empiric treatment for GAS if secondary prophylaxis uptake is suboptimal.

Vaccines for GAS are currently being investigated. One important issue with the vaccine is to ensure that it does not itself induce the ARF it is intended to prevent (Cunningham, 2000).

4. NEW ZEALAND INFECTION RATES

The highest estimated incidence of ARF among school children is in Sub-Saharan Africa, but the highest published incidence in recent times is among the indigenous populations of Australia and New Zealand (Cilliers, 2006).

ARF is a notifiable disease in New Zealand (Jaine et al., 2008), and data on ARF rates are available. Annual rates of first time ARF cases in New Zealand between 1996 and 2005 were found to be 3.4 per 100,000 (Jaine et al., 2008). This equates to an average of 125 first time ARF hospital admissions per year. Ethnicity is an important risk factor for ARF in New Zealand. ARF rates are shown in Figure 1 for different ethnicities and age groups in 2010. There were 103 cases (18.2 per 100,000) among Maori, 58 (25.6 per 100,000) among Pacific peoples and five cases (0.2 per 100,000) among all the other ethnicities combined (New Zealand Public Health Observatory, 2012). Geographically, incidence is highest in the upper North Island with low incidence in the South Island. This geographic variation is strongly correlated with ethnic distribution in New Zealand. Recurrences are also more likely among the Maori and Pacific Island peoples when compared with the rest of the population, accounting for well over 90% of recurrences. Overall recurrence rates in New Zealand are low, with an average of only six cases per year for the years 1996 to 2005 (Jaine et al., 2008). The patterns seen in age and ethnicity provide useful categories from which we develop a model for ARF incidence.

![Figure 1](image-url)  
**Figure 1.** Rheumatic fever rates for 2010 by age group and ethnicity. Rates are per 100,000. Source: Adapted from Notifiable Disease page of the New Zealand Public Health Observatory website (2012). The numbers of acute rheumatic fever among other ethnicities are not visible on this scale because they are only five cases in total or 0.2 per 100,000 individuals.
5. MODEL FOR A HOMOGENEOUS POPULATION

ARF is an autoimmune response to infection by GAS. This means individuals move from being infected to developing ARF. For brevity, we use a single label to represent both the state label and the corresponding total number of individuals in that state. If $I$ is the total number of individuals with GAS, and $A$ the total number infected with ARF, individuals change from state $I$ (GAS) to state $A$ (ARF) at the rate they develop ARF. If $S$ is the total number of individuals susceptible to infection with GAS, susceptible individuals change from state $S$ to state $I$ if they become infected with GAS, and then to $A$ if they become infected with ARF (Figure 2).

As GAS is an illness from which no immunity is retained upon recovery, we need an SIS type model. All individuals move back to the susceptible compartment as they recover. Individuals may recover from either the $I$ or $A$ compartment as not everyone develops ARF after having a GAS infection. We refer to this as the SIAS model:

$$
\begin{align*}
S'(t) &= -\beta S(t)I(t) + \gamma I(t) + \kappa A(t), \\
I'(t) &= \beta S(t)I(t) - \gamma I(t) - \omega I(t), \\
A'(t) &= \omega I(t) - \kappa A(t).
\end{align*}
$$

We assume a constant rate, $\beta$, of contact per person per day resulting in infection; $\gamma$ is the rate of recovery of infected individuals (per day) back into the susceptible population; $\omega$ is the rate at which infected individuals develop ARF (per day) and $\kappa$ is the rate of recovery (per day). The flow of individuals and the rates at which these individuals move between compartments are shown in Figure 2.

In the most basic model we assume that the population is homogeneous, with individuals mixing evenly and each individual having the same chance of being infected and developing ARF. We also assume that individuals with ARF are no longer infectious and cannot be infected with GAS. Due to the immune response resulting in ARF, these individuals are unlikely to contract a new GAS infection while in compartment $A$ (Stollerman, 2001).

$N = S(t) + I(t) + A(t)$ is the constant total population size. Substituting $A(t) = N - S(t) - I(t)$ into Eq. (1) gives the reduced system:

$$
\begin{align*}
S'(t) &= -\beta S(t)I(t) + \gamma I(t) + \kappa(N - S(t) - I(t)), \\
I'(t) &= \beta S(t)I(t) - \gamma I(t) - \omega I(t).
\end{align*}
$$

Figure 2. The SIAS epidemic model, given by Eq. (1), showing the transition rates between compartments as individuals move from susceptible through infectious to acute rheumatic fever states and the different paths they can take back to the susceptible compartment.
5.1. Equilibrium Points for the SIAS Model

Setting \( I(t) \) equal to zero gives

\[
\beta S(t)I(t) = \gamma I(t) + \omega I(t) \implies I(t) = 0 \text{ or } \beta S(t) = \gamma + \omega. \tag{3}
\]

If \( I(t) = 0 \), the first expression in Eq. (2) gives \( N = S(t) \), as \( \kappa \) is constant and non-zero. Therefore the disease-free equilibrium point is at \((S(t), I(t)) = (N, 0)\).

If \( I(t) \neq 0 \) then \( \beta S(t) = \gamma + \omega \). By substituting this into the first equation of Eq. (2) we get

\[
I(t) = \frac{\kappa (\beta N - \gamma - \omega)}{\beta (\omega + \kappa)} \left( \frac{\gamma + \omega}{\beta}, \frac{\kappa (\beta N - \gamma - \omega)}{\beta (\omega + \kappa)} \right). \tag{4}
\]

5.1.1. Stability of the equilibrium points. The Jacobian matrix for Eq. (2) is

\[
\begin{pmatrix}
-\beta I - \kappa & -\beta S + \gamma - \kappa \\
\beta I & \beta S - \gamma - \omega
\end{pmatrix}. \tag{5}
\]

At the disease free equilibrium \((N, 0)\), this becomes

\[
\begin{pmatrix}
-\kappa & -\beta N + \gamma - \kappa \\
0 & \beta N - \gamma - \omega
\end{pmatrix}. \tag{6}
\]

which has two eigenvalues, \(- \kappa\) and \(\beta N - \gamma - \omega\). Because \(\kappa > 0\) always, the disease free equilibrium is stable if \(\beta N < \gamma + \omega\) and unstable if \(\beta N > \gamma + \omega\). This means that if the initial rate of infection, \(\beta N\), is less than the rate \(\gamma + \omega\) at which individuals leave the infectious compartment, then the total number \(I\) of infectious people with GAS eventually decreases until the disease dies out in the population.

At the endemic equilibrium Eq. (4), the Jacobian matrix is:

\[
\begin{pmatrix}
-\kappa & -\beta N + \gamma - \kappa \\
0 & \beta N - \gamma - \omega
\end{pmatrix}. \tag{7}
\]

The determinant of the matrix in Eq. (7) is \(\kappa (\beta N - \gamma - \omega)\), which is positive if \(\beta N > \gamma + \omega\). The trace of this matrix is \(-\kappa \frac{\beta N - \gamma + \kappa}{\omega + \kappa} - \omega - \kappa\), which is negative if \(\beta N > \gamma - \kappa\). For \(\kappa > 0\) and \(\omega > 0\), \(\gamma - \kappa < \gamma < \gamma + \omega\). Therefore, the endemic equilibrium point is stable, provided that \(\beta N > \gamma + \omega\).

The condition for stability is also a condition for the existence of this equilibrium point. At the endemic equilibrium, \(\beta S(t) = \gamma + \omega\), so \(\beta N\) must be greater than \(\beta S(t)\), as \(N = S(t) + I(t) + A(t)\), and we cannot have a negative total number of individuals in any compartment. This means that \(\beta N > \beta S = \gamma + \omega\). That is, when the equilibrium is achievable, it is also stable. The change of stability about the point \(\beta N = \gamma + \omega\) is called a transcritical bifurcation.
At the endemic equilibrium, $A(t)$ is directly proportional to $I(t)$ as

$$A(t) = \frac{\omega (\beta N - \gamma - \omega)}{\beta (\omega + \kappa)} = \frac{\omega I(t)}{\kappa}.$$ (8)

This is also implied in the third equation in Eq. (1):

$$A'(t) = 0 \Rightarrow \omega I(t) = \kappa A(t).$$ (9)

Sample paths for GAS and ARF numbers for $N=100$ people, $\beta=0.02$ per person per day, $\gamma=0.5$ per day, $\omega=0.2$ per day, and $\kappa=0.8$ per day are presented in Figure 3. Under these conditions, the total numbers with GAS tend to 52 people, and those with ARF tend to 12 people. These are the equilibrium values.

6. STOCHASTIC MODEL

Using our basic ARF model, we derive transition probabilities for a continuous time Markov chain (CTMC), in which changes occur over time steps of varying size, allowing a more accurate representation of changes taking place in continuous time than if a constant time-step model was used. These transition probabilities are referred to as infinitesimal transition probabilities. By including the term $o(\Delta t)$ in definitions of the infinitesimal transition probabilities, we vary the sizes of the time steps according to an exponential distribution to simulate continuous time (Allen, 2008).
For the SIAS model with \( S(t) = N - I(t) - A(t) \), the equivalent CTMC infinitesimal transition probabilities are defined as:

\[
p_{(j,k),(i,a)}(\Delta t) = \begin{cases} 
\frac{\beta_i(N-i-a)}{N} \Delta t + o(\Delta t) & \text{for } (j, k) = (1, 0) \\
\gamma i \Delta t + o(\Delta t) & \text{for } (j, k) = (-1, 0) \\
\omega i \Delta t + o(\Delta t) & \text{for } (j, k) = (-1, 1) \\
\kappa a \Delta t + o(\Delta t) & \text{for } (j, k) = (0, -1) \\
1 - \left( \frac{\beta_i(N-i-a)}{N} + i(\gamma + \omega) + \kappa a \right) \Delta t + o(\Delta t) & \text{for } (j, k) = (0, 0) \\
o(\Delta t) & \text{otherwise.}
\end{cases}
\]

\( p_{(j,k),(i,a)}(\Delta t) \) is the probability that the total number\( I \) of individuals infected with GAS changes from\( i \) to\( j \) over the time step\( \Delta t \), while the total number\( A \) of people infected with ARF changes from\( a \) to\( k \).

Two sample paths for the SIAS model with continuous time Markov chain infinitesimal transition probabilities are shown in Figure 3, together with the deterministic plot from Eq. (1). The stochastic model sample paths follow the deterministic curve but with some variation induced by the random choice made at each time step.

### 7. THE CASE OF NEW ZEALAND

Data for rates of ARF in New Zealand are available because ARF is a notifiable disease. The availability of GAS data is much poorer. As effective treatment for GAS will prevent development of ARF (Olivier, 2000), we assume that individuals who receive treatment for GAS will not develop ARF. We also treat differently those individuals who, without receiving treatment, do not develop ARF following a GAS infection. Treatments for ARF include carbamazeprine for chorea (Harel et al., 2000) and steroids for ARF-related myocarditis (Cilliers et al., 2003), although data are limited.

#### 7.1. Defining Risk Groups

The New Zealand guideline for sore throat management contains an algorithm in which ethnicity, age, socioeconomic status, geographic location, and past history of rheumatic fever determine a treatment procedure for individuals presenting with a sore throat (National Heart Foundation, NZ and Cardiac Society of Australia and New Zealand, 2008). We simplify the model by ignoring socioeconomic status and geographic location, and focusing on age, ethnicity, and ARF history. By ignoring geographic location, we assume homogenous mixing of individuals in the population.

GAS and ARF have increased prevalence among school aged children (Cunningham, 2000; Olivier, 2000; Cilliers, 2006). Individuals under three years of age have a low risk of contracting GAS or developing rheumatic fever (Sharpe et al., 2011). Their mixing in the population is also limited. To simplify the model, we do not count individuals as being “born” into the population until they are three
years of age. We include under threes in the same group with the over 45 year olds to
avoid having to introduce an extra subgroup or loop the age groups around. An indi-
vidual spends 12 years in the under 15 age group, so the rate of movement out of this
group is \( \frac{1}{12} \) years or \( \frac{1}{4380} \) per day. Individuals spend 30 years in the 15 to 45 age group,
so leave this group at a rate of \( \frac{1}{10950} \) per day. To create the risk groups, we first defined
two ethnic groups, Maori or Pacific Island and other ethnicity. We split each ethnic
group into three age groups. To account for individual history of ARF and GAS, we
included three additional groups, giving a total of nine subgroups. The risk groups are:

Maori and Pacific Island groups

Group \( M_1 \): Maori and Pacific Islanders under 15 have the highest risk of developing
ARF after a GAS infection. This age group also has the highest risk of contracting a GAS infection.

Group \( M_2 \): Maori and Pacific Island peoples between the ages of 15 and 45 inclusive
have less risk of contracting GAS than Group \( M_1 \). They still have a high
risk of developing ARF after an infection, however, if it should occur.

Group \( M_3 \): Maori and Pacific Island peoples over the age of 45 have less risk of contract-
ing a GAS infection than Groups \( M_1 \) and \( M_2 \). They also have a reduced risk
of developing ARF compared with those in the younger age groups.

Other ethnic groups

Other ethnicities have a reduced risk of developing ARF after a GAS infection
but their risk of this and GAS varies with age.

Group \( E_1 \): Individuals in other ethnicities under the age of 15 have the highest risk of con-
tracting a GAS infection, like Maori and Pacific Islanders in the same age
group. Their risk of developing ARF after such an infection, however, is lower.

Group \( E_2 \): Individuals of other ethnicities between the ages of 15 and 45 have less
risk of contracting GAS but their risk of developing ARF afterwards
is still similar to the younger age group.

Group \( E_3 \): Individuals of other ethnicities over 45 have reduced risk of contracting a
GAS infection and a low likelihood of developing ARF after the infection.

Rheumatic fever history groups:

Group \( H \): Individuals who develop ARF after a case of GAS recover into a separate group
of susceptible individuals. This group has increased risk of developing ARF if
they do not receive treatment for a GAS infection (Rammelkamp et al., 1997).

Group \( G \): Individuals who recover from a GAS infection without treatment and do
not develop ARF afterwards may have a reduced susceptibility to
developing ARF. If individuals in this group recover from a GAS
infection without developing ARF, we assume their risk is low.

Group \( L \): Individuals who start in a group with low risk of GAS or ARF who
contract GAS but do not develop ARF after the infection, move into a
subgroup with low ARF risk upon recovery. Individuals can only move
into this subgroup from groups \( G \) or \( E_3 \).
Table 1. Risk of Group A Streptococcus (GAS) and acute rheumatic fever (ARF) for each group, and parameters for rates of movement into and out of the infectious compartment

<table>
<thead>
<tr>
<th>Group</th>
<th>GAS Risk</th>
<th>ARF Risk</th>
<th>$S \rightarrow I$</th>
<th>ARF $I \rightarrow A$</th>
<th>Recovery $I \rightarrow S$</th>
<th>Treatment $I \rightarrow T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>High</td>
<td>High</td>
<td>$\beta$</td>
<td>$\omega$</td>
<td>$\sigma$</td>
<td>$r$</td>
</tr>
<tr>
<td>M2</td>
<td>Medium</td>
<td>High</td>
<td>$\kappa$</td>
<td>$\omega$</td>
<td>$\sigma$</td>
<td>$0$</td>
</tr>
<tr>
<td>M3</td>
<td>Low</td>
<td>Medium</td>
<td>$\gamma$</td>
<td>$\alpha$</td>
<td>$\lambda$</td>
<td>$0$</td>
</tr>
<tr>
<td>E1</td>
<td>High</td>
<td>Medium</td>
<td>$\beta$</td>
<td>$\alpha$</td>
<td>$\lambda$</td>
<td>$0$</td>
</tr>
<tr>
<td>E2</td>
<td>Medium</td>
<td>Medium</td>
<td>$\kappa$</td>
<td>$\alpha$</td>
<td>$\lambda$</td>
<td>$0$</td>
</tr>
<tr>
<td>E3</td>
<td>Low</td>
<td>Low</td>
<td>$\gamma$</td>
<td>$\phi$</td>
<td>$\gamma$</td>
<td>$q$</td>
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<tr>
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<td>$\beta$</td>
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<tr>
<td>G</td>
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<td>Medium</td>
<td>$\kappa$</td>
<td>$\alpha$</td>
<td>$\lambda$</td>
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<tr>
<td>L</td>
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<td>$\kappa$</td>
<td>$\phi$</td>
<td>$\gamma$</td>
<td>$q$</td>
</tr>
</tbody>
</table>

Risk levels for ARF and GAS for each group and parameters for rates of transfer between compartments are shown in Table 1.

Figure 4. The acute rheumatic fever model includes ethnicity and rheumatic fever history. The arrows relating to vital dynamics and aging have been left out for simplicity.
7.2. Model

If individuals in group $L$ develop ARF, upon recovery their risk of ARF is increased and they become part of group $M3$. Although these individuals are not of Maori or Pacific Island ethnicity, they are assumed to have the same risk level for ARF. This gives individuals time to re-establish their low risk status or to move into the high risk group $H$.

Figure 4 shows the flow of individuals between groups. Each group contains three or four compartments, giving 29 compartments in total.

The model is

\[
S_{M1}'(t) = M - \beta S_{M1}(t)I(t) + \rho T_{M1}(t) - \mu S_{M1}(t) - \frac{S_{M1}(t)}{4380}
\]

\[
I_{M1}'(t) = \beta S_{M1}(t)I(t) - I_{M1}(t)(\omega + \sigma + r + \mu)
\]

\[
T_{M1}'(t) = r I_{M1}(t) - (\rho + \mu) T_{M1}(t)
\]

\[
S_{M2}'(t) = \frac{S_{M1}(t)}{4380} - \kappa S_{M2}(t)I(t) + \rho T_{M2}(t) - \mu S_{M2}(t) - \frac{S_{M2}(t)}{10950}
\]

\[
I_{M2}'(t) = \kappa S_{M2}(t)I(t) - I_{M2}(t)(\omega + \sigma + \theta + \mu)
\]

\[
T_{M2}'(t) = \theta I_{M2}(t) - (\rho + \mu) T_{M2}(t)
\]

\[
S_{M3}'(t) = \frac{S_{M2}(t)}{10950} - \gamma S_{M3}(t)I(t) + \rho T_{M3}(t) + \phi A_L(t) - \mu S_{M3}(t)
\]

\[
I_{M3}'(t) = \gamma S_{M3}(t)I(t) - I_{M3}(t)(\lambda + \lambda + \mu)
\]

\[
T_{M3}'(t) = \theta I_{M3}(t) - (\rho + \mu) T_{M3}(t)
\]

\[
S_{E1}'(t) = E - \beta S_{E1}(t)I(t) + \rho T_{E1}(t) - \mu S_{E1}(t) - \frac{S_{E1}(t)}{4380}
\]

\[
I_{E1}'(t) = \beta S_{E1}(t)I(t) - I_{E1}(t)(\alpha + \lambda + \mu)
\]

\[
T_{E1}'(t) = \theta I_{E1}(t) - (\rho + \mu) T_{E1}(t)
\]

\[
S_{E2}'(t) = \frac{S_{E1}(t)}{4380} - \kappa S_{E2}(t)I(t) + \rho T_{E2}(t) - \frac{S_{E2}(t)}{10950} - \mu S_{E2}(t)
\]

\[
I_{E2}'(t) = \kappa S_{E2}(t)I(t) - I_{E2}(t)(\alpha + \lambda + \mu)
\]

\[
T_{E2}'(t) = \theta I_{E2}(t) - (\rho + \mu) T_{E2}(t)
\]

\[
S_{E3}'(t) = \frac{S_{E2}(t)}{10950} - \gamma S_{E3}(t)I(t) + \rho T_{E3}(t) - \mu S_{E3}(t)
\]

\[
I_{E3}'(t) = \gamma S_{E3}(t)I(t) - I_{E3}(t)(\alpha + \phi + q + \mu)
\]

\[
T_{E3}'(t) = \theta I_{E3}(t) - (\rho + \mu) T_{E3}(t)
\]

\[
A_H'(t) = \omega (I_{M1}(t) + I_{M2}(t) + I_H(t)) + \alpha (I_{M3}(t) + I_{E1}(t) + I_{E2}(t)
\]

\[+ I_G(t) - (\phi + \mu) A_H(t)
\]

\[
S_H'(t) = \phi A_H(t) - \beta S_H(t)I(t) + \rho T_H(t) + \sigma I_H(t) - \mu S_H(t)
\]

\[
I_H'(t) = \beta S_H(t)I(t) - I_H(t)(r + \sigma + \omega + \mu)
\]

\[
T_H'(t) = r I_H(t) - (\rho + \mu) T_H(t)
\]
\[ S_G(t) = \sigma (I_{M1} + I_{M2}) + \lambda (I_{M3} + I_{E1} + I_{E2}) + \rho T_G(t) - \kappa S_G(t) I(t) - \mu S_G(t) \]

\[ I_G(t) = \kappa S_G(t) I(t) - I_G(t)(\theta + \lambda + \mu) \]

\[ T_G(t) = \theta I_G(t) - (\rho + \mu) T_G(t) \]

\[ S_L(t) = \chi (I_{E3} + I_L(t)) + \lambda I_G(t) - \kappa S_L(t) I(t) + \rho T_L(t) - \mu S_L(t) \]

\[ I_L(t) = \kappa S_L(t) I(t) - (\phi + \chi + \mu) I_L(t) \]

\[ T_L(t) = q I_L(t) - (\rho + \mu) T_L(t) \]

\[ A_L(t) = \phi (I_{E3} + I_L(t)) - (\phi + \mu) A_L(t). \] (11)

\[ \mathcal{R}^*(t)_{M1} = \frac{\beta S_{M1}(t)}{E} \frac{E}{r + \omega + \sigma + \mu} = \frac{\beta S_{M1}(t)}{r + \omega + \sigma + \mu}. \] (12)

We do the same calculation for each subgroup and sum to find the overall running reproduction number \( \mathcal{R}^*(t) \) as:

\[ \mathcal{R}^*(t) = \beta \left( \frac{S_{M1}(t) + S_{H}(t)}{r + \omega + \sigma + \mu} + \frac{S_{E1}(t)}{\theta + \chi + \lambda + \mu} \right) \]

\[ + \kappa \left( \frac{S_{M2}(t)}{\theta + \omega + \sigma + \mu} + \frac{S_{E2}(t) + S_G(t)}{\theta + \chi + \lambda + \mu} + \frac{S_L(t)}{q + \chi + \phi + \mu} \right) \]

\[ + \gamma \left( \frac{S_{M3}(t)}{\theta + \chi + \lambda + \mu} + \frac{S_{E3}(t)}{q + \chi + \phi + \mu} \right), \] (13)

which is also the largest eigenvalue of the next generation matrix. The basic reproduction number, \( \mathcal{R}_0 \), is \( \mathcal{R}^* \) at time zero, so \( \mathcal{R}_0 = \mathcal{R}^*(0) \).

### 8. DATA

We use the ARF and GAS information from section 2 to estimate parameters such as recovery rate with and without treatment, and rates of ARF development. Parameters such as population size, proportions of ethnicities, and birth or death rates are available from Statistics New Zealand. Using data tables from Statistics New Zealand (Bascand, 2012), we estimate the birth rate to be \( \mu = 0.000027 \) births.
per person per day. To obtain a constant population size for the numerical experiments we will conduct, we set the death rate in our model to be equal to the birth rate. A death rate of \( \mu = 0.000027 \) deaths per person per day corresponds to a lifespan of about 100 years, which is longer than New Zealand life expectancy. To keep the model simple, we assume no other sources of mortality aside from natural causes. The population size is fixed at \( N = 4 \) million.

### 8.1. Ethnic Proportions

Proportions of the relevant ethnicities in each age group based on 2006 census data provided by Statistics New Zealand (Bascand, 2012) are presented in Table 2. We altered the upper limit of the second age group to suit age limits for data on ARF rates provided by the New Zealand Public Health Observatory (2012). This alteration means that individuals spend 25 years in the second age group and that the rate at which individuals leave this group due to aging then becomes \( \frac{1}{9725} \) people per person per day.

### 8.2. Rates of Rheumatic Fever Development

The parameters \( \omega, \alpha, \) and \( \varphi \) are used to represent rates of rheumatic fever development in each risk group. It takes about three weeks for an individual to show symptoms of ARF after a GAS infection (section 2). This gives an approximate rate of ARF development of 0.05 per day for individuals susceptible to ARF. \( \alpha \) represents the rate of ARF for groups \( M3, E1, E2, \) and \( G. \) Approximately 3% of individuals in these groups are likely to develop ARF after an untreated GAS infection, which gives an estimated value for \( \alpha \) of \( \alpha = 0.03 \times 0.05 = 0.0015 \) per day. \( \omega \) represents the rate of ARF development for Maori and Pacific peoples under 40 years old and individuals with a history of ARF (\( M1, M2, \) and \( H). \) The upper limit of the second age group was modified from 45 to 40 because of data availability in age group distribution. Individuals with a history of ARF have an increased chance of 30% to 80% of recurrence after another GAS infection (Ayoub and Ahmed, 1997), assuming they do not undergo secondary prophylaxis. Maori rates are 22 times that of New Zealand Europeans, while rates for Pacific peoples are more than 75 times the New Zealand European rate (Jaine et al., 2008). Based on this information, we estimate that an average of 60% of these subgroups develop ARF after a GAS infection. This gives \( \omega = 0.6 \times 0.05 = 0.03 \) per day. \( \varphi \) is the rate of ARF development for those with a low risk, that is those in groups \( E3 \) and \( L. \) The lowest risk of developing ARF is 0.3% for the general population (section 2.2). We assume \( \varphi = 0.003 \times 0.05 = 0.00015 \) per day.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Ethnicity</th>
<th>0 to 14</th>
<th>15 to 40</th>
<th>40+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>European and Other</td>
<td>15.7</td>
<td>28.3</td>
<td>34.5</td>
<td>78.5</td>
<td></td>
</tr>
<tr>
<td>Maori and Pacific</td>
<td>7.5</td>
<td>8.2</td>
<td>5.8</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23.2</td>
<td>36.4</td>
<td>40.4</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>
8.3. Rates of Recovery

An untreated GAS infection can last for seven to 10 days (Somro and Rehman, 2011), after which ARF develops or recovery occurs. The rate of recovery if untreated is 0.1 multiplied by the proportion of individuals likely to recover. For groups $M_1$, $M_2$, and $H$, $\beta = 0.4 \times 0.1 = 0.04$ per day. For groups $E_3$ and $L$, we use $\gamma = 0.997 \times 0.1 = 0.0997$ per day. For all the other groups, we use $\gamma = 0.97 \times 0.1 = 0.097$ per day.

Treatment of GAS reduces the duration of symptoms and, in our model, eliminates the risk of developing rheumatic fever. The duration of symptoms is reduced by one to two days, but 10 days of treatment with antibiotics is recommended for routine strep throat treatment (National Heart Foundation, NZ and Cardiac Society of Australia and New Zealand, 2008). So an individual spends 10 days in the treatment compartment then recovers to the relevant susceptible compartment, implying $\phi = 0.01$ per day. Following treatment for rheumatic fever symptoms, the attacks usually cease within two months of the initial infection. This is about sixty days minus the time spent in a GAS compartment. So assuming that everyone recovers, 40 days full recovery time gives $\phi = 0.025$ per day.

8.4. Rates of Infection

Due to the lack of data on strep throat, infection rates were obtained by working backwards from total numbers of rheumatic fever cases. We use known rates of development and simpler models to estimate the overall rate of infection, then try various values for $\beta$, $\kappa$, and $\gamma$. Using data from the New Zealand Public Health Observatory (2012), we estimate an average of thirteen ARF cases per month from 1997 to 2010, that is 0.45 case per day. We also know $\beta > \kappa > \gamma > 0$, with the majority of cases occurring in the under 15 age group. Table 3 shows the average rate of ARF development for each subgroup.

Rheumatic fever rates are slowly increasing; therefore, $R_0(t) \geq 1$. Using Eq. (13) with our current parameters we get

$$R_0 = \beta \left( \frac{0.0752 N}{0.04 + 0.03 + 0.04 + 0.000027} + \frac{0.157 N}{0.04 + 0.0015 + 0.097 + 0.000027} \right) + \kappa \left( \frac{0.0817 N}{0.04 + 0.03 + 0.04 + 0.000027} + \frac{0.2826 N}{0.04 + 0.0015 + 0.097 + 0.000027} \right) + \gamma \left( \frac{0.0581 N}{0.04 + 0.0015 + 0.097 + 0.000027} + \frac{0.3454 N}{0.04 + 0.00015 + 0.0997 + 0.000027} \right) = (1.8169 \beta + 2.7828 \kappa + 2.8887 \gamma)N.$$  

(14)

Table 3. Average total number of cases per person per day between 2008 and 2011. $N$ represents the total population size. The total average number of acute rheumatic fever cases is $1.1134 \times 10^{-7}N$ cases per person per day. Data provided by the New Zealand Public Health Observatory (2012)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Age group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to 14</td>
<td>15 to 40</td>
<td>40+</td>
<td></td>
</tr>
<tr>
<td>European and other</td>
<td>$2.74 \times 10^{-9}N$</td>
<td>$2.06 \times 10^{-9}N$</td>
<td>$6.85 \times 10^{-10}N$</td>
<td></td>
</tr>
<tr>
<td>Maori and Pacific</td>
<td>$8.1 \times 10^{-8}N$</td>
<td>$2.4 \times 10^{-8}N$</td>
<td>$8.55 \times 10^{-10}N$</td>
<td></td>
</tr>
</tbody>
</table>
Using $R_0 = 1$ and simpler models, we estimate $\beta$, $\kappa$, and $\gamma$. The total number of individuals in group $M_1$ infected with GAS is governed by:

$$I'_M(t) = \beta S(t) I(t) - (r + \omega + \sigma + \mu) I_M(t).$$  \hspace{1cm} \text{(15)}$$

The total number of individuals with ARF in group $M_1$ is governed by:

$$A'_M(t) = \omega I_M(t) - (\phi + \mu) A_M(t).$$  \hspace{1cm} \text{(16)}$$

Setting $I'_M(t) = A'_M(t) = 0$ and using

$$I(t) = (\phi + \mu) \left( \frac{A_M(t) + A_{M2}(t)}{\omega} + \frac{A_{M3}(t) + A_{E1}(t) + A_{E2}(t) + A_{E3}(t)}{\phi} \right),$$  \hspace{1cm} \text{(17)}$$

an expression for estimating $\beta$ in terms of ARF total numbers and the population size $N$ is:

$$\hat{\beta} S_M(t) I(t) = (r + \omega + \sigma + \mu) I_M(t)$$

$$0.0752 \hat{\beta}(N - I(t) - A(t)) = \frac{(\phi + \mu)(r + \omega + \sigma + \mu) A_M(t)}{\omega I(t)}.$$  \hspace{1cm} \text{(18)}$$

Using values for $I(t)$ and $A(t)$ from Table 3 and known values for the other parameters gives

$$0.0752 \hat{\beta}(N - 2.96 \times 10^{-7} N - 1.1134 \times 10^{-7} N) = \frac{(r + \omega + \sigma + \mu) 8.1 \times 10^{-8}}{1.1837 \times 10^{-5} \omega} \Rightarrow \hat{\beta}N = 0.212 \text{ per day.}$$  \hspace{1cm} \text{(19)}$$

Using a similar method we find $\hat{\gamma}N = 0.08166 \text{ individual per day.}$ We use Eq. (14) to find $\kappa$ after which we check that it fits the criteria $\beta > \kappa > \gamma$. So our estimation equations for rates of infection are:

$$\begin{align*}
\beta N &= 0.212 \text{ per day,} \\
\kappa N &= 0.136 \text{ individuals per day, and} \\
\gamma N &= 0.082 \text{ individuals per day.}
\end{align*}$$  \hspace{1cm} \text{(20)}$$

For a population size of $N = 4$ million, $\hat{\beta} = 5.31 \times 10^{-8}$ per individual per day, $\kappa = 3.40 \times 10^{-8}$ per day, and $\hat{\gamma} = 2.04 \times 10^{-8}$ per day. Figure 5 shows the numerical solution and how the reproduction number changes over time using these rates of infection but assuming no treatment of GAS. The model starts with one individual in each of the six infected GAS categories. The total number of individuals with GAS increases very quickly after 200 days, and plateaus after two years at about 1.1 million. The total numbers of ARF and GAS are approaching an endemic equilibrium. ARF numbers plateau at about 130,000 individuals. These numbers are unrealistically high compared with the data provided by the New Zealand Public Health Observatory (2012). Incorporating a treatment compartment is one way to reduce them. The fact that the reproduction number value approaches a value near one
supports the presence of an endemic equilibrium. $R_0$ is about 1.45, which seems high, but this may be partly due to the fact that we are starting the model with such a small number of a total of six infectious individuals.

9. MATCHING ARF DATA

Data from Statistics New Zealand indicate a rate of about 0.45 of a new case per day. With each case taking about 40 days to fully recover, we expect about 18 individuals with ARF at any point in time, once the system has reached the endemic equilibrium.

As GAS is treatable, we incorporate a treatment rate in the model. A numerical solution with a GAS treatment rate of 1% is shown in Figure 6. We estimate that it takes an individual an average of five days to receive treatment for a GAS infection, so $\tau = \theta = \phi = 0.2 \times 0.01 = 0.002$ per day. This level of treatment reduces the total number of individuals with GAS to one million at the endemic equilibrium as shown in Figure 6a, and ARF numbers now plateau at about 120,000 individuals.

The numerical solution when the duration of recovery is reduced from 10 to eight days is presented in Figure 6b, with $\hat{\sigma} = 0.050$ per day, $\hat{\lambda} = 0.121$ per day, and $\hat{\chi} = 0.125$ per day. This remains in our range of seven to 10 days given earlier and reduces the total number of ARF cases as well. GAS numbers plateau at a lower value than in Figure 6a, and ARF numbers settle at 6,200 individuals, fewer than in Figure 6a. Model predictions are still too high, though a reduction in recovery time has led to a reduction in the total number of infected cases.

We further reduce ARF total numbers in our model by reducing the rate of GAS infection or the rate of ARF development. We also reduce recovery time or increase the basic treatment rate. If we truncate the estimates for the rates of infection, making them slightly smaller, we get $\beta = 5.0185 \times 10^{-8}$ per individual per day, $\kappa = 3.0000 \times 10^{-8}$ per individual per day, and $\gamma = 2.0000 \times 10^{-8}$ per individual.
per day. Using these values in the model we produce a numerical solution that does not die out but is greatly reduced in the total number of individuals with GAS or ARF. Figure 6c shows the numerical solution for our model using these slightly reduced infection rates. There is a large initial spike in GAS and ARF total numbers, which then reduce to about 289 individuals with ARF. These numbers of infected individuals persist for about 50 years, though with some fluctuations over a long time period that plateau at slightly higher values.

We divide the rates at which individuals develop ARF by 10. The results are in Figure 6d. The total number of individuals with GAS has increased because fewer individuals are leaving in each time step but the total number of individuals with ARF has decreased to 153 at the endemic equilibrium.

We slightly increase the rate at which individuals recover from GAS without treatment to account for the decrease in those developing ARF. An initial spike is followed by very low infected numbers for 20 years, then an increase to a steady level with ARF numbers at 64 (Figure 7).

Increasing the rate of treatment from $\tilde{r} = \tilde{\theta} = \tilde{q} = 0.002$ to $0.0025$ per day causes a drop in ARF to 20 individuals, a good fit to data (Figure 7c). The $R^*$ value tends to one, indicating an endemic equilibrium that persists for up to 140 years and
matches New Zealand ARF numbers. Attempts to run the model for longer than 140 years leads to the total number of infected individuals tending to zero. We use this model in the next section as a base model to compare the effectiveness of different treatment strategies.

10. TREATMENT STRATEGIES

In Figure 7c, we used treatment parameters $q = r = 0.0025$ per day. We vary the treatment rates and keep all other parameters unchanged. We start the model with initial conditions corresponding to the stable endemic numbers obtained after 70 years of iterating our fitted model in Figure 7c.

In the first case, we consider giving treatment only to groups with a high risk of rheumatic fever, by setting $\tilde{r} = 0.02$ and $\tilde{q} = \tilde{h} = 0$ per day. This shift of focus to treatment only of those most at risk of rheumatic fever leads to an increase in total rheumatic fever numbers, approaching about 200, as shown in Figure 8a. The reproduction number $R^*$ remains close to one throughout this time.

In the second case, we proportionally allocate the same level of treatment according to risk of developing ARF. Figure 8b shows results over the first three years, for treatment rates $\tilde{r} = 0.01$, $\tilde{h} = 0.006$, and $\tilde{q} = 0.004$ per day. This proportional method of treatment is successful in eventually eliminating ARF and GAS numbers completely. $R^*$ is reduced to 0.97 at the point of treatment introduction, and rises slowly no higher than 0.985 before decreasing again.
The final case we consider is to halve the proportional treatment levels of this second case. The result is that eventually the total number of infected individuals reduces to zero, as shown in Figure 8c. The $R/C_3$ value plotted in Figure 8d starts just below one, and eventually begins a decline toward zero.

11. CONCLUSION

Rates of ARF remain an issue in New Zealand, especially for Maori and Pacific Island people. An anonymous reviewer pointed out that the variation in ARF rates among ethnic groups is more likely due to underlying health determinants, given historic high rates of ARF in other groups such as people of Anglo-Celtic origin in the past. We have developed a model for ARF development, which uses different rates of GAS and ARF among different age groups and ethnic groups. The accuracy of this model may be limited by the absence of factors such as geographic location and socioeconomic status. It does however tend toward a stable rate of ARF, at values similar to those indicated by New Zealand data. The original version of the model with no manipulation of parameter values produces a stable, if overestimated, value for ARF numbers in New Zealand. Overestimation may be due to our assumptions that mixing is homogeneous and that further prevention measures, such as secondary prophylaxis, are not taken. Further development of the model and the inclusion of seasonality, socioeconomic status, and geographic...
location, in some combination, may lead to a more satisfactory model where parameter values required to match the real data are closer to expected values.

Jaine et al. (2008) suggested that primary prevention of ARF be targeted at high-risk individuals, rather than the whole population, as a possibly efficient means of managing the ethnic inequality in ARF numbers. Our investigations of different treatment protocols suggest that focusing treatment of strep throat on those at high risk of developing ARF to the exclusion of other groups could increase ARF numbers. However, a proportional treatment protocol, where higher risk groups had higher treatment rates, resulted in lower ARF numbers. This suggests that if each risk group receives some treatment for GAS infections, with greater focus on those at higher risk of developing ARF, then the reproduction number and ARF numbers could be reduced.

REFERENCES


