Primary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease With Penicillin in South African Children With Pharyngitis
A Cost-Effectiveness Analysis

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Background—Acute rheumatic fever and subsequent rheumatic heart disease remain significant in developing countries. We describe a cost-effective analysis of 7 strategies for the primary prevention of acute rheumatic fever and rheumatic heart disease in children presenting with pharyngitis in urban primary care clinics in South Africa.

Methods and Results—We used a Markov model to assess the cost-effectiveness of treatment with intramuscular penicillin using each of the following strategies: (1) empirical (treat all); (2) positive throat culture (culture all); (3) clinical decision rule (CDR) score ≥2 (CDR 2+); (4) CDR score ≥3 (CDR 3+); (5) treating those with a CDR score ≥2 plus those with CDR score <2 and positive cultures (CDR 2+, culture CDR negatives); (6) treating those with a CDR score ≥3 plus those with CDR score <3 and positive cultures (CDR 3+, culture CDR negatives); and (7) treat none. The strategies ranked in order from lowest cost were treat all ($11.19 per child), CDR 2+ ($11.20); the CDR 3+ ($13.00); CDR 2+, culture CDR negatives ($16.42); CDR 3+, culture CDR negatives ($23.89); and culture all ($27.21). The CDR 2+ is the preferred strategy at less than $150/quality-adjusted life year compared with the treat all strategy. A strategy of culturing all children compared with the CDR 2+ strategy costs more than $125 000/quality-adjusted life year gained.

Conclusions—Treating all children presenting with pharyngitis in urban primary care clinics in South Africa with intramuscular penicillin is the least costly. A strategy of using a clinical decision rule without culturing is overall the preferred strategy. A strategy of culturing all children may be prohibitively expensive. (Circ Cardiovasc Qual Outcomes. 2013;6:343-351.)

Key Words: cost-benefit analysis ■ prevention ■ rheumatic heart disease
WHAT IS KNOWN

• Acute rheumatic fever remains the most important cause of acquired heart disease in children and young adults in the world.
• Secondary prevention of rheumatic heart disease has been shown to be cost-effective. However, controversy still exists on primary prevention.

WHAT THE STUDY ADDS

• Using a Markov model to assess different treatment strategies, this study concluded that treatment with penicillin was cost-effective in all pharyngitis cases.
• The results also suggest that use of a clinical decision rule aids in the cost-effective management of pharyngitis, but use of throat cultures in all cases of pharyngitis was not cost-effective in low- and middle-income countries.

in a high endemic area with relatively low labor costs and low screening costs because of the opportunistic nature of presentation. In the South African setting, a marginal cost of an IM penicillin injection of R300 ($46) per case of ARF prevented has been estimated, suggesting that it may be cost-effective.5,7 However, diagnostic strategies are not 100% sensitive or specific and can be costly or unavailable in resource-limited settings. In addition, penicillin reactions can be both mild and severe, even though they are rare. Therefore, the challenge is to find a relatively sensitive strategy that ascertains the greatest proportion of GAS infections, limits costly testing, and minimizes unwarranted antibiotic treatment.

We describe a cost-effective analysis of 7 diagnostic and treatment strategies for the primary prevention of ARF in children presenting with pharyngitis in urban primary care settings in South Africa.

Methods

Decision Analysis Model

The decision of whom to treat with pharyngitis is complex. Providers must weigh the health benefits of preventing ARF and subsequent RHD, which has considerable morbidity and mortality, against the small risks of potentially significant drug reactions. Furthermore, the costs of diagnosis and initial management of GAS pharyngitis with IM penicillin must be weighed against the costs of later treatment for ARF and RHD. This set of complex choices with both clinical and diagnostic uncertainty is best facilitated by a medical decision analysis. We therefore developed a Markov decision analysis cohort model to evaluate common strategies for managing children (3–15 years) presenting with an acute sore throat (pharyngitis) and no history of ARF in an urban primary care clinic setting in South Africa (Figure 1).

The model incorporates annual recurrent rates of pharyngitis in this pediatric population and thus does not reflect the risk of RHD from 1 episode of pharyngitis but the possibility of multiple infections. The model follows the cohort through the annual probability of having GAS, developing ARF or peritonsillar abscess (PTA) acutely, developing complications from penicillin treatment, developing RHD on an annual basis, developing congestive heart failure requiring valve surgery, and ultimately premature death from RHD or other causes. Furthermore, the model incorporates the sensitivity and specificity of the various screening tools for GAS infection. The probability of developing ARF or complications from treatment and incurring costs are affected by a patient’s treatment status, which in turn is affected by the likelihood of treatment based on the diagnostic strategies described below.

Strategies Compared

We compared 7 strategies for the evaluation and management of children between the ages of 3 to 15 years who present to an urban primary care clinic with a complaint of sore throat and no history of ARF. Given the resource constraints in many parts of South Africa, the following 7 strategies were compared in our model. The strategies regarding screening and initiating treatment for possible GAS are based on a clinical decision rule, throat culture results, or a combination of the 2 in multistage screening strategies. We also compared these screening strategies to a treat all strategy with no screening and compared all strategies to no treatment. Several symptom-based clinical decision rules (CDRs) of varying sensitivity and specificity have been developed and evaluated to assist in diagnosis in resource-limited settings, which typically have limited access to lab culture and...
Table 1. Components* and Performance of 3-Variable Clinical Decision Rule

<table>
<thead>
<tr>
<th>Cumulative Score of Components (Range 0–3)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>99</td>
<td>3</td>
</tr>
<tr>
<td>≥2</td>
<td>92</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>83</td>
</tr>
</tbody>
</table>

*Clinical components of decision rule: enlarged cervical nodes, no rhinitis, no rash.

rapid testing and higher incident rates of ARF and RHD.4 The CDR used in the model is a modification of the World Health Organization (WHO)-recommended CDR7 that uses a 3-variable cumulative score (ie, presence of enlarged anterior cervical lymph nodes, absence of rash, and absence of rhinitis) to guide decisions about whether to treat with antibiotics. This rule has been tested and validated in Egypt in a population with health and socioeconomic status similar to that in sub-Saharan Africa.10 In the Egyptian study, children presenting with pharyngitis were assigned a point for each clinical variable for a cumulative score with a range of 0 to 3 points. The sensitivity and specificity of diagnosing GAS infection with 1, 2, or 3 of the variables are presented in Table 1. We used scores ≥2 or ≥3 as part of our strategies.

We included 5 single-stage strategies and two 2-stage screening strategies: (1) empirical treatment with IM penicillin (treat all); (2) treatment based on a positive throat culture (culture all); (3) treatment based on a CDR score ≥2 (CDR 2+); (4) treatment based on a CDR score ≥3 (CDR 3+); (5) treating those with a CDR score ≥3 (CDR 3+); (6) treating those with a CDR score ≥3 (CDR 3+); and (7) observation without treatment (treat none). The 2-stage strategies were included to improve sensitivity and specificity of diagnosing GAS infection with 1, 2, or 3 of the variables are presented in Table 1. We used scores ≥2 or ≥3 as part of our strategies.

Data Sources
The probabilities, costs, and utilities used in the decision model were derived from the published literature and local sources where available. The MEDLINE database was searched using the terms “pharyngitis” or “rheumatic fever” or “rheumatic heart disease” and “cost-effectiveness.” The references of relevant articles and evidence-based clinical guidelines were examined for additional studies.

Epidemiology
Table 2 lists the probabilities of GAS pharyngitis and its progression to RHD with and without treatment, as well as the associated complications. Anywhere from 1.6% to 30% of children with sore throat have GAS as the cause.2 The prevalence of GAS pharyngitis was 15.3% (95% confidence interval, 11.2%–20.4%) among 255 children presenting with sore throat at 3 urban primary care clinics in Cape Town between June 2008 and June 2010 (unpublished data). We have therefore used a baseline probability of 15% with a sensitivity range of 1.6% to 30% to reflect the above estimates. The incidence of pharyngitis in the same population is 870 per 100,000 patient years.

Published estimates of the incidence of ARF in school-aged children after untreated GAS pharyngitis range from 0.3% to 5% per year depending on crowding conditions,2,13–16 although some studies have used much lower probabilities for nonendemic areas.20,30 We have used a base case estimate of 0.3% and a wide range from 0.1% to 5% to explore in sensitivity analyses, given the large uncertainty in this variable. We have used an estimate of the annual risk of death from ARF of 1% (range, 0.5%–2%) based on prior studies.14,15,16,17 The PTA risk was estimated to be 1.5%.14,20–22

On the basis of a review of epidemiological data, there is a life-time risk of about 50% to 75% of developing RHD among those with untreated ARF, with either mild, moderate, or severe cardiomegaly (24%) or congestive heart failure leading to death.23,24 Therefore, assuming a constant hazard with an average life expectancy after infection, we estimated an annual probability of developing RHD of 1.8% with a range from 1.4% to 2.7%. Mortality from RHD has been estimated in our model as 1.5% per year, ranging from 1% to 2%, based on an analysis by Carapetis et al.23 The annual probability of death from chronic causes in South Africa is derived from the age-specific mortality rates in South Africa for the year 2006.31,32 We also adjust the annual risk of developing RHD based on treatment with monthly IM penicillin injections among those known to have ARF.

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Base Case</th>
<th>Range</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAS prevalence</td>
<td>0.15</td>
<td>0.016–0.3</td>
<td>Michaud,2 Carapetis1</td>
</tr>
<tr>
<td>ARF given GAS+</td>
<td>0.003</td>
<td>0.001–0.05</td>
<td>Michaud,2 Stollereman,13 Tsevat,14 Denny,15 Robertson16</td>
</tr>
<tr>
<td>Risk of death from ARF</td>
<td>0.01</td>
<td>0.005–0.02</td>
<td>Neuner,17 Tsevat,14 Feinstein,19 Hillner19</td>
</tr>
<tr>
<td>Risk of PTA</td>
<td>0.015</td>
<td>0.00–0.03</td>
<td>Van Howe,16 Tsevat,14 Lieu,21 Dippel19</td>
</tr>
<tr>
<td>Annual incidence of RHD, untreated ARF</td>
<td>0.018</td>
<td>0.014–0.027</td>
<td>Carapetis,21 Michaud24</td>
</tr>
<tr>
<td>Annual risk of death from RHD</td>
<td>0.015</td>
<td>0.01–0.02</td>
<td>Carapetis1</td>
</tr>
<tr>
<td>Probability of patients with ARF receiving secondary prevention</td>
<td>0.12</td>
<td>0.00–0.90</td>
<td>RHD registry at GSH, Kumar,25 Grayson26</td>
</tr>
<tr>
<td>Annual incidence of pharyngitis</td>
<td>0.0087</td>
<td>0.0001–0.017</td>
<td>ARF registry in Vanguard community</td>
</tr>
<tr>
<td>Treatment effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR of IM penicillin vs ARF among GAS+</td>
<td>0.2</td>
<td>0.11–0.5</td>
<td>Robertson27</td>
</tr>
<tr>
<td>RR of monthly penicillin vs RHD if ARF+</td>
<td>0.45</td>
<td>0.08–0.78</td>
<td>Padmavati20</td>
</tr>
<tr>
<td>RR of IM penicillin vs PTA</td>
<td>0.15</td>
<td>0.05–0.47</td>
<td>del Mar19</td>
</tr>
<tr>
<td>Probability of penicillin-induced rash</td>
<td>0.015</td>
<td>0.005–0.04</td>
<td>Neuner17</td>
</tr>
<tr>
<td>Incidence of penicillin-induced anaphylaxis</td>
<td>0.0001</td>
<td>0–0.0005</td>
<td>Tsevat14</td>
</tr>
<tr>
<td>Probability of death from anaphylaxis</td>
<td>0.10</td>
<td>0.00–0.25</td>
<td>Neuner,17 Tsevat14</td>
</tr>
</tbody>
</table>

*ARF indicates acute rheumatic fever; GAS, group A streptococcus; IM, intramuscular; PTA, peritonsillar abscess; RHD, rheumatic heart disease; and RR, risk reduction.
Table 3. Diagnostic Parameters*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case</th>
<th>Range</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity of CDR (score of 2+)</td>
<td>0.92</td>
<td>0.50–1.00</td>
<td>Steinhoff10</td>
</tr>
<tr>
<td>Specificity of CDR (score of 2+)</td>
<td>0.38</td>
<td>0.00–0.50</td>
<td>Steinhoff10</td>
</tr>
<tr>
<td>Sensitivity of CDR (score of 3+)</td>
<td>0.38</td>
<td>0.00–0.50</td>
<td>Steinhoff10</td>
</tr>
<tr>
<td>Specificity of CDR (score of 3+)</td>
<td>0.83</td>
<td>0.50–1.00</td>
<td>Steinhoff10</td>
</tr>
<tr>
<td>Sensitivity of throat culture</td>
<td>0.90</td>
<td>0.90–1.00</td>
<td>Webb,12 Kellogg13</td>
</tr>
<tr>
<td>Specificity of throat culture</td>
<td>0.95</td>
<td>0.90–1.00</td>
<td>Webb,12 Kellogg13</td>
</tr>
</tbody>
</table>

*CDR indicates clinical decision rule.

Treatment Effects
A 2005 fixed-effects meta-analysis of 9 trials found a protective effect of IM penicillin against ARF of 80% (risk ratio, 0.20; 95% confidence interval, 0.11–0.36),27 whereas a 2006 meta-analysis of 14 penicillin trials found a 73% reduction in ARF (risk ratio, 0.27; 95% confidence interval, 0.14–0.50).28 We use the risk ratio estimate of 0.2 with a range from 0.11 to 0.5 for IM penicillin. Penicillin effectiveness against PTA was estimated to be 85%.29 The probabilities of allergic30 and anaphylactic14 reactions to penicillin were derived from previously published estimates.

Test Characteristics
Table 3 displays the sensitivity and specificity of the diagnostic throat cultures and CDRs for GAS pharyngitis. The CDR we used30 performed the best (with a sensitivity of 92% and specificity of 38%) using a cutoff score of 2) in comparison with 6 other CDRs in predicting children with and without GAS in an Egyptian data set with a GAS prevalence of 24.6% (n=410),8 under conditions most similar to South African population. As expected, a CDR score of 3+ had a lower sensitivity (38%) but much higher specificity (83%) than a score of 2+. Throat culture sensitivity has been estimated to range from 75% to 95% and specificity from 90% to 100%.30,31 We used 90% sensitivity and 95% specificity as a base case and conduct sensitivity analyses around the ranges above.

Costs
The model uses a societal perspective to include all healthcare costs related to the identification and management of those with sore throat and subsequent ARF and RHD. The analysis includes health provider costs related to the diagnosis and treatment of GAS pharyngitis with IM penicillin, the treatment of any penicillin-induced rash and anaphylaxis or supplicative complications of GAS, and the ongoing inpatient and outpatient treatment of rheumatic fever and RHD (Table 4) incurred by the health system and the patient. Costs are reported in 2010 $US, and discounting of future costs and outcomes at 3% per year was applied, with a sensitivity analysis around a range of 0% to 10% to reflect local inflation rates.

The provider costs of outpatient clinic visits and inpatient days at different levels of public hospital care in South Africa are derived from a model of the estimated resource requirements of alternative healthcare financing reforms in South Africa,34 which used utilization and recurrent expenditure data from the South African District Health Information System and the National Treasury. Costs of throat culture diagnosis and medical treatment were sourced from the National Health Laboratory Service and the hospital pharmacy, respectively, and for surgical procedures from the hospital case managers. Costs to patients for subsistence and transport to attend the health facilities are based on questionnaires that were administered to parents or guardians of children with a sore throat attending a primary care clinic (n=49) and to adult patients with RHD (n=48) attending the cardiac clinic at Groote Schuur Hospital in Cape Town, South Africa, in 2010.

The standard of care for treating adverse effects of penicillin, PTA, rheumatic fever, and RHD is based on several sources, as detailed in Table 4. These sources include the National Guidelines on Primary Prevention of Rheumatic Fever and RHD at the primary level,32 the South African Medicines Formulary,35 the Standard Treatment Guidelines and Essential Drugs List,36 local hospital treatment protocols, and expert opinion. Patient data from Groote Schuur Hospital were used in some of the cost calculations: inpatients with RHD on the CLINICOM information system of the hospital department of Medical Informatics, outpatients with RHD on the REMEDY registry,37 and patients on the database of the Division of Cardiothoracic Surgery at Groote Schuur Hospital who had valve surgery.

Utilities
Utility values were derived from the literature (Table 5), with the exception of the utility of RHD, which was derived from a local survey of 48 adult patients with RHD attending the Cardiac Clinic at Groote Schuur Hospital during September to December 2010. Patients were asked 5 questions related to the dimensions of mobility, self-care,
Table 5. Utility Variables Used in the Decision Tree Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case</th>
<th>Range</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility of ARF</td>
<td>0.995</td>
<td>0.9000–0.999</td>
<td>Neuner 17</td>
</tr>
<tr>
<td>Utility of RHD without surgery</td>
<td>0.848</td>
<td>0.7500–1.000</td>
<td>Patient survey†</td>
</tr>
<tr>
<td>Utility of RHD post-surgery (adults)</td>
<td>0.881</td>
<td>0.8000–0.950</td>
<td></td>
</tr>
<tr>
<td>Disutility of ARF‡</td>
<td>−0.208</td>
<td>−0.0250 to −2.04</td>
<td>Neuner 17</td>
</tr>
<tr>
<td>Disutility of anaphylaxis</td>
<td>−0.025</td>
<td>−0.0080 to −0.050</td>
<td>Neuner 17</td>
</tr>
<tr>
<td>Disutility of PTA</td>
<td>−0.014</td>
<td>−0.0050 to −0.027</td>
<td>Neuner 17</td>
</tr>
<tr>
<td>Disutility of rash</td>
<td>−0.002</td>
<td>−0.0004 to −0.004</td>
<td>Neuner 17</td>
</tr>
</tbody>
</table>

ARF indicates acute rheumatic fever; PTA, peritonsillar abscess; and RHD, rheumatic heart disease.
†Grote Schuur Hospital September to December 2010 (n=48).
‡ Disutility measured in years lost in 1 year a maximum if death occurs.

Data Analyses
All analyses were conducted using TreeAge Pro Version 2011. Incremental cost-effectiveness ratios (ICERs) are calculated as the incremental cost per quality-adjusted life year (QALY) gained. One-way sensitivity analyses were performed on all variables with sensitivity ranges as tabulated in Tables 2 to 5. In addition to the absolute ICERs, we also highlight where strategies would not be acceptable at various willingness to pay (WTP) thresholds. The WHO Commission on Macroeconomics and Health suggested that interventions that add 1 QALY for less than the annual income per capita are very cost-effective and those that cost <3 times the per capita income are considered cost-effective. Interventions above this WTP of 3 times the per capita income are thus not considered cost-effective. For South Africa, the gross domestic product per capita was approximately $10000 for the year 2010, and thus using the WHO criteria, $30000/QALY when compared with the CDR 3 strategy was eliminated because it both costs more and leads to fewer QALYs than the treat all strategy and was thus eliminated. The CDR 2+, culture CDR negatives and the CDR 3+, culture CDR negatives strategies are eliminated by extended dominance by a blend of the CDR 2+ and the culture all strategy. Extended dominance is defined as those strategies with a higher ICER than a more effective option. The next strategy that was on the efficiency frontier was the culture all strategy, at $127600/QALY, it is well above the WTP for South Africa.

Sensitivity Analyses
In the base case analysis, the prevalence of GAS was estimated at 15%. However, the results were sensitive to the prevalence across a plausible range of 1.6% to 30%. At a GAS prevalence of 1.6%, the least costly strategy was CDR 3+ alone, with culture all being the most effective but with an ICER of $130000/QALY when compared with the CDR 3+ strategy. All other strategies were eliminated. This value is well above the 3 times gross domestic product/capita that the WHO recommends for a cost-effective intervention. Once the prevalence exceeds 2.9%, however, the CDR 2+ strategy becomes the lowest cost strategy, with the CDR 3+ strategy being the next best strategy with an ICER of $198/QALY. From 2.9% until 7.3% prevalence, the CDR 2+ strategy remains the lowest cost strategy and the ICER for CDR 3+ below the $300000/QALY threshold of 3 times gross domestic product/capita. Beyond a prevalence of 12.9% up to 30%, the treat all strategy has the lowest cost, with

Results
In evaluating the ICERs, each strategy’s costs and effects were evaluated compared with the least costly intervention. Compared with the treat all strategy, the CDR 2+ strategy yielded greater discounted QALYs, which resulted in an ICER of $136/QALY compared with the treat all strategy and thus is the preferred strategy with a WTP of $30000/QALY. Compared with the CDR 2+ strategy, the CDR 3+ strategy was dominated because it both costs more and leads to fewer QALYs than the treat all strategy and was thus dominated. The CDR 2+, culture CDR negatives and the CDR 3+, culture CDR negatives strategies are eliminated by extended dominance by a blend of the CDR 2+ and the culture all strategy. Extended dominance is defined as those strategies with a higher ICER than a more effective option. The next strategy that was on the efficiency frontier was the culture all strategy, but at $127600/QALY, it is well above the WTP for South Africa.

Table 6. Costs, Effects, and Incremental Cost-Effectiveness of Strategies for Primary Prevention of Acute Rheumatic Fever/ Rheumatic Heart Disease* 

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost, $US</th>
<th>Incremental Cost</th>
<th>Effect (QALY)</th>
<th>Incremental Effect</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat all</td>
<td>11.19</td>
<td>0.01</td>
<td>22.939936</td>
<td>0.000066</td>
<td>136</td>
</tr>
<tr>
<td>CDR 2+</td>
<td>11.20</td>
<td>0.01</td>
<td>22.940002</td>
<td>0.000066</td>
<td>136</td>
</tr>
<tr>
<td>CDR 3+</td>
<td>13.00</td>
<td>1.80</td>
<td>22.939961</td>
<td>−0.000041</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>Treat none</td>
<td>14.39</td>
<td>3.19</td>
<td>22.938999</td>
<td>−0.000103</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>CDR 2+, culture CDR negatives</td>
<td>16.42</td>
<td>5.22</td>
<td>22.940017</td>
<td>0.000015</td>
<td>(Dominated)*</td>
</tr>
<tr>
<td>CDR 3+, culture CDR negatives</td>
<td>23.89</td>
<td>12.69</td>
<td>22.940101</td>
<td>0.000099</td>
<td>(Dominated)*</td>
</tr>
<tr>
<td>Culture all</td>
<td>27.21</td>
<td>16.01</td>
<td>22.940128</td>
<td>0.000126</td>
<td>127600</td>
</tr>
</tbody>
</table>

CDR indicates clinical decision rule; ICER, incremental cost-effectiveness ratio; and QALY, quality-adjusted life year.
*Eliminated by extended dominance—those strategies that are not eliminated by any 1 strategy but by a mixed strategy of 2 other programs and have higher ICERs than a more effective option.
the CDR 2+ strategy remaining preferred and having an ICER below $30,000/QALY.

We assumed in our base case that 0.3% of those with GAS will develop ARF if untreated. In our sensitivity analysis, we varied the probability from 0.1% to 5%. At a probability of 0.1% to 0.29% and a WTP of $30,000/QALY, the CDR 2+ is the least costly ($10–$12 per patient) and the preferred strategy. Above 0.29%, the treat all strategy is the lowest cost strategy. However, from 0.29% to 1%, the CDR 2+ is still the preferred strategy, with ICERs ranging from $5/QALY to $29,000/QALY using the standard WHO WTP threshold of $30,000/QALY. Beyond 1%, the treat all strategy is preferred. The culture all strategy never has an ICER of below $120,000/QALY, which is found when the risk of developing ARF from GAS is 0.3%, and the ICER rises as the probability increases.

The results were also sensitive to the probability of anaphylaxis from treatment. Using a WTP of $30,000, both 2-stage strategies were preferred once the risk of anaphylaxis reached >3.4 per 10,000. However, the culture all strategy was never preferred unless the WTP was increased to $100,000, and this only occurred as the risk of anaphylaxis approached 4.1 of 10,000 or 4 times the baseline assumption.

When we varied the lifetime risk of developing RHD subsequent to ARF from 50% to 75%, there was no significant change in the results. Similarly, the results were not sensitive to a change in the probability of patients with ARF receiving secondary prevention from 0% to 90%. Using a very conservative WTP of $200,000, the results were also insensitive to the effectiveness of antibiotic treatment to prevent PTA, ARF (primary), or RHD (secondary) across the range of values tested. Furthermore, the results were not sensitive to the whole range of estimates for the probability of dying from ARF, induction of rash, and dying from anaphylaxis.

We further evaluated the sensitivity to changes in the test characteristics. At no level below our base case estimate (0.92) for the sensitivity of the CDR 2+ screening test were there significant changes in the results. However, with a CDR 2+ sensitivity of 0.97, the CDR 2+ strategy would be the preferred strategy. Regardless of the specificity of the CDR 2+, the treat all strategy remained dominant, with no changes in the results using a WTP of $30,000. The results were not changed in the various ranges for the sensitivity or specificity of the CDR 3+ either. When testing the range of values for the sensitivity of the throat culture from 90% to 100%, the treat all strategy remained the lowest cost strategy, and there were no changes in the results until the sensitivity of throat culture exceeded 98%. In this case, it made both 2-stage strategies using both CDR and cultures acceptable only when using a WTP of $200,000. Only at a sensitivity of >98% does the culture all strategy have an ICER at $186,000/QALY. The results were insensitive to changes across the range of specificity values we tested. The results did not change significantly across the whole range of sensitivity and specificity values we tested for the CDR 3+ criterion. All results assumed a rate of 100% return for culture results. If the follow-up rate declines, however, then the ICERs increase even more for the culture all strategy.

We assumed that the cost of throat culture requires a return visit. Even when we allowed for a low-cost ($1) value for phone follow-up, there is still a patient cost to return to the clinic to get the injection, so the cost is only minimally reduced. Even under these assumptions, the culture all strategy was not acceptable compared with the clinical scores or treat all strategies. The results were not sensitive to the cost of the IM injection, the clinic visit cost, the cost of managing ARF, throat cultures, valve surgery, managing RHD long term, discount rate, or any other costs tested across the ranges reported in Table 4. The only utility for which the results were sensitive was for those who survived a prior ARF attack. Because the utility was lowered from our base case of 0.995, the ICER for the CDR 2+, culture CDR negatives increased; and at a threshold of 0.91, all strategies were dominated by the treat all strategy.

Our probabilistic sensitivity findings were similar to the above findings (Figure 2). At a WTP of $10,000/QALY, the CDR 2+ strategy was the preferred strategy in 60% of the iterations and >20% in treat all, with the remainder of the iterations being made up of CDR 3+ (10%) or no treatment. At $30,000/QALY, the results were similar, with a slight decrease in preference of the CDR 2+. At $150,000/QALY, the CDR 2+ and the treat all strategy were still the preferred strategy >50% of the time. Culture all is only a preferred strategy 22% of the time at this very high ratio. The analyses were not sensitive to changes in the range of utilities for RHD, anaphylaxis, or the disutility of ARF, anaphylaxis, rash, or PTA.

**Discussion**

ARF and RHD have a relatively high incidence in South Africa and are a significant health concern in developing countries.\(^\text{41,42}\) Our analyses show that in an urban South African setting, a strategy of treating all children with IM penicillin who present to primary care centers with pharyngitis is the least costly strategy, costing about $11 per case of pharyngitis. The most cost-effective strategy, however, was using a CDR with ≥2 or more clinical criteria of enlarged cervical nodes, absence of rhinitis, or absence of rash. It was minimally more expensive, resulting in a very good return of about $150 per QALY gained. This value is well below the recommended threshold of 3 times the GDP/capita recommended by the WHO for ICER.\(^\text{43}\) The remaining strategies either did not result in long-term QALYs gained or resulted in too high an incremental cost per QALY gained. Culturing everyone compared with the clinical score was prohibitively expensive at more than $125,000 per QALY. Our analysis is sensitive to 2 key variables: the likelihood of developing ARF with GAS pharyngitis, also known as the attack rate; and the prevalence of GAS. The literature suggests a fairly broad range of estimates for the attack rate from as high as 5%\(^\text{44}\) in epidemics to as low as 0.3%\(^\text{44}\) and possibly lower in stable endemic situations. When the attack rate is closer to the epidemic rate, treating everyone may be a preferred strategy, especially if skin testing for drug allergy is possible. When the attack rate is closer to the endemic rates reported in the United States, then clinical scoring is a preferred strategy. Given that it is unlikely that studies to evaluate attack rates will be conducted for ethical reasons, a region may not be able to assess its attack rate and will thus have to assume the lower attack rate unless an epidemic is occurring. When the prevalence of GAS is <13%, then the clinical rules with either 2 or 3 positive
findings become preferred strategies, and treating everyone is no longer a preferred option. Therefore, it remains essential for countries or regions to know their local GAS prevalence.

Treating everyone is a low-cost strategy because it essentially has a sensitivity of 100%, and the potential downstream costs of ARF and RHD that are prevented per GAS case outweigh the costs of the relatively cheap IM injection of about $1. Overall, the incremental costs of the program to treat all cases of pharyngitis during the lifetime of children from ages 3 to 15 years would cost about $580 per 100,000 children per year. Furthermore, the health benefits gained from preventing ARF or RHD outweigh the relatively minimal risk of severe reactions from anaphylaxis in aggregate, provided the incidence of ARF after untreated pharyngitis remains >1%. The same was found in a US study that reported that treating all children with antibiotics is the least costly strategy. Lieu et al also found that a treat all strategy leads to the greatest reduction in potential GAS complications (suppurative and non-suppurative) but led to many minor drug reactions and rare fatal reactions. They did not calculate the QALYs, however, but only the cost per ARF, RHD, or suppurative complication, which was lowest with the treat all strategy. Because they did not examine overall mortality, they could not make an overall comparison of the strategies. Tsevat et al found the culture strategy less costly, but they did not include the long-term costs of secondary prophylaxis or the cost of RHD and its adverse health consequences, which are some of the major motivations for ARF prevention. Van Howe et al included RHD complications and costs but grossly underestimated the probability of GAS pharyngitis. They used one fiftieth of Siegel’s estimate of 0.3% as the likely probability of untreated GAS converting to ARF, citing more recent evidence suggesting that the incidence of ARF has decreased 50-fold since 1961. This value represents incidence in the US population, however, which has markedly increased treatment rates for pharyngitis and different crowding and socioeconomic conditions. It may not reflect the natural history of the disease in a relatively untreated population. We therefore used the estimate of 0.3% to reflect the relatively low treatment rates and more crowded conditions in South African urban townships. Michaud et al, using the estimated attack rate of ARF from GAS of 3%, estimated the cost-effectiveness of primary prevention at $22,000 to $33,000 per disability-adjusted life year averted for treatment of all GAS, including asymptomatic cases. This assumed that 50% of patients never come to the clinic and that 30% are asymptomatic. Because we only evaluated symptomatic patients that present, this would be about $3500 per disability-adjusted life year averted, according to their estimates in high endemic settings.

The authors of the 2 studies, which show that a treat all strategy leads to fewer total deaths, still did not recommend this strategy. Their resistance stems from 2 concerns. The first concern is about unnecessary severe reactions from the treatment as part of the desire to fulfill the Hippocratic oath’s “primum, non nocere.” Certainly, there are negative health consequences to treat false positives, as well as not treating false negatives. However, we are also reminded of Benjamin Franklin’s lament of not inoculating his son, whom he lost to smallpox in 1736:

“I bitterly regretted that I had not given it to him by inoculation. This I mention for the sake of parents who omit that operation, on the supposition, that they should never forgive themselves if a child died under it. My example shows the regret may be the same either way, and that therefore the safer should be chosen.”

The second concern relates to the potential risk of drug resistance with the overuse of antibiotics. There have been several instances of large-scale use of penicillin to treat suspected streptococcal pharyngitis in Puerto Rico, Guadeloupe and Martinique, and Cuba for the primary prevention of ARF. There were no reports of drug resistance to penicillin in GAS in these countries, and to the best of our knowledge, all
GAS strains remain sensitive to penicillin, and even the minimum inhibitory concentrations have not changed in >70 years. Therefore, the concern about drug resistance to penicillin in GAS is not supported by the present evidence. Therefore, we were unable to calculate the potential health or medical costs of drug resistance, and neither have any other cost-effectiveness analyses of primary prevention.

If a society wishes to value death averted from anaphylaxis greater than death averted from ARF, suppurative complications, or from RHD, then this valuation should be made explicit and quantifiable so that appropriate decisions could be made. However, we are not sure whether this rationale would not also need to be applied to all interventions where there is some acceptable up-front risk for some long-term reduction in overall risk, as is seen with procedures such as cardiac surgery for ischemic heart disease. Similarly, if there is a concern about antibiotic resistance, then models to evaluate this harm should be developed. If either of these concerns is heavily weighted, a strategy using a clinical rule first and then culturing only those who do not meet clinical thresholds could be a more palatable but perhaps more expensive alternative.

Our analysis differs from previous models in other ways as well. Lieu et al23 do not place utilities on different health states or follow a full life course, and thus they did not report a cost/QALY, only a cost per case averted of ARF. Tsevat et al14 report costs per life years saved, but no utility adjustments a cost/QALY, only a cost per case averted of ARF. Tsevat et al14 report costs per life years saved, but no utility adjustments are made for the various health states, and the long-term costs of secondary prevention or RHD are not included. Our model considers the full set of downstream events and costs associated with untreated GAS infection, including increased risk of ARF, development of RHD, heart failure, and the need for valve surgery. Fewer missed diagnoses (false negatives) in a setting with a relatively high incidence of post-GAS cardiac sequelae minimize the costs of later treatment of ARF and RHD, weighed against the comparatively minor expense and possible antibiotic resistance arising from the treatment of false-positive cases.

We did not consider the use of rapid antigen testing in this analysis for several reasons. First, this study was designed to assess the cost-effectiveness of diagnostic approaches that are in use in a South African urban setting. Rapid antigen testing is not used in the South African public health service, which caters to >80% of the population. Second, this study was designed to delineate the optimal strategy within the available resources, which is likely to be rapidly translated into policy and practice. Finally, the performance of the rapid antigen test is more appropriate for countries with low endemicity of ARF and RHD, given the high specificity and low sensitivity of this screening test. Our study shows that approaches with a high sensitivity are preferable in settings with a high incidence of ARF. An additional limitation is that we report on the cost-effectiveness only on those who report to the clinic for care. We recognize that children do not always have access or are unable to present with pharyngitis in low-income settings or that many cases of GAS are asymptomatic. Wider efforts to reduce ARF and RHD must therefore not be neglected if the burden is to be controlled.

In conclusion, we demonstrate that a strategy of treating all patients presenting in urban primary care clinics with symptomatic pharyngitis and at least 2 additional features is the most cost-effective intervention for the prevention of ARF and RHD in populations with a high burden of these diseases, such as among children living in sub-Saharan Africa and other developing countries. The findings of this study have implications for public health policy.

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Disclosures

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