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Development, Validation, and Cost Effectiveness of Clinical Prediction Rules for Group A Beta Hemolytic Streptococcal Pharyngitis In Children From Lower and Upper Middle Income Countries

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Development, Validation, and Cost Effectiveness of Clinical Prediction Rules for Group A Beta Hemolytic Streptococcal Pharyngitis In Children From Lower and Upper Middle Income Countries

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

by

Mehret Tsega Assefa

2014

ABSTRACT OF THE DISSERTATION

Development, Validation, and Cost Effectiveness of
Clinical Prediction Rules for
Group A Beta Hemolytic Streptococcal Pharyngitis
In Children From Lower and Upper Middle Income Countries

by

Mehret Tsega Assefa
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2014
Professor Anne Rimoin, Chair

Background: An estimated 3% of untreated group A beta hemolytic streptococcal (GABHS) pharyngitis can lead to rheumatic fever (RF), resulting in rheumatic heart disease (RHD) and other serious nonsuppurative sequelae of infection (1-5). Prevalence of disease is disproportionate with the greatest burden among children and adolescents of developing countries; an estimated 95% of RF and 79% of RHD cases are from low income countries (5). Accurate diagnosis and prompt antibiotic treatment of GABHS pharyngitis is a simple and effective strategy for primary prevention of RF and RHD. Accurate diagnosis is difficult without laboratory testing due to similarities in signs and symptoms with other causes of pharyngitis.

Due to financial constraints, laboratory capabilities are often limited, forcing many physicians in low and middle income countries (LMICs) to either prescribe antibiotics indiscriminately or rely on clinical prediction rules (CPRs). CPRs provide a practical alternative for diagnosis in the absence of laboratory testing. However, few CPRs have been derived specifically for LMICs. Studies have shown that CPRs can be cost effective in hospital settings, but few have been conducted for children from LMICs (6, 7).

Methods: Children 2-12 years of age presenting with complaint of sore throat were enrolled in four urban university pediatric outpatient clinics from September 2001 to August 2005 in Rio de Janeiro, Brazil, Cairo, Egypt; Riga Latvia and Zagreb, Croatia. The diagnostic component of the study (Chapters 4-5) consisted of generating CPRs for the 1,993 children enrolled in the study. It also consisted of external validation of a) published CPRs from the literature, and b) study developed CPRs. The cost effectiveness analysis component of the study (Chapter 6) assessed the cost effectiveness of the CPR developed for Egypt versus five alternative diagnostic and management strategies.

Summary: The dissertation consists of findings from three papers (Chapters 4-6). In paper 1 (Chapter 4), five different CPRs were developed for use in Egypt, Brazil, Latvia, Croatia, and the combined study population. In paper 2 (Chapter 5), external validation of published and study CPRs suggested country specific CPRs were better

in the population for which they were developed. In paper 3 (Chapter 6), Culture Only was the most cost effective strategy at baseline estimates; however, the Egypt CRP was cost effective when sensitivity and specificity were at or above 88%.

The dissertation of Mehret Tsega Assefa is approved.

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2014

DEDICATION

This dissertation is dedicated to my wonderful family and friends for their unending love, support, and encouragement throughout this process. Thank you.

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CHAPTER 1. INTRODUCTION

Chapter 1. Introduction

PROJECT RATIONALE

Group A beta hemolytic streptococcal (GABHS) pharyngitis is the precipitating cause of rheumatic fever (RF) and rheumatic heart disease (RHD). GABHS pharyngitis is a common illness, which left untreated can cause disease of the cardiac valves known as RF (1-5). Primary prevention of RF is accomplished through identification and antibiotic treatment of GABHS infection to eradicate the organism from the pharynx (7, 8).

Current understanding of the epidemiological and clinical presentation of GABHS derives largely from studies in high-income settings where sore throat is a common complaint in pediatric populations (5). In low and middle-income settings, there are few prospective studies that provide data on the epidemiological and clinical presentation of GABHS pharyngitis. GABHS presentation can vary by region (6, 9) and therefore, it is important to understand how it presents in low and middle-income countries (LMICs).

Improved diagnosis of GABHS pharyngitis will have two major impacts: 1) decrease in burden of preventable cardiac disease; and 2) decrease in indiscriminate antibiotic use when lab diagnosis is not available.

There is little information on effective clinical prediction rules (CPRs) for these settings where laboratory diagnosis may not be

readily available. Therefore, this study aims to develop CPRs with improved sensitivity and specificity.

Although antibiotic resistance to penicillin has not been reported, resistance to other antibiotics for treatment of GABHS pharyngitis has been reported in several countries (10-21). As long as penicillin sensitivity remains, cost-effective treatment of pharyngitis and prevention of RF/RHD is possible. However, indiscriminate antibiotic use threatens the sensitivity of penicillin by increasing the risk of antimicrobial resistance (AMR). Antimicrobial resistant GABHS can circumvent antibiotics, preventing treatment and lead to an increase in transmission (of penicillin-resistant GABHS), increased healthcare costs, morbidity, and mortality (22). This analysis will provide important new information to improve accurate diagnosis of GABHS pharyngitis in LMICs and therefore reduce indiscriminate use of antibiotic treatment.

The age structure of most LMICs is younger compared to higher income countries (HICs) and since GABHS pharyngitis is greatest among children 5 – 15 years, the proportion of susceptible individuals is of great public health concern (3, 5, 6). While there are few epidemiological studies on GABHS in LMICs, the few that have been conducted have demonstrated the burden of GABHS pharyngitis and its complications are still prevalent in LMICs. A recent school based study estimated the prevalence of RHD among Egyptian children to be 1.5 cases per 1,000 versus the 3.6 cases per 1,000 found among

Brazilian children (5). Another study of Egyptian school children conducted suggested that there is also variability within the same country reporting a prevalence of 5.1 cases per 1,000 (6). While these estimates are high[1], they are most likely an underestimate of the true burden of RF/RHD[2] (5, 6).

In Brazil, a 1992 study among 10 – 20 year olds documented the incidence of acute RF incidence as 360 cases per 100,000/year; this represents the highest reported incidence from the Latin American and Caribbean region and nearly as high as those reported from Indigenous Australians (374 – 815 cases per 100,000 per year), the highest rates (5). Although recent reports have shown a steady decease in crude mortality rates from RF and RHD in Brazil and other Latin American countries, this decrease more likely reflects issues with data collection methodologies and reporting strategies rather than the same decline seen in high-income countries. Therefore, the 1995 crude mortality rate of 1.0 is likely an underestimate of the true burden of RF and RHD (5).

These studies illustrate the burden of GABHS pharyngitis and RF/RHD are still major public health problems. The need for an improved CPR to accurately diagnose cases of streptococcal pharyngitis and ensure appropriate treatment of infected individuals is evident. By accurately and cost effectively predicting culture positive

[1] Some of the highest rates are found in indigenous populations of Australia and New Zealand (126).
[2] Most studies are conducted in schools (where more severe cases of RF don't present) and hospitals (where mild to moderate RF don't present)(5,6).

streptococcal pharyngitis, CPRs can limit treatment of non-cases and thereby decrease the probability of AMR, and facilitate primary prevention of RF.

PROJECT OBJECTIVES/AIMS

This dissertation project has three main objectives:

1. Develop five CPRs (four country specific and one for all countries combined)
2. Establish external validity of each study developed CPR, and several published CPRs
3. Estimate the cost effectiveness of the Egypt CPR (study developed) versus five alternative diagnostic and management strategies

Country Specific and Overall CPR Development (Chapter 4)

The first aim was to generate five CPRs – a single CPR for each of the four countries (Egypt, Brazil, Latvia, and Croatia) and one CPR for all countries combined. The CPRs were developed based on clinical presentations (signs/symptoms) and epidemiologic factors for each of the study populations for the presumptive diagnosis of GABHS pharyngitis in the absence of laboratory testing. Individual epidemiological and clinical factors, and various combinations of both, and their association with GABHS pharyngitis were explored to identify an optimum set of factors for the new rules. Regression models were used to determine which factors were predictive of GABHS

pharyngitis and a simple additive scoring system using beta coefficients was developed to provide an estimate of the probability of a GABHS positive culture.

External CPR Validation (Chapter 5)

The second aim was to determine the external validity of published CPRs from the literature and study developed CPRs. The study validated the efficacy of CPRs for GABHS pharyngitis proposed by Steinhoff, Smeesters, Sahin, Attia, Nandi, Breese, Centor, Wald, Abu Reesh, and McIsaac (3, 4, 23-31); and for the five study developed CPRs (Chapter 4) in the Egypt, Brazil, Latvia, Croatia, and combined study populations. It assessed the association between clinical diagnosis and culture status utilizing diagnostic test performance measures to estimate the accuracy of the CPRs developed for (and validated in) high, middle, and low-income countries. These rules were assessed to determine if comparable or improved sensitivity and specificity values could be found for the study populations, where sensitivity was high enough to prevent complications of GABHS pharyngitis by ensuring appropriate treatment of true cases and high enough specificity to prevent drug resistance from over prescription of antibiotics.

Cost Effectiveness Analysis (Chapter 6)

The third aim was to conduct a cost effectiveness analysis (CEA) of the CPR developed for Egypt versus five alternative diagnostic and management strategies for GABHS pharyngitis. The CEA was conducted to estimate the costs and effects of each of the six diagnostic and

management strategies to determine which strategy was the least expensive and most effective. A decision tree incorporating the alternatives was generated to examine the costs and benefits associated with the following six strategies: 1) No test, no treatment; 2) No test, treat all (empirical); 3) Clinical diagnosis, treat positives only (CPR only); 4) Culture, treat positives only (culture only); 5) Rapid antigen detection test (RADT), treat positives only (RADT only); and 6) Clinical diagnosis and rapid test, treat positives only (CPR + RADT). The CEA was conducted from the societal perspective and examined short-term costs and benefits. Sensitivity analysis was used to assess the accuracy of the estimates and assumptions used in the analysis.

CHAPTER 2. LITERATURE REVIEW OF GROUP A BETA HEMOLYTIC STREPTOCOCCAL PHARYNGITIS: EPIDEMIOLOGY, DIAGNOSIS, TREATMENT, AND COST EFFECTIVENESS

Chapter 2. Literature Review of Group A Beta Hemolytic Streptococcal Pharyngitis: Epidemiology, Diagnosis, Treatment, and Cost Effectiveness

EPIDEMIOLOGY OF GROUP A BETA HEMOLYTIC STREPTOCOCCAL PHARYNGITIS, RHEUMATIC FEVER, AND RHEUMATIC HEART DISEASE

Group A Beta Hemolytic Streptococcal Pharyngitis

Group A beta hemolytic streptococcus (GABHS) is a bacteria that is commonly found in the throat or on the skin and can cause a wide spectrum of disease from subclinical (asymptomatic) to severe infection (Table 1) (1, 3, 5, 32). GABHS diseases infections are common among children and adolescents of LMICs where conditions which promote efficient transmission (poverty, overcrowding, etc.) are present, and where prevention and treatment are not readily available (5).

Streptococcal pharyngitis is the most common group A streptococcal disease worldwide with nearly 616 million new cases each year; however, distribution of disease is disproportionate as the incidence is 5 – 10 times higher in developing countries and 3 times higher among children and adolescents under 15 years (1, 4, 5). Furthermore, GABHS is the most common bacterial cause of pharyngitis, particularly among children between 5 – 15 years, and is responsible for 15 – 30% of cases among children and 5 – 10% among adults (Table 2) (6, 33).

The burden of GABHS pharyngitis is highest among children 5 – 15; however, this age group is often neglected in global health disease monitoring.[3] Consequently, epidemiological data on GABHS pharyngitis and its sequelae are difficult to obtain from LMICs. Untreated, GABHS pharyngitis can lead to rheumatic fever (RF), rheumatic heart disease (RHD), and other serious sequelae of infection causing major health problems for children of developing countries (Table 3) (1-5). According to the World Health Organization (WHO), the global estimate for the prevalence for RF is 1.88 million cases with 188,000 new cases annually (5). The global estimate for the prevalence of RHD is 15.6 million cases with 282,000 additional cases annually and 233,000 deaths per year (5). Of these global estimates, 95% of RF and 79% of RHD cases are from lower income countries (5).

Incidence of GABHS varies greatly by age, geographic region (intracountry and intercountry), climate zones (temperate versus tropical)[4], environmental factors, socioeconomics, and health care accessibility (6, 34-36). Humans (especially children) are the natural reservoir and the primary carriage sites are the nasopharnx and oropharynx, however, it can also reside in skin, anal, and vaginal mucosal sites (37, 38). This highly infectious pathogen is transmitted person to person during the symptomatic phase of infection by close contact through inhalation of large droplets or via direct contact

[3] Generally, global health disease monitoring targets children under age 5 or adolescents. Data on children between the ages of 5 and 15 in LMICs is limited.
[4] In temperate climates, GABHS transmission occurs typically in the winter an early spring, whereas marked seasonal variation has not been observed as frequently in tropical climates.

with respiratory secretions (nasal and throat exudates) (6, 35, 37, 38).[5] Period of communicability for GABHS is greatest when acutely ill, however, can be infectious for an average of 2 - 3 weeks after infection when untreated (37, 39).

Rheumatic Fever and Rheumatic Heart Disease

Rheumatic fever and rheumatic heart disease are the result of a delayed host immune response (6). Data from observational and experimental studies on GABHS pharyngitis and subsequent complications have demonstrated the link between GABHS pharyngitis and RF/RHD. Approximately 0.3 – 3% of untreated GABHS pharyngitis will result in RF 1 – 5 after infection (6, 40). While various host, pathogen[6], and environmental factors may influence the presence and severity of infection, an individual's risk of RF increases to 75% with recurrent GABHS pharyngitis (Figure 1)(6, 40). The prevalence of recurrent RF is greatest in developing countries where likelihood increases immediately following the initial RF attack. Without prompt and appropriate treatment, recurrent attacks of RF can progress to RHD (41). RHD is one of the most common causes of cardiac disease in LMICs.[7] The majority of cases of RF occur in school age children (92%) and are seen equally in both males and females (42).

[5] Indirect transmission from contact with contaminated objects (utensils, toys, etc.) is also possible; however, its potential as an effective mode of transmission is limited (6, 34, 35).

[6] Rheumatogenic GABHS serotypes

[7] An estimated 50 – 80% of patients in developing countries suffering from carditis (inflammation of the heart) develop RHD (128). It is possible to diagnose RF in children younger than 3 years or older than 23, however, since 92% of cases are school age, disease occurrence outside this range is rare (42).

Although the pathogenic and immunogenic mechanism(s) involved in the development of RF and RHD are not clearly defined or understood, GABHS is recognized as the causal agent of RF/RHD (6, 41, 42). The direct and indirect determinates of RF/RHD include: 1) socioeconomic and environmental factors;[8] 2) other environmental factors such as seasonal variation;[9] and 3) healthcare factors.[10] These factors affect the exposure to and diagnosis of GABHS, the treatment of GABHS, and the disease progression to RF/RHD.

Pathogenesis

Group A beta hemolytic streptococcus (GABHS), a bacterial pathogen, is responsible for pharyngitis in 15 – 30% of children, 5 – 9% of adolescents, and 5 – 10% of adults (26, 35, 38, 39, 43). For successful GABHS infection, the organism must evade both the innate and adaptive immune systems. First, it must avoid the physical and mechanical barriers of the innate system to allow adhesion and secondly, it must circumvent opsonization by complement and type-specific antibodies of the adaptive system to prevent phagocytosis. Following a 2 – 3 week asymptomatic window, an autoimmune response to virulence factors (especially M proteins) of rheumatogenic GABHS serotypes begins the pathogenesis of RF and RHD (44, 45).

[8] Such as overcrowding and poverty, which increase the spread of GABHS and decreasing access to healthcare services, thereby resulting in increased incidence of GABHS, RF, and recurrent episodes. This also includes rheumatogenic serotypes, which vary geographically (6, 46, 47).
[9] Especially in temperate climates, which influences transmission by increasing close interpersonal contacts
[10] Especially for resource poor settings, where diagnostic ability, treatment availability, healthcare worker access, and public knowledge are adversely impacted due to restricted financial and personnel availabilities

While other streptococci can also cause pharyngitis, only group A has been shown to result in a cascade of autoimmune response leading to RF and subsequently RHD (6). The association between clinical manifestation and host immune response (i.e., severity) is influenced by three known factors of pathogenesis: the streptococcal pathogen, individual genetic predisposition[11], and environmental determinants (Figure 2) (6, 45).

The "rheumatogenic" GABHS strain infects a susceptible host resulting in pharyngitis (6, 46, 47). While the majority of RF cases follow symptomatic streptococcal infection of the upper respiratory tract, 30% - 50% can result from clinically inapparent pharyngitis (48, 49).

The CPRs developed in this analysis will aid in the prevention of RF/RHD by providing physicians with more sensitive and specific methods of diagnosis in the absence of laboratory diagnosis. Onset of RF is usually 2 – 3 weeks after the antecedent GABHS infection. The main objective is to prevent this period of autoimmune development (6, 40, 44).[12]

Lower Middle Income Countries (Egypt and Brazil) versus Upper Middle Income Countries (Latvia and Croatia)

[11] Genetic susceptibility is also evident by the fact that 0.3 – 3% of GABHS pharyngitis leads to RF (6, 22, 41, 43, 50). The reason certain individuals are predisposed is not entirely clear; however, findings from family studies illustrates the involvement of genetic predisposition (45).

Several studies addressing GABHS, RF, and RHD have been conducted in Egypt and Brazil; however, data from Latvia and Croatia are limited. The studies below have helped to clarify the epidemiology and clinical aspects of region specific GABHS infection and its suppurative and nonsuppurative complications. Geographic variability influences the genetic diversity of GABHS, which are important to the understanding of GABHS pathogenesis, disease, and complication. Differences in epidemiological and clinical presentation of GABHS pharyngitis between LMICs and HICs have been documented.

Egypt and Brazil

An assessment of cardiovascular pathology in Brazil suggested that 22% of adult cardiac failure admissions were due to valvular heart disease and 9.4% of all medical admissions (5). Another study found that 0.62% - 0.35% of hospital admissions were due to RF, with a 4 – 7% mortality rate (5). The average age of RHD is generally much younger in lower resource settings compared with higher income areas, possibly reflecting a younger population, higher RHD prevalence, more aggressive disease progression, and diminished access to healthcare (50).

Variability in incidence due to age has also been documented. A two year prospective study from the late 1960’s in Egypt demonstrated that the incidence of GABHS pharyngitis was inversely proportional to age, where incidence decreased as age increased with the highest incidence was among 2 to 4 year olds (5). Previous studies have shown that

Egyptian children present with GABHS pharyngitis at an earlier age (<5 years) compared with Brazilian children (more likely to be ≥ 5 years old), but that the highest frequency was 5 – 9 years for both countries (9).

Latvia and Croatia

From 1955 – 1994, Croatia experienced a significant reduction (95%) in the number and severity of RF and RHD cases (5, 50, 51). Nevertheless, studies from Eastern Europe on RF incidence in children demonstrate RF incidence is still higher compared to rates from HICs (5). In a nine year study conducted in Serbia, average incidence of tonsillopharyngitis was 76.2% and 166 cases of rheumatic fever were observed (20). Incidence among 4 – 18 year olds was highest in 1998, where 108.4 cases per 100,000 population were recorded. The study also tested GABHS sensitivity to penicillin, and resistance to penicillin was not found. Rimoin et al examined clinical variation and found that frequency of GABHS pharyngitis was highest among older children in Latvia (10 – 12 years) compared with Croatia (5 – 9 years) and little difference in incidence by age was observed in Croatia (9). Differences in seasonality were also reported, where most Croatian cases were seen in the autumn and Latvian cases in the winter (9).

DIAGNOSIS OF GROUP A BETA HEMOLYTIC STREPTOCOCCAL PHARYNGITIS, RHEUMATIC FEVER, AND RHEUMATIC HEART DISEASE

Clinical Presentation of GABHS Pharyngitis

The signs (Sx) and symptoms (Sy) of GABHS and non-GABHS overlap broadly and can be non-specific. Therefore, under ideal conditions, unless the physician is able to confidently exclude diagnosis of GABHS on clinical grounds, a laboratory test should be performed. In the U.S. and other high-income settings, antibiotic treatment is indicated after a lab test to confirm presence of GABHS. In low-income settings where bacterial culture or rapid tests are not readily available, clinicians must rely solely on clinical diagnosis and offer presumptive treatment. Therefore, the objective of this analysis is to find groups of signs and symptoms that are indicative of GABHS pharyngitis because independently, non-GABHS pharyngitis can present similarly. Common signs and symptoms include fever, sore throat, a lack of cough (and other signs/symptoms suggestive of viral infection), headache, tender anterior cervical lymph nodes, tonsil or pharyngeal exudates, abdominal pain, and palatal petechiae (Table 4) (26, 34, 35, 38, 52). These signs/symptoms generally have a rapid onset (38). After a short incubation period of 2 – 5 days, most children experience symptomatic pharyngitis, but asymptomatic infection is not uncommon (39).

Clinical Diagnosis of GABHS Pharyngitis

RF and RHD can be prevented with antibiotic treatment of streptococcal pharyngitis; however, accurate diagnosis of pharyngitis is initially required (1-3, 53). Clinical diagnosis of GABHS pharyngitis is not always accurate because signs and symptoms are difficult to

differentiate from other causes of pharyngitis, including viral and other bacterial causes (2, 3, 38, 39, 43, 53). Therefore, confirmation via laboratory diagnosis of streptococcal pharyngitis using throat-swab culture or rapid antigen testing is necessary for accurate diagnosis (1-3, 53). However, this may not be economically feasible for many developing counties where access to laboratory facilities is unavailable or restricted due to limited resources. Because of the higher incidence of RF/RHD, physicians in low-income regions must either prescribe antibiotics indiscriminately for all patients regardless of GABHS pharyngitis or alternatively rely on CPRs (combinations of signs and symptoms) for diagnosis, thereby limiting treatment to GABHS infected patients (2, 4). Since systematic use of antibiotic treatment for all patients infected with pharyngitis (regardless of GABHS status) may result in antimicrobial resistance, the use of CPRs is preferred; however, few have been generated or validated in developing countries (1).

Clinical Prediction Rules for GABHS Pharyngitis

The majority of CPRs were generated for use among adults in resource rich settings and they had a tendency to be complex with numerous clinical and epidemiological variables or requisite laboratory work; however, more recent efforts have lead to validation of these rules in other populations, and creation of new rules targeting new populations. Studies by Stillerman, Hoffman, and Walsh included numerous signs and symptoms and were conducted in resource rich setting like the United States and Europe (54-56). While Breese

created a CPR for children, it included white blood cell count which required laboratory access, and therefore is not applicable (57). Some of the original CPRs including those by Centor, Breese, and Walsh, although originally developed among adult populations, have been validated and modified in different age and geographic populations (26-28, 58-63). Of these, Centor considered is the best validated rule, with only four signs/symptoms (tonsillar exudate, swollen/tender cervical lymph nodes, no cough, and fever >38.5°C) (25, 52).

While most studies have been focused on resource-rich settings, there have been rules validated in children of lower income countries. A recent study conducted in Indian children, used a CPR adopted from Breese (a 9 item additive score with clinical and epidemiological variables) that was applied. Eight variables (age, seasons, fever, erythema of pharynx, size of tonsil, pharyngeal exudate, lymphadenopathy, and pain in throat) were identified where a score of 15 or more (range: 4 – 36) was highly predicative of GABHS pharyngitis (91% sensitivity, 98% specificity) (28). The Breese rule was also validated in two different age groups of Turkish children and found that the rule had greater sensitivity among children older than 3 years (61). However, there has been evidence of diminished effectiveness of CPRs developed in higher income countries for use in lower income countries (1, 2). Fisher et al found great variability when the Breese, Centor, Wald, and McIsaac rules for the original North American populations were applied to Egyptian children (1).

Clinical prediction rules with low sensitivity are another problem for developing countries with high RF/RHD. The WHO Acute Respiratory Infection (ARI) Control Programme devised a clinical decision rule for countries without access to laboratory testing, where children under 5 years with both pharyngeal exudate and tender, enlarged anterior cervical lymph nodes, should be diagnosed as positive for streptococcal pharyngitis and treated with antibiotics (1-4, 53). Recent studies conducted in low and middle-income countries evaluated the effectiveness of the WHO clinical decision rule and found it to have high specificity, but low sensitivity (93 – 97.4 and 0 – 12 respectively)(1-4). While high specificity limits unnecessary antibiotic use, for developing countries where the burden of RF/RHD is greatest, high sensitivity decision rules are essential to prevent further cases of RF/RHD and therefore the WHO rule is an inappropriate choice for resource poor settings.

The two rules generated for Egyptian children, Abu Reesh (3) and Steinhoff (4), were critical in demonstrating the transportability of CPRs developed in low income settings to other similarly low settings. The Abu Reesh rule, found that the presence of pharyngeal exudate or enlarged anterior cervical nodes was more sensitive (84%) than specific (39%), but that for children of developing countries, a more sensitive rule was preferable (3). The study conducted by Steinhoff et al suggested the use of a three-variable rule (enlarged cervical nodes, no rhinitis, no rash) with high sensitivity, but low specificity (92 and 38 respectively) when two or more clinical signs

are present (4). When Smeesters et al applied the Steinhoff rule to a population of Brazilian children, there was only a 20% reduction in unnecessary antibiotic use (versus 37.5%) and 12.5% undetected cases of GABHS pharyngitis (versus 9%) (30). While geographic fluctuation is expected due to variation in the clinical presentation of GABHS pharyngitis, the rule was still able to reduce unnecessary antibiotic use, although not to the extent of the Smeesters rule developed for the identification of non-GAS pharyngitis (9, 30). The Abu Reesh rule (also proposed by Steinhoff et al) was validated in Turkish children, which found a reduced sensitivity and slightly increased specificity compared to the original Egyptian population, but overall it was similar to one of two new recommended combinations based on results from the study population (29).

Clinical prediction rules ranging from high to low income countries between 1975 and 2006 for patients of various years are listed in Table 5. Generally, most rules for school age children and adolescents include variation of the following clinical signs/symptoms and epidemiological variables: tender (swollen/enlarged) cervical anterior nodes; tonsillar or pharyngeal exudate; fever of at least 38°C; no cough; difficulty/pain swallowing; no rhinitis; and season.

Laboratory Diagnosis of GABHS Pharyngitis

The microbiological tests used in the laboratory diagnosis of GABHS are either throat-swab culture or rapid antigen detection test (RADT). Identification of *Streptococcus pyogenes* by throat-swab culture on

blood agar at 35 – 37°C and confirmation with bacitracin is the gold standard for diagnosis of streptococcal infection because of its high sensitivity and specificity (6, 32, 53). Samples must be properly collected from the tonsils and posterior pharyngeal wall with swabs by vigorous rubbing to ensure accurate results and increase culture sensitivity (6, 35). Once plated, 18 – 24 hours are required for incubation and are reexamined at 48 hours if culture is negative (6, 43). Bacitracin discs (0.04 units) are used to differentially diagnose GABHS from non-GABHS (groups B, C, F, and G) and because 95 – 100% of GABHS are unable to grow around the disc, a large zone of growth inhibition is predictive of GABHS (6, 34, 38, 43, 64). The delay in results, the lack of standard culture guidelines and practices (differences in selection of medium, incubation duration, and atmosphere), and the occasional false-positives (most likely due to non-GABHS) and false-negatives (either due to flawed culture or bacteriologic techniques, undisclosed antibiotic use, or carrier states), are drawbacks to using cultures (34, 38, 43, 65).

Rapid antigen detection tests (RADTs), which primarily rely on the detection of antibodies against the carbohydrate antigen of the GABHS cell wall, provide quicker results and are more specific than throat cultures (90 – 99% range), but have reduced and varying sensitivity, can be more expensive, and some still require refrigeration (6, 26, 38). Confirmation of negative RADT results by throat culture is recommended by various guidelines, especially for children and

adolescents (6, 34, 66).[13] False-positives are rare with RADT, which make unnecessary antibiotic treatment unlikely, but false-negatives are more common than with cultures and likely to be a combination of carriers and acute (due to low colony counts) infections (67, 68). There is no clear international consensus on rapid testing; however, it has become standard practice in many developed countries with culture confirmation of negative RADT results (69). The logistic and economic advantage of RADT over culture has helped increase its use. Immediate results reduce loss to follow-up, prevent inappropriate antibiotic treatment either due to delay in treatment initiation or failure to terminate treatment after negative culture results, and reduce indirect costs (e.g., cost of treatment to patient or cost to healthcare system for follow-up) (70-72).

Use of the study derived CPRs in LMICs, especially in the study populations, may provide a more useful tool for diagnosis in the absence of laboratory diagnosis.

Recommendations/Policies for Management of Respiratory Diseases in Low and Middle Income Countries

Generally, global health recommendations and guidelines for children and adolescents target either children under 5 or adolescents,

[13] The varying sensitivity of the RADT is in part due to varying disease severity or "spectrum bias," where the ability of the test to detect GABHS pharyngitis across the clinical spectrum of disease influences the tests ability to accurately detect infection (67). Other influencing factors of RADT sensitivity include: quality of swabbing; use of simultaneous double swabs; regular training of sample collectors; and periodic check of RADT sensitivity (68-71).

neglecting children between these age groups. Therefore, recommendations and guidelines for children between ages 5 and 15 years are often limited, and finding recommendations, guidelines, and polices on the management of signs and symptoms, and respiratory illness in this population from LMICs difficult.

WHO has published recommendations on the management of children with acute respiratory infections, but specifically for children under 5. The recommendation includes a decision tree to determine the most appropriate management strategy for children under five presenting with acute respiratory infections to outpatient health facilities (73). First, the presence/absence of three major signs/symptoms (cough or difficulty breathing, ear problem, and/or sore throat) are assessed. Second, the lack of cough or difficulty of breathing and the presence of sore throat indicates use of the sore throat management chart. Lastly, management of sore throat involves three main components: assessment of signs/symptoms, classification of illness, and treatment. During assessment and classification, presence of difficulty swallowing, enlarged and tender nodes, and white exudates on the throat are used to classify children with sore throat that are then differentiated according to etiology (i.e., whether sore throat is due to GABHS). For children classified as having GABHS sore throat (pharyngitis), injectable penicillin (benzathine) is the recommended treatment to prevent non-compliance. For non-GABHS sore throats, symptomatic treatment is recommended such as warm, sweetened drinks (e.g., tea with honey) and paracetamol (i.e., for pain or fever).

Management of some signs/symptoms were included in the WHO recommendations such as treatment of fever (common sign/symptom of acute respiratory infections), where paracetamol was recommended for high fever (≥39°C), and copious fluids, loose clothing, and single dose of antibiotics (but no paracetamol) for low fever (38-39°C). In the US, recommendations for sign/symptom improvement associated with sore throat (non GABHS pharyngitis) include acetaminophen or ibuprofen, warm salt water gargle, throat lozenges, ice, hard candy (older children), soft foods, cool beverages or warm liquids, and popsicles or other frozen desserts (74). According to the California Medical Association (CMA) and the American Medical Association (AMA), the pediatric acute respiratory tract (ART) infection guideline includes both home remedies and over-the-counter medicine for treatment of symptoms associated with ART infections. However, these are treatment options for viral causes; antibiotics are recommended when symptoms are due to ART illness with bacteriological etiologies (see Table 6) (75).

Clinical and Laboratory Diagnosis of Rheumatic Fever and Rheumatic Heart Disease

Rheumatic fever involves inflammation of multiple organs including the heart (carditis), joints (arthritis), nervous system (chorea), subcutaneous nodules, and skin (erythema marginatum) (40, 44, 47). In low income countries, clinical diagnosis of RF can be made using the

set of clinical guidelines known as the Jones criteria (6). The original 1944 criteria was updated by the WHO in 2003 and consists of major and minor manifestations (Table 7) (6). The five major manifestations consist of: carditis; polyarthritis; chorea; subcutaneous nodules; and erythema marginatum (6). Minor manifestations (clinical) consist of: fever (≥39°C); polyarthralgia; and epistaxis, abdominal pain, and anemia (6). Because of recurrent infection, history of RF or recent GABHS infection also constitute major manifestations (6). Sensitivity and specificity of RF diagnosis based on Jones criteria vary according to the combination (number and type) of clinical manifestations (major and/or minor) present. In populations with high rates of RF and RHD, the Jones criteria should be adapted to allow for greater sensitivity (47).[14] While carditis is an important and serious predictive factor among children with the potential to cause permanent damage, in LMICs recurrent attacks of RF is the most common clinical presentation (6, 44, 47). RF can also be diagnosed by laboratory methods such as: the presence of elevated acute phase reactants (minor manifestation); detection of prolonged P-R interval via electrocardiogram (minor manifestation); rising streptococcal antibodies titers (anti-streptolysin O or anti-DNAse B); GABHS positive throat culture or RADT; or by the detection of carditis (mitral or aortic regurgitation with heart murmur) via echocardiography (46, 47).

[14] For example, the prevalence of manifestations vary where among high incidence populations chorea is usually due to RF, whereas subcutaneous nodules is rare, but highly specific (46).

TREATMENT OF GROUP A BETA HEMOLYTIC STREPTOCOCCAL PHARYNGITIS AND PREVENTION OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Treatment of GABHS Pharyngitis

Primary prevention of RF entails the prompt and accurate diagnosis of GABHS (within 9 days of onset of signs/symptoms), and subsequent antibiotic treatment (7, 8). Although GABHS pharyngitis is a self-limiting illness and generally resolves within a few days even in the absence of antibiotic therapy, antibiotic treatment is necessary for symptomatic relief, reduced GABHS transmission, and more importantly the prevention of suppurative and nonsuppurative complications (26, 35, 38, 43). The only form of commonly occurring pharyngitis indicated for antibiotic treatment is GABHS pharyngitis (34). Treatment of pharyngitis is indicated only for individuals with a positive GABHS test (culture or RADT) result per Infectious Disease Society of America (IDSA), the American Heart Association (AHA), and the American Academy of Pediatrics (AAP) recommendations (66).

The standard treatment recommended by various studies for GABHS pharyngitis among children is oral penicillin V (250mg) 2 – 3 times/day for 10 days and continues to effectively eradicate GABHS pathogen from the pharynx and prevent RF/RHD (Table 8).(6, 76) To ensure adherence, administration of a single intramuscular injection of benzathine benzylpenicillin (600,000 units for children < 27 kg) is recommended (77). For children with known penicillin allergies,

erythromycin is a widely used substitute (dosage varies) (6). While there are several antibiotic options for the effective treatment of GABHS, including penicillin (oral and injectable), penicillin congeners (e.g., amoxicillin and ampicillin), cephalosporins, macrolides, and clindamycin, the optimum first line therapy is penicillin as recommended by the American Academy of Family Physicians (AAFP), the WHO, the IDSA, the AHA, and the AAP because of its advantageous properties such as its effectiveness, narrow spectrum of activity, lower cost, and lower incidence of adverse side effects (26, 38).

The list of essential drugs developed by the World Health Organization (WHO) for children includes the appropriate drugs necessary for treatment of GABHS pharyngitis (Table 8) (78). Essential Drugs Lists are available for most countries, including the four countries in this study. All four countries have the proper antibiotics necessary to treat GABHS, on their list. The efficaciousness, safety, and affordability of a drug required for basic public health influences its placement on the core list of essential drugs, and the ability to successfully manage GABHS and prevent RF/RHD is influenced by the availability of these drugs.

Some studies have reported treatment failures for GABHS (77). Potential reasons for antibiotic failure include: (1) quality of antibiotic (non-uniformity in antibiotic formulation/manufacturing can lead to inadequate treatment); (2) compliance (either due to time of

administration, number of daily doses, taste, and/or perception of side effects); (3) recurrent GABHS exposure (different or same serotype); (4) suppressed natural immunity due to early treatment; (5) co-pathogens (beta-lactamase producing bacteria inhibit penicillin); (6) viral pharyngitis; (7) modification of normal bacterial flora (elimination or suppression of normal flora increases host susceptibility to GABHS infection); and/or (8) GABHS carriers (penicillin cannot eliminate carrier state) (38). In LMIC settings, regulatory (quality assurance) and economic (affordability) factors can influence antibiotic failure. For example, due to financial constraints, patients may adjust treatment course to financial capability as opposed to prescribed treatment course (e.g., take until symptoms improve). In addition, poor quality drugs due to no/limited regulation, is an issue that affects the patient, community, and health care system (79, 80). The patient is impacted by an increase in morbidity/mortality due to treatment failure, adverse effects, and economic loss. The community is impacted by an increased risk of infection, development of drug resistance, loss of efficacious medicine, mistrust of the health system, and economic loss. The health system is impacted by an increase in burden for health workers and economic loss (80).

Despite instances of occasional treatment failure, treatment of GABHS with penicillin and other antibiotics is simple and efficacious. According to the Centers for Disease Control and Prevention (CDC), penicillin is 90% effective in clearing GABHS infection and reduces

risk of RF by 70% for oral administration and up to 80% with intramuscular injection (6, 42, 81, 82). Although in some instances infection may persist after antibiotic therapy is complete, there are currently no penicillin-resistant strains of GABHS (6, 77, 81). Penicillin sensitive GABHS is important for the treatment of pharyngitis and the prevention of RF/RHD. Moreover, its availability and cost effectiveness makes it an ideal treatment option for LMICs, especially since reports of macrolides (erythromycin and azithromycin), tetracycline, and lincosamides (clindamycin) resistance have been documented in several countries (10-21). While antibiotic treatment of GABHS pharyngitis to prevent RF/RHD may not be entirely cost-effective for LMICs (7), it is an effective preventative method provided penicillin sensitivity remains. This research is relevant for its potential contribution to the improved prescribing practices of LMIC physicians and therefore prevention of RF/RHD.

Treatment of Rheumatic Fever and Rheumatic Heart Disease

Primary prevention of RF consists of antibiotic treatment of GABHS pharyngitis to prevent the onset of acute RF and treatment to interrupt transmission of the GABHS pathogen (Figure 3) (6, 7). Effective treatment of GABHS pharyngitis can reduce the risk of RF by approximately 90%.[15] RF prognosis is reasonably good for the first occurrence and with appropriate prophylaxis, the risk of reoccurrence

[15] A remaining 10% will have GABHS present in the throat even after adequate treatment and therefore there still remains a very small possibility of RF (i.e., for those in high risk settings)(6, 7, 44, 84). Nevertheless, it is generally accepted that these chronic streptococcal carriers are not at risk of RF since carriers do not trigger the autoimmune response that infection with active (acute) streptococcal infection does (6).

and therefore RHD is diminished (45). This is especially important during the first 3 – 5 years, after the initial incidence of RF, as the likelihood of relapse is greater during those years (45). Since recurrent RF can lead to RHD and more than 70% of RF cases develop RHD, prompt and adequate treatment of RF via intramuscular injection of benzathine penicillin G for an extended duration is necessary for preventing recurrent RF and irreversible damage due to RHD (47). This is secondary prevention of RF.[16] Once RHD has developed, antibiotics can prevent morbidity due to RHD including cardiac failure, stroke, and endocarditic (8). Without clinical management (combination of medical and surgical care) involving heat failure medication, anticoagulation medication, surgery, constant monitoring, and tests, death can occur (47). These tertiary preventative measures are effective, but economically burdensome for LMICs (8, 41, 47).

COST EFFECTIVENESS ANALYSIS OF GROUP A BETA HEMOLYTIC STREPTOCOCCAL PHARYNGITIS

Costs, Effectiveness, and Cost Effectiveness Analysis

Cost effectiveness analysis (CEA) is an economic evaluation technique used to compare costs and health effects (outcomes) of an intervention where the ability of the intervention to provide the most effective and least costly outcome is assessed (83). The goal of CEA is to determine which intervention will provided the best health outcome for a community with economic constraints (84). This is especially

[16] It also includes the administration of antibiotics to patients with RHD (6).

important in LMICs where healthcare budgets are limited, in some cases to as little as five dollars per person (84). Therefore, the objective is to select the least expensive and most effective intervention under evaluation. For this study, the least costly and most effective diagnostic and management strategy for GABHS pharyngitis in a lower middle-income country, Egypt, was assessed.

The two main components of CEA include costs and effectiveness. Costs are defined as the value of all resources used to produce a product or service (85). These resources can be classified as direct (e.g., diagnostic tests and physician visits), indirect (e.g., time loss), and intangible (e.g., pain and suffering); and are used to estimate true economic cost (85, 86). Effectiveness or benefits is an indicator of how well the selected strategies perform and health outcomes can be measured as cases prevented, years of life saved, and/or quality adjusted life years (QALYs)(84, 87). Utilities (quality of life weights) are a type of effectiveness measure used to examine the quality (not just quantity) life lived in a health condition [range from poor (0) to excellent health (1.0)] (88).

Perspective is important, as it determines which costs are applicable to the CEA, and determines who pays and who benefits from the intervention (85). Perspective can range from the individual (patient or family) to societal, however, most GABHS pharyngitis studies employ the societal perspective as recommended by Gold et al (89). The time frame (another important component) must be long enough to capture

costs of strategies and consequences (e.g., diagnostic and management strategies and nonsuppurative complications) (85). Once the main objective of the analysis is defined (for this study, the cost effectiveness of the CPR developed for Egypt for the diagnosis and management of GABHS pharyngitis), all relevant alternative strategies can be outlined in a decision tree; a visual representation of all likely options and the consequences of each option (90). The decision tree, with probabilities, costs, and utilities for all strategies, along with assumptions are used to generate a base case analysis. For the base-case analysis, the expected values of each strategy is determined by multiplying the probability of an chance node by the outcome for that node and adding all branches from a decision node (91). The findings obtained from the base case analysis are full of uncertainty and vary enormously due to generated estimates and assumptions. Therefore, a sensitivity analysis is employed to assess the impact of changes on baseline estimates and test all assumptions (87).

Cost Effectiveness Analysis of GABHS Pharyngitis Diagnosis and Management

The prohibitive costs of laboratory supplies and equipment, shortage of qualified laboratory personnel, and absence of suitable facilities leaves many physicians in economically developing countries with diagnostic and management strategies, specifically: no testing or treatment; treat all without testing; and clinical/observational diagnosis with treatment only for those diagnosed GABHS pharyngitis

positive. Due to the higher prevalence of RD/RHD in lower income countries, the first strategy is not recommended. The second strategy is most often employed and can significantly reduce RF/RHD incidence and complications, but increases the risk of allergic reactions, which are more prevalent among children and adolescents (ranging from mild to severe), and antibiotic resistance, which is a growing concern (70, 92). The third strategy is one that can be employed with little cost to patients, hospitals, and communities at large, and can be used within the economic confines of areas with limited economic resources. It allows physicians to follow a guideline, helping them to make informed decisions on the management of pharyngitis, thereby improving patient health outcome. However, few CPRs have been developed and/or validated for/in children from LMICs (2).

Costs of complications due to GABHS pharyngitis are: immediate (e.g., medical costs for managing RF/RHD) and distal (e.g., any additional economic burden due to RF/RHD in stressed LMIC settings may contribute to further inequalities in health care access and delivery); easily quantifiable (e.g., medical charges) and unquantifiable [e.g., pain and suffering, and loss of “intellectual opportunities” due to school dropout (patients) or absenteeism/work loss (parents)]; and direct (e.g., patient costs including drugs, transport, etc.) and indirect (e.g., time or productivity loss) (6). A Brazilian study on the socioeconomic costs of RF and RHD found that RF and RHD in low income children increased hospital consultations and admissions, increased school failure rates, increased parent absenteeism (in some instances

job loss), increased morbidity and mortality, and reduced intellectual opportunities (93). The annual societal cost of RF was estimated to be $51,144,347 USD (i.e., 1.3% of the average family income). These costs are not just immediate, but continue to have distal effects on children, families, communities, and the economies of developing countries. A U.S. study calculating the societal economic burden and cost of GABHS pharyngitis in children and adolescents estimated that the average cost per pharyngitis case was $205 and the total annual cost was $224 – 539 million USD per year, where approximately 50% were nonmedical related costs (e.g., time costs) (94).

Cost effectiveness analysis studies of diagnosis and management of pediatric GABHS pharyngitis have been conducted HICs (e.g., United States, France, New Zealand, and Spain) and/or not recent (which effects costs, use and effectiveness of RADT, etc.) (70, 72, 91, 95-101). One study performed a CEA for adults with pharyngitis (88) and another examined effectiveness without costs (102). There are also studies that explored the economic burden of GABHS pharyngitis, but did not perform a CEA to determine which diagnostic and management strategy was the most effective (94, 103, 104). Data for children and adolescents in low and middle-income countries is not available and needs to be addressed.

Cost effectiveness analyses may reach different conclusions due to differences in the assumptions and estimates used in the models. The type of perspective used (societal vs. parents), the costs used (which

is influenced by time and location), the type of RADT used (EIA vs. optical immunoassay), the prevalence (probability) of GABHS pharyngitis, the prevalence (probability) of RF and RHD, and the type of testing strategies and management options included (e.g., not all studies included the strategy “no treatment”) all influence results (105). At 10% prevalence of GABHS pharyngitis, one study found that culture was the most effective and least expensive strategy for streptococcal management among U.S. adults (88). Even when the probabilities, costs, and utilities were varied, only slight differences were observed. Other studies examining the cost effectiveness of pharyngitis management in U.S. children came to different conclusions. Tsevat et al (95) found that throat culture (vs. rapid antigen testing) was the best strategy among (adherent) children whereas two other studies (70, 72) recommended (high sensitivity) antigen testing (without culture confirmation). This contradicts an earlier study that determined antigen testing with culture confirmation was the most beneficial and cost effective strategy for prevention of nonsuppurative complications (91). Only one study found observation to have the lowest morbidity and cost (as parental time off) (96). However, a Spanish study found that using a clinical scoring method followed by rapid testing for those with high scores was the most cost effective (while culture was most effective, it was also most expensive) (99). Not surprisingly, these differences are due to variations in probabilities, costs, and utilities; model assumptions influence the outcomes and therefore the results from each study. A consensus is difficult to reach and therefore a CEA is needed

for each setting to determine, based on local estimates, which strategy is the most effective and least expensive. A summary of CEA studies conducted is listed in Table 9.

Probability, Cost, and Utility Estimates

Estimates used for CEA include probability, cost, and utility variables. Variables are derived from numerous and varied sources of information, but the main sources of information are published literature, medical records, questionnaires/surveys, accounting records, professional guidelines/practice (85). Often, variables are adjusted for time, inflation, etc. to reflect current estimates.

Current estimates for GABHS pharyngitis, especially from LMICs, are limited. Estimates from high income countries are available, but reflect epidemiological, economical, and medical patterns found in resource rich settings and therefore differences in probabilities of disease and complications (morbidity and mortality); characteristics of diagnostic tests (sensitivities and specificities); and diagnostic and management costs (testing, treatment, and complications) are expected. These differences mean that results from cost-effectiveness analyses conducted in high income countries may not be applicable to LMICs (106). GABHS to RHD probabilities (Figure 1) have been reported in epidemiological studies of GABHS pharyngitis and RF/RHD. Probability of GABHS pharyngitis ranges from 15-30% due to geographic and age variability. Untreated GABHS pharyngitis leads to acute RF (initial) 0.3 – 3% and increases to 75% with recurrent GABHS

pharyngitis. Probability of RHD is 70% among individuals with RF (recurrent) (6, 40, 107).

The probability, cost, and utility variables used in cost-effectiveness analysis studies for the diagnosis and management of GABHS pharyngitis are outlined in Tables 10 – 12. These tables include estimates and ranges (when available) used to generate the cost effectiveness models. Time loss estimates are also available (Table 13). These estimates (along with other country-specific information sources) were used (adjusted for inflation, pricing, and currency) for the CEA portion of this study.

TABLES AND FIGURES

Table 1. Group A Beta Hemolytic Streptococcal (GABHS) Associated Infections (38)

Affected Area/System	Associated Infections		
Upper Respiratory Tract	Pharyngitis	Otitis media	Sinusitis
Lower Respiratory Tract	Pneumonia	Empyema	
Skin and Soft Tissue	Impetigo	Cellulitis	Erysipelas
Cardiovascular	Endocarditis	Myocarditis	Pericarditis
Musculoskeletal	Septic arthritis	Osteomyelitis	Pyomyositis
Lymphatic	Lymphadenitis		
Central Nervous System	Meningitis	Brain abscess	
Systemic	Septicemia		

Modified from Pichichero (38)

Table 2. Selected Microbial Etiologies of Pharyngitis (34, 35, 38, 52)

Etiology	Pathogen	Associated Disorders/Symptoms
Bacterial	Streptococci Group A	Tonsillitis and scarlet fever
	Streptococci Group C and G	Tonsillitis and scarlatiniform rash
	Neisseria gonorrhoeae	Tonsillitis
	Corynebacterium diphtheriae	Diphtheria
	Arcanobacterium haemolyticum	Scarlatiniform rash
	Yersinia pestis	Plague
	Yersinia enterocolitica	Enterocolitis
	Francisella tularensis	Tularemia
	Frequency (%): 15 – 30%	
Viral	Rhinovirus	Common cold
	Coronavirus	Common cold
	Adenovirus	Pharyngoconjunctival fever
	Parainfluenza	Cold and croup
	Influenza A and B	Influenza
	Herpes simplex virus	Gingivostomatitis
	Epstein-Barr virus	Mononucleosis
	Cytomegalovirus	Mononucleosis
	Human immunodeficiency virus	HIV infection
	Frequency (%): 70 – 85%	
Mycoplasmal	*Mycoplasma pneumonia*	Pneumonia and bronchitis
Chlamydial	*Chlamydia psittaci*	Pneumonia
	Chlamydia pneumonia	Pneumonia
	Frequency (%): < 5%	

Modified from Bisno (34), Ebell (52), Jaggi (35), Pichichero (38)

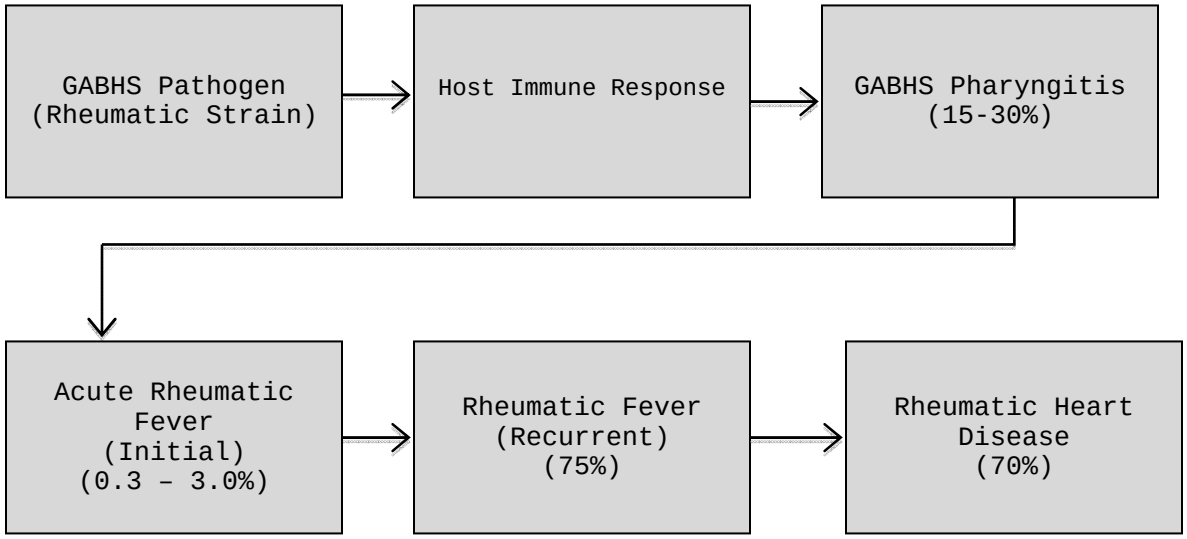
Table 3. Group A Beta Hemolytic Streptococcal (GABHS) Pharyngitis Complications (26)

Suppurative Complications[17]	Nonsuppurative Complications
Pneumonia	Poststreptococcal glomerulonephritis
Endocarditis	Rheumatic Fever
Meningitis	Rheumatic Heart Disease
Otitis media	
Mastoiditis	
Cervical lymphadenitis	
Bacteremia	
Peritonsillar/retropharyngeal	

Modified from Choby (26)

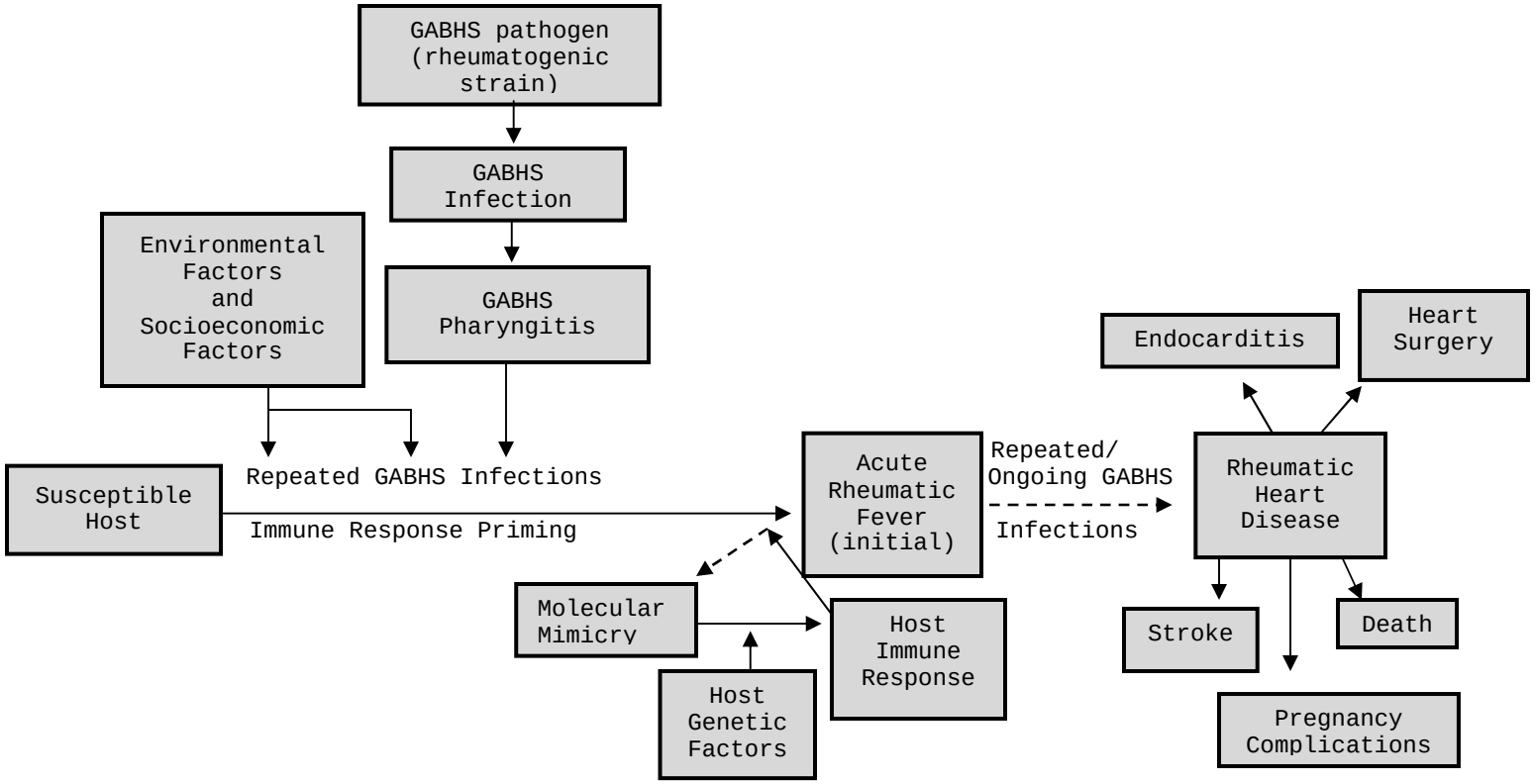
[17] Data on global burden of GABHS complications is not available for all GABHS sequelae. The following data was available for suppurative complications: 1) Pneumonia occurs in 0.3% of febrile patients (43) and among patients with GAS pneumonia, up to 30% have a history of GABHS pharyngitis (42); 2) Endocarditis estimates for less developed countries is based on a population study conducted in Israel which found 33,700 cases of endocarditis and 8,4000 deaths (41); and 3) Meningitis is uncommon in high income countries and global estimates are not available, but neurological complications from GAS meningitis are 36 – 46%, among the highest bacterial meningitis. The following data was available for nonsuppurative complications: 1) Poststreptococcal glomerulonephritis global prevalence is an estimated 456,000 cases and 5,000 deaths; 2) Rheumatic fever has an estimated 1,8880,000 cases; and 3) Rheumatic heart disease cases was 15,600,000 worldwide and is the cause of 233,000 deaths (5, 41).

Figure 1. Flow Diagram From Group A Beta Hemolytic Streptococci (GABHS) Pathogen to Rheumatic Heart Disease (RHD) (6, 40, 107)



Modified from Nkomo (40), WHO (6), Michaud (107)

Figure 2. Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) Pathogenic Pathway (47, 108)



Modified from Carapetis (108), Steer (47)

Table 4. Common Clinical and Epidemiological Factors of Pharyngitis Presentation Due to Group A Beta Hemolytic Streptococci (GABHS) (6, 26, 33-35, 38, 52, 109, 110)

	Factors	Sensitivity (%)	Specificity (%)
Clinical Factors[18] (Present)	Fever	22 – 58	53 – 92
	Sore throat	18 – 93	9 – 86
	Headache	48	50 – 80
	Abdominal pain	.	.
	Inflamed pharynx and tonsils	.	.
	Tonsil or pharyngeal exudates	45	75
	Palatal petechiae	7	95
	Scarlatiniform rash	4	79 – 99
	Tender, enlarged anterior cervical lymph nodes	55 – 82	34 – 73
Clinical Factors (Absent)	Cough	51 – 79	36 – 68
	Conjunctivitis	.	.
	Diarrhea	.	.
	Coryza (rhinitis)	42 – 84	20 – 70
	Hoarseness	.	.
Epidemiological Factors	Recent exposure to GABHS	19	91
	Season (winter – spring)	.	.
	Age (5 – 15 years)	.	.

Modified from Bisno (34), Choby (26), Ebell (52)

[18] These signs/symptoms generally have a sudden or rapid onset

Table 5. Clinical Prediction Rules (Clinical Signs and Symptoms)

Publication Year	Authors	Study Site(s)	Study Year (s)	Sample Size (n)	Ages (yr)	Clinical Signs/Symptoms	Method (Score/Regression)
2006	Smeesters (30)	Brazil	2004	220	0-15yr	Age (≤35, 36-59, ≥60 mo); Viral signs (coryza, conjunctivitis, cough, diarrhea, viral-like exanthema); and Bacterial signs (tender CN, headache, palate petechia, fever >38.5, abdominal pain, sudden onset (<12hr))	Score (Additive score -4-20) Regression model (2 different scoring methods)
2005	Steinhoff (4)	Egypt	2001-2003	451	2-12yr	Enlarged CN No Rhinitis No Rash	Score (Additive score 0-3) (Points ≥1, ≥2, ≥3)
2004	McIsaac (59) (Modified Centor)	Canada	1999-2002	787	3-69 yr	Fever (>38C) No Cough Tender CLN Tonsil swell/exudates Age (3-14; 15-44; ≥45)	Score (Additive score -1-5) (Points ≤0 - ≥4)
2003	McGinn (62) (Simplified Walsh)	USA	1995-1997	171	18-74yr	Fever (>38.3C) Exposure to known strep contact Pharyngeal or tonsillar exudates Enlarged, tender nodes Recent cough	Score (Additive score -1 – 4) (Points -1 – 3)
2003	Sahin (29)	Turkey	2001-2002	245	0-17 yr	Sore throat Fever Pharyngeal erythema	Regression
2002	Nandi (28) (Adopted from Breese)	India		536	5-15yr	Age Seasons Fever Erythema of pharynx Size of tonsil Pharyngeal exudate Lymphadenopathy Pain in throat	Score (Additive score 4-36)
2001	Attia (111)	USA	1999-2000	587	1-18yr	Cervical lymphadenopathy* Tonsillar swelling* No Coryza* Scarlatiniform rash (*Moderate – severe)	Score (Additive score 0- 5) (Points 0-10)

Table 5 (continued)

2000	Ulukol (61)	Turkey		716 total n1=202 n2=514	n1≤3yr n2>3yr	Comparison of Breese scoring system (see Breese)	Score (Additive score 0-9)
1999	Attia (23)	USA	1996	297 total (263 LR)	6mo - 18yr	Model 1: Scarlatiniform rash Tonsillar swelling* Tender, enlarged CN* No coryza* Model 2:Tonsillar swelling* No coryza* Tender, enlarged CN* (*Moderate – severe)	Stepwise multiple logistic regression models (model 1 and model 2)
1998	McIsaac (26, 27) (Modified Centor)	Canada	1995-1997	521	3-76	No cough Swollen/tender ACN Fever (>38C) Tonsillar exudate or swelling Age (3-14; 15-44; ≥45)	Score (Additive score -1-5) (Points 0 – 4)
1998	Wald (31)	USA	1990-1992	365	2-16yr	Age (5-15 yr) Season (Nov-May) Fever (≥38.3C) Adenopathy (CLN ≥1cm or tender) Pharyngitis (erythema, swelling, or exudates of phar/tons) No upper resp sympt (no rhinorrhea, cough, conjunctivitis)	Score (Additive score 0 – 6) (Points 1 – 6)
1997	Steinhoff (3) (Abu Reesh Rule)	Egypt	1992-1993	451	2-13yr	Pharyngeal exudate OR Enlarged anterior cervical nodes	Score
1995	WHO, ARI (73) and IMCI (49) Adaptation Guidelines				<5yr	Pharyngeal exudate AND Enlarge, tender CLN	Score
1993	Meland (63)	Norway	1988-1989	133	Childr en and Adults	No Cough Swollen lymph nodes Age (≥5yrs) Rubor (red/inflamed)	Regression

Table 5 (continued)

1992	Hoffman (54)	Denmark	187-1988	1783	Children and adults	Pain on swallowing Cough/coryza Age Enlarged or hyperaemic tonsils Exudate Enlarged or tender angular LN Fever (≥38C)	Score
1981	Centor (25)	USA	1980	286	>15yr	Tonsillar Exudate Swollen tender CLN No cough Fever (>38.5C)	Score (Additive score 0-4)
1977	Breese (24)	USA	1973-1975	670	Children	Season Age WB count Fever >38C Sore throat Headache Abnormal pharynx Abnormal cervical glands Cough	Score (Additive score 0-9)
1975	Walsh (56)	USA				Fever (>36.1C) Exposure to known strep Recent cough Pharyngeal/tonsillar exudates Enlarged/tender nodes	Score (Additive score -10-40)

Table 6. Recommendations on the Management of Selected Signs/Symptoms of Acute Respiratory Tract Infections (75)

Symptoms	Home Remedies	Over-the-counter Treatments
Fever, Aches, and Pain	1. Cool compress 2. Bed Rest 3. Heating pad on sore muscles	Analgesics 1. Acetaminophen 2. Ibuprofen 3. Naproxen
Cough or Sore Throat	1. Drink more fluids 2. Room humidifier 3. Gargle (warm salt water) 4. Avoid smoke	Expectorant 1. Guaifenesin Antitussives 1. Dextromethorphan
Stuffy or Runny Nose	1. Steam inhalation 2. Saline nose drops or spray 3. Petroleum jelly, salve, or tissue with lotion (for red, raw nose)	Decongestants 1. Pseudoephedrine 2. Oxymetazoline 3. Phenylephrine Antihistamines 1. Diphenhydramine 2. Chlorpheniramine 3. Loratadine 4. Clemastine

Modified from CMA Foundation (75)

Table 7. World Health Organization (WHO) 2003 Revised Jones Criteria (6, 35, 45, 47, 108)

Method	Major Manifestation	Minor Manifestation	Evidence of Streptococcal Infection
Clinical Diagnosis	Carditis Polyarthritis Chorea Subcutaneous nodules Erythema marginatum	Fever (≥39°C) Polyarthralgia Epistaxis Abdominal pain Anemia	
Laboratory Diagnosis	Echocardiogram identified carditis	Elevated acute phase reactants Electrocardiogram identified prolonged P-R interval	Rising streptococcal antibody titers GABHS positive throat culture or RADT

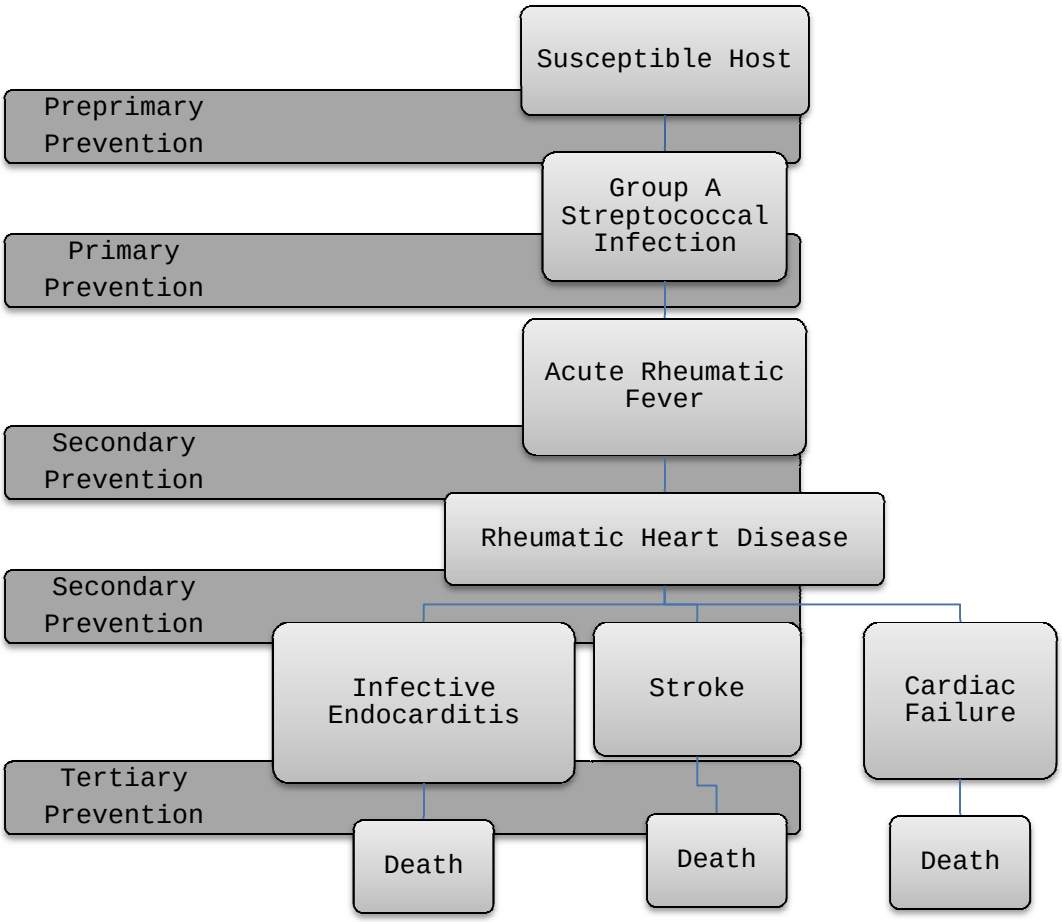
Modified from WHO (6), Steer (47)

Table 8. Treatment of Group A Beta Hemolytic Streptococcal Pharyngitis (GABHS) and Primary Prevention of Rheumatic Fever (RF) / Rheumatic Heart Disease (RHD) (6, 26, 34, 35, 38, 43, 45, 66, 108, 109)

Antibiotic	Route of Admin	Dosage	Duration	Effect/Impact	Comments
Penicillin V	Oral	250 mg 2 -3 times/day	10 Days	1. Symptomatic relief 2. Reduce GABHS transmission 3. Primary prevention: RF/RHD 4. Secondary prophylaxis: RF/RHD (same dose, longer duration)	-Rec 1st line therapy -No known resistance
Amoxicillin	Oral	250 mg 2 -3 times/day	10 Days	1. Symptomatic relief 2. Reduce GABHS transmission 3. Primary prevention: RF/RHD	-Improved taste alt -Broad spectrum
Erythromycin	Oral	Varies	10 Days	1. Symptomatic relief 2. Reduce GABHS transmission 3. Primary prevention: RF/RHD 4. Secondary prophylaxis: RF/RHD (250 mg 2 times/day, longer duration)	-Alt for known penicillin allergy -Contra in high macrolide resistance areas
Cephalosporins	Oral	Varies	10 Days	1. Symptomatic relief 2. Reduce GABHS transmission 3. Primary prevention: RF/RHD	-Contra for immediate-type hypersensitivity to beta-lactam antibiotic -Narrow spectrum
Benzathine penicillin G	Intra-muscular	Single injection: $6.0X10^5$ U (< 27 kg) $1.2X10^6$ U (> 27 kg)	1 Day	1. Symptomatic relief 2. Reduce GABHS transmission 3. Primary prevention of RF/RHD 4. Secondary prophylaxis of RF: same dose every 3-4 weeks, longer duration	-Alt to ensure adherence

Modified from Bisno (34), WHO (6)

Figure 3. Flow Diagram of Preventative Measures For Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) (41, 47)



Modified from Steer (47), Carapetis (41)

Table 9. Summary of Cost Effectiveness Analysis Studies

Author(s)	Year	Cost Assumptions	Benefits Assumptions	Findings
Neuner et al (88)	2003	• Cost represent actual resource cost (versus charges)[19] • Costs converted to 2000 USD • Published manufacturers' estimates used to determine rapid and culture costs • Assumed culture costs included test, patient notification, calling in prescription • Culture costs based on assumption conducted in physician's office • Cost of penicillin, erythromycin (penicillin allergy), and diphenhydramine (allergic reactions) estimated using wholesale and pharmacy dispensing costs • Resource-based relative value scale to estimate physician visit • Anaphylaxis estimated using previous analysis[20] • RF costs based on resource-based relative value scale and the Centers for Medicare & Medicaid fee schedule (primary care and specialist visits, electro- and echo- cardiography, and laboratory tests)	• Assumed utility associated with minor symptoms such as diarrhea and dyspepsia equivalent to pharyngitis • Assumed pharyngitis associated with a 0.95 utility • Other utilities estimated using a patient survey • Converted utilities to lost quality adjusted life days	Base Case: • Empirical treatment least effective (at 10% GABHS pharyngitis prevalence • Similar effectiveness for other strategies • Culture was least expensive Sensitivity Analysis: • Results sensitive to prevalence of GABHS pharyngitis o At >20%, rapid (first) and culture (second) were most effective o At <6%, observation was least expensive o At >71%, empirical was least expensive • Results sensitive to probability of anaphylaxis

[19] Time Horizon: 1 year; Perspective: Societal; and examined short-term cost-effectiveness
[20] Drug Topics Red Book. Montvale. NJ: Medical Economics; 2000

Table 9 (continued)

Ehrlich et al (70)	2002	• Culture, rapid testing, and treatment estimated using provider's resource costs[21] • Culture costs based on tests processed in outside laboratories • GABHS pharyngitis complications estimated using Children's Hospital of Philadelphia data	• Effectiveness expressed in cases of RHD prevented annually in US pediatric population (5-17) • US Census data used • A 0.004 probability of RF following GABHS pharyngitis • Morbidity/mortality: 0.038 probability of serious RHD sequelae • Treatment failure probability was 0.30	Base Case: • Rapid test was the most cost effective • Rapid test + culture was the most expensive • Treat all was the most effective (prevented the most RF, RHD, and complications), but also most allergic reactions and costly Sensitivity Analysis: • Results sensitive to rapid test sensitivity o As sensitivity increases, rapid increases in effectiveness and less costly than culture • Strategies not sensitive to increase in antibiotic sensitivity o Cost per RHD case prevented decreases o Number of RHD cases prevented increases
Tsevat et al (95)	1999	• Costs represent actual resource costs (versus charges) [22] • Costs converted to 1995 USD • No discount costs • Manufacture internal data for rapid and culture • Survey to estimate call time and salary for costs of notifying patients and calling in prescription • Treatment costs (penicillin and amoxicillin) included wholesale and dispensing costs	• Effectiveness expressed in terms of lives saved[24] • A 3% probability of ARF following GABHS pharyngitis • Mortality: 1% case fatality • Morbidity: 10% nonfatal complications • Assumed 75% reduction in ARF risk due to penicillin	Base Case: • At 20.8% GABHS pharyngitis prevalence, culture most cost-effective Sensitivity Analysis: • Results sensitive to: GABHS pharyngitis prevalence; RF attack rate; costs of EIA test;[25] and cost of culture (and result reporting) • Culture still best strategy when penicillin replaced by amoxicillin • Do nothing and empiric

[21] Perspective: Societal
[22] Perspective: Societal (base case) and Parental (sensitivity)
[24] Does not expressly state what the effectiveness assumptions or how it's estimated/defined.
[25] Enzyme immunoassay test. Note: assessed cost-effectiveness of both EIA and OIA (optical immunoassay) rapid tests.

		• Allergic reactions (penicillin rash and anaphylaxis) based on survey and resource-based relative scale reimbursement rate; and previous analysis[23] • ARF costs estimated from study hospital financial data (1994-96) on 34 cases • Co-pay and prescription costs assumed • Bureau of Labor Statistics used for time cost		treatment least expensive from parental perspective; culture most expensive
Van Howe et al (96)	2006	• Marginal differences in costs computed for each strategy[26] • A strategy preferred if cost < $200,00 per QALY • Discount rate of 3% used • Costs adjusted using Consumer Price Index to 2003 USD • Culture costs based on tests processed in outside laboratories (private and Medicaid costs) • Cost of death estimated from medical costs before death • Red book costs and pharmacy fee used to estimate cephalosporin costs	• Marginal differences in utilities computed for each strategy • A strategy was preferred if more health was preserved • Utilities estimated using the General Health Policy Model and Quality of Well-being Scale	Base case: • Societal perspective o Culture had the best cost-utility with Medicaid reimbursement o Observing had the lowest morbidity and highest cost • Payer perspective o Rapid test had the best cost-utility with private insurance reimbursement o Observing had the lowest morbidity and lowest cost Sensitivity Analysis: • Results were most sensitive to ARF incidence
Lieu et al (91)	1990	• Provider's resource costs used for culture, rapid, treatment, and follow-up[27] o Estimated using consultation from microbiology laboratory and emergency department of study hospital o Laboratory costs include materials and personnel	• Benefit expressed as number of GABHS pharyngitis complication prevented • Assumed a 10 fold reduction in rheumatic complications due to penicillin treatment • Assumed a 0.9 treatment effectiveness • Assumed the probability of ARF and ARF/RHD due to	Base Case: • Treat all prevented the most number of ARF and RHD cases, but had the greatest morbidity and was least cost-effective • Rapid test is the least expensive • Rapid + culture was the most cost-effective (if

[23] Tsevat et al. Neonatal screening for sickle cell disease: cost effectiveness analysis. J Pediatr. 1991; 118:546-554
[26] Perspective: Societal and Payer
[27] Perspective: Societal; Population: Hypothetical cohort of 100,000 children

		time o Follow-up costs include notification time and second visit o Assumed no second visit for oral penicillin treatment option • For extended cost analysis o Direct dollar costs of treatment for ARF and allergic reaction o Estimated using two methods: previous study[28] updated to 1985 USD; and actual charges for ARF from two patients at hospital in 1985	untreated GABHS pharyngitis to be 0.00288 and 0.00012	costs of GABHS streptococcal complications included) Sensitivity Analysis: • Strategies sensitive to rapid test sensitivity and follow-up rate (culture vs. rapid) • Strategies not sensitive to varying assumptions • Strategies cost effectiveness influenced by extended cost analysis • Two-way sensitivity (follow-up rate and rapid sensitivity) influenced testing strategies • Rapid + culture prevented greatest morbidity under all conditions
Pfoh et al (94)	2008	• Medical costs calculated by linking health service utilization with national service costs • Rapid and culture costs were estimated using Medicaid reimbursement survey • Antibiotic costs estimated using 2005 Red Book • Nonmedical costs (i.e., work loss, personal time costs, childcare costs, transportation, and nonprescription medicines) estimated o National median wage rate used to estimate work loss o Assumed personal and work time similarly valued o Overall transportation costs included costs for driving and public transportation	• Not Available/Applicable	• Total (societal) costs per GABHS pharyngitis case: $205 o Medical: $118 o Nonmedical: $87 • Total GABHS pharyngitis cost for US children: $224 – $539 million/yr

[28] Tompkins et al. An analysis of the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention. Ann Intern Med. 1977; 86:481-492

		o Red Book used for average wholesale prices • Costs adjusted to 2006 USD		
Terreri et al (93)	2001	• Direct costs from direct interventions attributed to the patient/family and society • Indirect costs relating to time loss for patient/family and production loss for society were estimated • Brazilian currency converted to 1998 USD • Utilization costs estimated using standard reimbursement fees and charges from the public health system • Medication costs were estimate from price index for public pharmacies and prices of the public Central of Medication • Transportation cost included public and private • Assumed private transportation for patients with private insurance • Loss of parental income calculated by deduction from monthly salary, and for society by sick pay	• Not Available/Applicable	• A 22.9% work absenteeism among patents o 901 days missed • Job loss was 5% • School failure among patients was 22% • Public system reference (societal costs): o Direct costs: $271/patient/yr o Indirect costs: $48/patient/yr o Total costs: $319/patient/yr • Healthcare plan reference: o Total costs: $423,550 • Private system reference: o Total costs: $684,351 • RF costs for families: 1.3% of annual income • RF annual costs for Brazil: $51,144,347
Webb et al (72)	1998	• Total treatment costs include visit and complication costs[29] • Wholesale costs of office visit, rapid test (plus direct and indirect costs for test administration), and culture (plus follow-up) • Penicillin allergy costs based on 1996 hospital charge data • ARF and RHD costs based on	• Benefit expressed as patients with disease prevented o Number of patients with ARF prevented o Percent of potential cases prevented o Complication prevented ARF • Assumed a treatment efficacy of 0.90 • Assumed ARF complications following untreated GABHS pharyngitis was 0.0003	Base Case: • Treat all was the least expensive, most cost-effective (cost/ complication prevented) • Among strategies involving diagnostic tests: o Rapid test (high sens) was least expensive, most cost-effective o Rapid + culture was most expensive, least cost-effective

[29] Perspective: Societal (base case) and Patient/Parental (sensitivity)

		estimates from the literature[30] and adjusted at a 3.5% annual inflation for 1997 USD costs • Financial proxy used to incorporate patient/parental preferences (not direct costs)		Sensitivity Analysis: • Treat all remained most cost-effective under most conditions o Exception: drug wholesale costs > $10.76 o Rapid becomes most cost-effective • Among diagnostic testing strategies, rapid the most cost-effective under most conditions o Exceptions: low GABHS pharyngitis prevalence; rapid sens < culture sens; and ARF epidemic
Giraldez-Garcia et al (99)	2011	• Direct medical costs for testing, treatment, and complications from Spanish National Health Service Source[31] o Rapid cost based on university hospital o Penicillin cost reduced by 40% to account for patient cost • Primary care costs from official costs of local health centers • Culture results and prescription costs included as second visit, assumed one for other strategies • RF/RHD and allergic reaction costs based on provision rates o Allergic reaction costs: visits and treatment • Costs expressed per 4 million children annually	• Effectiveness measured as proportion of patients cured without: o Disease complications (RF/RHD) o Allergic reaction (due to penicillin) • Effectiveness expressed per 4 million children annually • Assumed treatment efficacy was 0.80 • Assumed RF probability was 0.0003	Base Case: • Clinical scoring + rapid was the most cost effective • Culture was the most effective, but most expensive Sensitivity Analysis: • Strategies were sensitivity to changes in clinical scoring sensitivity and specificity o Rapid test most cost effective strategy when clinical scoring sens <91% and spec ≤9% o Clinical scoring triage + rapid for high scores most cost effective, and rapid for all when sens/spec is low

[30] Tompkins et al. An analysis of the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention. Ann Intern Med. 1977;86:481-492
North et al. Analysis of costs of acute rheumatic fever and rheumatic heart disease in Auckland. *N Z Med J.* 1993;106:400–403

[31] Perspective: Payer

Table 9 (continued)

Tompkins et al (101)	1977	• Charges for culture, visit, and treatment based on rates charged by a prepaid group clinic o Visit costs included travel and patient time o Assumed all strategies included medical care provider at initial visit o Culture positive treatment require two visits and no treatment have no second visit o Hospitalization cost based on general internal medical practice per diem (bed, meds, fees) • Assumed premature death costs from other patients similar to RF risk patients • RHD costs assumed four visits, two 14 day/year hospitalization, survive average 6.2 years o Includes premature death costs and medical care for 6.2 years • Estimated costs for allergic reaction based on assumptions that: o Serious reactions require hospitalization followed by disability period o Mild reactions require office visit, treatment, and patient time	• Effectiveness expressed as predicted cases per 1000 sore throat patients • Recurrent RF and RHD o Assuming antibiotic prophylaxis, cardiac disease from initial RF (w/in 8 yrs) probability: 0.011 o Death or debilitating RHD (and death w/in 6 yrs) probability: 14/771 • Assumed the probability (children) of RF after penicillin treated GABHS pharyngitis (endemic) was $6.43x10^{-4}$ • Assumed the probability of RF without treatment $6.43x10^{-3}$ • Assumed a 8-10 fold reduction in risk of RF with antibiotic treatment o Assuming patient compliance with oral treatment, oral penicillin and benzathine penicillin equally effective for initial RF	Base Case: • Treat all was the most effective, least expensive strategy under epidemic situations • Treat all was the most cost-effective strategy under endemic conditions when: o Oral penicillin used o Positive culture rate > 20% • Treat positive cultures strategy most cost effective with benzathine and rate 5 – 20% • Treat none most cost effective when rate <5% Sensitivity Analysis: • Epidemic situation was not sensitive to changes from sensitivity analysis • Endemic situation was sensitive to changes in positive culture rates

Table 10. Probability Variables Used in GABHS Pharyngitis Cost Effectiveness Analysis (CEA) Studies

Variable	Source	Probability		
		Baseline	Low Estimate	High Estimate
GABHS Prevalence	Neuner et al	0.097	0.02	0.68
	Ehrlich et al	0.20	-	-
	Tsevat et al	0.208	0.0	1.0
	Van Howe et al	0.26	-	-
	Lieu et al	0.29	0.0	1.0
	Webb et al	0.29	0.0	1.0
	Giraldez-Garcia et al	0.25	0.10	0.45
	Tompkins et al	-	0.095	0661
Rapid Test Sensitivity	Neuner et al	0.884	0.70	0.99
	Ehrlich et al	0.80	-	-
	Tsevat et al	0.859(EIA)/ 0.808(OIA)[32]	0.5 (EIA/OIA)	1.0 (EIA/OIA)
	Van Howe et al	0.891	0.80	0.95
	Lieu et al	0.55	0.0	1.0
	Webb et al	0.891	0.75[33]	1.0
	Giraldez-Garcia et al	0.90	-	-
Rapid Test Specificity	Neuner et al	0.944	0.80	0.99
	Ehrlich et al	0.99	-	-
	Tsevat et al	0.943 (EIA)/ 0.895 (OIA)	0.5 (EIA/OIA)	1.0 (EIA/OIA)
	Van Howe et al	0.95	0.90	0.99
	Lieu et al	0.90	-	-
	Webb et al	0.950	0.89	0.988
	Giraldez-Garcia et al	0.78	-	-
Culture Sensitivity	Neuner et al	1.0	-	-
	Ehrlich et al	0.90	-	-
	Tsevat et al	0.78	-	-
	Van Howe et al	0.834	0.77	0.93
	Lieu et al	0.90	-	-
	Webb et al	0.834	0.752	0.971
	Giraldez-Garcia et al	0.95	-	-
	Tompkins et al	0.90	-	-

[32] EIA = Enzyme immunoassay test; OIA = optical immunoassay test

[33] The range for the rapid test sensitivity is based on the range used for the sensitivity analysis. The range for rapid sensitivity from the 13 published studies was 0.77 – 0.974. The ranges for rapid test specificity, culture sensitivity, and culture specificity are based on the published studies

Table 10 (continued)

Culture Specificity	Neuner et al	1.0	-	-
	Ehrlich et al	0.99	-	-
	Tsevat et al	0.99	-	-
	Van Howe et al	0.99	0.95	0.995
	Lieu et al	1.0	-	-
	Webb et al	0.990	0.962	1.00
	Giraldez-Garcia et al	0.99	-	-
	Tompkins et al	0.82	-	-
Mild Allergic Reaction	Neuner et al	0.02[34]	0.005	0.04
	Ehrlich et al	0.10	-	-
	Tsevat et al	0.015	0	0.1
	Van Howe et al	0.02	0.007	0.04
	Lieu et al	0.003	0.001732	-
	Webb et al	0.0525	-	-
	Giraldez-Garcia et al	0.09499	-	-
	Tompkins et al	0.003(I)/0.00525(O)[35]	-	-
Severe Allergic Reaction	Neuner et al	0.0001[36]	0.00005	0.0002
	Ehrlich et al	0.005	-	-
	Tsevat et al	0.0001[28]	0	0.0005
	Van Howe et al	0.0064	0.0025	0.0075
	Lieu et al	0.0064	0.000083	-
	Webb et al	0.00025	-	-
	Giraldez-Garcia et al	0.005	-	-
	Tompkins et al	0.0064(I)/0.00025(O)	-	-
Death From Allergic Reaction	Neuner et al	0.10	0.05	0.2
	Ehrlich et al	0.00001	-	-
	Tsevat et al	0.10	0	1.0
	Van Howe et al	0.00001	0.000005	0.000015
	Lieu et al	0.000003	0	-
	Giraldez-Garcia et al	0.00001	-	-
	Tompkins et al	0.000003 (I/O)	-	-

[34] Penicillin induced rash
[35] I = Intramuscular penicillin (Benzathine penicillin); O = Oral penicillin (penicillin G)
[36] Penicillin induced anaphylaxis

Table 10 (continued)

Treatment Efficacy	Neuner et al	0.70[37]	0.55	0.80
	Ehrlich et al	0.70	-	-
	Tsevat et al	0.75[29]	0.0	1.0
	Van Howe et al	0.80	0.70	0.90
	Lieu et al	0.90	0.50	-
	Webb et al	0.90		
	Giraldez-Garcia et al	0.80	0.70	0.90
	Tompkins et al	--	0.80	0.90
Rheumatic Fever (Untreated GABHS Pharyngitis)	Neuner et al	0.0005	0.0	0.03
	Ehrlich et al	0.004	-	-
	Tsevat et al	0.03	0	0.05
	Van Howe et al	0.00000656	0.0	0.000328
	Lieu et al	0.00288	0.01	0.0001
	Webb et al	0.0003	0.0001	0.01
	Giraldez-Garcia et al	0.0003	-	-
	Tompkins et al	0.00643	-	-
Rheumatic Fever Complications (C)/ Death (D)	Neuner et al	0.1(C)/0.01 (D)	0.05(C)/0.0005(D)	0.2(C)/0.02(D)
	Tsevat et al	0.1(C)/0.01(D)	0.0 (C/D)	0.20(C)/0.25(D)
	Van Howe et al	0.10	-	-
	Tompkins et al	0.011(C)	-	-
Rheumatic Heart Disease	Ehrlich et al	0.038	-	-
	Van Howe et al	0.01	-	-
	Lieu et al	0.00012	-	-
	Tompkins et al	0.0182	-	-

Modified from Neuner (88), Ehrlich (70), Tsevat (95), Van Howe (96), Lieu (91), Webb (72), Giraldez-Garcia (99), and Tompkins (101)

[37] Effectiveness of penicillin vs. acute rheumatic fever

Table 11. Cost Variables Used in GABHS Pharyngitis Cost Effectiveness Analysis (CEA) Studies

Variable	Source	Cost[38]		
		Baseline	Low Estimate	High Estimate
Visit[39]	Lieu et al	8.00 (I)	16.00 (O)	31.00 (O)
	Webb et al	27.00	-	-
	Giraldez-Garcia et al	37.00	-	-
	Tompkins et al	10.00	-	-
Follow-up[40]	Neuner et al	1.29(CRN)/1.28(CIP)	0.65(CRN)/0.64(CIP)	2.58(CRN)/2.56(CIP)
	Tsevat et al	0.63(CRN)/0.43(CIP)	0.00 (CRN/CIP)	24.00 (CRN/CIP)
	Van Howe et al	5.73	0.00	10.00
	Lieu et al	5.00 (I)	0.00 (O)	0.00 (O)
	Webb et al	5.00	-	-
	Giraldez-Garcia et al	2.70	-	-
	Tompkins et al	4.00	-	-
Rapid Test	Neuner et al	7.67	3.84	15.34
	Tsevat et al	3.90(EIA)/6.50(OIA)	0.00 (EIA/OIA)	20.00 (EIA/OIA)
	Van Howe et al	15.00 (Private); 7.84 (Medicaid)	3.93	15.69
	Lieu et al	3.00 (I)	-	9.00 (O)
	Webb et al	7.00	-	-
	Giraldez-Garcia et al	2.67	-	-
Culture	Neuner et al	2.83	1.42	5.66
	Ehrlich et al	40.00	-	-
	Tsevat et al	2.40	0.00	15.00
	Van Howe et al	30.00 (Private)/ 5.00 (Medicaid)	1.45	40.00
	Lieu et al	5.00 (I)	-	15.00 (O)
	Webb et al	5.00	-	-
	Giraldez-Garcia et al	5.43	-	-
	Tompkins et al	2.00	-	-

[38] Neuner et al (2000 USD); Ehrlich et al (USD); Tsevat et al (1995 USD); Van Howe et al (2003 USD); Lieu et al (1985 USD); Webb et al (1997 USD); Giraldez-Garcia et al (EURO); Tompkins et al (1977 USD)
[39] Visit includes: initial hospital, general practice, office, diagnostic, etc.
[40] Follow-up includes: culture result notification, calling in prescriptions, therapy only, etc.

Table 11 (continued)

Penicillin (Oral)	Neuner et al	10.05	5.03	20.10
	Ehrlich et al	10.00	-	-
	Tsevat et al	9.06	0.00	20.00
	Van Howe et al	10.23	5.14	20.56
	Lieu et al	1.00 (I)	-	5.00 (O)
	Webb et al	2.00	-	-
	Giraldez-Garcia et al	6.22	-	-
	Tompkins et al	3.00	-	-
Other Antibiotics[41]	Ehrlich et al	10.00 (Am)	-	-
	Tsevat et al	8.22 (Am)	0.00	20.00
	Van Howe et al	20.29 (C)	-	-
	Lieu et al	4.00 (I)	-	8.00 (O)
	Giraldez-Garcia et al	7.51 (Az)	-	-
	Tompkins et al	3.00 (I)	-	-
Mild Allergic Reaction	Neuner et al	50.94	25.47	102.00
	Ehrlich et al	30.00	-	-
	Tsevat et al	49.99	25.99	73.99
	Van Howe et al	52.10	26.05	104.32
	Lieu et al	30.00	-	-
	Webb et al	35.00	-	-
	Giraldez-Garcia et al	44.51	-	-
	Tompkins et al	15.00	-	-
Severe Allergic Reaction	Neuner et al	1,772.54	886.00	3,545.00
	Ehrlich et al	5,495.00	-	-
	Tsevat et al	1,500.00	0.00	5,000
	Van Howe et al	4,808.07	1,812.94	8,546.75
	Lieu et al	5,495.00	-	-
	Webb et al	4,194.00	-	-
	Giraldez-Garcia et al	1,249.58	-	-
	Tompkins et al	826.00	-	-
Rheumatic Fever	Neuner et al	1,883.98	942.00	3,768.00
	Ehrlich et al	6,000.00	-	-
	Tsevat et al	700.00	0.00	20,000
	Van Howe et al	6,000.00	2,000.00	22,928.35
	Lieu et al	14,674.00 (T) / 925.00(CHP)[42]	-	-
	Webb et al	20,000.00	-	-
	Giraldez-Garcia et al	2,468.41	-	-
	Tompkins et al	10,560.00	-	-

[41] Other antibiotics include: Azithromycin (Az); Cephalosporin (C); Amoxicillin (Am); Intramuscular Penicillin (I), etc.
[42] T = Tompkins et al (updated to reflect inflation); CHP = Children's Hospital of Philadelphia

Table 11 (continued)

Rheumatic Heart Disease	Van Howe et al	20,000.00	5,000.00	25,000.00
Daily Cost Hospitalization	Tompkins et al	94.00	-	-
Death	Van Howe et al	10,000	8,000	12,000
Premature Death	Tompkins et al	72,000.00	-	-
Parental Wages (per hour)	Van Howe et al	17.18	13.00	25.00
Patient Time (per office visit)	Tompkins et al	4.50	-	-

Modified from Neuner (88), Ehrlich (70), Tsevat (95), Van Howe (96), Lieu et al (91), Webb (72), Giraldez-Garcia (99), and Tompkins (101)

Table 12. Utility Variables Used in GABHS Pharyngitis Cost Effectiveness Analysis (CEA) Studies

Variable[43]	Source	Utility, QALDs[44]		
		Baseline	Low Estimate	High Estimate
Untreated GABHS Pharyngitis	Neuner et al Van Howe et al	0.25	0	0.5
Treated GABHS Pharyngitis After Rapid	Neuner et al Van Howe et al	0.15	0.1	0.25
Treated GABHS Pharyngitis After Culture	Neuner et al Van Howe et al	0.20	0.15	0.25
Mild Allergic Reaction	Neuner et al Van Howe et al	0.625	0.15	1.50
Severe Allergic Reaction	Neuner et al Van Howe et al	9	3	18
Uncomplicated Rheumatic Fever	Neuner et al Van Howe et al	76.5	9	744
Complicated Rheumatic Fever	Neuner et al	744	56	744
Rheumatic Heart Disease	Van Howe et al	744	56	744
Death	Neuner et al Van Howe et al	14,874 22,995	- 14,000	- 25,00

Modified from Neuner (88) and Van Howe (96)

[43] Untreated GABHS pharyngitis (5 days); treated GABHS pharyngitis after rapid test (2 day reduction in sore throat) vs. culture (1 day reduction in sore throat); complicated rheumatic fever (with valvular disease)/rheumatic heart disease (Van Howe et al); and death (from allergic reaction or rheumatic fever)

[44] Lost Quality-Adjusted Life Days (QALDs)

Table 13. Time Loss Estimates Used in a GABHS Pharyngitis Cost Effectiveness Analysis (CEA) Study

Condition	Source	Work Lost, Hour		
		Baseline	Low Estimate	High Estimate
Untreated GABHS	Van Howe et al	16	8	24
Immediate Treatment	Van Howe et al	8	0	16
Delayed Treatment	Van Howe et al	8	0	16
Death	Van Howe et al	80	40	120
Rheumatic Fever[45]	Van Howe et al Tsevat et al	80 40	40 -	120 -
Rheumatic Heart Disease	Van Howe et al	80	40	120
Mild Allergic Reaction	Van Howe et al Tsevat et al	8 4[46]	4 -	12 -
Severe Allergic Reaction	Van Howe et al Tsevat et al	40 16	20 -	60 -

Modified from Van Howe (96) and Tsevat (95)

[45] Tsevat el al examined missing work/school, but used days of work/school missed without specifying number of hours in a work/school day. Therefore, not added to table.

CHAPTER 3. METHODOLOGY

Chapter 3. Methodology

STUDY DESIGN

This dissertation study was based on secondary data from a previous study that collected data from Egypt, Brazil, Latvia, and Croatia. The original study that generated this data has published results (2, 9, 77, 92).

The study was a cross sectional study of children. Data was collected from children (ages 2 – 12 y/o) presenting with acute respiratory infection at major urban outpatient clinics in university hospitals in Cairo, Egypt; Rio de Janeiro, Brazil; Riga, Latvia; and Zagreb, Croatia from 2001 to 2005. Patients who met the inclusion criteria (see below) and gave informed consent/assent were consecutively enrolled into the study. Upon parental/guardian consent and child/youth assent (ages 7 – 12 y/o), patients enrolled in the study provided study physicians with identification and demographic data, medical history, physical examination, and biological specimens (throat-swab) at the time of the hospital visit. Uniform data collection across the four countries was possible as all sites used a standard protocol outlining data collection, specimen collection, and laboratory analysis.[47]

[47] Study personnel ensured that: (1) parents/guardians and children/youth were properly informed of the study prior to consent and subsequent enrollment; and (2) the detailed and accurate collection of data occurred. Patients were enrolled for the duration of the study (one calendar year); however, subject participation was not required beyond the initial meeting at the time of hospital admission.

For clinical diagnosis of pediatric GABHS pharyngitis to prevent indiscriminate antibiotic therapy, and RF/RHD and other complications, data (clinical and laboratory) was used in this dissertation to: 1) develop a CPR for each country population and for the combined population for clinical diagnosis of GABHS pharyngitis in resource poor settings without laboratory access; 2) externally validate published CPRs and study developed CPRs; and 3) examine the cost effectiveness of the CPR developed for Egypt versus five other diagnostic and management strategies for pediatric pharyngitis.

DATA COLLECTION

Participant Characteristics

Study participants were children between the ages of 2 and 12 years presenting with sore throat, pharyngeal erythema, cough, or cold at the outpatient clinic of a major university hospital in Egypt, Brazil, Latvia, and Croatia. Table 1 provides basic descriptive data of study participants.

Selection of the Study Population

The study enrolled all eligible children ages 2 to 12 years seeking medical attention for symptoms of acute respiratory infection for the full study duration. The study enrolled a total of 2,055 children, with 1,421 from Egypt; 249 from Brazil; 185 from Latvia; and 200 from Croatia. The participants were drawn from the outpatient populations of University of Cairo, Egypt; Federal University of Rio de Janeiro, Brazil; Medical Academy of Latvia, Latvia; and University Hospital for

Infectious Diseases, Croatia. All pediatric outpatient clinics were in urban areas. Enrollment into the study was determined by inclusion and exclusion criteria. Patients satisfying all three of the following inclusion criteria were eligible for study participation: 1) Children ages 2 – 12 years old; 2) Present with sore throat, pharyngeal erythema, cough, or cold at outpatient clinics at one of the four study sites; and 3) Provide signed informed consent/assent. Patients reporting any of the following exclusion criteria were not eligible for study participation: 1) History of RF or RHD; 2) Any antibiotic treatment within the past 3 days (oral) or 28 days (intramuscular); 3) Hospitalization due to another illness (except malnutrition or tuberculosis); 4) Another infection requiring antibiotics; 5) Observation of impetigo or ear discharge during physical examination; 6) Physician diagnosis of pneumonia, bronchitis, or wheezing; and 7) Fails to provide informed consent/assent.

Data Collection (Study Procedures/Evaluations)

Children presenting to the outpatient clinics with sore throat were screened for study eligibility. Those who met all the eligibility criteria and did not meet any of the exclusion criteria were invited to enroll, and asked to provide written informed consent. Following informed consent/assent, study physicians collected identification and demographic information, ascertained medical history, conducted physical examination, and obtained biological specimens (throat swab). All information and samples collected during visit were recorded on corresponding designated study forms (see Appendix 1). Each patient

was assigned a unique study id number (alphanumerical) that accompanied all forms and samples.

Laboratory testing involved throat culture. First, biological specimens were collected using throat swabs from each participant. Throat swab cultures were collected by the standard method outlined by the American Heart Association, which is to depress the tongue and using light to illuminate the oropharyngeal area, swab the tonsillar and posterior pharyngeal wall vigorously with a sterile cotton swab stick. Throat swabs were placed in a sterile transportation carrier containing a label with the study id and transported to the participating laboratory at each site. At each site laboratory, swabs were plated within 4 hours of collection for optimal testing (3). Suboptimal conditions can alter survival of the streptococci organism; therefore, once biological samples were collected from patients, care was taken to ensure appropriate transport conditions were satisfied (i.e., avoid high temperatures, prolonged exposure to excessive moisture, and delayed arrival) (6). The swab was then used to test for GABHS according to the WHO Reference Manual: Laboratory Diagnosis of Group A Streptococcal Infections. Laboratory personnel at each site, plated throat swabs on 5% sheep blood agar which after incubation in 5% CO_2 at 35 – 37°C, was examined at 24 and 48 hours (112). The presence of beta hemolytic colonies was examined and recorded, and sensitivity to bacitracin was used for confirmation of *S. pyogenes* (2, 6). All laboratory personnel were blinded to the presence of clinical

findings and all results were recorded on study forms (see Appendix 1).

Forms were collected and entered into the database using EPI INFO software on computers at each study office. For quality assurance, at the time of data collection, data was centrally aggregated.

Biological and data collection took place at each of the study sites, the pediatric outpatient clinics, at the time of clinic visit. All study sites were university affiliated hospitals in large urban areas (i.e., located in the country capital, expect Brazil). Participating physicians from all sites were trained (uniformly) prior to the start of the study and regular site visits were made throughout the year for quality assurance. The regular visits were conducted to ensure accurate and consistent identification of signs and symptoms of streptococcal pharyngitis, uniform biological sample collection, proper delivery preparation of throat swab for culture, standardization of forms, and review of aid materials (manual of operations, contact information, etc.). All data collection forms were translated into the local language of each study site and back translated for accuracy. All laboratory personnel were trained uniformly at all sites to avoid contamination of biological samples during transport. Laboratory personnel were also trained to ensure accurate and consistent identification of positive cultures, standardization of forms, review of laboratory safety procedures, and

review of aid materials (manual of operations, contact information, etc.).

Figure 1 is a schematic representation of the original study data collection procedures that took place from 2001- 2005 from hospital admissions to laboratory analysis and results.

This dissertation study analyzed data collected from each site for the original study to be able to address the three main aims/objectives of the study (develop CPRs, validate CPRs, and evaluate cost effectiveness of developed CPR).

Study Variables

For the diagnostic component of the study, variables used to generate country specific and combined CPRs, and validate literature and study CPRs are presented in Table 2. Definitions of these variables are also available. Forms used to collect these variables can be found in the appendix (Appendix 1). For the cost effectiveness component of the study, variables used to conduct the CEA for Egypt is in Table 3. Definitions of the variables are also presented. Sources of information used for variable estimates include original study, published literature, outpatient clinic at University of Cairo Hospital, manufacturer (diagnostic tests), and other relevant sources.

DATA ANALYSIS

CRP Development and Validation Statistical Analysis

The study used STATA software to analyze data collected from the original strep study (GRASP). Data analysis began with data editing where checks for completeness, accuracy, and consistency were conducted. Every effort was made before and after data entry to limit missing/incomplete data including checks on all study forms for completeness and internal consistency, and contacting clinical personnel to obtain missing/incomplete data so that correct information was inserted. However, missing data was inevitable. Missing data on the outcome of interest (GABHS culture results) was minimal, representing approximately 3% of enrolled cases. These cases were excluded from the analysis. Sensitivity analyses were not performed given the low proportion (113-115). Missing data on some demographic and clinical data was present, but low (approximately 3%, except for sign of enlarged cervical lymph node which was near 10%). While the sample size was still large enough to perform analysis, it could have introduced bias, most likely nondifferential with regard to GABHS status and therefore most probably biased results towards the null. Data editing was also performed to highlight any potential data entry errors (e.g., out of range values). Following data editing, data description and summarization was conducted to assess distribution and frequency of study variables such as demographic and clinical data. Descriptive statistics was used to assess if assumptions of subsequent analyses were met. When necessary, new variables were created from

existing variable (i.e., recoding of variables). This is especially true for the diagnostic component of the study (Chapters 4-5).

Prevalence of GABHS was also analyzed. Chi square (X^2) analysis for categorical variables and Student's *t*-test for continuous variables were calculated to evaluate whether or not clinical or epidemiological factors were associated with GABHS pharyngitis according to culture results. Correlation analysis was also conducted to determine the inclusion of interaction terms among continuous, independent variables. Variables associated with GABHS were selected for the logistic regression. Predictors selected for stepwise regression (stepwise procedure) were based logistic regression. Several models were examined including those with only statistically significant predictors from the logistic regression, those with all predictors in the model, and combinations of both. A final multiple logistic regression model was derived for each study site by including only statistically significant predictors ($p<0.05$). The final models provided the subset of variables predictive of GABHS pharyngitis used for the CPR. Each coefficient from the model was defined in such a way that the predictors were positive. The predictors in the final model were used to generate the score, which was a simple additive scoring system based on beta coefficients. The cutoff score with the highest sensitivity and specificity (without compromising sensitivity) was used as the final rule for each of the five populations.

Statistics used for the evaluation of diagnostic tests such as sensitivity, specificity, PPV, NPV, diagnostic OR, J statistic, likelihood ratio, and ROC curves were performed for the five study developed CPRs. Test performance measures were also used for the validation component of the study where CPRs from the literature and study CPRs were validated in Egypt, Brazil, Latvia, Croatia, and combined populations. The variables used in published CPRs were recreated using original (and when not available, recoded) study variables.

Cost Effectiveness Analysis Statistical Analysis

The cost effectiveness analysis component of the study was conducted using TreeAge decision analysis software. The variables listed in Table 3 were used to generate a decision tree for the Egypt developed CPR (and treatment for GABHS positive only) compared to five alternative diagnostic and management strategies for pediatric GABHS pharyngitis. The strategies were as follows: 1) No test, no treatment (Do Nothing); 2) No test, treat all (Empirical); 3) Clinical diagnosis, treat positives only (CPR Only); 4) Culture, treat positives only (Culture Only); 5) RADT, treat positives only (RADT Only); and 6) Clinical diagnosis and RADT, treat positives only (CPR + RADT). Although RADT with culture confirmation (and treatment for positives from either RADT/culture test) is a recommended diagnostic and management strategy, its feasibility in LMICs is limited and for the purposes of this study, alternatives were limited to feasible

strategies so that practical application of study findings can be implemented for Egypt and other LMICs.

Probability, cost, and utility estimates for each strategy were computed and entered into the model. Probability estimates were estimated from published literature, the original study, and the University of Cairo. For example, diagnostic test sensitivity and specificity estimates were based on sensitivity and specificity of the throat culture and OIA rapid test used in the original study, and estimate ranges included test characteristics from published literature. Cost estimates (direct costs) were obtained from different sources including published literature, manufacturer, and other sources such as medical charges from the University of Cairo Hospital and adjusted to 2013 USD. Utilities (quality adjusted life years) obtained from the literature were used. Sensitivity analysis was conducted to evaluate uncertainty and assess the influence of estimates used in the cost effectiveness of the baseline estimates. Sensitivity analysis for certain assumptions were assessed, including: prevalence of GABHS, test characteristics, clinical prediction rule characteristics, rheumatic fever and rheumatic heart disease probability, diagnostic test and treatment costs, and utilities. These variables are often examined in sensitivity analyses, as they are most likely to influence cost effectiveness of strategies.

The cost effectiveness analysis was conducted from a societal perspective and was limited to a short-term time frame. The model was

used to examine the effect of six diagnostic and management strategies on the study outcomes: allergic reaction to penicillin, rheumatic fever, and rheumatic heart disease. Outcome measures were cost effectiveness ratios and incremental cost effectiveness ratios. Cost effectiveness ratios ($USD/lost quality adjusted life days) were estimated by dividing the cost of each strategy by the effectiveness (QALDs) for the strategy. The incremental cost effectiveness ratios (ICERs) were estimated by dividing the incremental costs (differences in cost between two different strategies) by the incremental effects (difference in health effects between two different strategies). According to results, the more expensive and less effective (dominated) strategies were eliminated. ICERs were recalculated until the only cost effective (dominant) strategies, which are less expensive and more effective, remained.

Outcome Measures Assessment

For country specific and combined CPR development, the outcome measures were culture positive for GABHS pharyngitis, clinical characteristics (signs and symptoms), patient and epidemiologic factors; and their relationship to each other. Assessment of the outcome measures included sensitivity (sens), specificity (spec), positive and negative predictive values (PPV and NPV), positive and negative likelihood ratios (PLR and NLR), diagnostic OR (DOR), and J statistic (JS). CPRs based on the optimal set of factors were derived from regression analysis for each of the five populations, which provided a simple additive scoring system using beta coefficients. The

cutoff score with the highest sensitivity (while maintaining high specificity) for each rule was selected as the most useful rule for LMICs.

For external CPR validation, the outcome measures were GABHS culture results and were used to assess sensitivity and specificity of the study generated CPRs and previously developed CPRs from the literature. Validation of the rules in each of the populations (country specific and combined) was assessed using test performance measures from the CPR development component. In addition, receiver operating characteristic (ROC) curve area or area under the curve (AUC) were also assessed for study CPRs.

For cost effectiveness analysis, the outcome measures were cost effectiveness ratios [cost per quality adjusted life years (QALYs)] and incremental cost effectiveness. Costs and effectiveness were calculated for each of the six strategies, where costs and effectiveness measures were derived from published literature, original study, or obtained from University of Cairo Hospital.

INFORMED CONSENT AND HUMAN SUBJECTS ISSUES

Institutional Review Board (IRB)

The original study (i.e., data collection component) was reviewed and approved by the ethics committees from each site, Johns Hopkins University IRB, and the World Health Organization IRB. This dissertation research is a modification of an earlier approved study

and which now exclusively involves the use of secondary data. Modifications were approved and continuation was granted from UCLA IRB (see Appendix 2).

Inclusion/Exclusion Procedures

An age criterion was necessary for participation in the study. Patients had to be between the ages of 2 and 12 years old. Inclusion/exclusion based on age was ethical because this is the age group most affected by GABHS pharyngitis and is the age group most commonly used in other studies on GABHS and its sequelae. There were no exclusion criteria based on ethnicity or gender.

Consent Procedures

In the original study, informed consent was obtained at the time of hospital admission. Those patients eligible for participation were invited to enroll in the study. Because eligible patients were children, parental/guardian informed consent was sought prior to enrollment. Child informed assent was sought for children 7 – 12 y/o after initially obtaining parental/guardian consent. The consent process was with study physicians in private examination rooms. Physicians ensured both patients and parents/guardians were properly informed prior to enrollment. Informed consent was orally obtained if parental/guardian literacy was in question. Patients and their parents/guardians were encouraged to ask questions and were provided contact information for later questions. Patients and their parents/guardians were informed that leaving the study at any time

without negative consequence was acceptable and medical attention according to clinic procedures would provided. The consent and assent forms will be translated and back translated into local languages.

Risks/Benefits

There was minimal risk for patients enrolled in the original study. They may have experienced some discomfort associated with the collection of throat cultures, but the discomfort was negligible and of short duration. GABHS pharyngitis is common and there is no stigmatization associated with illness. The benefits associated with participation included physical exam and laboratory testing of GABHS pharyngitis. However, patients still received a physical exam per hospital protocol regardless of study participation. Therefore, the only additional benefit to the patient was laboratory testing for diagnosis of streptococcal pharyngitis.

This dissertation research involves no patient contact or interaction as it involves analyses of secondary data; therefore there are no risks involved.

Societal benefits include expanding the literature on clinical diagnosis of GABHS pharyngitis in the absence of laboratory testing, validating (external) published and study CPRs, and evaluating cost effectiveness of clinical (versus laboratory) diagnosis of GABHS pharyngitis in a lower middle-income country.

Confidentiality

In the original study, the informed consent process, medical and demographic data collection, and clinical diagnosis were all performed with study physicians in individual examination rooms and therefore were conducted in privacy. Several measures were implemented to ensure confidentiality including: patient-doctor confidentiality rules; unique study identification numbers which were used at all sites, throughout the study, and on all forms, biological specimens, and database; all paper forms were kept locked in a file cabinet in each study office; and the database was password protected and only program managers has the required password/username to access the database.

For the dissertation study, the data was stored and saved on a password protected computer which only I had access to, and was backed up on a hard drive that was kept locked in a cabinet.

METHODOLOGICAL ISSUES

There are some methodological issues and limitations with the study.

First, this is a cross sectional study using secondary data. However, many studies on clinical diagnosis are cross sectional studies. Also, budgetary constraints made secondary data analyses a necessary option.

Second, this study used culture results for GABHS pharyngitis status. Although this is the gold standard, culture has several drawbacks. For example, occasional false positives, likely due to carries, are

possible as without serological data, definitive GABHS pharyngitis status is not possible. Therefore, misclassification of outcome is possible where carriers are classified as cases, which would affect the efficacy and effectiveness of generated CPRs. While this is a limitation faced by this study, it is one that is faced by many studies, as it is cost probative to do serological testing.

Third, culture results, although standardized, can yield differing results due to flawed culture or bacteriologic techniques, especially by different personnel, across different study sites. Studies have shown that various other factors can influence culture results such as undisclosed antibiotic use or carrier states (34, 38, 43, 65). Laboratory issues, due to differences in study sites, were another methodological issue. A centralized laboratory may have limited differences in accuracy and results; however, this was not feasible. These limitations are not limited to this study, and steps to limit laboratory issues were taken. Efforts to mitigate these limitations included standardization of protocol (translated into local language), training of laboratory personnel, periodic inspections at each site, and provision of National Committee on Clinical Laboratory Standards GABHS strains for accurate identification of GABHS.

Fourth, observer bias due to differences in identifying and recording signs and symptoms within and between study sites was possible. Variability in clinical diagnosis could have biased study results. To address the issue, standardized training was given to study physicians

along with standardized protocol for use at each site. Site visits were also done throughout study duration.

Fifth, selection bias towards more severe clinical presentation is also a potential methodological issue due to hospital setting. This is a problem for many GABHS pharyngitis studies; most studies of child and adolescent GABHS pharyngitis are conducted in either schools or hospitals. In addition, lack of representation of patients from rural areas might be is an issue as the outpatient clinics were part of university hospitals in urban centers (i.e., in the capital city for all sites, except Brazil). Although the urban settings provide socioeconomic variability, the four different countries from different economic levels lend the study results some generalizability.

Sixth, missing data and small sample size were methodological issues. The proportion of missing data on the outcome of interest (throat culture) was very low (about 3%) and therefore sensitivity analysis was not performed. These were excluded from the analysis, reducing the combined sample size to 1,933. While the sample size was still large enough to perform analysis, it could have introduced bias. A larger sample size would have been preferable to develop and validate CPRs.

Seventh, new variables were created for the validation component of the study using variables collected during the original study. All newly created variables for external validation of CPRs from the literature were approximations of variables used either because the

original study did not collect that information, or because not all studies were explicitly clear on how they defined their variables. Differences in variable definitions are a potential limitation of the study. The initial study collected numerous predictors for GABHS pharyngitis, which allowed for recreation of those not available. Furthermore, predictors not included in the original study would likely have detracted from the simplicity and ease of assessing signs/symptoms of patients during an outpatient clinic in resource poor settings.

Eighth, the cost effectiveness component of the study was based on strategies selected for the decision tree, estimates used in the base case analysis, and assumptions made.

Six strategies were used for the CEAs; all possible diagnostic and management strategies were not explored. This is a potential limitation of the study, influencing results. The reason for this however was to simply the strategies by limiting them to viable options for LMICs. Therefore, rapid with culture confirmation strategy was not included. While this testing strategy is commonly included in CEAs, conducting both types of laboratory testing is not feasible and therefore finding would not be applicable. The study goal was to limit alternative strategies to ones that could feasibly implemented for practical application of study finding in Egypt and other LMICs.

Results of the base case analysis are sensitive to the estimates used for probabilities, costs, and utilities. In this study, the best available data from the University of Cairo Hospital and the literature were used. When good estimates were not available, conservative estimates were used. For example, because the cost of RF complications was unavailable in the literature or from Egypt, costs were based on RF and RHD estimates from another study (96). Other assumptions based on lack of data from the literature include: assumed cost and utility of death due to allergic reaction and RHD were the same (same assumption made in two other studies (88, 96)); assumed the utility of treated GABHS pharyngitis after empirical and CPR only diagnostic strategies were the same as utility of treated GABHS pharyngitis after RADT diagnostic strategy, as there is no treatment delay for either strategy (prompt treatment); and assumed ineffective treatment was the same as untreated GABHS pharyngitis as signs and symptoms are not resolved because of treatment failure which is essentially untreated GABHS pharyngitis. To address these limitations, sensitivity analyses were conducted. Sensitivity analyses of estimates most likely to influence the outcome were assessed.

The CEA made several other assumptions and not all aspects of GABHS pharyngitis and its sequelae were addressed. First, the ability to differentiate clinically between acute GABHS infection and GABHS carriers is not possible. Moreover, serological testing to observer change in antibody titer is the only method that can differentiate between active and carrier. This is rarely if ever done. Therefore,

the assumption that both GABHS infections have similar risk of RF/RHD complication is a limitation, but cannot differentiate between carriers and acute infection (see Chapter 2). Furthermore, it was assumed that only symptomatic patients with positive laboratory tests (i.e., for strategies with laboratory testing) are treated. Assuming nondifferential laboratory diagnosis of carriers, the strategy outcomes will not change relative to each other. Second, this study focuses only on non-suppurative complications of GABHS pharyngitis, specifically RF and RHD. There suppurative complications of GABHS pharyngitis were not included in the CEA as the overall focus of the dissertation was on the prevention of RF and RHD. Third, the CEA was from a societal perspective and direct costs were used. Indirect costs such as loss of productivity were not addressed. While studies have demonstrated the indirect cost of RF/RHD including lost school days or school drop out for patients and lost workdays or unemployment, this analysis did not address these and instead focused on direct costs. In addition, culture strategy did not include time costs associated with 24-48 hour delay in culture results such as taking time off. Lastly, the assumptions were based on endemic rates of GABHS pharyngitis, RF, and RHD. Results of this CEA do not apply for non-endemic situations.

CONTRIBUTION

This study was based on secondary data. I performed all secondary data analyses.

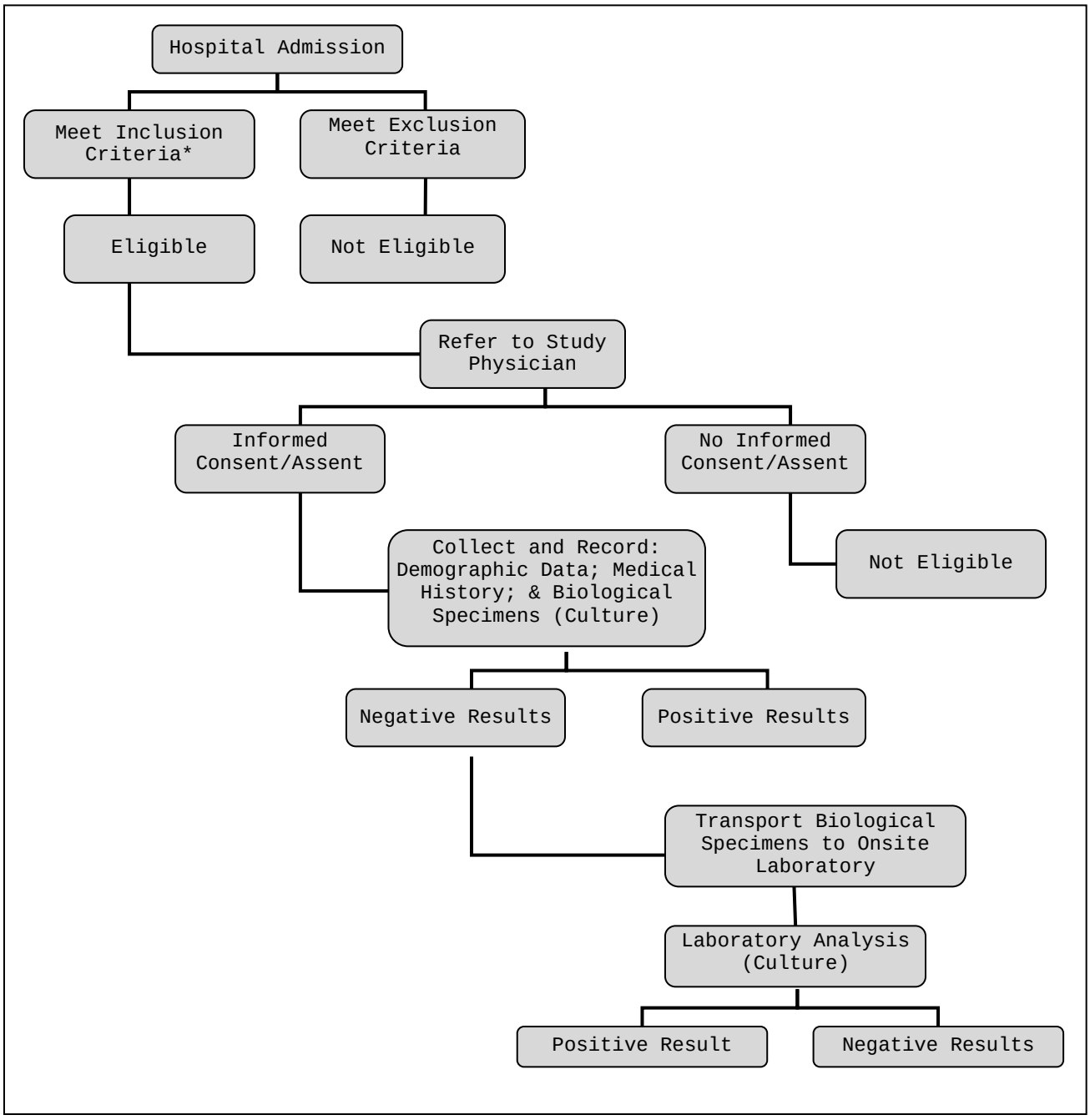
TABLES AND FIGURES

Table 1. Demographic and Clinical Characteristics of Study Participants by Study Site and Combined (92)

Characteristics	Study Site				
	Egypt	Brazil	Latvia	Croatia	Combined
Total Number of Patients	1,421	249	185	200	2,055
Mean Age, years (± SD)	4.9 (±2.4)	6.7 (± 3.1)	6.7 (±3.1)	6.4 (± 2.6)	5.4 (± 2.7)
Females, n (%)	600 (42.2)	122 (49.0)	83 (44.9)	84 (42.0)	889 (43.3)
History of Fever, n (%)	1,168 (82.4)	170 (89.0)	165 (89.7)	134 (67.0)	1,637 (82.1)
Absence of Cough, n (%)	1,022 (72.1)	128 (67.0)	125 (67.9)	109 (54.4)	1384 (69.4)
Pharyngeal or tonsillar exudates, n (%)	351 (24.8)	58 (30.4)	123 (66.8)	89 (44.5)	621 (31.2)
Cervical lymphadenopathy, n (%)	277 (19.5)	172 (90.1)	121 (65.8)	109 (54.4)	679 (34.1)

Modified from Rimoin (92)

Figure 1. Schematic Representation of Study Schedule (2001 – 2005)



*Inclusion criteria 1-2 (criteria 3 is a separate step).

Table 2. Variables for CPR Development and Validation Study

Variables Type	Variable	Definition[48]
Demographics	Age	Children ages 2 – 12 years
	Gender	Female, Male
Geographic	Country	Egypt, Brazil, Latvia, Croatia
	Season	Autumn, Winter, Spring, Summer
Signs	Fever	Temperature above 38.1°C (rectal) or 38.5°C (oral)
	Cough	Observation of coughing during consultation
	Hoarseness	Presence of harsh quality of voice different from normal
	Nares Excoriations	Scratches or lesions around nostrils
	Palatal Petechiae	Presence of lesions on the palate
	Strawberry Tongue	Tongue with papillar swelling
	Pharyngeal Erythema	Redness of pharynx greater than buccal mucosa, excluding tonsils
	Faucial Erythema	Redness of the passage from mouth to pharynx
	Tonsillar Erythema	Redness of the tonsils
	Erythema Posterior	Redness of the throat posterior wall
	Tonsillar Enlargement	Degree to which tonsils exceed more than 25% into the midline
	Enlarged Cervical Lymph Nodes	Any palpable anterior cervical lymph node greater than 1 cm in diameter
	Cervical Lymph Node Tenderness	Tenderness of node on gentle palpation, confirmed by statement or facial expression
	Pharyngeal Exudate	White or yellow matter on pharynx
	Tonsillar Exudate	White or yellow matter on tonsils
Symptoms[49]	Fever	Parent/patient report of history of high temperature (rectal: >38.1°C or oral: 38.5°C)
	Chills	Recent history of the sensation of cold (with/without shivering)
	Runny Nose	History of nasal discharge
	Nasal Congestion	History of increased difficulty of breathing
	Sore Throat	History of throat pain
	Difficulty/Pain Swallowing	History of child complaint of difficulty or pain when swallowing
	Cough	Any history of more than one episode of coughing
	Vomiting	History of vomiting
	Earache	History of ear pain
	Abdominal Pain	History of pain in the abdominal area
	Activity Level Below Normal	History of change (reduction) in level of activity compared to normal
	Disturbed Sleep	Parent report of history of change in sleep patterns compared to normal
	Hoarseness	History of presence of hash quality of voice that is different from normal

[48] Definitions for signs and symptoms based on original study questionnaire (Physical Examination Form – Visit 1)
[49] History refers to report of child experiencing any of the symptoms in the past five days

Table 3. Variables for the Cost Effectiveness Analysis (CEA) Study

Variable Type	Variable	Definition
Probability	GABHS Pharyngitis	Prevalence of GABHS pharyngitis in children, defined as the proportion of throat cultures that grow GABHS
	Rapid Test Sensitivity	Sensitivity of OIA rapid antigen detection test*
	Rapid Test Specificity	Specificity of OIA rapid antigen detection test
	Culture Sensitivity	Sensitivity of throat culture
	Culture Specificity	Specificity of throat culture
	Clinical Score Sensitivity	Sensitivity of the study developed CPR
	Clinical Score Specificity	Specificity of the study developed CPR
	Mild Allergic Reaction	Probability of penicillin-induced rash
	Severe Allergic Reaction	Probability of penicillin-induced anaphylaxis
	Death From Allergic Reaction	Probability of death from anaphylaxis
	Treatment Efficacy	Effectiveness of penicillin in preventing acute rheumatic fever
	Acute Rheumatic Fever	Probability of acute rheumatic fever following untreated GABHS pharyngitis
	Recurrent Rheumatic Fever	Probability of complications from recurrent rheumatic fever
	Rheumatic Heart Disease	Probability of rheumatic heart disease
	Death	Probability of death from rheumatic heart disease
Costs (USD)	Visit	Cost of urban pediatric clinic visit
	Follow-up	Costs of culture result notification and calling in prescription to pharmacy
	Rapid Test (OIA)	Cost of OIA rapid antigen detection test, including test and quality control
	Culture	Cost of culture, including materials, quality control, and labor
	Penicillin (Oral)	Cost of penicillin therapy, including wholesale cost of penicillin[50] and pharmacy dispensing cost
	Mild Allergic Reaction	Cost of treating a penicillin-induced rash, including healthcare worker time, diphenhydramine, and erythromycin ethylsuccinate[51]
	Severe Allergic Reaction	Cost of treating anaphylaxis, including hospitalization and treatment
	Death	Cost of approximate estimate of the medical costs incurred before death either from allergic reaction or rheumatic heart disease
	Acute Rheumatic Fever	Cost of rheumatic fever, including costs for hospitalization, disability, and penicillin prophylaxis

[50] Wholesale cost for 10 day course of oral Amoxicillin (250 mg 3 times daily)
[51] Wholesale and dispensing costs for 2 day course of diphenhydramine (12.5 mg 4 times daily) and 10 day course of erythromycin ethylsuccinate (200 mg 4 times daily)

Table 3 (continued)

	Recurrent Rheumatic Fever Rheumatic Heart Disease	Cost of rheumatic fever complications, including recurring rheumatic fever, visits, penicillin prophylaxis, hospitalization, disability, and medical care Cost of rheumatic heart disease, including costs for visits, hospitalization, disability, premature death, and medical care
Utilities	Untreated GABHS Pharyngitis	Quality adjusted life years for untreated GABHS pharyngitis
	Treated GABHS Pharyngitis After Rapid	Quality adjusted life years for treated GABHS pharyngitis after rapid test
	Treated GABHS Pharyngitis After Culture	Quality adjusted life years for treated GABHS pharyngitis after throat culture
	Mild Allergic Reaction	Quality adjusted life years for mild penicillin-induced rash
	Severe Allergic Reaction	Quality adjusted life years for anaphylaxis
	Acute Rheumatic Fever	Quality adjusted life years for uncomplicated rheumatic fever
	Recurrent Rheumatic Fever	Quality adjusted life years for complicated rheumatic fever
	Rheumatic Heart Disease	Quality adjusted life years for rheumatic heart disease
	Death	Quality adjusted life years for death

CHAPTER 4. PAPER ONE: “GROUP A BETA HEMOLYTIC STREPTOCOCCAL PHARYNGITIS: CLINICAL PREDICTION RULES FOR CHILDREN FROM LOWER AND UPPER MIDDLE INCOME COUNTRIES”

Chapter 4. Paper One: "Group A Beta Hemolytic Streptococcal Pharyngitis: Clinical Prediction Rules For Children From Lower and Upper Middle Income Countries"

ABSTRACT

Introduction: Untreated infection with group A beta hemolytic streptococcal (GABHS) pharyngitis can lead to serious sequelae including rheumatic fever (RF) and rheumatic heart disease (RHD). Accurate diagnosis and prompt treatment with antibiotics can prevent complications due to GABHS pharyngitis. In most high-income countries (HICs), diagnosis is identified via culture of rapid testing whereas in low and middle-income countries (LMICs), where laboratory access may be limited and expensive, indiscriminate antibiotic use or clinical diagnosis are employed. However, few clinical prediction rules (CPRs) have been developed for use in LMICs.

Methods: In this study, five CPRs were developed for the study population – children ages 2 – 12 years presenting with sore throat to outpatient clinics in Egypt, Brazil, Latvia, and Croatia. Patient demographic and clinical data were analyzed using chi square (X^2) and student t-test, and univariate and multiple logistic regression to derive CPRs, which were evaluated using test performance measures.

Results: Country specific and combined population CPRs varied by study site. Sensitivity and specificity of the CPRs ranged from 60.00 – 91.74% and 43.36 – 69.44%, respectively.

Conclusion: Results show that country specific CPRs are preferable to combined CPRs. This suggests that CPRs derived for HICs may not be applicable for LMICs and therefore, country specific CPRs are needed for resource poor settings with limited or no laboratory testing.

INTRODUCTION

Streptococcal pharyngitis is a common infection of the throat and/or tonsils caused by the bacterium S. pyogenes (1, 3, 5, 32). Untreated, GABHS pharyngitis can lead to rheumatic fever (RF), which can result in rheumatic heart disease (RHD) (40). Primary prevention of acute RF is accomplished by proper identification and adequate antibiotic treatment of GABHS pharyngitis (1-3, 53). Before penicillin was readily available, RF was the number one cause of cardiac illness in the U.S. It remains the number one cause of acquired heat disease in children in the developing world (5, 45).

Diagnosis of GABHS pharyngitis is best accomplished by combining clinical judgment and diagnostic test results, the gold standard for which is throat culture (53). In high-income countries (HICs), this is easily accomplished; however, in low and middle income countries (LMICs) and other resource poor settings, adhering to the gold standard may be difficult due to limited access to laboratory facilities and/or the expense of laboratory testing.

Clinical prediction rules (CPRs) may provide a reasonable option for physicians who do not have access to testing. Unfortunately, most CPRs have been developed using data from HICs where GABHS pharyngitis may present differently than in LMICs (Table 1) (1, 2, 4). Therefore, the objective of this study was to generate five CPRs (a single CPR for each of the four countries and one CPR for the combined countries) based on clinical presentations (signs/symptoms) and epidemiologic

factors for the presumptive diagnosis of GABHS pharyngitis in the absence of laboratory testing.

METHODS

Study Population

Children 2-12 years of age presenting with complaint of sore throat were enrolled in four urban university pediatric outpatient clinics from September 2001 to August 2005 in Rio de Janeiro, Brazil, Cairo, Egypt; Riga Latvia and Zagreb, Croatia. Patients were excluded on the basis of oral antibiotic use within 3 days or intramuscularly administered antibiotics within 28 days prior to the clinic visit; a history of previous rheumatic fever or rheumatic heart disease; or hospitalization for any reason.

Study Design

In this cross-sectional prospective study, all participating sites used a common protocol, standard methods for biological specimen collection and laboratory analysis and standard data collection forms translated into local language. Ethical approval was obtained by all participating institutions. Informed consent was obtained from the parent or guardian accompanying the child to the clinic and child assent was obtained from all participating children age 5 and older.

After enrollment, demographic data and medical history were recorded, a physical examination conducted, and two throat-swabs were obtained from each participant. One throat swab was used for a rapid test and

the other was plated onto 5% sheep blood agar, incubated at 37°C and examined at 24 and 48 hours for the presence of beta-hemolytic streptococci and confirmed by bacitracin disc (2, 6, 112).

Statistical Methods

Data analysis began with distribution and frequency of predictor variables such as demographic and clinical data (signs and symptoms). Table 2 lists the variables (and definitions) used for CPR development. These predictors were then assessed for association with culture positive and negative GABHS pharyngitis status. Chi square (X^2) analysis (categorical variables) and student t-test (continuous variables) were calculated to evaluate whether or not clinical or epidemiological factors were associated according to culture results.

Univariate analysis of independent variables was then assessed using logistic regression. Variables significantly associated with GABHS pharyngitis were used in the following stages of analyses. Predictors used in the final model were based on extensive exploratory analyses and all negative coefficients were recoded/redefined such that the predictors of GABHS pharyngitis were positive. Following univariate analysis, stepwise regression of predictors were examined using the stepwise procedure with an entry criterion of $p=0.15$ and a removal criterion of $p=0.30$. Various models were explored including models with statistically significant predictors ($p<0.05$) from univariate analysis, models with all predictors, and combinations of both. A final model was derived for each study site based on the conservative

criterion of including only predictors with $p<0.05$. Adjusted odds ratios and 95% confidence intervals were obtained from multiple logistic regression models.

The final models provided the subset of variables predictive of GABHS pharyngitis in each population. A GABHS score was calculated for each country and for the combined population. The score was based on a simple additive scoring system, where the beta coefficient for each predictor was used to generate a score.

Finally, diagnostic tests performance measures were calculated for each of the five rules at varying cutoff scores in the population it was derived for (e.g., Egypt CPR in Egypt population). At each cutoff score, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were calculated. This was done to determine which cutoff score was the most useful (i.e., balance sensitivity and specificity for a given rule such that sensitivity was high without sacrificing specificity). Consequently, five rules were developed – one for each of the four countries and one for the combined population. Additional test performance measures were used to evaluate the final country specific and combined CPRs including, J statistic (JS), and diagnostic odds ratio (DOR).

Data analyses were conducted using STATA (v12.1).

RESULTS

Patient Characteristics

A total of 2,055 children met the enrollment criteria and participated in the study. Of these, 1,993 study participants (Egypt, n=1,418; Brazil, n=191; Latvia, n=184; Croatia, n=200) had the outcome of interest (GABHS pharyngitis) and were included in the analysis. Selected patient characteristics by study site and combined are presented in Table 3. Patient characteristics of the 1,993 children varied by country. The majority of patients enrolled in the study were from Egypt (71%) compared to the 9% from Latvia (Brazil and Croatia each had 10%). Children from Egypt were younger (mean age 4.9 years) than children from the other three countries (Croatia mean age was 6.4 years and 6.7 years for Brazil and Latvia). These differences were statistically significant (Student t-test, $p \leq 0.000$) (Supplemental, Table 15). Other differences included proportion of children above 5 years. Croatia, Latvia, and Brazil had more than 50% of patients enrolled over the age 5 years whereas Egypt only had 32.86% (X^2 test, $p \leq 0.01$). The proportion of females varied less ranging from 42 – 50%. Of the 1,993 patients, nearly 30% tested culture positive for GABHS pharyngitis. With the exception of Croatia, which had 42% GABHS positive culture, the proportion of GABHS positive culture was similar for the other countries (24 – 29%). Although Egypt had the highest number of culture positive GABHS pharyngitis (387), Croatia had a greater proportion of GABHS positive children (42% of the study site population).

Clinical Presentation of Signs and Symptoms

Data on clinical presentation of signs and the association of individual signs with GABHS pharyngitis is presented in supplemental materials (Table 16). Clinical presentation varied significantly by site. Of the 15 signs that had significant differences in proportion children with each predictor for GABHS positivity (cough; hoarseness; palatal petechiae; strawberry tongue; pharyngeal, tonsillar, and faucial erythema; erythema posterior; tonsillar enlargement; 1+, 3+, and 4+ tonsillar enlargement; enlarged and tender cervical lymph nodes; and tonsillar exudate), 14 were in the combined population. Cervical lymph node tenderness and cough were significantly different in all study sites, except Latvia. There was no significant difference in the proportion of patients with fever, nares excoriations, 2+ tonsillar enlargement, and pharyngeal exudate at any of the study sites. The lowest percent of GABHS positivity were for nares excoriations, palatal petechiae, strawberry tongue, and 4+ tonsillar enlargement (<3%) and the highest were pharyngeal, faucial, and tonsillar erythema; erythema posterior; and tonsillar enlargement (>20%). Overall, pharyngeal erythema was the most commonly presented sign for (93.02%) and strawberry tongue was the least with less than 5% of GABHS positive and negative patients presenting across all sites.

Clinical presentation of symptoms (history of symptom within last five days) are presented in Table 17. Most symptoms were statistically

significant different in at least one site, but only difficulty/pain swallowing was different for all sites ($p<0.04$). Symptom presentation was different more for the combined population; Latvia and Croatia had the least. Fever, nasal congestion, vomiting, earache, and abdominal pain were not statistically different for any site. Overall, vomiting was the least reported symptom by patients or parents/guardians (23.22%), whereas history of sore throat was the most frequently reported symptom with more than 96% of GABHS positive and negative reporting at time of clinical visit.

There were over 19 signs and 13 symptoms; therefore, due to the large quantity of predictors and exploratory analysis conducted, not all results are not explicitly reported here, but are presented in the tables at the end of the chapter. Results of student t-test are not presented.

Clinical Presentation and Demographic Characteristics and Association of Predictors with Group A Beta Hemolytic Streptococcal Pharyngitis

Clinical and demographic characteristics were evaluated in terms of frequency and association with GABHS pharyngitis. Tables 18-20 present results of logistic regression of individual predictors of GABHS pharyngitis.

In Table 18, demographic predictors associated with GABHS pharyngitis were presented. Age below 5 years and age above 5 years were both significantly associated with GABHS pharyngitis in the Egypt, Brazil,

and combined population ($p \leq 0.008$). Winter season (which was defined as October - April) was also associated with GABHS pharyngitis in Egypt and the combined populations ($p=0.000$). Female gender was not associated for any site. In addition, there were no demographic factors associated with GABHS pharyngitis in either Latvia or Croatia.

Clinical signs associated with GABHS pharyngitis are shown in Table 19. Association of individual signs with GABHS pharyngitis varied by site. For example, in the Latvia study population, hoarseness and palatal petechiae were the only signs significantly associated ($p \leq 0.03$), whereas in the combined population, most signs were significantly associated (14/19). Fever, nares excoriations, 2+ tonsillar enlargement, and pharyngeal exudate were not associated in any of the study sites; and cough and cervical lymph node tenderness were significantly associated for all sites, except Latvia ($p \leq 0.39$).

Table 20 is results for symptoms and GABHS pharyngitis association. Symptoms of cough and difficulty/pain swallowing were identified in the logistic regression as independent predictors of GABHS pharyngitis for each of the five populations (cough was not significantly associated in Latvia; $p=0.478$). Some symptoms were not associated with GABHS pharyngitis in any of study sites including: fever; nasal congestion, vomiting; earache; and abdominal pain.

Model Section

Multivariate analysis of multiple GABHS pharyngitis predictors included stepwise procedure and multiple logistic regression. Statistically significant predictors from the univariate analysis were selected for stepwise procedure. In addition, all study variables were included and a combination of both was used. The best subset of combined predictors ($p<0.05$) was then used in multiple logistic regression to generate the final model. Tables 4 – 8 show the final model (derived by multiple logistic regression) for each of the five populations and odds ratios and 95% confidence intervals are presented for each selected predictor. The score for each of the predictors in the final model are also presented.

For the Egypt (Table 4) clinical prediction rule, a total of twelve variables were selected as potential predictors of GABHS pharyngitis from stepwise regression. Two of the predictors were negative and were redefined such that they had positive coefficients. A final model was created based on the conservative criterion of $p<0.05$. Therefore, there were seven predictors in the final model (early summer/autumn season, age above 5 years, no symptom of cough, sign of faucial erythema, symptom of nasal congestion, symptom of hoarseness, and no symptom of runny nose).

In Brazil (Table 5), according to the stepwise regression, thirteen predictors were selected. Both sign of fever and symptom of disturbed sleep were redefined. The final model had five predictors of GABHS pharyngitis which included: sign of faucial erythema; sign of cervical

lymph node tenderness; no symptom of disturbed sleep; no sign of fever; and symptom of difficulty/pain swallowing.

For Latvia, three predictors were eliminated with from the model by stepwise regression analysis (Table 6). The final model included three predictors of GABHS pharyngitis, which were sign of palatal petechiae, symptom of activity level below normal, and no sign of enlarged cervical lymph node.

In Croatia, stepwise regression removed eight predictors. The final logistic regression model had four predictors of GABHS pharyngitis including: sign of palatal petechiae; sign of cervical lymph node tenderness; no symptom of sore throat; and symptom of difficulty/pain swallowing (Table 7).

For the Combined population (Table 8), there were a total of sixteen predictors from which eight predictors of GABHS pharyngitis were selected in the final model. The clinical prediction rule for combined was early summer/autumn season, age above 5 years, sign of palatal petechiae, no symptom of cough, sign of faucial erythema, sign of erythema posterior, symptom of hoarseness, and symptom of difficulty/pain swallowing.

Test Performance Measures

Tables 9 – 13 present data on the performance of the clinical prediction rules for each population. Performance of CPRs was based on

cutoff scores. Test performance measures were calculated for each CPR (in its own population) at each possible cutoff score to determine which cutoff score was most useful for the given population. Evaluation of each rule in its site specific population was assessed using test performance measures such as sensitivity and specificity, positive and negative predictive value, and positive and negative likelihood ratio. Balancing sensitivity and specificity, a score of three or more (3+) was the most useful cutoff score for Egypt, Latvia and Croatia. For Brazil populations, a cutoff score of six or more (6+) was the most useful; for Combined, a score of four or more (4+). Therefore, five rules were created – one for each of the four countries and one for all countries combined.

In Table 14, a summary of the five population specific rules at the selected cutoff scores from Tables 9 – 13 plus two additional test performance measures [J statistic and diagnostic odds ratio (DOR)] are presented. For the Egypt and Combined populations, the created rules had similar results, where sensitivity and specificity were 73.13% and 43.36%; and 74.35% and 46.13%, respectively. The Latvia rule had the lowest sensitivity (60.00%) and Croatia had the second highest sensitivity and specificity compared to the other populations (75.00% and 68.97%, respectively). The rule created for the Brazil population had the highest sensitivity at 91.74% and specificity of 69.44%. Additionally, Brazil had the highest diagnostic odds ratio (25.00), whereas Egypt had the lowest (2.081). The negative and positive predictive values ranged from 79.21 – 91.74% and 32.64 – 69.44%,

respectively. The positive likelihood ratios range from 1.29 – 3.00, with the Brazil rule having the highest likelihood. The negative likelihood ratio for the Brazil rule had the largest decrease in the likelihood of disease (0.12).

DISCUSSION

This study developed five new clinical prediction rules for use in children from LMICs for improved clinical diagnosis of GABHS pharyngitis and prevention of RF and RHD. Rules for children from Egypt, Brazil, Latvia, Croatia, and the combined population were developed and validated in the population for which they were developed.

According to study results, there was great variability in patient characteristics (Tables 3 and S1) and clinical presentation of signs and symptoms (Tables S2 – S3). In addition, the association of individual predictors with GABHS pharyngitis varied by study population (Tables S4 – S6). Several models were generated based on clinical and statistical significant predictors of GABHS pharyngitis. Stepwise regression eliminated predictors and the final model with the best subset of predictors ($p<0.05$) for each study population was obtained using multiple logistic regression (Tables 4 - 8). Cutoff scores based on the beta coefficients of predictors in the final model were determined using diagnostic test performance measures (Tables 9 – 14).

In the effort to make the rules simple for use, predictors were defined as positive by redefining negative coefficients to generate a simple additive scoring system. Furthermore, the main performance measures of interest were sensitivity and specificity, as they were used to determine which cutoff score was the most helpful for LMICs (which favors high sensitivity for the prevention of RF/RHD without compromising specificity for prevention of AMR due to overuse antibiotics and allergic reaction, in particular to penicillin). The preference of sensitivity and specificity over other measures such as positive and negative predictive value (PPV and NPV) relates to the properties of these test measures. The drawback of predictive values is that, unlike sensitivity and specificity, they are susceptible to disease prevalence. Since prevalence of GABHS varies by country, the transportability of the rules is affected and its performance compromised. However, PPV and NPV are still important and relevant measures and therefore still used.

Egypt and the Combined population had a large number of predictors (seven and eight, respectively) compared to Brazil, Latvia, and Croatia. It would have been preferable if they had five predictors or less for parsimony and ease of use, but a more conservative p-value (for example $p \leq 0.005$) would have resulted in only one or two predictors for some study sites. While eight predictors may seem a lot, this is still easy to use compared to other CPRs in the literature.

Performance of the CPRs varied according to population. The rules were evaluated in their own population (validation of study CPRs in other populations were evaluated in Chapter 5). In Egypt, a cutoff score of three or more (3+) had the most useful balance of sensitivity and specificity. It had a sensitivity of 73.13% and specificity of 43.36%. At a score of six or more (6+), Brazil had the highest sensitivity (91.74%); specificity was 69.44%. The Latvia CPR had similar sensitivity and specificity (60.00% and 65.12%, respectively) when the cutoff score was three or more. Croatia had the second highest specificity (68.97%) and sensitivity (75.00%) after Brazil. The Combined CPR performed similar to the Egypt CPR, which may be a result of the size of the Egypt population as it constituted more than 70% of the Combined population. To address this potential limitation, importance weights were employed; however, there was no significant difference, and interpretation of results did not change.[52] At a score of four or more, the Combined CPR had 74.35% sensitivity and 46.13% specificity. Overall, sensitivities could have been higher, but cut off scores with higher sensitivities severely compromised specificity of the rules and were comparable to empirical treatment. For example, when cutoff scores were reduced by a single score (a lower cutoff score), specificity of all rules (except Egypt) dropped to less than 25% (12.22 – 21.55%). This is too low. Therefore, the cutoff score for the CPRs were selected because they best balanced the need for high

[52] Importance weights weigh each observation by importance according to population size; therefore, the larger the size, the greater the importance. Therefore, Egypt was considered imported and up-weighted in analysis.

sensitivity in RF/RHD prevalent populations with high enough specificity to prevent the global public health problem of AMR.

There are several CPRs for GABHS pharyngitis in the literature. However, the majority of rules were generated for use in adults in resource rich settings and they have a tendency to be complex with numerous clinical and epidemiological variables or requisite laboratory work. More recently efforts have lead to validation of these rules in other populations and creation of new rules targeting new populations. Studies by Stillerman, Hoffman, and Walsh included numerous signs and symptoms and were conducted in resource rich setting like the United States and Europe (54-56). While Breese created a CPR for children, it included white blood cell count which required laboratory access, and therefore is not applicable (57). Some of the original CPRs including those by Centor, Breese, and Walsh, although originally developed among adult populations, have been validated and modified in different age and geographic populations (26-28, 58-63). Of these, Centor considered is the best validated rule, with only four signs/symptoms (tonsillar exudate, swollen/tender cervical lymph nodes, no cough, and fever >38.5°C) (25, 52).

While most studies have been focused on resource-rich settings, there have been rules validated in children of lower income countries. A recent study conducted in Indian children, used a CPR adopted from Breese (a 9 item additive score with clinical and epidemiological variables) that was applied. Eight variables (age, seasons, fever,

erythema of pharynx, size of tonsil, pharyngeal exudate, lymphadenopathy, and pain in throat) were identified where a score of 15 or more (range: 4 – 36) was highly predicative of GABHS pharyngitis (91% sensitivity, 98% specificity) (28). The Breese rule was also validated in two different age groups of Turkish children and found that the rule had greater sensitivity among children older than 3 years (61). However, there has been evidence of diminished effectiveness of CPRs developed in higher income countries for use in lower income countries (1, 2). Fisher et al found great variability when the Breese, Centor, Wald, and McIsaac rules for the original North American populations were applied to Egyptian children (1).

Clinical prediction rules with low sensitivity are another problem for developing countries with high RF/RHD. The WHO Acute Respiratory Infection (ARI) Control Programme devised a clinical decision rule for countries without access to laboratory testing, where children under 5 years with both pharyngeal exudate and tender, enlarged anterior cervical lymph nodes, should be diagnosed as positive for streptococcal pharyngitis and treated with antibiotics (1-4, 53). Recent studies conducted in low and middle-income countries evaluated the effectiveness of the WHO clinical decision rule and found it to have high specificity, but low sensitivity (93 – 97.4% and 0 – 12% respectively) (1-4). While high specificity limits unnecessary antibiotic use, for developing countries where the burden of RF/RHD is greatest, high sensitivity decision rules are essential to prevent

further cases of RF/RHD and therefore the WHO rule is an inappropriate choice for resource poor settings.

The two rules generated for Egyptian children, Abu Reesh (3) and Steinhoff (4), were critical in demonstrating the transportability of CPRs developed in low income settings to other similarly low settings. The Abu Reesh rule, found that the presence of pharyngeal exudate or enlarged anterior cervical nodes was more sensitive (84%) than specific (39%), but that for children of developing countries, a more sensitive rule was preferable (3). The study conducted by Steinhoff et al suggested the use of a three-variable rule (enlarged cervical nodes, no rhinitis, no rash) with high sensitivity, but low specificity (92% and 38% respectively) when two or more clinical signs are present (4). When Smeesters et al applied the Steinhoff rule to a population of Brazilian children, there was only a 20% reduction in unnecessary antibiotic use (versus 37.5%) and 12.5% undetected cases of GABHS pharyngitis (versus 9%) (30). While geographic fluctuation is expected due to variation in the clinical presentation of GABHS pharyngitis, the rule was still able to reduce unnecessary antibiotic use, although not to the extent of the Smeesters rule developed for the identification of non-GAS pharyngitis (9, 30). The Abu Reesh rule (also proposed by Steinhoff et al) was validated in Turkish children, which found a reduced sensitivity and slightly increased specificity compared to the original Egyptian population, but overall it was similar to one of two new recommended combinations based on results from the study population (29).

Generally, most rules for school age children and adolescents include variation of the following clinical signs/symptoms and epidemiological variables: tender (swollen/enlarged) cervical anterior nodes; tonsillar or pharyngeal exudate; fever of at least 38°C; no cough; difficulty/pain swallowing; no rhinitis; and season. Similarly, the rules generated in this study included at least one of these predictors for all sites.

This study has several strengths. First, the data was obtained from a cross section of lower and upper middle-income countries for a span of four years in four different countries. Second, although there were four different study sites, a single standardized protocol was developed and used at each site. In addition, all study personnel, including physicians and laboratory staff were trained. Lastly, the probability of identifying significant predictors was increased due to the amount of data collected on signs and symptoms.

This study provides clinicians in resource poor settings with limited laboratory capabilities to diagnose and treat children with GABHS pharyngitis effectively and efficiently. This study provides cost effective primary prevention in a hospital setting. It also adds to the literature on the clinical diagnosis of GABHS pharyngitis in LMICs that can be used for further validation.

There are some limitations to the study. First, this is a cross sectional study using secondary data. However, many studies on clinical diagnosis are cross sectional studies. Also, budgetary constraints made secondary data analyses a necessary option.

Second, selection bias towards more severe clinical presentation is also a potential limitation due to hospital setting. This is a problem for many GABHS pharyngitis studies. In addition, differences in presentation according to study site may also bias results. To mitigate differences in recognition and recording of presenting signs and symptoms, standardized training for physicians was conducted at all sites to standardized diagnosis and standardized protocols were utilized.

Third, this study used culture results for GABHS pharyngitis status. Although this is the gold standard, culture has several drawbacks. For example, occasional false positives, likely due to carries, are possible. This is because without serological data, definitive GABHS pharyngitis status is not possible. Therefore, misclassification of outcome is possible where carriers are classified as cases, which would affect the efficacy and effectiveness of generated CPRs. While this is a limitation faced by this study, it is one that is faced by many studies, as it is cost probative to do serological testing.

Fourth, culture results, although standardized, can yield differing results due to flawed culture or bacteriologic techniques, especially

by different personnel, across different study sites. Studies have shown that various other factors can influence culture results such as undisclosed antibiotic use or carrier states (34, 38, 43, 65). To address this issue, standardized training of laboratory personnel was conducted at all sites and standardized protocol was utilized.

Lastly, analyses involved only covariates collected during the initial study. While the initial study collected numerous predictors for GABHS pharyngitis, there are several other predictors it could have included such as sign of chills or sign of vomiting. This study was only able to assess the ones that were collected from the initial study. However, the study did collect information on several key predictors, and predictors not included would likely include variables that would detract from the simplicity and ease of the rule. The rules include predictors that clinicians with restricted resources and limited time can easily assess in a hospital setting during a visit.

CONCLUSION

The sensitivity and specificity of the rules were not as high as expected (sensitivity range: 60.00 – 91.74%; specificity range: 43.36-69.44%); however, all five clinical rules generated in this study had higher sensitivity than the current WHO rule for children (under 5 years) in settings with no access to laboratory testing. The WHO decision rule although specific, had low sensitivity, ranging from 0-12% (1-4). However, the rules from this study had significantly higher sensitivity. While the specificity was not as high as the WHO rule

(93-97.4%), the higher sensitivity found in this study is essential (over higher specificity) to setting where GABHS pharyngitis prevalence is high and therefore the risk of RF and RHD is higher.

These rules will help prevent the leading cause of acquired heart disease in children from developing countries and therefore meet a current and ongoing public health need. While the specificity could be higher and efforts should be made to increase specificity without sacrificing the high sensitivity, in settings with higher prevalence of RF and RHD, higher sensitivity is of greater importance. Further validation of study rules is needed and can address these issues.

TABLES AND FIGURES

Table 1. Clinical Prediction Rules (Clinical Signs and Symptoms)

Publication Year	Authors	Study Site(s)	Study Year (s)	Sample Size (n)	Ages (yr)	Clinical Signs/Symptoms	Method (Score/Regression)
2006	Smeesters (30)	Brazil	2004	220	0-15yr	Age (≤35, 36-59, ≥60 mo); Viral signs (coryza, conjunctivitis, cough, diarrhea, viral-like exanthema); and Bacterial signs (tender CN, headache, palate petechia, fever >38.5, abdominal pain, sudden onset (<12hr))	Score (Additive score -4-20) Regression model (2 different scoring methods)
2005	Steinhoff (4)	Egypt	2001-2003	451	2-12yr	Enlarged CN No Rhinitis No Rash	Score (Additive score 0-3) (Points ≥1, ≥2, ≥3)
2004	McIsaac (59) (Modified Centor)	Canada	1999-2002	787	3-69 yr	Fever (>38C) No Cough Tender CLN Tonsil swell/exudates Age (3-14; 15-44; ≥45)	Score (Additive score -1-5) (Points ≤0 - ≥4)
2003	McGinn (62) (Simplified Walsh)	USA	1995-1997	171	18-74yr	Fever (>38.3C) Exposure to known strep contact Pharyngeal or tonsillar exudates Enlarged, tender nodes Recent cough	Score (Additive score -1 – 4) (Points -1 – 3)
2003	Sahin (29)	Turkey	2001-2002	245	0-17 yr	Sore throat Fever Pharyngeal erythema	Regression
2002	Nandi (28) (Adopted from Breese)	India		536	5-15yr	Age Seasons Fever Erythema of pharynx Size of tonsil Pharyngeal exudate Lymphadenopathy Pain in throat	Score (Additive score 4-36)
2001	Attia (111)	USA	1999-2000	587	1-18yr	Cervical lymphadenopathy* Tonsillar swelling* No Coryza* Scarlatiniform rash (*Moderate – severe)	Score (Additive score 0- 5) (Points 0-10)

Table 1 (continued)

2000	Ulukol (61)	Turkey		716 total n1=202 n2=514	n1≤3yr n2>3yr	Comparison of Breese scoring system (see Breese)	Score (Additive score 0-9)
1999	Attia (23)	USA	1996	297 total (263 LR)	6mo - 18yr	Model 1: Scarlatiniform rash Tonsillar swelling* Tender, enlarged CN* No coryza* Model 2:Tonsillar swelling* No coryza* Tender, enlarged CN* (*Moderate – severe)	Stepwise multiple logistic regression models (model 1 and model 2)
1998	McIsaac (26, 27) (Modified Centor)	Canada	1995-1997	521	3-76	No cough Swollen/tender ACN Fever (>38C) Tonsillar exudate or swelling Age (3-14; 15-44; ≥45)	Score (Additive score -1-5) (Points 0 – 4)
1998	Wald (31)	USA	1990-1992	365	2-16yr	Age (5-15 yr) Season (Nov-May) Fever (≥38.3C) Adenopathy (CLN ≥1cm or tender) Pharyngitis (erythema, swelling, or exudates of phar/tons) No upper resp sympt (no rhinorrhea, cough, conjunctivitis)	Score (Additive score 0 – 6) (Points 1 – 6)
1997	Steinhoff (3) (Abu Reesh Rule)	Egypt	1992-1993	451	2-13yr	Pharyngeal exudate OR Enlarged anterior cervical nodes	Score
1995	WHO, ARI (73) and IMCI (49) Adaptation Guidelines				<5yr	Pharyngeal exudate AND Enlarge, tender CLN	Score
1993	Meland (63)	Norway	1988-1989	133	Childr en and Adults	No Cough Swollen lymph nodes Age (≥5yrs) Rubor (red/inflamed)	Regression

Table 1 (continued)

1992	Hoffman (54)	Denmark	187-1988	1783	Children and adults	Pain on swallowing Cough/coryza Age Enlarged or hyperaemic tonsils Exudate Enlarged or tender angular LN Fever (≥38C)	Score
1981	Centor (25)	USA	1980	286	>15yr	Tonsillar Exudate Swollen tender CLN No cough Fever (>38.5C)	Score (Additive score 0-4)
1977	Breese (24)	USA	1973-1975	670	Children	Season Age WB count Fever >38C Sore throat Headache Abnormal pharynx Abnormal cervical glands Cough	Score (Additive score 0-9)
1975	Walsh (56)	USA				Fever (>36.1C) Exposure to known strep Recent cough Pharyngeal/tonsillar exudates Enlarged/tender nodes	Score (Additive score -10-40)

Table 2. Variables For Clinical Prediction Rule Development

Variables Type	Variable	Definition[53]
Demographics	Age	Children ages 2 – 12 years
	Gender	Female, Male
Geographic	Country	Egypt, Brazil, Latvia, Croatia
	Season	Autumn, Winter, Spring, Summer
Signs	Fever	Temperature above 38.1°C (rectal) or 38.5°C (oral)
	Cough	Observation of coughing during consultation
	Hoarseness	Presence of harsh quality of voice different from normal
	Nares Excoriations	Scratches or lesions around nostrils
	Palatal Petechiae	Presence of lesions on the palate
	Strawberry Tongue	Tongue with papillar swelling
	Pharyngeal Erythema	Redness of pharynx greater than buccal mucosa, excluding tonsils
	Faucial Erythema	Redness of the passage from mouth to pharynx
	Tonsillar Erythema	Redness of the tonsils
	Erythema Posterior	Redness of the throat posterior wall
	Tonsillar Enlargement	Degree to which tonsils exceed more than 25% into the midline
	Enlarged Cervical Lymph Nodes	Any palpable anterior cervical lymph node greater than 1 cm in diameter
	Cervical Lymph Node Tenderness	Tenderness of node on gentle palpation, confirmed by statement or facial expression
	Pharyngeal Exudate	White or yellow matter on pharynx
	Tonsillar Exudate	White or yellow matter on tonsils
Symptoms[54]	Fever	Parent/patient report of history of high temperature (rectal: >38.1°C or oral: 38.5°C)
	Chills	Recent history of the sensation of cold (with/without shivering)
	Runny Nose	History of nasal discharge
	Nasal Congestion	History of increased difficulty of breathing
	Sore Throat	History of throat pain
	Difficulty/Pain Swallowing	History of child complaint of difficulty or pain when swallowing
	Cough	Any history of more than one episode of coughing
	Vomiting	History of vomiting
	Earache	History of ear pain
	Abdominal Pain	History of pain in the abdominal area
	Activity Level Below Normal	History of change (reduction) in level of activity compared to normal
	Disturbed Sleep	Parent report of history of change in sleep patterns compared to normal
	Hoarseness	History of presence of hash quality of voice that is different from normal

[53] Definitions for signs and symptoms based on original study questionnaire (Physical Examination Form – Visit 1)
[54] History refers to report of child experiencing any of the symptoms in the past five days

Table 3. Selected Patient Demographic Characteristics By Study Site and Combined

Demographic Characteristics	Study Site				
	Egypt	Brazil	Latvia	Croatia	Combined
Total Number of Patients	1,418	191	184	200	1,993
GABHS Positive N (%)	387 (27.3)	47 (24.6)	55 (29.9)	84 (42.0)	573 (28.8)
Female N (%)	600 (42.3)	96 (50.1)	83 (44.9)	84 (45.1)	863 (43.3)
Age Above 5 Years N (%)	465 (32.8)	110 (57.6)	105 (57.1)	114 (57.0)	794 (40.1)
Age (Years) (Mean/Median)	4.9 / 4	6.7 / 6	6.7 / 6	6.4 / 6	5.4 / 5

Table 4. Egypt: Odds Ratio (OR) and 95% Confidence Interval (CI) For Predictive Demographic and Clinical Characteristics (p<0.05) of GABHS Pharyngitis According to Multiple Logistic Regression

Egypt: Demographic and Clinical Characteristics	Beta Coeff	Odds Ratio	P-value (OR)	95% Confidence Interval (OR)	Score
Season (Early Summer/Autumn)	0.092	1.599	0.000	(1.246, 2.052)	1
Age Above 5 Years	0.059	1.357	0.020	(1.049, 1.756)	1
No Cough Sx[55]	0.077	1.467	0.004	(1.129, 1.905)	1
Faucial Erythema Sg	0.122	1.995	0.000	(1.402, 2.839)	1
Nasal Congestion Sx	0.062	1.389	0.024	(1.044, 1.847)	1
Hoarseness Sx	0.069	1.436	0.013	(1.079, 1.912)	1
No Runny Nose Sx	0.077	1.509	0.004	(1.142, 1.994)	1

[55] Key: Sx = symptom
Sg = sign
Beta Coeff = beta coefficient

Table 5. Brazil: Odds Ratio (OR) and 95% Confidence Interval (CI) For Predictive Demographic and Clinical Characteristics (p<0.05) of GABHS Pharyngitis According to Multiple Logistic Regression

Brazil: Demographic and Clinical Characteristics	Beta Coeff	Odds Ratio	P-value (OR)	95% Confidence Interval (OR)	Score
Faucial Erythema Sg[56]	0.213	4.104	0.002	(1.670, 10.088)	2
Cervical Lymph Node Tenderness Sg	0.253	4.879	0.000	(2.097, 11.353)	3
No Disturbed Sleep Sx	0.162	3.873	0.003	(1.566, 9.580)	2
No Fever Sg	0.145	2.523	0.048	(1.009, 6.303)	1
Difficulty/Pain Swallowing Sx	0.155	4.407	0.011	(1.412, 13.749)	2

Table 6. Latvia: Odds Ratio (OR) and 95% Confidence Interval (CI) For Predictive Demographic and Clinical Characteristics (p<0.05) of GABHS Pharyngitis According to Multiple Logistic Regression

Latvia: Demographic and Clinical Characteristics	Beta Coeff	Odds Ratio	P-value (OR)	95% Confidence Interval (OR)	Score
Palatal Petechiae Sg	0.275	3.933	0.003	(1.578, 9.810)	3
Activity Level Below Normal Sx	0.248	4.840	0.011	(1.442, 16.243)	2
No Enlarged Cervical Lymph Nodes Sg	0.132	2.035	0.046	(1.012, 4.092)	1

[56] Key: Sx = symptom
Sg = sign
Beta Coeff = beta coefficient

Table 7. Croatia: Odds Ratio (OR) and 95% Confidence Interval (CI) For Predictive Demographic and Clinical Characteristics (p<0.05) of GABHS Pharyngitis According to Multiple Logistic Regression

Croatia: Demographic and Clinical Characteristics	Beta Coeff	Odds Ratio	P-value (OR)	95% Confidence Interval (OR)	Score
Palatal Petechiae Sg[57]	0.307	4.365	0.000	(1.914, 9.956)	3
Cervical Lymph Node Tenderness Sg	0.188	2.586	0.004	(1.355, 4.938)	2
No Sore Throat Sx	0.364	6.581	0.001	(2.169, 19.970)	4
Difficulty/Pain Swallowing Sx	0.247	3.730	0.000	(1.787, 7.784)	2

Table 8. Combined: Odds Ratio (OR) and 95% Confidence Interval (CI) For Predictive Demographic and Clinical Characteristics (p<0.05) of GABHS Pharyngitis According to Multiple Logistic Regression

Combined: Demographic and Clinical Characteristics	Beta Coeff	Odds Ratio	P-value (OR)	95% Confidence Interval (OR)	Score
Season (Early Summer/Autumn)	0.063	1.372	0.004	(1.109, 1.700)	1
Age Above 5 Years	0.065	1.392	0.002	(1.124, 1.722)	1
Palatal Petechiae Sg	0.170	2.139	0.001	(1.342, 3.411)	2
No Cough Sx	0.093	1.604	0.000	(1.287, 1.998)	1
Faucial Erythema Sg	0.067	1.435	0.006	(1.107, 1.860)	1
Erythema Posterior Sg	0.083	1.639	0.002	(1.204, 2.230)	1
Hoarseness Sx	0.088	1.560	0.000	(1.230, 1.977)	1
Difficulty/Pain Swallowing Sx	0.083	1.620	0.001	(1.205, 2.177)	1

[57] Key: Sx = symptom
Sg = sign
Beta Coeff = beta coefficient

Table 9. Egypt Test Performance Measures of Country Specific Clinical Prediction Rule At Varying Cut Off Scores. Egypt Clinical Prediction Rule: Season (Early Summer/Autumn), Age Above 5 Years, No Cough Sx, Faucial Erythema Sg, Nasal Congestion Sx, Hoarseness Sx, No Runny Nose Sx

Egypt Clinical Prediction Rule Cut Off Score	Test Performance Measures[58]					
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR
1+	99.48	1.36	27.46	87.50	1.01	0.38
2+	94.32	12.22	28.74	85.14	1.07	0.46
3+	**73.13**	**43.36**	**32.64**	**81.13**	**1.29**	**0.62**
4+	44.44	73.91	39.00	77.99	1.70	0.75
5+	15.25	92.73	44.03	74.45	2.10	0.91
6+	4.65	97.96	46.15	73.24	2.28	0.97
7+	1.29	98.64	26.32	72.69	0.95	1.00

[58] Key: Sens = Sensitivity; Spec = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value; PLR = Positive Likelihood Ratio; NLR = Negative Likelihood Ratio
(**bold**) selected cutoff score

Table 10. Brazil Test Performance Measures of Country Specific Clinical Prediction Rule At Varying Cut Off Scores. Brazil Clinical Prediction Rule: Faucial Erythema Sg, Cervical Lymph Node Tenderness Sg, No Disturbed Sleep Sx, No Fever Sg, Difficulty/Pain Swallowing Sx

Brazil Clinical Prediction Rule Cut Off Score	Test Performance Measures[59]					
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR
1+	100.00	1.39	24.87	100.00	1.01	0.00
2+	100.00	10.42	26.70	100.00	1.12	0.00
3+	100.00	15.28	27.81	100.00	1.18	0.00
4+	97.87	38.19	34.07	98.21	1.58	0.06
5+	95.74	47.22	37.19	97.14	1.81	0.09
6+	**91.74**	**69.44**	**69.44**	**91.74**	**3.00**	**0.12**
7+	68.09	75.69	47.76	87.90	2.80	0.42
8+	44.68	88.89	56.76	83.12	4.02	0.62
9+	31.91	95.14	68.18	81.07	6.57	0.72
10+	19.15	95.83	60.00	78.41	4.60	0.84

[59] Key: Sens = Sensitivity; Spec = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value; PLR = Positive Likelihood Ratio; NLR = Negative Likelihood Ratio
(**bold**) selected cutoff score

Table 11. Latvia Test Performance Measures of Country Specific Clinical Prediction Rule At Varying Cut Off Scores. Latvia Clinical Prediction Rule: Palatal Petechiae Sg, Activity Level Below Normal Sx, and No Enlarged Cervical Lymph Nodes Sg

Latvia Clinical Prediction Rule Cut Off Score	Test Performance Measures[60]					
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR
1+	94.55	12.40	31.52	84.21	1.08	0.44
2+	92.73	17.05	32.28	84.62	1.12	0.43
3+	**60.00**	**65.12**	**42.31**	**79.25**	**1.72**	**0.61**
4+	25.45	91.47	56.00	74.21	2.99	0.81
5+	23.64	93.80	61.90	74.23	3.81	0.81
6+	5.45	100.00	100.00	71.27	-	0.95

[60] Key: Sens = Sensitivity; Spec = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value; PLR = Positive Likelihood Ratio; NLR = Negative Likelihood Ratio
(**bold**) selected cutoff score

Table 12. Croatia Test Performance Measures of Country Specific Clinical Prediction Rule At Varying Cut Off Scores. Croatia Clinical Prediction Rule: Palatal Petechiae Sg, Cervical Lymph Node Tenderness Sg, No Sore Throat Sx, and Difficulty/Pain Swallowing Sx

Croatia Clinical Prediction Rule Cut Off Score	Test Performance Measures[61]					
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR
1+	97.62	21.55	47.40	92.59	1.24	0.11
2+	97.62	21.55	47.40	92.59	1.24	0.11
3+	**75.00**	**68.97**	**63.64**	**79.21**	**2.42**	**0.36**
4+	71.43	68.97	62.50	76.92	2.30	0.41
5+	35.71	86.21	65.22	64.94	2.59	0.75
6+	17.86	94.83	71.43	61.45	3.45	0.87
7+	13.10	95.69	68.75	60.33	3.04	0.91
8+	5.95	98.28	71.43	59.07	3.45	0.96
9+	58.29	100.00	100.00	58.29	-	0.42

[61] Key = Sens = Sensitivity; Spec = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value; PLR = Positive Likelihood Ratio; NLR = Negative Likelihood Ratio
(**bold**) selected cutoff score

Table 13. Combined Test Performance Measures of Combined Specific Clinical Prediction Rule At Varying Cut Off Scores. Combined Clinical Prediction Rule: Season (Early Summer/Autumn), Age Above 5 Years, Palatal Petechiae Sg, No Cough Sx, Faucial Erythema Sg, Erythema Posterior Sg, Hoarseness Sx, Difficulty/Pain Swallowing Sx

Combined Clinical Prediction Rule Cut Off Score	Test Performance Measures[62]					
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR
1+	100.00	0.99	28.95	100.00	1.01	0.00
2+	98.78	4.72	29.94	90.54	1.04	0.26
3+	93.37	17.25	31.29	86.57	1.13	0.38
4+	**74.35**	**46.13**	**35.77**	**81.67**	**1.38**	**0.56**
5+	48.34	74.30	43.15	78.09	1.88	0.70
6+	20.24	90.92	47.35	73.86	2.23	0.88
7+	10.30	96.06	51.30	72.63	2.61	0.93
8+	6.46	97.04	46.84	72.00	2.18	0.96
9+	5.24	97.46	45.45	71.82	2.07	0.97

[62] Key: Sens = Sensitivity; Spec = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value; PLR = Positive Likelihood Ratio; NLR = Negative Likelihood Ratio
(**bold**) selected cutoff score

Table 14. Summary of Test Performance Measures For Site Specific Clinical Prediction Rules By Site and Combined

Clinical Prediction Rule	Test Performance Measures[63]							
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR
Egypt	73.13	43.36	32.64	81.13	1.29	0.62	0.165	2.081
Brazil	91.74	69.44	69.44	91.74	3.00	0.12	0.612	25.000
Latvia	60.00	65.12	42.31	79.25	1.72	0.61	0.251	2.820
Croatia	75.00	68.97	63.64	79.21	2.42	0.36	0.440	6.722
Combined	74.35	46.13	35.77	81.67	1.38	0.56	0.205	2.464

[63] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, and DOR = Diagnostic Odds Ratio

SUPPLEMENTAL MATERIAL

Table S1. Individual Demographic Characteristics Compared to Culture Positive and Negative GABHS Pharyngitis Using Chi Square By Site and Combined

Demographic Characteristics	GABHS Status	Study Site				
		Egypt	Brazil	Latvia	Croatia	Combined
Gender (Female)	n	1418	191	184	200	1993
	% Positive	11.71	10.47	10.87	16.00	11.94
	% Negative	30.61	39.79	34.24	26.00	31.36
	P-value	0.786	0.22	0.12	0.34	0.312
	Ratio	2.61	3.80	3.15	1.63	2.63
Gender (Male)	n	1418	191	184	200	1993
	% Positive	15.59	14.14	19.02	26.00	16.81
	% Negative	42.10	35.60	35.87	32.00	39.89
	P-value	.	.	.	.	.
	Ratio	2.70	2.52	1.89	1.23	2.37
Season (Winter/ Spring)[64]	n	1403	-	183	161	1938
	% Positive	14.90	-	15.30	22.98	16.56
	% Negative	47.47	-	36.07	37.89	48.35
	P-value	**0.000**	-	0.932	0.656	**0.000**
	Ratio	3.19	-	2.36	1.65	2.92
Season (Summer/Autumn)	n	1403	-	183	161	1938
	% Positive	12.62	-	14.21	16.15	11.82
	% Negative	25.02	-	34.43	22.98	23.27
	P-value	.	-	.	.	.
	Ratio	1.98	-	2.42	1.42	1.97
Age Above 5 Years	n	1418	191	184	200	1993
	% Positive	10.44	18.32	19.57	23.50	13.35
	% Negative	22.36	39.27	37.50	33.50	26.49
	P-value	**0.007**	**0.007**	0.133	0.799	**0.000**
	Ratio	2.14	2.14	1.92	1.43	1.98
Age Below 5 Years	n	1418	191	184	200	1993
	% Positive	16.85	6.28	10.33	18.50	15.40
	% Negative	50.35	36.13	32.61	24.50	44.76
	P-value	.	.	.	.	.
	Ratio	2.99	5.75	3.16	1.32	2.91

[64] Key: (-) unable to compare due to missing data
(.) same p-value
(bold) p-values <0.05

Table S2. Individual Clinical Characteristics (Signs) Compared to Culture Positive and Negative GABHS Pharyngitis Using Chi Square By Site and Combined

Clinical Presentation: Signs	GABHS Status	Study Site				
		Egypt	Brazil	Latvia	Croatia	Combined
Fever	n	1418	191	184	200	1993
	% Positive	11.71	5.76	16.85	11.00	11.54
	% Negative	30.18	21.99	36.41	14.50	28.40
	P-value	0.639	0.444	0.582	0.849	0.908
	Ratio	2.58	3.82	2.16	1.32	2.46
Cough	n	1416	189	183	200	1988
	% Positive	6.21	3.70	9.84	15.50	7.24
	% Negative	21.61	28.57	21.86	30.00	23.14
	P-value	**0.010**	**0.003**	0.758	**0.038**	**0.001**
	Ratio	3.48	7.71	2.22	1.94	3.19
Hoarseness[65]	n	1417	*190*	184	200	1991
	% Positive	2.47	*2.63*	13.04	17.00	4.92
	% Negative	5.22	*3.16*	19.02	21.00	7.89
	P-value	0.235	*0.144*	**0.028**	0.539	**0.000**
	Ratio	2.11	*1.20*	1.46	1.24	1.60
Nares Excoriations	n	1417	*184*	*184*	*200*	1985
	% Positive	3.39	*0.54*	*2.72*	*2.00*	2.92
	% Negative	9.32	*4.89*	*8.70*	*3.00*	8.21
	P-value	0.853	*0.456*	*0.619*	*1.00*	0.371
	Ratio	2.75	*9.00*	*3.20*	*1.50*	2.81
Palatal Petechiae	n	*1417*	189	184	200	1990
	% Positive	*0.21*	3.17	7.61	12.50	2.41
	% Negative	*0.42*	7.41	7.61	6.50	2.36
	P-value	*0.711*	0.574	**0.012**	**0.001**	**0.000**
	Ratio	*2.00*	2.33	1.00	0.52	0.98
Strawberry Tongue	n	1416	-	183	200	1989
	% Positive	0.56	-	8.74	9.00	2.11
	% Negative	0.99	-	13.11	5.50	2.51
	P-value	0.330	-	0.121	**0.018**	**0.000**
	Ratio	1.75	-	1.50	0.61	1.19

[65] Key: (*italics*) Fisher Exact Test (cell frequency less than or equal to 5)
(-) Unable to compare to due missing data
(**bold**) p-value <0.05

Table S2 (continued)

Pharyngeal Erythema	n	1417	190	184	200	1991
	% Positive	26.53	21.05	28.80	37.50	27.32
	% Negative	68.81	55.79	66.30	52.50	65.70
	P-value	**0.024**	0.122	0.606	0.774	**0.020**
	Ratio	2.59	2.65	2.30	1.40	2.40
Faucial Erythema	n	1417	190	184	200	1991
	% Positive	23.92	20.00	23.91	10.00	22.15
	% Negative	58.15	29.47	51.09	8.00	49.72
	P-value	**0.001**	**0.000**	0.306	0.069	**0.001**
	Ratio	2.43	1.47	2.14	0.80	2.24
Tonsillar Erythema	n	1417	190	184	200	1991
	% Positive	24.91	22.11	28.26	38.00	26.27
	% Negative	65.00	46.84	67.39	51.00	62.08
	P-value	0.238	**0.000**	0.631	0.570	**0.006**
	Ratio	2.61	2.12	2.38	1.34	2.36
Erythema Posterior	n	1417	189	184	200	1990
	% Positive	23.78	20.11	26.63	38.00	25.13
	% Negative	59.77	31.75	59.24	47.50	55.83
	P-value	**0.020**	**0.000**	0.413	0.089	**0.000**
	Ratio	2.51	1.58	2.22	1.25	2.22
Tonsillar Enlargement (2 - 4)	n	1417	188	181	199	1985
	% Positive	20.54	19.15	25.41	29.15	21.71
	% Negative	52.29	32.98	58.01	30.15	48.77
	P-value	0.185	**0.000**	0.678	**0.017**	**0.001**
	Ratio	2.55	1.72	2.28	1.03	2.25
1+ Tonsillar Enlargement	n	1417	190	184	200	1991
	% Positive	4.38	3.68	4.35	11.50	5.02
	% Negative	15.67	24.21	11.96	22.00	16.78
	P-value	**0.022**	**0.022**	0.673	0.119	**0.003**
	Ratio	3.58	6.57	2.75	1.91	3.34
2+ Tonsillar Enlargement	n	1417	190	184	200	1991
	% Positive	11.36	10.53	14.13	14.00	11.80
	% Negative	34.37	21.05	40.22	15.50	31.74
	P-value	0.063	0.062	0.208	0.312	0.160
	Ratio	3.02	2.00	2.85	1.11	2.69
3+ Tonsillar Enlargement	n	1417	190	184	200	1991
	% Positive	7.55	7.37	10.33	11.50	8.19
	% Negative	15.03	7.37	17.39	11.00	14.11
	P-value	**0.005**	**0.001**	0.177	0.160	**0.000**
	Ratio	1.99	1.00	1.68	0.96	1.72

Table S2 (continued)

4+ Tonsillar Enlargement	n	1417	*189*	*183*	200	1989
	% Positive	1.62	*2.12*	*1.64*	3.50	1.86
	% Negative	2.89	*4.23*	*1.09*	5.00	3.07
	P-value	0.110	*0.497*	*0.161*	0.943	**0.044**
	Ratio	1.78	*2.00*	*0.67*	1.43	1.65
Enlarged Cervical Lymph Nodes	n	1417	40	162	200	1819
	% Positive	6.00	25.00	18.52	26.50	9.79
	% Negative	13.48	27.50	42.59	28.00	17.98
	P-value	0.139	0.987	0.412	**0.038**	**0.002**
	Ratio	2.25	1.10	2.30	1.06	1.84
Cervical Lymph Node Tenderness	n	1416	190	184	200	1990
	% Positive	6.21	14.21	23.37	23.00	10.25
	% Negative	12.22	16.84	53.80	21.50	17.44
	P-value	**0.009**	**0.000**	0.832	**0.013**	**0.000**
	Ratio	1.97	1.19	2.30	0.93	1.70
Pharyngeal Exudate	n	1417	190	184	200	1991
	% Positive	3.88	3.68	4.35	4.50	3.97
	% Negative	8.61	6.84	8.70	7.00	8.29
	P-value	0.221	0.261	0.693	0.767	0.179
	Ratio	2.218	1.86	2.00	1.56	2.09
Tonsillar Exudate	n	1417	190	184	200	1991
	% Positive	5.65	12.63	20.11	17.50	8.84
	% Negative	8.89	14.21	45.65	20.50	13.96
	P-value	**0.000**	**0.000**	0.778	0.363	**0.000**
	Ratio	1.58	1.13	2.27	1.17	1.58

Table S3. Individual Clinical Characteristics (Symptoms) Compared to Culture Positive and Negative GABHS Pharyngitis Using Chi Square By Site and Combined

Clinical Presentation: Symptoms	GABHS Status	Study Site				
		Egypt	Brazil	Latvia	Croatia	Combined
Fever	n	1417	189	184	200	1990
	% Positive	22.94	22.75	27.17	28.00	23.82
	% Negative	59.49	67.20	62.50	39.00	58.44
	P-value	0.284	0.685	0.719	0.932	0.653
	Ratio	2.59	2.95	2.30	1.39	2.45
Chills	n	1417	190	184	200	1991
	% Positive	10.59	9.47	22.83	15.00	12.05
	% Negative	24.35	23.16	46.74	21.50	26.02
	P-value	0.058	0.340	0.191	0.844	**0.023**
	Ratio	2.30	2.44	2.05	1.43	2.16
Runny Nose	n	1417	190	184	200	1991
	% Positive	12.07	7.89	10.87	19.50	12.31
	% Negative	40.01	37.89	26.63	31.00	37.67
	P-value	**0.000**	**0.028**	0.835	0.327	**0.000**
	Ratio	3.32	4.80	2.45	1.59	3.06
Nasal Congestion	n	1417	189	184	200	1990
	% Positive	9.39	8.99	16.30	17.50	10.80
	% Negative	23.85	34.92	38.59	32.00	27.09
	P-value	0.552	0.217	0.951	0.059	0.860
	Ratio	2.54	3.88	2.37	1.83	2.51
Sore Throat	n	1417	188	184	200	1989
	% Positive	26.68	25.00	28.26	35.00	27.50
	% Negative	70.71	71.81	65.22	54.00	68.63
	P-value	0.437	0.151	0.702	**0.029**	0.463
	Ratio	2.65	2.87	2.31	1.54	2.50
Difficulty/Pain Swallowing	n	1417	188	183	200	1988
	% Positive	24.49	22.34	23.50	31.50	24.90
	% Negative	62.24	45.21	45.36	31.50	55.99
	P-value	**0.032**	**0.000**	**0.042**	**0.003**	**0.000**
	Ratio	2.54	2.02	1.93	1.00	2.25
Cough	n	1417	190	184	200	1991
	% Positive	15.95	7.89	10.87	12.50	14.36
	% Negative	50.74	50.00	21.74	26.50	45.55
	P-value	**0.000**	**0.000**	0.478	**0.023**	**0.00**
	Ratio	3.18	6.33	2.00	2.12	3.17
Vomiting	n	1417	189	184	200	1990
	% Positive	6.56	4.76	8.15	10.50	6.93
	% Negative	16.16	17.46	13.59	18.50	16.28
	P-value	0.452	0.559	0.235	0.289	0.542
	Ratio	2.46	3.67	1.67	1.76	2.35

Table S3 (continued)

Earache[66]	n	1417	189	*184*	200	1990
	% Positive	2.47	3.17	*2.17*	3.00	2.56
	% Negative	7.13	8.99	*3.80*	4.50	68.59
	P-value	0.678	0.835	*0.735*	0.870	0.722
	Ratio	2.89	2.83	*1.75*	1.50	26.76
Abdominal Pain	n	1417	186	184	200	1987
	% Positive	9.95	6.99	10.33	13.00	10.02
	% Negative	26.68	26.88	16.30	23.50	25.42
	P-value	0.963	0.354	0.113	0.166	0.732
	Ratio	2.68	3.85	1.58	1.81	2.54
Activity Level Below Normal	n	1417	190	183	200	1990
	% Positive	14.75	14.74	26.78	28.50	17.24
	% Negative	33.52	37.37	55.19	37.00	36.23
	P-value	**0.007**	0.237	**0.046**	0.551	**0.000**
	Ratio	2.27	2.54	2.06	1.30	2.10
Disturbed Sleep	n	1416	190	183	200	1989
	% Positive	10.45	6.32	18.03	23.00	12.02
	% Negative	24.36	32.11	36.07	30.50	26.80
	P-value	0.088	**0.036**	0.218	0.761	0.077
	Ratio	2.33	5.08	2.00	1.33	2.23
Hoarseness	n	1416	190	183	200	1989
	% Positive	7.06	7.89	12.02	15.50	8.45
	% Negative	15.61	20.00	15.30	20.50	16.49
	P-value	0.070	0.479	**0.008**	0.821	**0.003**
	Ratio	2.21	2.53	1.27	1.32	1.95

[66] Key: (*italics*) Fisher's Exact (cell frequency less than or equal to 5)
(**bold**) p-value <0.05

Table S4. Univariate Logistic Regression of Individual Demographic Predictors and GABHS Pharyngitis Culture Status. Odds Ratios (OR) and 95% Confidence Interval (CI) For Each Predictor By Site and Combined

Demographic Characteristics	Odds Ratio	Study Site				
		Egypt	Brazil	Latvia	Croatia	Combined
Gender (Female)	N	1418	191	184	200	1993
	OR	1.033	0.663	0.599	0.757	0.904
	95% CI	(0.816, 1.309)	(0.341, 1.288)	(0.313, 1.145)	(0.427, 1.343)	(0.743, 1.10)
	P-value	0.786	0.225	0.121	0.342	0.312
Season (Winter)[67]	n	1403	-	183	161	1938
	OR	0.622	-	1.028	0.863	0.675
	95% CI	(0.490, 0.790)	-	(0.544, 1.941)	(0.452, 1.648)	(0.551, 0.827)
	P-value	**0.000**	-	0.932	0.656	**0.000**
Age Below 5 Years	n	1418	191	184	200	1993
	OR	1.395	2.683	1.648	0.929	1.464
	95% CI	(1.093, 1.780)	(1.290, 5.583)	(0.856, 3.171)	(0.527, 1.638)	(1.203, 1.781)
	P-value	**0.008**	**0.008**	0.135	0.799	**0.000**
Age Above 5 Years	n	1418	191	184	200	1993
	OR	0.717	0.373	0.607	1.076	0.683
	95% CI	(0.562, 0.915)	(0.179, 0.775)	(0.315, 1.168)	(0.611, 1.897)	(0.561, 0.831)
	P-value	**0.008**	**0.008**	0.135	0.799	**0.000**

[67] Key: (-) omitted because of collinearity
(**bold**) p-value < 0.05

Table S5. Univariate Logistic Regression of Individual Clinical (Signs) Predictors and GABHS Pharyngitis Culture Status. Odds Ratios (OR) and 95% Confidence Interval (CI) For Each Predictor By Site and Combined

Clinical Presentation: Signs	Odds Ratio	Study Site				
		Egypt	Brazil	Latvia	Croatia	Combined
Fever	n	1418	191	184	200	1993
	OR	1.058	0.742	1.195	1.065	1.012
	95% CI	(0.835, 1.340)	(0.345, 1.595)	(0.633, 2.256)	(0.560, 2.024)	(0.830, 1.233)
	P-value	0.639	0.445	0.582	0.849	0.908
Cough	n	1416	189	183	200	1988
	OR	0.699	0.285	1.113	0.546	0.702
	95% CI	(0.532, 0.918)	(0.119, 0.682)	(0.565, 2.191)	(0.308, 0.969)	(0.564, 0.874)
	P-value	**0.010**	**0.005**	0.758	**0.039**	**0.002**
Hoarseness	n	1417	190	184	200	1991
	OR	1.290	2.718	2.079	1.198	1.662
	95% CI	(0.847, 1.963)	(0.790, 9.357)	(1.075, 4.020)	(0.673, 2.134)	(1.264, 2.185)
	P-value	0.236	0.113	**0.030**	0.539	**0.000**
Nares Excoriations	n	1417	184	184	200	1985
	OR	0.967	0.309	0.706	0.917	0.865
	95% CI	(0.679, 1.377)	(0.038, 2.508)	(0.245, 2.034)	(0.250, 3.355)	(0.630, 1.188)
	P-value	0.853	0.272	0.519	0.895	0.371
Palatal Petechiae	n	1417	189	184	200	1990
	OR	1.338	1.338	2.805	3.357	2.672
	95% CI	(0.333, 5.377)	(0.483, 3.707)	(1.233, 6.382)	(1.598, 7.055)	(1.765, 4.045)
	P-value	0.681	0.575	**0.014**	**0.001**	**0.000**

Table S5 (continued)

Strawberry Tongue[68]	n	1416	-	183	200	1989
	OR	1.541	-	1.778	2.603	2.172
	95% CI	(0.642, 3.704)	-	(0.855, 3.696)	(1.157, 5.857)	(1.424, 3.314)
	P-value	0.333	-	0.123	**0.021**	**0.000**
Pharyngeal Erythema	n	1417	190	184	200	1991
	OR	2.160	1.995	1.520	0.873	1.649
	95% CI	(1.090, 4.277)	(0.822, 4.837)	(0.306, 7.563)	(0.345, 2.211)	(1.076, 2.525)
	P-value	**0.027**	0.127	0.609	0.775	**0.022**
Faucial Erythema	n	1417	190	184	200	1991
	OR	1.812	6.560	1.489	1.953	1.459
	95% CI	(1.288, 2.548)	(2.946, 14.61)	(0.692, 3.205)	(0.943, 4.047)	(1.164, 1.828)
	P-value	**0.001**	**0.000**	0.308	0.072	**0.001**
Tonsillar Erythema	n	1417	190	184	200	1991
	OR	1.278	5.097	0.699	1.304	1.580
	95% CI	(0.850, 1.921)	(1.90, 13.674)	(0.161, 3.032)	(0.521, 3.265)	(1.134, 2.201)
	P-value	0.239	**0.001**	0.632	0.571	**0.007**
Erythema Posterior	n	1417	189	184	200	1990
	OR	1.494	6.571	1.498	2.100	1.952
	95% CI	(1.064, 2.098)	(2.86, 15.093)	(0.567, 3.963)	(0.881, 5.004)	(1.477, 2.580)
	P-value	**0.020**	**0.000**	0.415	0.094	**0.000**
Tonsillar Enlargement (2-4)	n	1417	188	181	199	1985
	OR	1.199	4.645	1.205	2.045	1.432
	95% CI	(0.917, 1.568)	(2.14, 10.084)	(0.500, 2.905)	(1.134, 3.688)	(1.147, 1.787)
	P-value	0.186	**0.000**	0.678	**0.017**	**0.001**

[68] Key: (-) data dropped
(**bold**) p-value < 0.05

Table S5 (continued)

1+ Tonsillar Enlargement	n	1417	190	184	200	1991
	OR	0.697	0.369	0.828	0.617	0.688
	95% CI	(0.512, .950)	(0.154, 0.886)	(0.344, 1.994)	(0.336, 1.134)	(0.537, 0.882)
	P-value	**0.022**	**0.026**	0.674	0.120	**0.003**
2+ Tonsillar Enlargement	n	1417	190	184	200	1991
	OR	0.799	1.907	0.666	1.371	0.868
	95% CI	(0.631, 1.012)	(0.963, 3.780)	(0.353, 1.256)	(0.743, 2.529)	(0.713, 1.057)
	P-value	0.063	0.064	0.210	0.313	0.160
3+ Tonsillar Enlargement	n	1417	190	184	200	1991
	OR	1.473	3.909	1.600	1.611	1.614
	95% CI	(1.125, 1.928)	(1.698, 8.998)	(0.807, 3.172)	(0.826, 3.140)	(1.291, 2.018)
	P-value	**0.005**	**0.001**	0.178	0.161	**0.000**
4+ Tonsillar Enlargement	n	1417	189	183	200	1989
	OR	1.530	1.558	3.635	0.964	1.537
	95% CI	(0.905, 2.585)	(0.447, 5.430)	(0.590, 22.39)	(0.351, 2.644)	(1.010, 2.341)
	P-value	0.112	0.486	0.164	0.943	**0.045**
Enlarged Cervical Lymph Nodes	n	1418	191	184	200	1993
	OR	1.257	0.315	0.625	1.832	1.161
	95% CI	(0.943, 1.674)	(0.119, 0.831)	(0.325, 1.201)	(1.032, 3.251)	(0.947, 1.422)
	P-value	0.118	**0.020**	0.159	**0.039**	0.150
Cervical Lymph Node Tenderness	n	1416	190	184	200	1990
	OR	1.463	4.683	1.086	2.055	1.711
	95% CI	(1.096, 1.952)	(2.327, 9.423)	(0.508, 2.320)	(1.161, 3.639)	(1.387, 2.110)
	P-value	**0.010**	**0.000**	0.832	**0.013**	**0.000**
Pharyngeal Exudate	n	1417	190	184	200	1991
	OR	1.238	1.750	1.202	0.874	1.218
	95% CI	(0.879, 1.743)	(0.654, 4.685)	(0.482, 2.999)	(0.359, 2.127)	(0.913, 1.624)
	P-value	0.221	0.265	0.693	0.767	0.179
Tonsillar Exudate	n	1417	190	184	200	1991
	OR	1.878	4.483	1.101	1.307	1.824
	95% CI	(1.379, 2.557)	(2.207, 9.108)	(0.564, 2.151)	(0.734, 2.327)	(1.463, 2.275)
	P-value	**0.000**	**0.000**	0.778	0.364	**0.000**

Table S6. Univariate Logistic Regression of Individual Clinical (Symptoms) Predictors and GABHS Pharyngitis Culture Status. Odds Ratios (OR) and 95% Confidence Interval (CI) For Each Predictor By Site and Combined

Clinical Presentation: Symptoms	Odds Ratio	Study Site				
		Egypt	Brazil	Latvia	Croatia	Combined
Fever	n	1417	189	184	200	1990
	OR	1.188	1.270	1.217	0.974	1.061
	95% CI	(0.866, 1.630)	(0.400, 4.034)	(0.416, 3.562)	(0.536, 1.770)	(0.821, 1.370)
	P-value	0.285	0.686	0.720	0.932	0.653
Chills	n	1417	190	184	200	1991
	OR	1.264	1.397	1.615	0.943	1.257
	95% CI	(0.992, 1.610)	(0.703, 2.776)	(0.785, 3.325)	(0.526, 1.691)	(1.031, 1.533)
	P-value	0.058	0.341	0.193	0.844	**0.023**
Runny Nose	n	1417	190	184	200	1991
	OR	0.651	0.462	0.933	0.755	0.668
	95% CI	(0.514, 0.824)	(0.231, 0.927)	(0.485, 1.795)	(0.430, 1.325)	(0.550, 0.813)
	P-value	**0.000**	**0.030**	0.835	0.328	**0.000**
Nasal Congestion	n	1417	189	184	200	1990
	OR	1.078	0.653	0.980	0.580	0.982
	95% CI	(0.8412, 1.38)	(0.330, 1.288)	(0.520, 1.848)	(0.329, 1.024)	(0.804, 1.200)
	P-value	0.552	0.219	0.951	0.06	0.860
Sore Throat[69]	n	1417	-	184	200	1989
	OR	1.368	-	1.300	0.370	0.834
	95% CI	(0.620, 3.018)	-	(0.338, 4.997)	(0.148, 0.929)	(0.512, 1.357)
	P-value	0.438	-	0.703	**0.034**	0.464

[69] Key: (-) data dropped
(**bold**) p-value <0.05

Table S6 (continued)

Difficulty/ Pain Swallowing	n OR 95% CI P-value	1417 1.503 (1.034, 2.184) **0.033**	188 5.534 (2.063, 14.84) **0.001**	183 2.166 (1.019, 4.604) **0.044**	200 2.524 (1.365, 4.665) **0.003**	1988 1.779 (1.354, 2.337) **0.000**
Cough	n OR 95% CI P-value	1417 0.613 (0.481, 0.781) **0.000**	190 0.237 (0.117, 0.479) **0.000**	184 1.271 (0.654, 2.470) 0.478	200 0.504 (0.278, 0.912) **0.024**	1991 0.564 (0.464, 0.687) **0.000**
Vomiting	n OR 95% CI P-value	1417 1.112 (0.844, 1.464) 0.452	189 0.782 (0.343, 1.784) 0.559	184 1.560 (0.747, 3.259) 0.237	200 0.712 (0.379, 1.336) 0.290	1990 1.074 (0.855, 1.349) 0.542
Earache	n OR 95% CI P-value	1417 0.918 (0.613, 1.375) 0.678	189 1.112 (0.410, 3.011) 0.835	184 1.367 (0.383, 4.873) 0.630	200 0.915 (0.313, 2.675) 0.870	1990 0.941 (0.671, 1.319) 0.722
Abdominal Pain	n OR 95% CI P-value	1417 0.994 (0.780, 1.267) 0.963	186 0.709 (0.342, 1.470) 0.355	184 1.742 (0.874, 3.471) 0.115	200 0.658 (0.364 1.191) 0.167	1987 0.965 (0.787, 1.183) 0.732
Activity Level Below Normal	n OR 95% CI P-value	1417 1.382 (1.093, 1.748) **0.007**	190 1.494 (0.766, 2.916) 0.239	183 2.717 (0.989, 7.466) 0.053	200 1.198 (0.661, 2.171) 0.551	1990 1.456 (1.196, 1.774) **0.000**
Disturbed Sleep	n OR 95% CI P-value	1416 1.235 (0.969, 1.574) 0.088	190 0.461 (0.221, 0.961) **0.039**	183 1.500 (0.785, 2.864) 0.219	200 1.091 (0.621, 1.917) 0.761	1989 1.195 (0.981, 1.457) 0.077
Hoarseness	n OR 95% CI P-value	1416 1.286 (0.980, 1.688) 0.070	190 1.295 (0.632, 2.652) 0.479	183 2.480 (1.249, 4.922) **0.009**	200 1.070 (0.597, 1.919) 0.821	1989 1.390 (1.117, 1.729) **0.003**

CHAPTER 5. PAPER TWO: “VALIDATION OF GROUP A BETA HEMOLYTIC STREPTOCOCCAL PHARYNGITIS CLINICAL PREDICTION RULES: EXTERNAL VALIDATION OF RULES FOR CHILDREN FROM LOWER AND UPPER MIDDLE INCOME COUNTRIES”

Chapter 5. Paper Two: "Validation of Group A Beta Hemolytic Streptococcal Pharyngitis Clinical Prediction Rules: External Validation of Rules for Children From Lower and Upper Middle Income Countries"

ABSTRACT

Introduction: Most clinical prediction rules (CPRs) for group a beta hemolytic streptococcal (GABHS) pharyngitis have been developed and/or validated in high-income countries (HICs), but are most useful in low and middle-income settings with limited access to laboratory testing.

Methods: We validated 5 CPRs developed in the context of a five country multi-national study and CPRs available from the medical literature. Clinical and demographic predictors were re-created using study variables to re-create published CPRs, and diagnostic test performance measures were used to assess all CPRs in the study populations.

Results: CPRs from the medical literature had better sensitivity in the original study compared to study populations, but comparable or improved specificity. Study developed CPRs had varied performance, but Egypt CPR performed well in other populations, whereas Latvia had poor sensitivity.

Conclusion: CPRs developed for use in HICs do not generally have both high enough sensitivity to prevent RF/RHD and high enough specificity to reduce unnecessary antibiotics to prevent AMR and allergic reactions. Our analysis suggests that country specific CPRs are preferable to CPRs developed for other populations.

INTRODUCTION

Group A beta hemolytic streptococcal (GABHS) pharyngitis is the most common bacterial cause of pharyngitis and is responsible for 5 – 10% of cases diagnosed among children between the ages of 5 and 15 years of age (Table 1) (6, 33). GABHS is responsible for an estimated 600 million new cases of pharyngitis each year; however, disease distribution is disproportionate as incidence is 5 – 10 times higher in developing countries and 3 times higher among children and adolescents under 15 years (1, 4, 5). There are several factors that influence the prevalence of GABHS infections. Primarily, GABHS infections are common among children and adolescents of LMICs where conditions promoting efficient transmission (poverty, overcrowding, etc.) are present, and where prevention and treatment are not readily available (5).

Untreated, GABHS pharyngitis can lead to rheumatic fever (RF), which can result in rheumatic heart disease (RHD), and other serious sequelae of infection (Table 2) (1-5). In HICs, RF and RHD rates have declined since 1950s with an annual incidence of RF less than 0.5 cases per 100,000 school age children (45). Before penicillin was readily available, RF was the number one cause of cardiac illness in the U.S. However, it remains the number one cause of acquired heart disease in children in low and middle-income countries (LMICs) where annual RF incidence is RF 100 – 200 times greater (5, 45).

Primary prevention of acute RF is accomplished by proper identification and adequate antibiotic treatment of GABHS pharyngitis (Figure 1) (6, 7). Diagnosis of GABHS pharyngitis is best accomplished by combining clinical judgment and diagnostic test results, the gold standard for which is throat culture (1-3, 38, 39, 43, 53). In HICs, this is easily accomplished; however, in low and middle income countries (LMICs) and other resource poor settings, adhering to the gold standard may be difficult due to limited access to laboratory facilities and/or the expense of laboratory testing.

Clinical prediction rules (CPRs) may provide a reasonable option for physicians who do not have access to testing. Unfortunately, most CPRs have been developed using data from HICs where GABHS pharyngitis may present differently than in LMICs (1, 2, 4).

The majority of CPRs were generated for use in adults from HICs with numerous and complex clinical and epidemiological predictors; however, more recent efforts have lead to validation of these rules in different populations and settings with different patients (Table 3) (25-28, 52, 54-63). Validating CPRs test the diagnostic accuracy and transportability of the rules. While the vast majority of studies have focused on HICs, few rules have been validated in children of LMICs. This is especially important for LMICs as they rely on CPRs in the absence of laboratory testing. Therefore, the study objective was to validate study derived and published CPRs from the medical literature in the five study populations for improved diagnosis and prompt

treatment of GABHS pharyngitis, and subsequent primary prevention of RF/RHD in children from LMICs.

METHODS

Study Population

Children 2-12 years of age presenting with complaint of sore throat were enrolled in four urban university pediatric outpatient clinics from September 2001 to August 2005 in Rio de Janeiro, Brazil; Cairo, Egypt; Riga, Latvia; and Zagreb, Croatia. Patients were excluded on the basis of oral antibiotic use within 3 days or intramuscularly administered antibiotics within 28 days prior to the clinic visit; a history of previous rheumatic fever or rheumatic heart disease; or hospitalization for any reason.

Study Design

In this cross-sectional prospective study, all participating sites used a common protocol, standard methods for biological specimen collection and laboratory analysis and standard data collection forms translated into local language. Ethical approval was obtained by all participating institutions. Informed consent was obtained from the parent or guardian accompanying the child to the clinic and child assent was obtained from all participating children age 5 and older.

After enrollment, demographic data and medical history were recorded, a physical examination conducted and two throat swabs were obtained from each participant. One throat swab was used for a rapid test and

the other was plated onto 5% sheep blood agar, incubated at 37 C and examined at 24 and 48 hours for the presence of beta-hemolytic streptococci and confirmed by bacitracin disc (2, 6, 112). Biological and data collection took place at each of the study sites, at the time of hospital admission.

Statistical Methods

This study evaluated the external validation of published and study derived CPRs. To assess external validity, published and study CPRs were examined using each of the five study populations (four countries and all countries combined). The previously developed CPRs examined in this study were from articles published by: Steinhoff et al (Abu Reesh CPR and Steinhoff CPR); Smeesters et al (Smeesters CPR); Sahin et al (Sahin CPR 1 and Sahin CPR 2); Attia et al (Attia CPR); Breese et al (Breese CPR); Centor et al (Centor CPR); Wald et al (Wald CPR); McIsaac et al (McIsaac CPR); WHO et al (WHO CPR); Walsh et al (Walsh CPR); and Nandi et al (Nandi CPR) (3, 4, 23, 25-31, 57). Table 3 lists CPRs found in the literature from 1975 – 2006, including those validated in the study populations. Table 3 also includes the predictors used to generate these CPRs. These predictors were re-created using study variables. Table 4 presents study variables used to recreate the published CPRs.

External validation also included validation of the five CPRs generated in development component of the study for each of the

populations (Table 5). Methodology on development of these rules has been reported elsewhere (Chapters 3-4).

The re-created CPRs from the published literature and study CPRs were tested and evaluated in each of the four countries and combined populations. Evaluation of the rules involved using diagnostic test performance measures including sensitivity and specificity, positive and negative predictive value (PPV and NPV), positive and negative likelihood ratio (PLR and NLR), J statistic (JS), and diagnostic odds ratio (DOR) which were calculated for both published and study CPRs. Additionally, receiver operating characteristic (ROC) curve area, or area under the curve (AUC) were calculated for the study derived prediction rules.

Data analyses were conducted using STATA (v12.1).

RESULTS

Patient Characteristics

Of the 2,055 children enrolled and participated in the study, a total of 1,993 participants were included in the analysis (patients without the outcome of interest were excluded from analyses). Data on patients from outpatient clinics in Egypt (n=1,418), Brazil (n=191), Latvia (n=184), and Croatia (n=200) were analyzed. Table 6 presents data on selected patient characteristics by study population. Brazil, Latvia, and Croatia, had the smaller sample size (≤10%). Over 70% of the

children came from Egypt, where patients were younger (median age 4 years) than in the other study sites (median age 6 years). In the combined population, median age was 5 years, where 40% were over the age of 5. Children in Brazil, Latvia, and Croatia were older with nearly 60% of their population above age 5 years. The proportion of males was slightly greater for all sites (42-49%). In addition, GABHS pharyngitis status varied by site, where Egypt, Brazil, Latvia, and combined GABHS positive was 24-29%, but in Croatia 42% of patients tested culture positive for GABHS pharyngitis.

External Validation of Published CPRs in Study Populations

External validation of published CPRs in study populations was the first component of the study. External validation of existing CPRs found in the literature was performed using 12 articles on GABHS pharyngitis clinical diagnosis. A total of 13 CPRs[70] were validated in Egypt, Brazil, Latvia, Croatia, and combined study populations. There was variation in the CPRs evaluated. They had additive scores, but not all were simple; most had several predictors, but some had as little as two predictors. Seven of the rules examined were from high-income countries and six were from LMICs.

In the Egypt population (Table 7), sensitivity varied greatly ranging from 0.26 – 96.38%; specificity also differed by CPR ranging from 5.72 – 99.81% (Figure 2). CPRs developed by Sahin (29) both had the highest sensitivity (greater than 95%), but also had the poorest specificity

[70] Note: Sahin CPR 1 and Sahin CPR 2 are both from the same article [Sahin et al (43)].

(less than 7%). Conversely, CPRs by Attia (111), Breese (24), WHO (49, 73), and Nandi (28) had high specificity (92.14 – 99.81%) and little to no sensitivity (0.26 – 10.59%). The remaining rules had varying degrees of sensitivity and specificity, where the CPRs by Steinhoff (4) and McIsaac (26, 27, 59) had the optimum balance of high sensitivity (65.03% and 75.06%, respectively) and high specificity (46.60% and 34.12%, respectively). Both CPRs have similar estimates for the other performance measures including positive and negative predicative value, positive and negative likelihood ratio, and diagnostic odds ratio (Table S1). When compared to the population they were developed for, sensitivity dropped for nearly all rules when applied to the Egypt population. The Sahin CPRs improved sensitivity, and the WHO CPR performed similarly. Specificity varied, but in general performed similar to original.

Brazil had several CPRs with high sensitivity and specificity (Table 8). However, sensitivities and specificities had a wide range (2.13 – 91.49% and 25 – 98.61%, respectively) (Figure 3). Of these, the CPRs by McIsaac (26, 27, 59) (87.23% sensitivity and 53.52% specificity) and Steinhoff (4) (89.36% sensitivity and 41.96% specificity) had the best balance of sensitivity and specificity for prevention of RF/RHD and AMR. Other test measures (Table S2) were similar and the diagnostic odds ratios were highest for McIsaac (26, 27, 59) (DOR: 7.83) and Steinhoff (4) (DOR: 6.16). Both CPRs did equivalent or slightly better in Brazil population compared to original. In general, the sensitivity of CPRs were better in original, and specificities

varied. Although rules by Abu Reesh (3) and Walsh (56) were also suitable, the lower sensitivity of Abu Reesh (3) (63.83%), lower specificity of Walsh (56) (31.25%), and lower diagnostic OR of both (4.6 and 4.93, respectively) made them alternative (although viable) options.

Clinical prediction rules from the literature applied to the Latvia study population resulted in a single best option; the Wald (31) CPR (Table 9). Although the Abu Reesh (3) rule has slightly higher sensitivity compared to the Wald (31) rule (80% vs. 72.73%, respectively), it also has a slightly lower specificity (23.26% vs. 38.76%, respectively) (Figure 4). As an upper middle-income country, the gain in specificity, along with other test performance measures (Table S3), made the Wald (31) rule a valid option for the Latvia population. Overall, sensitivity and specificity was lower for the CPRs when validated in the Latvia population than in their original population.

The Croatia population (Table 10) had varying sensitivity (2.38 – 90.48%) and specificity (12.93 - 98.28%). Although sensitivity and specificity were higher in the original population, Steinhoff (4) and McIsaac (26, 27, 59) CPRs had the best balance of high sensitivity and specificity. Both CPRs performed similarly when applied to the Croatia population (Figure 5). In fact, both had 73.81% sensitivity and correctly similar specificity (Steinhoff, 37.07%; and McIsaac, 40.52%). Other tests performance measures were also similar (Table

S4). For three of the four study sites, Steinhoff (4) and McIsaac (26, 27, 59) rules were the best option with high sensitivity and specificity.

Table 11 presents results of published CPRs in the Combined population. The Attia CPR (23) had the lowest sensitivity, less than 1%, but also had the highest specificity, greater than 99%. In general, the CPRs had low sensitivity, especially when compared to how they performed in the original populations. Specificity were either similar to original or had slight improvement. The two CPRs with the highest sensitivity and specificity were Steinhoff (4) and McIsaac (26, 27, 59). Of the two, McIsaac (26, 27, 59) had the highest sensitivity (77.41%), and Steinhoff (4) had the highest specificity at 41.61%. Although the Walsh (56) rule had higher sensitivity than either McIsaac (26, 27, 59) or Steinhoff (4), it also had lower specificity (21.97%) (Figure 6). For LMICs dealing with the dual burden of RF/RHD and risk of AMR, Steinhoff (4) and McIsaac (26, 27, 59) CPRs are a good option, balancing sensitivity and specificity for Egypt, Brazil, Croatia, and the Combined population (Table S5).

External Validation of Study CPRs in Study Populations

External validation of study derived CPRs were performed in the second component of the study. Tables 7 – 11 present test performance measures for CPRs developed for each of the four countries and the combined population. Tables S6 – S10 present additional test

performance measures. Not surprisingly, country specific rules did best in the populations for which they were developed.

When evaluating the validity of the study CPRs in the Egypt population (Table 7), the Brazil CPR had dropped in sensitivity and specificity (62.02% versus 91.74% and 46.65 versus 69.44%, respectively) when validated in Egypt. Croatia CPR had the highest specificity (82.06%), but it also had the lowest sensitivity (23.36%). Egypt CPR performed the best, balancing sensitivity and specificity, in the Egypt population. The Egypt CPR performed better on most performance measures, expect the area under the curve (AUC) (Table S6).

Although the Brazil CPR was best in the Brazil population (Table 8), the Egypt and Combined CPRs both had high sensitivity (87.23% and 80.85%, respectively) and specificity (53.47% and 68.75%, respectively). The Latvia CPR had the poorest sensitivity (25.53%) and Croatia had the highest AUC (Table S7). The Brazil CPR had the highest sensitivity, positive and negative predictive values, positive likelihood ratio, J statistic, and diagnostic odds ratio.

Table 9 shows the Latvia population. The Latvia CPR had the lowest sensitivity for its own population (60.00%) and the highest specificity (65.12%). However, when assessing other measures (Table S8), it did have the highest diagnostic OR (2.820), performed better in other measures, and had specificity greater than 36% (specificity of other CPRs were low, ranging from 7.75 – 36.43%).

When examining the Croatia study population (Table 10), the Croatia CPR was best (75.00% sensitivity and 68.97% specificity). Furthermore, it performed better on all test performance measures except AUC, which was higher in Brazil (Table S9). However, the Combined CPR had the highest sensitivity and would have also provided a good alternative (83.33% sensitivity and 49.14% specificity).

For the Combined study population (Table 11), the Egypt CPR and Combined CPR were similar for most measures including sensitivity and specificity. Both had high sensitivity (74.35% and 76.44%, respectively) and specificity (46.13% and 40.21%, respectively); however, the Combined CPR was selected as the rule of choice. While Brazil CPR had similar specificity (49.79%), sensitivity was lower than either the Combined or Egypt (61.26%), which is why it was not selected. Latvia and Croatia had too low sensitivity.

Figures S1-5 show the AUC for each of the populations. Croatia CPR had the highest AUC in all populations, except in its own population, where the Brazil CPR had highest AUC.

Overall, the Egypt CPR had high sensitivity in the other study populations, but there was great fluctuation in the specificity of the rule when validated in other study populations. Combined CPR also, had high sensitivity when validated in other study populations and moderate to poor specificity.

DISCUSSION

In this study, 13 CPRs were evaluated for their effectiveness in clinically diagnosing GABHS pharyngitis in children from LMICs without laboratory testing. External validation of CPRs from the literature is difficult to compare directly because of variations in GABHS pharyngitis characteristics (e.g., prevalence, duration, severity, etc.); and because of differences in methodology used in the various studies (e.g., inclusion/exclusion, performance measures, etc.) (1). However, when applied to a single population, validity of different CPRs can be assessed and performance evaluated in new populations. Published and study derived CPRs were validated in the Egypt, Brazil, Latvia, Croatia, and Combined populations.

There was variation between the CPRs in their original population and when applied to the five study populations. In general, sensitivity was lower and specificity was either similar or slightly higher. The McIsaac (26, 27, 59) and Steinhoff CPRs (4) had the best balance of high sensitivity and specificity for all populations, except Latvia. In Latvia, the Wald CPR (31) was selected as the most useful CPR. However, these rules still performed better in their original populations for sensitivity (except Brazil); and had equivalent or higher specificity for all. Across all populations, Attia CPR (23) had poor diagnostic value (0.28 – 2.38% sensitivity), especially for LMICs with high risk of RF/RHD prevalence. Sensitivity and specificity were the main performance measures of interest because they are not

affected by fluctuations in GABHS pharyngitis; however, other performance measures were also evaluated. Positive and negative predictive values (which are influenced by GABHS prevalence, especially PPV) were assessed because of their importance to clinicians. In general, the ability of the CPRs to confirm GABHS pharyngitis when positive was lower than their ability to rule out GABHS pharyngitis when negative. Diagnostic odds ratios were close to 1 for most rules at each site, except for the Brazil CPR in the Brazil population, where the ability to discriminate between patients with GABHS pharyngitis and those without was highest at 7.8. In Egypt, Croatia, and the combined population, there was minimal to no change in likelihood of disease; in Brazil and Latvia there were small changes in the likelihood of disease.

Validating the study CPRs in the five populations was the second component of the study. Site-specific CPRs did better in the populations they were developed for, and had varying performances when validated in other populations. Overall, the Egypt CPR had high sensitivity in other study populations, but there was great fluctuation in the specificity of the rule when validated in other populations. Combined CPR also had high sensitivity when validated in other populations and moderate to poor specificity. Sensitivity and specificity were the main performance measures assessed as it is not influenced by changes in prevalence, but other performance measures were also examined. Positive and negative predicative values are affected by disease prevalence, but often used by clinicians. In each

population, a positive test was poorer at confirming GABHS pharyngitis than a negative test was at excluding GABHS negative patients. Diagnostic odds ratio and J statistic were highest in selected rule, but generally low and not very discriminating, except for the DOR of the Brazil CPR in Brazil which was 25.00. Rules had minimal or no change in the likelihood of disease in Egypt, Latvia, and the Combined population. However, in Brazil, the Brazil CPR had a large decrease in the likelihood (NLR) of disease. In each population, the Croatia CPR was more discriminating, with the highest AUC, except in its own population, where the Brazil CPR was best. However, when assessing sensitivity and specificity of the Croatia CPR, it was less sensitive, but more specific than the selected CPRs (except in Latvia). Because high sensitivity is of greater concern, it wasn’t the best performing CPR outside its own population.

External validation of CPRs from the literature in LMICs found Steinhoff (4) and McIsaac (26, 27, 59) had the highest sensitivity and specificity, balancing prevention of RF/RHD and AMR in four of the five study populations. If LMICs do not want to generate country specific CPRs and instead use existing CPRs from the literature, they may want to validate the usefulness of these rules along with the study generated rules and decide which to use. Deciding which of these CPRs to apply to their population will be dependent on several factors including rates of GABHS pharyngitis, RF, RHD, and AMR; and ease of clinical prediction rule. For example, when debating between Steinhoff (4) and McIsaac (26, 27, 59) CPRs, physicians may wish to employ the

Steinhoff CPR as it has less clinical criteria and therefore would be that much faster to diagnose. Overall, the recommendation is to generate country specific prediction rules as presentation of clinical signs and symptoms vary geographically.

External validation of study generated CPRs in other LMICs found that some of the rules (e.g., Latvia CPR) had poor sensitivity when applied to other study populations. This could be due to differences in clinical presentation of GABHS pharyngitis, which has been reported in other studies (9). Differences in disease prevalence also influence the transportability of CPRs to other countries. Consequently, the Latvia CPR would not be an effective CPR for LMICs because of its low sensitivity. However, it might be useful in high-income (and some upper middle income) countries where specificity is more important. Not all rules had poor validity in other study populations. For example, the Egypt CPR in Brazil had high sensitivity and although not especially high specificity, for countries where burden of RF/RHD is still a public health concern, high enough specificity to reduce indiscriminate antibiotic use and retain its high sensitivity.

To be useful in a clinical setting, percent of false positive and false negative were examined. Ideally, the CPRs would have small numbers of false positives and false negatives; however, analysis revealed that the percent of unnecessary antibiotic use was high for most CPRs and percent of undetected cases of GABHS pharyngitis lower, which is expected since high sensitivity was preferable for RF/RHD

prevention. For most populations, the increase in undetected cases was low at less than 12% compared to Steinhoff and McIsaac CPRs (Egypt and Croatia CPRs had a slight decrease in undetected cases). Increase in unnecessary treatment was less than 4% for Egypt CPR compared to Steinhoff CPR; all other study CPRs had a reduction in unnecessary treatment compared to the published CPRs. In Latvia, when compared to the Wald CPR, the Latvia CPR had a 27% reduction in unnecessary antibiotic use and 12% increase in undetected cases of GABHS pharyngitis. For Croatia, Steinhoff and McIsaac CPRs performed similarly (both had a 30% increase in unnecessary treatment of GABHS negative patients and 2% increase in undetected GABHS positive cases) compared to Croatia CPR.

This study shows the importance of validating CPRs as performance usually differs when applied to another population. Without testing rules developed in other populations and settings, their effectiveness is unknown. While most studies have focused on adults in HICs, a few studies have validated rules in children from lower income countries. A recent study conducted in Indian children, used a CPR adopted from Breese was applied and a score of 15 or more predictors was found to be highly predicative of GABHS pharyngitis (91% sensitivity, 98% specificity) (28). The Breese rule was also validated in two different age groups of Turkish children and found that the rule had greater sensitivity among children older than 3 years (61). However, there has been evidence of diminished effectiveness of CPRs developed in high-income countries for use in lower income countries (1, 2). Fisher et

al found great variability when the Breese, Centor, Wald, and McIsaac rules (for the original North American populations) were applied to Egyptian children (1).

Clinical prediction rules with low sensitivity are another problem for developing countries with high RF/RHD. For example, recent studies conducted in LMICs evaluated the effectiveness of the WHO CPR and found it to have high specificity, but low sensitivity (93 – 97.4% and 0 – 12% respectively) (1-4). While high specificity limits unnecessary antibiotic use, for LMICs where the burden of RF/RHD is greatest, high sensitivity decision rules are essential to prevent further cases of RF/RHD.

The two rules generated for Egyptian children, Abu Reesh (3) and Steinhoff (4) were critical in demonstrating the transportability of CPRs developed in low income settings to other similarly low settings. The study found the Abu Reesh CPR, was more sensitive (84%) than specific (39%), but for children from LMICs, a more sensitive rule was preferable (3). Steinhoff et al also proposed the Steinhoff CPR, which had high sensitivity, but low specificity (92% and 38%, respectively) for two or more predicators (4). When Smeesters et al applied the Steinhoff CPR to a population of Brazilian children, there was only a 20% reduction in unnecessary antibiotic use (versus 37.5%) and 12.5% undetected cases of GABHS pharyngitis (versus 9%) (30). While geographic fluctuation is expected due to variation in the clinical presentation of GABHS pharyngitis, the rule was still able to reduce

unnecessary antibiotic use, although not to the extent of the Smeesters CPR (9, 30). The Abu Reesh CPR was validated in Turkish children, which found a reduced sensitivity and slightly increased specificity compared to the original Egyptian population, but overall was similar to a CPR developed for their study population (29).

This study provides clinicians in LMICs with limited laboratory capabilities to diagnose and treat children with GABHS pharyngitis effectively and efficiently. This study provides a cost effective primary prevention tool for physicians in a hospital setting. It also adds to the literature on external validation of CPRs for GABHS pharyngitis among children in LMICs.

There are some limitations to the study. First, this is a cross sectional study using secondary data. However, many studies on clinical diagnosis are cross sectional studies. Also, budgetary constraints made secondary data analyses a necessary option.

Second, selection bias towards more severe clinical presentation is also a potential limitation due to the hospital setting. In addition, differences in presentation according to study site may also bias results. To address this issue, standardized training and protocol for all sites were utilized.

Third, this study used culture results for GABHS pharyngitis status. Although this is the gold standard, culture has several drawbacks. For

example, occasional false positives, likely due to carries, are possible. This is because without serological data, definitive GABHS pharyngitis status is not possible. Therefore, misclassification of outcome is possible, where carriers are misclassified as cases, affecting the efficacy and effectiveness of generated CPRs. Furthermore, standardized culture results can still yield differing results due to flawed culture or bacteriologic techniques, especially by different personnel, across different study sites. Studies have shown that various other factors can influence culture results such as undisclosed antibiotic use or carrier states (34, 38, 43, 65). These limitations are not limited to this study and are faced by many, as it is cost prohibitive to do serological testing. Efforts to mitigate these limitations include standardization of protocol, training, and periodic checks.

Lastly, validation of published CPRs involved using covariates collected during the initial study. Therefore, new covariates were recreated using available study variables. All newly created variable for external validation of CPRs from the literature were best approximations of variables used in the literature either because the original study did not collect the information, or because not all studies were explicitly clear on how they defined their variables. Differences in predictor definitions are a potential limitation of the study. While the initial study collected data on numerous covariates, several other predictors, such as conjunctivitis, headache or sudden onset (<12 hours), and severity of signs/symptoms, could have been

valuable, if collected. While this study was only able to assess covariates collected from the initial study, the study did collect information on several key predictors, which allowed for recreation of those not available. Furthermore, predictors not included in the original study would likely have detracted from the simplicity and ease of assessing signs/symptoms of patients during an outpatient clinic in resource poor settings.

CONCLUSION

External validation of CPRs is an essential part of the process of generating and implementing effective rules for resources poor settings. These CPRs are important for the accurate diagnosis and appropriate treatment of GABHS pharyngitis. This study was conducted to ensure that clinicians are equipped with CPRs developed for and validated in LMICs. In the previous study, five CPRs were generated for LMICs and this study was able to assess the validity of those rules. In addition, other rules identified from the medical literature were also validated in the five study populations.

Studies often tout the need for further validation, but fail to do so. This study addresses this shortcoming. Evaluating validity of rules helps ensure the effectiveness of CPRs in preventing one of the leading causes of preventable heart disease in children from LMICs and therefore meets a current and ongoing public health need.

TABLES AND RESULTS

Table 1. Selected Microbial Etiologies of Pharyngitis (34, 35, 38, 52)

Etiology	Pathogen	Associated Disorders/Symptoms
Bacterial	Streptococci Group A	Tonsillitis and scarlet fever
	Streptococci Group C and G	Tonsillitis and scarlatiniform rash
	Neisseria gonorrhoeae	Tonsillitis
	Corynebacterium diphtheriae	Diphtheria
	Arcanobacterium haemolyticum	Scarlatiniform rash
	Yersinia pestis	Plague
	Yersinia enterocolitica	Enterocolitis
	Francisella tularensis	Tularemia
	Frequency (%): 15 – 30%	
Viral	Rhinovirus	Common cold
	Coronavirus	Common cold
	Adenovirus	Pharyngoconjunctival fever
	Parainfluenza	Cold and croup
	Influenza A and B	Influenza
	Herpes simplex virus	Gingivostomatitis
	Epstein-Barr virus	Mononucleosis
	Cytomegalovirus	Mononucleosis
	Human immunodeficiency virus	HIV infection
	Frequency (%): 70 – 85%	
Mycoplasmal	*Mycoplasma pneumonia*	Pneumonia and bronchitis
Chlamydial	*Chlamydia psittaci*	Pneumonia
	Chlamydia pneumonia	Pneumonia
	Frequency (%): < 5%	

Modified from Bisno (34), Ebell (52), Jaggi (35), Pichichero (38)

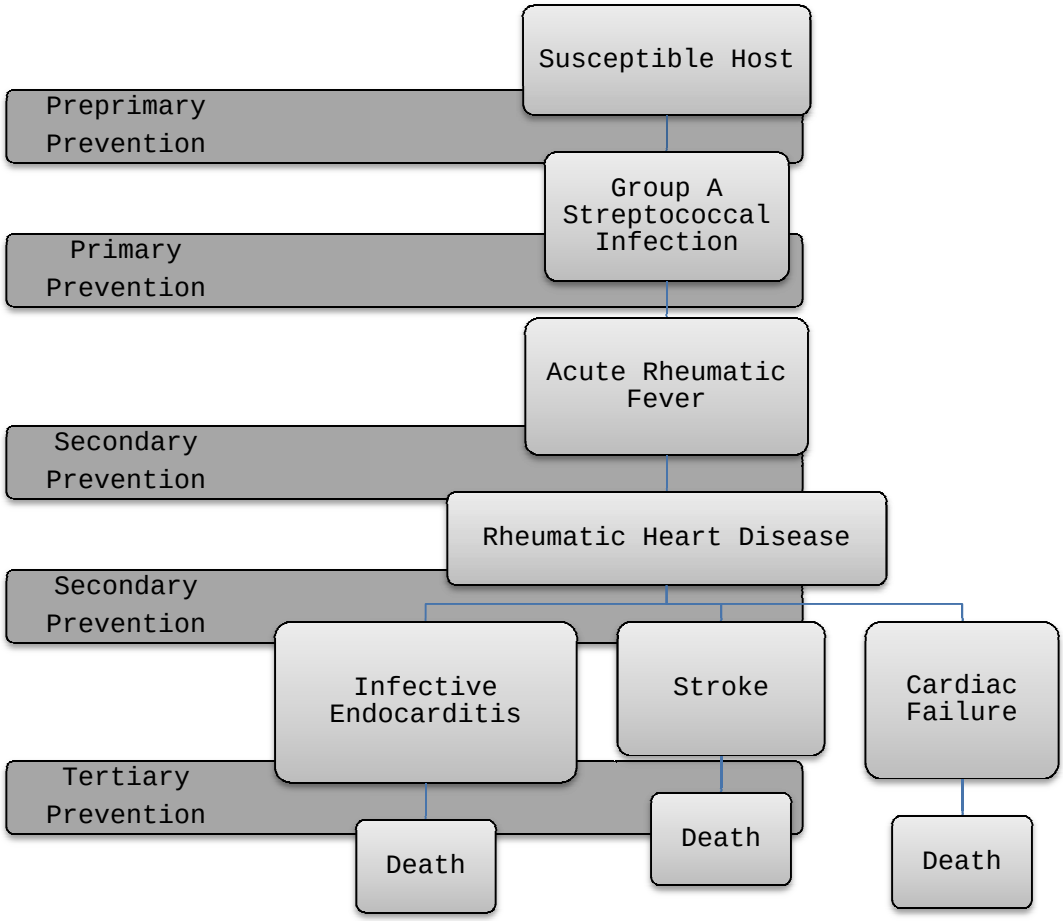
Table 2. Group A Beta Hemolytic Streptococcal (GABHS) Pharyngitis Complications (26)

Suppurative Complications[71]	Nonsuppurative Complications
Pneumonia	Poststreptococcal glomerulonephritis
Endocarditis	Rheumatic Fever
Meningitis	Rheumatic Heart Disease
Otitis media	
Mastoiditis	
Cervical lymphadenitis	
Bacteremia	
Peritonsillar/retropharyngeal	

Modified from Choby (26)

[71] Data on global burden of GABHS complications is not available for all GABHS sequelae. The following data was available for suppurative complications: 1) Pneumonia occurs in 0.3% of febrile patients (43) and among patients with GAS pneumonia, up to 30% have a history of GABHS pharyngitis (42); 2) Endocarditis estimates for less developed countries is based on a population study conducted in Israel which found 33,700 cases of endocarditis and 8,4000 deaths (41); and 3) Meningitis is uncommon in high income countries and global estimates are not available, but neurological complications from GAS meningitis are 36 – 46%, among the highest bacterial meningitis. The following data was available for nonsuppurative complications: 1) Poststreptococcal glomerulonephritis global prevalence is an estimated 456,000 cases and 5,000 deaths; 2) Rheumatic fever has an estimated 1,8880,000 cases; and 3) Rheumatic heart disease cases was 15,600,000 worldwide and is the cause of 233,000 deaths (5, 41).

Figure 1. Flow Diagram of Preventative Measures For Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) (41, 47)



Modified from Steer (47), Carapetis (41)

Table 3. Clinical Prediction Rules (Clinical Signs and Symptoms)

Publication Year	Authors	Study Site(s)	Study Year (s)	Sample Size (n)	Ages (yr)	Clinical Signs/Symptoms	Method (Score/Regression)
2006	Smeesters (30)	Brazil	2004	220	0-15yr	Age (≤35, 36-59, ≥60 mo); Viral signs (coryza, conjunctivitis, cough, diarrhea, viral-like exanthema); and Bacterial signs (tender CN, headache, palate petechia, fever >38.5, abdominal pain, sudden onset (<12hr))	Score (Additive score -4-20) Regression model (2 different scoring methods)
2005	Steinhoff (4)	Egypt	2001-2003	451	2-12yr	Enlarged CN No Rhinitis No Rash	Score (Additive score 0-3) (Points ≥1, ≥2, ≥3)
2004	McIsaac (59) (Modified Centor)	Canada	1999-2002	787	3-69 yr	Fever (>38C) No Cough Tender CLN Tonsil swell/exudates Age (3-14; 15-44; ≥45)	Score (Additive score -1-5) (Points ≤0 - ≥4)
2003	McGinn (62) (Simplified Walsh)	USA	1995-1997	171	18-74yr	Fever (>38.3C) Exposure to known strep contact Pharyngeal or tonsillar exudates Enlarged, tender nodes Recent cough	Score (Additive score -1 – 4) (Points -1 – 3)
2003	Sahin (29)	Turkey	2001-2002	245	0-17 yr	Sore throat Fever Pharyngeal erythema	Regression
2002	Nandi (28) (Adopted from Breese)	India		536	5-15yr	Age Seasons Fever Erythema of pharynx Size of tonsil Pharyngeal exudate Lymphadenopathy Pain in throat	Score (Additive score 4-36)
2001	Attia (111)	USA	1999-2000	587	1-18yr	Cervical lymphadenopathy* Tonsillar swelling* No Coryza* Scarlatiniform rash (*Moderate – severe)	Score (Additive score 0- 5) (Points 0-10)

Table 3 (continued)

2000	Ulukol (61)	Turkey		716 total n1=202 n2=514	n1≤3yr n2>3yr	Comparison of Breese scoring system (see Breese)	Score (Additive score 0-9)
1999	Attia (23)	USA	1996	297 total (263 LR)	6mo - 18yr	Model 1: Scarlatiniform rash Tonsillar swelling* Tender, enlarged CN* No coryza* Model 2:Tonsillar swelling* No coryza* Tender, enlarged CN* (*Moderate – severe)	Stepwise multiple logistic regression models (model 1 and model 2)
1998	McIsaac (26, 27) (Modified Centor)	Canada	1995-1997	521	3-76	No cough Swollen/tender ACN Fever (>38C) Tonsillar exudate or swelling Age (3-14; 15-44; ≥45)	Score (Additive score -1-5) (Points 0 – 4)
1998	Wald (31)	USA	1990-1992	365	2-16yr	Age (5-15 yr) Season (Nov-May) Fever (≥38.3C) Adenopathy (CLN ≥1cm or tender) Pharyngitis (erythema, swelling, or exudates of phar/tons) No upper resp sympt (no rhinorrhea, cough, conjunctivitis)	Score (Additive score 0 – 6) (Points 1 – 6)
1997	Steinhoff (3) (Abu Reesh Rule)	Egypt	1992-1993	451	2-13yr	Pharyngeal exudate OR Enlarged anterior cervical nodes	Score
1995	WHO, ARI (73) and IMCI (49) Adaptation Guidelines				<5yr	Pharyngeal exudate AND Enlarge, tender CLN	Score
1993	Meland (63)	Norway	1988-1989	133	Children and Adults	No Cough Swollen lymph nodes Age (≥5yrs) Rubor (redness/inflammation)	Regression

Table 3 (continued)

1992	Hoffman (54)	Denmark	187-1988	1783	Children and adults	Pain on swallowing Cough/coryza Age Enlarged or hyperaemic tonsils Exudate Enlarged or tender angular LN Fever (≥38C)	Score
1981	Centor (25)	USA	1980	286	>15yr	Tonsillar Exudate Swollen tender CLN No cough Fever (>38.5C)	Score (Additive score 0-4)
1977	Breese (24)	USA	1973-1975	670	Children	Season Age WB count Fever >38C Sore throat Headache Abnormal pharynx Abnormal cervical glands Cough	Score (Additive score 0-9)
1975	Walsh (56)	USA				Fever (>36.1C) Exposure to known strep Recent cough Pharyngeal/tonsillar exudates Enlarged/tender nodes	Score (Additive score -10-40)

Table 4. Variables For CPR Development and Validation Study

Variables Type	Variable	Definition[72]
Demographics	Age	Children ages 2 – 12 years
	Gender	Female, Male
Geographic	Country	Egypt, Brazil, Latvia, Croatia
	Season	Autumn, Winter, Spring, Summer
Signs	Fever	Temperature above 38.1°C (rectal) or 38.5°C (oral)
	Cough	Observation of coughing during consultation
	Hoarseness	Presence of harsh quality of voice different from normal
	Nares Excoriations	Scratches or lesions around nostrils
	Palatal Petechiae	Presence of lesions on the palate
	Strawberry Tongue	Tongue with papillar swelling
	Pharyngeal Erythema	Redness of pharynx greater than buccal mucosa, excluding tonsils
	Faucial Erythema	Redness of the passage from mouth to pharynx
	Tonsillar Erythema	Redness of the tonsils
	Erythema Posterior	Redness of the throat posterior wall
	Tonsillar Enlargement	Degree to which tonsils exceed more than 25% into the midline
	Enlarged Cervical Lymph Nodes	Any palpable anterior cervical lymph node greater than 1 cm in diameter
	Cervical Lymph Node Tenderness	Tenderness of node on gentle palpation, confirmed by statement or facial expression
	Pharyngeal Exudate	White or yellow matter on pharynx
	Tonsillar Exudate	White or yellow matter on tonsils
Symptoms[73]	Fever	Parent/patient report of history of high temperature (rectal: >38.1°C or oral: 38.5°C)
	Chills	Recent history of the sensation of cold (with/without shivering)
	Runny Nose	History of nasal discharge
	Nasal Congestion	History of increased difficulty of breathing
	Sore Throat	History of throat pain
	Difficulty/Pain Swallowing	History of child complaint of difficulty or pain when swallowing
	Cough	Any history of more than one episode of coughing
	Vomiting	History of vomiting
	Earache	History of ear pain
	Abdominal Pain	History of pain in the abdominal area
	Activity Level Below Normal	History of change (reduction) in level of activity compared to normal
	Disturbed Sleep	Parent report of history of change in sleep patterns compared to normal
	Hoarseness	History of presence of hash quality of voice that is different from normal

[72] Definitions for signs and symptoms based on original study questionnaire (Physical Examination Form – Visit 1)
[73] History refers to report of child experiencing any of the symptoms in the past five days

Table 5. Study Population Specific Clinical Prediction Rule By Site and Combined

Study Population Specific Clinical Prediction Rule[74]								
Egypt	Season (Early Summer/ Autumn)	Age Above 5 Years	Faucial Erythema (Sg)	Nasal Congestion (Sx)	Hoarseness (Sx)	No Runny Nose (Sx)		
Brazil	Faucial Erythema (Sg)	Cervical Lymph Node Tenderness (Sg)	No Disturbed Sleep (Sx)	No Cough (Sx)	No Fever (Sg)	Difficulty /Pain Swallowing (Sx)		
Latvia	Palatal Petechiae (Sg)	Activity Level Below Normal (Sx)	No Enlarged Cervical Lymph Nodes (Sg)					
Croatia	Palatal Petechiae (Sg)	Cervical Lymph Node Tenderness (Sg)	No Sore Throat (Sx)	Difficulty /Pain Swallowing (Sx)				
Combined	Age Above 5 Years	Season (Early Summer/ Autumn)	Difficulty /Pain Swallowing (Sx)	Hoarseness (Sx)	Erythema Posterior (Sg)	Faucial Erythema (Sg)	No Cough (Sx)	Palatal Petechiae (Sg)

[74] Key: Sg = Signs
Sx = Symptoms

Table 6. Selected Patient Demographic Characteristics By Study Site and Combined

Study Site	Demographic Characteristics				
	Sample Size N (%)	GABHS Positive N (%)	Female N (%)	Age Above 5 Years N (%)	Age (Years) (Mean/Median)
Egypt	1,418 (71.15)	387 (27.29)	600 (42.22)	467 (32.86)	4.9 / 4
Brazil	191 (9.58)	47 (24.61)	122 (49.09)	137 (55.02)	6.7 / 6
Latvia	184 (9.23)	55 (29.89)	83 (44.86)	106 (57.30)	6.7 / 6
Croatia	200 (10.04)	84 (42.00)	84 (42.00)	114 (57.00)	6.4 / 6
Combined	1,993 (100.00)	573 (28.75)	889 (43.26)	824 (40.10)	5.4 / 5

Table 7. External Validation of Selected Clinical Prediction Rules From the Literature and Study in Egypt Population

Clinical Prediction Rules	Egypt Population			
	Sensitivity (%)	Specificity (%)	PPV[75] (%)	NPV (%)
Steinhoff CPR (4)	**65.03**	**46.60**	**31.34**	**78.05**
Smeesters CPR[+] (30)	26.87	83.71	38.24	75.31
Sahin CPR 1 (29)	95.87	6.21	27.73	80.00
Sahin CPR 2 (29)	96.38	5.72	27.73	80.82
Attia CPR (111)	0.26	99.81	33.33	72.72
Breese CPR (24)	4.39	97.09	36.17	73.01
Centor CPR (25)	36.95	68.96	30.89	74.45
Wald CPR (31)	30.75	76.33	32.78	74.60
Abu Reesh CPR (3)	33.07	74.39	32.65	74.76
McIsaac CPR (26, 27, 59)	**75.06**	**34.12**	**30.01**	**78.43**
WHO CPR (49, 73)	8.81	95.44	41.98	73.63
Walsh CPR* (56)	81.65	23.67	28.65	77.46
Nandi (28) CPR	10.59	92.14	33.61	73.30
Brazil CPR	62.02	46.65	30.38	76.59
Latvia CPR	41.34	62.17	29.09	73.85
Croatia CPR	23.26	82.06	32.73	74.02
Combined CPR	70.28	44.71	32.30	80.03

[75] Key: PPV = Positive Predicative Value, NPV = Negative Predictive Value
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best published CPR (best study CPR was site specific CPR).

Figure 2. Graph of the Sensitivity and Specificity of Selected Clinical Prediction Rules From the Literature and Study in Egypt Population

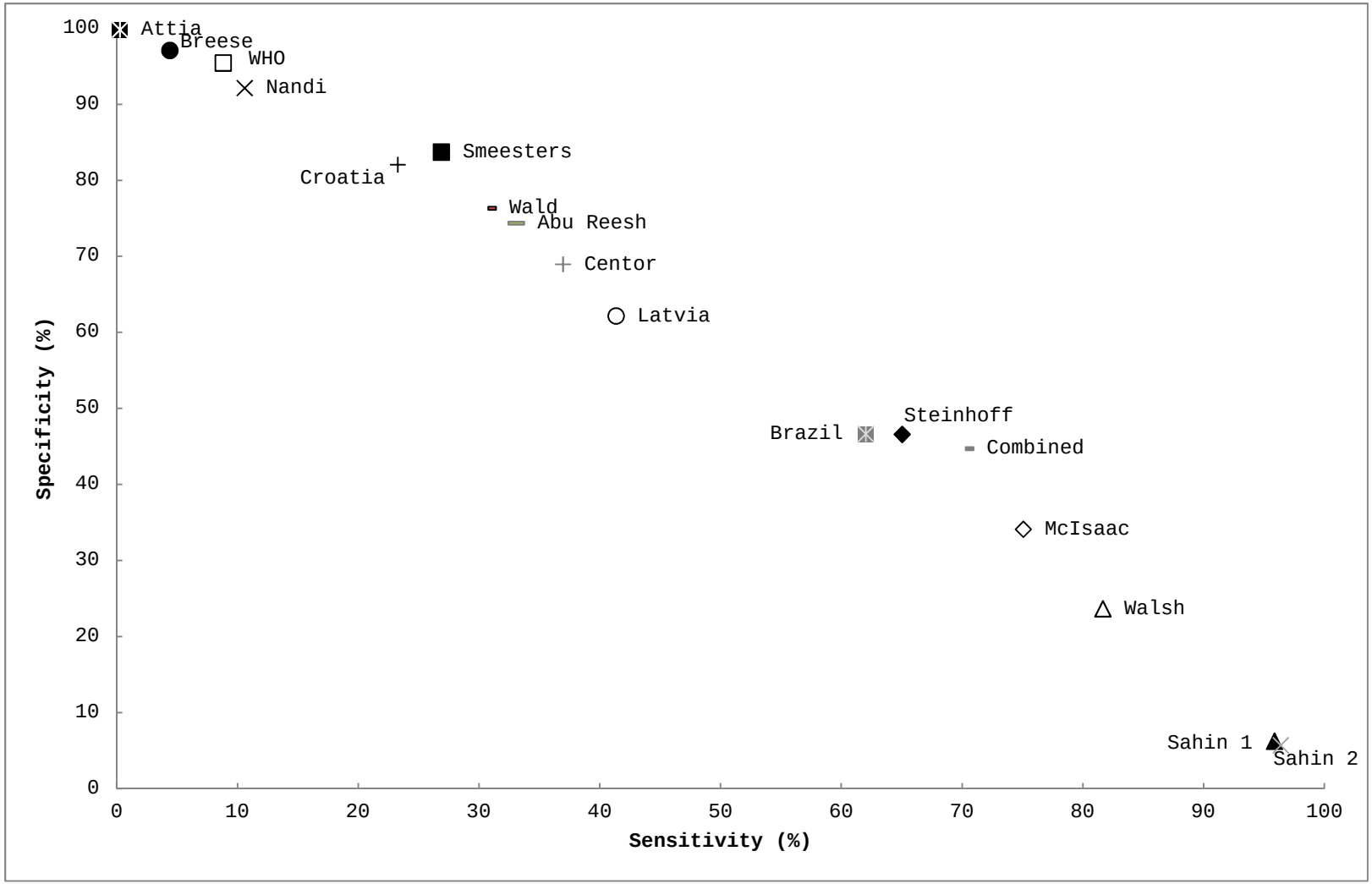


Table 8. External Validation of Selected Clinical Prediction Rules From the Literature and Study in Brazil Population

Clinical Prediction Rules	Brazil Study Population			
	Sensitivity (%)	Specificity (%)	PPV[76] (%)	NPV (%)
Steinhoff CPR (4)	**89.36**	**41.96**	**33.60**	**92.31**
Smeesters CPR+ (30)	31.91	78.47	32.61	77.93
Sahin CPR 1 (29)	85.11	27.08	27.59	84.78
Sahin CPR 2 (29)	85.11	25.00	27.03	83.72
Attia CPR (111)	2.13	98.61	33.33	75.53
Breese CPR (24)	10.64	96.53	50.00	76.80
Centor CPR (25)	51.06	72.92	38.10	82.03
Wald CPR (31)	34.04	63.89	23.53	74.80
Abu Reesh CPR (3)	63.83	72.22	42.86	85.95
McIsaac CPR (26, 27, 59)	**87.23**	**53.52**	**38.32**	**92.68**
WHO CPR (49, 73)	31.91	91.61	55.56	80.37
Walsh CPR* (56)	91.49	31.25	30.28	91.84
Nandi CPR (28)	14.89	73.61	15.56	72.60
Egypt CPR	87.23	53.47	37.96	92.77
Latvia CPR	25.53	86.81	38.71	78.12
Croatia CPR	51.06	71.53	36.92	81.75
Combined CPR	80.85	68.75	45.78	91.67

[76] Key: PPV = Positive Predicative Value, NPV = Negative Predictive Value
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best published CPR (best study CPR was site specific CPR).

Figure 3. Graph of the Sensitivity and Specificity of Selected Clinical Prediction Rules From the Literature and Study in Brazil Population

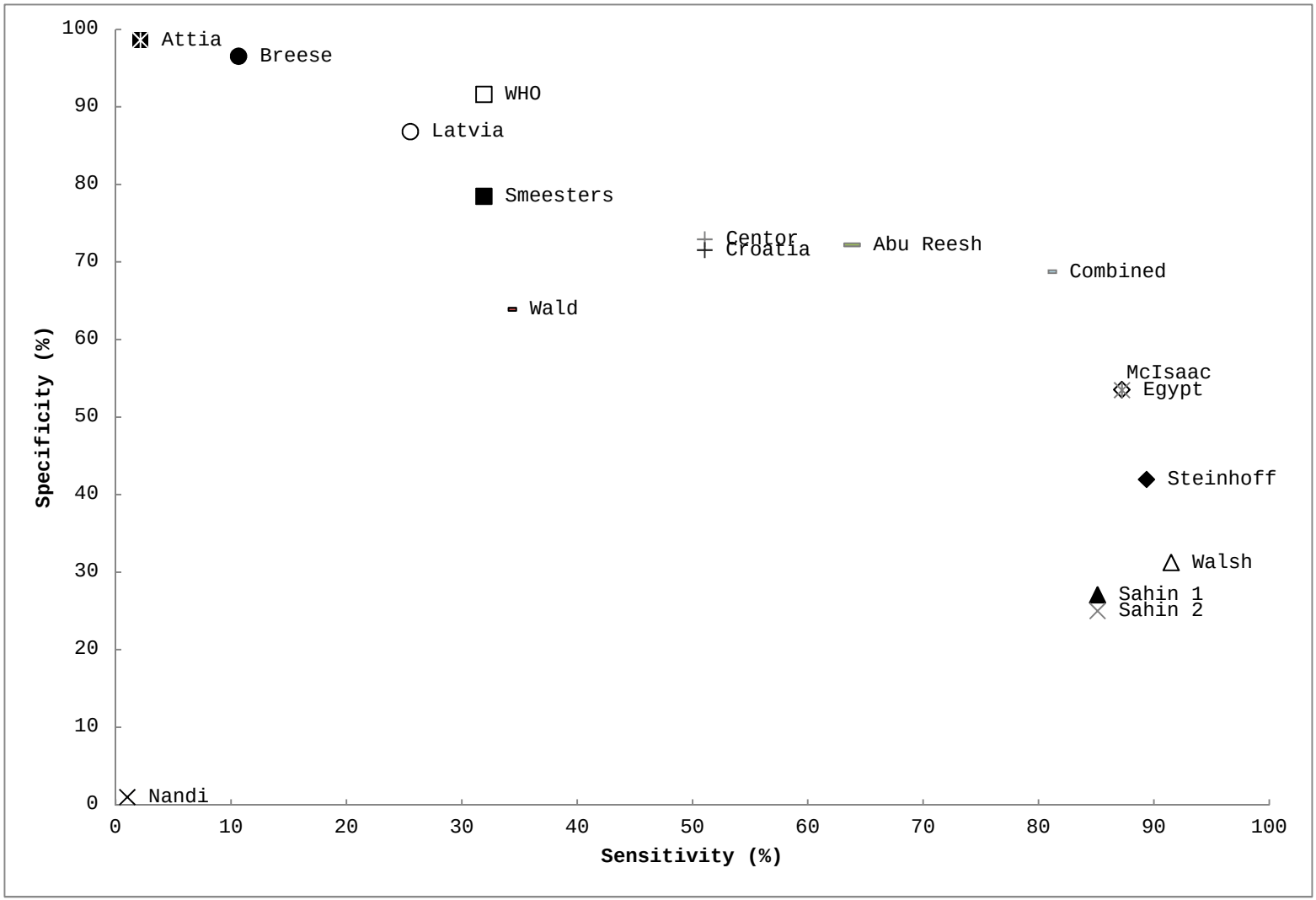


Table 9. External Validation of Selected Clinical Prediction Rules From the Literature and Study in Latvia Population

Clinical Prediction Rules	Latvia Study Population			
	Sensitivity (%)	Specificity (%)	PPV[77] (%)	NPV (%)
Steinhoff CPR (4)	90.91	5.43	29.07	58.33
Smeesters CPR+ (30)	36.36	66.67	31.75	71.07
Sahin CPR 1 (29)	92.73	10.85	30.72	77.78
Sahin CPR 2 (29)	92.73	6.98	29.82	69.23
Attia CPR (111)	1.82	98.45	33.33	70.17
Breese CPR (24)	12.73	93.80	46.67	71.60
Centor CPR (25)	70.91	29.46	30.00	70.37
Wald CPR (31)	**72.73**	**38.76**	**33.61**	**76.92**
Abu Reesh CPR (3)	80.00	23.26	30.77	73.17
McIsaac CPR (26, 27, 59)	90.91	10.85	30.30	73.68
WHO CPR (49, 73)	58.18	43.41	30.48	70.89
Walsh CPR* (56)	94.55	3.10	29.38	57.14
Nandi CPR (28)	7.27	98.45	66.67	71.35
Egypt CPR	87.27	7.75	28.74	58.82
Brazil CPR	70.91	31.01	30.47	71.43
Croatia CPR	74.55	36.43	33.33	77.05
Combined CPR	83.64	29.46	33.58	80.85

[77] Key: PPV = Positive Predicative Value, NPV = Negative Predictive Value
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best published CPR (best study CPR was site specific CPR).

Figure 4. Graph of the Sensitivity and Specificity of Selected Clinical Prediction Rules From the Literature and Study in Latvia Population

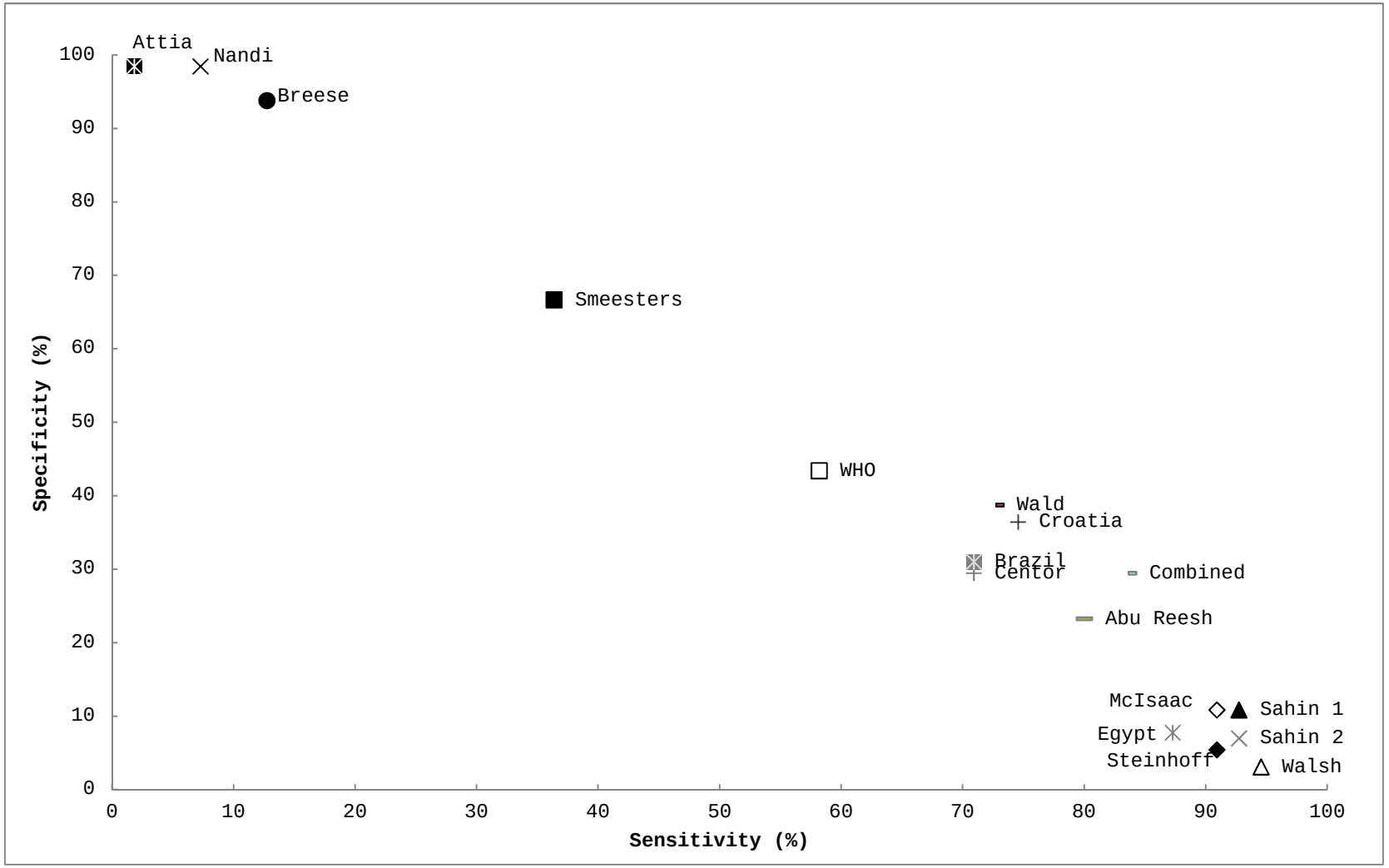


Table 10. External Validation of Selected Clinical Prediction Rules From the Literature and Study in Croatia Population

Clinical Prediction Rules	Croatia Study Population			
	Sensitivity (%)	Specificity (%)	PPV[78] (%)	NPV (%)
Steinhoff CPR (4)	**73.81**	**37.07**	**45.93**	**66.15**
Smeesters CPR[+] (30)	35.71	82.76	60.00	64.00
Sahin CPR 1 (29)	77.38	13.79	39.39	45.71
Sahin CPR 2 (29)	78.57	12.93	39.52	45.45
Attia CPR (111)	2.38	98.28	50.00	58.16
Breese CPR (24)	28.57	81.90	53.33	61.29
Centor CPR (25)	36.90	76.72	53.45	62.68
Wald CPR (31)	58.33	48.28	44.95	61.54
Abu Reesh CPR (3)	59.52	56.90	50.00	66.00
McIsaac CPR (26, 27, 59)	**73.81**	**40.52**	**47.33**	**68.12**
WHO CPR (49, 73)	20.24	86.21	51.52	59.88
Walsh CPR* (56)	90.48	16.38	43.93	70.37
Nandi CPR (28)	26.19	76.72	44.90	58.94
Egypt CPR	78.57	31.90	45.52	67.27
Brazil CPR	40.48	74.14	53.12	63.24
Latvia CPR	47.62	60.34	46.51	61.40
Combined CPR	83.33	49.14	54.26	80.28

[78] Key: PPV = Positive Predicative Value, NPV = Negative Predictive Value
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best published CPR (best study CPR was site specific CPR).

Figure 5. Graph of the Sensitivity and Specificity of Selected Clinical Prediction Rules From the Literature and Study in Croatia Population

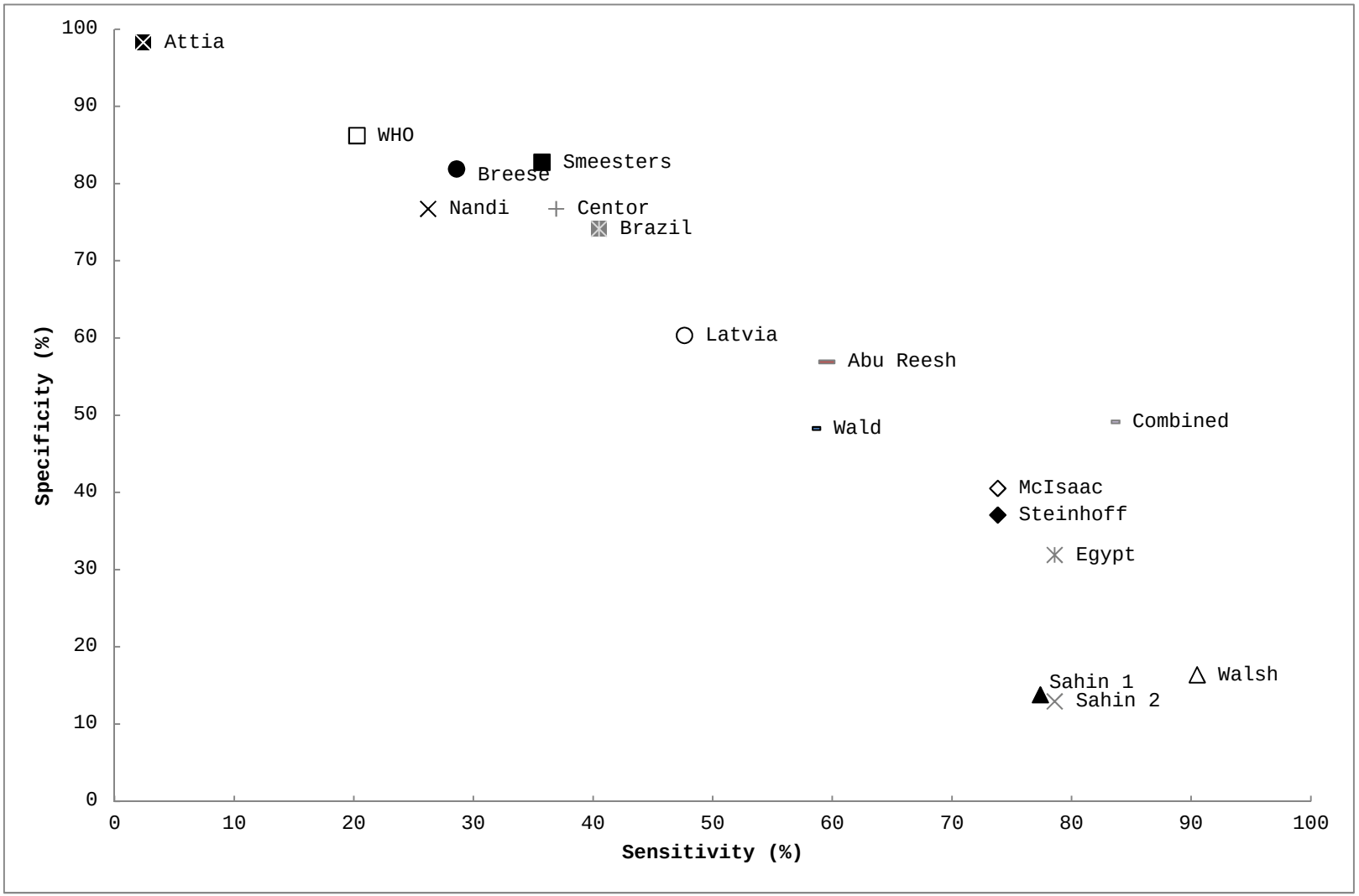
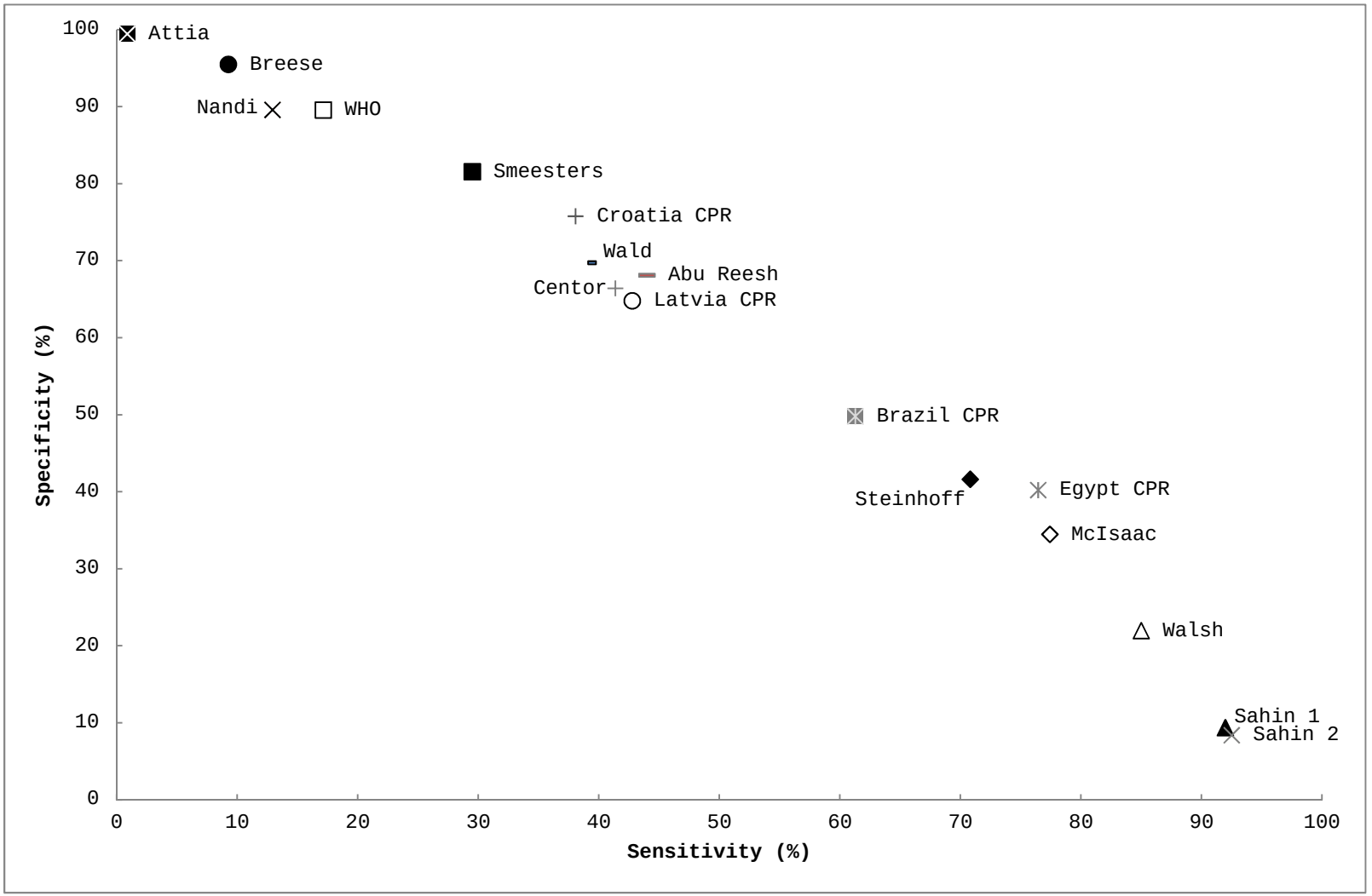


Table 11. External Validation of Selected Clinical Prediction Rules From the Literature and Study in Combined Population

Clinical Prediction Rules	Combined Study Population			
	Sensitivity (%)	Specificity (%)	PPV[79] (%)	NPV (%)
Steinhoff CPR (4)	**70.80**	**41.61**	**32.85**	**77.94**
Smeesters CPR[+] (30)	29.49	81.55	39.21	74.14
Sahin CPR 1(29)	91.97	9.37	29.05	74.30
Sahin CPR 2 (29)	92.50	8.38	28.95	73.46
Attia CPR (111)	0.87	99.44	38.46	71.31
Breese CPR (24)	9.25	95.49	45.30	72.28
Centor CPR (25)	41.36	66.41	33.19	73.73
Wald CPR (31)	39.09	69.73	33.99	73.84
Abu Reesh CPR (3)	43.98	68.10	35.74	75.08
McIsaac CPR (26, 27, 59)	**77.41**	**34.47**	**32.36**	**79.02**
WHO CPR (49, 73)	17.13	89.56	39.84	72.82
Walsh CPR* (56)	84.99	21.97	30.53	78.39
Nandi CPR (28)	12.91	89.58	33.33	71.82
Egypt CPR	76.44	40.21	34.03	80.88
Brazil CPR	61.26	49.79	32.99	76.10
Latvia CPR	42.76	64.79	32.89	73.72
Croatia CPR	38.05	75.77	38.79	75.19

[79] Key: PPV = Positive Predicative Value, NPV = Negative Predictive Value
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best published CPR (best study CPR was site specific CPR).

Figure 6. Graph of the Sensitivity and Specificity of Selected Clinical Prediction Rules From the Literature and Study in Combined Population



SUPPLEMENTAL MATERIAL

Table S1. External Validation of Selected Clinical Prediction Rules From the Literature in Egypt Study Population

Clinical Prediction Rules	Egypt Study Population							
	Test Performance Measures[80]							
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR
Steinhoff CPR (4)	**65.03**	**46.60**	**31.34**	**78.05**	**1.22**	**0.75**	**0.116**	**1.627**
Smeesters CPR+ (30)	26.87	83.71	38.24	75.31	1.65	0.87	0.106	1.897
Sahin CPR 1 (29)	95.87	6.21	27.73	80.00	1.02	0.67	0.021	1.522
Sahin CPR 2 (29)	96.38	5.72	27.73	80.82	1.02	0.63	0.021	1.619
Attia CPR (111)	0.26	99.81	33.33	72.72	1.33	1.00	0.001	1.330
Breese CPR (24)	4.39	97.09	36.17	73.01	1.51	0.98	0.015	1.541
Centor CPR (25)	36.95	68.96	30.89	74.45	1.19	0.91	0.059	1.308
Wald CPR (31)	30.75	76.33	32.78	74.60	1.30	0.91	0.071	1.429
Abu Reesh CPR (3)	33.07	74.39	32.65	74.76	1.29	0.90	0.075	1.433
McIsaac CPR (26, 27, 59)	**75.06**	**34.12**	**30.01**	**78.43**	**1.14**	**0.73**	**0.092**	**1.562**
WHO CPR (49, 73)	8.81	95.44	41.98	73.63	1.93	0.96	0.043	2.010
Walsh CPR* (56)	81.65	23.67	28.65	77.46	1.07	0.78	0.053	1.372
Nandi (28) CPR	10.59	92.14	33.61	73.30	1.35	0.97	0.027	1.392

[80] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best CPR

Table S2. External Validation of Selected Clinical Prediction Rules From the Literature in Brazil Study Population

Clinical Prediction Rules	Brazil Study Population							
	Test Performance Measures[81]							
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR
Steinhoff CPR (4)	**89.36**	**41.96**	**33.60**	**92.31**	**1.54**	**0.25**	**0.313**	**6.160**
Smeesters CPR+ (30)	31.91	78.47	32.61	77.93	1.48	0.87	0.104	1.701
Sahin CPR 1 (29)	85.11	27.08	27.59	84.78	1.17	0.55	0.122	2.127
Sahin CPR 2 (29)	85.11	25.00	27.03	83.72	1.13	0.60	0.101	1.883
Attia CPR (111)	2.13	98.61	33.33	75.53	1.53	0.99	0.007	1.545
Breese CPR (24)	10.64	96.53	50.00	76.80	3.06	0.93	0.072	3.290
Centor CPR (25)	51.06	72.92	38.10	82.03	1.89	0.67	0.240	2.821
Wald CPR (31)	34.04	63.89	23.53	74.80	0.94	1.03	-0.021	0.913
Abu Reesh CPR (3)	63.83	72.22	42.86	85.95	2.30	0.50	0.361	4.600
McIsaac CPR (26, 27, 59)	**87.23**	**53.52**	**38.32**	**92.68**	**1.88**	**0.24**	**0.408**	**7.833**
WHO CPR (49, 73)	31.91	91.61	55.56	80.37	3.80	0.74	0.235	5.135
Walsh CPR* (56)	91.49	31.25	30.28	91.84	1.33	0.27	0.227	4.926
Nandi CPR (28)	14.89	73.61	15.56	72.60	0.56	1.16	-0.115	0.483

[81] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best CPR

Table S3. External Validation of Selected Clinical Prediction Rules From the Literature in Latvia Study Population

Clinical Prediction Rules	Latvia Study Population							
	Test Performance Measures[82]							
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR
Steinhoff CPR (4)	90.91	5.43	29.07	58.33	0.96	1.68	-0.037	0.571
Smeesters CPR+ (30)	36.36	66.67	31.75	71.07	1.09	0.95	0.030	1.147
Sahin CPR 1 (29)	92.73	10.85	30.72	77.78	1.04	0.67	0.036	1.552
Sahin CPR 2 (29)	92.73	6.98	29.82	69.23	1.00	1.04	-0.003	0.962
Attia CPR (111)	1.82	98.45	33.33	70.17	1.17	1.00	0.003	1.170
Breese CPR (24)	12.73	93.80	46.67	71.60	2.05	0.93	0.065	2.204
Centor CPR (25)	70.91	29.46	30.00	70.37	1.01	0.99	0.004	1.020
Wald CPR (31)	**72.73**	**38.76**	**33.61**	**76.92**	**1.19**	**0.70**	**0.115**	**1.700**
Abu Reesh CPR (3)	80.00	23.26	30.77	73.17	1.04	0.86	0.033	1.209
McIsaac CPR (26, 27, 59)	90.91	10.85	30.30	73.68	1.02	0.84	0.018	1.214
WHO CPR (49, 73)	58.18	43.41	30.48	70.89	1.03	0.96	0.016	1.073
Walsh CPR* (56)	94.55	3.10	29.38	57.14	0.98	1.76	-0.024	0.557
Nandi CPR (28)	7.27	98.45	66.67	71.35	4.69	0.94	0.057	4.989

[82] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best CPR

Table S4. External Validation of Selected Clinical Prediction Rules From the Literature in Croatia Study Population

Clinical Prediction Rules	Croatia Study Population							
	Test Performance Measures[83]							
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR
Steinhoff CPR (4)	**73.81**	**37.07**	**45.93**	**66.15**	**1.17**	**0.71**	**0.109**	**1.648**
Smeesters CPR+ (30)	35.71	82.76	60.00	64.00	2.07	0.78	0.185	2.654
Sahin CPR 1 (29)	77.38	13.79	39.39	45.71	0.90	1.64	-0.088	0.549
Sahin CPR 2 (29)	78.57	12.93	39.52	45.45	0.90	1.66	-0.085	0.542
Attia CPR (111)	2.38	98.28	50.00	58.16	1.38	0.99	0.007	1.394
Breese CPR (24)	28.57	81.90	53.33	61.29	1.58	0.87	0.105	1.816
Centor CPR (25)	36.90	76.72	53.45	62.68	1.59	0.82	0.136	1.939
Wald CPR (31)	58.33	48.28	44.95	61.54	1.13	0.86	0.066	1.314
Abu Reesh CPR (3)	59.52	56.90	50.00	66.00	1.38	0.71	0.164	1.944
McIsaac CPR (26, 27, 59)	**73.81**	**40.52**	**47.33**	**68.12**	**1.24**	**0.65**	**0.143**	**1.908**
WHO CPR (49, 73)	20.24	86.21	51.52	59.88	1.47	0.93	0.065	1.581
Walsh CPR* (56)	90.48	16.38	43.93	70.37	1.08	0.58	0.069	1.862
Nandi CPR (28)	26.19	76.72	44.90	58.94	1.13	0.96	0.029	1.177

[83] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best CPR

Table S5. External Validation of Selected Clinical Prediction Rules From the Literature in Combined Study Population

Clinical Prediction Rules	Combined Study Population							
	Test Performance Measures[84]							
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR
Steinhoff CPR (4)	**70.80**	**41.61**	**32.85**	**77.94**	**1.21**	**0.70**	**0.124**	**1.729**
Smeesters CPR+ (30)	29.49	81.55	39.21	74.14	1.60	0.86	0.110	1.860
Sahin CPR 1(29)	91.97	9.37	29.05	74.30	1.01	0.86	0.013	1.174
Sahin CPR 2 (29)	92.50	8.38	28.95	73.46	1.01	0.90	0.009	1.122
Attia CPR (111)	0.87	99.44	38.46	71.31	1.55	1.00	0.003	1.550
Breese CPR (24)	9.25	95.49	45.30	72.28	2.05	0.95	0.047	2.158
Centor CPR (25)	41.36	66.41	33.19	73.73	1.23	0.88	0.078	1.398
Wald CPR (31)	39.09	69.73	33.99	73.84	1.28	0.88	0.088	1.455
Abu Reesh CPR (3)	43.98	68.10	35.74	75.08	1.38	0.82	0.121	1.683
McIsaac CPR (26, 27, 59)	**77.41**	**34.47**	**32.36**	**79.02**	**1.18**	**0.66**	**0.119**	**1.788**
WHO CPR (49, 73)	17.13	89.56	39.84	72.82	1.64	0.93	0.067	1.763
Walsh CPR* (56)	84.99	21.97	30.53	78.39	1.09	0.68	0.070	1.603
Nandi CPR (28)	12.91	89.58	33.33	71.82	1.24	0.97	0.025	1.278

[84] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio
(+) CRP for Unavailable Bacteriological Diagnosis
(*) Modified Walsh CPR
(**bold**) best CPR

Table S6. External Validation of Study Clinical Prediction Rules in Egypt Study Population

Clinical Prediction Rule	Egypt Study Population								
	Test Performance Measures[85]								
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR	AUC
Egypt CPR	**73.13**	**43.36**	**32.64**	**81.13**	**1.29**	**0.62**	**0.165**	**2.081**	**0.541**
Brazil CPR	62.02	46.65	30.38	76.59	1.16	0.81	0.087	1.432	0.670
Latvia CPR	41.34	62.17	29.09	73.85	1.09	0.94	0.035	1.160	0.481
Croatia CPR	23.26	82.06	32.73	74.02	1.30	0.94	0.053	1.383	0.862
Combined CPR	70.28	44.71	32.30	80.03	1.27	0.66	0.150	1.924	0.543

[85] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio (**bold**) best CPR

Table S7. External Validation of Study Clinical Prediction Rules in the Brazil Study Population

Clinical Prediction Rule	Brazil Study Population								
	Test Performance Measures[86]								
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR	AUC
Egypt CPR	87.23	53.47	37.96	92.77	1.87	0.24	0.407	7.792	0.672
Brazil CPR	**91.74**	**69.44**	**69.44**	**91.74**	**3.00**	**0.12**	**0.612**	**25.000**	**0.780**
Latvia CPR	25.53	86.81	38.71	78.12	1.94	0.86	0.123	2.256	0.722
Croatia CPR	51.06	71.53	36.92	81.75	1.79	0.68	0.226	2.632	0.793
Combined CPR	80.85	68.75	45.78	91.67	2.59	0.28	0.496	9.250	0.674

[86] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio (**bold**) best CPR

Table S8. External Validation of Study Clinical Prediction Rules in Latvia Study Population

Clinical Prediction Rule	Latvia Study Population								
	Test Performance Measures[87]								
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR	AUC
Egypt CPR	87.27	7.75	28.74	58.82	0.95	1.64	-0.050	0.579	0.503
Brazil CPR	70.91	31.01	30.47	71.43	1.03	0.94	0.019	1.096	0.592
Latvia CPR	**60.00**	**65.12**	**42.31**	**79.25**	**1.72**	**0.61**	**0.251**	**2.820**	**0.530**
Croatia CPR	74.55	36.43	33.33	77.05	1.17	0.70	0.110	1.671	0.616
Combined CPR	83.64	29.46	33.58	80.85	1.19	0.56	0.131	2.125	0.479

[87] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio (**bold**) best CPR

Table S9. External Validation of Study Clinical Prediction Rules in Croatia Study Population

Clinical Prediction Rule	Croatia Study Population								
	Test Performance Measures[88]								
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR	AUC
Egypt CPR	78.57	31.90	45.52	67.27	1.15	0.67	0.105	1.716	0.459
Brazil CPR	40.48	74.14	53.12	63.24	1.57	0.80	0.146	1.963	0.712
Latvia CPR	47.62	60.34	46.51	61.40	1.20	0.87	0.080	1.379	0.503
Croatia CPR	**75.00**	**68.97**	**63.64**	**79.21**	**2.42**	**0.36**	**0.440**	**6.722**	**0.589**
Combined CPR	83.33	49.14	54.26	80.28	1.64	0.34	0.325	4.824	0.430

[88] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio (**bold**) best CPR

Table S10. External Validation of Study Clinical Prediction Rules in Combined Study Population

Clinical Prediction Rule	Combined Study Population								
	Test Performance Measures[89]								
	Sens (%)	Spec (%)	PPV (%)	NPV (%)	PLR	NLR	JS	DOR	AUC
Egypt CPR	76.44	40.21	34.03	80.88	1.28	0.59	0.167	2.169	0.581
Brazil CPR	61.26	49.79	32.99	76.10	1.22	0.78	0.111	1.564	0.663
Latvia CPR	42.76	64.79	32.89	73.72	1.21	0.88	0.075	1.375	0.527
Croatia CPR	38.05	75.77	38.79	75.19	1.57	0.82	0.138	1.915	0.797
Combined CPR	**74.35**	**46.13**	**35.77**	**81.67**	**1.38**	**0.56**	**0.205**	**2.464**	**0.547**

[89] Key: Sens = Sensitivity, Spec = Specificity, PPV = Positive Predicative Value, NPV = Negative Predictive Value, PLR = Positive Likelihood Ratio, NLR = Negative Likelihood Ratio, JS = J Statistic, DOR = Diagnostic Odds Ratio (**bold**) best CPR

Figure S1. Comparison of Receiver Operating Curves (ROC) in Egypt Population

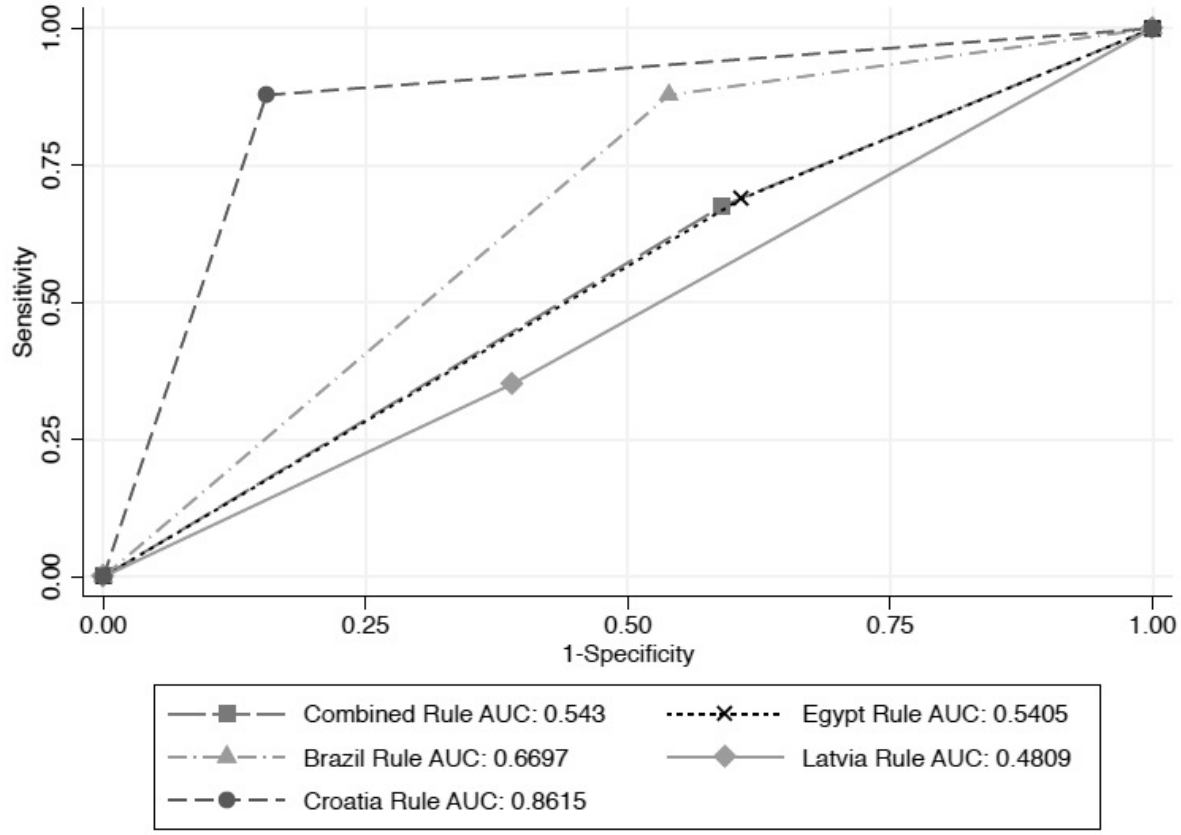


Figure S2. Comparison of Receiver Operating Curves (ROC) in Brazil Population

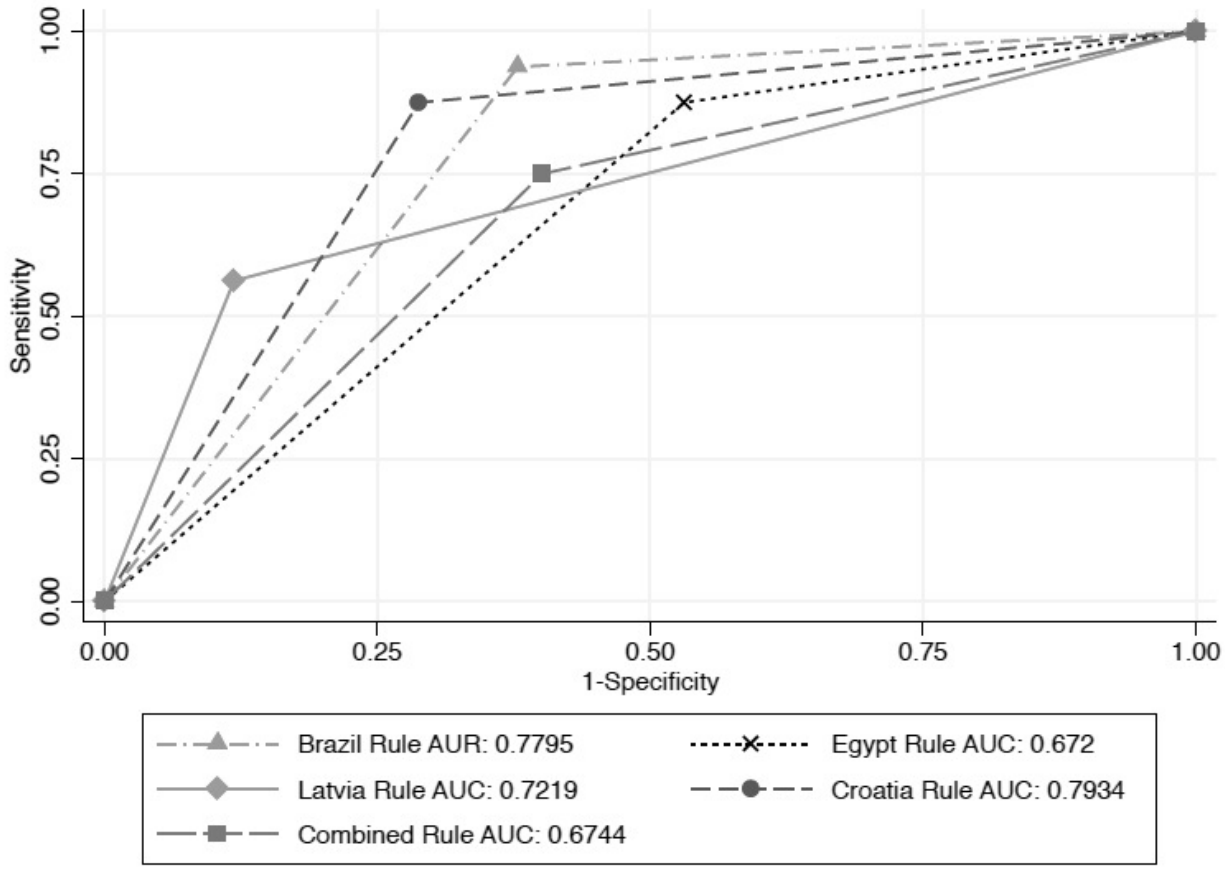


Figure S3. Comparison of Receiver Operating Curves (ROC) in Latvia Population

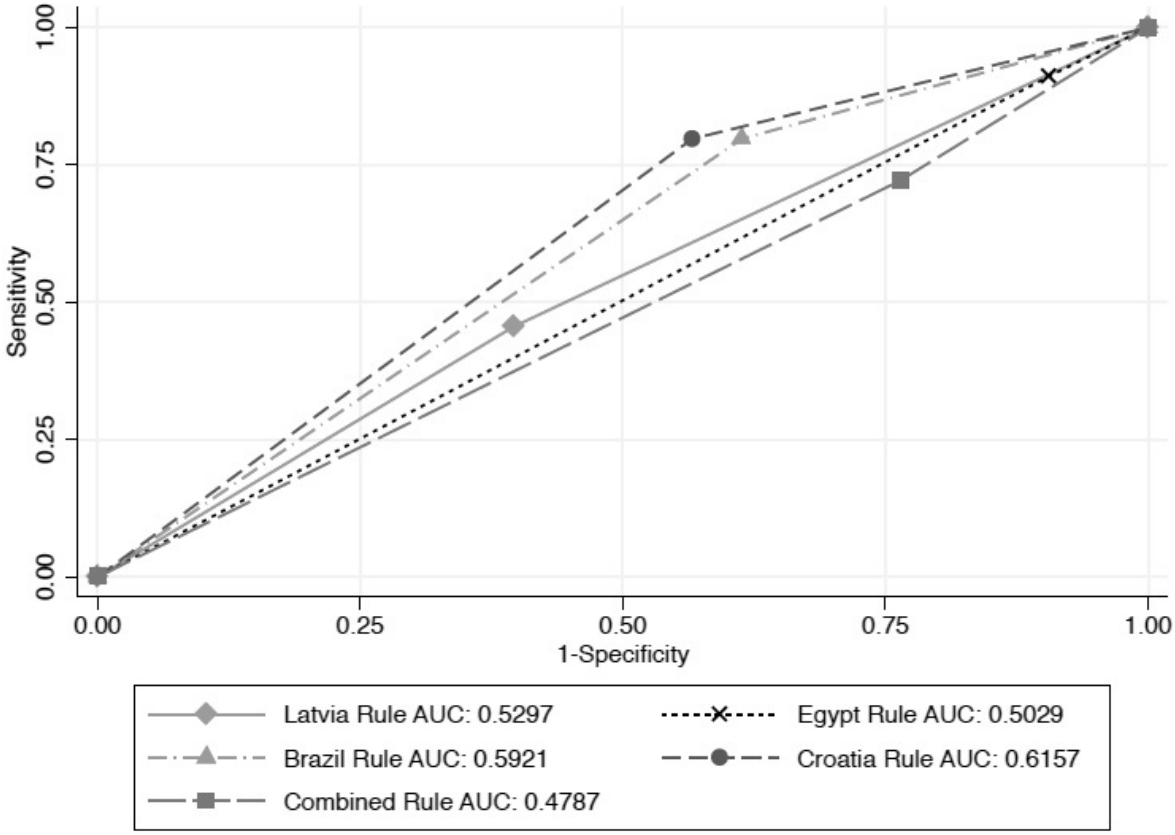


Figure S4. Comparison of Receiver Operating Curves (ROC) in Croatia Population

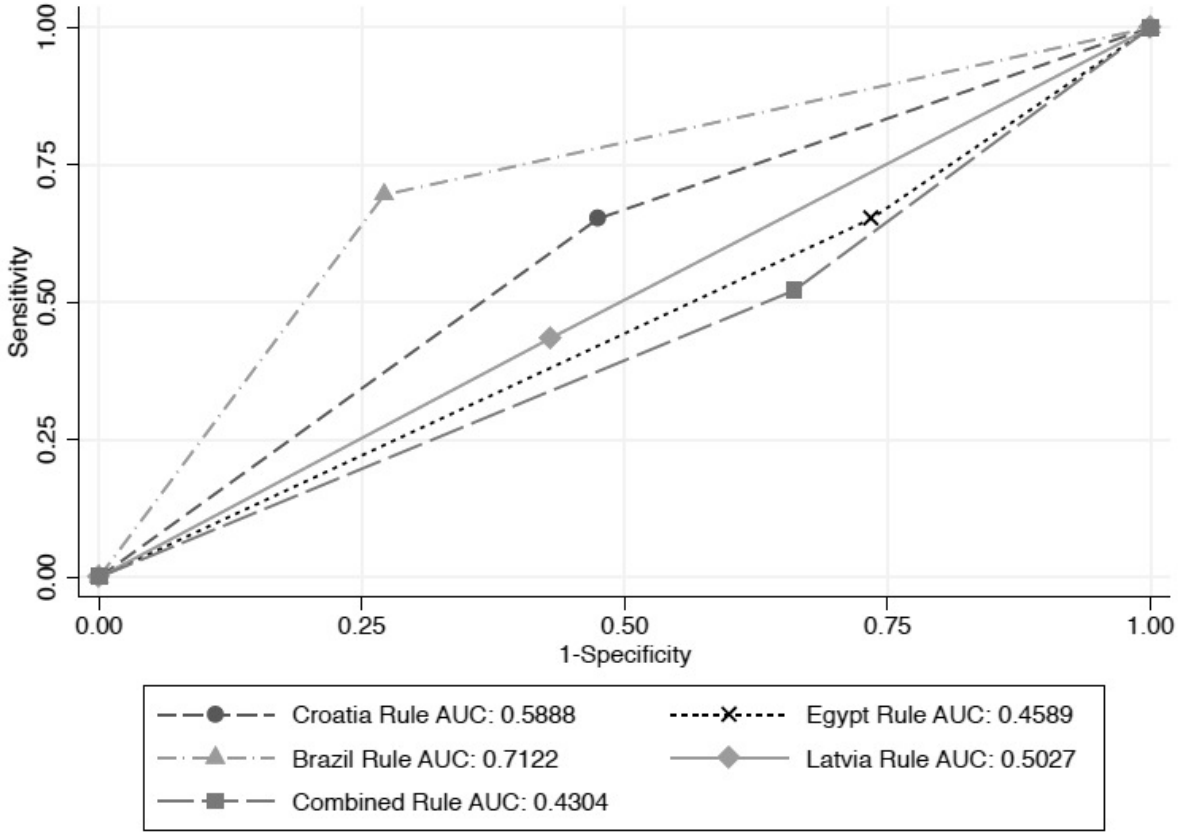
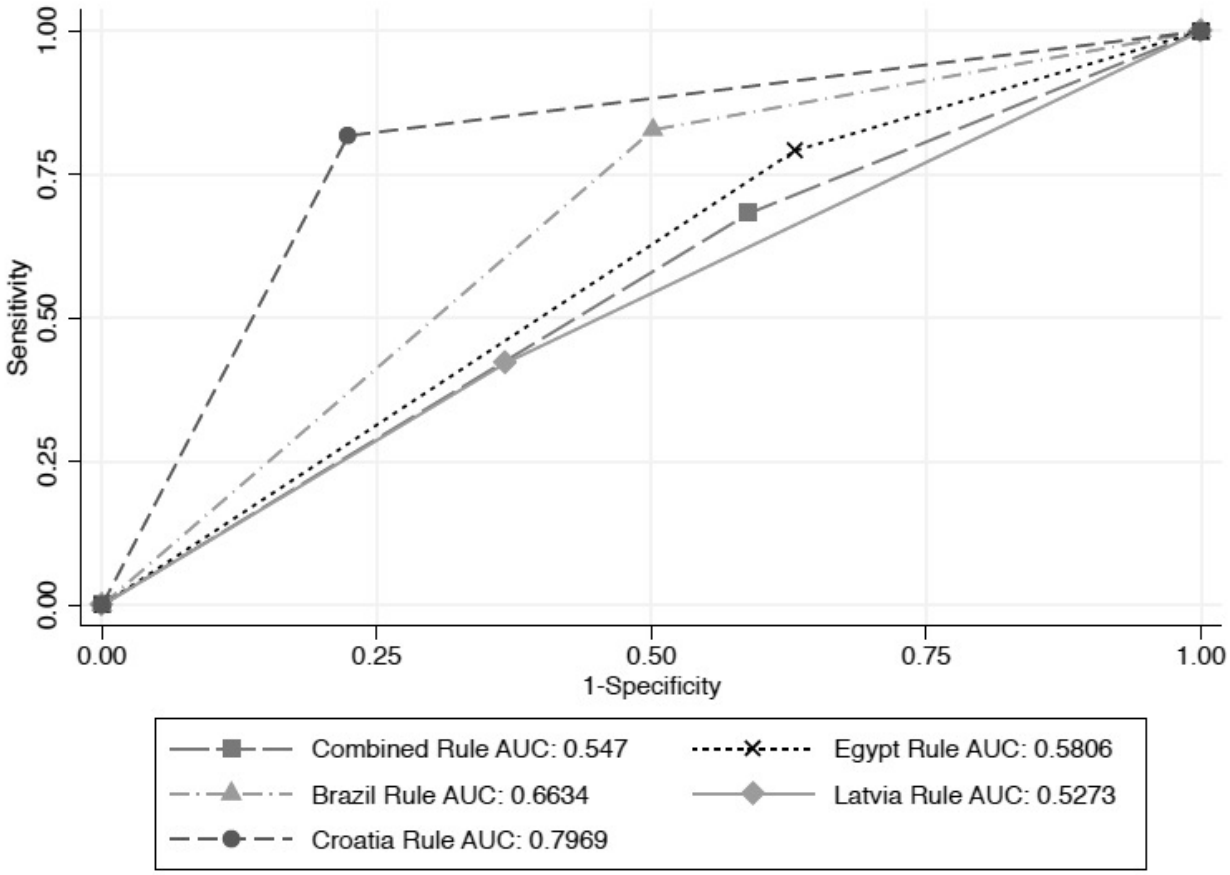


Figure S5. Comparison of Receiver Operating Curves (ROC) in Combined Population



CHAPTER 6. PAPER THREE: “COST EFFECTIVENESS OF A CLINICAL PREDICTION RULE FOR GROUP A BETA HEMOLYTIC STREPTOCOCCAL PHARYNGITIS FOR CHILDREN FROM A LOWER MIDDLE INCOME COUNTRY: EGYPT”

Chapter 6. Paper Three: “Cost Effectiveness Of A Clinical Prediction Rule For Group A Beta Hemolytic Streptococcal Pharyngitis For Children From A Lower Middle Income Country: Egypt”

ABSTRACT

Introduction: Group A beta hemolytic streptococcal (GABHS) pharyngitis is a common bacterial infection in children, especially between 5 and 15 years (5). Accurate diagnosis and treatment of GABHS pharyngitis can prevent complications such as rheumatic fever (RF) and rheumatic heart disease (RHD), but there is no consensus on the most cost effective diagnostic and management strategy for children.

Methods: A cost effectiveness analysis of the Egypt clinical prediction rule (CPR) compared to five other diagnostic and management strategies: 1) Do Nothing; 2) Empirical; 3) Culture Only; 4) Rapid antigen detection test (RADT) Only; and 5) CPR + RADT was evaluated. A decision tree analysis of the six strategies was performed and cost effectiveness analysis of the baseline estimates was calculated. Sensitivity analysis of estimates and assumptions were also performed.

Results: Culture Only strategy was the most cost effective strategy when GABHS pharyngitis prevalence is 27.29% according to cost effectiveness analysis of baseline estimates. Sensitivity analysis of most probability and cost parameters changed results, but remained consistent at varying utility estimates. GABHS pharyngitis prevalence had the greatest influence on results; Do Nothing was most cost effective for prevalence below 25% compared to Empirical above 80%. In

addition, CPR Only was cost effective when sensitivity and specificity was at or above 88%.

Conclusion: This was the first cost effectiveness analysis for children from low and middle-income countries (LMICs). For LMICs with laboratory capability, Culture Only is the most cost effective strategy for pediatric GABHS diagnosis and management. For setting without laboratory capability, RADT Only and/or CPR Only were cost effective under certain parameters estimates.

INTRODUCTION

Streptococcal pharyngitis is a common infection worldwide with most children developing at least one episode per year (6). Of these, 15 - 30% are due to group A beta hemolytic streptococcal (GABHS) pharyngitis (6, 33). Untreated, 3% of GABHS pharyngitis can lead to rheumatic fever (RF) 1-5 weeks after infection (1-5, 40). The risk of RF increases to 75% with recurrent RF, which may result in rheumatic heart disease (RHD), and other serious nonsuppurative sequelae of infection (see Figure 1) (1-5, 40). These life threatening cardiac complications are predominantly found in children and adolescents of developing countries, where an estimated 95% of RF and 79% of RHD cases are from lower income countries (5).

Diagnosis of GABHS pharyngitis is best accomplished by combining clinical judgment and diagnostic test results, the gold standard for which is throat culture (1-4, 38, 39, 43, 53). In high-income countries (HICs), this is easily accomplished; however, in low and middle income countries (LMICs) and other resource poor settings, adhering to the gold standard may be difficult due to limited access to laboratory facilities and/or the expense of laboratory testing. Clinical prediction rules (CPRs) may provide a reasonable option for physicians who do not have access to testing. Unfortunately, most CPRs have been developed using data from HICs where GABHS pharyngitis may present differently than in LMICs (1, 2, 4).

Treatment of GABHS pharyngitis can effectively interrupt transmission of GABHS pathogen and prevent[90] RF and RHD (Figure 2) (6, 7). Pharyngitis caused by GABHS is the only form of commonly occurring pharyngitis indicated for antibiotic treatment and is indicated only for patients diagnosed as GABHS positive (either via laboratory or clinical diagnosis) (34, 66). Effective treatment of GABHS pharyngitis provides symptomatic relief, reduced GABHS transmission, and more importantly, can reduce the risk of RF by approximately 90% (26, 35, 38, 43).[91]

Antimicrobial resistance (AMR) and the potential for morbidity and mortality due to allergic reactions are part of GABHS pharyngitis management. Indiscriminate antibiotic is a common management tool used by physicians in LMICs, which increases the risk of AMR (an emerging global concern) and allergic reactions (2, 4). Allergic reactions ranging from mild to severe, are more prevalent in children and adolescents, and risk increases with widespread, indiscriminate antibiotic use. (70, 92).

Secondary prevention of RF is effective if adequate prophylaxis is supplied; the risk of reoccurrence and therefore RHD is diminished (45). The first 3–5 years are critical as the likelihood of relapse is greatest during this period (45). More than 70% of RF cases develop

[90] Primary prevention
[91] For approximately 10%, GABHS remains present the throat following adequate treatment and therefore a small probability of RF still remains (i.e., in high risk settings (1, 12, 17-18). Nevertheless, chronic streptococcal carriers are not at risk of RF because they do not trigger the autoimmune response an active (acute) streptococcal infection triggers (6).

RHD; therefore, recurrent RF requires extended treatment (benzathine penicillin G) for recurrent RF prevention and secondary prevention of irreversible damage due to RHD (47).[92] Antibiotics can also prevent morbidity due to RHD including cardiac failure, stroke, and endocarditic (8). Tertiary preventative measures such as surgery although effective, are inefficient and economically burdensome for LMICs; therefore, primary prevention of RF/RHD is important (8, 41, 47).

Cost effectiveness analysis (CEA) of GABHS diagnosis and management have been conducted for HICs, but currently none have been conducted for lower income countries. Current estimates of probability, cost, and utility parameters for GABHS, especially from LMICs, are limited. Estimates from HICs are available, but reflect epidemiological, economical, and medical patterns found in resource rich settings and therefore, differences in probabilities of disease and complications (morbidity and mortality); characteristics of diagnostic tests (sensitivities and specificities); and diagnostic and management costs (testing, treatment, and complications) are expected. Due to these differences, CEAs from HICs might not provide the best estimates for LMICs; however, limited data from lower income countries necessitates use of these estimates (with additional adjustments and assumptions) (106).

[92] Secondary prevention also includes the administration of antibiotics to patients with RHD (6).

Effective use of CPRs for diagnosis of GABHS has been demonstrated in HICs (23, 25-27, 31, 57). However, fewer CPRs have been developed and/or validated in LMICs, and cost effectiveness of these CPRs has yet to be determined. Evaluating cost effectiveness of CPRs is important for countries with several demands on limited budgets. RF/RHD complications are major expenses for LMICs; therefore, a study to determine which strategy is most effective is needed. Therefore, the study conducted a cost effectiveness analysis to examine the cost effectiveness of the Egypt CPR (Chapter 4) versus five alternative GABHS pharyngitis diagnostic and management strategies for the prevention of RF/RHD.

METHODS

Study Population

Children 2-12 years of age presenting with complaint of sore throat were enrolled in four urban university pediatric outpatient clinics from September 2001 to August 2005 in Rio de Janeiro, Brazil, Cairo, Egypt; Riga Latvia and Zagreb, Croatia. Patients were excluded on the basis of oral antibiotic use within 3 days or intramuscularly administered antibiotics within 28 days prior to the clinic visit; a history of previous rheumatic fever or rheumatic heart disease; or hospitalization for any reason.

Study Design

The original study design has been described elsewhere (Chapters 3-5). For this study, a CEA was conducted for the diagnosis and management of GABHS pharyngitis among children from Egypt, a lower middle-income country. A decision analysis model with six diagnostic and management strategies for children ages 2 – 12 years presenting with complaints of sore throat to an urban university pediatric outpatient clinic in Cairo, Egypt was conducted. It tested the CEA of the study generated Egypt CPR (Chapter 4) against five alternative strategies.

Statistical Methods

Literature Search

An extensive review of the literature on recommended diagnostic and management strategies for GABHS pharyngitis was conducted. A summary of reviewed studies is presented in Table 1. Probability, cost, and utility estimates found in CEA studies from the literature are outlined in Tables 2 – 4. These tables include estimates and rages (when available) used to generate the study cost effectiveness model (in addition to estimates from the Egypt study site, and the RADT manufacture).[93] Table 5 is of time loss estimates (these were not included in the study analysis).

Decision Analysis Model

A decision analysis model was constructed to determine the short-term costs and cost effectiveness of six diagnostic and management strategies for GABHS pharyngitis. The costs and effectiveness of each

[93] The estimates used in this CEA were adjusted for inflation, currency, and pricing.

of the strategies were assessed to ascertain if the Egypt CPR was the most effective and least expensive strategy. The six strategies examined in this study are described below and shown in Figure 3:

1) No test, no treatment (Do Nothing). Patients are not diagnosed by either laboratory or clinical prediction methods, and treatment with antibiotics (penicillin) is not provided regardless of GABHS pharyngitis status. This strategy is not recommended due to risk of RF/RHD, but is a reality for many developing countries with poor resources.

2) No test, treat all (Empirical). Patients are not diagnosed by either laboratory or clinical prediction methods, and treatment with antibiotics (penicillin) is provided to all patients regardless of GABHS pharyngitis status. This strategy of indiscriminate use of antibiotics is not recommended due to increased risk of antimicrobial resistance (AMR) and allergic reaction, but is a common strategy in developing countries, with poor resources.

3) Clinical diagnosis with Egypt CPR, treat positives only (CPR Only). Patients are clinically diagnosed with clinical prediction rule (Egypt CPR), and treatment with antibiotics (penicillin) is provided only to patients diagnosed as GABHS pharyngitis positive (i.e., those with a high score). This is another common strategy. Diagnosis based on clinical presentation may be common, but CPRs developed and/or validated in LMICs are less common.

4) Culture, treat positives only (Culture Only). Patients are tested using throat culture, and treatment with antibiotics (penicillin) is provided only to patients who test GABHS pharyngitis positive. Laboratory diagnosis is less common in LMICs due to limited access to laboratory facilities and/or the expense of laboratory testing. However, culture diagnosis is the gold standard for GABHS pharyngitis and therefore, was included.

5) Rapid antigen detection test, treat positives only (RADT Only). Patients are tested using a rapid test, and treatment with antibiotics (penicillin) is provided only to patients who test GABHS pharyngitis positive. Laboratory diagnosis is less common in LMICs due to limited access to laboratory facilities and/or the expense of laboratory testing. However, RADT is increasingly used in HICs and can be used in the absence of laboratory facilities, and therefore, was included.

6) Clinical diagnosis with Egypt CPR and rapid antigen detection test (RADT), treat positives only (CPR + RADT). Patients are triaged using the Egypt CPR, where those with high score are tested using a rapid test, and treatment with antibiotics (penicillin) is provided only to patients who test GABHS pharyngitis positive. Patients with low scores are not tested or provided treatment. Laboratory diagnosis is less common due to limited access therefore the use of RADT for likely GABHS pharyngitis cases is a way to limit testing and therefore costs. This strategy was included in another study (99), which found CPR +

RADT to be the most cost effective strategy, and therefore, was included.

Feasibility for LMICs was a major consideration in determining which strategies to include in this CEA. For example, RADT with culture confirmation (and treatment for patients testing GABHS pharyngitis positive from either RADT/culture test) is a recommended diagnostic and management strategy; however, its feasibility in LMICs is limited. Therefore, for the purposes of this study, alternatives were limited to feasible strategies so that practical application of study findings can be implemented for Egypt and other LMICs.

Perspective

The CEA was conducted from the societal perspective and short-term direct costs and benefits (or health outcomes) associated with each of the six diagnostic and management strategies were examined.

Probabilities, Cost, and Utility Estimates

Tables of probability, cost, and utility estimates used in the cost effectiveness analysis of the baseline estimates and the sensitivity analysis of the low and high estimates are presented in Tables 7 - 9. Estimates used to conduct the CEA for Egypt were derived from various sources. Sources included original study, published literature (estimates and costs), University of Cairo Hospital (UCH) and outpatient clinical (medical), and manufacturer (diagnostic testing costs). Estimates specific to Egypt (or UCH) would have been

preferable and less biased (fewer assumptions); however, estimates specific to Egypt were not available (unless otherwise specified). Extensive search of the literature (and/or specific estimates from UCH) were unsuccessful in finding the necessary estimates of the parameters used in the CEA. Lack of available data (epidemiological, costs, etc.) is a major limitation of conducting research in LMICs. Therefore, data from HICs were used.

Probability Estimates

Probability estimates used in the cost effectiveness analysis of the baseline estimates are summarized in Table 7. The baseline estimate of GABHS prevalence was 27.29%. This was based on findings from the original study (92). Other studies have found the prevalence of GABHS in Egypt to range from 17 – 31% (3, 4, 116-120). This prevalence range is similar to the one estimated for children from developing and developed countries (6). However, for the sensitivity analysis, a prevalence range of 0 – 100%. This is common practice in CEAs and can be useful to different LMICs with varying prevalence of GABHS pharyngitis (72, 91, 95).

The CPR used in this study was from the diagnostic component of the study (Chapter 4). The CPR developed for the Egypt population was based on a simple additive scoring system where each predictor was defined as positive and given a score based on beta coefficient. The Egypt CPR had seven demographic and clinical (signs/symptoms) predictors including: early summer/autumn season; age above 5 years;

no cough; faucial erythema; nasal congestion; hoarseness; and no runny nose. A score of three or more predicators was considered predictive of GABHS (GABHS positive) and a score less than three was considered not predicative (GABHS negative). At this cutoff score, the CPR has a sensitivity of 73.13% and a specificity of 43.36%.

Sensitivity and specificity of laboratory diagnostic methods were based on the manufacturer, original study, and other studies using optical immunoassay rapid test. The specific OIA RADT used in the original study was the STREP A OIA MAX (Thermo Biostar/Inverness Medical Professional Diagnostics, Princeton, NJ, USA). The manufacturer reported 85% sensitivity (95% CI: 79-90%) and 95% specificity (95% CI: 93-96%); studies using this RADT have reported sensitivity and specificity ranges of 74.7 – 98.1% and 93.1 – 99%, respectively (92, 121). Therefore, the estimate ranges for the sensitivity analysis were 74.7 – 100% for sensitivity and 93.1 – 100% for specificity, according to the original study and modified from another (97). The only study found on rapid testing in Egyptian children did not provide information on the type of rapid test used (i.e., EIA vs. OIA and therefore was not included in the analysis (119). Nevertheless, the sensitivity and specificity of the RADT used (80.65% and 96.88%, respectively) falls withing the setimate range used for the sensitivity analysis. The estimate for culture sensitivity (83.5%) and specificity (99%) as well as the estimate ranges for sensitivity and specificity (75 – 100% sensitivity, and 95

– 100% specificity) were based on estimates found in the literature (70, 72, 88, 91, 92, 95, 96, 99, 101).

Estimates for treatment efficacy (penicillin), mild to severe penicillin allergic reaction, and death due to penicillin allergy, used in the cost effectiveness analysis of baseline estimates and sensitivity analysis were obtained from the literature (5, 6, 70, 72, 88, 91, 95, 96, 99, 101). Penicillin was the treatment option selected for this model, as it is readily available, widely used, and relatively inexpensive. Furthermore, penicillin is the antimicrobial treatment used at the outpatient clinic at UCH. Specifically, the outpatient clinic of UCH uses amoxicillin. Studies suggest that oral amoxicillin is as effective as oral penicillin V, well tolerated, and an inexpensive option (77). Therefore, this CEA used oral amoxicillin. Treatment efficacy and allergic reaction are based on estimates from the literature, as Egypt specific estimates were not available (88, 95, 96).

Nonsuppurative complications of GABHS pharyngitis were explored – RF (acute and recurrent) and RHD; suppurative complications were not assessed. Probability estimates specific for Egypt were unavailable; therefore, estimates specific to LMICs was used when available (6, 40, 107). Otherwise, estimates from HICs were used (70, 88, 95, 96).

Cost Estimates

Cost estimates used in the cost effectiveness analysis of the baseline estimates and sensitivity analysis are summarized in Table 8. Costs estimates not found in Egypt were obtained from the literature (70, 72, 88, 91, 95, 96, 99, 122). Costs from the literature (primarily from the U.S.) were adjusted for inflation using the consumer price index and converted to 2013 USD (123). Costs from Egypt were converted from the Egyptian Pound (EGP) to 2013 USD using a currency converter (124). Estimates included: cost of initial and follow-up physician visit[94]; RADT test (OIA); culture; penicillin (oral amoxicillin for recommended 10 day course of treatment); mild and severe allergic reaction; nonsuppurative complications (acute RF, recurrent RF, and RHD); and death due to RHD or allergic reaction.

Utility Estimates

Utility estimates used in the cost effectiveness analysis of the baseline estimates and sensitivity analysis are summarized in Table 9. Effectiveness of health outcomes were assessed using quality adjusted life years (QALYs). QALYs were the utility measures used in this analysis because they are most commonly used measure of disease burden in CEA studies (96). QALYs allow for comparisons with other GABHS pharyngitis studies (when available) and studies on other health outcomes (125). The utility (QALY) estimates used in the CEA were “off the shelf” and obtained from the literature (88, 125, 126). Because primary collection of QALY data specific to pediatric GABHS pharyngitis and associated outcomes was not conducted, QALYs specific

[94] Includes culture result notification, and antibiotic dispensed on a ticket which the patient picks up from the institute pharmacy

to some of the health outcomes were unavailable. Therefore, utility estimates with similar outcomes were used. For instance, untreated GABHS pharyngitis was based on utilities for chronic tonsillitis/adenitis and hay fever/rhinitis; mild allergic reaction was based on utilities for dermatitis and non-specific penicillin reaction; severe allergic reaction was based on utilities for congestive heart failure; recurrent RF was based on utilities for congenital heart disease; and RHD was based on utilities for congestive heart failure/other. Although these were derived using a U.S. population and included adults, estimates specific to Egyptian children and adolescents are unavailable; therefore, these estimates were used. In addition, estimate ranges for sensitivity analysis were wide to account for uncertainty.

Assumptions

Several assumptions were made in this CEA. First, it was assumed that estimates from HICs could be used when estimates from Egypt or other LMICs were unavailable. Second, in the context of risk of RF/RHD complications, it was assumed that ineffective treatment was equivalent to no treatment (does not include risk of allergic reaction). Third, it was assumed that the wait time for results after CPR diagnosis was equivalent to that of RADT (i.e., no waiting for results compared to culture). Forth, cost of recurrent RF was not available in the literature and therefore, made assumptions on the cost of recurrent RF based on estimates for acute RF and RHD. Fifth, cost of death due to RHD and allergic reaction were assumed equivalent

(the estimate was obtained from other CEA studies which did not differentiate between cost of death due to RHD and cost of death due to allergic reaction). Sixth, it was assumed that this was an endemic situation (the probability estimates of GABHS pharyngitis, RF, and RHD were based on endemic rates and therefore, results are not applicable to non-endemic or epidemic situations). Seventh, because health outcome specific estimates were unavailable for some parameters, it was assumed that utilities (QALYs) for similar health outcomes could be used (assumed they were interchangeable). Eight, the CEA assumed that both active and carrier GABHS pharyngitis had the same risk of RF/RHD complications as differentiating between the two via culture and rapid testing is impossible (only serological testing can differentiate between active and carrier GABHS pharyngitis). Lastly, it was assumed that treatment was limited to all symptomatic patients with positive laboratory tests (i.e., for strategies with laboratory testing). Assuming nondifferential laboratory diagnosis of carriers, can assume the strategy outcomes will not change relative to each other.

Cost Effectiveness Analysis

Cost effectiveness analysis of the baseline estimates was conducted using TreeAge decision analysis software. Variable estimates and estimate source are listed in Tables 7 – 9. These parameters were used to generate a decision tree analysis. The decision tree analysis included total direct costs and health outcomes of six pediatric GABHS diagnostic and management strategies to determine the cost

effectiveness of the study developed Egypt CPR (and treatment for children positive for GABHS pharyngitis) compared to five alternative diagnostic and management strategies for pediatric GABHS pharyngitis. The following five strategies were examined: 1) No test, no treatment (Do Nothing); 2) No test, treat all (Empirical); 3) Clinical diagnosis, treat positives only (CPR Only); 4) Culture, treat positives only (Culture Only); 5) RADT, treat positives only (RADT Only); and Clinical and RADT, treat positives only (CPR + RADT). Although RADT with culture confirmation (and treatment for positives from either test) is a recommended diagnostic and management strategy, its feasibility in LMICs is limited and therefore was not included. For the purposes of this study, alternatives were limited to either current practices or to feasible alternative strategies, so practical application of study findings can be implemented in Egypt and other LMICs.

Probabilities at each chance node, total costs of each strategy, and utilities for all health outcomes were computed and entered into the model. The CEA was conducted by calculating the payoff values for each of the health outcomes (summed all costs divided by outcome specific utility). The expected value for each strategy was then calculated by summing the probability-payoff products for each strategy (multiplied the probability of a chance node by the payoff values) (87, 91). The estimates and ranges used to derive the CEA were from various sources. Probability estimates were obtained from the published literature and original study. Cost estimates were obtained from different sources

including the published literature, manufacturer, and UCH. All cost estimates were adjusted to 2013 USD. Utilities were obtained from the literature.

This CEA was conducted from a societal perspective[95] and limited to short-term costs. The model examined the affect of six strategies on the main study outcomes: allergic reaction to penicillin, acute RF, recurrent RF, and RHD. Outcome measures were cost effectiveness ratios and incremental cost effectiveness ratios. Cost effectiveness ratios ($USD/ quality adjusted life years) were estimated by dividing the cost of each strategy by the effectiveness (QALYs) for the strategy. Incremental cost effectiveness ratios (ICERs) were estimated by dividing the incremental costs (difference in cost between two strategies) by the incremental effects (difference in health effects between two strategies). The more expensive and less effective strategies were dominated by cost effective (dominant) strategies, which were less expensive and more effective.

Sensitivity Analysis

Sensitivity analysis was also conducted using TreeAge decision analysis software. Low and high estimates for each of the variables used to conduct the sensitivity analysis (and the estimate source) are listed in Tables 7 – 9. The sensitivity analysis was used to evaluate uncertainty and assess the influence of estimates used in the cost effectiveness analysis of baseline estimates. Sensitivity analyses for

[95] Considers costs incurred by all parties, allows comparisons across programs and conditions, and is useful for resource allocation/policy purposes (87).

certain assumptions were assessed, including: prevalence of GABHS, laboratory test characteristics, CPR characteristics, probability of complications, costs of laboratory tests, costs of complications, and utilities. These variables are often examined in sensitivity analyses, as they are most likely to influence cost effectiveness of strategies. Tables 7 - 9 list the ranges in estimates for probabilities, costs, and utilities.

RESULTS

Cost Effectiveness Analysis

Based on baseline assumptions, probabilities, costs, and utility estimates (Tables 7 – 9) obtained from the literature, UCH, and RADT manufacturer, the six strategies had similar results (Table 10). Culture Only strategy was the least expensive and most effective (dominant)[96] with an average cost of $5.22 and an average effectiveness of 0.9814 quality adjusted life years (Figure 4). While RADT Only had the highest average effectiveness (0.9833), it also was the second most expensive strategy ($11.02). The cost effectiveness ratio for RADT Only was 11.20; however, it was the only other strategy not dominated and the incremental cost effectiveness ratio (ICER) compared to Culture Only was an additional $3,024.92 per QALY (compared to Do Nothing the ICER was $304.74 per QALY). CPR Only, CPR + RADT, and Do Nothing were dominated by Culture Only. Compared to Do Nothing, CPR Only cost an additional $3.35 and the cost effectiveness ratio (CER)

[96] A dominant (or undominated) strategy is a cost effective strategy (i.e., it is effective and not expensive), whereas a dominated strategy is not cost effective (i.e., expensive and less effective) (88).

was 8.77. CPR Only and CPR + RADT performed similarly for both cost and effectiveness. Empirical was the most expensive strategy at $11.54 and was dominated by RADT Only. Do Nothing strategy was the second least expensive ($5.23), but had the lowest effectiveness (0.9643).

Sensitivity Analysis

Sensitivity analysis was performed on the estimates most likely to influence the results or because of greater uncertainty. These included prevalence of GABHS pharyngitis, laboratory test characteristics (RADT and culture), CPR characteristics, probability of complications (RF, RHD, and allergic reactions), costs of laboratory tests (RADT and culture), costs of complications (RF, RHD, and allergic reactions), and utilities.

Prevalence of GABHS Pharyngitis

The prevalence of GABHS pharyngitis in the cost effectiveness analysis in children and adolescents from Egypt with sore throat was 27.29%. Results of the one-way sensitivity analysis of GABHS pharyngitis prevalence are shown in Figure 5. When prevalence of GABHS pharyngitis was 25% or less, Do Nothing was the dominant strategy; however, as GABHS pharyngitis prevalence rose, the effectiveness of Do Nothing dropped from 1.0 to 0.87 (comparatively, the other strategies had very little variation in effectiveness across the prevalence range). Culture Only remained the most cost effective strategy for prevalence between 26% and 80%. For prevalence greater than 80%, Empirical was the most cost effective strategy.

Laboratory Test Characteristics

Test characteristics of culture and RADT were explored. Culture Only strategy remained the most cost effective between 83% and 100% culture sensitivity, where cost of culture decreased as sensitivity increased. If specificity of culture was less than 99% then Do Nothing was the least costly strategy. Cost of RADT decreased as sensitivity and specificity of RADT increased, and was undominated at sensitivity greater than 78% and specificity greater than 70%. However, Culture Only strategy remained the least expensive strategy at various ranges of RADT characteristics.

CPR Characteristics

Test characteristics of the Egypt CPR are show in Figure 6 - 8. As the sensitivity of CPR increased, the cost of the CPR Only strategy decreased (Figure 6). CPR Only was undominated at sensitivity greater than 88%, but Culture Only was still the most cost effective strategy. Figure 7 shows the cost effectiveness ratios for the six strategies at varying CPR specificity. When the Egypt CPR specificity was at or above 88%, CPR Only was the most cost effective strategy. Two-way sensitivity analysis of CPR sensitivity and specificity is depicted in Figure 8, where sensitivity and specificity of CPR had an impact on cost effectiveness such that CPR Only was most cost effective when specificity and sensitivity were greater than 28% and 84%,

respectively.[97] Elsewhere, RADT Only strategy was cost effective (CPR + RADT strategy was cost effective for a very small area – sensitivity greater than 99% and specificity between 20% and 28%).

Results of the two-way sensitivity analysis were dependent on the willingness to pay (WTP). It was set to the standard $50,000/QALY, but its applicability to Egypt is unknown (127). Therefore, additional analyses were run with different WTP thresholds. As the willingness to pay additional cost per QALY decreased, the most cost effective strategy went from RADT Only (at lower sensitivity and higher specificity), CPR Only (at higher sensitivity and lower specificity), and CPR + RADT (at higher sensitivity and lower specificity) to Culture Only, CPR Only, and CPR + RADT (same relationship). Culture Only became cost effective when the WTP was less than $4,000/QALY. As the WTP threshold decreased, the sensitivity and specificity ranges where CPR Only was cost effective decreased (e.g., when the WTP was set to $500/QALY, CPR Only was cost effective when the sensitivity and specificity were 68% and 60%, respectively). In addition, at WTP less than $3,000/QALY, CPR + RADT was no a longer cost effective strategy.

Probability of Complications

Probability of nonsuppurative complications (RF and RHD) and allergic reactions (mild, severe, and death) estimates were assessed. In the cost effectiveness analysis of baseline estimates, probability of acute RF and recurrent RF were 0.4% and 20%, respectively. Do Nothing

[97] Two way CE (Net Benefit) sensitivity analysis on Egypt CPR sensitivity and specificity, where willingness to pay was set at standard $50,000/QALY (127).

was the cost effective strategy when the probability of acute RF and recurrent RF fell below 0.4% and 22%, respectively. At higher probabilities, Do Nothing (acute RF) and RADT Only (recurrent RF) were the most expensive strategies (dominated), and Culture Only was the most cost effective for both acute RF and recurrent RF. Culture Only was cost effective across the range of RHD probability, except at 3.5% (Do Nothing). No variation in the probability of death due to RHD altered the results; Culture Only remained the most cost effective.

Risk of a mild allergic reaction ranged from 0.0 – 10%. Do Nothing became the most cost effective for probabilities of mild allergic reaction greater than 2.5%. For probabilities ranging from 0 – 2% Culture Only was the least costly strategy and Empirical was the most expensive when greater than 0.5%. Culture Only strategy remained cost effective for severe allergic reaction probability ranges between 0.25% and 0.65%; Do Nothing was cost effective at probabilities above 0.65%.

Costs of Laboratory Tests

In the cost effectiveness analysis of the baseline estimates, cost of culture was $1.02. When cost of culture was more than $1.36, Culture Only was no longer the cost effective strategy. At $7.50, Culture Only was the least cost effective strategy. Culture Only remained most cost effective at different RADT costs. Two-way sensitivity analysis of cost of culture and cost of RADT resulted in RADT Only strategy as the most cost effective at all ranges of laboratory test costs.

Costs of Complications

For costs of complications, costs of acute RF and recurrent RF changed results, where Do Nothing was cost effective at costs below $2,430.86 and $9,600.00, respectively. Although Do Nothing was cost effective for RHD costs below $24,150.34, the incremental cost effectiveness (ICER) was less than $7 ($0.14 – $6.99) per additional QALY compared to Culture Only.

In addition, cost of mild allergic reaction did not alter results until cost was $62.92 when Do Nothing was more cost effective than Culture Only. Cost of severe allergic reaction above $1,381.78 changed Do Nothing to the most cost effective strategy. Cost of Death did not alter results.

Utilities

Culture Only remained the cost effective strategy for untreated and treated GABHS pharyngitis (after culture or RADT testing) utilities. Utilities for complications due to allergic reaction or secondary sequelae also did not alter results.

DISCUSSION

In this study, cost effectiveness of six GABHS pharyngitis diagnostic and management strategies for children from LMICs were assessed. The six strategies (Do Nothing, Empirical, CPR Only, Culture Only, RADT Only, and CPR + RADT) were included as they are either in use or can

be implemented in LMICs. Most of the strategies have been examined in other studies; however, this study also included Do Nothing, which has not routinely been evaluated in other studies. Its inclusion was based on its frequent use in some lower income countries, rather than a recommended strategy for GABHS pharyngitis diagnosis or RF/RHD prevention.

Of the six strategies studied, Culture Only was the most cost effective (least expensive and most effective) strategy at the baseline GABHS pharyngitis prevalence estimate of 27.29%. More notably, CPR Only [Egypt CPR from previous study (Chapter 4)] performed similarly to CPR + RADT, but was not as cost effective as the other strategies (less expensive and effective than RADT Only and Empirical, but more expensive and effective than Do Nothing). These finding although unexpected, are consistent with other CEA studies.

Results were changed by most probability and cost estimates during sensitivity analysis. Prevalence of GABHS pharyngitis had the greatest influence on results (both costs and effectiveness). When probability of GABHS pharyngitis prevalence was below 25%, Do Nothing was more cost effective, whereas prevalence above 80% had Empirical strategy as most cost effective. However, prevalence of GABHS pharyngitis greater than 80% is improbable under endemic situations, even in LMICs. Therefore, empirical treatment in LMICs should be discontinued. When laboratory test characteristics were assessed, reduction in sensitivity and specificity altered results from Culture Only to Do

Nothing. Although, CPR Only was not cost effective in the cost effectiveness analysis of the baseline estimates, the Egypt CPR was cost effective when sensitivity and specificity were greater than 88%. At lower probabilities of nonsuppurative complications, higher probabilities of allergic reaction, and higher costs, Do Nothing replaced Culture Only as most cost effective.

Although Do Nothing was the most cost effective strategy under certain parameter estimates, this strategy is not recommended for use in children in LMICs. Estimates were primarily from HICs and could have biased estimates in favor of Do Nothing and Culture Only (or laboratory testing). Generally, other strategies (mainly Culture Only and/or RADT Only) were also dominant (next cost effective strategy). Therefore, instead of Do Nothing, Culture Only is recommended for Egyptian healthcare facilities with laboratory testing capability, and RADT (or CPR) for those without laboratory capability for little additional cost/QALY. Laboratory facilities are not necessary for either RADT or CPR. For instances where CPR Only was a dominant strategy (e.g., when cost of culture increased, CPR sensitivity and specificity increased, and/or utility of treated GABHS pharyngitis after culture treatment decreased), CPR is preferable to RADT Only. Not all estimates were influenced by sensitivity analysis. For example, Culture Only remained the most cost effective strategy even when utility estimates were varied in sensitivity analysis. This shows the robustness of the baseline estimates.

The results of the cost effectiveness and sensitivity analysis were unexpected. Therefore, further analysis was conducted to explore the affects of an alternative approach, where Do Nothing strategy was excluded from analysis. Results of the alternative decision model remained consistent for the cost effectiveness analysis of the baseline estimates; Culture Only remained the most cost effective strategy. Culture Only was also the most cost effective for one-way sensitivity analysis of all variables, except for cost of culture and CPR specificity (CPR Only was the most cost effective at costs above $4.54 and specificity above 89%), and prevalence of GABHS pharyngitis 85% and higher (Empirical most cost effective). For two-way sensitivity analysis, CPR Only was cost effective when sensitivity and specificity were greater than 84% and 28%, respectively. RADT Only was cost effective elsewhere, except for a small area where CPR + RADT was cost effective (sensitivity above 99% and specificity between 20% and 28%). Although not the most cost effective, RADT Only was dominant for nearly all estimates during baseline and sensitivity analysis.

Currently, this is the first CEA conducted for children from LMICs. While there have been some studies on the cost effectiveness of GABHS pharyngitis diagnosis and management among children, these studies were conducted in high income counties (e.g., United States, France, New Zealand, and Spain) and/or not current (which influences costs, use and effectiveness of RADT, etc.) (70, 72, 91, 95-101). Other studies found in the literature either targeted adult pharyngitis, examined effectiveness without costs (88, 102), or explored the

economic burden of GABHS pharyngitis, but not effectiveness (94, 103, 104).

Cost effectiveness analyses often reach different conclusions due to differences in assumptions and estimates used. Factors influencing results include: type of perspective (societal vs. individual); costs (influenced by time and location); type of rapid test (EIA vs. optical immunoassay); probabilities of GABHS pharyngitis, RF, and RHD; type of effectiveness used (e.g., the two studies using utilities, used lost QALDs vs. standard QALYs); and type of strategies included (e.g., not all studies included the strategy “Do Nothing”) all influence CEAs (105). For example, when the prevalence of GABHS pharyngitis was low, culture was most cost effective strategy for U.S. adults (88). However, studies conducted in U.S. children came to differing conclusions; while one study (95) suggested culture was the best strategy, two other studies recommended rapid antigen testing alone (70, 72). Rapid testing alone contradicts an earlier study that determined rapid testing with culture confirmation was the most cost effective strategy for nonsuppurative complications prevention (91). Only one study found observation to have the lowest morbidity and cost (96). A recent Spanish study included a strategy with CPR, but with rapid testing confirmation and although it was the least expensive strategy, it was not as effective as culture (99). These studies (Table 1) illustrate how variations in probabilities, costs, and utilities account for differences in findings; model assumptions influence the outcomes and therefore the results from each study.

Because consensus is difficult, setting specific CEAs based on local estimates should be evaluated to determine which strategy is the most cost effective. However, results from this study can be helpful to Egypt and other LMICs with similar estimates.

Obtaining probability and cost estimates for LMICs is logistically complex because of a lack of systematic surveillance and reporting, but other CEAs for GABHS pharyngitis in LMICs are needed. Based on this CEA, it is recommended that empirical treatment of GABHS pharyngitis be discontinued as it is the most costly strategy and increases risk of antimicrobial resistance. In addition, while Do Nothing was the second least expensive strategy, it was also the least effective. Therefore, Egypt and other lower middle-income countries (with similar baseline estimates) with laboratory capability should consider laboratory testing, especially culture.

The cost effectiveness analysis component of the study had several strengths. First, this was a study of the cost effectiveness of pediatric GABHS pharyngitis clinical diagnosis and management in a lower middle-income country. There are a limited number of CEA studies on the diagnosis and management of GABHS pharyngitis among children, and currently none for children from LMICs (there are few cost analyses, but no evaluation of effectiveness). This study not only adds to the literature, but also addresses a practical need that can be implemented in Egypt and other LMICs with major public health problems and limited resources. In addition to being the first CEA for

LMICs, it is the first CEA to use standard utility estimates (i.e., QALYs), which can be used in other CEAs. QALYs were selected as the utility measure because they are most commonly used in CEA studies (96). QALYs allow for comparisons with other studies similar or other health outcomes (125). Other measures of effectiveness such as number of health outcomes prevented are easier to interpret, but QALYs incorporate not just the quantity of life (mortality), but also the quality (disability). Additionally, standardization of CEA effectiveness measures is beneficial when a community with a limited budget is comparing multiple health outcomes. Using “off the self” utilities enabled the study to conduct the CEA without having to collect primary data on GABHS pharyngitis utilities in Egypt (125). The only GABHS studies to use utility measures, used lost QALDs/QALYs, which is counter-intuitive and difficult to interpret (88, 96). Therefore, use of QALYs was one of the study strengths. Second, a sensitivity analysis was done to test the assumptions of the cost effectiveness analysis of the baseline estimates, which strengthens the findings.

Cost effectiveness results are based on assumptions and should be interpreted in the context of CEA limitations. There were several limitations in this study. First, the CEA was based on strategies selected for the decision tree. All possible diagnostic and management strategies were not explored; therefore, influencing results. For example, some studies included both culture and rapid testing as a strategy. However, for this study, strategies were limited to viable

options for LMICs. Conducting both types of laboratory testing is not feasible and therefore finding would not be applicable. The study goal was to limit alternative strategies to ones that could feasibly implemented for practical application of study finding in Egypt and other LMICs.

Second, results of the cost effectiveness analysis of the baseline estimates were sensitive to the estimates used for probabilities, costs, and utilities. Extensive search of the literature on Egypt specific data was limited. Data on GABHS pharyngitis, RF, and RHD are limited for LMICs and therefore, most of the data came from HICs. When data specific to Egypt or the University of Cairo Hospital were available, they were used. However, when best estimates were not available, assumptions were made on HIC estimates from literature. For example, because the cost of RF complications was unavailable in the literature or from UCH, costs were based on RF and RHD estimates from a recent U.S. CEA study (96). Other assumptions include: assumed cost and utility of death due to allergic reaction and RHD were the same (same assumptions made in other studies (88, 96)); assumed the utility of treated GABHS pharyngitis after empirical and CPR only diagnostic strategies were the same as utility of treated GABHS pharyngitis after RADT diagnostic strategy, as there is no treatment delay for either strategy (prompt treatment); and assumed ineffective treatment was the same as untreated GABHS pharyngitis as signs and symptoms are not resolved because of treatment failure which is essentially untreated GABHS pharyngitis. To attempt to address these limitations,

sensitivity analyses were conducted. Sensitivity analyses of estimates most likely to influence the outcome were assessed.

Third, the ability to differentiate clinically between acute GABHS infection and GABHS carriers is not possible without serological testing to observer change in antibody titer. However, this study used culture and RADT and therefore was unable to differentiate between the two GABHS infections. Therefore, the assumption that both GABHS infections have similar risk of RF/RHD complication is a study limitation due to inability to differentiate (see Chapter 2). Furthermore, it was assumed that treatment was limited to all symptomatic patients with positive laboratory tests (i.e., for strategies with laboratory testing). Assuming nondifferential laboratory diagnosis of carriers, can assume the strategy outcomes will not change relative to each other.

Fourth, this study focuses only on non-suppurative complications of GABHS pharyngitis, specifically RF and RHD. There suppurative complications of GABHS pharyngitis were not included in the CEA as the overall focus of the dissertation was on the prevention of RF and RHD.

Fifth, the CEA was conducted from a societal perspective (taking into account costs incurred by all parties) and direct costs were used. Indirect costs such as loss of productivity were not addressed. While studies have demonstrated the indirect cost of RF/RHD including lost school days or school drop out for patients and lost workdays or

unemployment, this analysis did not address these and instead focused on direct costs. In addition, Culture Only strategy did not include time costs associated with 24-48 hour delay in culture results such as taking time off from work.

Lastly, the assumptions were based on endemic rates of GABHS pharyngitis, RF, and RHD. Results of this CEA do not apply for non-endemic situations.

CONCLUSION

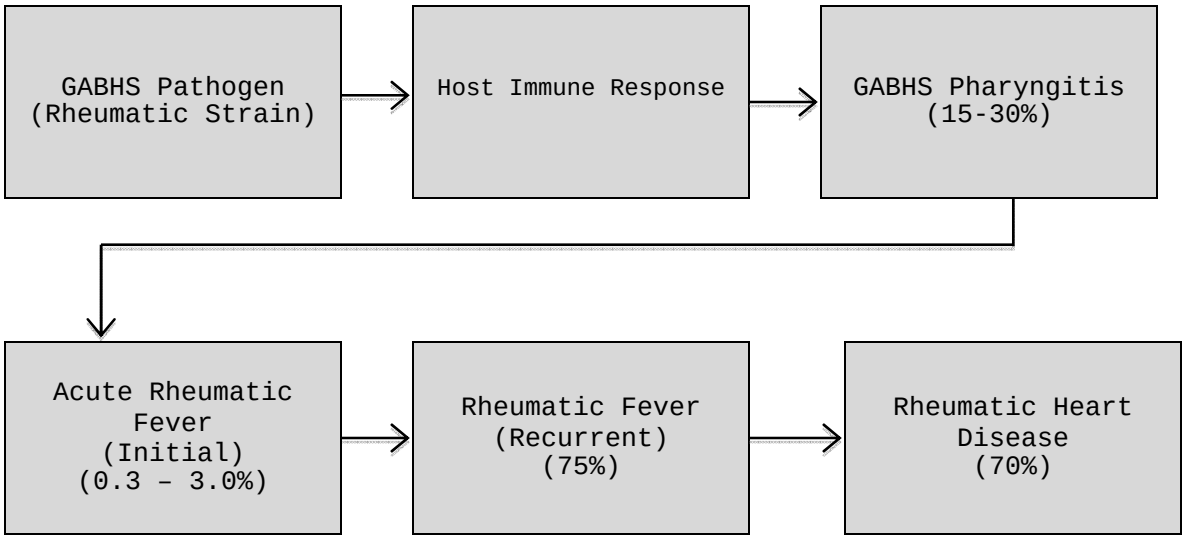
GABHS pharyngitis is manageable with prompt and adequate treatment, but when untreated, RF/RHD complications are complex and costs exorbitant (5, 6). The socioeconomic costs of RF and RHD among low-income children can increase hospital consultations and admissions, increase school failures, increase parent absenteeism, increase morbidity and mortality, and reduce intellectual opportunities (93). Studies estimating the annual cost of RF range from $51 to $539 million USD per year and the average cost per pediatric pharyngitis case approximately $205 USD (94).

Healthcare costs due to RF and RHD can represent a tremendous financial burden to LMICs where the burden of RF and RHD is high. For countries like Egypt, the RF and RHD estimates for children and adolescents range from 4.4 – 40 cases per 100,000 per year and 0.7 – 5.1 per 1,000, respectively (5, 6, 128). The results of this CEA indicate that Egypt healthcare facilities with laboratory capability

can reduce healthcare costs and increase effectiveness in preventing a neglected topical disease by implementing culture testing to the diagnostic practices in pediatric primary healthcare. For Egypt healthcare facilities without laboratory capability, can implement RADT Only or CPR Only strategies. It is also recommended that further research on cost effectiveness of GABHS pharyngitis diagnosis and management among children ages 5 – 15 years in developing countries be conducted, particularly since the majority of GABHS pharyngitis and its nonsuppurative sequelae burden are greatest among this population. Further recommendations include: country or facility specific estimates; improved CPRs with higher sensitivity and specificity; and explore CEA with additional alternative strategies such as CPR with RADT confirmation. Hopefully, this will be the first of many CEAs conducted for children in LMICs.

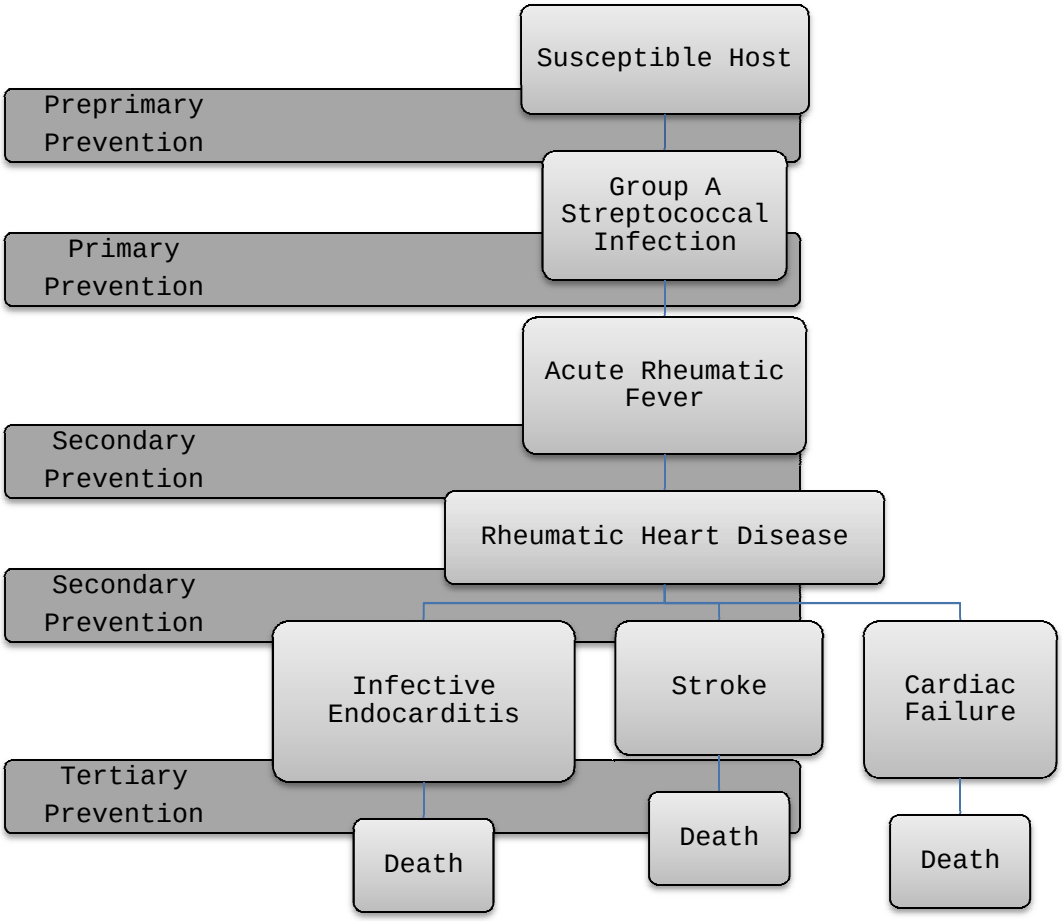
TABLES AND FIGURES

Figure 1. Flow Diagram From Group A Beta Hemolytic Streptococci (GABHS) Pathogen to Rheumatic Heart Disease (RHD) (6, 40, 107)



Modified from Nkomo (40), WHO (6), Michaud (107)

Figure 2. Flow Diagram of Preventative Measures For Rheumatic Fever (RF) and Rheumatic Heart Disease (RHD) (41, 47)



Modified from Steer (47), Carapetis (41)

Table 1. Summary of Cost-Effectiveness Analysis Studies

Author(s)	Year	Cost Assumptions	Benefits Assumptions	Findings
Neuner et al (88)	2003	• Cost represent actual resource cost (versus charges)[98] • Costs converted to 2000 USD • Published manufacturers' estimates used to determine rapid and culture costs • Assumed culture costs included test, patient notification, calling in prescription • Culture costs based on assumption conducted in physician's office • Cost of penicillin, erythromycin (penicillin allergy), and diphenhydramine (allergic reactions) estimated using wholesale and pharmacy dispensing costs • Resource-based relative value scale to estimate physician visit • Anaphylaxis estimated using previous analysis[99] • RF costs based on resource-based relative value scale and the Centers for Medicare & Medicaid fee schedule (primary care and specialist visits, electro- and echo- cardiography, and laboratory tests)	• Assumed utility associated with minor symptoms such as diarrhea and dyspepsia equivalent to pharyngitis • Assumed pharyngitis associated with a 0.95 utility • Other utilities estimated using a patient survey • Converted utilities to lost quality adjusted life days	Base Case: • Empirical treatment least effective (at 10% GABHS pharyngitis prevalence • Similar effectiveness for other strategies • Culture was least expensive Sensitivity Analysis: • Results sensitive to prevalence of GABHS pharyngitis o At >20%, rapid (first) and culture (second) were most effective o At <6%, observation was least expensive o At >71%, empirical was least expensive • Results sensitive to probability of anaphylaxis
Ehrlich et al (70)	2002	• Culture, rapid testing, and treatment estimated using provider's resource costs[100] • Culture costs based on	• Effectiveness expressed in cases of RHD prevented annually in US pediatric population (5-17)	Base Case: • Rapid test was the most cost effective • Rapid test + culture was

[98] Time Horizon: 1 year; Perspective: Societal; and examined short-term cost-effectiveness
[99] Drug Topics Red Book. Montvale. NJ: Medical Economics; 2000
[100] Perspective: Societal

		tests processed in outside laboratories • GABHS pharyngitis complications estimated using Children's Hospital of Philadelphia data	• US Census data used • A 0.004 probability of RF following GABHS pharyngitis • Morbidity/mortality: 0.038 probability of serious RHD sequelae • Treatment failure probability was 0.30	the most expensive • Treat all was the most effective (prevented the most RF, RHD, and complications), but also most allergic reactions and costly Sensitivity Analysis: • Results sensitive to rapid test sensitivity o As sensitivity increases, rapid increases in effectiveness and less costly than culture • Strategies not sensitive to increase in antibiotic sensitivity o Cost per RHD case prevented decreases o Number of RHD cases prevented increases
Tsevat et al (95)	1999	• Costs represent actual resource costs (versus charges) [101] • Costs converted to 1995 USD • No discount costs • Manufacture internal data for rapid and culture • Survey to estimate call time and salary for costs of notifying patients and calling in prescription • Treatment costs (penicillin and amoxicillin) included wholesale and dispensing costs • Allergic reactions (penicillin rash and anaphylaxis) based on survey and resource-based relative scale reimbursement rate; and previous analysis[102]	• Effectiveness expressed in terms of lives saved[103] • A 3% probability of ARF following GABHS pharyngitis • Mortality: 1% case fatality • Morbidity: 10% nonfatal complications • Assumed 75% reduction in ARF risk due to penicillin	Base Case: • At 20.8% GABHS pharyngitis prevalence, culture most cost-effective Sensitivity Analysis: • Results sensitive to: GABHS pharyngitis prevalence; RF attack rate; costs of EIA test;[104] and cost of culture (and result reporting) • Culture still best strategy when penicillin replaced by amoxicillin • Do nothing and empiric treatment least expensive from parental perspective; culture most expensive

[101] Perspective: Societal (base case) and Parental (sensitivity)
[102] Tsevat et al. Neonatal screening for sickle cell disease: cost effectiveness analysis. J Pediatr. 1991; 118:546-554

		• ARF costs estimated from study hospital financial data (1994-96) on 34 cases • Co-pay and prescription costs assumed • Bureau of Labor Statistics used for time cost		
Van Howe et al (96)	2006	• Marginal differences in costs computed for each strategy[105] • A strategy preferred if cost < $200,00 per QALY • Discount rate of 3% used • Costs adjusted using Consumer Price Index to 2003 USD • Culture costs based on tests processed in outside laboratories (private and Medicaid costs) • Cost of death estimated from medical costs before death • Red book costs and pharmacy fee used to estimate cephalosporin costs	• Marginal differences in utilities computed for each strategy • A strategy was preferred if more health was preserved • Utilities estimated using the General Health Policy Model and Quality of Well-being Scale	Base case: • Societal perspective o Culture had the best cost-utility with Medicaid reimbursement o Observing had the lowest morbidity and highest cost • Payer perspective o Rapid test had the best cost-utility with private insurance reimbursement o Observing had the lowest morbidity and lowest cost Sensitivity Analysis: • Results were most sensitive to ARF incidence
Lieu et al (91)	1990	• Provider's resource costs used for culture, rapid, treatment, and follow-up[106] o Estimated using consultation from microbiology laboratory and emergency department of study hospital o Laboratory costs include materials and personnel time o Follow-up costs include notification time and second visit o Assumed no second visit for oral penicillin	• Benefit expressed as number of GABHS pharyngitis complication prevented • Assumed a 10 fold reduction in rheumatic complications due to penicillin treatment • Assumed a 0.9 treatment effectiveness • Assumed the probability of ARF and ARF/RHD due to untreated GABHS pharyngitis to be 0.00288 and 0.00012	Base Case: • Treat all prevented the most number of ARF and RHD cases, but had the greatest morbidity and was least cost-effective • Rapid test is the least expensive • Rapid + culture was the most cost-effective (if costs of GABHS streptococcal complications included) Sensitivity Analysis: • Strategies sensitive to

[103] Does not expressly state what the effectiveness assumptions or how it's estimated/defined.
[104] Enzyme immunoassay test. Note: assessed cost-effectiveness of both EIA and OIA (optical immunoassay) rapid tests.
[105] Perspective: Societal and Payer
[106] Perspective: Societal; Population: Hypothetical cohort of 100,000 children

		treatment option • For extended cost analysis o Direct dollar costs of treatment for ARF and allergic reaction o Estimated using two methods: previous study[107] updated to 1985 USD; and actual charges for ARF from two patients at hospital in 1985		rapid test sensitivity and follow-up rate (culture vs. rapid) • Strategies not sensitive to varying assumptions • Strategies cost effectiveness influenced by extended cost analysis • Two-way sensitivity (follow-up rate and rapid sensitivity) influenced testing strategies • Rapid + culture prevented greatest morbidity under all conditions
Pfoh et al (94)	2008	• Medical costs calculated by linking health service utilization with national service costs • Rapid and culture costs were estimated using Medicaid reimbursement survey • Antibiotic costs estimated using 2005 Red Book • Nonmedical costs (i.e., work loss, personal time costs, childcare costs, transportation, and nonprescription medicines) estimated o National median wage rate used to estimate work loss o Assumed personal and work time similarly valued o Overall transportation costs included costs for driving and public transportation o Red Book used for average wholesale prices • Costs adjusted to 2006 USD	• Not Available/Applicable	• Total (societal) costs per GABHS pharyngitis case: $205 o Medical: $118 o Nonmedical: $87 • Total GABHS pharyngitis cost for US children: $224 – $539 million/yr

[107] Tompkins et al. An analysis of the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention. Ann Intern Med. 1977; 86:481-492

Table 1 (continued)

Terreri et al (93)	2001	• Direct costs from direct interventions attributed to the patient/family and society • Indirect costs relating to time loss for patient/family and production loss for society were estimated • Brazilian currency converted to 1998 USD • Utilization costs estimated using standard reimbursement fees and charges from the public health system • Medication costs were estimate from price index for public pharmacies and prices of the public Central of Medication • Transportation cost included public and private • Assumed private transportation for patients with private insurance • Loss of parental income calculated by deduction from monthly salary, and for society by sick pay	• Not Available/Applicable	• A 22.9% work absenteeism among patents o 901 days missed • Job loss was 5% • School failure among patients was 22% • Public system reference (societal costs): o Direct costs: $271/patient/yr o Indirect costs: $48/patient/yr o Total costs: $319/patient/yr • Healthcare plan reference: o Total costs: $423,550 • Private system reference: o Total costs: $684,351 • RF costs for families: 1.3% of annual income • RF annual costs for Brazil: $51,144,347
Webb et al (72)	1998	• Total treatment costs include visit and complication costs[108] • Wholesale costs of office visit, rapid test (plus direct and indirect costs for test administration), and culture (plus follow-up) • Penicillin allergy costs based on 1996 hospital charge data • ARF and RHD costs based on	• Benefit expressed as patients with disease prevented o Number of patients with ARF prevented o Percent of potential cases prevented o Complication prevented ARF • Assumed a treatment efficacy of 0.90 • Assumed ARF complications following untreated GABHS	Base Case: • Treat all was the least expensive, most cost-effective (cost/ complication prevented) • Among strategies involving diagnostic tests: o Rapid test (high sens) was least expensive, most cost-effective o Rapid + culture was most expensive, least cost-effective

[108] Perspective: Societal (base case) and Patient/Parental (sensitivity)

		estimates from the literature[109] and adjusted at a 3.5% annual inflation for 1997 USD costs • Financial proxy used to incorporate patient/parental preferences (not direct costs)	pharyngitis was 0.0003	Sensitivity Analysis: • Treat all remained most cost-effective under most conditions o Exception: drug wholesale costs > $10.76 o Rapid becomes most cost-effective • Among diagnostic testing strategies, rapid the most cost-effective under most conditions o Exceptions: low GABHS pharyngitis prevalence; rapid sens < culture sens; and ARF epidemic
Giraldez-Garcia et al (99)	2011	• Direct medical costs for testing, treatment, and complications from Spanish National Health Service Source[110] o Rapid cost based on university hospital o Penicillin cost reduced by 40% to account for patient cost • Primary care costs from official costs of local health centers • Culture results and prescription costs included as second visit, assumed one for other strategies • RF/RHD and allergic reaction costs based on provision rates o Allergic reaction costs: visits and treatment • Costs expressed per 4 million children annually	• Effectiveness measured as proportion of patients cured without: o Disease complications (RF/RHD) o Allergic reaction (due to penicillin) • Effectiveness expressed per 4 million children annually • Assumed treatment efficacy was 0.80 • Assumed RF probability was 0.0003	Base Case: • Clinical scoring + rapid was the most cost effective • Culture was the most effective, but most expensive Sensitivity Analysis: • Strategies were sensitivity to changes in clinical scoring sensitivity and specificity o Rapid test most cost effective strategy when clinical scoring sens <91% and spec ≤9% o Clinical scoring triage + rapid for high scores most cost effective, and rapid for all when sens/spec is low

[109] Tompkins et al. An analysis of the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention. Ann Intern Med. 1977;86:481-492
North et al. Analysis of costs of acute rheumatic fever and rheumatic heart disease in Auckland. *N Z Med J.* 1993;106:400–403
[110] Perspective: Payer

Table 1 (continued)

Tompkins et al (101)	1977	• Charges for culture, visit, and treatment based on rates charged by a prepaid group clinic o Visit costs included travel and patient time o Assumed all strategies included medical care provider at initial visit o Culture positive treatment require two visits and no treatment have no second visit o Hospitalization cost based on general internal medical practice per diem (bed, meds, fees) • Assumed premature death costs from other patients similar to RF risk patients • RHD costs assumed four visits, two 14 day/year hospitalization, survive average 6.2 years o Includes premature death costs and medical care for 6.2 years • Estimated costs for allergic reaction based on assumptions that: o Serious reactions require hospitalization followed by disability period o Mild reactions require office visit, treatment, and patient time	• Effectiveness expressed as predicted cases per 1000 sore throat patients • Recurrent RF and RHD o Assuming antibiotic prophylaxis, cardiac disease from initial RF (w/in 8 yrs) probability: 0.011 o Death or debilitating RHD (and death w/in 6 yrs) probability: 14/771 • Assumed the probability (children) of RF after penicillin treated GABHS pharyngitis (endemic) was $6.43x10^{-4}$ • Assumed the probability of RF without treatment $6.43x10^{-3}$ • Assumed a 8-10 fold reduction in risk of RF with antibiotic treatment o Assuming patient compliance with oral treatment, oral penicillin and benzathine penicillin equally effective for initial RF	Base Case: • Treat all was the most effective, least expensive strategy under epidemic situations • Treat all was the most cost-effective strategy under endemic conditions when: o Oral penicillin used o Positive culture rate > 20% • Treat positive cultures strategy most cost effective with benzathine and rate 5 – 20% • Treat none most cost effective when rate <5% Sensitivity Analysis: • Epidemic situation was not sensitive to changes from sensitivity analysis • Endemic situation was sensitive to changes in positive culture rates

Table 2. Probability Variables Used in GABHS Pharyngitis Cost Effectiveness Analysis (CEA) Studies

Variable	Source	Probability		
		Baseline	Low Estimate	High Estimate
GABHS Prevalence	Neuner et al	0.097	0.02	0.68
	Ehrlich et al	0.20	-	-
	Tsevat et al	0.208	0.0	1.0
	Van Howe et al	0.26	-	-
	Lieu et al	0.29	0.0	1.0
	Webb et al	0.29	0.0	1.0
	Giraldez-Garcia et al	0.25	0.10	0.45
	Tompkins et al	-	0.095	0.661
Rapid Test Sensitivity	Neuner et al	0.884	0.70	0.99
	Ehrlich et al	0.80	-	-
	Tsevat et al	0.859(EIA)/ 0.808(OIA)[111]	0.5 (EIA/OIA)	1.0 (EIA/OIA)
	Van Howe et al	0.891	0.80	0.95
	Lieu et al	0.55	0.0	1.0
	Webb et al	0.891	0.75[112]	1.0
	Giraldez-Garcia et al	0.90	-	-
Rapid Test Specificity	Neuner et al	0.944	0.80	0.99
	Ehrlich et al	0.99	-	-
	Tsevat et al	0.943 (EIA)/ 0.895 (OIA)	0.5 (EIA/OIA)	1.0 (EIA/OIA)
	Van Howe et al	0.95	0.90	0.99
	Lieu et al	0.90	-	-
	Webb et al	0.950	0.89	0.988
	Giraldez-Garcia et al	0.78	-	-
Culture Sensitivity	Neuner et al	1.0	-	-
	Ehrlich et al	0.90	-	-
	Tsevat et al	0.78	-	-
	Van Howe et al	0.834	0.77	0.93
	Lieu et al	0.90	-	-
	Webb et al	0.834	0.752	0.971
	Giraldez-Garcia et al	0.95	-	-
	Tompkins et al	0.90	-	-

[111] EIA = Enzyme immunoassay test; OIA = optical immunoassay test

[112] The range for the rapid test sensitivity is based on the range used for the sensitivity analysis. The range for rapid sensitivity from the 13 published studies was 0.77 – 0.974. The ranges for rapid test specificity, culture sensitivity, and culture specificity are based on the published studies

Table 2 (continued)

Culture Specificity	Neuner et al	1.0	-	-
	Ehrlich et al	0.99	-	-
	Tsevat et al	0.99	-	-
	Van Howe et al	0.99	0.95	0.995
	Lieu et al	1.0	-	-
	Webb et al	0.990	0.962	1.00
	Giraldez-Garcia et al	0.99	-	-
	Tompkins et al	0.82	-	-
Mild Allergic Reaction	Neuner et al	0.02[113]	0.005	0.04
	Ehrlich et al	0.10	-	-
	Tsevat et al	0.015	0	0.1
	Van Howe et al	0.02	0.007	0.04
	Lieu et al	0.003	0.001732	-
	Webb et al	0.0525	-	-
	Giraldez-Garcia et al	0.09499	-	-
	Tompkins et al	0.003(I)/0.00525(O)[114]	-	-
Severe Allergic Reaction	Neuner et al	0.0001[115]	0.00005	0.0002
	Ehrlich et al	0.005	-	-
	Tsevat et al	0.0001[28]	0	0.0005
	Van Howe et al	0.0064	0.0025	0.0075
	Lieu et al	0.0064	0.000083	-
	Webb et al	0.00025	-	-
	Giraldez-Garcia et al	0.005	-	-
	Tompkins et al	0.0064(I)/0.00025(O)	-	-
Death From Allergic Reaction	Neuner et al	0.10	0.05	0.2
	Ehrlich et al	0.00001	-	-
	Tsevat et al	0.10	0	1.0
	Van Howe et al	0.00001	0.000005	0.000015
	Lieu et al	0.000003	0	-
	Giraldez-Garcia et al	0.00001	-	-
	Tompkins et al	0.000003 (I/O)	-	-

[113] Penicillin induced rash
[114] I = Intramuscular penicillin (Benzathine penicillin); O = Oral penicillin (penicillin G)
[115] Penicillin induced anaphylaxis

Table 2 (continued)

Treatment Efficacy	Neuner et al	0.70[116]	0.55	0.80
	Ehrlich et al	0.70	-	-
	Tsevat et al	0.75	0.0	1.0
	Van Howe et al	0.80	0.70	0.90
	Lieu et al	0.90	0.50	-
	Webb et al	0.90		
	Giraldez-Garcia et al	0.80	0.70	0.90
	Tompkins et al	--	0.80	0.90
Rheumatic Fever (Untreated GABHS Pharyngitis)	Neuner et al	0.0005	0.0	0.03
	Ehrlich et al	0.004	-	-
	Tsevat et al	0.03	0	0.05
	Van Howe et al	0.00000656	0.0	0.000328
	Lieu et al	0.00288	0.01	0.0001
	Webb et al	0.0003	0.0001	0.01
	Giraldez-Garcia et al	0.0003	-	-
	Tompkins et al	0.00643	-	-
Rheumatic Fever Complications (C)/ Death (D)	Neuner et al	0.1(C)/0.01 (D)	0.05(C)/0.0005(D)	0.2(C)/0.02(D)
	Tsevat et al	0.1(C)/0.01(D)	0.0 (C/D)	0.20(C)/0.25(D)
	Van Howe et al	0.10	-	-
	Tompkins et al	0.011(C)	-	-
Rheumatic Heart Disease	Ehrlich et al	0.038	-	-
	Van Howe et al	0.01	-	-
	Lieu et al	0.00012	-	-
	Tompkins et al	0.0182	-	-

Modified from Neuner (88), Ehrlich (70), Tsevat (95), Van Howe (96), Lieu (91), Webb (72), Giraldez-Garcia (99), and Tompkins (101)

[116] Effectiveness of penicillin vs. acute rheumatic fever

Table 3. Cost Variables Used in GABHS Pharyngitis Cost Effectiveness Analysis (CEA) Studies

Variable	Source	Cost[117]		
		Baseline	Low Estimate	High Estimate
Visit[118]	Lieu et al	8.00 (I)	16.00 (O)	31.00 (O)
	Webb et al	27.00	-	-
	Giraldez-Garcia et al	37.00	-	-
	Tompkins et al	10.00	-	-
Follow-up[119]	Neuner et al	1.29(CRN)/1.28 (CIP)	0.65(CRN)/0.64 (CIP)	2.58(CRN)/2.56 (CIP)
	Tsevat et al	0.63(CRN)/0.43 (CIP)	0.00 (CRN/CIP)	24.00 (CRN/CIP)
	Van Howe et al	5.73	0.00	10.00
	Lieu et al	5.00 (I)	0.00 (O)	0.00 (O)
	Webb et al	5.00	-	-
	Giraldez-Garcia et al	2.70	-	-
	Tompkins et al	4.00	-	-
Rapid Test	Neuner et al	7.67	3.84	15.34
	Tsevat et al	3.90(EIA)/6.50(OIA)	0.00 (EIA/OIA)	20.00 (EIA/OIA)
	Van Howe et al	15.00 (Private); 7.84 (Medicaid)	3.93	15.69
	Lieu et al	3.00 (I)	-	9.00 (O)
	Webb et al	7.00	-	-
	Giraldez-Garcia et al	2.67	-	-
Culture	Neuner et al	2.83	1.42	5.66
	Ehrlich et al	40.00	-	-
	Tsevat et al	2.40	0.00	15.00
	Van Howe et al	30.00 (Private)/ 5.00 (Medicaid)	1.45	40.00
	Lieu et al	5.00 (I)	-	15.00 (O)
	Webb et al	5.00	-	-
	Giraldez-Garcia et al	5.43	-	-
	Tompkins et al	2.00	-	-

[117] Neuner et al (2000 USD); Ehrlich et al (USD); Tsevat et al (1995 USD); Van Howe et al (2003 USD); Lieu et al (1985 USD); Webb et al (1997 USD); Giraldez-Garcia et al (EURO); Tompkins et al (1977 USD)
[118] Visit includes: initial hospital, general practice, office, diagnostic, etc.
[119] Follow-up includes: culture result notification, calling in prescriptions, therapy only, etc.

Table 3 (continued)

Penicillin (Oral)	Neuner et al	10.05	5.03	20.10
	Ehrlich et al	10.00	-	-
	Tsevat et al	9.06	0.00	20.00
	Van Howe et al	10.23	5.14	20.56
	Lieu et al	1.00 (I)	-	5.00 (O)
	Webb et al	2.00	-	-
	Giraldez-Garcia et al	6.22	-	-
	Tompkins et al	3.00	-	-
Other Antibiotics[120]	Ehrlich et al	10.00 (Am)	-	-
	Tsevat et al	8.22 (Am)	0.00	20.00
	Van Howe et al	20.29 (C)	-	-
	Lieu et al	4.00 (I)	-	8.00 (O)
	Giraldez-Garcia et al	7.51 (Az)	-	-
	Tompkins et al	3.00 (I)	-	-
Mild Allergic Reaction	Neuner et al	50.94	25.47	102.00
	Ehrlich et al	30.00	-	-
	Tsevat et al	49.99	25.99	73.99
	Van Howe et al	52.10	26.05	104.32
	Lieu et al	30.00	-	-
	Webb et al	35.00	-	-
	Giraldez-Garcia et al	44.51	-	-
	Tompkins et al	15.00	-	-
Severe Allergic Reaction	Neuner et al	1,772.54	886.00	3,545.00
	Ehrlich et al	5,495.00	-	-
	Tsevat et al	1,500.00	0.00	5,000
	Van Howe et al	4,808.07	1,812.94	8,546.75
	Lieu et al	5,495.00	-	-
	Webb et al	4,194.00	-	-
	Giraldez-Garcia et al	1,249.58	-	-
	Tompkins et al	826.00	-	-

[120] Other antibiotics include: Azithromycin (Az); Cephalosporin (C); Amoxicillin (Am); Intramuscular Penicillin (I), etc.

Table 3 (continued)

Rheumatic Fever	Neuner et al	1,883.98	942.00	3,768.00
	Ehrlich et al	6,000.00	-	-
	Tsevat et al	700.00	0.00	20,000
	Van Howe et al	6,000.00	2,000.00	22,928.35
	Lieu et al	14,674.00 (T) / 925.00(CHP)[121]	-	-
	Webb et al	20,000.00	-	-
	Giraldez-Garcia et al	2,468.41	-	-
	Tompkins et al	10,560.00	-	-
Rheumatic Heart Disease	Van Howe et al	20,000.00	5,000.00	25,000.00
Daily Cost Hospitalization	Tompkins et al	94.00	-	-
Death	Van Howe et al	10,000.00	8,000.00	12,000.00
Premature Death	Tompkins et al	72,000.00	-	-
Parental Wages (per hour)	Van Howe et al	17.18	13.00	25.00
Patient Time (per office visit)	Tompkins et al	4.50	-	-

Modified from Neuner (88), Ehrlich (70), Tsevat (95), Van Howe (96), Lieu (91), Webb (72), Giraldez-Garcia (99), and Tompkins (101)

[121] T = Tompkins et al (updated to reflect inflation); CHP = Children's Hospital of Philadelphia

Table 4. Utility Variables Used in GABHS Pharyngitis Cost Effectiveness Analysis (CEA) Studies

Variable[122]	Source	Utility, QALDs[123]		
		Baseline	Low Estimate	High Estimate
Untreated GABHS Pharyngitis	Neuner et al Van Howe et al	0.25	0	0.5
Treated GABHS Pharyngitis After Rapid	Neuner et al Van Howe et al	0.15	0.10	0.25
Treated GABHS Pharyngitis After Culture	Neuner et al Van Howe et al	0.20	0.15	0.25
Mild Allergic Reaction	Neuner et al Van Howe et al	0.625	0.15	1.50
Severe Allergic Reaction	Neuner et al Van Howe et al	9	3	18
Uncomplicated Rheumatic Fever	Neuner et al Van Howe et al	76.5	9	744
Complicated Rheumatic Fever	Neuner et al	744	56	744
Rheumatic Heart Disease	Van Howe et al	744	56	744
Death	Neuner et al Van Howe et al	14,874 22,995	- 14,000	- 25,00

Modified from Neuner (88) and Van Howe (96)

[122] Untreated GABHS pharyngitis (5 days); treated GABHS pharyngitis after rapid test (2 day reduction in sore throat) vs. culture (1 day reduction in sore throat); complicated rheumatic fever (with valvular disease)/rheumatic heart disease (Van Howe et al); and death (from allergic reaction or rheumatic fever)

[123] Lost Quality-Adjusted Life Days (QALDs)

Table 5. Time Loss Estimates Used in a GABHS Pharyngitis Cost Effectiveness Analysis (CEA) Study

Condition	Source	Work Lost, Hour		
		Baseline	Low Estimate	High Estimate
Untreated GABHS	Van Howe et al	16	8	24
Immediate Treatment	Van Howe et al	8	0	16
Delayed Treatment	Van Howe et al	8	0	16
Death	Van Howe et al	80	40	120
Rheumatic Fever[124]	Van Howe et al Tsevat et al	80 40	40 -	120 -
Rheumatic Heart Disease	Van Howe et al	80	40	120
Mild Allergic Reaction	Van Howe et al Tsevat et al	8 4[125]	4 -	12 -
Severe Allergic Reaction	Van Howe et al Tsevat et al	40 16	20 -	60 -

Modified from Van Howe (96) and Tsevat (95)

[124] Tsevat el al examined missing work/school, but used days of work/school missed without specifying number of hours in a work/school day. Therefore, not added to table.

Table 6. Variables for the Cost Effectiveness Analysis (CEA) Study

Variable Type	Variable	Definition
Probability	GABHS Pharyngitis	Prevalence of GABHS pharyngitis in children, defined as the proportion of throat cultures that grow GABHS
	Rapid Test Sensitivity	Sensitivity of OIA rapid antigen detection test*
	Rapid Test Specificity	Specificity of OIA rapid antigen detection test
	Culture Sensitivity	Sensitivity of throat culture
	Culture Specificity	Specificity of throat culture
	Clinical Score Sensitivity	Sensitivity of the study developed CPR
	Clinical Score Specificity	Specificity of the study developed CPR
	Mild Allergic Reaction	Probability of penicillin-induced rash
	Severe Allergic Reaction	Probability of penicillin-induced anaphylaxis
	Death From Allergic Reaction	Probability of death from anaphylaxis
	Treatment Efficacy	Effectiveness of penicillin in preventing acute rheumatic fever
	Acute Rheumatic Fever	Probability of acute rheumatic fever following untreated GABHS pharyngitis
	Recurrent Rheumatic Fever	Probability of complications from recurrent rheumatic fever
	Rheumatic Heart Disease	Probability of rheumatic heart disease
	Death	Probability of death from rheumatic heart disease
Costs (USD)	Visit	Cost of urban pediatric clinic visit
	Follow-up	Costs of culture result notification and calling in prescription to pharmacy
	Rapid Test (OIA)	Cost of OIA rapid antigen detection test, including test and quality control
	Culture	Cost of culture, including materials, quality control, and labor

Table 6 (continued)

Costs (USD)	Penicillin (Oral)	Cost of penicillin therapy, including wholesale cost of penicillin[126] and pharmacy dispensing cost
	Mild Allergic Reaction	Cost of treating a penicillin-induced rash, including healthcare worker time, diphenhydramine, and erythromycin ethylsuccinate[127]
	Severe Allergic Reaction	Cost of treating anaphylaxis, including hospitalization and treatment
	Death	Cost of approximate estimate of the medical costs incurred before death either from allergic reaction or rheumatic heart disease
	Acute Rheumatic Fever	Cost of rheumatic fever, including costs for hospitalization, disability, and penicillin prophylaxis
	Recurrent Rheumatic Fever	Cost of rheumatic fever complications, including recurring rheumatic fever, visits, penicillin prophylaxis, hospitalization, disability, and medical care
	Rheumatic Heart Disease	Cost of rheumatic heart disease, including costs for visits, hospitalization, disability, premature death, and medical care
Utilities	Untreated GABHS Pharyngitis	Quality adjusted life years for untreated GABHS pharyngitis
	Treated GABHS Pharyngitis After Rapid	Quality adjusted life years for treated GABHS pharyngitis after rapid test
	Treated GABHS Pharyngitis After Culture	Quality adjusted life years for treated GABHS pharyngitis after throat culture
	Mild Allergic Reaction	Quality adjusted life years for mild penicillin-induced rash
	Severe Allergic Reaction	Quality adjusted life years for anaphylaxis
	Acute Rheumatic Fever	Quality adjusted life years for acute (uncomplicated) rheumatic fever
	Recurrent Rheumatic Fever	Quality adjusted life years for recurrent (complicated) rheumatic fever
	Rheumatic Heart Disease	Quality adjusted life years for rheumatic heart disease
	Death	Quality adjusted life years for death

[126] Wholesale cost for 10 day course of oral Amoxicillin (250 mg 3 times daily)
[127] Wholesale and dispensing costs for 2 day course of diphenhydramine (12.5 mg 4 times daily) and 10 day course of erythromycin ethylsuccinate (200 mg 4 times daily)

Figure 3. Decision Tree of Six GABHS Pharyngitis Diagnostic and Management for Children From Low and Middle Income Countries (LMICs)

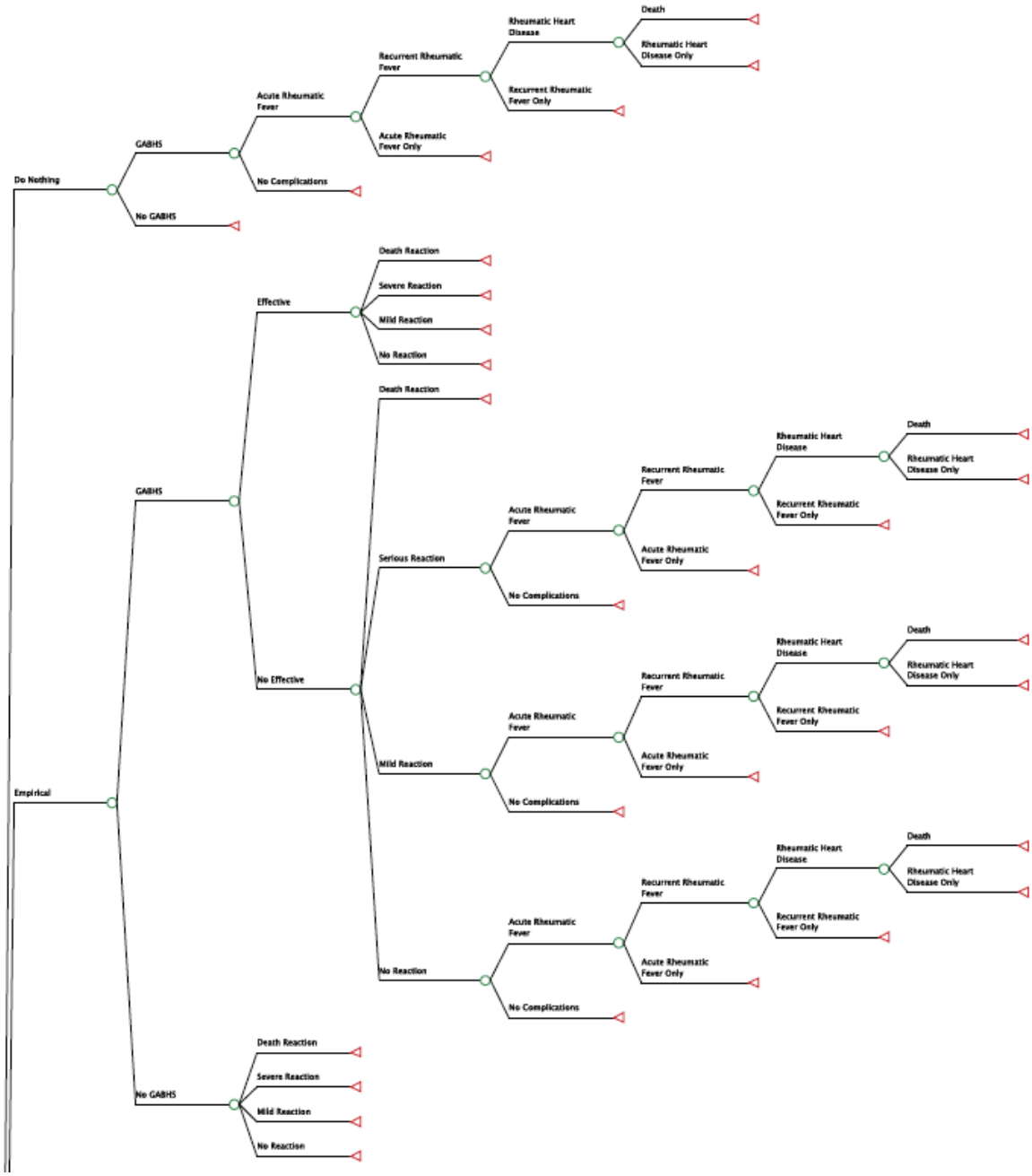


Figure 3 (continued)

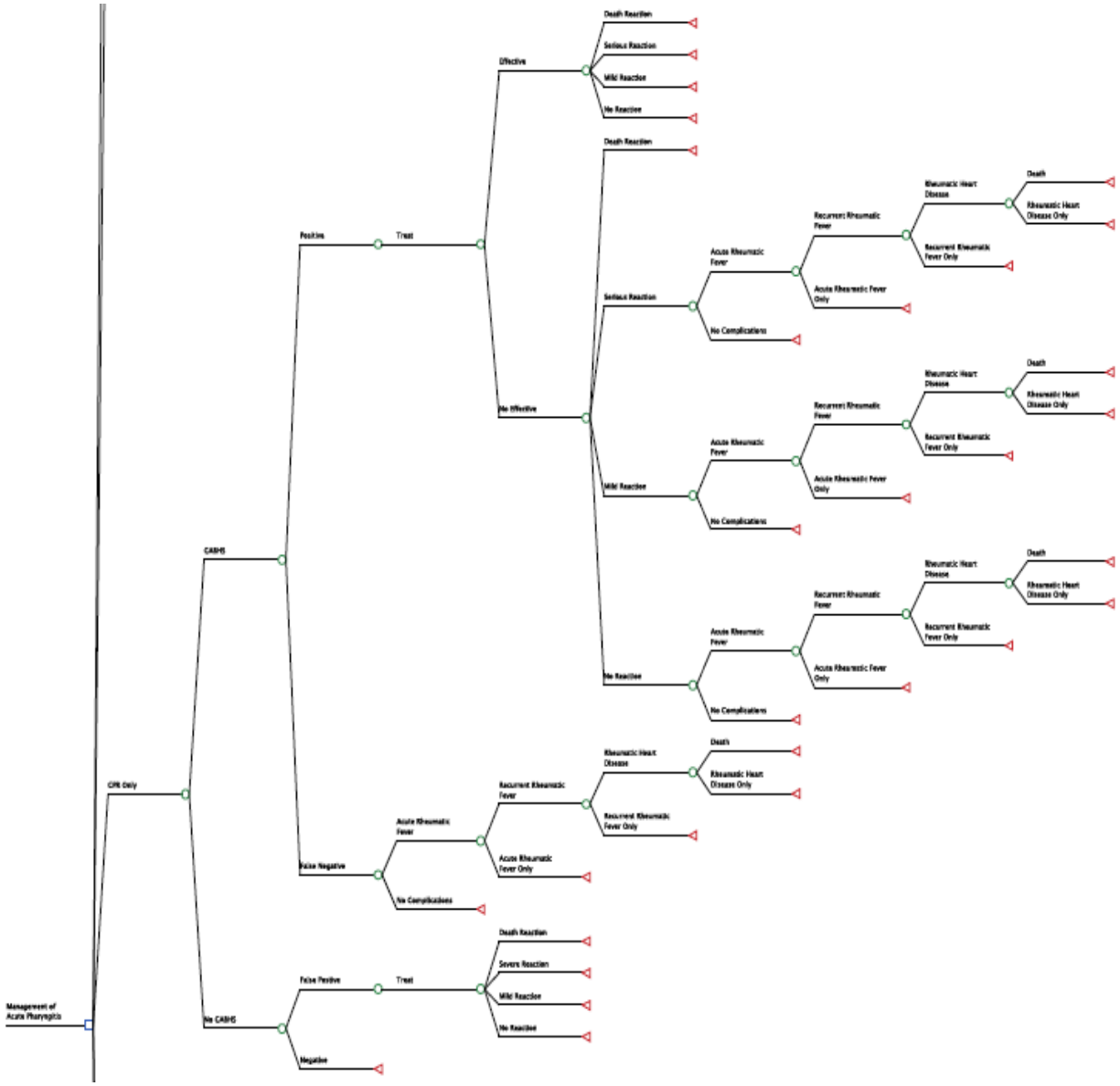


Figure 3 (continued)

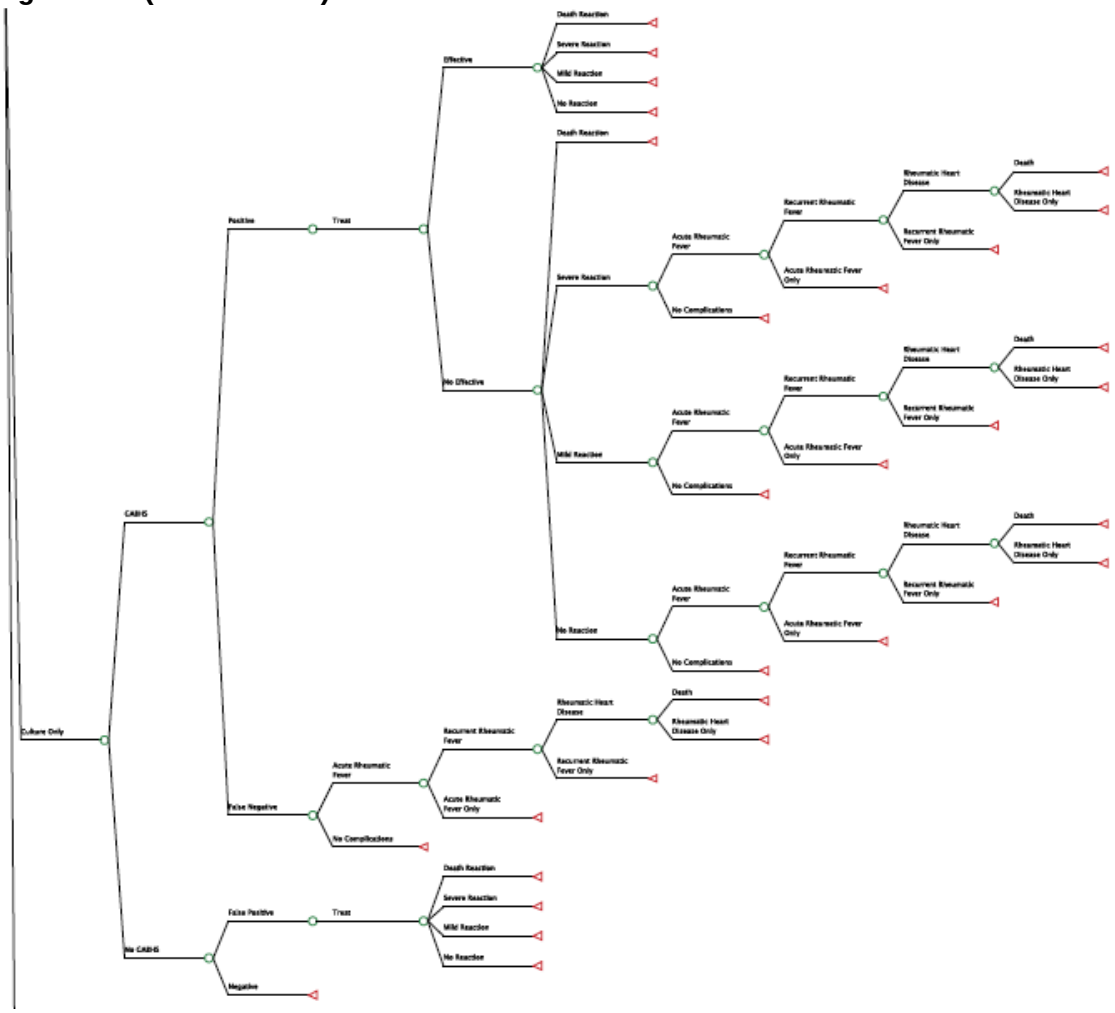


Figure 3 (continued)

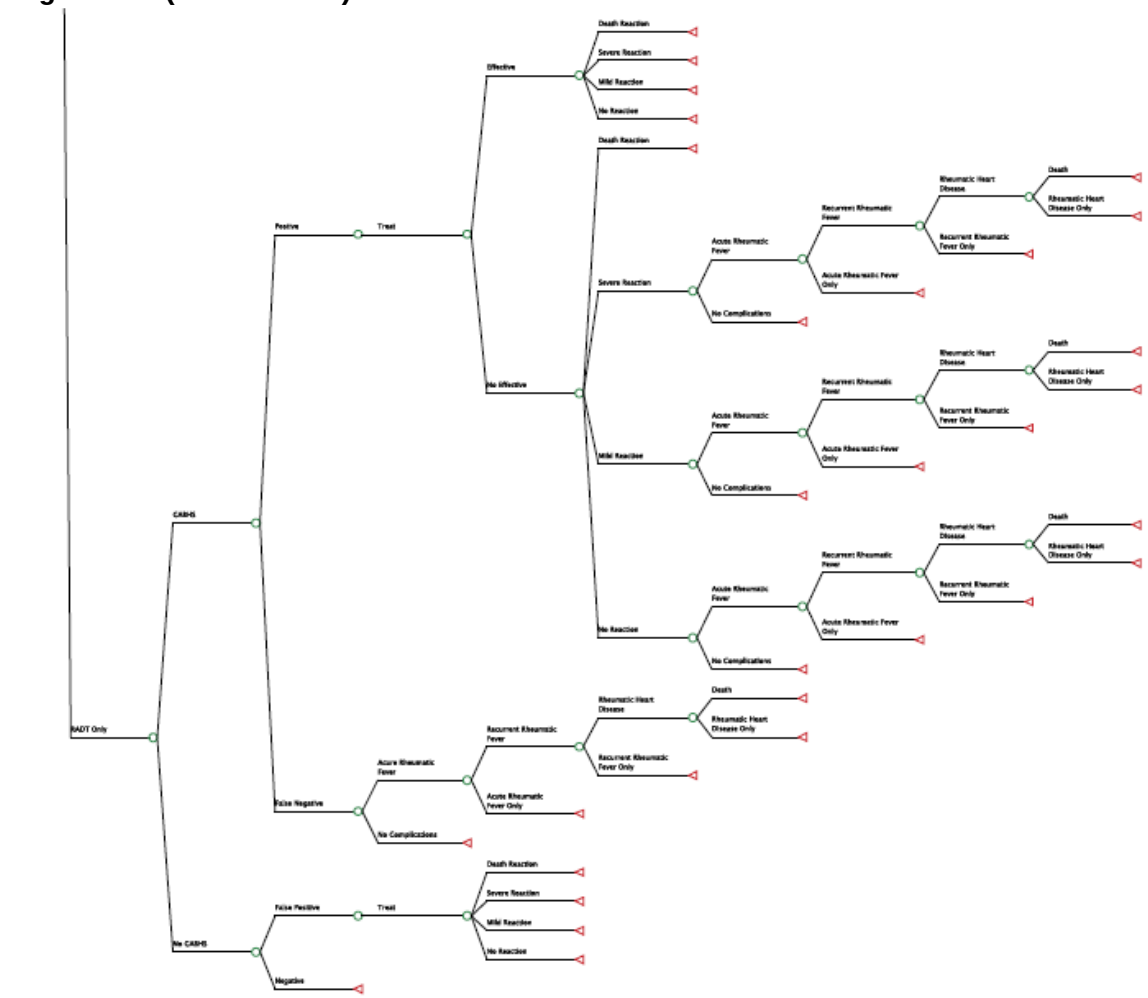


Figure 3 (continued)

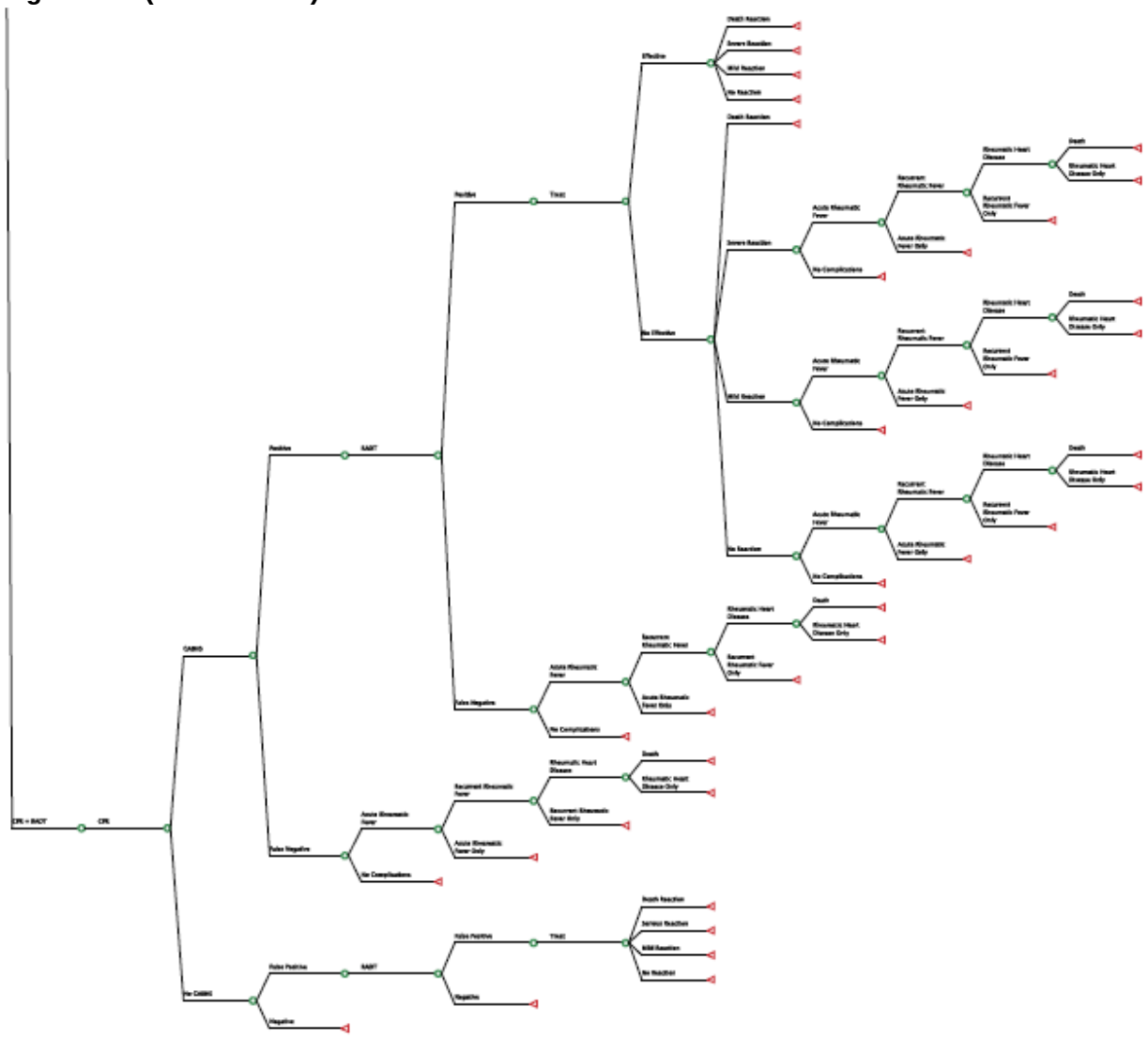


Table 7. Probability Variable Estimates Used in the Study Cost Effectiveness Analysis of GABHS Pharyngitis Diagnosis and Management

Variable	Source*	Probability		
		Baseline	Low Estimate	High Estimate
GABHS Prevalence	Tsevat et al Web et al Lieu et al Rimoin et al	0.2729	0.0	1.0
Clinical Prediction Rule[128] Sensitivity	Chapter 4	0.7313	0.6	1.0
Clinical Prediction Rule Specificity	Chapter 4	0.4336	0.2	1.0
OIA[129] Rapid Test Sensitivity	Thermo Biostar/Inverness Medical Rimoin et al	0.85	0.747	1.0
OIA Rapid Test Specificity	Biostar Rimoin et al	0.95	0.931	1.0
Culture Sensitivity	Web et al Rimoin et al	0.835	0.7965	1.0
Culture Specificity	Web et al Rimoin et al Van Howe et al	0.99	0.85	1.0
Mild Allergic Reaction	Neuner et al Van Howe et al Tsevat et al	0.02	0.00	0.10
Severe Allergic Reaction	Van Howe et al	0.0064	0.0025	0.0075
Death From Allergic Reaction	Van Howe et al	0.00001	0.000005	0.000015
Treatment Efficacy	Van Howe et al	0.80	0.70	0.90
Acute Rheumatic Fever	Nkomo WHO Michaud et al Ehrlich et al	0.004	0.003	0.03
Recurrent Rheumatic Fever	Neuner et al Tsevat et al Van Howe et al	0.20	0.05	0.75
Rheumatic Heart Disease	Ehrlich et al	0.045	0.035	0.70
Death From Rheumatic Fever/Rheumatic Heart Disease	WHO Tsevat et al Neuner et al	0.015	0.0	0.25

*Neuner (88), Ehrlich (70), Tsevat (95), Van Howe (96), Lieu (91), Webb (72), Rimoin (92), WHO (5, 6), Nkomo (40), Michaud et al (107), Thermo Biostar/Inverness Medical Professional Diagnostics

[128] Egypt CPR

[129] OIA = optical immunoassay test

Table 8. Cost Variables Estimates Used in the Study Cost Effectiveness Analysis of GABHS Pharyngitis Diagnosis and Management

Variable	Source*	Cost[130]		
		Baseline	Low Estimate	High Estimate
Visit	UCH	0.00	0.00	29.02
Follow-up[131]	UCH	0.00	0.00	10.00
Rapid Test[132]	UCH Biostar/Inverness	6.53	1.60	14.51
Culture	UCH	1.02	0.00	13.64
Penicillin (Oral Amoxicillin)[133]	UCH	1.65	0.00	5.25
Mild Allergic Reaction	Tsevat et al Van Howe et al Giraldez-Garcia et al	61.01	33.05	132.60
Severe Allergic Reaction	Neuner et al Giraldez-Garcia et al	1,170.50	1,000.34	4,814.72
Acute Rheumatic Fever	Neuner et al Giraldez-Garcia et al	2,558.77	1,279.40	5,117.59
Recurrent Rheumatic Fever	Neuner et al Giraldez-Garcia et al Van Howe et al[134]	10,000.00	3,000.00	25,000.00
Rheumatic Heart Disease	Van Howe et al	25,421.41	6,355.35	31,776.77
Death	Van Howe et al	12,710.71	10,168.57	15,252.85

*Neuner (88), Ehrlich (70), Tsevat (95), Van Howe (96), Lieu (91), Webb et al (72), Giraldez-Garcia (99), University of Cairo Hospital (UCH), Biostar/Inverness (122)

[130] All costs adjusted for inflation and converted to 2013 USD
[131] Follow-up includes: culture result notification, and antibiotic dispensed on a ticket which the patient picks up from the institute pharmacy
[132] Includes manufacture cost and hospital cost
[133] Penicillin treatment (oral Amoxicillin) for 10 day course treatment
[134] There is no specific estimate for recurrent RF in the literature. Therefore assumed costs for recurrent RF based on estimates for acute RF and RHD, which were available in from the literature.

Table 9. Utility Variables Estimates Used in the Study Cost Effectiveness Analysis of GABHS Pharyngitis Diagnosis and Management

Variable[135]	Source*	Utility, QALYs[136]		
		Baseline	Low Estimate	High Estimate
No GABHS Pharyngitis / No Allergic Reaction	Gold et al	1.0	0.935	1.0
Untreated GABHS Pharyngitis	Gold et al Neuner et al	0.87	0.855	0.99
Treated GABHS Pharyngitis After Rapid	Gold et al Neuner et al	0.98	0.90	1.0
Treated GABHS Pharyngitis After Culture	Gold et al Neuner et al	0.97	0.90	0.99
Mild Allergic Reaction	Gold et al Dodek et al	0.82	0.79	1.0
Severe Allergic Reaction	Gold et al	0.50	0.10	0.79
Acute Rheumatic Fever	Gold et al	0.72	0.52	0.92
Recurrent Rheumatic Fever	Gold et al	0.65	0.47	0.92
Rheumatic Heart Disease	Gold et al	0.53	0.29	0.79
Death	Gold et al	0.0	-	-

*Gold (125), Neuner (88), and Dodek (126)

[135] No GABHS/No allergic reaction has a range because some respondents had less than 1.0 even when not reporting a condition; Untreated GABHS pharyngitis (5 days); treated GABHS pharyngitis after rapid test (2 day reduction in sore throat) vs. culture (1 day reduction in sore throat); recurrent rheumatic fever (with valvular disease)/rheumatic heart disease; and death (from allergic reaction or RF/RHD)

[136] Quality-Adjusted Life Years (QALDs)

Table 10. Cost Effectiveness of GABHS Pharyngitis Diagnosis and Management Strategies: Costs, Effectiveness, and Cost Effectiveness of Base Case Analysis

Strategy	Average Cost[137] (USD)	Incremental Cost (USD)	Average Effectiveness (QALYs)	Incremental Effectiveness (QALY)	Cost Effectiveness Ratio (CER)	Incremental Cost Effectiveness (ICER)
Culture Only	$5.22	-$0.01	0.9814	0.0171	5.32	(Dominant)
Do Nothing	$5.23	-	0.9643	-	5.42	(Dominated)
CPR Only	$8.58	$3.35	0.9781	0.0138	8.77	(Dominated)
CPR + RADT	$8.62	$3.39	0.9783	0.0140	8.81	(Dominated)
RADT Only	$11.02	$5.79	0.9833	0.0190	11.21	3,024.92
Empirical	$11.54	$6.31	0.9820	0.0176	11.75	(Dominated)

[137] Key: USD = 2013 United States dollars
QALYs = Quality Adjusted Life Years
CPR = Clinical prediction rule
RADT = Rapid Antigen Detection Test
Dominated = strategy less effective and more costly

Figure 4. Cost and Effectiveness of Six GABHS Pharyngitis Strategies

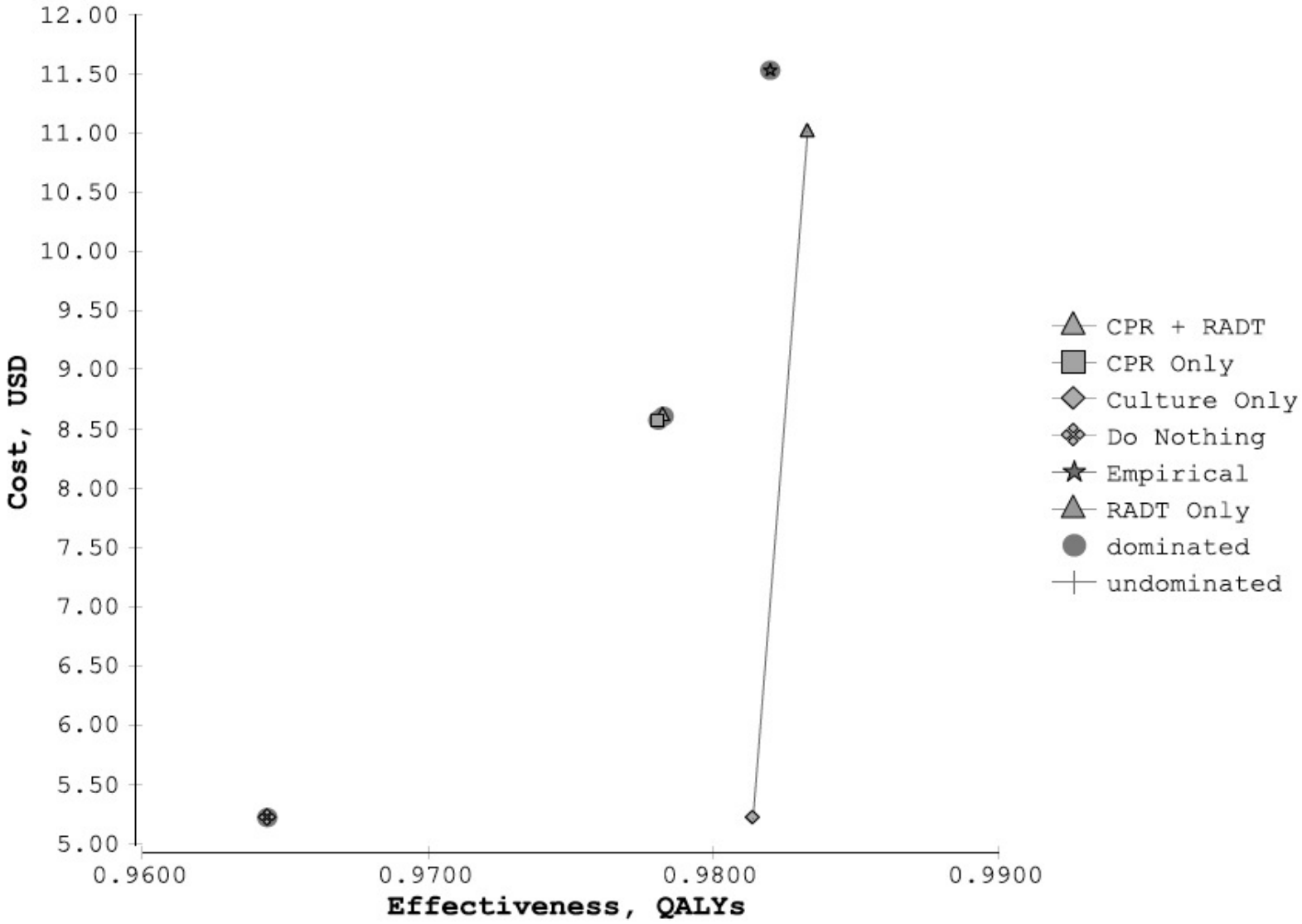


Figure 5. One Way Sensitivity Analysis of the Prevalence of Group A Beta Hemolytic Streptococcal (GABHS) Pharyngitis

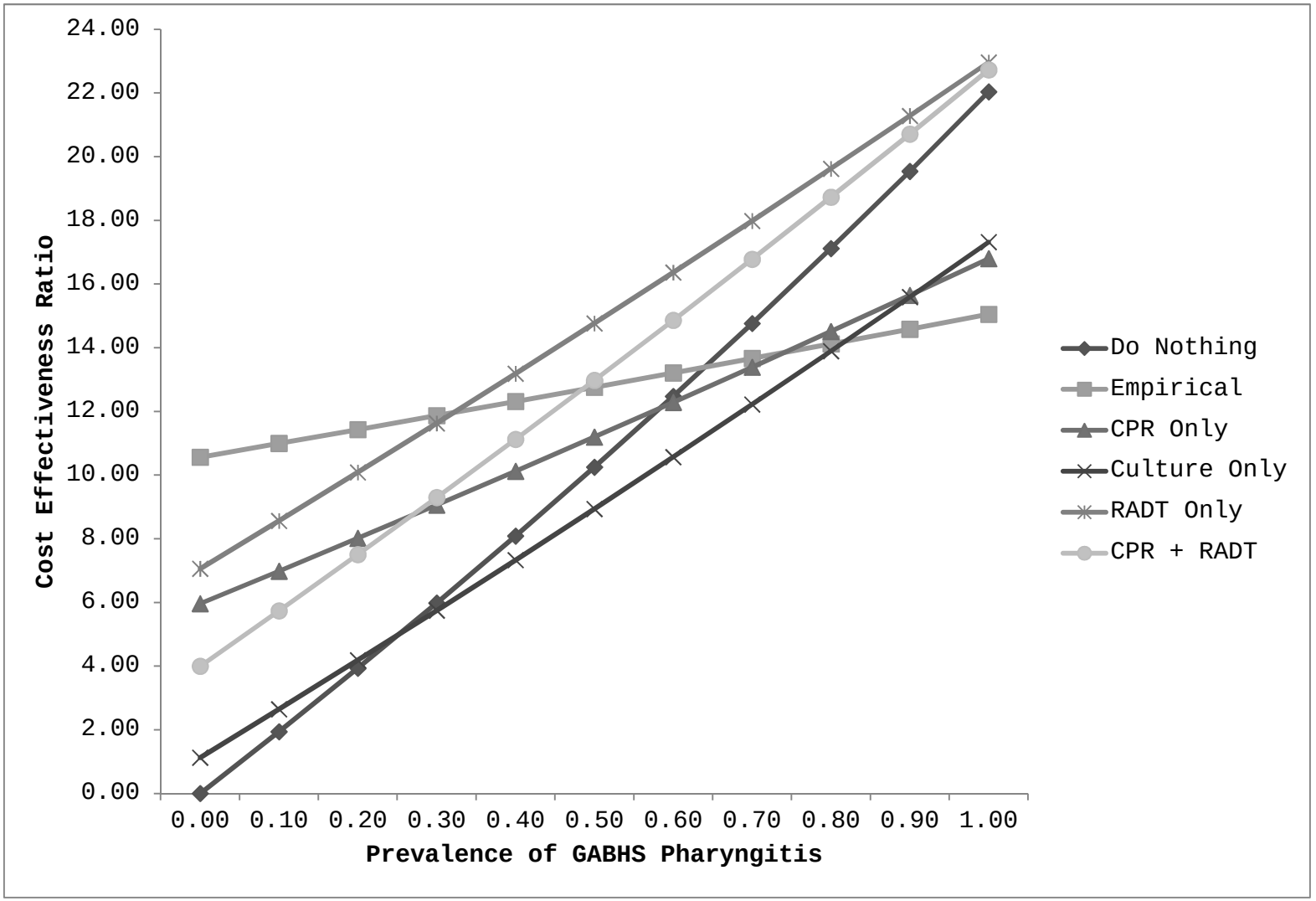


Figure 6. One Way Sensitivity Analysis of the Egypt Clinical Prediction Rule Sensitivity

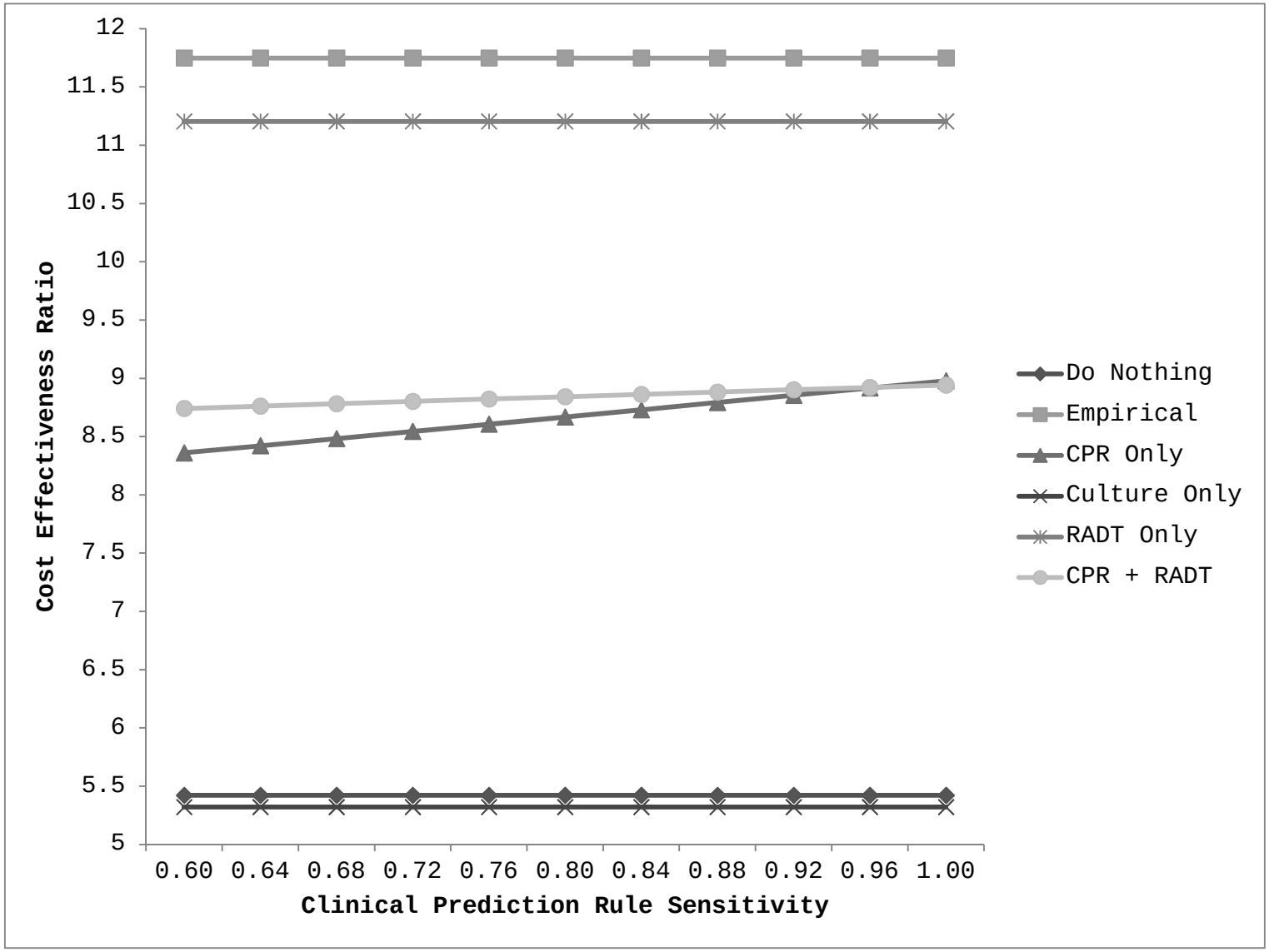


Figure 7. One Way Sensitivity Analysis of the Egypt Clinical Prediction Rule Specificity

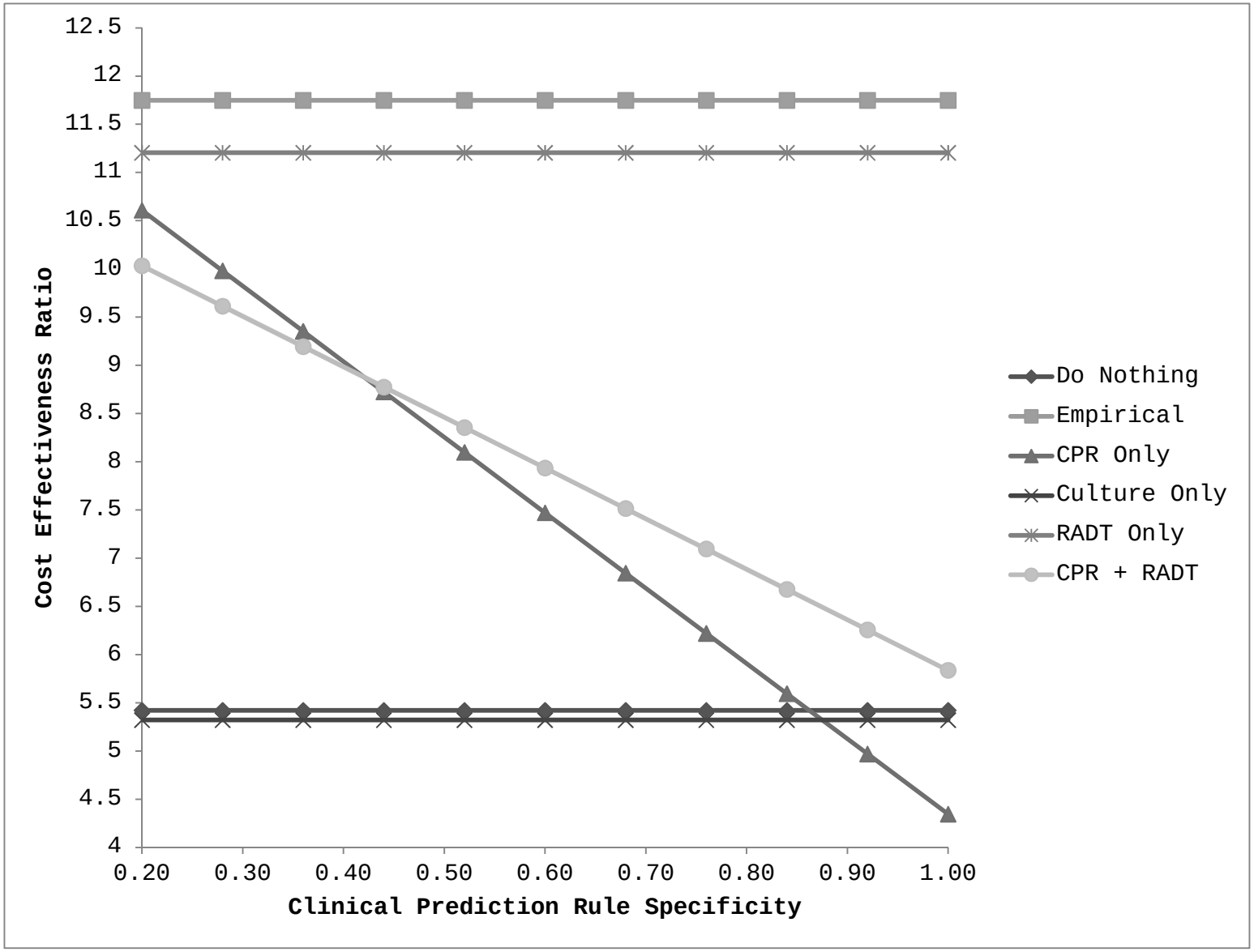
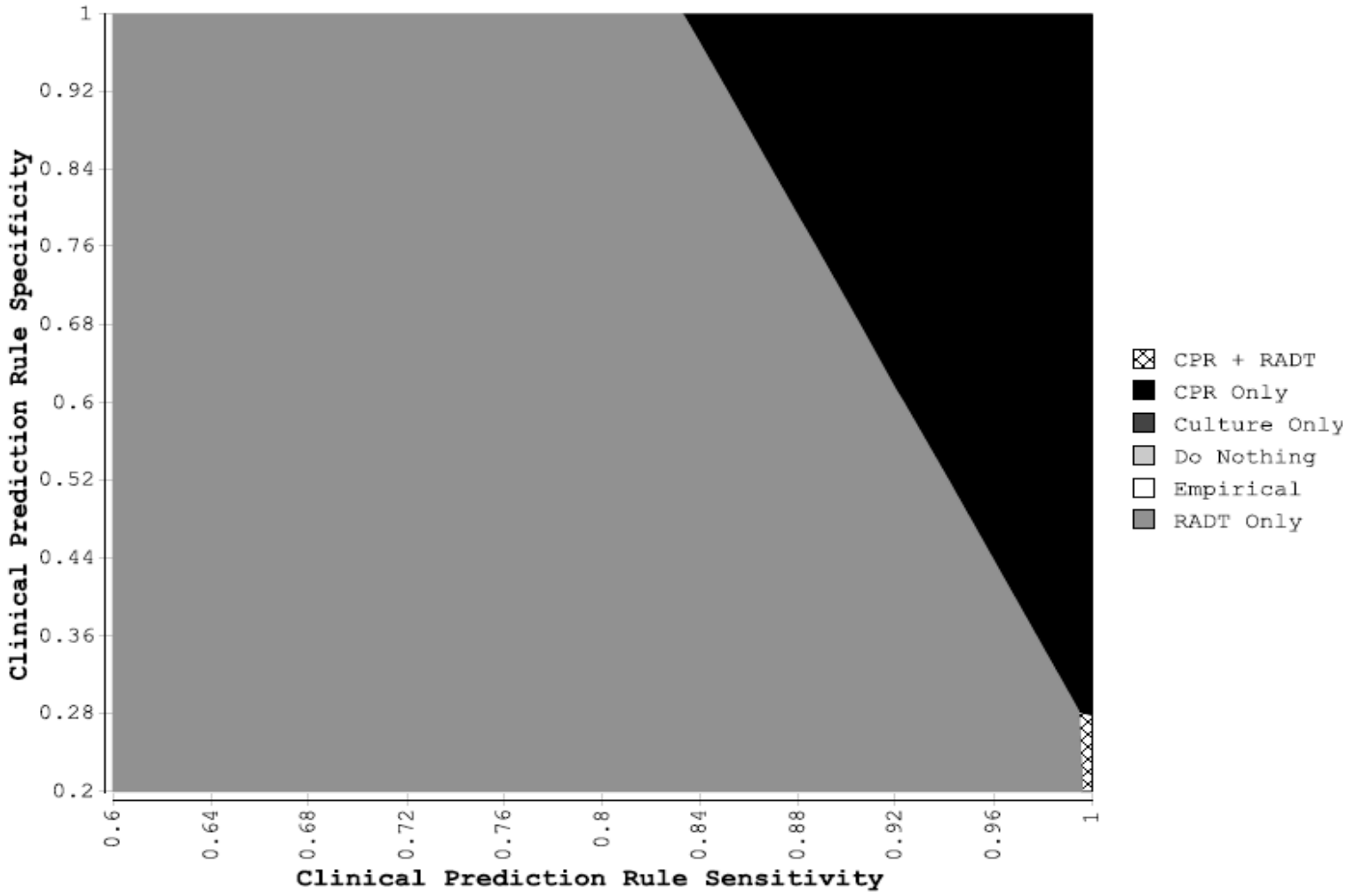


Figure 8. Two Way Sensitivity Analysis of Sensitivity and Specificity of the Egypt Clinical Prediction Rule[138]



[138] Net Benefit, Willingness to pay $50,000/QALY

CHAPTER 7. SUMMARY/CONCLUSION

Chapter 7. Summary/Conclusion

STUDY STRENGTHS AND LIMITATIONS

Study Strengths

Clinical Prediction Rule Development and Validation

The CPR development and validation component of the study had several strengths. First, the data was obtained from a cross section of lower and upper middle-income countries over a span of four years in four different countries. Second, although there were four different study sites, a single standardized protocol was developed and used at each site. In addition, all study personnel, including physicians and laboratory staff were trained. Lastly, the probability of identifying significant predictors was increased due to the amount of data collected on signs and symptoms.

This study is significant in that it addresses a major public health need in LMICs. RF and RHD are serious cardiac complications that are still prevalent in developing countries. This study allows clinicians in LMICs with limited laboratory capabilities to diagnose and treat children with GABHS pharyngitis effectively and efficiently. This study provides a cost effective primary prevention tool for physicians in a hospital setting. In addition, it adds to the literature on clinical diagnosis of GABHS pharyngitis in LMICs that can be used for further validation. It also all adds to the literature on external

validation of study and published CPRs for GABHS pharyngitis in LMIC children.

Cost Effectiveness Analysis

The cost effectiveness analysis component of the study had several strengths. First, this was a study of the cost effectiveness of pediatric GABHS pharyngitis clinical diagnosis and management in a lower middle-income country. There are a limited number of CEA studies on the diagnosis and management of GABHS pharyngitis among children, and currently none for children from LMICs (there are few cost analyses, but effectiveness was not evaluated). This study not only adds to the literature, but also addresses a practical need that can be implemented in Egypt and other LMICs with major public health problems and limited resources. In addition to being the first CEA for LMICs, it is the first CEA to use standard utility estimates (i.e., QALYs), which can be used in other CEAs. QALYs were selected as the utility measure because they are most commonly used in CEA studies (96). QALYs allow for comparisons with other studies similar or other health outcomes (125). Other measures of effectiveness such as number of health outcomes prevented are easier to interpret, but QALYs incorporate not just the quantity of life (mortality), but also the quality (disability). Additionally, standardization of CEA effectiveness measures is beneficial when a community with a limited budget is comparing multiple health outcomes. Using “off the self” utilities enabled the study to conduct the CEA without having to collect primary data on GABHS pharyngitis utilities in Egypt (125).

The only GABHS studies to use utility measures, used lost QALDs/QALYs, which is counter-intuitive and difficult to interpret (88, 96). Therefore, use of QALYs was one of the study strengths. Second, a sensitivity analysis was done to test the assumptions of the cost effectiveness analysis of the baseline estimates, which strengthens the findings.

Study Limitations

Clinical Prediction Rule Development and Validation

There wee several limitations to CPR development and validation component of the study. First, this is a cross sectional study using secondary data. However, many studies on clinical diagnosis are cross sectional studies. Also, budgetary constraints made secondary data analyses a necessary option.

Second, selection bias towards more severe clinical presentation is also a potential limitation due to hospital setting. This is a problem for many GABHS pharyngitis studies in similar settings. In addition, differences in presentation by to study site may also bias results. To address the issue of differences in clinical diagnosis (identifying and recording signs and symptoms), standardized training was given to study physicians along with standardized protocol for use at each site. Site visits were also done throughout study duration.

Third, this study used culture results for GABHS pharyngitis status. Although this is the gold standard, culture has several drawbacks. For

example, occasional false positives, likely due to carries, are possible as without serological data, definitive GABHS pharyngitis status is not possible. Therefore, misclassification of outcome is possible where carriers are classified as cases, which would affect the efficacy and effectiveness of generated CPRs. While this is a limitation faced by this study, it is one that is faced by many studies, as it is cost probative to do serological testing.

Fourth, culture results, although standardized, can yield differing results due to flawed culture or bacteriologic techniques, especially by different personnel, across different study sites. Studies have shown that various other factors can influence culture results such as undisclosed antibiotic use or carrier states (34, 38, 43, 65). These limitations are not limited to this study and are faced by many, as it is cost prohibitive to do serological testing. Efforts to mitigate these limitations include standardization of protocol, training, and periodic checks.

Lastly, for the validation component, recreating predictors for published CPR involved using covariates collected during the initial study. All newly created predictors were best approximations of variables used either because the original study did not collect the information, or because not all studies were explicitly clear on how they defined their variables. Differences in predictor definitions are a potential limitation of the study. While the initial study collected data on numerous covariates, several other predictors, such as

conjunctivitis, headache or sudden onset (<12 hours), and severity of signs/symptoms, could have been valuable, if collected. While this study was only able to assess covariates collected from the initial study, the study did collect information on several key predictors, which allowed for recreation of those not available. Furthermore, predictors not included in the original study would likely have detracted from the simplicity and ease of assessing signs/symptoms of patients during an outpatient clinic in resource poor settings.

Cost Effectiveness Analysis

First, the CEA was based on strategies selected for the decision tree. All possible diagnostic and management strategies were not explored; therefore, influencing results. For example, some studies included both culture and rapid testing as a strategy. However, for this study, strategies were limited to viable options for LMICs. Conducting both types of laboratory testing is not feasible and therefore finding would not be applicable. The study goal was to limit alternative strategies to ones that could feasibly implemented for practical application of study finding in Egypt and other LMICs.

Second, results of the cost effectiveness analysis of the baseline estimates were sensitive to the estimates used for probabilities, costs, and utilities. Extensive search of the literature on Egypt specific data was limited. Data on GABHS pharyngitis, RF, and RHD are limited and therefore, more of the data came from HICs. When data specific to Egypt or the University of Cairo (UCH) were available,

they were used. However, when best estimates were not available, assumptions were made based on HIC estimates from the literature. To attempt to address this limitation, a sensitivity analysis was conducted. Sensitivity analyses of estimates most likely to influence the outcome were assessed.

Third, the ability to differentiate clinically between acute GABHS infection and GABHS carriers is not possible without serological testing to observer change in antibody titer. However, this study used culture and RADT and therefore was unable to differentiate between the two GABHS infections. Therefore, the assumption that both GABHS infections have similar risk of RF/RHD complication is a study limitation due to inability to differentiate (see Chapter 2). Furthermore, it was assumed that only symptomatic patients with positive laboratory tests (i.e., for strategies with laboratory testing) were treated. Assuming nondifferential laboratory diagnosis of carriers, the strategy outcomes will not change relative to each other.

Fourth, this study focuses only on non-suppurative complications of GABHS pharyngitis, specifically RF and RHD. There suppurative complications of GABHS pharyngitis were not included in the CEA as the overall focus of the dissertation was on the prevention of RF and RHD.

Fifth, the CEA was conducted from a societal perspective and direct costs were used. Indirect costs such as loss of productivity were not

addressed. While studies have demonstrated the indirect cost of RF/RHD including lost school days or school drop out for patients and lost workdays or unemployment, this analysis did not address these and instead focused on direct costs. In addition, Culture Only strategy did not include time costs associated with 24-48 hour delay in culture results such as taking time off from work.

Lastly, the assumptions were based on endemic rates of GABHS pharyngitis, RF, and RHD. Results of this CEA do not apply for non-endemic situations.

PUBLIC HEALTH RELEVANCE

Rheumatic fever and rheumatic heart disease are preventable cardiac diseases prevalent in children from LMICs. This dissertation research was implemented to address this public health problem and prevent RF/RHD through diagnosis and treatment of GABHS pharyngitis. Based on study results, there was great variation in presentation of GABHS pharyngitis, which resulted in five different CPRs with differing predictors of GABHS pharyngitis. Clinical diagnosis of GABHS pharyngitis is difficult, but this study developed five rules for use in LMICs. When validated across different populations, the CPRs did best in the population they were developed for. This suggests that while LMICs can use other CPRs from the literature, including the ones developed for this study, they may want to consider generating a CPR for their population. The cost effectiveness of using the Egypt CPR

for diagnosis can be a feasible and effective strategy for LMICs when sensitivity and specificity of the CPR are above 80% and 88%, respectively. However, for Egypt and other LMICs with similar baseline estimates with laboratory capability, the most cost effective strategy is culture and therefore is recommended for the cost effective diagnosis and management of GABHS pharyngitis and for the prevention of RF/RHD and allergic reaction. Currently, there is a gap in the literature on clinical diagnosis of GABHS pharyngitis and its cost effectiveness. This dissertation attempts to address this issue by adding to the literature.

FUTURE DIRECTIONS

While this study developed five clinical prediction rules for four lower and upper middle income countries and the combined population, more studies should develop CPRs across a wider economic cross section of countries. The need for country specific rules was suggested by study results. If possible, studies should be conducted where outcome can be serologically tested to accurately differentiate between active and carrier GABHS pharyngitis. This would improve study developed CPRs. The study derived CPRs were validated in the five study populations, but further validation is needed in various LMICs and in different settings.

Rheumatic fever and rheumatic heart disease are still public health problems in LMICs, despite the rapid decline in cases from high-income countries after the 1950s. As such, GABHS pharyngitis and its

complications are often neglected, but continued research in diagnosis and management of GABHS pharyngitis, and prevention of RF/RHD are needed. In addition, global health monitoring and surveillance by local and international agencies (such as ministries of health, WHO, etc.) needs to include GABHS pharyngitis, especially among children 5 – 15 years of age, as they are often neglected, but most affected.

APPENDICES

APPENDIX 1. STUDY FORMS

Form 1. Screening Form

WHO / USAID / JHSPH GRASP/TOPS STUDY

Date: __ __/__ __/__ __ GRASP Patient ID#: ☐☐☐☐-☐☐☐
DD / MM / YY

TOPS Patient ID#: ☐☐☐☐-☐☐☐

PATIENT SCREENING FORM (VISIT 1)

Complete this form for children age more than 24 months and less than 12 completed years with cough or cold or sore throat, or pharyngeal erythema.

Identification

1. Child's Name: _____

2. Parent or Guardian's Name _____

3. Telephone Number _____

4. Address: _____

5. Distance of residence from clinic: _____ (kilometers)

5a. Time it takes to get to clinic __ __ Hours __ __ Minutes

6. Date of Birth: __ __ / __ __ / __ __
DD / MM / YY

6a. Age __ __

6b. If less than one year of age, use months: __ __

7. Sex: (Please circle one)

1. Male

2. Female

Study Eligibility

8. ***Children are eligible for the study if they meet the following criteria:***

Age: More than 24 completed months and less than 12 completed years

0. No
1. Yes

and

Physician observes or parent/child reports one or more of the following symptoms:

Cough	0. No	1. Yes
Cold	0. No	1. Yes
Sore Throat	0. No	1. Yes
Pharyngeal erythema	0. No	1. Yes

WHO / USAID / JHSPH GRASP/TOPS STUDY

Date: __ __/__ __/__ __ GRASP Patient ID#: □□□□-□□□
DD / MM / YY

TOPS Patient ID#: □□□□-□□□

Exclusion Criteria

Children are NOT eligible for the study if they meet any of the following criteria:

(Please circle yes or no for each criteria)

Documented antibiotic use in the last 3 days	0. No 1. Yes
Documented intramuscular penicillin G in the last 28 days	0. No 1. Yes
Presence of ear discharge or impetigo at the time of examination	0. No 1. Yes
History of previous rheumatic fever or rheumatic heart disease	0. No 1. Yes
History of allergy to amoxicillin or penicillin	0. No 1. Yes
Any other infection requiring antibiotics	0. No 1. Yes
Presence of other severe illness or major system disease that requires hospitalization	
EXCEPT: Malnutrition or Tuberculosis	0. No 1. Yes
Previous enrollment in the study	0. No 1. Yes
Physician diagnosis of wheezing, bronchitis, or pneumonia	0. No 1. Yes
Patient unable to return for follow up visit	0. No 1. Yes
Parent or guardian not available to give informed consent	0. No 1. Yes

Form 2. Patient Physical Exam Form

Date: __ __/__ __/__ __ GRASP Patient ID#: □□□□-□□□
DD / MM / YY

TOPS Patient ID#: □□□□-□□□-□

PATIENT PHYSICAL EXAM FORM (VISIT 1)

HISTORY OF SYMPTOMS PRESENT WITHIN THE LAST 5 DAYS			
Parent/guardian and child should be asked if child has exhibited any of the following symptoms in the past five days:	Please check the appropriate box:		If PRESENT, please indicate number of days symptom has been present
SYMPTOM	**PRESENT**	**ABSENT**	**DURATION (Number of days symptom has been present)**
Fever (Report by parent/guardian of fever or Temperature above 38.1 °C Rectal or 38.5 °C Oral)			
Chills (Sensation of cold)			
Runny Nose (History of nasal discharge)			
Nasal Congestion (Increased difficulty breathing)			
Sore Throat (Throat pain)			
Difficulty or Pain Swallowing			
Cough			
Vomiting			
Earache (Ear pain)			
Abdominal Pain			
Activity Level Below Normal (Change in activity compared to normal)			
Disturbed Sleep (Change in sleep patterns from normal)			
Hoarseness (Presence of harsh quality of voice that is different from normal)			
Other Remarks (Please list)			

History	**Yes**	**No**	**Number of Episodes**
Does this child have a history of streptococcal infection (confirmed by a health professional) in the last year?			
Has another person in the family had a sore throat in the past 5 days?			

Date: __ __/__ __/__ __ GRASP Patient ID#: □□□□-□□□
DD / MM / YY

TOPS Patient ID#: □□□□-□□□-□

VITAL SIGNS

Heart Rate: __ __ __ beats per minute

Temperature: __ __. __ C° (Please fill in temperature and circle method)

1. Axillary
2. Oral
3. Ear

Height: __ __ __ centimeters (Height in nearest centimeter of standing child)

Weight: __ __.__ kilograms (Weight of child to the nearest 0.1 kg)

SIGNS PRESENT			
Please examine child and indicate if sign is absent or present	Please check the appropriate box:		
SIGNS	**PRESENT**	**ABSENT**	**REMARKS**
Cough (Observation of coughing during consultation)			
Hoarseness (Presence of harsh quality of voice that is different from normal)			
Pharyngeal Erythema (Redness of the pharynx that is greater than that of the buccal mucosa, excluding tonsils)			
Tonsillar Erythema (Redness of the tonsils)			
Erythema Posterior (Redness of the posterior wall of throat)			
Faucial Erythema (Redness of the passage from mouth to pharynx)			
1**+ Tonsillar Enlargement** Degree to which tonsils extend into the midline. Defined as ≤ 25% of distance of midline			
2+ Tonsillar Enlargement Degree to which tonsils extend into the midline. Defined as tonsils are >25% and ≤ 50% of distance of midline.			

WHO / USAID / JHSPH GRASP/TOPS STUDY

Date: __ __/__ __/__ __ GRASP Patient ID#: □□□□-□□□
DD / MM / YY

TOPS Patient ID#: □□□□-□□□-□

3+ Tonsillar Enlargement Degree to which tonsils extend into the midline. Defined as tonsils >50% and ≤75% of distance of midline.			
4+ Tonsillar Enlargement Degree to which tonsils extend into the midline. Defined as tonsils are touching			
Tonsillar Exudate (White or yellow matter on tonsils)			
Cervical Lymph Node Tenderness (Tenderness of node on gentle palpation, confirmed by statement or facial expression)			
Nares Excoriations (Scratches or lesions around nostrils)			
Pharyngeal Exudate (White or yellow matter on the pharynx)			
Palatal Petechiae (Presence of lesions on the palate)			
Strawberry Tongue (Tongue with papillar swelling)			

Diameter of largest Cervical Lymph Node (any diameter >1): __ . __ (centimeters)

WHO / USAID / JHSPH GRASP/TOPS STUDY

Date: __ __/__ __/__ __ GRASP Patient ID#: □□□□-□□□
DD / MM / YY

TOPS Patient ID#: □□□□-□□□-□

OTHER CONDITIONS PRESENT			
Please examine child and indicate if conditions are present	Please check the appropriate box:		
OTHER CONDITIONS	**PRESENT**	**ABSENT**	**REMARKS**
Severe Malnutrition (Marasmus, Kwashiorkor, Protein Energy Malnutrition)			
Vitamin A Deficiency (physician observation of Bitot's spots or report of night blindness)			
Diarrhea (More than 3 abnormal stools in the past 24 hours)			
Tuberculosis (diagnosis by health care professional)			
Other (Please list)			

TREATMENT GIVEN

(Please check appropriate box and indicate dosage)

Drug	Daily Dosage (mg)	Duration (# Days)
Oral Penicillin		
Intramuscular Penicillin (Benzathine G)		
Oral Ampicillin		
Oral Erythromycin		
Oral Azithromycin		
Oral Amoxicillin		
Other (Please list)		

REMINDER:

1. ***PLEASE TAKE THROAT CULTURE AND BLOOD SPECIMEN***
2. ***PLEASE ASK PARENT/GUARDIAN TO MAKE APPOINTMENT AND BRING CHILD BACK IN 21 – 32 DAYS.***

IF PARTICIPATING IN TOPS THERAPEUTIC TRIAL:

1. ***TAKE NASOPHARYNGEAL CULTURE***
2. ***GIVE PARENT/GUARDIAN FILTER STRIP FOR URINE TEST***
3. ***RANDOMIZE PATIENT TO TREATMENT REGIMEN***

Form 3. Throat Culture Collection and Results Form

WHO / USAID / JHSPH GRASP/TOPS STUDY

Date: __ __/__ __/__ __ GRASP Patient ID#: □□□□-□□□
DD / MM / YY

TOPS Patient ID#: □□□□-□□□-□

THROAT CULTURE COLLECTION AND RESULTS FORM
(VISIT 1)

THROAT CULTURE SPECIMEN COLLECTION

1. Patient Name: _____

2. Time specimen collected: __ __:__ __ (24 Hour Time, for example 3pm = 15:00)

3. Time received by laboratory: __ __:__ __ (24 Hour Time)

LABORATORY THROAT CULTURE SPECIMEN RESULTS

1. Growth (Please circle one):
   - 1+ <10 colony-forming units (CFU)
   - 2+ ≥10 to <50 CFU
   - 3+ ≥50 CFU, streptococci not predominant
   - 4+ ≥50 CFU, streptococci predominant or pure culture

2. Bacitracin Disc Test (Please circle one):
   - 1) Positive
   - 2) Negative
   - 3) Indeterminate
   - 4) Not Done

3. Group A Beta Hemolytic Streptococci (Please circle one):
   - 0) No
   - 1) Yes

4. Name of Laboratory Technician: _____

5. Date: __ __/__ __ / __ __
   DD MM YY

Form 4. Parental/Guardian Consent Form

CLINICAL INVESTIGATION CONSENT FORM
GRASP STUDY

STUDY TITLE:	**DEVELOPMENT OF A CLINICAL PREDICTION INSTRUMENT FOR GROUP A STREPTOCOCCAL PHARYNGITIS (GRASP) IN CHILDREN**
PRINCIPLE INVESTIGATOR:	**<INSERT LOCAL PRINCIPAL INVESTIGATOR AND CONTACT INFORMATION>**

Because your child has a cough, a cold, or a red or sore throat, you and your child are invited to participate in a study on strep throat. This study is being run by <Insert name of Local Principle Investigator>. This form explains the study. Please read it carefully and ask questions about anything you do not understand.

PURPOSE OF STUDY

The purpose of the study is to find an easy way to diagnose strep throat. This type of sore throat can be the cause of heart disease if not treated.

The goal of this study is to make the treatment of sore throat by doctors better. A second goal is to reduce the use of antibiotics in patients who probably do not have strep throat.

DURATION

You will be in our study for 4 weeks

PROCEDURES

If you choose to be in this study,
You will be asked questions by a member of the study team.
A throat culture will be taken. (A throat swab will be rubbed on the back of the child’s throat.)
A blood sample will be taken
A urine sample may be taken.
You will be asked to return with your child in 3 weeks for another visit. This may include another throat culture and blood sample. The doctor may also examine your child again.

INCLUSION AND EXCLUSION CRITERIA

Your child can be in this study if:

He or she is between 24 months and 12 years of age.
He or she has had a cough, a cold, or a red or sore throat in the past five days.
Your child cannot be in the study:
If your child has used antibiotics in the last three days.
If your child has had a shot of penicillin in the last twenty-eight days.
If your child currently has ear discharge or impetigo.
If your child has had previous rheumatic fever or rheumatic heart disease.
If your child has another infection requiring antibiotics.
If your child has another severe illness requiring a hospital stay expect Malnutrition or Tuberculosis.
If your child has been diagnosed with wheezing, bronchitis, or pneumonia.
If your child has already been enrolled in this study.
If a parent or guardian is not available to sign this form.
If the patient not able to return for the follow up visit.

RISKS AND DISCOMFORTS

The risks and discomforts of being in this study are:
Collection of 2 blood samples.
Collection of 2 throat culture.
Two trips to the clinic.

BENEFITS

The benefits of being in this study are:
Both physical exams will be provided free of charge.
Medicine will be provided free of charge.
Your child will be tested for strep throat.
We will pay your travel costs to come to the follow up exam.

ALTERNATIVES TO PARTICIPATION

If you do not want your child to be in this study, he/she will receive the care from your doctor and this hospital.

The participation of your child in this study is entirely voluntary. If you agree to let your child be in the study, you can take him or her out at any time. Your decision not to be in the study or to stop being in the study will not affect how your child is treated or your relationship with your doctor.

CONFIDENTIALITY

The records from this research study will be kept confidential and will not be given to anyone who is not helping on this study. We will keep the study information private to the extent possible by law. However, under certain conditions, people responsible for making sure the research is done properly may review your records. This might include people from <Insert Local Institution>, John Hopkins, or the World Health Organization. All of these people are also required to keep your identity confidential. Otherwise, the information that identifies you will not be given out to people who are not working on the study, unless you give permission.

IF YOU ARE HURT BY PARTICIPATING IN THE STUDY

If you think you have been hurt by being in the study, or not treated fairly, you should contact <Insert Local Information Here> to receive help or advice, including help finding medical care if needed.

RIGHT TO REFUSE OR TERMINATE PARTICIPATION IN STUDY

The participation of your child in this study is entirely voluntary. If you agree to let your child be in the study, you can take him or her out at any time. Your decision not to be in the study or to stop being in the study will not affect how your child is treated. It will also not affect relationship with your doctor at <insert name of hospital>.

QUESTIONS OR CONCERNS

If you have any questions or concerns about participation, treatment, or any other issues related to the study, you should contact <Insert Local Principle Investigator>. You may ask him/her questions in the future if you do not understand something that is being done.

INSTITUTIONAL APPROVAL

This project has been approved by <Insert name of local IRB>, the World Health Organization, and the John Hopkins Medical Institutions, USA. If you have any questions about the institutional approval of the study you should contact <Local IRB information> or call the Johns Hopkins University Joint Committee on Clinical Investigation at (410) 955-3008.

If you sign this form, you are willing to join the research project described to you on the other side of this page. Your doctors, or the investigators, did explain the other kinds of treatment that are available to you and to others. The investigators (or doctors) will share with you any new findings that may develop while you are participating in this study.

If you agree to join this study, please sign your name below.

_____

Subject's signature Date
(including children, when applicable)

_____

Signature of Parent or Guardian (when applicable) Date

_____

Signature of Investigator or Approved Designee Date

_____

Witness to Consent Procedures* Date

* Optional unless subject is illiterate, or unable to sign.

NOTE: Signed copies of this consent form **must** be a) retained on file by the Principle Investigator; b) deposited in the patient's medical record; and c) given to the patient.

Form 5. Child Assent Form

GRASP STUDY CHILD ASSENT DOCUMENT

Project Title: Development of a Clinical Prediction Instrument For Group A Streptococcal Pharyngitis in Children

Investigators: Dr. Mark C. Steinhoff, Dr. Antonio Ledo Alves da Cunha; Dr. Adriana Vince; Dr. Hala Hamza; Dr. Shammim Qaiz; Anne W. Rimoin, MPH

We are doing a research study about sore throats. A research is a way to learn more about people. If you decide that you want to be a part of this study, you will be asked to:

Have a swab subbed on the inside of your throat, which might be uncomfortable for a few seconds.
Let us take a blood sample. We will use a needle and it will be uncomfortable for a brief time.
Come back for another visit in 3 weeks to have the throat swab, another blood sample, and be asked some questions.

When we are finished with the study we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that’s ok too.

If you decide you want to be in this study, please sign your name.

I, _____ ,want to be in this research study.
(Print your name here)

_____ _____
(Sign your name here) (Date)

APPENDIX 2. INSTITUTIONAL REVIEW BOARD APPROVAL

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APPROVAL NOTICE

DATE:	7/26/2013
TO:	MEHRET ASSEFA EPIDEMIOLOGY
FROM:	DANIEL CLEMENS, MD, PhD Chair, MIRB1
RE:	IRB#11-001886-CR-00002 2013 Review for IRB#11-001886 A Clinical Prediction Rule for Group A Beta Hemolytic Streptococcal Pharyngitis Among Children in Addis Ababa, Ethiopia Version: GABHS Project Proposal (3.21.2011)

The UCLA Institutional Review Board (UCLA IRB) has approved the submission listed below. The UCLA IRB's Federalwide Assurance (FWA) with Department of Health and Human Services is FWA00004642 (IRB00000172).

Submission and Review Information

Type of Submission	Continuing Review
Type of Review	Expedited Review
Approval Date for this Submission	7/25/2013
Expiration Date of the Study	6/16/2014
Funding Source(s)	1) Other: Hewlett Foundation/IIE Dissertation Fellowship 2) Other: UCLA Fieldwork Fellowship 3) Other: UCLA Graduate Research Mentorship

Specific Conditions for Approval

-- **Data Analysis Only** - the remaining research activities are limited to data analysis.

Regulatory Determinations

-- The UCLA IRB determined that the research meets the requirements for expedited review per 45 CFR 46.110 categories 3 and 4.

Important Note: Approval by the Institutional Review Board does not, in and of itself, constitute approval for the implementation of this research. Other UCLA clearances and approvals or other external agency or collaborating institutional approvals may be required before study activities are initiated. Research undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the entity.

General Conditions of Approval
As indicated in the PI Assurances as part of the IRB requirements for approval, the PI has ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the IRB.

The PI and study team will comply with all UCLA policies and procedures, as well as with all applicable Federal, State, and local laws regarding the protection of human subjects in research, including, but not limited to, the following:

- Ensuring that the personnel performing the project are qualified, appropriately trained, and will adhere to the provisions of the approved protocol,
- Implementing no changes in the approved protocol or consent process or documents without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of human subjects and then notifying the IRB as soon as possible afterwards),
- Obtaining the legally effective informed consent from human subjects of their legally responsible representative, and using only the currently approved consent process and stamped consent documents, as appropriate, with human subjects,
- Reporting serious or unexpected adverse events as well as protocol violations or other incidents related to the protocol to the IRB according to the OHRPP reporting requirements.

- Assuring that adequate resources to protect research participants (i.e., personnel, funding, time, equipment and space) are in place before implementing the research project, and that the research will stop if adequate resources become unavailable.
- Arranging for a co-investigator to assume direct responsibility of the study if the PI will be unavailable to direct this research personally, for example, when on sabbatical leave or vacation or other absences. Either this person is named as co-investigator in this application, or advising IRB via webIRB in advance of such arrangements.

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