Existing cost-effectiveness analyses for diseases caused by Group A Streptococcus: A systematic review to guide future research [version 1; peer review: awaiting peer review]

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Abstract

**Background:** Group A Streptococcus (Strep A) causes a broad spectrum of disease manifestations, ranging from benign symptoms including throat or skin infections, to fatal illness such as rheumatic heart disease, or chronic renal failure. Currently, there is no vaccine available against Strep A infections. Despite the high burden of Strep A-associated infections worldwide, little attention has been paid to the research of these diseases, including standardized surveillance programs, resulting in a lack of economic evaluations for prevention efforts. This study aims at identifying existing cost-effectiveness analyses (CEA) on any Strep A infections.

**Methods:** A systematic literature review was conducted by searching the PubMed electronic database.

**Results:** Of a total of 321, 44 articles met the criteria for inclusion. Overall, CEA studies on Strep A remain limited in number. In particular, a number of available CEA studies on Strep A are disproportionately lower in low-income countries than in high-income countries. Decision-analytic models were the most popular choice for CEA on Strep A. A majority of the models considered pharyngitis and acute rheumatic fever, but it was rare to observe a model which covered a wide range of disease manifestations.

**Conclusions:** Future research is needed to address missing clinical outcomes, imbalance on study locations by income group, and the transmission dynamic of selected diseases.

**Keywords**
cost-effectiveness analysis, Group A Streptococcus, S. Pyogenes, economic evaluation, decision analytic models, Strep A
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Introduction

Group A Streptococcus (Strep A), also known as Streptococcus pyogenes (S. pyogenes) is a Gram-positive bacterium, often identified in the throat or on the skin. Strep A is a major public health concern causing significant morbidity and mortality worldwide. While the World Health Organization (WHO) prioritized Group A Strep vaccine development in 2014, there are no vaccines available. Strep A infections include a broad spectrum of diseases. Relatively minor infections can be a precursor for acute and invasive diseases, both of which can lead to long-term morbidity. Acute conditions include throat and skin diseases, as well as toxin-mediated diseases. If relatively benign infections (i.e. Strep throat or skin infections) are not properly treated, the infection may further develop into post infectious autoimmune diseases (i.e. acute rheumatic fever (ARF), glomerulonephritis), which can lead to chronic diseases such as rheumatic heart disease (RHD) and chronic renal failure.

The absolute numbers of episodes of Strep A throat infections and skin infections are much higher than those associated with more severe illness. This raises the possibility that although the symptoms of pharyngitis or skin infections may not be as severe as the ones of ARF or RHD, their economic and social burdens at the population level could be noticeably high considering direct treatment costs and indirect costs.

While vaccines against Strep A are absent, the use of antibiotics such as oral or intramuscular penicillin has proved effective and been recommended to treat patients with Strep A infections. In addition, several prevention strategies were developed. Primary prevention of ARF involves the detection and timely treatment of streptococcal pharyngitis. In order to identify patients with Strep A infections, the following test options are often considered: clinical diagnosis (with or without the use of clinical scoring algorithms), throat or skin cultures, and point of care testing (e.g., rapid Strep A antigen detection test and nucleic acid amplification tests). Once confirmed positive, antibiotics are prescribed to treat patients. However, this process may result in prescription and consumption of unnecessary antibiotics for those tests who are false positives or in missing true cases (false negative). While this primary prevention strategy is effective, this approach is also costly considering only 10–20% of pharyngitis is caused by Strep A. A study estimating the rates of inappropriate outpatient antibiotic use in the United States reported that 56.2% and 72.4% of ambulatory care visits for pharyngitis were associated with antibiotic prescribing in children (0–19 years) and adults (20–64 years), respectively. However, streptococcal prevalence for pharyngitis was 37% for children and 18% for adults, indicating the existence of inappropriate use of antibiotics in pharyngitis treatment.

The secondary prevention strategy is to use intramuscular antibiotics as a prophylaxis to prevent recurrent ARF, but it was shown that increasing patients’ compliance to the recommended schedule of injections occurring every 28 days over a minimum of 10 years is challenging. The tertiary prevention scenario involves increasing the coverage of valve surgery by building local surgical capacity especially in resource-limited settings. While the tertiary approach will enhance local health capacity to treat patients with severe illness, this process will require a long-term plan and consensus among decision makers who need to consider various competing health problems in a nation.

Few health economic studies have been conducted on the entire spectrum of Strep A diseases. This may be due in part to the significant reduction in the rates of autoimmune diseases (i.e., acute rheumatic fever) and its sequelae (i.e., RHD) in high-income countries (HIC) during the late 20th century. The reduction was mainly attributable to improvements in socioeconomic conditions and to the increase in the use of antibiotics. However, the diseases are still highly prevalent in lower- and middle-income countries, and the burden of Strep A throat or skin infections is not negligible in HIC either. It is also worth noting that Strep A causes a wide range of disease manifestations, and there is a lack of available data points for each disease category, making it difficult to establish a universal model that covers all symptoms which progress over time.

The primary interest of the current review lies in identifying existing health economic models (i.e., those used in cost-effectiveness analyses) for Strep A-associated diseases. This review aims to summarize the types of model structures and evaluation perspectives which have been frequently emphasized by others, as well as to identify the gap in existing literature.

Methods

A systematic literature review was conducted by searching the PubMed electronic database. Search terms were divided into two groups and developed separately: (1) disease category and (2) economic evaluation terminology category. Considering that Strep A causes a broad spectrum of diseases from seemingly benign throat and skin infections to chronic RHD or CHF, search strategies in the disease category closely followed the terms previously defined in texts on the burden of group A streptococcal diseases. For the current search, “group A streptococcus” was additionally included as a separate search term to expand the search to papers which did not mention the specific names of Strep A-related diseases. In addition to the disease category, all search terms related to health-economic evaluation were developed in the economic evaluation category. Table 1 summarizes the search terms used for the current review.

All lines of the search terms in each of the two categories were combined using “OR”, and the two categories were eventually joined by “AND” in order to identify papers associated with health-economic models for Strep A-related diseases. The search terms were not limited to a title or an abstract. Any papers published up to May 2020 were included, and papers written in non-English languages were excluded. Additional search was done by going through bibliographies for eligible articles. The initial screening was carried out by going through all abstracts and shortlisting the papers that indicated the use of a CEA in the economic analyses. For the shortlisted papers, a more comprehensive (full-length) assessment was carried...
out by reviewing the full text against a list of inclusion and exclusion criteria. The search was performed independently by JSL and cross-checked by JSL and SK. Any discrepancies were discussed and resolved between the two independent reviewers.

Given that the studies were conducted under varying conditions (i.e. different country-contexts, study designs, disease types), a standardized set of criteria would be useful to make systematic assessments among the articles identified at the final stage of the literature review. First, disease category was defined. Sanyahumbi et al. (2016) previously categorized Strep A-related diseases into four groups: superficial and locally invasive disease, immune-mediated disease, disease sequelae, and invasive- and toxin-mediated disease. The same categorization was applied for the current study. Second, given that Strep A causes a wide range of disease presentations, age groups chosen for an intervention may also differ depending on disease types and the peak incidence of a disease. Thus, target cohorts were also identified. Third, given that model structure is one of the key factors that determine the final outcome of an intervention (i.e. cost-effectiveness strategy), the types of health economic models were compared. Fourth, cost perspective was identified. For the current review, any costs related to healthcare costs such as drug, hospitalization, treatment, etc. were termed “health system perspective”. On the other hand, any studies which considered broader cost items such as healthcare costs, productivity losses, caregiving, etc. were defined as “societal perspective”. Fifth, a CEA model often compares total costs with intervention benefits which can be measured in various ways. For example, while some studies use the Quality-Adjusted Life Year (or Day) (QALY(D)) as an outcome measure, others adopt the Disability-Adjusted Life Year (DALY). In addition, there are studies which directly utilize the number of episodes prevented by converting into saved costs. Hence, outcome measure was described for each study. Lastly, while some studies calculated cost-effectiveness based on primary data sources obtained from a trial, many studies estimated cost-effectiveness outcomes by constructing a decision analytic model. Given that such a model often utilizes multiple health states, more details on health states were further investigated for these studies.

Results

The initial search using the key words identified 321 articles from the database, as shown in Figure 1. After going through the abstracts and titles, 274 articles were omitted, resulting in 47 articles for a more comprehensive review. The full-length assessment was carried out for these articles. Of the 47 articles, nine studies were further excluded, and six articles were additionally identified through the bibliography search of the eligible articles. A total of 44 articles were selected at the final stage of the current literature review search. These final papers were assessed based upon the six criteria described above.

Table 2 summarizes the final 44 articles identified by the systematic literature review. The majority of studies (93%) were done in countries classified as high-income or upper-middle-income by the World Bank. There were only three studies that were carried out in lower-middle-income economies or below: two studies from Africa and one study from India. While most studies conducted a cost-effectiveness analysis for a single country or sub-population of a country, Watkins et al. and Manji et al. covered multiple African countries by taking into account evidence reported in existing
Literature. About 25% of the studies (n = 11) solely considered superficial diseases such as throat or skin infections. Among those 11 studies, six of them were not Strep A-specific but more general, resulting in only five studies with a specific focus on Strep A. Another 34% of the studies (n = 15) included immune-mediated- (i.e. acute rheumatic fever) or locally invasive diseases (i.e. peritonsillar abscess) in addition to superficial diseases. As described above, Strep A causes a broad spectrum of diseases from benign superficial infections to severe cardiac failures. Five studies investigated disease sequelae (i.e. RHD) along with superficial- and immune-mediated-diseases, and two studies further included locally invasive diseases on top of these. There was only one study that covered at least a subset of each of the four disease categories: superficial and locally invasive, immune-mediated, sequelae, and invasive- and toxin-mediated diseases.

Forty-one percent and 43% of the studies applied a health system perspective and a societal perspective, respectively. Of the 44 articles, five studies adopted both perspectives. For example, the health system perspective was chosen for a primary analysis, but the societal perspective was also considered as a sensitivity or scenario analysis. A total of 18 studies used health-related quality of life such as QALY(D) or DALY as an outcome measure, and others directly utilized the number of episodes prevented or the number of patients free of recurrence which were in most cases converted into saved costs. While some studies conducted cost-effectiveness analyses alongside (randomized) clinical trials (n = 7) or simple comparisons between costs and benefits (n = 8), the majority of the studies (66%) used decision analytic models. Among the studies with decision analytic models, 72% of them (n = 21) adopted decision tree models, and eight studies employed Markov models.

Since decision analytic models take into account multiple health states and transition probabilities from one health state to another, more details on health states were further investigated as shown in Table 3. The most common health states chosen for the models were Strep A pharyngitis and ARF.
| No. | Article | Year | Region | Country | Disease category | Target cohort | Model type | Cost perspective | Outcome measure | Source |
|-----|---------|------|--------|---------|-----------------|--------------|------------|----------------|----------------|--------|
| 1   | Ubels et al. | 2020 | Latin America | Brazil | Sequelae | Adults aged 11 years (socioeconomically disadvantaged children) | Markov cohort | Health system perspective | DALY | 17 |
| 2   | Oetzel et al. | 2019 | Asia & Pacific | New Zealand | Immune-mediated; Sequelae | 14-21 years; Waikato RF registry receiving secondary prophylaxis, Maori and Pacific Island populations | Decision tree (cohort) | Health system perspective | QALD | 3 |
| 3   | Behnamfar et al. | 2019 | Middle East | Iran | Superficial; Local invasive; Immune-mediated | Children, adults | Decision tree (cohort) | Health system perspective | QALD | 3 |
| 4   | Cannon et al. | 2018 | Asia & Pacific | Australia | Superficial; Local invasive; Immune-mediated; Sequelae; Invasive | Three vaccination scenarios: (1) Infants, (2) 5 years old, (3) 65 years (non-indigenous), (4) 65 years (indigenous) | Markov cohort | Societal perspective | DALY | 4 |
| 5   | Burns et al. | 2018 | Europe | UK | Superficial | Adults between 18 and 70 years with acute sore throat and painful swallowing | RCT | Health system perspective excluding out-of-pocket expense, societal perspective analysis | QALY | 14 |
| 6   | CADTH Common drug review | 2018 | North America | Canada | Superficial | Patients with impetigo aged two months and older | Decision tree (cohort) | Health system perspective | QALY | 20 |
| 7   | Roberts et al. | 2017 | Asia & Pacific | Australia | Immune-mediated; Sequelae | Indigenous populations in the Northern Territory of Australia, (1) 8 and 12 years (Echo A), (2) 5 to 12 years (Echo B) | Markov patient-level | Health system perspective | QALY | 21 |
| 8   | Watkins et al. | 2016 | Africa | Pinnel del Bio | Immune-mediated; Sequelae | 5-24 years; hypothetical African cohort for the application of the model | Decision tree (cohort) | Health system perspective | QALY | 22 |
| 9   | Watkins et al. | 2015 | South America | Cuba | Immune-mediated; Sequelae | 5-24 years | Decision tree (cohort) | Health system perspective | QALY | 23 |
| 10  | Zachariah et al. | 2014 | Asia & Pacific | Australia | Superficial | Indigenous children aged 5 years | Markov cohort | Societal perspective | DALY | 24 |
| 11  | Little et al. | 2014 | Europe | UK | Superficial | Adults, children aged 5 years | RCT | Health system perspective | QALY | 25 |
| No | Article | Year | Region | Country | Disease category | Target cohort | Model type | Cost perspective | Outcome measure | Source |
|----|---------|------|--------|---------|------------------|---------------|------------|-----------------|----------------|--------|
| 12 | Irlam et al. | 2013 | Africa | South Africa | Superficial; Local invasive; Immune-mediated; Sequelae | 3–15 years (presenting with an acute sore throat (pharyngitis) and no history of ARF; Urban primary care clinics) | Markov cohort | Societal perspective (base analysis); Health system perspective (sub-analysis) | QALY | 25 |
| 13 | Klepser et al. | 2012 | North America | USA | Superficial; Local invasive; Immune-mediated | Adults | Decision tree (cohort) | Health system perspective | QALD | 26 |
| 14 | Manji et al. | 2013 | Africa | Sub-Saharan Africa | Superficial; Local invasive; Immune-mediated; Sequelae | 5 years | Decision tree (cohort) | Health system perspective | QALD | 27 |
| 15 | Wilson et al. | 2011 | Europe | UK | Superficial | 4–15 years; five secondary care otolaryngology Departments in the northern UK | RCT | Health system perspective | QAL | 28 |
| 16 | Gilzadeh-Sarrafzadeh et al. | 2007 | Asia & Pacific | India | Superficial; Local invasive; Immune-mediated; Sequelae | 5–15 years; Pondicherry Union Territory | Decision tree (cohort) | Health system perspective | QALD | 29 |
| 17 | Saudarsanam et al. | 2006 | North America | USA | Superficial; Local invasive; Immune-mediated | Children & adolescents | Decision tree (cohort) | Societal perspective (also, Health system perspective) | QALD | 30 |
| 18 | Howe et al. | 2006 | Europe | Spain | Superficial; Local invasive; Immune-mediated; Sequelae | Cost-effectiveness analysis | Break-even analysis | Societal perspective | QALD | 31 |
| 19 | Fujihara et al. | 2002 | Asia & Pacific | Japan | Superficial | 2–15 years (109 children); 15–66 (123 adults), Wakayama | Break-even analysis | Societal perspective | QALD | 32 |
| 20 | Neuner et al. | 2003 | North America | USA | Superficial; Local invasive; Immune-mediated | Adults | Decision tree (cohort) | Societal perspective | QALD | 33 |
| 21 | King et al. | 2002 | North America | USA | Superficial; Local invasive; Immune-mediated; Sequelae | Hypothetical 2,000 birth cohort | Decision tree (cohort) | Health system perspective | QALD | 34 |
| 22 | Ehrlich et al. | 1999 | North America | USA | Superficial; Local invasive; Immune-mediated | Children older than 3 years with signs or symptoms of pharyngitis | Decision tree (cohort) | Societal perspective | QALD | 35 |
| 23 | Tsevat et al. | 1999 | North America | USA | Superficial; Local invasive; Immune-mediated | Decision tree (cohort) | Health system perspective (baseline); societal perspective in the sensitivity analysis | QALD | 36 |
| No | Article | Year | Region | Country | Disease category | Target cohort | Cost perspective | Model type | Outcome measure |
|---|---------|------|--------|---------|-----------------|---------------|----------------|------------|----------------|
| 24 | Giraldes | 1999 | Europe | Portugal | Superficial | Overall | Cost-utility analysis (cost of a healthy day) (Cost / Utility changes between treatment and non-treatment) | Decision tree (cohort) | Own measure |
| 25 | Webb | 1998 | North America | USA | Superficial | Children with symptoms of pharyngitis (n = 1000 children with pharyngitis) | Health system perspective (baseline) | RCT (cost-minimization approach) | Societal perspective | Own measure |
| 26 | Carbon et al. | 1996 | Europe | France | Superficial | 18-65 years with symptoms of pharyngitis (n = 259-362) | Decision tree (cohort) | RCT | Societal perspective |
| 27 | Pelc et al. | 1996 | Europe | France | Superficial | 515 adults (older than 15 years) | Decision tree (cohort) | RCT | Societal perspective |
| 28 | Majed et al. | 1993 | Middle East | Kuwait | Superficial | 1-14 years with symptoms of pharyngitis (n = 1016) | Decision tree (cohort) | RCT | Societal perspective |
| 29 | Rice et al. | 1992 | North America | USA | Superficial | 5-14 years with symptoms of pharyngitis (n = 83) | RCT | Patient perspective (no financial costs of treatment-related components) | Decision tree (cohort) | QALD |
| 30 | Dippel et al. | 1992 | Not mentioned | Not mentioned | Superficial | 14 years hypothetical patients with sore throat | Decision tree (cohort) | RCT | Societal perspective |
| 31 | Makela et al. | 1991 | Europe | Finland | Superficial | All (n = 2,016; 22-28% of less than 15 years, 1-2% of greater than 65 years) | Decision tree (cohort) | RCT | Societal perspective |
| No | Article | Year  | Region         | Country  | Disease category                                                                 | Target cohort                                                                 | Model type                          | Cost perspective                  | Source                  | Outcome measure                                                                 |
|----|---------|-------|----------------|----------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------|-----------------------------------|--------------------------|----------------------------------------------------------------------------------|
| 32 | Li et al. | 1990  | North America  | USA      | Superficial; Local invasive; Immune-mediated; Sequelae                           | Children (hypothetical cohort of 100,000 children with pharyngitis)             | Decision tree (cohort)             | Health system perspective        | Lieu et al.              | Number of patients with ARF and suppurative complications prevented               |
| 43 | DeNeef et al. | 1987  | North America  | USA      | Superficial; Immune-mediated                                                    | Hypothetical cohort of 1,000 adults with pharyngitis                            | Decision tree (cohort)             | Societal perspective            | DeNeef et al.             | Number of episodes of illness (ARF and suppurative complications prevented)    |
| 33 | DeNeef et al. | 1987  | North America  | USA      | Superficial; Immune-mediated                                                    | 1,000 hospital employees                                                        | Decision tree (cohort)             | Health system perspective        | DeNeef et al.             | Number of episodes (ARF and suppurative complications prevented)                |
| 44 | DeNeef et al. | 1987  | North America  | USA      | Superficial; Immune-mediated                                                    | Adults with pharyngitis                                                          | Decision tree (cohort)             | Societal perspective            | DeNeef et al.             | Number of episodes (ARF and suppurative complications prevented)                |
| 34 | DeNeef et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | Hypothetical cohort of 1,000 patients with pharyngitis                           | Decision tree (cohort)             | Health system perspective        | DeNeef et al.             | Number of days (illness) saved                                                  |
| 45 | DeNeef et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | Non-mentioned                                                                    | Decision tree (cohort)             | Societal perspective            | DeNeef et al.             | Number of days (illness) saved                                                  |
| 35 | Hillner et al. | 1987  | North America  | USA      | Superficial; Local invasive; Immune-mediated; Sequelae                           | Adults with pharyngitis                                                          | Decision tree (cohort)             | Health system perspective        | Hillner et al.            | Number of days (illness) saved                                                  |
| 46 | Hillner et al. | 1987  | North America  | USA      | Superficial; Immune-mediated                                                    | Adults with pharyngitis                                                          | Decision tree (cohort)             | Societal perspective            | Hillner et al.            | Number of days (illness) saved                                                  |
| 36 | DeNeef et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | 310 patients with sore throat during the study period                            | Decision tree (cohort)             | Health system perspective        | DeNeef et al.             | Number of days (illness) saved                                                  |
| 47 | DeNeef et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | Non-mentioned                                                                    | Decision tree (cohort)             | Societal perspective            | DeNeef et al.             | Number of days (illness) saved                                                  |
| 37 | Hedges et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | 310 patients with sore throat during the study period                            | Decision tree (cohort)             | Societal perspective            | Hedges et al.             | Number of days (illness) saved                                                  |
| 48 | Hedges et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | Non-mentioned                                                                    | Decision tree (cohort)             | Health system perspective        | Hedges et al.             | Number of days (illness) saved                                                  |
| 38 | Cebul et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | 310 patients with sore throat during the study period                            | Decision tree (cohort)             | Societal perspective            | Cebul et al.              | Number of days (illness) saved                                                  |
| 49 | Cebul et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | Non-mentioned                                                                    | Decision tree (cohort)             | Health system perspective        | Cebul et al.              | Number of days (illness) saved                                                  |
| 39 | Brant et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | Inuit children of 3–18 years old in Alaska (Norton Sound, Yukon-Kuskokwim, Bristol Bay) | Cost-benefit analysis             | Health system perspective        | Brant et al.              | Number of days (illness) saved                                                  |
| 50 | Brant et al. | 1986  | North America  | USA      | Superficial; Immune-mediated                                                    | Inuit children of 3–18 years old in Alaska (Norton Sound, Yukon-Kuskokwim, Bristol Bay) | Cost-benefit analysis             | Societal perspective            | Brant et al.              | Number of days (illness) saved                                                  |
| 40 | Coulehan et al. | 1982  | North America  | USA      | Superficial; Immune-mediated                                                    | Navajo patients of 5–16 years hospitalized for ARF or chorea                     | Cost-benefit analysis             | Societal perspective            | Coulehan et al.          | Number of days (illness) saved                                                  |
| No | Article          | Year | Region     | Country | Disease category                  | Target cohort                                                                 | Model type         | Cost perspective             | Outcome measure                                      | Source |
|----|------------------|------|------------|---------|----------------------------------|------------------------------------------------------------------------------|--------------------|-------------------------------|------------------------------------------------------|--------|
| 41 | Smith et al.     | 1981 | North America | USA     | Superficial                      | 86 patients with clinical diagnosis of pharyngitis; Missouri                  | Cost comparison    | Health system perspective    | Treatment cost comparison                           | 52     |
| 42 | Tompkins et al.  | 1977 | North America | USA     | Superficial; Immune-mediated; Sequelae | Children, adults                                                                | Decision tree (cohort) | Societal perspective           | Costs of medical evaluation and treatment (dollar costs) by strategy | 53     |
| 43 | Forsyth          | 1975 | North America | USA     | Superficial; Immune-mediated      | Adult (15 and over) and Pediatric (14 and under)                              | Cost-risk analysis | Societal perspective           | Risk of incorrect clinical diagnosis (clinical accuracy was compared to throat culture outcomes) | 54     |
| 44 | Saslaw et al.    | 1965 | North America | USA     | Immune-mediated; Sequelae        | Children of 6 - 15 years                                                       | Cost-benefit analysis | Societal perspective           | ARF episodes prevented (expressed as a cost)          | 55     |
Table 3. Health states considered in existing decision analytic models.

| Existing models | Year | Healthy (stable) | Superficial infections | Strep A Pharyngitis | Suppurative complications | Strep A skin infections | ARF1 | ARF>1<sup>a</sup> | RHD | Severe RHD (or heart failure, surgery, etc.) | Death | Allergic reaction | Others |
|-----------------|------|------------------|------------------------|--------------------|--------------------------|------------------------|------|------------------|-----|---------------------------------------------|-------|------------------|--------|
| Ubels et al.    | 2020 | ✓                | ✓                      | ✓ (pharyngitis)    | ✓ (PTA)                 | ✓                      | ✓ (differentiated by diagnosis, severity, treatment, and confirmation) | ✓    | ✓ |
| Behnamfar et al.| 2019 | ✓ (pharyngitis)  | ✓                      | ✓ (PTA)            | ✓                        | ✓                      | ✓ (moderate, severe) | ✓ |
| CADTH            | 2018 | ✓ (impetigo)     | ✓                      | ✓ (PTA, tonsillitis) | ✓ (multiple)            | ✓                      | ✓ (moderate, severe) | ✓ |
| Roberts et al.  | 2017 | ✓                | ✓                      | ✓ (PTA, tonsillitis) | ✓ (multiple)            | ✓                      | ✓ (moderate, severe) | ✓ |
| Watkins et al.  | 2016 | ✓                | ✓                      | ✓ (PTA, tonsillitis) | ✓ (multiple)            | ✓                      | ✓ (moderate, severe) | ✓ |
| Watkins et al.  | 2015 | ✓                | ✓                      | ✓ (PTA, tonsillitis) | ✓ (multiple)            | ✓                      | ✓ (moderate, severe) | ✓ |
| Zachariah et al.| 2015 | ✓                | ✓                      | ✓ (PTA, tonsillitis) | ✓ (multiple)            | ✓                      | ✓ (moderate, severe) | ✓ |
| Islam et al.    | 2013 | ✓                | ✓                      | ✓ (PTA)            | ✓ (sub-clinical, clinical) | ✓ (moderate, severe) | ✓ (moderate, severe) | ✓ |
| Manji et al.    | 2013 | ✓                | ✓                      | ✓ (PTA)            | ✓ (moderate, severe) | ✓ (moderate, severe) | ✓ (moderate, severe) | ✓ |
| Klepser et al.  | 2012 | ✓ (pharyngitis)  | ✓                      | ✓ (PTA)            | ✓ (ARF, valve damage due to ARF) | ✓ (moderate, severe) | ✓ (moderate, severe) | ✓ |
| Giraldez-Garcia et al. | 2011 | ✓ (acute pharyngitis) | ✓ | ✓ | ✓ | ✓ | ✓ (moderate, severe) | ✓ |
| Howe et al.     | 2006 | ✓                | ✓ (PTA)                | ✓                  | ✓ (moderate, severe) | ✓ (moderate, severe) | ✓ (moderate, severe) | ✓ |
| Neuner et al.   | 2003 | ✓ (pharyngitis)  | ✓                      | ✓ (PTA)            | ✓ (ARF, valve damage due to ARF) | ✓ (moderate, severe) | ✓ (moderate, severe) | ✓ |
| Existing models | Year | Year | Healthy (stable) | Superficial infections | Strep A Pharyngitis | Suppurative complications | Strep A skin infections | ARF1 | ARF>1 | RHD | Severe RHD (or heart failure, surgery, etc.) | Death | Allergic reaction | Others |
|-----------------|------|------|------------------|------------------------|---------------------|--------------------------|-------------------------|-------|-------|------|---------------------------------------------|-------|-------------------|--------|
| King et al.     | 2002 | √    |                  |                        |                     |                          |                         | √     |       | √    | (RF among high risk subjects)               | √     |                   |        |
| Ehrlich et al.  | 2002 | √    |                  | (sore throat suspected GAS) |                     |                          |                         | √     |       | √    |                                           | √     | (severe, mild) |        |
| Tsevat et al.   | 1999 | √    | (pharyngitis)    |                        | √                   | (PTA or retropharyngeal abscess) |                         | √     |       | √    |                                           | √     | (anaphylaxis, rash, death) |        |
| Webb et al.     | 1998 | √    | (pharyngitis)    |                        | √                   | (PTA)                    |                         | √     |       | √    |                                           | √     | (severe, mild) |        |
| Dippel et al.   | 1992 | √    | (acute pharyngitis) |                        | √                   | (PTA, retropharyngeal abscess, otitis) |                         | √     |       | √    | (carditis)                                  | √     | (severe, mild, death) |        |
| Makela et al.   | 1991 | √    | (pharyngitis)    |                        |                     |                          |                         |       |       | √    | (severe, mild, death)                      |       |                   |        |
| Lieu et al.     | 1990 | √    | (pharyngitis)    |                        |                     |                          |                         |       |       | √    |                                           | √     | (severe, mild, death) |        |
| DeNeef (a)      | 1987 | √    | (pharyngitis)    |                        |                     |                          |                         |       |       | √    |                                           | √     | (severe, mild) |        |
| DeNeef (b)      | 1987 | √    | (pharyngitis)    |                        |                     |                          |                         |       |       | √    |                                           | √     |                   |        |
| Hillier et al.  | 1987 | √    | (pharyngitis)    |                        | √                   | (PTA)                    |                         |       |       | √    |                                           | √     | (severe, mild, death) |        |
| DeNeef          | 1986 | √    | (pharyngitis)    |                        |                     |                          |                         |       |       | √    |                                           | √     | (severe, mild) |        |
| Cebul et al.    | 1986 | √    | (pharyngitis)    |                        | √                   | (infected, carrier)      |                         |       |       | √    |                                           | √     | (severe, mild, death) |        |
| Hedges et al.   | 1986 | √    | (pharyngitis)    |                        |                     |                          |                         |       |       | √    |                                           | √     | (serious, mild, death) |        |
| Tompkins et al. | 1977 | √    | (pharyngitis)    |                        | √                   | (infected, carrier)      |                         |       |       | √    |                                           | √     | (serious, mild, death) |        |

| Total           | 7    | 19   | 22               | 13                     | 1                   | 22                        | 6                        | 14    | 8     | 21   | 18                           | 2     |

* Superficial infections prior to Strep A confirmation
* Recurrent ARF
* Peritonsillar abscess
* Acute post-streptococcal glomerulonephritis
* Invasive GAS
followed by death, superficial infections prior to Strep A con-
firmation, and allergic reactions due to antibiotics. Health
states such as RHD, and suppurative complications were also
moderately selected. Six models included a health state of recur-
rent ARF. Eight models took account of severe RHD or other
manifestations of cardiovascular disease. It should be noted
that the inclusion of this health state is relatively new, reflect-
ing that six of these models have been developed since 2015.
It was rare to observe models that included Strep A skin
infection, acute post-streptococcal glomerulonephritis (APSGN),
or invasive and toxin-mediated diseases, showing that there
was only one model with each of these health states. This rar-
ity reflects the complex nature of Strep A infections and
implies the limited number of surveillance data points for each
health state.

Discussion
The current review focuses on the identification of exist-
ing CEA studies on Strep A infection. Given a wide range of
disease presentations caused by Strep A, a large variation exists
across the identified models in terms of disease types cov-
ered in the studies. Overall, CEA studies on Strep A remain
limited in number. In particular, the number of the existing stud-
ies was highly concentrated in upper-middle income coun-
tries or higher, and there were only four studies focused on
lower-middle income countries or below. This is problematic
because the burden of more severe illnesses caused by Strep A
(i.e. RHD and CHF) has been greatly reduced in advanced
countries but remains disproportionately high in developing
countries. This does not mean that high income econom-
ies are free of Strep A. Superficial diseases such as pharyngi-
tis or impetigo are sometimes thought of as small-time players
compared to the ensuing diseases that cause more severe ill-
ness. However, pharyngitis is one of the most common diseases
observed globally, including in more advanced countries. In
addition, there is a growing concern that Strep A skin infections
may play a significant role in developing ARF. Unlike dur-
ing an episode of immune-mediated diseases or its sequelae,
Strep A can be transmitted from host to host during episodes
of acute diseases such as sore throat, which puts emphasis on
the dynamic nature of the disease; that is, preventing or treat-
ing an acute Strep A infection in an individual can reduce the
risk of transmission, resulting in indirect benefits for the broader
population. None of the existing studies identified through this
review took into account the indirect benefits from reducing
Strep A transmission.

Some areas of uncertainty deserve attention. The current study
used one database which may have excluded potentially eli-
gible articles. However, we compared our findings with the
ongoing systematic review of the broader societal and economic
evaluations of Group A Streptococcus under the Strep A Vac-
cine Global Consortium (SA VAC), and confirmed that there
was no difference in terms of the final set of articles which
reported CEA on Strep A. It should be also noted that the cur-
rent review only included articles written in English, and this
may have omitted eligible articles published in non-English
languages.

In the context of health economic models on Strep A-associated
diseases, cohort-level models have been widely used by
incorporating varying health-states and predicting disease
progression among patient groups. While there were more
decision tree models observed than Markov models in this
review, a decision tree model may not be appropriate when
dealing with the long-term progression of diseases and treat-
ment effects. On the other hand, a Markov-cohort model is suit-
able for chronic diseases because the model can incorporate
repetitive cycles. With the Markov-cohort model, events are
considered stochastic processes over time, allowing to evalu-
ate costs and effects of intervention strategies over a long time
period. However, Markov-cohort models are limited to the
lack of memory when transitioning from one health state to
another (i.e. Markovian assumption). While this property can
be circumvented by setting up temporary tunnel states, this
procedure results in a more complex model due to dividing
one health state into multiple sub health states. Patient-level
(or microsimulation) models can improve the drawback of
the cohort model as patient-level models follow an individual
trajectory across multiple health states. However, this type of
microsimulation model often requires a high level of com-
putational power, more input parameters, and detailed data
sources at the individual-level, which is often challenging in
resource-constrained settings.

While health officials have implemented various intervention
strategies (i.e., primary, secondary, and/or tertiary prevention
strategies) to reduce the burden of the diseases associated
with Strep A, the existing control strategies almost always
involve the use of antibiotics. The use of oral or intramuscular
penicillin has proved effective in reducing the disease pro-
gression and treating rheumatic fever. However, it should
be noted that the use of such drugs may also cause allergic
reactions such as rash, anaphylaxis, or sometimes, death.
In addition, antibiotics can be unnecessarily prescribed to
patients who are false positive or carriers, which may contrib-
ute to the increasing trend of antimicrobial resistance. Thus,
there is no doubt that preventive measures such as a safe vac-
cine will reduce the concerns raised by excessive antibiotic
uses. Currently, there is no vaccine available for Strep A
infections. The development of safe, efficacious, and afford-
able vaccines may open a new era to control Strep A infections
in a more effective manner. In other words, with a vaccine that
protects populations from contracting superficial Strep A infec-
tions, vaccination will likely limit chances for benign symp-
toms to be developed further into more severe illnesses such
as autoimmune diseases or its sequelae, and reduce not only
the burden of a broad spectrum of the Strep A diseases but also
antimicrobial resistance.

Data availability
Underlying data
No data are associated with this article.

Reporting guidelines
Zenodo: PRISMA checklist for “Existing cost-effectiveness
analyses for diseases caused by Group A Streptococcus: A
systematic review to guide future research”, https://doi.org/10.5281/zenodo.5178543

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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