SYSTEMATIC REVIEW

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

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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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view

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Any reports and responses or comments on the article can be found at the end of the article.

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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 illness¹. 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^{2,3}.

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^{4,5}. 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 A⁵. 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 treatment⁶. 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 challenging⁵. The tertiary prevention scenario involves increasing the coverage of valve surgery by building local surgical capacity especially

in resource-limited settings⁴. 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^{7–9}. However, the diseases are still highly prevalent in lower- and middle-income countries¹⁰, and the burden of Strep A throat or skin infections is not negligible in HIC either¹¹. 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^{1,12,13}. 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

Table 1. Search terms.

Group	Search terms
Disease category	<ol style="list-style-type: none"> 1. Rheumatic fever OR rheumatic heart disease 2. Glomerulonephritis AND (streptococcus OR streptococcal OR post-streptococcal OR post-streptococcal OR streptococcus) 3. Invasive OR bacteremia OR bacteraemia OR toxic shock syndrome OR necrotizing fasciitis AND (group A streptococcus OR group A streptococcal OR streptococcus pyogenes) 4. Stroke AND (Rheumatic fever OR rheumatic heart disease) 5. Endocarditis AND (Rheumatic fever OR rheumatic heart disease) 6. Impetigo OR pyoderma or scabies 7. (Bacteremia OR bacteraemia) AND developing country 8. Pharyngitis 9. Group A streptococcus OR group A streptococcal OR streptococcus pyogenes
Economic evaluation category	<ol style="list-style-type: none"> 1. Cost-effectiveness 2. Cost-benefit 3. Cost-utility 4. Incremental cost-effectiveness ratio 5. QALY OR quality adjusted life year 6. DALY OR disability adjusted life year

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 disease¹. 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”¹⁴. 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 Bank¹⁵. There were only three studies that were carried out in lower-middle-income economies or below: two studies from Africa^{4,5} and one study from India¹⁶. While most studies conducted a cost-effectiveness analysis for a single country or sub-population of a country, Watkins *et al.*⁴ and Manji *et al.*⁵ covered multiple African countries by taking into account evidence reported in existing

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA).

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

Table 2. Summary of the final 44 articles identified for the systematic literature review.

No	Article	Year	Region	Country	Disease category	Target cohort	Model type	Cost perspective	Outcome measure	Source
1	Ubels <i>et al.</i>	2020	Latin America	Brazil	Sequelae	A hypothetical cohort of 11 years (socioeconomically disadvantaged children)	Markov cohort	Health system perspective	DALY	17
2	Oetzel <i>et al.</i>	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	Number of successful secondary prophylaxis injections	18
3	Behnamfar <i>et al.</i>	2019	Middle East	Iran	Superficial; Local invasive; Immune-mediated	Children, adults	Decision tree (cohort)	Societal perspective	QALD	19
4	Cannon <i>et al.</i>	2018	Asia & Pacific	Australia	Superficial; Local invasive; Immune-mediated; Sequelae; Invasive	Non-indigenous & indigenous Australian populations; Three vaccination scenarios: (1) Infants (2) 5 years old (3) 65 years (non-indigenous), 50 years (indigenous)	Markov cohort	Societal perspective	DALY	3
5	Burns <i>et al.</i>	2018	Europe	UK	Superficial	Adults between 18 and 70 years with acute sore throat and painful swallowing; 42 primary care clinics	RCT	Primary: Health system perspective excluding out-of-pocket expense; societal perspective in the scenario analysis	QALY (EQ5D-5L)	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 <i>et al.</i>	2017	Asia & Pacific	Australia	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	DALY	21
8	Watkins <i>et al.</i>	2016	Africa	African nations	Immune-mediated; Sequelae	5–24 years; hypothetical African cohort for the application of the model	Markov cohort	Health system perspective	DALY	4
9	Watkins <i>et al.</i>	2015	South America	Cuba	Immune-mediated; Sequelae	5–24 years in Pinar del Rio	Decision tree (cohort)	Health system perspective	DALY	22
10	Zachariah <i>et al.</i>	2015	Asia & Pacific	Australia	Sequelae	5–49 years; Northern Territory	Markov cohort	Societal perspective	QALY	23
11	Little <i>et al.</i>	2014	Europe	UK	Superficial	Adults or children aged ≥ 5 years presenting acute sore throat; Southern and central areas of England	RCT	Health system perspective	(1) Symptom severity score, (2) QALY (EQ5D)	24

No	Article	Year	Region	Country	Disease category	Target cohort	Model type	Cost perspective	Outcome measure	Source
12	Irlam <i>et al.</i>	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	Manji <i>et al.</i>	2013	Africa	Sub-Saharan Africa	Superficial; Sequelae	5 years	Markov cohort	Societal perspective	QALY	5
14	Klepser <i>et al.</i>	2012	North America	USA	Superficial; Local invasive; Immune-mediated	Adults	Decision tree (cohort)	Health system perspective	QALD	26
15	Wilson <i>et al.</i>	2012	Europe	UK	Superficial	4–15 years; five secondary care otolaryngology Depts. in the northern UK	RCT	Health system perspective	QoL (PedsQL)	27
16	Giraldez-García <i>et al.</i>	2011	Europe	Spain	Superficial; Immune-mediated	2–14 years who consult with a primary care physician due to acute pharyngitis	Decision tree (cohort)	Health system perspective	Proportion of patients cured	28
17	Soudarssanane <i>et al.</i>	2007	Asia & Pacific	India	Superficial; Immune-mediated; Sequelae	5–15 years; Pondicherry Union Territory	Cost-benefit analysis	Societal perspective	RF/RHD episodes prevented (expressed as a cost)	16
18	Howe <i>et al.</i>	2006	North America	USA	Superficial; Local invasive; Immune-mediated	Children & adolescents	Decision tree (cohort)	Societal perspective (also, Health system perspective)	QALD	29
19	Fujihara <i>et al.</i>	2006	Asia & Pacific	Japan	Superficial	2–15 years (39 children), 16–66 (129 adults); Wakayama	Break-even analysis	Societal perspective	Total health care cost savings (i.e. decreases in physician visits, work days missed, etc.)	30
20	Neuner <i>et al.</i>	2003	North America	USA	Superficial; Local invasive; Immune-mediated	Adults	Decision tree (cohort)	Societal perspective but excluding productivity loss	QALD	31
21	King <i>et al.</i>	2002	North America	USA	Superficial; Immune-mediated; Sequelae	Hypothetical 2,000 birth cohort	Markov cohort	Societal perspective	QALY	32
22	Ehrlich <i>et al.</i>	2002	North America	USA	Superficial; Immune-mediated	5–17 years	Decision tree (cohort)	Health system perspective	RHD cases prevented	33
23	Tsevat <i>et al.</i>	1999	North America	USA	Superficial; Local invasive; Immune-mediated	Children older than 3 years with signs or symptoms of pharyngitis	Decision tree (cohort)	Health system perspective (baseline); societal perspective in the sensitivity analysis	The number of cases prevented	34

No	Article	Year	Region	Country	Disease category	Target cohort	Model type	Cost perspective	Outcome measure	Source
24	Giraldes	1999	Europe	Portugal	Superficial	Overall	Cost-utility analysis (cost of a healthy day) (Cost / Utility changes between treatment and non-treatment)	Health system perspective	Own measure	35
25	Webb	1998	North America	USA	Superficial; Local invasive; Immune-mediated	Children (hypothetical cohort of 100,000 children with pharyngitis)	Decision tree (cohort)	Health system perspective (baseline); societal perspective in the sensitivity analysis	Number of patients with ARF and suppurative complications prevented	36
26	Carbon <i>et al.</i>	1996	Europe	France	Superficial	18-65 years with symptoms of pharyngitis (n = 259 (=262-3))	RCT (cost-minimization approach)	Societal perspective	Drug compliance and symptoms averted based on 10-cm visual analogue scale	37
27	Pelc <i>et al.</i>	1996	Europe	France	Superficial	575 adults (older than 15 years) with recurrent pharyngotonsillitis (who had at least 2 episodes of tonsillitis in the previous 12 months); 204 general practice clinics throughout France	RCT	Societal perspective	Number of patients free of recurrence	38
28	Majeed <i>et al.</i>	1993	Middle East	Kuwait	Superficial; Immune-mediated; Sequelae	5-14 years with symptomatic pharyngitis; 12 districts representing three socio-economic levels	RCT (with existing literature on ARF and RHD)	Health system perspective	Number of Strep A pharyngitis episodes not missed (thus treated) by using the rapid test (compared to clinical diagnosis)	39
29	Rice <i>et al.</i>	1992	North America	USA	Superficial	3 months to 16 years with impetigo (n = 83)	RCT	Societal perspective	Clinical and bacteriologic response (cured, improved), time to resolution (days)	40
30	Dippel <i>et al.</i>	1992	Not mentioned	Not mentioned	Superficial; Local invasive; Immune-mediated; Sequelae	14 years hypothetical patients with sore throat	Decision tree (cohort)	Patient perspective (no financial costs of treatment-related components)	QALD	41
31	Makela <i>et al.</i>	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)	Societal perspective	Treatment cost comparison	42

No	Article	Year	Region	Country	Disease category	Target cohort	Model type	Cost perspective	Outcome measure	Source
32	Lieu <i>et al.</i>	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	Number of patients with ARF and suppurative complications prevented	43
33	DeNeef	1987	North America	USA	Superficial; Immune-mediated	Hypothetical cohort of 1,000 adults with pharyngitis	Decision tree (cohort, written as "probability trees")	Societal perspective	Number of episodes prevented (utility expressed as a cost in dollars)	44
34	DeNeef	1987	North America	USA	Superficial; Immune-mediated	1,000 hospital employees	Decision tree (cohort)	Health system perspective	Person-days of illness saved	45
35	Hillner <i>et al.</i>	1987	North America	USA	Superficial; Local invasive; Immune-mediated; Sequelae	Adults with pharyngitis	Decision tree (cohort)	NA	Well days (net well days = 10 well days - sickday equivalents for adverse outcomes such as ARF, penicillin reactions)	46
36	DeNeef	1986	North America	USA	Superficial; Immune-mediated	Hypothetical cohort of 1,000 patients with pharyngitis	Decision tree (cohort)	Health system perspective	Person-days of illness saved	47
37	Hedges <i>et al.</i>	1986	North America (not clearly mentioned)	USA (not clearly mentioned)	Superficial; Immune-mediated	Not mentioned	Decision tree (cohort)	Societal perspective	Number of episodes (ARF, allergic reaction, etc.) prevented (expressed as a cost in dollars)	48
38	Cebul <i>et al.</i>	1986	North America	USA	Superficial; Immune-mediated; Sequelae	310 patients with sore throat during the study period	Decision tree (cohort)	Societal perspective	Correct decision (culture-positive patients who were treated and culture-negative patients who were not treated)	49
39	Brant <i>et al.</i>	1986	North America	USA	Superficial; Immune-mediated	Inuit children of 3–18 years (during school session, all children regardless of symptoms, but during the summer, only children with pharyngitis); 9 villages in western Alaska (Norton Sound, Yukon-Kuskokwim, Bristol Bay)	Cost-benefit analysis	Health system perspective	ARF episodes prevented (expressed as a cost)	50
40	Coulehan <i>et al.</i>	1982	North America	USA	Superficial; Immune-mediated	Navajo patients of 5–16 years hospitalized for ARF or chorea	Cost-benefit analysis	Societal perspective	ARF episodes prevented (expressed as a cost)	51

No	Article	Year	Region	Country	Disease category	Target cohort	Model type	Cost perspective	Outcome measure	Source
41	Smith <i>et al.</i>	1981	North America	USA	Superficial	86 patients with clinical diagnosis of pharyngitis; Missouri	Cost comparison	Health system perspective	Treatment cost comparison	52
42	Tompkins <i>et al.</i>	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 <i>et al.</i>	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	Health states											
		Healthy (stable)	Superficial infections ^a	Strep A Pharyngitis	Suppurative complications	Strep A skin infections	ARF1	ARF>1 ^b	RHD	Severe RHD (or heart failure, surgery, etc.)	Death	Allergic reaction	Others
Ubels <i>et al.</i>	2020	✓							✓ (differentiated by diagnosis, severity, treatment, and confirmation)	✓			
Behnamfar <i>et al.</i>	2019		✓ (pharyngitis)	✓	✓ (PTA)		✓				✓		
CADTH common drug review	2018		✓ (impetigo)										
Cannon <i>et al.</i>	2018	✓		✓	✓ (PTA, tonsillitis)	✓ (multiple)	✓	✓	✓	✓			APSGN ^d , iGAS ^e
Roberts <i>et al.</i>	2017								✓ (moderate, severe)	✓			
Watkins <i>et al.</i>	2016	✓					✓	✓	✓	✓			
Watkins <i>et al.</i>	2015	✓					✓	✓	✓ (mild, moderate)	✓ (severe)	✓		
Zachariah <i>et al.</i>	2015	✓		✓					✓ (sub-clinical, clinical)	✓ (congestive heart failure, post-valve replacement)	✓		
Irlam <i>et al.</i>	2013		✓ (pharyngitis)	✓	✓ (PTA)		✓		✓	✓	✓ (anaphylaxis, rash)		
Manji <i>et al.</i>	2013	✓		✓					✓	✓			
Klepser <i>et al.</i>	2012		✓ (pharyngitis)	✓	✓ (PTA)		✓ (ARF, valve damage due to ARF)			✓	✓ (anaphylaxis, rash)		
Giraldez-Garcia <i>et al.</i>	2011		✓ (acute pharyngitis)	✓	✓		✓			✓	✓ (anaphylaxis: severe, mild)		
Howe <i>et al.</i>	2006			✓	✓ (PTA)		✓			✓	✓ (severe, mild, death)		
Neuner <i>et al.</i>	2003		✓ (pharyngitis)	✓	✓ (PTA)		✓ (ARF, valve damage due to ARF)			✓	✓ (anaphylaxis, rash)		

Existing models	Year	Health states											
		Healthy (stable)	Superficial infections ^a	Strep A Pharyngitis	Suppurative complications	Strep A skin infections	ARF1	ARF>1 ^b	RHD	Severe RHD (or heart failure, surgery, etc.)	Death	Allergic reaction	Others
King <i>et al.</i>	2002	✓		✓			✓	✓ (RF among high risk subjects)	✓	✓ (moderate, severe, with CHF and surgery)	✓		
Ehrlich <i>et al.</i>	2002		✓ (sore throat suspected GAS)	✓	✓		✓				✓ (severe, mild, death)		
Tsevat <i>et al.</i>	1999		✓ (pharyngitis)	✓	✓ (PTA or retropharyngeal abscess)		✓				✓	✓ (anaphylaxis, rash, death)	Non-fatal complications due to ARF
Webb <i>et al.</i>	1998		✓ (pharyngitis)	✓	✓ (PTA)		✓				✓ (severe, mild)		
Dippel <i>et al.</i>	1992		✓ (acute pharyngitis)	✓ (infected, carrier)	✓ (PTA, retropharyngeal abscess, otitis)		✓		✓ (carditis)	✓ (chronic RHD, heart failure)	✓	✓ (severe, mild, death)	
Makela <i>et al.</i>	1991		✓ (pharyngitis)	✓									
Lieu <i>et al.</i>	1990		✓ (pharyngitis)		✓		✓		✓		✓ (severe, mild, death)		
DeNeef (a)	1987		✓ (pharyngitis)	✓			✓				✓	✓ (severe, mild)	
DeNeef (b)	1987		✓ (pharyngitis)	✓			✓				✓		
Hillner <i>et al.</i>	1987		✓ (pharyngitis)	✓	✓ (PTA)		✓		✓		✓ (serious, mild, death)		
DeNeef	1986		✓ (pharyngitis)	✓			✓				✓ (severe, mild)		
Cebul <i>et al.</i>	1986		✓ (pharyngitis)	✓ (infected, carrier)			✓	✓	✓		✓ (serious, mild, death)		
Hedges <i>et al.</i>	1986		✓ (pharyngitis)	✓			✓				✓ (serious, mild, death)		
Tompkins <i>et al.</i>	1977		✓ (pharyngitis)	✓ (infected, carrier)			✓	✓	✓		✓ (serious, mild, death)		
Total		7	19	22	13	1	22	6	14	8	21	18	2

^a Superficial infections prior to Strep A confirmation^b Recurrent ARF^c Peritonsillar abscess^d Acute post-streptococcal glomerulonephritis^e Invasive GAS

followed by death, superficial infections prior to Strep A confirmation, 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 recurrent 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, reflecting 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 rarity 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 existing 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 covered in the studies. Overall, CEA studies on Strep A remain limited in number. In particular, the number of the existing studies was highly concentrated in upper-middle income countries 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^{7,8,56}. This does not mean that high income economies are free of Strep A. Superficial diseases such as pharyngitis or impetigo are sometimes thought of as small-time players compared to the ensuing diseases that cause more severe illness. 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^{3,56}. Unlike during 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 treating 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 eligible 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 Vaccine Global Consortium (SAVAC), and confirmed that there was no difference in terms of the final set of articles which reported CEAs on Strep A. It should be also noted that the current 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 treatment effects. On the other hand, a Markov-cohort model is suitable for chronic diseases because the model can incorporate repetitive cycles. With the Markov-cohort model, events are considered stochastic processes over time, allowing to evaluate costs and effects of intervention strategies over a long time period⁵. 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 computational 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 progression 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 contribute to the increasing trend of antimicrobial resistance. Thus, there is no doubt that preventive measures such as a safe vaccine will reduce the concerns raised by excessive antibiotic uses^{57–61}. Currently, there is no vaccine available for Strep A infections. The development of safe, efficacious, and affordable 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 infections, vaccination will likely limit chances for benign symptoms 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>⁶²

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

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Version 1

Reviewer Report 25 January 2023

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The literature review does not seem to follow the recommended methods for this type of synthesis. The search in one single database (PubMed) may not be sufficient. The author should be aware of other databases where this type of study exists as well as other sources. The study reporting does not follow PRISMA statement and many important details are missing e.g., study inclusion and exclusion criteria, systematic review protocol registration number, explicit statement of questions being addressed with reference to PICO, method of data extraction, quality assessment etc.

My specific comments for each section are as follows:

1. Abstract: The abstract is not clear about the rationale and the focus of the review whether it is the cost-effectiveness of prevention or treatment against Strep A infection and the primary outcome e.g., NMB, ICER etc. The period of publication covered should have been mentioned. The result section should present the details of study selection e.g., the number of studies included, types of study design, and characteristics etc. to provide an overview of study characteristics. The conclusions should be clear and drawn from the findings.
2. Introduction: In the introduction the author should have specified the specific EEs to be included e.g., CUA, CEA, CBA etc. The explicit statement of questions being addressed with reference to PICO should have been mentioned.
3. The study reporting is not according to PRISMA statement. For example, an explicit statement of questions being addressed with reference to PICO was not indicated. The protocol registration, inclusion and exclusion criteria were not mentioned, etc. Have the authors registered the study protocol? The protocol registration number and the link to access should be provided. I would recommend the authors use and provide the completed PRISMA checklist showing the page number where each component was presented. The search strings/strategy with the inception date for each database should also be provided.
4. The search for one single database may not be sufficient and comprehensive enough. The

inception up to May 2020 may not be up to date. The author should consider including more databases and expanding the period.

5. There was no risk of bias assessment for the included studies. The author should have selected the appropriate tool e.g., the Drummond checklist, the CHEERS checklist to assess the study quality. A summary table with the details of RoB should be presented in the manuscript.
6. The data extraction was not properly carried out. There was no mention of the findings of EEs included. The outcomes should have been inflated to be the same year value. The authors should consider extracting/making the outcomes as NMB, ICER to be comparable. Please see a few examples of a systematic review of EEs: <https://journals.hh-publisher.com/index.php/pmmb/article/view/627>, <https://link.springer.com/article/10.1007/s40273-016-0439-3>) and consider citing them in the discussion section.

The above are only a few examples of things to be improved. I would recommend the authors work on the main issues concerning its methodology, analysis, and presentations before working on the manuscript.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

No

Is the statistical analysis and its interpretation appropriate?

No

Are the conclusions drawn adequately supported by the results presented in the review?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Evidence synthesis, infectious diseases, HIV, public health, epidemiology, and outcome research.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.