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Prevalence of Streptococcal Pharyngitis and Streptococcal Carriage in Children: A Meta-analysis

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KEY WORDS
Streptococcus, carriage, pediatrics, prevalence, meta-analysis

ABBREVIATIONS
GAS—group A *Streptococcus*
CI—confidence interval

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WHAT'S KNOWN ON THIS SUBJECT: The prevalence of group A streptococcal pharyngitis and carriage has not been systematically studied.

WHAT THIS STUDY ADDS: In this meta-analysis the authors provide clinicians with quantitative estimates of the prevalence of GAS infection and carriage in children of various ages.

abstract

OBJECTIVES: Prevalence estimates can help clinicians make informed decisions regarding diagnostic testing of children who present with symptoms of pharyngitis. We conducted a meta-analysis to determine the (1) prevalence of streptococcal infection among children who presented with sore throat and (2) prevalence of streptococcal carriage among asymptomatic children.

METHODS: We searched Medline for articles on pediatric streptococcal pharyngitis. We included articles in our review when they contained data on the prevalence of group A *Streptococcus* (GAS) from pharyngeal specimens in children who were younger than 18 years. Two evaluators independently reviewed, rated, and abstracted data from each article. Prevalence estimates were pooled in a meta-analysis and stratified according to age group.

RESULTS: Of the 266 articles retrieved, 29 met all inclusion criteria. Among children of all ages who present with sore throat, the pooled prevalence of GAS was 37% (95% confidence interval [CI]: 32%–43%). Children who were younger than 5 years had a lower prevalence of GAS (24% [95% CI: 21%–26%]). The prevalence of GAS carriage among well children with no signs or symptoms of pharyngitis was 12% (95% CI: 9%–14%).

CONCLUSIONS: Prevalence rates of GAS disease and carriage varied by age; children who were younger than 5 years had lower rates of throat cultures that were positive for GAS. *Pediatrics* 2010;126: e557–e564

Clinicians are frequently faced with the decision of whether to obtain a pharyngeal swab for rapid antigen testing and/or culture to assess for the presence of group A *Streptococcus* (GAS) pharyngitis. Because GAS can lead to serious sequelae, particularly rheumatic fever, clinicians may be inclined to test children with the slightest suspicion of pharyngitis. Conversely, it is widely known that a subgroup of asymptomatic children have GAS detected in the pharynx as part of their flora (hereinafter referred to as carriers of GAS).

Knowledge of the prevalence of GAS infection among various subgroups of children can assist clinicians in selecting children who are likely to benefit from additional diagnostic testing. Using prevalence rates as an estimate of the previous probability of disease is the first step in evidence-based practice. In children with a very low pretest probability of GAS pharyngitis, routine diagnostic testing is not necessary. In such children, an indiscriminate approach to diagnostic testing might lead to more harm than benefit, especially if the rate of carriage of GAS is high. Prevalence estimates also help clinicians in the interpretation of test results and in the treatment of children with suspected GAS pharyngitis. We conducted a meta-analysis of the prevalence of GAS infection and carriage with the aim of providing clinicians with quantitative estimates for children of various ages.

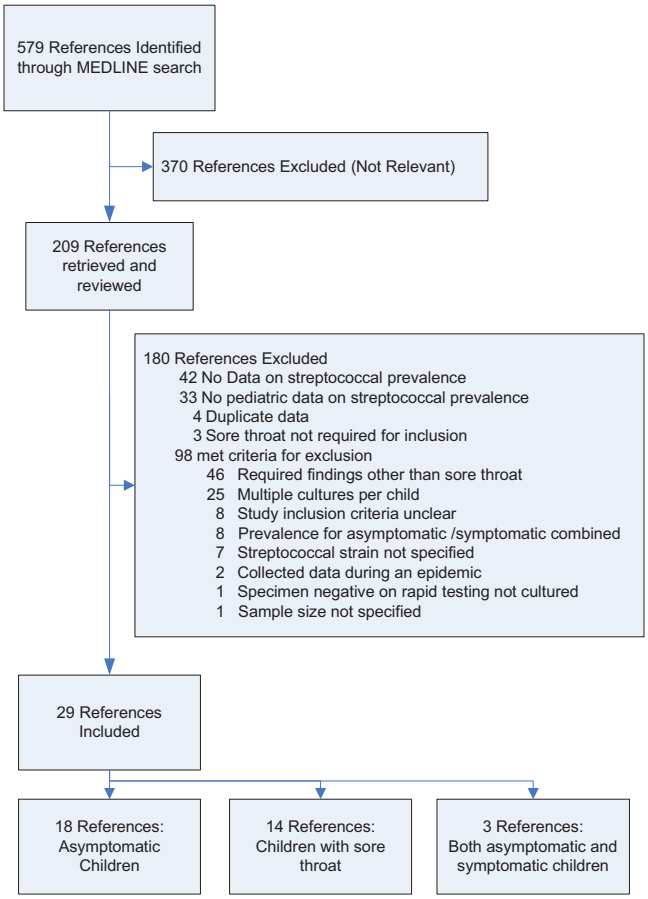

FIGURE 1
Flow diagram outlining the study selection process.

METHODS

We searched Medline (1950 through November 4, 2008) for articles on GAS pharyngitis or asymptomatic carriage in children who were younger than 18 years (Fig 1). Search terms included the following: Streptococcus infections (MeSH), streptococc*, pharyngitis, sore throat, strep throat, throat culture, tonsillitis, tonsillopharyngitis, subclinical, carrier*, carriage, coloni*, prevalence, incidence, and epidemiology. We reviewed full-text versions of articles that might contain data regarding prevalence of GAS infection and/or carriage. Only articles that were written in English, French, Italian, Spanish, and German were reviewed. Two evaluators (Drs Shaikh and Leonard) independently abstracted data from each article.

Explicit a priori inclusion and exclusion criteria were applied. We included an article when it reported data on the prevalence of GAS in children who presented to a clinician for evaluation of sore throat. Only studies that used throat cultures as the gold standard were included; studies in which rapid antigen tests were used were included only when specimens that were negative on the rapid antigen test were sent for culture confirmation. Although streptococcal grouping is ideally determined by using latex agglutination in a microbiological laboratory, sensitivity to bacitracin is often used in an office setting; therefore, we decided to include studies that used either test and to investigate whether the results differed on the basis of the test used. Because we were interested in the point prevalence of GAS, not the incidence of GAS over time, longitudinal studies in which the same child was cultured multiple times were excluded.

We excluded studies that (1) did not specifically identify the *Streptococcus* as group A, (2) included only children who lived in isolated communities or residential homes, (3) reported on an unusual epidemic of GAS, (4) included

a large proportion (>30%) of children who had received antibiotics before the throat culture, and (5) required children to have signs and symptoms other than sore throat (eg, required fever). We excluded studies that did not describe the exact signs and symptoms required for patient enrollment. For example, some of the studies reviewed stated that enrollment was based on the presence of "pharyngitis." Because pharyngitis may be defined in many ways, when no additional clarification was provided in the methods, these studies were excluded.

Because various studies enrolled children of various ages, we planned to group the studies into 2 clinically relevant age categories: <5 years and 5 to 18 years. In a number of articles, however, the lower age cutoff was not specified (eg, "we enrolled children ≤15 years of age"). Because it is likely that the majority of the children in these studies were school-aged children, we analyzed all articles that included school children together despite the different lower age cutoffs used and examined the effect of the age cutoff on the prevalence rates. Finally, when the original study presented data stratified by age, we used the data in each stratum; therefore, data from 1 article may appear in several analyses. We also examined studies that reported streptococcal prevalence among asymptomatic children; however, studies that included both asymptomatic and symptomatic children were excluded when data for the groups could not be separated.

Quality Rating

We adapted a quality assessment system for prevalence articles.[1] Two investigators (Drs Shaikh and Leonard) assessed each study independently to determine whether (1) the study was prospective, (2) the study was consecutive (defined as the systematic and unbiased enrollment of potentially eligible patients), and (3) children who had recently (≤30 days) used antibiotics were excluded. We assessed these quality indicators separately for each article; a total quality score was not calculated.[2]

Statistical Methods

Prevalence was calculated by dividing the number of children with positive cultures for GAS by the number of children who underwent throat swabs.[3] We pooled the prevalence estimates by using standard meta-analytic techniques. All reported confidence intervals (CIs) represent the 95% CIs. We planned regression analyses with regard the following factors: lower age limit of children included in the study (see previous section), setting (emergency department versus outpatient clinic), and country (United States/Canada/Europe/Australia versus others), study quality (prospective, consecutive, excluded recent antibiotic use), and year of publication.

We also examined the effect of seasonality on prevalence rates by comparing streptococcal prevalence from studies that enrolled children during their respective winter season (November through April in the northern hemisphere and May through September in the southern hemisphere) with studies that enrolled children during the entire year. For this particular analysis, only studies that were conducted in cities that were not located between the Tropic of Cancer and the Tropic of Capricorn were included.

Data were imported into Stata 10.1, and a pooled estimate of GAS prevalence was calculated by using a random-effects model with inverse-variance weighting by using the DerSimonian and Laird method.[4] Statistical heterogeneity between and within groups was measured by using the χ^2 test for heterogeneity.

Because prevalence is clearly affected by the spectrum of patients included, we expected to find significant heterogeneity among studies. To deal with heterogeneity, we used meta-regression to identify subgroups in which pooling may be acceptable. Meta-regression, a modification of linear regression, investigates the extent to which heterogeneity among studies is related to various study characteristics. Finally, we used Galbraith plots to assess visually which studies were the most heterogeneous.

To evaluate the weight of particular articles on the pooled estimates, we performed influence analysis. This method recalculates the pooled prevalence estimate omitting 1 study at a time. We also conducted sensitivity analysis by examining the effect of (1) restricting the analysis to studies conducted in the United States or Canada, (2) restricting the analysis to studies that were conducted in an outpatient setting, and (3) excluding the most heterogeneous studies.

RESULTS

Description of Articles

A total of 515 articles were found through the described search strategy. From these, we retrieved 209 that were relevant for full-text review (Fig 1). Twenty-nine articles met all criteria for inclusion; 14 reported the prevalence of GAS recovered from children who presented with sore throat, 18 reported the prevalence of GAS carriage among asymptomatic patients, and 3 reported both.

Prevalence of GAS Among Children With Sore Throat

There was significant heterogeneity ($P < .001$) among the estimates from the 14 studies that reported data on the prevalence of GAS among children with sore throat (Table 1). On

TABLE 1 Prevalence of GAS Infection Among Children Presenting With Sore Throat

Source	Age Range, y	*N*	Setting	Country	Prevalence (%)
All ages					
Romoin et al,[15] 2005	5–12	916	Clinic	Egypt/Croatia/Brazil	33
McIsaac et al,[16] 2004	3–17	454	Clinic	Canada	34
McIsaac et al,[17] 2000	3–14	158	Clinic	Canada	35
de Silva et al,[18] 1998	3–12	137	Clinic	Sri Lanka	45
McIsaac et al,[19] 1998	3–14	94	Clinic	Canada	36
Gunnarsson et al,[11] 1997	3–15	106	Clinic	Sweden	34
Dobbs et al,[20] 1996	4–11	86	Clinic	Ireland	48
Dagnelie et al,[21] 1993	4–14	80	Clinic	Netherlands	58
Pichichero et al,[22] 1992	<18	65 463	Clinic	United States	23
Hoffman et al,[23] 1992	≤14	466	Clinic	Denmark	42
Reed et al,[24] 1990	<19	375	ED	United States	33
Reed et al,[25] 1988	2–12	136	Clinic	United States	32
Feery et al,[26] 1976	6–16	47	Clinic	Australia	45
Forsyth et al,[27] 1975	≤14	213	Clinic	United States	31
Pooled prevalence (95% CI)					37 (32–43)
Younger than 5 y					
Romoin et al,[15] 2005	2–5	894	Clinic	Egypt/Croatia/Brazil	24
Gunnarsson et al,[11] 1997	0–2	40	Clinic	Sweden	18
Feery et al,[26] 1976	0–5	30	Clinic	Australia	17
Pooled prevalence (95% CI)					24 (21–26)

ED indicates emergency department.

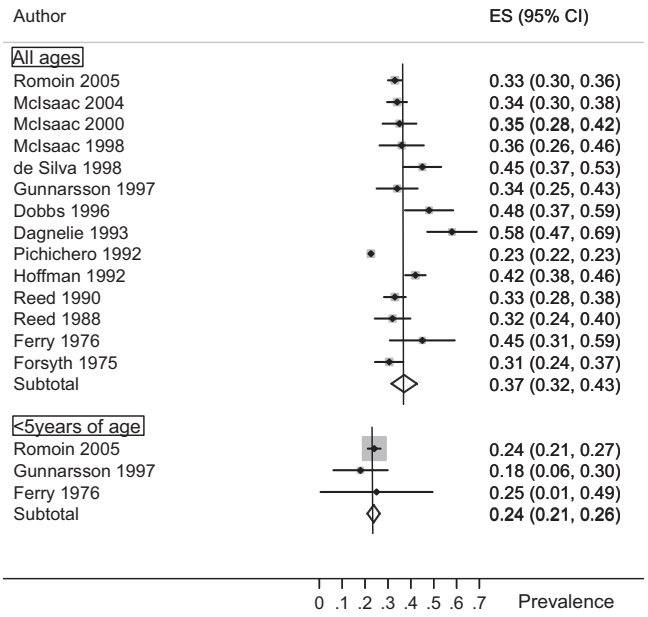

FIGURE 2
Prevalence (rectangles), 95% CI (lines), and pooled prevalence rate (diamonds) of streptococcal pharyngitis in children with sore throat, stratified by age.

stratified analysis, prevalence of GAS carriage was lower in studies that included only children who were younger than 5 years as compared with studies that included children of all ages ($P = .026$). Accordingly, we present separate analyses for GAS according to age group (Fig 2).

Only 3 studies provided data on the prevalence of GAS in children who had sore throat and were younger than 5 years (Fig 2). There was no heterogeneity among the estimates ($P = .6$) from these 3 studies, and the pooled prevalence of GAS was 24% (95% CI: 21%–26%).

Fourteen studies presented data on the prevalence of GAS among children of all ages with sore throat. The pooled prevalence of GAS from these studies was 37% (95% CI: 32%–43%). There was substantial heterogeneity among these studies ($P < .001$). To explore the reasons for this heterogeneity, we conducted meta-regression and sensitivity analysis. On meta-regression, there was no association between publication year, study quality, season, country, antibiotic use, laboratory test used to determine streptococcal group, or clinical setting and prevalence estimates. Influence analysis showed that omission of no single study significantly affected the pooled prevalence values. The Galbraith plot identified the populations studied by Dagnelie and Pichichero as the most heterogeneous; however, exclusion of 1 or both of these studies did not significantly alter the results; the prevalence of GAS was 36% (95% CI: 33%–39%) with both studies excluded. Sensitivity analysis revealed that prevalence of GAS was very similar when the analysis was restricted to studies that were conducted in the United States or Canada (37% [95% CI: 31%–43%]). Restricting the analysis to studies that were conducted in an outpatient setting also did not change the estimated significantly (38% [95% CI: 32%–43%).

Prevalence of GAS Carriage Among Asymptomatic Children

Eighteen studies presented data on GAS carriage among asymptomatic children who were younger than 18 years (Table 2). There was significant heterogeneity among the estimates from the studies ($P < .001$).

On stratified analysis, prevalence of GAS carriage was found to be lower in studies that included only children who were younger than 5 years as compared with studies that included children of all ages. Accordingly, we

TABLE 2 Prevalence of GAS carriage Among Asymptomatic Children

Source	Age Range, y	*N*	Setting	Country	Prevalence (%)
All ages					
Unceta et al,[28] 2005	0.5–14	413	Clinic	Spain	12
Kim et al,[29] 2004	School aged	581	School	Korea	17
Fazeli et al,[30] 2003	6–13	1588	School	Iran	11
Gür et al,[31] 2002	6–16	1161	School	Turkey	14
Attia et al,[32] 2001	1–18	194	Clinic/ED	United States	15
Jasir et al,[33] 2000	School-aged	1885	School	Iran	21
Pichichero et al,[34] 1999	2–16	227	Clinic	United States	3
Gunnarsson et al,[11] 1997	3–15	565	School	Sweden	10
Edmond et al,[35] 1996	4–17	85	ED	Australia	5
Cimolai et al,[a] 1991	2–18	247	Clinic	Canada	13
Lieu et al,[36] 1988	1–17	100	ED	United States	20
Hofkosh et al,[37] 1988	3–15	414	Clinic	United States	5
Reed et al,[25] 1988	2–12	96	Clinic	United States	26
McMillan et al,[38] 1986	4–18	307	Clinic	United States	12
Ginsburg et al,[39] 1985	5–14	622	Clinic	United States	5
Karoui et al,[40] 1982	6–16	1041	School	Kuwait	10
Feery et al,[26] 1976	6–16	26	Clinic	Australia	15
Koshi et al,[41] 1971	<15	110	Clinic	India	5
Pooled prevalence (95% CI)					12 (9–14)
Younger than 5 y					
Gunnarsson et al,[11] 1997	0–2	216	School	Sweden	3
Edmond et al,[35] 1996	0–3	50	ED	Australia	10
Ginsburg et al,[39] 1985	0–5	740	Clinic	United States	2
Feery et al,[26] 1976	0–5	30	Clinic	Australia	17
Pooled prevalence (95% CI)					4 (1–7)

ED indicates emergency department.

[a] Cimolai N, Morrison BJ, MacCulloch L, Smith DF, Hlady J. Beta-haemolytic non-group A streptococci and pharyngitis: a case-control study. *Eur J Pediatrics*. 1991;150:776–779

present separate analyses for GAS carriage according to age group (Fig 3).

Only 4 studies provided data on the prevalence of GAS carriage in asymptomatic children who were younger than 5 years. Although there was some remaining heterogeneity among the estimates from these 4 studies ($P = .04$), the small sample of studies did not allow for meaningful meta-regression or sensitivity analysis. The pooled prevalence of GAS from these studies was 3.8% (95% CI: 1%–7%).

Eighteen studies provided data on the prevalence of GAS carriage among children of all ages. The pooled prevalence of GAS carriage in these studies was 12% (95% CI: 9%–14%). There was substantial heterogeneity among these studies ($P < .001$). On meta-regression, none of the variables investigated (see Methods) was associated with the prevalence estimates. Influence analysis showed that omission of no single study significantly changed the pooled prevalence estimates. The Galbraith plot identified the populations studied by Jasir and Pichichero as the most heterogeneous; however, exclusion of 1 or both of these studies did not significantly alter the results; the pooled prevalence with both studies excluded was 11% (95% CI: 9%–13%). Sensitivity analysis revealed that the pooled prevalence was very similar when the analysis was restricted to studies that were conducted in the United States or Canada (11% [95% CI: 7%–15%).

DISCUSSION

This study demonstrates that children who present with sore throat have a high probability of having GAS pharyngitis: 37% of children who presented to an outpatient clinic or emergency department with sore throat were found to have a throat culture that was positive for GAS. The prevalence of GAS in an unselected, office-based adult population has been estimated to be in the range of 5% to 10%.[5] The relatively high probability of GAS disease and acute rheumatic fever in school-aged children, as compared with adults and children who are younger than 5 years, suggests that testing of school-aged children who present with sore throat is beneficial. This is in accordance with the strategies endorsed by the Committee on Infectious Diseases of the American Academy of Pediatrics,[6] the American Heart Association,[7] and the Infectious Disease Society of America.[8]

Only 3 studies provided data on the prevalence of GAS in children who were younger than 5 years and had a sore throat. In those studies, 24% of children who were younger than 5 years and presented with sore throat were positive for GAS; however, because acute rheumatic fever occurs infrequently among preschool children,[9] more data are needed to determine whether routine testing in this age group is justified. It may be the case that presence of other risk factors (eg, age >3 years, older sibling with GAS infection, other signs and symptoms) can be used to select a subgroup of children who have sore throat and would benefit from routine testing.

Twelve percent of children who were older than 5 years were found to be carriers of GAS. This is in agreement with previous epidemiologic studies to date.[10–14] Because it is not possible to distinguish between a child who has a viral infection and is a carrier for GAS and a child who has an acute streptococcal infection and because the prevalence of GAS carriage is relatively high in the school-aged population (~1 in 8), children who have repeated episodes of sore throat and continue to test positive for GAS should be carefully evaluated. Although posttreatment cultures are unnecessary in the majority of patients with GAS pharyngitis,[7] in selected children with recurrent pharyngitis, posttreatment test-

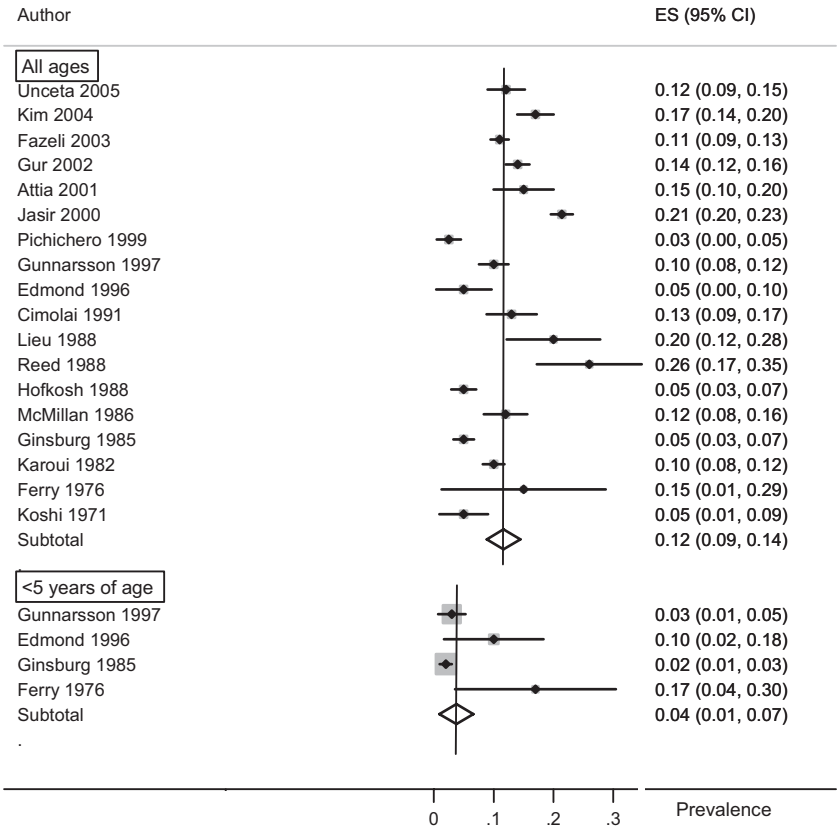

FIGURE 3
Prevalence (rectangles), 95% CI (lines), and pooled prevalence rate (diamonds) of streptococcal carriage in asymptomatic children, stratified by age.

ing may help to differentiate children with true recurrent GAS pharyngitis from carriers; children who are carriers are likely to have persistent GAS even after being treated with appropriate antimicrobial agents.

A somewhat surprising finding was that the prevalence of GAS infection and carriage did not vary significantly among studies that enrolled children only in the winter and those that enrolled children all year. Previous longitudinal studies, which are clearly better at identifying seasonal trends, have convincingly documented that GAS is a seasonal disease. There may be 2 reasons that this seasonality was not observed in our analysis. First, prevalence of GAS was not stratified by season in most of the articles. As such, we could not compare prevalence rates from the winter months with the prevalence rates in the rest of the year. Rather, we compared studies that enrolled children only during the winter with studies that enrolled children all year long. No studies enrolled children during the summer months only. In studies that enrolled children throughout the year, the majority of children were likely to have been enrolled during the winter months; therefore, because of how the data were reported, we were limited in our ability to discern seasonal trends in the data; our data do not conflict with the well-documented seasonality of GAS pharyngitis.

Our analysis had several limitations. The first limitation relates to the paucity of studies with data on children who were younger than 5 years. Additional study on the prevalence of GAS in preschool children is warranted. Second, the heterogeneity among studies could be considered a limitation. We used our clinical judgment and results of the meta-regression analysis to determine when studies were "too different" to be pooled. For example, rather than blindly pooling data from all of the studies, we present data for less heterogeneous subgroups of patients on the basis of age. Much of the remaining heterogeneity is likely attributable to the differences in implicit criteria used by investigators during enrollment. This would have led to differences in the clinical spectrum of patients who were included in various studies. In other words, although all studies met our inclusion criteria, the severity of symptoms of the children enrolled may have varied on the basis of the approach of the investigators or the objectives of the study. Nevertheless, by conducting a comprehensive review of the literature and by using strict a priori inclusion and exclusion criteria, our results provide a more complete picture of GAS prevalence than has previously been reported. Our results were robust to changes in the assumptions tested by sensitivity analyses, and the pooled estimates have relatively narrow CIs.

CONCLUSIONS

This study provides important information for the clinician regarding the expected prevalence of GAS from pharyngeal specimens obtained from children with sore throat and from children who are asymptomatic. The pooled prevalence values presented in this study can be used as an estimate of baseline probability and provide a basis for an evidence-based approach to the treatment of children with this frequently occurring condition.

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