

Prevalence of Group C *Streptococcus* and *Fusobacterium Necrophorum* in Patients With Sore Throat: A Meta-Analysis

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ABSTRACT

PURPOSE The prevalence of Group C beta-hemolytic *streptococcus* and *Fusobacterium necrophorum* among patients with sore throat in the outpatient setting has not been previously summarized. We set out to derive prevalence information from the existing literature.

METHODS We performed a systematic review of MEDLINE for studies reporting the prevalence of *F necrophorum* or Group C *streptococcus* or both in prospective, consecutive series of outpatients with sore throat, as well as laboratory-based studies of throat cultures submitted from primary care. We limited searches to studies where the majority of data was collected after January 1, 2000, to reflect contemporary microbiological methods and prevalences. Each author independently reviewed the articles for inclusion and abstraction of data; we resolved discrepancies by consensus discussion. We then performed a meta-analysis to calculate the pooled prevalence estimates using a random effects model of raw proportions.

RESULTS A total of 16 studies met our inclusion criteria. The overall prevalences of Group C *streptococcus* and *F necrophorum* were 6.1% (95% CI, 3.2%-9.0%) and 18.9% (95% CI, 10.5%-27.2%), respectively. When stratified by study type, the prevalences of Group C *streptococcus* and *F necrophorum* in laboratory-based studies were 6.6% (95% CI, -1.0% to 14.2%) and 18.8% (95% CI, 6.5%-31.1%), respectively. In primary care patients with sore throat, Group C *streptococcus* had a prevalence of 6.1% (95% CI, 3.1%-9.2%), while *F necrophorum* had a prevalence of 19.4% (95% CI, 14.7%-24.1%).

CONCLUSIONS Group C *streptococcus* and *Fusobacterium necrophorum* are commonly detected in patients with acute pharyngitis. Research is needed, however, to determine whether these bacteria are truly pathogenic in patients with pharyngitis and whether antibiotics reduce the duration of symptoms or the likelihood of complications.

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INTRODUCTION

Pharyngitis is an important cause of morbidity, and was responsible for 1.4% of all visits¹ to ambulatory care physicians in 2012, making it the 10th most common reason for such visits. While most cases of pharyngitis are viral, Group A beta-hemolytic *streptococci* are responsible for approximately 10% of episodes in adults and up to 30% in children.² Recently, it has been suggested that 2 other bacteria may be important causes of pharyngitis, but their prevalence has not been well described.

The first, Group C beta-hemolytic *streptococcus*, is often found in patients with acute pharyngitis. While it is traditionally not thought to be a pathogen, recent studies have found that it appears to cause symptoms similar to those caused by Group A *streptococcus*.^{3,4} For example, in a study of 606 adults in primary care who had sore throat, those with Group C or G streptococcal infection resembled those with Group A *streptococcus* in rapidity of onset, likelihood of adenopathy, intensity of pharyngeal inflammation, and likelihood of purulence.⁵ In addition, Group C *streptococcus* appears to share some of the virulence factors found in Group A.⁶ While

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it is not known to cause rheumatic fever, identification and treatment may reduce the duration of symptoms and the period of communicability of the infection.

The second organism, *Fusobacterium necrophorum*, is a known cause of serious complications of acute pharyngitis and is associated with recurrent sore throat, persistent sore throat syndrome, peritonsillar abscess, and Lemierre's syndrome.⁷ The latter is characterized by unilateral neck swelling due to suppurative thrombophlebitis of the internal jugular vein and may lead to sepsis, pulmonary abscess, and death.⁸

The prevalence of both of these pathogens, particularly in outpatient primary care, is not well known and has not been previously summarized. Therefore, we performed a meta-analysis to describe the prevalence of Group C *streptococcus* and *Fusobacterium necrophorum* among patients with sore throat in primary care.

METHODS

Inclusion and Exclusion Criteria

We included 2 types of studies: those that reported the prevalence of *F necrophorum* or Group C *streptococcus* in prospective, consecutive series of outpatients presenting with sore throat or clinically diagnosed pharyngitis, and laboratory-based studies that reported the prevalence of *F necrophorum* or Group C *streptococcus* in throat cultures submitted entirely or largely from outpatient or primary care (presumably for sore throat or clinically diagnosed pharyngitis). We report results separately for these groups, since laboratory-based studies may reflect a more highly selected group of patients with persistent, ambiguous, or severe symptoms. Acceptable reference standards included culture and polymerase chain reaction (PCR). In order to reflect contemporary microbiology and prevalences, we limited searches to studies where the majority of data was collected after January 1, 2000. We also limited our search to studies set in high-income countries that are also members of the Organisation for Economic Cooperation and Development (OECD)⁹ (Supplemental Appendix A, <http://www.annfammed.org/content/14/6/567/suppl/DC1>). We defined outpatient care as including patients presenting to a primary care physician, an urgent care clinic, or an emergency department.

We excluded studies without an abstract; studies that included only or predominantly immunocompromised patients; studies that included predominantly patients with hospital-acquired or recurrent tonsillitis, peritonsillar abscess, or invasive streptococcal disease; and studies of special or unusual populations. We also excluded case-control studies, case reports, case series, retrospective studies, outbreak investigations, and studies that did not use throat culture or PCR as a reference standard test.

Search Strategy

For Group C *streptococcus*, we conducted a systematic review of MEDLINE using 2 search strategies. The first focused on the prevalence, incidence, and epidemiology of Group C *streptococcus* among patients with pharyngitis in outpatient care and was limited to studies in English or German. Because this search identified only 42 abstracts, we performed a second search on the differential diagnosis of pharyngitis without language limits, resulting in a total of 202 abstracts for Group C *streptococcus*. For *F necrophorum*, we performed a search similar to the initial search for Group C *streptococcus* but included complications such as peritonsillar abscess and Lemierre's syndrome. This returned only 79 abstracts, so again we used a secondary search that excluded peritonsillar abscess and Lemierre's syndrome but added pharyngitis. The *F necrophorum* search strategies returned a total of 191 abstracts. Appendix B includes detailed search terms used for each strategy (Supplemental Appendix B, <http://www.annfammed.org/content/14/6/567/suppl/DC1>). We also searched the first 200 studies identified by MEDLINE as related to a highly relevant publication by Amess and colleagues in 2007,¹⁰ as well as the reference lists of included studies and of any review articles that were identified. We reran the searches in December, 2015, just before we wrote the manuscript.

Data Abstraction

Both investigators reviewed abstracts for each search in tandem, and both reviewed in full studies that seemed likely to meet our inclusion criteria. For each included study, we both abstracted study characteristics and data regarding prevalence, resolving any discrepancies by consensus discussion. Results were stored in a series of Google Drive spreadsheets and imported into the statistics package for analysis.

Study Quality

There are no widely accepted standard instruments for evaluating the quality of studies of prevalence like those used in meta-analyses of diagnosis or therapy studies.^{11,12} Characteristics that we felt were important to ensure generalizability were built into our inclusion and exclusion criteria to assure a uniformly high level of quality for the included studies. Specifically, for studies of outpatients with sore throat or pharyngitis, we included only studies of consecutive, prospective samples of patients. We excluded case-control and retrospective clinical studies. For laboratory-based studies, we included only those reporting on a consecutive series of all submitted throat swabs or a random sample of throat swabs from a defined period. Finally, we included only studies with a high quality, valid reference standard (PCR or culture).

Analysis

Pooled prevalence estimates were calculated with random effects model of raw proportions. The double arcsine transformation has been recommended for the meta-analysis of prevalence,¹³ but we found that pooled estimates do not vary significantly following transformation. Therefore, we used raw proportions for clarity and understanding of true prevalence numbers. Statistical analysis was performed in R, version 3.2.2, including plots of prevalences for each infection using the metafor procedure. We quantified heterogeneity using the I^2 statistic, which represents the proportion of total variance that is due to between-study rather than within-study variability.¹⁴ It is important to note that I^2 is of limited value and may give exaggerated estimates of heterogeneity when there are a small number of studies, as in our analysis.¹⁵

RESULTS

Our initial search of the literature returned 404 articles for Group C *streptococcus* and 391 for *F necrophorum*. After review of the abstracts, we reviewed 21 articles for Group C *streptococcus* and 26 for *F necrophorum* in detail. Review of the reference lists identified an additional 16 studies for Group C *streptococcus* and 2 for *F necrophorum* that we reviewed in full. In the end, a total of 14 studies from these 2 searches met our inclusion criteria.^{4,5,10,16,17-26} An updated search made just before we wrote the manuscript identified 2 additional studies^{7, 27} for a final count of 16 included studies (Figure 1). Table 1 summarizes the study characteristics: 6 reported the prevalence of Group C *streptococcus*,^{4,5,17-20} 3 the prevalence of *F necrophorum*,^{16,21,22} and 7 the prevalence of both pathogens.^{7,10, 23-27} Data collection ranged from 2000 to 2014 and took place in 9 countries.

The prevalence of Group C *streptococcus* is summarized in the forest plot in Figure 2. The overall prevalence of Group C *streptococcus* was 6.1% (95% CI, 3.2%-9.0%) with a range from 0.5%¹⁴ to 24.8%.¹⁰

As mentioned above, we stratified studies into 2 types: studies of outpatients with sore throat and laboratory-based studies that reported the results of any throat swabs sent to a participating laboratory. The prevalence of Group C *streptococcus* was similar in the two groups of studies (6.1%, 95% CI, 3.1%-9.2% in outpatients with sore throat and 6.6%, 95% CI, -1.0% to 14.2% in laboratory studies). There was significant heterogeneity, with an I^2 statistic of 98% for all studies. As we said above, though, heterogeneity may be inflated when the number of studies is small,¹⁵ and 8 of 13 studies of Group C *streptococcus* reported a prevalence between 0.5% and 5.0%, while only 2 studies reported a prevalence greater than 10%. Heteroge-

neity for Group C *streptococcus* prevalence calculated separately for outpatient studies was 94% and for laboratory-based studies was 98%, although dropping an outlier with a prevalence of 25%²⁵ lowered the heterogeneity to 68% for laboratory-based studies.

Figure 3 shows a forest plot summarizing the prevalence of *F necrophorum*. The overall prevalence was 18.9% (95% CI, 10.5%-27.2%). Again, the forest plot is stratified by study type: studies of outpatients with sore throat and laboratory-based studies reporting on throat swabs sent to a participating laboratory. *F necrophorum* prevalence ranged widely in the studies, from 4.9%¹⁰ to 51.4%.²⁵ Stratified by setting, the summary estimate of prevalence was 18.8% (95% CI, 6.5%-31.1%) in laboratory-based studies and 19.4% (95% CI, 14.7%-24.1%) in outpatient studies. Again, there was a large amount of heterogeneity, with an overall I^2 statistic of 99%. Visual inspection of the forest plot confirmed significant heterogeneity for studies of *F necrophorum*, especially among the laboratory-based studies. Considered separately, the outpatient studies had an I^2 of 62%, although this may be inflated by the small number of studies, and all of the CIs overlapped.

Four studies included primarily patients from what may be described as a late adolescent and young adult or "college age" populations. They found prevalences of Group C *streptococcus* of 6.4%²¹ and 24.8%,²⁵ and prevalences of *F necrophorum* of 20.5%,⁷ 22.2%,²² 23.4%,²¹ and 51.4%.²⁵ In each case, the prevalence of the pathogen was higher than the overall mean prevalence, consistent with previous observations that these pathogens are more common in young adult populations.⁷

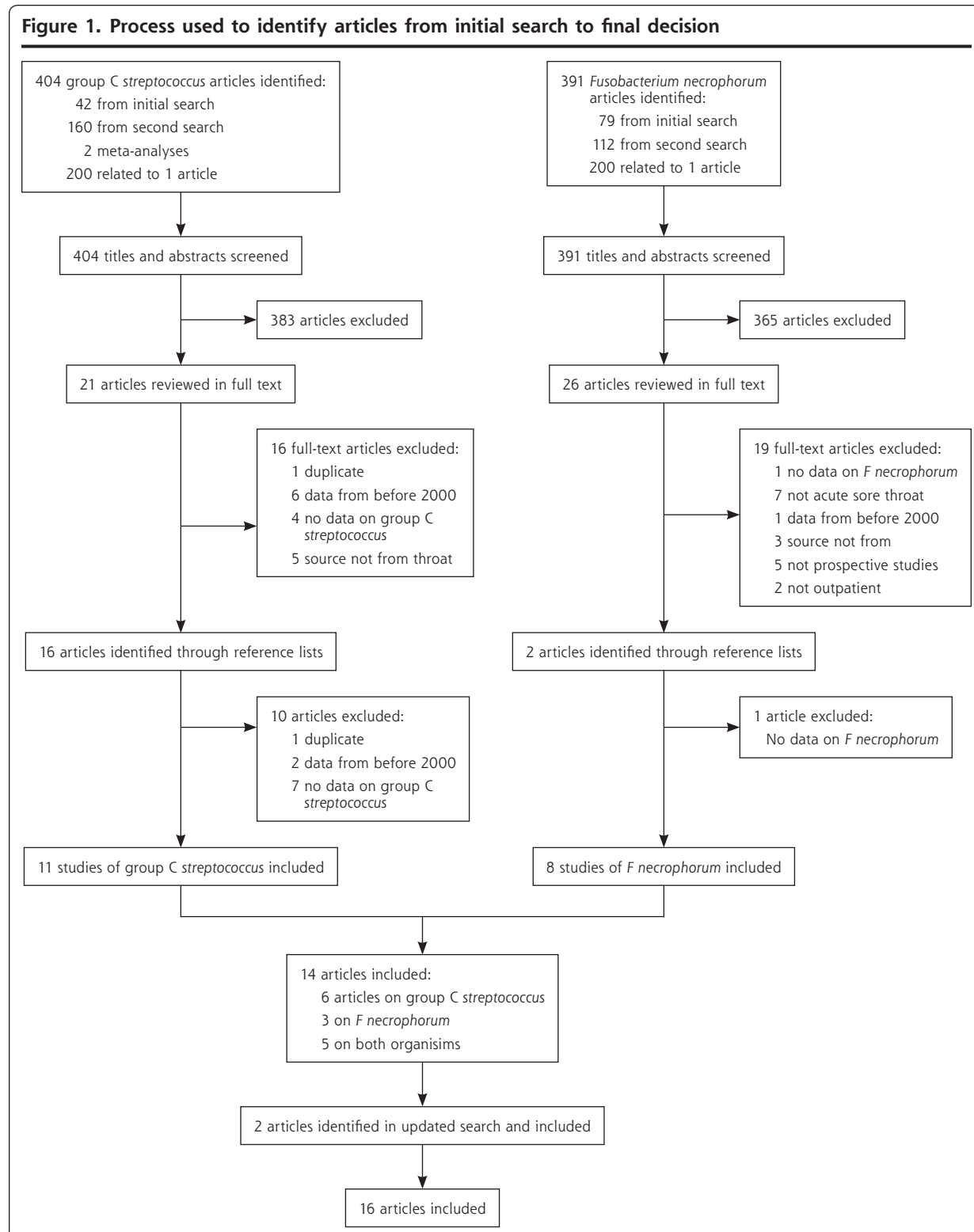
DISCUSSION

In patients with acute pharyngitis or tonsillitis, Group C *streptococcus* and *F necrophorum* are both relatively common. Whether this is clinically important remains to be determined; it depends on whether they are merely colonizing the pharynx or are pathogens. One study compared the bacteria and viruses detected in throat cultures from 220 patients with acute pharyngotonsillitis with those found in 128 asymptomatic controls. They found higher percentages of patients with Group C *streptococcus* (3.6% vs 0.8%, $P = .16$) and *F necrophorum* (15.0% vs 3.1%, $P = .001$) in the symptomatic patients, ratios similar to those for Group A *streptococcus* (30% vs 2.3%, $P < .001$) and rhinovirus (6.4% vs 2.3%, $P = .09$).²⁷ Another found *F necrophorum* in 14 of 85 university students with sore throat (16.5%), compared with 29 of 326 who were asymptomatic (8.9%).²¹ Most recently, Centor and colleagues found higher rates of both *F necrophorum* (20.5% vs 9.4%) and Group C *streptococcus* (9.0% vs 3.9%) in university students with sore throat than in asymptomatic controls.⁷ Little and colleagues argue

that Group C *streptococcus* is a likely pathogen because it has the same virulence factors as Group A *streptococcus* (streptokinase, M proteins, peptidase, and a hyaluronic capsule), can cause septicemia, and is associated with

signs and symptoms similar to those of Group A *streptococcus*.⁵ *Fusobacterium necrophorum* is clearly a pathogen in rare patients with Lemierre's syndrome and is often found in patients with peritonsillar abscess, but based on our findings may

Figure 1. Process used to identify articles from initial search to final decision



be a more common cause of pharyngitis than previously recognized, especially in younger adults.

Table 2 summarizes the clinical signs and symptoms of patients with pharyngitis associated with Group A *streptococcus*, Group C *streptococcus*, and *F necrophorum* from 3 studies, 1 of which included *F necrophorum*.^{4,5,7} The clinical presentations are very similar for patients with any of the 3 bacteria, again supporting the idea that they may be pathogenic.

The argument for detection and treatment is three-fold. While Group C *streptococcus* is not a cause of rheumatic fever, this is an exceedingly rare complication

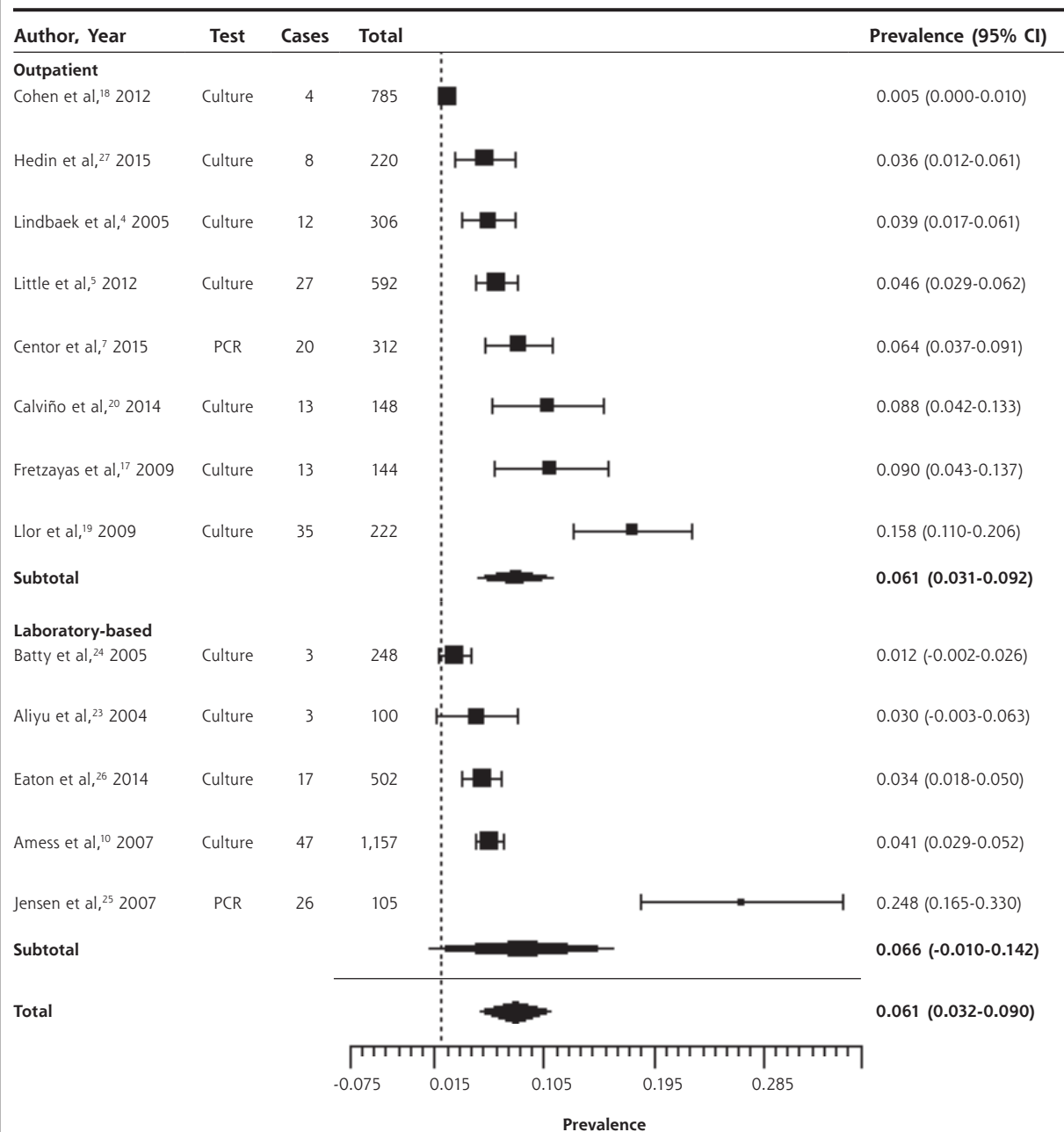
of Group A *streptococcus*, and treatment solely for that purpose is not cost-effective.²⁸ Treatment of all 3 infections, however, may reduce the duration of symptoms, decrease the likelihood of spread (particularly in communal living settings such as universities), and for *F necrophorum* it has may prevent rare complications such as peritonsillar abscess and Lemierre's syndrome. It is premature, however, to recommend antibiotic treatment for these pathogens. The natural history of *F necrophorum* and Group C *streptococcus* are currently poorly understood, and we agree with others that randomized trials of antibiotic treatment are needed.²⁹

Table 1. Characteristics of Studies Reporting the Prevalence of Group C beta hemolytic *Streptococcus* and *Fusobacterium necrophorum*

Author, Year (Country)	Population	Age	Setting ^a	Years of Data Collection	Diagnostic Method
Group C <i>Streptococci</i>					
Lindbaek et al, ⁴ 2005 (Norway)	Adults and children with sore throat for <7 d and no recent antibiotic presenting to GP.	Mean 23.9 y; 244 adults, 62 children <10 y	Primary care	2000-2002	Culture
Fretzayas et al, ¹⁷ 2009 (Greece)	Children with pharyngitis and no recent antibiotics presenting to an outpatient clinic.	Mean 6.5 y, range 4 y-14 y	Primary care	2006	Culture
Little et al, ⁵ 2012 (England)	Adults and children presenting to a GP with sore throat for <14 d as the primary symptom.	≥5 y; 11% were 5 y-9 y	Primary care	2007-2008	Culture
Cohen et al, ¹⁸ 2012 (France)	Children with pharyngitis and no recent antibiotics presenting to their pediatrician.	Mean 6.1 y, range 3 y-5 y	Primary care	2008-2010	Culture
Llor et al, ¹⁹ 2009 (Spain)	Adults presenting to GP with acute pharyngitis and ≥2 Centor criteria.	Mean 30.6 y, range ≥14 yr	Primary care	2007-2008	Culture
Calvino et al, ²⁰ 2014 (Spain)	Adults presenting to an outpatient health center with pharyngitis and all 4 Centor criteria.	Mean 28.5 y, range 18 y-51 y	Primary care	2010-2012	Culture
<i>Fusobacterium necrophorum</i>					
Ludlam et al, ²¹ 2009 (United Kingdom)	Two groups: 411 students, of whom 85 had a sore throat, and 103 patients presenting to a GP with sore throat.	University students: median 20 y, range 18 y-39 y GP patients: median 26 y, range 2 y-77 y	Primary care	2005-2006	PCR
Bank et al, ¹⁶ 2010 (Denmark)	All throat swabs submitted to a regional laboratory from primary care practice during 2 mo.	Median 20 y, range 0 y-57 y	Laboratory-based	2009	PCR
Bank et al, ²² 2013 (Denmark)	All throat swabs submitted to a regional laboratory from primary care practices for patients age 15 y-24 y.	Range 15 y-24 y	Laboratory-based	2007-2009	Culture
Both pathogens					
Aliyu et al, ²³ 2004 (United Kingdom)	Random sample of 100 throat swabs submitted by primary care physicians during 7 mo.	Mean 25 y, range 5 mo-79 y	Laboratory-based	2003	Culture
Batty et al, ²⁴ 2005 (United Kingdom)	All throat swabs received during a 4 wk period.	1 y-47 y	Laboratory-based	2005	Culture
Amess et al, ¹⁰ 2007 (United Kingdom)	All throat swabs received during 6 mo.	<1 y to 88 y	Laboratory-based	2004-2005	Culture
Jensen et al, ²⁵ 2007 (Denmark)	All throat swabs received during 7 mo from patients with a diagnosis consistent with tonsillitis or pharyngitis.	Range 18 y-32 y	Laboratory-based	2005-2006	PCR
Eaton et al, ²⁶ 2014 (United Kingdom)	All throat swabs received during 1 y.	Not reported; largely 10 y-49 y	Laboratory-based	2011-2012	Culture
Hedin et al, ²⁷ 2015 (Sweden)	Adults presenting to a GP with acute pharyngo-tonsillitis.	Median 33 y, range 15 y-48 y	Primary care	2011-2012	Culture
Centor et al, ⁷ 2015 (United States)	Adults with sore throat presenting to a college health center.	Mean 22.3 y, range 15 y-30 y	Primary care	2013-2014	PCR

GP = general practitioner; PCR = polymerase chain reaction.

^a Primary care includes outpatient generalist clinics such as general practice, family medicine, general internal medicine, and pediatrics.

Figure 2. Forest plot of Group C streptococcus prevalence in sore throats in the outpatient and laboratory-based setting, sorted by prevalence

$I^2 = 97.28$; PCR = polymerase chain reaction

Centor argues that a randomized trial of antibiotics would be unethical in patients with *F necrophorum* associated pharyngitis.⁷ We respectfully disagree, since the serious complication of Lemierre's syndrome is exceedingly rare. A college health population would be the ideal setting for such a trial, given the frequency of both bacteria in young adults with sore throat. One could obtain throat cultures in all patients presenting with sore

throat, and randomize those with a Centor score of 2 or more and a negative rapid test for Group A streptococcus to antibiotic or placebo. The antibiotic or placebo could be discontinued for those with a negative culture for Group C streptococcus or *F necrophorum*, but continued for those with a positive culture for 1 of these pathogens.

Most of the included studies excluded patients who had received antibiotics before enrollment. Seven stud-

ies did not mention including or excluding patients with prior antibiotic use.^{5,10,16,20,22,24,26} Of these 7, 5 were laboratory-based. It was because the laboratory-based studies did not indicate why swabs were submitted or provide details regarding previous antibiotics that we stratified our analysis by setting. The prevalence in laboratory-based studies was similar to that in outpatient primary care studies, however, suggesting that they were including similar patients.

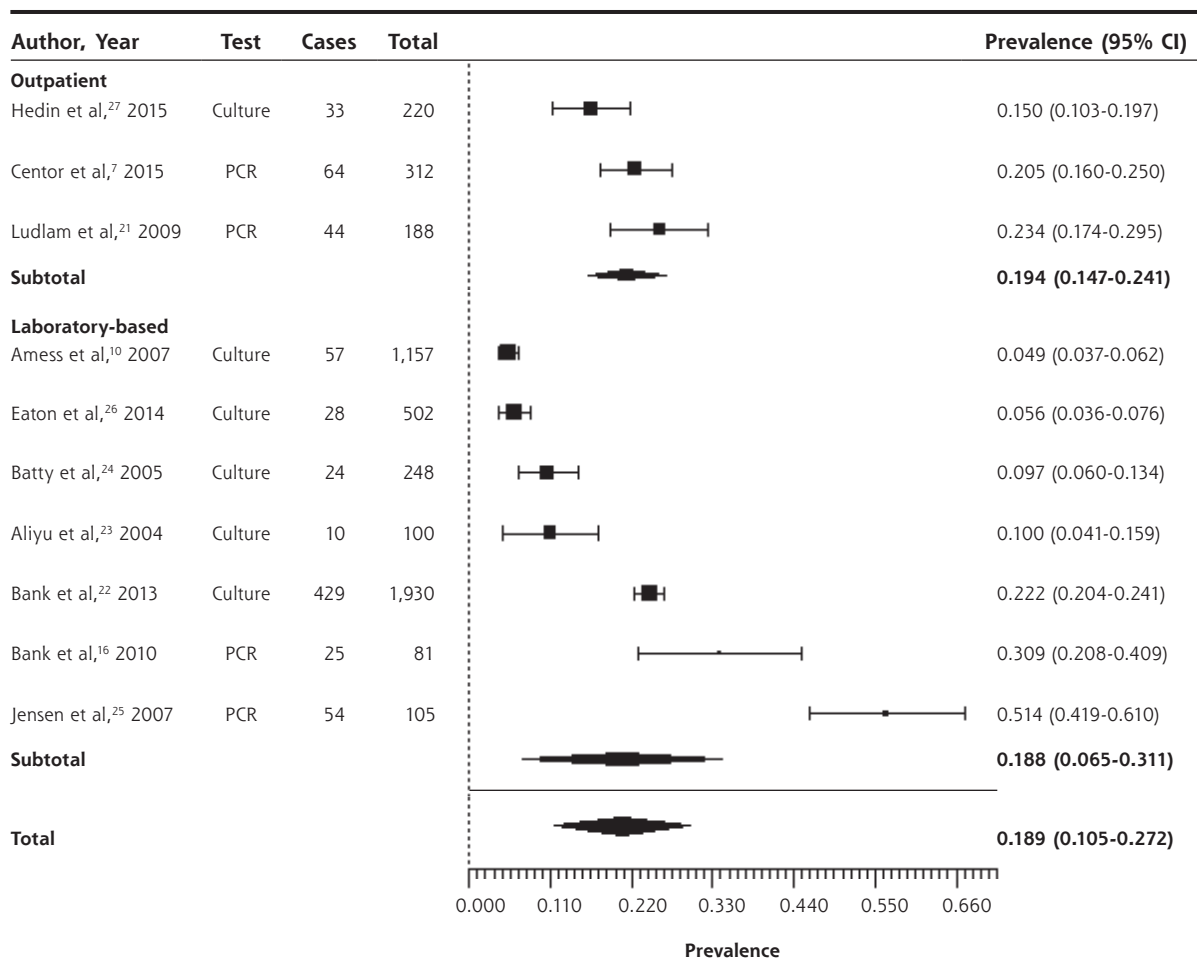
Our analysis had several limitations. First, most of the studies of outpatients that we included, especially for *F necrophorum*, were in young adults and university health centers. The prevalence in other age groups is therefore less certain. Second, we found considerable unexplained heterogeneity, especially in

Table 2. Prevalence of Signs and Symptoms in Patients With Pharyngitis Associated With Group A streptococcus, Group C streptococcus, and Fusobacterium necrophorum

Symptom or Sign	Percentage With this Sign or Symptom		
	Group A streptococcus	Group C streptococcus	<i>F necrophorum</i>
Cervical adenopathy ^{4,5,7}	71-91	82-93	66
Absence of cough ^{4,5,7}	67-90	63-80	62
Fever ^{4,5,7}	29-80	47-76	38
Tonsillar exudates ^{4,5,7}	25-52	24-56	34
Redness in pharynx ⁴	88	79	NT
Pain on swallowing ⁴	57	36	NT
Duration ≤3 d ⁵	70	64	NT
Severely inflamed tonsils ⁵	30	38	NT
Absence of runny nose ⁵	71	76	NT

NT = not tested.

Figure 3. Forest plot of Fusobacterium necrophorum prevalence in sore throats in the outpatient and laboratory-based setting, sorted by prevalence



I² = 98.71; PCR = polymerase chain reaction

the laboratory-based studies of *F necrophorum*. This may be due to differences in laboratory techniques or the gathering of samples, in study populations, or in other unrecognized factors. Furthermore, PCR is an evolving technology for the detection of *Fusobacterium*, and the sensitivity may vary based on the specific sequences used and may be falsely elevated due to contamination with other samples. Last, our search was limited to the only database available to us, MEDLINE; the inclusion of other databases may reveal additional studies not included in this analysis.

In summary, our systematic review confirms that both Group C streptococcus and *F necrophorum* are commonly found in patients with acute pharyngitis, especially in young adult populations, and further study (including randomized controlled trials of treatment) is needed to determine whether treatment is beneficial.

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Key words: pharyngitis, Group C streptococcus prevalence, *Fusobacterium necrophorum* prevalence, primary care

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