OPEN

A Longitudinal Study of Group A Streptococcal Colonization and Pharyngitis in US Children

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Background: Group A streptococci (GAS) are a major cause of pharyngitis in children. Recently, there were severe GAS outbreaks. The aims of this study were to assess pharyngeal colonization prevalence in healthy children, to assess different diagnostic definitions for GAS pharyngitis and to estimate incidence rates for these infections.

Methods: A 2-year longitudinal study was conducted in healthy children in the United States. Pharyngeal swabs were cultured every 3 months for GAS colonization. Serum antistreptolysin O, antideoxyribonuclease B (DNaseB) and antistreptococcal C5a peptidase (SCP) antibody titers were assessed at baseline. When participants developed a sore throat, pharyngeal swabs were collected for rapid antigen detection test (RADT) and culture, and antibody titers were determined in serum samples. A range of case definitions were used for GAS pharyngitis.

Results: A total of 422 children 3–12 years old were enrolled (140, 141 and 141 were 3–5, 6–9 and 10–12 years of age, respectively). The overall prevalence of GAS colonization during the study was 48%. Baseline antistreptolysin O, anti-DNaseB and anti-SCP antibody titers were higher for children older than 5 years. The incidence of GAS pharyngitis per 100 person-years was 15.9 for RADT/culture-proven and 4.6 for serologically confirmed pharyngitis.

Conclusions: GAS throat colonization and pharyngitis were frequent in children 3–12 years old. The case definition employed impacted the measured incidence of GAS pharyngitis, with higher rates detected using RADT/culture-based definitions. These data suggest that case definition is important and that young children are exposed to GAS, which may inform plans for vaccine development and implementation.

Key Words: group A streptococcus, GAS pharyngitis, antistreptococcal C5a peptidase antibodies, antistreptolysin O, deoxyribonuclease B

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Streptococcus pyogenes or group A streptococcus (GAS) colonizes human mucosa, including the throat,[1] and can cause acute exudative pharyngitis (known as "strep throat") common in school-age children with some winter and spring seasonality in the United States[2] and Australia.[3] In the United States, ~12 million pediatric outpatient visits are attributable to pharyngitis each year,[4–6] with GAS estimated to account for 24%–37% of childhood sore throat visits.[1,7,8] Recent years have seen outbreaks of more severe GAS.[9,10]

GAS is also the leading cause of childhood-acquired heart disease worldwide. In 5–14-year-old children, GAS results in 336,500 cases of acute rheumatic fever, an estimated 282,000 new cases of rheumatic heart disease (RHD), and >233,000 associated deaths annually.[11] Global prevalence of RHD is >34.2 million cases,[12] and >100 million cases of impetigo occur yearly.[11,13] Episodic life-threatening invasive GAS infections in North America[14,15] and worldwide[15,16] and the persistence of poststreptococcal sequelae (PSS), such as rheumatic fever and RHD, globally,[11,16] result in significant morbidity, mortality and worldwide health and economic costs.[17–19]

Accurate diagnosis of streptococcal pharyngitis, especially in the context of severe outbreaks of highly pathogenic GAS,[20–23] is essential for the prevention of suppurative and nonsuppurative complications of infection, including rheumatic fever and RHD, as well as preventing the spread of infection.[2] However, signs and symptoms of GAS and viral pharyngitis broadly overlap, rendering diagnosis of GAS pharyngitis on clinical grounds alone difficult.[2] Diagnosis of GAS pharyngitis is further complicated by asymptomatic GAS carriage.[1] Therefore, detection of GAS in the throat, by culture-positive pharyngeal swab or rapid test, is not necessarily pathognomonic of GAS pharyngitis.

Measurements of GAS-specific antibody responses have been employed to evaluate GAS infection, but increases in titer only occur after infection so cannot reliably inform acute treatment decisions.[2,24] Indeed, antistreptolysin O (ASO) titers peak 3–5 weeks after infection, while antideoxyribonuclease B (anti-DNaseB) titers peak 4–6 weeks after infection and may remain elevated for months.[25,26] Even so, studies have prospectively examined rises in ASO,[3,27] anti-DNaseB and antistreptococcal C5a peptidase (anti-SCP)[27] antibody titers associated with episodes of GAS pharyngitis in children, with a suggestion that these measurements might improve diagnostic specificity.[3,27]

No licensed vaccine is available to prevent GAS-mediated infections.[28] While the low frequency of PSS would require a large efficacy study, GAS pharyngitis is both common and a precursor to PSS. A GAS pharyngitis vaccine efficacy trial requires an appropriate case definition for GAS pharyngitis. Paired collection of pharyngeal swabs and blood samples could show the relationship between antibody levels, asymptomatic carriage and pharyngitis. These data can identify when children are first exposed to GAS and thus inform appropriate vaccination timing. A point prevalence study in 0–10-year-old children demonstrated that after the maternal GAS-associated antibodies waned, they increased at ~10 months of age, indicating the need for early intervention via vaccination.[29] This study aimed to enhance the understanding of clinical and epidemiological

features of GAS colonization and antibody responses during episodes of GAS pharyngitis in US children, with the potential to inform future vaccine development and implementation.

METHODS

Study Design

This 2-year longitudinal, prospective, cohort study assessed GAS throat colonization and pharyngitis incidence in US children at 9 clinical sites following the International Conference on Harmonization guidelines.[30,31] Written informed consent was obtained from all parents/legal guardians (with the child's assent as applicable) prior to study enrollment, following local Institutional Review Board approval of study documents.

Study Participants

Eligible participants were healthy children 3–12 years old at enrollment. Children with a history of culture-confirmed invasive streptococcal disease, RHD, glomerulonephritis, confirmed streptococcal pharyngitis or impetigo within the preceding month, bleeding disorder, known/suspected immunodeficiency condition or receipt of immunoglobulins within the past year were ineligible.

Assessments

At study entry, a physical examination was performed, and a pharyngeal swab and a blood sample were taken.

GAS Pharyngeal Carriage

At healthy visits (months 3, 6, 9 12, 15, 18, 21 and 24), a pharyngeal swab for microbiological culture was obtained. Healthy visits could not occur until ≥6 weeks after any sick visit.

GAS Pharyngitis

An episode of sore throat triggered sick visit 1, which was followed by 2 subsequent sick visits (sick visits 2 and 3), depending on the initial evaluation (Fig. 1A).

1. Sick visit 1 included physical examination, temperature recording and examination of pharynx, tonsils and cervical nodes. Two throat swabs for rapid antigen detection test (RADT) and culture and a blood sample were collected. Children with pharyngitis and a positive RADT/throat swab culture received antibiotic treatment as per local guidelines and returned for sick visit 2.
2. Sick visit 2 occurred 7–10 days after antibiotic completion and included a physical examination with examination of pharynx, tonsils and cervical nodes and collection of a throat swab and a blood sample.
3. Sick visit 3 (convalescent, 4–6 weeks after sick visit 1) included collection of a throat swab for culture and a blood sample.

Microbiology

At study entry, healthy and sick visits, 1 pharyngeal swab was collected from both tonsils and postpharyngeal wall and shipped at ambient temperature same-day to Quest Laboratories for plating on sheep blood agar for up to 48 hours. Beta-hemolytic streptococcus colonies were grouped by latex agglutination using Streptex (Thermo Fisher Scientific; Waltham, MA).

A color immunographic assay, RADT, was performed at point-of-care using the Sure-Vue Signature Strep A Test Kit (Fisher HealthCare; Houston, TX) on throat swabs for all subjects attending sick visit 1. The result was recorded as either positive or negative.

Serology

Blood samples processed to serum were assessed for antibody levels to streptolysin O, DNaseB and SCP.

ASO and anti-DNaseB titers were determined using standardized immunoturbidometric and nephelometric assays, respectively, at Quest Laboratories and reported in international units per milliliter (I U/mL). Anti-SCP titers were determined using a competitive Luminex immunoassay and reported in units per milliliter (U/mL).[29]

GAS Carriage Case Definition

GAS carriage was defined as:

1. Positive healthy visit GAS culture.
2. A RADT- or culture-confirmed GAS-positive result at sick visit 1 that remained positive at sick visit 2 (7–10 days postantibiotic treatment completion).

GAS Pharyngitis Case Definitions

Five case definitions were explored for GAS pharyngitis.[3,27]

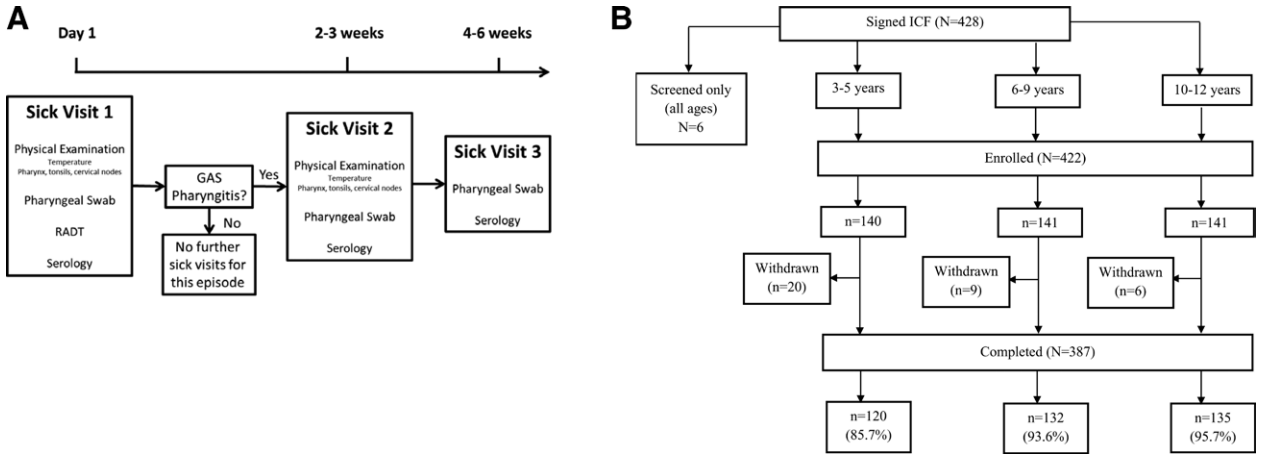

FIGURE 1. A: Sequence of sick visits and assessments following a sore throat episode. B: Subject disposition. ICF indicates informed consent form.

Primary case definition included:
1. Sore throat at sick visit 1.
2. GAS-positive RADT/throat swab at sick visit 1.
3. GAS-negative throat swab at sick visit 2.[32]

Exploratory case definition included:
1. Primary case definition.
2. ≥2-fold increase in ASO, anti-DNaseB and/or anti-SCP antibody titer 4–6 weeks after pharyngitis.[27]

Alternate case definition A included:
1. Primary case definition.
2. Fever (>100.4°F).

Alternate case definition B included:
1. Alternate case definition A.
2. Tender, enlarged cervical lymph nodes, exudate, tonsil inflammation and/or pharynx inflammation.

Alternate case definition C (aligning with the Centor criteria for GAS pharyngitis[33]) included:
1. Alternate case definition A.
2. Tender, enlarged cervical lymph nodes.
3. Exudate, tonsillar inflammation or pharynx inflammation.

Safety

Serious adverse events and protocol-related adverse events were collected Days 1–7 following each visit involving throat swabs/blood draws.

Statistical Analysis

Descriptive statistics were calculated for continuous variables, along with incidence, prevalence and 95% confidence intervals for pharyngitis and carriage.

Serology

Fold rises (exploratory case definition) and ASO, anti-DNaseB and anti-SCP kinetic and reverse cumulative distribution curves were generated for the first episode of GAS pharyngitis. Percent of children with a prespecified rise[3,27] in titers from sick visit 1 to sick visit 3 or control were also calculated. Geometric mean fold rises were calculated from baseline to sick visit 1, sick visit 1 to sick visit 2 and sick visit 1 to sick visit 3 for the primary and exploratory case definitions by age group, and overall.

RESULTS

Individual Disposition and Baseline Characteristics

The study enrolled 422 subjects (140, 141 and 141 were 3–5, 6–9 and 10–12 years of age, respectively); ≥85.7% of the subjects by age group completed the study. The most common reasons for withdrawal included parent/legal guardian request in the 3–5 age group (5%), subject request in the 6–9 age group (2.1%) and subject request and lost to follow-up in the 10–12 age group (1.4% each) (Fig. 1B).

The 3 age groups were comparable with respect to sex, race and ethnicity. The subjects in each group were predominantly White. The proportion of subjects categorized as Black/African American, Hispanic or Latino was higher in the 3–5 age group compared with the 6–9 and the 10–12 age groups. The overall mean age in years (± standard deviation) at enrollment was 8.0 (±2.99), and was 4.5 (±0.90) in the 3–5 age group, 8.1 (±1.11) in the 6–9 age group and 11.5 (±0.85) in the 10–12 age group (Table 1).

TABLE 1. Demographic Characteristics (Enrolled Population)

	Age Group*			
	3–5 Years N† = 140	6–9 Years N = 141	10–12 Years N = 141	Total N = 422
Sex, n‡ (%)				
Male	81 (57.9)	74 (52.5)	84 (59.6)	239 (56.6)
Female	59 (42.1)	67 (47.5)	57 (40.4)	183 (43.4)
Race, n (%)				
White	101 (72.1)	123 (87.2)	118 (83.7)	342 (81.0)
Black or African American	28 (20.0)	15 (10.6)	18 (12.8)	61 (14.5)
Other	9 (6.4)	2 (1.4)	3 (2.1)	14 (3.3)
Asian	2 (1.4)	1 (0.7)	2 (1.4)	5 (1.2)
Ethnicity, n (%)				
Non-Hispanic and Non-Latino	130 (92.9)	140 (99.3)	138 (97.9)	408 (96.7)
Hispanic or Latino	10 (7.1)	1 (0.7)	3 (2.1)	14 (3.3)
Age at enrollment, years				
Mean (standard deviation)	4.5 (0.90)	8.1 (1.11)	11.5 (0.85)	8.0 (2.99)
Median	4.5	8.1	11.5	8.1

*Age at enrollment.
†N = number of participants in the specified age group, or total sample.
‡n = number of participants in the specified category.

GAS Throat Carriage

GAS throat carriage was common in all 3 age groups, with an overall prevalence rate of 48%, declining with age from 63% in the 3–5 age group to 52% in the 6–9 age group to 30% in the 10–12 age group. Prevalence of GAS throat carriage ranged from 12% to 20% across each of the individual quarterly visits. Overall incidence was 24.9/100 patient-years, falling from 39.2/100 patient-years in the 3–5 age group to 15.1/100 patient-years in the 10–12 age group (Fig. 2A). Overall incidence rate of GAS colonization was higher in winter (36.7/100 patient-years) and lowest in summer (9.7/100 patient-years) (Fig. 2B, Table, Supplemental Digital Content 1, http://links.lww.com/INF/F262). The age group highest point estimate was in spring for the 3–5 age group (68.1/100 patient-years) and winter for older children (44.5 and 26.9/100 patient-years for 6–9 and 10–12 age groups, respectively); all groups were lowest in summer (15.7, 9.1 and 5.3/100 patient-years for 3–5, 6–9 and 10–12 age groups, respectively) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/F262).

GAS Pharyngitis

According to the primary case definition, GAS pharyngitis incidence was higher in the 3–5 age group (19.5/100 person-years) compared with the other age groups (14.7 and 13.9/100 person-years for the 6–9 and 10–12 age groups, respectively) (Fig. 2A).

GAS pharyngitis incidence by the exploratory case definition (the primary case definition plus a ≥2-fold increase in ASO, anti-DNaseB and/or anti-SCP antibody titers[27]) was lower (4.6 vs. 15.9/100 person-years, respectively) and skewed toward the older age group (5.9/100 person-years in the 10–12 age group), compared with the younger age groups (4.1/100 person-years in the 3–5 age group, 3.9/100 person-years in the 6–9 age group) (Fig. 2A).

GAS pharyngitis incidence was evaluated by 3 additional case definitions that included clinical symptoms. Inclusion of fever in case definition A resulted in a lower incidence of GAS pharyngitis in the 3–5 age group (19.5 to 8.3/100 patient-years) (Fig. 2A).

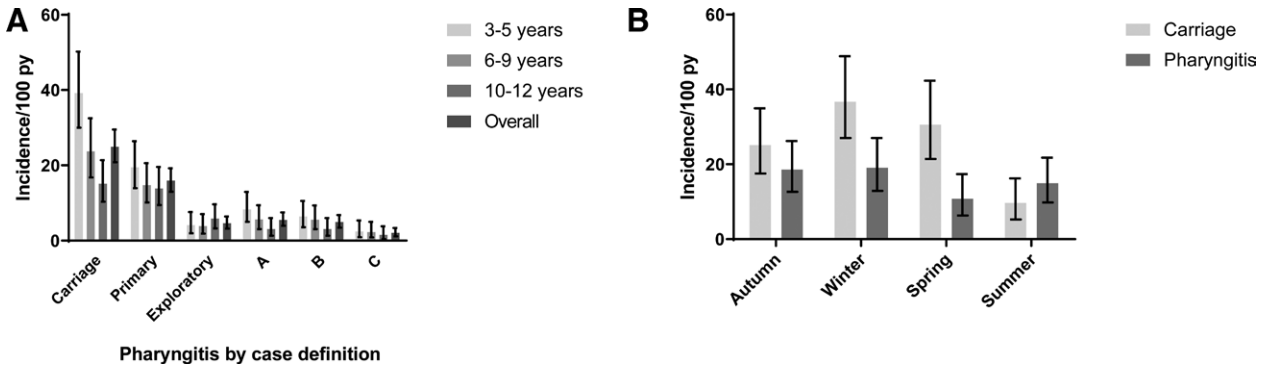

FIGURE 2. A: Incidence/100 patient-years (py) of GAS pharyngeal carriage and of GAS pharyngitis by case definition. For details of GAS pharyngeal carriage and GAS pharyngitis case definitions see Methods. Bars are 95% confidence intervals. B: Incidence/100 patient-years (py) of GAS pharyngeal carriage by season and of GAS pharyngitis by primary case definition by season. For definition of seasons, GAS pharyngeal carriage and GAS pharyngitis primary case definition see Methods. Bars are 95% confidence intervals.

Inclusion of additional clinical signs further reduced GAS pharyngitis incidence, to 6.4/100 and 2.5/100 patient-years with alternate case definitions B and C, respectively. Similar trends were observed in the 6–9 and 10–12 age groups (Fig. 2A).

Overall, GAS pharyngitis incidence was seasonal, with an incidence of 18.6/100 and 19.1/100 patient-years observed in autumn and winter, respectively (Fig. 2B). The age group highest point estimate was in winter (27.7/100 patient-years) for the 3–5 age group, and autumn for older children (20.4 and 15.3/100 patient-years for 6–9 and 10–12 age groups, respectively) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/F262). The 3–5 and 10–12 age groups were lowest in spring (12.3 and 9.2/100 patient-years, respectively), and the 6–9 age group was lowest in spring and summer (11.2/100 patient-years for each of seasons) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/F262).

Impact of GAS Pharyngitis on Antibody Titers

Kinetic curves of ASO, anti-DNaseB and anti-SCP antibody titers were lower at baseline and throughout the sick visits for the 3–5 age group at the first pharyngitis episode compared with the older age groups (Fig. 3). For the 3–5 age group, there was a modest increase in titers from baseline to sick visit 2, whereas the older age groups curves were relatively flat.

Differences in ASO RCDF curves between sick visits 1, 2 and 3 by the primary case definition are only seen at sick visit 1 for the youngest age group (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/F263). Similar RCDF curves generated for anti-DNaseB and anti-SCP antibody titers showed no differences between sick visits for any age group (data not shown).

The proportion of subjects with GAS pharyngitis with a prespecified increase in antibody titer was compared with the proportion of subjects without GAS pharyngitis with a prespecified increase in titer. Generally, a higher proportion of subjects with GAS pharyngitis met a prespecified increase in titer,[27] especially in the youngest age group, particularly for ASO. This was not observed for DNaseB in the youngest age group, however. By combining the 3 antigens, 60%–68% of subjects with GAS pharyngitis had a prespecified rise in titer to at least one antigen, although 35%–45% of subjects without GAS pharyngitis also had a prespecified rise in titer (Fig. 4).

DISCUSSION

This 2-year longitudinal epidemiology study conducted in the United States assessed GAS carriage and pharyngitis in healthy children 3–12 years of age according to various case definitions, the criteria for which went beyond the requirements of guidelines available at the time of study execution.[32] Recently, an updated GAS pharyngitis case definition has been proposed.[34] Relatively few studies examine longitudinal GAS carriage and pharyngitis from both a microbiology and a serology standpoint, and no studies included children under 5. Previous reports include an Australian study[3] and a study[25] designed to examine possible association between GAS infection and pediatric autoimmune psychiatric disorders in conjunction with streptococcal syndromes.

Here, GAS throat carriage was common, with an overall prevalence of 48% across all 3 age groups, with higher prevalence in the 3–5 age group (63%), as compared to the 6–9 age group (52%) and the 10–12 age group (30%). The prevalence rates of GAS throat

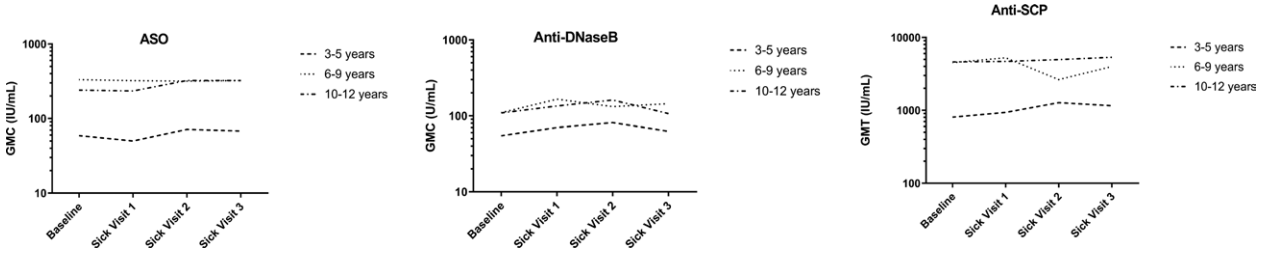

FIGURE 3. Kinetics of ASO and anti-DNaseB antibody geometric mean concentrations (GMC) and anti-SCP antibody geometric mean titers (GMT), by age group.

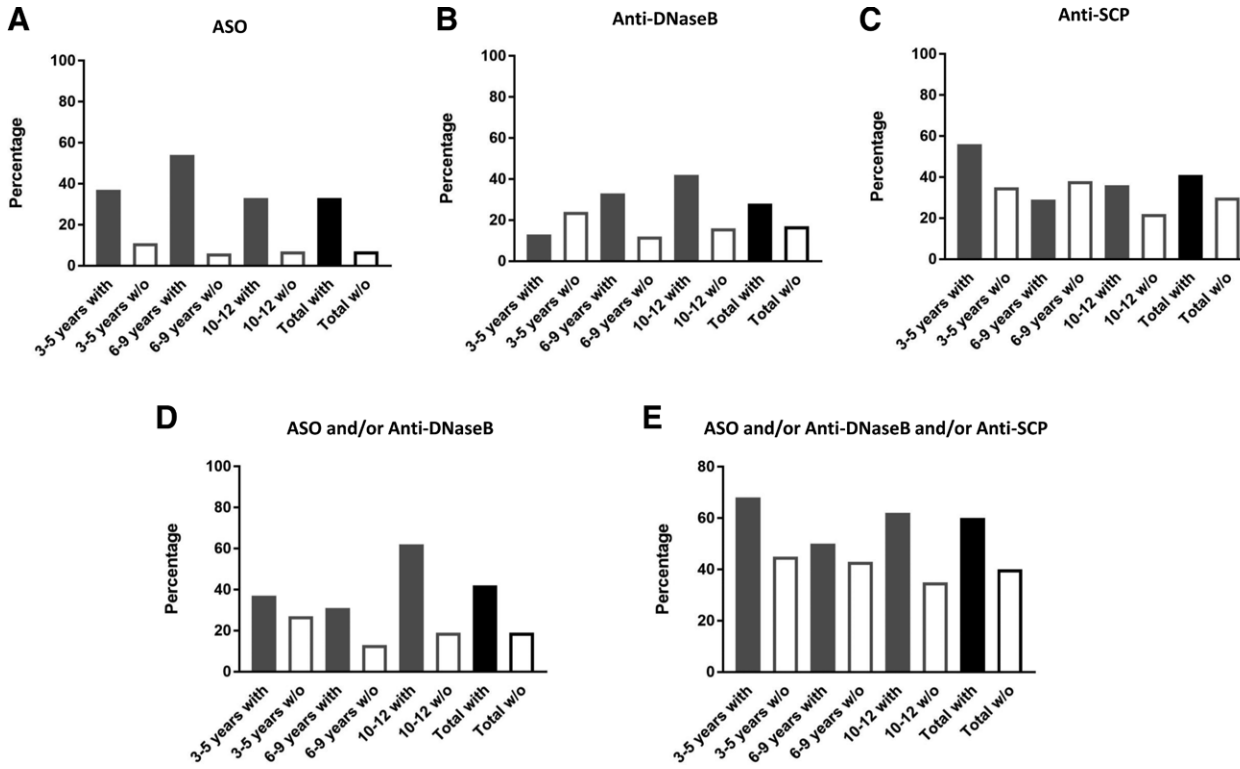

FIGURE 4. Percentages of subjects with GAS pharyngitis showing a 0.2 log rise in ASO or anti-DNaseB or 15% rise in anti-SCP titer associated with a first episode of GAS pharyngitis or with sick visits but no GAS identified.

carriers was 12% to 20% across each individual quarterly visit, consistent with previous point prevalence studies[1,29] where the pooled prevalence from 18 GAS carriage studies was 12%.[1] However, in this study the prevalence in 3–5-year-olds was higher than pooled point prevalence from 4 studies in children <5 years.[1]

GAS pharyngitis incidence by the primary case definition was also common, 15.9/100 person-years overall, and consistent with the 13% GAS pharyngitis incidence rate in Australian children 5–12 years of age.[3] In this study, the incidence rate was higher in 3–5-year-olds (19.5/100 person-years) compared to the older age groups (14.7 and 13.9/100 person-years in 6–9-year-olds and 10–12-year-olds, respectively). While the incidence rate in older children in this study was consistent with previous reports, the incidence rates observed in the youngest age group are somewhat higher than previously reported, which may indicate differences in childcare practices in the populations studied.[3]

High rates of GAS carriage raise the question of whether GAS detected by RADT or culture in the presence of pharyngitis is causally related or coincidental.[24] Improved case definition specificity could reduce unnecessary antibiotic use, but would also impact efficacy study design for GAS vaccines. Two approaches were taken to attempt to increase case definition specificity. The first approach included an exploratory case definition where antibody responses to GAS antigens (ASO, DNaseB and/or SCP) were evaluated for the ability to discriminate GAS infection from carriage. The second approach was to limit the GAS pharyngitis case definition to subjects with bacterial infection signs and symptoms.

Inclusion of antibody responses as a marker of GAS infection reduced measured incidence rates (Fig. 2A), consistent with previous findings with ASO and anti-DNaseB titers.[3] Healthy children in the study had baseline antibody titers to streptolysin O, DNaseB and SCP that increased with age, as was observed previously for SCP.[29] In a previous study evaluating ASO and DNaseB as markers of GAS pharyngitis, a 0.2 log rise in ASO or anti-DNaseB titers occurred in 54% and 45% of subjects, a 15% rise in anti-SCP titer was seen in 67% of subjects with confirmed GAS pharyngitis, and 69% of subjects had a rise in titer for at least one of the antigens. During GAS pharyngitis episodes in this study, ASO, anti-DNaseB and anti-SCP geometric mean titers did not change dramatically from baseline through the sick visits, although modest increases were seen, primarily in the youngest children. Thus, inclusion of a 2-fold increase in antibody titers against ASO, DNaseB and/or SCP in the exploratory case definition resulted in substantially fewer events than the primary case definition, but likely did not improve the specificity of the diagnosis, similar to what was found previously.[35] For inclusion of serology to have utility in a GAS pharyngitis case definition, any increase in titer must be larger than the normal fluctuation in titers seen in these age groups. When assessed by age group, ASO had the greatest utility in discriminating GAS pharyngitis from non-GAS pharyngitis in the 3–5 and 10–12 age groups, but not 6–9-year-olds. Similarly, an anti-SCP titer was seen in 56% of 3–5-year-olds with GAS pharyngitis compared to 35% of controls, while this parameter was unable to discriminate between cases and controls in the 6–9-year-olds and 10–12-year-olds. This could suggest that anti-SCP, and potentially ASO, titers are acquired during early infection events and then remain high throughout childhood, irrespective of infection status. If this is the case, anti-SCP, ASO and/or anti-DNaseB antibody measurements may have limited utility as part of a GAS pharyngitis case definition. Indeed, while ASO and anti-DNaseB titers can be useful in the diagnosis of nonsuppurative sequelae of GAS infections, they are not routinely used for the diagnosis of acute GAS pharyngitis due to the lag between infection and antibody production. However, a

higher rate of GAS carriage in the younger age group, along with antibody peaking in 6–9-year-olds, suggests that young children are exposed to GAS, which could inform preventative immunization strategies.

The second approach to improving GAS case definition specificity involved inclusion of bacterial infection signs and symptoms, which also led to much lower measured incidence estimates. Unfortunately, no reference standard exists to allow calculation of GAS pharyngitis case definition sensitivity and specificity; thus, it is unclear whether the addition of serological responses or signs and symptoms of bacterial infection would improve the specificity of GAS pharyngitis case definitions over RADT/culture, but it does not seem likely.

Overall, the utility of expanding the case definition for GAS pharyngitis to include serological endpoints is not expected to better discriminate true GAS pharyngitis from carriage due to high baseline titers in children >5 years. Additional clinical endpoints, such as those indicated in Miller et al.,[34] may better discriminate true GAS pharyngitis from GAS carriage plus non-GAS pharyngitis. One limitation of the study is that only United States sites were included, with a predominance of White children. Also, testing for alternate pharyngitis-causing pathogens was not included to determine if pharyngitis was associated with a non-GAS pathogen, and the design of sampling timepoints did not allow for detailed GAS carriage kinetics assessment.

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