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Research Article

The Nose Knows: Identified Organisms in Community Pediatric Sinusitis and Febrile URI-A Retrospective Study

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ABSTRACT

Objective: Viruses and bacteria comprising the nasal microbiome are both commensals and pathobionts, existing in a dynamic niche that is influenced by many factors including age, genetics, seasons, immunization status, as well as environmental and social factors such as daycare status and number of siblings. The aim of this study is to characterize the nasopharyngeal bacteria and viruses present at the time of URI diagnosis, to determine bacterial and viral co-infections, and to correlate the results to the day care status of the patient or patient's siblings.

Study Design: 186 patients who had a respiratory PCR panel test obtained during an illness visit to a community outpatient pediatric clinic were included. Ages included children from 4 months to 17 years of age.

Results: 47.8% of the patients included in this study had a bacterial-viral co-infection. In non-daycare attending children who presented with febrile illness and had a daycare or school attending sibling, non-SARS human coronavirus was found in all of the patients.

Conclusion: Our data support a correlation between age, daycare status, and etiology of upper respiratory infection. Viral and bacterial co-infection are common in younger aged children and becomes less frequent as children age.

Keywords: Pediatrics; Infectious disease; Virus; Bacteria; Respiratory PCR

INTRODUCTION

Previous studies have discussed the role of host nasopharyngeal microbiota and its dynamics following Upper Respiratory Infection (URI). Normal nasopharyngeal microbiotas confer immune defense and respiratory health [1]. Viruses and bacteria comprising the nasal microbiome are both commensals and pathobionts, existing in a dynamic niche that is influenced by many factors including age, genetics, seasons, immunization status, as well as environmental and social factors such as daycare status and number of siblings [1,2]. Some previously identified commensal organisms in nasopharyngeal microbiota include *Staphylococcus aureus, Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae, Corynebacterium,* and *Neisseria* meningitides [1-3]. Of note, *S. pneumoniae, M. catarrhalis,* and *H. influenzae* are well-known colonizers of the nasopharynx after birth and have been found in highest density after febrile URI [3]. *S. pneumoniae* colonization begins within the first 6 months and increases with age up to 5 years of age, then declines; preschool age is associated with highest prevalence [4]. The rate of *M. catarrhalis* colonization decreases with age [5]. The early colonization of these organisms is an important consideration as treating previously colonized bacteria can prove more difficult than treating invasive species [6]. Furthermore, competition and symbiosis between various organisms contributes to the diverse composition of the nasopharyngeal microbiome. While the presence of bacteria and viruses in the nasal microbiome is observed in asymptomatic patients, competition and overdominance of one species has been evidenced in the setting of symptomatic URIs [2]. Distinct, ongoing changes in microbiota composition have been observed at the onset of URI symptoms and three weeks after [1]. Viruses have also been found occupying the nasopharynx in both asymptomatic and symptomatic patients [2,7]. In asymptomatic children, it has been suggested there is co-presence of adenovirus and human rhinovirus with *M. catarrhalis* and *H. influenza* in the nasopharyngeal microbiota. Symptomatic patients were correlated with higher concentrations of nasal bacteria at the time of viral infection, further suggesting a symbiotic relationship [2].

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Certain bacteria and viruses interact and potentiate inflammation and infection, and previous studies have discovered that bacterial and viral pairings or clusters and overall organism diversity in the nasopharyngeal microbiota influence disease state of the host. Lower diversity of viruses and bacteria has been associated with more frequent upper respiratory infections, particularly in infants up to 12 months old [1]. One study found that the nasopharyngeal microbiota of infants presenting with frequent URIs were overrepresented by *M. catarrhalis* and lower diversity overall; these infants were also found to be at an increased risk of atopy [1]. In addition, patients whose microbiota demonstrated increased *H. influenzae* and *S. pneumoniae* pairings experienced more clinically severe infection with RSV [8]. Other research has correlated an overabundance of *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *S. aureus* clusters with RSV infection [8]. There is a paucity of data from the community pediatric setting which looks at the nasal microbiota implicated during febrile upper respiratory infections or clinical sinusitis symptoms. While the vast majority of pediatric URI and sinusitis treatment decisions are based on classical correlations between symptoms and seldomly cultured bacteria or viral pathogens, newer multiplex polymerase chain reaction tests are available to identify multiple viral and/or bacterial pathogens that may be causative agents during illness. Daycare status is also known to play a role in the transmission of upper respiratory tract infections in young children [9]. There is some discrepancy among the literature of whether daycare status provides a protective role or serves as a risk factor for URIs. Some research suggests that the highest risk for URI occurs when the child first begins daycare; the risk subsequently declines the longer the child attends daycare. Early daycare status has been associated with increased risk for recurrent acute otitis media (AOM), asthma, and invasive pneumococcal infections [9]. Contact with other children, poor hygiene, and close physical proximity of daycares have been associated with the risk of opportunistic infections (including *S. pneumoniae*) [4]. Acute otitis media is often caused by streptococcus pneumoniae infection; one study found that daycare status was associated with a 3-fold increased risk of pneumococcal infection and that having a sibling increased the risk by 2.5 times [10].

DEMOGRAPHICS

We conducted a retrospective study where patients who had presented to an outpatient pediatric office and had a respiratory Polymerase Chain Reaction (PCR) panel nasal swab performed were reviewed. Chart review revealed that all patients with the PCR test performed had febrile upper respiratory symptoms of at least 3 days duration and/or clinical sinusitis symptoms of at least 10 days duration at the time the sample was obtained. Patients were tested using a nasopharyngeal swab for 20 different bacterial and viral infections. The total number of subjects was 186 and included ages 4 months to 17 years old. There were 77 females and 109 males (Table 1).

It should be noted that all subjects above the age of 3 years were immersed in a day care setting or school environment at the time of PCR testing. Information has been provided whether or not those under the age of 3 were in daycare or had siblings in daycare.

Table 1: Age and gender of subjects.

	Total	Males	Females
<1 year old	31	17	14
1 - 3 years old	77	51	26
4 - 7 years old	43	21	22
8+ years old	35	20	15

All subjects had received age-appropriate routine vaccinations based on the Center for Disease Control guidelines by age at the time of PCR testing.

This retrospective study evaluated patients who were tested with a multiplex PCR respiratory pathogen nasal swab. Further investigation aimed to reveal environmental factors that may contribute to these pathologies. Upper Respiratory Tract Infection (URI) symptoms were defined as fever, cough, rhinorrhea, and/or non-streptococcal pharyngitis.

DAYCARE ATTENDANCE

The participants who were age 3 years and below were categorized in three different groups: Attend daycare, Do not attend daycare, and Do not attend daycare but have siblings that do. Daycare was defined as a large group, center-based care provided by professional caregivers (Table 2).

DESIGN/METHODS

From 2016 to 2018 nasopharyngeal respiratory PCR swabs obtained on patients who presented with febrile upper respiratory symptoms of at least 3 days duration or clinical sinusitis in an outpatient community general pediatric office were included. The physician obtained the nasopharyngeal swab by having the patient blow their nose (if age appropriate) to produce secretions and then tilt their head about 70 degrees and inserted a single swab with cotton wool into the nasopharynx and rotated per standard nasal PCR protocol. The swab was then placed into a tube filled with a virus transport medium and capped. All swabs in the study were outsourced to the same laboratory. The lab performed a multiplex PCR panel that screened for 20 different viral and bacterial infections (Table 3).

Human coronavirus infections were positive if they included any of the four common cold subtypes-229E, NL63, OC43, or HKU1. Multiplex PCR is a molecular biology technique which amplifies multiple targets of bacterial and viral infections in one single experiment. This is very efficient in both cost and time by performing one experiment for a multiplex assay without compromising the results. The lab reported results approximately 1 day from retrieval. All data was recorded and then statistically analyzed to determine

Table 2: Daycare status by age.

	Attended daycare	Did not attend daycare	Did not attend daycare but have siblings that do
<1 Years Old	10	19	2
1- 3 Years Old	59	10	8

Table 3: Pathogens identified via PCR testing.

Bacterial Infections		Viral infections	
Bordetella pertussis	0	Enterovirus group	48
Chlamydophila pneumoniae	0	Human Bocavirus	0
Haemophilus influenzae (non-typeable)	36	Human Coronavirus (subtypes-229E, NL63, OC43, or HKU1)	20
Haemophilus influenza Type B	0	Human Metapneumovirus	8
Moraxella catarrhalis	81	Influenza A-Human Influenza	0
Mycoplasma pneumoniae	4	Influenza A-H1N1-09	4
Neisseria meningitidis	0	Influenza B	4
Streptococcus pneumoniae	47	Parainfluenza	16
Streptococcus pyogenes (Group A Strep)	6	Respiratory Syncytial Virus	25
Adenovirus	3	Rhinovirus	43

any correlations. All patients who had received oral antibiotics for treatable infections were prescribed the appropriate medications as recommended by the Infectious Disease Society of America (ISDA) (Table 4).

For the purpose of this study, co-infections are defined as having two or more positive pathogens identified on the resulted PCR panel.

RESULTS

All data was gathered and constructively analyzed to allow for a conducive discussion. It was found that as age increases, the presence of all-cause infections decreases ($p<0.05$). Ages 1-3 years old had the highest presence of bacterial and viral co-infections, supporting that co-infections in that subpopulation are most common (Figure 1).

Specifically, in the <1 year old subpopulation, the most common virus present in the subpopulation was enterovirus group. The most common bacteria identified was *M. catarrhalis* (Figure 2).

In Figure 3, the influence of daycare is assessed, and it was found that there were zero patients who attended daycare and did not have an infectious source identified, as well as zero patients who did not attend day care and also had no infectious source identified. Figure 4 focuses on the coinfections within the <1 year old population and it was found that the most common interaction was that between enterovirus group and *M. catarrhalis*.

Whereas the most common interaction in the 1-3 years old subpopulation was between *M. catarrhalis* and rhinovirus (Figure 5) ($p>0.05$).

In the 4-7 years old subpopulation, the most common coinfection was non-typeable *H. influenzae* with rhinovirus (Figure 6).

Table 4: IDSA guidelines on treatment recommendation for particular pathogen presence [11].

Pathogen	First Line of Therapy	Alternative Therapy
Haemophilus influenzae	Amoxicillin or Augmentin	Cefdinir or Azithromycin
Moraxella catarrhalis	Augmentin	Cefdinir or Ceftriaxone
Streptococcus pneumoniae	Amoxicillin or Augmentin	Cefdinir or Azithromycin
Streptococcus pyogenes (Group A Strep)	Penicillin V or Amoxicillin	First generation cephalosporin, oral macrolide
Influenza A	Antiviral	
Influenza B	Antiviral	

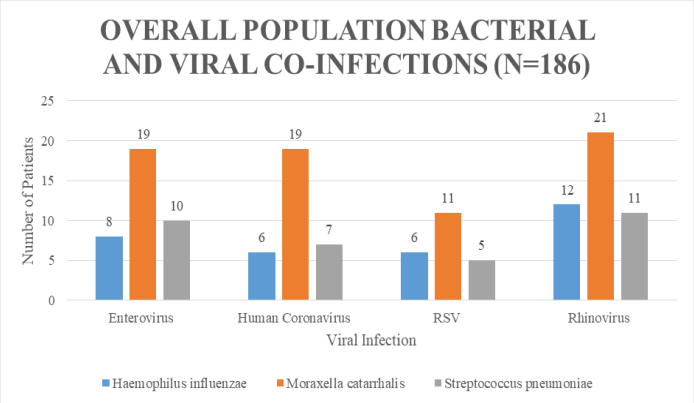

Figure 1: Overall study population bacterial and viral co-infections.

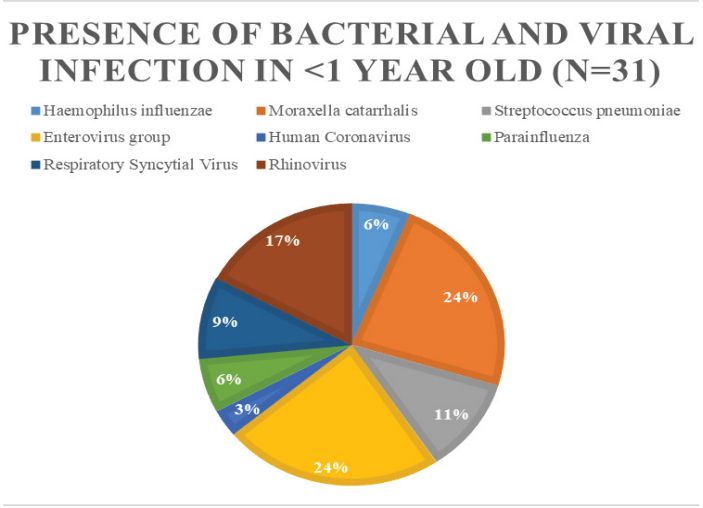

Figure 2: Presence of bacterial and viral infection in <1 year olds.

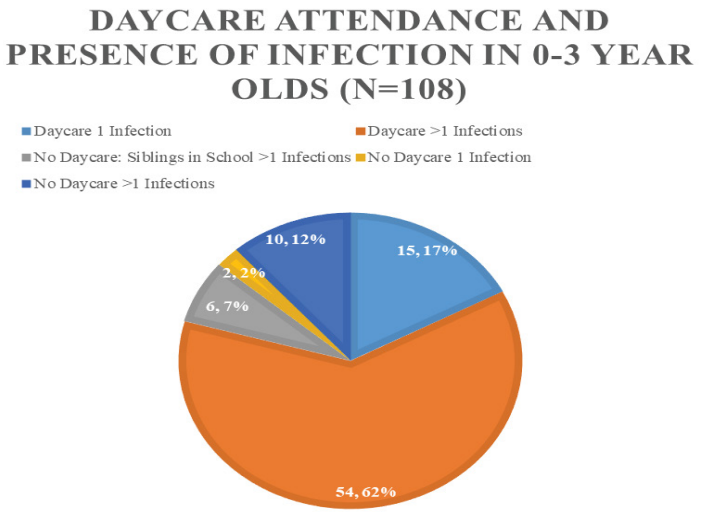

Figure 3: Daycare attendance and presence of infection in 0-3 year olds.

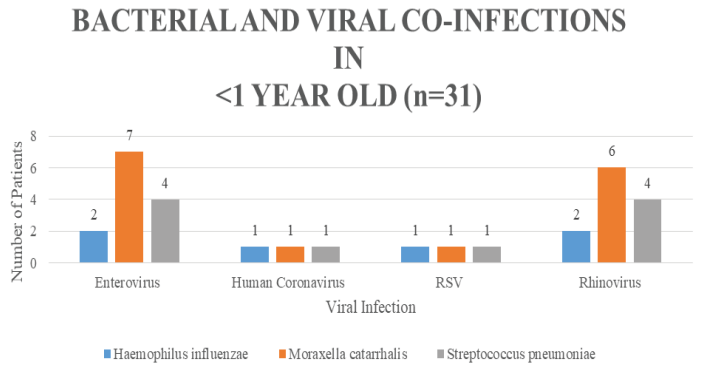

Figure 4: Bacterial and viral co-infections in <1 year olds.

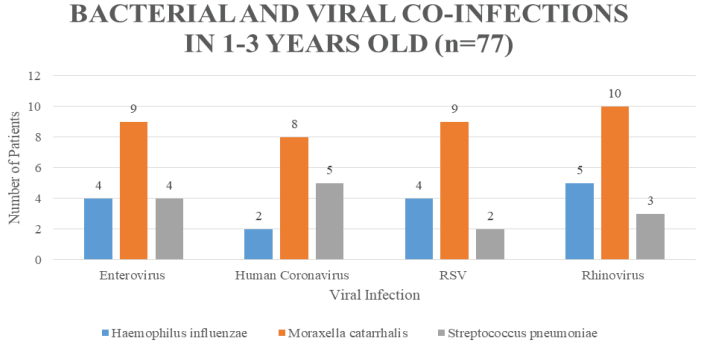

Figure 5: Bacterial and viral co-infections in 1-3 year olds.

There was no significant common trend for co-infections in the 8 years and older age group (Figure 7).

In the overall population, the most common coinfection of the population was *M. catarrhalis* with rhinovirus (Figure 8) ($p<0.05$).

Overall, 47.8% of the patients included in this study had a bacterial-viral co-infection. 6.5% of patients overall did not have a positive result via PCR panel testing (Table 5).

Figure 9 provides for an illustrative view of the common etiologies of the viral and bacterial co-infection and also organized in appropriate subpopulation categories.

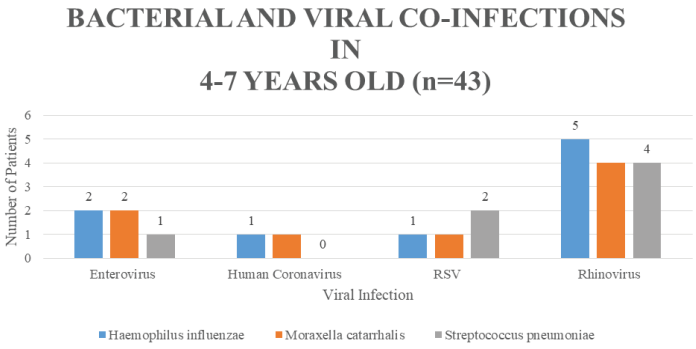

Figure 6: Bacterial and viral co-infections in 4-7 years old.

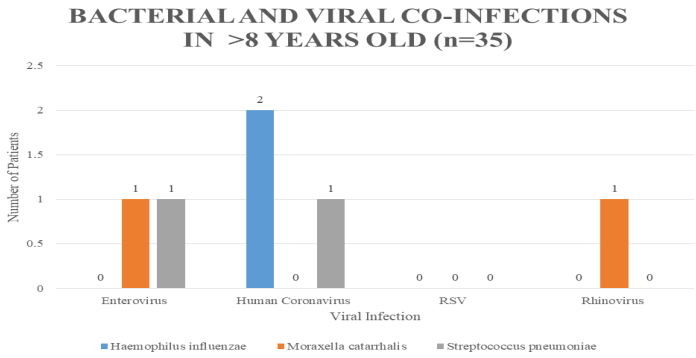

Figure 7: Bacterial and viral co-infections in >8 years old.

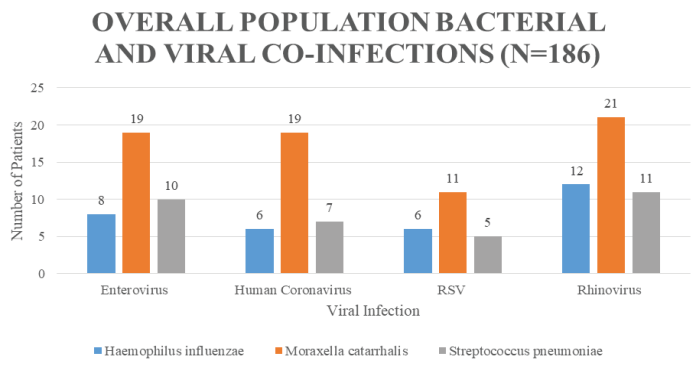

Figure 8: Overall study population presence of bacterial and viral co-infection.

Table 5: Overall Infections Identified

Overall (N=186)		
No infection present	12	Only Bacterial
1 infection present	63	18
>1 infection present	111	16
Streptococcus pyogenes (Group A Strep)	Penicillin V or Amoxicillin	First generation cephalosporin, oral macrolide
Influenza A	Antiviral	
Influenza B	Antiviral	

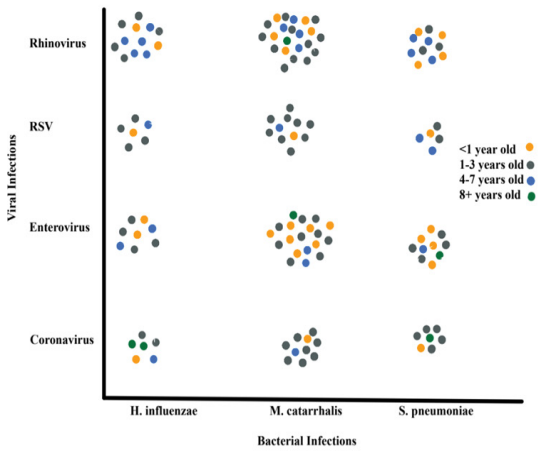

Figure 9: Scatter diagram displaying co-infection etiology by age group.

DISCUSSION

In the age group less than 1 year (n=31), there were 3 subgroups: those who attended daycare (41.9%), those who did not attend daycare (51.6%), and those who did not attend daycare but had a sibling who did (6.5%). Of those that attended daycare, all but one patient was found to have an identified infection present. Of note, the most common co-infection of the day care attendees was *S. pneumoniae* and rhinovirus, with 38.5% of the subgroup having this co-infection. Rhinovirus and *S. pneumoniae* have previously been found to have synergistic effects such that rhinovirus can increase epithelial adherence of *S. pneumoniae*, which explains the co-presence of these two pathogens [12]. It was found statistically significant that daycare attendance corresponded with the presence of an infection ($p<0.05$) (Figure 3). Of those that did not attend daycare, all but one patient had an identified infection present. 33.3% had one viral infection present with no other pathogens identified. The most common viral infection was enterovirus. The remaining non-daycare attending patients had a bacterial-viral co-infection with the most common co-infection being enterovirus and *M. catarrhalis*. The link between *M. catarrhalis* and enteroviral co-infection may be more likely to occur because they are both responded to by the IgG subclass 3 antibody [13,14]. All patients in the group who did not attend daycare but had a sibling in daycare were found to be positive for human coronavirus (subtype 229E, NL63, OC43, or HKU1) along with different bacterial co-infections. One of these patients was found to be positive for *S. pneumoniae*, *M. catarrhalis*, and non-typeable *H. influenzae* infection. It is known that these three bacteria colonize the nasopharynx from an earlier age (as early as 6 months) and that viral disturbance of the microbiome can predispose to bacterial infection and colonization of the middle ear [3,4,7].

In the age group 1-3 years old (n=77) there were 3 subgroups: those who attended daycare (76.6%), those who did not attend daycare (10.3%), and those who did not attend daycare but had a sibling who did (13.1%). Of those that attended daycare, bacterial infections were more common than viral, and *M. catarrhalis* was the most common bacteria identified with 61% of the subgroup positive for this species. *M. catarrhalis* is a known colonizer of the nasopharynx and common oto-pathogen, causing AOM in children after viral illness. 6.7% of the 1-3 years old who attended daycare presented with positive results for *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*. In this age group, of those who did not attend daycare 75% of patients had either a solitary bacterial

infection or a solitary viral infection with the remaining having a bacterial and viral co-infection (Figure 3). The most common bacterial-viral co-infections in this age group were rhinovirus and *M. catarrhalis* (Figure 5). Patients in this age group who had siblings in daycare but did not themselves attend daycare, all but one had co-infections. Of note, there was a high incidence of *S. pneumoniae* and *M. catarrhalis* present together (40%).

All patients above 4 years old (n=43) who had received a respiratory PCR test attended daycare or regular schooling. 7.0% of this group had no identified infection present on the nasopharyngeal swab. 23.3% of this subpopulation had only bacterial infections with the most common being *M. catarrhalis*. 18.6% of the subpopulation had only viral infections with the most common being the parainfluenza virus. 48.9% of patients in this group had bacterial-viral co-infection present, with the most common being non-typeable *H. influenzae* and rhinovirus (11.6%) (Figure 6).

Of the thirty-five results from subjects who were 8 years and older it was found that 14.3% presented with both bacterial and viral infection. There was not a significant pair of bacterial and viral coinfections in the >8 years old subpopulation (Figure 7). 11.4% of the patients presented with a solitary bacterial infection and 54.3% with a solitary viral infection. Although not statistically significant, the most common viral infection present in the >8 years population was enterovirus. Of the 105 subjects with bacterial infections identified, 25 had clinical improvement in symptoms at the time of test result and were not treated with antibiotics (Table 6).

S. pneumoniae, *M. catarrhalis*, and *H. influenzae* are well-known colonizers of the nasopharynx after birth and have been found in highest density after febrile URI [3]. *S. pneumoniae* colonization begins within the first 6 months and increases with age up to age 5, then declines; preschool age is associated with highest prevalence [4]. Similarly, the rate of *M. catarrhalis* colonization has been found to decrease with age [5].

CONCLUSION

Our data support a correlation between age, daycare status, and etiology of upper respiratory infection. Most standard PCR panels obtained by hospitals and health systems include similar pathogens used on our panel with the exception of *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*, which are not commonly included on test results. The current widely used panels include atypical bacteria only. Additionally, our study separated rhinovirus from the rest of the enterovirus family. Most respiratory PCR panels combine rhinovirus and enterovirus as one result. None of the patients who had PCR tests required hospitalization related to their illness.

In our overall study population, we found that *S. pneumoniae* was highly associated with either the patient attending daycare or having a sibling in daycare/school. This finding supports what has been found in previous studies: *S. pneumoniae* is an opportunistic pathogen that can easily infect children in close contact in daycare settings. Additionally, *S. pneumoniae* is a known colonizer of the nasopharyngeal microbiome. Our data supports daycare attendance was most strongly associated with risk for greater than one infection present at time of nasal swab collection in the ages 0-3 group. Of this group, those who had more than one infection present were more likely to have a bacterial-viral co-infection. In the age group 4-7 years old, all of whom attended daycare/school, it was more common to have an infection with more than one pathogen rather than a single pathogen, and a majority of these patients' collections showed a bacterial-viral co-infection. However, in the 8+ years old age group, single infections were more common than multi-infections, with a single viral infection being more common than bacterial. Overall in our study, as age increases the number of bacteria identified on PCR decreases.

This retrospective study helps to illustrate the likelihood of bacterial presence in the nasal microbiome during acute illness which further helps the clinician to choose the appropriate antibiotic treatment when antibiotic use is indicated. This is especially true when co-infections are most likely given the child's age and daycare status. An important finding was that children who do not attend daycare but having a sibling who does, are also at increased risk for having a bacterial co-infection similar to their daycare attending counterparts. A limitation of this study was not including any nasal PCR swabs from asymptomatic subjects. Prior studies have shown that asymptomatic patients have viral and/or bacterial pathogens present in their nasal microbiome. Thus, future studies may be better able to determine when pathogens identified are causative, commensal, or related to a carrier-state. Additionally, our study identified 25 subjects with positive bacterial identification on the test panel who had complete or at least significant resolution at the time of test result which prompted continued observation without antibiotics. Future studies may also be able to delineate which subjects with positive bacterial identification on PCR test may be able to continue with close observation in lieu of antibiotic treatment following the test result despite continued URI or sinusitis symptoms at the time of result.

The emergence of the novel coronavirus, SARS-CoV-2, has brought respiratory pathogen PCR panels into use more often as a way to essentially rule out SARS-CoV-2 with the idea that having one pathogen would preclude the novel coronavirus from also causing symptoms. This was based on initial un-published reports of a very low co-infection rate found in China. The type of PCR panel with a number of co-infection pathogens tested for was unable to be determined with any confidence. In the United States, due to limited resources with testing kits for SARS-CoV-2, if a patient, especially a child, was found to have an identified pathogen on the standard respiratory PCR panel, they were presumed to only have the identified infection and further work-up looking for SARS-CoV-2 was not done unless there was significant clinical worsening. While the identification of SARS-CoV-2 would be unlikely to change the treatment course in an otherwise healthy child who can be managed as an outpatient, it would help with infection tracking and public health monitoring. Our retrospective study also found that in non-daycare attending children who presented with febrile illness and had a daycare or school attending sibling, non-SARS human coronavirus was found in all of the patients. This further illustrates that children can be vectors of transmission for human coronavirus infection and can spread to other children as well. Our study helps to provide additional evidence that co-infections are common in pediatrics and finding one pathogen on a PCR panel may not preclude that patient from having another virus and/or bacterium present, which may complicate the clinical course or help to determine best treatments.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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