# COMPARISON OF NASOPHARYNGEAL AND MID-TURBINATE SWABS IN CHILDREN WITH UPPER RESPIRATORY TRACT INFECTION SYMPTOMS AND THE FEASIBILITY OF USING ELECTRONIC DIARIES IN CLINICAL RESEARCH

by

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## ABSTRACT

**Background** Acute bacterial sinusitis is the inflammation of the sinuses resulting from a bacterial infection. Sinusitis is the fifth most common condition for which antimicrobials are prescribed to children in the United States. According to the literature, 40% of children diagnosed with sinusitis do not have a true bacterial infection. The development of antibiotic resistance has become a significant public health concern among this pediatric population. **Methods** Participants between the ages of 6 months and 11 years were recruited from Children's Hospital of Pittsburgh (CHP) and the Primary Care Center in Oakland of CHP. Two studies, the Cold Swab study and the Sinus Diary study were designed to investigate acute bacterial sinusitis in children. Nasopharyngeal (NP) and mid-turbinate (MT) swabs were obtained from children presenting with upper respiratory tract infection (URI) symptoms enrolled in the Cold Swab study. NP and MT swab results were compared in order to determine success of colonization. All laboratory work was conducted at the Infectious Disease Research Laboratory of CHP. The Sinus Diary study investigated the feasibility of having parents electronically report their child's URI symptoms daily.

**Results** The Cold Swab study enrolled 96 children and the Sinus Diary study enrolled 68 participants. Based on the results of the Cold Swab study, 9.4% of children were colonized with

both SPN and HFLU, 48% were colonized with SPN only, 25% were colonized with HFLU only, and 36.4% were not colonized with either pathogen. Seventy-six percent of paired NP/MT swabs were concordant for SPN and HFLU, and 87.5% of paired swabs were concordant for only SPN or only HFLU. The compliance of the electronic diary study was assessed. Of parents who successfully completed all of the diary entries, only 50% did not require a reminder phone call.

**Conclusion** The NP/MT swabs were highly concordant for SPN and HFLU in the Cold Swab study. Electronic diaries are an effective way of collecting data for clinical research, however reminders are essential for achieving a high compliance rate. The results from these pilot studies will be used as preliminary data for a larger acute bacterial sinusitis study.

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# PREFACE

I would like to thank my thesis director, Dr. Judith Martin from Children's Hospital of Pittsburgh (CHP), Department of Pediatrics, Division of General Academic Pediatrics, for her guidance and support throughout the year. I appreciate you trusting me to be a part of the investigation team for this study.

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# 1.0 INTRODUCTION

Sinuses are mucus-filled hollow cavities located within the cheekbones, around the eyes, and behind the nose. The maxillary, frontal, sphenoid, and ethmoid make up the four paired sinus cavities in humans.[8] The mucus in these cavities helps warm, moisten, and filter the air that is breathed in. When mucus is blocked from draining normally, the tissue lining the sinuses gets inflamed resulting in sinusitis.[17] Sinusitis is the inflammation of the paranasal sinuses and the mucosa of the nose.[3] Common symptoms include nasal congestion, facial pressure, cough, and nasal discharge.

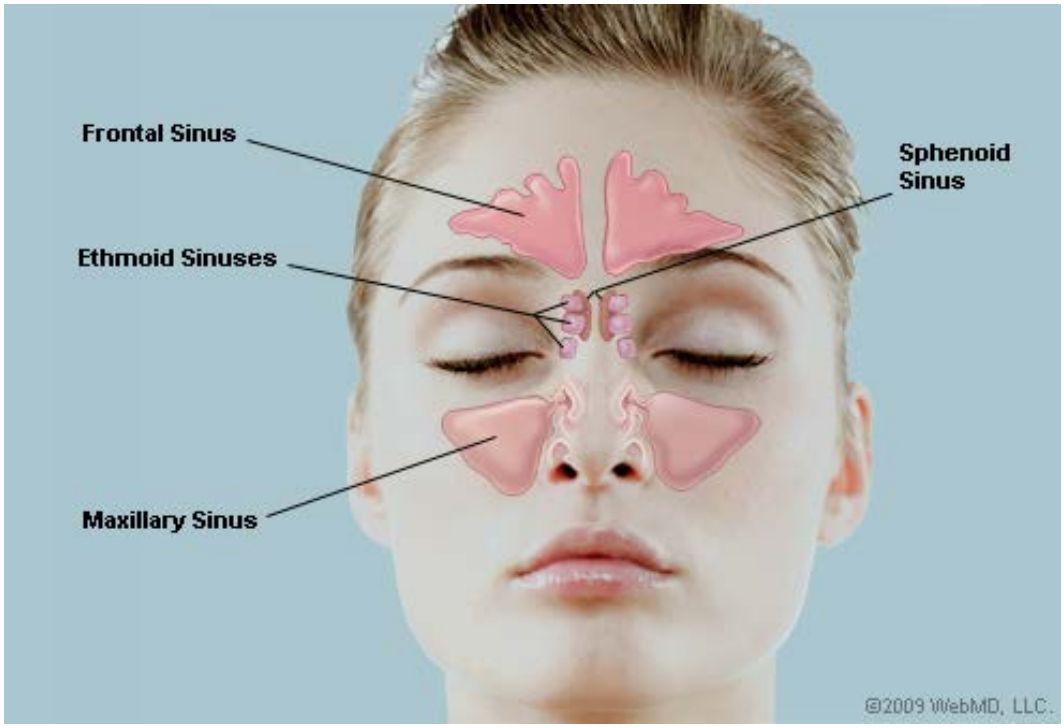


**Figure 1. Anatomical Location of the Four-Paired Sinus Cavities**

**[16] WebMD, (2009) *Picture of the Sinuses*, [Image]. Retrieved 14 December 2015, from WebMD http://www.webmd.com/allergies/picture-of-the-sinuses**

**Included with permission from WebMD.**

There are five subtypes of sinusitis: acute, subacute, chronic, allergic, and hyperplastic.[16,17] Sinusitis is considered to be acute when the infection presents rapidly and persists for less than four weeks.[17] Subacute sinusitis presents with continual nasal discharge and persists for less than twelve weeks. Chronic sinusitis presents with episodes of prolonged inflammation and symptoms remain persistent for twelve or more weeks.[17] Allergic sinusitis results from allergic rhinitis.[1] When an individual breathes in a substance to which he or she is allergic, the inside of his or her nose becomes inflamed and swollen. This causes the sinuses to be blocked and filled with fluid, giving sinusitis the ideal conditions to prosper. Hyperplastic

sinusitis is due to a chronic inflammation of the sinuses, which leads to the development of polyps.[5] Sinusitis can be caused by a viral, bacterial, or fungal pathogen.

Antibiotics are generally considered the recommended course of treatment for acute bacterial sinusitis. The first-line treatment for acute bacterial sinusitis is amoxicillin with or without the addition of clavulanate.[19] In cases where acute sinusitis is not bacterial, nasal sprays, decongestants, and over-the-counter pain relievers are recommended.[17] Chronic sinusitis is rarely caused by a bacterial infection. Patients with conditions such as allergic rhinitis and asthma are at a higher risk of developing chronic sinusitis because their airways are more likely to become inflamed.[17] Intranasal corticosteroids or antifungal medications are often recommended to patients, depending on the causative pathogen. In some cases, endoscopic sinus surgery is an option. However, in general sinus surgery is not recommended for children.[17]

Approximations of one billion sinusitis cases occur in the United States each year. Americans spend roughly $2.2 billion on medications to treat sinusitis.[3] Although viral illness is the most common type of sinusitis, acute bacterial sinusitis is also prevalent across all age groups in the United States.[3] Sinusitis has become a public health issue due to its high prevalence and financial burden.

## 1.1 ACUTE BACTERIAL SINUSITIS

Acute bacterial sinusitis is the inflammation of the sinuses due to a bacterial infection. It is often the complication of a viral upper respiratory tract infection or allergic inflammation.[13,19] Presenting symptoms and temporal patterns of upper respiratory tract infections are key factors for diagnosing acute bacterial sinusitis. Symptoms may include nasal discharge of any quality,

daytime cough, or a combination of nasal discharge and cough. Symptoms for acute bacterial sinusitis usually persist for at least ten days and less than four weeks. Stringent clinical presentation is the key factor to diagnosing acute bacterial sinusitis.[19]

## 1.2 CONCERNS

Sinusitis is the fifth most common condition for which antimicrobials are prescribed to children each year.[14] Approximately 82% of children with acute bacterial sinusitis are prescribed antibiotics in the United States.[19] However, it is estimated that 40% of children diagnosed with the condition do not have true acute bacterial sinusitis. Currently, a diagnostic laboratory test and specific clinical examination findings do not exist to confirm the diagnosis.[14] Therefore, physicians rely on the clinical presentation to guide them when making a diagnosis of acute bacterial sinusitis for diagnosis.

Acute bacterial sinusitis and uncomplicated viral upper respiratory tract infections present with similar symptoms. This makes the diagnosis problematic because physicians have a difficult time differentiating between a viral and bacterial infection based on clinical symptoms. A key factor that differentiates the two diagnoses is the duration of symptoms. Symptoms of a viral upper respiratory tract infection tend to resolve within ten days without the use of antimicrobial therapy.[19] As mentioned earlier, symptoms should be present for at least ten days to consider a diagnosis of acute bacterial sinusitis. Therefore, persistence of symptoms without improvement suggests acute sinusitis.

In the past, imaging has been used to diagnose acute bacterial sinusitis in patients presenting with respiratory infections. Recently, research has concluded that imaging, including

computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography, is not an effective method for confirming diagnosis.[19] Although a normal radiograph suggests the absence of acute bacterial sinusitis, an abnormal radiograph is not enough evidence to confirm the diagnosis.[19] For these reasons, routine imaging is no longer recommended to distinguish between a viral upper respiratory tract infection and acute bacterial sinusitis.

Over-diagnosing acute bacterial sinusitis has become a concern in clinical settings. The course of treatment differs drastically between a viral and bacterial infection. Incorrectly diagnosing acute bacterial sinusitis in cases where the patient should have been diagnosed with a viral upper respiratory tract infection, can lead to the unnecessary administration of antibiotics. This raises further concern regarding overprescribing antibiotics, which can lead to adverse side effects and facilitate the development of antimicrobial resistance.[12]

## 1.3 NASAL SPECIMEN COLLECTION

*Streptococcus pneumoniae* (SPN) and *Haemophilus influenzae* (HFLU) are the common pathogens and primary causes of acute bacterial sinusitis.[2,19] SPN and HFLU account for 60% of acute bacterial sinusitis cases in children. *Moraxella catarrhalis* accounts for 10% of acute bacterial sinusitis cases and *Staphylococcus aureus* is considered to be an uncommon isolate from children presenting with the condition.[19]

The nasopharynx is the anatomical site where pathogens that infect the paranasal sinuses originate.[13] According to previous research, nasopharyngeal swabs (NP) swabs are not effective in determining the etiology of acute bacterial sinusitis.[19] NP swabs can be used to identify which bacteria are present in the nasopharynx. This may represent colonization. A culture of the

nasopharynx is obtained by introducing the NP swab into the nares and advancing it gently back to the pharynx (5.5cm) causing minor discomfort. NP swabs are the traditional method used in clinical settings to identify presence of pathogens in the nasopharynx.

## 1.4 DIARIES IN CLINICAL RESEARCH

Daily symptom diaries are often used in clinical research settings to assess daily changes in the clinical status for conditions like sinusitis. Pain, mood, and stress are some of the common and effective reasons why diaries are used in clinical research settings.[10] In contrast to questionnaire studies used in clinical research, diaries are considered to be less prone to recall bias.[4] Patients are likely to introduce recall bias in questionnaire studies if they incorrectly recollect events or cannot remember them at all. Diaries allow study participants to self-report their symptoms within shorter timeframes and on a consistent schedule and therefore reduce bias.

Paper diaries have been the traditional method used in clinical studies involving diaries in the past. With advancements in technology, researchers are now incorporating the use of electronic diaries in clinical research settings. The use of electronically submitted diaries allows researchers to know exactly what day and time the diary entry was completed. This method has the potential to reduce bias suspected of traditional paper diaries.

## 1.5 OBJECTIVES

Researchers from the Primary Care Center, Department of Pediatrics, Division of General Academic Pediatrics at Children's Hospital of Pittsburgh were designing a large randomized acute bacterial sinusitis trial that would investigate the benefit of antimicrobial therapy in children. In order to prepare for this study, researchers wanted to refine the methods of specimen collection from the nasopharynx for bacterial culture, and the collection of sinusitis symptoms on a day-to-day basis.

There were two clinical studies designed to obtain additional information to prepare for this larger study: the Cold Swab study and the Sinus Diary study. The objectives of the Cold Swab study were to identify respiratory pathogens found in the nasal secretions of children who present with sinusitis-like symptoms, and to compare the accuracy of two swabs, the traditional NP swab and the mid-turbinate (MT) swab, used to collect nasal specimens. The objective of the Sinus Diary study was to assess the feasibility and compliance of daily electronic diaries completed by parents of children who present with upper respiratory symptoms.

# 2.0 METHODOLOGY

## 2.1 STUDY DESIGN

Study participants were recruited from Children's Hospital of Pittsburgh (CHP) and the Primary Care Center in Oakland of CHP. Two studies, the Cold Swab study and the Sinus Diary study were designed to investigate acute bacterial sinusitis in children. Each study was made up of different cohorts, meaning the same child was not enrolled in both the Cold Swab and the Sinus Diary study. Both observational cross-sectional studies received Institutional Review Board (IRB) approval from the University of Pittsburgh. Written informed consent was obtained from parents of all study participants prior to enrollment.

## 2.2 COLD SWAB STUDY

Inclusion criteria: Children between the ages of six months and eleven years with an upper respiratory tract infection were recruited for the Cold Swab study. Children who had taken antimicrobials or nasally administered medications within the last 14 days were excluded from the study. The duration of the cold swab study was one visit for participants. Children enrolled in this study received an NP and MT swab on enrollment day. All swabs were processed for bacterial culture at the Infectious Disease Research Laboratory at CHP.

## 2.3 SINUS DIARY STUDY

Inclusion criteria: Children between the ages of one to eleven years with persistent or worsening acute sinusitis were recruited for the Sinus Diary study (n=68). Persistent acute bacterial sinusitis was defined as presence of nasal discharge, cough, or both for more than ten days but less than 30 days. Worsening acute bacterial sinusitis presents with the onset of fever or severe headache. Symptoms tend to worsen after a period of improvement. Subjects who had taken antimicrobials within the last seven days, who were wheezing during the visit, or had history of asthma, rhinitis, cystic fibrosis, an underlying immunodeficiency, other respiratory tract infections, or neurodevelopmental disorders were excluded from the study. Parental inability to read or write in English was also an exclusion factor for the sinus diary study.

One nasopharyngeal swab was obtained on enrollment day and the swab was processed for bacterial culture at the Infectious Disease Research Laboratory at CHP. The duration of the study was eighteen days, including the day of enrollment. Parents of children who presented with sinusitis-like symptoms received a total of three phone calls on the second, third, and fourth days of the study. (see Appendix C for a copy of the phone call/missed diary entry questionnaire) Parents were asked to complete eleven consecutive diary entries on behalf of their children. (see Appendix B for an example of a Sinus Diary entry completed by a parent) Diary entry links via email or text message were sent directly to smartphones or tablets each day of the study. Families who did not own smartphones or tablets were lent a CHP research tablet throughout the duration of the study. Additional phone calls were made to parents who did not complete a diary entry the morning following the missing diary entry day. Children were asked to come in for a final visit between the twelfth and eighteenth day of the study for a final assessment.

The Pediatric Rhinosinusitis Symptom Scale (PRSS) is used to assess sinusitis symptoms.[15] (see Appendix A for a copy of the PRSS) The electronic diary questions for the Sinus Diary study were developed from the PRSS scale. The Sinus Diary questions focused on the following eight symptoms: runny nose, stuffy nose, daytime cough, nighttime cough, trouble sleeping, trouble breathing from the nose, irritability/mood, and feeling tired/energy level. Parents were asked to rate the severity of the eight symptoms experienced by their child over the past 24 hours. These questions were scored on a 6-point Likert scale (no=0, almost none=1, a little=2, some=3, a lot=4, an extreme amount=5) and a total score was obtained by summing up each individual score.

## 2.4 LABORATORY METHODS

All swabs were processed for culture at the Infectious Disease Research Laboratory at CHP. Specimen collection required the use of a sterile, flexible, thin, flocked swab that was introduced into one of two nares (Copan Liquid Amies Elution Swab (eSwab) 482C). The NP swab extended back to the pharynx, approximately 5.5 centimeters, causing minor discomfort. The MT swab extended approximately 2.5 centimeters into the nasal cavity and usually without any discomfort. Specimen collection was performed by one of the pediatric primary care experts on the investigative team. After obtaining the specimen, the investigator placed the swab into a transport tube with the tip immersed into the media. The specimen could only be stored at room temperature for no longer than twenty minutes. The transport tube was stored in a specimen refrigerator at 4-8°C until it was transported to the Infectious Diseases Research Laboratory at CHP with a cold pack.

Upon arrival to the laboratory, the specimen was either immediately cultured or frozen for processing at a later time. The lead technician at the Infectious Disease Research Laboratory of CHP carried out all laboratory methods. Swabs were inoculated onto a chocolate agar plate and a 5% sheep's blood agar plate. Plates were then incubated at 37°C. Plates were inspected for initial growth at 24 hours. If the plates did not display colony growth or displayed inadequate colony growth, they were incubated for an additional 24 hours and inspected again at 48 hours. Plates were then evaluated for the presence of SPN or HFLU and results were recorded. Laboratory results were shared with study investigators and entered into an electronic database.

# 3.0 RESULTS

## 3.1 ENROLLMENT

A total of 96 paired NP/MT swabs were available for analysis from children enrolled in the Cold Swab study. The Cold Swab study enrolled participants from August 20, 2014 to November 12, 2015. Of the 96 children enrolled, 58.3% were males and 79% were African Americans. The mean age of participants at enrollment was 2.45 years.

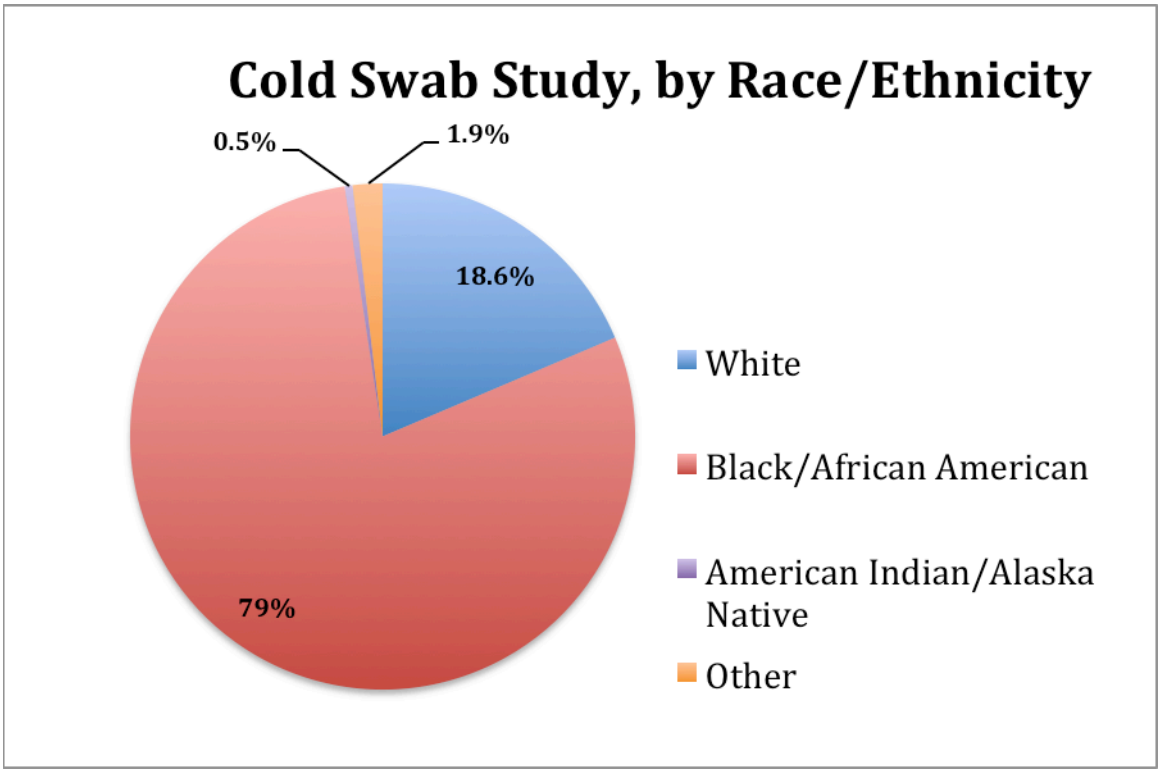


**Figure 2. Race/ethnicity of Cold Swab Study Participants**

A total number of 68 participants were enrolled in the Sinus Diary study and 54 nasal swabs were obtained. Methods for processing the bacterial culture of the swabs were identical to the Cold Swab study. The Sinus Diary study enrolled participants from October 15, 2014 to May 15, 2015. Of the 68 children enrolled, 52.3% were males and 67.7% were African Americans. The mean age of participants at enrollment was 4.08 years.

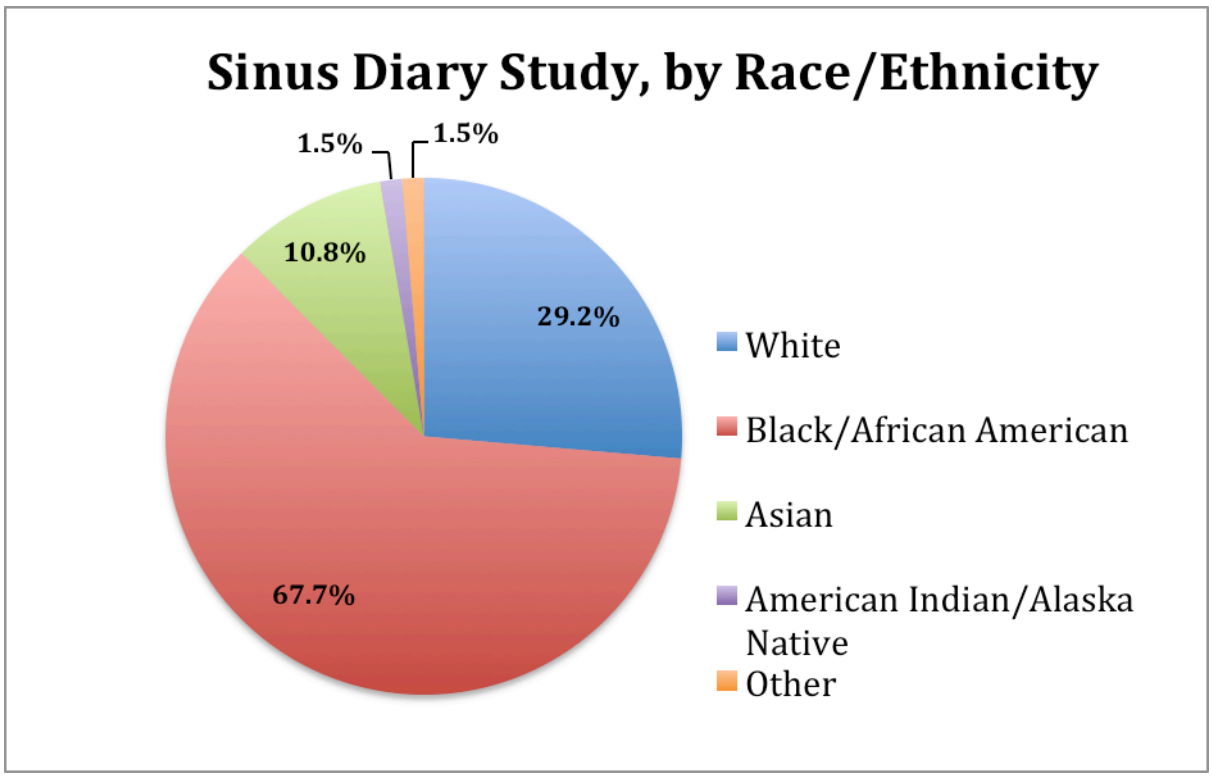


**Figure 3. Race/ethnicity of Sinus Diary Study Participants**

## 3.2 COLD SWAB STUDY

### 3.2.1 Pathogen Identification

SPN and HFLU were identified in the nasal swab cultures of participants. Of the 96 swabs obtained, neither pathogen was isolated from 35 participants (36.4%). Nine participants (9.4%) had cultures positive for both SPN and HFLU. Forty-six participants (48%) had cultures positive for SPN and 24 (25%) participants had cultures positive for HFLU.

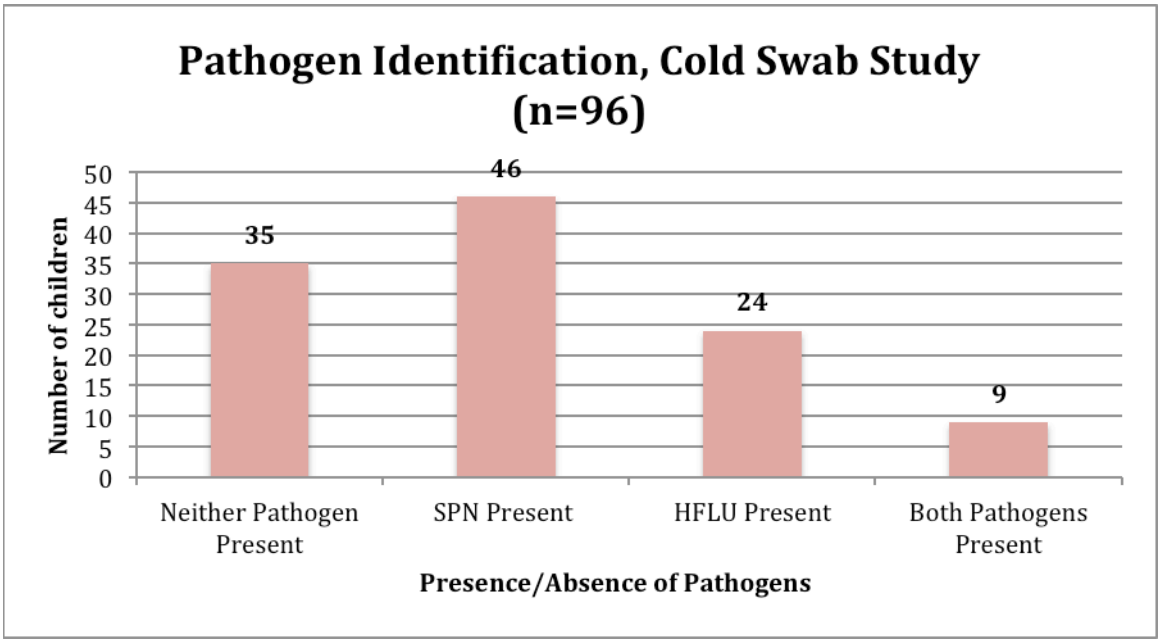


**Figure 4. Results comparing the presence verses absence of SPN and HFLU in cultures from Cold Swab Study participants**

### 3.2.2 Swab Comparison

A total of 96 paired NP/MT swabs were obtained from participants in the study. Seventy-three of 96 (76%) paired swabs were concordant for SPN and HFLU and 23 of 96 (24%) were discordant. Eighty-four of 96 (87.5%) paired swabs were concordant for SPN, and 84 of 96 (87.5%) paired swabs were concordant for HFLU.

Based on a McNemar test using Stata 14, the NP/MT swab comparison for SPN had an exact McNemar significance probability of 0.0005. This indicates that the differences observed between the NP/MT swabs were statistically significant for SPN. The NP/MT swab comparison for HFLU resulted in an exact McNemar significance probability of 1.0. This indicates that the differences observed between the NP/MT swabs were not statistically significant for HFLU.

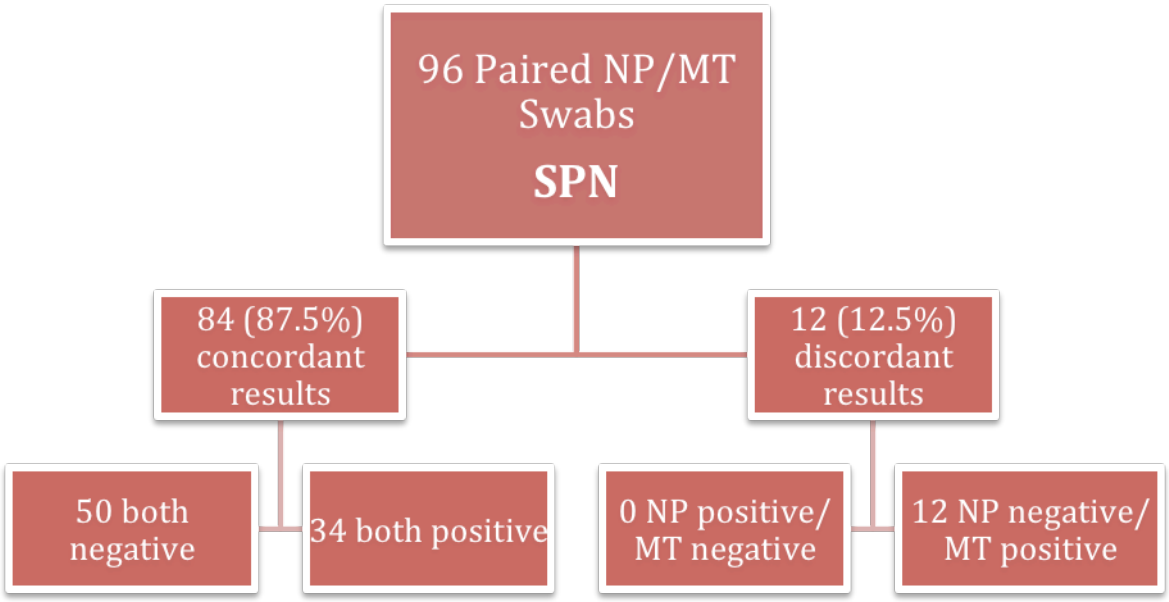


**Figure 5. Results for SPN in 96 paired NP/MT swabs**

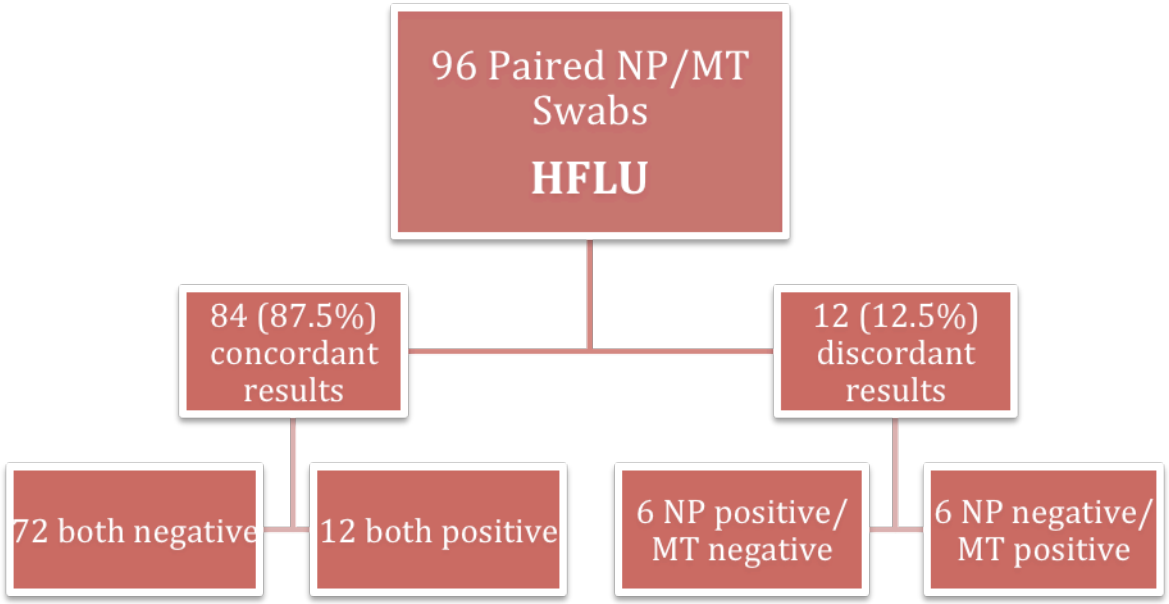


**Figure 6. Results for HFLU in 96 paired NP/MT swabs**

## 3.3 SINUS DIARY STUDY

### 3.3.1 Pathogen Identification

SPN and HFLU were identified in the nasal swab cultures of participants. Of the 54 nasal swabs obtained, neither pathogen was isolated from 25 participants (46%). Two participants (3.7%) had cultures positive for both SPN and HFLU. Twelve children (22.2%) had cultures positive for HFLU only and 19 (35.2%) had cultures positive for SPN only.

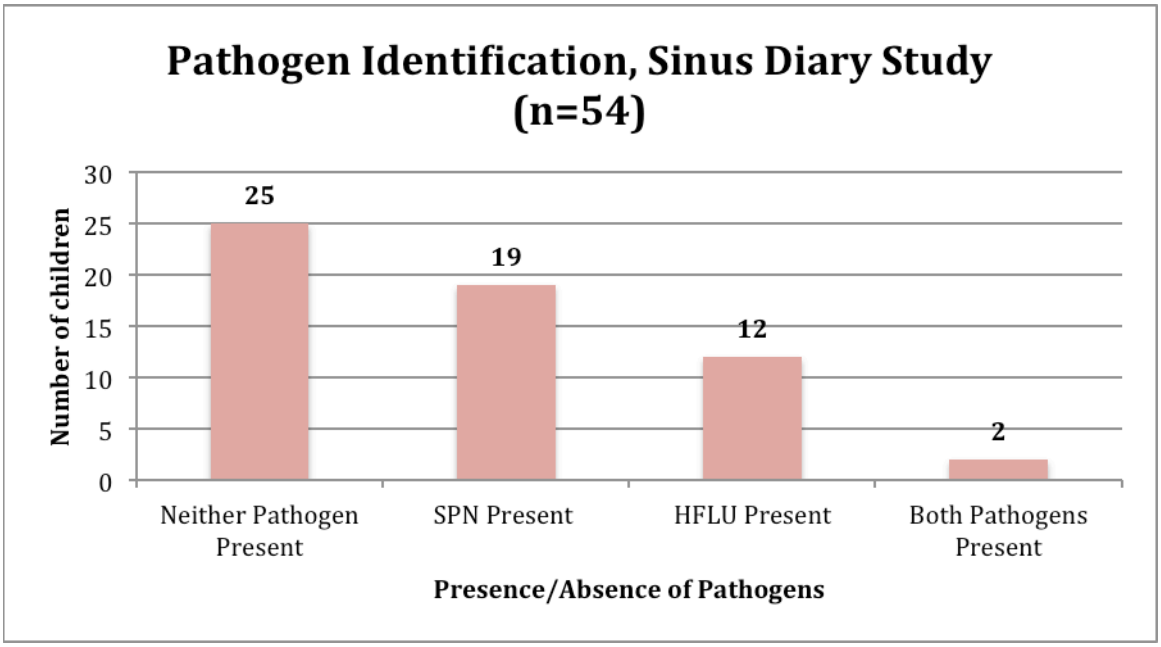


**Figure 7. Results comparing the presence versus absence of SPN and HFLU in cultures from Sinus Diary study participants**

### 3.3.2 Diary Compliance

There were a total of eleven diary entries throughout the duration of the Sinus Diary study. Twenty-seven percent of parents completed all diary entries. At least nine of eleven diary entries were completed by 59% of participant parents. Of parents who completed eleven diary entries, only 50% of them did so without the need of a reminder phone call.

# 4.0 DISCUSSION

## 4.1 COLD SWAB STUDY

### 4.1.1 Pathogen Identification

Forty-six of 96 (48%) children enrolled in the Cold Swab study had cultures positive for SPN, whereas 24 of 96 (25%) children had cultures positive for HFLU. Only nine of 96 (9%) children were colonized with both pathogens. According to a study conducted by Shaikh et al. in 2014, children with acute bacterial sinusitis whose nasopharynx was colonized with SPN responded better to antimicrobial therapy compared to those who were not colonized with SPN in the nasopharynx.[15] Their results did not confirm a similar response to antimicrobial therapy in children who were colonized with some of the other common pathogens such as, HFLU and *Moraxella catarrhalis*, involved in acute bacterial sinusitis. Investigators suspect the antibiotic response differences were due to the host's immune response to different bacterial pathogens.[15] Additional research is necessary to determine if certain pathogens respond better to antimicrobial therapy, but researchers suspect the presence versus absence of a pathogen could direct the course of treatment in acute bacterial sinusitis.

### 4.1.2 Swab Comparison

The combined SPN and HFLU concordance rate for the NP/MT swabs was 76%. The concordance rate for SPN in matched NP/MT swabs was 87.5%. All 12 of discordant results were NP negative and MT positive. The HFLU concordance rate was also 87.5% in matched NP/MT swabs. Six of the 12 discordant results were NP positive and MT negative and the other six were NP negative and MT positive. The differences observed could have been due to specimen collection technique, a delay before processing, or handling methods in the laboratory. Trained professionals swabbed NP/MT swabs together to eliminate prolonged discomfort for children. However, NP/MT swabs were not assigned to specific nares. There is a possibility that pathogens can differ in the nares. If this holds to be true, different swabs would pick up different pathogens depending on what exists in the nares.

According to Copan Diagnostics, eSwab can support bacteria for up to 48 hours at refrigerator temperature before pathogen viability is at stake.[7] Specimens that were left at refrigerator temperature for greater than 48 hours at the Primary Care Center may have been inviable before being processed at the Infectious Disease Research Laboratory of CHP. In the beginning of the study, some specimens that were collected on Fridays were left at the Primary Care Center over the weekend, and then transported to the Infectious Disease Research Laboratory the following week. It is possible that this delay could have caused an underestimation of SPN or HFLU in the NP/MT swab results.

In 2011, Larios et al. compared self-collected MT swabs with nurse-collected NP swabs for acute respiratory illnesses.[9] This study was conducted in adults and aimed to detect viruses specifically. The conclusions from this study showed a 91% concordance rate. In contrast to the

Cold Swab study, this study swabbed most participants more than once. There was no indication about which of the two nares were swabbed with the NP versus MT swab.

## 4.2 SINUS DIARY STUDY

### 4.2.1 Diary Compliance

Electronic diaries are an effective way of gathering data to assess symptoms for conditions like acute bacterial sinusitis. Fifty-nine percent of parent participants completed at least nine of 11 diary entries in the sinus diary study. Compared to prior diary studies, the electronic diary compliance rate was lower in the Sinus Diary study.[10,18] This may have been due to a difference in sample size number, gender, racial status, duration of the study, number of entries per day, and the fact that the Sinus Diary study was not a self-assessment. These variables varied among studies investigating the compliance and accuracy of electronic diaries for symptoms research in clinical settings. Therefore, the lower compliance rate seen in the Sinus Diary study may have been due to a variety of factors.

### 4.2.2 Electronic and Paper Diary Comparison

The benefit of using electronic diaries in clinical research settings is that researchers know exactly when the diary entry was submitted. Advancements in technology have allowed clinical researchers to excel beyond basic data collection methods on paper. Paper diaries have been the traditional method for gathering data to assess symptoms in the past. However, this

method of data collection always had to account for reporter bias. In most studies, participants would have brought in all their diary entries for submission during their final visit, and this always raised potential concern for diary hoarding. Hoarding is when study participants fail to complete diary entries at correct time intervals, and instead fill out multiple entries at once. Although this would result in a high compliance rate for the study, the data in the entries would be inaccurate.

A study performed by Stone et al. compared paper and electronic diary compliance among patients.[18] Study participants submitted their paper diaries 90% of the time. However, the study was designed to record how often and at what time the paper diary binder had been opened. Although 90% of diary entries had been completed and submitted, electronic records showed that only 11% of paper diary entries were completed at their appropriate times. Electronic records indicated that the diary binder had not been opened on one-third of all study days even though diary entries were completed. In comparison, the electronic diary compliance was 94%. The results of this study raise concern about diary hoarding, backfilling, and forward-filling of diary entries when using the traditional paper method.[18]

The purpose of using diaries in clinical studies is to understand the course of a disease in order to prescribe the best treatment available to patients. The purpose of clinical diaries would be jeopardized if participants were failing to comply with the diary study protocols. Many studies have questioned the validity of paper diary information due to research confirming the low compliance rates of paper diaries.[18]

The use of electronic diaries has shown to reduce costs over long periods of time in clinical research settings. Using electronic diaries reduce the cost and processing time allocated for data transcription.[4,6] Even though clinical research centers purchase the software and

technology needed for electronic diary studies, they can reuse these programs and devices for future studies as well. In addition to saving time and money for data transcription, electronic diaries can reduce the potential for transcription errors made when transcribing data from paper diaries to software programs for data analysis.[6] Lastly, the study performed by Dale and Hagen claims participants preferred the electronic diaries to the paper diaries.[6]

Although electronic diaries confirm higher rates of compliance, they are not perfect. Electronic diaries have shown to result in higher percentage of missing data when compared to paper diaries. Investigators believe this is due to technical difficulties of electronic devices and programs. Using electronic diaries in clinical research poses its own drawbacks. As noted, the use of technology in any setting raises potential for technical problems.[6] Device or program failure is always a possibility which is why researchers should make sure that data is being backed-up regularly.[4] When using technology in clinical research, researchers must keep in mind that not all participants are on the same comfort level with computers, smartphones, and the Internet.[4] This can become a big disadvantage if a study involves an older age population who is still adjusting to the idea of the Internet. In addition, researchers must keep in mind that access to the Internet is not universal among all participants. For this reason, the Sinus Diary study provided CHP tablets to participants without smartphones, tablets, computers, or Internet access throughout the duration of the study. Researchers did not want access to technology to be a restricting factor for participants. Although electronic diaries have many drawbacks, they are still considered to outperform paper diaries in clinical research settings.[6]

### 4.2.3 Reminders

Only half of parents who completed all of eleven diary entries completed them without the need of a reminder phone call. Most parents required a reminder phone call the morning after missing a diary entry. Research assistants then completed the diary entry over the phone as an additional phone call session. This way data was still being collected for symptom assessment. This concludes that parents often need to be reminded to complete their diary entries even though they receive the diary entry link daily in email or text message formatting.

In the study performed by Burton et al., researchers concluded that electronic diaries were an effective method for collecting valid data for clinical studies involving symptoms research.[4] Stone et al. concluded that incorporating compliance-enhancing features to the electronic diary studies has potential of achieving good compliance rates.[18] Therefore, reminder messages and phone calls are an essential and necessary component of the electronic diary study.

## 4.3 LIMITATIONS

### 4.3.1 Cold Swab Study

Due to funding limitations, SPN and HFLU were the only pathogens screened for throughout the study. Although *Moraxella catarrhalis* and *Staphylococcus aureus* are pathogens that may be isolated from the nares of children presenting with sinusitis, researchers focused their efforts on the two most common pathogens, SPN and HFLU. In the future, researchers can expand on other pathogens involved in the development and persistence of sinusitis.

A delay before processing the NP/MT swabs could potentially impact the results observed. This is a limitation because there was a delay before processing some of the swabs in this study, and therefore could have impacted the pathogen identification and swab comparison results. The specimen collection technique was a limitation in this study as well. The NP swab was taken from one of two nares, whereas the MT swab was taken from the other. There is a possibility that pathogen colonization can differ in each of the nares, which in turn could impact the results observed in this study.

### 4.3.2 Sinus Diary Study

The main limitation of the Sinus Diary study was that parents were answering the diary questions on behalf of their children. If this study involved an older population, participants would have filled out the diary entries themselves. This brings into question the accuracy of the day-to-day symptom assessment and parental compliance rate. In addition, if this study involved a pediatric population who did not have to rely on their parents to complete the diary entries, there may have been a difference seen in the compliance rate. In 2003, Palermo et al. investigated the compliance, accuracy and acceptability of electronic and paper diaries in children.[10] Their diaries assessed pain and disability in children for headaches and juvenile idiopathic arthritis. Unlike the Sinus Diary study, the pain study enrolled children ages eight to 16 and asked the children to complete the daily diary entries. The results from this study showed a compliance rate of 83.3% in the group randomized to the electronic diary and 46.7% in children who were randomized to the paper diary study. The Sinus Diary study enrolled children one to 11 years of age and therefore could not rely on children to self-assess their symptoms for diary entries.

## 4.4 PUBLIC HEALTH SIGNIFICANCE

The diagnosis and treatment of sinusitis involves a financial burden due to high costs and socioeconomic status. Children often miss school days, which may require parents take time off from work as well.[2] The financial burden that results from sinusitis can tremendously affect families of low socioeconomic status, especially if they do not have access to healthcare. Children who are misdiagnosed with a viral upper respiratory infection instead of acute bacterial sinusitis will require additional visits to their provider. Depending on the socioeconomic status and geographic location of these families, parents who rely on public transit or live far from hospitals or provider offices, will have to arrange transportation for these visits. Lastly, poor education can become a concern for children repeatedly taking time off of school.

Over-prescribing antibiotics in sinusitis patients has become a major concern in clinical settings. The emergence of antimicrobial resistance has been noted in sinusitis patients. These resistant strains include the most common bacterial strains, especially SPN, involved in the development of sinusitis.[12] This emergence is suspected to be a result of inappropriately diagnosing acute bacterial sinusitis and prescribing antibiotics in patients who have a viral upper respiratory infection. When prescribing antibiotics to bacterial sinusitis patients, the agent should be active against the most common strains, SPN, HFLU and MCAT. If symptoms do not show signs of improvement within three to five days, providers should suspect a resistant pathogen.

There is limited research on the optimal duration of antimicrobial therapy in sinusitis patients. Currently, a ten-day duration of antibiotics is the recommended course of treatment in patients presenting with uncomplicated sinusitis. Previous studies have compared a three verses ten-day antibiotic therapy and results have shown rates of similar success. The results from this study are not entirely reliable since researchers did not rule out viral sinusitis cases

beforehand.[12,20] Therefore, it is suspected that their study population involved viral and bacterial sinusitis cases.

In addition to the concerns of antimicrobial resistance, prolonged antimicrobial therapy also gives rise to reduced patient compliance. This can also lead to development of bacterial resistance in patients.[12] Acute bacterial sinusitis is suspected less in pediatric patients who present with mild upper respiratory infection symptoms. Therefore, these patients are thought to benefit less from antibiotics since the purpose of prescribing these antibiotics is to relieve symptoms. For these reasons, symptoms should be observed in children presenting with mild symptoms before immediately prescribing antibiotics.[12]

## 4.5 FUTURE DIRECTION

### 4.5.1 Larger Acute Bacterial Sinusitis Study

Researchers designed the Cold Swab and Sinus Diary studies to function as pilot studies for a larger randomized acute bacterial sinusitis trial. The aim of the larger study is to determine if certain subgroups of children are more likely to benefit from antimicrobial therapy based on the presence of certain pathogens in the nares. Investigators designed the pilot studies in order to evaluate the accuracy of the MT swab in comparison to the traditional NP swab. Their goal was to determine whether the MT swab could replace the NP swab for specimen collection in acute bacterial sinusitis patients. Investigators hypothesize that children who are not colonized with respiratory pathogens are unlikely to benefit from antimicrobial therapy.

In May 2015, the larger acute bacterial sinusitis study received funding from the National Institutes of Health (NIH). The study will use the effective methods from the Cold Swab study and Sinus Diary study to focus on enhancing diagnosis and treatment measures of acute bacterial sinusitis.

### 4.5.2 Nasal Cytokines

Cytokines are cell-signaling molecules secreted in response to inflammation. Cytokines have a variety of functions and their levels can be detected in nasal secretions.[21] The literature suggests that cytokine levels can help aid in the diagnosis of acute bacterial sinusitis.[2,11] A handful of studies have looked into identifying nasal biomarkers in nasal secretions from sinusitis patients.

Although a few studies have investigated nasal cytokines involved in acute sinusitis, most studies have failed to reach statistical significance in their findings. A study conducted by Bachert et al. in 1998 concluded upregulation of the proinflammatory cytokine interleukin (IL)-8. Their work also concluded proinflammatory cytokines IL-1β and IL-6 upregulations but these cytokine levels slightly failed to reach statistical significance.[2] Researchers believed the significant upregulation of IL-8 was due to an early release of IL-1β and tumor-necrosis factor (TNF)-α. Samples from acute sinusitis study subjects were collected five days after symptoms had been present. Due to this delay in specimen collection, researchers believe they missed the initial release of proinflammatory cytokines. The cytokines found to be upregulated in acute bacterial sinusitis were also upregulated in viral upper respiratory tract infections; therefore these findings would not be able to differentiate between the two respiratory infections.

Riechelmann et al. attempted to investigate nasal biomarkers in acute and chronic sinusitis in 2005.[11] This study did not include comparisons to viral upper respiratory tract infections. The nasal cytokine levels of acute and chronic sinusitis patients were compared to those of healthy controls. Their study concluded upregulations in IL-13, IL-12, IL-10 and IL-4 with statistical significance. However, upregulations in IL-6 and IL-8 were detected without reaching statistical significance. Investigators indicated detecting high levels of IL-6 and IL-8 in the healthy control subjects enrolled in their study.

Using nasal cytokine levels could become helpful in diagnosing acute bacterial sinusitis. The goal would be to identify cytokines specific to acute bacterial sinusitis that are not also upregulated in viral upper respiratory tract infections. Although the literature suggests certain cytokines are involved in acute bacterial sinusitis, the conclusions from these studies tend to be inconsistent and lack statistical significance.

Researchers used the nasal specimens obtained from the Cold Swab study to investigate the cytokine types and levels involved in acute bacterial sinusitis. Due to the interest of time and lack of correlation over a short time span, investigation efforts and results were not included in this dataset. Based on the cytokine signals seen in the laboratory and the suggestions in the literature, investigators plan to revisit this area of research in the future.

## APPENDIX A: PEDIATRIC RHINOSINUSITIS SYMPTOM SCALE (PRSS)

### Pediatric Rhinosinusitis Symptom Scale (PRSS)

## How has your child been doing?

We are interested in finding out how your child has been doing over the last 24 hours. Please answer these questions with the help of your child. For each question, please place a check (✓) in the box corresponding to your child's symptoms. Please answer all questions.

Did your child…

| | No | Almost None | A Little | Some | A Lot | An Extreme Amount |
|---|---|---|---|---|---|---|
| Have a **stuffy nose today**? | ❒ | ❒ | ❒ | ❒ | ❒ | ❒ |
| Have a **runny nose today**? | ❒ | ❒ | ❒ | ❒ | ❒ | ❒ |
| **Cough during the day**? | ❒ | ❒ | ❒ | ❒ | ❒ | ❒ |
| Act **more tired** than usual today? | ❒ | ❒ | ❒ | ❒ | ❒ | ❒ |
| Act **irritable or fussy** today? | ❒ | ❒ | ❒ | ❒ | ❒ | ❒ |
| Have **trouble breathing** through the nose today? | ❒ | ❒ | ❒ | ❒ | ❒ | ❒ |
| **Cough last night**? | ❒ | ❒ | ❒ | ❒ | ❒ | ❒ |
| Have **trouble sleeping last night**? | ❒ | ❒ | ❒ | ❒ | ❒ | ❒ |



**Thank you**

## APPENDIX B: SINUS DIARY ENTRY EXAMPLE

1001 | Day: 1

Over the last 24 hours, did your child...

| | No (0) | Almost none (1) | A little (2) | Some (3) | A lot (4) | An extreme amount (5) | Yesterday you said |
|---|---|---|---|---|---|---|---|
| Have a runny nose? | ○ | ○ | ○ | ○ | ○ | ● | N/A |
| Have a stuffy nose? | ○ | ○ | ○ | ○ | ● | ○ | N/A |
| Cough during the day? | ○ | ● | ○ | ○ | ○ | ○ | N/A |
| Cough during the night? | ○ | ○ | ○ | ○ | ● | ○ | N/A |
| Have trouble sleeping? | ○ | ○ | ○ | ● | ○ | ○ | N/A |
| Have green or yellow mucus from the nose? | ○ | ○ | ○ | ○ | ● | ○ | N/A |
| Act irritable or fussy? | ○ | ○ | ○ | ● | ○ | ○ | N/A |
| Act more tired than usual? | ○ | ○ | ○ | ● | ○ | ○ | N/A |
| Have thick mucus from the nose? | ○ | ○ | ○ | ○ | ● | ○ | N/A |

N/A = not available

Is your child's health back to normal?

○ Yes ● No

Compared to yesterday, is your child now...

○ A lot better
● A little better
○ About the same
○ A little worse
○ A lot worse

Did your child take their doses of antibiotics today?

○ Yes ● No

If yes, how many doses (1 or 2)

## Compared to yesterday, how is your child's...

| | Better | Same | Worse | Back to normal |
|---|---|---|---|---|
| Runny nose? | ○ | ● | ○ | ○ |
| Stuffy nose? | ○ | ● | ○ | ○ |
| Daytime cough? | ● | ○ | ○ | ○ |
| Nightime cough? | ○ | ● | ○ | ○ |
| Sleep? | ○ | ● | ○ | ○ |
| Green or yellow mucus from the nose? | ○ | ● | ○ | ○ |
| Mood? | ● | ○ | ○ | ○ |
| Activity level/energy? | ● | ○ | ○ | ○ |
| Thick mucus from the nose? | ○ | ● | ○ | ○ |

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## APPENDIX C: PHONE CALL/MISSED DIARY ENTRY QUESTIONNAIRE

*Confidential*



# Phone Call

Study ID _____

Study Day
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ Missing Diary

Day missed _____

Was contact made?
- ☐ Yes
- ☐ No

Date and time of call _____

Person contacted
- ☐ Mother
- ☐ Father
- ☐ Grandmother
- ☐ Grandfather
- ☐ Other

Other: _____

**Compared to yesterday, how is your child's...**

| | Better | Same | Worse | Back to Normal |
|---|---|---|---|---|
| Runny nose? | ☐ | ☐ | ☐ | ☐ |
| Stuffy nose? | ☐ | ☐ | ☐ | ☐ |
| Daytime cough? | ☐ | ☐ | ☐ | ☐ |
| Nighttime cough? | ☐ | ☐ | ☐ | ☐ |
| Sleep? | ☐ | ☐ | ☐ | ☐ |
| Green or yellow mucus from the nose? | ☐ | ☐ | ☐ | ☐ |
| Mood? | ☐ | ☐ | ☐ | ☐ |
| Activity level/ energy? | ☐ | ☐ | ☐ | ☐ |
| Thick mucus from the nose? | ☐ | ☐ | ☐ | ☐ |

**Over the past 24 hours, did your child....**

| | No | Almost none | A little | Some | A lot | An extreme amount |
|---|---|---|---|---|---|---|
| Have a runny nose? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Have a stuffy nose? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Cough during the day? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Cough during the night? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Have trouble sleeping? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Have green or yellow mucus from the nose? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |





| | | | | | | |
|---|---|---|---|---|---|---|
| Act irritable or fussy? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Act more tired than usual? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Have thick mucus from the nose? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

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