ETIOLOGY OF ACUTE RESPIRATORY TRACT INFECTIONS AND PREDICTORS FOR SEEKING CARE

by

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((Under the Direction of Mark Ebell, MD, MS)

ABSTRACT

Problem: There are very few recent studies on the etiology of ARTIs done in the US. Care seeking behavior of college-aged students has not been researched. Our primary goal is to identify bacterial and/or viral organisms that are pathogenic and ones that could be commensal. Our secondary goal is to identify symptoms and illness severity that influences students' likelihood for seeking care or antibiotic treatment. **Methods:** We performed a meta-analysis to identify etiologies associated with symptomatic illness and etiologies that could be commensal. We conducted a case-control study composed of cases with symptomatic ARTIs and controls to determine identify etiology of ARTIs. A survey was administered to University of Georgia students as a cross-sectional study to identify symptoms and illness severity associated with seeking care or seeking antibiotic treatment. **Results:** The meta-analysis identified 15 studies that reported etiology for ARTIs. We found that the etiology of symptomatic ARTIs was most often viral. Bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* were detected more often in asymptomatic persons. A total of 1,215 individuals met the inclusion criteria for our case-control study. Viral etiology was more often association with being symptomatic. Bacteria had the potential to be commensal as they were detected more frequently

in healthy individuals. A total of 2,000 students completed our vignette survey. Recent antibiotic use was a predictor for seeking care and/or seeking antibiotic treatment for all conditions (aOR 1.5 – 3.8, 95% CI [1.0, 5.4]). Being an undergraduate in school was an independent predictor for seeking an antibiotic for all conditions (aOR 1.5 – 3.8, 95% CI [1.0, 5.4]). **Conclusion:** Etiology of symptomatic ARTIs were determined to most often be viral. Certain bacterial organisms, when present, have the potential of being commensal as they are identified more often in healthy individuals than patients with symptoms. Students are more likely to seek care and antibiotics with more severe illness when compared to mild or moderate. Students were also more likely to seek antibiotic treatment if they had recently been prescribed an antibiotic. Other common predictors for seeking care included non-white race and younger age in school.

INDEX WORDS: Acute respiratory tract infections, upper respiratory tract infections, sore throat, lower respiratory tract infections, etiology, commensal, care seeking behavior, college students

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CHAPTER 1

INTRODUCTION

1.1 Pathophysiology of Acute Respiratory Tract Infections

Acute respiratory infections (ARIs) are the most common reasons for encounter in the outpatient setting[1]. They are also the most common diagnoses for which a patient receives any prescription (i.e. antibiotics, antitussives, and inhalers)[2]. ARIs can occur as upper respiratory tract infections (URTIs) or lower respiratory tract infections (LRTIs). The World Health Organization (WHO) and Centers for Disease Control (CDC) define acute respiratory tract infections based on the location of the infection and the symptoms associated (Table 1.1).

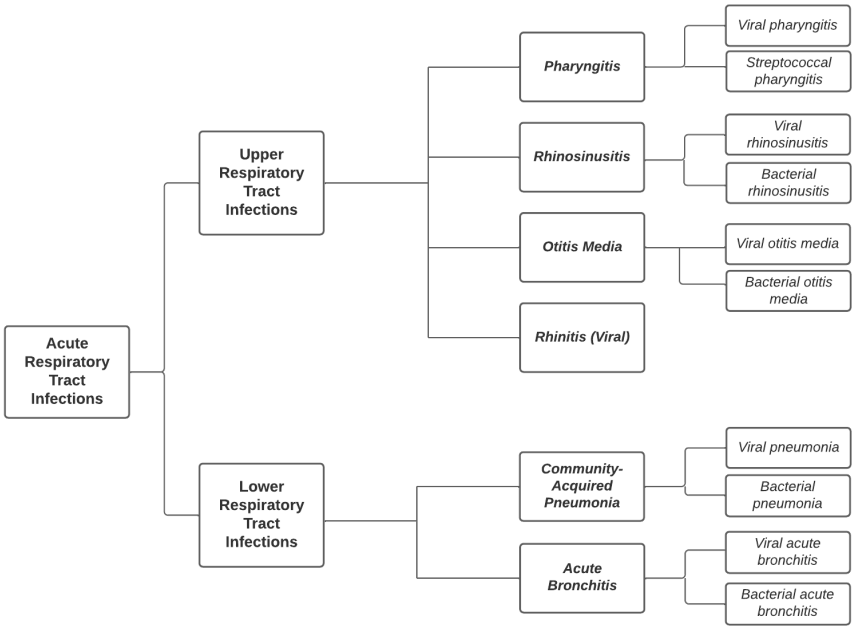
Table 1.1 Duration of acute illness for the most common acute respiratory tract infections

Acute Respiratory Infections	**Common Symptoms**	**Duration of Symptoms**
Upper Respiratory Tract		
Pharyngitis	Sore throat, cough, runny nose, fever, swollen tonsils and/or lymph nodes	2 to 5 days
Rhinosinusitis	Runny/congested nose, facial pain, headache, mucus in throat, sore throat, cough	3 days to 10 days

Otitis Media	Ear pain, fever, irritability, difficulty sleeping, discharge from ear	2 to 3 days
Rhinitis	Sneezing, runny/congested nose, sore throat, coughing, mucus in throat, watery eyes, fever	10 to 14 days
Lower Respiratory Tract		
Community-Acquired Pneumonia	Shortness of breath, cough, sputum, fever/chills, chest pain with cough, nausea, vomiting or diarrhea	2 weeks to 1 month
Acute Bronchitis	Cough, chest pain with cough, fatigue, headache, body aches, sore throat	1 to 3 weeks

URTI diagnoses include pharyngitis, rhinosinusitis, otitis media, and rhinitis (Figure 1.1). Acute upper respiratory tract infections are caused by a virus and/or bacterium which produces acute inflammation of nasal and pharyngeal mucosa[3]. Symptoms of acute URTIs typically include mild cough, fever, fatigue, nasal congestion, sore throat, and swollen lymph nodes.

Figure 1.1 Taxonomy of acute respiratory tract infections



LRTI diagnoses include community-acquired pneumonia (CAP) and non-pneumonia lower respiratory tract infections or acute bronchitis, as it is also known. Acute lower respiratory tract infections affect the lungs and typically cause cough and at least one of the following symptoms: sputum production, dyspnea, wheezing, or chest pain/discomfort. The median duration of lower respiratory symptoms is approximately 18 days[4].

1.2 Microbiology of Acute Respiratory Tract Infections

Acute upper and lower respiratory tract infections can be caused by both bacterial and viral pathogens. Bacterial URTI diagnoses include streptococcal pharyngitis, pharyngitis caused by *Fusobacterium necrophorum*[5], bacterial rhinosinusitis, and bacterial otitis media. Bacteria commonly associated with both URTIs and LRTIs include *Streptococcus pneumoniae*

(pneumococcus), *Haemophilus influenzae*, and *Moraxella catarrhalis. Staphylococcus aureus* is a bacterium that is associated solely with LRTIs[6].

However, it is thought that some of these bacterial pathogens could be commensal and not pathogenic. Commensal bacteria are those that colonize the respiratory tract but are not associated with illness[7]. Bacteria that are suspected to be commensals in the respiratory tract, with the potential to become pathogenic, include *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*[8].

Viral URTI diagnoses include viral pharyngitis, viral rhinosinusitis, viral otitis media, and viral rhinitis. Viruses associated with URTIs and LRTIs include human rhinovirus, human metapneumovirus (hMPV), respiratory syncytial virus (RSV), influenza A and B viruses, parainfluenza virus, adenovirus, and coronavirus[6]. Bacterial LRTIs can include pneumonia and acute bronchitis. Viral LRTIs are viral pneumonia and viral acute bronchitis.

1.3 Testing for Acute Respiratory Tract Infections

Respiratory illnesses can be caused by bacterial and/or viral pathogens making diagnostic practices vital for guiding proper treatment. Clinicians can utilize conventional culture, rapid antigen testing, and polymerase-chain reaction (PCR) testing to identify the presence of viral/bacterial pathogens in patients with acute respiratory tract infections[9]. Conventional culture is the "gold standard" but is rarely used in outpatient practice due to how labor intensive and time consuming the process is. PCR testing has a sensitivity approaching 100% for many pathogens but is often not used because it is costly and may not be available in many settings. Due to its high sensitivity, PCR can detect chronic colonization or low viral loads from previous infections. This can make interpreting results challenging. Rapid antigen testing availability is available for influenza, RSV, hMPV, adenovirus, parainfluenza, and now SARS-CoV-2[10]. While

the rapid test for SARS-CoV-2 has good specificity, the sensitivity of these tests is lower (68.9%, CI: 61.8 – 75.1) than PCR[11,12]. Also, the sensitivity of these test has been shown to significantly decrease after 7 days of disease onset especially in cases where COVID-19 was suspected[11].

1.4 Transmission and Prevention of Acute Respiratory Tract Infections

All acute respiratory illnesses are spread from person-to-person primarily via droplets produced from coughing, sneezing, and talking. Often, pathogens causing respiratory infections are contained in large droplets that are spread over short distances. However, aerosols are small particles that can remain suspended in the air and follow airflow. SARS-CoV-2 is a highly transmissible aerosol because it can be spread over a short or long distance through airborne routes[13]. Respiratory infections are prevented through infection control measures such as proper hand hygiene, wearing of facemasks, disinfecting frequently touched surfaces, socially distancing from persons who are symptomatic, and respiratory hygiene and cough etiquette[14]. Some respiratory illnesses, both viral and bacterial, can be prevented with vaccinations. Vaccine preventable infections include influenza, COVID-19, RSV, pertussis, *Haemophilus influenzae* type B, and pneumococcal pneumonia.

1.5 Prognosis and Treatment of Acute Respiratory Tract Infections

Infections in the respiratory tract are often self-limited with symptoms resolving in between one week and one month. Prognosis of upper respiratory illness is typically thought to be good among healthy patients without underlying conditions. However, lower respiratory tract infections can cause severe illness, especially in patients who have other health conditions, are immunocompromised, are older (especially over 65 years of age), and/or are under 5 years of age[15]. Even though most RTIs are viral, antibiotics are often prescribed as a form of treatment. These prescriptions comply with current recommendations in only 25% of cases[16]. This could, in

part, be due to patient expectations. Non-antibiotic treatments include over-the-counter medications and supportive therapies for the management of symptoms such as cough suppressants, oral and nasal decongestants, anti-inflammatory drugs, inhalers, systemic corticosteroids, and nasal saline. Alternative treatments like zinc and Umcka (South African Geranium) have also been shown to decrease the duration and severity of acute respiratory tract infections[17,18].

1.6 Statement of Problem

In previous studies, viruses have been identified as the causative agent in respiratory tract infections approximately 90% of the time[19]. However, antibiotic prescriptions are often still provided in the absence of testing that can confirm a viral cause. This has led to overprescribing of antibiotics in cases when the illness would have been self-limiting[20]. Inappropriate prescribing of antibiotics is the leading cause of antimicrobial resistant pathogens, which are a threat to global health[21]. Also, the diagnostic and treatment strategies for acute respiratory tract infections are often variable due to overlap of symptoms of infections involving different anatomical sites[22].

Additionally, care seeking trends and behaviors for acute RTIs have not been studied thoroughly in college-aged individuals. College students are in the unique position of making their own health decisions for the first time. Also, respiratory infections are easily spread on college campuses due to congregate living conditions and lifestyle factors. It is important to investigate this demographic group because the information obtained could influence RTI treatments prescribed, diagnostic practices, and long-term medical behaviors. This research will also help to identify gaps in the health education of college-aged students as it relates to RTIs.

1.7 Aims of this Dissertation

Our overall goal for these three aims is to better understand the diagnosis, treatment, and natural history of respiratory tract infections in the outpatient setting. We also plan to identify trends in student care seeking behaviors/ understanding of respiratory illnesses to mitigate overprescribing and over diagnosis at early ages. Each aim has its own set of objectives and methods, which are described in detail in chapter 3. Below is a brief description of each aim, presented in Table 1.2.

Table 1.2 Brief description of objectives, data sources, and methods of dissertation aims

Aim	Objectives	Data Sources	Methods
1	- Identify the most common pathogens associated with outpatient RTI based on published literature - Compare respiratory pathogens seen in symptomatic and asymptomatic outpatients, and to use that information to estimate likelihood that each pathogen is commensal versus pathogenic	- PubMed, EMBASE, Web of Science, Google Scholar	- Systematic review - Meta-analysis
2	- Using the Enhancing Antibiotic Stewardship in Primary Care (EAST-PC) dataset as cases, collect swabs from asymptomatic patients and compare the pathogens detected with those from symptomatic patients - Use this information to estimate the likelihood that a pathogen is commensal, and compare those findings with those in the systematic review	- RedCap (East-PC) - Recruitment documents	- Case-control study - EAST-PC recruitment of symptomatic individuals - Convenience sampling of asymptomatic people (campus, UHC, farmers market) - X^2

3	- Investigate college-aged students RTI-related care seeking behaviors through assessing their responses to a series of clinical vignettes	- Survey data – administered via UGAMail and Qualtrics - Review responses to the UHC "Respiratory Illness Questionnaire" - RedCap (EAST-PC) care seeking responses	- Logistic regression - Qualitative analysis

Aim 1 is focused on determining what pathogens are commonly associated with respiratory tract infections among outpatients. We will conduct a systematic review of the literature to identify outpatient studies that compare the detection of respiratory pathogens present among asymptomatic, healthy individuals and cases with symptomatic acute RTI. This information will be used first, to identify the most common pathogens associated with acute upper and lower respiratory tract infections in the outpatient setting and second, to determine which bacteria and/or viruses are likely commensal. We hypothesize that the majority of symptomatic respiratory infections are caused by viruses and as such, do not require antibiotic treatment, and that several commonly identified viruses and bacteria are always or usually commensal.

Aim 2 focuses on determining if the data summarized in Aim 1 are consistent with the findings of our own case-control study of the same topic. Symptomatic patients will be recruited in one of six primary care sites in the US based on their presence of cough for less than 14 days and are 18 years to 75 years of age. Demographic data, signs, symptoms, c-reactive protein (CRP), and a PCR panel for both viral and bacterial pathogens will be gathered (Table 1.3). Asymptomatic patients will be recruited on campus (faculty and staff), in outpatient clinic

settings affiliated with UGA, Georgetown and the University of Wisconsin, and at other community settings. We hypothesize that the findings of our case-control study are similar to those identified in the systematic review.

Table 1.3 Pathogens (n=43) included in PCR panel for symptomatic and asymptomatic patients

PCR Panel Pathogens		
Bacterial Pathogens		
P. aeruginosa	*C. trachomatis*	*B. pseudomallei*
S. pneumoniae	*K. pneumoniae*	*H. influenzae (all types)*
Group A and B Streptococcus	*S. aureus*	*C. pneumoniae*
M. pneumoniae	*A. baumannii*	*M. catarrhalis*
C. diptheriae	*C. ulcerans/pseudotb*	*Bordetella spp. (IS481)*
Bordetella spp. (pIS1001)	*M. tuberculosis*	*P. jirovecii (PCP)*
DT (toxin)	PT (toxin)	
Viral Pathogens		
Varicella zoster virus	MERS coronavirus	Coronavirus HKU1
Measles virus	MERS-CoV upE	Coronavirus 229E
Parainfluenza virus 1, 2, 3, 4	Coronavirus NL63	Coronavirus OC43
Influenza A and B	Cytomegalovirus	RSV
Enterovirus	Adenovirus	Rhinovirus
Rubella virus	Human metapneumovirus	

Aim 3 addresses the behavior of university students seeking care for RTI. It is important to study this demographic as it is the first time that medical decision-making falls solely on the

individual student. Vignettes will be created based on common RTI encounters that systematically varies key signs and symptoms such as fever, sputum color, dyspnea, and severity. Students will be asked to indicate on a Likert scale their likelihood of seeking outpatient care, over-the-counter (OTC) treatments, their perception of if they need an antibiotic, and other care-seeking behaviors. We hypothesize that for scenarios with less severe symptoms, students will opt not to go to an outpatient setting but will try treating symptoms with OTC options first. In addition to these vignettes, we will utilize the UHC patient portal respiratory illness questionnaire to identify their reason for scheduling a respiratory related illness appointment. Lastly, we will quantify responses to care seeking questions for the symptomatic young adults, aged 18 – 30 years, recruited in the EAST-PC study. This information will help identify common reasons for scheduling appointments as they pertain to their illness and symptoms and also identify any outside factors (i.e. guardian advice, insurance coverage, upcoming event) that may have influenced their decision. These qualitative data could also inform health education in an effort to reduce antibiotic requests. This information will complement that obtained from the clinical vignettes.

1.8 Dissertation Outline

Chapter 1 of this dissertation has provided a brief introduction to respiratory tract infections. Chapter 2 will thoroughly describe the literature surrounding RTIs, their treatment and testing, and student behavior with regards to RTIs. Chapter 3 will describe the methods used in each aim of this dissertation. Chapter 4 is a brief introduction to the results for each aim. Chapters 5, 6, 7, will be manuscripts prepared for publication representing each of the three aims. Chapter 8 will be a summarization of the findings of each aim and conclusions.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of Acute Respiratory Tract Infections

Acute respiratory tract infections remain a common cause of outpatient visits globally[23]. The World Health Organization indicated in 2004 that LRTIs ranked first in the burden of infectious disease measured by years lost through death or disability[15]. In 2013, respiratory infections were responsible for 120 million disability-adjusted life years (DALYs) worldwide[24]. Acute respiratory tract infections can be caused by bacterial and/or viral pathogens. Coinfection competition that ultimately results in infection is not completely understood[25]. Similarly, there is significant overlap of symptoms associated with different acute respiratory tract infections, making diagnosis difficult. The most commonly used point-of-care tests (POCT) for acute respiratory tract infections in the outpatient setting are those for *streptococcus* pharyngitis (strep throat), influenza, and in recent years COVID-19[26,27]. However, rapid tests to differentiate between most bacterial and viral infections are lacking[28]. This has led to widespread overprescribing of antibiotics despite the fact that most cases are caused by viral pathogens. It was estimated in 2003 that in the United States (US), 500 million non-influenza, viral acute RTIs occur annually with approximately $40 billion spent in associated costs[29].

2.2 Etiology of Acute Respiratory Tract Infections

As previously mentioned, the etiology of acute upper and lower respiratory tract infections can be bacterial and/ or viral. However, viral pathogens are more frequently associated with acute respiratory illness than bacteria[30]. Creer and colleagues conducted a study in the United

Kingdom (UK) in 2004 assessing the etiology in adults with lower respiratory tract infections. Out of the 80 patients recruited with acute LRTI the identification rate for pathogens present was 63% for viruses and 26% for bacteria[31]. Among the LRTI cases, rhinovirus (33%) and influenza (24%) were among the most commonly detected viruses. Bacterial pathogens most frequently detected in this study population were *S. pneumoniae* (19%) and *H. influenzae* (6%). Multiple organisms were found in 18 of the 80 acute LRTI patients (22.5%).

A 2019 study conducted in three primary care centers in Sweden also confirmed these findings in a study population of cases with acute upper or lower respiratory tract infections. Sundell and colleagues enrolled 103 patients with respiratory tract infections in their study (46 with URTI and 57 with LRTI)[32]. They found that 51 (50%) of the patients with respiratory tract infection were positive for at least one respiratory pathogen. In 37 (36%) of these cases, a virus was detected. Rhinovirus was the most commonly detected virus (22%) followed by coronavirus (5.8%).

Most recently, a study was conducted in six inpatient settings in low to middle income countries. Researchers found that among the 2,388 patients enrolled with acute upper and lower respiratory tract infections, 77% of cases had one or more pathogens detected when nasopharyngeal (NP) and oropharyngeal (OP) swabs were tested[33]. Unlike the previously mentioned studies, bacterial pathogens were the most commonly identified pathogens overall. The most commonly identified bacteria being *S. pneumoniae*, *H. influenzae* (all types), and *M. catarrhalis*. Rhinovirus, influenza A and B, and RSV were the most common viruses.

2.2.1 Commensal Pathogens

As shown in the studies conducted by Creer and Milucky, there are instances when multiple pathogens can be detected in an individual simultaneously. This brings into question

which pathogen detected is likely causing symptoms of acute respiratory tract infection. The respiratory tract is colonized with bacteria and/or viruses, much like our skin. The commensal microbiome is housed primarily in the upper respiratory tract which includes the nasal cavity, nasal pharynx, and larynx[7]. The normal bacteria that colonize the respiratory tract are thought to be commensal or "healthy" and unlikely to cause harm[34]. In contrast, it is thought that the presence of these commensal organisms can assist the body with fighting new, opportunistic bacterial or viral pathogens that may cause invasive diseases[6,35]. Disruption of the respiratory tract commensal bacteria can lead to imbalances in the microbiota that can result in new bacterial or viral infection, multiple bacterial infections, or viral co-infections[6,36].

2.2.2 Bacterial Colonization

Unfortunately, many pathogens that reside in the upper respiratory have the ability to colonize and cause disease. Such bacterial pathogens that lead to imbalances in the upper respiratory tract microbiota are *S. pneumoniae, H. influenzae, M. catarrhalis*, and *S. aureus*, which have been identified as the most frequently detected bacterial pathogens in previous studies[7,37]. Over-colonization of commensal bacteria causing respiratory tract infections can result from the airway becoming inflamed which causes a decrease in mucus production leading to less clearance of the bacteria[37]. Competition amongst bacterial pathogens is not the only driver of infection. Upper and lower respiratory tract infections can also arise from bacterial and viral co-infections.

2.2.3 Viral-bacterial Co-infections

It is no surprise that the viruses most commonly detected in outpatient and inpatient settings are also the same viruses associated with co-infections. These viruses include influenza A, influenza B, respiratory syncytial virus, and rhinovirus[7,38]. Individuals often become co-

infected with bacterial infections when a viral respiratory tract infection has preceded it, weakening the immune system and allowing the bacteria in[38]. For example, secondary bacterial pneumonia caused by *S. pneumonia* can be a complication of influenza virus infection[36,38,39]. In this scenario, bacteria and influenza virus act synergistically resulting in increased colonization of bacteria, increased viral replication, and altered inflammatory response[39].

2.2.4 Biofilm and Otitis Media

Acute otitis media (AOM) is a common upper respiratory tract infection among children[40]. It is estimated that 80% of children less than three years of age will experience at least one acute otitis media infection[40,41]. The estimated global incidence rate of AOM in 2012 was 709 million cases per year with approximately 50% occurring in children under five years[40]. It has been hypothesized that biofilms may play a significant role in both initial acute infections and recurrent infections causing otitis media. A biofilm is an accumulation of microbial cells that form a highly-structured matrix that are associated with certain surfaces of the body[36,42]. One surface that biofilms can be found in is the middle ear. Pathogens associated with AOM are *Streptococcus pneumoniae* and *Haemophilus influenzae* which are thought to colonize the biofilm structures. Acute otitis media infections arise when bacteria escape from the biofilm and enter surrounding areas such as the adenoids and Eustachian tube that leads to the middle ear[41,43].

2.3 Epidemiology of Acute Respiratory Tract Infections

All age groups are susceptible to contracting upper and lower respiratory tract infections. In 2018, sinusitis accounted for 2.7 million physician visits in the US[44]. 11.6% of these sinusitis diagnoses occurred in adults 18 and older[45]. Children and the elderly are at the highest risk for severe complications from upper and lower respiratory tract illnesses. In the UK and Europe, community acquired lower respiratory tract infections including CAP are major causes of

morbidity and mortality among those ≥ 65 years of age[46]. In 2017, lower respiratory tract infections caused an estimated 808,920 deaths among children less than 5 years of age in lower – and lower-middle income countries[47]. In 2021, LRTIs were documented as a leading cause of morbidity and mortality, contributing to 4.4% of deaths across all age groups worldwide[48].

Vaccinations for *H. influenzae* type B (Hib), pertussis (DTaP or Tdap), and pneumococcal pneumonia (PCV) have aided in reducing mortality for these illnesses[49]. Most recently, in December of 2020, the COVID-19 vaccine became available for individuals 16 years and older under the Federal Drug Administration's (FDA) Emergency Use Authorization (EUA)[50]. In May of 2021, the authorization was updated to include individuals 12 to 15 years[50]. According to the US Department of Health and Human Services (HHS), they estimate that the uptake of the COVID vaccination is associated with the reduction of approximately 25 million cases, 1.3 million hospitalizations, and 213,000 deaths[51]. In 2018, 89.9% of infants in Georgia received ≥1 dose of the Hib vaccine by 3 months of age (1.3% higher than the national average)[52]. Only 75.1% of Georgian children had received the Hib-full dose series by age 24 months compared to 81.4% of US infants[52]. Rates for ≥4 doses of DTap coverage were much lower among children in Georgia aged 19 months compared to the rest of the United States (58.4% vs. 72.8%)[52]. Subsequent Tdap vaccinations among those aged 18 and older across the US were 43.6% in 2019 based on Behavioral Risk Factor Surveillance System (BRFSS) estimates[53]. Rates for ≥4 doses of PCV was 71.0% in Georgia in 2018 among those aged 19 months. This was 9.2% less than the percent vaccination coverage for this age group overall in the US[52]. Lastly, in 2020, pneumococcal vaccination coverage among adults 65 years and older in Georgia was 71.7 % which higher than the overall coverage in the US for this age group (70.3%)[53].

2.3.1 Seasonal Trends in Respiratory Tract Infection

Seasonal changes often coincide with the rise and fall in incidence of upper and lower respiratory tract infections. In temperate regions of the northernmost and southernmost parts of each hemisphere, respiratory illness peaks during the winter months[54–56]. In the 19th century it was hypothesized that this increase in incidence was a result of the decrease in temperature. In other words, that exposure to the cold was the cause of the "common cold"[56]. However, better understanding of acute respiratory tract infections has determined that additional environmental influences, human behavior, and viral factors play a role in increased transmission during colder seasons[55].

2.3.1.1 Environmental Influences on Respiratory Tract Infection Seasonality

Environmental factors such as outdoor absolute humidity and indoor relative humidity are believed to play an important role in acute respiratory tract infection transmission. As previously mentioned, the majority of acute respiratory tract infections are spread via droplets or aerosols through direct or indirect contact[55,57]. In studies conducted in guinea pigs and ferrets, it was concluded that during the winter season, the outdoor absolute humidity (AH) is low and indoor relative humidity (RH) ranges from 10-40%[57]. This creates a suitable environment for airborne transmission where respiratory virus stability, proportion of droplet nuclei, and virus viability are high[57,58]. In spring and fall seasons, the outdoor AH was moderate and indoor RH of 40-60%, which yields itself suitable for all forms of transmission in guinea pigs and ferrets (i.e. long-range airborne, short-range droplet, direct or indirect contact, fomites)[57,58]. Lastly, tropical climates, having a high outdoor AH and indoor RH ranging from 60-100% was found to be optimal for fomite and direct transmission[57,58]. Influenza, human coronavirus, and RSV are typically classified as winter viruses with peak transmission typically occurring between

November and April[59]. Adenovirus, rhinovirus and human metapneumovirus can be detected at all times of the year, but typically peak in the spring and fall[59,60]. Incidence peaks for enterovirus in the summer months[60].

2.3.1.2 Influences of Human Behavior on Respiratory Tract Infection Seasonality

Weather is not the only factor that influences the seasonality of acute respiratory tract infections. Human behavioral changes can also play a role in increased incidence of respiratory illnesses during certain times of the year. These behavioral factors include spending more time indoors during winter months, varying travel patterns by season, and school calendar breaks throughout the year[61]. During winter months, individuals often spend less time outside as a result of colder temperatures and shorter day-light hours. Fewer sunlight hours can lead to a decrease in vitamin D levels which is associated with weakened immune response[61–64]. Colder temperatures are also associated with an increase of indoor gatherings, especially during holiday periods, which creates ideal settings for increased respiratory pathogen droplet and/or aerosol transmission[62]. Air travel has also been researched as a possible cause for surges in seasonal respiratory infections[61,65]. A 2006 study found that domestic air travel during November was a significant predictor for the spread of influenza across the US[65]. These findings coincide with previous findings of increased spread during holiday months due to an increase of travel and indoor gatherings.

Lastly, schools (including colleges and universities) have also been considered an influential factor in the seasonality of respiratory tract infections. A French study using transmission modeling methods found that holiday school closures were associated with a 20-29% reduction in the rate of flu transmitted among children[66]. In recent years, school closures as a mitigation strategy for reducing SARS-CoV-2 transmission have been a frequently debated

topic. In March of 2020, schools, childcare centers, and virtually all colleges and universities in the United States experienced closures. This affected approximately 21 million children in childcare, 57 million K-12 students, and 20 million college and university students[67]. In 2020, a population based observational study was conducted in the US to assess the association between school closures and COVID-19 incidence and mortality[68]. This was done by using time-series analysis of the "cumulative incidence of COVID-19 grouped in quartiles by date of school closure" and "daily COVID-19 incidence and mortality". Data used was publicly available through Johns Hopkins School of Public Health and the CDC. Based on their analyses, the researchers found that school closures were associated with a -62% (95% CI: -71%, -49%) relative change in COVID-19 incidence per week[68].

2.4 Clinical Management of Respiratory Tract Infections

While some persons experience severe complications from respiratory tract infections, most experience only mild to moderate symptoms. However, these can still impair quality of life and productivity[69]. Acute respiratory tract infection symptoms differ based on anatomical location. Symptoms of acute upper respiratory infections typically include sore throat, runny nose, nasal congestion, ear pain, low-grade fever, facial pressure, sneezing, and less commonly cough, malaise, and myalgia. Depending on the pathogen symptom onset usually begins one to three days after exposure and can continue for up to three weeks[70]. Symptoms of acute lower respiratory tract infection can include cough, sputum or phlegm production, shortness of breath, wheezing, chest pain or discomfort with cough, dyspnea, fever, myalgias, and malaise. These can also last up to 3 weeks[4,71,72].

2.4.1 Diagnosis

2.4.1.1 Clinical Impression and Clinical Scores

Diagnosis of acute respiratory tract infections combines assessing the patient for signs and symptoms and if appropriate diagnostic testing typically by PCR or a rapid antigen test. While clinical impression alone often cannot be used to reliably distinguish the presence of bacteria or viruses, it is sometimes all clinicians in primary care have to guide them in diagnostic decision making[73,74]. Likewise, clinical impression does not simply rely on a single sign or symptom for diagnosis, but instead a culmination of signs and symptoms and other factors (i.e. age, risk factors, lifestyle factors). A qualitative study conducted by Howell et al. used clinician interview data from 80 clinicians across 9 European cities to determine what influence clinical impression had on antibiotic prescribing for LRTIs[74]. Clinical factors most frequently identified for guiding antibiotic prescribing were auscultation findings, fever, discolored sputum, and shortness of breath. Many clinicians also considered clinical factors such as patient age and existing comorbidities. Lastly, "consideration of illness course, clinician intuition, and the clinicians' familiarity with the patient" also influenced decision making.

In 2019, a systematic review and meta-analysis was conducted to assess the accuracy of overall impression for GABHS pharyngitis, acute rhinosinusitis, and CAP. The study found that clinical impression helped clinicians to differentiate Strep. pharyngitis from non-Strep. pharyngitis 73% of the time[75]. The same study also assessed diagnosis based on clinical impression for acute rhinosinusitis and found that clinical impression led to accurate diagnosis 77% of the time. Additionally, logistic regression led to the development of well-defined clinical decision rules that aid in diagnosing community- acquired pneumonia[75,76]. Cough, fever, shortness of breath, tachycardia, absence of rhinorrhea, sputum production, and abnormal lung

exam were identified as the best independent predictors of CAP[76–78]. Similar to the pharyngitis scoring rubrics, based on the presence or absence of these signs or symptoms, a clinician may opt do the following: 1. Rule out CAP; 2. Evaluate further with a chest radiograph; 3. Treat with antibiotic[77]. Clinical impression guiding diagnosis of CAP was found to be 80% accurate in adults and children[75].

Researchers have developed scoring systems that use individual signs and symptoms to aid in diagnosing Group A beta- haemolytic streptococcal pharyngitis (GABHS) and rhinosinusitis. The pharyngitis scoring systems most commonly used are the "Modified Centor Criteria (or the McIsaac Criteria)" and the "FeverPAIN Score"[79–81]. The Modified Centor Criteria includes signs and symptoms such as fever (subjective or measured), cervical lymphadenopathy, tonsillar exudate, absence of cough, and patient age[79,80]. The FeverPAIN Score evaluates patients for fever (within 24 hours of visit), purulent tonsils, symptom onset (≤ 3 days), inflamed tonsils, and absence of cough or coryza[79,81]. For both clinical decision scores, a point is given for each item and is used to determine which of the following clinical courses will be taken for treatment: 1) antibiotic therapy, 2) rapid test or delayed prescription, or 3) symptomatic therapy[79–81]. Table 2.1 Shows the Modified Centor Criteria and Table 2.2 provides a key for how to interpret it[82,83].

Table 2.1 Modified Centor Criteria (McIsaac Score)- For each Centor Criteria score 1 point for a possible maximum score of 5 (depending on age)

Modified Centor Criteria (McIsaac)	Score
Fever > 38ºC	1
Tonsillar exudate	1
Absent cough	1
Cervical lymphadenopathy	1

3 – 14 years	1
15 – 44 years	0
≥ 45 years	- 1

Table 2.2 Modified Centor score interpretation

Modified Centor Score	Interpretation
< 1	Low likelihood of Strep. pharyngitis; no rapid test, culture or antibiotic required
2 – 3	Moderate likelihood of Strep. pharyngitis; rapid strep test is recommended with culture; antibiotic prescription given based on test/culture results
≥ 4	High likelihood of Strep. pharyngitis; rapid strep test is recommended with culture; give antibiotic therapy empirically

2.4.1.2 Diagnostic Testing

The most reliable method for determining presence of bacterial or viral pathogens is through diagnostic testing. PCR testing is generally the most sensitive test for identifying viral and bacterial pathogens. However, interpretation can be difficult as a positive result may simply indicate prolonged viral shedding after a symptomatic infection or an asymptomatic infection[32]. PCR is not generally used in practice for this reason and because it is also not efficient with turnaround times ranging from a few hours to multiple days depending on the number of tests

being performed and the pathogen[27,84]. PCR tests are generally conducted in a reference laboratory with specialized equipment and specific specimen handling requirements[27,85,86]. These factors also make PCR more costly.

Rapid diagnostics or point-of-care testing are another way to differentiate between bacterial and viral infection in the outpatient setting[28]. Point of care testing options, are much more efficient with results typically being available within 5 to 20 minutes[85,87]. Additionally, POCT can be conducted virtually anywhere, including at home. Rapid antigen testing for strep throat, influenza, RSV, hMPV, adenovirus, parainfluenza, and now COVID-19 have been widely used in the US[26,85,88]. However, uptake of POCTs in other countries is much lower. A systematic review was conducted that assessed primary clinicians' attitudes towards these tests[89]. The study determined that while some clinicians believe that POCTs can be used as an effective tool for targeting treatment, there were also concerns about the accuracy of the tests. Some clinicians believed that POCTs could negatively affect clinical practice by undermining their knowledge. They were also concerned that implementation of POCTs in primary practice could lead to over-testing.

Lastly, many European countries have adopted the use of C-reactive protein (CRP) blood tests to aid in determining diagnosis and appropriate treatment for acute respiratory tract infections. CRP is an inflammatory biomarker that can be elevated when the body is experiencing a bacterial infection. Normal CRP levels can range from 2 to 20 mg/L[90]. CRP levels are considered to be high when they are greater than or equal to 100 mg/L[91]. The United Kingdom's (UK) National Institute for Health and Care Excellence (NICE) guidelines state that antibiotics should not be prescribed for acute RTI if the CRP levels are below 100 mg/L[92]. In 2021 a prospective pilot study was conducted in Australia to investigate CRP use in pharmacy

settings. Clinical outcomes, rate of service, and feasibility of pharmacists to use CRP measurements for RTI management were considered[93]. Participants were recruited if they presented to one of the pilot pharmacy locations inquiring about an RTI-related product, experiencing symptoms of RTI, or seeking advice for antibiotic use or needing a primary care visit. Upon being recruited, CRP tests were administered, and pharmacists' provided management advice based on their findings and clinical impression. Of patients that presented with symptoms, the most common complaints were sore throat (73.3%), cough (69.5%), and congested nose (67.2%). CRP was statistically significantly associated with the presence of cough, fever, and runny nose when headache was absent. OTC medications for symptom management was recommended for 100% of the participants. During follow-up, 38% of participants reported a full recovery by day 3 and 65% reported recovery by day 5. 34.2% of participants had seen a primary care clinician by day 5 which resulted in an antibiotic prescription for 55% of patients.

A large clinical trial conducted in Spain concluded that having access to CRP point of care testing reduced the number of antibiotics prescribed to patients with acute upper respiratory symptoms that specifically asked for them[94]. A previous study conducted in the Netherlands also had a similar result with reduced antibiotic prescribing in patients with acute LRTI and the use of CRP tests[95]. However, no point of care CRP test has been formally approved for use in the US to determine viral or bacterial pathogen presence in acute respiratory tract infections[28].

2.4.2 Treatment

2.4.2.1 Over-the-Counter Regimens, Antivirals, and Corticosteroids

As most acute respiratory infections are caused by viral pathogens, they are generally self-limiting meaning that they are expected to resolve without specific antiviral treatment. Patients

can often take over-the-counter (OTC) medications to minimize or resolve symptoms and help them to feel better faster. OTC treatments include nasal saline spray, acetaminophen, non-steroidal anti-inflammatory drugs, antihistamines, oral or nasal decongestants, oral or nasal corticosteroids, and cough suppressants. However, not all viral ARTIs are self-limiting. Exceptions may occur in at risk populations such as infants and elderly adults. In 2015, RSV in children under 5 years was associated with 118, 200 deaths worldwide[48]. The CDC reported in 2014 that 34% of viral pneumonia and influenza deaths occurred in persons 65 year of age or older[96].

For some pathogens, if viral respiratory infections are identified within 24-48 hours of symptom onset, anti-viral treatments can be successful in decreasing the duration of illness. Baloxavir, zanamivir and oseltamivir are used for the treatment of influenza[97,98], while molnupiravir and ritonavir-boosted nirmatrelvir are effective for SARS-CoV-2 infection in outpatients. It is also common in outpatient settings for clinicians to prescribe corticosteroids for short term use when upper and/ or lower respiratory tract infection is likely[99]. However, there is no good quality evidence supporting that the use of corticosteroids for these indications (acute bronchitis, pharyngitis, and sinusitis) leads to greater improvement of symptoms[100].

2.4.2.2 Antibiotic Prescribing

Despite most acute RTIs being viral in nature, approximately 49.7% of patients receive an inappropriate prescription for antibiotics in inpatient settings[101]. A study conducted using regional health data from the southeastern US found that among acute respiratory tract infection visits, 49.4% of antibiotic prescriptions were filled[102]. In this study antibiotics were most commonly prescribed for acute bronchitis. Prescribing rates for suspected viral RTIs was between 42.2% and 51.4%. The majority of antibiotic prescriptions for respiratory illnesses are

written in outpatient settings[20]. In 2016, it was estimated that approximately 41% of outpatient antibiotic prescriptions are written by family physicians and 23% were written by physician assistants and nurse practitioners[103]. In 2018 it was estimated that 75% of antibiotic prescribing took place in a primary care setting[104]. This overuse of antibiotics contributes to the growing concern regarding antibiotic resistance. While overall antibiotic prescribing in the US is decreasing, broad spectrum antibiotic use is increasing[103]. A clinician's decision to prescribe antibiotics in acute respiratory illness cases is multifactorial. Some of these factors include lack of time for education of appropriate antibiotic use, patient expectation or request of antibiotics, race of patient, and geographic location[20,94,102,105,106].

2.5 Acute Respiratory Tract Infections in Colleges and Universities

Upper respiratory illnesses are common among college students and are a substantial cause of morbidity[107]. One study conducted at the University of Minnesota – Twin Cities campus in 2006 found that 83% of its study population self-reported experiencing at least one "cold" and 36.7% experienced an influenza like illness (ILI) between the months of November and April[108]. With these illnesses, students stated they not only felt the negative effects from the symptoms associated with their illnesses, but they were unable to perform regular activities, missed class and work, and missed extracurricular activities[108]. A small study conducted in a university setting determined that 46.5% of participants diagnosed with an acute respiratory infection (ARI) tested positive for a viral pathogen[109]. Social contacts of these symptomatic participants were also invited to participate in the study. These contacts were "presumed to be 'healthy'" however, some reported experiencing ARI symptoms at the time of specimen collection. Social contacts tested positive for at least one viral pathogen in 28.3% of symptomatic individuals and 13.3% of asymptomatic individuals. The viruses detected most often in the entire study population were

human coronaviruses (22.0%), rhinovirus (7.6%), and influenza A (6.4%)[109]. Based on the study population, they did find a statistically significant difference in the number of Influenza A cases among confirmed ARI participants compared to symptomatic social contacts. However, these estimates were likely biased due to the inclusion of symptomatic social contacts in the sample.

College students, especially undergraduates, live in environments where transmission of acute upper and lower respiratory tract infections may be more likely. Student living typically consist of congregate settings such a dormitories or apartment buildings in which they share a space with one or more roommates. Living in close contact with others in small spaces in addition to stressful workloads, lack of sleep, lack of adherence to preventative measures, and attending social activities in large group settings could put students at increased risk for acute respiratory tract infections. However, this has not been determined from previous studies.

In 1968, a study was conducted to compare the rates and clinical classification of common acute illnesses among university students (18-24 years old), military air force trainees (18-21 years old), and industrial workers (25-40 years old)[110]. These participants were chosen as the populations of interest because they are normally considered to be healthy individuals but have differing living and working conditions. The most commonly detected pathogens among university students over a 4-year period were influenza A, parainfluenza 1, rhinovirus, adenovirus, group A streptococci, and *M. pneumoniae*. Similar findings were found in air force trainees and industrial personnel. The only exception was the rate and clinical presentation of influenza among the airmen, because of strict vaccination requirement imposed by the US military.

University students must make their own medical decisions (typically for the first time) when they are away at school. The decisions they make in regards to seeking medical care for

acute RTIs may be based on their perceptions of the severity of their symptoms, the length of their symptoms, and their perceived need for a prescription. Other factors may include missing a social event due to illness or effects on the ability to do schoolwork. One study conducted in college students in 2000 showed that students would use antibiotics for symptoms of "common cold" especially in the presence of symptoms like low-grade fever and purulent nasal discharge[106].

2.6 Gaps in Literature

While respiratory tract infection research has been conducted for many years, there are few studies that systematically review the etiology of acute upper and lower respiratory tract infections among symptomatic with acute respiratory infection compared to healthy individuals. Likewise, research that has been conducted in these populations have primarily been conducted in inpatients settings, with very few in outpatient settings. Also, very few studies have been conducted to assess the likelihood of isolated bacteria and/or viruses being pathogenic or commensal. This limits our understanding of the true cause of these illnesses and best practices for diagnosing and treating them, as the misuse of antibiotics is common. Since the annual burden of respiratory tract infections in outpatient settings is so great, it is important to determine which type of organism is likely leading to specific clinical presentations.

Finally, a study was conducted 20 years ago assessing antibiotic perceptions and care seeking behaviors of college students. Little has been studied on the subject since that time. It is important that university students be studied to assess trends in antibiotic beliefs and identify gaps in health and antibiotic-use education. It also helps to guide clinical practice with the understanding of patient expectations.

We will address these gaps in the literature through the three aims of this dissertation. First, we will conduct a systematic review of the published literature that compares the bacteria and viruses detected in outpatients with respiratory tract infections and in healthy, asymptomatic controls. We will also identify signs and symptoms most commonly associated with each pathogen. We will then investigate if the etiology identified in the systematic review is similar to that of our own study population. We will recruit symptomatic respiratory tract infection patients and asymptomatic persons and compare organisms identified in the PCR results of their NP and OP swabs. We will then determine the likelihood of certain bacteria/viruses identified as being pathogenic versus commensal. Lastly, we will assess the care seeking behaviors of college-aged students by providing them with vignettes that detail common clinical presentations for both acute URTI and LRTIs. It is our hope that we can also extend our research from college students and compare their perceptions to that of general adult population.

CHAPTER 3

METHODS

3.1 Introduction

3.1.1 Aim 1: Importance of Systematic Review and Meta-Analysis

Many research studies spanning multiple years have often addressed the same topic. To read through all available literature on a specific topic can be exhaustive and time consuming. Additionally, studies addressing the same question with similar study designs sometimes have conflicting results making interpretation of best practices difficult[111]. These differences could be due to changes in population health, differences in dose or exposure, subtle differences in design, differences in duration of follow-up, improvements in medical care over time, and many other reasons. Limitations of simply reviewing single articles are that their results could be influenced by bias, data errors, and inappropriate research methods. Systematic reviews and meta-analyses help to inform readers of findings from previously conducted research on specific topics in a concise manner while also highlighting the limitations of the included studies[112]. Systematic reviews and meta-analyses achieve this by identifying, critiquing, and if appropriate synthesizing the results of studies and offering an overall impression as it relates to the research question of interest[111,112]. Systematic reviews do this by presenting the qualitative data from the identified studies, while a meta-analysis provides a quantitative synthesis of the results. These two review types assist readers in being able to interpret the results of all available literature on a specific topic. Systematic reviews can also aid in identifying gaps in literature, lack of evidence, and areas where new primary research is needed[113]. Also, because systematic reviews can include

studies with contrasting methods and measures, they can justify drawing broader conclusions, typically outside of the scope of one single study. The ability of systematic reviews to draw broad conclusions plays a crucial role in guiding evidence-based practice in healthcare and impact health policy[114].

3.1.2 Aim 1: Conducting a Good Systematic Review and Meta-analysis

A systematic review is "an article that identifies, evaluates, and synthesizes empirical evidence that meets pre-determined inclusion criteria to answer a specific research question"[115]. The Cochrane organization was one of the first to create and publish such systematic reviews. They have since helped to change the systematic review process by setting rigorous methods that are still followed by researchers[116]. The steps highlighted below can be found in the Cochrane Handbook and will be used to address Aim 1.

Many systematic reviews and meta-analysis are done in order to effect change in health policy or provide up-to-date guidance for healthcare practices. Therefore, when starting a systematic review, it is vital that the study question and inclusion/exclusion criteria be prespecified and methods for reviewing and abstracting data should follow a strict systematic approach. This will ensure that the work is reliable, transparent, and replicable, and reduces the likelihood of bias. First, the research question should follow the FINER criteria meaning that it should be Feasible, Interesting, Novel, Ethical, and Relevant in order to warrant doing a systematic review[117]. The inclusion and exclusion criteria for studies in a systematic review ultimately define the scope of the review and include the population, interventions, comparators and outcomes (PICO) of interest for the review question[116,118]. The question and scope set the tone for the entire review and dictate the types of studies that will be included.

While systematic reviews can be written to address any topic, Cochrane reviews specifically address questions that impact healthcare treatment decisions and some diagnostic practices[116,118]. As such, these reviews rely on data that typically comes from randomized trials when possible. Randomized trials are considered to be the "gold standard" experimental study design because they uphold the counterfactual theory that participants in the intervention group and participants in the comparator group are no different to each other except for their random allocation to their different interventions. However, there are instances when randomized trials are not ethical, so non-randomized study designs must be included in the review instead. Non-randomized studies have a greater susceptibility to bias which must be assessed and addressed when summarizing conclusions[119]. Assessing risk of bias will be discussed in the following section.

After the review question has been defined and the types of studies to be included in the review have been set, a detailed search strategy must be formulated. Systematic reviews require a search strategy that is thorough, objective, and reproducible to identify as many eligible studies as possible[116,120]. Creating a search strategy is one of the most complex steps of completing a systematic review and, like all the methods, relies heavily on the review question and scope of the review (i.e. the types of primary research included) being determined a priori. The structure of the search strategy should be specific and represent the important concepts of the review. However, the strategy should also be broad as it may miss important studies that should be included if the search terms are too stringent[116,120,121]. Multiple databases should be searched for studies to be included in the systematic review. Optimal databases to search include Embase, MEDLINE, Web of Science and Google Scholar[122]. To ensure that the search is reproducible by other investigators, the search strategy should be clearly documented.

Once a search has been completed and a comprehensive list of all studies has been compiled, the articles must be reviewed for inclusion or exclusion. Included studies should meet the predetermined criteria in terms of study design, population, intervention, comparator, and outcome of interest. This is done by first examining titles and abstracts in an effort to remove any studies that are obviously irrelevant. Next, studies not excluded during title and abstract review, should be read in full for final decisions for inclusion or exclusion. An important feature of this step of the review is that it should be done in parallel by at least two reviewers to ensure irrelevant studies are excluded, relevant studies are not overlooked, and to ensure that studies are not included more than once[116,120,123].

After identifying studies for inclusion, the next steps are extracting and combining or manipulating data available reported by each study. As with many other steps in the systematic review and meta-analysis process, determining the type of data that you will need and how it will be synthesized and analyzed should be chosen before beginning the review. Generally, the types of data that will be gathered and effect measures that will be calculated are based on the review question and scope of the review. Every systematic review should have a table that presents the baseline characteristics of each study included in the review. Information in this table should include, but is not limited to, the author and year of publication, participants studied, setting, interventions used (if applicable), and outcomes being measured[116,124].

Based on the data available, one can choose to combine the numerical data that is presented in order to give an overall effect measure. This is referred to as a meta-analysis and usually accompanies a systematic review. The basic steps for conducting a meta-analysis are first calculating a summary statistic for each study included and second calculating a weighted average of the summary statistics for each study. These data are typically presented in the form

of a forest plot[116,125,126]. Heterogeneity is an important factor to consider when data from multiple different studies are being brought together. Heterogeneity could arise from random variation and also variability in clinical factors such as the study population, setting, duration of follow-up, interventions used, and outcomes being measured. Differing study design methods, outcome measurements, and biases within the studies can also lead to heterogeneity[116,125]. Heterogeneity can be assessed by quantifying it with the I^2 statistic. The I^2 value is the proportion of variance that is due to between study variance versus within study variance[127].

3.1.3 Aim 1: Assessing Risk of Bias in Systematic Reviews and Meta-analysis

Bias is defined as a systematic deviation from the truth[116,128,129]. Like heterogeneity, bias within studies included in a systematic review is inevitable. An important feature of systematic reviews is that primary research included in the review are assessed for risk of bias based on many factors of their methodology. Risk of bias is commonly defined by a grade of low, moderate, or high based on the number of biases or threats to validity identified by a formal quality assessment tool. There are various tools to assess risk of bias and they are differentiated by study design[130]. Additionally, in the meta-analysis stage, sensitivity analysis can be used to assess how low or high risk of bias affects overall estimates of effect in the review.

3.1.4 Aim 2: Differentiating Pathogen versus Commensal Bacteria and Viruses

As previously discussed, the cause of acute respiratory tract infections can be bacterial and/or viral. Also, it has been mentioned that the microbiome of the human body can be colonized with the pathogens that are also commonly associated with infection. Aim 1 and Aim 2 will attempt to determine which organisms identified in the respiratory tract of a person with acute respiratory tract infection are likely commensal and not pathogenic. Aim 1 will do this through systematic review and meta-analysis as outlined below. Aim 2 will conduct an etiology

study comparing patients with symptomatic respiratory infection and asymptomatic, healthy individuals. Identifying bacteria and viruses found in the respiratory tract among symptomatic and asymptomatic patients has been done in other studies but identifying possible commensalism is less common due to multiple individual factors influence the development of disease. These factors include but are not limited to age, antibiotic usage, vaccination status, and smoking status[131,132].

A 2000 prospective study conducted in Sweden aimed to "investigate whether a nasopharyngeal sample could yield information concerning the etiology of long-standing coughs in patients with a respiratory tract infection"[133,134]. Cases consisted of patients that presented to an outpatient setting or school clinic with the chief complaint of cough lasting more than 9 days. Controls were identified as adults and children who were not experiencing respiratory tract infections symptoms at the time of their visit to a primary care clinic or school clinic setting. Healthy individuals were also required to not have received antibiotics 4 weeks prior to their visit. Participants were recruited from January to February and July to September of 1991 as part of a previously completed study to investigate potential pathogenic bacteria identified in healthy controls. A nasopharyngeal swab was collected for all participants at the time of recruitment and sent to a laboratory for testing using culture methods. The four bacterial pathogens being tested for were *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Beta-haemolytic streptococci* (BHS). Pearson's chi- squared test with Yates correction was used to determine whether there was a statistically significant difference between the expected bacterial frequencies and observed bacterial frequencies for symptomatic cases and asymptomatic controls. Yates correction is typically applied to Pearson's chi-squared to prevent overestimation of statistical significance[135,136]. When numbers were very small, Fisher's exact test was used to

determine if the proportion of bacterial pathogens among cases differed from the proportion of bacterial pathogens among controls. The most common symptom combinations among cases were cough and sneezing and cough and throat pain. At least on potentially pathogenic bacterium was identified in 83% of NP samples taken from participants aged 0 to 6 years. In children (0 – 6 years) and adults (≥ 16 years), *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* were found significantly more often in symptomatic cases than in asymptomatic controls of the same age. Growth of more than one bacterium was most common in children 0 to 6 years of age. The combinations identified most often in symptomatic children were *M. cattarhalis* + *S. pneumoniae*, *M. cattarhalis* + *H. influenzae*, and *H. influenzae* + *S. pneumoniae*.

A similar study was conducted in 2018 in 3 inpatient and 3 outpatient centers in the UK[32]. The study aimed to "determine the prevalence of respiratory pathogens in the upper airways of asymptomatic adults compared with patients with respiratory tract infections (RTI) and to investigate risk factors associated with the detection of respiratory pathogens"[32]. Symptomatic individuals consisted of patients who presented to an inpatient or outpatient setting with symptoms of RTI lasting 10 or more days. Healthy, asymptomatic individuals consisted of individuals presenting to inpatient or outpatient setting with no RTI symptoms at least 2 weeks prior to and during the time of recruitment. Both symptomatic and asymptomatic participants were required to be 18 years of age or older. NP swabs were taken from all participants at the time of enrollment into the study. PCR was used to test samples for 16 viral pathogens and 4 bacterial pathogens. Like Gunnarsson et al, Sundell et al. utilized Pearson's chi-squared and Fisher's exact test to compare the differences in bacterial and viral pathogens identified in the asymptomatic and symptomatic groups. Differences in cycle threshold (C_T) values and clinical factors among both groups were compared using simple linear regression and Pearson correlation

coefficient. Cycle threshold was defined as the number of PCR cycles required to identify a pathogen. A respiratory pathogen was detected in 11% of asymptomatic persons and 50% of symptomatic persons. The most common virus detect among asymptomatic participants was Rhinovirus. *S. pneumoniae* and *H. influenzae* were the most common bacteria found in asymptomatic individuals. *H. influenzae* was significantly more frequent among symptomatic individuals compared to asymptomatic. When comparing C_T values, low pathogen load was associated with asymptomatic cases while higher pathogen load was associated with symptomatic cases. However, the differences were not statistically significant.

In 2020, Gunnarsson and Manchal. conducted a systematic review and meta-analysis to determine "the pathogenicity of beta-hemolytic Streptococcus group C (GCS) in patients with uncomplicated acute sore throat"[137]. Studies included in the systematic review were prospective and retrospective case-control studies comparing the prevalence of GCS in patients with sore throat to health controls. Researchers assumed that patients with symptomatic sore throat and healthy controls could potentially carry GCS. Based on this assumption, GCS was considered to be "clinically irrelevant" if the prevalence of GCS was the same among both groups. However, GCS was considered to be "potentially clinically relevant" if ill patients tested positive for GCS more often than healthy controls. The positive etiologic predictive value (P-EPV) was calculated for all included studies and an overall summary P-EPV was calculated for studies when stratified by age. The P-EPV was defined as the post-test probability of an association between sore throat and identifying GCS in the throat, while also understanding that other pathogens might be influencing pathogenicity. The P-EPV ranges from 0 to 100% and requires the assumed sensitivity of the etiologic test used to detect the pathogen. In this case, the etiologic test used by all included studies was culture which had an assumed 90% sensitivity. From the studies

included in the meta-analysis, 11% of ill adult patients tested positive for GCS while 5.6% of healthy controls had GCS identified in their samples. The summary P-EPV for adult studies was 53%, indicating the GCS may play a role in sore throat diagnoses in adults. Among studies included that were conducted in children (younger than 15 – 19 years) with sore throat, 3.15% of ill patients tested positive for GCS and GCS was identified in 2.87% of healthy controls. The summary P-EPV for studies conducted in children was 9.3% indicating that GCS was unlikely to play a role in sore throat in that age group. The analytic approaches used by Gunnarsson et al. and Sundell et al. described above, will be used to address Aim 2.

3.1.5 Aim 3: Patient Care Seeking Behaviors

Acute upper and lower respiratory tract infections (ARIs) are among the most common illnesses for which patients seek care. However, there are instances when a visit may not be necessary. Office visits can be inconvenient, require time off from work and/or school, and cost money. Additionally, office visits can sometimes result in an inappropriate antibiotic prescription. For this reason, a 2016 retrospective study was conducted in Massachusetts to "measure the proportion of primary care ARI visits that may not require an office visit"[138]. The study utilized electronic health record to identify ARI visits that took place between May 2011 and May 2012 in 14 primary care practices. Researchers randomly selected 500 ARI visit records. Records were excluded (N=61) if they did not have ARI symptom information, were follow-up visits for ARI, or if the ARI symptom duration was > 30 days. Data on symptom duration, presence, and absence of ARI symptoms (cough, phlegm production, colored sputum, chest congestion, sore throat, fever, chills, ear pain, red eyes, headache, fatigue, myalgias, nasal symptoms, sinus symptoms, wheezing, and shortness of breath). Based on this information along with patient age and co-morbidities, researchers determined their diagnosis and whether their

visit was necessary or unnecessary for further management. If a patient's symptoms at the time of their visit led to a researcher diagnosis of acute bronchitis and pneumonia, the visit was labeled necessary to rule out pneumonia. However, if the researcher diagnosis was a non-severe upper respiratory tract infection (NS URI), the visit was labeled as unnecessary for further management. The researcher diagnoses were termed "HPI diagnosis" and cross-referenced with clinician diagnoses for final determination of necessity of visit. If the HPI diagnosis was "unnecessary for further management" and clinicians' diagnosis matched exactly, the visit was ultimately determined to be unnecessary. Similarly, if there was a discrepancy between the HPI diagnosis and clinicians' diagnosis but there was no change in antibiotic management as a result of the visit, the visit was determined to be unnecessary. A visit was determined to necessary if the HPI diagnosis indicated it was necessary regardless of the clinicians' diagnosis. "Antibiotic-appropriate diagnoses" were pneumonia, sinusitis (with prolonged, worsening symptoms), streptococcal pharyngitis, and otitis media. "Non-antibiotic appropriate diagnoses" were NS URI, acute bronchitis, sinusitis (without prolonged, worsening symptoms), viral pharyngitis, and influenza. Necessity of visit was determined by two independent reviewers. Disagreements were resolved by consensus.

The most common symptoms recorded were cough (64%), sore throat (55%), and nasal symptoms (47%). Clinicians ordered rapid testing for strep pharyngitis in 80 visits and chest X-rays in 24. Antibiotics were prescribed in 213 visits (49%) and non-antibiotic prescriptions were provided in 123 visits (28%). The most common diagnoses were non-specific upper respiratory tract infection (39%), sinusitis (24%) and acute bronchitis (22%). Researchers concluded that 276 of the visits (63%) included in the study were unnecessary and could have been managed without an office visit.

A similar study was conducted in 2018 in rural China to "investigate the occurrence of reported respiratory tract infection (RTI) symptoms and their effects on the use of self and professional care among patients in the community"[139]. Researchers assessed this research question using a cross-sectional retrospective household survey. A stratified-clustered randomized sampling approach was used to recruit villages and residents. The study survey consisted of questions addressing the 4 following categories: 1) social demographics, 2) last episode of symptomatic RTI, including symptoms experienced, 3) action taken to treat RTI, and 4) whether antibiotics were obtained for illness. Dry cough (58.9%), rhinorrhea (51.7%), and sore throat were the most common symptoms associated with previous RTIs. Professional care was sought by 55.7% of participants, 13.4 % bought over-the-counter treatments, and 23.1% used leftover medicine from previous illness and 20.8% did nothing. Logistic regression was used to model the association between care seeking behaviors and demographics. Educational level was negatively associated with seeking help from clinics (OR = 0.79) and positively related to buying over the counter medication (OR = 1.23) and using leftover medication (OR = 1.28). Women were more likely than men to use leftover medication (OR = 2.02). Age was found to have no effect on care-seeking behavior. Controlling for demographic factors, having a cough was positively associated with purchasing over the counter medication (OR = 1.49). Also, controlling for demographics, seeking care was positively associated with having a sore throat (OR = 1.35), cough (OR = 1.49), shortness of breath (OR 1.70), and fever (OR = 2.14).

While there are retrospective studies that assess care seeking behaviors, there very few studies that assess patient decisions to seek care in real-time. In Aim 3, our goal is to determine patient perceptions regarding the need to seek clinical care for an ARI using clinical vignettes. The information regarding the most common symptoms leading to seeking care as identified in

previous research will aid in the development of our vignettes. We will also determine patients' reasoning for seeking care among college students upon making an appointment, by reviewing appointment questionnaires.

3.2 Aim 1: Identify pathogens commonly associated with symptomatic respiratory tract infections and classify pathogens that could likely be commensal.

3.2.1 Objective

We will perform a systematic review of previously published studies that identify respiratory viruses and bacteria found among outpatients with a respiratory tract infection, including the subset that compare those viruses and bacteria with those found in healthy, asymptomatic controls. We will also identify studies reporting signs and symptoms associated with specific pathogens. This information will inform us of which bacterial and/ or viral pathogens are most associated with developing symptoms of acute RTI. In addition, we will use the data from these studies to identify possible commensal pathogens by comparing the frequency of pathogens found in symptomatic cases to pathogens found in asymptomatic controls.

3.2.2 Methods

3.2.2.1 Data Sources

We will use PubMed, EMBASE, Web of Science, and Google Scholar to identify all previously published studies reporting the etiology of acute respiratory tract infections in outpatient settings. This will include studies only reporting on symptomatic outpatients with RTI, as well as studies reporting only on asymptomatic controls, and studies reporting on both populations. In addition, we will review the reference lists of included studies for additional articles that were not initially identified in our search.

3.2.2.2 Inclusion Exclusion Criteria

We will include only prospective studies of patients of all ages presenting with any symptomatic acute respiratory tract infection (lower or upper) in the outpatient setting. We will also include studies of asymptomatic patients that are tested for NP and OP pathogens in outpatient or non-clinical settings. Studies that report both symptomatic and asymptomatic etiology will also be included. Testing for viral and/or bacterial pathogens had to use PCR or culture. Adequate count data for assessing how often bacteria and/ or viruses were detected is required for inclusion. Pathogen data could be obtained as a result of prospective data collection or retrospective health record review, depending on the study design. We will exclude studies that were performed in a specialized population (i.e. immunocompromised) or in an inpatient facility.

3.2.2.3 Search Strategy

We systematically reviewed studies in PubMed, EMBASE, Web of Science, and Google Scholar using the following search strategy:

> (“respiratory tract infection”[TIAB] OR “respiratory tract infection”[MH] OR “acute bronchitis”[MH] OR “pneumonia”[MH] OR “viral rhinitis”[MH] OR “rhinosinusitis”[MH] OR “sinusitis”[tiab] OR “otitis media”[MH] OR “pharyngitis”[MH] OR “respiratory virus”[MH]) AND
>
> (“bacteria”[MH] OR “S. pneumoniae”[MH] OR “Streptococcus”[MH] OR “H. influenzae”[MH] OR “M. catarrhalis”[MH] “virus”[MH] OR “viral” OR “influenza virus”[MH] OR “enterovirus”[MH] OR “adenovirus”[MH] OR “coronavirus”[MH] OR “respiratory syncytial virus”[MH] OR “rhinovirus”[MH] OR “parainfluenza”[MH] OR “metapneumovirus”[MH] OR “microbiome”[MH]) AND

(“etiology”[TIAB] OR “aetiology”[TIAB] OR “etiological role” [TIAB] OR “prevalence”[MH] OR “prevalence”[TIAB] OR “commensal”[MH] OR “commensal”[TIAB] OR “pathogenic”[TIAB] OR “pathogenic”[MH]) NOT (“nosocomial”[TIAB] OR “nosocomial” [MH] OR “ventilator-acquired pneumonia”[TIAB] OR “ventilator-acquired” [MH])

The search strategy will be developed based on key words and MESH terms of previously identified etiologic studies. We will also review studies included in previous systematic reviews or meta-analysis, as well as the reference list of all included studies. The search will not be restricted by language or date of publication. A secondary systematic review will be conducted using PubMed to include studies that assessed symptoms of specific etiologies of ARTIs or specific ARTI diagnoses. The following search strategy will be used:

(“Influenza”[TIAB] OR “rhinovirus”[TIAB] OR “rhinovirus”[MH] OR “common cold virus”[MH] OR “catarrhalis”[TIAB] OR “M. catarrhalis”[MH] OR “S. pneumoniae”[TIAB] OR “strep pneumoniae”[TIAB] OR “streptococcal pneumonia”[TIAB] OR “S. pneumoniae”[MH] OR “H. influenzae”[TIAB] OR “H. influenzae”[MH] OR “Haemophilus influenzae”[TIAB]) AND (“signs and symptoms”[TIAB] OR “signs or symptoms”[TIAB} or “history and physical”[TIAB] OR “physical examination”[TIAB]) NOT (“Nosocomial”[TIAB] OR “Nosocomial”[MH] OR “children” [TIAB] OR “pediatric”[TIAB] OR “childhood” [TIAB]).

Filters for human only research, with abstract, and in adults were applied.

3.2.2.4 Data Abstraction

Abstracts will be reviewed by 2 investigators for possible inclusion. Abstracts identified for full text review by either reviewer will then be reviewed in detail for possible inclusion in the

study, again in parallel. Study characteristics, study quality, and etiology data will be abstracted in parallel by 2 investigators. The same data abstraction template will be used by both investigators. Any discrepancies in data abstraction will be resolved by consensus after discussion, involving a third investigator if necessary.

3.2.2.5 Quality Assessment

Despite the importance of prevalence studies for guiding clinical practice, a tool has not been adopted as the standard for assessing risk of bias in these types of studies. One systematic review of quality assessments for prevalence studies concluded that the Joanna Briggs Institute (JBI) Prevalence Critical Appraisal Tool is the most comprehensive[140]. Therefore, we will assess prevalence study quality using the JBI criteria (Appendix A). Studies in this systematic review will consist of prospective observational designs (i.e. cohort and case-control). Two different versions of the JBI criteria will be used to assess risk of bias based on the study design. Investigators will review the studies in tandem and resolved any discrepancies by consensus discussion.

3.2.3 Analysis

In this Aim, the prevalence of bacteria and/or viruses in symptomatic patients with ARTI and in asymptomatic controls will be obtained from studies included in our systematic review. The pooled prevalence estimates and 95% confidence intervals for pathogens in each group will be calculated with a random effects model of raw proportions. The inverse variance method will be used to calculate the overall proportion of a specific pathogen identified the among symptomatic or asymptomatic groups. This information will be presented graphically using forest plots. A random effects model will be used because we assume that there will be some degree of heterogeneity across the included studies. We suspect there will be heterogeneity

because we are including research conducted in children and adults, and our research is not limited to as specific type of acute respiratory tract infection. As there will likely be varying ages included in our study, we could address resulting heterogeneity by stratifying the data by age group. Similarly, because our meta-analysis will include data for all acute respiratory tract infections, we will stratify them by upper and lower respiratory tract infection or by specific diagnosis, if possible.

Heterogeneity will be quantified using the I^2 estimate. The following scale will be used to determine the degree of heterogeneity: I^2 estimates less than 40% indicate little to no heterogeneity; 40 – 60% indicates moderate heterogeneity; 60 – 90% indicates substantial heterogeneity; 75 – 100% indicates considerable heterogeneity. The first analysis presented will be the prevalence of bacteria and/or viral pathogens detected in outpatients with acute respiratory tract infections who are symptomatic. The second will be the prevalence of bacteria and/or viral pathogens detected in outpatients without acute respiratory tract infections who are asymptomatic. The third analysis presented will compare the prevalence of bacteria and/or viruses found in symptomatic patients with acute respiratory tract infections to asymptomatic, healthy patients. We will assess the clinical relevance of any statistical differences between the bacterial and/or viral pathogens being carried by symptomatic and asymptomatic persons by calculating the positive etiologic predictive value (P-EPV) and 95% confidence interval. The P-EPV is the probability of finding an association between symptomatic lower respiratory tract infections and bacterial and/or viral pathogens[137]. Based on our study design, we will assume that the sensitivity of the PCR test used is 100%. P-EPV will range from 0 – 100%. If a bacterial and/or viral organism is found equally often in symptomatic and asymptomatic individuals, the estimated P-EPV will be 0% and as such we will assume that it is likely to be commensal. If the

difference in the prevalence of pathogens identified between both groups increases, the P-EPV will approach 100%. The equation used to calculate P-EPV is provided below[141]. All analyses will be conducted in R.

$$P(D^+|S^+T^+) = 1 - \left(\frac{\frac{\text{Sen}}{P(T^+|S^+)} - 1}{\frac{\text{Sen}}{P(T^+|S^+D^-)} - 1} \right)$$

D = Disease

S = Symptoms

T = Test

Sen = Sensitivity

$$P(T^+|S^+D^-) = P(T^+|S^-) \times \theta$$

θ = ratio between symptomatic and asymptomatic carriers

Lastly, we will broadly assess signs and symptoms commonly associated with specific pathogens for each diagnosis if this data is available. It is our hope to identify the prevalence of certain signs and symptoms among symptomatic patients. Likewise, we would also like to assess if signs and symptoms of acute respiratory tract infections coincide with a specific pathogen or group of pathogens. Table 3.1 and 3.2 contain the details that we will aim to provide. All analysis will be completed in R.

Table 3.1 Proportion of symptomatic patients with specific acute respiratory tract signs/symptoms (SAMPLE DATASET)

Signs/Symptoms	# Studies Reporting Data for Symptom	# Symptomatic Patients with that Symptom	Total # Symptomatic Patients
Cough	5	250	500
Fever			

Sore Throat			

Table 3.2 Proportion of symptomatic patients with a sign/symptom of acute respiratory tract infection given that at least one pathogen was identified (SAMPLE DATASET)

Signs/ Symptoms	S. pneumoniae	H. influenzae	Influenza A	Rhinovirus
Cough	100	200	50	75
Fever				
Sore throat				
Sputum				

3.2.3.4 Publication Bias

Publication bias is often a problem in systematic reviews and meta-analyses and must be addressed[142,143]. Publication bias arises when the chance of a study being published is positively associated with the statistical significance of its findings and, as a result, being included in the systematic review and meta-analysis[142]. Publication bias could lead to incorrect conclusions of the systematic review. In this aim, publication bias will be assessed using a funnel plot of prevalence estimates plotted against their standard errors. If the funnel plot is asymmetrical or skewed, we will conclude that publication bias is likely in our meta-analysis. In addition to assessing for publication visually, we will assess for publication bias statistically using Begg's rank test and Egger's regression test. Begg's test assesses if there is a correlation between the ranks of effect estimates and their variances. Egger's test assesses the relationship between the effect estimates and their standard errors[144]. If the test produces a p-value less than 0.05, we will conclude that there is evidence of publication bias.

3.3. Aim 2: Conduct an acute respiratory tract infection etiology study comparing symptomatic and asymptomatic individuals from diverse US populations

3.3.1 Objective

The objective of this aim is to conduct our own observational study comparing pathogens found in persons with acute lower respiratory tract infection symptoms to bacterial and/or viral organisms found in healthy individuals. We will use this data to determine the likelihood that bacteria and/ or viruses are pathogenic or commensal or both.

3.3.2 Methods

3.3.2.1 Settings

Outpatient clinic settings associated with the University of Georgia, Georgetown University, and University of Wisconsin were used as recruiting sites for symptomatic patients, suspected of having a lower respiratory tract infection. One urgent care center and one university health center are located in Athens, Georgia. Two outpatient clinics are located in Madison, Wisconsin, while 17 clinics and/ or urgent care centers are located in the District of Columbia and surrounding Virginia cities. Farmers markets, university campuses and other community settings, associated with the previously mentioned universities and in the same geographical areas, will be used as recruitment sites for asymptomatic, healthy participants.

3.3.2.2 Participants and Procedures

In this study, the outcome of interest is symptomatic lower acute respiratory tract infection. The exposures being studied are pathogenic organisms associated with symptomatic upper and lower acute respiratory tract infection. Symptomatic patients were recruited prospectively to participate in the Enhancing Antibiotic Stewardship in Primary Care study

(EAST-PC) between June 2018 and April 2023. Symptomatic participants are 18 to 75 years of age that presented to one of the aforementioned settings with cough lasting less than 14 days. In addition, they needed to have at least one of the following symptoms for inclusion: shortness of breath, sputum and phlegm production, body or muscle aches, chest discomfort with cough, chest congestion, fever (subjective or measured), and chills or sweats. One of these of symptoms was required for inclusion because it was the goal of the EAST-PC study to recruit only or majority of patients with lower respiratory tract infections. Signs and symptoms of illness, pre-existing conditions, and demographic information were also obtained from these patients.

Asymptomatic, healthy individuals aged 18 to 75 years will be recruited prospectively between September 2022 and February 2023. Participants will be identified in medical clinics, university campuses, and various community settings. Age, sex, and recruitment location will be recorded for these individuals.

Nasopharyngeal and oropharyngeal swabs were taken at the time of recruitment for both symptomatic and asymptomatic individuals participating in the study. Swabs were stored in viral transport media (VTM) in sub-zero freezers until time for testing. Testing was conducted using PCR at the Centers for Disease Control and Preventions. Bacteria and viruses tested for can be found in Table 1.3.

3.3.2.3 IRB Approval and Funding

IRB approval was received for the recruitment of symptomatic patients for all recruitment sites prior to the initiation of the EAST-PC study. IRB approval will be obtained for the recruitment of asymptomatic patients. The EAST-PC study is funded by a research grant from the Agency for Healthcare Research and Quality (AHRQ) through the Department of Health and Human Services (HHS). All symptomatic patients received $40 for agreeing to participate in the

study, provide swabs, and complete additional study materials. All asymptomatic patients received $10 for providing nasal and pharyngeal samples and basic demographic information.

3.3.3 Analysis

Bivariate analysis will be conducted using Pearson's chi-squared (X^2) to determine if there is a significant difference in the prevalence of certain pathogens between symptomatic and asymptomatic patients. As we expect that some pathogens may not be identified as frequently in the asymptomatic or symptomatic groups, we will utilize Yates correction factor in the chi-squared test to reduce overestimation of statistical significance that could be a result of a small cell counts in the 2 x 2 table. The X^2 equation used is shown below. Fisher's exact test will also be used to compare the differences in prevalence of bacterial and viral pathogens identified in the asymptomatic and symptomatic groups. However, it will only be used when sample size for the pathogen identified is small (cell count less than 5 in one or more cells in the 2 x 2 table). Differences in PCR cycle threshold (C_T) values among both groups will be compared using simple linear regression and Pearson correlation coefficient (r). Cycle threshold was defined as the number of PCR cycles required to identify a pathogen.

$$X^2 = \sum \frac{(|O_i - E_i| - 0.5)^2}{E_i}$$

O = Observed value

E = Expected value

Logistic regression will be used to determine whether a viral or bacterial pathogen is independently associated with symptomatic infection. We will assess the clinical relevance of any statistical differences between the bacterial and/or viral pathogens being carried by symptomatic and asymptomatic persons by calculating the positive etiologic predictive value (P-

EPV) and 95% confidence interval. The P-EPV is the probability of finding an association between symptomatic lower respiratory tract infections and bacterial and/or viral pathogens[137]. Based on our study design, we will assume that the sensitivity of the PCR test used is 100%. P-EPV will range from 0 – 100%. If a bacterial and/ or viral organism is found equally often in symptomatic and asymptomatic individuals, the estimated P-EPV will be 0% and as such we will assume that it is likely to be commensal. If the difference in the prevalence of pathogens identified between both groups increases, the P-EPV will approach 100%. The equation used to calculate P-EPV is provided below[141]. All analyses will be conducted in R.

$$P(D^+|S^+T^+) = 1 - \left(\frac{\frac{\text{Sen}}{P(T^+|S^+)} - 1}{\frac{\text{Sen}}{P(T^+|S^+D^-)} - 1} \right)$$

D = Disease

S = Symptoms

T = Test

Sen = Sensitivity

$$P(T^+|S^+D^-) = P(T^+|S^-) \times \theta$$

θ = ratio between symptomatic and asymptomatic carriers

3.4 Aim 3: Assess care seeking behaviors of university students for respiratory tract infections

3.4.1 Objective

The objective of our third and final aim is to identify independent predictors of care seeking behaviors for university students with acute respiratory symptoms. We will do this by conducting a mixed methods study that includes an email survey, a review of questionnaire responses of students with ARTI in the University Health Center's electronic medical records and data obtained from participants in the Enhancing Antibiotic Stewardship in Primary Care Study (EAST-PC). This study will inform clinicians in the university health setting and more

broadly clinicians caring for young adults regarding why they choose to seek care for respiratory symptoms. This population is important to study because these students are often acting for the first-time as decision makers in regards to their health. We will also identify areas where more health education is needed as it applies to acute respiratory tract infections and their treatments.

3.4.2 Methods

3.4.2.1 Setting and Population

Data collection will be conducted at the University of Georgia and UGA's University Health Center (UHC) located in Athens, Georgia. According to the 2021 University of Georgia Diversity Report, there are approximately 38,920 students currently enrolled at the university, of whom 28,175 are undergraduate students, and 7,005 are graduate students. Among full-time (enrolled in at least 12 credit hours) undergraduate students, 58% are female and 42% are male. Among full-time (enrolled in at least 9 credit hours) graduate students, 59% are female and 41% are male. Approximately 62% of students are considered to be "traditional college aged" or between the ages of 18 and 21 years. Approximately 14,681 students (37.7%) are 22 years and older.

All students at the University of Georgia have access to the campus's University Health Center. The health center provides a variety of healthcare services including primary care, a gynecology clinic, sports medicine, mental health care, vision care, and dental care. The health center has its own on-site pharmacy, laboratory, and radiology capabilities. Upon enrolling at UGA, each student is assigned a primary care clinic for them to access by appointment throughout their tenure at the university. UHC has three primary care clinics tasked with addressing student health concerns needs such as suspected respiratory tract infections.

Symptomatic patients were recruited prospectively to participate in the Enhancing Antibiotic Stewardship in Primary Care Study (EAST-PC) between June 2018 and April 2023. Symptomatic participants were 18 to 75 years of age that presented to an outpatient setting with a cough lasting less than 14 days. In addition, they needed to have at least one of the following symptoms for inclusion: shortness of breath, sputum and phlegm production, body or muscle aches, chest discomfort with cough, chest congestion, fever (subjective or measured), and chills or sweats.

3.4.2.2 Sample Size

We will be utilizing multivariate analysis to identify symptoms of ARTI that are predictors for seeking care and antibiotic treatment for three categories of respiratory illnesses: 1) upper respiratory tract infections, 2) sore throat, and 3) lower respiratory tract infections. Therefore, the number of predictors will be used identify the ideal sample size for survey respondents. It is a general rule that there should be at least 10 observations per independent variable, but the number of desired observations can be greater based on preference. In a 2018 study, Bujang et al. presented a sample size calculation with the formula $N = 100 + xi$, where "x" represents the desired of number of observations per variable and "i" represents the number of independent variables in the study[145]. The 9 independent predictors that will be systematically varied in the vignettes in our survey are provided below (Table 3.3). To increase the precision of our findings and provide our study with more power to draw conclusions from our findings, we will set our x value as 20. Based on the formula, our sample size of survey respondents should be at least 280 (N = 100 + (20 * 9).

Table 3.3 Independent predictors that will systematically varied in 12 vignettes. Vignettes will consist of scenarios that fit into the 3 categories listed: 1) Upper Respiratory Tract Infection, 2) Sore Throat, and 3) Lower Respiratory Tract Infection

Variables	**Code for Variable**
Outcome (Continuous)	
Seeking Care	1 – 10
Seeking Antibiotics	1 - 10
Predictors (Categorical)	
Symptoms of Upper Respiratory Tract Infections	
Nasal Discharge (and color)	
None	0
Clear	1
Yellow/Green	2
Face Pain/ Pressure	
Absent	0
Present	1
Symptoms of Sore Throat	
Sore Throat	
Absent	0
Present	1
Swollen Glands	
Absent	0
Present	1
Symptoms of Lower Respiratory Tract Infections	

Cough	
Absent	0
Present	1
Sputum Color	
None	0
Clear or Yellow	1
Green	2
Bloody	3
Chest pain with Cough	
Absent	0
Present	1
Symptoms Associated with all Categories	
Fever	
Absent	0
Present	1
Symptom Duration	
< 3 days	0
3 – 7 days	1
8 – 14 days	2
> 14 days	3

3.4.2.3 Data Collection

3.4.2.3.1 Survey

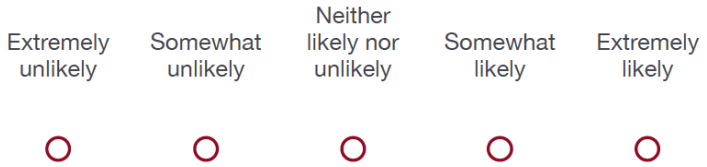
To address Aim 3, the first part of the study will consist of sending an electronic survey to the UGA student population via the Outlook *listserv* feature. Outlook *listserv* will be used to ensure that survey vignettes will be disseminated to the entire UGA student body in an effort to reach our desired sample size for survey responses. Qualtrics will be used to create the vignette survey and track survey responses. This platform was chosen because the University of Georgia has a license that is available free for student use. Students will be asked to provide the following demographic information: age, sex, and grade level (to determine the difference in care seeking behaviors between undergraduate and graduate level students). The survey will consist of 12 vignettes. Each vignette will provide a summary of common clinical presentations for specific acute respiratory tract infections with varying severity and onset of symptoms. A table indicating signs and symptoms to be included or excluded in each vignette is provided below (Table 3.4). Patients will be asked to read each vignette and rate, on a linear numeric response scale, their likelihood of seeking clinical care and their perception of the likelihood that prescription antibiotics are needed to treat the signs and symptoms described in each scenario. The numeric scale will range from 1 to 5. A score of 1 will indicate “extremely unlikely” whereas a score of 5 will indicate “extremely likely”. A sample scale is shown below (Figure 3.1). Completion of this survey will be entirely voluntary. IRB approval will be obtained to conduct this data collection. Data collection will be conducted between August 2022 and December 2022.

Table 3.4 Indicators for which signs/symptoms will be included in each vignette

Vignette Number	**Fever**	**Cough**	**Sputum Color**	**Chest Pain with Cough**	**Sore Throat**	**Swollen Glands**	**Nasal Discharge (and color)**	**Face Pain**	**Symptom Duration**
Upper Respiratory Tract Infection									
1	1	1	0	0	0	1	0	0	0
2	0	1	1	0	1	0	2	1	1
3	1	0	0	0	0	1	2	1	2
4	0	1	1	0	0	0	1	0	0
Sore Throat									
5	0	0	0	0	1	0	1	0	1
6	1	0	0	0	1	1	0	0	0
7	1	0	0	0	1	1	0	0	2
8	0	0	0	0	1	1	1	0	1

Lower Respiratory Tract Infection									
9	0	1	1	1	1	0	0	0	2
10	1	1	3	1	0	0	0	0	3
11	1	1	1	1	1	0	0	0	2
12	0	1	0	1	0	0	0	0	0

Figure 3.1 Scale that will be used to rate likelihood for seeking care and antibiotic treatment in vignette survey



3.4.2.3.2 University Health Center Point and Click (UHC PNC) Questionnaire

As previously mentioned, UGA students have access to the UHC for their health concerns by appointment. Appointments can be made over the phone or online. Prior to each appointment students are asked to complete pre-visit questionnaires that are specific to their chief complaint for their visit. Respiratory illness is one such complaint with an associated questionnaire (Appendix B). In the questionnaire, students are asked to provide information in regards to their illness. Patients are asked to rank the severity of their cough, body or muscles aches, and overall weakness as either “none”, “mild, “moderate” or “severe”. Patients are also asked to check “yes” or “no” to having specific acute upper and lower respiratory tract infection symptoms, and approximate the number of days they have been experiencing symptoms prior to making the appointment. This questionnaire also includes the following open-ended questions: “how has your illness evolved” and “what measures have you tried to get or feel better”. We will use UHC PNC to download de-identifiable data from patient questionnaire responses. Questionnaires completed between August 2022 and January 2023 will be obtained. This information will be used for qualitative data analysis to inform common treatments used prior to seeking care and reasoning for seeking care. IRB approval will be obtained to access patient records.

3.4.2.3.3 Enhancing Antibiotic Stewardship in Primary Care Study

Upon enrollment in our study, symptomatic patients were asked to describe their expectation for how long their cough would last and to indicate from a prespecified list why they sought care for their illness. IRB approval was received for the recruitment of symptomatic patients for all recruitment sites prior to the initiation of the EAST-PC study. The EAST-PC study is funded by a research grant from the Agency for Healthcare Research and Quality (AHRQ) through the Department of Health and Human Services (HHS). All symptomatic patients received $40 for agreeing to participate in the study, provide swabs, and complete additional study materials.

3.4.3 Analysis

3.4.3.1 Vignette Survey Analysis

Exploratory data analysis will be done first to identify any necessary data cleaning. Then an item analysis will be done for each variable to assess for missing data. As vignettes will differ systematically on the severity of the scenario and symptoms included, it is our goal to identify independent predictors of seeking care versus not seeking care. Based on the survey responses, we will achieve this by using multivariate analysis that will be conducted on the 3 predetermined categories of acute respiratory tract infection. Participants will rank their perception of the need for clinical intervention and antibiotic treatment on a numerical scale for all 12 vignettes. Responses on the numeric scale for seeking care and antibiotics will be analyzed as categorical variables ranging from 1 (extremely unlikely) to 5 (extremely likely). Agreeing to seek care or antibiotic will be defined by a response of somewhat likely or extremely likely. Disagreeing to seek care or antibiotic will be defined by a response of neutrality, somewhat unlikely, or extremely unlikely. Symptoms included or excluded from vignettes will be defined as categorical

variables. The presence of a specific symptom in a vignette will be defined by a 1, 2, or 3. If the symptom is absent from the vignette, the symptom will be defined by a 0. An example dataset is provided below (Table 3.5).

Table 3.5 Sample dataset of vignette survey responses

Participant ID	Vignette Number	Seek Care (1-5)	Seek Antibiotics (1-5)	Fever	Cough	Sputum Color	Chest Pain with Cough	Sore Throat	Swollen Glands	Nasal Discharge (with color)	Face Pain	Symptom Duration
1	1	5	3	1	0	0	1	0	1	0	0	0
1	2	4	4	0	1	1	0	1	0	2	1	1
2	1	3	2	1	0	0	1	0	1	0	0	0
2	2	5	4	0	1	1	0	1	0	2	1	1

A logistic regression model will be created in STATA. P-values that are included in the summary statistics of the regression model will be reviewed to determine if the independent predictors included in the model, significantly contribute to seeking care or antibiotic treatment. Symptoms that have p-values greater than 0.05 will be concluded as not being a predictor for a college student seeking care for a respiratory tract infection.

3.4.3.2 University Health Center Questionnaire Qualitative Analysis

Deidentified respiratory illness questionnaire data retrieved from UHCs electronic health records will be assessed in order to present the clinical characteristics of patients being seen in the university health setting for suspected upper and lower respiratory tract infections. We will determine the most common symptoms patients present to the clinic with by quantifying the yes or no responses (Table 3.6). We will also calculate the mean and median number of days the patients have been experiencing these symptoms prior to scheduling an appointment at the health center. Responses for the severity of cough, body aches, and weakness will be combined to determine the student's perception of the severity of their illness (Table 3.7). Lastly, we aim to conduct conventional content analysis to identify common reasons for respiratory visits. Conventional content analysis is generally used to describe a topic of interest, when existing theories or research about the topic are limited[146]. Our aim will be addressed by reviewing student responses on how their illness evolved and whether or not any measures were used to get or feel better prior to making the appointment. We will consider the content of this open–ended question and attempt to categorize them based on themes identified. We expect that there will be certain over-the-counter medications and regimens that have been used prior to making the appointments, therefore we would like to identify the most common measures tried. We also suspect that no measures are tried, which would also be important to note. In terms of symptom

and illness evolution, we hope to identify common reasons for scheduling the appointment such as “symptoms were not going away”, “encouraged to seek care by parent or guardian”, “symptoms are very bad and do not want to miss event or class”, or “roommate was diagnosed with illness; therefore, I suspect I have it”, etc. Using the themes that we identify through our content analysis, we hope to develop a theoretical model to better understand individual factors that commonly lead to students making appointments for respiratory tract infections[147].

Table 3.6 Proportion of patients by signs/symptoms who completed the University Health Center Respiratory Tract Infection Questionnaire (SAMPLE DATASET)

N = 500	Respiratory Illness Questionnaire	
	Present	Not Present
Cough	200/500	300/500
Fever		
Sneezing		
Fatigue		
Avg # Days	10 days (1 – 30 days)	

Table 3.7 Proportion of patients who reported severity of cough, body aches, and/or weakness on the University Health Center Respiratory Illness Questionnaire (SAMPLE DATASET)

N = 500	Severity			
Symptoms	None	Mild	Moderate	Severe
Cough	200/500	150/500	50/500	100/500
Body aches				
Weakness				

3.4.3.3 Enhancing Antibiotic Stewardship in Primary Care Descriptive Analysis

Supplementary descriptive analysis will be done using data obtained from individuals enrolled in the Enhancing Antibiotic Stewardship in Primary Care study. For our analysis we will utilize a subset of the data that contained only responses from young adults aged 18 – 30 years. From this data we will calculate the mean and median number of days that patients expected their cough to last with or without an antibiotic. Responses to a prespecified list of options for seeking care will be quantified. Analysis of this data was done using STATA.

CHAPTER 4

RESULTS

Introduction

The results of each aim of this dissertation are presented individually as manuscripts in chapters 5, 6, and 7. This corresponds to aims 1, 2, and 3 respectively. Each manuscript contains a title page, abstract, introduction, results, discussion, and applicable tables or figures. A single references list is included at the end of this dissertation. There may be some repetition between information presented in chapters 1 – 3. After presenting the results of each aim in the form of a manuscript, chapter 8 summarizes and discusses the future directions for research for all three aims.

CHAPTER 5

Etiology of Acute Respiratory Tract Infections in Outpatients: A Systematic Review and Meta-Analysis to Identify Likelihood of Commensalism

INTRODUCTION

Acute respiratory tract infections remain a common cause of outpatient visits globally[22]. They are also the most common diagnoses for which a patient receives any prescription (i.e. antibiotics, antitussives, and inhalers)[2]. Upper respiratory tract infection (URTI) diagnoses include pharyngitis, rhinosinusitis, otitis media, and rhinitis. Lower respiratory tract infection (LRTI) diagnoses include community-acquired pneumonia (CAP) and non-pneumonia lower respiratory tract infections or acute bronchitis, as it is also known.

The etiology of acute upper and lower respiratory tract infections can be bacterial and/ or viral. Bacterial URTI diagnoses include streptococcal pharyngitis, pharyngitis caused by *Fusobacterium necrophorum*[5], bacterial rhinosinusitis, and bacterial otitis media. Bacteria commonly associated with both URTIs and LRTIs include *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae*, and *Moraxella catarrhalis. Staphylococcus aureus* is a bacterium that is associated solely with LRTIs[6]. However, viral pathogens are more frequently associated with acute respiratory illness than bacteria[29]. Viral URTI diagnoses include viral pharyngitis, viral rhinosinusitis, viral otitis media, and viral rhinitis. Viruses associated with URTIs and LRTIs include human rhinovirus, human metapneumovirus (hMPV), respiratory syncytial virus (RSV), influenza A and B viruses, parainfluenza virus, adenovirus, and

coronavirus[6]. Bacterial LRTIs can include pneumonia and acute bronchitis. Viral LRTIs are viral pneumonia and viral acute bronchitis.

The respiratory tract is colonized with bacteria and/or viruses, much like our skin. The commensal microbiome is housed primarily in the upper respiratory tract which includes the nasal cavity, nasal pharynx, and larynx[7]. The normal bacteria that colonize the respiratory tract are thought to be commensal or "healthy" and unlikely to cause harm[33]. In contrast, it is thought that the presence of commensal genera such as *Staphylococcus, Streptococcus, Corynebacterium, Prevotella, Veillonella, Propionibacterium, and Fusobacterium* can assist the body with fighting new, opportunistic bacterial or viral pathogens that may cause invasive diseases in adults[7,148–151] .

Our systematic review will identify outpatient studies that determine the etiology of acute upper and lower respiratory tract infections. This information will be used first, to identify the most common pathogens associated with acute upper and lower respiratory tract infections in the outpatient setting and second, to determine the likelihood that specific bacteria and/or viruses are commensal versus pathogenic.

METHODS

Inclusion and Exclusion Criteria

To be considered for inclusion in the meta-analysis, studies had to recruit outpatients presenting with any symptomatic acute respiratory tract infection (ARTI) (lower or upper). Studies were also considered for inclusion if their research population included asymptomatic patients that were tested for nasopharyngeal (NP) and oropharyngeal (OP) pathogens in outpatient or non-clinical settings. Studies that reported both symptomatic and asymptomatic ARTI etiology were also included. Testing for viral and/or bacterial pathogens had to use

polymerase chain reaction (PCR) or culture methods. Adequate count data for assessing how often bacteria and/ or viruses were detected was required for inclusion. Pathogen data could be obtained via prospective data collection or retrospective health record review, depending on the study design.

Studies were excluded from the meta-analysis if their population consisted of primarily children. We also excluded studies that were performed in specialized populations such as individuals with cancer, HIV, immunosuppressed, chronic lung disease, or pregnant women. Lastly, studies were excluded if they were conducted in an inpatient facility.

Search Strategy

A search of PubMed, EMBASE, Web of Science, and Google Scholar were done to identify etiological studies of outpatients with acute respiratory tract infections. The search strategy was developed based on key words and MESH terms of previously identified etiologic studies. The search strategy for each database is included in Appendix A, Table A1. We also reviewed studies included in previous systematic reviews or meta-analyses, as well as the reference lists of all included studies. The search was not restricted by language or publication date. A secondary systematic review was conducted to include studies that assessed symptoms of specific etiologies of ARTIs or specific ARTI diagnoses. This search yielded an additional five studies to be included in the descriptive analysis. The study characteristics and data obtained from these studies is detailed in Appendix A, Table A5. The search strategy of our secondary systematic review can be found in Appendix A, Table A4.

Data Abstraction

All abstracts were reviewed in parallel by two investigators. For any abstract of interest, the full article was obtained and reviewed by two investigators. Full articles were screened for

the following data: inclusion criteria, type of care setting, age of patients, study design, diagnostic testing, country, years of data collection, pathogens identified in study, and viral and/or bacterial etiology count data for acute respiratory tract infections. A final list of included studies was developed, and all data were abstracted in parallel by two investigators. The same data abstraction template was used by both investigators. Any discrepancies in data abstraction were discussed and resolved by consensus.

Quality Assessment

Study quality was assessed using the Joanna Briggs Institute (JBI) Prevalence Critical Appraisal Tool (Appendix A, Figures A1 and A2). Studies in this systematic review consisted of prospective and retrospective observational designs (i.e., cohort and case-control). Two different versions of the JBI criteria were used to assess risk of bias based on the study design. Investigators reviewed the studies in tandem and resolved any discrepancies by consensus discussion. Overall risk of bias was determined for all included studies. Studies that addressed all categories of the JBI criteria were considered low risk of bias. Those that did not address one or two categories were considered moderate risk of bias. If more than two categories were not addressed from the criteria studies were considered high risk of bias.

Analytic Strategy

R version 4.1.2 and the meta package was used to perform a random effect meta-analysis of data gathered from included studies. The prevalence of bacteria and/or viruses in symptomatic patients with ARTI and in asymptomatic controls were obtained from studies included in our systematic review. Data were stratified into two groups, acute respiratory tract infection (ARTI) and lower respiratory tract infection (LRTI), based on the condition type being studied. The ARTI group included upper respiratory tract infections (URTIs) and studies that did not specify

whether the condition of interest was upper or lower respiratory tract infection. The LRTI group included studies researching non-specific LRTIs, acute bronchitis, and community acquired pneumonia (CAP). The pooled prevalence estimates and 95% confidence intervals for pathogens in each group were calculated with a random effects model of Freeman-Tukey transformed prevalence proportions. The inverse variance method was used to calculate the overall proportion of a specific pathogen identified among symptomatic or asymptomatic groups. This information is presented graphically using forest plots. Each plot reports an I^2 statistic to quantify the proportion of the observed variance that would remain if we could eliminate sampling error. The following scale will be used to determine the degree of heterogeneity between studies: I^2 estimates less than 40% indicate little to no heterogeneity; 40 – 60% indicates moderate heterogeneity; 60 – 90% indicates substantial heterogeneity; 75 – 100% indicates considerable heterogeneity. For forest plots with less than ten studies included, it is noted that the I^2 estimate can underestimate between study variability[152].

The P-EPV is the probability that a bacterial and/or viral pathogen detected in a symptomatic person's respiratory tract is causing those symptoms[137]. Based on previous research findings, we will assume that the sensitivity of the PCR test used is 99%[153,154]. P-EPV will range from 0 – 100%. If a bacterial and/ or viral organism is found equally often in symptomatic and asymptomatic individuals, the estimated P-EPV will be near 0% and as such we will assume that it is likely to be commensal. For pathogens primarily detected in symptomatic persons and rarely seen in asymptomatic persons, the P-EPV will approach 100%. The P-EPV equation is provided in Appendix A, Figure 3[144]. The online EPV Calculator version 2.21 tool was used to calculate P-EPV and their corresponding 95% confidence intervals[155].

Lastly, we will descriptively analyze the signs and symptoms commonly associated with specific pathogens for each diagnosis if this data is available. It is our hope to identify the prevalence of certain signs and symptoms among symptomatic patients. Likewise, we would also like to assess if signs and symptoms of acute respiratory tract infections coincide with a specific pathogen or group of pathogens. STATA version 18/ SE will be used to conduct Pearson's Chi-square test to determine the likelihood of having acute respiratory infection symptoms based on etiology.

Assessment of Publication Bias

The 'funnel' function in the R meta package will be used to generate funnel plots to visually assess publication bias. A plot for each etiology with five or more studies will be generated for symptomatic and asymptomatic groups[156]. Plots will then be analyzed for visual symmetry. Publication bias will be statistically assessed using Egger's test for etiologies with ten or more studies included in the analysis. This cut-off will be used because if there are too few studies included in the meta-analysis, the power of Egger's test can be too low. A statistically significant association will indicate that the relationship between the pooled prevalence effect measure and the study size is more than chance. We will report statistically significant results from this test as potential publication bias.

RESULTS

Search Results

Figure 5.1 includes a summary of our search process for relevant studies. A total of 3, 670 studies were identified from our search and 135 were reviewed in full for inclusion. There were 19 studies remaining for inclusion in the meta-analysis. Of these studies, 4 were excluded because their etiology data presented pediatric data only or combined data for pediatric and adult

populations. Therefore, complete analysis was conducted on 15 studies, all of which presented etiology in adult populations.

Characteristics of the included studies are shown in Table 5.1. Studies were performed worldwide including 6 in European countries, 5 in Asian countries, and 3 in the United States. Data were collected between 1992 to and 2019. Etiology in only symptomatic persons was reported in 6 studies. The remaining 9 studies reported etiology in both symptomatic and asymptomatic adults. The mean or median age ranged from 31 to 69 years. In general, all studies had similar recruitment of males and females.

Study Quality

The quality of all included studies was evaluated using the Joanna Briggs Institute (JBI) Prevalence Critical Appraisal Tool. Tables 5.2 and 5.3 include these results for case-control and cohort designs, respectively. Overall, 11 studies had a low risk of bias, in either a cohort or case-control design, across all JBI categories. We classified three studies as having an overall moderate risk of bias for not addressing one to three JBI categories. This classification was given due to studies not highlighting potential confounders or mentioning how confounding was addressed in analyses. A moderate risk of bias was also given to three studies based on their recruitment strategies for their study populations. High risk of bias was present in one study due to the article not addressing three of the categories in the appraisal tool. The three categories that were not addressed were adequate matching strategies for a case-control studies, confounding factors, and appropriate statistical analysis for confounding.

Etiologic Prevalence

Summary estimates of etiologic prevalence and their corresponding 95% confidence intervals for symptomatic and asymptomatic groups are shown in Table 5.3. All forest plots for

symptomatic and asymptomatic etiology pooled prevalence estimates and their I^2 values are included in Appendix A, Figures A4 and A5. Overall, viruses that were identified most often in symptomatic individuals included influenza A or B, rhinovirus (RV), bocavirus, and enterovirus. Amongst individuals recruited with acute respiratory tract infection symptoms (ARTI) influenza A or B, bocavirus, rhinovirus, and enterovirus were the most identified. In patients with lower respiratory tract infection symptoms (LRTI), influenza A or B, rhinovirus, human coronavirus, and respiratory syncytial virus (RSV) were most common. Bacteria that were most common overall among patients included *Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae*. Overall heterogeneity between studies was high amongst symptomatic study populations and the respective etiologies by illness type. Heterogeneity ranged from 0% to 99%, with the majority being greater than 85%. Parainfluenza virus 3 and Enterovirus were the only etiologies to have low heterogeneity between studies with an I^2 value equal or close to 0%.

The isolation of bacteria and viruses in asymptomatic study populations (individuals with no signs or symptoms of acute respiratory tract infections) was lower compared to symptomatic populations. Viruses such as human metapneumovirus and parainfluenza virus (all types) were nearly non-existent in these groups. The most identified viruses among asymptomatic groups were rhinovirus, influenza, respiratory syncytial virus (RSV), and enterovirus. Bacterial etiology was found to have a higher prevalence in asymptomatic persons. *Streptococcus pneumoniae* and *Haemophilus influenzae* were both found most often in those who were asymptomatic for respiratory tract symptoms. There was a range of heterogeneity 0 – 97% amongst this group with the majority being greater than 75%. RV had a moderate I^2 value of 60%, and hCoV and

bocavirus had low I^2 values below 10% indicating low heterogeneity between studies for these viruses.

Determining Commensalism

The positive etiologic predictive values (P-EPV) for viruses and bacteria that were present in both the symptomatic and asymptomatic groups is included in Table 5.4. Etiologies that were determined to likely be pathogenic, as they were present amongst symptomatic groups more frequently than asymptomatic groups, were influenza A or B, human metapneumovirus, respiratory syncytial virus, and parainfluenza virus. These viral etiologies all had P-EPVs that were greater than 90%. However, all viral etiologies, except for adenovirus, had P-EPVs greater than 70%. There were three bacterial etiologies, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* that had the potential to be commensal with P-EPV values less than 0%. This occurred because these pathogens were present more often in healthy participants than patients with symptomatic ARTIs. However, negative values for the P-EPV are not interpretable according to its developer (personal communication, R. Gunnarsson). *Chlamydia pneumoniae* was the only bacteria identified to be pathogenic with a P-EPV greater than 70%.

Etiology Associated with Symptoms

There were nine studies that provided data on etiology specific symptoms, in adults, from our original search. Overall, cough, headache, fever, sore throat, and abdominal symptoms were the most frequently reported in studies of acute respiratory tract etiology. Sneezing was only reported in one study. Most symptoms were reported for viral etiologies (N = 24850). These viral etiologies included adenovirus, SARS-CoV2, human metapneumovirus, and influenza virus A or B. Individuals diagnosed with these viruses most often had complaints of cough (85.8%),

headache (77.7%), and fever (77.7%) while complaints of sputum production (0.1%), sneezing (0.1%), and chills/sweats (5.0%) were less common. Two studies, with an interest in diagnosing community-acquired pneumonia etiology, reported symptoms that were specific to the bacterial etiology *Mycoplasma pneumoniae* (N = 63) and *Chlamydia pneumoniae* (N = 21). The isolation of *M. pneumoniae* coincided with increased complaints of cough (91.7%) and sputum production (40.5%). Abdominal symptoms (10.7%), chest pain (10.7%) and dyspnea (7.1%) were reported less often for these bacterial pathogens.

Count data for adenovirus symptoms was reported the most in our subset of studies. Therefore, we conducted a X^2 tests to determine the likelihood of specific ARTI symptoms in patients with adenovirus compared to those diagnosed with other viral pathogens. Based on the reported data, patients with complaints of cough, headache, abdominal symptoms, dyspnea, fever, myalgia, sore throat, and nasal congestion were all significantly associated with an adenovirus diagnosis. Notably, sore throat (OR 11.85; 95% CI 10.98, 12.78) and nasal congestion (OR 8.02; 95% CI 7.57, 8.50) were more frequent in the group of patients with adenovirus compared to those without.

Publication Bias

Funnel plots for viral and bacterial etiologies for symptomatic and asymptomatic groups that were reported in three or more studies can be found in Appendix A, Figures A6 and A7. Upon visual assessment, none of the funnel plots appear to be symmetrical. Therefore, we do not see any evidence of bias in publication due to sample size. As there were no etiologies that were reported in at least 10 studies, Egger's test was not conducted.

DISCUSSION

The objective of this meta-analysis was to identify viral and/or bacterial etiologies that were associated with symptomatic acute respiratory tract infections (ARTI). We also wanted to look at organisms detected in asymptomatic persons that could possibly be associated with disease but that can also be commensal. We were able to identify viruses and bacteria that were significantly associated with symptomatic ARTI diagnoses and being asymptomatic. From the studies included in out meta-analysis, we were able to determine that bocavirus, influenza virus A or B, rhinovirus, and *M. catarrhalis* are the most common causes of acute respiratory tract infections. Influenza virus A or B, rhinovirus, *S. pneumoniae*, and *H. influenzae* were the most common causes of lower respiratory tract infection. Overall, when detected influenza A or B, human metapneumovirus, and respiratory syncytial virus are highly likely to be pathogenic, as they were much more prevalent in symptomatic individuals compared to asymptomatic individuals. *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are often commensal, but could become invasive and cause disease.

While we did find these associations, there are several limitations to consider with the studies included in this meta-analysis. First, this meta-analysis included a small number of studies. Many etiologies in the symptomatic subgroups and the asymptomatic group only had data from single studies. Heterogeneity was moderate to high for all groups. This is likely a result of inconsistent recruitment methods and ascertainment of infection and pathogen data across studies. Definitions of signs and symptoms used for recruitment varied slightly across studies. Similarly, many studies combined upper and lower respiratory tract data. Lastly, there were relatively few studies that compared symptomatic and asymptomatic groups therefore providing little evidence to make conclusions on commensalism and pathogenicity. The studies

that did compare symptomatic and asymptomatic persons often included patients that were from different communities across different time periods.

Further research on this topic is needed to address these limitations. Studies should strive to prospectively recruit symptomatic and asymptomatic participants from the same source populations and using the same testing procedures in both groups. Inclusion criteria should provide clear definitions for the conditions that they will be researching as it is important to separate upper respiratory and lower respiratory etiology because they are associated with different pathogens, symptoms, and severity of disease. Participants should also be tested for bacterial and or viral organisms using the same methods, ideally PCR or culture.

Conclusion

In conclusion, this systematic review highlights the importance of research in the field of respiratory tract infection etiology. We found that viruses such as influenza A or B, human metapneumovirus, and respiratory syncytial virus are most often pathogenic and bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* could be commensal when they are not invasive. However, due to the lack of studies available for inclusion in the meta-analysis, there is little evidence to make causal claims about these associations. There is a clear need for both large and small studies that include symptomatic and asymptomatic groups to determine the etiologies of upper and lower acute respiratory tract infections. This information is crucial for guiding prescribing practices for these conditions as they are the most frequent reason for seeking care in clinical settings.

TABLES AND FIGURES

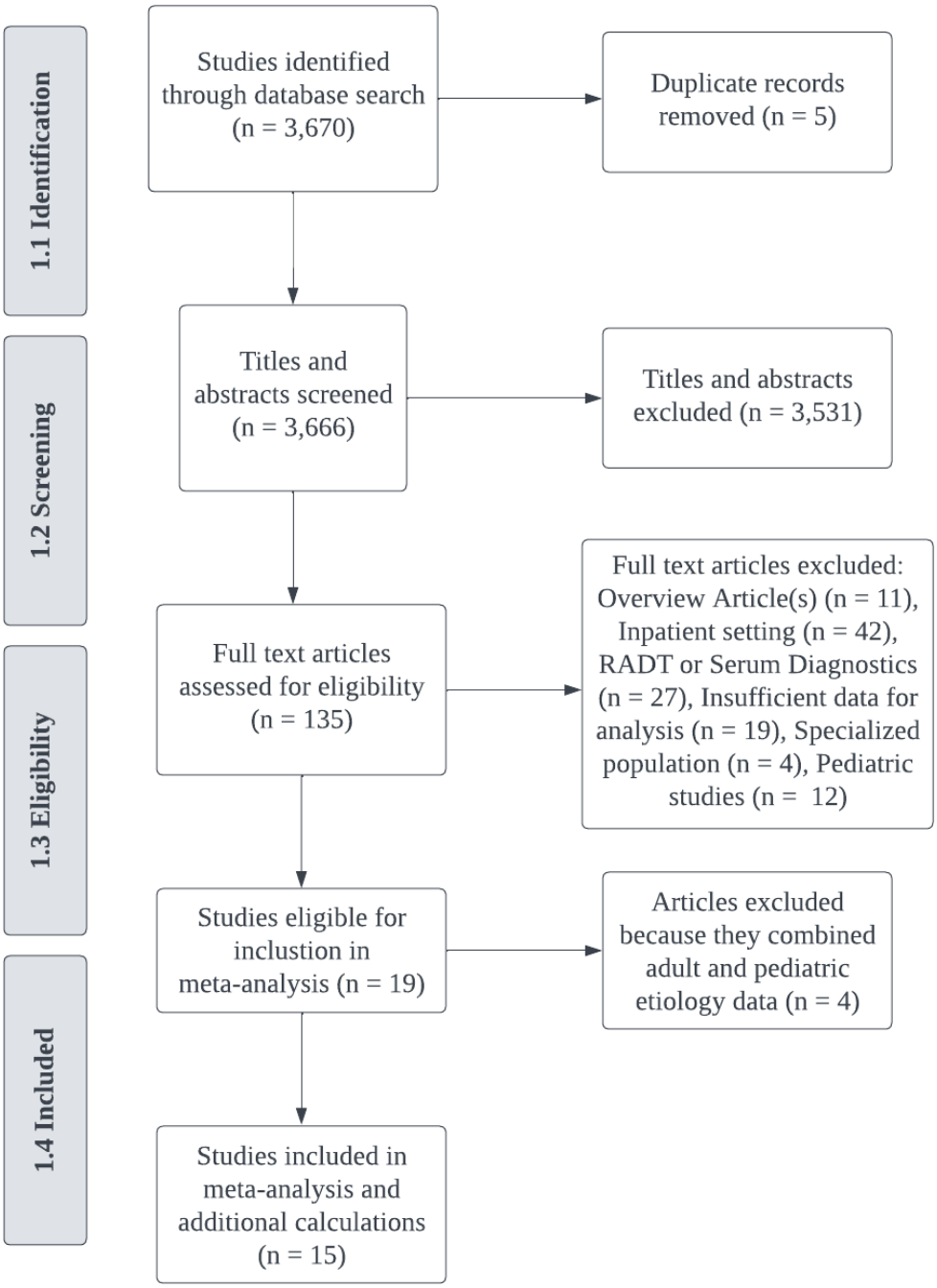


Figure 5.1 PRISMA Diagram for the systematic review of etiology of acute respiratory tract infections in outpatient settings

Table 5.1 Study characteristics of articles included in the etiology systematic review and meta-analysis.

Author, Year	Country	Setting	Year Data Collected	Mean Age in Years (Range)	Detection Method	Diagnosis of Interest	Type of Patients	Sex
Studies Reporting Data on any Acute Respiratory Tract Infection (ARTI)								
Shih et al, 2015[157]	Taiwan	Clinic	2012 - 2013	42.7 (19 - 92)	PCR	ARTIs	Symptomatic/ Asymptomatic	46.1% Male
Sundell et al, 2019[32]	Sweden	Clinic	2015 - 2016	Symptomatic: Median 66 (57 - 76); Asymptomatic: Median 69 (54 - 77)	PCR	ARTIs	Symptomatic/ Asymptomatic	Symptomatic: 45% Male; Asymptomatic: 37% Male
Zimmerman et al, 2014[158]	United States	Clinic	2012	(6 mos – 82 yrs)	PCR	ARTI	Symptomatic	Not Reported
Studies Reporting Data on any Upper Respiratory Tract Infection (URTI)								
Chi et al, 2003[159]	United States	Community (university)	1999 - 2000	37 (20 - 62)	Culture	Bacterial Otitis Media and Sinusitis	Symptomatic/ Asymptomatic	Not Reported
Han et al, 2011[160]	United States	Community	2003 - 2006	Not Reported	Culture	Acute Viral Rhinosinusitis	Symptomatic/ Asymptomatic	Not Reported
Layani-Milon et al, 1999[161]	France	Clinic	1992 - 1997	Not Reported	PCR	URTI	Symptomatic	Not Reported

Lu et al, 2013[162]	China	Clinic	2009 - 2010	Median 31 (14 - 88)	PCR	Acute URTIs	Symptomatic	51% Male
Studies Reporting Data on any Lower Respiratory Tract Infection (LRTI)								
Creer et al, 2006[31]	United Kingdom	Clinic	2000 - 2001	Symptomatic: 49.9 (18 – 90) Asymptomatic : 49.7 (22 -83)	Culture/ PCR	LRTIs	Symptomatic/ Asymptomatic	37% Male
Graffelman et al, 2008[163]	Netherlands	Clinic	1998 - 2001	50	Culture	CAP	Symptomatic	47% Male
Holm et al, 2007[164]	Denmark	Clinic	2002 - 2003	Median 50 (18 - 94)	PCR	CAP and LRTI	Symptomatic	49% Male
Ieven et al, 2018[166]	11 European Countries	Clinic	2007 - 2010	49.8 (18 - 92)	Culture/ PCR	LRTI with or without CAP	Symptomatic/ Asymptomatic	40% Male
Liu et al, 2013[167]	China	Clinic	2010 - 2011	Not Reported	Culture/ PCR	CAP	Symptomatic	Not Reported
Studies Reporting Data for SARS-CoV-2								
Karamese et al, 2021[169]	Turkey	Clinic/ Lab Database	2020	38.1	PCR	SARS-CoV-2	Symptomatic/ Asymptomatic	59.1% Male
Setiadi et al, 2022[170]	Indonesia	Clinic/ Lab Database	2020 - 2021	Not Reported	PCR	SARS-CoV-2	Symptomatic/ Asymptomatic	38.4% Male
Viera-Segura et al, 2021[171]	Mexico	Clinic/Lab Database	2020	37.4	PCR	SARS-CoV-2	Symptomatic/ Asymptomatic	46.4% Male

PCR = Polymerase chain reaction, ARTI = acute respiratory tract infection, ILI = influenza like illness, URTI = upper respiratory tract infection, LRTI = lower respiratory tract infection, CAP = community acquired pneumonia

Table 5.2 Summary of pathogen detection by study. The numbers shown are the number and percentage of patients in each category for each study.

Author, Year	Pathogens Reported	Any virus N (%)	Any bacteria N (%)	> 1 pathogen N (%)	No pathogens detected N (%)
Chi et al, 2003[159]	*M. catarrhalis, s. pneumoniae, H. influenzae*	0 (0.0%)	106 (54.3%)	47 (24.1%)	42 (21.5%)
Creer et al, 2006[31]	*S. pneumoniae, H. influenzae, M. catarrhalis, M. pneumoniae, C. pneumoniae, L. pneumophila* RV, IV, HCoV, PIV, RSV, EV	55 (36.9%)	24 (16.1%)	20 (13.4%)	50 (33.6%)
Graffelman et al, 2008[163]	*S. pneumoniae, H. influenzae, M. pneumoniae* IV (A, B)	43 (33.3%)	33 (25.6%)	8 (6.2%)	45 (34.9%)
Han et al, 2011[160]	*M. catarrhalis, s. pneumoniae, H. influenzae*	0 (0.0%)	72 (51.8%)	48 (34.5%)	19 (13.7%)
Holm et al, 2007[164]	*S. pneumoniae, H. influenzae, M. pneumoniae, M. catarrhalis, C. pneumoniae, L. pneumophilia, S. aureus* RV, IV (A,B), RSV, HMPV, PIV, ADV	89 (23.1%)	69 (17.9%)	22 (5.7%)	206 (53.4%)

Karamese et al, 2021[169]	SARS- CoV-2	373 (4.8%)	0 (0.0%)	Not Reported	7480 (95.3%)
Layani-Milon et al, 1999[161]	*M. pneumoniae*, IV (A, B), RSV, HCoV, RV, ADV, PIV	1385 (32.4%)	283 (6.6%)	375 (8.8%)	2229 (52.2%)
Liu et al, 2013[167]	*M. pneumoniae*	122 (24.4%)	82 (16.2%)	67 (13.4%)	229 (45.8%)
Lu et al, 2013[162]	IV (A,B,C), HBoV, RV, EV, RSV, PIV, HMPV, ADV, HCoV	203 (35.2%)	0 (0.0%)	8 (1.4%)	365 (63.4%)
Setiadi et al, 2022[170]	SARS- CoV-2	10130 (15.7%)	0 (0.0%)	Not Reported	54234 (84.3%)
Shih et al, 2015[157]	IV A, RV, EV, HMPV, HCoV, AV, RSV, PIV, EBV	126 (31.2%)	0 (0.0%)	137 (33.9%)	141 (34.9%)
Sundell et al, 2019[32]	*S. pneumoniae, H. influenzae, M. pneumoniae,* IV (A,B,C), HboV, RV, EV, RSV, PIV, HMPV, ADV, HCoV	56 (10.2%)	48 (8.7%)	0 (0.0%)	447 (81.1%)
Viera-Segura et al, 2021[171]	SARS- CoV-2	6918 (29.8%)	0 (0.0%)	Not Reported	16293 (70.0%)
Zimmerman et al, 2014[158]	AV, HCoV, IV, HMPV, RV, PIV, RSV	349 (52.7%)	0 (0.0%)	46 (6.9%)	267 (40.3%)

* IVAB = Influenza A or B, RSV = Respiratory syncytial virus, RV = Rhinovirus, hMPV = Human metapneumovirus, hCoV = Human Coronavirus, BV = Bocavirus, EV = Enterovirus, PIV = Parainfluenza virus, AV = Adenovirus

Table 5.3 Prevalence estimates of acute respiratory tract infection etiology

Etiology	Studies	Patients	Prevalence (95% CI)	Prevalence Range	I^2
Symptomatic					
Viral Etiology					
Influenza A or B	8	7903	0.102 (0.049, 0.172)	0.007 – 0.279	98.0 %
ARTI	4	2114	0.076 (0.003, 0.227)	0.007 – 0.210	99.0 %
LRTI	4	5789	0.132 (0.062, 0.222)	0.059– 0.279	95.0 %
Rhinovirus	7	7774	0.084 (0.054, 0.121)	0.042 – 0.202	94.0 %
ARTI	4	2114	0.053 (0.041, 0.067)	0.042 – 0.081	46.0 %
LRTI	3	5660	0.129 (0.095, 0.168)	0.102 – 0.202	75.0 %
Influenza A	4	1816	0.070 (0.011, 0.172)	0.004 – 0.210	98.0 %
ARTI	3	1452	0.073 (0.002, 0.224)	0.004 – 0.210	99.0 %
LRTI	1	364	0.063 (0.040, 0.093)		
Influenza B	3	1507	0.041 (0.000, 0.142)	0.004 – 0.126	98.0 %
ARTI	2	1143	0.045 (0.000, 0.234)	0.004 – 0.126	99.0 %
LRTI	1	364	0.033 (0.017, 0.057)		

Bocavirus	2	6171	0.030 (0.000, 0.153)	0.003 – 0.082	99.0 %
ARTI	1	596	0.082 (0.061, 0.107)		
LRTI	1	5167	0.003 (0.002, 0.006)		
Enterovirus	3	1034	0.030 (0.020, 0.042)	0.016 – 0.037	0.0 %
ARTI	2	905	0.033 (0.022, 0.046)	0.026 – 0.037	0.0 %
LRTI	1	129	0.016 (0.002, 0.055)		
Human Coronavirus*	6	7410	0.025 (0.011, 0.043)	0.007 – 0.045	91.0 %
ARTI	4	2114	0.018 (0.007, 0.034)	0.007 – 0.042	81.0 %
LRTI	2	5296	0.043 (0.038, 0.049)	0.039 – 0.045	0.0 %
Respiratory Syncytial Virus	7	7774	0.019 (0.011, 0.029)	0.004 – 0.041	79.0 %
ARTI	4	2114	0.014 (0.006, 0.026)	0.004 – 0.025	73.0 %
LRTI	3	5660	0.028 (0.020, 0.037)	0.016 – 0.041	25.0 %
Human Metapneumovirus	6	7645	0.015 (0.006, 0.026)	0.002 - 0.032	86.0 %
ARTI	4	2114	0.011 (0.003, 0.024)	0.002 – 0.032	80.0 %
LRTI	2	5531	0.025 (0.018, 0.032)	0.016 – 0.027	22.0 %

Parainfluenza Virus 1	1	309	0.010 (0.002, 0.028)		
Parainfluenza Virus	6	7112	0.009 (0.004, 0.016)	0.002 – 0.023	67.0 %
ARTI	3	1452	0.006 (0.001, 0.015)	0.002 – 0.013	54.0 %
LRTI	3	5660	0.013 (0.006, 0.032)	0.005 – 0.023	42.0 %
Adenovirus	3	6072	0.009 (0.005, 0.015)	0.008 – 0.019	45.0 %
ARTI	2	905	0.012 (0.004, 0.026)	0.008 – 0.019	49.0 %
LRTI	1	5167	0.008 (0.006, 0.011)		
Parainfluenza Virus 3	2	673	0.004 (0.000, 0.011)	0.003 – 0.005	0.0 %
ARTI	1	309	0.003 (0.000, 0.018)		
LRTI	1	364	0.005 (0.001, 0.020)		
SARS-CoV-2	3	95428	0.153 (0.059, 0.281)	0.047 – 0.298	100.0 %
Bacterial Etiology					
*Haemophilus influenzae**	7	6575	0.069 (0.037, 0.110)	0.018 – 0.198	93.0 %
ARTI	3	786	0.113 (0.008, 0.304)	0.018 – 0.198	97.0 %
LRTI	4	5789	0.044 (0.026, 0.066)	0.032 – 0.093	70.0%

Moraxella catarrhalis	4	732	0.069 (0.004, 0.192)	0.008 – 0.187	96.0 %
ARTI	2	239	0.175 (0.129, 0.227)	0.169 – 0.187	0.0 %
LRTI	2	493	0.010 (0.002, 0.021)	0.008 – 0.011	0.0 %
Streptococcus pneumoniae	7	6575	0.049 (0.029, 0.074)	0.013 – 0.116	86.0 %
ARTI	3	786	0.041 (0.005, 0.105)	0.013 – 0.110	88.0 %
LRTI	4	5789	0.058 (0.029, 0.095)	0.033 – 0.116	86.0 %
Mycoplasma pneumoniae	7	10733	0.031 (0.017, 0.050)	0.002 – 0.101	94.0 %
ARTI	3	4944	0.029 (0.002, 0.082)	0.002 – 0.098	97.0 %
LRTI	4	5789	0.034 (0.015, 0.059)	0.008 – 0.101	80.0 %
Bordetella pertussis	1	5167	0.018 (0.015, 0.022)		
Chlamydia pneumoniae	2	5531	0.017 (0.001, 0.051)	0.005 – 0.032	92.0 %
Staphylococcus aureus	1	364	0.005 (0.001, 0.020)		
Legionella pneumophilia	1	5167	0.001 (0.000, 0.003)		

Asymptomatic					
Viral Etiology					
Rhinovirus	3	6152	0.013 (0.006, 0.022)	0.002 – 0.026	60.0 %
Influenza A or B	2	5296	0.007 (0.000, 0.044)	0.001 – 0.023	88.0 %
Respiratory Syncytial Virus	2	5296	0.005 (0.000, 0.027)	0.002 – 0.016	77.0 %
Enterovirus	2	676	0.005 (0.000, 0.026)	0.002 – 0.016	68.0%
Human Coronavirus*	3	5843	0.004 (0.002, 0.007)	0.004 – 0.016	9.0 %
Adenovirus	1	5167	0.004 (0.003, 0.007)		
Bocavirus	2	5714	0.003 (0.001, 0.004)	0.002 – 0.003	0.0 %
Human Metapneumovirus	2	5714	0.001 (0.000, 0.002)	0.001 – 0.002	23.0 %
Parainfluenza virus	1	5167	0.001 (0.001, 0.003)		
SARS-CoV-2	1	23211	0.023 (0.021, 0.025)		
Bacterial Etiology					
Moraxella catarrhalis	2	239	0.150 (0.064, 0.263)	0.099 – 0.203	78.0 %
Streptococcus pneumoniae	3	786	0.116 (0.019, 0.276)	0.046 – 0.257	96.0 %

Haemophilus influenzae	3	786	0.090 (0.001, 0.279)	0.011 – 0.209	97.0 %
Chlamydia pneumoniae	1	129	0.008 (0.000, 0.042)		

*Human coronavirus detected does not include SARS-CoV-2. H. influenzae detected was not typable in all studies.

Table 5.4 Positive Etiologic Predictive Value (P-EPV) calculations with 95% confidence intervals (CI) of pathogens that were included in the meta-analysis for symptomatic and asymptomatic patients.

Pathogen	T+S+	T+S-	T-S+	T-S-	P-EPV (95% CI)
Influenza A or B	592	10	7311	5286	97.7 (95.6, 99.4) %
Human metapneumovirus	169	4	7476	5710	96.9 (92.0, 100.0) %
Respiratory syncytial virus	193	12	7581	5284	91.1 (82.4, 97.3) %
Parainfluenza virus	96	7	7016	5160	90.1 (76.2, 98.8) %
SARS-CoV-2	17421	536	78007	22675	89.7 (88.4, 90.8) %
Rhinovirus	798	88	6979	6064	87.2 (82.6, 91.0) %
Enterovirus	32	3	1002	673	86.1 (46.7, 100.0) %
Human coronavirus*	275	33	7135	5810	85.3 (76.2, 92.1) %
Bocavirus	67	17	5696	5697	74.6 (46.0, 90.9) %
Adenovirus	52	23	6020	5144	48.2 (0.00, 79.0) %

Chlamydia pneumoniae	167	1	5364	128	74.9 (0.0, 100.0) %
Haemophilus influenzae	254	47	6321	739	-58.3 (0.00, 7.4) %
Streptococcus pneumoniae	238	71	633	715	-164.6 (0.00, 100.00) %
Moraxella catarrhalis	47	39	685	200	-184.6 (0.0, 100.0) %

T = diagnostic test, S = symptoms

Table 5.5 Pearson's chi-square test for symptoms associated with adenovirus etiology compared to other viral etiology.

Clinical Symptoms	Adenovirus (N = 13725)	Other Viruses* (N = 11125)	OR (95% CI)	P value
Cough				
Yes	12559 (91.5 %)	8766 (78.8 %)	2.90 (2.69, 3.13)	<0.0001
No	1166 (8.5 %)	2359 (21.2 %)		
Headache				
Yes	11571 (84.3 %)	7743 (69.6 %)	2.35 (2.21, 2.50)	<0.0001
No	2154 (15.7 %)	3382 (30.4 %)		
Vomiting/ Diarrhea				
Yes	7135 (52.0 %)	3224 (29.0 %)	2.65 (2.52, 2.80)	<0.0001
No	6590 (48.0 %)	7901 (71.0 %)		
Dyspnea				
Yes	5010 (36.5 %)	2221 (20.0 %)	2.30 (2.17, 2.44)	<0.0001
No	8715 (63.5 %)	8904 (80.0 %)		
Fever (subjective or measured)				
Yes	11945 (87.0 %)	7359 (66.1 %)	3.43 (3.22, 3.66)	<0.0001
No	1780 (13.0 %)	3766 (33.9 %)		
Muscle pain/ Weakness				
Yes	9804 (71.4 %)	6056 (54.4 %)	2.09 (1.99, 2.21)	<0.0001
No	3921 (28.6 %)	5069 (45.6 %)		
Sore throat				
Yes	12771 (93.0 %)	5902 (53.1 %)	11.85 (10.98, 12.78)	<0.0001
No	954 (6.95 %)	5223 (46.9 %)		
Nasal congestion				
Yes	11223 (81.8 %)	3991 (35.9 %)	8.02 (7.57, 8.50)	<0.0001
No	2502 (18.2 %)	7134 (64.1 %)		

* Other viruses included influenza virus A or B (n = 3785), human metapneumovirus (n = 49), and SARS-CoV-2 (n = 7291)

CHAPTER 6

Determining Etiology of Acute Respiratory Tract Infections and Potential Commensalism in Outpatients: A Case-Control Study

INTRODUCTION

Acute respiratory infections (ARIs) are the most common reasons for visiting an outpatient setting[1]. ARIs can occur as upper respiratory tract infections (URTIs) or lower respiratory tract infections (LRTIs). The World Health Organization (WHO) and Centers for Disease Control (CDC) define acute respiratory tract infections based on the location of the infection and the symptoms associated. URTI diagnoses include pharyngitis, rhinosinusitis, otitis media, and rhinitis. Acute upper respiratory tract infections are caused by a virus and/or bacteria which produces acute inflammation of nasal and pharyngeal mucosa[3]. Symptoms of acute URTIs typically include mild cough, fever, fatigue, nasal congestion, sore throat, and swollen lymph nodes. LRTI diagnoses include community-acquired pneumonia (CAP) and non-pneumonia lower respiratory tract infections or acute bronchitis, as it is also known. Acute lower respiratory tract infections affect the lungs and typically cause cough and at least one of the following symptoms: sputum production, dyspnea, wheezing, or chest pain/discomfort. The median duration of lower respiratory symptoms is approximately 18 days[4].

Acute upper and lower respiratory tract infections can be caused by both bacterial and viral pathogens. Bacterial URTI diagnoses include streptococcal pharyngitis, pharyngitis caused by *Fusobacterium necrophorum*[5], bacterial rhinosinusitis, and bacterial otitis media. Bacteria commonly associated with both URTIs and LRTIs include *Streptococcus pneumoniae*

(pneumococcus), *Haemophilus influenzae*, and *Moraxella catarrhalis. Staphylococcus aureus* is a bacterium that is associated solely with LRTIs[6].

However, it is thought that some of these bacterial pathogens could be commensal and not pathogenic. Commensal bacteria are those that colonize the respiratory tract but are not associated with illness[7]. Bacteria that are suspected to be commensals in the respiratory tract, with the potential to become pathogenic, include *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*[8].

Viral URTI diagnoses include viral pharyngitis, viral rhinosinusitis, viral otitis media, and viral rhinitis. Viruses associated with URTIs and LRTIs include human rhinovirus, human metapneumovirus (hMPV), respiratory syncytial virus (RSV), influenza A and B viruses, parainfluenza virus, adenovirus, and coronavirus[6]. Bacterial LRTIs can include pneumonia and acute bronchitis. Viral LRTIs are viral pneumonia and viral acute bronchitis.

Multiple pathogens can be detected in an individual simultaneously. This brings into question which pathogen detected is likely causing symptoms of acute respiratory tract infection. The respiratory tract is colonized with bacteria and/or viruses, much like our skin. The commensal microbiome is housed primarily in the upper respiratory tract which includes the nasal cavity, nasal pharynx, and larynx[7]. The normal bacteria that colonize the respiratory tract are thought to be commensal or "healthy" and unlikely to cause harm[33]. In contrast, it is thought that the presence of these commensal organisms can assist the body with fighting new, opportunistic bacterial or viral pathogens that may cause invasive diseases[6,34]. Disruption of the respiratory tract commensal bacteria can lead to imbalances in the microbiota that can result in new bacterial or viral infection, multiple bacterial infections, or viral co-infections[6,35].

The aim of our case-control study is to identify pathogens that are likely causing ARI symptoms and identify organisms in the respiratory tract that are likely not causing disease.

METHODS

Settings

Data collection was conducted at outpatient clinic settings associated with the University of Georgia, Georgetown University, and University of Wisconsin were used as recruiting sites for symptomatic patients, suspected of having a lower respiratory tract infection. Farmers markets, university campuses and other community settings, associated with the previously mentioned universities and in the same geographical areas, were used as recruitment sites for asymptomatic, healthy participants.

Study Design

We conducted a prospective case-control study to identify etiology of acute respiratory tract infections among symptomatic persons compared with bacterial/viral nasopharyngeal findings among asymptomatic, healthy individuals. Symptomatic patients were recruited prospectively to participate in the Enhancing Antibiotic Stewardship in Primary Care Study (EAST-PC) between June 2018 and April 2023. Symptomatic participants were 18 to 75 years of age that presented to one of the settings with a cough lasting less than 14 days. In addition, they needed to have at least one of the following symptoms for inclusion: shortness of breath, sputum and phlegm production, body or muscle aches, chest discomfort with cough, chest congestion, fever (subjective or measured), and chills or sweats. Signs and symptoms of illness, pre-existing conditions, and demographic information were also obtained from these patients.

Asymptomatic, healthy individuals aged 18 to 75 years were recruited prospectively between September 2022 and April 2023. Participants were identified in medical clinics,

university campuses, and various community settings. Age, sex, and recruitment location were recorded for these individuals.

Nasopharyngeal and oropharyngeal swabs were taken at the time of recruitment for both symptomatic and asymptomatic individuals participating in the study. Swabs were stored in viral transport media (VTM) in sub-zero freezers until time for testing. Testing was conducted using polymerase chain reaction (PCR) at the Centers for Disease Control and Preventions. A list of the organisms that were included in the PCR panel can be found in Appendix B, Table B1. This study was approved by the University of Georgia Internal Review Board (IRB) and Western Internal Review Board (WIRB). The EAST-PC study is funded by a research grant from the Agency for Healthcare Research and Quality (AHRQ) through the Department of Health and Human Services (HHS).

Analysis

Bivariate analysis was conducted using Pearson's chi squared (X^2) to determine if there is a significant difference in the prevalence of certain pathogens between symptomatic and asymptomatic patients. The mean PCR cycle threshold (C_T) was recorded for all samples. Cycle thresholds were categorized into categories based on their likelihood of pathogenicity. C_T values greater than 34 were defined as low pathogenicity. C_T values greater than 28 or less than or equal to 34 were defined as moderate pathogenicity. C_T values less than or equal to 28 were defined as high pathogenicity.

We assessed the clinical relevance of any statistical differences between the bacterial and/or viral pathogens being carried by symptomatic and asymptomatic persons by calculating the positive etiologic predictive value (P-EPV) and 95% confidence interval. The P-EPV is the probability of finding an association between symptomatic lower respiratory tract infections and

bacterial and/or viral pathogens[137]. Based on our study design, we assumed that the sensitivity of the PCR test used was 99%[153,154]. P-EPV will range from 0 – 100%. If a bacterial and/ or viral organism was found equally often in symptomatic and asymptomatic individuals, the estimated P-EPV was 0% and as such we assumed that it was likely to be commensal. If the difference in the prevalence of pathogens identified between both groups increased, the P-EPV approached 100%. A value of 100% for P-EPV meant the pathogen was only identified in symptomatic persons. A continuity correction of 1 was used in instances where there was a zero value for a positive test with no symptoms. The equation used to calculate P-EPV is provided in Appendix B[144]. All analyses were conducted in STATA 18/SE.

RESULTS

Participant Characteristics

Demographic characteristics of symptomatic and asymptomatic participants can be found in Table 6.1 and Appendix B, Tables B2 and B3. The average age of symptomatic patients was 39.4 years (18 – 74) and asymptomatic individuals was 36.8 years (18 – 74). Female sex accounted for 66.5 percent of our study population. These statistics were consistent across both groups. White race was the most common among symptomatic (76.4 %) and asymptomatic persons (74.9 %). Only 11.4 percent of symptomatic patients and 8.2 % of healthy individuals were Hispanic. Most symptomatic patients (60.5%) were recruited in the Washington D.C. area and 45.3% of asymptomatic participants were recruited in Athens, Georgia. Over half of asymptomatic individuals (63.9%) responded that their most recent antibiotic use was more than one year from when they were recruited.

Etiologic Prevalence in Study Population

Summary estimates of etiologic prevalence for symptomatic and asymptomatic groups are shown in Table 6.2 and Appendix B, Table B4. Overall, viruses were identified most often (28.3%) in symptomatic patients when compared to other infection types. The most common viruses in the symptomatic group included rhinovirus, influenza A and B, and SARS-CoV-2. Bacterial pathogens were detected in 28.0 percent of symptomatic individuals, most commonly *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*.

Asymptomatic individuals were carriers of bacterial pathogens (30.6%) more often than viral pathogens (11.5%). The most identified bacteria in this group were *Staphylococcus aureus, Haemophilus influenzae, and Streptococcus pneumoniae.* Viral organisms detected among asymptomatic participants included rhinovirus and seasonal human coronavirus (all types but not including SARS-CoV-2). No etiology was detected in 15.4% of symptomatic and 53.1% of asymptomatic nasal and oropharyngeal swabs collected in our study population.

Determining Commensalism (P-EPV)

The overall positive etiologic predictive values (P-EPV) for viruses and bacteria that were present in the symptomatic and asymptomatic groups are included in Tables 6.3 and 6.4. Among viruses, influenza A and B virus, parainfluenza virus, SARS-CoV-2, human metapneumovirus, and respiratory syncytial virus were detected in symptomatic patients only and as such were determined to always be pathogenic with a P-EPV value near 100.0%. Other viral etiologies that were determined to usually be pathogenic, as they were present in symptomatic participants more frequently than asymptomatic participants were adenovirus, rhinovirus, and enterovirus. These etiologies had P-EPVs that were greater than 40%. There were only two viral etiologies that had the potential to be commensal as they were present more often

in healthy participants than patients with symptomatic acute lower respiratory tract infections. These viruses included cytomegalovirus and human coronavirus (all types) with a P-EPV less than or equal to 0%.

Among bacteria, Group A *streptococcus*, *Moraxella catarrhalis,* and *Mycoplasma pneumoniae* bacteria were detected in symptomatic patients only and as such were determined to be pathogenic with a P-EPV value greater than 50%. *Pseudomonas aeruginosa, Chlamydia pneumoniae, Hemophilus influenzae,* and *Bordetella* (all types) are also usually pathogenic with P-EPVs greater than 20%. There were eight bacterial etiologies that had the potential to be commensal with P-EPVs approaching or less than 0%. These bacteria were Group B streptococcus, *Streptococcus pneumoniae*, *Ureaplasma urealyticum, Pneumocysitis jirovecii*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Staphylococcus aureus*, and *Ureaplasma parvum*. However, it is important to note that negative values for the P-EPV are not interpretable according to its developer (personal communication, R. Gunnarsson).

The mean polymerase chain reaction (PCR) cycle threshold (C_T) was recorded for all samples collected. The etiologic predictive values (P-EPV) for viruses and bacteria that were present in symptomatic and asymptomatic groups with a C_T less than 34 are included in Table 6.4. A cycle threshold less than 34 was determined to be indicative of a higher likelihood of pathogenicity[172,173]. Similar trends for pathogenicity were seen for the subset of individuals with C_T values less than 34 except for human coronavirus (all types). With a P-EPV of -1.3 (0.0, 85.8) %, this viral etiology could potentially be commensal.

DISCUSSION

The objective of our prospective case-control study was to identify viral and/ or bacterial organisms that were associated with symptomatic acute respiratory infections (ARTIs) in

outpatients. Furthermore, we wanted to determine organisms detected in asymptomatic individuals that could possibly be associated with disease but could also be commensal. We were able to identify trends in pathogenicity when comparing organisms identified in symptomatic patients to those detected in asymptomatic individuals. Overall, we found that viral pathogens were more prevalent in symptomatic patients than asymptomatic patients. In our study population, rhinovirus, influenza virus, and SARS-CoV-2 were the most common viral organisms detected. These organisms are highly likely to be pathogenic because they are more much common in symptomatic individuals compared to asymptomatic individuals. *Hemophilus influenzae*, *Moraxella catarrhalis*, and Staph*ylococcus aureus* were the most common bacterial pathogens detected in symptomatic and asymptomatic groups. Group B streptococcus, *Streptococcus pneumoniae*, *Ureaplasma urealyticum, Pneumocysitis jirovecii*, *Klebsiella pneumoniae, Acinetobacter baumanii*, *Staphylococcus aureus,* and *Ureaplasma parvum* were determined to potentially be commensal but could become invasive and cause disease.

Comparison to current literature

There are some similarities and differences in our study findings when compared to results of similar studies. Based on our study population, seasonal human coronavirus (all types) was detected almost as often in symptomatic patients as in asymptomatic individuals when the data was limited to those with low or moderate cycle times ($C_T \leq 34$). This result differs greatly from previous findings that human coronavirus is highly associated with being a common cause of symptomatic acute respiratory tract infections[174,175]. Human coronavirus types one and three were most likely to be pathogenic with P-EPVs of 62.3%. However, based on P-EPV estimates, human coronaviruses type two (-52.4%) and four (-286.7%) were more likely to be commensal. It has been estimated that up to 30% of cold-like illnesses for which symptomatic patients seek

care are due to human coronavirus infections[176,177]. The differences found in our study could be a result of the natural recombination of genomic sequences overtime coupled with changes in the host immune system, specifically when looking at our findings for human coronaviruses type two and four[176,178,179]. This idea is supported by a 2020 cohort study that found infection rates for seasonal coronaviruses are higher amongst children under 5 years, who are less likely to have developed any protective immunity against these viruses[180,181]. Studies on seasonality of respiratory viruses suggest that human coronaviruses one and three follow a seasonal pattern with high circulation in winter and spring. Likewise, these coronavirus types are more prevalent compared to type two and four[182].

Similarly, *Klebsiella pneumoniae* were found almost as often in symptomatic and asymptomatic individuals. This is consistent with our current knowledge of *Klebsiella* organisms[183–186]. *Klebsiella pneumoniae* and all *Klebsiella species* are primarily opportunistic pathogens that affect individuals with weakened immune systems and as such have been identified as a leading cause of nosocomial infections[187–190]. *K. pneumoniae* is best known in the outpatient setting as a cause of bacterial community - acquired pneumonia[188,189,191,192]. While *K. pneumoniae* is highly virulent it can also be a commensal organism. An Indonesian study found that in healthy adults, *K. pneumoniae* carriage was roughly 15 percent. This study focused on socioeconomic factors associated with carriage and determined that age and poor food and water hygiene were determinants of nasopharyngeal colonization[193]. Research done in mice also found that colonization and pathogenesis of *K. pneumoniae* could depend on the host microbiota present[194].

Streptococcus pneumoniae was also found almost as often in symptomatic and asymptomatic individuals in our study population, meaning it is a commensal organism despite

its association with diseases such as otitis media, pneumonia, sepsis, and meningitis[195–197]. *S. pneumoniae* has been detected as a commensal colonizer of the human upper respiratory tract but the prevalence is generally low (<10%) in adult populations[198,199]. Like human coronavirus, *S. pneumoniae* can remodel its genome to become resistant to antibiotics allowing it to colonize and become pathogenic. However, there has been some decline in high *S. pneumoniae* carriage and transmission due to the development of the pneumococcal conjugate vaccine (PCVs)[200]. *S. pneumoniae* pathogenesis can also be influenced by an individual's microbiota much like *K. pneumoniae*. For instance, a study done in mice found that *S. pneumonia* viral co-infections could result in a higher density of the bacteria in the nasal cavity[201–203].

Strengths and limitations

Our study did have some limitations. First, symptomatic patients were recruited over a longer period and more consistently in comparison to the asymptomatic group. Certain organisms, like influenza, have detection that can be variable based on the time of year. The data in this study might underestimate viral and bacterial carriage in the asymptomatic group. Additionally, the varying timeframes likely introduced selection bias. While the symptomatic group were recruited prospectively over time in a clinic setting, asymptomatic persons were recruited by convenience sampling in community settings that had similar groups of people (i.e. college students and college faculty/ staff members). Therefore, the data in this study may not be truly representative of the population. Future research should consider initiating case and control recruitment at the same time and continue for the same length of time. Cases and controls should also be recruited from the same settings, if possible.

Despite these limitations, our study did have some strengths. We used a prospective design which allows us to draw conclusions more accurately about causality between pathogens

and acute respiratory tract infections. Symptomatic and asymptomatic groups were recruited from similar source populations reducing selection bias. Additionally, symptomatic patients and healthy controls were recruited using the same inclusion criteria and the groups only differed by the presence of the outcome of interest. This made the groups demographically comparable and reducing confounding in our interpretation. Nasopharyngeal swabs were all sampled and tested using identical lab procedures. This reduces sampling and confirmation bias which strengthens the interpretation of results across our study groups.

Conclusion

From our research we were able to identify viral and bacterial organisms that were associated with symptomatic acute respiratory infections (ARTIs). When found in the respiratory tract, viruses such as influenza viruses, parainfluenza, SARS-CoV-2, human metapneumovirus, RSV, adenovirus, rhinovirus, and enterovirus are most often or usually pathogenic. Bacteria such as Group B streptococcus, *Streptococcus pneumoniae*, *Ureaplasma urealyticum, Pneumocysitis jirovecii*, *Klebsiella pneumoniae, Acinetobacter baumanii, Staphylococcus aureus,* and *Ureaplasma parvum* could be commensal when they do not colonize at a high density. However, due to some of our limitations, there is little evidence to make causal claims about these associations. There is a clear need for more studies that aim to include symptomatic and asymptomatic groups to determine the etiologies of upper and lower acute respiratory tract infections. This information is important to better understand the human pathogenesis of certain organisms like *K. pneumoniae* and *S. pneumoniae*. Furthermore, this research can be used to guide prescribing practices for ARTIs. As our findings suggest that symptomatic ARTIs are most often viral, there is no indication for antibiotic prescribing. In cases where clinicians believe a bacterial etiology might be present, antibiotics can be prescribed with a delayed start if

symptoms persist. Lastly, our research findings can also guide the interpretation of multi-pathogen PCR results in outpatients. In PCR results that detect viral pathogens they are likely the cause of disease even if accompanied by bacterial organisms. Bacterial organisms identified by PCR of individuals who are otherwise healthy are likely part of the normal human microbiota.

TABLES AND FIGURES

Table 6.1 Demographics of study participants with valid nasopharyngeal samples

	Symptomatic (N = 618)	**Asymptomatic (N = 497)**	**Total (N = 1115)**
Age *Mean (Range)*	39.2 (18 - 74)	36.8 (18 – 74)	38.0 (18 – 74)
Sex			
Male	205 (33.3%)	153 (31.4.2%)	358 (32.1%)
Female	408 (66.2%)	333 (68.2%)	741 (66.5%)
Other	3 (0.5%)	2 (0.4%)	5 (0.4%)
Race			
White	472 (76.4%)	367 (74.9%)	839 (75.2%)
Asian/Pacific Islander	63 (10.2%)	32 (6.5%)	95 (8.5%)
Black	43 (7.0%)	57 (11.6%)	100 (8.9%)
American Indian/Alaska Native	4 (0.7%)	4 (0.8%)	8 (0.7%)
No Race	25 (4.0%)	17 (3.5%)	42 (3.8%)
Other	12 (1.9 %)	13 (2.6%)	25 (2.2%)
Ethnicity			
Non-Hispanic	529 (86.2%)	437 (89.6%)	966 (86.6%)
Hispanic	70 (11.4 %)	40 (8.2%)	110 (9.9%)
Prefer not to answer	15 (2.4%)	11 (2.3%)	26 (2.3%)

Table 6.2 Etiology data of study participants and bivariate analysis

Organism	Symptomatic N = 618	Asymptomatic N = 497	X^2	P - value
Viral Etiology				
Rhinovirus	107 (17.3%)	17 (3.4%)	51.02	< 0.001
Influenza ANY	79 (12.8%)	0 (0.0%)	68.4	< 0.001
Influenza A	54 (7.5%)	0 (0.0%)	44.75	< 0.001
Influenza B	25 (3.5%)	0 (0.0%)	20.57	< 0.001
SARS-CoV-2	68 (9.5%)	7 (0.0%)	40.42	< 0.001
Human coronavirus ANY	50 (8.1%)	10 (2.0%)	15.34	< 0.001
Human coronavirus 1	7 (1.1%)	2 (0.4%)	1.31	0.253
Human coronavirus 2	12 (1.9%)	2 (0.4%)	4.15	0.042
Human coronavirus 3	23 (3.7%)	0 (0.0%)	16.23	<0.001
Human coronavirus 4	8 (1.3%)	6 (1.2%)	0.02	0.881
Parainfluenza virus ANY	21 (3.4%)	0 (0.0%)	17.21	< 0.001
Parainfluenza virus type 2	3 (0.5%)	0 (0.0%)	2.42	0.120
Parainfluenza virus type 3	14 (2.3%)	0 (0.0%)	11.40	0.001
Parainfluenza virus type 4	4 (0.7%)	0 (0.0%)	3.23	0.072
Human Metapneumovirus	18 (2.9%)	0 (0.0%)	14.71	< 0.001
Respiratory syncytial virus	18 (2.9%)	0 (0.0%)	14.71	< 0.001
Enterovirus	4 (0.7%)	0 (0.0%)	3.23	0.072
Adenovirus	7 (1.1%)	0 (0.0%)	5.67	0.017
Cytomegalovirus	0 (0.0%)	1 (0.2%)	1.24	0.265

Bacterial Etiology				
Haemophilus influenzae (All types)	173 (28.0%)	53 (10.7%)	51.2	< 0.001
Moraxella catarrhalis	100 (16.2%)	19 (3.8%)	44.13	< 0.001
Staphylococcus aureus	96 (15.5%)	109 (21.9%)	7.51	0.006
Streptococcus pneumoniae	63 (10.2%)	41 (8.2%)	1.23	0.267
Klebsiella pneumoniae	17 (2.8%)	15 (3.0%)	0.07	0.790
Group B Strep	14 (2.4%)	6 (1.2%)	2.22	0.136
Group A Strep (*Streptococcus pyogenes*)	12 (2.1%)	2 (0.4%)	5.26	0.022
Acinetobacter baumanii	9 (1.5%)	8 (1.6%)	0.04	0.835
Mycoplasma pneumoniae	5 (0.8%)	0 (0.0%)	4.04	0.044
Pseudomonas aeruginosa	5 (0.8%)	2 (0.4%)	0.73	0.393
Chlamydia pneumoniae	4 (0.7%)	0 (0.0%)	3.23	0.072
Bordetella ANY	3 (0.5%)	1 (0.2%)	0.62	0.430
Bordetella (IS481)	1 (0.2%)	1 (0.2%)	0.02	0.877
Bordetella pertussis toxin	1 (0.2%)	0 (0.0%)	0.80	0.370
Bordetella (IS1001)	1 (0.2%)	0 (0.0%)	0.80	0.370
Pneumocysitis jirovecii	2 (0.3%)	3 (0.6%)	0.48	0.487
Ureaplasma urealyticum	2 (0.3%)	2 (0.4%)	0.05	0.827
Ureaplasma parvum	1 (0.2%)	4 (0.8%)	2.55	0.110

Table 6.3 Positive Etiologic Predictive Value (P-EPV) calculations with 95% confidence intervals (CI) of pathogens identified in symptomatic and asymptomatic patients.

Organism	T+S+	T-S+	T+S-	T-S-	P-EPV (95% CI)
Viral Etiology					
Influenza virus (All types)	79	539	0	497	98.6 (94.0, 100.0) * %
Influenza A	54	564	0	497	97.9 (90.1, 100.0) * %
Influenza B	25	593	0	497	95.2 (71.8, 100.0) * %
Parainfluenza virus (All types)	21	597	0	497	94.3 (63.5, 100.0) * %
Parainfluenza virus type 2	3	615	0	497	58.7 (0.0, 100.0) * %
Parainfluenza virus type 3	14	604	0	497	91.3 (29.7, 100.0) * %
Parainfluenza virus type 4	4	614	0	497	69.1 (0.0, 100.0) * %
Human Metapneumovirus	18	600	0	497	93.3 (53.7, 100.0) * %
Respiratory syncytial virus	18	600	0	497	93.3 (53.7, 100.0) * %
SARS-CoV-2	68	550	7	490	88.5 (70.2, 98.6) %
Rhinovirus	107	511	17	480	83.8 (65.8, 93.8) %
Adenovirus	7	611	0	497	82.4 (0.0, 100.0) * %
Human coronavirus (All types)	50	568	10	487	76.7.12 (40.7, 94.9) %

Human coronavirus 1	7	611	2	495	64.7 (0.0, 100.0) %
Human coronavirus 2	12	606	2	495	79.6 (0.0, 100.0) %
Human coronavirus 3	23	595	0	497	94.8 (68.1, 100.0) * %
Human coronavirus 4	8	610	6	491	6.82 (0.0, 95.4) %
Enterovirus	4	614	0	497	69.1 (0.0, 100.0) * %
Cytomegalovirus	0	618	1	496	0.0 (0.0, 0.0) %
Bacterial Etiology					
Group A Streptococcus (*Streptococcus pyogenes*)	12	605	2	495	79.6 (0.0, 100.0) * %
Moraxella catarrhalis	100	518	19	478	79.5 (58.7, 92.0) %
Mycoplasma pneumoniae	5	613	0	497	75.3 (0.0, 100.0) * %
Chlamydia pneumoniae	4	614	0	497	69.1 (0.0, 100.0) * %
Haemophilus influenzae (All types)	173	545	53	444	62.5 (38.2.5, 78.7) %
Bordetella (All types)	3	615	1	496	58.7 (0.0, 100.0) %
Bordetella pertussis toxin	1	617	0	497	-24.4 (0.0, 100.0) * %
Bordetella (IS1001)	1	617	0	497	-24.4 (0.0, 100.0) * %

Bordetella (IS481)	1	617	1	496	-24.4 (0.0, 100.0) %
Pseudomonas aeruginosa	5	613	2	495	50.5 (0.0, 100.0) %
Group B Streptococcus	14	604	6	491	47.3 (0.0, 97.1) %
Streptococcus pneumoniae	63	555	41	456	20.8 (0.0, 60.9) %
Klebsiella pneumoniae	17	601	15	482	-10.0 (0.0, 70.2) %
Acinetobacter baumanii	9	609	8	489	-10.7 (0.0, 86.7) %
Ureaplasma urealyticum	2	616	2	495	-24.5 (0.0, 100.0) %
Staphylococcus aureus	96	522	109	388	-52.9 (0.0, 6.6) %
Pneumocysitis jirovecii	2	616	3	494	-87.1 (0.0, 100.0) %
Ureaplasma parvum	1	617	4	493	-400.6 (0.0, 100.0) %

T = diagnostic test, S = symptoms

*Continuity correction of 1 was used for instances where T+S- = 0 to avoid dividing by 0.

Table 6.4 Positive Etiologic Predictive Value (P-EPV) calculations with 95% confidence intervals (CI) of pathogens with low and moderate cycle times ($C_T \leq 34$) among symptomatic and asymptomatic participants.

Organism	T+S+	T-S+	T+S-	T-S-	P-EPV (95% CI)
Viral Etiology					
Influenza virus (All types)	77	390	0	205	97.5 (88.9, 100.0) * %
Influenza virus A	52	415	0	205	96.1 (81.3, 100.0) * %
Influenza virus B	25	442	0	205	91.3 (48.5, 100.0) * %
Parainfluenza virus (All types)	20	447	0	205	89.1 (28.2, 100.0) * %
Parainfluenza virus 2	2	465	0	205	-14.0 (0.0, 100.0) * %
Parainfluenza virus 3	14	453	0	205	84.1 (0.0, 100.0) * %
Parainfluenza virus 4	4	463	0	205	43.3 (0.0, 100.0) * %
SARS-CoV-2	66	401	4	201	87.9 (63.5, 100.0) %
Human Metapneumovirus	14	453	0	205	84.1 (0.0, 100.0) * %
Respiratory syncytial virus	14	453	0	205	84.1 (0.0, 100.0) * %
Adenovirus	7	460	0	205	67.8 (0.0, 100.0) * %
Rhinovirus	97	370	17	188	66.2 (27.8, 88.0) %

Enterovirus	4	463	0	205	43.3 (0.0, 100.0) * %
Cytomegalovirus	0	467	1	204	0.0 (0.0, 0.0) %
Human coronavirus (All types)	18	449	8	197	-1.30 (0.0, 85.8) %
Human coronavirus 1	6	461	1	204	62.3 (0.0, 100.0) %
Human coronavirus 2	3	464	2	203	-52.4 (0.0, 100.0) %
Human coronavirus 3	6	461	0	205	62.3 (0.0, 100.0) * %
Human coronavirus 4	3	464	5	200	-286.7 (0.0, 98.3) %
Bacterial Etiology					
Group A Streptococcus (*Streptococcus pyogenes*)	12	457	2	203	62.5 (0.0, 100.0) %
Moraxella catarrhalis	97	370	19	186	61.7 (19.7, 85.6) %
Mycoplasma pneumoniae	5	462	0	205	54.7 (0.0, 100.0) * %
Pseudomonas aeruginosa	4	463	1	204	46.6 (0.0, 100.0) %
Chlamydia pneumoniae	4	463	0	205	43.3 (0.0, 100.0) * %
Hemophilus influenzae (All types)	164	303	51	154	40.3 (0.0, 68.6) %
Bordetella (All types)	3	464	1	204	24.2 (0.0, 100.0) %

Bordetella pertussis toxin	1	466	1	204	-128.50 (0.0, 100.0) %
Bordetella (IS1001)	1	466	0	205	-128.50 (0.0, 100.0) * %
Bordetella (IS481)	1	466	0	205	-128.50 (0.0, 100.0) * %
Group B Streptococcus	12	455	5	200	5.2 (0.0, 99.4) %
Streptococcus pneumoniae	58	409	25	180	2.1 (0.0, 60.1) %
Ureaplasma urealyticum	2	465	1	204	-14.0 (0.0, 100.0) %
Pneumocysitis jirovecii	2	465	2	203	-129.2 (0.0, 100.0) %
Klebsiella pneumoniae	14	453	14	191	-138.3 (0.0, 40.8) %
Acinetobacter baumanii	5	462	6	199	-179.2 (0.0, 86.7) %
Staphylococcus aureus	90	377	105	100	-384.7 (0.0, 100.0) %
Ureaplasma parvum	1	466	3	202	-593.1 (0.0, 100.0) %

T = diagnostic test, S = symptoms

*Continuity correction of 1 was used for instances where T+S- = 0 to avoid dividing by 0.

CHAPTER 7

Identifying Predictors of Care-Seeking Behavior for Acute Respiratory Tract Infection in College Students

INTRODUCTION

Upper respiratory illnesses are common among college students and are a substantial cause of morbidity despite them being a generally healthy demographic[107]. Research conducted in 2006 found that 83% of its study population, composed of college students, self-reported experiencing at least one "cold" and 36.7% experienced an influenza like illness (ILI) between the months of November and April[108]. With these illnesses, students stated they not only felt the negative effects from the symptoms associated with their illnesses, but they were unable to perform regular activities, missed class and work, and missed extracurricular activities[108]. Another study found that the most detected pathogens amongst this group were influenza A, parainfluenza 1, rhinovirus, adenovirus, group A streptococci, and *M. pneumoniae.* College students, especially undergraduates, live in environments where transmission of acute upper and lower respiratory tract infections may be more likely. Student living typically consists of congregate settings such as dormitories or apartment buildings in which they share a space with one or more roommates. Living in close contact with others in small spaces in addition to stressful workloads, lack of sleep, lack of adherence to preventive measures, and attending social activities in large group settings could put students at increased risk for acute respiratory tract infections.

Research on the care seeking behaviors of college students for acute respiratory tract infections (ARTIs) is limited. While this age group is not thought to be at increased risk of

adverse outcomes from ARTIs, university students must make their own medical decisions (typically for the first time) when they are away at school. The decisions they make regarding seeking medical care for ARTIs may be based on their perceptions of the severity of their symptoms, the length of their symptoms, and their perceived need for a prescription. Further research is needed to understand why college students seek care and/or treatment for ARTIs, to be able to tailor interventions to reduce inappropriate antibiotic use and improve the appropriateness of healthcare visits. This is important because college is the first environment where young adults are given the opportunity to make healthcare decisions on their own and is the foundation for life-long care seeking habits. Our goal is to identify signs and symptoms of ARTIs that influence students to seek care at the University of Georgia (UGA).

METHODS

To address our goal of identifying signs and symptoms of acute respiratory tract infections (ARTIs) among young adults that influence them to seeking care and to describe trends in their care seeking behavior, we utilized three data sources. These data sources include, a vignette survey distributed to UGA students, UGA health center electronic records, and a subset of young adult data obtained from the Enhancing Antibiotic Stewardship in Primary Care study.

Setting and Population

Data collection was conducted at the University of Georgia and UGA's University Health Center (UHC) located in Athens, Georgia. According to the 2023 University of Georgia Admissions Statistics, there are 40,118 students currently enrolled at the university, of whom 30,166 are undergraduate students, and 9,952 are graduate students[204]. All students at the University of Georgia have access to the campus's University Health Center. The health center

provides a variety of healthcare services including primary care. The health center has its own on-site pharmacy, laboratory, and radiology capabilities. This population is ideal for our study as it captures a large young adult population that can be easily contacted via email. Additionally, this population has access to expansive healthcare services for ARTIs which utilizes an electronic health record (EHR) that stores information for each student encounter and can be used to generate reports.

Study Design

We conducted a cross-sectional study and retrospective cohort study in students at UGA. This study was approved by the University of Georgia Internal Review Board (IRB). The outcomes of interest were seeking care and seeking antibiotic treatment. Seeking care and antibiotic treatment were defined by a rank scale based on students' perceptions of theoretical ARTI cases. Seeking care was investigated further using student electronic health record responses. To be included in the study, participants had to be at least 18 years of age and be enrolled at UGA for both Fall 2022 and Spring 2023.

Data Collection – Vignette Survey

To capture information on predictors for students' care seeking behavior for upper and lower respiratory tract illnesses, and sore throat, we created a survey using Qualtrics. The Qualtrics survey consisted of 12 vignettes that differed systematically on the severity of the scenario and the symptoms included. Students were asked to respond to only 4 randomly assigned vignettes. Protocols, consent forms, and the survey were approved by UGA's IRB before data collection started. The consent letter and survey that were provided to participants can be found in Appendix C.

We contacted students by obtaining a list of email addresses for all students enrolled at UGA for the Fall 2022 semester. Our email included a description of our study, the inclusion criteria, consent information, and a link to the survey. To complete the survey, students had to answer questions to confirm that they met our inclusion criteria and that they agree to participate in the study. Students that did not meet the inclusion criteria or did not wish to participate were excluded from the analysis. The student participation email was sent on September 19, 2022, and remained open for one month.

Data Collection - Electronic Health Record Questionnaire

To investigate reasons that UGA students sought care at the University Health Center (UHC), we obtained de-identified data from the UHC electronic health record (EHR) questionnaire. This questionnaire is a required form for any student that makes an appointment at UHC for a respiratory illness. The protocol for this study was approved by the UGA IRB. This project was defined as a non-human subjects research as we requested no identifying data and as such, did not require informed consent. The snapshots of the EHR questionnaire are included in Appendix C.

With the assistance of UHC personnel, we obtained batch data in a Microsoft Excel report that contained a list of all student responses to the respiratory illness questionnaire from November 2, 2022, to January 31, 2022. To be included in the report, students had to be enrolled at UGA for both Fall 2022 and Spring 2023 semesters. To complete the questionnaire, students had to make an appointment at UHC and choose that respiratory illness was their chief complaint.

Data Collection – Enhancing Antibiotic Stewardship in Primary Care Study

Symptomatic patients were recruited prospectively to participate in the Enhancing Antibiotic Stewardship in Primary Care Study (EAST-PC) between June 2018 and April 2023. Symptomatic participants were 18 to 75 years of age that presented to one of the settings with a cough lasting less than 14 days. In addition, they needed to have at least one of the following symptoms for inclusion: shortness of breath, sputum and phlegm production, body or muscle aches, chest discomfort with cough, chest congestion, fever (subjective or measured), and chills or sweats. Upon enrollment in our study, symptomatic patients were asked to describe their expectation for how long their cough would last and to indicate from a prespecified list why they sought care for their illness.

Analysis

Vignette Survey Analysis

All survey analysis was done using STATA version 18/SE statistical software. Exploratory data analysis was done first to identify any necessary data cleaning. Then an item analysis was done for each variable to assess for missing data. Responses on the numeric scale for seeking care and antibiotics were analyzed as categorical variables ranging from 1 (extremely unlikely) to 5 (extremely likely). Agreeing to seek care or antibiotic was defined by a response of somewhat likely or extremely likely. Disagreeing to seek care or antibiotic was defined by a response of neutrality, somewhat unlikely, or extremely unlikely. Symptoms included or excluded from vignettes were defined as categorical variables. We began our analysis by assessing trends of student responses based on vignette severity. This was achieved by conducting bivariate analysis of student binary responses (agree vs disagree) to seeking care or

seeking antibiotic treatment based on vignette severity by condition described (URTI, sore throat, and LRTI). We also determined the frequency these responses.

Pairwise correlation analysis was conducted using the pwcorr command in STATA to identify variables that were highly correlated and likely to result in collinearity. Bivariate analysis was conducted using the tabulate command to determine the association between independent and dependent variables. Variables with a p-value less than 0.2 in bivariate analysis were included in multivariate model. Multivariate analysis was conducted using stepwise backwards selection logistic regression for each condition (URTI, sore throat, and LRTI) for the outcomes of seeking care or seeking an antibiotic. P-values that were included in the summary statistics of the regression model were reviewed to determine if the independent predictors included in the model significantly contribute to seeking care or antibiotic treatment. Independent predictors that could be included in the model were fever, cough, sputum production, chest pain with cough, sore throat, swollen glands, nasal discharge, face pain, duration of symptoms, sex, race, ethnicity, year in school, and recent antibiotic usage. For this analysis, our dependent variables were agreeing or disagreeing to seek care and seek antibiotic treatment. Variables with p-values less than 0.05 were deemed statistically significant for being an independent predictor of college students seeking care or seeking antibiotic treatment for a respiratory tract infection.

University Health Center Questionnaire Qualitative Analysis

We determined the most common symptoms with which patients present to the clinic by quantifying the yes or no responses from the University Health Center (UHC) respiratory illness questionnaire. We also calculated the mean and median number of days the patients have been experiencing these symptoms prior to scheduling an appointment at the health center. Responses

for the severity of cough, body aches, and weakness were also quantified to determine the student's perception of the severity of their illness. All descriptive analysis was conducted using STATA 18/SE. NVivo qualitative analysis software was used to identify themes in the health center's open-ended question regarding the evolution of a students' respiratory illness. We used the content of these questionnaires to better understand individual factors that commonly lead to students making appointments for respiratory tract infections[147].

Enhancing Antibiotic Stewardship in Primary Care Descriptive Analysis

Supplementary descriptive analysis was done using data obtained from individuals enrolled in the Enhancing Antibiotic Stewardship in Primary Care study. For our analysis we utilized a subset of the data that contained only responses from young adults aged 18 – 30 years. From this data we calculated the mean and median number of days that patients expected their cough to last with or without an antibiotic. Responses to a prespecified list of options for seeking care were also quantified. Analysis of this data was done using STATA 18/SE.

RESULTS

Study population for survey

A flow diagram of student participation is included in Figure 7.1. Emailed invitations were sent to 40,454 students. Overall, 2,664 students began the survey and 2070 consented to participation. Among those who consented to participation, 6 were not at least 18 years of age, and therefore they did not meet our inclusion criteria and were excluded. There were 64 students who consented to participation, but then chose not to complete the survey. In total, 2,000 UGA students completed the survey.

Survey participant characteristics

Characteristics of participating students including demographics, year in school, and history of recent antibiotic usage are included in Table 7.1. The average age of the study population was about 21 years old. This was comparable to the student population, as of the Fall 2021 semester, with an average age of 22 years. About 75 percent of participants were female, 74.7 percent were of white race, and approximately 7 percent of participants were Hispanic. Overall, the UGA student body is about 60 percent female, 66 percent white race, and 7.5 percent Hispanic. Graduate students consisted of 27.9% of survey responses which closely approximates the UGA population of graduate students (25%). However, only 14 percent of our population were undergraduate year 4 and 5 students. This is less than the UGA population of 26 percent for that group. Less than half (41.3%) of participants responded that their most recent antibiotic use was more than one year from the time that they completed the survey[205].

Vignette Symptoms and Care Seeking Decisions

Upon consenting to participation, participants were randomly assigned to read and complete questions for three vignettes. The frequency data of these responses can be found in Appendix C, Tables C1 and C2. Vignettes were designed to represent possible symptom scenarios for upper respiratory tract infections, lower respiratory tract infections, and sore throat. These scenarios ranged in severity from mild to very severe based on the symptoms that were included. Table 7.2 shows that the likelihood of wanting an antibiotic was only slightly lower than the likelihood of wanting to see a doctor for the scenarios. Similarly, the likelihood for seeking care or antibiotic treatment significantly increased by scenario severity. Students indicated that they were significantly more likely to seek care or an antibiotic for lower respiratory tract infections than sore throat and upper respiratory tract infections.

Multivariate Analysis of Vignette Responses

The results of our multivariate analysis can be found in table 7.3 (a-c). Independent predictors of seeking care in upper respiratory tract infection scenarios were the presence of fever (aOR 12.47, 95% CI [9.20, 16.90]), sore throat (aOR 6.12, 95% CI [4.61, 8.12]), nasal discharge (aOR 2.92, 95% CI [2.52, 3.38]), Black/ African American race (aOR 1.78, 95% CI [1.15, 2.77]), and recent antibiotic use (aOR 1.5 - 2.5, 95% CI [1.0, 3.6]). Independent predictors of seeking antibiotic treatment in URTI scenarios were the presence of sore throat (aOR 3.54, 95% CI [2.80, 4.49]), non-White race, and recent antibiotic use (aOR 1.7 - 3.8, 95% CI [1.1, 5.4]).

Independent predictors of seeking care in sore throat scenarios were the presence of swollen glands (aOR 2.73, 95% CI [2.10, 3.55]), symptom duration of 8-14 days (aOR 3.55, 95% CI [2.69, 4.69]), and recent antibiotic use (aOR 1.5 - 2.7, 95% CI [1.1, 3.8]). Independent predictors of seeking antibiotic treatment in sore throat scenarios were the presence of swollen glands (aOR 2.95, 95% CI [2.24, 3.88]), longer symptom duration of 8-14 days (aOR 1.97, 95% CI [1.52, 2.70]), Asian race (aOR 1.55, 95% CI [1.16, 2.05]) and recent antibiotic use (aOR 1.7 - 2.9, 95% CI [1.2, 4.0]).

Independent predictors of seeking antibiotics in lower respiratory tract infection scenarios were the presence of sputum and Black/ African American race (aOR 2.10, 95% CI [1.18, 3.74]). Independent predictors of seeking care in LRTI scenarios were the presence of sputum and recent antibiotic use (aOR 1.5 - 2.2 95% CI [1.0, 3.2].

University Health Center Respiratory Illness Questionnaire

Students seeking care at for a respiratory illness at UGA's University Health Center are required to complete a questionnaire prior to their appointment. From November 2022 to January

2023, 2,678 students completed the respiratory illness questionnaire. The data from these questionnaires are provided in Table 7.5. The median duration of symptoms at the time of completion of the form was three days (Range = 0 - 750.0). The duration of symptoms was highly skewed (Appendix C, Figure C2), showing that students were more likely to seek care if they had been experiencing ARTI symptoms for less than a week. When asked to rank on a scale from zero to ten the impact of their illness on their daily activity, the mean impact that their illness had on their activity was 5.72 (SD = 2.7). Students scheduled an appointment most often when they were experiencing sore throat (79.1%), nasal congestion (71.6%), fatigue (70.7%), and cough (70.3%). Students with cough described its intensity as being moderate or worse 40.1% of the time. Students experiencing fatigue and muscle pain with respiratory illness ranked its intensity as mild 34.8% and 28.8% of the time respectively. When scheduling an appointment for respiratory illness, students rarely complained of vision changes (1.5%), loss of smell (4.7%), hearing loss (4.9%), or eye pain (9.5%).

Of the 2,678 respiratory questionnaires that were completed, 1,215 (45.4%) had responses to the open-ended question regarding illness evolution. Themes that were identified in these responses using NVivo included sore throat (32.5%), cough (13.6%), congestion (9.3%), nose (8.8%), and aches (8.6%) (Figure 7.2). NVivo was also used to identify sentiments of the open-ended responses. Sentiments were identified as being either positive (5.4%) or negative (53.8%) based on words included in the student's response. Figure 7.3 shows the intersecting relationship between the themes and sentiments. While sore throat was the most common theme identified in the open-ended responses, it was often not accompanied with descriptive language. Cough was most often described with negative phrases such as "severe cough", "horrible cough", "bad cough", or "worsening cough".

Care seeking behaviors in young adults presenting with acute cough to an outpatient clinic

Lastly, additional data regarding care seeking behavior was obtained from the Enhancing Antibiotic Stewardship in Primary Care (EAST-PC) study. This data can be found in Table 7.6. Patients aged 18 to 30 with a cough for less than 14 days expected that their cough would last, on average, 7 additional days if they did not receive an antibiotic compared to only 4 more days if they received an antibiotic. When asked to choose an option for why they came to the doctor, most patients stated either they were "not getting any better" (50.4%) or their "symptoms were severe" (45.2%). Only 23.2 % indicated that they sought care for an antibiotic.

DISCUSSION

The objective of our cross-sectional and retrospective studies was to identify signs and symptoms of ARTIs that influence students to seek care and seek antibiotic treatment at the University of Georgia (UGA). We were able to identify symptoms and student characteristics that were associated with seeking care and antibiotic treatment across three acute respiratory tract infection condition types: upper respiratory tract infection (URTI), sore throat, and lower respiratory tract infection (LRTI) with varying severities. Overall, we found that the likelihood of wanting an antibiotic was only slightly lower than the likelihood of wanting to see a doctor based on the scenarios described in the vignettes. This suggests that when students seek care for acute respiratory tract infections, they are likely also expecting to receive a prescription as their rankings for each action (seeking care and seeking antibiotic) were often the same.

For each condition, we identified independent predictors that were associated with being more likely to seek care or antibiotic treatment. These findings were presented in six separate logistic regression models. Overall, recent antibiotic use was the most consistent predictor for seeking antibiotic treatment across all illness types. It was also identified as a predictor for

seeking care for sore throat and upper respiratory tract infections. Additionally, being non-white and/or an undergraduate were also predictors for seeking antibiotic treatment. Change is sputum color was a predictor for seeking care and seeking antibiotic treatment for lower respiratory tract infections. Swollen glands without a fever were predictors for seeking care and antibiotic treatment for sore throat illnesses.

Comparison to current literature

There are some similarities and differences in our final models when compared to results of similar literature that are important to highlight. Recent antibiotic use was a predictor for increased likelihood of seeking care and seeking antibiotic treatment among college aged students across all condition types. Previous randomized control trials found that active or recent antibiotic prescriptions for sore throat increased the likelihood of reattendance in general practice when compared to no or delayed prescribing of antibiotics. It was found that immediate prescribing "medicalized" otherwise self-limiting conditions to meet patient expectations for the care that they receive during their visit. This was thought to prompt patients to seek care more frequently for similar symptoms[206–208]. Our findings highlight that this trend in reattendance following recent antibiotic use remains true across all acute respiratory tract illnesses (ARTI). Based on these findings, clinicians should consider no prescription or delayed prescription for uncomplicated ARTIs to reduce antibiotic use[209].

Students indicated that they were more likely to seek care and antibiotic treatment when their cough was accompanied by green or bloody sputum production. Other studies have also noted that a change in sputum color is considered, by both patients and clinicians, to be indicative of bacterial infection[210–212]. A common symptom of bacterial (classically pneumococcal) pneumonia is brown or blood-stained sputum. The rust-colored sputum is usually

produced from the lungs when a patient has been coughing for long periods because of a bacterial chest infection. However, a 2009 study concluded that green sputum was only a weak diagnostic marker for differentiating between viral and bacterial infection as the cause for acute cough[210]. On the other hand, a similar study found that green, yellow-green, and rust-colored sputum had a higher bacterial-yield in sputum samples than clear samples[213]. This highlights an educational gap regarding seeking care, which could potentially result in inappropriate prescribing of antibiotics if physical examinations are not paired with proper diagnostic tests.

Swollen glands combined with sore throat for 8 – 14 days was a predictor for increased likelihood of seeking care and seeking antibiotic treatment. While sore throat could be indicative of a bacterial infection, it could also be a result of allergies, tonsillitis, acid reflux, overuse of irritants (yelling, spicy food, smoking, etc.) or mouth breathing[214]. Since no single feature from a patient's physical examination can confirm or exclude the presence of bacterial infection, clinical decision rules like the Centor score and FeverPAIN risk score have been created to help identify indications for antibiotic treatment[82,215]. Based on these scores, sore throat should be accompanied by swollen glands and recent onset of fever to rule in strep throat. Yet, in our study population, fever was associated with a decreased likelihood for seeking care or antibiotic treatment in sore throat illnesses. Students also appeared to associate increased symptom duration with strep throat. However, previous studies have determined that streptococcal pharyngitis has an incubation period of two to five days and can resolve in approximately a week with or without antibiotic treatment[214,216,217]. This suggests that the illness that they are more likely to seek care and/ or antibiotic treatment for is infectious mononucleosis which exhibits similar symptoms with a symptom duration of four weeks or longer[218]. Another survey study conducted in 2020 suggests that while much of their study population sought care for a sore

throat, the desire was to "limit the worsening of symptoms" due to its impact to their daily life. A much lower proportion of the population reported "wanting an antibiotic" as their reasoning for visiting their general practitioner[219].

Being an undergraduate student and identifying as a non-white race were predictors for seeking care and antibiotic treatment. From 2009 - 2016 a national study was conducted in the United States to identify disparities in antibiotic prescribing. Overall, patients who were less than 18 had the highest rate of antibiotic prescriptions[220]. While this could be due to a high incidence of acute respiratory tract infections among this age group, it could also be influenced by the medicalization of self-limiting illness[206,221,222]. Additionally, this age group is likely to have a lack of experience making their own healthcare decisions. Inappropriate prescribing rates were high across all ages. The study also found that overall prescribing rates and inappropriate prescribing rates were highest among African Americans and Hispanics. This could be a result of socioeconomic, societal, or cultural factors such as educational level, living conditions, expectation of care, and social pressure[220,223].

Strengths and limitations

Our study did have some limitations. First, all data included for these analyses were self-reported. Responses of all students that chose to complete the survey may not be representative of all college-aged students' sentiments on seeking care or seeking antibiotic treatment for ARTIs. Likewise, responses were based on vignette scenarios that were created a priori with specific conditions and severities in mind. This places constraints on the complexity of information that we were able to obtain from respondents. Future research should consider assessing reasoning for seeking care or antibiotic treatment using responses that are prospectively collected in open-ended questions or more comprehensive multiple-choice

questions. Lastly, our study population only consisted of University of Georgia (UGA) students who were living in similar conditions and similar access to care. It is likely that these results are representative of other college-aged students but may not be generalized to larger populations.

Conclusion

Overall, students indicated that they were significantly more likely to seek care or an antibiotic for lower respiratory tract infections than sore throat and upper respiratory tract infections. We found that students were more likely to seek antibiotics for URTIs if they were experiencing a sore throat. These findings matched the responses from student EHR questionnaires as most students that sought care at the university health center indicated they were experiencing sore throat. The presence of swollen glands for 8 -14 days accompanied by recent antibiotic use, identifying as non-white race, and/ or being an undergraduate increased the likelihood of a student seeking care and seeking antibiotic for illnesses with sore throat. The likelihood of seeking care or antibiotic treatment for a LRTI increased if the presence of cough was accompanied by bloody or green sputum. These predictors help to identify gaps in health education and clinical research. Educational efforts should be focused on highlighting specific symptoms, illness severity, and symptom duration that are important and not important when considering seeking care. Future research should consider addressing misconceptions about symptom development such as sputum color or length of sore throat, with the need for an antibiotic. Another major takeaway of our study is that for all conditions, having an antibiotic more recently increased a student's desire for an antibiotic. This highlights the importance of antibiotic stewardship and minimizing unnecessary antibiotic prescribing. Larger prospective studies should be done in that age group to determine more in-depth reasoning for seeking care and the perceived need for an antibiotic among college-aged students to guide long-term care

seeking behaviors. Additionally, public health agencies should consider implementing campaigns that are inclusive with regards to racial and ethnic groups regarding expectations about the need for antibiotics.

TABLES AND FIGURES

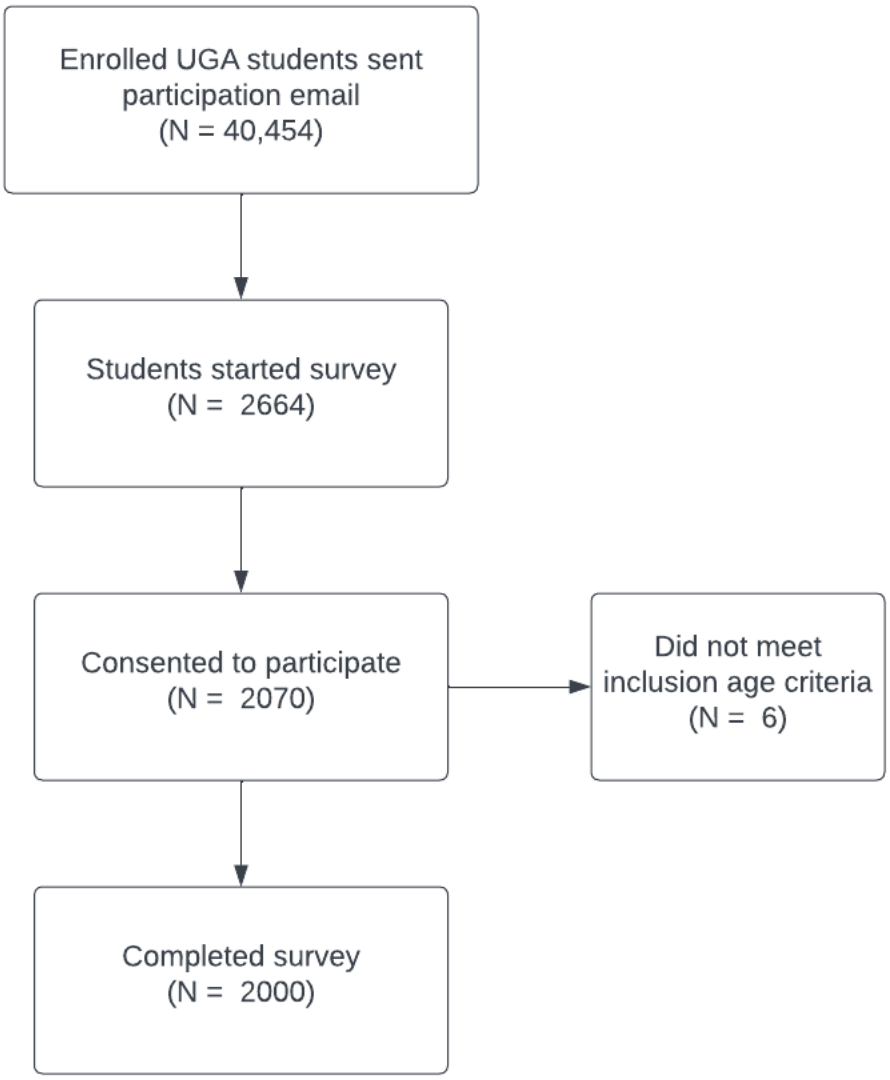


Figure 7.1 Flow diagram of student participation

Table 7.1 Demographics of study participants

	Total (N = 2000)
Age (years)	
Median [Min, Max]	21.0 [18.0, 68.0]
Gender	
Male	445 (22.3%)
Female	1503 (75.2%)
Non-binary/ third gender/ other	45 (2.3%)
Prefer not to answer	7 (0.4%)
Race	
White	1,494 (74.7%)
Black/ African American	107 (5.4%)
Asian/ Pacific Islander	255 (12.8%)
Alaska Native/ American Indian/ Native Hawaiian	2 (0.1%)
Other	116 (5.8%)
Prefer not to answer	26 (1.3%)
Ethnicity	
Hispanic	142 (7.2%)
Non-Hispanic	1,800 (90.8%)
Prefer not to answer	40 (2.0%)
Year in School	
Undergraduate Year 1	385 (19.3%)
Undergraduate Year 2	319 (16.0%)
Undergraduate Year 3	306 (15.3%)
Undergraduate Year 4	248 (12.4%)
Undergraduate Year 5	59 (2.6%)
Graduate	558 (27.9%)

Professional	120 (6.0%)
Other	5 (0.3%)
Last Antibiotic Usage	
Less than 1 month	207 (10.4%)
1 – 2 month(s) ago	130 (6.5%)
3 – 5 month(s) ago	213 (10.7%)
6 – 12 month(s) ago	474 (23.7%)
More than 1 year	826 (41.3%)
Unsure	150 (7.5%)

Table 7.2 Description of vignettes and bivariate analysis of student responses (agree vs disagree) to seeking care or seeking antibiotic treatment based on vignette severity by illness condition (URTI, sore throat, and LRTI)

Vignette #, Symptoms present	**Severity**	**Seek Care** OR (95% CI)	**P value**	**Seek Antibiotic** OR (95% CI)	**P value**
Upper Respiratory Tract Infection					
Vignette 4 Cough with clear sputum Yellow/ green nasal discharge 2 days symptom duration	Mild	REF	REF	REF	REF
Vignette 1 Dry cough Fever Swollen glands in throat 1 day symptom duration	Moderate	5.43 (4.13, 7.14)	<0.001	3.12 (2.39, 4.07)	<0.001
Vignette 2 Cough with yellow sputum Sore throat Yellow nasal discharge Facial pain/ pressure 7 days symptom duration	Severe	1.38 (1.03, 1.85)	0.0.030	1.05 (0.79, 1.40)	0.755
Vignette 3 Fever for 2 days Swollen glands in throat Yellow/ green nasal discharge Facial pain/ pressure 10 days symptom duration	Very Severe	10.23 (7.63, 13.72)	<0.001	4.45 (3.39, 5.84)	<0.001
Sore Throat					
Vignette 1 Sore throat Runny nose	Mild	REF	REF	REF	REF

Clear/ nasal discharge 5 days symptom duration					
<u>Vignette 4</u> Sore throat Swollen glands in throat Runny nose Yellow/green nasal discharge 7 days symptom duration	Moderate	2.69 (2.08, 3.48)	<0.001	2.82 (2.17, 3.67)	<0.001
<u>Vignette 2</u> Fever Sore throat Swollen glands in throat 1 day symptom duration	Severe	2.08 (1.61, 2.68)	<0.001	1.91 (1.46, 2.48)	<0.001
<u>Vignette 3</u> Fever for 2 days Sore throat Swollen glands in throat 14 days symptom duration	Very Severe	6.55 (4.96, 8.63)	<0.001	3.42 (2.63, 4.45)	<0.001
Lower Respiratory Tract Infection					
<u>Vignette 4</u> Dry cough 2 days duration	Mild	REF	REF	REF	REF
<u>Vignette 1</u> Chest pain with cough Yellow sputum Sore throat 10 days symptom duration	Moderate	5.69 (4.36, 7.44)	<0.001	5.19 (3.96, 6.80)	<0.001
<u>Vignette 3</u> Fever for 1 day Chest pain with cough Green sputum	Severe	21.05 (14.57, 30.41)	<0.001	8.91 (6.70, 11.86)	<0.001

Sore throat 12 days symptom duration					
<u>Vignette 2</u> Fever for 2 days Chest pain with cough Bloody sputum 14 days symptom duration	Very Severe	23.78 (16.11, 35.10)	<0.001	13.37 (9.85, 18.13)	<0.001

Table 7.3 (a – c) Multivariate analysis of survey responses of seeking care and seeking an antibiotic by upper respiratory tract infection, sore throat, and lower respiratory tract infection.

a. Final models of survey responses to upper respiratory tract infection vignettes.

Upper Respiratory Tract Infection			
Independent variables	Adjusted Odds Ratio (95% CI)	® coefficient	P-value
Dependent = "Seeking Care"*			
Fever	12.5 (9.2, 16.9)	2.52	<0.001
Sore throat	6.1 (4.6, 8.1)	1.81	<0.001
Nasal discharge	2.9 (2.5, 3.4)	1.07	<0.001
Black/ African American	1.8 (1.2, 2.8)	0.58	0.010
Recent antibiotic use			
12 – 6 months	1.5 (1.2, 2.0)	0.43	0.001
5 – 3 months	2.0 (1.4, 2.8)	0.69	<0.001
2 – 1 month(s)	1.9 (1.2, 2.9)	0.63	0.003
< 1 month	2.5 (1.8, 3.6)	0.93	<0.001
Unsure	1.5 (1.0, 2.2)	0.41	0.043
Dependent = "Seek Antibiotic"+			
Cough	0.2 (0.1, 0.2)	-1.71	<0.001
Sore throat	3.5 (2.8, 4.5)	1.26	<0.001
Race			
Black/ African American	2.4 (1.6, 3.7)	0.88	<0.001
Asian/ Pacific Islander	1.6 (1.2, 2.1)	0.46	0.002

Non-Hispanic	0.5 (0.3, 0.7)	-0.80	<0.001
Undergraduate year 5/ Graduate/ Professional/ Other	0.6 (0.5, 0.8)	-0.49	<0.001
Recent antibiotic use			
12 – 6 months	2.0 (1.6, 2.6)	0.70	<0.001
5 – 3 months	2.7 (2.0, 3.8)	1.00	<0.001
2 – 1 month(s)	2.5 (1.6, 3.7)	0.90	<0.001
< 1 month	3.8 (2.7, 5.4)	1.35	<0.001
Unsure	1.7 (1.1, 2.4)	0.50	0.011

*Variables included in model of seeking care for URTI that were not statistically significant ($p > 0.05$) were swollen glands, cough, face pain, symptom duration, sex, non-African American race, grades prior to undergraduate year 5.
+Variables included in model of seeking antibiotic treatment for URTI that were not statistically significant ($p > 0.05$) were nasal discharge and age.

b. Final models of survey responses to sore throat vignettes.

Sore Throat			
Independent variables	Adjusted Odds Ratio (95% CI)	® coefficient	P-value
Dependent = "Seeking Care"*			
Fever	0.8 (0.6, 1.0)	-0.26	0.048
Swollen glands	2.7 (2.1, 3.6)	1.00	<0.001
8 – 14 days of symptoms	3.6 (2.7, 4.7)	1.27	<0.001
Recent antibiotic use			
12 – 6 months	1.7 (1.4, 2.2)	0.54	<0.001
5 – 3 months	1.5 (1.1, 2.1)	0.41	0.012
< 1 month	2.7 (1.9, 3.8)	1.00	<0.001
Dependent = "Seek Antibiotic"+			
Fever	0.7 (0.5, 0.9)	-0.40	0.003
Swollen glands	3.0 (2.2, 3.9)	1.08	<0.001
8 – 14 days of symptoms	2.0 (1.5, 2.7)	0.68	<0.001
Non-binary/Third Gender/Other	0.3 (0.2, 0.6)	-1.17	0.002
Asian/ Pacific Islander	1.6 (1.2, 2.1)	0.44	0.003
Ethnicity			
Non-Hispanic	0.6 (0.4, 0.9)	-0.49	0.010
Prefer not to answer	0.2 (0.1, 0.6)	-1.47	0.001
Grade			

Undergraduate year 3 & 4	0.7 (0.6, 0.9)	-0.32	0.008
Undergraduate year 5/ Graduate/ Professional/ Other	0.6 (0.5, 0.7)	-0.58	<0.001
Recent antibiotic use			
12 – 6 months	2.3 (1.8, 2.9)	0.82	<0.001
5 – 3 months	1.8 (1.3, 2.4)	0.56	0.001
2 – 1 month(s)	2.1 (1.4, 3.1)	0.75	<0.001
< 1 month	2.9 (2.1, 4.0)	1.06	<0.001
Unsure	1.7 (1.2, 2.5)	0.54	0.005

*Variables included in the model for seeking care for sore throat that were not statistically significant ($p > 0.05$) was nasal discharge, symptom duration less than 8-14 days, sex, race, and recent antibiotic use from 2-1 months.

+Variables included in the model for seeking antibiotic treatment for sore throat that were not statistically significant ($p > 0.05$) was nasal discharge, symptom duration less than 8-14 days, female sex, and non-Asian races.

c. Final models of survey responses to lower respiratory tract infection vignettes.

Lower Respiratory Tract Infection			
Independent variables	Adjusted Odds Ratio (95% CI)	® coefficient	P-value
Dependent = "Seeking Care"*			
Sputum			
Clear or yellow	6.6 (5.0, 8.7)	1.89	<0.001
Green	24.4 (16.6, 35.9)	3.20	<0.001
Bloody	25.6 (17.5, 37.5)	3.24	<0.001
Race			
Black/ African American	2.1 (1.2, 3.7)	0.74	0.011
Other	0.6 (0.4, 0.9)	-0.56	0.020
Dependent = "Seek Antibiotic"+			
Sputum			
Clear or yellow	6.5 (4.9, 8.6)	1.87	<0.001
Green	16.2 (11.8, 22.3)	2.79	<0.001
Bloody	10.8 (8.0, 14.6)	2.38	<0.001
Sex			
Female	0.8 (0.6, 1.0)	-0.29	0.029
Non-Binary/Third Gender/Other	0.3 (0.1, 0.5)	-1.35	<0.001
Prefer not to answer	0.1 (0.0, 0.9)	-2.30	0.041
Ethnicity			

Non-Hispanic	0.6 (0.4, 0.9)	-0.48	0.024
Prefer not to answer	0.4 (0.2, 0.9)	-0.92	0.029
Undergraduate year 5/ Graduate/ Professional/ Other	0.6 (0.5, 0.8)	-0.45	<0.001
Recent antibiotic use			
12 – 6 months	1.9 (1.5, 2.5)	0.65	<0.001
5 – 3 months	2.0 (1.4, 2.9)	0.70	<0.001
2 – 1 month(s)	1.8 (1.2, 2.9)	0.60	0.008
< 1 month	2.2 (1.5, 3.2)	0.78	<0.001
Unsure	1.5 (1.0, 2.3)	0.43	0.043

*Variables included in the model for seeking care for sore throat that were not statistically significant ($p > 0.05$) were fever, chest pain, sore throat, symptom duration, and recent antibiotic use.

+Variables included in the model for seeking antibiotic treatment for sore throat that were not statistically significant ($p > 0.05$) were fever, chest pain, sore throat, symptom duration, age, and grades prior to undergraduate year 5.

Table 7.4 Summary of predictors that were identified by multivariate analysis to be significantly associated with seeking care or seeking antibiotic treatment by illness type

Outcome	URTI	Sore throat	LRTI
Seeking care	Recent antibiotic use	Recent antibiotic use	Bloody sputum
	Fever	Fever absent	Green sputum
	Black/ African American	8 – 14 days of symptoms	Black/African American
	Nasal discharge	Swollen glands	
	Sore throat		
Seeking antibiotics	Recent antibiotic use	Recent antibiotic use	Recent antibiotic use
	Undergraduate year 1, 2 3, and 4	Undergraduate year 1 and 2	Undergraduate year 1, 2 3, and 4
	Asian/ Pacific Islander	Asian/ Pacific Islander	Male
	Black/African American	Hispanic	Hispanic
	Hispanic	Male and Female	Bloody sputum
	Cough absent	8 – 14 days of symptoms	Green sputum
	Sore throat	Swollen glands	
		Fever absent	

Table 7.5 Descriptive analysis of student response to University Health Center respiratory illness questionnaire

	Total Responses (N = 2678)
Symptoms	
Symptom Duration (days) Mean (SD) Median [Min, Max]	 7.72 (23.74) 3.0 [0.0, 750.0]
Activity Impact Mean (SD) Median [Min, Max]	 5.72 (2.68) 6.0 [0.0, 10.0]
Symptoms with severity	Number (%)
Cough	**1927 (72.0%)**
Mild	832 (31.1%)
Moderate	895 (33.4%)
Severe	200 (7.5%)
Asthenia	**1770 (66.1%)**
Mild	933 (34.8%)
Moderate	692 (25.8%)
Severe	145 (5.4%)
Myalgia	**1582 (59.1%)**
Mild	770 (28.8%)
Moderate	661 (24.7%)
Severe	151 (5.6%)
Symptoms without severity	Number (%)
Pharyngitis	2118 (79.1%)
Nasal congestion	1917 (71.6%)
Fatigue	1892 (70.7%)
Headache	1696 (63.3%)
Rhinorrhea	1565 (58.4%)
Sneezing	1565 (58.4%)

Chills/ sweats	1242 (46.4%)
Adenopathy	1189 (44.4%)
Insomnia	1109 (41.4%)
Chest congestion	1043 (39.0%)
Fever	832 (31.1%)
Shortness of breath	668 (24.9%)
Otalgia	654 (24.4%)
Nausea	556 (20.8%)
Wheezing	511 (19.1%)
Facial pain/ pressure	486 (18.2%)
Chest pain	453 (16.9%)
Itchy eyes	416 (15.5%)
Eye pain	255 (9.5%)
Diarrhea	255 (9.5%)
Abdominal pain	216 (8.1%)
Vomiting	172 (6.4%)
Hearing loss	131 (4.9%)
Anosmia	125 (4.7%)
Vision changes	41 (1.5%)

Figure 7.2 Composite hierarchy chart of symptom themes identified by NVivo in open-ended student responses regarding illness evolution.

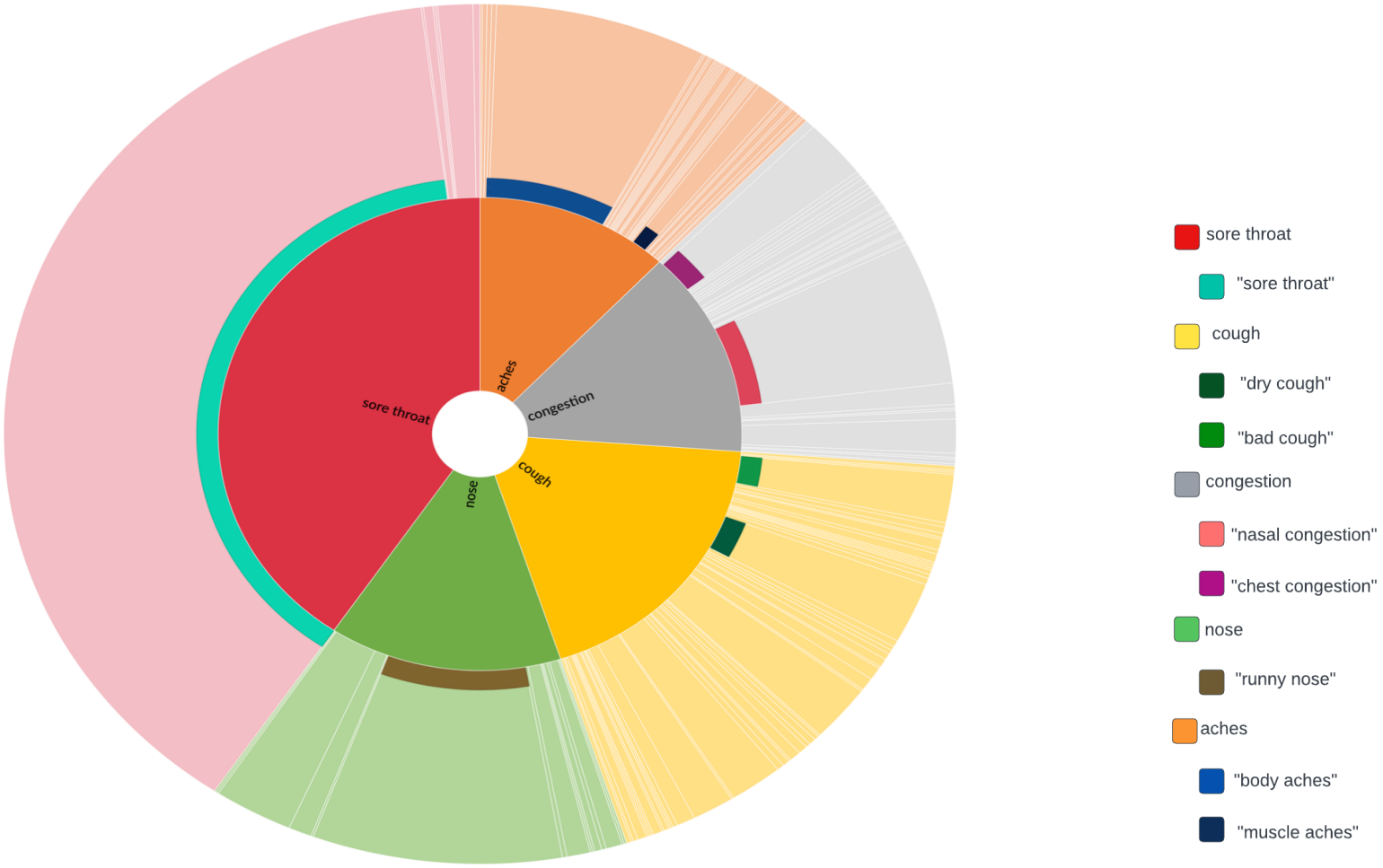


Figure 7.3 Composite hierarchy chart of themes by sentiment classification (positive or negative) identified by NVivo in open-ended student responses regarding illness evolution.

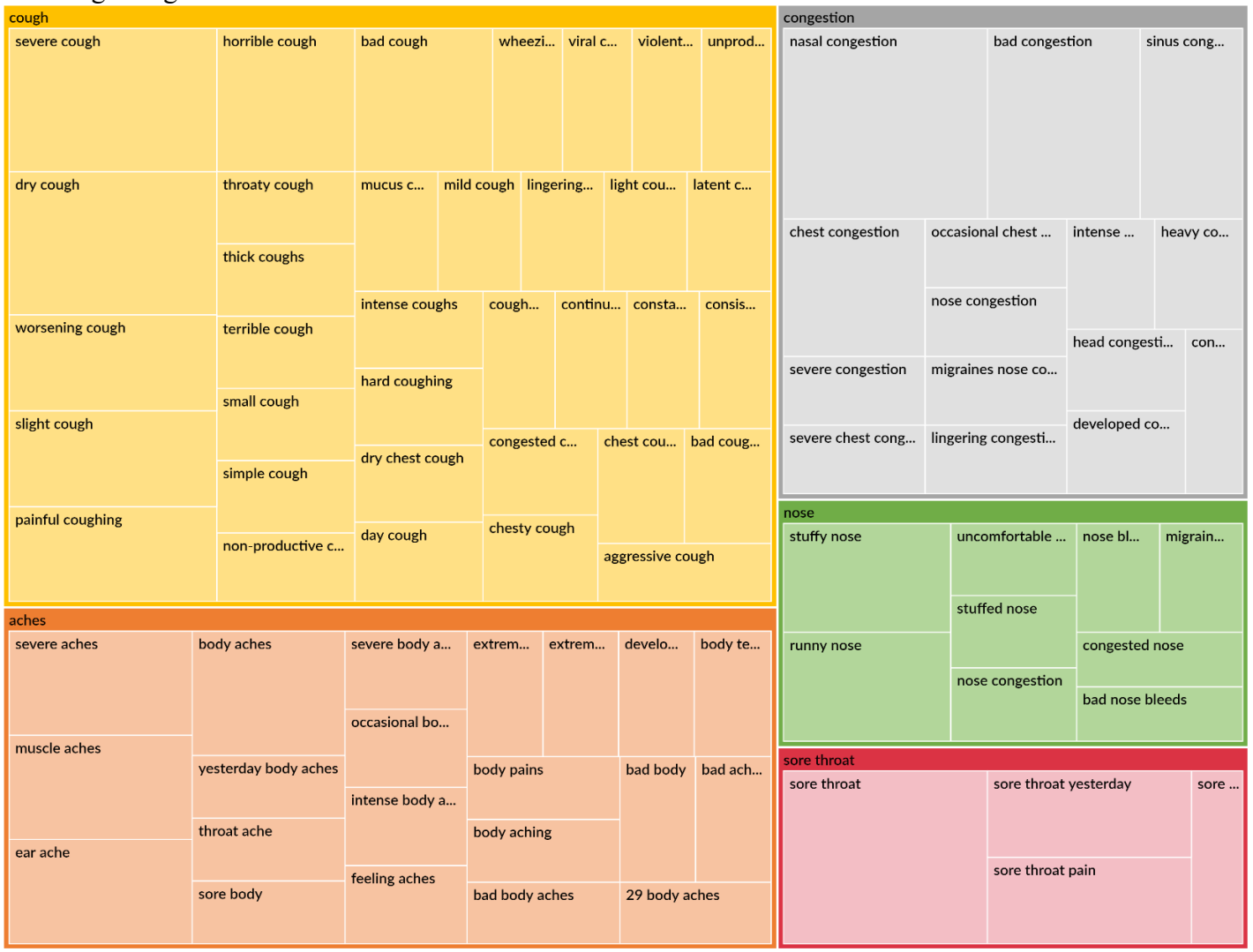


Table 7.6 Care seeking behaviors of symptomatic patients aged 18 – 30 years in the EAST-PC study (N = 250)

Age (years) Mean (SD) Median [Min – Max]	 23.3 (3.7) 23 [18 – 30]
Expected cough duration with antibiotic (days) Mean (SD) Median [Min – Max]	 4.1 (3.1) 3 [0 – 30]
Expected cough duration without antibiotic (days) Mean (SD) Median [Min – Max]	 7.6 (7.7) 7 [0 – 90]
Reason for Seeking Care	
Not getting better	126 (50.4%)
Severe symptoms	113 (45.2%)
Thought the illness was serious	81 (32.4%)
Antibiotic	58 (23.2%)
Encouraged by family member	55 (22.0%)
No reason	0 (0.0%)

CHAPTER 8

CONCLUSIONS

This concluding chapter serves as a summary of the problems addressed by this dissertation, the results of three aims, a comparison of their results, and discusses future directions for research.

The Problem

In previous studies, viruses have been identified as the causative agent in respiratory tract infections approximately 90% of the time[19]. However, antibiotic prescriptions are often still provided in the absence of testing that is able to confirm a viral cause. This has led to overprescribing of antibiotics in cases when the illness would have been self-limiting[20]. Inappropriate prescribing of antibiotics is the leading cause of antimicrobial resistant pathogens, which are a threat to global health[21]. Also, the diagnostic and treatment strategies for acute respiratory tract infections are often variable due to overlap of symptoms of infections involving different anatomical sites[22].

Additionally, care seeking trends and behaviors for acute RTIs have not been studied thoroughly in college-aged individuals. College students are in the unique position of making their own health decisions for the first time. Also, respiratory infections are easily spread on college campuses due to congregate living conditions and lifestyle factors. It is important to investigate this demographic group because the information obtained could influence RTI treatments prescribed, diagnostic practices, antibiotic stewardship interventions, and long-term medical behaviors. This research will also help to identify gaps in the health education of college-aged students as it relates to RTIs.

Aim 1: Etiology of Acute Respiratory Tract Infections in Outpatients: A Systematic Review and Meta-Analysis to Identify Likelihood of Commensalism

In our first aim, we analyzed current literature describing the etiology of acute respiratory tract infections (ARTIs). Our search yielded 15 studies that were included in our meta-analysis. Data for these studies were collected from 1992 to 2019 with the age of participants in the studies ranging from 31 to 69 years old.

Our meta-analysis identified significant associations of bacteria and viruses with symptomatic acute respiratory tract infection diagnoses and being asymptomatic. Overall, viruses that were identified most often in symptomatic individuals included influenza A or B, rhinovirus (RV), bocavirus, enterovirus, human coronavirus (hCoV), and respiratory syncytial virus (RSV) (hCoV did not include SARS-CoV-2). Bocavirus, influenza virus, rhinovirus, and *M. catarrhalis* are the most common causes of any acute respiratory tract infection. In patients with lower respiratory tract infection symptoms (LRTI), influenza, rhinovirus, human coronavirus, and RSV were most common. Bacteria that were most common overall among patients included *Haemophilus influenzae and Moraxella catarrhalis*. These were also the bacteria that were most common among ARTI patients. Bacteria that were identified most frequently in patients with LRTI were *Streptococcus pneumoniae* and *Haemophilus influenzae.*

The isolation of bacteria and viruses in asymptomatic study populations (individuals with no signs or symptoms of acute respiratory tract infections) was lower compared to symptomatic populations. The most identified viruses among asymptomatic groups were rhinovirus, influenza, respiratory syncytial virus (RSV), and enterovirus. *Moraxella catarrhalis* and *Streptococcus pneumoniae* were both found most often in those who were asymptomatic for respiratory tract symptoms.

Aim 2: Determining Etiology of Acute Respiratory Tract Infections and Potential Commensalism in Outpatients: A Case-Control Study

The second aim of this dissertation used a case-control design to investigate the etiology of lower respiratory tract infections (LRTIs) amongst adults 18 to 75 years old. Patients with ARTI symptoms and asymptomatic individuals were recruited from areas in or surrounding Athens, Georgia, Madison, Wisconsin, and Washington D.C. A total of 1,215 participants met the inclusion for our study: 718 symptomatic patients and 497 asymptomatic persons.

Overall, viruses were identified most often (35.8%) in symptomatic patients when compared to other infection types. The most common viruses in the symptomatic group included rhinovirus, influenza A and B, and SARS-CoV-2. Influenza, parainfluenza, and SARS-CoV-2 were determined to be pathogenic with positive etiologic predictive values (P-EPVs) greater than 85%[133,141]. Bacterial pathogens were detected in 12.4 percent of symptomatic individuals and mostly included *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. Group A *streptococcus*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae, Pseudomonas aeruginosa, Chlamydia pneumoniae, and Haemophilus influenzae* are also likely pathogenic with P-EPVs greater than 40%. Mixed samples accounted for 21.9% of symptomatic samples and 4.8% of asymptomatic samples. There were 29.9% of symptomatic samples and 53.1% of asymptomatic samples with no growth.

Asymptomatic individuals were carriers of bacterial pathogens (30.6%) more often than viral pathogens (11.5%). The most identified bacteria in this group were *Staphylococcus aureus, Haemophilus influenzae, and Streptococcus pneumoniae.* Group B *streptococcus*, *Streptococcus pneumoniae*, *Ureaplasma urealyticum*, *Pneumocysitis jirovecii, Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Staphylococcus aureus*, and *Ureaplasma parvum* had the potential to

be commensal with P-EPVs approaching or less than 0%. Viral organisms detected among asymptomatic participants included rhinovirus and seasonal human coronavirus (all types but not including SARS-CoV-2). Cytomegalovirus and human coronaviruses had the potential to be commensal with P-EPVs less than or equal to 0%.

Aim 3: Identifying Predictors of Care-Seeking Behavior for Acute Respiratory Tract Infections in College Students

The third aim of this dissertation used a cross – sectional study design to identify care seeking and antibiotic seeking behaviors among college students, age 18 or older, at the University of Georgia. An email survey was sent to all enrolled students as of Fall 2022 semester (n = 40,454) and 2,000 students met the inclusion criteria and fully completed the survey. Upon consenting to participation, participants read and completed questions for three vignettes randomly selected from a total of 12 vignettes. Vignettes were designed to represent possible symptom scenarios for upper respiratory tract infections, lower respiratory tract infections, and sore throat. These scenarios ranged in severity from mild to very severe based on the symptoms that were included.

We were able to identify symptoms and student characteristics that were associated with seeking care and antibiotic treatment across three acute respiratory tract infection condition types: upper respiratory tract infection (URTI), sore throat, and lower respiratory tract infection (LRTI) with varying severities. Overall, we found that the likelihood of wanting an antibiotic was only slightly lower than the likelihood of wanting to see a doctor based on the scenarios described in the vignettes. This suggests that when students seek care for acute respiratory tract infections, they are likely also expecting to receive a prescription as their rankings for each action (seeking care and seeking antibiotic) were often the same.

For each condition, we identified independent predictors that were associated with being more likely to seek care or antibiotic treatment. These findings were presented in six separate logistic regression models. Overall, recent antibiotic use was the most consistent predictor for seeking antibiotic treatment across all illness types. It was also identified as a predictor for seeking care for sore throat and upper respiratory tract infections. Additionally, being non-white and/or an undergraduate were also predictors for seeking antibiotic treatment. Change is sputum color was a predictor for seeking care and seeking antibiotic treatment for lower respiratory tract infections. Swollen glands without a fever were predictors for seeking care and antibiotic treatment for sore throat illnesses.

Comparison of Results

Together, aims one and two of this dissertation were able to identify etiologies that are associated with symptomatic acute respiratory tract infections and etiologies that could be commensal in adult populations. This information can be used to guide antibiotic prescribing practices and care seeking behaviors. These aims determined that viruses such as influenza and rhinovirus remain highly associated with symptomatic disease as supported by previous research. As such, symptomatic treatments should be encouraged and an antibiotic prescription would be inappropriate. Bacterial organisms are often present in symptomatic individuals but sometimes equally as present in healthy participants which leads us to believe that these organisms could be commensal when they are not invasive. Bacterial pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis* were detected in symptomatic patients more often than asymptomatic. They are typically associated with the diagnosis of acute bacterial rhinosinusitis (ABRS) which is a secondary infection caused by a blockage of the sinus cavity[224]. ABRS differentiates from viral rhinosinusitis with severe symptoms that persist more than 10 days without any

improvement[224,225]. Management for ABRS could include the use of antibiotics such as amoxicillin-clavulanate, doxycycline, or fluoroquinolone. However, the Infectious Diseases Society of America (IDSA) has found that there is no evidence to support that these treatments are superior to supportive care in most cases[224–226]. Lastly, our research found that bacteria such as *Klebsiella pneumoniae* and *Streptococcus pneumoniae* could be commensal as they were detected more often in healthy individuals. This is consistent with our current knowledge of these organisms and as such, it is not suggested that these be treated with antibiotics unless pneumonia is suspected[183,196].

The understanding of ARTI etiology is vital as we consider care seeking behaviors and antibiotic stewardship efforts for young adult populations in college settings when they are often making their own health decisions for the first time. In aim three we identified symptom and illness severities that influenced care and antibiotic seeking behaviors of college students. We determined that being an undergraduate student and identifying as non-white race were predictors for seeking care and antibiotic treatment. While this could be result of a higher incidence of ARTIs amongst this age group, it could also be influenced by their lack of experience making their own health decisions. A higher likelihood of seeking care among non-white races could be a result of socioeconomic, societal, or cultural factors such as educational level, living conditions, expectation of care, and social pressure[220,223]. Students also indicated they were more likely to seek care and seek antibiotic treatment for scenarios that were categorized as severe or very severe based on the symptom descriptions and symptom duration. However, for some of these scenarios, we identified potential gaps in education as there was no previous evidence to support seeking antibiotic treatments out of fear of bacterial infection. These scenarios include sore throat and swollen glands for 8 – 14 months and cough with green

or bloody sputum production. While sore throat could be indicative of a streptococcal pharyngitis, it could also be a result of allergies, tonsillitis, acid reflux, overuse of irritants (yelling, spicy food, smoking, etc.) or mouth breathing[214]. Additionally, sore throat accompanied by swollen glands with an extended symptom duration is more often associated with mononucleosis when compared to the illness progression of strep throat[216,217]. A common symptom of bacterial (classically pneumococcal) pneumonia is brown or blood-stained sputum and as such aligns with a greater likelihood for seeking care. However, there is little diagnostic evidence to support that green sputum is indicative of a bacterial infection more often than viral infections[210,213]. Recent antibiotic use was identified as a predictor for increased likelihood of seeking care and seeking antibiotic treatment among college aged students across all ARTI condition types. Our findings highlight that there is a trend in reattendance following recent antibiotic use and this could likely be due to clinicians' perceived expectations of patients[206,207].

These findings suggest that there is likely a lack of understanding of the etiology of ARTIs and its influence on care seeking behaviors that should be addressed with future research and health education measures. As our research found that the majority of ARTIs had a viral etiology, there is little to no indication for antibiotic prescribing for acute symptomatic respiratory illness in outpatient settings. Cases when symptoms have persisted and/ or when pneumonia is suspected should be tested for bacterial etiology. In these instances, antibiotics can be prescribed. However, when possible, clinicians should delay prescribing if possible and educate patients on proper antibiotic use. Other educational efforts should be focused on specific symptoms, illness severity, and symptom duration that are important and not important when considering seeking care

Future Directions

Further research should include large prospective studies that recruit both symptomatic and asymptomatic participants. These larger studies will allow for direct measurement of symptoms that patients are experiencing during infection as well as how those symptoms progress and evolve overtime. Larger prospective studies will also allow for the measurement of common vital signs and laboratory tests for both groups. In particular, both groups should be recruited and undergo nasopharyngeal swabs that are tested via polymerase chain reaction (PCR) to determine the presence of bacterial and/or viral organisms during the same times so that they are presentative of seasonal changes that could influence etiology. Symptomatic groups should be asked to describe their symptoms in detail in an effort to identify trends in seeking care. Additionally, symptomatic participants should be asked to explain why they sought care to determine if gaps in understanding of antibiotic prescribing exist. Lastly, it is also important to consider outside factors such as finances, insurance and access to quality care, that could also influence individuals to seek care and antibiotic treatment.

REFERENCES

1. Yoshino T, Takada T, Horiba Y, Watanabe K. Classification of acute phase febrile upper respiratory tract infection: Retrospective chart review. *Tradit Kampo Med*. 2017;4(1):31-37. doi:10.1002/TKM2.1064
2. Vodicka TA, Thompson M, Lucas P, et al. Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review. *Br J Gen Pract*. 2013;63(612):e445. doi:10.3399/BJGP13X669167
3. Gonzales R, Bartlett JG, Besser RE, Hickner JM, Hoffman JR, Sande MA. Principles of appropriate antibiotic use for treatment of nonspecific upper respiratory tract infections in adults: Background. *Ann Intern Med*. 2001;134(6):490-494. doi:10.7326/0003-4819-134-6-200103200-00015
4. Ebell MH, Lundgren J, Youngpairoj S. How Long Does a Cough Last? Comparing Patients' Expectations With Data From a Systematic Review of the Literature. *Ann Fam Med*. 2013;11(1):5. doi:10.1370/AFM.1430
5. Centor RM, Atkinson TP, Ratliff AE, et al. The Clinical Presentation of Fusobacterium-Positive and Streptococcal-Positive Pharyngitis in a University Health Clinic. *https://doi.org/107326/M14-1305*. 2015;162(4):241-247. doi:10.7326/M14-1305
6. Bosch AATM, Biesbroek G, Trzcinski K, Sanders EAM, Bogaert D. Viral and Bacterial Interactions in the Upper Respiratory Tract. *PLoS Pathog*. 2013;9(1). doi:10.1371/JOURNAL.PPAT.1003057
7. Clark SE. Commensal bacteria in the upper respiratory tract regulate susceptibility to infection. *Curr Opin Immunol*. 2020;66:42. doi:10.1016/J.COI.2020.03.010
8. Watson K, Carville K, Bowman J, et al. Upper respiratory tract bacterial carriage in aboriginal and non-aboriginal children in a semi-arid area of Western Australia. *Pediatr Infect Dis J*. 2006;25(9):782-790. doi:10.1097/01.INF.0000232705.49634.68
9. Walter JM, Wunderink RG. Testing for Respiratory Viruses in Adults With Severe Lower Respiratory Infection. *Chest*. 2018;154(5):1213. doi:10.1016/J.CHEST.2018.06.003
10. Bruning AHL, Leeflang MMG, Vos JMBW, et al. Rapid Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review and Meta-analysis. *Clin Infect Dis An Off Publ Infect Dis Soc Am*. 2017;65(6):1026. doi:10.1093/CID/CIX461
11. Mori K, Imaki S, Ohyama Y, Satoh K, Abe T, Takeuchi I. Rapid screening for severe acute respiratory syndrome coronavirus 2 infection with a combined point-of-care antigen test and an immunoglobulin G antibody test. *PLoS One*. 2022;17(2):e0263327. doi:10.1371/JOURNAL.PONE.0263327
12. Dinnes J, Deeks JJ, Adriano A, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane database Syst Rev*. 2020;8(8). doi:10.1002/14651858.CD013705
13. Tellier R, Li Y, Cowling BJ, Tang JW. Recognition of aerosol transmission of infectious agents: A commentary. *BMC Infect Dis*. 2019;19(1):1-9. doi:10.1186/S12879-019-3707-

Y/FIGURES/1
14. Respiratory Hygiene/Cough Etiquette in Healthcare Settings | CDC. https://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm. Accessed March 25, 2022.
15. Troeger C, Blacker B, Khalil IA, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis*. 2018;18(11):1191. doi:10.1016/S1473-3099(18)30310-4
16. Martin D, Konrad M, Adarkwah CC, Kostev K. Reduced antibiotic use after initial treatment of acute respiratory infections with phytopharmaceuticals- a retrospective cohort study. *Postgrad Med*. 2020;132(5):412-418. doi:10.1080/00325481.2020.1751497/SUPPL_FILE/IPGM_A_1751497_SM1459.DOCX
17. Rao G, Rowland K, Hickner J. Zinc for the common cold—not if, but when. *J Fam Pract*. 2011;60(11):669. /pmc/articles/PMC3273967/. Accessed March 25, 2022.
18. Patrick G, Hickner J. This obscure herb works for the common cold. *J Fam Pract*. 2008;57(3):157. /pmc/articles/PMC3183890/. Accessed March 25, 2022.
19. Gačina A, Botica MV, Botica I, Hodžić AH, Žuti IB, Kobaš A. Antibiotic prescription rate for upper respiratory tract infections in general practice - a Croatian study. *Med Glas (Zenica)*. 2020;17(1):79-85. doi:10.17392/1074-20
20. Shaver AL, Jacobs DM, Lamonte MJ, Noyes K. Antibiotic prescribing for acute respiratory tract infections in the United States outpatient setting. *BMC Fam Pract*. 2019;20(1). doi:10.1186/S12875-019-0980-1
21. Antibiotic resistance. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance. Accessed March 25, 2022.
22. Kardos P, Malek FA. Common Cold - an Umbrella Term for Acute Infections of Nose, Throat, Larynx and Bronchi. *Pneumologie*. 2017;71(4):221-226. doi:10.1055/S-0042-116112
23. Carvajal LA, Pérez CP. Epidemiology of Respiratory Infections. *Pediatr Respir Dis*. 2020;no. 48:263. doi:10.1007/978-3-030-26961-6_28
24. Charlton CL, Babady E, Ginocchio CC, et al. Practical guidance for clinical microbiology laboratories: Viruses causing acute respiratory tract infections. *Clin Microbiol Rev*. 2019;32(1). doi:10.1128/CMR.00042-18/ASSET/41B0F3BB-FAE2-41E5-9342-25029343E7C6/ASSETS/GRAPHIC/ZCM0011926520002.JPEG
25. Obasi CN, Barrett B, Brown R, et al. Detection of viral and bacterial pathogens in acute respiratory infections. *J Infect*. 2014;68(2):125. doi:10.1016/J.JINF.2013.10.013
26. Sohn AJ, Hickner JM, Alem F. Use of Point-of-Care Tests (POCTs) by US Primary Care Physicians. *J Am Board Fam Med*. 2016;29(3):371-376. doi:10.3122/JABFM.2016.03.150249
27. Karako K, Song P, Chen Y, Tang W. Increasing demand for point-of-care testing and the potential to incorporate the Internet of medical things in an integrated health management system. *Biosci Trends*. 2022;16(1):4-6. doi:10.5582/BST.2022.01074
28. Dhesi Z, Enne VI, O'Grady J, Gant V, Livermore DM. Rapid and Point-of-Care Testing in Respiratory TractInfections: An Antibiotic Guardian? *ACS Pharmacol Transl Sci*. 2020;3(3):401. doi:10.1021/ACSPTSCI.0C00027
29. Fendrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of non-

influenza-related viral respiratory tract infection in the United States. *Arch Intern Med*. 2003;163(4):487-494. doi:10.1001/ARCHINTE.163.4.487
30. Shi T, Arnott A, Semogas I, et al. The Etiological Role of Common Respiratory Viruses in Acute Respiratory Infections in Older Adults: A Systematic Review and Meta-analysis. *J Infect Dis*. 2020;222(Supplement_7):S563-S569. doi:10.1093/INFDIS/JIY662
31. Creer DD, Dilworth JP, Gillespie SH, et al. Aetiological role of viral and bacterial infections in acute adult lower respiratory tract infection (LRTI) in primary care. *Thorax*. 2006;61(1):75-79. doi:10.1136/THX.2004.027441
32. Sundell N, Andersson LM, Brittain-Long R, et al. PCR Detection of Respiratory Pathogens in Asymptomatic and Symptomatic Adults. *J Clin Microbiol*. 2019;57(1). doi:10.1128/JCM.00716-18
33. Milucky J, Pondo T, Gregory CJ, et al. The epidemiology and estimated etiology of pathogens detected from the upper respiratory tract of adults with severe acute respiratory infections in multiple countries, 2014-2015. *PLoS One*. 2020;15(10). doi:10.1371/JOURNAL.PONE.0240309
34. Normal Respiratory Microbiota in Health and Disease. https://asm.org/Articles/2020/February/Normal-Respiratory-Microbiota-in-Health-and-Diseas. Accessed March 25, 2022.
35. Khan R, Petersen FC, Shekhar S. Commensal Bacteria: An Emerging Player in Defense Against Respiratory Pathogens. *Front Immunol*. 2019;10(MAY):1203. doi:10.3389/FIMMU.2019.01203
36. Murphy TF, Bakaletz LO, Smeesters PR. Microbial interactions in the respiratory tract. *Pediatr Infect Dis J*. 2009;28(10 Suppl). doi:10.1097/INF.0B013E3181B6D7EC
37. Prat C, Lacoma A. Bacteria in the respiratory tract-how to treat? Or do not treat? *Int J Infect Dis*. 2016;51:113-122. doi:10.1016/J.IJID.2016.09.005
38. Bakaletz LO. Viral–bacterial co-infections in the respiratory tract. *Curr Opin Microbiol*. 2017;35:30. doi:10.1016/J.MIB.2016.11.003
39. Rothberg MB, Haessler SD, Brown RB. Complications of Viral Influenza. *Am J Med*. 2008;121(4):258. doi:10.1016/J.AMJMED.2007.10.040
40. Monasta L, Ronfani L, Marchetti F, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS One*. 2012;7(4). doi:10.1371/JOURNAL.PONE.0036226
41. Vermee Q, Cohen R, Hays C, et al. Biofilm production by Haemophilus influenzae and Streptococcus pneumoniae isolated from the nasopharynx of children with acute otitis media. *BMC Infect Dis*. 2019;19(1). doi:10.1186/S12879-018-3657-9
42. Donlan RM. Biofilms: microbial life on surfaces. *Emerg Infect Dis*. 2002;8(9):881-890. doi:10.3201/EID0809.020063
43. Coticchia JM, Chen M, Sachdeva L, Mutchnick S. New paradigms in the pathogenesis of otitis media in children. *Front Pediatr*. 2013;1(DEC). doi:10.3389/FPED.2013.00052
44. Summary Health Statistics: National Health Interview Survey. https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2018_SHS_Table_A-2.pdf. Published 2018. Accessed March 25, 2022.
45. Akinbami LJ, Moorman JE, Bailey C, et al. *NCHS Data Brief, Number 94, May 2012*.; 2001. http://www.cdc.gov/nchs/data/databriefs/db94_tables.pdf#2. Accessed April 14, 2021.

46. Millett ERC, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. *PLoS One*. 2013;8(9). doi:10.1371/JOURNAL.PONE.0075131
47. Claassen-Weitz S, Lim KYL, Mullally C, Zar HJ, Nicol MP. The association between bacteria colonizing the upper respiratory tract and lower respiratory tract infection in young children: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2021;27(9):1262-1270. doi:10.1016/J.CMI.2021.05.034/ATTACHMENT/7EB9D7BD-B567-4302-B3E8-172F0D955856/MMC5.DOCX
48. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet (London, England)*. 2017;390(10098):946. doi:10.1016/S0140-6736(17)30938-8
49. le Roux DM, Zar HJ. Community-acquired pneumonia in children - a changing spectrum of disease. *Pediatr Radiol*. 2017;47(11):1392-1398. doi:10.1007/S00247-017-3827-8
50. FDA Approves First COVID-19 Vaccine | FDA. https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine. Accessed April 4, 2022.
51. Holtkamp N, Kolbe A, Beleche T. COVID-19 Vaccination Associated with Reductions in COVID-19 Mortality and Morbidity in the United States, and an Approach to Valuing these Benefits | ASPE. https://aspe.hhs.gov/reports/economic-health-benefits-covid-19-vaccination. Published December 15, 2021. Accessed April 6, 2022.
52. ChildVaxView | CDC. https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/index.html. Accessed March 25, 2022.
53. AdultVaxView | General Population Reports | Vaccination Coverage | CDC. https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/data-reports/general-population/index.html. Accessed March 25, 2022.
54. Audi A, AlIbrahim M, Kaddoura M, Hijazi G, Yassine HM, Zaraket H. Seasonality of Respiratory Viral Infections: Will COVID-19 Follow Suit? *Front Public Heal*. 2020;8:576. doi:10.3389/FPUBH.2020.567184/BIBTEX
55. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of Respiratory Viral Infections. *Annu Rev Virol*. 2020;7(1):83-101. doi:10.1146/ANNUREV-VIROLOGY-012420-022445
56. Eccles R. An explanation for the seasonality of acute upper respiratory tract viral infections. *Acta Otolaryngol*. 2002;122(2):183-191. doi:10.1080/00016480252814207
57. Lowen AC, Steel J. Roles of Humidity and Temperature in Shaping Influenza Seasonality. *J Virol*. 2014;88(14):7692-7695. doi:10.1128/JVI.03544-13/ASSET/1A25AC9B-B171-4DDE-9117-F6CD17978F69/ASSETS/GRAPHIC/ZJV9990992450001.JPEG
58. Yang W, Marr LC. Dynamics of Airborne Influenza A Viruses Indoors and Dependence on Humidity. *PLoS One*. 2011;6(6):e21481. doi:10.1371/JOURNAL.PONE.0021481
59. Morikawa S, Kohdera U, Hosaka T, et al. Seasonal variations of respiratory viruses and etiology of human rhinovirus infection in children. *J Clin Virol*. 2015;73:14. doi:10.1016/J.JCV.2015.10.001
60. Rodgers L, Sheppard M, Smith A, et al. Changes in Seasonal Respiratory Illnesses in the United States During the COVID-19 Pandemic. *Clin Infect Dis An Off Publ Infect Dis Soc Am*. 2021;73:S110-S117. doi:10.1093/CID/CIAB311

61. Fisman D. Seasonality of viral infections: mechanisms and unknowns. *Clin Microbiol Infect*. 2012;18(10):946-954. doi:10.1111/J.1469-0691.2012.03968.X
62. Willem L, van Kerckhove K, Chao DL, Hens N, Beutels P. A Nice Day for an Infection? Weather Conditions and Social Contact Patterns Relevant to Influenza Transmission. *PLoS One*. 2012;7(11):e48695. doi:10.1371/JOURNAL.PONE.0048695
63. Flasche S, Hens N, Boëlle PY, et al. Different transmission patterns in the early stages of the influenza A(H1N1)v pandemic: a comparative analysis of 12 European countries. *Epidemics*. 2011;3(2):125-133. doi:10.1016/J.EPIDEM.2011.03.005
64. Dowell SF. Seasonal variation in host susceptibility and cycles of certain infectious diseases. *Emerg Infect Dis*. 2001;7(3):369-374. doi:10.3201/EID0703.010301
65. Brownstein JS, Wolfe CJ, Mandl KD. Empirical Evidence for the Effect of Airline Travel on Inter-Regional Influenza Spread in the United States. *PLOS Med*. 2006;3(10):e401. doi:10.1371/JOURNAL.PMED.0030401
66. Cauchemez S, Valleron AJ, Boëlle PY, Flahault A, Ferguson NM. Estimating the impact of school closure on influenza transmission from Sentinel data. *Nat 2008 4527188*. 2008;452(7188):750-754. doi:10.1038/nature06732
67. Donohue JM, Miller E. COVID-19 and School Closures. *JAMA*. 2020;324(9):845-847. doi:10.1001/JAMA.2020.13092
68. Auger KA, Shah SS, Richardson T, et al. Association Between Statewide School Closure and COVID-19 Incidence and Mortality in the US. *JAMA*. 2020;324(9):859-870. doi:10.1001/JAMA.2020.14348
69. Jin X, Ren J, Li R, et al. Global burden of upper respiratory infections in 204 countries and territories, from 1990 to 2019. *EClinicalMedicine*. 2021;37. doi:10.1016/J.ECLINM.2021.100986
70. Thomas M, Bomar PA. Upper Respiratory Tract Infection. *Medscape*. June 2021:1-18. https://www.ncbi.nlm.nih.gov/books/NBK532961/. Accessed March 25, 2022.
71. Mahowald M, Shahan B, Forbes D. Respiratory Conditions: Lower Respiratory Tract Infections - PubMed. *FP Essent*. November 2019. https://pubmed.ncbi.nlm.nih.gov/31710454/. Accessed May 1, 2022.
72. Mahashur A. Management of lower respiratory tract infection in outpatient settings: Focus on clarithromycin. *Lung India*. 2018;35(2):143. doi:10.4103/LUNGINDIA.LUNGINDIA_262_17
73. Thornton H V., Hay AD, Redmond NM, et al. Throat swabs in children with respiratory tract infection: associations with clinical presentation and potential targets for point-of-care testing. *Fam Pract*. 2017;34(4):407-415. doi:10.1093/FAMPRA/CMW136
74. Brookes-Howell L, Hood K, Cooper L, et al. Clinical influences on antibiotic prescribing decisions for lower respiratory tract infection: a nine country qualitative study of variation in care. *BMJ Open*. 2012;2(3):795. doi:10.1136/BMJOPEN-2011-000795
75. Dale AP, Marchello C, Ebell MH. Clinical gestalt to diagnose pneumonia, sinusitis, and pharyngitis: a meta-analysis. *Br J Gen Pract*. 2019;69(684):E444-E453. doi:10.3399/BJGP19X704297
76. Van Vugt SF, Verheij TJM, De Jong PA, et al. Diagnosing pneumonia in patients with acute cough: clinical judgment compared to chest radiography. *Eur Respir J*. 2013;42(4):1076-1082. doi:10.1183/09031936.00111012
77. Ebell MH, Locatelli I, Mueller Y, Senn N, Morgan K. Diagnosis and treatment of

community-acquired pneumonia in patients with acute cough: a quantitative study of decision thresholds in primary care. *Br J Gen Pract*. 2018;68(676):e765-e774. doi:10.3399/BJGP18X699545
78. Moore M, Stuart B, Little P, et al. Predictors of pneumonia in lower respiratory tract infections: 3C prospective cough complication cohort study. *Eur Respir J*. 2017;50(5). doi:10.1183/13993003.00434-2017
79. Ebell M. Diagnosis of Streptococcal Pharyngitis - Point-of-Care Guides - American Family Physician. American Family Physician. https://www.aafp.org/afp/2014/0615/p976.html. Published June 15, 2014. Accessed March 25, 2022.
80. McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE. Empirical Validation of Guidelines for the Management of Pharyngitis in Children and Adults. *J Am Med Assoc*. 2004;291(13):1587-1595. doi:10.1001/jama.291.13.1587
81. Little P, Richard Hobbs FD, Moore M, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). *BMJ*. 2013;347(7930). doi:10.1136/BMJ.F5806
82. Choby B. Diagnosis and treatment of streptococcal pharyngitis - PubMed. *Am Fam Physician*. August 2013. https://pubmed.ncbi.nlm.nih.gov/19275067/. Accessed May 1, 2022.
83. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55(10):1279-1282. doi:10.1093/CID/CIS847
84. Yüce M, Filiztekin E, Özkaya KG. COVID-19 diagnosis -A review of current methods. *Biosens Bioelectron*. 2021;172. doi:10.1016/J.BIOS.2020.112752
85. Basile K, Kok J, Dwyer DE. Point-of-care diagnostics for respiratory viral infections. *Expert Rev Mol Diagn*. 2018;18(1):75-83. doi:10.1080/14737159.2018.1419065
86. Xu G, Hsieh TM, Lee DYS, et al. A self-contained all-in-one cartridge for sample preparation and real-time PCR in rapid influenza diagnosis. *Lab Chip*. 2010;10(22):3103-3111. doi:10.1039/C005265E/
87. Hazelton B, Nedeljkovic G, Ratnamohan VM, Dwyer DE, Kok J. Evaluation of the Sofia Influenza A + B fluorescent immunoassay for the rapid diagnosis of influenza A and B. *J Med Virol*. 2015;87(1):35-38. doi:10.1002/JMV.23976
88. Ganesh M, Brawley CC, Khanwalkar A, et al. Utility of Point-of-Care COVID-19 Testing in an Outpatient Otolaryngology clinic. *OTO open*. 2021;5(4). doi:10.1177/2473974X211049328
89. Jones CHD, Howick J, Roberts NW, et al. Primary care clinicians' attitudes towards point-of-care blood testing: A systematic review of qualitative studies. *BMC Fam Pract*. 2013;14(1):1-9. doi:10.1186/1471-2296-14-117/TABLES/3
90. Lykkegaard J, Olsen JK, Sydenham RV, Hansen MP. C-reactive protein cut-offs used for acute respiratory infections in Danish general practice. *BJGP open*. 2021;5(1):1-9. doi:10.3399/BJGPOPEN20X101136
91. Cooke J, Butler C, Hopstaken R, et al. Narrative review of primary care point-of-care testing (POCT) and antibacterial use in respiratory tract infection (RTI). *BMJ Open Respir Res*. 2015;2(1):1-10. doi:10.1136/BMJRESP-2015-000086
92. The technology | QuikRead go for C-reactive protein testing in primary care | Advice |

NICE. https://www.nice.org.uk/advice/mib78/chapter/the-technology. Accessed March 25, 2022.
93. Sim TF, Chalmers L, Czarniak P, et al. Point-of-care C-reactive protein testing to support the management of respiratory tract infections in community pharmacy: A feasibility study. *Res Soc Adm Pharm*. 2021;17(10):1719-1726. doi:10.1016/J.SAPHARM.2021.01.004
94. Llor C, Bjerrum L, Munck A, Cots JM, Hernández S, Moragas A. Access to point-of-care tests reduces the prescription of antibiotics among antibiotic-requesting subjects with respiratory tract infections. *Respir Care*. 2014;59(12):1918-1923. doi:10.4187/RESPCARE.03275
95. Cals JWL, Butler CC, Hopstaken RM, Hood K, Dinant GJ. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ*. 2009;338(7703):1112-1115. doi:10.1136/BMJ.B1374
96. Al-Baadani A, Elzein F, Alhemyadi S, Khan O, Albenmousa A, Idrees M. Characteristics and outcome of viral pneumonia caused by influenza and Middle East respiratory syndrome-coronavirus infections: A 4-year experience from a tertiary care center. *Ann Thorac Med*. 2019;14(3):179. doi:10.4103/ATM.ATM_179_18
97. Abed Y, Boivin G. Treatment of respiratory virus infections. *Antiviral Res*. 2006;70(2):1-16. doi:10.1016/J.ANTIVIRAL.2006.01.006
98. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. *N Engl J Med*. 2018;379(10):913-923. doi:10.1056/NEJMOA1716197
99. Waljee AK, Rogers MAM, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ*. 2017;357:j1415. doi:10.1136/BMJ.J1415
100. Dvorin E, Ebell M. Short-Term Systemic Corticosteroids: Appropriate Use in Primary Care - American Family Physician. American Family Physician. https://www.aafp.org/afp/2020/0115/p89.html. Published January 15, 2020. Accessed March 25, 2022.
101. Donnelly JP, Baddley JW, Wang HE. Antibiotic utilization for acute respiratory tract infections in U.S. emergency departments. *Antimicrob Agents Chemother*. 2014;58(3):1451-1457. doi:10.1128/AAC.02039-13
102. Ebell M, Radke T. Antibiotic Use for Viral Acute Respiratory Tract Infections Remains Common. The American Journal of Managed Care. https://www.ajmc.com/view/antibiotic-use-for-viral-acute-respiratory-tract-infections-remains-common. Published November 10, 2015. Accessed April 5, 2022.
103. Suda KJ, Roberts RM, Hunkler RJ, Taylor TH. Antibiotic prescriptions in the community by type of provider in the United States, 2005-2010. *J Am Pharm Assoc*. 2016;56(6):621-626.e1. doi:10.1016/J.JAPH.2016.08.015
104. O'connor R, O'doherty J, O'regan A, Dunne C. Antibiotic use for acute respiratory tract infections (ARTI) in primary care; what factors affect prescribing and why is it important? A narrative review. doi:10.1007/s11845-018-1774-5
105. Andrews T, Thompson M, Buckley DI, et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and

meta-analysis. *PLoS One*. 2012;7(1). doi:10.1371/JOURNAL.PONE.0030334
106. Zoorob R, Lazelere M. Use and perceptions of antibiotics for upper respiratory infections among college students - PubMed. J Fam Pract. https://pubmed.ncbi.nlm.nih.gov/11195478/. Published January 2001. Accessed March 25, 2022.
107. Lanthier-Veilleux M, Baron G, Généreux M. Respiratory Diseases in University Students Associated with Exposure to Residential Dampness or Mold. *Int J Environ Res Public Health*. 2016;13(11). doi:10.3390/IJERPH13111154
108. Nichol KL, D'Heilly S, Ehlinger E. Burden of upper respiratory illnesses among college and university students: 2002-2003 and 2003-2004 cohorts. *Vaccine*. 2006;24(44-46):6724-6725. doi:10.1016/J.VACCINE.2006.05.033
109. Davis BM, Foxman B, Monto AS, et al. Human coronaviruses and other respiratory infections in young adults on a university campus: Prevalence, symptoms, and shedding. *Influenza Other Respi Viruses*. 2018;12(5):582-590. doi:10.1111/IRV.12563
110. Mogabgab WJ. Acute respiratory illnesses in university (1962-1966), military and industrial (1962-1963) populations. *Am Rev Respir Dis*. 1968;98(3):359-379. doi:10.1164/ARRD.1968.98.3.359
111. Siddaway AP, Wood AM, Hedges L V. How to Do a Systematic Review: A Best Practice Guide for Conducting and Reporting Narrative Reviews, Meta-Analyses, and Meta-Syntheses. *Annu Rev Psychol*. 2019;70:747-770. doi:10.1146/ANNUREV-PSYCH-010418-102803
112. Baumeister RF. Writing a Literature Review. *The Portable Mentor*. 2013:119-132. doi:10.1007/978-1-4614-3994-3_8
113. Macleod MR, Michie S, Roberts I, et al. Biomedical research: increasing value, reducing waste. *Lancet (London, England)*. 2014;383(9912):101-104. doi:10.1016/S0140-6736(13)62329-6
114. Muka T, Glisic M, Milic J, et al. A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. *Eur J Epidemiol*. 2020;35(1):49-60. doi:10.1007/S10654-019-00576-5
115. About Cochrane Reviews | Cochrane Library. https://www.cochranelibrary.com/about/about-cochrane-reviews. Accessed March 29, 2022.
116. Higgins J, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. version 6.3. Cochrane; 2022. https://training.cochrane.org/handbook. Accessed March 29, 2022.
117. Cummings SR, Browner WS, Hulley SB. Conceiving the research question and developing the study plan. In: *Designing Clinical Research: An Epidemiological Approach*. 4th ed. Philadelphia: Lippincott William & Wilkins; 2007:14-22.
118. Mckenzie J, Brennan S, Ryan R, Thomson H, Johnston R, Thomas J. Chapter 3: Defining the criteria for including studies and how they will be grouped for the synthesis | Cochrane Training. In: *Cochrane Handbook for Systematic Reviews of Interventions*. ; 2022. https://training.cochrane.org/handbook/current/chapter-03. Accessed May 1, 2022.
119. Valentine JC, Thompson SG. Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions. *Res Synth Methods*. 2013;4(1):26-35. doi:10.1002/JRSM.1064

120. Lefebvre C, Glanville J, Briscoe S, et al. Chapter 4: Searching for and selecting studies | Cochrane Training. In: *Cochrane Handbook for Systematic Reviews of Interventions*. ; 2022. https://training.cochrane.org/handbook/current/chapter-04. Accessed May 1, 2022.
121. Frandsen TF, Bruun Nielsen MF, Lindhardt CL, Eriksen MB. Using the full PICO model as a search tool for systematic reviews resulted in lower recall for some PICO elements. *J Clin Epidemiol*. 2020;127:69-75. doi:10.1016/J.JCLINEPI.2020.07.005
122. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: A prospective exploratory study. *Syst Rev*. 2017;6(1):1-12. doi:10.1186/S13643-017-0644-Y/TABLES/5
123. Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. *BMJ*. 1997;315(7109):635-640. doi:10.1136/BMJ.315.7109.635
124. Li T, Higgins J, Deeks J. Chapter 5: Collecting data | Cochrane Training. In: *Cochrane Handbook for Systematic Reviews of Interventions*. ; 2022. https://training.cochrane.org/handbook/current/chapter-05. Accessed May 1, 2022.
125. Deeks J, Higgins J, Altman D. Chapter 10: Analysing data and undertaking meta-analyses | Cochrane Training. In: *Cochrane Handbook for Systematic Reviews of Interventions*. ; 2022. https://training.cochrane.org/handbook/current/chapter-10. Accessed May 1, 2022.
126. Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. *BMJ*. 2001;322(7300):1479-1480. doi:10.1136/BMJ.322.7300.1479
127. Borenstein M, Higgins JPT, Hedges L V., Rothstein HR. Basics of meta-analysis: I2 is not an absolute measure of heterogeneity. *Res Synth Methods*. 2017;8(1):5-18. doi:10.1002/JRSM.1230
128. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372. doi:10.1136/BMJ.N71
129. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ*. 2001;323(7303):42-46. doi:10.1136/BMJ.323.7303.42
130. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: What are they and which is better? *Mil Med Res*. 2020;7(1):1-11. doi:10.1186/S40779-020-00238-8/TABLES/1
131. Edouard S, Million M, Bachar D, et al. The nasopharyngeal microbiota in patients with viral respiratory tract infections is enriched in bacterial pathogens. *Eur J Clin Microbiol Infect Dis*. 2018;37(9):1725-1733. doi:10.1007/S10096-018-3305-8
132. Man WH, De Steenhuijsen Piters WAA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. *Nat Rev Microbiol*. 2017;15(5):259-270. doi:10.1038/NRMICRO.2017.14
133. Gunnarsson RK, Holm SE, Söderström M. The prevalence of potentially pathogenic bacteria in nasopharyngeal samples from individuals with a long-standing cough-clinical value of a nasopharyngeal sample. *Fam Pract*. 2000;17(2):150-155. doi:10.1093/FAMPRA/17.2.150
134. Gunnarsson RK, Holm SE, Söderström M. The prevalence of potential pathogenic bacteria in nasopharyngeal samples from healthy children and adults. *Scand J Prim Health Care*. 1998;16(1):13-17. doi:10.1080/028134398750003340
135. Glannini EH. Design, measurement, and analysis of clinical investigations. *Textb Pediatr*

Rheumatol. 2005:142-173. doi:10.1016/B978-1-4160-0246-8.50012-7
136. Riffenburgh RH. Statistical Testing, Risks, and Odds in Medical Decisions. *Stat Med*. 2006:93-114. doi:10.1016/B978-012088770-5/50045-9
137. Gunnarsson RK, Manchal N. Group C beta hemolytic Streptococci as a potential pathogen in patients presenting with an uncomplicated acute sore throat - a systematic literature review and meta-analysis. *Scand J Prim Health Care*. 2020;38(2):226-237. doi:10.1080/02813432.2020.1753374
138. Renati S, Linder JA. Necessity of office visits for acute respiratory infections in primary care. *Fam Pract*. 2016;33(3):312-317. doi:10.1093/FAMPRA/CMW019
139. Diao M, Shen X, Cheng J, et al. How patients' experiences of respiratory tract infections affect healthcare-seeking and antibiotic use: insights from a cross-sectional survey in rural Anhui, China. *BMJ Open*. 2018;8(2):e019492. doi:10.1136/BMJOPEN-2017-019492
140. Borges Migliavaca C, Stein C, Onica Colpani V, Munn Z, Falavigna M. Quality assessment of prevalence studies: a systematic review. *J Clin Epidemiol*. 2020;127:59-68. doi:10.1016/j.jclinepi.2020.06.039
141. Gunnarsson RK, Lanke J. The predictive value of microbiologic diagnostic tests if asymptomatic carriers are present. *Stat Med*. 2002;21(12):1773-1785. doi:10.1002/SIM.1119
142. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics*. 2018;74(3):785-794. doi:10.1111/BIOM.12817
143. Sutton AJ, Higgins JPT. Recent developments in meta-analysis. *Stat Med*. 2008;27(5):625-650. doi:10.1002/SIM.2934
144. Van Enst WA, Ochodo E, Scholten RJ, Hooft L, Leeflang MM. Investigation of publication bias in meta-analyses of diagnostic test accuracy: A meta-epidemiological study. *BMC Med Res Methodol*. 2014;14(1):1-11. doi:10.1186/1471-2288-14-70/TABLES/3
145. Bujang MA, Sa'At N, Tg Abu Bakar Sidik TMI, Lim CJ. Sample Size Guidelines for Logistic Regression from Observational Studies with Large Population: Emphasis on the Accuracy Between Statistics and Parameters Based on Real Life Clinical Data. *Malays J Med Sci*. 2018;25(4):122-130. doi:10.21315/MJMS2018.25.4.12
146. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005;15(9):1277-1288. doi:10.1177/1049732305276687
147. Teherani A, Martimianakis T, Stenfors-Hayes T, Wadhwa A, Varpio L. Choosing a Qualitative Research Approach. *J Grad Med Educ*. 2015;7(4):669. doi:10.4300/JGME-D-15-00414.1
148. Bassis CM, Erb-Downward JR, Dickson RP, et al. Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. *MBio*. 2015;6(2). doi:10.1128/MBIO.00037-15
149. Segal LN, Alekseyenko A V., Clemente JC, et al. Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. *Microbiome*. 2013;1(1). doi:10.1186/2049-2618-1-19
150. Bosch AATM, De Steenhuijsen Piters WAA, Van Houten MA, et al. Maturation of the Infant Respiratory Microbiota, Environmental Drivers, and Health Consequences. A Prospective Cohort Study. *Am J Respir Crit Care Med*. 2017;196(12):1582-1590. doi:10.1164/RCCM.201703-0554OC

151. Teo SM, Mok D, Pham K, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. *Cell Host Microbe*. 2015;17(5):704-715. doi:10.1016/J.CHOM.2015.03.008
152. Von Hippel PT. The heterogeneity statistic I2 can be biased in small meta-analyses. *BMC Med Res Methodol*. 2015;15(1):1-8. doi:10.1186/S12874-015-0024-Z/FIGURES/4
153. Nomanpour B, Ghodousi A, Babaei T, Jafari S, Feizabadi MM. Single tube real time PCR for detection of Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydophila pneumoniae and Legionella pneumophila from clinical samples of CAP. *Acta Microbiol Immunol Hung*. 2012;59(2):171-184. doi:10.1556/AMICR.59.2012.2.3
154. Luo X, Zhou W, Yan X, et al. Prognostic value of C-reactive protein in patients with COVID-19. *Clin Infect Dis*. May 2020. doi:10.1093/cid/ciaa641
155. Gunnarsson R. EPV Calculator – INFOVOICE.SE. https://infovoice.se/epv-calculator/. Published September 1, 2001. Accessed July 17, 2023.
156. 10.4.3.1 Recommendations on testing for funnel plot asymmetry. https://handbook-5-1.cochrane.org/chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_plot_asymmetry.htm. Accessed July 17, 2023.
157. Shih HI, Wang HC, Su IJ, et al. Viral Respiratory Tract Infections in Adult Patients Attending Outpatient and Emergency Departments, Taiwan, 2012–2013: A PCR/Electrospray Ionization Mass Spectrometry Study. *Medicine (Baltimore)*. 2015;94(38). doi:10.1097/MD.0000000000001545
158. Zimmerman RK, Rinaldo CR, Nowalk MP, et al. Influenza and other respiratory virus infections in outpatients with medically attended acute respiratory infection during the 2011-12 influenza season. *Influenza Other Respi Viruses*. 2014;8(4):397. doi:10.1111/IRV.12247
159. Chi D, Hendley JO, French P, Arango P, Hayden F, Winther B. Nasopharyngeal reservoir of bacterial otitis media and sinusitis pathogens in adults during wellness and viral respiratory illness - PubMed. https://pubmed.ncbi.nlm.nih.gov/12962190/. Published 2003. Accessed January 17, 2023.
160. Han JK, Hendley JO, Winther B. Bacterial pathogens of acute sinusitis in the osteomeatal complex during common colds and wellness. *Int Forum Allergy Rhinol*. 2011;1(5):356-360. doi:10.1002/ALR.20080
161. Layani-Milon MP, Gras I, Valette M, et al. Incidence of Upper Respiratory Tract Mycoplasma pneumoniae Infections among Outpatients in Rhône-Alpes, France, during Five Successive Winter Periods. *J Clin Microbiol*. 1999;37(6):1721. doi:10.1128/JCM.37.6.1721-1726.1999
162. Lu Y, Tong J, Pei F, et al. Viral Aetiology in Adults with Acute Upper Respiratory Tract Infection in Jinan, Northern China. *Clin Dev Immunol*. 2013;2013. doi:10.1155/2013/869521
163. Graffelman AW, Willemssen FEJA, Zonderland HM, Knuistingh Neven A, Kroes ACM, van den Broek PJ. Limited value of chest radiography in predicting aetiology of lower respiratory tract infection in general practice. *Br J Gen Pract*. 2008;58(547):93. doi:10.3399/BJGP08X264054
164. Holm A, Nexoe J, Bistrup LA, et al. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. *Br J Gen Pract*. 2007;57(540):547. /pmc/articles/PMC2099637/. Accessed January 17, 2023.

165. Huijskens EGW, Koopmans M, Palmen FMH, van Erkel AJM, Mulder PGH, Rossen JWA. The value of signs and symptoms in differentiating between bacterial, viral and mixed aetiology in patients with community-acquired pneumonia. *J Med Microbiol*. 2014;63(PART 3):441-452. doi:10.1099/JMM.0.067108-0/CITE/REFWORKS
166. Ieven M, Coenen S, Loens K, et al. Aetiology of lower respiratory tract infection in adults in primary care: a prospective study in 11 European countries. *Clin Microbiol Infect*. 2018;24(11):1158. doi:10.1016/J.CMI.2018.02.004
167. Liu YF, Gao Y, Chen MF, Cao B, Yang XH, Wei L. Etiological analysis and predictive diagnostic model building of community-acquired pneumonia in adult outpatients in Beijing, China. *BMC Infect Dis*. 2013;13(1):309. doi:10.1186/1471-2334-13-309
168. Vos LM, Bruyndonckx R, Zuithoff NPA, et al. Lower respiratory tract infection in the community: associations between viral aetiology and illness course. *Clin Microbiol Infect*. 2021;27(1):96. doi:10.1016/J.CMI.2020.03.023
169. Karamese M, Ozgur D, Tarhan C, et al. Prevalence of COVID-19 in 10,000 samples from 7853 patients in Eastern Turkey by positive real-time PCR. *Future Microbiol*. 2021;16(10):697. doi:10.2217/FMB-2020-0134
170. Setiadi W, Rozi IE, Safari D, et al. Prevalence and epidemiological characteristics of COVID-19 after one year of pandemic in Jakarta and neighbouring areas, Indonesia: A single center study. *PLoS One*. 2022;17(5). doi:10.1371/JOURNAL.PONE.0268241
171. Viera-Segura O, Vega-Magaña N, García-Chagollán M, et al. A Comprehensive Descriptive Epidemiological and Clinical Analysis of SARS-CoV-2 in West-Mexico during COVID-19 Pandemic 2020. *Int J Environ Res Public Health*. 2021;18(20):10644. doi:10.3390/IJERPH182010644
172. Bolotin S, Deeks SL, Marchand-Austin A, et al. Correlation of Real Time PCR Cycle Threshold Cut-Off with Bordetella pertussis Clinical Severity. *PLoS One*. 2015;10(7):e0133209. doi:10.1371/JOURNAL.PONE.0133209
173. Caraguel CGB, Stryhn H, Gagné N, Dohoo IR, Hammell KL. Selection of a cutoff value for real-time polymerase chain reaction results to fit a diagnostic purpose: Analytical and epidemiologic approaches. *J Vet Diagnostic Investig*. 2011;23(1):2-15. doi:10.1177/104063871102300102/ASSET/IMAGES/LARGE/10.1177_1040638711023001 02-FIG5.JPEG
174. Park S, Lee Y, Michelow IC, Choe YJ. Global Seasonality of Human Coronaviruses: A Systematic Review. *Open Forum Infect Dis*. 2020;7(11). doi:10.1093/OFID/OFAA443
175. Nickbakhsh S, Nickbakhsh S, Ho A, et al. Epidemiology of Seasonal Coronaviruses: Establishing the Context for the Emergence of Coronavirus Disease 2019. *J Infect Dis*. 2020;222(1):17-25. doi:10.1093/INFDIS/JIAA185
176. Harrison CM, Doster JM, Landwehr EH, et al. Evaluating the Virology and Evolution of Seasonal Human Coronaviruses Associated with the Common Cold in the COVID-19 Era. *Microorganisms*. 2023;11(2). doi:10.3390/MICROORGANISMS11020445
177. Liu DX, Liang JQ, Fung TS. Human Coronavirus-229E, -OC43, -NL63, and -HKU1 (Coronaviridae). *Encycl Virol Vol 1-5, Fourth Ed*. 2021;1-5:428-440. doi:10.1016/B978-0-12-809633-8.21501-X
178. Lau SKP, Lee P, Tsang AKL, et al. Molecular Epidemiology of Human Coronavirus OC43 Reveals Evolution of Different Genotypes over Time and Recent Emergence of a Novel Genotype due to Natural Recombination. *J Virol*. 2011;85(21):11325.

doi:10.1128/JVI.05512-11
179. Woo PCY, Lau SKP, Yip CCY, et al. Comparative Analysis of 22 Coronavirus HKU1 Genomes Reveals a Novel Genotype and Evidence of Natural Recombination in Coronavirus HKU1. *J Virol*. 2006;80(14):7136. doi:10.1128/JVI.00509-06
180. Ljubin-Sternak S, Meštrović T, Lukšić I, Mijač M, Vraneš J. Seasonal Coronaviruses and Other Neglected Respiratory Viruses: A Global Perspective and a Local Snapshot. *Front Public Heal*. 2021;9:691163. doi:10.3389/FPUBH.2021.691163/BIBTEX
181. Monto AS, DeJonge PM, Callear AP, et al. Coronavirus Occurrence and Transmission Over 8 Years in the HIVE Cohort of Households in Michigan. *J Infect Dis*. 2020;222(1):9-16. doi:10.1093/INFDIS/JIAA161
182. Kong D, Zheng Y, Hu L, et al. Epidemiological and co-infection characteristics of common human coronaviruses in Shanghai, 2015–2020: a retrospective observational study. *Emerg Microbes Infect*. 2021;10(1):1660. doi:10.1080/22221751.2021.1965498
183. Lau HY, Huffnagle GB, Moore TA. Host and microbiota factors that control Klebsiella pneumoniae mucosal colonization in mice. *Microbes Infect*. 2008;10(12-13):1283. doi:10.1016/J.MICINF.2008.07.040
184. De Gutierrez RC, De Nader OM, Pesce De Ruiz Holgado A, Nader-Macias ME. Microbial flora variations in the respiratory tract of mice. *Mem Inst Oswaldo Cruz*. 1999;94(5):701-707. doi:10.1590/S0074-02761999000500027
185. Niemela SI, Vaatanen P, Mentu J, Jokinen A, Jäppinen P, Sillanpää P. Microbial incidence in upper respiratory tracts of workers in the paper industry. *Appl Environ Microbiol*. 1985;50(1):163. doi:10.1128/AEM.50.1.163-168.1985
186. Ostfeld E, Segal J, Segal A, Bogokovski B. Bacterial colonization of the nose and external ear canal in newborn infants. *Isr J Med Sci*. 1983;19(12):1046-1049. https://europepmc.org/article/med/6363353. Accessed August 19, 2023.
187. Martin RM, Bachman MA. Colonization, infection, and the accessory genome of Klebsiella pneumoniae. *Front Cell Infect Microbiol*. 2018;8(JAN):314961. doi:10.3389/FCIMB.2018.00004/BIBTEX
188. Paczosa MK, Mecsas J. Klebsiella pneumoniae: Going on the Offense with a Strong Defense. *Microbiol Mol Biol Rev*. 2016;80(3):629-661. doi:10.1128/MMBR.00078-15
189. Li B, Zhao Y, Liu C, Chen Z, Zhou D. Molecular pathogenesis of Klebsiella pneumoniae. *Future Microbiol*. 2014;9(9):1071-1081. doi:10.2217/FMB.14.48
190. Magill SS, Edwards JR, Bamberg W, et al. Multistate Point-Prevalence Survey of Health Care–Associated Infections. *N Engl J Med*. 2014;370(13):1198-1208. doi:10.1056/NEJMOA1306801/SUPPL_FILE/NEJMOA1306801_DISCLOSURES.PDF
191. Podschun R, Ullmann U. Klebsiella spp. as Nosocomial Pathogens: Epidemiology, Taxonomy, Typing Methods, and Pathogenicity Factors. *Clin Microbiol Rev*. 1998;11(4):589. doi:10.1128/CMR.11.4.589
192. Carpenter JL. Klebsiella pulmonary infections: occurrence at one medical center and review. *Rev Infect Dis*. 1990;12(4):672-682. doi:10.1093/CLINIDS/12.4.672
193. Farida H, Severin JA, Gasem MH, et al. Nasopharyngeal carriage of Klebsiella pneumoniae and other Gram-negative bacilli in pneumonia-prone age groups in Semarang, Indonesia. *J Clin Microbiol*. 2013;51(5):1614-1616. doi:10.1128/JCM.00589-13
194. Sequeira RP, McDonald JAK, Marchesi JR, Clarke TB. Commensal Bacteroidetes protect

against Klebsiella pneumoniae colonization and transmission through IL-36 signalling. *Nat Microbiol 2020 52*. 2020;5(2):304-313. doi:10.1038/s41564-019-0640-1
195. Alpern ER. Bacteremia. *Pediatr Emerg Med*. January 2007:530-534. doi:10.1016/B978-141600087-7.50071-4
196. Chhatwal GS, Graham R. Streptococcal diseases. *Int Encycl Public Heal*. 2008:231-241. doi:10.1016/B978-012373960-5.00616-X
197. Mazer BD. Otitis Media. *Pediatr Allergy Princ Pract Third Ed*. 2016:219-227.e3. doi:10.1016/B978-0-323-29875-9.00025-2
198. Weiser JN, Ferreira DM, Paton JC. Streptococcus pneumoniae: transmission, colonization and invasion. *Nat Rev Microbiol*. 2018;16(6):355. doi:10.1038/S41579-018-0001-8
199. Mitchell AM, Mitchell TJ. Streptococcus pneumoniae: virulence factors and variation. *Clin Microbiol Infect*. 2010;16(5):411-418. doi:10.1111/J.1469-0691.2010.03183.X
200. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348(18):1737-1746. doi:10.1056/NEJMOA022823
201. Nakamura S, Davis KM, Weiser JN. Synergistic stimulation of type I interferons during influenza virus coinfection promotes Streptococcus pneumoniae colonization in mice. *J Clin Invest*. 2011;121(9):3657. doi:10.1172/JCI57762
202. Avadhanula V, Rodriguez CA, DeVincenzo JP, et al. Respiratory Viruses Augment the Adhesion of Bacterial Pathogens to Respiratory Epithelium in a Viral Species- and Cell Type-Dependent Manner. *J Virol*. 2006;80(4):1629. doi:10.1128/JVI.80.4.1629-1636.2006
203. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. *J Infect Dis*. 2002;186(3):341-350. doi:10.1086/341462
204. Admission Statistics - UGA Undergraduate Admissions. https://www.admissions.uga.edu/admissions/admission-statistics/. Accessed July 31, 2023.
205. University of Georgia 2019 Fact Book. https://oir.uga.edu/_resources/files/factbook/UGA_FactBook2019.pdf. Accessed September 17, 2020.
206. Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ*. 1997;315(7104):350-352. doi:10.1136/BMJ.315.7104.350
207. Little P, Rumsby K, Kelly J, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. *JAMA*. 2005;293(24):3029-3035. doi:10.1001/JAMA.293.24.3029
208. Ebell MH. Antibiotic prescribing for cough and symptoms of respiratory tract infection: do the right thing. *JAMA*. 2005;293(24):3062-3064. doi:10.1001/JAMA.293.24.3062
209. Spurling GKP, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotic prescriptions for respiratory infections. *Cochrane database Syst Rev*. 2017;9(9). doi:10.1002/14651858.CD004417.PUB5
210. Altiner A, Wilm S, Da¨ubenerda¨da¨ubener W, et al. Sputum colour for diagnosis of a bacterial infection in patients with acute cough. *Scand J Prim Health Care*. 2009:70-73. doi:10.1080/02813430902759663

211. Wilm S, Knauf A, Kreilkamp R, Schlegel U, Altiner A. The Doctor, his Patient and the Sputum. *Z Allgemeinmed*. 2006;(2):67-73. https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,shib&db=edsbl&AN=RN183312960&site=eds-live&custid=uga1.
212. Mainous A, Zoorob R, Oler M, Haynes D. Patient knowledge of upper respiratory infections: implications for antibiotic expectations and unnecessary utilization - PubMed. *J Fam Pract*. 1997;45:75-83. https://pubmed.ncbi.nlm.nih.gov/9228917/. Accessed August 7, 2023.
213. Johnson AL, Hampson DF, Hampson NB. Sputum Color: Potential Implications for Clinical Practice. 2008.
214. Sore Throat: Symptoms, Causes & Treatment. https://my.clevelandclinic.org/health/symptoms/8274-sore-throat-pharyngitis#. Accessed August 7, 2023.
215. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination. Does this patient have strep throat? *JAMA*. 2000;284(22):2912-2918. doi:10.1001/JAMA.284.22.2912
216. Kenealy T. Sore throat. *BMJ Clin Evid*. 2014;2014. /pmc/articles/PMC3948435/. Accessed August 7, 2023.
217. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane database Syst Rev*. 2013;2013(11). doi:10.1002/14651858.CD000023.PUB4
218. Mononucleosis (Mono): Symptoms, Treatment & Diagnosis. https://my.clevelandclinic.org/health/diseases/13974-mononucleosis. Accessed August 19, 2023.
219. Velden AW van der, Sessa A, Altiner A, Pignatari ACC, Shephard A. Patients with Sore Throat: A Survey of Self-Management and Healthcare-Seeking Behavior in 13 Countries Worldwide. *Pragmatic Obs Res*. 2020;11:91. doi:10.2147/POR.S255872
220. Young EH, Strey KA, Lee GC, et al. National Disparities in Antibiotic Prescribing by Race, Ethnicity, Age Group, and Sex in United States Ambulatory Care Visits, 2009 to 2016. *Antibiotics*. 2023;12(1). doi:10.3390/ANTIBIOTICS12010051/S1
221. Hersh AL, Shapiro DJ, Pavia AT, Shah SS. Antibiotic Prescribing in Ambulatory Pediatrics in the United States. *Pediatrics*. 2011;128(6):1053-1061. doi:10.1542/PEDS.2011-1337
222. McCaig LF, Besser RE, Hughes JM. Trends in Antimicrobial Prescribing Rates for Children and Adolescents. *JAMA*. 2002;287(23):3096-3102. doi:10.1001/JAMA.287.23.3096
223. Mangione-Smith R, Elliott MN, Stivers T, McDonald L, Heritage J, McGlynn EA. Racial/ethnic variation in parent expectations for antibiotics: implications for public health campaigns. *Pediatrics*. 2004;113(5). doi:10.1542/PEDS.113.5.E385
224. Harris AM, Hicks LA, Qaseem A. Appropriate antibiotic use for acute respiratory tract infection in adults: Advice for high-value care from the American college of physicians and the centers for disease control and prevention. *Ann Intern Med*. 2016;164(6):425-434. doi:10.7326/M15-1840/SUPPL_FILE/M15-1840_SUPPLEMENT.PDF
225. Chow AW, Benninger MS, Brook I, et al. IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. *Clin Infect Dis*. 2012;54(8):e72-e112. doi:10.1093/CID/CIS370

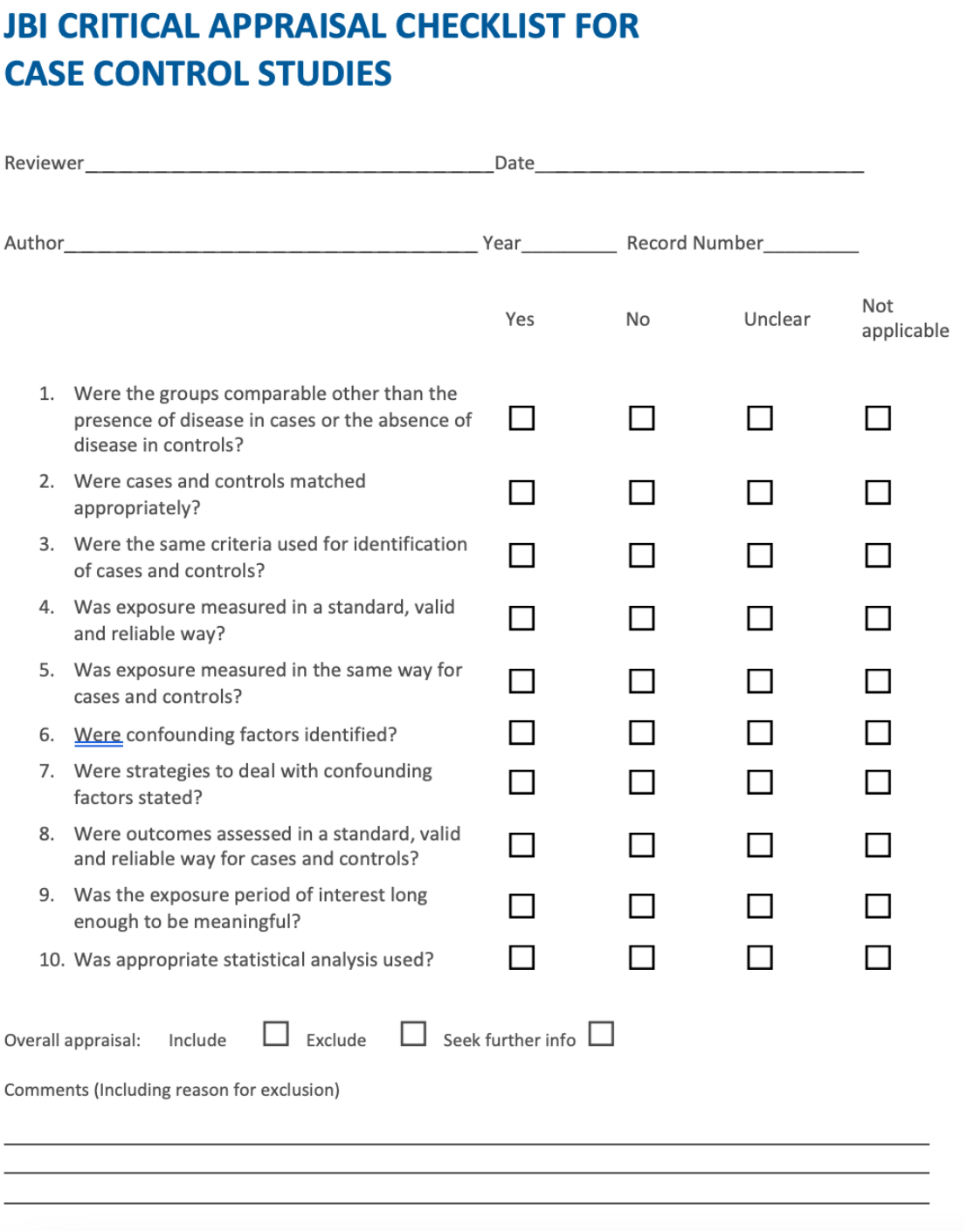
226. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): Adult sinusitis. *Otolaryngol - Head Neck Surg (United States)*. 2015;152:S1-S39. doi:10.1177/0194599815572097/ASSET/IMAGES/LARGE/10.1177_0194599815572097-FIG5.JPEG
227. Al-Mahrezi A, Samir N, Al-Zakwani I, Al-Muharmi Z, Balkhair A, Al-Shafaee M. Clinical characteristics of influenza A H1N1 versus other influenza-like illnesses amongst outpatients attending a university health center in Oman. *Int J Infect Dis*. 2012;16(7):e504-e507. doi:10.1016/j.ijid.2012.02.015
228. Kiertiburanakul S, Morasert T, Sirinavin S, Chantratita W. Comparisons of Clinical Characteristics between Adult Patients with 2009 H1N1 Influenza and Those with Seasonal Influenza during the 2009 Epidemic in Thailand. *Jpn J Infect Dis*. 2014;67:33-39.
229. Ouchi D, García-Sangenís A, Moragas A, et al. Clinical prediction of laboratory-confirmed influenza in adults with influenza-like illness in primary care. A randomized controlled trial secondary analysis in 15 European countries. *Fam Pract*. 2022;39(3):398-405. doi:10.1093/FAMPRA/CMAB122
230. Padin DS, Faix D, Brodine S, et al. Retrospective analysis of demographic and clinical factors associated with etiology of febrile respiratory illness among US military basic trainees. *BMC Infect Dis*. 2014;14(1). doi:10.1186/S12879-014-0576-2
231. Thom DH, Grayston JT, Campbell LA, Kuo CC, Diwan VK, Wang SP. Respiratory infection with Chlamydia pneumoniae in middle-aged and older adult outpatients. *Eur J Clin Microbiol Infect Dis*. 1994;13(10):785-792. doi:10.1007/BF021113

APPENDIX A

Table A1 Search strategies for the three databases included in our systematic review.

Database	Search Terms	Link to Database and Notes
PubMed	(“respiratory tract infection”[TIAB] OR “respiratory tract infection”[MH] OR “acute bronchitis”[MH] OR “pneumonia”[MH] OR “viral rhinitis”[MH] OR “rhinosinusitis”[MH] OR “sinusitis”[TIAB] OR “otitis media”[MH] OR “pharyngitis”[MH] OR “respiratory virus”[MH]) AND (“bacteria”[MH] OR “S. pneumoniae”[MH] OR “Streptococcus”[MH] OR “H. influenzae”[MH] OR “M. catarrhalis”[MH] “virus”[MH] OR “viral” OR “influenza virus”[MH] OR “enterovirus”[MH] OR “adenovirus”[MH] OR “coronavirus”[MH] OR “respiratory syncytial virus”[MH] OR “rhinovirus”[MH] OR “parainfluenza”[MH] OR “metapneumovirus”[MH] OR “microbiome”[MH]) AND (“etiology”[TIAB] OR “aetiology”[TIAB] OR “etiological role” [TIAB] OR “prevalence”[MH] OR “prevalence”[TIAB] OR “commensal”[MH] OR “commensal”[TIAB] OR “pathogenic”[TIAB] OR “pathogenic”[MH]) NOT (“nosocomial”[TIAB] OR “nosocomial” [MH] OR “ventilator-acquired pneumonia”[TIAB] OR “ventilator-acquired” [MH])	https://pubmed.ncbi.nlm.nih.gov/searches/6599945/?mode=full&sort=date
Web of Science	“etiology of acute respiratory tract infections in outpatients”	https://www.webofscience.com
Google Scholar	“etiology of acute respiratory tract infections”	https://scholar.google.com

Figure A1 Joanna Bridges Institute (JBI) Appraisal Tool used to assess risk of bias in case-control studies.



JBI CRITICAL APPRAISAL CHECKLIST FOR CASE CONTROL STUDIES

Reviewer_____Date_____

Author_____ Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	☐	☐	☐	☐
2. Were cases and controls matched appropriately?	☐	☐	☐	☐
3. Were the same criteria used for identification of cases and controls?	☐	☐	☐	☐
4. Was exposure measured in a standard, valid and reliable way?	☐	☐	☐	☐
5. Was exposure measured in the same way for cases and controls?	☐	☐	☐	☐
6. Were confounding factors identified?	☐	☐	☐	☐
7. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	☐	☐	☐	☐
9. Was the exposure period of interest long enough to be meaningful?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

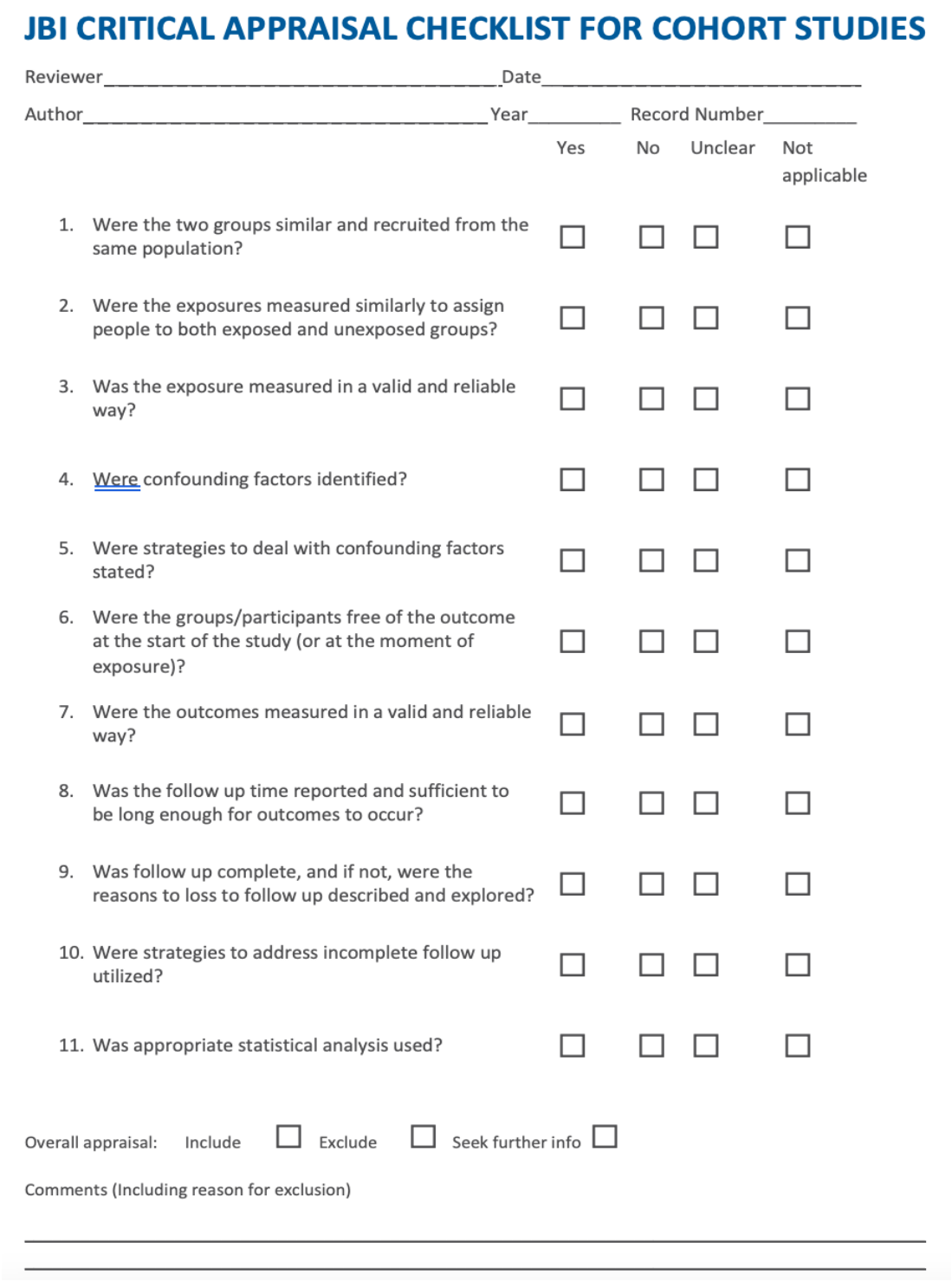
Comments (Including reason for exclusion)

_____

_____

_____

Figure A2 Joanna Bridges Institute (JBI) Appraisal Tool used to assess risk of bias in cohort studies.



JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____Date_____

Author_____Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

Figure A3 P-EPV Equation

$$P(D^+|S^+T^+) = 1 - \left(\frac{\frac{\text{Sen}}{P(T^+|S^+)} - 1}{\frac{\text{Sen}}{P(T^+|S^+D^-)} - 1} \right)$$

D = Disease

S = Symptoms

T = Test

Sen = Sensitivity

$$P(T^+|S^+D^-) = P(T^+|S^-) \times \theta$$

θ = ratio between symptomatic and asymptomatic carriers

Table A2 Joanna Bridges Institute quality assessment of case-control studies included in our systematic review.

Author, Year	Groups were comparable other than the presence of disease*	Cases and controls matched appropriately*	Same criteria were used for the identification of cases and controls*	Valid and reliable measurement of exposure*	Exposure was measured in the same way for cases and controls*	Confounding factors were identified*	Strategies to address confounding were stated*	Valid and reliable measurement of outcome*	Exposure period of interest was meaningful*	Appropriate statistical analysis*	Overall+
Creer et al, 2006	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	L
Han et al, 2011	Y	N	Y	Y	Y	N	N	Y	NA	Y	H
Ieven et al, 2018	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	L
Sundell et al, 2019	Y	N	Y	Y	Y	Y	Y	Y	NA	Y	M

* Y = yes, N = no, U = unclear, NA = not applicable in this study
+ L = low bias, M = moderate bias, H = high bias

Table A3 Joanna Bridges Institute quality assessment of cohort studies included in our systematic review.

Author, Year	Group(s) were similar and recruited from the same population*	Valid and reliable measure of exposure*	Confounding factors were identified*	Participants were free of outcome at the start of the study*	Valid measurement of the outcome*	Reported sufficient follow-up time*	Loss to follow-up was described*	Utilized strategies to address incomplete follow-up*	Appropriate statistical analysis*	Overall+
Chi et al, 2003	Y	Y	N	Y	Y	NA	NA	NA	Y	M
Graffelman et al, 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	L
Holm et al, 2007	Y	Y	Y	Y	Y	Y	Y	Y	Y	L
Karamese et al, 2021	Y	Y	Y	Y	Y	NA	NA	NA	Y	L
Layani-Milon et al, 1999	Y	Y	Y	Y	Y	Y	Y	Y	Y	L
Liu et al, 2013	Y	Y	Y	Y	Y	NA	NA	NA	Y	L
Lu et al, 2013	Y	Y	Y	Y	Y	NA	NA	NA	Y	L

Setiadi et al, 2022	Y	Y	Y	N	Y	NA	NA	NA	Y	M
Shih et al, 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	L
Viera-Segura et al, 2021	Y	Y	Y	Y	Y	NA	NA	NA	Y	L
Zimmerman et al, 2014	Y	Y	Y	Y	Y	NA	NA	NA	Y	L

* Y = yes, N = no, U = unclear, NA = not applicable in this study

+ L = low bias, M = moderate bias, H = high bias

Table A4 Raw etiology data used to create forest plots and calculate P-EPV

Study	Total Participants	Total with etiology	Total with other etiology
Symptomatic			
Influenza Virus A or B			
Creer et al, 2006	129	19 (14.7%)	110 (85.3%)
Holm et al, 2007	364	35 (9.6%)	329 (90.4%)
Graffelman et al, 2008	129	36 (27.9%)	93 (72.1%)
Ieven et al, 2018	5167	307 (5.9 %)	4860 (94.1%)
Lu et al, 2002	596	121 (20.3%)	475 (79.7%)
Shih et al, 2015	309	65 (21.0%)	244 (79.0%)
Sundell et al, 2019	547	4 (0.7%)	543 (99.3%)
Zimmerman et al, 2014	662	5 (0.76%)	657 (99.2%)
Influenza Virus A			
Holm et al, 2007	364	23 (6.3%)	341 (93.7%)
Lu et al, 2002	596	46 (7.7%)	550 (92.3%)
Shih et al, 2015	309	65 (21.0%)	244 (79.0%)
Sundell et al, 2019	547	2 (0.27%)	545 (99.6%)
Influenza Virus B			
Holm et al, 2007	364	12 (3.3%)	352 (96.7%)
Lu et al, 2002	596	75 (7.6%)	521 (87.4%)
Sundell et al, 2019	547	2 (0.4%)	545 (99.6%)
Respiratory Syncytial Virus			
Creer et al, 2006	129	2 (1.6%)	127 (98.4%)
Holm et al, 2007	364	15 (4.1%)	349 (95.9%)
Ieven et al, 2018	5167	144 (2.8%)	5023 (97.2%)
Lu et al, 2002	596	15 (2.5%)	581 (97.5%)
Shih et al, 2015	309	6 (1.9%)	303 (98.1%)
Sundell et al, 2019	547	2 (0.4%)	545 (99.6%)
Zimmerman et al, 2014	662	9 (1.4%)	653 (98.6%)
Rhinovirus			
Creer et al, 2006	129	26 (20.2%)	103 (79.8%)
Holm et al, 2007	364	37 (10.2%)	327 (89.8%)
Ieven et al, 2018	5167	623 (12.1%)	4544 (87.9%)
Lu et al, 2002	596	30 (5.0%)	566 (95.0%)
Shih et al, 2015	309	25 (8.1%)	284 (91.9%)
Sundell et al, 2019	547	23 (4.2%)	524 (95.8%)
Zimmerman et al, 2014	662	34 (5.1%)	628 (94.9%)
Human Metapneumovirus			
Holm et al, 2007	364	6 (1.6%)	358 (98.4%)
Ieven et al, 2018	5167	138 (2.7%)	5029 (97.3%)
Lu et al, 2002	596	5 (0.8%)	591 (99.2%)
Shih et al, 2015	309	10 (3.2%)	299 (96.8%)

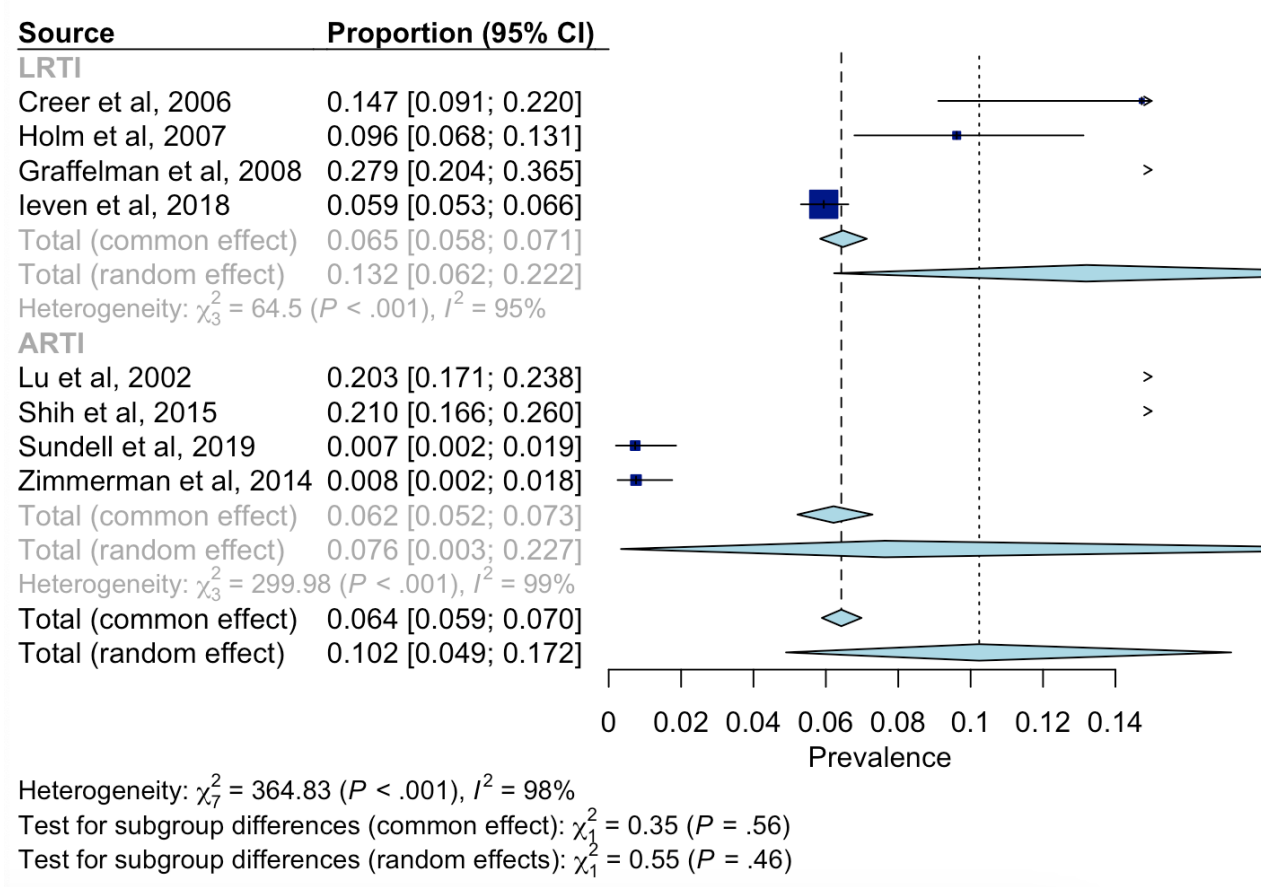
Sundell et al, 2019	547	1 (0.2%)	546 (99.8%)
Zimmerman et al, 2014	662	9 (1.4%)	653 (98.6%)
Adenovirus			
Ieven et al, 2018	5167	41 (0.8%)	5126 (99.2%)
Lu et al, 2002	596	5 (0.8%)	591 (99.2%)
Shih et al, 2015	309	6 (1.9%)	303 (98.1%)
Human Coronavirus			
Creer et al, 2006	129	5 (3.9%)	124 (96.1%)
Ieven et al, 2018	5167	231 (4.5%)	4936 (95.5%)
Lu et al, 2002	596	4 (0.67%)	592 (99.3%)
Shih et al, 2015	309	13 (4.2%)	296 (95.8%)
Sundell et al, 2019	547	6 (1.1%)	541 (98.9%)
Zimmerman et al, 2014	662	16 (2.4%)	646 (97.6%)
SARS-CoV-2			
Setiadi et al, 2022	64364	10130 (15.7%)	54234 (84.3%)
Karamese et al, 2021	7853	373 (4.7%)	7480 (95.3%)
Viera-Segura et al, 2021	23211	6918 (29.8%)	16293 (70.2%)
Enterovirus			
Creer et al, 2006	129	2 (1.6%)	127 (98.4%)
Lu et al, 2002	596	22 (3.7%)	574 (96.3%)
Shih et al, 2015	309	8 (2.6%)	301 (97.4%)
Bocavirus			
Ieven et al, 2018	5167	18 (0.3%)	5149 (99.7%)
Lu et al, 2002	596	49 (8.2%)	547 (91.8%)
Parainfluenza virus			
Creer et al, 2006	129	3 (2.3%)	126 (97.7%)
Holm et al, 2007	364	2 (0.5%)	362 (99.5%)
Ieven et al, 2018	5167	81 (1.6%)	5086 (98.4%)
Lu et al, 2002	596	5 (0.8%)	591 (99.2%)
Shih et al, 2015	309	4 (1.3%)	305 (98.7%)
Sundell et al, 2019	547	1 (18.3%)	546 (99.8%)
Parainfluenza virus 1			
Shih et al, 2015	309	3 (1.0%)	306 (99.0%)
Parainfluenza virus 3			
Holm et al, 2007	364	2 (0.5%)	362 (99.5%)
Shih et al, 2015	309	1 (0.3%)	308 (99.7%)
Moraxella catarrhalis			
Chi et al, 2003	148	25 (16.9%)	123 (83.1%)
Creer et al, 2006	129	1 (0.8%)	128 (99.2%)
Han et al, 2011	91	17 (18.7%)	74 (81.3%)
Holm et al, 2007	364	4 (1.1%)	360 (98.9%)
Streptococcus pneumoniae			
Chi et al, 2003	148	5 (3.4%)	143 (96.6%)

Creer et al, 2006	129	15 (11.6%)	114 (88.4%)
Graffelman et al, 2008	129	6 (4.7%)	123 (95.3%)
Han et al, 2011	91	10 (11.0%)	81 (89.0%)
Holm et al, 2007	364	23 (6.3%)	341 (93.7%)
Ieven et al, 2018	5167	172 (3.3%)	4995 (96.7%)
Sundell et al, 2019	547	7 (1.3%)	540 (98.7%)
Mycoplasma pneumoniae			
Creer et al, 2006	129	1 (0.8%)	128 (99.2%)
Graffelman et al, 2008	129	13 (10.1%)	116 (89.9%)
Holm et al, 2007	364	11 (3.0%)	353 (97.0%)
Ieven et al, 2018	5167	150 (2.9%)	5017 (97.1%)
Layani-Milon et al, 1999	3897	83 (2.1%)	3814 (97.9%)
Liu et al, 2013	500	49 (9.8%)	451 (90.2%)
Sundell et al, 2019	547	1 (0.2%)	546 (99.8%)
Haemophilus influenzae			
Chi et al, 2003	148	27 (18.2%)	121 (81.8%)
Creer et al, 2006	129	5 (3.9%)	124 (96.1%)
Graffelman et al, 2008	129	12 (9.3%)	117 (90.7%)
Han et al, 2011	91	18 (19.8%)	73 (80.2%)
Holm et al, 2007	364	15 (4.1%)	349 (95.9%)
Ieven et al, 2018	5167	167 (3.2%)	5000 (97.8%)
Sundell et al, 2019	547	10 (1.8%)	537 (98.2%)
Chlamydia pneumonia			
Ieven et al, 2018	5167	165 (3.2%)	5002 (96.8%)
Holm et al, 2007	364	2 (0.5%)	362 (99.5%)
Staphylococcus aureus			
Holm et al, 2007	364	2 (0.5%)	362 (99.5%)
Legionella pneumophilia			
Ieven et al, 2018	5167	6 (0.1%)	5161 (99.9%)
Bordetella pertussis			
Ieven et al, 2018	5167	95 (1.8%)	5072 (98.2%)
Asymptomatic			
Influenza virus A or B			
Ieven et al, 2018	5167	7 (0.1%)	5160 (99.9%)
Creer et al, 2006	129	3 (0.23%)	126 (97.7%)
Respiratory syncytial virus			
Ieven et al, 2018	5167	10 (0.19%)	5157 (99.8%)
Creer et al, 2006	129	2 (0.16%)	127 (98.4%)
Rhinovirus			
Creer et al, 2006	129	1 (0.8%)	128 (99.2%)
Ieven et al, 2018	5167	72 (1.4%)	5095 (98.6%)
Shih et al, 2015	309	1 (0.3%)	308 (99.7%)
Sundell et al, 2019	547	14 (2.6%)	533 (97.4%)

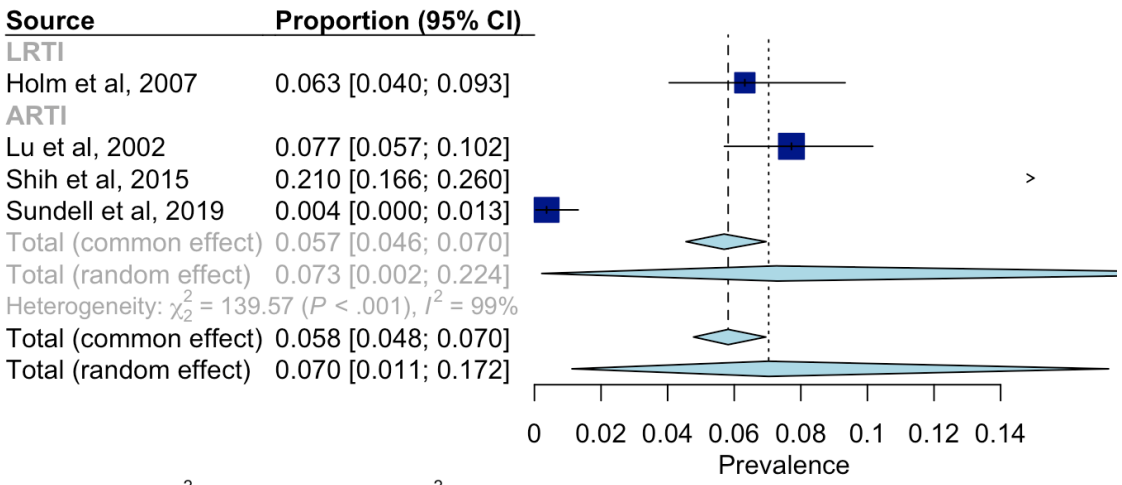
Human Coronavirus			
Creer et al, 2006	129	2 (1.6%)	127 (98.4%)
Ieven et al, 2018	5167	29 (5.6%)	5138 (99.4%)
Sundell et al, 2019	547	2 (0.4%)	545 (99.6%)
Human metapneumovirus			
Ieven et al, 2018	5167	3 (0.1%)	5164 (99.9%)
Sundell et al, 2019	547	1 (0.2%)	546 (99.8%)
Adenovirus			
Ieven et al, 2018	5167	23 (0.4%)	5144 (99.6%)
SARS-CoV-2			
Viera-Segura et al, 2021	23211	536 (2.3%)	22675 (97.7%)
Enterovirus			
Sundell et al, 2019	547	1 (0.2%)	546 (99.8%)
Creer et al, 2006	129	2 (1.6%)	127 (98.4%)
Bocavirus			
Ieven et al, 2018	5167	16 (0.3%)	5151 (99.7%)
Sundell et al, 2019	547	1 (0.2%)	546 (99.8%)
Parainfluenza virus			
Ieven et al, 2018	5167	7 (0.1%)	5160 (99.9%)
Streptococcus pneumoniae			
Chi et al, 2003	148	38 (2.6%)	110 (74.3%)
Han et al, 2011	91	8 (8.8%)	83 (91.2%)
Sundell et al, 2019	547	25 (4.6%)	522 (95.4%)
Haemophilus influenzae			
Chi et al, 2003	148	31 (20.9%)	117 (79.1%)
Han et al, 2011	91	10 (11.0%)	81 (89.0%)
Sundell et al, 2019	547	6 (1.1%)	541 (98.9%)
M. catarrhalis			
Han et al, 2011	91	9 (9.9%)	82 (90.1%)
Chi et al, 2003	148	30 (20.8%)	118 (79.7%)
C. pneumoniae			
Creer et al, 2006	129	1 (0.78%)	128 (99.2%)

Figure A4 (a – v) Forest Plots of Symptomatic Etiology

a. Influenza virus A or B

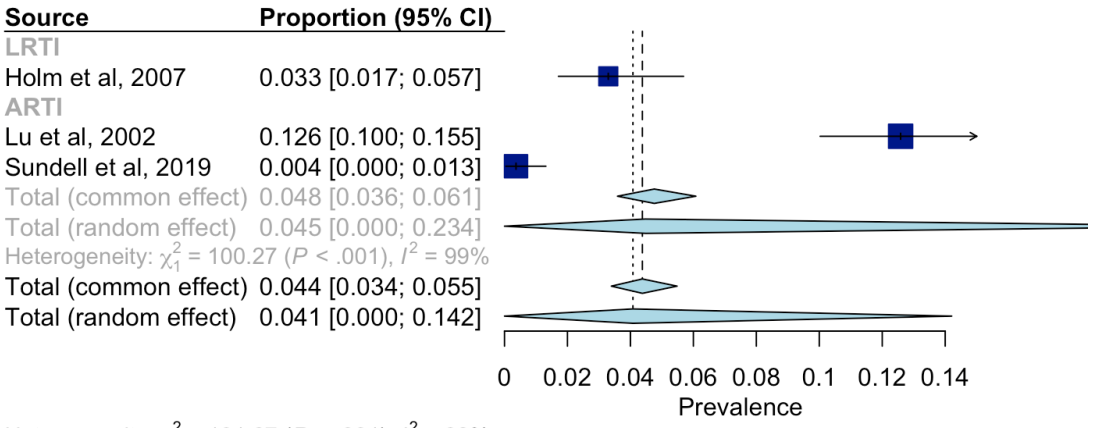


b. Influenza virus A



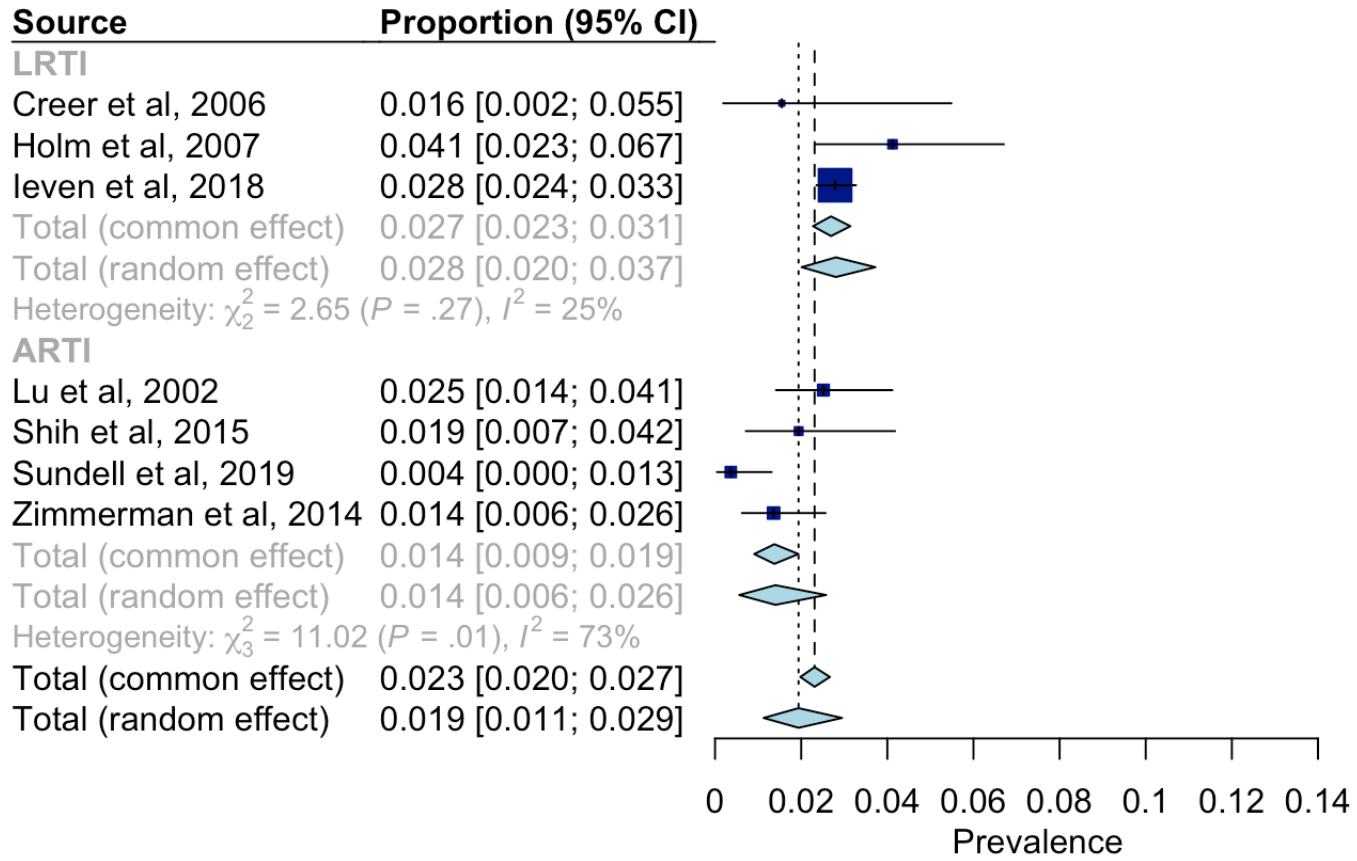
Heterogeneity: χ^2_3 = 139.78 (*P* < .001), I^2 = 98%
Test for subgroup differences (common effect): χ^2_1 = 0.21 (*P* = .65)
Test for subgroup differences (random effects): χ^2_1 = 0.03 (*P* = .87)

c. Influenza virus B



Heterogeneity: χ^2_2 = 101.67 (*P* < .001), I^2 = 98%
Test for subgroup differences (common effect): χ^2_1 = 1.41 (*P* = .24)
Test for subgroup differences (random effects): χ^2_1 = 0.04 (*P* = .85)

d. Respiratory syncytial virus

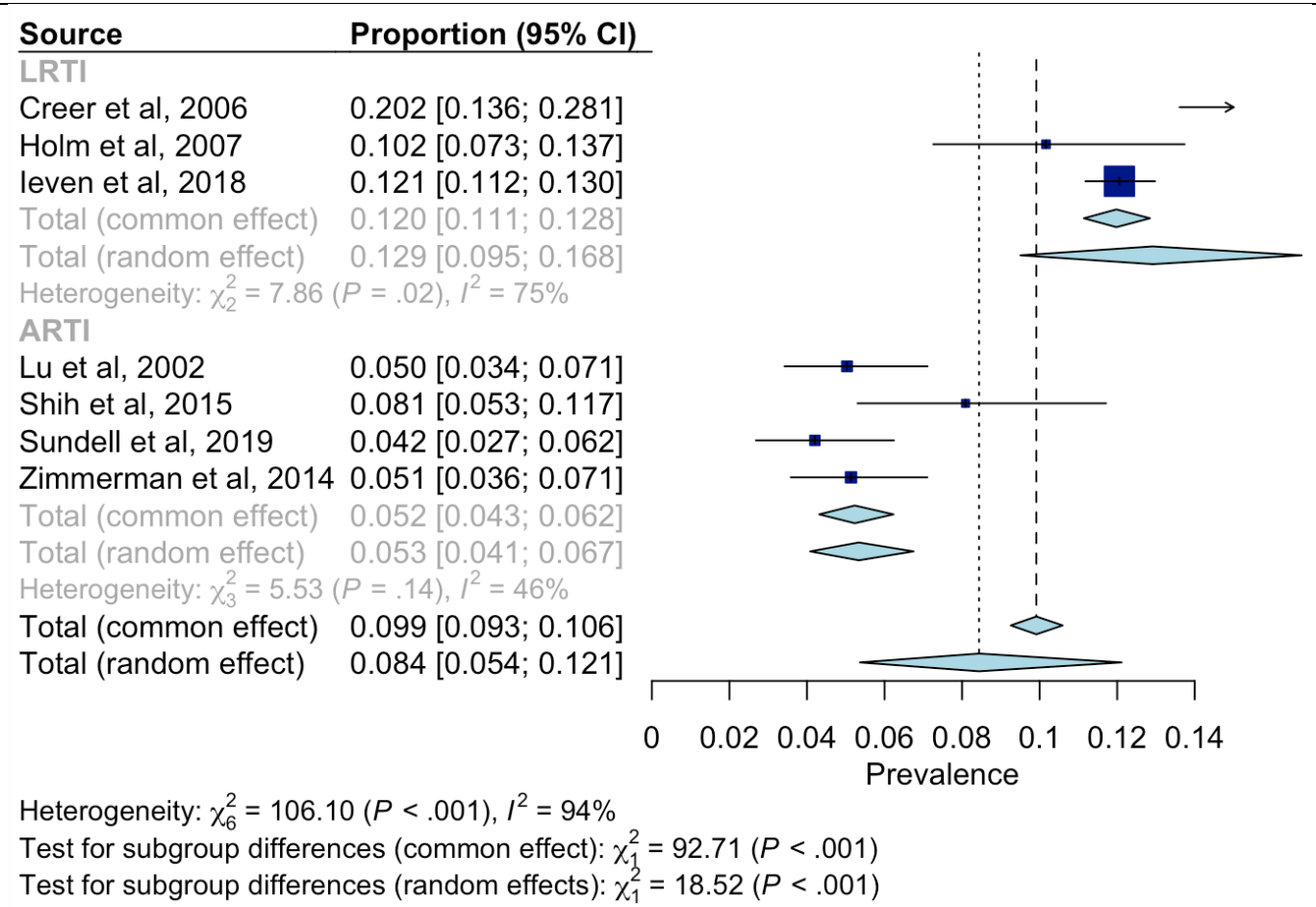


Heterogeneity: χ^2_6 = 27.91 (P < .001), I^2 = 79%

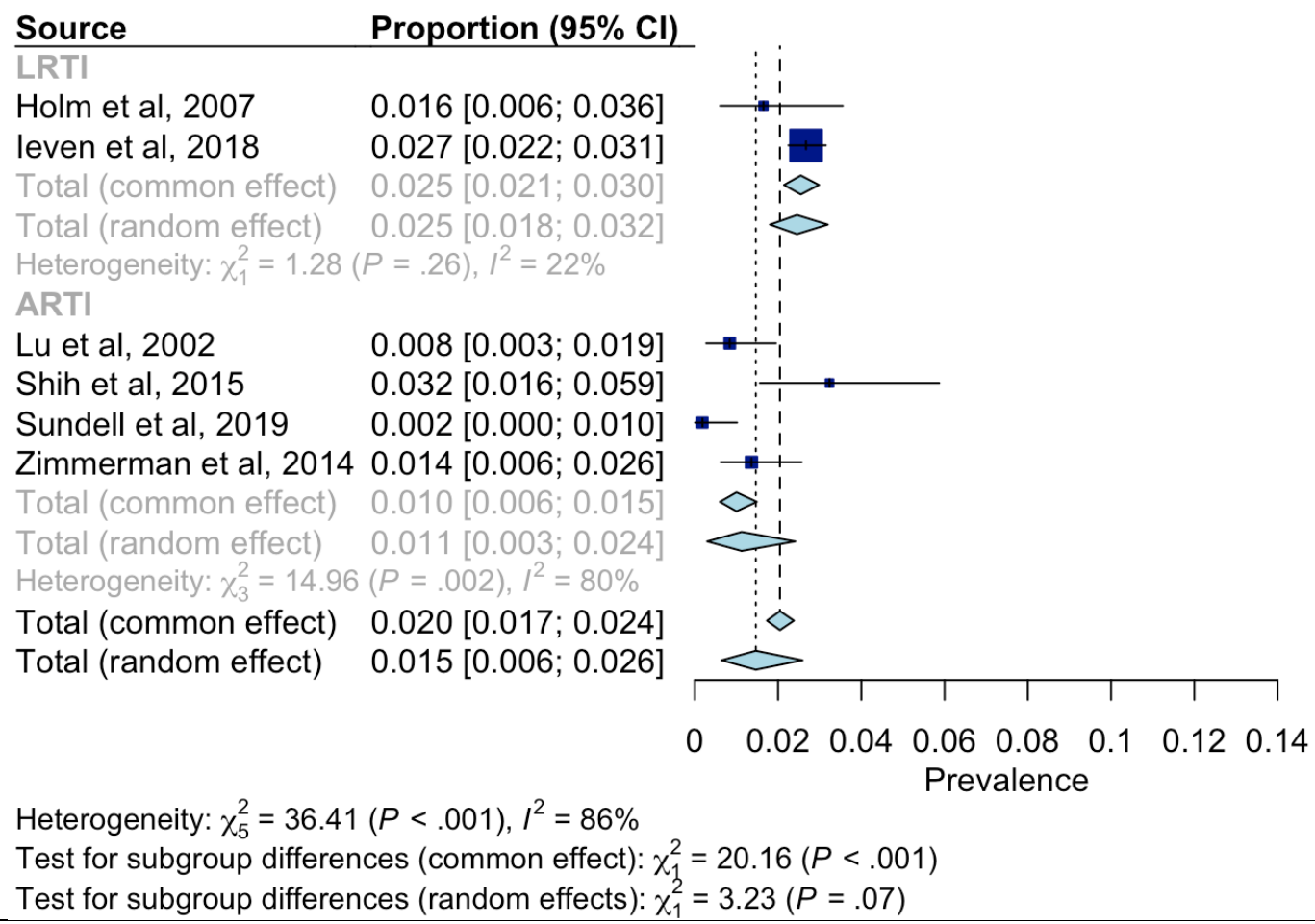
Test for subgroup differences (common effect): χ^2_1 = 14.23 (P < .001)

Test for subgroup differences (random effects): χ^2_1 = 4.15 (P = .04)

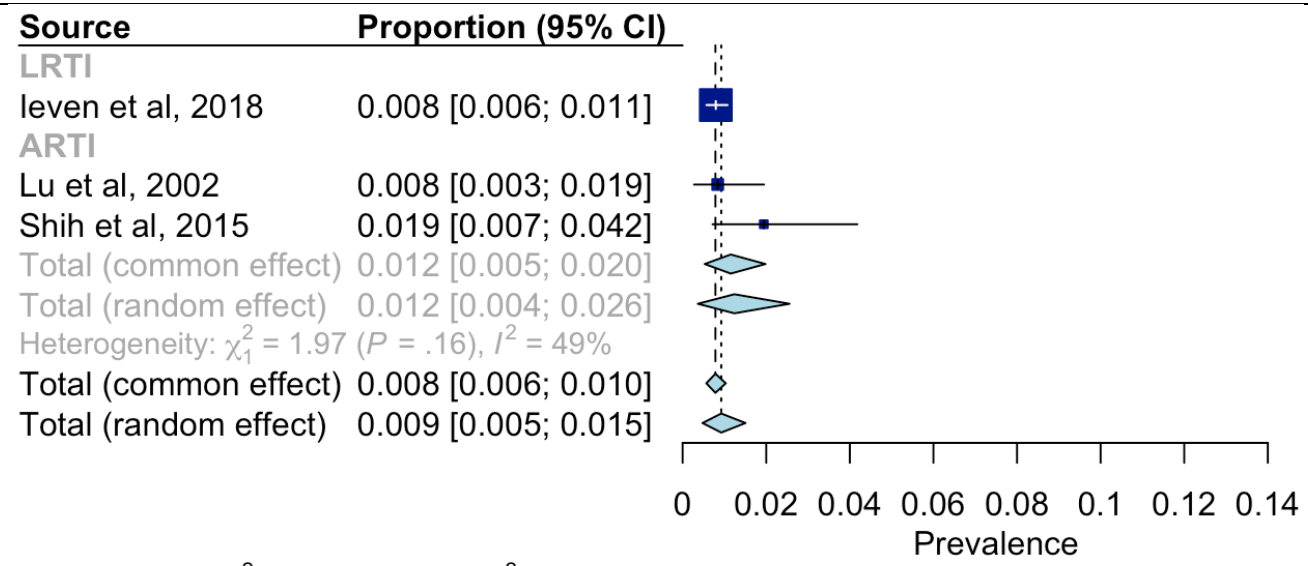
e. Rhinovirus



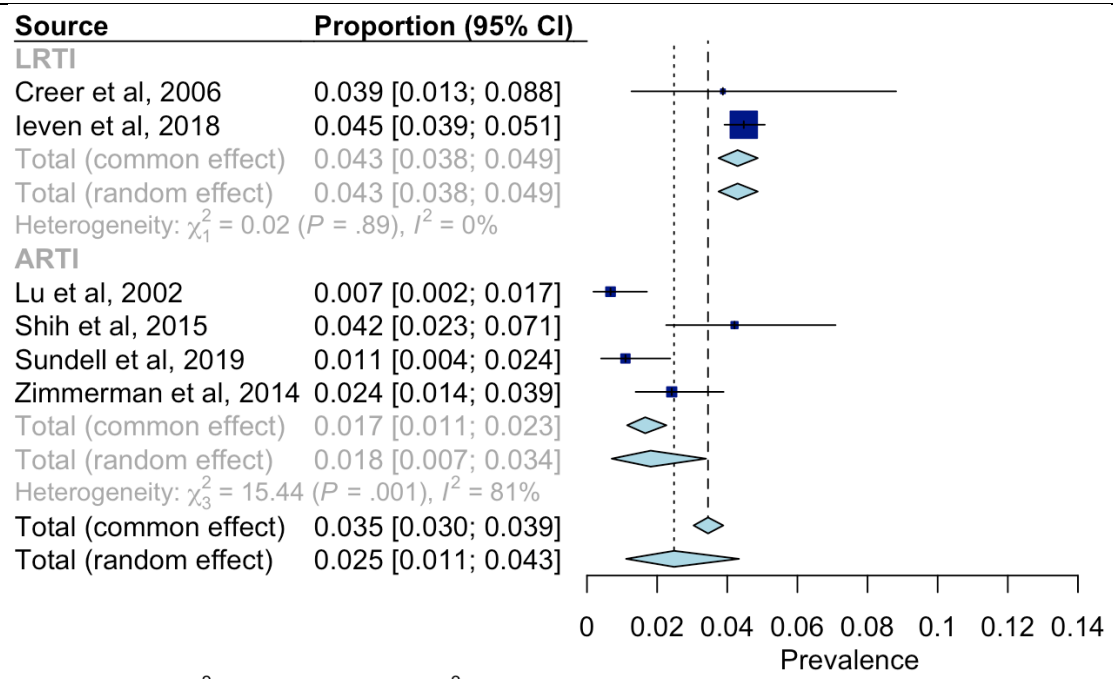
f. Human metapneumovirus



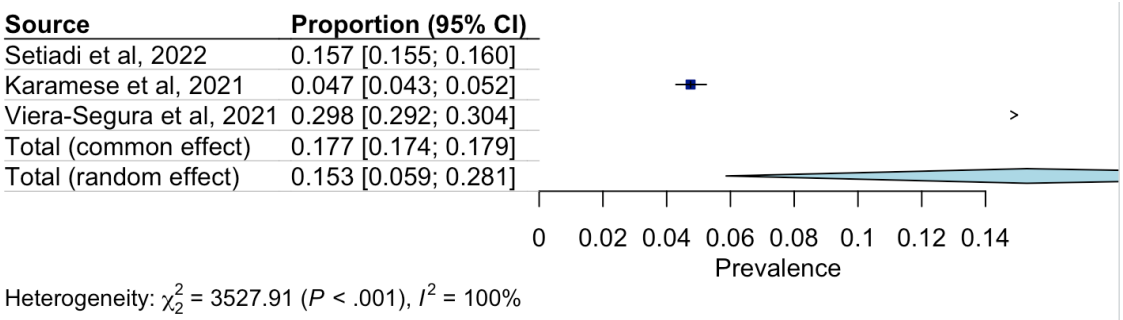
g. Adenovirus



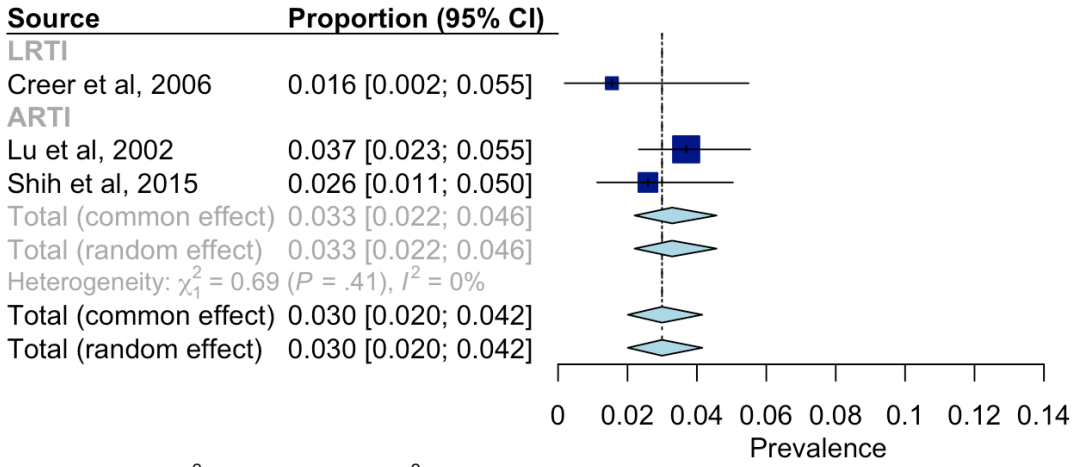
h. Human coronavirus


Source
Proportion (95% CI)
LRTI
Creer et al, 2006 0.039 [0.013; 0.088]
Ieven et al, 2018 0.045 [0.039; 0.051]
Total (common effect) 0.043 [0.038; 0.049]
Total (random effect) 0.043 [0.038; 0.049]
Heterogeneity: χ^2_1 = 0.02 (P = .89), I^2 = 0%
ARTI
Lu et al, 2002 0.007 [0.002; 0.017]
Shih et al, 2015 0.042 [0.023; 0.071]
Sundell et al, 2019 0.011 [0.004; 0.024]
Zimmerman et al, 2014 0.024 [0.014; 0.039]
Total (common effect) 0.017 [0.011; 0.023]
Total (random effect) 0.018 [0.007; 0.034]
Heterogeneity: χ^2_3 = 15.44 (P = .001), I^2 = 81%
Total (common effect) 0.035 [0.030; 0.039]
Total (random effect) 0.025 [0.011; 0.043]
0 0.02 0.04 0.06 0.08 0.1 0.12 0.14
Prevalence
Heterogeneity: χ^2_5 = 54.25 (P < .001), I^2 = 91%
Test for subgroup differences (common effect): χ^2_1 = 38.79 (P < .001)
Test for subgroup differences (random effects): χ^2_1 = 8.19 (P = .004)

i. SARS-CoV-2

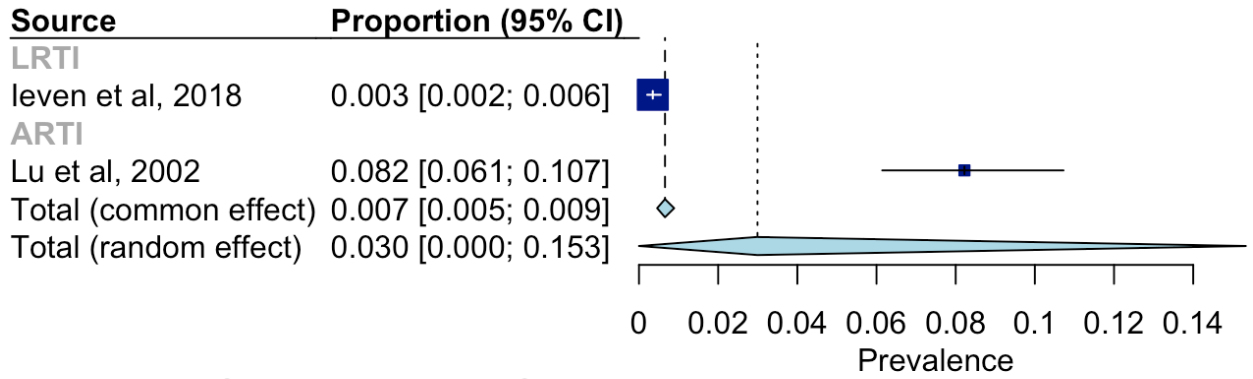

Source
Proportion (95% CI)
Setiadi et al, 2022 0.157 [0.155; 0.160]
Karamese et al, 2021 0.047 [0.043; 0.052]
Viera-Segura et al, 2021 0.298 [0.292; 0.304]
Total (common effect) 0.177 [0.174; 0.179]
Total (random effect) 0.153 [0.059; 0.281]
0 0.02 0.04 0.06 0.08 0.1 0.12 0.14
Prevalence
Heterogeneity: χ^2_2 = 3527.91 (P < .001), I^2 = 100%

j. Enterovirus



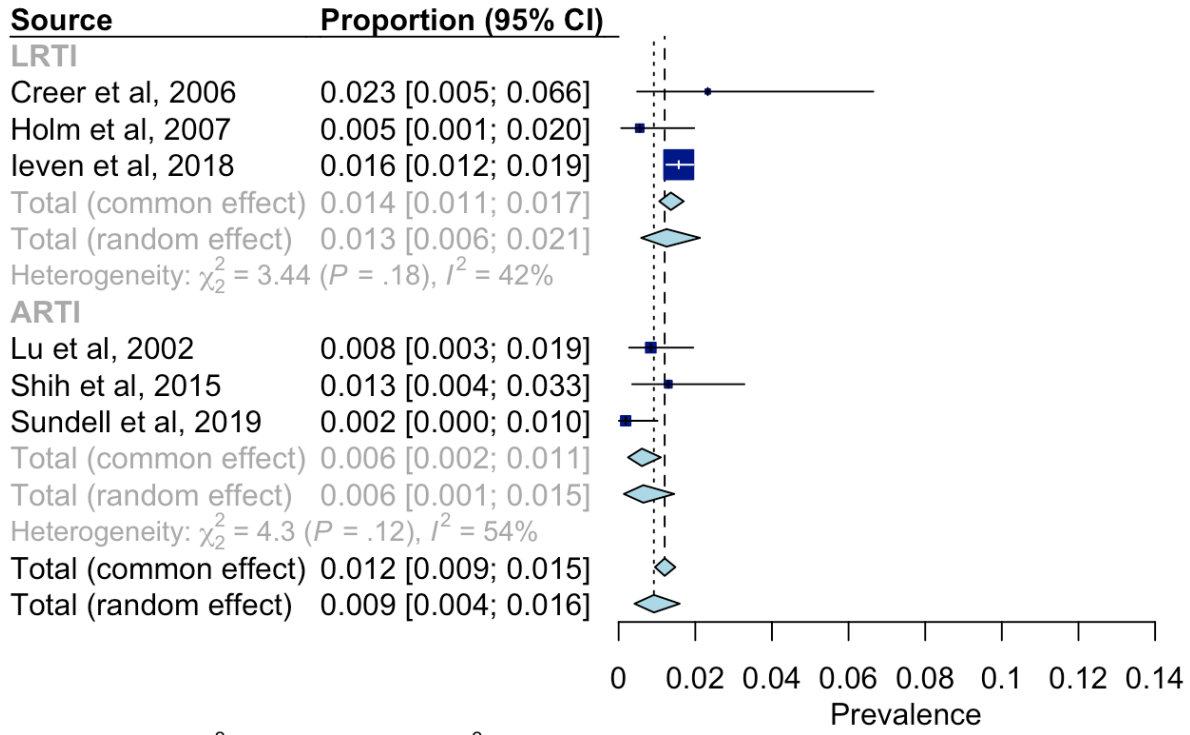
Heterogeneity: χ^2_2 = 1.69 (*P* = .43), I^2 = 0%
Test for subgroup differences (common effect): χ^2_1 = 1.00 (*P* = .32)
Test for subgroup differences (random effects): χ^2_1 = 1.00 (*P* = .32)

k. Bocavirus



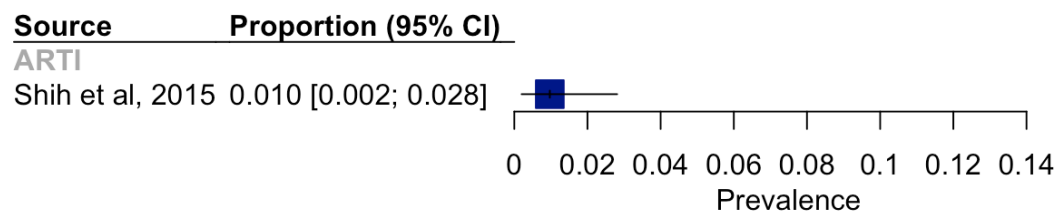
Heterogeneity: χ^2_1 = 115.35 (*P* < .001), I^2 = 99%
Test for subgroup differences (common effect): χ^2_1 = 115.35 (*P* < .001)
Test for subgroup differences (random effects): χ^2_1 = 115.35 (*P* < .001)

l. Parainfluenza virus

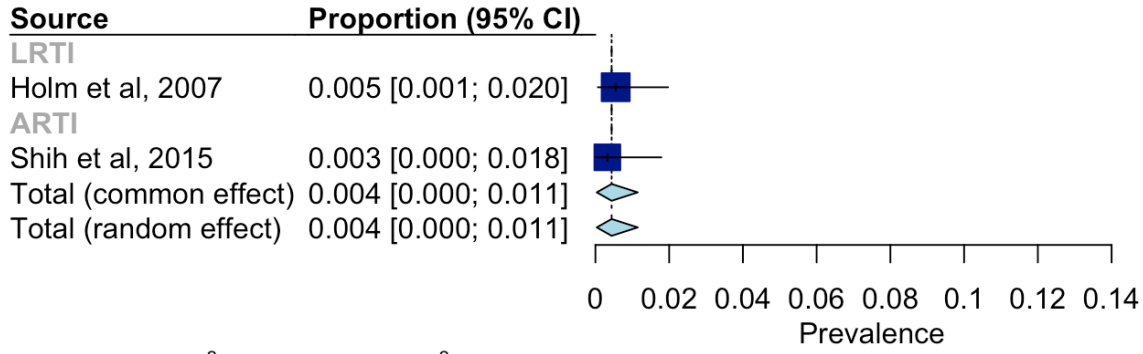


Heterogeneity: χ^2_5 = 14.95 (P = .01), I^2 = 67%
Test for subgroup differences (common effect): χ^2_1 = 7.21 (P = .007)
Test for subgroup differences (random effects): χ^2_1 = 1.61 (P = .20)

m. Parainfluenza virus 1

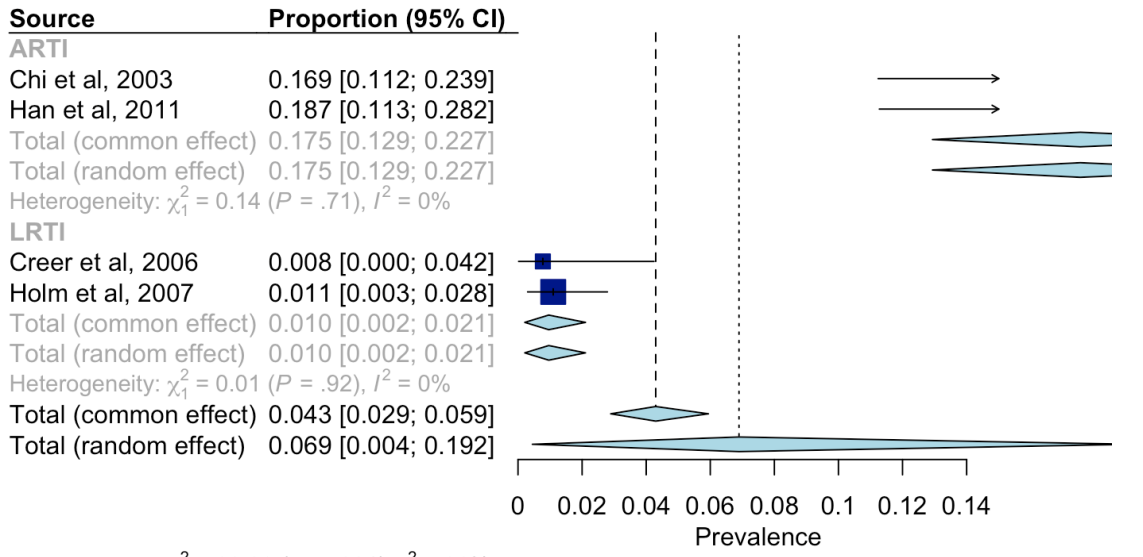


n. Parainfluenza virus 3



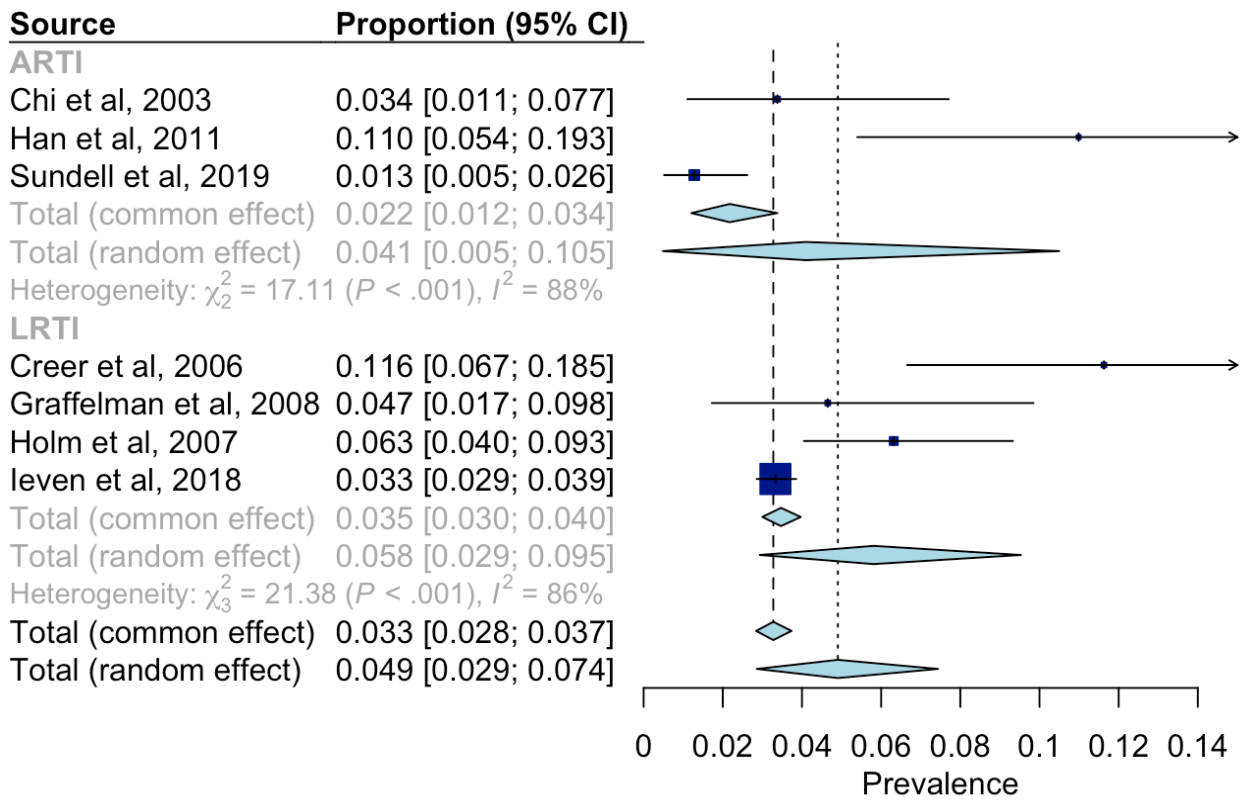
Heterogeneity: $\chi^2_1 = 0.13$ ($P = .72$), $I^2 = 0\%$
Test for subgroup differences (common effect): $\chi^2_1 = 0.13$ ($P = .72$)
Test for subgroup differences (random effects): $\chi^2_1 = 0.13$ ($P = .72$)

o. Moraxella catarrhalis



Heterogeneity: $\chi^2_3 = 68.88$ ($P < .001$), $I^2 = 96\%$
Test for subgroup differences (common effect): $\chi^2_1 = 68.73$ ($P < .001$)
Test for subgroup differences (random effects): $\chi^2_1 = 68.73$ ($P < .001$)

p. Streptococcus pneumoniae

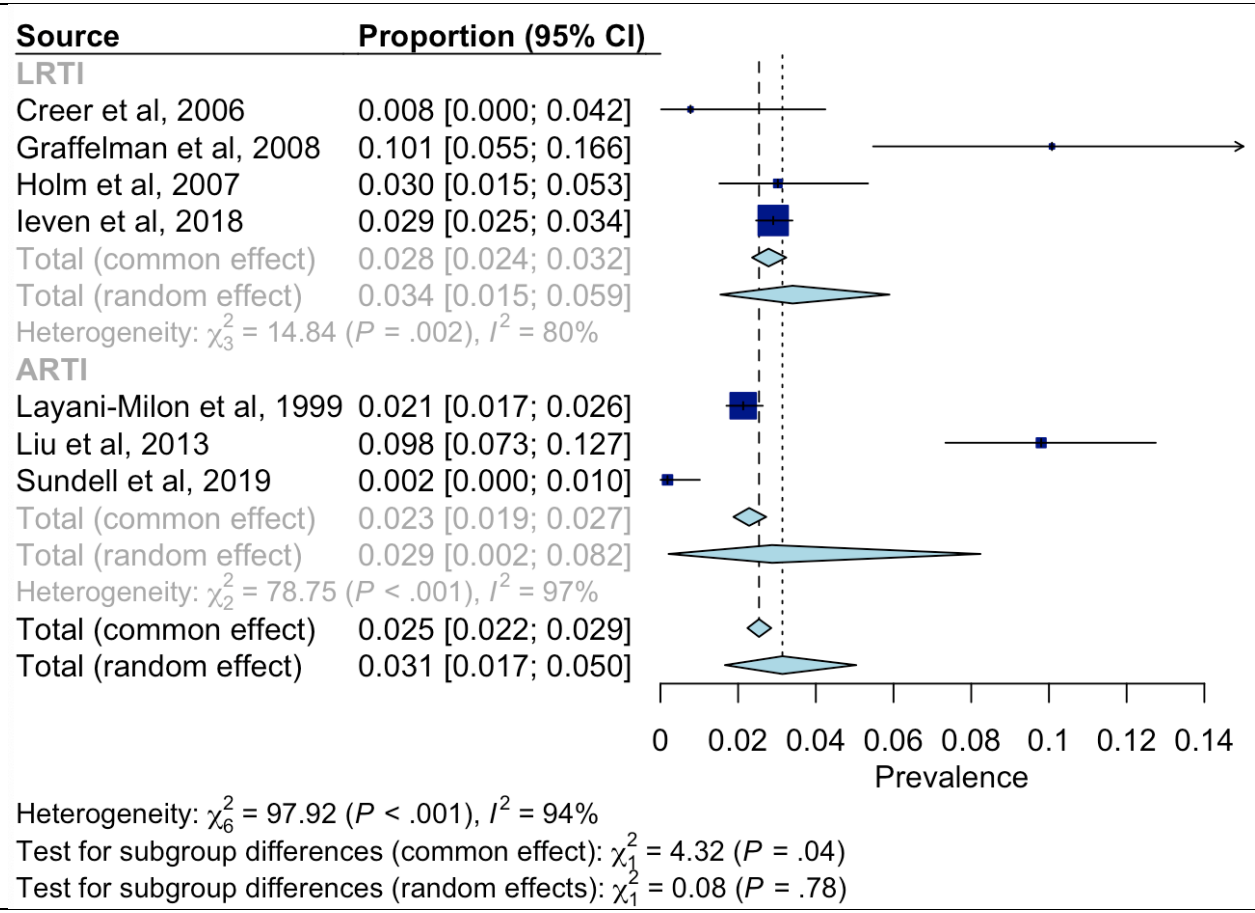


Heterogeneity: χ^2_6 = 41.91 (*P* < .001), I^2 = 86%

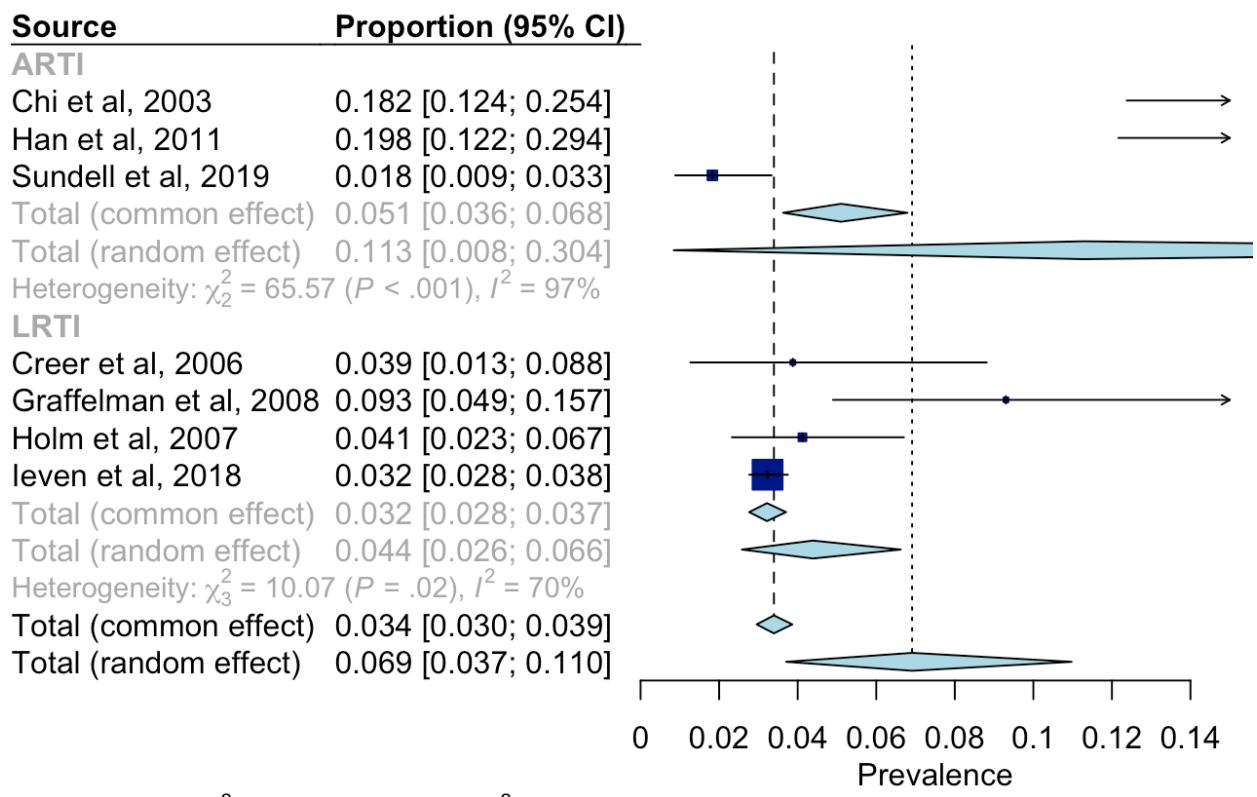
Test for subgroup differences (common effect): χ^2_1 = 3.41 (*P* = .06)

Test for subgroup differences (random effects): χ^2_1 = 0.26 (*P* = .61)

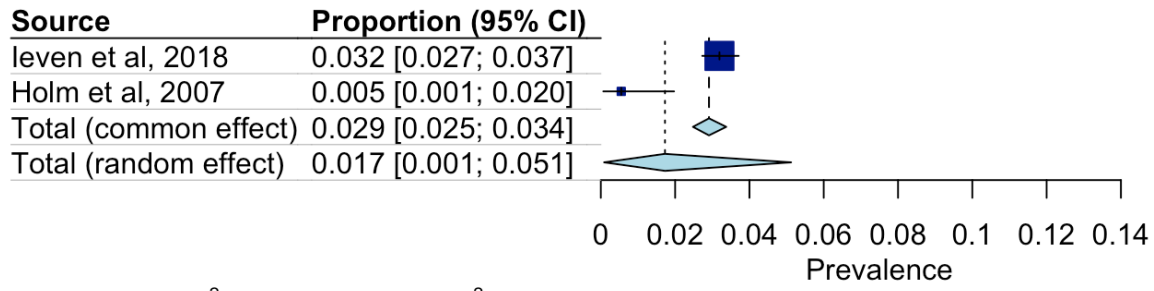
q. Mycoplasma pneumoniae



r. Haemophilus influenzae

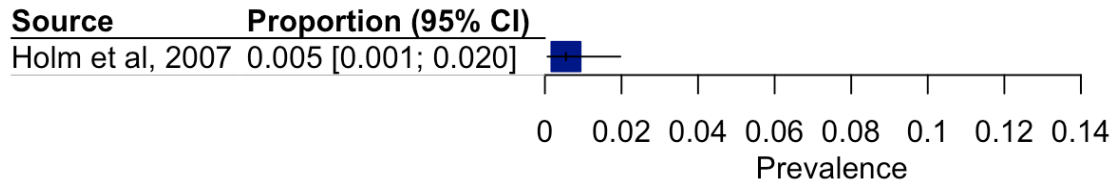


s. Chlamydia pneumoniae

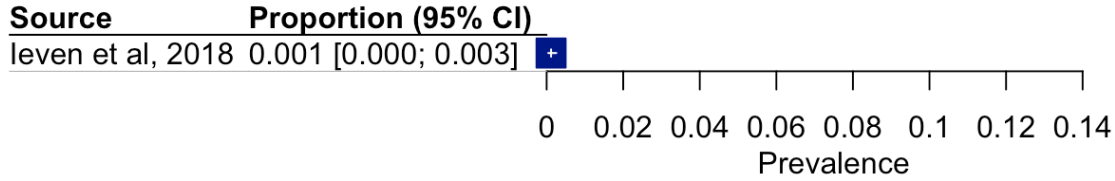


Heterogeneity: $\chi^2_1 = 12.94$ ($P < .001$), $I^2 = 92\%$

t. Staphylococcus aureus



u. Legionella pneumophilia



v. Bordetella pertussis

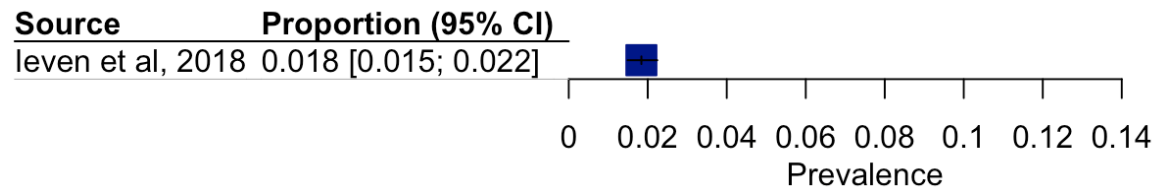
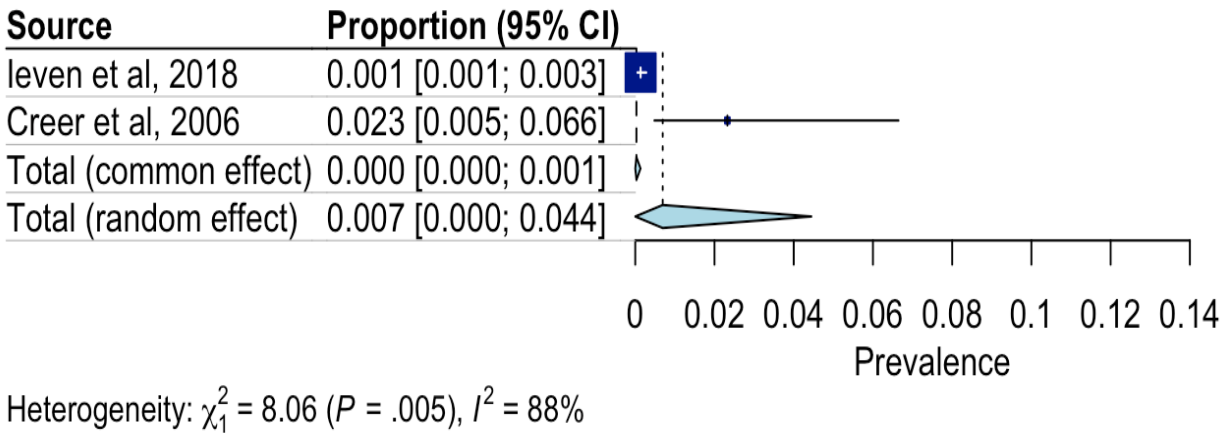


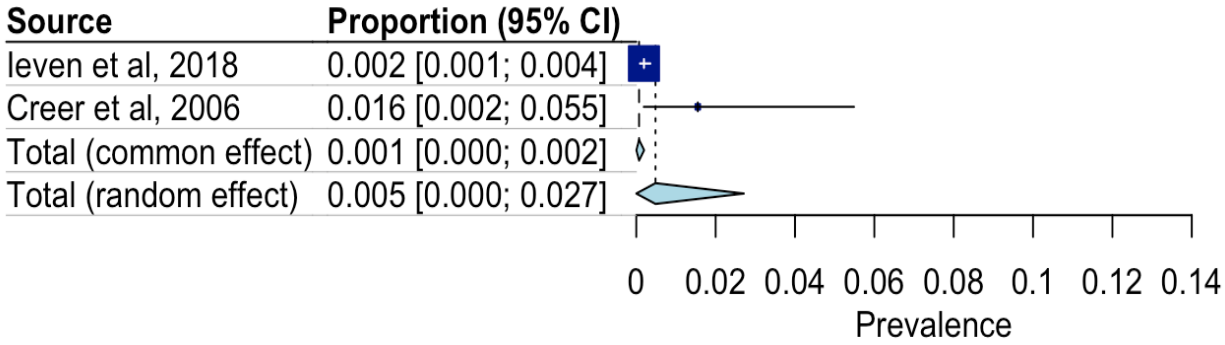
Figure A5 (a - n) Forest Plots of Asymptomatic Etiology

a. Influenza A or B



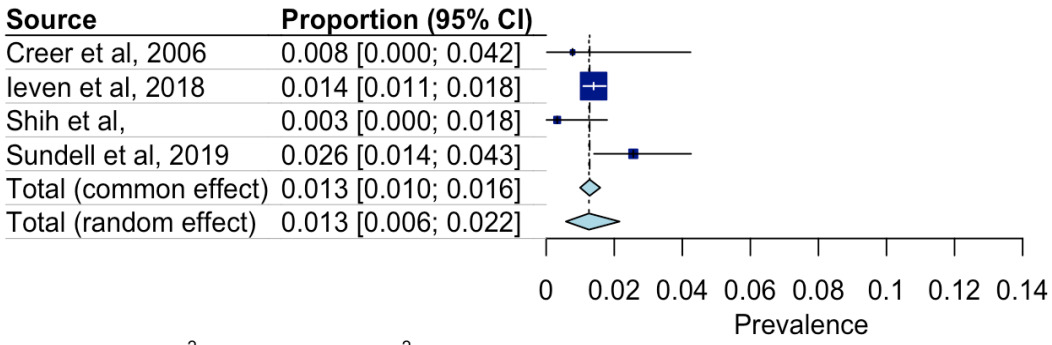
Heterogeneity: $\chi^2_1 = 8.06$ ($P = .005$), $I^2 = 88\%$

b. Respiratory syncytial virus



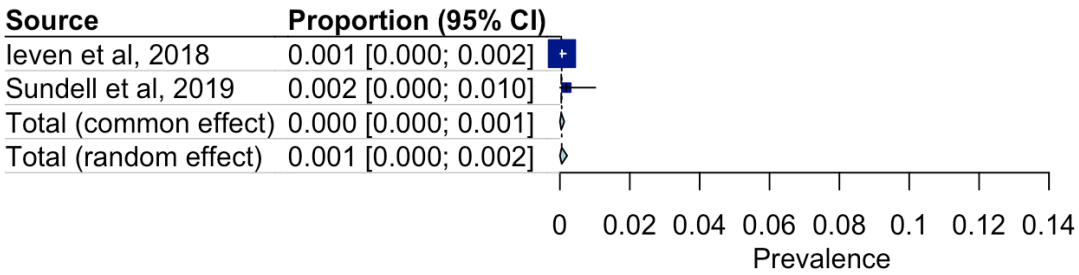
Heterogeneity: $\chi^2_1 = 4.40$ ($P = .04$), $I^2 = 77\%$

c. Rhinovirus



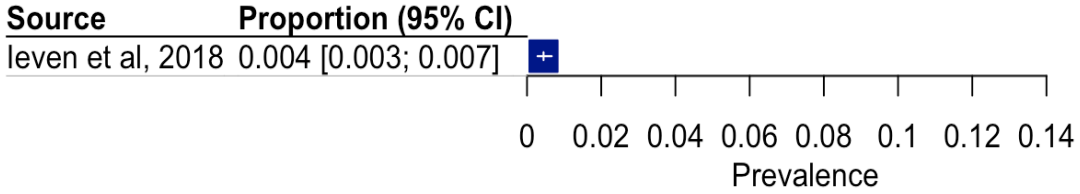
Heterogeneity: $\chi^2_3 = 7.52$ ($P = .06$), $I^2 = 60\%$

d. Human metapneumovirus

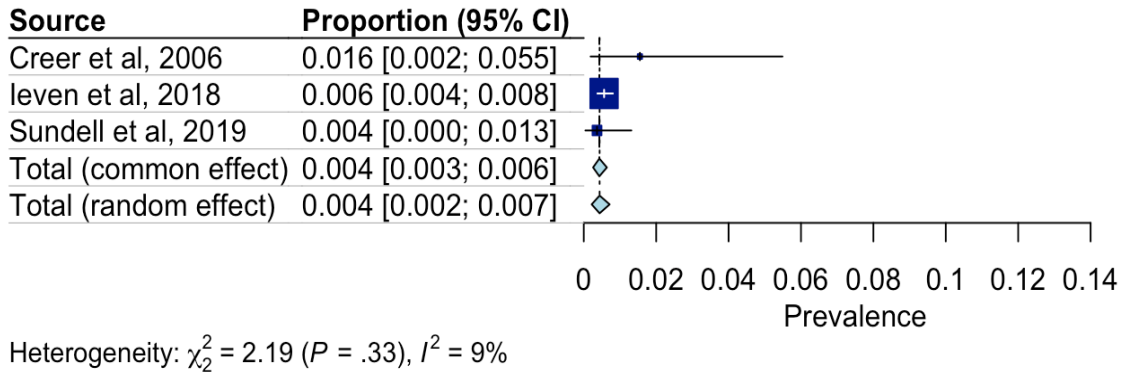


Heterogeneity: $\chi^2_1 = 1.30$ ($P = .25$), $I^2 = 23\%$

e. Adenovirus

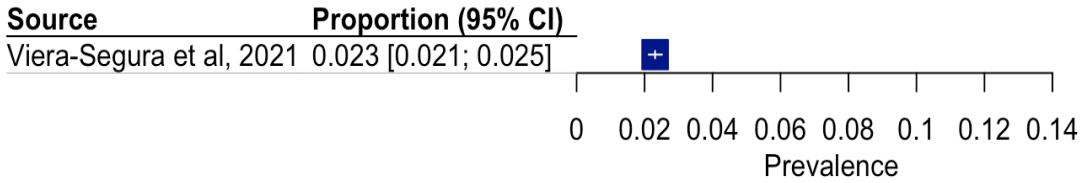


f. Human coronavirus

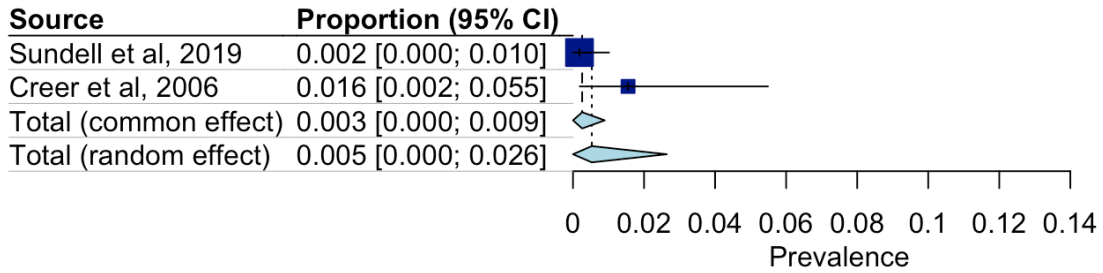


Heterogeneity: $\chi^2_2 = 2.19$ ($P = .33$), $I^2 = 9\%$

g. SARS-CoV-2

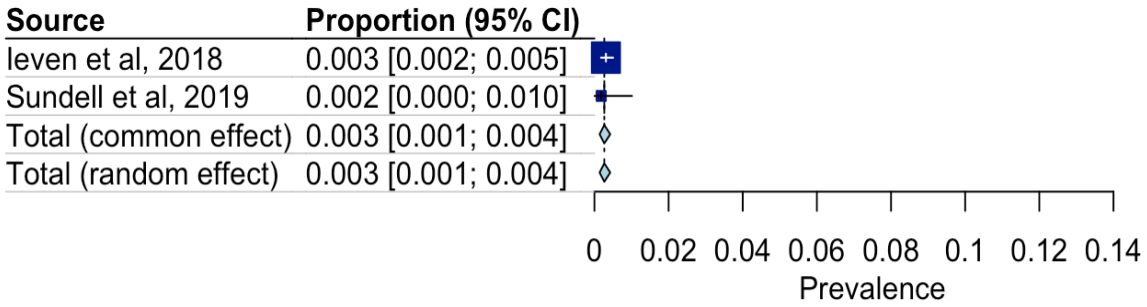


h. Enterovirus



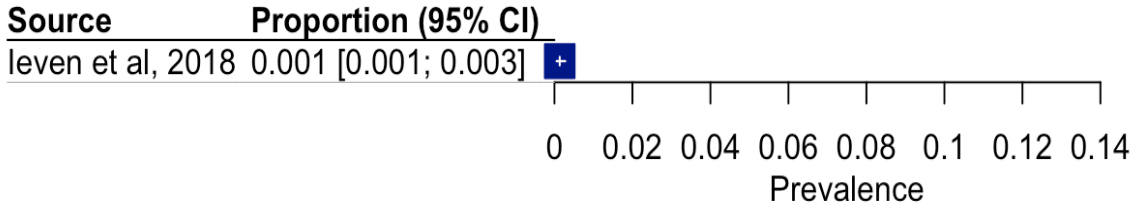
Heterogeneity: $\chi^2_1 = 3.16$ ($P = .08$), $I^2 = 68\%$

i. Bocavirus

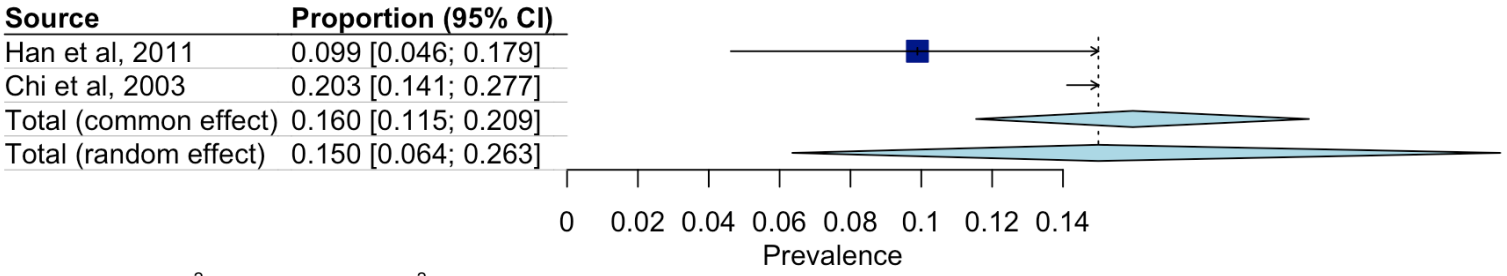


Heterogeneity: $\chi^2_1 = 0.05$ ($P = .83$), $I^2 = 0\%$

j. Parainfluenza Virus



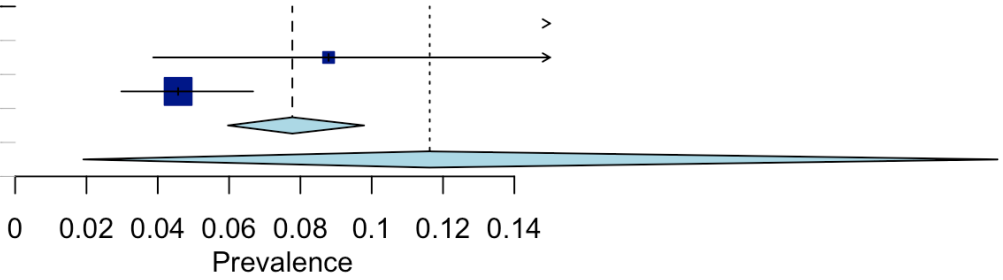
k. M. catarrhalis



Heterogeneity: $\chi^2_1 = 4.59$ ($P = .03$), $I^2 = 78\%$

l. Streptococcus pneumoniae

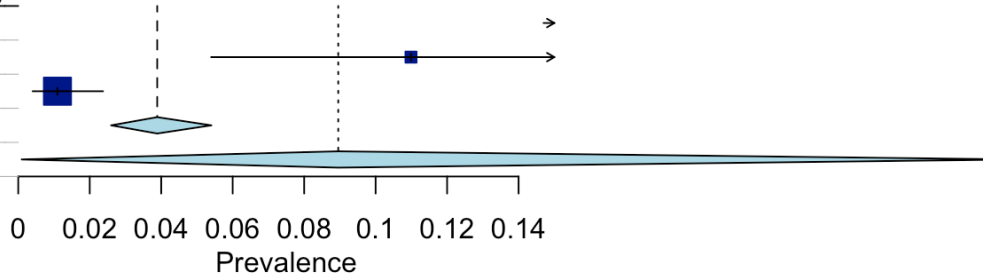
Source	Proportion (95% CI)
Chi et al, 2003	0.257 [0.189; 0.335]
Han et al, 2011	0.088 [0.039; 0.166]
Sundell et al, 2019	0.046 [0.030; 0.067]
Total (common effect)	0.078 [0.060; 0.098]
Total (random effect)	0.116 [0.019; 0.276]



Heterogeneity: $\chi^2_2 = 46.79$ ($P < .001$), $I^2 = 96\%$

m. H. influenzae

Source	Proportion (95% CI)
Chi et al, 2003	0.209 [0.147; 0.284]
Han et al, 2011	0.110 [0.054; 0.193]
Sundell et al, 2019	0.011 [0.004; 0.024]
Total (common effect)	0.039 [0.026; 0.054]
Total (random effect)	0.090 [0.001; 0.279]



Heterogeneity: $\chi^2_2 = 71.48$ ($P < .001$), $I^2 = 97\%$

n. C. pneumoniae

Source	Proportion (95% CI)
Creer et al, 2006	0.008 [0.000; 0.042]

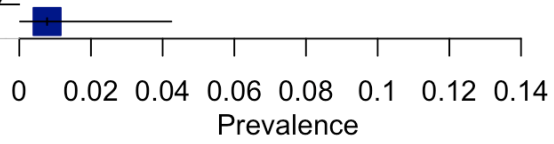
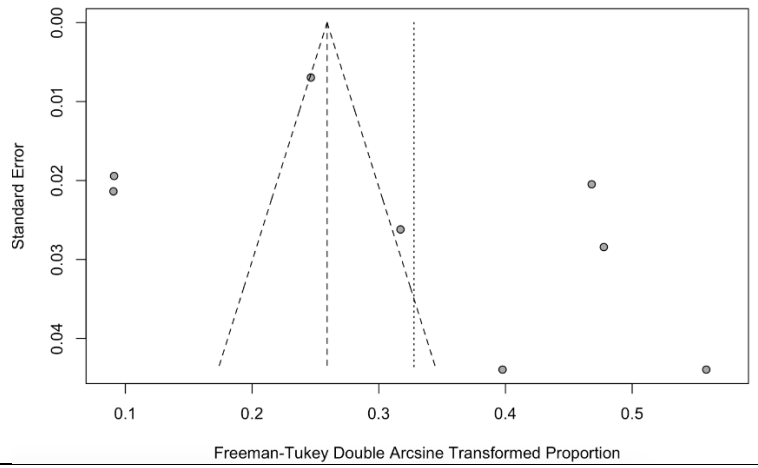
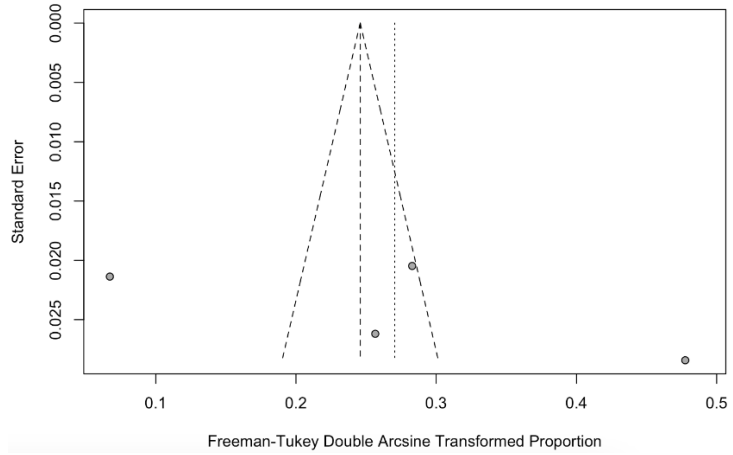


Figure A6 (a - q) Funnel Plots of Symptomatic Etiology

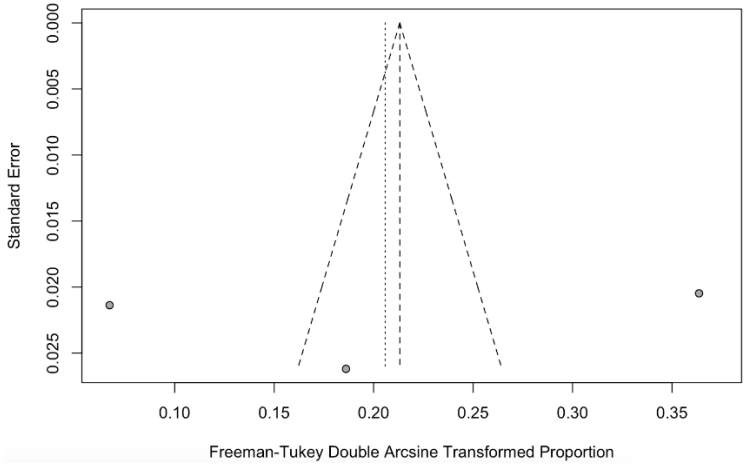
a. Influenza virus A or B



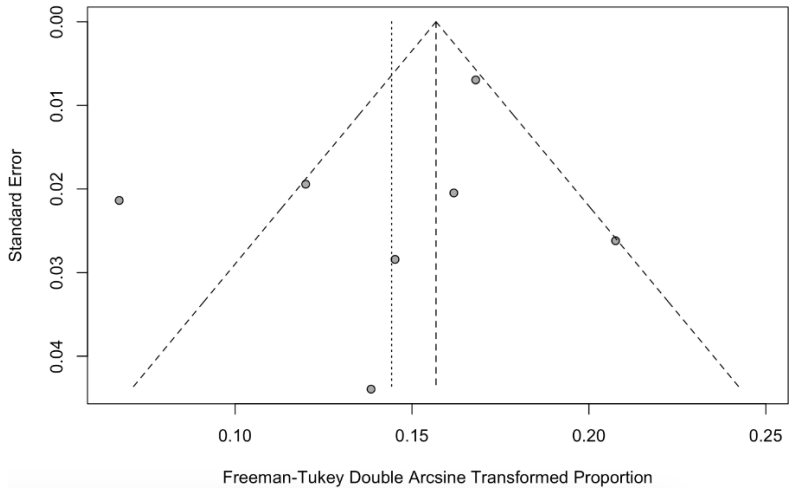
b. Influenza virus A



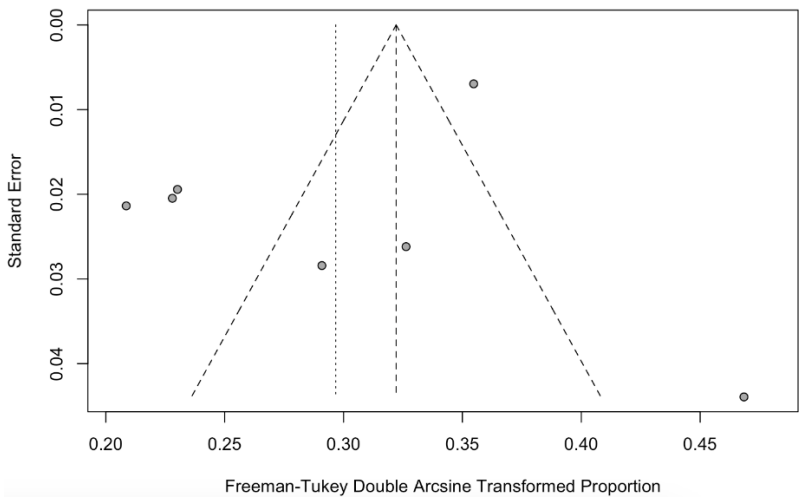
c. Influenza virus B



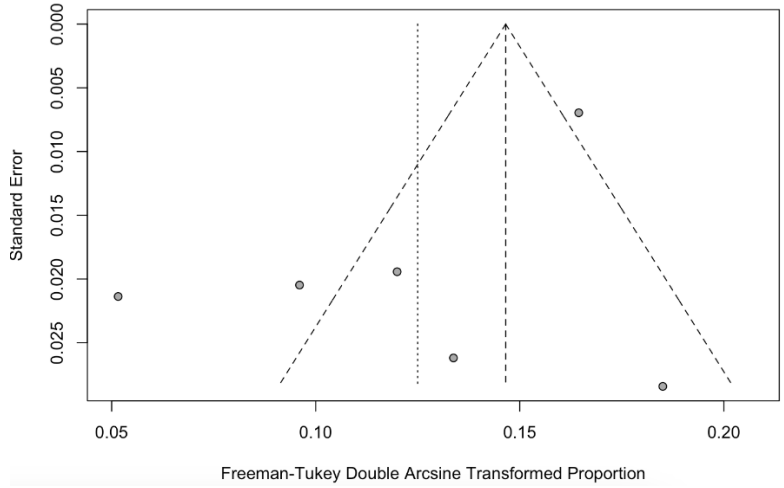
d. Respiratory syncytial virus



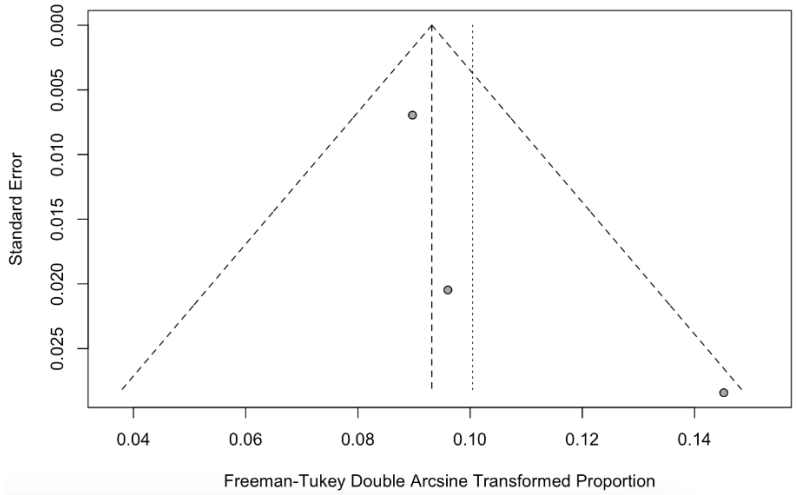
e. Rhinovirus



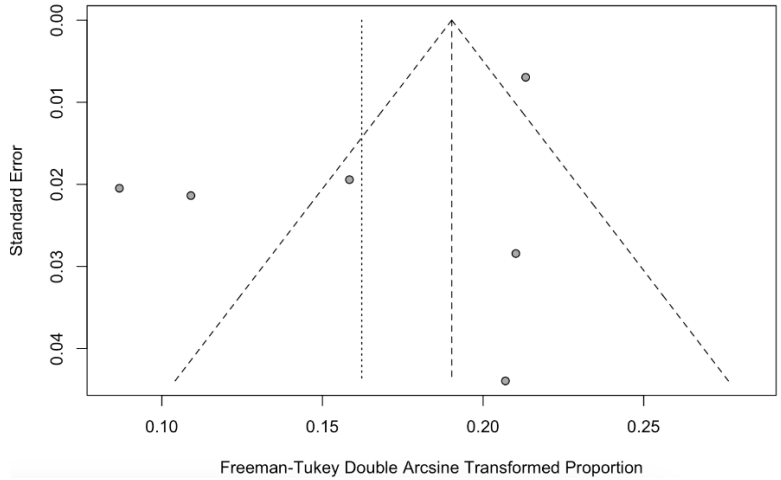
f. Human metapneumovirus



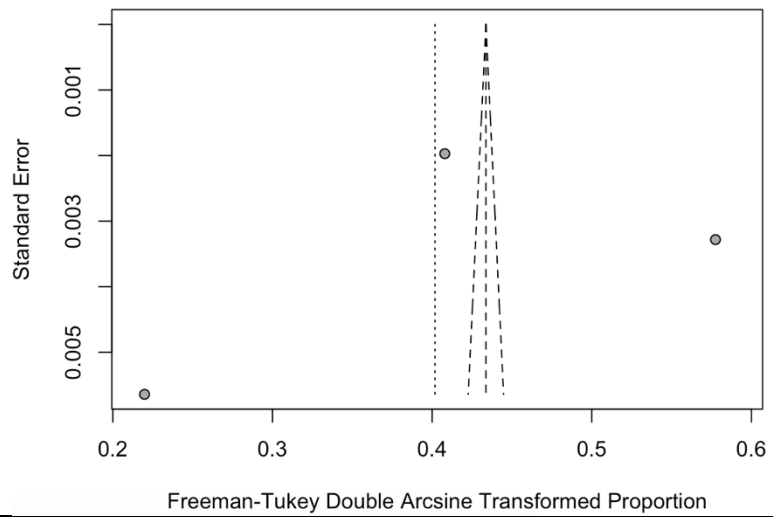
g. Adenovirus



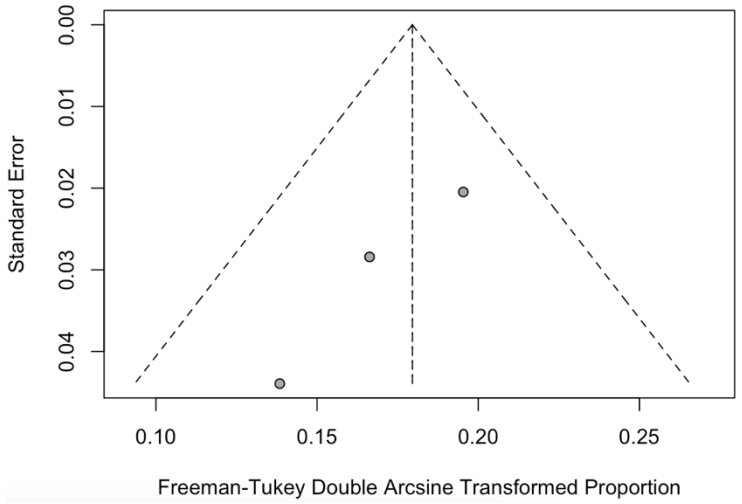
h. Human coronavirus



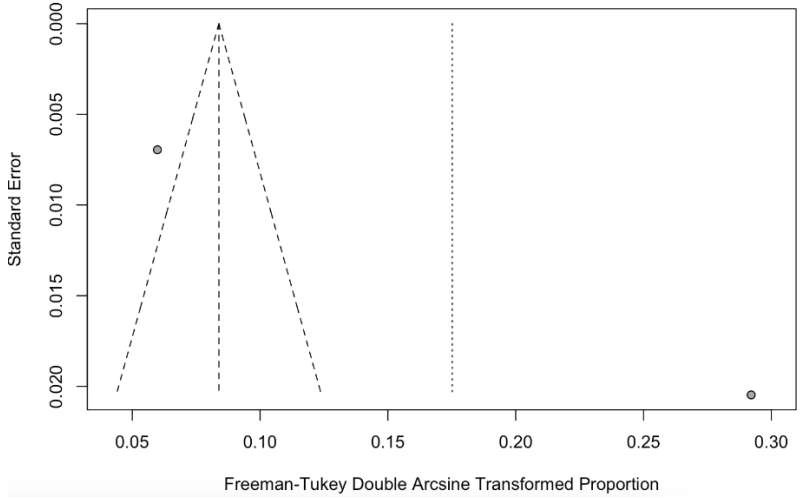
i. SARS-CoV-2



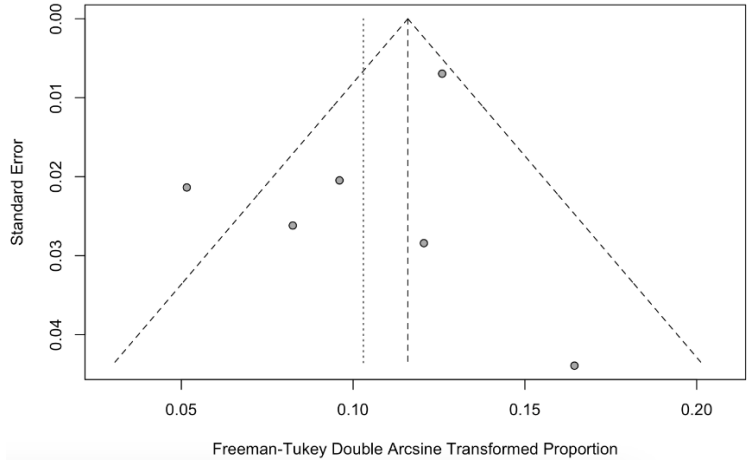
j. Enterovirus



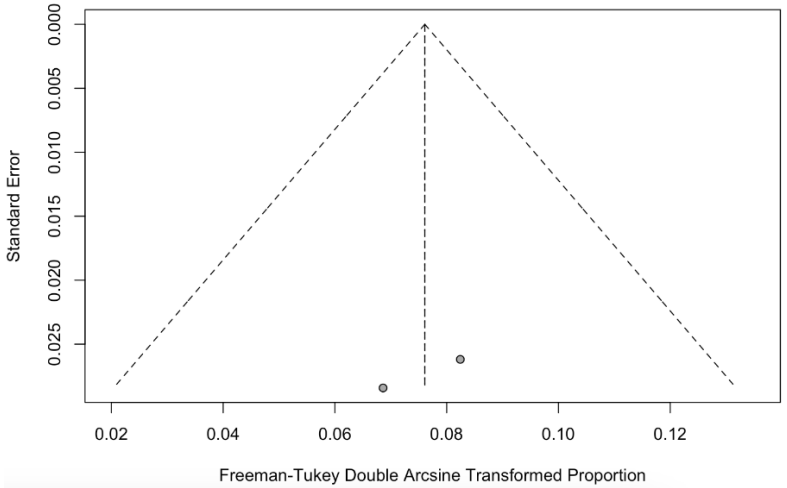
k. Bocavirus



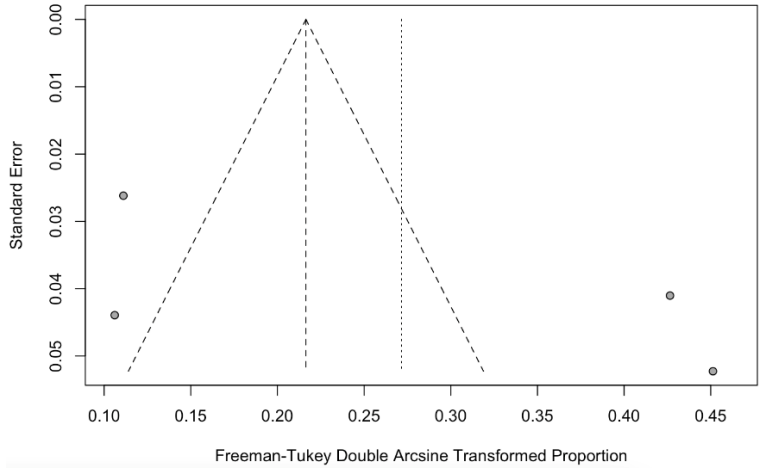
l. Parainfluenza virus



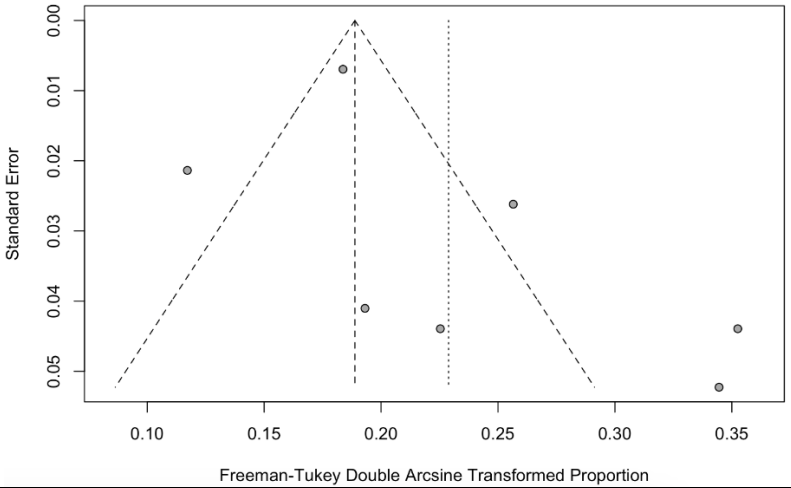
m. Parainfluenza virus3



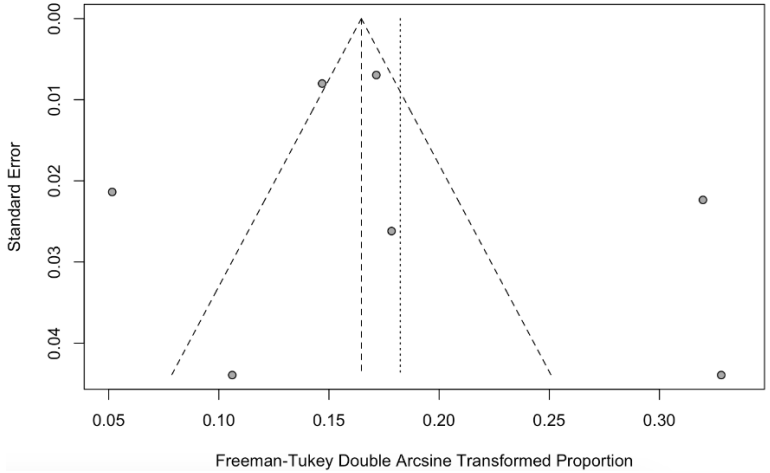
n. *Moraxella catarrhalis*

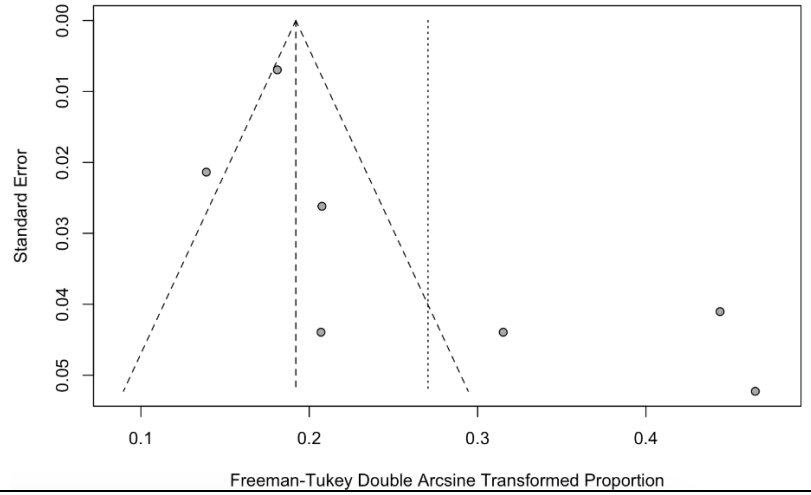


o. *Streptococcus pneumoniae*



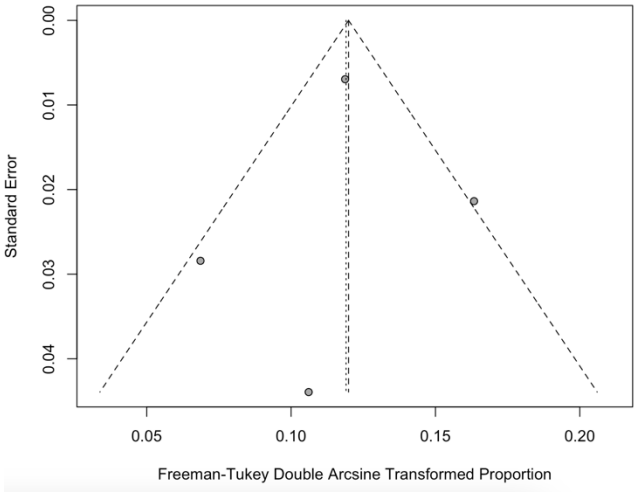
p. *Mycoplasma pneumoniae*



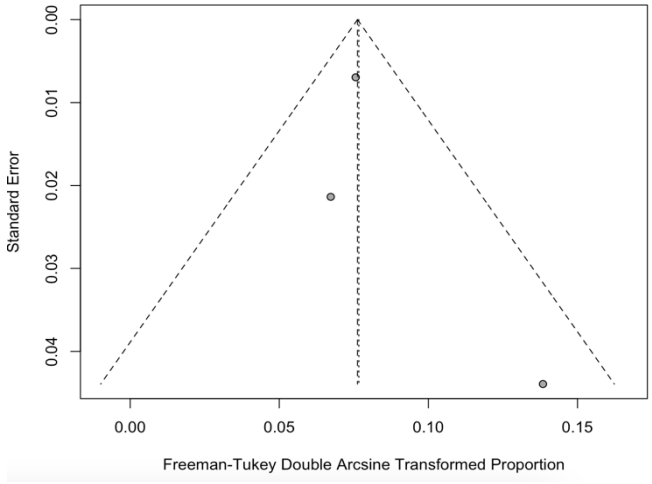
q. *Haemophilus influenzae*  	

Figures A7 (a – d) Asymptomatic forest plots

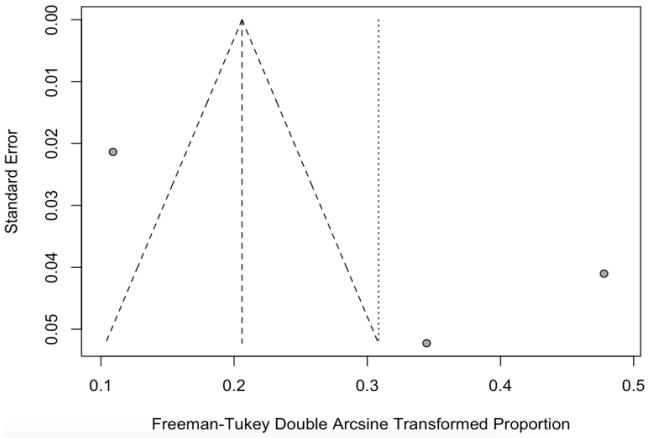
a. *Rhinovirus*



b. *Human coronavirus*



c. *H. influenzae*



d. *S. pneumoniae*

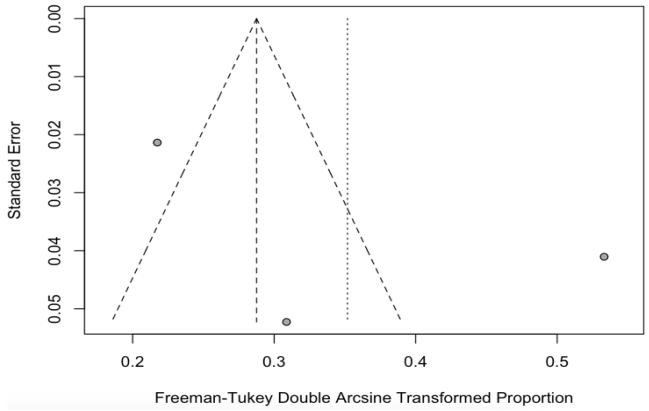


Table A5 Secondary search strategies for symptom sitology systematic review.

Database	Search Terms	Link to Database and Notes
PubMed	(“Influenza”[TIAB] OR “rhinovirus”[TIAB] OR “rhinovirus”[MH] OR “common cold virus”[MH] OR “catarrhalis”[TIAB] OR “M. catarrhalis”[MH] OR “S. pneumoniae”[TIAB] OR “strep pneumoniae”[TIAB] OR “streptococcal pneumonia”[TIAB] OR “S. pneumoniae”[MH] OR “H. influenzae”[TIAB] OR “H. influenzae”[MH] OR “Haemophilus influenzae”[TIAB]) AND (“signs and symptoms”[TIAB] OR “signs or symptoms”[TIAB} or “history and physical”[TIAB] OR “physical examination”[TIAB]) NOT (“Nosocomial”[TIAB] OR “Nosocomial”[MH] OR “children” [TIAB] OR “pediatric”[TIAB] OR “childhood” [TIAB])	https://pubmed.ncbi.nlm.nih.gov Filters used: Humans, with Abstract, Adults

Figure A8 PRISMA for secondary systematic review for additional studies reporting clinical characteristics by etiology.

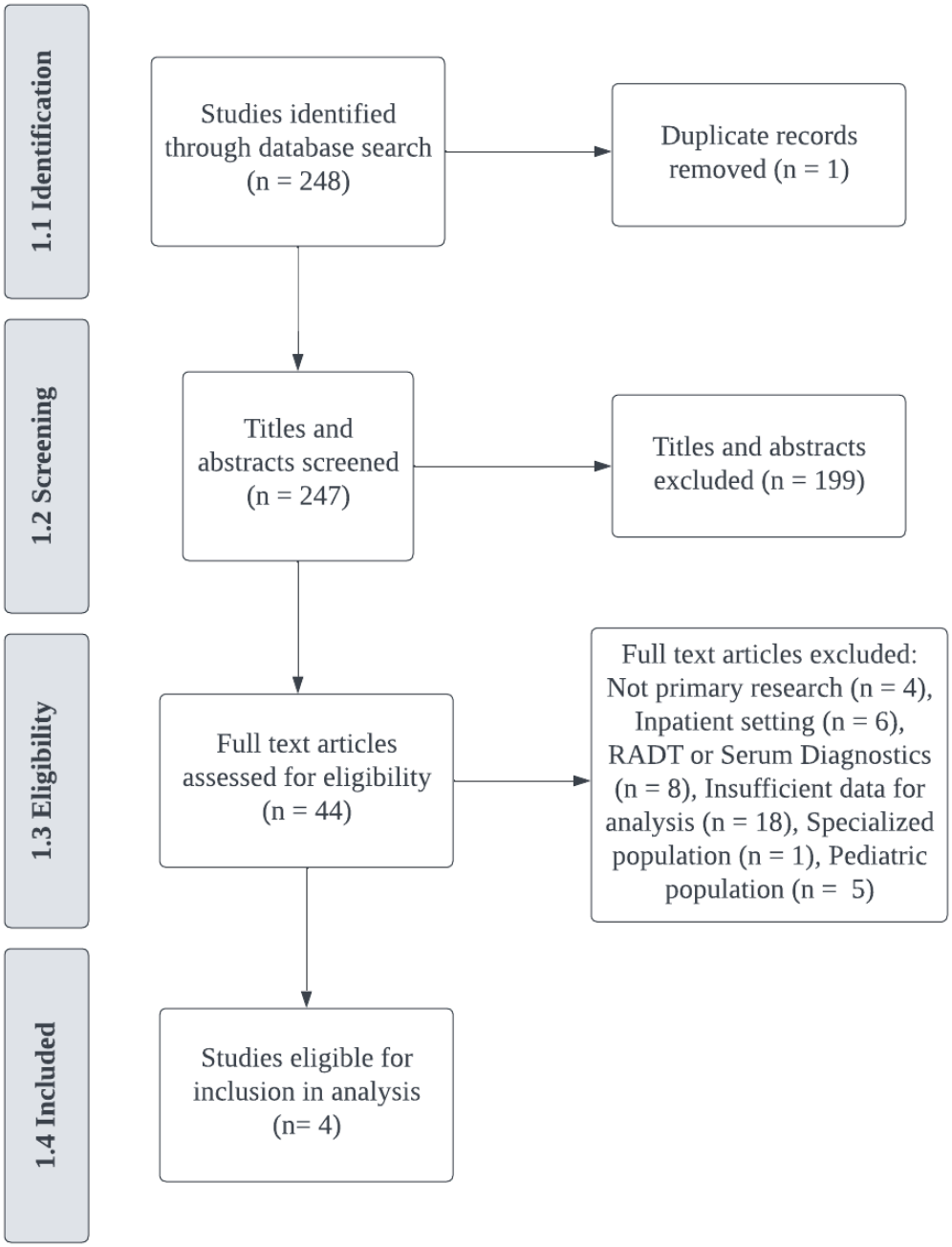


Table A6 Study characteristics of all articles chosen for inclusion in the analysis of symptom specific etiology

Author, Year	Country	Clinic or Community Setting	Month/ Year Data Collected	Inclusion Criteria	Detection Method	Sex	Age (mean or median) and Range (in yrs)
Al-Mahrezi et al., 2012[227]	Oman	Clinic/ Database	August - November 2009	Patients ≥17 years with ILI symptoms including fever, cough, sore throat, headache, nasal symptoms, and myalgia	PCR	54.0% Male	Median 25 (21 - 34)
Karamese et al. 2021	Turkey	Clinic/ Lab Database	April - May 2020	Suspected cases who had typical respiratory infection symptoms such as fever, cough, and SOB or close contact with a COVID-19 patient	PCR	59.1% Male	Mean 38.14
Kiertiburanakul et al, 2014[228]	Thialand	Clinic	April - August 2009	Any patients attending an outpatient clinic diagnosed with ILI	PCR	38.1% Male	Not reported
Li et al., 2012	China	Clinic	July 2008 - Jun 2010	Patients ≥14 years with acute respiratory symptoms, acute fever, and normal or low leukocyte count	PCR	46% Male	Mean 33.9
Liu et al., 2013	China	Clinic	November 2010 - October 2011	Patients ≥18 with signs and symptoms of CAP such as new cough with or without sputum, fever, normal or low	Culture/ PCR	Not reported	Not reported

				leukocyte, and CXR with new infiltrate			
Ouchi et al., 2022[229]	15 European Countries	Clinic	2015 - 2018	Patients >18 years with ILI of ≤ 72 hours from symptoms onset	PCR	42.1% Male	Mean 41.8
Padin et al., 2014[230]	United States	Clinic	2004 - 2009	Military trainees >18 years with fever ≥ $38°C$ with either cough or sore throat or provider diagnosed pneumonia	PCR	86.8% Male	Mean 20.8
Thom et al, 1994[231]	United States	Clinic	December 1984 - February 1986	Adult patients with ARI symptoms more severe than simple rhinitis, with mild or no fever	PCR	36.6% Male	Mean 40.9
Viera-Segura et al., 2021	Mexico	Clinic/Lab Database	April - December 2020	All individuals who presented to COVID testing sites with COVID symptoms and/or those in close contact with patients diagnosed with COVID in the last 15 days	PCR	46.4% Male	Mean 37.4

Table A7 Raw count data of symptoms that were present by etiology.

		Viral Pathogens				**Bacterial Pathogens**	
Clinical Symptoms Present	**# of Studies Reporting Symptom**	Adenovirus (N = 13725)	Influenza Virus A or B (N = 3785)	Human metapneumovirus (N = 49)	SARS-CoV-2 (N = 7291)	*Chlamydia pneumoniae* (N = 21)	*Mycoplasma pneumoniae* (N = 63)
Cough	9	12559 (91.5%)	3543 (93.6 %)	30 (61.2%)	5193 (71.2%)	17 (81.0%)	60 (95.2%)
Headache	9	11571 (84.3%)	2655 (70.1 %)	36 (73.5%)	5052 (69.3%)	9 (42.9%)	17 (27.0%)
Fever (subjective or measured)	7	11945 (87.0%)	3378 (89.2 %)	0 (0.0%)	3981 (54.6%)	8 (38.1%)	10 (15.9%)
Sore throat	7	12771 (93.0%)	2507 (66.2 %)	33 (67.3%)	3362 (46.1%)	12 (57.1%)	9 (14.3%)
Vomiting/ Diarrhea	7	7135 (52.0%)	1604 (42.3 %)	1 (2.04%)	1619 (22.2%)	0 (0.0%)	9 (14.3%)
Dyspnea	6	5010 (36.5%)	1323 (35.0 %)	0 (0.0%)	898 (12.3%)	0 (0.0%)	6 (9.52%)
Muscle pain/ Weakness	6	9804 (71.4%)	2866 (75.7 %)	24 (49.0%)	3166 (43.4%)	0 (0.0%)	0 (0.0%)
Rhinorrhea	4	0 (0.0%)	1384 (36.6 %)	30 (61.2%)	1611 (22.1%)	0 (0.0%)	0 (0.0%)
Nasal congestion	3	11223 (81.8%)	1570 (41.5 %)	0 (0.0%)	2421 (33.2%)	0 (0.0%)	0 (0.0%)
Chest pain	2	0	0	0	1264	0	9

		(0.0%)	(0.0%)	(0.0%)	(17.3%)	(0.0%)	(14.3%)
Chills/ Sweats	2	0 (0.0%)	1212 (32.0%)	37 (75.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatigue	2	0 (0.0%)	1300 (34.3%)	0 (0.0%)	3622 (49.6%)	0 (0.0%)	0 (0.0%)
Sputum production	2	0 (0.0%)	0 (0.0%)	25 (51.0%)	0 (0.0%)	0 (0.0%)	34 (54.0 %)
Sneezing	1	0 (0.0%)	0 (0.0%)	25 (51.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

APPENDIX B

UNIVERSITY OF GEORGIA CONSENT FORM
Enhancing Antibiotic Stewardship in Primary Care (EAST-PC)

Researcher's Statement
You are being asked to take part in a research study. The information in this form will help you decide if you want to be in the study. Please ask the researcher(s) below if there is anything that is not clear or if you need more information.

Protocol no.:	1R01HS025584-01A1 WCG IRB Protocol #20190108
Sponsor:	National Institutes of Health
Principal Investigator:	Mark Ebell BA, MD, MS Department of Epidemiology, College of Public Health University of Georgia 706-247-4953 or ebell@uga.edu
Site(s):	University of Georgia, University Health Center 55 Carlton Street Athens, Georgia 30602 United States Piedmont Athens Regional Urgent Care 485 Highway 29 North Athens, Georgia 30601 United States
Phone Number(s):	Mark Ebell BA, MD, MS 706-247-4953 706-247-5953 (24 Hours)

Purpose of the Study
The purpose of this study is to better understand lower respiratory tract infections. These infections are sometimes called "acute bronchitis" or a "chest cold". This information will help us design tools that physicians and patients can use to decide about antibiotics and other treatments. The assays being used in this study are experimental and have not been approved by the FDA

Study Procedures and Time Commitment

Patients with cough and other symptoms

If you agree to participate, we will ask you questions about your signs and symptoms, and information about yourself like your age and education. This will take about 10 to 15 minutes. We will take a swab from your nose and mouth to detect viruses and bacteria, and we will poke your finger for a small blood sample to check a blood test for inflammation. All of this will be done while you are waiting to see the doctor.

Next, your doctor will do their usual examination and will record their findings and their treatment plan. Your care by the doctor is in no way affected by the study. We will obtain their findings and treatment plan to use in the study. Over the next week, we will ask you to fill out a simple symptom diary that will take just 1 or 2 minutes a day. At the end of the week, we will email or text you and ask you to mail the diary to us or take a photo of the diary and email or text it to us. We will ask you to keep recording information in the diary while you still have a cough, for up to 4 weeks. When you feel well, you can stop. If you don't respond to our email or text, we will try to call you, and ask the same questions that take 2 or 3 minutes to answer.

Persons without any cough or symptoms

If you agree to participate, we will ask you questions about your signs and symptoms, and information about yourself like your age and sex. This will take about 10 minutes. We will take a swab from your nose and mouth to detect viruses and bacteria. If you are in a medical setting all of this will be done while you are waiting to see the doctor.

Next, your doctor will do their usual examination and will record their findings and their treatment plan. Your care by the doctor is in no way affected by the study.

The specimens from your nose and throat will be tested for the presence of 41 viruses and bacteria at the CDC lab some time in the future, up to 6 months from now. If a virus or bacteria is detected that is important for you to know about, because it could affect your healthcare decisions (for example, COVID-19) we will contact you with the result. In general, though, we will not contact you with the test results. If a virus is detected that could affect the health of others, we will contact local public health officials so they can work with you to determine the risk to you and to your contacts.

Risks and discomforts

The questions are about ordinary signs and symptoms of cold and cough and are not sensitive or likely to cause embarrassment. If you are a symptomatic patient, we will ask you about your race, income category, and educational level, but you don't have to answer those questions if you don't want to. Asymptomatic patients will be asked to provide their age, sex, race, and antibiotic usage, but can choose not to answer any of the questions. The mouth swab is the same as would be taken for a throat culture, and the nasal swab gathers mucus from the back of your nose. The blood test, for symptomatic patients only, is a finger stick like that used to check blood sugar and is

done in a sterile way so we minimize any risk of infection. A sterile band-aid is applied afterward to control any bleeding.

Benefits
We expect that the information will provide important benefits for society and humankind by helping doctors take better care of patients with lower respiratory tract infections like yours. This includes making sure the right patients get an antibiotic, that patients know how long their infection is likely to last, and which treatments are most effective. There are no expected direct benefits to you, though. The test that tells us which virus or bacteria were present will be run only once every 6 months by a laboratory at the CDC. In rare instances, if a virus or bacteria is detected that it would be important for you to know about, we will contact you with those results. If your doctor tests you for COVID-19 or flu, you will learn those results as soon as they are available. If your doctor doesn't test for COVID-19, the CDC lab will test for it and if present we will let you know if it was positive, even if it is several months later.

Alternatives to Participation
If you choose not to participate in the study, you will receive usual care from your clinician. The clinician will not be told that you declined to participate and declining to participate will have no impact on your care today.

Confidentiality of records
Patients with cough and other symptoms
Your name and contact information only be recorded on the Enrollment Form and linked to the other forms and data using a code number. During the time you are in the study, the information will be stored on a secure computer server protected by password and can only be accessed by the researchers. We will only keep information that could identify you long enough to match your responses with your medical records. We do not plan to share this identifying information with anyone who is not connected to this research study. Once you have completed your participation in the study, the name and contact information will be deleted.
After any identifying information has been removed, it is possible that the data and samples from this study may be used by other researchers for future research without your consent. Also, the US Food and Drug Administration (FDA), the US Department of Health and Human Services Office for Human Research Protections, the Institutional Review Board (IRB), and departments at the University of Georgia is responsible for regulatory and research oversight and may access the records. Researchers will not release identifiable results of the study to anyone other than individuals working on the project without your written consent unless required by law.

Persons without any cough or symptoms
Your name and contact information will not be recorded. During the time you are in the study, the information about your test results will not be linked to any identifiers other than age and sex will be stored on a secure computer server protected by password and can only be accessed by the researchers.

Participant rights
If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

Your involvement in the study is voluntary, and you may choose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. If you have any questions, concerns or complaints about the research, or questions regarding your rights as a research participant in this study, you may contact the WCG IRB at 855-818-2289 or researchquestions@wcgirb.com or Institutional Review Board (IRB) Chairperson at 706.542.3199 or irb@uga.edu. An IRB is a group of people who perform independent review of research studies.

Incentives/compensation for participation
Patients with cough and other symptoms
You will receive $20 after the first session, $10 after submitting the first weekly diary, and $10 after submitting at least one other diary for a total of up to $40. We will not track identifying information other than to note that you have received the money. The funds will be distributed either in cash as a VISA debit card, or as a gift card for a major retailer such as Amazon or Target.

Persons without any cough or symptoms
You will receive $10 after the completing the recruitment questions and providing your samples.

Detailed Description of Procedures and Visits
Symptomatic Patients
Today you will be asked about signs, symptoms, age, education, race, and income. We will also obtain a swab of your nose and throat, and a drop of blood from your finger to test for inflammation. If you are coughing up phlegm and have fever, chills, sweats, rapid breathing, or low blood pressure and you feel at least moderately ill, we will ask you to cough into a cup to collect your sputum (phlegm/mucus). We will also record information about what your doctors has diagnosed, what tests he or she has ordered, and what treatments are recommended.

Until you are feeling better (2 days without symptoms) we will ask you to complete a brief set of questions every day to tell us how you are feeling, whether you have missed work or school, and whether you are taking any medication to treat you cough. This should only take a minute or two and can be done from your phone or on a paper diary. We will also text or email you once a week to ask you to send us a photo of your diary or put it in the mail postage free.

Patients with cough and other symptoms

	Day 1	Days 2 to recovery	Day 7 and optionally 14, 21, 28 if not recovered
Consent discussion, signs and symptoms	X		
Nasal/throat swab, finger stick blood test	X		
Daily symptom diary		X	
Weekly text or email			X
Time needed in minutes:	**15**	**1-2 per day**	**3 per week**

Persons without any cough or symptoms

Today you will be asked about signs, symptoms, age, sex, race, and antibiotic usage. We will also obtain a swab of your nose and throat.

	Day 1
Consent discussion, signs and symptoms	X
Nasal/throat swab	X
Antibiotic usage questions	X
Time needed in minutes:	**10**

Internet Data Collection

This research involves the transmission of data over the Internet using the REDCap system developed at Vanderbilt University. This system is designed to gather data at multiple sites and save it in a single, secure repository on a secure server at the University of Georgia. Every reasonable effort has been taken to ensure the effective use of available technology; however, confidentiality during online communication cannot ever be completely guaranteed.

Sponsored Research

This study is funded by the Agency for Healthcare Quality and Research, which is part of the US Department of Health and Human Services.

UGA Health Center involvement

This study will be performed, in part, at the University Health Center (UHC). Refusal to participate or decision to stop participating at any time will not compromise your access to care, treatment, and UHC services not related to the research, if you otherwise have such access. If you have a health record at UHC, your participation in this project will be noted on the summary list unless you specifically request that it not be added.

If you agree to participate in this research study, please sign below:

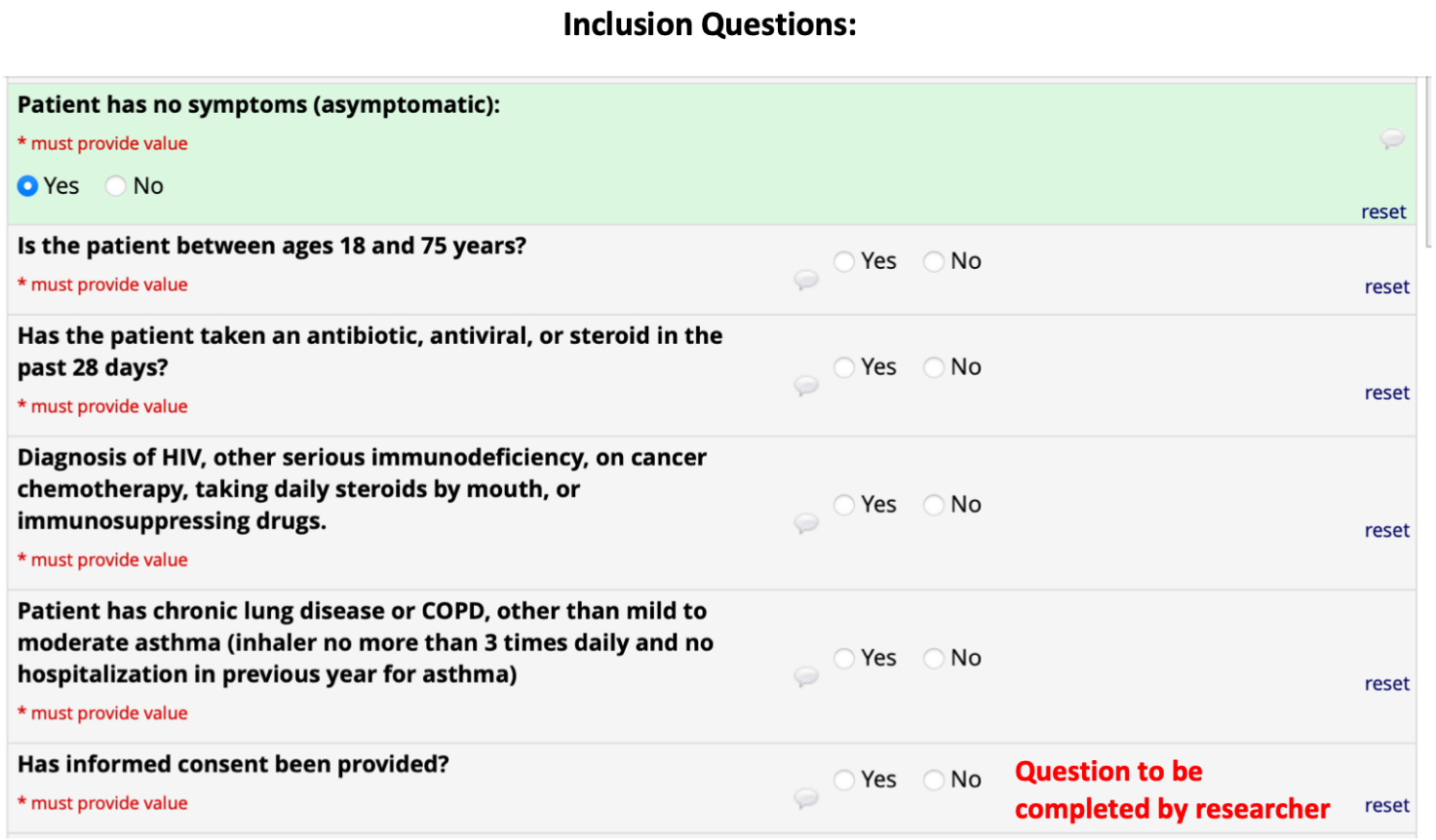
Name of Researcher	Signature	Date
Name of Participant	Signature	Date

Please keep one copy and return the signed copy to the researcher.

Table B1 Pathogens (n = 43) included in PCR panel used to test nasal and pharyngeal swabs of symptomatic and asymptomatic patients

PCR Panel Pathogens		
<u>Bacterial Pathogens</u>		
P. aeruginosa	*C. trachomatis*	*B. pseudomallei*
S. pneumoniae	*K. pneumoniae*	*H. influenzae (all types)*
Group A and B Streptococcus	*S. aureus*	*C. pneumoniae*
M. pneumoniae	*A. baumannii*	*M. catarrhalis*
C. diptheriae	*C. ulcerans/pseudotb*	*Bordetella spp. (IS481)*
Bordetella spp. (pIS1001)	*M. tuberculosis*	*P. jirovecii (PCP)*
DT (toxin)	PT (toxin)	
<u>Viral Pathogens</u>		
Varicella zoster virus	MERS coronavirus	Coronavirus HKU1
Measles virus	MERS-CoV upE	Coronavirus 229E
Parainfluenza virus 1, 2, 3, 4	Coronavirus NL63	Coronavirus OC43
Influenza A and B	Cytomegalovirus	RSV
Enterovirus	Adenovirus	Rhinovirus
Rubella virus	Human metapneumovirus	

Figure B1 Asymptomatic recruitment questionnaire



Inclusion Questions:

Patient has no symptoms (asymptomatic): * must provide value	● Yes ○ No	reset
Is the patient between ages 18 and 75 years? * must provide value	○ Yes ○ No	reset
Has the patient taken an antibiotic, antiviral, or steroid in the past 28 days? * must provide value	○ Yes ○ No	reset
Diagnosis of HIV, other serious immunodeficiency, on cancer chemotherapy, taking daily steroids by mouth, or immunosuppressing drugs. * must provide value	○ Yes ○ No	reset
Patient has chronic lung disease or COPD, other than mild to moderate asthma (inhaler no more than 3 times daily and no hospitalization in previous year for asthma) * must provide value	○ Yes ○ No	reset
Has informed consent been provided? * must provide value	○ Yes ○ No **Question to be completed by researcher**	reset

If you answered **"yes" to any of the questions following the age question** you are not eligible to participate
If you answered **"no" to ALL of these questions following the age question** you are eligible to participate, please sign and consent form then complete the questions on the back of this page.

Recruitment Questions:

Participant age (years):
* must provide value

Gender: ○ Male ○ Female ○ Other
reset

Patient race (may select more than one option):

- ☐ Prefer not to answer
- ☐ White
- ☐ Black
- ☐ Asian/Pacific Islander
- ☐ American Indian/Alaska Native

Patient ethnicity:

- ○ Prefer not to answer
- ○ Hispanic
- ○ Non-Hispanic

reset

Please indicate when the patient last took an antibiotic:

- ○ Patient has never taken an antibiotic
- ○ 1 to 2 months ago
- ○ > 2 to 6 months ago
- ○ > 6 to 12 months ago
- ○ > 12 months ago

reset

Nasal and pharyngeal specimen has been obtained: ○ Yes ○ No **Question to be completed by researcher**
reset

Figure B2 Equation used to calculate P-EPV

$$P(D^+|S^+T^+) = 1 - \left(\frac{\frac{\text{Sen}}{P(T^+|S^+)} - 1}{\frac{\text{Sen}}{P(T^+|S^+D^-)} - 1} \right)$$

D = Disease

S = Symptoms

T = Test

Sen = Sensitivity

$$P(T^+|S^+D^-) = P(T^+|S^-) \times \theta$$

θ = ratio between symptomatic and asymptomatic carriers

Table B2 Asymptomatic demographics by recruitment site

Asymptomatic				
	Athens/UGA (N = 225)	**Madison/UW (N = 143)**	**Washington/ GU (N = 122)**	**Total (N = 497)**
Age *Mean (Range)*	34.3 (18 – 74)	42.7 (18 – 65)	34.18 (19 – 71)	36.8 (18 – 74)
Sex				
Male	78 (34.8%)	40 (28.2%)	31 (26.7%)	149 (30.9%)
Female	144 (64.3%)	102 (71.8%)	85 (73.3%)	331 (68.7%)
Other	2 (0.9%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Race				
White	178 (79.1%)	117 (81.8%)	72 (59.0%)	367 (74.9%)
Black	28 (12.4%)	7 (4.9%)	22 (18.0%)	57 (11.6%)
Asian/Pacific Islander	5 (2.2%)	10 (7.0%)	17 (13.9%)	32 (6.5%)
American Indian/Alaska Native	2 (0.9%)	0 (0.0%)	2 (1.6%)	4 (0.8%)
No Race	7 (3.1%)	2 (1.4%)	8 (6.6%)	17 (3.5%)
Other	5 (2.2%)	7 (4.9%)	1 (0.8%)	13 (2.7%)
Ethnicity				
Hispanic	25 (11.1%)	4 (2.8%)	11 (9.1%)	40 (8.2%)
Non-Hispanic	194 (86.2%)	137 (95.8%)	107 (88.4%)	438 (89.6%)
Prefer not to answer	6 (2.7%)	2 (1.4%)	3 (2.5%)	11 (2.3%)
Antibiotic use				
1 to 2 month(s) ago	14 (6.2%)	1 (0.7%)	6 (4.5%)	21 (4.2%)
>2 to 6 months ago	32 (14.2%)	8 (5.8%)	23 (17.2%)	63 (12.7%)
>6 to 12 months ago	48 (21.3%)	13 (9.5%)	21 (15.7%)	82 (16.5%)
>12 months ago	122 (54.2%)	113 (82.5%)	82 (61.2%)	317 (63.9%)
Never taken an antibiotic	9 (4.0%)	2 (1.5%)	2 (1.5%)	13 (2.6%)

Table B3 Symptomatic demographics by recruitment site with valid nasopharyngeal samples

Symptomatic				
	Athens/UGA (N = 46)	**Madison/UW (N = 196)**	**Washington/ GU (N = 374)**	**Total (N = 618)**
Age *Mean (Range)*	32.0 (18 – 65)	34.3 (18 – 69)	42.7 (18 – 74)	39.2 (18 - 74)
Sex				
Male	14 (30.0%)	56 (38.6%)	135 (36.1%)	205 (66.2%)
Female	31 (67.4%)	138 (70.4%)	239 (63.9%)	408 (66.2%)
Other	1 (2.2%)	2 (1.0%)	0 (0.0%)	3 (0.5 %)
Race				
White	36 (78.3%)	170 (86.7%)	266 (71.1%)	472 (76.4%)
Black	6 (13.0%)	14 (7.1%)	23 (6.1%)	43 (7.0%)
Asian/Pacific Islander	2 (4.3%)	3 (1.6%)	58 (1.6%)	63 (10.2%)
American Indian/Alaska Native	0 (0.0%)	2 (0.6%)	2 (0.5%)	4 (0.6%)
No Race	1 (2.1%)	5 (1.5%)	19 (5.1%)	25 (4.0%)
Other	2 (4.3%)	3 (1.6%)	9 (2.4%)	14 (2.3%)
Ethnicity				
Hispanic	1 (2.2%)	15 (7.7%)	54 (14.5%)	70 (11.4%)
Non-Hispanic	44 (95.7%)	178 (91.3%)	307 (82.3%)	529 (86.2%)
Prefer not to answer	1 (2.2%)	2 (1.0%)	12 (3.2 %)	15 (2.4%)

Table B4 Infection types identified in the nasal and oropharyngeal swabs of symptomatic and asymptomatic study participants.

Infection Type	Symptomatic (N = 618)	Asymptomatic (N = 497)
Bacterial	173 (28.0%)	152 (30.6%)
Viral	175 (28.3%)	57 (11.5%)
Mixed	175 (28.3%)	24 (4.8%)
No growth	95 (15.4%)	264 (53.1%)

$X^2 = 213.5$, P-value = <0.0001

Table B5 Description of cycle time categories for the first pathogen identified in symptomatic and asymptomatic participants.

Pathogen Likelihood	Symptomatic (N = 618)	Asymptomatic (N = 497)
Low $C_T > 34$ to $C_T < 50$	34 (5.5%)	28 (5.6%)
Moderate $C_T > 28$ to $C_T \leq 34$	196 (31.7%)	166 (33.4%)
High $C_T \leq 28$	270 (43.7%)	39 (7.9%)
Undetected	118 (19.1%)	264 (53.1%)

$X^2 = 218.3$, P-value = <0.0001

APPENDIX C

UNIVERSITY OF GEORGIA
CONSENT LETTER

Study of Care Seeking Behaviors of College Aged Students for Respiratory Illnesses

Dear Participant,

My name is Cassie Hulme, and I am a doctoral candidate in the Department of Epidemiology and Biostatistics at the University of Georgia under the supervision of Faculty Advisor Dr. Mark Ebell. I am inviting you to take part in a research study.

I am doing research to identify the most common respiratory symptoms for which students believe that they need to seek care or seek antibiotic treatment. The goal of this research is to inform clinicians in the university health setting and more broadly clinicians caring for young adults regarding why they choose to seek care for respiratory symptoms. We will also use this research to identify areas where more health education is needed as it applies to acute respiratory tract infections and their treatments. Any University of Georgia students aged 18 years and older can participate.

If you agree to take part in this study, you will be asked to take an online survey that will take about 10 minutes to complete. All responses will be kept confidential and used only for the purposes of this research study. We will not be collecting any direct identifying information from you. Only your responses to survey questions will be stored.

We will ask you to provide your email address to enter you in a drawing for 1 of 10, $50 Amazon electronic gift cards for your participation. Participation in this study is not required to be entered in the drawing. By providing your email address of the first page of the survey, you will be entered. While the internet is insecure, your email address will be stored securely. We will not use your email address to contact you other than described above, and once the study is over, we will delete the email address.

Participation is voluntary. You can refuse to take part or stop completing the survey at any time without penalty. We do not think that any of the questions will make you uncomfortable. However, you are free to skip any questions if you do not wish to answer them. The information you provide will not be used or distributed for future research.

There are no direct benefits to you for participating, but we hope that your responses may help us understand students reasoning for seeking (or not seeking) medical treatment for acute respiratory tract infections.

If you are interested in participating or have questions about this research, please feel free to contact me at cchupp@uga.edu or Dr. Mark Ebell at ebell@uga.edu If you have any complaints or questions about your rights as a research volunteer, contact the IRB at 706-542-3199 or by email at IRB@uga.edu.

By completing this survey, you are consenting to participate in this study.

Sincerely,

Cassie Hulme, MPH

UGA Care Seeking Behavior for ARTI Study

Start of Block: Introduction

Thank you for considering participation in our survey. Our goal is to better understand the most common reasons that university students seek care for acute respiratory tract infections. Below is a copy of the informed consent form for download. Please click on the PDF link below to download and review.

After reviewing the consent form, if you choose to participate, please click the next button to proceed. By clicking this button, you agree that you give consent to participate in this study.

Complete the survey questions to the best of your ability. If you do not want to answer a question, please choose 'prefer not to answer' or simply skip the question.

End of Block: Introduction

Start of Block: Demographics

What is your age in years?

_____

Skip To: End of Survey If Condition: What is your age in years? Is Less Than 18. Skip To: End of Survey.

Page Break

Which sex do you identify with?

- ○ Male (1)
- ○ Female (2)
- ○ Non-binary / third gender / other (3)
- ○ Prefer not to answer (4)

Which race do you identify as (you may check more than one)?

- ☐ White (1)
- ☐ Black or African American (2)
- ☐ American Indian or Alaska Native (3)
- ☐ Asian (4)
- ☐ Native Hawaiian or Pacific Islander (5)
- ☐ Other (6) _____
- ☐ Prefer not to answer (7)

Which ethnicity do you identify as?

- ○ Hispanic (1)
- ○ Non-Hispanic (2)
- ○ Prefer not to answer (3)

Which of the following best describes your year in school at UGA at the time that you are taking this survey?

- ○ Undergraduate Year 1 (1)
- ○ Undergraduate Year 2 (2)
- ○ Undergraduate Year 3 (3)
- ○ Undergraduate Year 4 (4)
- ○ Undergraduate Year 5 (5)
- ○ Graduate (MS, MA, MFA, MPH, MSW, or other Masters; PhD, EdD, DrPH, or other doctoral) (6)
- ○ Professional (DVM, MD, JD, or Pharmacy) (7)
- ○ Other (8) _____

End of Block: Demographics

Start of Block: Antibiotic usage

Indicate the approximate time frame of when you received your last antibiotic prescription:

- ○ > 1 year ago (1)
- ○ 12 - 6 months ago (2)
- ○ 6 - 3 months ago (3)
- ○ 3 - 1 month(s) ago (4)
- ○ < 1 month ago (5)
- ○ Unsure (6)

End of Block: Antibiotic usage

Start of Block: Upper Respiratory Tract Scenarios

Imagine that you have had a dry cough (without sputum production), fever, and swollen glands in your throat for 1 day. You have not had a sore throat or nasal discharge, and are otherwise healthy with no other health concerns. Based on these signs and symptoms:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you have had a cough with yellow sputum production, a sore throat, yellow nasal discharge, and facial pressure pain. You have been experiencing these symptoms for

approximately 7 days. You have not had a fever or swollen glands in your throat and you are otherwise healthy with no other health concerns. Based on these signs and symptoms:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you have had a fever for 2 days. Additionally, you have had swollen glands in your throat, yellow/green nasal discharge, and been experiencing facial pain/ pressure for

approximately 10 days. You are otherwise healthy with not other health concerns. Based on these signs and symptoms:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you have had a cough with clear/yellow sputum production and yellow/green nasal discharge for 2 days. You are otherwise healthy with no other health concerns. Based on these signs and symptoms:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

End of Block: Upper Respiratory Tract Scenarios

Start of Block: Sore Throat Scenarios

Imagine that you have had a sore throat and a runny nose with clear/ yellow nasal discharge for 5 days. You are otherwise healthy with no other health concerns. Based on the signs and symptoms described:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you woke up with a fever, sore throat and the glands in their neck are swollen. You are otherwise healthy with no other health concerns. Based on the signs and symptoms described:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you have been experiencing a fever for 2 days. Additionally, you have had a sore throat with swollen glands 2 weeks (14 days). You are otherwise healthy with no other health concerns. Based on the signs and symptoms described:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you have had a sore throat with swollen glands and a runny nose with yellow/ green nasal discharge for 7 days. You are otherwise healthy with no other health concerns. Based on

the signs and symptoms described:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

End of Block: Sore Throat Scenarios

Start of Block: Lower Respiratory Tract Scenarios

Imagine that you have had a cough with chest pain. When you cough, you noticed that your sputum is slightly yellow. You have also had a sore throat. You have been experiencing all of

these symptoms for approximately 10 days. You are otherwise health with no other health concerns. Based on the signs and symptoms described:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you have had a fever for 2 days. You have also had a cough for over 2 weeks. When you cough, you feel a slight pain in your chest and sometimes your sputum is bloody. You are otherwise healthy with no other health concerns. Based on the signs and symptoms described:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you woke up with a fever and have been experiencing a cough and sore throat for 12 days. When you cough, you have a pain in your chest and you noticed that your sputum is

green. You are otherwise healthy with no other health concerns. Based on the signs and symptoms described:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

Imagine that you have had a cough for 2 days. When you cough, you notice that it causes you to have a slight pain in your chest. You are otherwise healthy with no other health concerns. Based on the signs and symptoms described:

	Extremely unlikely (1)	Somewhat unlikely (2)	Neither likely nor unlikely (3)	Somewhat likely (4)	Extremely likely (5)
How likely are you to want to visit a doctor? (1)	○	○	○	○	○
How likely are you to want an antibiotic? (2)	○	○	○	○	○

End of Block: Lower Respiratory Tract Scenarios

Table C1. Vignette response frequencies

Vignette Type, #	**Seek Care**	**Seek Antibiotic**
URTI 1 (Moderate) **N = 472**		
Extremely Unlikely	154 (32.2%)	172 (36.4%)
Somewhat Unlikely	167 (34.9%)	115 (24.4%)
Neither	24 (5.0%)	69 (14.6%)
Somewhat Likely	105 (21.9%)	94 (19.9%)
Extremely Likely	29 (6.1%)	22 (4.7%)
URTI 2 (Severe) **N = 536**		
Extremely Unlikely	48 (8.9%)	62 (11.6%)
Somewhat Unlikely	128 (23.7%)	93 (17.4%)
Neither	36 (6.7%)	110 (20.5%)
Somewhat Likely	221 (40.9%)	182 (34.0%)
Extremely Likely	107 (19.8%)	89 (16.6%)
URTI 3 (Very Severe) **N = 298**		
Extremely Unlikely	21 (4.2%)	33 (6.6%)
Somewhat Unlikely	84 (16.8%)	60 (12.1%)
Neither	17 (3.4%)	109 (21.9%)
Somewhat Likely	206 (41.3%)	177 (35.5%)
Extremely Likely	171 (34.3%)	119 (23.9%)
URTI 4 (Mild) **N = 498**		

Extremely Unlikely	175 (35.1%)	194 (39.0%)
Somewhat Unlikely	193 (38.7%)	119 (23.9%)
Neither	23 (4.6%)	59 (11.9%)
Somewhat Likely	79 (15.8%)	97 (19.5%)
Extremely Likely	29 (5.8%)	29 (5.8%)
ST 1 (Mild) **N = 503**		
Extremely Unlikely	134 (26.5%)	155 (30.8%)
Somewhat Unlikely	169 (33.4%)	137 (27.2%)
Neither	38 (7.5%)	68 (13.5%)
Somewhat Likely	121 (23.9%)	103 (20.5%)
Extremely Likely	44 (8.7%)	40 (8.0%)
ST 2 (Severe) **N = 505**		
Extremely Unlikely	77 (15.2%)	88 (17.4%)
Somewhat Unlikely	148 (29.3%)	135 (26.7%)
Neither	30 (5.9%)	72 (14.3%)
Somewhat Likely	179 (35.4%)	142 (28.1%)
Extremely Likely	72 (14.2%)	68 (13.5%)
ST 3 (Very Severe) **N = 498**		
Extremely Unlikely	26 (5.6%)	39 (7.8%)
Somewhat Unlikely	63 (12.6%)	75 (15.0%)
Neither	25 (5.0%)	97 (19.4%)

Somewhat Likely	213 (42.6%)	174 (34.7%)
Extremely Likely	173 (34.6%)	116 (23.2%)
ST 4 (Moderate) **N = 488**		
Extremely Unlikely	55 (11.2%)	66 (13.5%)
Somewhat Unlikely	120 (24.5%)	89 (18.2%)
Neither	40 (8.2%)	80 (16.4%)
Somewhat Likely	177 (36.1%)	170 (34.8%)
Extremely Likely	98 (20.0%)	84 (17.2%)
LRTI 1 (Moderate) **N = 525**		
Extremely Unlikely	16 (3.1%)	27 (5.1%)
Somewhat Unlikely	72 (13.7%)	74 (14.1%)
Neither	43 (8.2%)	105 (20.0%)
Somewhat Likely	192 (36.6%)	192 (34.0%)
Extremely Likely	202 (38.5%)	141 (26.8%)
LRTI 2 (Very Severe) **N = 483**		
Extremely Unlikely	6 (1.2%)	8 (1.7%)
Somewhat Unlikely	14 (2.9%)	26 (5.4%)
Neither	15 (3.1%)	99 (20.5%)
Somewhat Likely	111 (22.8%)	138 (28.6%)
Extremely Likely	341 (70.0%)	212 (43.9%)
LRTI 3 (Severe) **N = 464**		

Extremely Unlikely	4 (0.9%)	10 (2.2%)
Somewhat Unlikely	18 (3.9%)	21 (4.5%)
Neither	13 (2.8%)	68 (14.6%)
Somewhat Likely	133 (28.7%)	144 (30.9%)
Extremely Likely	296 (63.8%)	223 (47.9%)
LRTI 4 (Mild) **N = 515**		
Extremely Unlikely	111 (21.5%)	157 (30.5%)
Somewhat Unlikely	176 (34.0%)	151 (29.3%)
Neither	60 (11.6%)	99 (19.2%)
Somewhat Likely	133 (25.7%)	79 (15.3%)
Extremely Likely	37 (7.2%)	29 (5.6%)

Table C2 Count and frequency of agreeing or disagreeing to seeking care or seeking antibiotic treatment by scenario severity (N = 2000).

Severity	Seek Care				Seek Antibiotic			
	Agree	**Disagree**	**X^2**	**P-value**	**Agree**	**Disagree**	**X^2**	**P-value**
Upper Respiratory Tract Infection								
Mild	109 (11.7%)	385 (36.2%)	379.6	<0.001	120 (15.0%)	374 (31.1%)	189.5	<0.001
Moderate	326 (34.8%)	212 (19.9%)			269 (33.7%)	269 (22.4%)		
Severe	133 (14.2%)	340 (32.0%)			119 (14.9%)	354 (29.5%)		
Very Severe	368 (39.3%)	127 (11.9%)			291 (36.4%)	204 (17.0%)		
Sore Throat								
Mild	164 (15.3%)	341 (36.8%)	195.2	<0.001	140 (15.7%)	365 (32.9%)	100.2	<0.001
Moderate	277 (25.8%)	314 (23.1%)			255 (28.6%)	236 (21.3%)		
Severe	251 (23.4%)	251 (27.1%)			212 (23.8%)	290 (26.2%)		
Very Severe	381 (35.5%)	121 (13.1%)			285 (32.0%)	217 (19.6%)		
Lower Respiratory Tract Infection								
Mild	177 (12.2%)	341 (62.0%)	566.4	<0.001	115 (10.0%)	403 (47.4%)	396.2	<0.001

Moderate	393 (27.1%)	133 (24.2%)			314 (27.3%)	212 (24.9%)		
Severe	432 (29.8%)	35 (6.4%)			370 (32.2%)	97 (11.4%)		
Very Severe	448 (30.9%)	41 (7.5%)			351 (30.5%)	138 (16.2%)		

Table C3a Bivariate analysis – Seeking Care for URTI

Variable	OR (95% CI)	P-value
Fever	1.51 (1.27, 1.81)	<0.001
Cough	0.20 (0.16, 0.25)	<0.001
Sore throat	2.17 (1.77, 2.66)	<0.001
Glands	1.51 (1.27, 1.81)	<0.001
Nasal discharge	1.71 (1.52, 1.91)	<0.001
Face pain	6.51 (5.35, 7.92)	<0.001
Duration		
< 3 days		REF
3 - 7days	4.80 (3.83, 6.02)	<0.001
8 - 14days	9.47 (7.36, 12.18)	<0.001
Age	0.99 (0.98, 1.00)	0.132
Sex		
Male		REF
Female	1.11 (0.90, 1.37)	0.345
Non-binary/ third gender/ other	1.04 (0.56, 1.90)	0.912
Prefer not to answer	2.46 (0.45, 13.60)	0.301
Race		
White		REF
Black or African American	1.57 (1.06, 2.32)	0.025
Asian	0.72 (0.55, 0.95)	0.018
Other	0.98 (0.67, 1.43)	0.917
Prefer not to answer	1.58 (0.70, 3.57)	0.276
Ethnicity		
Hispanic		REF
Non-Hispanic	0.87 (0.62, 1.23)	0.436
Prefer not to answer	0.86 (0.43, 1.74)	0.681

Grade		
Undergraduate year 1 - 2		REF
Undergraduate year 3 - 4	0.90 (0.72, 1.27)	0.364
Undergraduate year 5, Graduate, Professional	0.83 (0.68, 1.23)	0.08
Antibiotics		
> 1 year		REF
12 - 6 months ago	1.37 (1.09, 1.72)	0.007
5 - 3 months ago	1.71 (1.26, 2.32)	0.001
2 - 1 month(s) ago	1.57 (1.08, 2.27)	0.018
< 1 month	1.84 (1.35, 2.50)	<0.001
Unsure	1.55 (1.10, 2.03)	0.013

Table C3b Bivariate analysis – Seeking Antibiotic Treatment for URTI

Variable	OR (95% CI)	P-value
Fever	1.18 (0.99, 1.41)	0.072
Cough	0.34 (0.28, 0.42)	<0.001
Sore throat	1.80 (1.47, 2.19)	<0.001
Glands	1.18 (0.99, 1.41)	0.072
Nasal discharge	1.64 (1.45, 1.84)	<0.001
Face pain	3.82 (3.15, 4.62)	<0.001
Duration		
< 3 days		REF
3 - 7days	3.20 (2.56, 4.00)	<0.001
8 - 14days	4.65 (3.68, 5.86)	<0.001
Age	0.97 (0.95, 0.99)	<0.001
Sex		
Male		REF
Female	1.10 (0.88, 1.36)	0.409
Non-binary/ third gender/ other	0.63 (0.32, 1.23)	0.173
Prefer not to answer	0.80 (0.14, 4.40)	0.795
Race		
White		REF
Black or African American	2.01 (1.36, 2.97)	<0.001
American Indian or Alaska Native	1.61 (0.10, 25.84)	0.736
Asian	1.16 (0.88, 1.52)	0.285
Other	1.10 (0.75, 1.61)	0.632
Prefer not to answer	1.61 (0.72, 3.61)	0.246
Ethnicity		
Hispanic		REF
Non-Hispanic	0.59 (0.42, 0.84)	0.003

Prefer not to answer	0.66 (0.33, 1.33)	0.246
Grade		
Undergraduate year 1 - 2		REF
Undergraduate year 3 - 4	0.80 (0.64, 1.00)	0.057
Undergraduate year 5, Graduate, Professional	0.53 (0.43, 0.66)	<0.001
Antibiotics		
> 1 year		REF
12 - 6 months ago	1.83 (1.45, 2.32)	<0.001
5 - 3 months ago	2.40 (1.77, 3.27)	<0.001
2 - 1 month(s) ago	2.19 (1.51, 3.19)	<0.001
< 1 month	3.06 (2.24, 4.19)	<0.001
Unsure	1.94 (1.36, 2.77)	<0.001

Table C3c Bivariate analysis – Seeking Care for Sore Throat

Variable	OR (95% CI)	P-value
Fever	2.22 (1.86, 2.66)	<0.001
Glands	3.18 (2.57, 3.93)	<0.001
Nasal discharge		
None		REF
Clear	0.28 (0.22, 0.35)	<0.001
Yellow	0.71 (0.57, 0.89)	0.003
Duration		
< 3 days		REF
3 - 7days	0.79 (0.64, 0.98)	0.031
8 - 14days	3.43 (2.61, 4.50)	<0.001
Age	0.99 (0.98, 1.01)	0.298
Sex		
Male		REF
Female	1.21 (0.97, 1.49)	0.085
Non-binary/ third gender/ other	1.56 (0.84, 2.91)	0.159
Prefer not to answer	1.00 (0.20, 5.03)	0.996
Race		
White		REF
Black or African American	1.29 (0.87, 1.93)	0.196
American Indian or Alaska Native	0.87 (0.05, 13.86)	0.918
Asian	0.94 (0.72, 1.22)	0.622
Other	0.93 (0.63, 1.35)	0.693
Prefer not to answer	1.02 (0.46, 2.30)	0.957
Ethnicity		
Hispanic		REF
Non-Hispanic	0.99 (0.70, 1.41)	0.979

Prefer not to answer	0.60 (0.30, 1.22)	0.16
Grade		
Undergraduate year 1 - 2		REF
Undergraduate year 3 - 4	0.96 (0.77, 1.20)	0.709
Undergraduate year 5, Graduate, Professional	0.86 (0.70, 1.06)	0.158
Antibiotics		
> 1 year		REF
12 - 6 months ago	1.61 (1.28, 2.02)	<0.001
5 - 3 months ago	1.52 (1.12, 2.05)	0.007
2 - 1 month(s) ago	1.46 (1.01, 2.12)	0.045
< 1 month	2.44 (1.77, 3.37)	<0.001
Unsure	1.14 (0.81, 1.62)	0.453

Table C3d Bivariate analysis – Seeking Antibiotic Treatment for Sore Throat

Variable	OR (95% CI)	P-value
Fever	1.52 (1.27, 1.82)	<0.001
Glands	2.56 (2.06, 3.19)	<0.001
Nasal discharge		
None		REF
Clear	0.40 (0.32, 0.50)	<0.001
Yellow	1.05 (0.85, 1.31)	0.645
Duration		
< 3 days		REF
3 - 7days	0.91 (0.73, 1.13)	0.385
8 - 14days	1.91 (1.49, 2.46)	<0.001
Age	0.96 (0.95, 0.98)	<0.001
Sex		
Male		REF
Female	1.13 (0.91, 1.40)	0.266
Non-binary/ third gender/ other	0.42 (0.21, 0.85)	0.015
Prefer not to answer	0.27 (0.03, 2.30)	0.229
Race		
White		REF
Black or African American	1.20 (0.81, 1.77)	0.361
American Indian or Alaska Native	1.31 (1.00, 1.71)	0.047
Asian	1.05 (0.72, 1.53)	0.814
Other	0.43 (0.17, 1.09)	0.075
Prefer not to answer		
Ethnicity		REF
Hispanic	0.70 (0.50, 0.99)	0.046
Non-Hispanic	0.25 (0.11, 0.56)	0.001

Prefer not to answer		
Grade		REF
Undergraduate year 1 - 2	0.77 (0.62, 0.97)	0.023
Undergraduate year 3 - 4	0.53 (0.43, 0.65)	<0.001
Undergraduate year 5, Graduate, Professional		
Antibiotics		REF
> 1 year	2.12 (1.68, 2.66)	<0.001
12 - 6 months ago	1.77 (1.31, 2.40)	<0.001
5 - 3 months ago	2.13 (1.47, 3.09)	<0.001
2 - 1 month(s) ago	2.79 (2.04, 3.81)	<0.001
< 1 month	1.84 (1.30, 2.62)	0.001
Unsure		

Table C3e Bivariate analysis – Seeking Care for LRTI

Variable	OR (95% CI)	P-value
Fever	9.79 (7.50, 12.78)	<0.001
Sputum		
None		REF
Clear	6.40 (4.88, 8.40)	<0.001
Green	23.99 (16.36, 35.17)	<0.001
Bloody	24.66 (16.89, 36.00)	<0.001
Chest pain	13.06 (10.31, 16.54)	<0.001
Sore throat	3.12 (2.52, 3.84)	<0.001
Duration		
< 3 days		REF
8 – 14 days	10.37 (8.09, 13.30)	<0.001
> 14 days	24.66 (16.89, 36.00)	<0.001
Age	1.00 (0.98, 1.01)	0.930
Sex		
Male		REF
Female	1.23 (0.97, 1.55)	0.082
Non-binary/ third gender/ other	0.91 (0.48, 1.74)	0.780
Prefer not to answer	0.88 (0.16, 4.88)	0.886
Race		
White		REF
Black or African American	1.67 (1.02, 2.75)	0.043
American Indian or Alaska Native	0.37 (0.02, 5.95)	0.484
Asian	0.85 (0.63, 1.13)	0.262
Other	0.71 (0.47, 1.05)	0.087
Prefer not to answer	0.90 (0.37, 2.19)	0.819
Ethnicity		

Hispanic		REF
Non-Hispanic	0.89 (0.60, 1.32)	0.565
Prefer not to answer	1.42 (0.60, 3.35)	0.430
Grade		
Undergraduate year 1 - 2		REF
Undergraduate year 3 - 4	1.14 (0.89, 1.47)	0.305
Undergraduate year 5, Graduate, Professional	1.02 (0.81, 1.28)	0.862
Antibiotics		
> 1 year		REF
12 - 6 months ago	1.24 (0.96, 1.60)	0.095
5 - 3 months ago	1.56 (1.09, 2.24)	0.014
2 - 1 month(s) ago	1.04 (0.69, 1.56)	0.861
< 1 month	1.31 (0.92, 1.86)	0.130
Unsure	0.97 (0.66, 1.41)	0.868

Table C3f Bivariate analysis – Seeking Antibiotic Treatment for LRTI

Variable	OR (95% CI)	P-value
Fever	4.29 (3.54, 5.19)	<0.001
Sputum		
None		REF
Clear	6.02 (4.57, 7.94)	<0.001
Green	14.66 (10.76, 19.95)	<0.001
Bloody	9.66 (7.24, 12.90)	<0.001
Chest pain	9.08 (7.14, 11.55)	<0.001
Sore throat	2.75 (2.29, 3.30)	<0.001
Duration		
< 3 days		REF
8 – 14 days	8.81 (6.85, 11.34)	<0.001
> 14 days	9.66 (7.24, 12.90)	<0.001
Age	0.98 (0.96, 0.99)	0.007
Sex		
Male		REF
Female	0.87 (0.70, 1.08)	0.207
Non-binary/ third gender/ other	0.34 (0.18, 0.65)	0.001
Prefer not to answer	0.13 (0.01, 1.11)	0.063
Race		
White		REF
Black or African American	1.30 (0.87, 1.94)	0.205
American Indian or Alaska Native	0.74 (0.05, 11.87)	0.832
Asian	1.08 (0.83, 1.42)	0.563
Other	0.77 (0.53, 1.12)	0.169
Prefer not to answer	0.63 (0.28, 1.41)	0.258
Ethnicity		

Hispanic		REF
Non-Hispanic	0.70 (0.48, 1.00)	0.052
Prefer not to answer	0.45 (0.22, 0.92)	0.027
Grade		
Undergraduate year 1 - 2		REF
Undergraduate year 3 - 4	0.92 (0.73, 1.15)	0.464
Undergraduate year 5, Graduate, Professional	0.68 (0.55, 0.84)	<0.001
Antibiotics		
> 1 year		REF
12 - 6 months ago	1.68 (1.33, 2.11)	<0.001
5 - 3 months ago	1.99 (1.45, 2.72)	<0.001
2 - 1 month(s) ago	1.42 (0.97, 2.06)	0.068
< 1 month	2.15 (1.56, 2.97)	<0.001
Unsure	1.28 (0.90, 1.82)	0.164

Respiratory History

** How long have you been having symptoms (in days)?

** How long did it take to feel this bad?

○ Less than a day

○ 1-2 days

○ 3 or more days

** Has someone you lived with been sick? ○ Yes ○ No

** In the past 24 hours, how much have you limited your activities due to illness?
(Normal activity level = 10 and completely confined to bed is 0)

○ 0 (Bed Ridden) ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 (No Limit)

General/Systemic:

** Fever..... ○ Yes ○ No

** Chills and/or Sweats ○ Yes ○ No

** Headache..... ○ Yes ○ No

** Fatigue..... ○ Yes ○ No

** Can't Sleep..... ○ Yes ○ No

Nose, sinus and throat:

** Nasal Congestion..... ○ Yes ○ No

** Runny Nose..... ○ Yes ○ No

** Sneezing..... ○ Yes ○ No

** Face Pain or Toothache..... ○ Yes ○ No

** Sore Throat..... ○ Yes ○ No

** Swollen/Tender Lymph Nodes ○ Yes ○ No

** Loss of taste of smell ○ Yes ○ No

Eyes and Ears:

** Ear Pain..... ○ Yes ○ No

** Loss of Hearing.... ○ Yes ○ No

** Eye Pain/Irritation.. ○ Yes ○ No

** Itchy, Watery Eyes.. ○ Yes ○ No

** Change of Vision.. ○ Yes ○ No

Chest:

** Cough..... ○ Yes ○ No

** Wheezing..... ○ Yes ○ No

** Shortness of Breath ○ Yes ○ No

** Chest pain..... ○ Yes ○ No

** Chest Congestion... ○ Yes ○ No

Abdomen:

** Nausea..... ○ Yes ○ No

** Vomiting..... ○ Yes ○ No

** Abdominal Pain.. ○ Yes ○ No

** Diarrhea..... ○ Yes ○ No

Please rank the intensity of the following (if they apply):

** Cough

○ None ○ Mild ○ Moderate ○ Severe

** Body or muscle aches.

○ None ○ Mild ○ Moderate ○ Severe

** Weakness

○ None ○ Mild ○ Moderate ○ Severe

** Have you had your flu shot this season (since August/September 2021)? ☐ Yes ☐ No

** Have you had previous COVID testing? ☐ Yes ☐ No

Please describe if yes.

How has your illness evolved??

What measures have you tried to get or feel better?

Indicate below any other concerns that you have (please note that time constraints may force us to address these in a separate appointment).

Supplemental Information

Thanks for submitting your questionnaire.

Figure C2 Histogram of symptom duration (days)

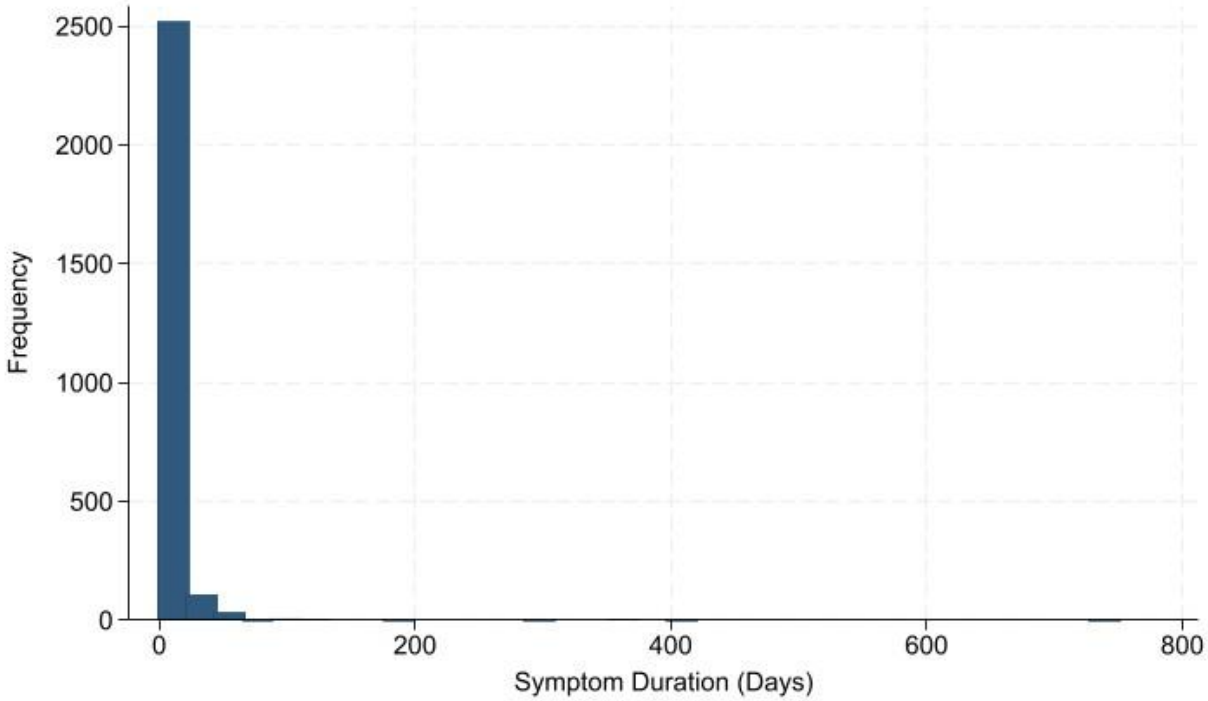


Table C4 Themes identified in “how has your illness evolved?” responses (N = 1,215).

Theme Name	Number of Times Referenced N (%)
Sore throat	395 (32.5%)
Cough	165 (13.6%)
Dry cough	21 (12.7%)
Bad cough	17 (10.3%)
Mild cough	17 (10.3%)
Severe cough	15 (9.1%)
Slight cough	12 (7.3%)
Small cough	6 (3.6%)
Lingering cough	5 (3.0%)
Light cough	4 (2.4%)
Persistent cough	4 (2.4%)
Wet cough	4 (2.4%)
Congested cough	3 (1.8%)
Painful coughing	3 (1.8%)
Productive coughing	3 (1.8%)
Congestion	113 (9.3%)
Nasal congestion	46 (40.7%)
Chest congestion	18 (15.9%)
Sinus congestion	12 (10.6%)

Head congestion	4 (3.5%)
Bad congestion	3 (2.7%)
Mild congestion	3 (2.7%)
Constant congestion	2 (1.8%)
Heavy congestion	2 (1.8%)
Severe congestion	2 (1.8%)
Nose	107 (8.8%)
Runny nose	66 (61.7%)
Stuffy/Stuffed nose	24 (22.4%)
Nose bleeds	3 (2.8%)
Aches	104 (8.6%)
Body aches	61 (58.7%)
Muscle aches	9 (8.7%)
Ear aches	2 (1.9%)
Severe aches	2 (1.9%)

*Description themes that were mentioned in ≤ 1% of responses were excluded from table