EPIDEMIOLOGY, CLINICAL PRESENTATION, MANAGEMENT, AND PROGNOSIS OF PROLONGED COUGH IN ADULTS IN THE OUTPATIENT SETTING

by

CHRISTIAN S. MARCHELLO

(Under the Direction of Mark Ebell)

ABSTRACT

Background: Approximately 20 million visits to an ambulatory physician per year are due to the primary complaint of a cough. Observed duration for an acute cough in the literature (15 to 28 days) is longer than patient expectations (7 to 9 days). Examining the clinical presentation and management decisions for the subset of patients with an uncomplicated acute cough of at least a week may help reduce the ordering of chest x-rays (CXR) and the overprescribing of antibiotics, steroids, and cough suppressants. **Methods**: A systematic review and meta-analysis of clinical decision rules (CDR) for low yield criteria of community-acquired pneumonia (CAP). In addition, adults 18 years or older presenting with a cough as their main or chief complaint were recruited for a mixed cross-sectional and prospective observational study. Patients were surveyed for demographics, signs and symptoms, and clinicians documented their management decisions. Participants recorded duration and severity of symptoms for up to 14 days after enrollment. **Results**: Normal vital signs combined with a normal pulmonary exam performed well as a CDR to rule out CAP (LR- 0.10, 95% CI 0.07-0.13). A total of 125 patients enrolled over the study period, 118 (94%) received an antibiotic, 39 (31%) CXR, 87 (70%) a systemic corticosteroid, and 97 (78%) a cough suppressant. A normal chest exam by the clinician is significantly associated with a longer duration of a cough (LR+ 2.11, 95% CI: 1.07-

4.16 and LR- 0.49, 0.32-0.75). Dyspnea was significantly associated with ordering a CXR (aOR 3.01, 95% CI 1.21-7.49). Clinician recorded crackles significantly decreased the likelihood of a systemic corticosteroid prescription (aOR 0.27, 95% 0.09-0.82). Increasing age was significantly associated with an increased likelihood of being prescribed a cough suppressant (aOR 1.04 per additional year of age, 95% CI 1.01-1.07). **Conclusions**: A combination of normal vital signs and a normal pulmonary exam in adults with acute respiratory infection can be used as low yield criteria for CAP. Chest x-rays, antibiotics, systemic corticosteroids and cough suppressants are commonly used in patients with uncomplicated acute cough of at least seven days duration in the urgent care setting.

INDEX WORDS: Community-acquired pneumonia, acute bronchitis, cough, outpatient, urgent care, clinical decision rules, clinical presentation, clinical management

EPIDEMIOLOGY, CLINICAL PRESENTATION, MANAGEMENT, AND PROGNOSIS OF PROLONGED COUGH IN ADULTS IN THE OUTPATIENT SETTING

by

CHRISTIAN S. MARCHELLO

BS, University of North Carolina at Chapel Hill, 2006

MS, Georgetown University, 2012

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2018

EPIDEMIOLOGY, CLINICAL PRESENTATION, MANAGEMENT, AND PROGNOSIS OF PROLONGED COUGH IN ADULTS IN THE OUTPATIENT SETTING

by

CHRISTIAN S. MARCHELLO

Major Professor:	Mark Ebell
Committee:	Christopher Whalen
	Ye Shen
	Eric Harvill

Electronic Version Approved:

Suzanne Barbour
Dean of the Graduate School
The University of Georgia
May 2018

DEDICATION

To my wife, Amy - I would not have been able to do this without you. Deciding for me to pursue this degree did not make things easy for you. From moving, finding work, and a place to live, you never once complained or second guessed. For that, I will forever be grateful. There were many long days and several frustrating moments with how my project was progressing and you were always there for me, never doubting that it would all work out. Your reassurance and always positive attitude kept me grounded. This experience was all worth it by having you by my side the entire way. Thank you. I love you.

To my parents, Vince and Pat - thank you for providing me with the tools necessary to get me to this point in life. You taught me that with self-discipline and determination, anything is possible. It has made me a better person, man, and husband. Without your love, support, and encouragement, I would not be who or where I am today.

ACKNOWLEDGEMENTS

First and foremost, an enormous thank you to my major dissertation advisor, Dr. Mark Ebell. I began working with you during my first semester as a student in the program and have learned an incredible amount from you throughout these four years. I continue to tell everyone that I can't believe how lucky I am to have you as a mentor. You always seemed to know when to be stern and when to encourage. Thank you for having patience and never doubting me.

Thank you to Dr. Whalen for meeting with me and my wife before I gave my acceptance to the program. Your demeanor, knowledge, and enthusiasm solidified our decision for me to come to UGA. Thank you for providing guidance and reassurance in my first two years and the same while serving on my committee over the last two.

Thank you Dr. Shen and Dr. Harvill for your flexibility and willingness to provide help when I needed it. Knowing I could always reach out made this process far less stressful.

Brian McKay, I greatly appreciate you taking personal time to help me recruit for this project. I may still be there if it wasn't for you. And to Ariella and Ben, thank you for keeping me sane and talking me off many ledges.

A special acknowledgment to my brother Vinson and sister Adrienne. I look up to you both far more than you realize. I know I can always count on you both to be there for me whenever I need you. Thank you.

I would also like to thank Dr. Navin Patel, Sherrer, and Pam at Athens Regional FirstCare. Your flexibility and willingness to work with us made this all possible. In addition, thank you again to Pam and to Dr. Pinholster, Ivy, Amy, Jill, Joey and the rest of the staff for making the day-to-day an easy and enjoyable experience.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

Acute respiratory tract infections are a significant source of morbidity in the United States. A common symptom experienced during these infections, particularly lower respiratory tract infections (LRTI) such as community-acquired pneumonia (CAP) and acute bronchitis, is coughing. Approximately 20 million visits to an ambulatory physician per year are due to the primary complaint of a cough.[1]

Patients significantly underestimate the time required for a cough to resolve. While an acute cough typically ranges from 15 to 28 days (mean of 18 days), patient expectations are that it will resolve in seven to nine days.[2] Therefore, many patients arrive at their primary care physician's office, emergency department, or urgent care clinic expecting treatment because they have not stopped coughing. While these LRTIs that cause a cough are often viral and usually self-limiting, antibiotics continue to be prescribed to most patients.

Antibiotic resistance and overprescribing is a significant issue. The Centers for Disease Control and Prevention (CDC) estimates $20 billion in excess direct healthcare costs and as much as $35 billion a year in lost productivity due to antibiotic resistance.[3] Despite the efforts of the CDC and other organizations to publicize the issues regarding antibiotic resistance, overprescribing for patients with RTI continues to occur, primarily in the ambulatory setting.[4-6]

An important issue is the difficulty in weighing the cost, convenience, and health implications of ordering a chest x-ray (CXR) to diagnose CAP and recognizing self-limiting infections that do not need treatment. They must also address the desire and pressure from a patient that has been coughing for an extended period and is seeking an antibiotic.[7-9]

Clinicians lack the information to accurately determine which patients are more likely to have a self-limiting acute cough that will resolve naturally within two weeks to avoid prescribing an antibiotic or corticosteroid. This includes what signs and symptoms rule out CAP so they don't unnecessarily order a CXR, as well as the clinical factors that predict a prolonged cough longer than 14 days.

Many studies have described the signs and symptoms of patients with CAP. In a large, multi-country study of 3106 adults presenting with acute cough in primary care centers, the combination of signs and symptoms showing moderate diagnostic accuracy for CAP included: absence of runny nose, presence of breathlessness, crackles, diminished breath sounds on auscultation, tachycardia, and fever.[10]

A combination of signs and symptoms, or clinical decision rule (CDR), is a useful tool clinically because it can be used to differentiate patients that are low, moderate, or high risk for CAP (and other outcomes). Stratifying risk allows the physician to make clinical decisions based on the patient's likelihood of having the outcome and rule it out without the need for additional testing.

To diagnose CAP, an infiltrate must be identified on a chest radiograph.[11] A patient at very low risk of CAP would not get a CXR, thus eliminating unnecessary exposure to radiation and reducing health system cost. However, there is currently no source that summarizes the literature as a systematic review or meta-analysis to identify the most useful combination of signs and symptoms to rule out CAP.

We conclude with four major points that led us to study the clinical presentation, management, and prognosis of prolonged cough in adults: 1.) LRTI with a chief complaint of cough is a common reason for an outpatient visit; 2.) There is a disconnect between patient expectations and the actual duration of a cough; 3.) There is a lack of information on the clinical presentation and management decisions of the subset of patients with prolonged cough in the

literature; and 4.) There are no published systematic reviews of the clinical characteristics that best rule out community-acquired pneumonia in adults with a cough.

Three Specific Aims

The overarching goal of this study is to examine the epidemiology, clinical presentation, management, and prognosis of prolonged cough in adults in the outpatient care setting. We attempt to address the clinical questions related to prolonged cough using three aims:

1. Systematically review, summarize and evaluate the current literature regarding the combination of signs and symptoms that rule out community-acquired pneumonia in adults with a cough in the outpatient setting.
2. To describe the epidemiology, clinical presentation, and prognosis for adults with a cough of seven or more days duration.
3. To measure the associations between demographics, signs, symptoms, and social factors on the odds of having a cough duration greater than 14 days among adults presenting with seven or more days of cough and determine which factors predict the management decisions of physicians.

To accomplish these aims, we will recruit a consecutive sample of at least 125 adults older than 18 years of age with a cough of at least seven days at two urgent care centers around Athens, Georgia. Adults were chosen for several reasons. Foremost, we have identified several gaps in the literature regarding cough duration in adults. We also chose adults to make it more likely that we reach our recruitment goal, avoiding the need for consent of a parent to recruit children and adolescents. We also felt that our second and third aims were more suited for adults, where symptoms will be recorded in a diary after their visit, making our data more

reliable. Finally, previous studies have suggested that the natural history of cough may be different in adults than in children.[2,12,13]

A minimum of seven days cough duration at recruitment was chosen for two reasons. Due to limited time and resources, we felt a longer cough duration would limit our ability to recruit an appropriate sample size given the restraints. Secondly, as mentioned previously, patients expect an acute cough to last less than seven days.[2] Thus, patients often seek care at that time.

We have set certain objectives to complete each aim. The instruments being used, objectives and hypotheses are presented below and are summarized in Table 1.1:

Aim 1

- Instrument: Systematic review of the literature by two investigators using a shared Google Document and DropBox folder for data abstraction and file keeping.
- Objective: Present a summary and quantitative analysis of the combinations of signs and symptoms that best rule out community-acquired pneumonia in adults with a cough.

Aim 2

- Instrument: A clinical record form to gather the signs and symptoms from the participant and clinical management from the physician (Appendix C and D). A follow up survey and diary for the participant to fill out up to 14 days after the urgent care visit (Appendix E and F).
- Objective: Present the prevalence of atypical bacterial pathogens and the mean duration of cough and symptoms. Calculate the accuracy of signs and symptoms for having a cough greater than 14 days using sensitivity, specificity, positive likelihood

ratio, negative likelihood ratio, and diagnostic odds ratio. Calculate differences of duration and severity between management decisions.

Aim 3

- Instrument: The information from the clinical record form used in Aim 2.
- Objective: Present the unadjusted and adjusted associations of the collected variables and the outcome of a cough greater than 14 days. Determine which factors predict the ordering of a CXR and prescribing of systemic corticosteroids and cough suppressants.

Our hypothesis for Aim 1 is that we will be able to identify several publications that describe the accuracy of combinations of at least two signs or symptoms that attempt to rule out pneumonia in adults with cough. The studies will include a variety of combinations, but we believe we will find at least one combination that is used across three studies to be able to perform a meta-analysis.

In Aim 2, we hypothesize that the prevalence of atypical bacterial pathogens among adults with prolonged cough will be low, from 0-3%. We believe we will be able to identify at least one sign or symptom that will have an acceptable sensitivity above 75% but low specificity (below 40%) and likelihood ratios significantly different than 1.0 (95% confidence interval does not cross 1.0) for predicting a cough greater than 14 days. There will be a significant impact on daily routine. More than 50% of adults will have missed more than 3 days of work and at least 75% will report trouble sleeping as a result of their cough.

Similar to Aim 2, we hypothesize that will be able to identify at least one sign or symptom that will increase the odds of a cough greater than 14 days in Aim 3. At least one sign, symptom, or demographic factor will be significant in a clinician's decision for ordering a CXR or giving a prescription.

Dissertation Outline

Chapter one of this dissertation has provided a basic overview of LRTI in the US, study goals, summary of our approaches to the study, and hypotheses. In chapter 2, we will expand on the background by providing a more detailed, complete review of the literature. It will cover causes of two common causes of prolonged cough (community-acquired pneumonia and *Bordetella pertussis*), including their epidemiology and diagnosis, and the gaps in the literature. Chapter 3 will describe the methods of each specific aim, including study design, data collection, and data analysis. Chapters 4 through 6 will be written manuscripts that will be submitted for publication. Each manuscript is expected to be traditionally formatted, with an introduction, methods, results, and discussion. As a result, there may be duplication of information that was presented in earlier chapters or in sections of other manuscripts. Lastly, Chapter 7 will summarize the findings of this dissertation, provide conclusions, and make suggestions for future research.

Chapter 1 Tables

Table 1.1 Summary of dissertation aims, instruments, objectives, and hypotheses

Aim	Instrument	Objectives	Hypothesis
One	Systematic review of the literature by two investigators using a shared Google Document and DropBox folder for data abstraction and file keeping.	Qualitative analysis of the combination of signs and symptoms that rule out community-acquired pneumonia in adults with a cough.	Identify several publications that describe a combination of at least two signs or symptoms. Meta-analysis of at least one CDR
Two	Clinical record form (Appendix C and D). Follow up survey and diary (Appendix E and F).	Prevalence of atypical bacterial pathogens and the mean duration of cough and symptoms. Accuracy of signs and symptoms for having a cough greater than 14 days.	Prevalences of atypical bacteria between 0-3% At least one sign or symptom will be sensitive (above 75%) but have low specificity (below 40%) with likelihood ratios significantly different than 1.0.
Three	Clinical record form used in Aim 2.	Unadjusted and adjusted associations of the collected variables and the outcome of cough longer than 14 days. Predictors of a CXR, steroid or cough suppressant being ordered.	At least one sign or symptom will increase odds of a prolonged cough and significant predictors for the clinical decision to order a CXR. At least one social and demographic factors will increase the risk of prolonged cough.

CHAPTER 2

LITERATURE REVIEW

Introduction

Coughing is a natural reflex and serves as a defense mechanism against environmental contaminants, infectious diseases, and as a response for clearing the airways of the lung and throat. A cough is characterized as either acute, subacute or chronic, depending on the etiology and duration.[14] Acute cough typically resolves in less than three weeks, subacute can last between three and eight weeks, and chronic cough is often classified as longer than eight weeks.

Other than a general medical exam or progress visit, coughing is a frequent reason for visiting an ambulatory physician in the United States (US). Approximately 2.8% of all visits were due to cough in 2012.[1] This has largely remained the same over the last 15 years: in 1991, it accounted for 3.6% of all visits.[15]

The most common reason for a cough is an acute respiratory infection. In a large four-country study of almost 10,000 patients, researchers used the International Classification of Primary Care (ICPC) to examined the differential diagnoses in encounters to a family physician when the reason for the visit was a cough.[16] The ICPC is analogous to the International Classification of Disease (ICD) used in the US and codes reasons for visits to a physician based on diseases, signs, symptoms, and causes for illness.

Across the four countries, when the reason for encounter was coded as cough (ICPC R05), the two most common diagnoses other than cough of non-specific origin were upper respiratory traction infection (URTI; common cold) and acute bronchitis. Incidence density rates were 47.2 to 292.3 per 1,000 patient-years for URTI and 17.1 to 42.0 per 1,000 patient-years for

acute bronchitis. Other notable respiratory infections that were diagnosed included whooping cough (0.1 to 1.8 per 1,000 person-years), pneumonia (1.8 to 9.4 per 1,000 person-years), and influenza (1.3 to 24.8 per 1,000 person-years).

An older study (1985 to 1995) explored the final diagnosis of patients that presented with a cough to a family physician with similar results.[17] In 11,092 encounters, about 33% of patients with a cough were diagnosed with URTI. Acute bronchitis was the second most common diagnosis at 25.4%. Pneumonia and influenza were diagnosed in about 2%, and whooping cough was diagnosed in 0.4% of encounters with cough.

An acute cough caused by a viral respiratory tract infection ("acute bronchitis") typically lasts a mean of 18 days[2], pushing the limits of the classical definition of acute. The median duration that patients expect an acute episode of cough to last is five to seven days.[2] We therefore define a prolonged or persistent cough as one lasting more than seven days (longer than patient expectations).

In this literature review, the epidemiology and diagnosis for two causes of prolonged cough and lower respiratory tract infections will be described: community-acquired pneumonia and *Bordetella pertussis*. In addition, the clinical management of patients with a cough in the outpatient setting will be given. Lastly, gaps in the literature and steps to address these will be summarized.

Epidemiology of Community-Acquired Pneumonia

Pneumonia has been a known illness for centuries, first described by Hippocrates around 400 BC.[18] Pneumonia is an encompassing term used to describe an infection of the lungs affecting alveoli and respiratory bronchioles and can be acquired via the community (CAP), hospital (HAP), or ventilator (VAP).[19] Etiology of pneumonia varies significantly, with many different viral, bacterial, or fungal pathogens responsible for the disease.[20] Common viruses causing pneumonia are influenza A and B, and respiratory syncytial virus, whereas

"typical" bacterial pathogens include *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Staphylococcus aureus.* Less common bacterial causes, often referred to as "atypical", include *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, and *Legionella pneumophila.*

The proportion of episodes of CAP caused by *M pneumoniae* can vary widely, depending on population and year. It has been shown to have a cyclical pattern using modeling methods,[21,22] and across prospective studies from 2002 to 2015 in a meta-analysis of its prevalence.[23] Prevalence varies from as low as less than 1% to as high as 24% in outpatient adults with CAP, with an overall mean prevalence of 7%. While its prevalence is well published (30 studies since 2000), the clinical presentation and natural history is poorly understood.

Traditionally believed to be more common in children, *C pneumoniae* has been documented to cause up to 20% of episodes of CAP in adults.[24,25] Overall prevalence is about 4% in adults and 1% in children with CAP in a recent meta-analysis.[23] Regarding clinical significance, another meta-analysis found an increased risk of lung cancer in patients with previous *C pneumoniae* infections.[26] In addition, there may also be an association between *C pneumoniae* and subsequent diagnosis with asthma.[27,28] Given these implications of possible more serious conditions, the clinical diagnosis of *C pneumoniae* in patients with prolonged cough is important but not yet described.

Infections with *L pneumophila* are rare. Case-based surveillance in the US reported 1.17 cases per 100,000 persons in 2012, and a recent meta-analysis of prospective studies found an overall mean prevalence of approximately 3% in adults with CAP.[23] The infection caused by *L pneumophila* is commonly known as Legionellosis, or "Legionnaire's Disease"; it is found naturally in environmental water sources such as hot tubs and cooling towers.[29] Recently, the CDC investigated a possible outbreak from two cooling towers at Disneyland that resulted in 12 cases of Legionnaire's disease in which 10 were hospitalized and one died.[30] Fifteen outbreaks

associated with environmental or undetermined water exposures occurred from 2011 to 2012 that resulted in 254 reported cases and 10 deaths.[31]

Pneumonia can be severe and life-threatening. Between 1900 and 1937, pneumonia (combined with influenza) was among the top three causes of death in the US, consistently accounting for over 100 deaths per 100,000 persons during that timeframe.[32] Mortality has decreased significantly; there were 51,811 deaths due to pneumonia in 2015, about 16 deaths per 100,000.[33] Older age groups are disproportionately affected compared to younger age groups. In 2015, 85% of all deaths caused by pneumonia were in adults older than 65 years.

Community-acquired pneumonia requiring hospitalization has an estimated annual incidence rate of 25 cases per 10,000 adults.[34] In 2010, 972,000 adults had a primary diagnosis of pneumonia at hospital discharge; the overwhelming majority of those (621,000) occurring in patients older than 65 years.[35] It is the second leading reason for a hospital stay, behind only live births.[36]

Diagnosis of community-acquired pneumonia

A chest x-ray (CXR) or computed tomography (CT scan) are the “gold standard” for diagnosing CAP. However, for such a common and non-specific symptom such as coughing, screening everyone with a CXR for CAP would expose patients to unnecessary harms with limited benefits since CAP only occurs in a low proportion of patients with a cough.[16,17] Therefore, physicians rely on signs and symptoms, and sometimes laboratory or point of care (POC) tests to make the decision for ordering a CXR and to diagnose CAP.

The combination of demographics, signs, symptoms, and POC tests, referred to as clinical decision rules (CDRs), stratify patients into risk categories.[37] A common CDR is the Centor Criteria. The combination of tonsillar exudates, swollen tender anterior cervical nodes, lack of a cough, and history of fever is used to categorize the risk of strep throat.[38] A patient in a

low risk group for CAP would likely not receive a CXR or antibiotic treatment, possibly reducing unnecessary radiation exposure and overall health system costs.

The clinical signs and symptoms to diagnose CAP has been studied extensively. A quick search of the clinical presentation of CAP in MEDLINE returns over 1,000 articles. The list of individual signs and symptoms is substantial. Some are more common though, including: temperature, heart rate, respiratory rate, crackles, wheezing, dullness on percussion, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and oxygen saturation. However, there are only a few studies that use a CDR to diagnose or rule out CAP.

A large, multi-center, prospective study developed a CDR using temperature (>37.8 C), heart rate (>100/min), rales, absence of asthma, and decreased breath sounds to diagnose CAP.[39] It had large sample size of over 1,400 and was developed using a derivation set and then externally validated in two other locations. However, the CDR is over 20 years old and has not been validated by any other independent studies.

An even older CDR, produced in 1984, classified patients as low, moderate, and high risk for CAP using a combination of temperature (>37.8 C), respiratory rate (>25/min), myalgia, night sweats, sputum, sore throat, and rhinorrhea.[40] While the sample size was again sufficient (1,712), it used very different factors than the CDR produced in the study above and is not validated.

A more recent CDR recruited patients across 12 different countries in Europe.[10] The POC test c-reactive protein (CRP) was included in this rule, combined with decreased breath sounds, crackles, breathlessness, vesicular breath sounds, absence of runny nose, temperature (>37.8 C) and heart rate (>100/min). The overall model of the CDR had an area under the receiver operating characteristic curve (AUC) of 0.77 (95% CI 0.73-0.81). The low-risk group with a score of zero, had 0.7% probability of CAP given a prevalence of 5.2%.

Another CDR employing CRP is a decision tree that ruled out pneumonia in all patients with a CRP less than 10 µg/mL.[41] When CRP was between 11 and 50 µg/mL, it was able to rule

out pneumonia with the addition of no dyspnea and no fever. This is a very simple tree that uses a maximum of three decision points to rule out CAP and could easily be implemented in clinical practice.

Epidemiology of *Bordetella pertussis*

Bordetella pertussis causes pertussis disease, a prolonged acute lower respiratory infection that is also called "whooping cough",[42] due to the sound made as patients inhale through narrowed airways. Pertussis is an aerobic, fastidious, gram-negative rod bacterium that was first isolated in 1906 by French scientists.[43-45] A vaccine was developed shortly after that in 1914 for use in the United States (US).[44]

Pertussis is a notifiable disease in the US. Surveillance of pertussis was reported by the US Public Health Service (PHS) prior to the 1950s.[46] Today, the Centers for Disease Control and Prevention (CDC) main systems for collecting information on notifiable diseases are the National Electronic Disease Surveillance System (NEDSS) and the Electronic Laboratory Reporting (ELR).[47] Although reporting has greatly improved because of the reliability and accuracy of electronic systems, it is limited due to still being based on passive surveillance.

Before the widespread use of the vaccine "Diphtheria, Tetanus, and Pertussis" (DTP), pertussis was a fairly common illness. The annual number of cases of pertussis reached its peak in 1934 at 265,269 (Figure 2.1).[48] The average annual incidence rate from 1930-1939 was about 150 cases per 100,000.[49] Because of the limited sensitivity of laboratory tests, use of summary reports instead of individual case reports, and lack of a consensus case definition at the time, it is estimated that the actual annual rate was in fact over 800 cases per 100,000.[50]

Annual incidence rates of pertussis dropped significantly after the introduction of the DTP in 1948. By the 1970s, they were about one case per 100,000 per year.[48,51] In the 1980s, there were a total of 27,826 pertussis cases, a mean of 1.2 cases per 100,000 per year. Through this period (1980-1989), annual incidence rates began to increase gradually, from 0.8

cases per 100,000 in 1981 to 1.7 cases per 100,000 in 1989. Rates started to increase dramatically in the late 1990s.

In the three years from 1997 to 2000, there were 29,134 cases (2.7 cases/100,000/year) of pertussis.[52] This three-year period had more cases than the entire 10-year period in the 1980s. This trend has continued into the 2000s. There were over 48,000 cases reported in the US in 2012, the highest number of cases since 1955.[53] This is an annual incidence rate of 15.4 cases per 100,000, a nearly 6-fold increase since 2000. Cases in the US declined slightly in 2013 to 28,639, but then increased again in 2014 to 32,971.[54] In Georgia, 317 cases (3.2 per 100,000) of pertussis were reported based on laboratory-based surveillance in 2013 and 408 (4.1 per 100,000) in 2014.[54,55]

The distribution of cases among different age groups has changed significantly. In the pre-vaccine era (prior to the 1940s), about 94% of cases were in children less than 10 years old.[56] During this period, only 7.5% were in infants less than a year old, meaning nearly 87% were in children 1 to 10 years of age. Adults older than 15 years accounted for less than one percent of reported cases. We begin to see the percentages shift from children to infants and adults in the late 1970s and early 1980s, where infant and adult infections rose to 53.5% and 6.5%, respectively.[57]

From 1997 to 2000, approximately 30% of pertussis infections were in infants less than a year old, 50% were in persons 1 to 20 years of age, while adults older than 20 years accounted for 20%.[52] In 2014, the most recent final report of notifiable diseases, cases among different age groups shifted again (Table 2.1).[54] Cases in infants less than a year old have dropped significantly, and they only account for 12.8% (4,205) of all cases. The majority of cases now occur in ages 1 to 20 years old, where there were 22,817 cases (69%). In the pre-vaccine era, 87% of cases were in ages 1 to 10 years old[56], which dropped to 35% in 2014[54]. There were 5,839 cases (17.7%) in 2014 in adults 20 years and older.

Depending on cough duration, age, vaccination, and setting, the prevalence of pertussis in patients with prolonged cough varies significantly. In the literature, a multi-country study of 3,074 adults with cough less than 28 days duration, the overall prevalence of pertussis was 3%, while in the subset of adults that had a cough longer than 14 days the prevalence was 5%.[58]

A meta-analysis found that 12% of all patients with prolonged cough in the outpatient setting have pertussis.[23] A study of 409 adolescents and adults in Korea (greater than 11 years old; mean age 44.3 years) that had a cough less than 30 days reported a prevalence of 6.9%.[59] Another study of 66 children (age 5-16 years) and 156 adults (age 17-49 years) in New Zealand with a cough longer than 14 days reported prevalences of pertussis of 17% and 7%, respectively.[60] Another study set in Germany had a prevalence of 10% in 971 adults and children with a cough longer than seven days.[61] Three studies not included in the meta-analysis because of design or time frame found prevalence of 5.4%, 13%, and 32% in different populations and different inclusion criteria.[62-64]

While there is no strong evidence of a seasonal temporal change in the incidence of pertussis, there may be slight increases in the late summer, typically July and August.[65-68] Reasons for this are not currently understood. There was no correlation between the increase in cases during these months and the opening of schools.[67] It could be considered that with its relatively mild symptoms, pertussis is missed by physicians focused on testing for more prominent diseases, such as influenza, during the winter months. [66] Pertussis has shown cyclical trends, in both the pre- and post-vaccine eras, peaking every two to five years.[50,67]

Some studies have suggested waning immunity in recipients of both DTaP (Diphtheria, Tetanus, and acellular Pertussis), and the Tdap booster (Tetanus, Diphtheria, and acellular Pertussis) given to adolescents and adults.[62,69-71] In children 4 to 12 years old in California from 2006 to 2011, the number of pertussis infections increased each successive year after receiving DTaP.[62] There were seven (0.8%) cases within the first year, increasing to 65 (18.5%) cases when it had been more than six years since vaccination. When controlling for calendar time,

age, sex, race, ethnicity, and locality, the odds ratio of pertussis infection was 1.50 for each additional year from immunization in polymerase chain reaction (PCR) positive children when compared to matched controls. Two additional studies came to the same conclusions[70,71]; as time since the fifth dose increased, the odds of infection increased.

Vaccine effectiveness of Tdap was evaluated in Wisconsin among young adolescents in 2012 who received the vaccine between 2008 and 2012.[69] Among those who received Tdap in 2012, effectiveness was 75.3%, whereas it was only 11.9% if they received the vaccine in 2008 or 2009. Again, increasing time since receiving the vaccine was associated with increased risk of infection.

Mortality for pertussis has declined significantly in the US. In 1934, the year that the most cases were ever reported, there were 7,518 deaths from pertussis.[72] There were 13 reported deaths in 2014 as a result of pertussis infection. Eight occurred in infants less than three months old and two in adults older than 55. No deaths were reported in persons between four and 55 years old.

Because adults have lower morbidity and mortality than younger patients, prevention is typically focused on infants. Although warranted, adults are the source for 56-69% of pertussis cases in infants.[73,74] Low rates of Tdap and waning immunity make adults important vectors for infection among children and susceptible adults. It is important they are properly diagnosed before the disease can be transmitted to others.

Clinical Diagnosis of pertussis

A clinical case definition for pertussis was established in 1991 by the World Health Organization (WHO).[75] The current clinical case definition is a person with a cough lasting two weeks or longer and at least one of the following: paroxysmal cough, inspiratory whooping or post-tussive vomiting.[76] The CDC uses the same definition in the US but adds apnea for infants less than a year old.[77]

Based on a meta-analysis, six individual symptoms are significantly associated with pertussis: whooping cough, post-tussive vomiting, paroxysmal cough, sputum, nighttime cough, and absence of headache.[78] The most sensitive single symptom was paroxysmal cough (80% sensitivity) but it lacked specificity (35% specific). The CDC clinical definition was very sensitive (90%) but again had an insufficient specificity (16%).

The best predictor of a pertussis infection is not a single symptom but the physician's overall clinical impression, which was 85% specific, 47% sensitive, and had a positive and negative likelihood ratio of 3.3 and 0.63, respectively. The majority of the studies included in the meta-analysis were based on symptoms in children. Two studies of low bias were in adults[58,79] and between the two, only paroxysmal cough was significantly associated with pertussis infection.[79]

As discussed above, there are several CDRs to diagnose CAP. However, there is only one such CDR in the literature for pertussis.[80] Medical records of infants at a pediatric emergency department at a large US hospital and local incidence data from pertussis culture results at the state laboratory were used to develop the CDR. Three models were used to develop a CDR: only clinical data, incidence data only, and a combination of the two. The combined model was the best, using two symptoms (cyanosis and cough longer than one week) and prevalence, with a receiver operating characteristic curve of 0.82. The data for development of this CDR was collected retrospectively and it has not been validated, limiting is clinical value. The exact algorithm was not described in the publication either.

Additional burdens that accompany a diagnosis of pertussis include multiple visits to the physician, hospitalizations, antibiotics, and missed school or work. Depending on the presence or absence of complications such as pneumonia, or hospitalization, and the age of patient, the direct and indirect cost of pertussis can vary widely. It is estimated that the mean direct cost of medical care in adults is $326.[81] Non-medical cost was significant, with 61% of adults missing a mean of 9.8 days from work, resulting in an estimated mean cost of $447 per case. The total

estimated mean cost per adult case is $773, but these estimates are from the most recent study available in the US which was performed from 1998 to 2000.[81] It is likely that the direct and indirect cost of a case of pertussis has likely risen substantially since then, given overall rise in healthcare costs.

Patient expectations and clinical management of a cough

As described previously, patient expectations for the duration of an acute cough is approximately seven to nine days, which is significantly less than the duration it actually takes to resolve.[2] A recent large, prospective study performed in 13 European countries found a cough lasts a mean duration of 17.3 days.[82] Two additional prospective studies conducted in within the last 15 years concluded similar mean durations, one 15.3 days[83] and the other 21.3 days.[84]

When the cough has not resolved within a week, patients begin to seek care and come with the anticipation of being treated. Nearly half (45%) of outpatient adults with an acute cough expect an antibiotic to be prescribed and 41% hoped for one.[85] Additionally, 61% of patients believe that antibiotics are effective for a cough of at least five days.[86] These expectations for duration and treatment influence physician behaviors as well. When patients express their desire for an antibiotic they are more likely to be given one.[7,8,85] Even when a physician believes an antibiotic is not necessary, they feel pressured to prescribe one anyway in order to satisfy the patient.[87,88]

For uncomplicated cases of acute bronchitis, clinical guidelines do not recommend the use of an antibiotic.[89,90] Despite these guidelines and the push from government bodies and other organizations to reduce antibiotic use, outpatient clinicians still prescribe them for up to 75% of patients presenting with acute respiratory infections.[4-6]

Two other commonly prescribed treatments for acute cough are corticosteroids and cough suppressants. A recent multi-center, placebo-controlled, randomized clinical trial showed no reduction in symptom duration or severity for oral corticosteroids in uncomplicated acute

respiratory infections,[91,92] and a systematic review failed to find conclusive evidence to recommend the use of inhaled corticosteroids.[93] In fact, prescribing corticosteroids to these patients may be harmful. A population-based cohort study concluded patients that took oral corticosteroids had an increased risk of serious adverse events such as sepsis and venous thromboembolism.[94] There may be no benefit to prescribing a cough suppressant as well.[95,96]

It is unclear how many patients are receiving these treatments; prospective observational studies describing the prevalence of these prescriptions for acute cough could not be found. Anecdotally, it is believed they are being increasingly prescribed for acute LRTI in the absence of asthma, chronic obstructive pulmonary disease, or CAP.

Gaps in the literature

Healthcare utilization in the US has changed over the last 10 to 15 years. Patients are increasingly seeking care from emergency departments and urgent care centers over their primary care physician.[97] This has been attributed to the convenience they provide (accepting walk-ins), decreasing numbers of primary care physicians, and the perceived urgency of the need for care by the patient.

This systematic review has highlighted several gaps in the literature. Several studies have documented the duration of uncomplicated acute cough but none recently in the US. Although the clinical signs and symptoms to diagnose CAP has been studied extensively, a systematic review or meta-analysis on which combinations best rule out CAP has not been presented previously. Additionally, studies on the clinical management decisions, especially the prescribing of systemic corticosteroids and cough suppressants, in patients with prolonged cough is limited. This is compounded by the changing landscape of healthcare in the US, where urgent care centers are becoming a more popular option.

We hope to improve these areas with our systematic review and study of adults who present in the outpatient setting with a prolonged cough of more than seven days. We will do

this by: 1.) Systematically reviewing the literature and present CDRs that best rule out CAP; 2.) Evaluating the accuracy of signs and symptoms in adults with a cough longer than seven days, comparing adults that cough for less than 14 days to those cough for longer; 3.) Determining prognosis of prolonged cough, by presenting the duration and severity of signs and symptoms, missed days of school or work and comparing patients that received a prescription; and 4.) Measure the associations of signs, symptoms and social factors on the odds of having prolonged cough and treatment decisions.

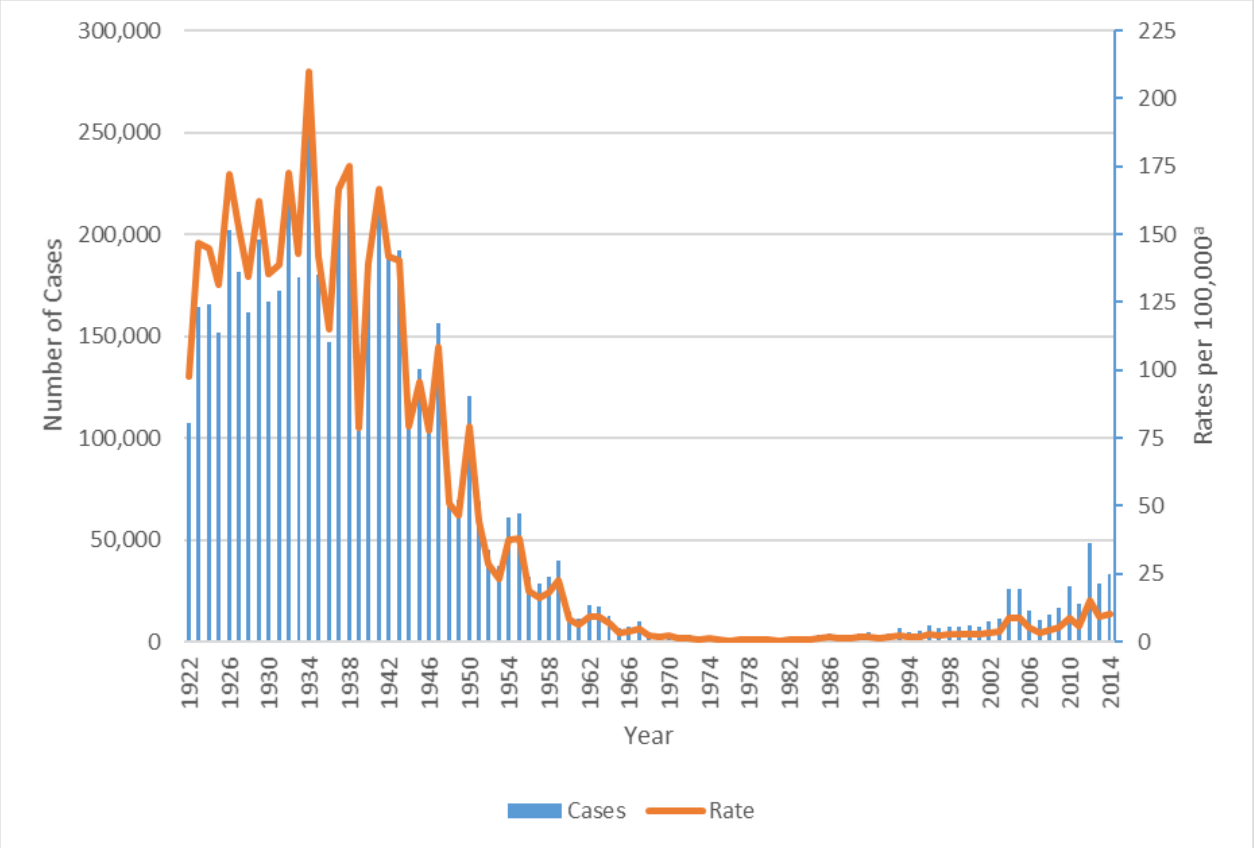
Chapter 2 Tables and Figures

Table 2.1 Epidemiology of *Bordetella pertussis* by age group in the United States in 2014[54]

Age*	Number of Cases	Percentage of all cases	Incidence Rate/100,000/year
< 6 months	3,330	10.1	169.0
6-11 months	875	2.7	44.4
1-6 years	6,082	18.5	25.1
7-10 years	5,576	16.9	34.0
11-19 years	11,159	33.8	29.6
> 20 years	5,839	17.7	2.2

* 110 cases were unknown age

Figure 2.1 National Notifiable Diseases Surveillance System reported cases of pertussis and incidence rates (cases/100,000/year) from 1922 to 2014[48,51]



CHAPTER 3

METHODS

Aim 1 Methods Overview

This aim will perform a systematic review of the literature to identify a comprehensive list of publications that use a combination of signs and symptoms to diagnose or rule out community-acquired pneumonia (CAP) in adults with a cough. To perform this review, two investigators will create a set of inclusion and exclusion criteria and develop a search strategy. The search strategy will be key words and phrases that are entered into MEDLINE to identify an initial set of publications to review. After the initial set of articles are identified, the two investigators will independently review the titles and abstracts of the articles using the inclusion and exclusion criteria to exclude irrelevant articles and to keep potential articles that need to be reviewed in full. The full text of the potential articles is reviewed independently and in tandem to identify a final list of included articles. The inclusion and exclusion criteria, search strategy to be used, and details on data abstraction, and analysis is provided below.

Inclusion and Exclusion Criteria

We will include articles that use a combination of signs, symptoms and/or point of care (POC) tests (e.g., c-reactive protein, lung ultrasound, sedimentation rate) to diagnose CAP. The study must have used chest radiography or CT as a reference standard for diagnosing CAP. Only studies in adults or adolescents who were seen in an outpatient setting (emergency department, urgent care, primary care, or hospital outpatient clinic) will be included. To limit bias, only cross-sectional or cohort studies with prospective data collection will be accepted.

Because we are interested in otherwise healthy adults and want to apply our analysis to a generalized population, studies where the majority of patients had hospital-acquired pneumonia or enrolled immunocompromised patients will be excluded. We will also exclude studies of specialized populations such as military recruits or nursing homes. Studies that are not prospective in nature (case-control, case reports, case series, retrospective studies and outbreak investigations) will be excluded. Lastly, all patients must have received the reference standard to identify and diagnose CAP.

Search Strategy

We will use the following search strategy to identify the initial list of publications to review in MEDLINE:

> ("clinical criteria"[TIAB] OR "diagnostic value"[TIAB] OR "predictive value"[TIAB] OR "rule out"[TIAB] OR decision[TIAB] OR prediction[TIAB]) AND ("pneumonia"[MeSH Terms] OR pneumonia[TIAB] OR pneumoniae[TIAB]) AND (community[TIAB] OR emergency[TIAB] OR urgent[TIAB] OR primary[TIAB] OR acute[TIAB] OR "general practice"[TIAB]) NOT ("hospital-acquired"[TIAB] OR "hospital-associated"[TIAB] OR "healthcare-associated"[TIAB] OR nosocomial[TIAB] OR stroke[TIAB] OR klebsiella[TIAB] OR tuberculosis[TIAB] OR surgery[TIAB] OR ventilator[TIAB] OR "intensive care unit"[TIAB] OR "ICU"[TIAB] OR retrospectively[TIAB] OR retrospective[TIAB] OR "case-control"[TIAB] OR "case report"[TIAB] OR "case series"[TIAB] OR gastrointestinal[TIAB] OR immunocompromised[TIAB] OR HIV[TIAB] OR cancer[TIAB]) AND hasabstract[text]

In addition to this search of MEDLINE, we will supplement it by searching previous systematic reviews. We will review the articles that were included in those reviews and their

reference lists. A Google search of “diagnostic accuracy of community-acquired pneumonia” will also be performed and the first five pages searched for relevant publications. Lastly, after a list of articles is finalized by the two investigators, each will review the references of those included articles.

Data Abstraction and Analysis

Review of the literature and abstraction of data occurs in two stages. During the first stage, two investigators identify an initial set of published articles using the above search strategy. They will independently review the titles and abstracts of each publication and document. In a Google Excel Document shared between investigators, the publications that needs its full text reviewed are saved in separate tabs using the article ID, author name, and year. The two lists of articles that each investigator felt needed to be fully reviewed are combined into a single list. This first stage keeps any article either reviewer feels should be reviewed and is designed to gather as many potentially relevant articles as possible so that the review of the literature is exhaustive.

In the second stage, only articles and data that each investigator both agree on is kept. If at any point during this second stage that there is a discrepancy between the investigators, a consensus discussion will occur and if an agreement is not agreed upon, a third investigator will review the discrepancy. The following steps of the systematic review are part of this second stage.

First, the full text of each article from the abstract list is evaluated for its inclusion. Inclusion criteria (combination of signs/symptoms/POC, chest radiograph or CT as reference standard, data for accuracy such as sensitivity/specificity/likelihood ratios, adolescents/adults, outpatient setting, and prospective data) is logged as a yes or no. The review for inclusion is performed independently and recorded on separate tabs. They are then combined into a single tab to compare the “yes’s” and “no’s”. Articles that were not common between the two

investigators are reviewed as described above. We will use a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram[98] to document the number of articles identified and excluded at each step and how many were included at the final review. The final list of included articles is then reviewed for data abstraction.

Study characteristics that will be abstracted are: author, year, language, country, design, setting, years recruited, sample size, population, and mean or median age. We will then abstract data on the accuracy of the combinations. When available, we will record true positive, false positive, true negative and false negative. If these values are not given, they will be calculated using the sensitivity, specificity, positive predictive value, or negative predictive values from the articles. Lastly, the abstracted data will be used to calculate likelihood ratios and posttest probabilities.

At this point, we will review how many of the signs, symptoms, and POC tests overlap to determine if a meta-analysis is possible. If more than three or more do, we will use summary receiver operating characteristic (ROC) curves using the Reitsma method to compare estimates of accuracy.[99] The analysis and plots will be generated using R (3.4.2).

Quality assessment of the included articles for the meta-analysis will be performed using QUADAS-2 framework.[100] This tool evaluates potential bias in four categories: patient selection, index test, reference standard, and flow and timing. Using the same protocol as during data abstraction, both investigators will review the articles for bias and disagreements resolved by consensus or a third party.

For each combination used, we will summarize the relevant summary statistics provided from the article and make comparisons, if possible. We will then discuss what potential impacts they may have on the care of patients with CAP.

Limitations

We are primarily limited by the quality of the published article and how the research was originally conducted. To limit this impact, we only included prospective studies where all participants received the same reference standard. This should improve the quality of the studies we included and limit potential bias. We are also limited to using MEDLINE, which is the only source currently available to us. As a result, our search strategy was broad to capture as many articles as possible. We also reviewed other systematic reviews, the references of included articles, and ran a Google search.

Aim 2 Methods Overview

We will attempt to recruit a prospective consecutive series of patients visiting an urgent care clinic with the chief complaint of a prolonged cough, defined as one lasting at least seven days and no more than 56 days. We will recruit consecutive patients during the approximately 40 hours per week that an investigator is on site. Some patients may be missed due the limitations of recruitment, including not being present at the clinic during all operating hours, patient refusal, and those that do not participate due to exclusion criteria.

Consenting patients who are 18 years or older will be asked several questions about their signs and symptoms and will then have a nasal swab and a throat swab collected. Only adults were chosen for recruitment based on reasons outlined in the introduction and literature review. The swab will be tested using polymerase chain reaction (PCR) for detection of *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Bordetella pertussis*. *Legionella pneumophila* was not considered due to its low prevalence and it was felt resources would be better utilized to detect the more common pathogens.

A symptom diary and follow-up survey will be given to each participant enrolled. We will ask participants about the duration and severity of symptoms and the impact of symptoms on daily living such as work and/or school. We will also collect information on social factors such as

prescription utilization and contact with children. Participants will document their symptoms in two ways. They will be sent home with a symptom diary and will also be sent a survey electronically via a hyperlink in a text message or email at seven days after their visit. If participants indicate they are still experiencing a cough on the electronic survey at seven days, they will be sent an additional survey seven days later. A minimum of one electronic survey will be sent to every participant recruited, while others may receive up two depending on the duration of their cough.

We decided to send a combination of a diary and survey for several reasons. Without an extensive research team to continuously contact patients and a relatively low compensation, there was concern of a low return rate for take home diaries. The electronic surveys are quicker, easier for the patient, and match the time commitment to the compensation but lack the comprehensive data that a diary provides. We will ask the patient to use the diary as a memory tool for filling out the electronic survey but also hope for a high return of the diaries. The electronic survey allows for a sufficient backup if diaries are not returned in the quantities we need. Details on delivery, non-responses, and loss to follow up are outlined below.

Study Population

Primary recruitment will occur at Regional FirstCare Athens. This urgent care center is part of Piedmont Athens Regional Health System and serves mainly urban/suburban Clarke County, but also serves more rural Madison, Jackson and Oglethorpe counties. All four counties have a combined population of adults over 18 years old of approximately 183,000; Clarke County had an adult population of approximately 102,000 in 2015.[101] About 61% of adults in Clarke County are White non-Hispanic, 25% African-American non-Hispanic, and 8.4% Hispanic. Over 85% of the population has at least a high school education and the median household annual income is $32,000 based on data from the 2010 census[102], well below the national average for median household annual income of $49,445.[103] Regional FirstCare Athens

sees an estimated 100 patients per day during the winter season. Institutional Review Board (IRB) approval was received on January 31, 2017. Recruitment will occur from February 2017 to December 2017. Regional FirstCare Barrow will be used as a secondary recruitment site whenever another investigator is available. A letter of support has been received from Dr. Navin Patel, the Medical Director of the Regional FirstCare sites (Appendix A).

Inclusion and Exclusion Criteria

Patients 18 years and older with an initial visit for a cough lasting at least seven and no more than 56 days (8 weeks) days will be included. Seven days was chosen to increase recruitment, versus 14 days or more days. To exclude patients with chronic cough, we selected eight weeks as the upper limit.[14] Patients with chronic respiratory illnesses such as chronic obstructive pulmonary disease (COPD), moderate or severe asthma, or immunodeficiency disorders will be excluded. They will also be excluded if they do not speak English or are judged unable to comprehend the informed consent forms.

Sample Size

A systematic review of the duration of an acute cough concluded that it ranges from 15 to 28 days, with a weighted mean duration of about 18 days.[2] We expect that less than 20% of our recruited patients to have a cough for less than 15 days. To calculate the appropriate sample size for this aim, the following formula was used[104]:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Formula 1.1

For this formula, *n* is sample size, *Z* the confidence level, *P* the expected prevalence, and *d* the precision. All calculations were made using a 95% confidence level. Based on the

limited time we have for recruitment (several months versus years) and available funding, sample sizes larger than 200 were deemed impractical.

Using these parameters, sample sizes for varying levels of prevalence and confidence intervals (precision) are summarized in Table 3.1. A larger confidence interval allows us to recruit fewer patients but reduces the value of our findings because our prevalence estimate would be less precise. A smaller confidence interval would give us more precise prevalence estimates but less flexibility in recruitment. To compromise, a margin of error of +/- 6.4 was selected, resulting in a recruitment goal of 120. For example, if the prevalence of those without prolonged cough is 15%, we will be 95% confident that the true prevalence is between 8.6% and 21.4%. We increased this sample size to a final 125 to provide flexibility in the event there are issues with a few participants and they must be dropped from the analysis.

We will send a diary and survey to each of the 125 participants enrolled in our study. The number of respondents needed to detect differences between answers based on a 95% confidence level depending on precision is summarized in Table 3.2. To achieve a margin of error of 5.8 at a 95% confidence level, we would need 88 responses. A non-response rate of 30% would return 88 surveys. These calculations were performed using the formula[105]:

$$\mathrm{s} = X^2 * \mathrm{NP}(1-\mathrm{P}) \div d^2(\mathrm{N}-1) + X^2\mathrm{P}(1-\mathrm{P})$$

Formula 1.2

X^2 = Chi-square (3.841 for 95% confidence level); N=Population; P = population proportion (50% used to maximize sample size); d=precision.

At a risk of having a high non-response rate, we will accept the larger margin of error of 6.4%, which also matches our precision used for the recruitment goal. As a result, a minimum of 82 (65%) returned diaries or surveys are needed.

Data Collection

The patient will arrive at Regional FirstCare and register with the receptionist. During registration, the patient records their chief complaint as coughing and is brought to the back to an exam room. After a medical assistant or nurse has recorded vitals and taken a medical history, a physician or nurse practitioner will perform their normal patient assessment. They will make a diagnosis independent of our study and will order any commercial laboratory tests or chest x-ray (CXR) that he or she deems necessary at their own discretion and make a diagnosis. After completing their time with the patient, he or she will notify the investigator of a potential candidate.

The investigator will enter the exam room and identify himself as being associated with the University of Georgia, and is seeking to recruit patients for a research study on prolonged coughing. The investigator will confirm the patient is eligible for the study by asking about the exclusion criteria. If they respond affirmatively and are interested in participating, they will then be given an informed consent form (Appendix B) describing the purpose, goal, risks, and benefits of the study. After signing the consent form (one copy for the patient and one for the investigator) and verbally confirming that the patient understands the process and details of the study, the investigator will begin data collection.

The investigator will first administer a short verbal survey (Appendix C). The patient will be assigned a unique identifier (ID) on the survey that will be used throughout the study and give their phone number and email address for follow up. The first section of the survey will consist of demographics (age, sex, race, and ethnicity) and signs and symptoms, including wheezing, paroxysmal cough, post-tussive vomiting, cyanosis, and dyspnea. Additional symptoms documented in the survey are duration of cough, fever, headache, sneezing, runny nose, redness or watery eyes, chills or sweats, and sputum production.

The second section will ask the patient about social factors such as smoking, education, and contact with children and infants. At the end of this section, the patient will be asked if they

are willing to enter their personal information (name and date of birth) into the Georgia Immunization Registry (GRITS) to confirm they've received either the DTP (diphtheria-tetanus-pertussis), Tdap (tetanus-diphtheria-acellular pertussis), or influenza vaccines. If yes, the investigator will enter their information on a secure PC and the immunizations and dates will be recorded. After the immunization records are collected, the investigator will sign out of GRITS.

After the survey, the investigator will collect a nasal and throat swab. A combined nose and throat swab (CNTS) instead of a nasopharyngeal (NP) swab is being used for two reasons. A CNTS is much less invasive for the patient and therefore more tolerable than NP. We believe we will have significantly more patients willing to participate with this collection procedure, resulting in more generalizable information. In addition to this, a CNTS procedure has been shown to be just as sensitive as NP in detecting respiratory viruses and bacterial pathogens.[106-111] When using PCR as the detection method, throat swabs alone are an acceptable replacement for NP in the detection of pertussis.[112] Using CNTS will insure there is adequate enough pathogen for detection via PCR while also providing a better experience for the patient.

Once collection of the swabs is complete, the participant will receive $5 cash. The investigator will then notify the staff to discharge the patient and hand the clinician a short survey regarding diagnosis, tests ordered, chest findings and treatment (Appendix D).

Swabs collected daily will remain at room temperature in a specially marked (biohazard stickers and research samples) cooler. At the end of the day, the samples are driven to the laboratory of Dr. Eric Harvill at the University of Georgia College of Veterinary Medicine where they will be refrigerated overnight. Laboratory staff will aliquot the sample medium and store the aliquot in a -80-degree Celsius freezer. The samples will remain in the freezer until they are ready to be tested as a batch.

Israel Rivera, a PhD candidate working under the direction of Dr. Eric Harvill, Professor at the University of Georgia, will perform PCR on the collected samples. Sample DNA will be extracted using the QIAamp DNeasy Blood & Tissue Kit (Quiagen, Hilden, Germany) following

manufacture's protocol. PCR primers were manually designed from GeneBank sequences using the IDT web base tool "OlioAnalyzer 3.1". Isolated DNA will be amplified using AmpliTaq Gold 360 DNA Polymerase kit following manufacturer's (ThermoFishers) protocol. The PCR product will be analyzed in a 1-2% gel for amplification success. Results of the PCR tests will be documented on an Excel Spreadsheet, matched to the unique ID given to the patient.

The participant will be given a symptom diary (Appendix F) before leaving the clinic and provide a mobile phone number and an email address to send them a hyperlink directing them to an online survey (Appendix E). The online survey will be administered using Qualtrics, provided through the University of Georgia (UGA). Qualtrics is a web application that provides an automated, secure method for sending surveys. It is designed to be user-friendly for both the researcher and participant. Respondents do not need a Qualtrics account and will be able to quickly access the survey whether on mobile phone or a personal computer.

The participant's phone number, email address, and matching unique ID will be uploaded to Qualtrics. The initial follow-up survey will be scheduled to automatically deliver a unique link specific to that participant seven days from the day of their visit to the clinic. A reminder will be sent three times within 24 hours if there is no response recorded on the first attempt. Text messages will be sent by an investigator due to not having this capability in Qualtrics. If the participant does not complete the survey within 24 hours, an investigator will call the following day and ask the questions over the phone. While on the phone, we will also ask that the participant please mail the diary back. If unable to contact the participant via phone, they will be considered lost to follow-up.

On the survey, there will be a question about duration of cough. If the participant reports still having a cough on the day they take the survey, an additional survey will be queued to be sent seven days later. Participants could potentially receive up to two surveys (at 7 and 14 days after the visit). The same procedures regarding delivery and follow-up to non-responses that are used for the first survey will be used for the second survey at 14 days.

The participant will receive a $10 e-gift card (Target or Amazon) sent electronically to their email address when they submit their last survey or when they return the diary. Those that do not have an email address will be asked for consent to record their physical address to mail them a physical gift card. Compensation will be the same for participants whether they return the diary or submitted one or two surveys. Combined with the $5 cash they received in the clinic, the participant's total compensation for completing our study is $15.

Our diary and survey were developed using the Wisconsin Upper Respiratory Symptom Survey (WURSS), the Bronchitis Severity Survey (BSS), and an acute lower respiratory tract infection diary (LRTi Diary) as guidance.[113-115] In addition to these surveys, we also referred to the protocols used in two large prospective cohort studies, the Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE), and the TARGET Cohort Study.[116,117]

The number of questions and the scale used in each study and protocol are summarized in Table 3.3. The BSS has been assessed for content, construct and predictive validity and was determined to be an effective tool for evaluating symptom severity of acute bronchitis.[113] There are several WURSS questionnaire lengths, from 11 to 44 questions. The WURSS-21 and WURSS-44 have been validated (construct, convergent, and face validity) to perform well in quality of life outcome measures.[114] The LRTi Diary is a six question, six-point Likert scale diary determined to be internally valid and have construct validity.[115] The GRACE study protocol involves a symptom diary of 13 respiratory associated questions on a seven-point Likert scale.[117] The TARGET protocol asked parents 20 questions about the symptoms present in their child with respiratory illness.[116]

With several sources available, we chose to construct the diary and survey using symptoms from the BSS, LRTi Diary and GRACE protocol (Appendix E and F). Signs and symptoms from the WURSS survey and TARGET protocol were not considered because they did not fit our study design or population (upper respiratory and children, respectively).

We will ask about the presence of cough, sputum production, wheeze, post-tussive vomiting, paroxysmal cough, and trouble sleeping. Duration will be evaluated from the diary by how many days after the urgent care visit they stopped having the symptom. Following duration, severity will be measured similar to the BSS. The BSS is a five-point Likert-scale (0-absent, 1-mild, 2-moderate, 3-severe, 4-very severe). We will use the same five points but preferred the descriptions from the LRTi Diary, where the participant is asked how bad is a symptom (0-absent, 1-slightly a problem, 2-moderately bad, 3-bad, 4-very bad, as bad as it could be).

Two symptoms will not be measured on a scale, post-tussive vomiting and paroxysmal cough. These will be asked as yes or no questions because we felt vomiting or uncontrollable coughing are not suited for rating on a scale. Having an uncontrollable coughing fit or vomiting as a result of coughing would often be considered “bad” or “very bad” symptoms to have and thus bias our ratings. We will also ask about the impact of cough on daily living by inquiring how many days of work or school were missed. Lastly, we will ask if they filled their prescription and if they’ve had contact with children less than five years old.

The diary will be split into two identical diaries, one for the first seven days and another for the next seven days. This was done for two reasons. First, we expect commitment to the study to taper off as time passes. A single diary of 14 days would likely result in fewer being returned. Secondly, our inclusion criteria set a minimum duration of cough at enrollment as seven days. If a patient is recruited at this minimum duration and they return at least one survey or diary, we can conclude the duration of cough is at least 14 days.

We will instruct the participant to fill out the diary at the end of the day before they go to sleep and fill out the diary based on whether they experienced any of the symptoms during their day and if they had trouble sleeping the night before. The diary will be self-addressed and pre-stamped to make it easier to be returned after they are completed.

The electronic survey will be a scaled back version of the diary, only asking when they stopped coughing, the presence of symptoms over the last two days, how many days of work or

school missed, if they filled their prescription, and if they had contact with children. We excluded questions about severity due to the unreliability of asking the participant to rate how they felt on average.

Data Analysis

We will first present the prevalence of atypical bacteria among adults with cough of at least seven days in the contemporary United States urgent care setting. Prevalence will be calculated by dividing the number of positive PCR results by the total number of participants in the study. It is then multiplied by 100 to get a percentage (Formula 1.3). This calculation and a 95% confidence interval for the prevalence estimate will be generated using SAS 9.4 (SAS Institute, Cary, NC, USA).

$$P = \frac{\#\text{ of positive PCR}}{\#\text{ of total participants}} x\ 100$$

Formula 1.3

We will then evaluate the accuracy of signs and symptoms for predicting a cough longer than 14 days by using sensitivity, specificity, likelihood ratios, and diagnostic odds ratios. How they are calculated and the statistical software being used are provided below.

Sensitivity is calculated by dividing the true positives (TP; those with the symptom who coughed longer than 14 days) by the false negatives (FN; those without the symptom and coughed longer than 14 days) plus the true positives.

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

Formula 1.4

Specificity is determined similarly, by dividing true negatives (TN; those without the symptom and coughed less than 15 days) by the false positives (FP; those with the symptom and coughed less than 15 days) plus true negatives.

$$\text{Specificity} = \frac{TN}{TN+FP}$$

Formula 1.5

Likelihood ratios are used to revise the probability a patient has a disease based on a result. The positive likelihood ratio (LR+) corresponds to how much a positive test increases the probability of disease and is calculated by dividing the sensitivity by one minus specificity:

$$LR+ = \frac{\text{sensitivity}}{1 - \text{specificity}}$$

Formula 1.6

A negative likelihood ratio (LR-) corresponds to how much a negative test decreases the probability of disease and is calculated by dividing one minus specificity by sensitivity:

$$LR- = \frac{1 - \text{specificity}}{\text{sensitivity}}$$

Formula 1.7

The diagnostic odds ratio (DOR) can be represented in several ways, using TP, FN, FP, and TN, sensitivity and specificity, or likelihood ratios. Here, the DOR is the ratio of the odds having a symptom with a cough longer than 14 days over the odds of having a symptom with cough less than 15 days. It corresponds to LR+/LR- and is an overall measure of diagnostic accuracy for dichotomous tests.

$$DOR = \frac{TP/FN}{FP/TN} = \frac{\text{sensitivity}/(1-\text{sensitivity})}{(1-\text{specificity})/\text{specificity}}$$

Formula 1.8

Likelihood ratios and the DOR will be considered statistically significant if their 95% confidence levels do not cross one. Sensitivity, specificity, LR+, LR-, and DOR will be performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

A survival analysis with a Kaplan-Meier curve will also be used to compare the differences of duration and severity of symptoms by clinical care (antibiotics, corticosteroids,

and cough suppressants). To do this, we will dichotomize the patient-rated severity to 0, 1 or 2 (absent, slightly a problem, moderately bad) versus 3 or 4 (bad, 4-very bad). The number of days until severity is below five will be compared between the type of clinical care the patient received. The same will be performed to determine the duration until all symptoms are scored less than three. Due to only our diary requesting the patient to rate their symptom, this analysis will be restricted to only those that returned at least one diary. Kaplan-Meier curves will be generated in SAS 9.4 (SAS Institute, Cary, NC, USA) and differences will be considered statistically significant using Log-Rank statistics with a p-value less than 0.05.

Limitations

Aim 2 has several potential limitations. Ideally, we would prefer to enroll all adults with a cough longer than seven days during all operating hours. Due to several limiting factors, an investigator will be present for approximately 40 hours per week. This means we will miss some potential subjects that may have otherwise enrolled but recruitment will still be a consecutive series while the investigator is present and using broad inclusion criteria will reduce the impact of this limitation.

Interviewer bias occurs when the interviewer elicits certain responses from the subject by encouraging them to respond a certain way or misinterpreting those responses. To prevent this, the survey has been developed to be as simple as possible for the subject to understand, with many of the responses to the questions being yes or no. The investigator will read the questions from the survey as written and will only record responses given as a yes or no. Recall bias may occur among subjects who are not able to remember experiencing some symptoms. Using a cough duration of seven days versus 14 or longer will help reduce this bias because subjects will have a shorter period to remember. In addition, the use of a standardized survey with yes or no responses rather than more complicated and detailed questions should allow for an easier recollection.

We understand there is a high likelihood that many of the diaries will not be returned. We will attempt to limit this by providing thorough instructions in the clinic on how to fill out the diary and explain the importance of understanding the duration of symptoms. We will also explain to the participant that they can use the diary as a memory tool when filling out the electronic survey, where they can reference the diary to note when a symptom subsided. We also attempted to simplify and shortened the survey as much as possible to reduce the time and hopefully increase response rate.

If we only receive the survey, there may be recall bias. We address this limitation by giving the patient a diary and tailored our follow-up survey to be quick and relatively simple for the participant to complete. Participants that return both the diary and survey will allow us to evaluate the recall bias.

Aim 3 Methods Overview

When the participant is first recruited at the urgent care center, the investigator will gather demographic information, specific signs and symptoms since their cough began, social factors, vaccine records, and vital signs. The sample size, data collection procedures, and forms have been previously described in Aim 2 methods. We will perform univariate and multivariate logistic regression to determine associations (unadjusted and adjusted odds ratios) between collected predictor variables and the outcome variable of having a prolonged cough greater than 14 days. In addition to the outcome of prolonged cough, we will also perform the same analysis on the outcome of a CXR being ordered and the prescribing of antibiotics, corticosteroids, and cough suppressants.

Data Analysis

The first objective of Aim 3 is to calculate the unadjusted and adjusted association of signs, symptoms, and social factors on the outcome of a cough greater than 14 days. Variables

will be assessed for collinearity using Spearman correlation, removing variables highly correlated above 0.80. The remaining variables will be used in a univariate logistic regression analysis to determine unadjusted odds ratios. Individual variables will be considered to have a statistically significant association with the outcome of cough greater than 14 days if they have a p-value less than 0.05.

Next, associations will be measured using multivariate logistic regression. Normally, before building the model, an assessment would be made for confounding variables between the exposure and outcome. However, in this analysis we are not measuring the association between a single exposure and single outcome but rather what variables (signs and symptoms) are independently associated with cough duration. Based on biological plausibility, there may be some interaction between symptoms. First and second order interactions that will be explored include: paroxysmal cough, post-tussive vomiting, wheezing, and dyspnea. We will use both forward selection with Akaike Information Criterion (AIC) and automatic forward and backward selection using the chi-square test and select the most parsimonious model for our final multivariate model.

With forward selection, we will add variables beginning with the lowest p-value from the univariate model. As we continue to add variables (up to p-value <0.20), we will compare the AIC statistic. The AIC statistic was chosen because it penalizes for using too many variables, which can limit accuracy and avoids attenuation of possible important variables.[118] The model with the lowest AIC is considered the better model, but this depends on the difference between the two models. Generally, if the difference between AIC models is less than two, the models being compared are considered equally as good.[118-121] If the difference in AIC between the two models is greater than 10, the one with the lower AIC is considered a better model. If our full model with the added variable has a lower AIC by more than 10, it will be kept. This is repeated until the difference between the models is less than 10 where the new full model is rejected because it didn't improve the AIC and we then have a final multivariate logistic model.

We will also use automatic forward and backward selection with -2 Log Likelihood (-2LL). Using -2LL is a more traditional approach that does not penalize for too many variables. This will give us the opportunity to evaluate a different model that may include important variables or interactions that were left out of the model using AIC. First, in backwards selection, a model with all the variables and interaction terms is created. Insignificant (p-value >0.20) variables, starting with interaction terms, are removed one at a time to produce a reduced model. At each step, the preceding 'full' model and the newly reduced model are compared with -2LL. The -2LL of the full model is subtracted from the -2LL of the reduced model, as well as the degrees of freedom (DF) from each. The resulting value of the -2LL and DF are used in a chi-square distribution table to determine if the difference between models are statistically significant. If the p-value is greater than 0.05, we keep the reduced model. This is repeated until the p-value is less than 0.05, which meant removing a variable had a significant impact on the model. The variables that are remaining result in a final multivariate model.

Comparing the models produced from manual and automated selection, we will choose the most parsimonious model. An example of the final multivariate logistic model is given in Formula 1.9, where β are the coefficients and X_i are the values of each independent variable.

$$Log\left[\frac{Y}{(1-Y)}\right] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_1 X_3 \ldots.$$

Formula 1.9

The individual signs and symptoms are the independent variables and the cough duration (greater than 14 days versus less than 15 days) is the dependent variable. The last two terms of the equation represent possible interaction. The adjusted odds ratios from the multivariate model with 95% confidence intervals will be presented in a separate table.

Our next objective is to determine if any of the collected variables predict the type of clinical management given to the patient. The univariate analysis will be performed by comparing binary variables using a chi-square test and means with Student's t-test, both

considered statistically significant if the p-value is less than 0.05. Variables with a p-value less than 0.20 from the univariate analysis will be used to determine the variables added to the multivariate logistic regression.

As was performed above for the multivariate logistic regression analysis of cough duration, the same procedures will be used for these outcomes. In the final multivariate model, independent variables could potentially be any combination of signs, symptoms, demographics, or social factors and the dependent variables are CXR, antibiotic, systemic corticosteroid, and cough suppressant. All of the above analysis, including the odds ratios and 95% confidence intervals from univariate and multivariate logistic regression will be performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

Lastly, to use a non-parametric method, we will create a Fast and Frugal Tree (FFT) for each outcome. A FFT is a decision tree that is based on limited variables, usually less than four,[122,123] which limits overfitting of the model.[124] Each tree is limited to only two branches, simplifying the decision to a dichotomous yes or no question. This is ideal for emergency and urgent care settings because decisions must be made quickly and with limited information available. They have been proven useful in medical practice previously.[125,126]

Because an FFT only has two possible exits (positive or negative), building the tree is directly influenced by sensitivity and specificity. For example, if the tree was built with all positive exits, it would have a high sensitivity but low specificity because every node was based on a positive decision. An FFT is constructed using an algorithm (ifan and dfan) that maximizes the weighted accuracy, where it balances sensitivity and specificity to produce the best model.[123]

This is in contrast to classification and regression trees (CART) that use recursive partitioning for its decision making.[127] To develop a CART model, a single parent node is split into two daughter nodes based on which variable was determined to best split the data. This process is repeated and applied separately to each daughter node, continuing until the final nodes reach a minimum size, usually determined *a priori*. The resulting model is usually one

with several terminal nodes, depending on the minimum size chosen. This makes CART models prone to high variance and overfitting.[128]

Usually the FFT would be created using cross-validation, where the data set is split into a training set (e.g., 70% of the data) and validated against a test set (the remaining 30%). With our relatively small sample size (goal of 125) and number of anticipated outcomes, the entire data set will be used to create each FFT. To supplement the lack of cross-validation, we will use random forests of FFTs. A random forest simulates many different decision trees to output which variables appear most often across all simulations.[128,129] One hundred random forests of FFTs using a 70/30 cross-validation split will be used to determine the most important (i.e., most common) variables associated with each outcome.

Decision trees and random forests were created with the FFTrees and FFForest package in R version 3.4.3, respectively.

Limitations

Because Aim 3 is completely dependent on the data collected during Aim 2, it is subject to all of the limitations previously described in Aim 2.

Chapter 3 Tables

Table 3.1 Aim 1 Sample Size Calculations+

Expected Prevalence[a]	Confidence interval (margin of error/precision)	Sample Size	Expected Cases*	Lower CI	Upper CI
0.14	0.058	137	19	0.082	0.198
0.14	0.060	128	18	0.080	0.200
0.14	0.062	120	17	0.078	0.202
0.14	0.064	113	16	0.076	0.204
0.14	0.066	106	15	0.074	0.206
0.15	0.058	146	22	0.092	0.208
0.15	0.060	136	20	0.090	0.210
0.15	0.062	127	19	0.088	0.212
0.15	0.064	120	18	0.086	0.214
0.15	0.066	112	17	0.084	0.216
0.16	0.058	153	25	0.102	0.218
0.16	0.060	143	23	0.100	0.220
0.16	0.062	134	21	0.098	0.222
0.16	0.064	126	20	0.096	0.224
0.16	0.066	119	19	0.094	0.226

+ Calculated using: $n= (Z^{\wedge 2})(P(1-P)/(d^{\wedge 2})$; Z = 1.96 (95% confidence level); d = precision; P = expected prevalence

* Expected cases = number of cases of cough duration less than 15 days. Sample size multiplied by expected prevalence

a – sorted by expected prevalence

Table 3.2 Sample Size to Determine Number of Responses Needed from Follow-up Surveys

Population Size from Aim 1	**Margin of Error (Precision)** 0.058	0.060	0.062	0.064
125	88	86	84	82
Non-response rate	20%	25%	30%	35%
Responses Received¥	100	94	88	82
Formula[105]: $s = X^2 * NP(1-P) \div d^2(N-1)+X^2P(1-P)$ X^2 = Chi-square (3.841 for 95% confidence level); N=Population; P = population proportion (50% used to maximize sample size); d=precision				

¥ - How many responses would be received if 125 surveys were sent

Table 3.3 Comparison of Three Validated Respiratory Surveys and Two Large Prospective Study Protocols

Survey or Protocol	Number of Questions	Point Scale (Likert)
Wisconsin Upper Respiratory Symptom Survey (WURSS)[114]	Varies (11, 21, 24, 44)	8-point (0 = Not sick, 1 = Very mildly, 3 = Mildly, 5 = Moderately, and 7 = Severely)
Bronchitis Severity Survey (BSS)[113]	5	5-point (0 = absent, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe)
Acute lower respiratory tract infection diary (LRTi Diary)[115]	6	7-point (0 = normal, 1 = very little problem, 2 = slight problem, 3 = moderately bad, 4 = bad, 5 = very bad, and 6 = as bad as it could be)
Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE)[117]	13	7-point (0 = normal, 1 = very little problem, 2 = slight problem, 3 = moderately bad, 4 = bad, 5 = very bad, and 6 = as bad as it could be)
TARGET Cohort Study[116]	20	3-point (1 = Mild, 2 = Moderate, 3 = Severe)

CHAPTER 4

SYSTEMATIC REVIEW AND META-ANALYSIS OF THE SIGNS AND SYMPTOMS THAT RULE OUT COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS PRESENTING WITH COUGH[1]

[1] Marchello, C., Ebell, M., Dale, A.P., Harvill, E., Shen, Y., and Whalen, C., To be submitted to Annals of Internal Medicine

Abstract

Background: Clinical decision rules (CDRs), using a combination of signs, symptoms, and point of care (POC) tests, are helpful tools for determining the risk of having a disease. A review of which CDR most accurately identifies patients at low risk for community-acquired pneumonia (CAP) has not been previously presented in the literature.

Design: Systematic review of the literature and meta-analysis

Methods: We performed a systematic review of MEDLINE for prospective studies that used at least two signs, symptoms, or POC tests to diagnose, predict, or rule out CAP. We included studies that enrolled adults and adolescents in the outpatient setting (emergency department, urgent care, primary care, or outpatient clinic) where all or random sample of patients received a chest radiograph as the reference standard. We excluded retrospective studies and studies that recruited a majority of patients with hospital-acquired CAP, who were immunocompromised, or from special populations such as military.

Results: A total of 974 articles were returned from our search strategy. Twelve studies were included in the final analysis. Of the 12, three used a score, one was a decision tree, and the remaining eight studies produced 17 CDRs. A meta-analysis of four CDRs using the absence of any abnormal vital signs (temperature, respiratory rate, and heart rate) to identify patients at low risk for CAP had a summary estimate of the negative likelihood ratio of 0.24 (95% CI: 0.17-0.34), and a sensitivity of 0.89 (95% CI: 0.79-0.94). Three CDRs using normal vital signs combined with a normal pulmonary exam had a summary estimate of the negative likelihood ratio of 0.10 (95% CI: 0.07-0.13) with a high area under the receiver operating characteristic curve of 0.92.

Conclusions: Normal vital signs or a combination of normal vital signs and a normal pulmonary exam in adults with acute respiratory infection can be used to identify those very unlikely to have CAP. Additional prospective studies validating these CDRs in a contemporary population are needed.

Introduction

Community-acquired pneumonia (CAP) is a significant source of morbidity and mortality for adults in the United States (US). Episodes requiring hospitalization occurs at an estimated annual incidence rate of 25 to 36 cases per 10,000 adults, trailing only live births as a reason for a hospital stay[34,36]. In 2015, there were over 50,000 deaths due to pneumonia (about 1.6 deaths per 10,000 persons) and when combined with influenza, is the eighth leading cause of mortality in the US.[33]

The recommended test for diagnosing CAP is by chest radiograph (CXR).[11] However, not all patients presenting in the outpatient setting with a cough should receive a CXR. Providing a CXR to everyone would be not only be costly but also exposes patients to radiation and inconvenience, especially if the risk for CAP is low. For a common and non-specific symptom such as coughing, the harms may outweigh the possible benefits.

A way to limit unnecessary testing of these patients is by stratifying risk, such as determining based on the clinical presentation whether a patient has a low, moderate, or high risk of CAP. Generally, the low risk group would not receive a CXR or antibiotic treatment, the moderate risk group might be considered for CXR, and the high-risk group might have a CXR or empiric antibiotic therapy if their risk was high enough. This could reduce overall health system costs and unnecessary radiation exposure.

A clinical decision rule (CDR) is often used to place patients into appropriate risk categories. A CDR is developed by analyzing multiple factors such as demographics, signs, symptoms, laboratory or point of care (POC) tests, and overall physician clinical impression to determine which combinations best categorize a patient's risk for disease. For example, a widely used CDR is the Centor Criteria, which uses tonsillar exudates, swollen tender anterior cervical nodes, lack of a cough, and history of fever to categorize the risk of strep throat.[38]

Many studies have summarized the clinical presentation of CAP, while some have used a CDR to diagnose, predict, or rule out CAP.[130-133] These CDRs vary, using different

combinations of vital signs, signs, symptoms, and laboratory tests. The specific combinations used in these studies have not been previously summarized in the literature with an eye toward identifying low risk criteria for CAP.

Our goal is to systematically review the literature to analyze and describe CDRs that may be used to rule out ("low risk criteria") CAP in otherwise healthy adults. We aim to present which combinations of signs (including vital signs), symptoms, and POC tests have the greatest negative predictive value so physicians can confidently rule out CAP without CXR in the outpatient setting.

Methods

Inclusion and Exclusion Criteria

Before performing a literature search, we set specific inclusion and exclusion criteria. Our goal was to only include articles that used a CDR to diagnose, predict, or rule out CAP. The study was included if it used a CXR or computed tomography (CT scan) as the primary reference standard and was given to all patients enrolled in the study. If the reference standard was used in a random or systematic sample of low risk CAP patients to minimize radiation exposure, the study was also included. Studies had to gather data prospectively, and could include cohort studies, clinical trials, cross-sectional studies, and consecutive series of enrolled patients. Lastly, only adults or adolescents who were seen in an outpatient setting (emergency department, urgent care, primary care, or outpatient clinic) were included.

We are interested primarily in healthy adults that developed pneumonia in the community, so studies where a majority of the patients enrolled had hospital-acquired or ventilator associated pneumonia, were immunocompromised, or special populations such as military or nursing homes were excluded. We excluded studies that were not prospective, such as case-control, case reports, retrospective studies, and outbreak investigations. An exception was made if the case-control study enrolled symptomatic patients in a prospective way such as

a consecutive series, where patients with similar symptoms but with and without CAP were matched.

Search Strategy

We performed a systematic review of articles published in MEDLINE using the following search strategy:

("clinical criteria"[TIAB] OR "diagnostic value"[TIAB] OR "predictive value"[TIAB] OR "rule out"[TIAB] OR decision[TIAB] OR prediction[TIAB]) AND ("pneumonia"[MeSH Terms] OR pneumonia[TIAB] OR pneumoniae[TIAB]) AND (community[TIAB] OR emergency[TIAB] OR urgent[TIAB] OR primary[TIAB] OR acute[TIAB] OR "general practice"[TIAB]) NOT ("hospital-acquired"[TIAB] OR "hospital-associated"[TIAB] OR "healthcare-associated"[TIAB] OR nosocomial[TIAB] OR stroke[TIAB] OR klebsiella[TIAB] OR tuberculosis[TIAB] OR surgery[TIAB] OR ventilator[TIAB] OR "intensive care unit"[TIAB] OR "ICU"[TIAB] OR retrospectively[TIAB] OR retrospective[TIAB] OR "case-control"[TIAB] OR "case report"[TIAB] OR "case series"[TIAB] OR gastrointestinal[TIAB] OR immunocompromised[TIAB] OR HIV[TIAB] OR cancer[TIAB]) AND hasabstract[text]

In addition to this search of MEDLINE, systematic reviews that appeared in our results were reviewed for relevant articles that fit our inclusion and exclusion criteria. We also searched the references of any article in which its full text was reviewed.

The systematic review was performed in parallel by two authors, with a third author who helped resolve any discrepancies. This occurred in two stages, with the goal of the first stage to maximize the number of articles to get a full and comprehensive list of possible studies. Each author executed the above search strategy separately, in parallel, to review the titles and

abstracts for articles that needed a full text review. Study ID, author, and year were recorded in a shared Google Doc Excel spreadsheet. The two lists were combined into one complete list and we moved to stage two.

The second stage (all methods described from this point forward) required the agreement of both authors and if a consensus could not be reached, a third author resolved the discrepancy. The full text of the articles in the combined list of titles and abstracts were reviewed for inclusion. After reviewing the full text of the article, each author separately documented if it met the inclusion criteria. The two lists were reviewed for agreement as previously described. Articles meeting the final inclusion list were then reviewed for data abstraction. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[98] to document our search process.

Data Abstraction and Analysis

We first abstracted the study characteristics (author, year, country, design, setting, years recruited, sample size, inclusion age, and mean or median age) for each article. Then, two authors reviewed the combination of signs, symptoms or POC tests that were used to diagnose CAP. The final list of these combinations was sorted by most commonly shared among the articles.

The next step was to evaluate the articles for bias using the QUADAS-2 framework.[100] The evaluation consists of four areas: patient selection, index test, reference standard, and flow and timing. For each, a set of questions assess the article for bias, answering yes, no, high, low, or unknown. Two authors reviewed the included articles and finalized an overall assessment for each article as being low, moderate, or high risk for bias.

We then abstracted data on the accuracy of the combinations for each CDR. When available, we recorded true positive (CDR+, CAP+), false positive (CDR+, CAP-), true negative (CDR-, CAP-) and false negative (CDR-, CAP+). When not directly provided, we calculated

them using data that were provided. These data were used to calculate positive and negative likelihood ratios (LR+ and LR-, respectively) for CDRs reporting a dichotomous outcome of CAP vs no CAP, and stratum specific likelihood ratios (SSLR) for CDRs reporting more than 2 possible outcomes (e.g. low, moderate, and high risk groups). Post-test probabilities were calculated for standardized low prevalence (4%) and high prevalence (20%) populations, consistent with outpatient primary care and emergency department populations respectively, using summary estimates of LRs for high performing CDRs.[39,130] Lastly, we calculated three risk groups (low, moderate, and high) as part of a post hoc analysis of any CDR based on a multichotomous score.[39,40] The risk groups were assigned based on the distribution of likelihood ratios from the studies' published data.

Where three or more CDRs matched, we performed a bivariate meta-analysis to calculate summary estimates and 95% confidence intervals for sensitivity, specificity, LR+, LR-, and receiver operating characteristic (ROC) curves. These were performed using the mada package in R, version 3.4.3 using the Reistma method.[99]

Institutional Review Board approval was exempt and no funding was provided for this research as this was a secondary analysis of previously published data.

Results

Our initial search strategy returned 974 articles (Figure 4.1). The title and abstract review eliminated 906 articles, resulting in 68 articles that needed a full text review. Forty-two additional articles were identified when we reviewed their reference lists, resulting in a total of 110 articles for full text review. Of these, we excluded 98. The most common reasons to exclude a study were because it was not prospective, was a literature review or guideline, did not report any usable patient data, or did not present data for something that met our criteria for a CDR.
A final total of 12 studies were included.[10,39-41,134-141] Study characteristics are summarized in Table 4.2. Almost half were performed in the United States[39,40,134,136,140], and no other country

appeared more than once. Enrollment of patients occurred from 1984 to 2010, with a mean age between 32 and 65 years. Half of the studies were performed in the emergency department setting and the other half in primary care. Sample sized ranged from 246 to 2820 patients.

The QUADAS-2 assessment of bias for the 12 studies is presented in Table 4.2. Overall, half (six) of the studies were determined to be at low risk of bias and the other half at moderate risk of bias. The moderate risk articles were only included after consideration of their limitations.[39,134,136,137,140,141] Two were initially excluded because they were classified as case control studies.[136,141] However, we included them after further review because they were not a traditional case control design. Each study enrolled patients prospectively in a consecutive series, and a CXR was performed on each patient. However, the researchers matched patients with a positive infiltrate (cases) on the CXR to a similar number of symptomatic patients without an infiltrate (controls). Since patients were enrolled prospectively, we chose to retain the studies in the final analysis.

In one article[137], not all patients received the reference standard CXR; those with a low probability of CAP were randomized to receive one or not. We included this article because this is common practice in studies where the reference standard is potentially harmful or costly. Randomization ensured the study avoided differential verification bias, which is the concern when not all patients receive the same reference standard.

The final three articles that we included[39,134,140] enrolled patients when a CXR was ordered because pneumonia was suspected or the physician considered the probability of pneumonia to be greater than zero. We chose to accept this limitation because we are interested in when it is appropriate to order a CXR for CAP. Indications for a CXR other than CAP (e.g. heart failure, pulmonary embolism, broken ribs) are not relevant in our case, so these articles were excluded.

There was a wide range of CDRs, with between three and 10 elements and many of them different (Table 4.3). The four individual signs or symptoms that appeared in at least half

of the studies were elevated temperature, elevated heart rate, crackles on auscultation, and decreased breath sounds. Elevated temperature was the most common shared sign or symptom, found in 10 of the 12 studies. The definition of elevated temperature was not consistent, with some using greater than 37.8 C, some greater than 38.0 C, and two described as just “fever”. The other three signs or symptoms were used in six studies.

Three studies produced a simple point score (Table 4.4).[10,39,40] The three scores were difficult to compare, as each score used different combinations of variables to identify the risk groups; the only sign or symptom shared across all three scores was a temperature greater than 37.8 C. One study used seven criteria overall[40]: temperature greater than 37.8C, respiratory rate greater than 25 breath/minute, night sweats, myalgia, sputum, sore throat, and rhinorrhea. A specific point value was assigned to each, for example, rhinorrhea was given negative two points while temperature greater than 37.8C was positive two points. In the post hoc assigned risk groups, patients with a score from -3 to 0 had a SSLR of 0.47, and a 1.2% probability of CAP given a baseline prevalence of 2.6%. The high-risk group had a 27.3% probability of CAP and a SSLR of 14.0.

Another study used a derivation set (Illinois) and then validated it with data from two other locations (Nebraska and Virginia).[39] The score is based on the number of abnormal findings present (>37.8C, HR >100/min, rales, absence of asthma, decrease breath sounds). The Illinois derivation set had an area under the ROC curve (AUC) of 0.82 (95% CI 0.78-0.86), while the Nebraska and Virginia validation sets had an AUC of 0.82 (0.74-0.90) and 0.76 (0.66-0.86), respectively. Low, moderate and high-risk groups were created post hoc for the derivation set and validation set, and were pooled for the entire study. Overall, patients presenting with no or one abnormal finding in the pooled set had a low risk of CAP, with a probability of 4.0% given a baseline prevalence of 29.2% and a SSLR of 0.19. The high-risk group with four or five abnormal findings had a 64.0% probability of CAP and a SSLR of 8.3.

The final study was the only one to do so with a POC test, c-reactive protein (CRP).[10] A score was developed using regression coefficients, assigning one point to each sign or symptom (decreased breath sounds, crackles, breathlessness, vesicular breath sounds, absence of runny nose, temperature greater than 37.8C, heart rate greater than 100/min) and for a CRP greater than 30 mg/L. The overall model had an AUC of 0.77 (0.73-0.81). The low-risk group with a score of zero, had 0.7% probability of CAP given a prevalence of 5.2%, with a SSLR of 0.14. The SSLRs for moderate and high-risk groups were 0.76 and 4.3, respectively.

The remaining nine studies reported the accuracy of 18 CDRs that predict a dichotomous outcome of CAP vs no CAP rather than a point score (Table 4.5). The CDRs used in each study are presented in two ways: to diagnose (ruling in CAP) and as low yield criteria (ruling out CAP). A CDR using solely normal vital signs to exclude CAP was the most common, appearing four times[135,136,140,141], while one using normal vital signs plus a normal pulmonary exam to exclude CAP appeared three times (REFs).

Measure of accuracy for each CDR are summarized in Table 4.6. Fourteen CDRs have good sensitivities (above 0.75) while 12 lacked specificity (below 0.60). The highest sensitivity was 1.00, a clinical decision tree that used CRP greater than 50 µg/mL or CRP 11-50 µg/mL and dyspnea or daily fever.[41] Only two CDRs were both sensitive and specific (0.86/0.72 and 0.81/0.64), and both used only abnormal vital signs (temperature 38C or greater, heart rate 100/min or greater, and respiratory rate greater than 20/min) in the CDR.[136,141]

The highest LR+ among these 18 CDRs was 4.0, for a CDR with that combined a positive overall physician impression of CAP and an oxygen saturation of 95% or less.[139] A patient positive for this combination had a probability of CAP of approximately 25% given an overall prevalence of 16.2%. Three other CDRs had a LR+ above 3.0.[137,139,141] Normal vital signs accompanied by no findings on a pulmonary exam rules out CAP well, with three studies of this CDR having negative likelihood ratios 0.09 to 0.11.[135,136,141]

A meta-analysis of the four CDRs that used normal vital signs[135,136,140,141] as low yield criteria for CAP had a summary estimate of sensitivity of 0.89 (95% CI: 0.79-0.94) and a summary LR- of 0.24 (95% CI: 0.17-0.34) (Table 4.7). The summary ROC curve (Figure 4.2A) has good discrimination and a narrow confidence interval, with an AUC of 0.89. For the CDRs using any normal vital signs plus normal findings on the pulmonary exam,[135,136,141] the overall sensitivity was 0.96 (95% CI: 0.92-0.98) and LR- 0.10 (95% CI: 0.07-0.13). The summary ROC curve for this CDR (Figure 4.2B) also had a narrow confidence range around the summary estimate, with an excellent AUC of 0.92.

Discussion

In this systematic review, we identified two potentially useful CDRs: abnormal vital signs, and abnormal vital signs plus abnormal pulmonary findings. The latter CDR performed very well, with very high sensitivity, low negative likelihood, and good AUC. The results of our meta-analysis suggest that normal vital signs plus a normal pulmonary exam is a CDR that could serve as low risk criteria for CAP.

The components of the pulmonary exam are parts of a physician's overall impression and weigh into the decision on whether to order a CXR. Only one study solely used a physician's overall clinical impressions as part of the CDR.[139] This CDR also included two POC tests, CRP and oxygen saturation. A systematic review of the accuracy of a physician's overall clinical impression would be helpful before making further conclusions.

The addition of POC tests could also be useful in ruling out pneumonia, depending on the probability of CAP in the setting. A systematic review evaluated the usefulness of CRP, indicating there may be value in settings where the probability is over 10%, such as emergency departments (EDs).[142] In our systematic review, five studies implemented the use of CRP in their CDR. Among those, a decision tree using CRP was able to rule out pneumonia in all patients with a CRP less than 10 µg/mL.[41] When CRP was between 11 and 50 µg/mL, it was

able to rule out pneumonia with the addition of no dyspnea and no fever. In a large, multi-country, prospective study of over 2,500 patients where the prevalence was 5%, the addition of CRP to the score improved discrimination based on the area under the ROC and diagnostic accuracy.[10]

Of the 12 studies included, three were multichotomous CDRs using a score or points. In a standardized low prevalence setting (4%), intended to simulate the prevalence of CAP among patients with acute cough in primary care, each score differentiated low, moderate and high-risk groups (Table 4.7). However, one score's high-risk group[10] had a lower probability of pneumonia (15.1%) compared to the others. In a high prevalence setting (20%), intended to simulate the prevalence of CAP in the ED, a post hoc calculated low-risk group had a relatively high probability of CAP (10.5%).[40]

One score,[39] which was externally validated, had a large sample size, and of all the CDRs produced in our review had the highest AUC, could be argued as a starting point for future research. However, the study has not been validated in over 20 years. Thus, validation of this CDR in a contemporary population of patients with acute RTI or clinically suspected CAP would be helpful. Additional prospective studies validating the vital signs and pulmonary exam CDRs, current published scores and decision trees are recommended.

Chapter 4 Tables and Figures

Figure 4.1 PRISMA flow diagram: visualization of process from initial search to final decision

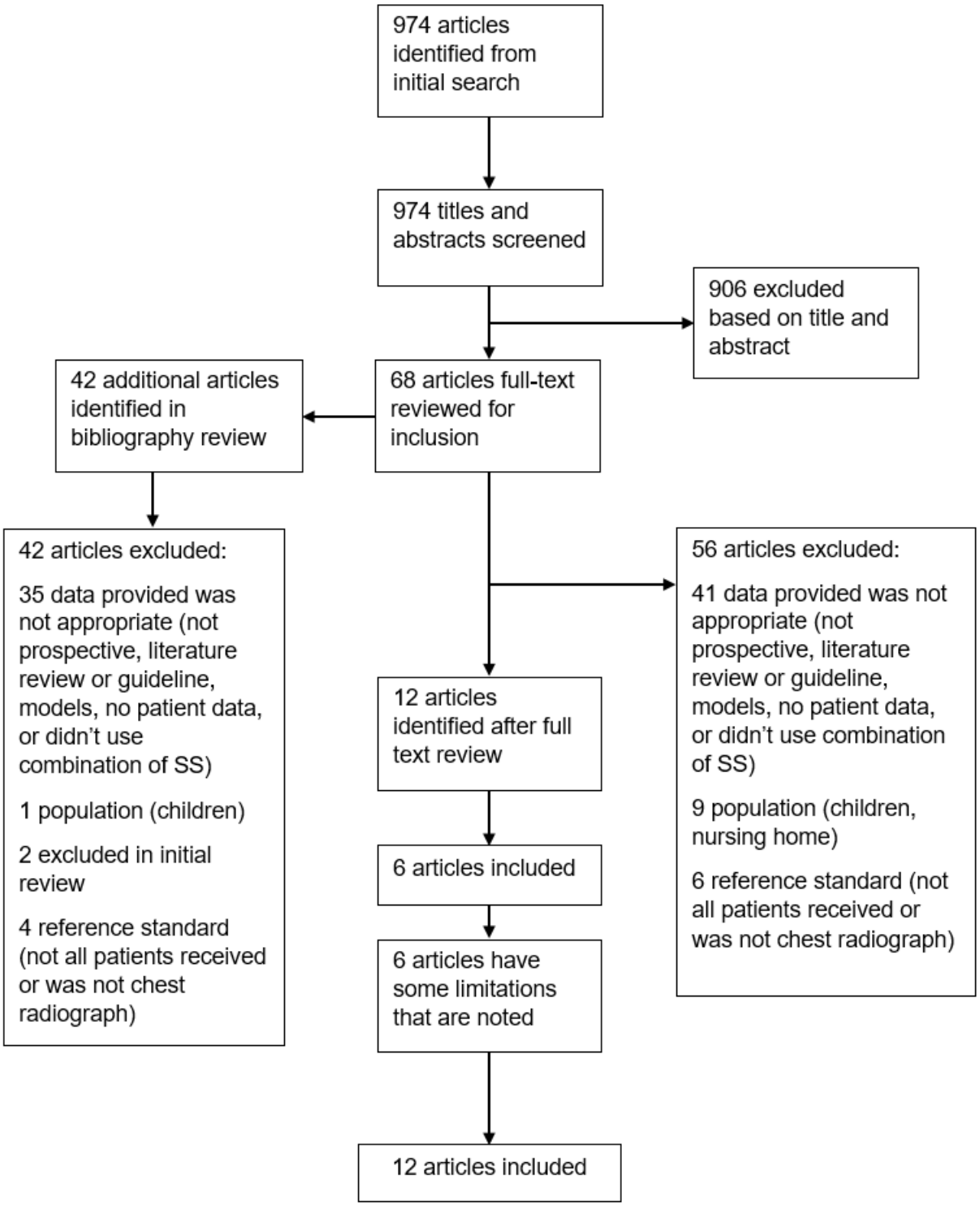


Table 4.1 Characteristics of included studies.

Author, Year	Country	Design	Setting	Year recruited	Sample Size	Inclusion Age	Mean or Median Age
Diehr, 1984[40]	United States	Prospective	ED	Not reported	1758	Adults	Not reported
[a]Gennis, 1989[140]	United States	Prospective	ED	1984-1985	308	>=16 years	53.6 years (mean)
[a]Singal, 1989[134]	United States	Prospective	ED	1986-1987	255	>=18 years	Not reported
[a]Heckerling, 1990[39]	United States	Prospective	ED	1987-1988	1436	>=16 years	45.4 years (mean): Illinois/Nebraska 41.4 years (mean): Virginia
[a]Melbye, 1992[137]	Norway	Prospective	ED	1988-1989	581	>=18 years	32.1 (mean)
Hopstaken, 2003[138]	The Netherlands	Cross-sectional / prospective	Primary care	1998-1999	246	>=18 years	52 years (mean)
[a]O'Brien, 2006[136]	United States	Case-control/prospective	Outpatient/ED	2004-2005	700	>=18 years	65 years (mean): cases; 66 years (mean): controls
Holm, 2007[139]	Denmark	Prospective	Primary care	2002-2003	364	>=18 years	50 years (median)
Saldias, 2007[135]	Chile	Prospective	ED	2005	325	>15 years	53.4 years (mean)
Steurer, 2011[41]	Switzerland	Prospective	Primary care	2006-2009	621	>=18 years	46.8 years (mean)
van Vugt, 2013[10]	12 European countries	Prospective	Primary care	2007-2010	2820	Adults	50 years (mean)
[a]Ebrahimzadeh, 2015[141]	Iran	Case-control/prospective	Outpatient/ED	2008-2009	840	>=18 years	60 years (mean): cases 63 years(mean): controls

a – limitations of these studies were noted in text in the Methods and Results; ED: emergency department

Table 4.2 Assessment of study quality using QUADAS-2 framework

Author, Year	Consecutive or random sample enrolled? (Y/N/U)	Case-control design avoided? (Y/N/U)	Avoided inappropriate exclusion criteria? (Y/N/U)	Likelihood that patient selection could have introduced bias? (H/L/U)	Concerns that included patients and setting do not match the review question? (Y/N/U)	CDR results interpreted without knowledge of reference standard? (Y/N/U)	Likelihood that conduct or interpretation of the CDR have introduced bias? (H/L/U)	Concerns that the CDR differs from the review question? (Y/N/U)	Reference standard likely to correctly classify patients as pneumonia? (Y/N/U)	Reference standard interpreted without knowledge of index test? (Y/N/U)	Likelihood that conduct or interpretation of reference standard introduced bias? (H/L/U)	Conditions defined by the reference standard do not match the review question? (Y/N/U)	All patients receive a reference standard? (Y/N/U)	Did all patients receive the same reference standard? (Y/N/U)	Were all patients included in the analysis? (Y/N/U)	Patient flow have introduced bias? (H/L/U)	**Overall assessment of risk of bias (H/M/L)**
Diehr, 1984	Y	Y	Y	L	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**L**
Ebrahimzadeh, 2015	U	N	Y	H	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**M**
Gennis, 1989	Y	Y	N	H	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**M**
Heckerling, 1990	Y	Y	N	H	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**M**
Holm, 2007	Y	Y	Y	L	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**L**
Hopstaken, 2003	Y	Y	Y	L	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**L**
Melbye, 1992	Y	Y	Y	L	N	Y	L	N	Y	Y	L	N	N	Y	Y	H	**M**

Obrien, 2006	U	N	Y	H	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**M**
Saldias, 2007	Y	Y	Y	L	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**L**
Singal, 1989	Y	Y	N	H	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**M**
Steurer, 2011	Y	Y	Y	L	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**L**
van Vugt, 2013	Y	Y	Y	L	N	Y	L	N	Y	Y	L	N	Y	Y	Y	L	**L**

Y: yes; N: No; U: unknown; H; high, M: moderate; L: low; CDR: clinical decision rule

Table 4.3 Individual signs, symptoms and point of care tests used in CDRs to diagnose or rule out pneumonia

Author, Year	Temp (C)	Pulse (per min)	Crackles	Decreased breath sounds	Resp (per min)	Other signs, symptoms or point of care tests				
Diehr, 1984	>37.8				>25	sore throat	night sweats	myalgia	rhinorrhea	sputum
Ebrahimzadeh, 2015	≥ 38	≥100	X	X	≥20	CRP	dullness on percussion	rhonchi	ESR	WBC
Gennis, 1989	>37.8	>100		X	>20	rales	wheezes	rhonchi		
Heckerling, 1990	>37.8	>100		X		rales	absence of asthma			
Holm, 2007						CRP	clinical pneumonia	SATO2		
Hopstaken, 2003	≥ 38					CRP<20	diarrhea	ESR <20	dry cough	
Melbye, 1992			X	X		pleural rubs	dullness on percussion			
Obrien, 2006	≥38	≥100	X	X	>20	rhonchi	dullness on percussion			
Saldias, 2007	≥38	≥100	X		≥20	orthopnea	dullness on percussion	abnormal auscultation		
Singal, 1989	X		X			cough				
Steurer, 2011	X					CRP >11	dyspnea			
van Vugt, 2013	>37.8	>100	X	X		CRP >30	breathlessness	Vesicular sounds	absence of runny nose	

Boxes in gray indicate not used in study. X: used in study but did not give specific value; Temp: temperature in Celsius; Resp: respiratory rate; CRP: c-reactive protein ESR: erythrocyte sedimentation rate; WBC: white blood cell count; SATO2: oxygen saturation

Table 4.4 Clinical decision rules that used a point score to diagnose pneumonia

Author, Year (signs, symptoms, tests used in CDR)	CDR score	CAP	No CAP	PV	LR
Diehr, 1984	-3	0	140	0.0%	0.00
(>37.8C,	-2	4	552	0.7%	0.27
>25 breath/min,	-1	8	504	1.6%	0.59
myalgia, night	0	7	316	2.2%	0.82
sweats, sputum,	1	12	124	8.8%	3.60
sore throat,	2	6	52	10.3%	4.29
rhinorrhea)	3	4	12	25.0%	12.41
	4	3	8	27.3%	13.96
	5	1	4	20.0%	9.30
	6	1	0	100.0%	*
	Total	46	1712		
	Low (-3 - 0)¥	*19*	*1512*	*1.2%*	*0.47*
	Mod (1-2)¥	*18*	*176*	*9.3%*	*3.81*
	High (3-6)¥	*9*	*24*	*27.3%*	*13.96*
Heckerling, 1990	Derivation: Illinois				
(>37.8C,	0	1	48	2.0%	0.12
HR >100/min,	1	11	316	3.4%	0.20
rales, absence of	2	28	232	10.8%	0.70
asthma, decrease	3	42	149	22.0%	1.64
breath sounds)	4	37	30	55.2%	7.18
	5	15	5	75.0%	17.46
	Total	134	780		
	Low (0-1)¥	*12*	*364*	*3.2%*	*0.19*
	Mod (2-3)¥	*70*	*381*	*15.5%*	*1.07*
	High (4-5)¥	*52*	*35*	*59.8%*	*8.65*
	Validation: Nebraska				
	0	0	5	0.0%	0.000
	1	3	28	9.7%	0.196
	2	11	26	29.7%	0.78
	3	12	16	42.9%	1.38
	4	11	2	84.6%	10.08
	5	5	0	100.0%	*
	Total	42	77		
	Low (0-1)¥	*3*	*33*	*8.3%*	*0.17*
	Mod (2-3)¥	*23*	*42*	*35.4%*	*1.00*
	High (4-5)¥	*16*	*2*	*88.9%*	*14.67*

	Validation: Virginia				
	0	1	7	12.5%	0.51
	1	2	30	6.3%	0.24
	2	8	44	15.4%	0.65
	3	6	16	27.3%	1.35
	4	11	8	57.9%	4.93
	5	1	0	100.0%	*
	Total	29	104		
	Low (0-1)¥	*3*	*37*	*7.5%*	*0.29*
	Mod (2-3)¥	*14*	*60*	*18.9%*	*0.84*
	High (4-5)¥	*12*	*8*	*60.0%*	*5.38*
	Pooled				
	0	2	60	3.2%	0.16
	1	16	374	4.1%	0.20
	2	47	302	13.5%	0.73
	3	60	181	24.9%	1.55
	4	59	40	59.6%	6.92
	5	21	5	80.8%	19.69
	Total	60	205		
	Low (0-1)¥	*18*	*434*	*4.0%*	*0.19*
	Mod (2-3)¥	*107*	*483*	*18.1%*	*1.04*
	High (4-5)¥	*80*	*45*	*64.0%*	*8.33*
van Vugt, 2013 (decreased breath sounds, crackles, breathlessness, vesicular breath sounds, absence of runny nose, >37.8C, HR >100/min, CRP >30)	CDR w/out CRP				
	<2.5% (low)	11	654	1.7%	0.32
	2.5-20% (interm)	105	1987	5.0%	1.01
	>20% (high)	24	39	38.1%	11.78
	Total	140	2680		
	CDR and CRP >30				
	0 (low)	4	568	0.7%	0.14
	1-2 (interm)	73	1829	3.8%	0.76
	≥3 (high)	63	283	18.2%	4.26
	Total	140	2680		

CDR: clinical decision rule; CAP: community-acquired pneumonia; PV: predictive value; LR: likelihood ratio; AUC: area under the receiver operating characteristic curve; CRP: c-reactive protein; C: temperature in Celsius; HR: heart rate; NR: not reported
* Unable to calculate due to zero value for CAP-;
¥ Risk groups calculated post hoc and were not in original publication

Table 4.5 Diagnostic accuracy of clinical decision rules using signs, symptoms, and point of care tests to diagnose (rule in) pneumonia

Author, Year	CDR used to diagnose CAP (rule in)	CDR expressed as low yield criteria (rule out)	Sensitivity (TP/TP+FN)	Specificity (TN/TN+FP)	LR+	LR-
Ebrahimzadeh, 2015	Any abnormal VS	Normal VS	0.86 (361/420)	0.72 (302/420)	3.06	0.20
	Any abnormal VS or PE finding	Normal VS and no PE findings	0.94 (395/420)	0.57 (241/420)	2.21	0.10
	Any abnormal lab (CRP, ESR, WBC)	Normal labs	0.60 (254/420)	0.74 (310/420)	2.31	0.54
Gennis, 1989	Any abnormal VS	Normal VS	0.97 (114/118)	0.19 (36/190)	1.19	0.18
	Any abnormal auscultatory findings	Normal auscultatory findings	0.78 (92/118)	0.38 (73/190)	1.27	0.57
Holm, 2007	GP diagnosis of CAP and CRP ≥ 20	GP diagnosis of CAP or CRP < 20	0.49 (23/47)	0.84 (249/297)	3.03	0.61
	GP diagnosis of CAP and SATO2 ≤ 95%	GP diagnosis of CAP or SATO2 > 95%	0.32 (15/47)	0.92 (268/291)	4.04	0.74
	GP diagnosis of CAP or CRP ≥ 20	GP diagnosis of CAP and CRP < 20	0.83 (39/47)	0.48 (144/297)	1.61	0.35
	GP diagnosis of CAP or SATO2 ≤ 95%	GP diagnosis of CAP and SATO2 > 95%	0.79 (37/47)	0.56 (164/291)	1.80	0.38

Hopstaken, 2003	>1 (diarrhea, dry cough, ≥ 38C) or CRP ≥ 20	<=1 of 3 sign/symptom + CRP <20	0.91 (29/32)	0.49 (104/211)	1.79	0.19
	>1 (diarrhea, dry cough, ≥ 38C) or ESR ≥ 20	<=1 of 3 sign/symptom + ESR <20	0.81 (26/32)	0.55 (115/211)	1.79	0.34
Melbye, 1992	Abnormal auscultatory signs	Normal auscultatory signs	0.40 (8/12)	0.88 (336/382)	3.32	0.68
O'Brien, 2006	Any abnormal VS	Normal VS	0.81 (282/350)	0.64 (225/350)	2.26	0.30
	Any abnormal VS or PE finding	Normal VS and no PE findings	0.95 (333/350)	0.56 (196/350)	2.16	0.09
Saldias, 2007	Any abnormal VS	Normal VS	0.86 (89/103)	0.44 (85/193)	1.54	0.31
	Abnormal VS or PE finding	Normal VS and no PE findings	0.98 (101/103)	0.19 (37/193)	1.21	0.10
Singal, 1989	Fever, cough, crackles	Absence of fever, cough, crackles	0.93 (37/40)	0.27 (57/215)	1.26	0.28
Steurer, 2011	CRP>50 or CRP 11-50 and dyspnea or daily fever	CRP < 10 or CRP 11-50, no dyspnea, and no daily fever	1.00 (127/127)	0.38 (190/494)	1.63	0.00

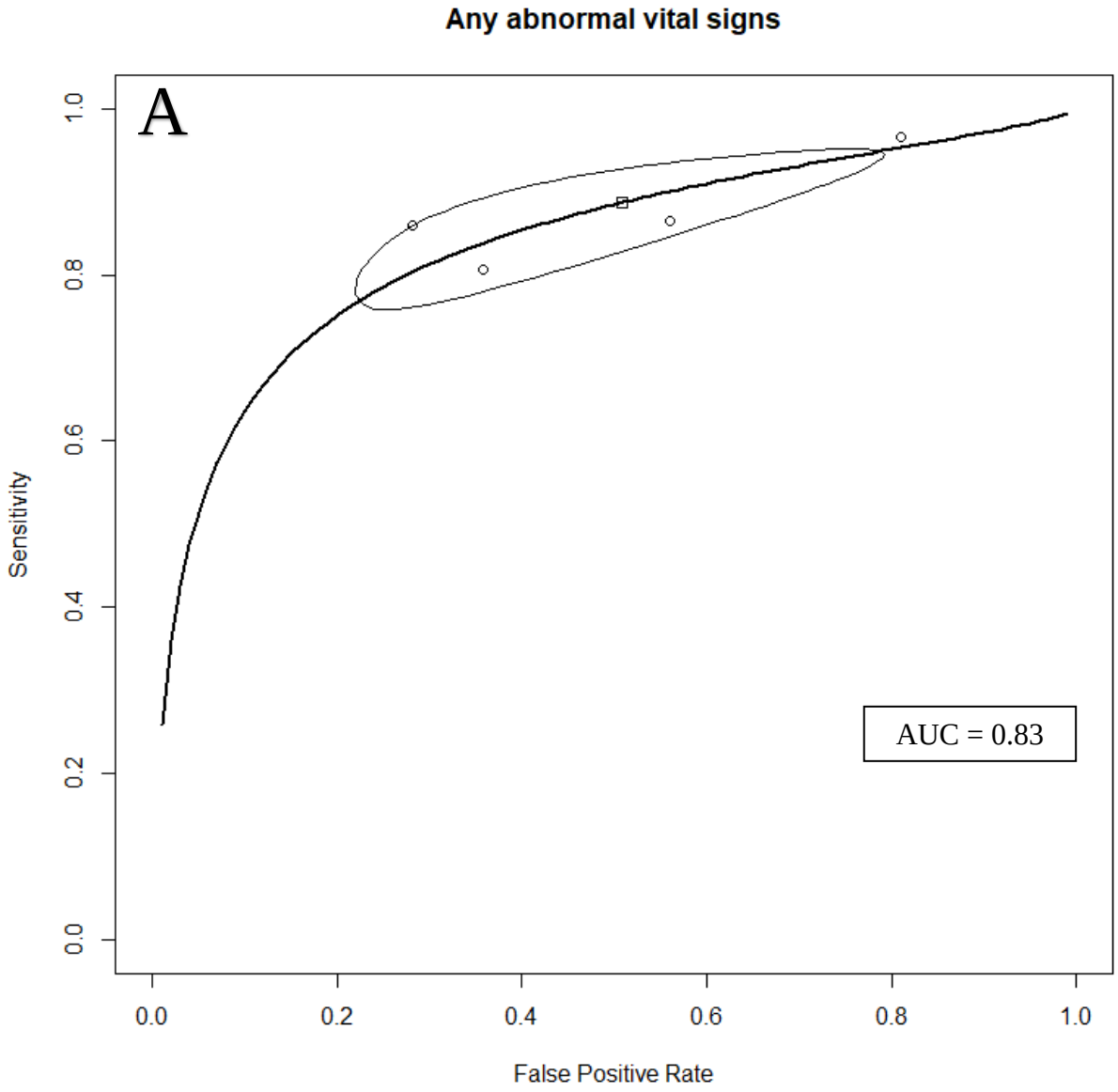
CDR: clinical decision rule; CAP; community-acquired pneumonia; VS: vital signs; PE: pulmonary exam; GP: general practitioner; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count; SATO2: oxygen saturation; Sensitivity and specificity calculated using ruling in criteria

Table 4.6 Summary estimates of meta-analysis for the diagnostic accuracy of clinical decision rules that diagnose (rule in) CAP

CDR used to diagnose CAP (rule in)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	AUROCC
Any abnormal vital signs	0.89 (0.79-0.94)	0.49 (0.25-0.73)	1.84 (1.25-3.03)	0.24 (0.17-0.34)	0.83
Any abnormal signs or any abnormal pulmonary exam finding	0.96 (0.92-0.98)	0.43 (0.20-0.69)	1.79 (1.22-3.01)	0.10 (0.07-0.13)	0.92

LR: likelihood ratio; AUROCC: area under the receiver operating characteristic curve; CDR: clinical decision rule; CAP: community-acquired pneumonia

Figure 4.2 Summary receiver operating characteristic curves for CDRs using any abnormal vital signs (A), and any abnormal vital sign and abnormal pulmonary exam (B) to diagnose (rule in) CAP



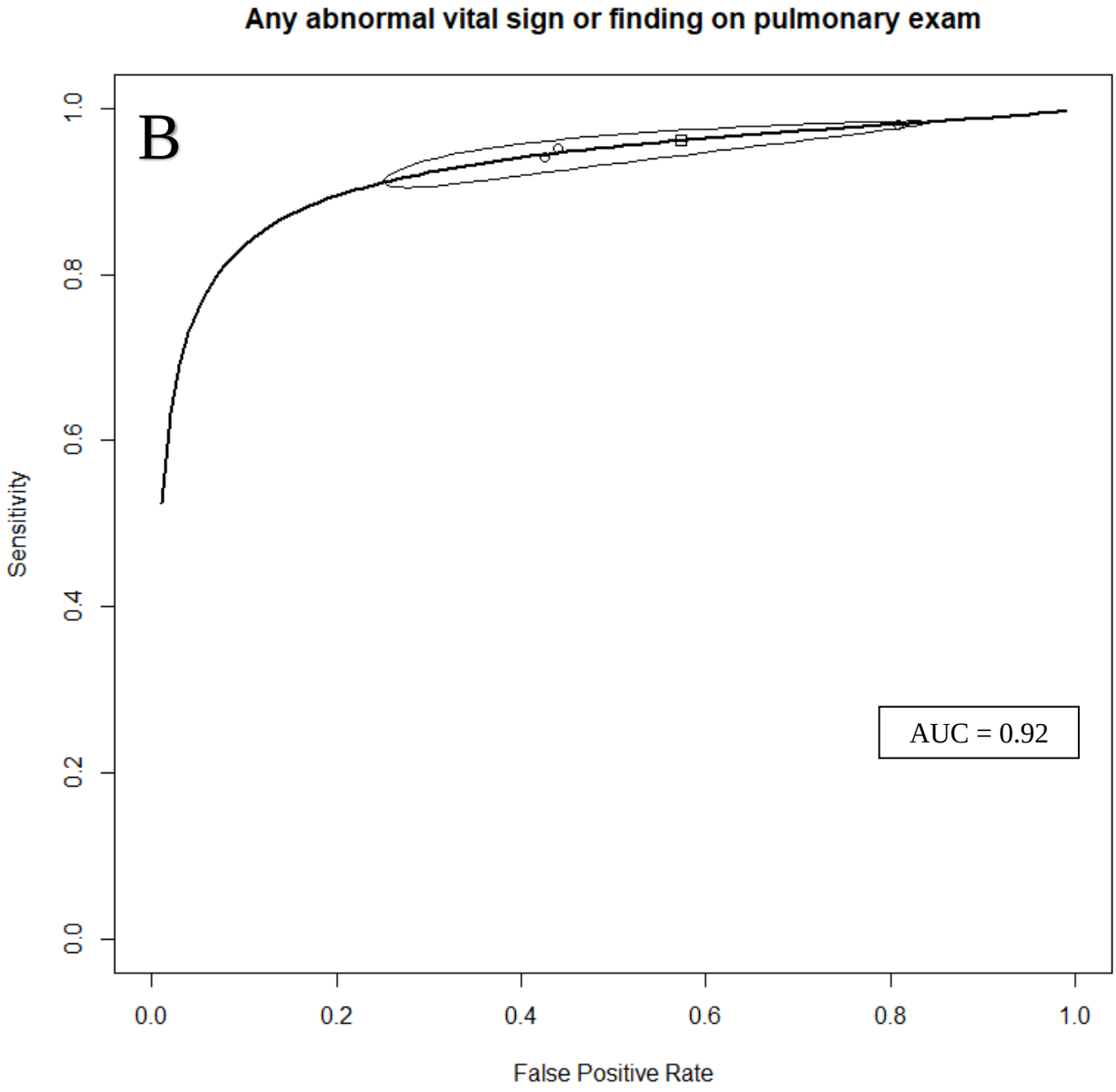

Any abnormal vital sign or finding on pulmonary exam
B
Sensitivity
False Positive Rate
0.0
0.2
0.4
0.6
0.8
1.0
AUC = 0.92

Table 4.7 Simulated primary care (4%) and emergency department (20%) prevalence rates for selected CDRs

Author(s), Year	Score or CDR	% CAP given baseline prevalence of: 4%	20%
Ebrahimzadeh, 2015 **Gennis, 1989** **O'Brien, 2006** **Saldias, 2007**	Normal vital signs	1.0%	5.7%
Ebrahimzadeh, 2015 **O'Brien, 2006** **Saldias, 2007**	Normal signs and no pulmonary finding	0.4%	2.4%
Diehr, 1984	*Low (-3 - 0)*¥	1.9%	10.5%
	Mod (1-2)¥	13.7%	48.8%
	High (3-6)¥	36.8%	77.7%
Heckerling, 1990	Derivation: Illinois		
	Low (0-1)¥	*0.8%*	*4.6%*
	Mod (2-3)¥	*4.3%*	*21.1%*
	High (4-5)¥	*26.5%*	*68.4%*
	Validation: Nebraska		
	Low (0-1)¥	0.7%	4.0%
	Mod (2-3)¥	4.0%	20.1%
	High (4-5)¥	37.9%	78.6%
	Validation: Virginia		
	Low (0-1)¥	1.2%	6.8%
	Mod (2-3)¥	3.4%	17.3%
	High (4-5)¥	18.3%	57.4%
	Pooled		
	Low (0-1)¥	0.8%	4.6%
	Mod (2-3)¥	4.1%	20.6%
	High (4-5)¥	25.8%	67.6%
van Vugt, 2013	CDR w/out CRP		
	<2.5% (low)	1.3%	7.4%
	2.5-20% (interm)	4.0%	20.2%
	>20% (high)	32.9%	74.7%
	CDR and CRP >30		
	0 (low)	0.6%	3.3%
	1-2 (interm)	3.1%	16.0%
	≥3 (high)	15.1%	51.6%

¥ Risk groups calculated post hoc and were not in original publication
CDR: clinical decision rule; CAP: community-acquired pneumonia

CHAPTER 5

ADULTS IN AN OUTPATIENT URGENT CARE SETTING WITH A COUGH OF AT LEAST SEVEN DAYS: EPIDEMIOLOGY, CLINICAL PRESENTATION, MANAGEMENT AND PROGNOSIS[2]

[2] Marchello, C., Ebell, M., McKay, B., Rivera, I., Harvill, E., Shen, Y., and Whalen, C., To be submitted to BMJ

Abstract

Background: Patient expectations for the duration of an acute cough (7 to 9 days) are significantly shorter than what has been observed for the actual duration (15 to 28 days). Clinical factors that predict a cough that will last longer than 14 days from onset of symptoms, as well as the clinical factors that predict whether a cough will persist longer than two weeks after presentation to an outpatient clinic, could help influence clinician management decisions in these patients.

Design: Mixed cross-sectional and prospective observational

Population: Adults 18 years or older presenting with a cough as their main or chief complaint for at least seven days but not longer than 56 days were included. Study performed at two urgent care clinics in the Athens, Georgia region from February to December 2017.

Methods: Patients were asked a series of questions regarding their demographics, signs, and symptoms, and a combination nasal and throat swab were taken for the detection of *Bordetella pertussis, Chlamydophila pneumoniae,* and *Mycoplasma pneumoniae* by polymerase chain reaction (PCR). Clinician examination and management decisions were recorded. A follow up diary and electronic survey were given to the patient to document the duration and severity of symptoms for up to 14 days post study entry.

Main outcome measures: Sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values, diagnostic odds ratios, and comparisons of mean values with Student's t-test.

Results: A total of 125 patients enrolled over the study period. The mean age was 41.8 years and the mean duration of cough from symptom onset to presentation to the clinic was 15.4 (95% CI: 13.6-17.2) days. Complete two week follow up was available for 91 patients (73%); in this subgroup, the total cough duration from symptom onset until it resolved was 22.4 (95% CI: 19.6-25.1) days. Almost 95% of the patients were prescribed an antibiotic, while 70% and 78% were prescribed a corticosteroid and cough suppressant, respectively. The absence of self-reported

wheezing by the patient was significantly associated with a decreased likelihood of cough duration more than 14 days from onset (LR- 0.54, 95% CI: 0.33-0.88). In addition, a normal chest exam by the clinician, when there was an absence of wheezing or crackles in the lungs (LR+ 2.11, 95% CI: 1.07-4.16 and LR- 0.49, 0.32-0.75), is significantly associated with a longer duration of a cough.

Conclusions: Both antibiotics and corticosteroids are heavily overused among patients with a cough of seven or more days duration in the urgent care. Chest sounds, as either reported by the patient or noted by a clinician on a chest exam, may be helpful in predicting cough persisting for at least 14 days after symptom onset. Additional prospective studies are recommended to validate our clinical signs and symptoms and additional education of clinicians in these settings on the guidelines for appropriate antibiotic, steroid and cough suppressant use for acute bronchitis is highly encouraged.

Introduction

Cough is a significant source of morbidity. In the United States (US), approximately 20 million visits to a physician in the ambulatory setting were due to the primary complaint of a cough in 2015.[1] Respiratory tract infections (RTI), a common cause of an acute cough, account for approximately 21% of all outpatient visits.[4] An acute cough has a mean duration of 18 days, while patient expectations for when an acute cough should resolve is significantly less, from seven to nine days.[2] As a result, patients may seek care if their cough is not resolving after a week, and may expect an antibiotic. In a large, multi-country, prospective study of outpatient adults with an acute cough, 45% of the patients expected, and 41% hoped for an antibiotic to be prescribed.[85] Furthermore, 61% of patients believe that antibiotics are effective for a cough of at least five days.[86]

For a large proportion of episodes of acute cough, an antibiotic is unnecessary due to viral etiology. However, they continued to be prescribed; outpatient practitioners prescribe antibiotics to 60-75% of patients with acute respiratory infections.[4,5] A patient's expectation influences this overprescribing. Those expecting an antibiotic are more often given one[7,8,85] and physicians report feeling pressured to prescribe an antibiotic when they believe one is not necessary.[87,88] This is leading to a growing public health problem, with the Centers for Disease Control and Prevention (CDC) estimating $20 billion in excess direct healthcare costs due to antibiotic resistance.[3]

Compounding the problem is the increase in number of patients seeking care from emergency departments (ED) and urgent care centers instead of a primary care practice in the last 20 years.[97] Determining appropriate clinical management is difficult in an urgent care setting due to the short duration of visits, lack of a continuity relationship in this setting, and the cost of diagnostic testing. Practitioners, therefore, are tasked with deciding which patients would benefit from interventions and which are likely to be self-limiting and resolve without intervention. What

type of care to provide to patients with an acute cough is typically based on clinical presentation, including signs, symptoms, recorded vital signs, and in some cases, point of care testing.

The clinical factors that predict whether a cough will last longer than 14 days from onset of symptoms are largely unknown, as well as the clinical factors that predict whether a cough will persist beyond two weeks after presentation to an outpatient clinic. There is a lack of recent prospective studies in the US, especially in the urgent care setting, on the clinical presentation, management decisions, and prognosis for patients that present with a cough of a week or longer.

We therefore set out to: 1.) Describe the epidemiology of adults presenting with an acute cough of at least seven days in an urgent care setting; 2.) Evaluate the diagnostic accuracy of clinical presentation for predicting a cough that is longer than 14 days from symptom onset; 3.) Evaluate the diagnostic accuracy of signs and symptoms for predicting whether a cough will persist for more than two weeks after presenting to a clinician; 4.) Present the diagnostic tests and prescriptions ordered by physicians for these patients; and 5.) Determine the prognosis based on the severity and duration of symptoms experienced after seeking care.

Methods

Design and population

This was a mixed cross-sectional and prospective observational study performed at two urgent care clinics in the Athens, Georgia region. The clinics serve a diverse population primarily from urban and suburban Clarke County but also five surrounding rural counties. Data was collected from February 8, 2017 to December 8, 2017. Consecutive patients fitting the inclusion criteria were recruited primarily from 9:00am to 6:00pm, Monday through Friday, totaling approximately 40 hours a week.

Inclusion and Exclusion Criteria

Eligible patients were adults at least 18 years of age presenting to the urgent care clinic with a cough of at least seven days but not longer than 56 days (8 weeks). Only patients where cough was their main or chief complaint were included. Patients with chronic lung conditions, such as moderate or severe asthma or chronic obstructive pulmonary disease (COPD), or who were immunodeficient, were excluded. They were also excluded if they were unable to speak and read English.

Clinic Data Collection

We first asked the patient a series of questions that included demographic information such as age, sex, race, and ethnicity (Appendix C). The patient then reported the duration of their cough, and whether they were experiencing sputum production, wheezing, post-tussive vomiting, dyspnea, paroxysmal cough, cyanosis, fever or felt warm, headaches, sneezing, runny nose, redness or watery eyes, chills or sweats, and trouble sleeping. We also asked how many days were missed from work or school due to the cough and social factors including education, income, and cigarette smoking.

Lastly, the patient provided consent for the investigator to log in and search for their record in the Georgia Immunization Registry (GRITS) to document if the patient received either the influenza vaccine, DTP (diphtheria-tetanus-pertussis), or Tdap (tetanus-diphtheria-acellular pertussis). The registry has several limitations. First, if the patient was not born in Georgia or moved to the state and had not received any vaccinations while a resident, there was no record. Secondly, the Georgia Department of Health has to authorize access, and as a result some facilities do not document in GRITS. We also asked if they could recall from memory if they received the Tdap in the last 10 years. Records found in GRITS were considered confirmed vaccination, while those based on recall were classified as probable.

Identification of bacteria

After administering the clinical survey, a separate nasal and throat swab were collected for the detection of *Bordetella pertussis, Chlamydophila pneumoniae,* and *Mycoplasma pneumoniae* by polymerase chain reaction (PCR). Testing was performed at a research laboratory in the Department of Infectious Diseases, College of Veterinary Medicine at the University of Georgia. Extracted DNA was amplified and run on a gel electrophoresis. Positive and negative controls were run alongside patient samples and bands matching the target base length on the gel electrophoresis were considered positive for the respective pathogen. Detailed information regarding kits, and procedures for extraction, amplification, and electrophoresis can be found in Chapter 3, Aim 2 methods.

Follow up

Each patient recruited was given a symptom diary to take home. Patients were asked to record their symptoms daily for up to 14 days or until their symptoms resolved (Appendix F). The diary included cough, sputum production, wheezing, trouble sleeping, dyspnea, vomited from coughing, and paroxysmal cough. We also asked the patient if they filled their prescription at any point before returning the diary and if they missed work or school that day. They rated the severity of each symptom (with the exception of vomiting and paroxysmal cough) using a 5-point Likert-scale: 0-absent, 1-slightly a problem, 2-moderately bad, 3-bad, 4-very bad. Vomiting and paroxysmal cough were asked as yes or no questions. The total possible score is 22 (5 symptoms times a score of 4 plus 1 point each answering yes) and the total number of possible symptoms is seven. Our score was developed from several validated surveys for respiratory infections.[113-117] Further information on the various scores and how our scale was selected is presented in Aim 2 Methods of Chapter 3.

To increase follow-up participation, patients were also sent an electronic survey on the seventh day after enrollment, and if they were still coughing on day 7, on the 14th day after

enrollment as well (Appendix E). The online survey asked the patient when they stopped cough, if they had sputum, wheezing, vomiting, paroxysmal cough, or trouble sleeping in the last two days, how many days of work or school were missed in the last week, and if they filled their prescription.

Analysis

For each sign and symptom, the sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), positive and negative likelihood ratios (LR+ and LR-, respectively), and diagnostic odds ratios (DOR) were calculated. These were calculated for two outcomes: predicting a total cough duration greater than 14 days from symptom onset, and predicting a cough persisting for at least 14 days after study entry. To be consistent with discussing the outcomes, when the positive likelihood ratio was less than 0.90, the accuracy was reported for the symptom being absent. A cough was resolved when the patient reported it was a 0 or 1 on the diary or indicated on the electronic survey the number of days since they stopped coughing.

Using the returned completed diaries, we compared the mean duration of symptoms for patients receiving steroids and cough suppressants. We classified symptoms as resolved in two ways: when total combined severity was less than five and when the number of symptoms was less than two. Mean duration was compared using Student's t-test, with a p-value less than 0.05 considered statistically significant. The cut off at less than five points for our score was based on several studies using a Bronchitis Severity Score (BSS) of five or greater as defining a patient with bronchitis.[143-145] A symptom was considered present if the patient scored the symptom from a 2 to 4 and resolved when the symptom was scored a 0 or 1.

A Kaplan-Meier curve was used to compare the duration of symptoms until they were resolved (using both severity and number of symptoms as described above) for patients given steroids, cough suppressants, and to compare different antibiotic classes, with Log-Rank p-

value less than 0.05 considered statistically significant. In addition, we also compared mean duration using Student's t-test. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

Comparing the use of antibiotics on each of our outcomes was originally planned as well. However, given the significant proportion of patients given an antibiotic, we were unable to perform these comparisons.

Ethics approval

The study was approved by the University of Georgia Institutional Review Board for Human Subjects Research. A letter of support and permission to recruit patients was received by the medical director of the urgent care centers.

Results

A total of 125 patients were enrolled during the recruitment period (Table 5.1). The mean age was 41.8 years, ranging from 18 to 88 years. Eighty-seven (69.6%) were female and 96 (76.8%) responded as White, non-Hispanic. Over 70% (93) were recruited in the first two months, between February and the end of March. The majority (83.2%) were diagnosed with acute bronchitis.

Eight-four patients had a record available in GRITS. Of those, 63 had the influenza vaccine at some point, but just 37 of them were current, receiving it within the current flu season. Forty patients (47.6%) had a confirmed completed DTP series (4 or 5 doses), while 39 (46.4%) had confirmed Tdap in the last 10 years. A little over half of the patients (67) were probable for having received the Tdap in the last 10 years and just under a third were unsure. One hundred patients (80%) were either probable or confirmed as having Tdap in the last 10 years.

Fifty-three (42.4%) patients reported that either before they were recruited or at some point during follow up that they missed at least one day of work or school because of their cough. The number of days missed ranged from one to seven days with a total of 146 combined days missed. From symptom onset until presentation to the clinic, nearly 90% of all patients said they had trouble sleeping at some point as a result of their cough.

Seventy-three percent (91) of the patients completed follow up. Baseline characteristics of those that completed follow up were not significantly different than those that were lost to follow up. Of the 91 to complete follow up, 72 patients reported they stopped coughing within the 14 days of follow up. The mean duration of cough from symptom onset until presenting to the clinic was 15.4 (95% CI: 13.6-17.2) days, with a range from 7 days to 56 days (Figure 5.1A). Eight-nine patients (71.2%) had a cough for less than 15 days when they were recruited. Among the 72 patients who reported that they stopped coughing during the follow up period, the mean duration from symptom onset to when their cough resolved was 22.4 (95% CI: 19.6-25.1) days (Figure 5.1B).

Predicting cough duration > 14 days from symptom onset

The diagnostic accuracy of self-reported symptoms and clinician recorded signs for predicting a total cough duration greater than 14 days from symptom onset is summarized in Table 5.2. Trouble sleeping was the most specific self-reported symptom (0.89; 95% CI: 0.82-0.95). The absence of self-reported wheezing, or any self-reported noises during their cough, were significantly associated with a decreased likelihood of cough duration more than 14 days from onset, with a LR- of 0.54 (95% CI: 0.33-0.88).

A normal chest exam, indicated by the absence of clinician recorded wheezing or crackles and absence of just crackles, was significantly associated with the duration of a cough (both LR+ and LR- were significantly different from 1.0). A respiratory rate of 20 or greater per

minute was associated with decreased likelihood (LR- 0.31, 95% CI: 0.14-0.71) of a cough greater than 14 days from onset.

Predicting cough duration > 14 days from presentation

When the patient reported post-tussive vomiting prior to study entry, it was a significant predictor of an increased likelihood that a cough will persist for 14 or more days from the time of study entry (LR+ 1.99, 95% CI: 1.12-3.54) (Table 5.3). Trouble sleeping was highly sensitive for this outcome as well (0.95, 95% CI: 0.85-1.00). No clinician recorded sign was significantly associated with a cough duration of 14 or more days after entering the study. All of the recorded vital signs (heart rate less than 100 beats per minute, respiratory rate less than 20 per minute, and temperature 37.7C or less) were sensitive for this outcome, above 0.84.

Diagnostic testing and treatment

Regarding diagnostic testing, 39/125 patients (31.2%) received a chest x-ray (CXR) and 36/125 (28.8%) had a rapid test for either influenza, strep, or mononucleosis (Table 5.4). Only two patients tested positive for one of the three bacterial pathogens by PCR, both with *M pneumoniae*. Almost all patients (94.4%) were prescribed an antibiotic. A macrolide (azithromycin or clarithromycin) was the most common antibiotic prescribed (55.1%), followed by a cephalosporin (23.7%) and penicillin (17.0%). Regarding other medications, 87 patients (69.6%) were prescribed a systemic corticosteroid, and 97 (77.6%) a cough suppressant.

Of those that returned at least the first diary, the mean total symptom severity on their first day of follow up was 12.0 and they had a mean of 4.3 symptoms and a median of 5 symptoms (Table 5.5). There was no significant difference for duration (measured using severity or number of symptoms) between patients receiving and not receiving any type of steroid or cough suppressant. A survival analysis using Kaplan Meier curves also found no significant

difference when comparing any steroid versus none, or cough suppressant versus none for all of the outcomes.

Discussion

There is potential diagnostic value of signs and symptoms for determining if a person is more or less likely to have a cough that is longer than 14 days from symptom onset. Trouble sleeping and paroxysmal coughing were fairly sensitive (0.89 and 0.80, respectively) for prolonged cough; their absence makes it less likely. Although no cases of *Bordetella pertussis* were documented in our population, these two factors are often associated with a pertussis infection.[146]

The absence of self-reported wheezing or any noises while they coughed was significantly associated with a decreased likelihood (LR- 0.54) of a cough longer than 14 days from onset. It also had the greatest diagnostic discrimination among the self-reported symptoms, with a DOR of 3.06. These noises experienced by the patient may be more upper respiratory, such as hoarseness or stridor, which are heard from the outside, usually while coughing. These are different than the wheezing or crackles that a clinician would hear on a chest exam, where they are listening with a stethoscope to the chest for noises inside the lung while breathing normally or taking deep breaths.

In fact, a normal chest exam (LR+ 2.11 and LR- 0.49) and the absence of crackles (LR+ 1.82 and LR- 0.30) on a chest exam by a clinician were both associated with duration of a cough that was longer than 14 days from onset. A meta-analysis on the clinical diagnosis for *Bordetella pertussis*, an infection often associated with prolonged coughing of more than two weeks, produced similar findings for the absence of wheezing.[146]

Patients that reported they had post-tussive vomiting prior to presentation to the clinic were more likely to not have their cough resolve within the next two weeks. Trouble sleeping

was sensitive in this scenario, which could be used to rule out the possibility of a cough continuing for more than two weeks after presentation if disturbed sleep is not reported.

Despite recommendations against the prescribing of antibiotics for uncomplicated acute bronchitis[89,147], we found they continue to be overprescribed. Limited analysis could be performed on if the antibiotics were able to reduce overall duration and severity due to all but two patients that completed the follow up diary receiving an antibiotic.

A recent, large, randomized clinical trial of oral prednisone found no significant difference in mean duration or severity for prednisone versus placebo in patients with uncomplicated acute lower respiratory infections and advises against the use of oral corticosteroids.[91] In our study, 72% received a systemic corticosteroid and over 78% a cough suppressant. There were no significant differences in any of the outcomes when comparing those that were prescribed a steroid or cough suppressant with those that were not.

Evaluation of patients with a cough of at least a week from onset to presentation should be focused on ruling out pneumonia, as community-acquired pneumonia (CAP) is the primary indication for an antibiotic and possibly a corticosteroid. Almost a third of our population received a CXR while only four were diagnosed with pneumonia. This is a significant proportion that received one unnecessarily.

From our results in Chapter 4, the combination of normal vital signs (temperature less than 37.7C, respiratory rate less than 20 per min, heart rate less than 100 per minute) plus normal pulmonary exam performs well at ruling out CAP. However, of the 58 patients in our population that fit that criteria, 14 received a CXR and none were diagnosed with CAP. Of the four diagnosed with pneumonia, all had a combination of at least two abnormal vital signs or abnormal chest sounds. A Cochrane Review recommends the use of corticosteroids for pneumonia, finding a reduction in morbidity in all patients with non-severe CAP.[148] One patient did not receive a steroid, while all received a macrolide, which is the recommended first-line antibiotic for otherwise healthy adults.[11]

Lastly, a systematic review estimated the duration of an acute cough to last between 15 and 28 days, with a mean duration of 18 days.[2] Our mean cough duration was slight longer, approximately 22 days. Our inclusion criteria of a cough for at least a week biases the duration to be longer, although our mean duration still falls within the range estimated by the review. Educating patients about the expected duration of cough may help mitigate demands for antibiotics, as may advice to not immediately fill the antibiotic.[149] Point of care testing using CRP has also been shown to reduce inappropriate antibiotic use for adults with acute cough.[150,151]

Additional prospective studies are recommended to validate our clinical signs and symptoms on the duration of a prolong cough longer than 14 days from onset. We encourage additional education of clinicians in the urgent care setting on the guidelines for appropriate antibiotic, steroid, and cough suppressant use for acute bronchitis.

Limitations

Due to a limitation of resources, investigators were not present during all operating hours of the clinic. Subsequently, some patients were likely missed during the enrollment period. However, we believe this did not have a significant impact on the patients that were eventually recruited. Investigators were present for the majority of the hours the clinic was open and we approached all patients meeting the inclusion criteria while an investigator was present resulting in more of a consecutive series than convenience sample.

Fewer diaries were returned than hoped but not more than expected given our resources. Anticipating this, we supplemented our follow up with the electronic surveys. Even though the diary is more robust in the type of data it provided, we met our overall follow up sample size goal with the combination of the two. Of those that completed follow up, 19 were still coughing. We could have benefited from a longer follow up period.

Because patients were recruited after they received care, selection bias may have occurred from the staff, where sometimes patients were not referred to an investigator.

However, this most likely did not impact our data because clinicians and assistants were staffed together randomly and on random days; we did not observe preferential selection of patients by the staff. In addition, although we did not document patients that declined, the acceptance rate was perceived to be above 80% among those that were asked to be part of the study.

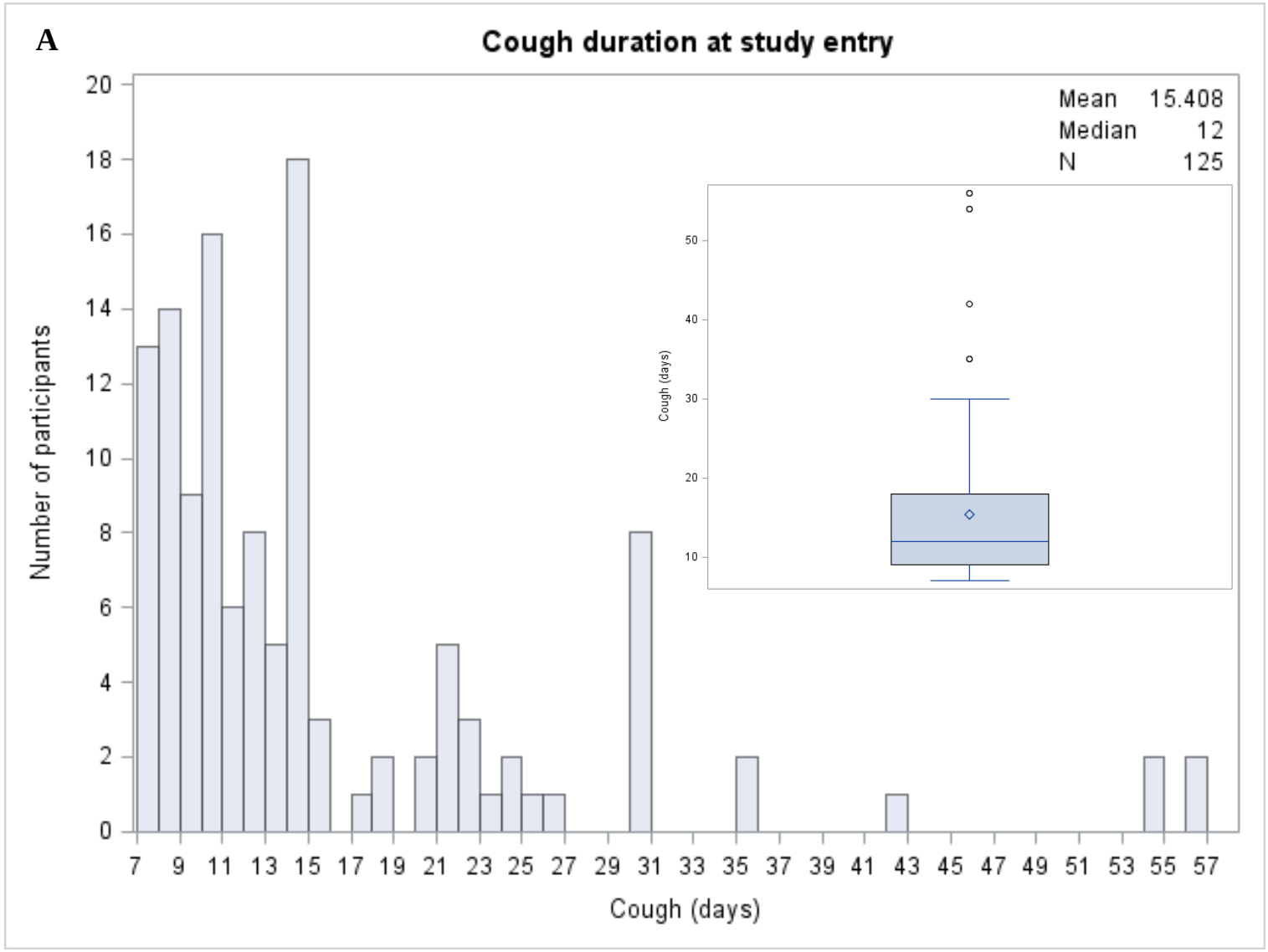
Chapter 5 Tables and Figures

Table 5.1: Patient characteristics and primary diagnosis

Characteristic		**n=125 (%)**	**Complete Follow up n=91 (%)**	**Lost to follow up n=34 (%)**	**p-value^**
Age, mean years (range)		41.8 (18-88)	42.1	40.9	0.710
Sex	Female	87 (69.6)	67 (73.6)	20 (58.8)	0.110
	Male	38 (30.4)	24 (26.4)	14 (41.2)	
Race	White, non-Hispanic	96 (76.8)	72 (79.1)	24 (70.6)	0.399
	White, Hispanic	2 (1.6)	2 (2.2)	0 (0.0)	
	African-American, non-Hispanic	19 (15.2)	12 (13.2)	7 (20.6)	
	Asian	2 (1.6)	2 (2.2)	0 (0.0)	
	Hispanic only (no race selected)	6 (4.8)	3 (3.3)	3 (8.8)	
Education	None	5 (4)	4 (4.4)	1 (2.9)	0.119
	High school graduate	29 (23.2)	16 (17.6)	13 (38.2)	
	Some college / Associate's degree	48 (38.4)	37 (40.7)	11 (32.4)	
	College graduate	43 (34.4)	34 (37.3)	9 (26.5)	
Income	<$25k	19 (15.2)	14 (15.4)	5 (14.7)	0.459
	$25-$49k	38 (30.4)	28 (30.8)	10(29.4)	
	$50-75k	29 (23.2)	18 (19.8)	11 (32.4)	
	>$75k	39 (31.2)	31 (34.0)	8 (23.5)	
Smoker	Never	75 (60)	58 (63.7)	17 (50.0)	0.241
	Former	22 (17.6)	16 (17.6)	6 (17.7)	
	Current	28 (22.4)	17 (18.7)	11 (32.3)	
Primary diagnosis	Acute bronchitis	104 (83.2)	75 (82.4)	29 (85.3)	0.684
	Sinusitis	11 (8.8)	9 (9.9)	2 (5.9)	
	Acute Upper Respiratory	2 (1.6)	2 (2.2)	0 (0.0)	
	Pneumonia	4 (3.2)	3 (3.3)	1 (2.9)	
	Other	4 (3.2)	2 (2.2)	2 (5.9)	

^ Comparison of completed versus lost to follow up. Mean age - Student's t-test; categorical - chi-square test and Fisher's Exact test.

Figure 5.1 Number of days coughing from symptom onset to study entry (A) and number of days coughing from onset until patient stopped (B).



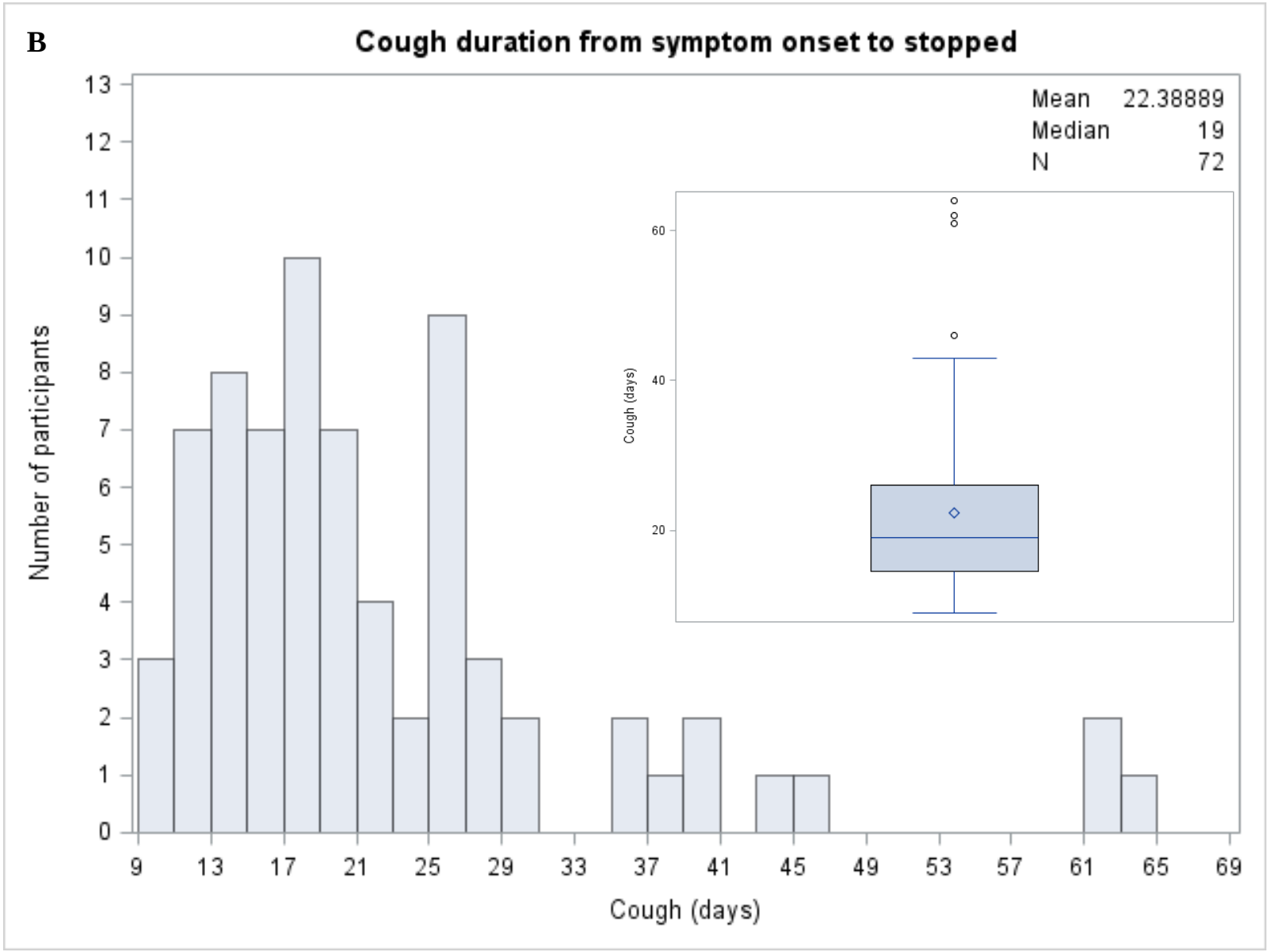

B
Cough duration from symptom onset to stopped
Mean 22.38889
Median 19
N 72
Number of participants
Cough (days)
Cough (days)

Table 5.2 Accuracy of self-reported symptoms and clinician recorded signs for predicting a total cough duration greater than 14 days from symptom onset

Self-reported Symptom	Cough >14 days (n=87)	Cough ≤14 days (n=19)	Sensitivity (95% CI)	Specificity (95%CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR
Absence of runny nose	22	2	0.25 (0.16-0.34)	0.89 (0.76-1.00)	0.92 (0.81-1.00)	0.21 (0.12-0.30)	2.40 (0.62-9.36)	0.84 (0.69-1.02)	2.88
Absence of headache	21	2	0.24 (015-0.33)	0.89 (0.76-1.00)	0.91 (0.80-1.00)	0.20 (0.12-0.29)	2.29 (0.59-8.96)	0.85 (0.70-1.03)	2.70
Wheezing or chest sounds	60	8	0.69 (0.59-0.79)	0.58 (0.36-0.80)	0.88 (0.81-0.96)	0.29 (0.15-0.43)	1.64 (0.95-2.83)	***0.54* (0.33-0.88)***	3.06
Post-tussive vomiting	30	4	0.34 (0.24-0.44)	0.79 (0.61-0.97)	0.88 (0.77-0.99)	0.21 (0.11-0.30)	1.64 (0.65-4.10)	0.83 (0.63-1.10)	1.97
Absence of fever	40	6	0.46 (0.36-0.56)	0.68 (0.48-0.89)	0.87 (0.77-0.97)	0.22 (0.11-0.32)	1.46 (0.72-2.93)	0.79 (0.55-1.13)	1.84
Sputum	63	11	0.72 (0.63-0.82)	0.42 (0.20-0.64)	0.85 (0.77-0.93)	0.25 (0.10-0.40)	1.25 (0.83-1.87)	0.66 (0.35-1.23)	1.91
Dyspnea	54	10	0.62 (0.52-0.72)	0.47 (0.25-0.70)	0.84 (0.75-0.93)	0.21 (0.09-0.34)	1.18 (0.75-1.86)	0.80 (0.46-1.38)	1.47
Paroxysmal cough	70	13	0.80 (0.38-0.59)	0.32 (0.11-0.52)	0.84 (0.77-0.92)	0.26 (0.08-0.44)	1.18 (0.85-1.62)	0.62 (0.28-1.36)	1.90
Chills or sweats	42	8	0.48 (0.38-0.59)	0.58 (0.36-0.80)	0.84 (0.74-0.94)	0.20 (0.09-0.30)	1.15 (0.65-2.03)	0.89 (0.58-1.38)	1.28
Red or watery eyes	52	10	0.60 (0.49-0.70)	0.47 (0.25-0.70)	0.84 (0.75-0.93)	0.20 (0.09-0.2)	1.14 (0.72-1.80)	0.85 (0.50-1.46)	1.34
Sneezing	57	11	0.66 (0.56-0.76)	0.42 (0.20-0.64)	0.84 (0.75-0.93)	0.21 (0.08-0.34)	1.13 (0.75-1.71)	0.82 (0.45-1.49)	1.38
Trouble sleeping	77	17	0.89 (0.82-0.95)	0.11 (0.00-0.24)	0.82 (0.74-0.90)	0.17 (0.00-0.38)	0.99 (0.83-1.17)	1.09 (0.26-4.58)	0.91

Clinician recorded	Cough >14 days (TP+FN)	Cough ≤14 days (FP+TN)	Sensitivity (95% CI)	Specificity (95%CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR
Chest exam									
normal (no wheezing or crackles)	58 (87)	6 (19)	0.67 (0.57-0.77)	0.68 (0.48-0.89)	0.91 (0.83-0.98)	0.31 (0.17-0.45)	***2.11* (1.07-4.16)***	***0.49* (0.32-0.75)***	4.33
absence of only crackles	58 (69)	6 (13)	0.84 (0.75-0.93)	0.54 (0.27-0.81)	0.91 (0.83-0.98)	0.39 (0.16-0.61)	***1.82* (1.00-3.31)***	***0.30* (0.14-0.62)***	6.15
absence of combined both wheezes and crackles	58 (60)	6 (9)	0.97 (0.92-1.01)	0.33 (0.03-0.64)	0.91 (0.83-0.98)	0.60 (0.17-1.00)	1.45 (0.91-2.31)	***0.10* (0.02-0.52)***	14.50
absence of only wheezes	58 (74)	6 (9)	0.78 (0.69-0.88)	0.33 (0.03-0.64)	0.91 (0.83-0.98)	0.16 (0.00-0.32)	1.18 (0.73-1.89)	0.65 (0.23-1.80)	1.81
Respiratory rate (<20/min)	77 (87)	12 (19)	0.89 (0.82-0.95)	0.37 (0.15-0.59)	0.87 (0.79-0.94)	0.41 (0.18-0.65)	1.40 (0.99-1.99)	***0.31* (0.14-0.71)***	4.49
Temperature (≤37.7C)	86 (87)	18 (19)	0.99 (0.97-1.00)	0.05 (0.00-0.15)	0.83 (0.75-0.90)	0.50 (0.00-1.00)	1.04 (0.94-1.16)	0.22 (0.01-3.34)	4.78
Heart rate (<100/min)	73 (87)	16 (19)	0.84 (0.76-0.92)	0.16 (0.00-0.32)	0.82 (0.74-0.90)	0.18 (0.00-0.36)	1.00 (0.80-1.24)	1.02 (0.32-3.20)	0.98

(sorted by LR+). PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; DOR: Diagnostic odds ratio; TP: true positive; FN: false negative; FP: false positive; TN: true negative

* Significant (95% confidence interval does not cross 1.0)

Table 5.3 Accuracy of self-reported symptoms to predict a cough persisting for at least 14 days after study entry

Self-reported Symptom	Continued after 14 days (n=19)	Stopped within 14 days (n=72)	Sensitivity (95% CI)	Specificity (95%CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR
Post-tussive vomiting	10	19	0.53 (0.30-0.75)	0.74 (0.63-0.84)	0.34 (0.17-0.52)	0.85 (0.77-0.94)	***1.99* (1.12-3.54)***	0.64 (0.39-1.05)	3.10
Sneezing	16	44	0.84 (0.68-1.00)	0.39 (0.28-0.50)	0.27 (0.15-0.38)	0.90 (0.80-1.00)	***1.38* (1.05-1.80)***	0.41 (0.14-1.19)	3.39
Dyspnea	14	40	0.74 (0.54-0.93)	0.44 (0.33-0.56)	0.26 (0.14-0.8)	0.86 (0.75-0.98)	1.33 (0.95-1.86)	0.59 (0.27-1.31)	2.24
Chills or sweats	11	32	0.58 (0.36-0.80)	0.56 (0.44-0.67)	0.26 (0.13-0.39)	0.83 (0.73-0.94)	1.30 (0.82-2.07)	0.76 (0.43-1.34)	1.72
Paroxysmal coughing	18	53	0.95 (0.85-1.00)	0.26 (0.16-0.37)	0.25 (0.15-0.35)	0.95 (0.85-1.00)	***1.29* (1.08-1.53)***	0.20 (0.03-1.40)	6.45
Sputum	15	48	0.79 (0.61-0.97)	0.33 (0.22-0.44)	0.24 (0.13-0.34)	0.86 (0.73-0.99)	1.18 (0.89-1.57)	0.63 (0.25-1.60)	1.88
Headache	16	54	0.84 (0.68-1.00)	0.25 (0.15-0.35)	0.23 (0.13-0.33)	0.86 (0.71-1.00)	1.12 (0.89-1.42)	0.63 (0.21-1.92)	1.78
Wheezes or chest sounds	13	44	0.68 (0.48-0.89)	0.39 (0.28-0.50)	0.23 (0.12-0.34)	0.82 (0.70-0.95)	1.12 (0.78-1.60)	0.81 (0.39-1.67)	1.38
Trouble sleeping	18	64	0.95 (0.85-1.00)	0.11 (0.04-0.18)	0.22 (0.13-0.31)	0.89 (0.68-1.00)	1.07 (0.93-1.22)	0.47 (0.06-3.56)	2.25
Runny nose	15	55	0.79 (0.61-0.97)	0.24 (0.14-0.33)	0.21 (0.12-0.31)	0.81 (0.64-0.98)	1.03 (0.79-1.35)	0.89 (0.34-2.34)	1.16
Red or watery eyes	11	44	0.58 (0.36-0.80)	0.39 (0.28-0.50)	0.20 (0.09-0.31)	0.78 (0.64-0.91)	0.95 (0.62-1.45)	1.08 (0.59-1.98)	0.88
Fever or felt warm	10	42	0.53 (0.30-0.75)	0.42 (0.30-0.53)	0.19 (0.09-0.30)	0.77 (0.64-0.90)	0.90 (0.56-1.44)	1.14 (0.66-1.96)	0.79

Clinician recorded	Cough >14 days (TP+FN)	Cough ≤14 days (TN+FP)	Sensitivity (95% CI)	Specificity (95%CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR
Chest exam									
normal (no wheezing or crackles)	12 (19)	40 (72)	0.63 (0.41-0.85)	0.44 (0.33-0.56)	0.23 (0.12-0.35)	0.82 (0.70-0.94)	1.14 (0.76-1.70)	0.83 (0.44-1.58)	1.37
absence of only crackles	12 (14)	40 (54)	0.86 (0.67-1.00)	0.26 (0.14-0.38)	0.23 (0.12-0.35)	0.88 (0.71-1.00)	1.16 (0.89-1.51)	0.55 (0.14-2.15)	2.10
absence of combined both wheezes and crackles	12 (17)	40 (53)	0.71 (0.49-0.92)	0.25 (0.13-0.36)	0.23 (0.12-0.35)	0.72 (0.52-0.93)	0.94 (0.66-1.32)	1.20 (0.50-2.88)	0.78
absence of only wheezes	12 (12)	40 (45)	1.00	0.11 (0.02-0.20)	0.23 (0.12-0.35)	1.00	***1.13* (1.01-1.25)***	0.00	X
Temperature (≤37.7C)	19 (19)	71 (72)	1.00	0.01 (0.00-0.04)	0.21 (0.13-0.30)	1.00	1.01 (0.99-1.04)	0.00	X
Respiratory rate (<20/min)	16 (19)	59 (72)	0.84 (0.68-1.00)	0.18 (0.09-0.27)	0.21 (0.12-0.31)	0.81 (0.62-1.00)	1.03 (0.82-1.28)	0.87 (0.28-2.76)	1.18
heart rate (<100/min)	16 (19)	59 (72)	0.84 (0.68-1.00)	0.18 (0.09-0.27)	0.21 (0.12-0.31)	0.81 (0.62-1.00)	1.03 (0.82-1.28)	0.87 (0.28-2.76)	1.18

(sorted by LR+). PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; DOR: Diagnostic odds ratio; TP: true positive; FN: false negative; FP: false positive; TN: true negative; X: denominator is zero;
* Significant (95% confidence interval does not cross 1.0)

Table 5.4 Bacterial pathogens detected and clinical management of adults presenting with a cough of at least 7 days

	n (%)
PCR results	
B. pertussis	0 (0.0%)
C. pneumoniae	0 (0.0%)
M. pneumoniae	2 (1.6%)
Diagnostic tests	
Chest x-ray	39 (31.2)
Rapid Flu	25 (20.0)
Rapid Strep	9 (7.2)
Mono spot	2 (1.6)
Antibiotics	118 (94.4)
Macrolide *	65 (55.1)
Cephalosporin#	28 (23.7)
Amoxicillin/Amoxi-clav	20 (17.0)
Levofloxacin	3 (6.8)
Clindamycin	1 (0.9)
Doxycycline	1 (0.9)
Other medications	
Steroid	90 (72.0)
Systemic+	87 (96.7)
Inhaled^	2 (0.2)
Nasal	1 (0.1)
Cough suppressant	97 (77.6)
Albuterol inhaler	16 (12.8)

* azithromycin or clarithromycin
# Cefdinir, Cefprozil, Ceftin, Cefzil, Omnicef
+ Medrol, Prednisone, Decadron, Depo medrol
^ Advair, Flovent

Table 5.5 Duration, severity and number of symptoms reported by patients when prescribed a steroid or cough suppressant

	Mean (95% CI)	p-value^
Severity and number of symptoms on first day of follow up		
Severity (maximum 22)	12 (10.8-13.3)	
Number of symptoms* (maximum 7)	4.3 (3.9-4.7)	
Duration until patient reported total severity < 5 points		
Steroid		
Yes	6.6 days (5.5-7.7)	p = 0.246
No	5.5 days (4.0-7.0)	
Cough suppressant		
Yes	6.4 days (5.4-7.4)	p = 0.528
No	5.7 days (3.9-7.5)	
Duration until patient reported number of symptoms < 2*		
Steroid		
Yes	6.1 days (4.9-7.3)	p = 0.463
No	5.3 days (3.9-6.7)	
Cough suppressant		
Yes	5.9 days (4.8-7.0)	p = 0.989
No	5.9 days (3.7-8.1)	

^ Student's t-test

* Definition: present = rating of 2 to 4; absent = rating of 0 or 1

CHAPTER 6

PROGNOSTIC FACTORS AND CLINICAL MANAGEMENT DECISIONS OF PATIENTS WITH 7 OR MORE DAYS OF COUGH IN AN URGENT CARE SETTING[3]

[3] Marchello, C., Ebell, M., McKay, B., Harvill, E., Shen, Y., and Whalen, C., To be submitted to BMJ

Abstract

Background: Healthcare utilization in the United States is changing and patients are seeking care from urgent care centers more often. Uncomplicated episodes of prolonged acute cough are usually viral and self-limited, but despite evidence and recommendations to the contrary are often treated with antibiotics, systemic corticosteroids, and cough suppressants.

Objective: Among patients with a prolonged cough, to determine factors associated with a cough duration longer than 14 days, as well as the association between these factors and management decisions.

Design: Mixed cross-sectional and prospective observational study.

Population: Adults 18 years or older presenting to two urgent care centers in the Athens, Georgia regional area with a cough as their main or chief complaint for at least seven days but not longer than 56 days were included. Patients were surveyed, recording their demographics, social factors, and signs and symptoms in addition to clinician exam and management decisions. A follow up diary and electronic survey were given to the patient to document the duration and severity of symptoms for up to 14 days post study entry.

Main outcome measures: Unadjusted and adjusted odds ratios using univariate and multivariate logistic regression. Sensitivity, specificity and area under the receiver operating characteristic curve (AUROCC) for fast and frugal decision trees (FFT).

Results: Of the 125 enrolled patients, 118 (94%) received an antibiotic, 39 (31%) a chest x-ray (CXR), 87 (70%) a systemic corticosteroid, and 97 (78%) a cough suppressant. Presence of wheezing and crackles by a clinician on a chest exam significantly decreased the likelihood that a cough would persist for longer than 14 days (aOR 0.03, 95% CI 0.00-0.27), while self-reported wheezing or noises when coughing significantly increased the likelihood (aOR 6.29, 95% CI 1.36-29.16). Clinician chest exam is the most influential factor in the FFT when determining cough duration (AUROCC 0.70). Dyspnea was significantly associated with ordering a CXR (aOR 3.01, 95% CI 1.21-7.49). It was also the first decision point in the FFT, followed by chills

and race (AUROCC 0.67). Clinician recorded crackles significantly decreased the likelihood of a systemic corticosteroid prescription (aOR 0.27, 95% 0.09-0.82). Increasing age was significantly associated with an increased likelihood of being prescribed a cough suppressant (aOR 1.04 per additional year of age, 95% CI 1.01-1.07).

Conclusions: Chest x-rays, antibiotics, systemic corticosteroids and cough suppressants are commonly used in patients with uncomplicated acute cough of at least 7 days duration in the urgent care setting. Chest sounds (both by the patient and clinician) are important predictors of a more prolonged course. Additional studies in the urgent care setting are warranted.

Introduction

Cough is a common reason for seeing an ambulatory physician in the United States; approximately 3% of all visits are due to a cough.[1] The most frequent diagnosis for a cough is upper respiratory tract infection, followed by acute bronchitis.[16,17] Only a small percentage of these episodes of cough, about 2%, are due to pneumonia.[17] A systematic review found an acute cough lasts a mean duration of 18 days after onset, with a range of 15 to 28 days. Patient expectations for duration is much less, between seven to nine days.[2] While most of these episodes are caused by a virus, antibiotics, systemic corticosteroids, and cough suppressants continue to be prescribed for uncomplicated cases, particularly in the outpatient setting.[5,152,153]

Between 1996 and 2010, antibiotic prescribing for acute non-pneumonia lower respiratory tract infections (LRTI) ("acute bronchitis") has increased[6] and up to 75% of patients seen by outpatient clinicians and diagnosed with acute LRTI are given an antibiotic.[4-6] This is despite guideline recommendations against it.[89,90] In addition, a multi-center, placebo-controlled, randomized clinical trial showed no reduction in symptom duration or severity for oral corticosteroids in uncomplicated acute respiratory infections,[91] and informal observations in practice suggest that corticosteroids are increasingly prescribed for acute LRTI in the absence of asthma or chronic obstructive pulmonary disease (COPD) exacerbation. There is also little evidence that indicates cough suppressants are beneficial.[95,96]

There has been a significant increase in the utilization of urgent care centers in the last decade, attributed to decreasing numbers of primary care physicians, perceived urgency of the need for care by patients, and demands for convenience.[97] Management of patients with a cough in these settings is difficult; the expectation from a patient is to have a quick visit and many expect to receive a prescription for treatment. This may influence clinicians, as does the lack of an ongoing continuity relationship and reliance on patient satisfaction as a quality measure and as a component of compensation.[7-9,85,154]

In the outpatient setting, treatment decisions are based mainly on the clinical presentation of the patient in the form of signs, symptoms, recorded vital signs, and rapid point of care tests for influenza and streptococcal pharyngitis. When community-acquired pneumonia (CAP) is suspected, a chest x-ray (CXR) may be ordered, but the frequency of ordering is unknown in urgent care centers. Most patients will have a cough lasting for 7 or more days from symptom onset, although patient expectations are that the cough will have resolved by then.[2] Thus, patients presenting with prolonged cough may have a greater expectation for a CXR or prescription.

As a result of the changing patterns in healthcare utilization, the clinical management of prolonged cough in the urgent care setting is understudied. The goal of this study was twofold: to determine the association between demographics, social factors, and clinical presentation with the likelihood of a cough lasting more than 14 days from onset, and the association between these same factors and treatment decisions.

Methods

Data collection

The data used in this chapter are the same that were gathered in the protocol for Aim 2. The data collection procedures have been previously described in detail in Chapter 3, Aim 2 methods, and were also summarized in the methods section of Chapter 5. Briefly, adults 18 years and older with a cough of 7 to 56 days were recruited at two urgent care centers around Athens, Georgia. Recruitment occurred from February 8, 2017 to December 8, 2017. Enrolled participants were surveyed with questions about their signs and symptoms (Appendix C). They were also given a diary to take home to record their symptom duration and severity for up to 14 days after their visit to the urgent care center (Appendix F). An electronic survey was sent via mobile text message or email at 7 and 14 days after enrollment to supplement the diary (Appendix E).

Analysis

A univariate and multivariate logistic regression analysis was performed to determine the associations of demographics, social factors, signs, and symptoms with the odds of two different outcomes. The first was a cough greater than 14 days from symptom onset, while the second was type of clinical management the patient received, specifically if the patient was given a CXR, systemic corticosteroid, or cough suppressant. Antibiotic prescriptions were originally included in the analysis plan but ultimately could not be analyzed because 95% of our population received one.

Item and collinearity analyses were performed first. The item analysis explored potential issues with variables, such as missing values or discrepancies in inputted data. Several variables were adjusted after item analysis. The continuous variables temperature, heart rate, and respiratory rate were dichotomized based on clinical relevance (>37.7C, ≥100/min, ≥20/min, respectively). Race was split into two categories, white non-Hispanic and "other" because of less than 7 observations each for white Hispanic, Asian, Hispanic only (race was not selected). Both Spearman and Pearson correlations were used and any variables with a correlation above 0.80 were explored further and determined if they should be adjusted for or removed.

Next, we used univariate logistic regression to determined unadjusted odds ratios (uOR) and 95% confidence intervals for each association. We also performed Student's t-test to compare mean values of continuous variables against the outcomes, for example the mean age for those that received a CXR versus those that did not. Variables in the univariate analysis had a statistically significant association if the p-value was less than 0.05 and were noted as a "trend" towards significance if the p-value was between 0.05 and 0.1.

Both manual forwards selection with the Akaike Information Criterion (AIC) statistic and automatic forward and backward selection using the chi-square statistic were used to build a multivariate logistic model. For the manual method, variables starting with the lowest AIC that had a p-value less than 0.20 were added. After each variable was added to the model, we

compared the difference in AIC between the two models. A difference greater than two indicates the addition of the variable improved the model, while a difference less than two means the two models are equally as good and the additional variable did not improve the model.[118,119,121] This process of adding variables and checking the AIC was repeated until the AIC difference was less than two, resulting in a final model.

The final model from the manual method was compared to the models produced from the automatic model selection and the most parsimonious model was chosen, producing adjusted odds ratios (aOR). Variables in the final multivariable model had a statistically significant association if the p-value was less than 0.05. Detailed information for the manual and automatic model building, including formula equations is presented in Chapter 3, Aim 3 methods. Logistic regression analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Lastly, we created a Fast and Frugal Tree (FFT) for each outcome. A FFT is a decision tree that is based on limited variables, usually less than four.[122,123] Due to the number of possible predictors in our data set (over 20), this approach is favorable because it restricts the model, preventing overfitting.[124] Each tree is limited to only two branches, simplifying the decision to a dichotomous yes or no question. This makes them useful in medical practice,[125,126] where time and information is limited. As a result, they are ideal for emergency and urgent care settings.

Each FFT was developed using all predictors, including demographics (e.g. age, sex), social factors (e.g. smoking), and signs and symptoms. Typically, the FFT would be created using cross-validation, where the data set is split into a training set (e.g. 70% of the data) and validated against a test set (the remaining 30%). However, given our relatively small sample size and number of outcomes, the entire data set was used to create each FFT.

To supplement the lack of cross-validation, we also produced random forests of FFTs. A random forest simulates many different decision trees to output which variables appear most

often across all simulations.[128,129] We simulated 100 random forests of FFTs using a 70/30 cross-validation split to determine the most important (i.e. most common) variables associated with each outcome. We presented the percentages of the top three variables and while exact percentages will fluctuate on each run, highly important variables will appear at the top on each consecutive run which provides an indication which variables are most influential. Decision trees and random forests were created with the FFTrees and FFForest package in R version 3.4.3, respectively.

Results

One hundred and twenty-five patients were enrolled during the recruitment period with a mean age of 41.8 years; 70% were female, 77% responded as White, non-Hispanic, and 83% were diagnosed with acute bronchitis. The mean duration of cough from symptom onset until presenting to the clinic was 15.4 days (95% CI: 13.6-17.2). Ninety-one patients completed follow up and of these, 72 patients (79%) reported they stopped coughing within the 14 days of follow up. Among the 72 patients who reported that they stopped coughing during the follow up period, the mean duration from symptom onset to when their cough resolved was 22.4 days (95% CI: 19.6-25.1). Antibiotics were given to 94% (118) of the patients. A CXR was given to 39 patients (31%), systemic corticosteroids were prescribed to 87 patients (70%), and 97 patients (78%) were given a cough suppressant.

Cough duration of greater than 14 days from symptom onset

Univariate Analysis

A total of 106 patients were included in the analysis for cough duration from symptom onset (Table 6.1). Nineteen were excluded due to them not returning at least one diary or survey. Patients that self-reported wheezing or noises when coughing were three times more likely to experience a cough that was longer than 14 days from symptom onset than those with it

absent (uOR 3.36, 95% CI 1.01-11.14). Patients with tachypnea (respiratory rate of 20 or greater per minute) had a decreased likelihood of a prolonged cough compared to those without tachypnea (uOR 0.16, 95% CI 0.04-0.55). Similarly, if a clinician heard wheezes or crackles (OR 0.24, 95% CI 0.07-0.86), or both (OR 0.04, 95% CI 0.01-0.35) on a chest exam, the patient was less likely to experience a cough for longer than 14 days after onset compared to patients with a normal chest exam.

Multivariate analysis

The same three variables from the univariate analysis were independently associated with a cough duration of more than 14 days from onset in the multivariate analysis (Table 6.3). Patients with self-reported wheezing were six times more likely to have a cough for longer than 14 days from onset than those without (aOR 6.29, 95% CI 1.36-29.16). Patients were very unlikely to experience a prolonged cough when wheezing and crackles were heard on the chest exam (aOR 0.03, 95% CI 0.00-0.27). Variables on a continuous scale (age, heart rate, respiratory rate, and temperature) were not associated with cough duration in either the univariate or multivariate models.

Ordering a chest x-ray

Univariate analysis

The unadjusted analysis for predicting CXR, corticosteroid, or a cough suppressant is summarized in Table 6.2. Patients with a cough for over three weeks were three times more likely than patients with a shorter cough to have received a CXR (uOR 3.03, 95% CI 1.20-7.67). However, when measured as a continuous variable, cough duration was not significantly associated with ordering a CXR. Self-reported difficulty breathing (uOR 2.64, 95% CI 1.12-6.22) and chills or sweats (uOR 2.37, 95% CI 1.08-5.17) were also significantly associated with an increased likelihood of receiving a CXR compared to when those symptoms were absent.

White, non-Hispanic were significantly more likely to receive a CXR than other races and patients of Hispanic origin (uOR 3.59, 95% CI 1.15-11.15).

Multivariate analysis

The adjusted analysis for predicting CXR, corticosteroid, or a cough suppressant is summarized in Table 6.3. The odds that a CXR was ordered were significantly higher for patients with dyspnea in the multivariate analysis (aOR 3.0, 95% CI 1.2 - 8.2). A cough duration greater than three weeks at the time of presentation (aOR 3.08, 95% CI 1.16-8.20) and race (aOR 3.58, 95% CI 1.10-11.66) were also independent predictors for receiving a CXR. While significantly associated with obtaining a CXR in the univariate analysis, chills or sweats were not included in the multivariate model.

Receiving a systemic corticosteroid or cough suppressant

Univariate analysis

Tachycardia was significantly associated with an increased likelihood of a systemic corticosteroid prescription (uOR 4.70, 95% CI 1.03-21.37). When clinicians heard wheezing on the chest exam (uOR 2.62, 95% CI 0.71-9.70) they were more likely to prescribe a systemic corticosteroid and when they heard crackles (uOR 0.35, 0.13-0.99), they were less likely. Overall, patients that received a cough suppressant were significantly older (mean 43.5 years) than those that did not receive one (mean 35.8 years, $p = 0.026$). For every additional year of age, patients were significantly more likely to receive a cough suppressant (uOR 1.03, 95% CI 1.00-1.06). Race was also significantly associated with receiving a cough suppressant (uOR 2.84, 95% CI 1.14-7.09)

Multivariate analysis

Patients with a heart rate 100 or greater were six times more likely than patients with a lower heart rate to receive a systemic corticosteroid in the multivariate analysis (aOR 6.10, 95% CI 1.22-30.64). Wheezing noted by the clinician was an independent predictor of an increased likelihood that a corticosteroid was prescribed (aOR 2.59, 0.69-9.73), while crackles on exam was an independent predictor of a lower likelihood that a steroid was prescribed (aOR 0.27, 0.09-0.82). Presence of a headache was associated with a decreased likelihood of cough suppressant prediction (aOR 0.16, 95% CI 0.03-0.75). Increasing age increased the likelihood that a cough suppressant was prescribed (aOR 1.04, 95% CI 1.01-1.07). When any chest sounds were heard by a clinician (wheezing, crackles, or both), patients were more likely to receive a cough suppressant (aOR 2.74, 95% CI 1.01-7.40).

Fast and Frugal Trees

The FFTs and forest FFTs summary statistics are presented in Table 6.4. For predicting a cough greater than 14 days from onset, the decision tree using clinician chest exam, patient reported wheezing, education, and respiratory rate was sensitive (0.93) and had an area under the receiving operating characteristic curve (AUROCC) of 0.70. A clinician's chest exam where any noises (wheezing, crackles, or both) were recorded was the most important variable, appearing in 93% of the 100 random FFT forests.

For the prediction of ordering a CXR, dyspnea, chills, and race (white, non-Hispanic versus all others) were included in the FFT. The tree was more specific (0.80) than sensitive (0.54), with an AUROCC of 0.67. Three variables appeared in over 50% of the random forests for CXR: dyspnea (74%), chills (66%), and cough (52%).

The FFT for the prescribing of a systemic corticosteroid was the worst performing of the four (AUROCC 0.63). Age was extremely important in predicting a cough suppressant prescription, appearing in 97% of the random forests.

Discussion

Chest sounds, when reported by the patient or heard in the lungs by a clinician during a chest exam, are the most important factors associated with the likelihood that a patient will cough more than 14 days. When experienced by a patient, likely as an audible upper respiratory noise (stridor), the likelihood of cough for more than 2 weeks was significantly increased (aOR 6.29, 95% CI 1.36-29.16). When the presence of wheezes and crackles in the lungs was noted on a clinician chest exam, it significantly decreased the patient's likelihood of prolonged cough (aOR 0.03, 95% CI 0.00-0.27). Similar results were also found in the FFT; the same two factors were at the top of the decision tree. Clinician chest exam was more influential than patient reported wheezing in the random forests, 93% compared to 67%.

Noises on a chest exam are an important indicator for the likelihood of a prolonged cough. After performing a chest exam, it also may be helpful for clinicians to ask the patient how they would describe their cough and whether they are experiencing any noises or chest sounds. In patients with acute cough ("acute bronchitis"), a clinician could use these two factors to judge that the patient is more likely to continuing coughing, and thus discuss with the patient the natural course and duration of a cough instead of prescribing an antibiotic or corticosteroid.

A duration of cough greater than three weeks (aOR 2.79) and self-reported dyspnea (aOR 2.96) were both significantly associated with an increased likelihood of receiving a CXR. The primary reasons to order a CXR are clinical suspicion of community-acquired pneumonia (CAP) or concern over malignancy. However, in our systematic review from Chapter 4, duration of cough was not used in any of the combination of signs and symptoms to rule out CAP, and only one combination incorporated dyspnea.[10] Instead, focus should be placed on normal vital signs and normal chest exam, which indicate a significantly lower risk of CAP. In our population, patients with a combination of normal vital signs and normal chest exam were only slightly less likely to receive a CXR (uOR 0.54, 95% CI 0.25-1.17).

There was a trend for patients 60 years and older to be more likely to receive a CXR (uOR 2.35, 95% CI 0.90-6.13). This is logical as the risk of both malignancy and CAP increases at this age. There was a trend for several other factors regarding their association with ordering a CXR: trouble sleeping (uOR 6.62, 95% CI 0.77-49.18), self-reported fever (uOR 2.21, 95% CI 0.98-5.01), self-reported wheezing (uOR 2.18, 95% CI 0.92-5.52), wheezing or crackles on a chest exam (uOR 1.97, 95% CI 0.91-4.26), and a fever over 37.7 C (uOR 7.08, 95% CI 0.71-70.40).

Wheezing on the clinician chest exam (aOR 2.59, 95% CI 0.69-9.73) and tachycardia (aOR 6.10, 95% 1.22-30.64) were both associated with an increased likelihood that a clinician would prescribe a systemic corticosteroid, although the wide confidence intervals limit the conclusions that can be made. In addition, the FFT predicted patients with wheezing noted by the clinician would get a systemic corticosteroid. Patients with crackles on the clinician exam were predicted to not receive a systemic corticosteroid according to the FFT and was the most important factor (52%) in the random forests. Corticosteroids are not recommended for patients with uncomplicated acute bronchitis,[91] and should be limited to patients with wheezing from acute exacerbations of asthma or COPD[155] and selected patients with CAP.[148] In fact, of the 97 patients that had no wheezing, 65 (67%) still received a systemic corticosteroid.

Interestingly, increasing age was associated with receiving a cough suppressant in this population. Patients that were given a cough suppressant were a mean of 7.7 years older than those that did not. In addition, white non-Hispanic were significantly more likely (uOR 2.84) compared to all others to receive a cough suppressant. It was also a very important predictor in the random forests we generated, present in 97% of trees, which was 30% higher than the next most common variable (headache). We were unable to find any literature addressing predictors of cough suppressant use in patients with prolonged cough. In general, there is insufficient evidence regarding the effectiveness of antitussive medication for the treatment of acute cough, and more generally of how ARTI are managed in the urgent care setting.[95,96]

This study provides evidence that despite continued efforts to reduce antibiotic use in uncomplicated lower respiratory infections, they continue to be overprescribed. Approximately 95% of our population received an antibiotic. In addition, 70% received a systemic corticosteroid, which appears to represent a new trend in treatment of ARTI in the ambulatory setting. The implications of this are important, as a recent, population-based cohort study found an increased risk of adverse events from short courses of oral corticosteroids, including sepsis, venous thromboembolism and fractures.[94]

The mean duration of cough (22 days) observed in this population of patients presenting with 7 or more days of cough was similar to that found in other studies.[82,84] Even though our inclusion criteria likely biased the duration to be longer, it was still within the range of 15 to 28 days found in a systematic review and well above the number of days patients expect their cough to resolve.[2]

Given the recent increase in patients using emergency and urgent care over a primary care practice,[97] we encourage additional observational prospective studies to determine if our findings are trends occurring at other urgent care settings. We also advocate for additional education to promote the appropriate use of CXRs, antibiotics, corticosteroids, and cough suppressants and discussion with patients about the expectations for duration of illness.

Chapter 6 Tables

Table 6.1 Unadjusted odds of having a cough duration greater than 14 days from onset (n=106)

Variable	uOR[a]	95% CI	p-value
Demographics and Social Factors			
Sex			
Female	1.00	Reference	
Male	0.53	(0.16-1.77)	0.299
Race			
Other+	1.00	Reference	
White, non-Hispanic	0.95	(0.28-3.22)	0.940
Ethnicity			
Non-Hispanic	1.00	Reference	
Hispanic	0.68	(0.07-6.34)	0.736
Income			
>$75k	1.00	Reference	
<$25k	0.46	(0.03-7.77)	0.595
$25k-$49k	0.12	(0.01-1.01)	0.068
$50k-$74k	0.14	(0.01-1.31)	0.175
Education			
College graduate	1.00	Reference	
No education	0.16	(0.01-2.29)	0.370
High school graduate	0.45	(0.06-3.45)	0.734
Some college	0.23	(0.05-1.16)	0.368
Current smoker			
Never	1.00	Reference	
Current	1.30	(0.27-6.49)	0.733
Self-reported signs and symptoms*			
Wheezing	*3.36*	***(1.01-11.14)***	***0.048^***
Sputum	2.21	(0.68-7.19)	0.188
Red or watery eyes	1.77	(0.55-5.67)	0.340
Paroxysmal cough	1.73	(0.48-6.23)	0.401
Post-tussive vomiting	1.67	(0.43-6.50)	0.462
Sneezing	1.63	(0.51-5.27)	0.411
Trouble sleeping	1.51	(0.29-7.81)	0.624
Chills or Sweats	1.50	(0.46-4.93)	0.504
Dyspnea	0.95	(0.29-3.12)	0.927
Runny nose	0.59	(0.12-2.85)	0.509
Felt warm or feverish	0.54	(0.16-1.88)	0.332

Headache	0.27	(0.03-2.19)	0.219
Clinician Recorded signs*			
Heart rate (≥100/min)	0.59	(0.14-2.42)	0.464
Chest sounds (any)	***0.24***	***(0.07-0.86)***	***0.027^***
Respiratory rate (≥20/min)	***0.16***	***(0.04-0.55)***	***0.004^***
Temperature (>37.7C)	0.13	(0.01-2.22)	0.159
Chest Exam			
Normal	1.00	Reference	
Wheezes	0.57	(0.10-3.36)	0.259
Crackles	0.23	(0.05-1.05)	0.748
Wheezes and crackles	*0.04*	***(0.01-0.35)***	***0.013^***
Continuous variables	**uOR[a]**	**95% CI**	**p-value**
Age, years	0.99	(0.96-1.02)	0.576
Heart rate per minute	1.01	0.98-1.05)	0.507
Respiratory rate per minute	0.89	(0.71-1.11)	0.293
Temperature, Celsius	0.64	(0.19-2.14)	0.471

a - unadjusted odds ratio: probability modeled had a cough greater than 14 days from onset; CI Confidence interval

* Reference value is not having sign or symptom

^ statistically significant p-value less than 0.05

+ White Hispanic, African-American, Asian, or Hispanic only (race not selected)

Table 6.2 Unadjusted odds of receiving a chest x-ray, or a prescription for a systemic corticosteroid or cough suppressant

	Chest X-ray			Systemic Corticosteroid			Cough Suppressant		
Variable	**uOR[a]**	**95% CI**	**p-value**	**uOR[a]**	**95% CI**	**p-value**	**uOR[a]**	**95% CI**	**p-value**
Demographics and Social Factors									
Sex									
Female	1.00	Reference		1.00	Reference		1.00	Reference	
Male	1.71	(0.77-3.82)	0.189	1.11	(0.48-2.55)	0.816	1.81	(0.67-4.89)	0.246
Age									
< 60 years old	1.00	Reference		1.00	Reference		1.00	Reference	
≥ 60 years old	2.35	(0.90-6.13)	0.080	1.11	(0.40-3.13)	0.842	3.17	(0.69-14.52)	0.138
Race									
Other+	1.00	Reference		1.00	Reference		1.00	Reference	
White, non-Hispanic	***3.59***	***(1.15-11.15)***	***0.027^***	0.84	(0.33-2.11)	0.707	***2.84***	***(1.14-7.09)***	***0.025^***
Ethnicity									
Non-Hispanic	1.00	Reference		1.00	Reference		1.00	Reference	
Hispanic	0.30	(0.04-2.50)	0.264	3.24	(0.38-27.27)	0.280	0.45	(0.10-2.03)	0.300
Income									
>$75k	1.00	Reference		1.00	Reference		1.00	Reference	
<$25k	1.04	(0.30-3.61)	0.586	1.40	(0.41-4.74)	0.679	0.38	(0.11-1.30)	0.114
$25k-$49k	1.18	(0.43-3.22)	0.763	1.23	(0.47-3.23)	0.895	0.97	(0.30-3.09)	0.392
$50k-$74k	2.36	(0.86-6.57)	0.076	1.11	(0.40-3.11)	0.872	0.69	(0.21-2.24)	0.941
Education									
College graduate	1.00	Reference		1.00	Reference		1.00	Reference	
No education	1.72	(0.26-11.62)	0.692	0.58	(0.09-3.92)	0.620	0.65	(0.06-6.84)	0.952
High school graduate	1.58	(0.58-4.31)	0.619	1.02	(0.36-2.91)	0.599	0.62	(0.18-2.16)	0.984
Some college	1.06	(0.43-2.65)	0.565	0.77	(0.32-1.90)	0.864	0.36	(0.12-1.03)	0.170

Current smoker									
Never or former	1.00	Reference		1.00	Reference		1.00	Reference	
Current	1.30	(0.54-3.16)	0.559	1.81	(0.67-4.89)	0.246	0.83	(0.31-2.21)	0.708
Self-reported signs and symptoms*									
Trouble sleeping	6.62	(0.77-49.18)	0.086	1.02	(0.29-3.54)	0.976	0.26	(0.03-2.11)	0.209
Cough >21 days	***3.03***	***(1.20-7.67)***	***0.019^***	0.62	(0.24-1.58)	0.316	1.46	(0.45-4.71)	0.526
Dyspnea	***2.64***	***1.12-6.22)***	***0.027^***	0.96	(0.43-2.10)	0.908	0.90	(0.38-2.16)	0.815
Chills or Sweats	***2.37***	***(1.08-5.17)***	***0.031^***	1.54	(0.72-3.33)	0.269	0.68	(0.29-1.58)	0.366
Felt warm or feverish	2.21	(0.98-5.01)	0.056	0.79	(0.36-1.73)	0.552	0.62	(0.26-1.51)	0.293
Wheezing or chest sounds	2.18	(0.92-5.52)	0.076	1.90	(0.86-4.17)	0.110	0.57	(0.22-1.46)	0.238
Paroxysmal cough	1.77	0.65-4.83)	0.260	0.76	(0.29-1.98)	0.569	0.54	(0.17-1.71)	0.291
Headache	1.48	(0.57-3.84)	0.423	0.71	(0.27-1.85)	0.482	***0.21***	***(0.05-0.95)***	***0.042^***
Sputum production	1.37	(0.57-3.29)	0.486	0.50	(0.20-1.28)	0.150	0.86	(0.33-2.27)	0.767
Runny nose	1.15	(0.47-2.79)	0.764	0.59	(0.23-1.53)	0.279	0.76	(0.29-2.16)	0.640
Post-tussive vomiting	1.09	(0.49-2.45)	0.830	1.23	(0.54-2.82)	0.629	1.23	(0.49-3.10)	0.659
Red or watery eyes	0.92	(0.43-1.98)	0.838	1.35	(0.63-2.90)	0.440	0.62	(0.26-1.47)	0.275
Sneezing	0.77	(0.35-1.68)	0.510	1.62	(0.74-3.53)	0.226	0.62	(0.25-1.55)	0.308
Clinician Recorded signs*									
Heart rate (≥100/min)	1.23	(0.45-3.37)	0.689	***4.70***	***(1.03-21.37)***	***0.046^***	0.84	(0.28-2.56)	0.761
Chest sounds (any)	1.97	(0.91-4.26)	0.086				2.11	(0.82-5.42)	0.123
Respiratory rate (≥20/min)	1.35	(0.49-3.74)	0.565	1.77	(0.55-5.74)	0.341	1.10	(0.33-3.62)	0.879
Temperature (>37.7C)	7.08	(0.71-70.40)	0.095	1.32	(0.13-13.13)	0.812	0.27	(0.04-2.04)	0.206
Chest Sounds									
Normal	1.00	Reference		1.00	Reference		1.00	Reference	
Wheezes	2.66	(1.02-6.97)	0.388	*2.62*	*(0.71-9.70)*	*0.014^*	1.33	(0.44-4.02)	0.508
Crackles	1.04	(0.33-3.24)	0.212	0.35	(0.13-0.99)	0.124	6.63	(0.83-52.81)	0.133

Wheezes and crackles	4.35	(0.68-27.94)	0.230	0.26	(0.04-1.68)	0.168	1.47	(0.16-13.95)	0.776
Continuous variables	**uOR[a]**	**95% CI**	**p-value**	**uOR[a]**	**95% CI**	**p-value**	**uOR[a]**	**95% CI**	**p-value**
Age, years	1.02	(0.99-1.04)	0.178	1.01	(0.98-1.03)	0.553	***1.03***	***(1.00-1.06)***	***0.029^***
Days coughing	1.03	(0.99-1.06)	0.160	0.99	(0.96-1.03)	0.575	1.01	(0.97-1.06)	0.609
Heart rate per minute	1.01	(0.99-1.04)	0.454	1.02	(0.99-1.05)	0.149	0.98	(0.95-1.00)	0.095
Respiratory rate per minute	1.08	(0.91-1.29)	0.370	0.99	(0.83-1.19)	0.967	0.98	(0.80-1.12)	0.815
Temperature, Celsius	1.64	(0.66-4.06)	0.287	1.14	(0.44-2.95)	0.782	0.51	(0.19-1.35)	0.174

a - unadjusted odds ratio: probability modeled patient received a chest x-ray, systemic corticosteroid or cough suppressant
* Reference value is not having sign or symptom; CI Confidence interval;
^ statistically significant p-value less than 0.05
+ White Hispanic, African-American, Asian, or Hispanic only

Table 6.3 Adjusted odds for a cough duration greater than 14 days from onset, or patient was given a chest x-ray, systemic corticosteroid, or cough suppressant

Variable	aOR[a]	95% CI	p-value
Coughing >14 days from onset			
Respiratory rate (≥20/min)*	0.20	(0.05-0.72)	0.014
Self-reported wheezes or noises while coughing	6.29	(1.36-29.16)	0.019
Clinician chest exam			
Normal	1.00	Reference	
Wheezes	0.18	(0.02-1.34)	0.797
Crackles	0.12	(0.03-0.50)	0.640
Wheezes and crackles	0.03	(0.00-0.27)	0.025
Chest x-ray ordered			
Dyspnea*	3.01	(1.21-7.49)	0.018
Cough >21 days*	3.08	(1.16-8.20)	0.024
Race			
Other+	1.00	Reference	
White, non-Hispanic	3.58	(1.10-11.66)	0.034
Prescribed a systemic corticosteroid			
Heart rate (≥100/min)*	6.10	(1.22-30.64)	0.028
Clinician chest exam			
Normal	1.00	Reference	
Wheezes	2.59	(0.69-9.73)	0.013
Crackles	0.27	(0.09-0.82)	0.051
Wheezes and crackles	0.31	(0.05-1.99)	0.273
Prescribed a cough suppressant			
Headache*	0.16	(0.03-0.75)	0.020
Age (continuous)	1.04	(1.01-1.07)	0.024
Clinician chest exam			
Normal	1.00	Reference	0.030
Wheezes, crackles or both	2.74	(1.01-7.40)	0.047

a - adjusted odds ratio: probability modeled patient had a cough greater than 14 days or was given a chest x-ray, systemic corticosteroid or cough suppressant
+ White Hispanic, African-American, Asian, or Hispanic only
* Reference value is not having sign or symptom; CI Confidence interval

Table 6.4 Summary statistics of Fast and Frugal Decision trees and Random FFT forests

	FFT Decision Tree^			100 Random FFT Forests	
Outcome	**Tree Sensitivity**	**Tree Specificity**	**AUC**	**Variable**	**Importance * (%)**
Cough >14 days from onset	0.93	0.47	.70	Clinician chest exam (any noises)	93%
	Tree Normal clinician chest exam ↓ Self-reported wheezing ↓ Some college or college graduate ↓ Respiratory rate <20/min			Self-reported wheezing	67%
				Education	60%
Chest x-ray	0.54	0.80	0.67	Self-reported Dyspnea	74%
	Tree Self-reported dyspnea ↓ Self-reported chills ↓ White, non-Hispanic			Self-reported chills	66%
				Cough duration	52%
Systemic corticosteroid	0.71	0.55	0.63	Clinician recorded crackles	52%
	Tree Crackles absent on Clinician chest exam ↓ Heart rate ≥ 20/min ↓ Clinician recorded wheezing ↓ Self-reported wheezing or noises			Self-reported wheezing	48%
				Heart rate ≥ 100/min	46%

Cough suppressant	0.66	0.71	0.69	Age	97%
	Tree Age > 49 years ↓ White, non-Hispanic ↓ Self-reported headache ↓ Some college or college graduate			Headache	63%
				White, non-Hispanic	58%

* Importance measured by % variable appeared in 100 random forests - displaying top 3
^ Variable presented in FFT predicted increased likelihood of outcome (e.g. normal clinician chest exam predicted increased likelihood of a cough for being longer than 14 days from onset)

CHAPTER 7

DISSERTATION CONCLUSIONS

The goal for this dissertation was to improve on the subject of adults with a prolonged acute cough longer than a week in the outpatient setting. In the literature review, we identified several key areas that had significant gaps that were addressed by this research. Briefly, three recently published studies have identified the duration of an acute cough between 15 and 22 days.[82-84] A systematic review concluded the mean duration is approximately 17 days.[2] In this same review, patients responded they expected their cough to resolve in seven to nine days.

Where patients are receiving their care is changing. In the United States, emergency departments and urgent care centers are becoming more popular. [97] In these settings, management decisions are difficult. Clinicians lack a continuous relationship with the patient and base treatment decisions mainly on the clinical presentation of the patient in the form of signs, symptoms, recorded vital signs, and rapid point of care tests. Decisions include when to order a chest x-ray (CXR) and when to treat with antibiotics, corticosteroids, and cough suppressants.

Two main reasons for ordering a CXR is suspected community-acquired pneumonia (CAP) or a malignancy. The literature review identified many clinical factors that are associated with CAP; four studies varied in the combinations used, in sample size, and in how long ago the study was conducted.[10,39-41] There was no study identified that summarized what combinations of signs and symptoms are best for low yield criteria to rule out CAP.

The literature also indicates that antibiotic prescribing is a common practice in the outpatient setting for acute lower respiratory infections.[4-6] This is also believed to be the case for corticosteroids and cough suppressants through discussion with other researchers and

professionals in healthcare. Studies describing the prevalence of the latter, especially in the urgent care setting, have not been published. There are guidelines that advise against the use of antibiotics in uncomplicated episodes of acute bronchitis,[89,90] and studies that suggest the prescribing of corticosteroids are not helpful in reducing duration or severity of symptoms[91,92] and actually pose significant harms.[94]

Understanding which clinical factors predict a cough that will last longer than 14 days from onset of symptoms and which clinical factors predict the management decisions of clinicians may help reduce the overprescribing of antibiotics, steroids, and cough suppressants for the subset of patients with an uncomplicated acute cough of at least a week.

In summary, we set out to: 1.) Systematically review the literature and present clinical decision rules (CDRs) that best rule out CAP; 2.) Evaluate the accuracy of signs and symptoms in adults with a cough longer than seven days, comparing adults that cough for less than 14 days to those cough for longer; 3.) Determine the prognosis of prolonged cough, by presenting the duration and severity of signs and symptoms, missed days of school or work and comparing patients that received a prescription; and 4.) Measure the associations of signs, symptoms and social factors on the odds of having prolonged cough and treatment decisions.

Summary of Results

In Chapter 4, we identified two CDRs that are possible low yield criteria for CAP. The absence of any abnormal vital signs (temperature, respiratory rate, and heart rate) identified patients as low risk for CAP and had a summary estimate of the negative likelihood ratio of 0.24, and a sensitivity of 0.89.

The combination of normal vital signs combined with a normal pulmonary exam had a summary estimate of the negative likelihood ratio of 0.10, with a high area under the receiver operating characteristic (ROC) curve of 0.92.

In Chapter 5, chest sounds, when reported by the patient or recorded by the clinician, are indicators for the duration of a cough. The absence of self-reported wheezing by the patient was significantly associated with a decreased likelihood of cough duration more than 14 days from onset (LR- 0.54). A normal chest exam by the clinician, when there was an absence of wheezing or crackles in the lungs (LR+ 2.11 and LR- 0.49), is significantly associated with a longer duration of a cough.

In addition, we found significant overprescribing. Almost 95% of the patients were prescribed an antibiotic, while 70% and 78% were prescribed a corticosteroid and cough suppressant, respectively. Thirty-nine patients were given a CXR while only four were diagnosed with CAP. The majority of patients were diagnosed with acute bronchitis (104 out of 125). The mean duration from symptom onset to when the cough resolved was 22.4 days.

In Chapter 6, chest sounds were again identified as being associated with a cough lasting longer than 14 days. Patients with self-reported wheezing were six times more likely to have a cough for longer than 14 days from onset than those without (aOR 6.29). Wheezing and crackles noted by the clinician indicated patients were very unlikely to experience a prolonged cough (aOR 0.03).

Several factors influence management decisions. Dyspnea, cough duration longer than three weeks, and race (white, non-Hispanic) were all associated with receiving a CXR (aOR 3.01, aOR 3.08, and aOR 3.58, respectively). The fast and frugal tree concluded these three factors (in the same order) increased the likelihood of a CXR (AUC 0.67).

Wheezing (by the clinician) was an independent predictor of an increased likelihood that a corticosteroid was prescribed (aOR 2.59). Crackles noted by the clinician on the chest exam was an independent predictor of a lower likelihood that a steroid was prescribed (aOR 0.27). Increasing age was significantly associated with increased likelihood of a prescribed cough suppressant in every analysis. In addition, presence of a headache (aOR 0.16) and any

abnormal chest sounds (aOR 2.74) were also associated with an increased likelihood of prescribing a cough suppressant.

Implications and Future Research

Our study has highlighted that chest x-rays, antibiotics, systemic corticosteroids, and cough suppressants are all frequently used in patients with prolonged cough. This is the one of the first studies to report the prevalence of these decisions, especially steroids and cough suppressants, in the urgent care setting. Since urgent care clinics are gaining popularity, it is unclear if the results we found are also occurring at other urgent care clinics in the United States. In addition, given the significant implications of overprescribing antibiotics, it is obvious that a better job needs to be done educating clinicians on appropriate management of patients with uncomplicated acute cough.

We also found potentially useful diagnostic criteria for predicting a cough will last longer than two weeks from onset and several factors that influence the likelihood of management decisions by clinicians. We encourage additional observational prospective studies to validate these findings.

REFERENCES

1. CDC. National Ambulatory Medical Care Survey: 2015 State and National Summary Tables 2015; https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf. Accessed November 8, 2017.

2. 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):5-13.

3. CDC. Antibiotc Resistance Threats in the United States 2013. 2013; https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf. Accessed November 9, 2017.

4. Lee GC, Reveles KR, Attridge RT, et al. Outpatient antibiotic prescribing in the United States: 2000 to 2010. *BMC medicine.* 2014;12:96.

5. Ebell MH, Radke T. Antibiotic use for viral acute respiratory tract infections remains common. *The American journal of managed care.* 2015;21(10):e567-575.

6. Barnett ML, Linder JA. Antibiotic prescribing for adults with acute bronchitis in the United States, 1996-2010. *Jama.* 2014;311(19):2020-2022.

7. Coenen S, Michiels B, Renard D, Denekens J, Van Royen P. Antibiotic prescribing for acute cough: the effect of perceived patient demand. *Br J Gen Pract.* 2006;56(524):183-190.

8. Sirota M, Round T, Samaranayaka S, Kostopoulou O. Expectations for antibiotics increase their prescribing: Causal evidence about localized impact. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 2017;36(4):402-409.

9. Welschen I, Kuyvenhoven M, Hoes A, Verheij T. Antibiotics for acute respiratory tract symptoms: patients' expectations, GPs' management and patient satisfaction. *Fam Pract.* 2004;21(3):234-237.

10. van Vugt SF, Broekhuizen BD, Lammens C, et al. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: diagnostic study. *BMJ.* 2013;346:f2450.

11. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44 Suppl 2:S27-72.

12. Gjelstad S, Lindbaek M. Prognosis of respiratory tract infections in primary care. *BMJ.* 2013;347:f7185.

13. Moore M, Little P, Rumsby K, et al. Predicting the duration of symptoms in lower respiratory tract infection. *Br J Gen Pract.* 2008;58(547):88-92.

14. Kwon NH, Oh MJ, Min TH, Lee BJ, Choi DC. Causes and clinical features of subacute cough. *Chest.* 2006;129(5):1142-1147.

15. Schappert SM. National Ambulatory Medical Care Survey: 1991 summary. *Vital and health statistics Series 13, Data from the National Health Survey.* 1994(116):1-110.

16. Soler JK, Okkes I, Oskam S, et al. The interpretation of the reasons for encounter 'cough' and 'sadness' in four international family medicine populations. *Informatics in primary care.* 2012;20(1):25-39.

17. Okkes IM, Oskam SK, Lamberts H. The probability of specific diagnoses for patients presenting with common symptoms to Dutch family physicians. *The Journal of family practice.* 2002;51(1):31-36.

18. Adams F, Society S. *The Genuine Works of Hippocrates.* Sydenham Society; 1849.

19. Harrison TR, Fauci AS. *Harrison's Manual of Medicine.* Vol 17th ed. New York: McGraw-Hill Professional; 2009.

20. Bennett JE, Dolin R, Blaser MJ. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 8th ed: Elsevier Health Sciences; 2014.

21. Omori R, Nakata Y, Tessmer HL, Suzuki S, Shibayama K. The determinant of periodicity in Mycoplasma pneumoniae incidence: an insight from mathematical modelling. *Sci Rep.* 2015;5:14473.

22. Nguipdop-Djomo P, Fine PEM, Halsby KD, Chalker VJ, Vynnycky E. Cyclic epidemics of Mycoplasma pneumoniae infections in England and Wales from 1975 to 2009: time-series analysis and mathematical modelling. *The Lancet.*382:S78.

23. Marchello C, Ebell M. The Prevalence of Atypical Pathogens in Patients with Cough and Community-Acquired Pneumonia: A Meta-Analysis. *Annals of Family Medicine.* 2016.

24. Beovic B, Bonac B, Kese D, et al. Aetiology and clinical presentation of mild community-acquired bacterial pneumonia. *Eur J Clin Microbiol Infect Dis.* 2003;22(10):584-591.

25. Shibli F, Chazan B, Nitzan O, et al. Etiology of community-acquired pneumonia in hospitalized patients in northern Israel. *Isr Med Assoc J.* 2010;12(8):477-482.

26. Zhan P, Suo LJ, Qian Q, et al. Chlamydia pneumoniae infection and lung cancer risk: a meta-analysis. *Eur J Cancer.* 2011;47(5):742-747.

27. Hahn DL, Schure A, Patel K, Childs T, Drizik E, Webley W. Chlamydia pneumoniae-specific IgE is prevalent in asthma and is associated with disease severity. *PLoS One.* 2012;7(4):e35945.

28. Johnston SL, Martin RJ. Chlamydophila pneumoniae and Mycoplasma pneumoniae: a role in asthma pathogenesis? *Am J Respir Crit Care Med.* 2005;172(9):1078-1089.

29. Phin N, Parry-Ford F, Harrison T, et al. Epidemiology and clinical management of Legionnaires' disease. *Lancet Infect Dis.* 2014;14(10):1011-1021.

30. Barboza T. Disneyland shuts down 2 cooling towers after Legionnaires' disease sickens park visitors. *Los Angeles Times.* November 11, 2017.

31. Beer KD, Gargano JW, Roberts VA, et al. Outbreaks Associated With Environmental and Undetermined Water Exposures - United States, 2011-2012. *MMWR Morbidity and mortality weekly report.* 2015;64(31):849-851.

32. CDC. Leading Causes of Death 1900-1998. *National Vital Statistics System.* 2009.

33. CDC. Deaths: Final Data for 2015. *National Vital Statistics Report* https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_06_tables.pdf. Accessed February 16, 2018.

34. Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med.* 2015;373(5):415-427.

35. CDC. National Hospital Discharge Survey. 2010; https://www.cdc.gov/nchs/data/nhds/3firstlisted/2010first3_numberage.pdf. Accessed November 10, 2017.

36. Pfuntner A, Wier LM, Stocks C. Most Frequent Conditions in U.S. Hospitals, 2011: Statistical Brief #162. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006.

37. Ebell M. AHRQ White Paper: Use of clinical decision rules for point-of-care decision support. *Med Decis Making.* 2010;30(6):712-721.

38. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K. The diagnosis of strep throat in adults in the emergency room. *Med Decis Making.* 1981;1(3):239-246.

39. Heckerling PS, Tape TG, Wigton RS, et al. Clinical prediction rule for pulmonary infiltrates. *Ann Intern Med.* 1990;113(9):664-670.

40. Diehr P, Wood RW, Bushyhead J, Krueger L, Wolcott B, Tompkins RK. Prediction of pneumonia in outpatients with acute cough--a statistical approach. *Journal of chronic diseases.* 1984;37(3):215-225.

41. Steurer J, Held U, Spaar A, et al. A decision aid to rule out pneumonia and reduce unnecessary prescriptions of antibiotics in primary care patients with cough and fever. *BMC medicine.* 2011;9:56.

42. Cherry JD. Historical review of pertussis and the classical vaccine. *Journal of Infectious Diseases.* 1996;174(Supplement 3):S259-S263.

43. Guiso N. Bordetella pertussis and pertussis vaccines. *Clin Infect Dis.* 2009;49(10):1565-1569.

44. Hamborsky J, Kroger A. *Epidemiology and prevention of vaccine-preventable diseases, E-Book: The Pink Book.* Public Health Foundation; 2015.

45. Bordet J, Gengou O. *Le microbe de la coqueluche.* 1906.

46. CDC. Notifiable disease surveillance and notifiable disease statistics--United States, June 1946 and June 1996. *MMWR Morbidity and mortality weekly report.* 1996;45(25):530.

47. NNDSS. Data Collection and Reporting. 2016; https://wwwn.cdc.gov/nndss/data-collection.html. Accessed October 28, 2016.

48. NNDSS. Pertussis Cases by Year (1922-2014). 2015; http://www.cdc.gov/pertussis/surv-reporting/cases-by-year.html. Accessed October 28, 2016.

49. Gambhir M, Clark TA, Cauchemez S, Tartof SY, Swerdlow DL, Ferguson NM. A change in vaccine efficacy and duration of protection explains recent rises in pertussis incidence in the United States. *PLoS Comput Biol.* 2015;11(4):e1004138.

50. Cherry JD. The epidemiology of pertussis: a comparison of the epidemiology of the disease pertussis with the epidemiology of Bordetella pertussis infection. *Pediatrics.* 2005;115(5):1422-1427.

51. Bureau UC. Population Estimates. 2016; https://www.census.gov/popest/index.html. Accessed October 28, 2016.

52. CDC. Pertussis--United States, 1997-2000. *MMWR Morbidity and mortality weekly report.* 2002;51(4):73-76.

53. CDC. Notice to readers: final 2012 reports of nationally notifiable infectious diseases. *MMWR Morbidity and mortality weekly report.* 2013;62(33):669.

54. CDC. 2014 Final Pertussis Surveillance Report. 2015; http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2014.pdf. Accessed October 28, 2016.

55. CDC. 2013 Final Pertussis Surveillance Report. 2014; http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2013.pdf. Accessed December 12, 2015.

56. Cherry JD. The science and fiction of the "resurgence" of pertussis. *Pediatrics.* 2003;112(2):405-406.

57. Cherry JD. The epidemiology of pertussis and pertussis immunization in the United Kingdom and the United States: a comparative study. *Current problems in pediatrics.* 1984;14(2):1-78.

58. Teepe J, Broekhuizen BD, Ieven M, et al. Prevalence, diagnosis, and disease course of pertussis in adults with acute cough: a prospective, observational study in primary care. *Br J Gen Pract.* 2015;65(639):e662-667.

59. Park S, Lee SH, Seo KH, et al. Epidemiological aspects of pertussis among adults and adolescents in a Korean outpatient setting: a multicenter, PCR-based study. *J Korean Med Sci.* 2014;29(9):1232-1239.

60. Philipson K, Goodyear-Smith F, Grant CC, Chong A, Turner N, Stewart J. When is acute persistent cough in school-age children and adults whooping cough? A prospective case series study. *Br J Gen Pract.* 2013;63(613):e573-579.

61. Riffelmannn M, et al. Pertussis incidence symptoms and costs. *Dtsch Med Wochenschr.* 2006;50(131):2829-2834.

62. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. *N Engl J Med.* 2012;367(11):1012-1019.

63. Strebel P, Nordin J, Edwards K, et al. Population-based incidence of pertussis among adolescents and adults, Minnesota, 1995-1996. *J Infect Dis.* 2001;183(9):1353-1359.

64. Gilberg S, Njamkepo E, Du Chatelet IP, et al. Evidence of Bordetella pertussis infection in adults presenting with persistent cough in a french area with very high whole-cell vaccine coverage. *J Infect Dis.* 2002;186(3):415-418.

65. Cherry JD, Seaton BL. Patterns of Bordetella parapertussis respiratory illnesses: 2008-2010. *Clin Infect Dis.* 2012;54(4):534-537.

66. Bhatti MM, Rucinski SL, Schwab JJ, Cole NC, Gebrehiwot SA, Patel R. Eight-Year Review of Bordetella pertussis Testing Reveals Seasonal Pattern in the United States. *J Pediatric Infect Dis Soc.* 2015.

67. De Greeff SC, Dekkers AL, Teunis P, Rahamat-Langendoen JC, Mooi FR, De Melker HE. Seasonal patterns in time series of pertussis. *Epidemiology and infection.* 2009;137(10):1388-1395.

68. Tanaka M, Vitek CR, Pascual FB, Bisgard KM, Tate JE, Murphy TV. Trends in pertussis among infants in the United States, 1980-1999. *Jama.* 2003;290(22):2968-2975.

69. Koepke R, Eickhoff JC, Ayele RA, et al. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. *J Infect Dis.* 2014;210(6):942-953.

70. Misegades LK, Winter K, Harriman K, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. *Jama.* 2012;308(20):2126-2132.

71. Tartof SY, Lewis M, Kenyon C, et al. Waning immunity to pertussis following 5 doses of DTaP. *Pediatrics.* 2013;131(4):e1047-1052.

72. Roush SW, Murphy TV. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *Jama.* 2007;298(18):2155-2163.

73. Bisgard KM, Pascual FB, Ehresmann KR, et al. Infant Pertussis. *The Pediatric Infectious Disease Journal.* 2004;23(11):985-989.

74. Wendelboe AM, Njamkepo E, Bourillon A, et al. Transmission of Bordetella pertussis to young infants. *Pediatr Infect Dis J.* 2007;26(4):293-299.

75. Organization WH. WHO meeting on case definition of pertussis, Geneva, 10-11 January 1991. 1991.

76. Organization WH. Monitoring team of the Department of Vaccines and Biologicals. WHO-recommended standards for surveillance of selected vaccine-preventable diseases. *World Health Organization.* 2003.

77. CDC. Pertussis / Whooping cough (Bordetella pertussis) 2014 Case Definition. 2014; https://wwwn.cdc.gov/nndss/conditions/pertussis/case-definition/2014/. Accessed October 28, 2016.

78. Ebell M, Marchello C, Callahan M. A Systematic Review of the Clinical Diagnosis of Pertussis Infection. *Publication in Review.* Submitted August 25, 2016.

79. Miyashita N, Akaike H, Teranishi H, et al. Diagnostic value of symptoms and laboratory data for pertussis in adolescent and adult patients. *BMC Infect Dis.* 2013;13:129.

80. Fine AM, Reis BY, Nigrovic LE, et al. Use of population health data to refine diagnostic decision-making for pertussis. *J Am Med Inform Assoc.* 2010;17(1):85-90.

81. Lee GM, Lett S, Schauer S, et al. Societal costs and morbidity of pertussis in adolescents and adults. *Clin Infect Dis.* 2004;39(11):1572-1580.

82. Butler CC, Hood K, Kelly MJ, et al. Treatment of acute cough/lower respiratory tract infection by antibiotic class and associated outcomes: a 13 European country observational study in primary care. *J Antimicrob Chemother.* 2010;65(11):2472-2478.

83. Nduba VN, Mwachari CW, Magaret AS, et al. Placebo found equivalent to amoxicillin for treatment of acute bronchitis in Nairobi, Kenya: a triple blind, randomised, equivalence trial. *Thorax.* 2008;63(11):999-1005.

84. 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.

85. Coenen S, Francis N, Kelly M, et al. Are patient views about antibiotics related to clinician perceptions, management and outcome? A multi-country study in outpatients with acute cough. *PLoS One.* 2013;8(10):e76691.

86. Mainous AG, 3rd, Zoorob RJ, Oler MJ, Haynes DM. Patient knowledge of upper respiratory infections: implications for antibiotic expectations and unnecessary utilization. *The Journal of family practice.* 1997;45(1):75-83.

87. 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).

88. Francois Watkins LK, Sanchez GV, Albert AP, Roberts RM, Hicks LA. Knowledge and Attitudes Regarding Antibiotic Use Among Adult Consumers, Adult Hispanic Consumers, and Health Care Providers--United States, 2012-2013. *MMWR Morbidity and mortality weekly report.* 2015;64(28):767-770.

89. Centre for Clinical Practice at N. National Institute for Health and Clinical Excellence: Guidance. *Respiratory Tract Infections - Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care*. London: National Institute for Health and Clinical Excellence; 2008.

90. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest.* 2006;129(1 Suppl):1s-23s.

91. Hay AD, Little P, Harnden A, et al. Effect of Oral Prednisolone on Symptom Duration and Severity in Nonasthmatic Adults With Acute Lower Respiratory Tract Infection: A Randomized Clinical Trial. *Jama.* 2017;318(8):721-730.

92. Hay AD, Downing HE, Brookes ST, et al. Are oral steroids effective in treating the symptoms of acute lower respiratory tract infection in non-asthmatic adults? The Oral Steroids for Acute Cough (OSAC) placebo-controlled randomised trial. *Thorax.* 2015;70(Suppl 3):A50.

93. El-Gohary M, Hay AD, Coventry P, Moore M, Stuart B, Little P. Corticosteroids for acute and subacute cough following respiratory tract infection: a systematic review. *Fam Pract.* 2013;30(5):492-500.

94. Waljee AK, Rogers MA, 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.

95. Holzinger F, Beck S, Dini L, Stoter C, Heintze C. The diagnosis and treatment of acute cough in adults. *Deutsches Arzteblatt international.* 2014;111(20):356-363.

96. Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *The Cochrane database of systematic reviews.* 2004(4):Cd001831.

97. Coster JE, Turner JK, Bradbury D, Cantrell A. Why Do People Choose Emergency and Urgent Care Services? A Rapid Review Utilizing a Systematic Literature Search and Narrative Synthesis. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine.* 2017;24(9):1137-1149.

98. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339.

99. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* 2005;58(10):982-990.

100. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011;155(8):529-536.

101. Health GDoP. Online Analytical Statistical Information System (OASIS). 2016; https://oasis.state.ga.us/. Accessed September 8, 2016.

102. Bureau USC. Georgia QuickFacts. 2016; http://www.census.gov/quickfacts/table/PST045215/13. Accessed August 8, 2016.

103. Walt-DeNavas C. Income, Poverty, and Health Insurance Coverage in the United States: 2010. In: Commerce USDo, ed2011:6.

104. Daniel W. *Biostatistics: A Foundation for Analysis in the Health Sciences.* 9th ed: John Wiley & Sons, Inc; 2009.

105. Krejcie RV, Morgan DW. Determining sample size for research activities. *Educ psychol meas.* 1970.

106. Lambert SB, Whiley DM, O'Neill NT, et al. Comparing nose-throat swabs and nasopharyngeal aspirates collected from children with symptoms for respiratory virus identification using real-time polymerase chain reaction. *Pediatrics.* 2008;122(3):e615-620.

107. van den Bergh MR, Bogaert D, Dun L, et al. Alternative sampling methods for detecting bacterial pathogens in children with upper respiratory tract infections. *J Clin Microbiol.* 2012;50(12):4134-4137.

108. Dawood FS, Jara J, Estripeaut D, et al. What Is the Added Benefit of Oropharyngeal Swabs Compared to Nasal Swabs Alone for Respiratory Virus Detection in Hospitalized Children Aged <10 Years? *J Infect Dis.* 2015;212(10):1600-1603.

109. Esposito S, Zampiero A, Terranova L, et al. Comparison of posterior pharyngeal wall and nasopharyngeal swabbing as a means of detecting the carriage of Neisseria meningitidis in adolescents. *Eur J Clin Microbiol Infect Dis.* 2013;32(9):1129-1133.

110. Irving SA, Vandermause MF, Shay DK, Belongia EA. Comparison of nasal and nasopharyngeal swabs for influenza detection in adults. *Clin Med Res.* 2012;10(4):215-218.

111. de la Tabla VO, Masia M, Antequera P, et al. Comparison of combined nose-throat swabs with nasopharyngeal aspirates for detection of pandemic influenza A/H1N1 2009 virus by real-time reverse transcriptase PCR. *J Clin Microbiol.* 2010;48(10):3492-3495.

112. Holberg-Petersen M, Jenum PA, Mannsaker T, Melby KK. Comparison of PCR with culture applied on nasopharyngeal and throat swab specimens for the detection of Bordetella pertussis. *Scand J Infect Dis.* 2011;43(3):221-224.

113. Lehrl S. The BSS - A Valid Clinical Instrument to Measure the Severity of Acute Bronchitis. *Journal of Lung, Pulmonary & Respiratory Research.* 2014;1(3).

114. Barrett B, Brown RL, Mundt MP, et al. Validation of a short form Wisconsin Upper Respiratory Symptom Survey (WURSS-21). *Health Qual Life Outcomes.* 2009;7:76.

115. Watson L, Little P, Moore M, Warner G, Williamson I. Validation study of a diary for use in acute lower respiratory tract infection. *Fam Pract.* 2001;18(5):553-554.

116. Redmond NM, Davies R, Christensen H, et al. The TARGET cohort study protocol: a prospective primary care cohort study to derive and validate a clinical prediction rule to improve the targeting of antibiotics in children with respiratory tract illnesses. *BMC Health Serv Res.* 2013;13:322.

117. Butler CC. Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe: GRACE. *Workpackage 8.*2006.

118. Burnham KP, Anderson DR. Multimodel inference understanding AIC and BIC in model selection. *Sociological methods & research.* 2004;33(2):261-304.

119. Symonds MRE, Moussalli A. A brief guide to model selection, multimodel inference and model averaging in behavioural ecology using Akaike's information criterion. *Behavioral Ecology and Sociobiology.* 2011;65(1):13-21.

120. Richards SA. Testing ecological theory using the information-theoretic approach: examples and cautionary results. *Ecology.* 2005;86(10):2805-2814.

121. Burnham K. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach.* Second Edition ed: Springer-Verlag New York; 2002.

122. Martignon L, Vitouch O, Takezawa M, Forster MR. Naive and Yet Enlightened: From Natural Frequencies to Fast and Frugal Decision Trees. *Thinking: Psychological Perspectives on Reasoning, Judgment and Decision Making*: John Wiley & Sons, Ltd; 2005:189-211.

123. Phillips ND, Neth H, Woike JK, Gaissmaier W. FFTrees: A toolbox to create, visualize, and evaluate fast-and-frugal decision trees. *Judgment and Decision Making.* 2017;12(4):344.

124. Gigerenzer G, Brighton H. Homo Heuristicus: Why Biased Minds Make Better Inferences. *Topics in Cognitive Science.* 2009;1(1):107-143.

125. Jenny MA, Pachur T, Lloyd Williams S, Becker E, Margraf J. Simple rules for detecting depression. *Journal of Applied Research in Memory and Cognition.* 2013;2(3):149-157.

126. Green L, Mehr DR. What alters physicians' decisions to admit to the coronary care unit? *The Journal of family practice.* 1997;45(3):219-226.

127. Therneau TM, Atkinson EJ. An introduction to recursive partitioning using the RPART routines. Technical Report 61.; 1997.

128. Hastie T. *The Elements of Stastical Learning: Data Mining, Inference, and Prediction.* Second Edition ed. Berlin: Springer; 2009.

129. Breiman L. Random forests. *Machine learning.* 2001;45(1):5-32.

130. van Vugt SF, Verheij TJ, de Jong PA, et al. Diagnosing pneumonia in patients with acute cough: clinical judgment compared to chest radiography. *The European respiratory journal.* 2013;42(4):1076-1082.

131. Shah SN, Bachur RG, Simel DL, Neuman MI. Does This Child Have Pneumonia?: The Rational Clinical Examination Systematic Review. *Jama.* 2017;318(5):462-471.

132. Schierenberg A, Minnaard MC, Hopstaken RM, et al. External Validation of Prediction Models for Pneumonia in Primary Care Patients with Lower Respiratory Tract Infection: An Individual Patient Data Meta-Analysis. *PLoS One.* 2016;11(2):e0149895.

133. Minnaard MC, de Groot JA, Hopstaken RM, et al. The added value of C-reactive protein measurement in diagnosing pneumonia in primary care: a meta-analysis of individual patient data. *Cmaj.* 2016.

134. Singal BM, Hedges JR, Radack KL. Decision rules and clinical prediction of pneumonia: evaluation of low-yield criteria. *Ann Emerg Med.* 1989;18(1):13-20.

135. Saldias PF, Cabrera TD, de Solminihac LI, Hernandez AP, Gederlini GA, Diaz FA. [Predictive value of history and physical examination for the diagnosis of community-acquired pneumonia in adults]. *Revista medica de Chile.* 2007;135(2):143-152.

136. O'Brien WT, Sr., Rohweder DA, Lattin GE, Jr., et al. Clinical indicators of radiographic findings in patients with suspected community-acquired pneumonia: who needs a chest x-ray? *Journal of the American College of Radiology : JACR.* 2006;3(9):703-706.

137. Melbye H, Straume B, Aasebo U, Dale K. Diagnosis of pneumonia in adults in general practice. Relative importance of typical symptoms and abnormal chest signs evaluated against a radiographic reference standard. *Scand J Prim Health Care.* 1992;10(3):226-233.

138. Hopstaken RM, Muris JW, Knottnerus JA, Kester AD, Rinkens PE, Dinant GJ. Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *Br J Gen Pract.* 2003;53(490):358-364.

139. 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):547-554.

140. Gennis P, Gallagher J, Falvo C, Baker S, Than W. Clinical criteria for the detection of pneumonia in adults: guidelines for ordering chest roentgenograms in the emergency department. *J Emerg Med.* 1989;7(3):263-268.

141. Ebrahimzadeh A, Mohammadifard M, Naseh G, Mirgholami A. Clinical and Laboratory Findings in Patients With Acute Respiratory Symptoms That Suggest the Necessity of Chest X-ray for Community-Acquired Pneumonia. *Iranian journal of radiology : a quarterly journal published by the Iranian Radiological Society.* 2015;12(1):e13547.

142. Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. *Fam Pract.* 2009;26(1):10-21.

143. Matthys H, Heger M. Treatment of acute bronchitis with a liquid herbal drug preparation from Pelargonium sidoides (EPs 7630): a randomised, double-blind, placebo-controlled, multicentre study. *Current medical research and opinion.* 2007;23(2):323-331.

144. Kemmerich B. Evaluation of efficacy and tolerability of a fixed combination of dry extracts of thyme herb and primrose root in adults suffering from acute bronchitis with productive cough. A prospective, double-blind, placebo-controlled multicentre clinical trial. *Arzneimittel-Forschung.* 2007;57(9):607-615.

145. Matthys H, Funk P. EPs 7630 improves acute bronchitic symptoms and shortens time to remission. Results of a randomised, double-blind, placebo-controlled, multicentre trial. *Planta Med.* 2008;74(6):686-692.

146. Ebell MH, Marchello C, Callahan M. Clinical Diagnosis of Bordetella Pertussis Infection: A Systematic Review. *J Am Board Fam Med.* 2017;30(3):308-319.

147. Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *The Cochrane database of systematic reviews.* 2017;6:Cd000245.

148. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *The Cochrane database of systematic reviews.* 2017;12:Cd007720.

149. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotic prescriptions for respiratory infections. *The Cochrane database of systematic reviews.* 2017;9:Cd004417.

150. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. *Br J Gen Pract.* 2013;63(616):e787-794.

151. Jakobsen KA, Melbye H, Kelly MJ, et al. Influence of CRP testing and clinical findings on antibiotic prescribing in adults presenting with acute cough in primary care. *Scand J Prim Health Care.* 2010;28(4):229-236.

152. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Danziger LH. A national evaluation of antibiotic expenditures by healthcare setting in the United States, 2009. *J Antimicrob Chemother.* 2013;68(3):715-718.

153. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. *Jama.* 2016;315(17):1864-1873.

154. Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *Bmj.* 1997;315(7117):1211-1214.

155. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *The Cochrane database of systematic reviews.* 2001(1):Cd002178.

APPENDICES

Appendix A. Letter of support from Dr. Navin Patel

From:Regional 1st Care Watkinsville 7067690320 01/02/2017 12:44 #864 P.001/001

Athens Regional

MEDICAL CENTER

1199 Prince Avenue, Athens, GA 30605

Mark H. Ebell MD, MS
125 Miller Hall
UGA Health Sciences Campus
Athens, GA 30602

Dear Dr. Ebell,

Thank you very much for inviting the Athens Regional FirstCare urgent care center to participate in a study on the prevalence, clinical presentation and natural history of Bordetella pertussis among adults with prolonged cough. This dissertation project will help estimate the burden of pertussis in the adult population and determine which signs and symptoms are most strongly associated with pertussis infection. This information will allow clinicians to make more informed decisions about ordering diagnostic testing and prescribing antibiotics, which will in turn give patients improved care.

We are looking forward to providing access to patients at the Athens Regional FirstCare site in Athens, Georgia (485 Highway 29 North Athens, GA 30601). We appreciate that your study will limit the impact as much as possible on our clinical practice and patient flow. By providing a research assistant for data collection at our site, we recognize we will not receive compensation for allowing the research. Patients, however, will receive monetary compensation in the form of a gift card.

We look forward to working with you and are eager to see the results of your study.

Sincerely,

Navin Patel, MD, FACEP
Medical Director, Athens Regional FirstCare

Appendix B. Informed Consent Form

Approved by University of Georgia
Institutional Review Board
Protocol # STUDY00003904
Approved on: 1/31/2017
For use through: 1/3/2018

UNIVERSITY OF GEORGIA ADULT CONSENT FORM

Name of Study: PERTUSSIS AMONG ADULTS WITH PROLONGED COUGH (PAPC)

Researcher's Statement

We are asking you to take part in a research study. Before you decide to participate in this study, it is important that you understand why the research is being done and what it will involve. This form is designed to give you the information about the study so you can decide whether to be in the study or not. Please take the time to read the following information carefully. Please ask the researcher if there is anything that is not clear or if you need more information. When all your questions have been answered, you can decide if you want to be in the study or not. This process is called "informed consent." A copy of this form will be given to you.

Principal Investigator: **Mark H. Ebell MD, MS**
Department of Epidemiology, College of Public Health
University of Georgia
706-247-4953 (m) or ebell@uga.edu

Purpose of the Study

The purpose of this study is to better understand the diagnosis and outcomes of a respiratory infection called pertussis. These infections are sometimes called "whooping cough" or a "chest cold". We also want to know how common this infection is in adults with a cough. This information will help us design tools that physicians and patients can use to better diagnose whooping cough in the future.

Study Procedures

If you agree to participate, you will be asked to answer some questions about your age, your signs and symptoms, and some social factors. This will include questions about your cough and whether you have headaches, sweats, and other symptoms. We will also ask you about smoking habits, if you have contact with children, and if you will let us check on previous vaccination for pertussis ("whooping cough") through the Georgia Immunization Registry (GRITS). The principal investigator, Dr. Ebell, is a licensed physician authorized by the state of Georgia to use GRITS. We will then take a swab from your nose and throat to detect bacteria. The entire process will take about 10 minutes, and will be done while you are waiting to see the doctor.

You will then be given 2 forms to bring with you when you see the nurse and doctor. You will give the forms to the nurse and doctor for them to complete. The nurse will use the form to record vital signs such as temperature and heart rate.

Next, your doctor will do their usual examination for a patient with acute cough. They will make their evaluation independent of our study and your care from the doctor will not change based on enrolling or declining this study. The doctor will record their findings as well as their treatment plan on the form you gave them. After you finished your visit with the doctor, you will return the forms to the researcher.

You will be asked to take a diary home and record your symptoms each day for 14 days. The diary should take less than 2 to 3 minutes each day to fill out. The diary can be returned with by folding, stapling and dropping it off in a US mailbox. The diary already has postage.

We will also contact you via email or text message at 7 and 14 days after your visit with a short survey to check your progress, and if you have recovered yet (standard data fees and text messaging rates may apply based on your plan with your mobile phone carrier). These electronic surveys will take 2 to 3 minutes. If you don't respond to the surveys, we will try to call you, and ask questions that take 2 or 3 minutes to answer.

It is important to know that the results of the nose and throat swabs will be performed at a research laboratory on the University of Georgia campus, and will not be available to your physician. The test results are for research only and will not be used by the physician for diagnostic purposes. It is also important that you know that any identifiable information will be kept confidential, and stored in secure computers without use of social security numbers.

Risks and discomforts

The questions are about ordinary signs and symptoms of cold and cough. These will not likely cause you to be embarrassed but some questions about social factors, like if you smoke, may make you to feel uncomfortable. However, your answers will not be shared with anyone and is no risk to you by answering truthfully. The throat swab is the same as would be taken for a strep throat test, and the nasal swab only gathers mucus from the front part of the nose. There are no physical risks for collecting these swabs.

Benefits

We expect that the information will provide important benefits for society and humankind by helping doctors take better care of patients with respiratory 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. You are not expected to directly benefit from participating other than the incentive described below.

Incentives for participation

In exchange for participating in the study, you will receive $5 cash for completing the survey in clinic today, and for providing the nose and throat swab. You will be sent home with a symptom diary and will receive a text or email with a link to a follow-up survey 7 and 14 days after your visit today. At the completion of your final survey, or when we receive your symptom diary, you will receive an additional $10 e-gift card which will be delivered to your email. Your total compensation for participating is $15.00.

Privacy/Confidentiality

In order to be able to contact you for follow-up emails and if necessary follow-up phone calls, we will record your phone number and email address. This information will be retained in a secure manner in an Excel spreadsheet on a password protected computer, and any paper files will be stored in a locked room. This identifiable information will be destroyed once we have gathered your follow-up data and emailed you your gift card. Otherwise, your clinical and laboratory findings will not be identifiable or linkable to you.

Receipts of delivered gift cards will be linked to your unique study ID. These could be shared with the business department within the Department of Epidemiology at the University of Georgia for billing, payment, and receipt logs. These receipts will not contain any personal identifying information that can be linked to you.

We are using a secure, well-regarded survey provider called Qualtrics to send you the electronic surveys via text message or email. Confidentiality can only be maintained to the degree of the technologies being used.

While unlikely, no guarantee can be made regarding the interception of data sent via the Internet by any third parties.

The project's research records may be reviewed by departments at the University of Georgia responsible for regulatory and research oversight. 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.

Taking part is voluntary

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. Your decision to take part or not to take part in this research study will not affect your treatment or health care services. If you decide to stop or withdraw from the study, the information/data collected from or about you up to the point of your withdrawal will be kept as part of the study and may continue to be analyzed.

If you are injured by this research

The researchers will exercise all reasonable care to protect you from harm as a result of your participation. In the event that any research-related activities result in an injury, the sole responsibility of the researchers will be to arrange for your transportation to an appropriate health care facility. If you think that you have suffered a research-related injury, you should seek immediate medical attention and then contact Mark H. Ebell MD, MS right away at 706-542-1585. In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

If you have questions

The main researcher conducting this study is Mark H. Ebell MD, MS, a Professor of Epidemiology at the University of Georgia. Please ask any questions you have now. If you have questions later, you may contact Dr. Ebell at ebell@uga.edu or at 706-5421585. If you have any questions or concerns regarding your rights as a research participant in this study, you may contact the Institutional Review Board (IRB) Chairperson at 706.542.3199 or irb@uga.edu.

Research Subject's Consent to Participate in Research:

To voluntarily agree to take part in this study, you must sign on the line below. Your signature below indicates that you have read or had read to you this entire consent form, and have had all of your questions answered.

_____	_____	____/____/_____
Name of Researcher	Signature	Date
_____	_____	____/____/_____
Name of Participant	Signature	Date

Please sign both copies, keep one and return one to the researcher.

Appendix C. Clinical Record Survey Form

PERTUSSIS AMONG ADULTS WITH PROLONGED COUGH (PAPC)
Site: Regional FirstCare Athens

Unique patient ID: _____

Enrollment date: _____ / _____ / _____

Contact Information for gathering follow-up data
Do you prefer text or email?

☐ Text message ☐ Email

What is your email address:

_____@_____

For text message and in case you do not respond to the email or text message, we need your phone number. What are the best phone numbers to reach you at? (Standard messaging fees apply)

Mobile phone number 1: _____

Other phone number 2: _____

Demographics

Patient age (years): _____

Sex: ☐ Male ☐ Female

Race (may select more than one): ☐ White ☐ Black
☐ Asian/Pacific Islander ☐ Other

Ethnicity: ☐ Hispanic ☐ Non-Hispanic

Symptoms

How many days have you had your cough: _____

Sputum (mucus when you cough):
☐ Green ☐ Yellow ☐ Rusty or bloody ☐ Mostly a dry cough

Have you experienced a “whooping” or “wheezing” or other noise before or during your cough?
☐ YES ☐ NO

Has your cough ever made you vomit or gag?
☐ YES ☐ NO

During a coughing spell, has it made you feel like you couldn’t breathe or had trouble breathing?
☐ YES ☐ NO

Have you had any violent, sudden episodes of coughing that are hard to control?
☐ YES ☐ NO

Have you noticed a blue or purplish skin color after a coughing episode?
☐ YES ☐ NO

Have you had any of the following symptoms since you began coughing?

Fever or Felt Warm: ☐ YES ☐ NO

Headache: ☐ YES ☐ NO

Sneezing: ☐ YES ☐ NO

Runny nose: ☐ YES ☐ NO

Red/watery eyes: ☐ YES ☐ NO

Chills or Sweats: ☐ YES ☐ NO

Have you had trouble sleeping as a result of your cough?

☐ YES ☐ NO

How many days of work or school have you missed because of your cough?

_____

Social Factors

Education: ☐ None or Some High School ☐ High School Graduate/GRE
☐ Some College or Associates Degree ☐ College graduate

Annual Household Income: ☐ Less than $25,000 ☐ $25,000 - $49,999
☐ $50,000-$74,999 ☐ Greater than $75,000

Cigarette smoking: ☐ Never smoked ☐ Former smoker ☐ Current smoker

Have you been in contact with anyone that you believe or have been told has pertussis or "whooping cough" since your cough began?

☐ No ☐ Yes ☐ Not sure

Do you have children in your household that are younger than 5 years old?

☐ No ☐ Yes

If yes, how many? _____

Why did you decide to come to the doctor/urgent care center? (mark all that apply)

☐ I wanted an antibiotic ☐ I am worried it might be something serious

☐ A person close to me told me to come ☐ Needed a note for work or school

☐ Other: _____

Have you had a tetanus vaccine, also known as Tdap, in the last 10 years?

☐ No ☐ Yes ☐ Not sure

I would like to log into the Georgia Immunization Registry (GRITS) to confirm whether you have been immunized against whooping cough (pertussis), is this ok?

☐ No ☐ Yes

If yes, list vaccines:

☐ No immunizations listed/patient not found

☐ Influenza Date: ____/_____/_____

☐ Tdap Date: ____/_____/_____

☐ DTaP Date: ____/_____/_____

Doses: _____

☐ DTwP Date: ____/_____/_____

Doses: _____

☐ Non-specific DTP:

Date: ____/_____/_____

Doses: _____

Appendix D. Clinician Survey Form

Test results:

Rapid Flu Test: ☐ N/A ☐ Negative ☐ Influenza A ☐ Influenza B

Rapid Strep Test: ☐ N/A ☐ Negative ☐ Positive

Vital signs

Heart rate: _____/ min Temperature (C): _____ Respiratory rate: _____/ min

Examination

Chest Findings: ☐ Normal ☐ Wheezes ☐ Crackles

Likelihood of pertussis infection: ☐ Unlikely ☐ Possible ☐ Likely

Tests and Referrals

☐ Chest x-ray

☐ Other test(s): _____

☐ Specialist referral to: _____

☐ Hospitalized

Treatments

☐ Antibiotic prescribed. If yes, select:

☐ Azithromycin ☐ Amoxicillin ☐ Amoxi-clav

☐ Clarithromycin ☐ Levofloxacin ☐ Other: _____

☐ Cough suppressant

☐ Steroid: _____

☐ Other: _____

Diagnosis

☐ Acute Bronchitis ☐ Acute pharyngitis ☐ Influenza ☐ Pertussis

☐ Other: _____

Appendix E. Qualtrics Follow-up Survey

How many days has it been since you stop coughing?

☐ 1 day ☐ 2 days ☐ 3 days ☐ 4 days

☐ 5 days ☐ 6 days ☐ I am still coughing today

Which of the following symptoms have you had in the last 2 days (select all that apply):

☐ Green, yellow or bloody sputum (mucus):

☐ Wheezing or noise when coughing:

☐ Vomited from coughing:

☐ Uncontrollable or violent coughing:

☐ Trouble sleeping because of my coughing:

How many days of work or school have you missed because of your cough in the past week?

☐ None ☐ 1 day ☐ 2 days ☐ 3 days ☐ 4 days

☐ 5 days ☐ 6 days ☐ 7 days

If you were given a prescription for an antibiotic or Tamiflu by your doctor, did you have this prescription filled?

☐ Was not given a prescription ☐ No, did not fill it ☐ Yes, I filled it

Have you had contact with children that are younger than 5 years old in the last 7 days?

☐ No ☐ Yes ☐ Not sure

Appendix F. Symptom Diary

SYMPTOM DIARY, DAYS 1 – 7

UNIVERSITY OF GEORGIA College of Public Health

Unique ID _____

FOR EACH DAY, PLEASE RATE HOW BAD YOUR SYMPTOMS WERE:
0 = Did not have symptom; 1 = Slightly a problem; 2 = Moderately bad; 3 = Bad; 4 = As bad as it could be (very bad)

Day of Record	1 (day of visit)	2	3	4	5	6	7
Date							
Cough	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Green, yellow or bloody sputum (mucus)	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Wheezing or noise when coughing ("whooping")	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Trouble sleeping because of coughing	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Shortness of breath or trouble breathing	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Vomited from coughing	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No
Uncontrollable or violent coughing	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No
Missed work or school today	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No
If you were given a prescription, did you have it filled before returning this diary?			❑ Yes ❑ No ❑ Not given a prescription				
Have you had contact with children less than 5 years old at any point before returning this diary?			❑ Yes ❑ No ❑ Not sure				

******* After completing day 7, please return by folding, stapling and dropping in a US mailbox********

How to rate your symptoms:
0 = Absent; did not have the symptom on that day
1 = Symptom was slightly a problem.
2 = Symptom was moderately bad.
3 = Symptom was bad.
4 = Symptom was very bad, it was as bad as it possibly could be.

If you have a medical emergency, please dial 911. If you have non-emergency questions regarding this diary or any part of this study, please contact: Dr. Mark Ebell at ebell@uga.edu.

It is extremely important you fill out the diary as careful and accurately as possible. Knowing your symptoms will allow us to understand how to better treat patients in the future. Thank you for your commitment. Please fold on the lines, staple, and return in a US mailbox

----------fold here----------

Mark H. Ebell MD, MS
125 Miller Hall
UGA Health Sciences Campus
Athens, GA 30602

Mark H. Ebell MD, MS
125 Miller Hall
UGA Health Sciences Campus
Athens, GA 30602

----------fold here----------

Staple

Staple

Staple

Staple

SYMPTOM DIARY, DAYS 8 – 14

UNIVERSITY OF GEORGIA College of Public Health

Unique ID _____

FOR EACH DAY, PLEASE RATE HOW BAD YOUR SYMPTOMS WERE:
0 = Did not have symptom; 1 = Slightly a problem; 2 = Moderately bad; 3 = Bad; 4 = As bad as it could be (very bad)

Day of Record	8	9	10	11	12	13	14
Date							
Cough	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Green, yellow or bloody sputum (mucus)	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Wheezing or noise when coughing ("whooping")	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Trouble sleeping because of coughing	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Shortness of breath or trouble breathing	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4	❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4
Vomited from coughing	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No
Uncontrollable or violent coughing	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No
Missed work or school today	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No	❑ Yes ❑ No
If you were given a prescription, did you have it filled before returning this diary?			❑ Yes ❑ No ❑ Not given a prescription				
Have you had contact with children less than 5 years old at any point before returning this diary?			❑ Yes ❑ No ❑ Not sure				

******* After completing day 14, please return by folding, stapling and dropping in a US mailbox*********

How to rate your symptoms:
0 = Absent; did not have the symptom on that day
1 = Symptom was slightly a problem.
2 = Symptom was moderately bad.
3 = Symptom was bad.
4 = Symptom was very bad, it was as bad as it possibly could be.

If you have a medical emergency, please dial 911. If you have non-emergency questions regarding this diary or any part of this study, please contact: Dr. Mark Ebell at ebell@uga.edu.

It is extremely important you fill out the diary as careful and accurately as possible. Knowing your symptoms will allow us to understand how to better treat patients in the future. Thank you for your commitment. Please fold on the lines, staple, and return in a US mailbox

----------fold here----------

Mark H. Ebell MD, MS
125 Miller Hall
UGA Health Sciences Campus
Athens, GA 30602

Mark H. Ebell MD, MS
125 Miller Hall
UGA Health Sciences Campus
Athens, GA 30602

----------fold here----------

Staple

Staple

Staple

Staple