“DIAGNOSIS, TREATMENT AND IMPACT ON FUNCTION OF INFLUENZA IN A COLLEGE HEALTH POPULATION”

by

ARIELLA PERRY DALE

(Under the Direction of Mark Ebell)

ABSTRACT

Problem: Studies of influenza in the college health population are primarily focused on outbreaks such as H1N1 in 2009. Our goal is to better understand the diagnosis, treatment, and impact of influenza in college students during a traditional influenza season. **Methods:** A quasi-experimental study at the University of Georgia Health Center from December 2016 to February 2017. Patients with a cough and at least one influenza-like symptom received a rapid PCR test for the diagnosis of influenza and were sent a follow up survey. A systematic review was conducted on the clinical decision rules (CDR) for the diagnosis of influenza which were validated in our population and a novel CDR was developed. The impact of PCR-guided care and PCR-confirmed diagnosis on treatment and behavior were also assessed. **Results:** A total of 265 patients were recruited during enrollment and 771 patients met our inclusion but did not receive the rapid PCR test were assigned as usual care. The systematic review yielded 16 studies that had five heuristics, 12 multivariate models, four influenza-like-illness case definitions, four classification and regression trees, and one-point score. Twelve CDRs were externally validated in our population. A CDR including myalgia, chills, fever, and the absence of tonsillar exudate as predictors of influenza performed well. (AUROCC: 0.77). A fast and frugal tree yielded a CDR with myalgia, chills, fever, and acute onset of less than or equal to 48 hours (AUROCC: 0.69). Guideline supported care did not significantly increase for patients who

received PCR-guided care (aOR: 1.24, 95%CI: 0.83, 1.88). PCR-guided care significantly decreased the likelihood of an antibiotic prescription (aOR: 0.61, 95%CI: 0.40, 0.94), increased the likelihood of an antiviral prescription (aOR: 1.57, 95%ci: 1.09, 2.28), and decreased the likelihood of return visit within 2 weeks (aOR: 0.19, 95%CI: 0.04, 0.81). Students with influenza were also more likely to report any absence from work or school (aOR: 3.86; 95% CI: 1.84,8.09). **Conclusion:** Influenza remains a burden in the college health population. The use of a rapid PCR test for diagnosis in outpatient care needs further assessment but shows a positive trend towards in promoting guideline consistent care.

INDEX WORDS: Influenza, Clinical prediction rules, College students, Stress, College health, Student health center, Rapid diagnostic testing, Antiviral, Antibiotic stewardship

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CHAPTER 1

INTRODUCTION

Statement of the Problem

Influenza is a highly infectious disease with a significant epidemiological burden for centuries. Influenza was originally attributed to the "influence of the stars" in the 15th century.[1] The influenza viruses are a group of negative-sense, single stranded ribonucleic acid viruses that belong to the *Orthomyxoviridae* family. There are three types of influenza: A, B, and C. Influenza A is the most common circulating type of influenza during outbreaks.[1] Influenza A is also the most prone to antigenic shifts and to lead to a pandemic.[2,3] So far, in the 2015-16 influenza season, 91.8% of influenza viruses reported by public health laboratories were influenza A.[4]

Influenza spreads primarily through droplets made when people with flu cough, sneeze, or talk. The typical symptoms of influenza include: fever, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, fatigue, vomiting, and diarrhea.[5] Most persons will present with a subset of these symptoms, as not all symptoms are found in every person. Persons with influenza are infectious beginning a day before symptoms present and for up to 7 days after. Most persons who are infected with influenza will become symptomatic after an average of 2 days (range 1-4 days), and typically recover without complications.[6] About one in every three people with influenza will be asymptomatic.[7] There are four groups that are at high risk for complications: persons 65 years of age and older, pregnant women, young children, and persons with chronic medical conditions.[8] Complications of influenza that can affect any person include bacterial pneumonia, ear or sinus infections, and dehydration.[8]

Diagnosis of influenza is difficult based on symptoms alone due to its overlap with many other respiratory illnesses. Therefore, many diagnostic tests have been developed. Currently, six major types of influenza tests exist: rapid influenza diagnostic tests, rapid molecular assays, immunofluorescence through direct or indirect fluorescent antibody staining, reverse transcription polymerase chain reaction (RT-PCR), rapid cell culture, and viral tissue culture.[9] Rapid influenza diagnostic tests are often used at the point of care since they can be completed in less than 15 minutes and are fairly simple to use.[9] This test relies on antigen detection from a nasopharyngeal, nasal, or throat swab or aspirate and wash. Rapid influenza diagnostic tests report a range of sensitivity values (10-80%); a recent meta-analysis found that the pooled sensitivity was 62.3% and the pooled specificity was 98.2%.[9] RT-PCR, rapid cell culture, and viral tissue culture (serology) take a significant amount of time but are less likely to misclassify a patient's influenza diagnosis. RT-PCR is a highly accurate testing method that takes approximately one to two days to complete.[10] RT-PCR is superior to cell culture at detecting influenza and is becoming the gold standard; however, the it's high cost and delay in setting results limits its use by clinicians.[9-11] Cell culture has the ability to detect other viruses within three to fourteen days.[10] Serology is an important research method that is also highly sensitive and specific, but the two to four week result timeline reduces its usefulness in clinical care.[10] Many options exist for the detection of influenza, but rapid influenza diagnostic tests continue to be widely available and used despite their failure to identify nearly four in ten patients with influenza.

Recently, Roche Diagnostics introduced the Cobas Liat system.[12] The Cobas Liat system performs RT-PCR in twenty minutes or less for the detection of influenza A and B as well as beta-hemolytic *Streptococcus* group A.[12] This test is 99.2% sensitive (95% CI: 95.1-99.9%) and 100% specific for influenza A virus (95%CI: not reported), and 100% sensitive

(95%CI: 83.1-100%) and 100% specific for influenza B viruses (95%CI: not reported) when compared to a reference laboratory influenza A and B real-time PCR assay.[12] The Cobas Liat influenza A/B test and machine will be used for all aims of this dissertation; Roche Diagnostics USA provided the funding and equipment for testing of participants.

Influenza has a significant annual burden in the United States. In the United States, influenza activity will typically peak between December and February. For the 2015-2016 influenza season, the epidemic peaked in March of 2016 with an estimated 25 million persons having had influenza by the end of influenza season.[13] There were 11 million influenza-related outpatient medical visits, 310,000 influenza related hospitalizations, and 12,000 pneumonia and influenza related deaths.[13] Despite this large morbidity and mortality burden, influenza vaccination coverage remains below 33% for adults 18-49 years of age.[13] Influenza vaccination can prevent illness, influenza-associated medical visits, influenza-associated hospitalizations and even deaths. A new influenza vaccination is released yearly based on research estimates of which viruses will be in circulation.[13] While the effect of influenza vaccination is highly dependent on vaccine efficacy, low coverage continues to be an issue.[13] University students have low vaccination rates (approximately 12-30%) due to a lack of understanding of both influenza burden and the benefits and harms of the vaccine.[14,15] This could contribute to the lack of vaccine coverage among adults 18-49 years of age, which includes university students.[13,14]

Further research to understand the diagnosis and prognosis of influenza in adults, particularly young adults, is important to prepare for future pandemics. University and college students live in more crowded living conditions, have a poor understanding of how influenza virus is spread, and a low vaccination rate.[14,15] University students at the University of Georgia benefit from a comprehensive care team at the University Health Center. Given the detailed electronic health record maintained at UHC and its high usage by UGA students, we can describe the course of an episode of influenza from onset of symptoms to diagnosis to recovery. We will follow a small cohort of UGA students (n=300) from enrollment at an appointment for

influenza like illness (ILI) to five days' post appointment with a follow up survey. With this cohort, we will be able to assess current clinical decision rules for diagnosis, describe the impact of a new, highly accurate rapid point of care PCR test and its effects on patient treatment, and better understand the effect of influenza diagnosis on the behaviors of university students post diagnosis.

Aims of this Dissertation

Our primary goal for these three aims is to better understand the diagnosis, treatment, natural history, and impact of influenza in college students. Our three aims are:

1. Identify and validate current clinical decision rules for the diagnosis of influenza and develop a novel clinical decision rule for the college health population.
2. Assess the impact of a new, highly accurate influenza diagnostic test on the guideline consistency of clinician's treatment decisions.
3. Assess the impact of a confirmed influenza diagnosis on university student's behavior with regards to participation in university life and social distancing.

To accomplish these three aims, we will recruit 300 patients at the University Health Center to receive rapid point of care PCR test. Participants will be current University of Georgia students that present with cough and one other symptom or at least two of the following symptoms: headache, fever, chills, sweats, fatigue, myalgia or arthralgia. Patients must present to UHC within seven days of symptom onset, and without previous evaluation by a clinician.

We chose university students at UHC for several reasons. First, as young adults, university students' behavior when infected with influenza has not been recently assessed.[16] Second, UHC has an excellent electronic health record (EHR). The EHR at UHC uses checkboxes, Booleans, and plus/minus controls to record symptoms, medical history, and laboratory results. This sophisticated system has the capability to require clinicians to answer specific fields. We have worked previously with UHC on a project for group A beta-hemolytic *Streptococcus* with success. We chose cough or suspected influenza symptoms to capture patients who present

with milder forms of influenza. Seven days is our symptomatic cut off because the most severe symptoms of influenza typically pass within a week.

Objectives of Aims

Each aim has its own set of objectives and methods, which are described in detail in chapter 3. Below is a brief description of each aim, presented as Table 1.1.

Table 1.1 Brief Description of the Objective, Data Source, and Methods for Each Aim

Aim	Objectives	Data Sources	Methods
1	-To identify published clinical decision rules for diagnosis of influenza through a systematic review and validate them using prospective data from UHC -To develop a new diagnostic clinical decision rule for the college health population using the UHC data	-Medline, Google Scholar, EMBASE, DARE, Cochrane Library, and CDR database from Dr. Tom Fahey (Dublin) - Symptom, history, and laboratory data from UHC	-Systematic review -ROC curve, Hosmer-Lemeshow plot, calibration statistics -Logistic Regression to build new model from UHC
2	-To identify whether the rapid point of care PCR significantly increases the number of patients who receive guideline consistent treatment -To assess the impact of the rapid point of care PCR test on return visits to the UHC.	-Symptom, patient history, and laboratory data from UHC electronic health record	-Logistic regression
3	-To assess the behavior of college students who have participated in the rapid point of care PCR test in the following composite variables: emotional impact and social distancing	-UHC EHR laboratory data -Qualtrics survey administered via UGAMail 5 days' post appointment	-Logistic Regression

Aim 1 is focused on clinical decision rules. We first conducted a systematic review of the literature to identify clinical decision rules (CDRs) for the diagnosis of influenza. We then validated all identified rules using the prospectively gathered data on patients with ILI from UHC. We hypothesized that most CDRs will be found to be valid in our patient population, defined as having an area under the curve greater than 0.70 and calibration slope close to 1. Following validation of each previously developed CDR, we then created our own CDR for influenza in a

university student population. We hypothesized that cough, fever, myalgia and headache will be clinically and statistically significant predictors of influenza in university students.

Aim 2 focused on the treatment of patients in the presence of the rapid point of care PCR test. We hypothesized that patients who received care guided by the rapid point of care PCR test will be more likely to receive guideline consistent treatment, because of greater clinician certainty and confidence in the diagnosis. We defined guideline consistent and guideline inconsistent treatment in Table 2.1 of chapter 3. Oseltamivir (Tamiflu) is guideline consistent when administered within 48 hours of symptom onset in patients with influenza confirmed by clinician diagnosis or PCR test (when used). Antibiotics are guideline consistent in patients with a high risk of pneumonia or with clinician diagnosed pneumonia, acute rhinosinusitis, streptococcal pharyngitis, acute otitis media, or other predominantly bacterial infection. Patients who do not have influenza and are at low risk for pneumonia or bacterial infection (for example, with a clinical diagnosis of acute bronchitis, viral pharyngitis, or viral upper respiratory infection) should not receive an antibiotic. In addition, patients diagnosed with influenza should not receive an antibiotic, with or without oseltamivir. We also assessed the number of return visits within seven days of the initial appointment. We hypothesized that patients who receive care guided by the rapid point of care PCR test will be significantly less likely to schedule a follow up appointment than those who received usual care, due to greater certainty in and comfort with the diagnosis.

Aim 3 addresses the behavior of university students after influenza diagnosis. We hypothesized that patients who are influenza positive, as confirmed by the rapid point of care PCR, are more likely to be socially distant. Patients who are socially distant will indicate a lowered use of public transportation and dining facilities, less interaction with friends and a decreased attendance to class or work. We also hypothesized that patients who are influenza positive, as confirmed by the rapid point of care PCR, will report more emotional impact. These

patients could possibly report higher levels of stress, increased reliance of family for health-related decision making, and reliance on a social network in relation to their health.

Dissertation Outline

Chapter 1 of this dissertation has provided a brief introduction to influenza and university student behavior. Chapter 2 describes the literature surrounding influenza, university student behavior, PCR testing, and CDRs thoroughly. Chapter 3 describes the methods used in each aim of this dissertation. Chapter 4 is a be brief introduction to the results. Chapters 5, 6, and 7 are manuscripts prepared for publication representing each of the three aims. Chapter 8 is a summarization of the findings of each aim and conclusions.

CHAPTER 2

LITERATURE REVIEW

Influenza Overview

Influenza is an airborne respiratory disease with potentially devastating effects, as seen in the 1918 “Spanish” influenza pandemic.[17] An estimated 21 million deaths are attributed to this pandemic.[17] The devastating aftermath of the 1918 influenza pandemic became the driving force for understanding the virus. In the 1930s, the influenza virus was first isolated from nasal secretions of infected patients.[18] By the 1940s, the first influenza vaccination had been created using an inactivated monovalent influenza A virus.[19] Vaccine development has continued throughout the decades. The first worldwide surveillance system for circulating influenza strains was developed by the World Health Organization (WHO) in 1952.[1]

While continued monitoring of influenza and development of vaccines occurred in the 1960s and 1970s, it was not until February 1980 that the naming convention for influenza viruses was accepted by the WHO.[20] Every influenza virus, regardless of type, receives a strain designation. That strain designation is comprised of information on the antigenic type of the virus the host of origin, geographical origin, strain number, and year of isolation.[20] Antigenic description of influenza A viruses was added based on the subtypes of hemagglutinin or “H” (15) and neuraminidase or “N” receptors (9).[20] We now refer to influenza viruses by their antigenic type, for example H3N2. Similar antigenic subtyping does not exist for influenza B or influenza C.

Epidemiology of Influenza in the United States

The influenza viruses were first isolated in the 1930s. Influenza has been responsible for four pandemics in the last 125 years (1918, 1957, 1968, 2009). Understanding the molecular epidemiology behind the influenza pathogens of this pandemic is essential to furthering understanding of pandemic influenza. Influenza viruses have persisted for centuries due to the antigenic variation and antigenic shift.[21] Antigenic variation is the accumulation of point mutations in the hemagglutinin and neuraminidase genes.[21] A viral RNA polymerase transcribes the influenza genome imperfectly causing some point mutations.[21] There is positive Darwinian selection for hemagglutinin antigenic sites that permit replication if conditions favor survival.[21] Continued antigenic variation means an individual is susceptible to infection of a new strain despite previous infections. Antigenic shift occurs when an influenza A virus with a new hemagglutinin occurs in humans. This shift can result from a virus being transmitted without re-assortment from an animal to a human. Antigenic shift can also occur when genetic re-assortment between animal and human influenza A viruses yields a new virus. Due to the potential for antigenic shift, influenza A virus is the primary concern for future epidemics.[3]

It is well accepted that influenza is spread through direct person to person transmission when an infected person expels viral particles through sneezing, coughing and talking.[21] Influenza is seasonal; most outbreaks occur within the first quarter of the year (January-March) [22]. Most outbreaks are dominated by influenza A virus H3N2 in the beginning with influenza B incidence rising later towards the end in the outbreak.[23] Influenza infection is generally self-limited and a majority of symptoms resolve within 1 to 7 days, with the exception of cough which may last several weeks. [10,121]

During a typical influenza outbreak, four groups are identified as high risk for serious complications: persons >65 years of age, young children, pregnant women, and persons with

chronic diseases.[8] Children less than 5 years of age and adults that were 65 years or older accounted for approximately 66% of the estimated excess deaths due to pneumonia and influenza in the 2015-16 influenza season.[13] In the 2009-10 H1N1 pandemic season, 12% of pregnancy related deaths were attributed to influenza.[24] While these groups are at the highest risk for mortality during seasonal influenza outbreaks, this pattern does not hold true during a pandemic. A study comparing mortality by age group during the 1918, 1957, and 1968 influenza A pandemics revealed that risk of mortality from influenza increases significantly during a pandemic for younger adults.[21,25] Following the pandemic, the number of deaths in younger adults decreases rapidly, suggesting an acquisition of protection against fatal influenza in younger persons.[25]

In the United States, weekly surveillance of influenza infections is performed by the Centers for Disease Control and Prevention (CDC). Since the WHO established influenza surveillance as a priority in 1952, the CDC has monitored influenza through five types of surveillance systems: viral surveillance, outpatient illness surveillance, mortality surveillance, hospitalization surveillance, and summaries of the geographic spread of influenza throughout the United States.[26] A brief description of each surveillance system is included below as Table 1.2. This information is compiled into FluView, CDC's interactive web based program for influenza surveillance statistics.[26] Surveillance allows the CDC to track influenza related illness, the time and states where influenza is occurring, which influenza viruses are circulating, the impact of influenza on hospitalizations and deaths, and finally to identify any changes in influenza viruses.[26] This information is important to public health response to influenza and assists in development of future vaccinations.

Table 1.2 Description of 5 Surveillance Systems that Contribute to FluView

System Name	System Description	Setting	Number of Sites
Viral surveillance	-public health laboratories test for surveillance of which viruses are circulating -clinical laboratories test for diagnosis of virus in patient	Public health and clinical laboratories	400 throughout the 50 states, Puerto Rico and DC
Pneumonia and Influenza Mortality	Deaths related to pneumonia and influenza identified by ICD-10 cause of death codes	National Center for Health Statistics (NCHS) mortality surveillance data	Not reported
Influenza-associated Pediatric Deaths	Laboratory confirmed influenza associated deaths of persons >18 years of age	Hospitals, doctor's offices, medical examiners, laboratories in the United States	Not reported
Influenza-associated Hospitalizations	population-based surveillance for laboratory-confirmed influenza-related hospitalizations in children and adults	Hospitals in 10 Emerging Infections Program states (CA, CO, CT, GA MD, MN, NM, NY, OR, TN)	70 counties throughout 10 EIP states
Outpatient Illness Surveillance	Providers report ILI to ILINet system	Outpatient providers throughout all 50 states, Puerto Rico, D.C., and the U.S. Virgin Islands	2,800 participating providers reporting +36 million visits

Influenza Treatment Options

Most patients receive only supportive care for influenza. Current pharmaceutical options for influenza are limited, in part due to virus evolution, medication cost and adverse effect, the rapidity with which the infection causes symptoms, and the difficulty surrounding rapid diagnosis of influenza. Influenza medications include M2 protein inhibitors (amantadine or rimantadine), neuraminidase inhibitors (oseltamivir or zanamivir), hemagglutinin inhibitors, and medications that target the RNA viral transcription (umifenovir) and replication (ribavirin).[3] In the US, the only medications recommended for influenza are the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir.[27] Recent reviews of published and unpublished data show that the use of these medications does not significantly reduce hospitalizations or complications, that they have

significant adverse effects, only modestly reduce the duration of illness, and are expensive.[28-30] Therefore, supportive treatment continues to be the primary means for assisting patients.

Influenza Vaccination

Influenza vaccinations are the primary public health strategy for reducing influenza impact.[19] Influenza vaccines are developed through two processes: an inactivated vaccine or a live attenuated vaccine. The first inactivated influenza vaccine was developed in the 1930s and the first bivalent vaccine followed shortly after.[19] A bivalent vaccine contains one influenza A and one influenza B virus strain. Today, inactivated vaccines are produced in embryonated hens' eggs. This method has it's challenges, as there is a limited availability of embryonated hens' eggs.[19] Live attenuated vaccines were first licensed in the late 1970s.[19] Live attenuated virus vaccines induce a immune system response that mimics the immune response to natural infection but without causing clinical disease.[19] Live attenuated virus vaccines should not be used in persons with confirmed severe allergic reactions, asthma, long-term aspirin use, or have altered immunocompetence.[19] Persons with altered immunocompetence should refer to the recommendation made by the Infectious Disease Society of America for detailed guidance on selection and timing of vaccines.[31]

In the United States, the Advisory Committee on Immunization Practices (ACIP) sets the recommendations for vaccinations. The ACIP recommends annual influenza vaccination in all persons 6 months of age and older. Either vaccine type, inactivated or live attenuated virus, may be used in persons aged 2 to 49 years without certain conditions. These conditions include severe allergic reaction, asthma, long-term asthma use or any indications of a depressed immune system.[19] Until 2012, a trivalent vaccine was widely used for influenza protection. The trivalent vaccine contains antigens for influenza A H3N2 and H1N1 and one influenza B virus.[19] The use of this trivalent vaccine often resulted in a mismatch between the circulating influenza B virus and the influenza B virus in the trivalent vaccine.[19] To combat this mismatch, a quadrivalent vaccine was developed and introduced into the United States in February of 2012.

The quadrivalent vaccine contains the viruses from the trivalent vaccine with an addition of another influenza B strain. The quadrivalent vaccine is more effective at producing an immunogenic response and is considered safe.[19] In a multicenter trial conducted during the 2011-2012 influenza season, the quadrivalent vaccine outperformed the trivalent vaccine when measuring geometric mean titers of antibody response were 3.08 (95%CI: 2.44, 3.90) and 3.27 (95%CI: 2.55,4.03) for the unmatched influenza B strains in adults.[32] Additionally, the quadrivalent vaccine was non-inferior to the trivalent vaccine when measuring geometric mean titers of antibody response were approximately 1 and included 1 in the 95% confidence interval to the four matched influenza strains.[32] Finally, the solicited reactions, unsolicited adverse events and serious adverse events are similar between the quadrivalent and trivalent vaccine; no serious adverse events or deaths were reported as related to treatment.[32] The quadrivalent vaccine has apparently accomplished its initial goal of reducing influenza B infections; with a 16% reduction of influenza B infections in the United States from 2000-2013.[33] Public health officials should continue to educate the US population and promote vaccine coverage for all persons, especially focused on high risk groups to reduce influenza morbidity and mortality.[34]

Vaccination rates in adults aged 18-49 remains low throughout the United States.[13] There are many reasons for the lack of vaccination by adults aged 18-49, the foremost being a failure to understand the risk of influenza infection.[35] To increase influenza vaccination acceptance in otherwise healthy adults, trust must be increased in the following areas: an increase in the perceived effectiveness of the vaccine, and improved knowledge regarding the low likelihood of vaccine side effects.[36] A lack of knowledge surrounding vaccination is a major hurdle to increasing vaccine coverage in young adults.[35] Vaccination rates are low among university students, even shortly after the H1N1 pandemic, demonstrating that education and public health messaging is still needed to increasing vaccine coverage.[37-39] Also, officials may consider placing a greater emphasis on non-pharmaceutical prevention measures such as self-isolation.

Influenza at Colleges and Universities

Influenza outbreaks at universities and colleges have a significant impact on the health of young adult students. Previous outbreaks have led to increased use of clinical care, loss of class and work time, and an increase in health costs, among many other significant consequences.[16,38] In June of 2009, the WHO declared the H1N1 outbreak the first pandemic of the 21st century. Worldwide, an estimated 284,500 people died because of H1N1 infection or its complications.[40] Many colleges and universities faced a large burden of disease throughout the duration of the H1N1 outbreak.[39,41-44] The rapid surge of patients to college health services was overwhelming when comparing the peak of influenza in 2009 to the same week in 2008.[41] Many patients presented to health services out of fear of a H1N1 infection despite their absence of fever or other influenza like symptoms.[41] A lack of adequate education of the community regarding H1N1 and media attention contributed to the doubling of clinical care visits, from 352 to 782.[41] Influenza like illnesses also impact academic and work performance.[16] Students with influenza miss school days, miss work days, and report worse performance on tests or class assignments.[16] For the university student, who is often balancing a job alongside a full course load, the impact of an acute illness like influenza can continue for weeks' post illness. While these consequences are disruptive for the life of a university student, many fail to perceive the risk of influenza infection.[35]

Gaps in Education of University Students

The H1N1 outbreak was a rich source for research around disease outbreak preparedness efforts for universities. In a pandemic, universities must prepare for a quick influx of patients as an influenza outbreak progresses; a possible solution is the establishment of temporary clinics for triaging patients.[41] Another possible solution is the creation of a telephone based clinical decision rule to triage patients during an outbreak. Education of the campus community is essential to the management of future outbreaks. Non-pharmaceutical interventions such as handwashing, home isolation, and social distancing have varied levels of

success in university students.[42,43,45] Education regarding influenza risk for university students consistently leads to increased hand washing during outbreaks.[42,45,46] Female students and students who perceived their illness severity to be great are more likely to wash their hands frequently.[42] However, students and staff at universities do not isolate themselves when infected; infected students still attend class and social activities.[41,47] Social activities include club and organization meetings as well as parties. In a study of a large public university during the H1N! pandemic of 2009 students, faculty and staff were asked to complete a survey regarding non-pharmaceutical interventions.[45] Students who reported being "somewhat concerned" or "very concerned" that they would contract H1N1 reported attending social activities significantly less.[45] Even during pandemic situations, students do not understand their increased risk for infection.[46] Since students are unlikely to practice social distancing behaviors, and given the social stigma to mask use, it isn't surprising that they also report low usage of face masks.[46,48,49]

Social contact networks are a contributor the propagation of influenza in communities.[50] A study of social distancing designs for pandemic influenza targeted elementary, middle, and high school contact networks in order to reduce the influenza attack rate by 90%.[51] The social contact networks of children, teenagers, and college students are similar in that they are highly assortative and interact primarily with people in their age group.[50, Guh, 2011 #33] Therefore, the implementation of targeted social distancing methods proposed by Glass are useful for colleges as well. In 2005, a simulated model of influenza in Southeast Asia determined that social distancing was necessary for pandemic control when combined with geographically targeted prophylaxis.[52] Social distancing can include self-isolation, the closing of schools and workplaces, the cancelling of major events on campus, and many other measures. Educating university students regarding infection risk and preventative measures is still needed.

Adapting education measures to university students is challenging. University officials must balance their message to not increase unnecessary fear or promote complacency to influenza risk.[53] Many options are available to universities in disseminating information about

influenza. Some of these options include: posters, announcements in lectures, university websites, simple message services, and e-mails.[53] The use of computer technology is potentially the most efficient way to reach students, faculty and staff during an outbreak.[53] Students report that classroom announcements and campus posters are the next preferred methods of communication of risk.[53]

Gaps in the Literature

While influenza research has been conducted for years, the research into university students has been centered around major pandemics.[15,16,41,42,47] This limits our understanding, as it is reactionary to the pandemic and does not continue once the threat has diminished. Since the influenza virus is undergoing constant antigenic evolution, it's impact in the university student population needs to be assessed in a non-pandemic setting. The most recent study of non-pandemic influenza in university students regarding their illness related behaviors was published in 2002.[16] Use of mobile and other technology has increased dramatically in the last 15 years, emphasizing a need for a new assessment of student behavior post influenza infection. It is important to assess whether the same hurdles to reducing influenza transmission in university students, such as crowded living and a lack of social distancing, still exist.[38,45,54]

In addition, validation of current clinical decision rules for influenza is key to the continued implementation of these tools.[55] By conducting a systematic review and validating current rules in a university population, we can strengthen the argument for the use of these clinical decision rules as a part of evidence-based practice. Currently, no clinical decision rule exists exclusively for university students. Given the atypical crowded living conditions and social behaviors of university students, it is important to develop a clinical decision rule that can be applied to the otherwise healthy university student.

Finally, the use a new highly accurate and rapid point of care PCR test has not been studied. The over-prescription of antibiotics and antivirals continues to remain a top public health concern. The misuse of antibiotics remains common for respiratory viral infections [56], and

anti-influenza drugs such as oseltamivir are often misused as well.[57] Therefore, the implementation of a rapid test with increased accuracy should be studied as a possible means to reduce over-prescription by improving patient and physician confidence in the accuracy of the diagnosis of influenza.

We will address these gaps in the literature through the three aims of this dissertation. First, we will conduct a systematic review of current clinical decision rules for influenza and validate them using original data collected from the University of Georgia's Health Center (UHC). We will then develop our own clinical decision rule for university students using the same data. From there, we will assess whether the implementation of the rapid point of care PCR test significantly decreases guideline inconsistent prescribing for patients with and without influenza-like illness. We will also assess the impact of the PCR test on return visits of patients at the UHC. Finally, we will assess the effect of an influenza diagnosis on emotional impact and social distancing of university students. It is possible that the attitude of university students has changed to include vaccination and non-pharmaceutical interventions as a priority.

CHAPTER 3

METHODS

AIM 1: Validation of Existing Influenza Prediction Rules and Development of an Influenza Prediction Rule Using University Student Health Data

1.1 Background

1.1.1 History and Utility of Clinical Decision Rules

While caring for patients, clinicians must make a diagnosis, choose a treatment and advise patients regarding prognosis. All three of those tasks require a judgment regarding the likelihood of a disease (or multiple diseases); the likelihood that a treatment will be effective; and the likelihood that a patient will experience an outcome such as recovery or death. Clinicians are increasingly relying on evidence-based practices including clinical decision (also known as clinical prediction) rules (CDRs).

Prediction models can be applied in medicine and public health to aid in diagnosis or screening processes.[58] These models are particularly useful in resource limited settings, and to minimize harms. For example, a prediction model applied to screening can identify high risk groups and exclude patients with minimal risk, who are less likely to experience a net benefit. When applied to clinical decisions, prediction models are typically diagnostic tools to help decrease the financial or physical burden on the patient [58] by avoiding unnecessary tests. Many medical outcomes are binary; you either have the outcome or do not. Examples of outcomes can range from simple presence versus absence of disease to time dependent outcomes such as 10-year mortality.[58]

Another important benefit of prediction models in medicine is the ability of the models to work in conjunction with clinician experience. While increasing years of clinical experience may be beneficial for patients, our understanding of disease changes as research continues. When a clinician fails to stay current, this can increase misdiagnosis or over diagnosis.[59] Therefore, a prediction model, called a clinical decision rule (CDR) in medicine, combines individual factors from a patient's history, physical exam, and in some cases laboratory tests to predict the diagnosis, treatment response, or prognosis for a patient. CDRs apply statistical methods to improve the processes of diagnosis, treatment selection and prognosis. For example, a CDR would be most useful as mentioned previously in a situation where the cost to the patient is high, where the test or treatment is risky, or where prognosis is uncertain.[59] CDRs help to inform and augment clinical judgement to improve the quality of care.

1.1.2 Clinical Decision Rules: Development, Validation, and Impact Analysis

The creation of a useful CDR involves three phases. These three phases are development, validation, and impact analysis, and each is discussed below.

1.1.2.1 Development

CDRs are typically developed following these steps: identification of potential clinical predictors, assessment of the presence or absence of these predictors and the outcome of interest (diagnosis, treatment success, or mortality) in a patient population, and finally statistical analysis.[59] To identify potential clinical predictors, researchers rely on an extensive literature review and existing knowledge of disease etiology. These clinical predictors as previously described can include symptoms, signs, medical history and laboratory tests. Once these potential clinical predictors have been identified, a susceptible patient population is identified. Each patient is then assessed for the presence or absence of each clinical predictor and the clinical outcome. This patient population can also be referred to as the development, derivation,

or training population, as this is the population on which we will train our prediction model to predict the clinical outcome. To address inaccuracy in the measurement of predictors or outcomes, researchers should strive to use prospective primary data collection and perform extensive training of assessors. Additionally, developing the model in a diverse population will increase the generalizability of the model to other populations and clinical practice. The training population should resemble the clinical population that we want to apply the model to in terms of spectrum of disease and diversity. Once data collection is complete, researchers will typically use logistic regression (or a variant) to build the most parsimonious model. From the final fitted logistic regression model, we will assign a point value of 1 to each included parameter.

Researchers collect data through primary and secondary methods. Primary data collection involves a researcher and their team prospectively collecting original information from a patient population. This method is advantageous because the researcher ensures that the data necessary for the objective of the study will be complete and accurate. Complete and accurate data is essential for trustworthy results. However, primary data collection is expensive, takes time to plan and execute, and involves dedication from a research team. Researchers must consider the planning, ethical decisions and institutional review boards, and execution of the project over a significant period. Secondary data comes from a source that has already collected the information for other purposes, such as medical records. These previously collected data sources are cheaper and do not involve as great an investment of time, money, and planning. A significant disadvantage of secondary data is that the researcher has no control over what data is obtained, it's quality, or the completeness. The decrease in quality can interfere with the model reliability, accuracy, and generalizability to answer the study's objective.

1.1.2.2 Validation

Once a CDR has been developed, the CDR must then be validated in an external population. External populations are patient populations that do not include patients from the training population that developed the original model. Validation is an important step in the

process to a successful CDR. There are many potential problems with a CDR that must be accounted for. Some of these problems include: overfitting, optimism, inaccuracy of measurement of predictors or outcomes, differences between training and validation populations, and the complexity of the CDR.[55,59] Overfitting occurs when a prediction model is fitted with too many degrees of freedom in the model development process.[55] Overfitting leads to a model that is will only perform well in the training population and does not generalize well to other populations. The development and validation populations should be diverse, provide an adequate spectrum of disease, and be representative of the target population for the CDR. Minimization of selection bias, interviewer bias, and loss to follow up is key to the successful validation of a CDR in a new population.[59] Once the CDR has been developed, it is important to assess whether the CDR is too complex or lacks face validity. CDRs that involve too many terms or are difficult to remember will not be successful in practice. Additionally, CDRs that do not make sense to clinicians and their existing knowledge will be ignored. It is important to develop a CDR that is simple and intuitive, fitting the known signs and symptoms of diagnosis.

The validity of a CDR is assessed via classification accuracy, discrimination, and calibration. Classification accuracy is the number of correct predictions made by the CDR divided by the total. We will use the CDR to classify patients into risk groups, and then compare to the risk groups to the final diagnosis. We will also calculate test and treatment thresholds. The test threshold occurs when a clinician has enough equipoise to decide whether to rule out a disease or order additional tests.[60] The treatment threshold occurs when a clinician has enough equipoise to decide to rule in disease for treatment or order additional tests[60]. The data below the test threshold should correspond to the low risk group for a typical CDR; values above treatment threshold corresponds to the high-risk group. The test threshold and treatment threshold equations are shown below as Equation 2.[60,61] The parameters are: p which is the probability of not ruling out, x is disease probability, a and b are model coefficients.[60,61]

$$\ln[\frac{p}{1+p}] = a + bx$$

Equation 2. Logistic Function to Calculate Test or Treatment Threshold [61]

Discrimination statistics tell us how well a model can discriminate those with the outcome from those without the outcome. We can assess the discrimination of a model through statistical measures such as diagnostic odds ratio and the calculation of area under a receiver operating characteristic curve (AUROCC).[55]

Calibration is another important aspect of model validation. Calibration quantifies the agreement between the predicted outcome and the observed outcome. To assess model calibration, calibration plots are produced with the outcome on the y axis and the prediction on the x axis. A calibration plot with perfect predictions will have a line along the 45 degrees with a slope of 1.0. With a binary outcome, the y axis will only contain values of 0 or 1. Smoothing techniques are used to estimate the relationship between observed and predicted probabilities. A common calibration plot is the Hosmer-Lemeshow plot, which groups outcome values into deciles. A well calibrated model will have a Hosmer-Lemeshow plot with an even distribution of outcome points across all deciles. There are many other goodness of fit tests available with their own strengths and weaknesses such as the Goeman-Le Cessie test or subgroup calibration.[55] We will focus on the Hosmer-Lemeshow test since we are using a binary outcome. The Hosmer-Lemeshow goodness of fit test uses a chi-square statistic to assess the ability of our model to fit the new data.

1.1.2.3 Impact Analysis

A CDR will only be successful at improving patient care if it is relatively easy to implement in a clinician's practice. The use of a CDR must have benefits that outweigh the costs of labor and time for the clinician. These benefits include improved patient outcomes or reduced costs to maintain current quality of clinical care. Barriers for use of a CDR center around the clinician and their practice setting. The difficulty increases with the number of clinical

predictors needed (due to the time needed to gather these data), variation in the number of points assigned to each predictor and calculations, and the time it takes to perform the calculation.[59] While a CDR may minimize the number of clinical predictors and keep the calculation simple, a clinician's fear of litigation or unwillingness to allow a CDR to overrule their clinical judgement may also decrease the use of the CDR. The cost of misdiagnosing or mistreating a patient varies amongst disease conditions; if the outcome involves a high burden to the patient, the clinician may be more inclined to order expensive and invasive testing to increase diagnostic certainty.[59]

To quantify the impact of a CDR, a large randomized study should be conducted to assess relevant outcomes such as morbidity, mortality, and cost.[59] We would ideally assess the impact of a CDR by randomizing patients, clinicians or groups of clinicians to usual care or usual care aided by the CDR. Then, we would assess the differences between groups in outcomes such as diagnostic accuracy, hospitalization rates, mortality, and cost. Successful implementation of a CDR occurs when a clinician uses the CDR in all or most relevant patients.[59]

CDRs are potentially most useful when they can be implemented in a wide range of settings with confidence that they will benefit patients and be used by clinicians.[59] CDRs are most trustworthy and clinically relevant when they have been validated in either a single, large diverse population or when they have been validated in multiple smaller populations. CDRs that are only validated in one small homogenous population will only be useful in similar populations.

1.1.3 Clinical Decision Rules in Current Practice

CDRs have been developed and validated for a wide range of conditions. In primary care, a commonly used CDR is the Centor score for diagnosis of group A beta-hemolytic *Streptococcus (GAS).* Criteria for this score were developed in 1981 in an adult patient population presenting to the emergency room to aid physicians in diagnosis of acute pharyngitis.[62] Consecutive patients (n=234) with complete clinical data and culture results were

collected over a 2-month period. This information was then used to build a logistic regression model with positive throat culture for GAS as the dependent variable. Four symptoms and signs were identified as independent predictors of a positive GAS culture: tonsillar exudate, swollen anterior cervical lymph nodes, absence of cough, and a history of fever. Each sign or symptom adds a point to the Centor score. Patients with all 4 variables had a 55.7% probability of a positive GAS culture in the derivation population, decreasing in probability as the total score decreases.[62] The Centor score has now been externally validated in many studies of both adults and children.[63-65] A review of guidelines for the management of pharyngitis in 2004 assessed the impact of modified Centor criteria (which add age as a variable) on the sensitivity and specificity for identifying GAS, total antibiotics prescribed, and the number of unnecessary antibiotic prescriptions.[65] Patients with a score of 2 or 3 received a throat culture, while patients with a score of 4 or more were treated empirically with an antibiotic, and those with a score of -1, 0 or 1 were neither tested nor treated.[65] This strategy was assessed alongside 5 other strategies based on practice guidelines.[65] The modified Centor criteria and culture combination strategy proved to be the best compromise in identifying GAS in a sample of 787 cultured confirmed GAS positive and negative (n=228 and n=559 respectively) children and adults (sensitivity 100%, specificity 93.2%). This strategy kept the number of unnecessary antibiotic prescriptions and the level of diagnostic testing low in children and adults.[65] This review and other studies have helped strengthen the acceptance and generalizability of the Centor score, and as a result it is widely used by clinicians today.

Objective

To use a systematic review to identify published clinical decision rules for influenza, and to validate them with data from the University of Georgia's Health Center (UHC). We will also develop a new clinical decision rule for the college health population using the UHC data.

Methods: Systematic Review and Validation

1.1.4 Data Sources

We will use PubMed, Embase, the Cochrane Library, the Database of Abstract of Reviews of Effectiveness, Google Scholar and the CDR registry developed by Dr. Tom Fahey in Dublin to identify all clinical decision rules in primary care for the diagnosis of influenza. Our search strategy is outlined in the next section.

To validate these CDRs, we will use data from patients who have received the Roche Cobas Liat Polymerase Chain Reaction (PCR) test as a part of their care. This is a novel and highly accurate rapid PCR test for the diagnosis of influenza A and B. Compared to reference laboratory PCR, it is 99% sensitive and specific for the diagnosis. We will perform this test at the University Health Center (UHC) and the University of Georgia. UHC is available to all fees paying students enrolled at the Athens, Georgia campus. The UHC setting is described in detail in section 1.3.2.1 below, and the patient population in 1.3.2.2. Students presenting with cough or at least two other suspected influenza symptoms within the last week will be included. Signs or symptoms of suspected influenza include: headache, cough, fever, chills, sweats, fatigue, myalgia or arthralgia.[66] The most severe symptoms of influenza typically resolve within 2 to 3 days, therefore for recruitment the duration of symptoms will be limited to one week. During seasonal influenza epidemics, cough and fever are strong indicators of influenza.[67] At UHC, an electronic health record is maintained for each patient, and includes structured data (e.g. checkboxes and plus/minus indicators) to record individual signs and symptoms. Given the ability to require aspects of each note generated for a patient visit, the risk of incomplete or missing data is low. In addition, key signs and symptoms for patients with acute respiratory tract infection (ARTI) are required to be completed by clinicians. The data collection strategy and further details are included later in section 1.4.2.

1.1.5 Search Strategy

The scope of our review will include CDRs in adults seeking outpatient care for clinically suspected influenza. We will conduct a systematic review following the PRISMA guidelines.[68] A flow diagram is presented below as Figure 1 to illustrate the PRISMA search process.[68] Each step of the search strategy and analysis will be performed by two researchers. Any disagreements will be resolved by a discussion between the two investigators. If an agreement cannot be reached, a third investigator will be contacted to make the final decision.

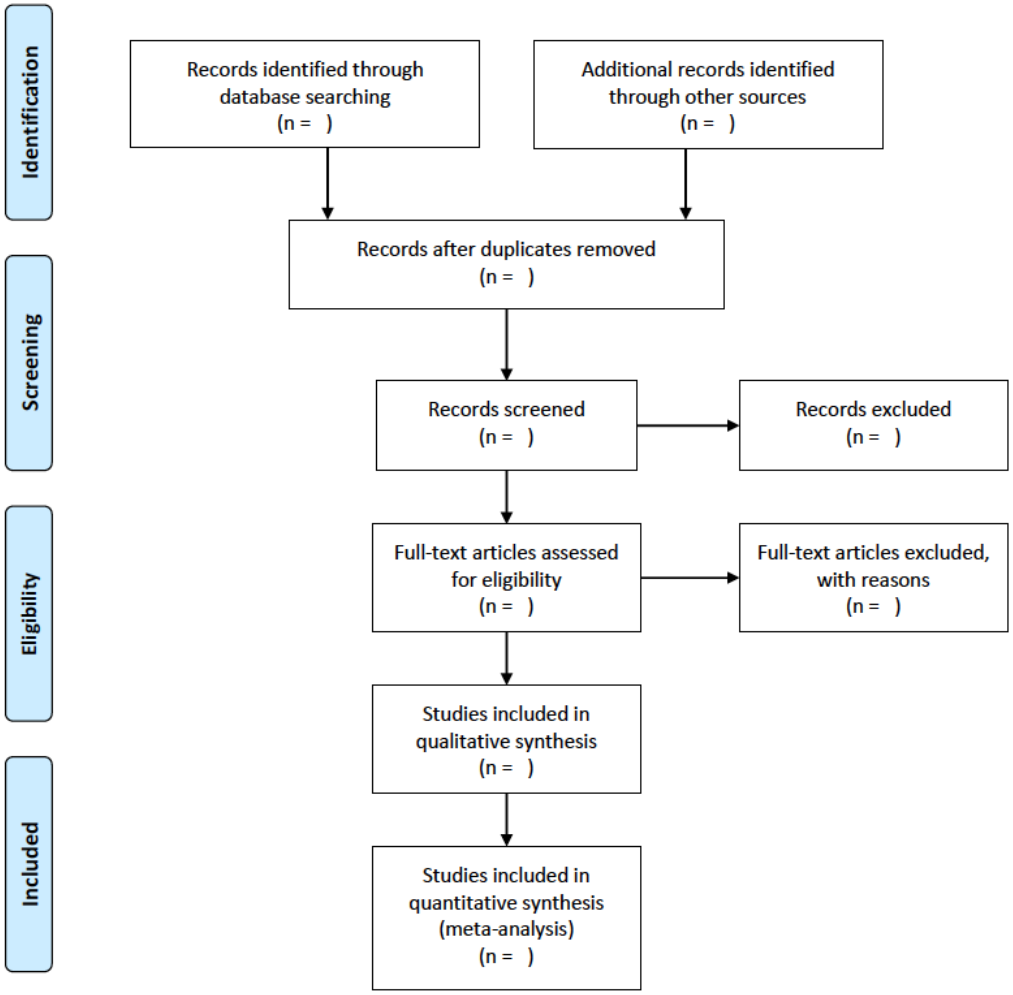

Figure 1.1 PRISMA Flow Diagram for a Systematic Review [68]

We will perform a literature search to identify prediction rules in Medline, EMBASE, Google Scholar, Database of Abstract of Reviews of Effectiveness (DARE), the Cochrane Library and the CDR registry (REF for Fahey). Many researchers have assessed best practices for search strategies in each of the previous databases.[68-73] Each of these articles was taken into consideration when developing the search strategy for each database. Additionally, we reviewed the search strategies of a recent systematic review that used PubMed, Clinical Queries, and Google Scholar.[5] The search strategy for each database is included in Table 5.1 in chapter 5. Our search strategies were developed to be as sensitive as possible to identify the all relevant articles. Currently, the CDR registry is not available to the public. We will communicate directly with the primary investigator, Dr. Tom Fahey, for our search until the registry is released. Each abstract from the search results will be reviewed to ensure that the inclusion and exclusion criteria are met.

In addition to the strategies for the six databases included in our search, we will contact experts in influenza as part of our search strategy. Also, we will review any studies included in a previous systematic review or meta-analysis for clinical diagnosis of influenza. Finally, we will also review the references lists of all included studies to identify additional studies. This will aid us in expanding our results to include all relevant articles, regardless of presence or absence of MeSH terms.

1.1.6 Inclusion and Exclusion Criteria

For a study to be included in the systematic review, it must report the accuracy of a combination of signs, symptoms and/or point of care tests (e.g. a CDR) for the diagnosis of influenza in humans. Studies will be excluded if they are conducted in a specialized population, conducted exclusively in children, conducted in immunocompromised persons, or were not published within the last 25 years. We exclude specialized populations (i.e. persons with chronic diseases such as HIV) and populations with children because our population is a young adult population of overall good health. Additionally, we exclude studies conducted in

immunocompromised individuals as we assume our patients are not immunocompromised young adults seeking care at UHC. Finally, we exclude studies that were published or did data collection greater than 30 years ago to keep information relevant to the current understanding and diagnosis of influenza. We will include all studies from any country. Articles will be excluded if they are case control design as temporality cannot be established in these studies. Articles for influenza outbreaks that are not seasonal, such as the swine flu (H3N1) outbreak of 2009, will also be excluded as these outbreaks are atypical to what is expected for the coming influenza season of 2016-17.

1.1.7 Data abstraction

Based on a review of the abstract, any study appearing to report the accuracy of a combination of signs or symptoms or a CDR for the diagnosis of influenza will be reviewed in full. We define a CDR as a point score or equation based on symptom history and physical examinations. All articles included in previous systematic reviews of influenza diagnosis will also be reviewed in full. The full text of each article will be pulled from PubMed using the PMID number. Articles will be screened for the following information: clinical decision rule, type of care setting, age of patients, study design, influenza prevalence, country, years of data collection, and type of test used to confirm influenza diagnosis. A final list of included studies will be developed, and study description data abstracted in parallel by two investigators.

1.2 Quality Assessment of Included Studies Using a Modified QUADAS-2

1.2.1 Quality Assessment using a modified QUADAS-2

In order to assess study quality of each of our CDRs for diagnostic accuracy, we will be using the Quality Assessment tool for Diagnostic Accuracy of Studies (QUADAS-2).[74] QUADAS-2 is the second iteration of the original QUADAS with the update beginning in January of 2010. QUADAS-2 is divided into four phases: 1) state the review question, 2) develop review specific guidance, 3) review the published flow diagram for the primary study or construct a flow diagram

if none is reported, 4) judgement of bias and applicability. All sections are judged as “low”, “high” or “unclear” risk of bias.[74]

Risk of bias and applicability share three subsections: patient selection, the reference standard, and patient flow.[74] To avoid spectrum bias, we will ensure that a consecutive, random, or convenience sample of patients is enrolled without applying unreasonable exclusion criteria in a prospective or retrospective cohort study. We will ensure that all patients are assessed prospectively and the CDR applied prior to knowledge of the laboratory test. Case control designs enroll patients with known disease and healthy controls; these studies tend to overestimate the accuracy of the test and will be excluded from our analyses. To assess the reference standard, we will examine each study to determine if the conduct or interpretation of the reference standard could have introduced bias. An acceptable reference standard for the CDR will be viral cultures or RT-PCR for influenza diagnosis. For each of these three subsections, applicability is assessed by comparison of the study to the overall review question [74]. We will assess the risk of bias using Appendix A adapted QUADAS criteria.

For each of the thirteen questions in our form the response is dichotomous. CDRs are either at low risk, high risk, or unclear risk for bias. We will describe what qualifies as low risk of bias for each question; failure to meet the described qualification would indicate a high risk of bias for that parameter. Starting with question one, a CDR will be at low risk of bias if a consecutive, convenience, or random sample of patients presenting with cough, influenza like illness symptoms, or suspected influenza was used. A study will be considered at low risk for bias if the selection criteria are clearly described. The study will be classified as low risk of bias if viral culture or RT-PCR was used to classify patients as having influenza or not. Clinical assessment should be obtained at the same time as the reference standard test to keep the risk of bias low. Additionally, all patients should receive the same reference standard test to minimize bias. This reference standard test should be administered regardless of the CDR result. The CDR should be described in sufficient detail that it can be replicated; this reduces

any bias introduced by interrater reliability. The reference standard test should also be clearly described to ensure replication. The CDR should be used by clinicians prior to the results of the reference standard test; the reference standard test should also be interpreted without knowledge of the results of the CDR to keep the risk of bias introduced by analysts' low. The CDR should only be implemented by personnel who would typically have access to the necessary patient data. Finally, any uninterpretable results or withdrawals from the study should be clearly explained to minimize risk of bias. Failing to meet any of the thirteen previously mentioned criteria will result in that criterion being considered at high risk for bias. Studies with nine or more criteria classified as high risk of bias will be considered unfit for validation.

A final assessment of the risk of bias for an included study assesses the flow and timing [74]. We will assess whether all patients were included in analysis and received an acceptable reference standard. Studies that are judged as "high" or "unclear" in most the subsections will be judged as at high risk of bias and excluded from analyses.

1.3 Validation of each Clinical Decision Rule in a College Health Population

We will perform all calculations using R. We will externally validate each clinical prediction rule identified through the literature search using data obtained from UHC at the University of Georgia. Data collection is fully described in the following sections.

1.3.1 Sample Size

A review of previous UHC data regarding influenza-like-illness demonstrated that approximately 600-1200 patients are seen each year. If we assume at least 2/3rds of those patients would be willing to participate, we anticipate a total eligible population of between 400 and 800 patients. Roche has provided 300 Cobas Liat PCR swab kits and reagents for the in-house UHC laboratory, so our final sample size will be 300 that receive PCR and at least 300 patients who will receive usual care. This calculation is described in section 2.3.3.1.

1.3.2 Data Collection

1.3.2.1 Setting

The University Health Center (UHC) at the University of Georgia (UGA) provides primary care, urgent care, and selected specialty services to the 35,000+ students enrolled at the university. The UHC has four primary care clinics, with 20 primary care clinicians available to students during traditional business hours; an urgent care clinic is available Sunday afternoons. UHC is unique in that it is one of just two college health facilities in the nation that has been accredit by the Joint Commission for Ambulatory Care and Primary Care Medical Home. In addition to primary and urgent care, UHC provides dental, counseling and psychiatric services, vision clinic services, a travel clinic, massages, physical therapy, and pharmacy services. Students can make same day appointments, so this health care facility serves as an ideal and convenient location for a study of acute respiratory illnesses such as influenza in a college health population of young adults.

1.3.2.2 Population

The University of Georgia student population demographics from 2014 are included in Table 1.3 in Appendix A. The UGA student population is racially comparable to the entire population of university students enrolled in the United States that identify as White or Asian. However, the percentage of African-American students (8.11% vs 16.0%) and Hispanic/Latino students (4.9% vs 18.0%) is significantly lower than in the overall US university student population.[75]

University students are an interesting subset of the population that often does not receive much research focus. This age group is typically 18 to 24 years of age, with approximately 79% of the US enrolled students falling in this range.[75] The first healthcare visit not accompanied by a parent or guardian often occurs at the UHC. Additionally, all UGA students must live on campus for their first year, other than students coming from one of the 5

counties surrounding UGA. These students live in dormitories and will go on to other crowded housing options for their remaining enrollment, presenting an ideal environment for pathogen circulation. Finally, university students interact with the age groups at highest risk for influenza complication: the very young and the very old. These interactions occur through family events with extended family such as nieces, nephews, grandparents, and great grandparents, often during the winter holiday break when influenza virus is beginning to circulate. Many university students also volunteer in the local community at nursing homes and hospitals. Therefore, the role of students as carriers to these vulnerable populations cannot be ignored. Rapid, accurate diagnosis and notification of a student has the potential to minimize the spread of seasonal influenza, particularly in a pandemic situation, and especially if accurate diagnosis affects their behavior around contact with others and being in crowds or public places.

1.3.2.3 Recruitment of Participants

1.3.2.3.1 Inclusion and Exclusion Criteria

Patients will be selected for the study if they report signs or symptoms of suspected influenza to their medical assistant. As described previously, students presenting with cough or at least two of the following suspected influenza symptoms within the last week at the time of the appointment will be included: headache, fever, chills, fatigue, myalgia, sore throat, or arthralgia. Patients will be excluded if they are less than 18 years of age, if English is not their preferred method of communication for the appointment, if they do not provide consent, or if they withdraw consent at any point in the study.

1.3.2.3.2 Data Collection: UHC Electronic Health Record

The UHC uses an electronic health record (EHR) that is customizable. The same EHR is used throughout the UHC and includes data for every clinic visit. We will work with Dr. Garth Russo, clinician and manager of the EHR at UHC, to access data recorded in the EHR. For the purposes of our study, the respiratory template will be modified to require answers to fields

pertaining to our question. These fields will be determined by our literature review of the signs and symptoms for influenza, signs and symptoms from previous clinical decision rules, and fields necessary to accommodate symptom severity and informed consent. Figure 1.2 below shows how the EHR populates for licensed practical nurses, registered nurses, and clinicians. The data from the EHR is stored on HIPAA secure servers and will be de-identified before being transported off site. Each patient will be assigned a random digit ID number, created and known only by Dr. Russo, to maintain confidentiality of the patient's medical record.

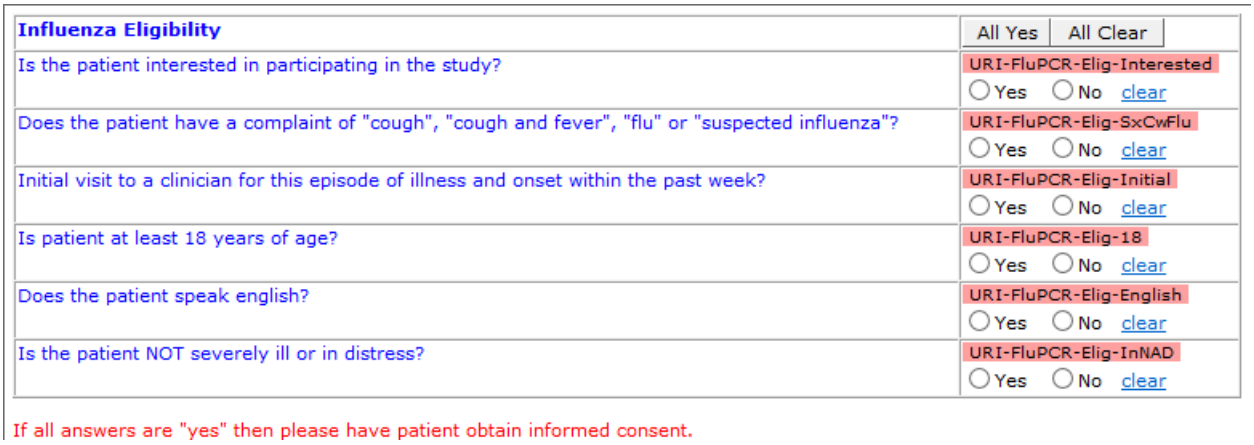

Figure 1.2 Example of Eligibility Criteria in Electronic Health Record from University Health Center

1.3.2.4 Description and Schedule of Clinic Recruitment

UHC has four primary care clinics with 3-5 clinicians in each clinic in a multistory building. It's not practical to randomize our patients given this setup, so we will be conducting a quasi-experimental study. Data collection will begin in Blue Clinic for the first week of enrollment, December 5-9, 2016. The study will resume on January 3, 2017 in the Blue and Green Clinics. We will recruit patients in the Blue and Green Clinics until we reach 130 patients recruited OR the peak of flu season. Once either is reached, we will then recruit exclusively in the Gold Clinic until all PCR kits have been used (approximately 300). Patients that meet inclusion criteria will be asked to participate in the study. For the first half of the study, the Gold Clinic patients will serve as our controls, receiving the standard of care. This standard of care

may or may not involve use of a rapid serologic point of care test (FluView, CDC), which is less accurate than the PCR test used in the intervention arm. For the second half of the study, the Blue and Green Clinics will serve as the controls, receiving usual care. This will help control for differences between providers and the care received at each clinic, by allowing each clinic to serve as a test site and control site throughout the study duration. The recruitment of usual care patients is described in 1.3.2.6.

The UHC has a full medical laboratory that performs most diagnostic testing for patients. The exception is patients on United HealthCare insurance, whose tests are sent off site to Quest Diagnostics. For patients in the “PCR group”, UHC laboratory staff will perform the PCR test, log results in the EHR and notify the clinician of the results in less than 30 minutes, and as soon as 15 minutes as previously described. UHC laboratory and clinic staff will be trained over a two-month period in September and October in the rapid point of care PCR test. The Diagnostic Services Manager in the UGAHC laboratory, Houston Taylor MT (ASCP), has conducted training of laboratory staff, and medical assistants have been trained in the proper technique for obtaining a nasopharyngeal specimen. Recruitment will begin December 5 and end by April 30. The study will be terminated early if 300 patients have received nasopharyngeal swabs.

1.3.2.5 Recruitment Procedures

Patients complete an intake questionnaire when scheduling their appointment online or upon their arrival for check in at the clinics in UHC. This questionnaire gathers chief complaint information, symptom history, and a brief updated medical history. Figure 1.3 below illustrates the patient experience through the study.

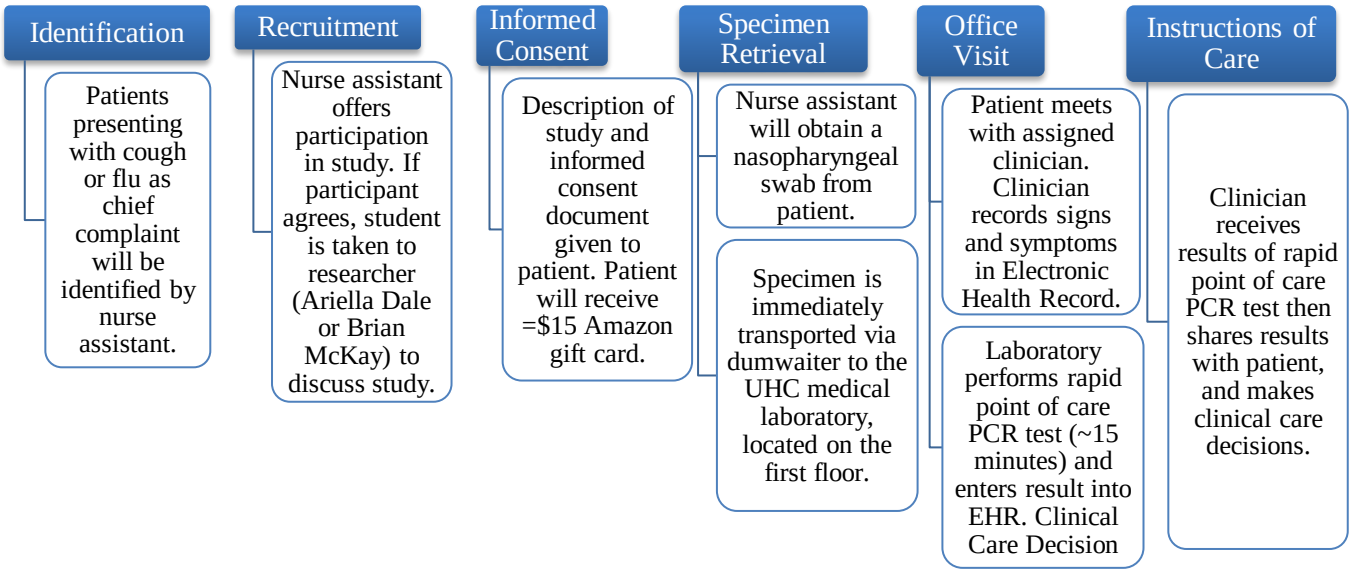

Figure 1.3 Methods of Patient Recruitment, Specimen Retrieval, and Clinician Care.

First, the clinic assistant will identify the patient as having a chief complaint of “cough”, “cough and fever”, “flu” or “suspected influenza”. Specifically, students presenting with cough or at least two of the following suspected influenza symptoms within the last week at the time of the appointment will be included: headache, fever, chills, fatigue, myalgia, sore throat, or arthralgia. if they would like to participate in the study. The study will begin in December of 2016 and continue until all PCR swabs are used or April 2016 is reached. If so, the clinic assistant will notify a study investigator (Ariella Dale, Brian McKay, or Mark Ebell) that the patient is interested. The study investigator will meet with the patient to obtain their informed consent. During the informed consent process, three forms will be used and are included in Appendix B. The first form, our patient recruitment script, will be read to each patient. After reading the script, the investigator will ask the patient the six questions listed at the bottom of the form. If the patient says yes to all six questions, the investigator will continue to the informed consent document.

The informed consent document is 3 pages, containing information as required by the Institutional Review Board at the University of Georgia. This document includes the researcher's statement, purpose of the study, principal investigator and contact information, study procedures, risks and discomforts, benefits, incentives for participation, privacy and confidentiality, voluntary participation statement, instructions for injury incurred during research, and a description of how to contact investigators with questions. Patients who wish to consent will sign the document witnessed by the investigator. They will also list their UGA email address to receive the follow up survey in Aim 3 as well as their "81 number". The "81 number" is a student identification number that will be used to link the surveys from Aim 3 to the EHR.

The final document included in the patient packet is a receipt for compensation for participation. This will be filled out by the patient and witnessed by the investigator. Upon completion of all forms, the patient will receive the $15 Amazon gift card.

Once informed consent is received, the investigator will notify the clinic assistant to collect a nasopharyngeal swab. This swab will then be sent to the UHC medical laboratory for Cobas Liat polymerase chain reaction (PCR) testing. Patients who receive a swab will receive their compensation from the investigator. The clinician will then be notified that the patient is ready for their office visit and meet with the patient. Simultaneously, the UHC medical laboratory will input the results of the PCR test into the EHR of the patient within approximately 35 minutes of collection (20 minutes for the test, 15 minutes for transport, preparation, and entering of results). Clinicians will then review the results of the test in the patient's EHR prior to making any care decisions. The clinician will then meet with the patient and assign treatment, which will be recorded in the EHR.

1.3.2.6 Patients Receiving Usual Care

Patients will be classified to the usual care group if they had an appointment in the Blue, Green, or Gold clinics from December-April of 2017 when PCR testing is not being conducted. Patients will be selected for the usual care group up until the final day of PCR testing, if that

comes before April 2017. Our usual care patient group will begin with patients who have a chief complaint of “cough”, “cough and fever”, “flu” or “suspected influenza” during the study timeframe. Specifically, the patient must have a cough or at least two suspected influenza symptoms. This must be the patients’ first medical visit since symptom onset. If a patient receives a rapid influenza test, this laboratory result will be included to classify the patients. Patients who are positive and receive an influenza diagnosis will be classified as having influenza. Patients who are negative for the rapid influenza test and/or do not have a final diagnosis of influenza will be classified as not having influenza. Patients that are influenza negative but receive a final diagnosis of influenza will be considered influenza positive. We will include a minimum of 300 patients in the usual care group; up to 600 patients will be included if possible. These patients will be pulled from the UHC EHR database by the Medical Information Officer, Dr. Garth Russo.

1.3.2.7 Dataset Development and Management

Sign, symptoms, demographics, laboratory results, final diagnosis, and prescription(s) for each patient will be retrieved from the EHR and de-identified by Dr. Garth Russo. The data will only include information from the single influenza related visit and will be exported in a .csv format to Ariella Perry Dale. Ms. Dale will maintain the dataset as it expands with increasing participants, linking informed consent with EHR information. A codebook will be developed and maintained on the “UGA Flu Study” Google Drive account (ugaflustudy@gmail.com).

1.3.3 Validation of a Clinical Decision Rule Developed Using Logistic Regression or CART

1.3.3.1 Data Cleaning

We will validate each CDR by first building a model that represents each rule in R. We will then calculate the prevalence of influenza in the UHC patient population [76]. Next, we will confirm that the variables we have collected are in the same format as the variables in each CDR. For example, if cough is simply “present” or “absent” in the CDR, we will ensure that our

variable is also dichotomous from the UHC data. After building a representative model for each CDR, we will then move to assessing its discrimination, calibration, and classification accuracy.

1.3.3.2 Discrimination

An ROC curve is a plot of the true positive rate (sensitivity, on the y axis) against the false positive rate (1 – specificity, on the x axis) for a range of possible cutoffs to define an abnormal test. We will apply each CDR to our data and calculate the sensitivities and specificities to build an ROC curve. For example, if a CDR provides a point score from 0 to 6, we will calculate and plot the sensitivity and specificity for cutoffs of >0, > 1, >2, >3, >4, and >5 to define an abnormal result. The area under the curve (AUC), also called the c-statistic, is proportional to the ability of a CDR to discriminate influenza positive patients from influenza negative patients. The c statistic is a forced choice comparison. An example of forced choice comparison is randomly selecting a person who is outcome positive and a person who is outcome negative. The c statistic is the probability that our test will correctly classify a patient with the outcome as having the outcome and a patient who does not have the outcome as not having the outcome. The c statistic ranges from 0.5 for a test that does not discriminate at all between patients with and without the disease, to 1.0 for a test that always classifies them correctly (perfect discrimination). (A c statistic of 0 means that the test misclassifies all patients with disease as healthy, and all healthy patients as diseased.) We will use the AUC to measure the discrimination of the CDR. Figure 1.4 presents an example ROC curve from SAS. Figure 1.4 was obtained from previous research regarding group A beta-hemolytic streptococcus (GAS) in the UHC population of adults. As denoted in the figure, the AUROCC=0.6614, which we would interpret as the model being fair at discriminating patients to their outcome (GAS) appropriately. We interpret this model as poor because it is slightly better than AUROCC=0.5, which is a worthless test.[77] There are guidelines for interpreting AUROCC; 1 is perfect, 0.99-0.9 is excellent, 0.89 to 0.8 is good, 0.79 to 0.70 is fair, 0.51 to 0.69 is poor, and 0.5 is worthless.[77] We

will report the AUROCC and the 95% confidence intervals for each CDR. We will use the pROC package in R to complete this part of the analysis.[78]

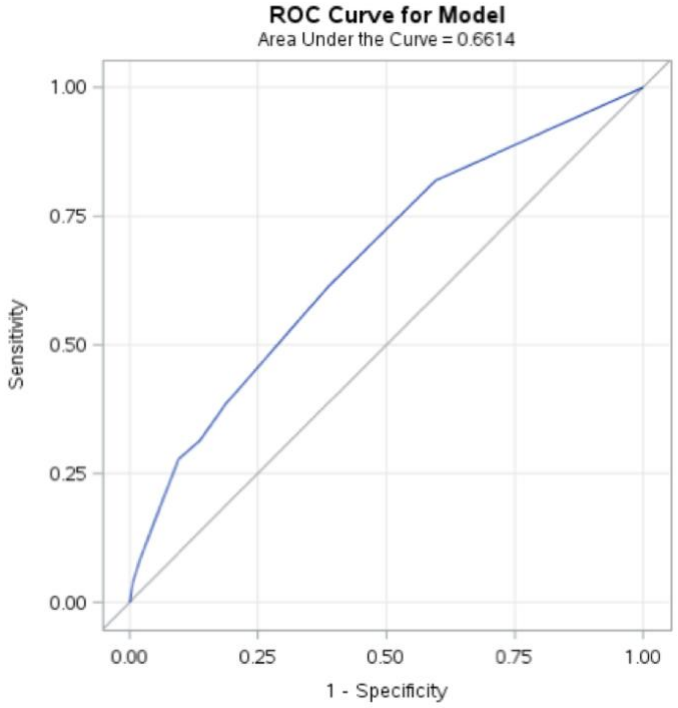

Figure 1.4 ROC Curve Example from SAS 9.4

1.3.3.3 Calibration

Next, we will create calibration plots for each CDR. Since our outcome is binary (patients either have influenza confirmed by PCR or they do not), we will use the Hosmer-Lemeshow test to produce calibration graphs. The Hosmer-Lemeshow test is related to goodness-of-fit statistics.[55] The Hosmer-Lemeshow test measures the difference between predicted and observed outcomes. This will produce a Pearson Chi-Square statistic ($\chi 2$) along with a calibration graph (Figure 1.5) and table. We will assess the Pearson Chi-Square statistic and determine if the clinical prediction rule is a reasonable fit. A $\chi 2$ with a p value <0.05 will be considered poorly calibrated.[55] We will also assess the calibration slope for each CDR. The calibration slope, when used for external validation, reflects the combined effect of overfitting and the true differences in effects of predictors. Ideally a calibration slope will be 1. A calibration

slope value <1 can indicate overfitting or the need for shrinkage of the regression coefficients.[58] A calibration slope value >1 indicates under fitting of the model.[79]

There are limitations to using the Hosmer-Lemeshow test for calibration. First, the test can have poor power in smaller samples.[55] Specifically, a Hosmer-Lemeshow test is not useful in validation as the results are often not statistically significant.[55] Neither of these points will be of concern in our analysis, as we will have a moderate sized sample (n=300) and are using the Hosmer-Lemeshow test for the purposes of external validation. An example of a calibration graph produced by the Hosmer Lemeshow test is included as Figure 1.5. Figure 1.5 is a calibration graph produced by the Hosmer-Lemeshow test in STATA for previous research about GAS in the UHC population. Based on Figure 1.5 and its accompanying statistics ($\chi 2=1.17$, $p=0.8830$), the model is well calibrated for the data. We will identify each CDR that meets Hosmer-Lemeshow test statistics for significance and report the results of each test.

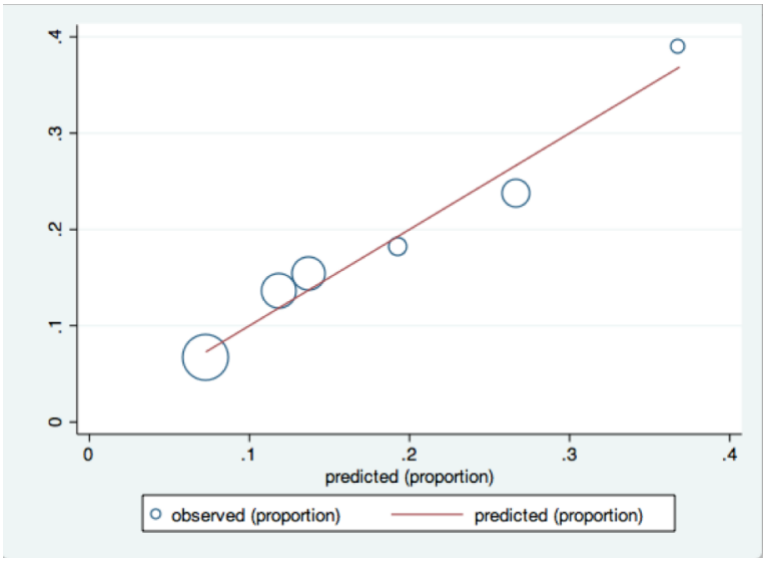

Figure 1.5 Example Calibration Graph of a Hosmer-Lemeshow Test

1.3.3.4 Classification Accuracy

We will then apply each model to our UHC data set to calculate individual patient scores. We will stratify the scores into the risk groups specified by the CDR; often this will be low vs high, or low vs intermediate vs high risk groups.[76] The stratum specific positive and negative

likelihood ratios, predictive values, and post-test probabilities for the risk groups will be calculated. The discrimination, calibration and classification accuracy measures can be applied to a CDR created through logistic regression or classification and regression trees.[76]

1.3.3.5 Selection of Best Clinical Decision Rule

The selection of the best clinical decision rule will be based on the discrimination, calibration, and classification accuracy. Additionally, the rule must be feasible and easy to implement in outpatient care. We will judge the number of parameters included in the CDR by its ease to remember and ease of assessment in a patient. An ideal CDR will be easy for a clinician to recall, not involve parameters that are subjective, and performs well when validated.

1.4 Analysis: Determining Clinical Predictors of Influenza in a College Health Population

1.4.1 Background

Development of a CDR has already been briefly described in this aim and includes: the identification of clinical predictors, assessment of these predictors and the outcome in an unbiased manner, then regression analyses will aid us in building a prediction model relevant to our patient population.

1.4.2 Objective

Determine the significant clinical predictors of influenza in a university student population. We hypothesize that cough, fever, myalgia and headache will be clinically and statistically significant predictors of influenza in university students.

1.4.3 Developing Clinical Decision Rule from University Student Patient Data

1.4.3.1 Identification of Clinical Predictors and Outcome

Symptoms of suspected influenza as previously described will be included in our model building. Additionally, any other signs or symptoms identified through our systematic review of

previously developed CDRs will be included. Our outcome is binary: influenza diagnosis as determined by the PCR test.

1.4.3.2 Assessment of Clinical Predictors in University Student Population

All analyses will be performed in R. First the frequencies, sensitivity, specificities, likelihood ratios and predictive values will be calculated for each sign and symptom.

1.4.3.3 Analysis: Logistic Regression

We will build a model for predicting influenza in university students based on signs and symptoms. We will use the lasso technique (least absolute shrinkage and selection operator) for logistic regression to build our model and explore other model building techniques such as a fast and frugal tree. Lasso logistic regression is advantageous for our model building since we are developing a prediction model that needs to be memorable for clinicians [80].

The lasso technique is a type of penalized regression, which is a flexible shrinkage approach that works well when the expected number of events per variable could possibly be less than 10.[80] The lasso constrains the sums of the absolute values of the regression coefficients, meaning it can exclude parameters from a final model by shrinking their coefficient to 0.[81] The lasso estimate of $(\widehat{\alpha, \beta})$ is defined below in equation 3. We will use the glmnet package in R to perform the lasso regression. The glmnet package builds the logistic regression model using the lasso in relation to the tuning parameter, lambda. The glmnet package also will cross validate the model to evaluate its performance.

$$\widehat{\alpha, \beta)} = \arg\min\{\sum_{i=1}^{N}(y - \alpha - \sum_j \beta_j x_{ij})^2\} \text{ subject to } \sum_j |\beta| < t$$

Equation 3. Definition of the Lasso Estimate [81]

1.4.3.4 Fast and Frugal Tree Analysis: FFTree Package

We will use a fast and frugal tree analysis, a non-parametric method, to identify predictors of influenza. Our outcome is binary and is influenza diagnosis as determined by the

PCR test. Developing a CART model consists of two phases: training and testing. We will use the FFTree package developed for R.[82]

We will split the data into a training and testing data sets at a 60:40 ratio. Using the training data set, the FFTree construction algorithm will complete four tasks. These four tasks may not be completed in this exact order; 1) select cues, 2) determine a decision threshold for each cue, 3) determine the order of the cues, and 4) determine the exit for each cue.[82] To accomplish these tasks, the FFTree construction algorithm relies on the "dfan" and "ifan", a class of the "fan" algorithms developed by Phillips and colleagues.[82] The "dfan" and "ifan" algorithms are advantageous for addressing the tree size issues and sensitivity weighting necessary for an fast and frugal tree.[82] This is accomplished by taking advantage of the very nature of a fast and frugal tree: each cue must produce at least one exit node. The combination of exit nodes in a fast and frugal tree is known as an "exit structure". fast and frugal tree are adaptable and can consider all exit structures. The "dfan" and "ifan" algorithms explore the "fan" of possible trees for an analysis that can include a positive rake or zig zag structure. After creating the fan, the "ifan" and "dfan" algorithms selected the fast and frugal tree that maximizes the weighted accuracy.[82] It is also possible to limit the tree to nodes that only substantially increase accuracy, limit the size of the fast and frugal tree, or nodes that do not classify enough cases.[82]

Following selection of the tree from the "ifan" and "dfan" algorithms that has the highest weighted accuracy we then enter the testing phase. In testing, we use the algorithms to predict the criterion values using new data (the testing data set, 40% of the original data).[82] These criterion values are determined by using the parameter values (i.e. the cues) developed in the training phase. The testing phase allows us to assess the algorithms abilities to make accurate predictions in a new data set. The FFTree package displays the final model fitted using the testing data, including a wide variety of statistics including sensitivity, specificity, and weighted accuracy.

A fast and frugal tree is advantageous for its speed and frugality. Speed refers to the mean number of cues (mcu) before a case is classified.[82] Frugality is the amount of information that the algorithm ignores in order to make a classification. This is quantified by “percent cues ignored” (PCI).[82] In addition to implementing the “ifan” and “dfan” algorithms, the FFTree package implements four additional analyses commonly used in classification. This includes logistic regression, supported vector machines, random forests, and a classification and regression tree. The FFtree implements the default parameters for these four analyses as set by their corresponding R packages. The 8 fast and frugal trees and four analyses are then all plotted on a single receiver operating characteristic curve for comparison. Selection of the best model for predicting the data is determined by weighted accuracy, this model also maximizes the area under the receiver operating characteristic curve (AUROCC). We will use the FFTree package to develop a novel CDR for influenza in our college health population.

AIM 2: Impact of using the Cobas Liat Polymerase Chain Reaction Test as a Diagnostic Test for Patients with Suspected Influenza

2.1 Background

2.1.1 Influenza in the United States and College Students

Influenza continues to be an important health problem in the United States, particularly for groups at high risk of hospitalization and death. This includes the very young (<5 years of age), the old (>65 years of age), pregnant women, residents of long term health care facilities, and those with comorbidities such as chronic pulmonary disease and neurological disorders.[83] The burden of influenza in the United States is determined by several factors including the timing of the influenza season, the number of people vaccinated, the subtypes of influenza virus included in the vaccine, and the characteristics of the viruses that are circulating.[83] The Centers for Disease Control and Prevention (CDC) Influenza Surveillance System and FluView monitors the number of outpatient visits, hospitalizations, and deaths attributed to influenza like illness.[83]

Previous influenza epidemics had a large burden in the United States, most notably the 1918 influenza pandemic. Recently, the 2009 influenza A (H1N1) epidemic in the United States affected approximately 10% of students on many college and university campuses.[15] The 2009 epidemic highlighted the need for further research about influenza in college and university students. These students tend to live in crowded dormitories or apartments, which may serve as a reservoir for diseases such as influenza to circulate.[84] While hospitalization rates are low, influenza can affect a student's academic performance, lead to unnecessary antibiotic and antiviral prescriptions, and increase the use of outpatient health care services. At the peak of the H1N1 influenza season, approximately 13% of primary care visits were for influenza like illness at college health services.[14] To address these effects, university and college students are encouraged to receive an annual influenza vaccination. Unfortunately, recent studies indicate that only 12-30% of these students receive their influenza vaccine.[14] A study in 2007 revealed

that 29% of students believed that the influenza vaccination could infect them with influenza.[85] Similarly, a study of the 2009 H1N1 outbreak in England revealed that college students were hesitant to receive the vaccine due to a lack of information, fear of side effects, lack of perceived risk, and inconvenience.[35] Therefore, there are many challenges surrounding the prevention of influenza and its burden on healthcare.

2.1.2 Treatment and Testing for Influenza

Current treatment of influenza is primarily supportive care. Antiviral medications, also known as neuraminidase inhibitors, may also be used. Antiviral medications currently recommended by CDC guidelines include oseltamivir (Tamiflu) and zanamivir.[27] Guideline consistent use of antiviral medications reduces the duration of symptoms, and in observational studies appears to reduce the risk of complications that require antibiotics, and potentially decrease hospitalization and mortality rates.[86] In addition, antiviral medications were viewed as a cost-effective treatment.[87] However, recent reviews of published and unpublished data show that the use of these medications does not significantly reduce hospitalizations or complications, and are costly.[28-30] Additionally, CDC guidelines have dictated that oseltamivir must be started within 48 hours of symptom onset.[27] This is not the case, as most published and unpublished clinical trial patients began antiviral medication within 36 hours of symptom onset.[28,29] Starting oseltamivir within 24 hours of symptom onset reduced symptom duration by approximately 28.8 hours; beginning treatment within 24 to 36 hours reduced symptom duration by approximately 14.8 hours.[28] As the medication costs approximately $145 for a 5-day prescription [88], the symptom benefits must be weighed against the financial burden or potential side effects including nausea and vomiting.[27] One study found that 38% of antiviral prescriptions are guideline inconsistent due to prescribing later than 48 hours after symptom onset or a in patients with a negative rapid influenza test.[57] The lack of data supporting a benefit for antiviral start more than 36 hours after symptom onset suggests that the percentage of guideline inconsistent antiviral prescriptions may in fact be higher.

Antibiotic prescriptions are also frequently given to patients with influenza. A recent study demonstrated that 25% of patients with a diagnosis of influenza received an antibiotic prescription.[56] In patients with influenza and a low risk for bacterial infections, antibiotics are guideline inconsistent. The use of antibiotics remains common for many viral acute respiratory infections, emphasizing the need for clinician and patient education regarding their ineffectiveness for these pathogens.[56] One reason for the over-prescription of antibiotics is the overlapping signs and symptoms between many respiratory infections. When a patient presents with cough and fever, it is important to be able to rule out pneumonia to eliminate the need for an antibiotic. Clinicians cite concern of a bacterial pneumonia infection as one of the leading reasons for prescribing an unnecessary antibiotic.[89] A recent validated CDR identified three criteria for ruling out pneumonia: absence of dyspnea, a daily feeling of increased body temperature since the onset of a cough, and C-reactive protein levels below 50 μg/mL.[89,90] This CDR can be easily used in clinical practice to increase the guideline consistent treatment of respiratory infections. However, the use of CRP is not currently an approved test for point of care use by the Food and Drug Administration. Therefore, alternative CDRs must be considered for our study to determine the guideline consistency of antibiotic use, such as the Gennis rule, the Hecklering rule, and the Diehr rule.[91-93] These CDRs are explained in section 2.3.5.

Another reason for the over-prescription of antibiotics is low confidence in the rapid influenza test. The use of rapid influenza tests for diagnosing patients is not advised [94]. For example, in a study of BinaxNOW, the rapid antigen test is 61% sensitive; many rapid influenza tests have a poor sensitivity [94, Hurt, 2007 #110]. This weakness in the rapid influenza test reduces its utility in clinical practice and can potentially lead to the overuse of antibiotics or antivirals. Polymerase chain reaction (PCR) tests are the gold standard in influenza diagnosis but until recently have taken 24 to 36 hours to yield results.[94] The recent introduction of a rapid point of care PCR test combines the timeliness of the rapid flu test with the increased sensitivity and specificity of traditional PCR. Using a nasopharyngeal swab, the rapid point of care PCR test

takes approximately 15 minutes to complete at point of care. The result is a qualitative PCR result for the presence or absence of Influenza A or Influenza B. This test is 99.2% sensitive (95% CI: 95.1-99.9%) and 100% specific for influenza A virus (95%CI: not reported), and 100% sensitive (95%CI: 83.1-100%) and 100% specific for influenza B viruses (95%CI: not reported) when compared to a reference laboratory influenza A and B real-time PCR assay.[12] With the increased certainty in the results from a rapid point of care PCR test, the clinician can now have greater confidence in the final diagnosis. This may decrease guideline inconsistent prescribing of antivirals and antibiotics in patients with acute respiratory infections. The rapid point of care PCR test has the potential to be a useful test in the clinical care of influenza but has yet to be independently tested.

2.2 Objective

The primary goal of our study is to identify whether the rapid point of care PCR test significantly increases the number of patients who receive guideline consistent treatment with antibiotics and/or oseltamivir (Table 2.1). Our secondary goal will be to assess the impact of the rapid PCR test on return visits.

2.3 Methods

2.3.1 Setting

The University Health Center (UHC) at the University of Georgia (UGA) provides primary care, urgent care, and selected specialty services to the 35,000+ students enrolled at the university. UHC has been previously described in 1.3.2.1.

2.3.2 Population

The population at UGA has been previously described in section 1.3.2.2.

2.3.3 Data Collection and Source

2.3.3.1 Sample Size

The sample size for this data set has been previously described section 1.3.1. Our final sample size will include 300 PCR tested patients and a minimum 300 influenza patients who received usual care (possibly more, depending on how many patients are available). We will use equation 2.1 below to calculate the expected difference between the two groups. We assume an 80% power, a standard deviation of 0.5, and an alpha of 5%. Given our parameters, we expect to detect an 8% difference between the two groups. If the standard deviation was 0.3, we can detect a 4.9% difference. If the standard deviation was 0.6, we can detect a 9.7% difference.

$$n = \frac{2\left(Z_\alpha + Z_\beta\right)^2 \sigma^2}{\Delta^2}$$

$$600 = \frac{2(1.96 + 0.8416)^2 (0.5)^2}{\Delta^2}$$

$$\Delta = 8.09\%$$

Equation 2.1 Aim 2 Sample Size Calculation

2.3.3.2 Collection

Data collection has been previously described in section 1.3.2. In summary, we will recruit participants from December 2016-April 2017 or until our 300 rapid PCR test kits are used at UHC. While patients are being actively recruited for the PCR treatment group, the other clinic will continue to treat patients with influenza using usual care. These patients, described as our usual care patients, are described in section 1.3.2. After data collection is complete at UHC, we will then assign each patient to their appropriate exposure and outcome definitions based on the section 2.3.5.

2.3.4 Institutional Review Board and Funding

Institutional Review Board approval has been obtained from the University of Georgia. Patients will give informed consent prior to administration of nasopharyngeal swab. Patients will be compensated $15 for participation in the nasopharyngeal swab and $10 for completion of our follow up survey at 5 days' post appointment.

2.3.5 Exposure and Outcome Variable Definitions

To address our objectives, we need clear definitions of our outcome and our exposure. Our exposure will be influenza diagnosis and our outcome will be guideline consistent or inconsistent treatment classification. For patients who have received the rapid PCR test, the exposure and outcome definitions are as follows. A patient will be considered influenza positive if they had a positive rapid point of care PCR test. A patient will be considered influenza negative if they had a negative rapid point of care PCR test. For patients who received usual care will be classified as influenza positive if they have a final diagnosis from their clinician of influenza. Patients who received usual care will be considered influenza negative if influenza is not listed as one of their final diagnoses.

Defining treatment as guideline consistent or inconsistent is more complex than defining our exposure, due to the overlapping symptom presentation of many respiratory diseases. We developed table 2.1 to illustrate what would be guideline consistent and guideline inconsistent treatment dependent on diagnosis. Tamiflu (oseltamivir phosphate) is only guideline consistent when administered within 48 hours of symptom onset in patients with influenza confirmed by PCR or clinician diagnosis per the drug companies' instructions. Antibiotics are guideline consistent in patients with a high risk of pneumonia or a final clinical diagnosis of a bacterial infection. Patients who are diagnosed with influenza greater than 48 hours of symptom onset, that do not have influenza, are at low risk for pneumonia, and do not have a bacterial infection as a clinical diagnosis should not receive Tamiflu or antibiotics. Unfortunately, our data collection does not include the measurement of C-reactive protein as this is not an approved

point of care test in the United States. C-reactive protein is necessary to apply several CDRs for ruling out pneumonia.[76,89,90] We must therefore consider other CDRs to identify patients at high risk for pneumonia that do not require CRP.

A 2007 review of predicting pneumonia in patients presenting with a cough identified three CDRs that have been validated.[91-93,95] Of the three validated CDRs, the Hecklering rule can be easily applied using our medical record data.[93] The Hecklering rule gives one point for the each of the following patient characteristics: temperature greater than 100.7*F, heart rate greater than 100 beats per minutes, crackles, decreased breath sounds, and the absence of asthma.[93] Patients with a score of 4 or 5 would be considered at increased risk for pneumonia. We therefore define that an antibiotic prescription would be guideline consistent for patients at an increased risk for pneumonia or with a diagnosis of a bacterial infection. Therefore, an antibiotic will be considered guideline inconsistent in patients who are influenza negative, are considered low risk of pneumonia based on the Hecklering rule, and/or do not have a diagnosis of another bacterial infection. Other bacterial infections that could guideline consistently be treated with an antibiotic include acute sinusitis, bronchitis, and urinary tract infection.

Table 2.1 Guide for Determining Guideline Consistency of Treatment

Diagnosis	**Guideline Treatment**	
	Oseltamivir	**Antibiotics**
Influenza positive (PCR confirmed or final clinical diagnosis)	Consistent **(<48 hours onset)**	Inconsistent
No influenza, but high risk for pneumonia and/or bacterial infection diagnosis	Inconsistent	Consistent
No influenza, low risk for pneumonia and no bacterial infection diagnosis	Inconsistent	Inconsistent

2.3.6 Analysis: Primary Objective

All statistical analyses will be performed in R. We will first describe the data by sociodemographic, signs, symptoms, and laboratory tests. We will use chi-square testing to

determine any differences between treatment groups; a p value less than 0.05 will be considered statistically significant.

We will then determine whether care guided by a rapid PCR test is an independent predictor of guideline consistent treatment. The outcome of our study will be the dichotomous variable treatment (guideline consistent vs inconsistent) (Table 2.1). Guideline inconsistent treatment will be coded as the reference group. We will first assess this relationship with a simple logistic regression model for y (treatment)= x (PCR tested vs. not). We recognize that there are other variables that potentially confounded this relationship. These variables include the signs, symptoms, patient demographics, clinic assignment, and clinician type (MD vs other). We will first assess these variables with a univariate analysis to determine outcome-variable and exposure-variable relationships. Any relationships that are greater than 10% different from the exposure-outcome relationship will be considered potential covariates and will be included in our model building. We recognize there could be interaction between potential covariates, as many signs and symptoms work synergistically. These will be identified prior to model building through correlation and bivariate analyses.

After we have identified our potential covariates, we will first build a logistic regression model through a manual forward addition using Aikake Information Criteria (AIC). The logistic regression model takes the form of equation 2.1 below no matter what strategy is used to obtain it.[96] The will be final model will be displayed in Table 2.5 in Appendix 2.

$$Logit\ P(x) = \ln\frac{P(x)}{1-P(x)} = \ln[\frac{{}^{1}\!/_{1+e^{-(\alpha+\sum\beta_i X_i)}}}{1-\left({}^{1}\!/_{1+e^{-(\alpha+\sum\beta_i X_i)}}\right)}] = \ln[e^{(\alpha+\sum\beta_i X_i)}] = \alpha + \sum\beta_i X_i$$

Equation 2.1 Logistic Regression Model

We can use the logistic regression model can be interpreted using odds, and from odds the odds ratio.[96] T calculate the odds and odds ratio, assume that the presence and absence of a symptom have values of X_1 and X_2. From the logistic regression model presented in Equation 2.1 the odds ratio can be calculated using equation 2.2.

$$\phi = \frac{\frac{P(X_1)}{1-P(X_1)}}{\frac{P(X_2)}{1-P(X_2)}} = \frac{\frac{1/}{1+e^{-(\alpha+\sum\beta_i X_{1i})}}}{1-\left(1/_{1+e^{-(\alpha+\sum\beta_i X_{1i})}}\right)} = \frac{e^{-(\alpha+\sum\beta_i X_{1i})}}{e^{-(\alpha+\sum\beta_i X_{2i})}} =$$

$$(continued\ from\ above) = e^{-(\alpha+\sum\beta_i X_i)} - e^{-(\alpha+\sum\beta_i X_i)} = e^{\sum_i^k \beta_i (X_{1i}-X_{2i})}$$

Equation 2.2. Calculating the Odds Ratio from a Logistic Regression Model

Given the equation for the odds ratio, for every unit increase in x the odds that the variable (i.e. characteristic, trait) is present is increased by a multiplicative factor of e^{β}.[96]

A logistic regression will be fitted to the data, using a manual forward selection process based on Aikake information criteria (AIC).[97] The change in AIC will be measured between the initial model with the addition of one covariate per model. Change in AIC is easy to interpret and allows a quick determination of strength of evidence when comparing a list of candidate models. The list of candidate models in each step will be compared to the best model selected in the previous step for a positive change in AIC. The model that gives the greatest change in AIC will be selected as the best model. Covariates continue to be added to this model until the change in AIC is less than 4.[97] If the change in AIC is less than 4, then no additional terms will be added to the model.

2.3.7 Analysis: Secondary Objective

All statistical analysis will be performed in R. We will define returning of patients as patients who schedule a follow up visit within two weeks of their diagnosis. This return visit can be scheduled by the patients calling in to the clinic or through the nurse follow up phone call. Not all patients receive a follow up phone call. Most of the patients who do have return visits will schedule the appointment themselves. This outcome variable will be dichotomous; if a patient had a return visit they are a “yes”, a “no” if they did not.

We will first assess the relationship between return visit and use of the PCR test with a simple logistic regression model for y (return visit) = x (PCR tested vs. not). We recognize that

there are other variables that potentially confounded this relationship. These variables include assess the signs, symptoms, patient demographic, clinic assignment, and clinician assignment. Investigators will first assess these variables with a univariate analysis to determine outcome-variable and exposure-variable relationships. Any relationships that are greater than 10% different from the exposure-outcome relationship will be considered potential covariates and included in our model building.

After we have identified our potential covariates a logistic regression will be fitted to the data, using a manual forward selection process based on Aikake information criteria (AIC).[97] The change in AIC will be measured between the initial model with the addition of one covariate per model. Change in AIC is easy to interpret and allows a quick determination of strength of evidence when comparing a list of candidate models. The list of candidate models in each step will be compared to the best model selected in the previous step for a positive change in AIC. The model that gives the greatest change in AIC will be selected as the best model. Covariates continue to be added to this model until the change in AIC is less than 4.[97] If the change in AIC is less than 4, then no additional terms will be added to the model.

2.3.8. Limitations

The use of the rapid point of care PCR test as our gold standard faces criticism for being a qualitative test. While the rapid point of care PCR test can only detect presence or absence of our pathogen, we are only testing in symptomatic patients. Therefore, we eliminate the concern of influenza being present without pathogenicity. Additionally, we are not randomizing the use of the PCR test because it is not feasible at UHC. We address this limitation by alternating between clinics. The lack of C reactive protein testing at UHC and its lack of FDA approval limits our ability to use a highly accurate CDR for classifying our patient's risk for pneumonia. Finally, we are not able to confirm all patients with a pneumonia diagnosis with a chest X-ray. However, some patients do receive chest x-rays at UHC as deemed necessary by their clinician.

AIM 3: Influenza Diagnosis and Student Behavior

3.1. Background

3.1.1. Influenza in College and University Students

Acute upper respiratory infections are a significant source of morbidity in adults each year with an annual incidence of 2 to 4 episodes per adult.[98] Influenza has a significant economic burden of over $87 billion per year in the United States.[99] Additionally, an average of 610,660 life-years lost, 3.1 million hospitalized days, and 31.4 million outpatient visits are attributed to seasonal influenza in the United States.[99] This represents a significant burden to the United States workforce, the elderly (>65 years of age), and the very young (>2 years of age).

The burden of influenza is also significant for university and college students.[16] The burden of influenza like illness (ILI) in university students is larger compared to other upper respiratory infections.[16] Specifically, students with ILI miss more days of class, work, and social activities as compared to students with other upper respiratory infections.[16] These students also report a longer duration of illness, number of days spent in bed, and number of days with physical impairment as compared to an upper respiratory infection.[16]

3.1.2. Influenza Transmission Reduction

There are many ways to reduce the burden of influenza, including seasonal influenza vaccination and non-pharmaceutical interventions. Unvaccinated persons report missing more work hours and a decrease in work productivity.[100] As previously discussed in section 2.1.1, university students have varying concerns about the vaccine and low compliance.

Other preventive behaviors are available to university students during an influenza outbreak. These non-pharmaceutical interventions include: handwashing, face masks, cough covering, and self-isolation.[101] Students are more likely to participate in these behaviors as perceived personal risk increases.[48] Frequent handwashing and covering of the mouth when coughing have the highest compliance among university students.[48] Self-perceived risk is the

main contributor to low compliance to face masks and self-isolation.[48, 49] Persons aged 16-24 are the least likely to use a face mask unless the threat of pandemic influenza is high.[49]

University students lead active social lives. Therefore, the low rates of compliance to self-isolating behaviors is not surprising.[45,48] Students are unlikely to forgo social events such as Greek Week or parties when infected with influenza.[45] Additionally, university students live in crowded conditions, but fewer than 40% recognize this as a health risk.[54] Crowded living conditions and social events are significant factors in the spread of influenza. Even during a pandemic influenza outbreak, such as the H1N1 outbreak of 2009, student compliance with preventative behaviors and risk perception were low.[44] The lack of understanding of risk and low compliance with many preventive behaviors is troubling, and requires a concentrated education effort by universities to overcome it.[16,44,48,101]

3.1.3. The University Student Experience: in Sickness and in Health

College students' lack of compliance with self-isolating behaviors may be linked to the social health and support system of the student. For most university students, influenza infection can represent the first time a student is making health-related decisions without consultation of their family or guardians. Colleges and universities attempt to create strong social networks and ties to campus culture to support students to graduation. Many universities now institute a first year live on campus requirement for students, as it is demonstrated to have numerous social and educational benefits.[102] This requirement yields a strong social network in a university; however, this network can also be a substantial risk for infection.

College students' understanding of risk as related to social networks and compliance to preventive behaviors is low. [35,33,44,54] However, these studies were conducted without the availability of a highly accurate test.[35] By introducing a highly accurate rapid PCR test it is possible that perceived risk will increase since a student will be more certain of their diagnosis. If perceived risk increases, the compliance with self-isolation may increase. Therefore, we hypothesize that students with PCR confirmed influenza may miss significantly more days of

school/work, report a decreased use in public facilities, and an increase in reliance on others for healthcare decision making.

3.2. Objective

To assess the behavior of college students who had the diagnosis of influenza confirmed by PCR, compared to those whose PCR test was negative, in the following categories: number of days of work or class missed, self-reported stress level, reliance on friends and family for health care decisions, use of public transportation, and use of dining facilities. These categories will be combined into two composite variables: emotional impact and social distancing.

3.3. Hypothesis

Students with PCR confirmed influenza will miss more days of work or class, have increased self-reported stress levels, and rely more on friends and family for health care decisions as compared to PCR influenza negative students. We also hypothesize that influenza positive students will also report a decrease in use of public dining facilities and public transportation as compared to influenza negative students.

3.4. Methods

3.4.1. Setting

The University Health Center (UHC) at the University of Georgia (UGA) provides primary care, urgent care, and selected specialty services to the 35,000+ students enrolled at the university. The UHC has four primary care clinics, with 20 primary care clinicians available to students for traditional business hours and Sunday urgent care hours. UHC is unique in that it is one of just two college health facilities in the nation that has been accredited by the Joint Commission for Ambulatory Care and Primary Care Medical Home. In addition to primary and urgent care, UHC provides dental, counseling and psychiatric services, vision clinic services, massages, physical therapy, and pharmacy services. Students can make same day appointments, so this health care facility serves as an ideal location for a study of suspected influenza in young adults.

3.4.2. Population

UGA is the nation's first land grant institution, with 36,130 students enrolled in 2015. Of those students, 27,547 are undergraduate students and 8,583 are graduate students.[103] UHC serves currently enrolled UGA students who attend the Athens campus. UGA students must have paid their $196 UHC student fee to schedule appointments. Once the semester has begun a student may log into the online patient portal or call in same day to receive an appointment. These college students are ideal for study for several reasons. First, they are at an age that typically is not highly vaccinated against influenza. Second, they are assigned to a primary care clinician who oversees their care and is the first doctor available for scheduling. Third, these student's records are easy to follow throughout their four years, as UHC uses a comprehensive electronic health record (EHR).

3.4.3. Sample Size

Our sample size is calculated below in Equation 3.1. We will have 300 patients who receive the PCR test and will be invited to complete the survey. We assume an 80% power, a standard deviation of 0.5, and an alpha of 5%. We will be able to detect an 11.44% difference between groups. If the standard deviation was 0.3, we can detect a 6.86% difference. If the standard deviation was 0.6, we can detect a 13.72% difference.

$$n = \frac{2\left(Z_\alpha + Z_\beta\right)^2 \sigma^2}{\Delta^2}$$

$$300 = \frac{2(1.96 + 0.8416)^2 (0.5)^2}{\Delta^2}$$

$$\Delta = 11.44\%$$

Equation 3.1 Aim 3 Sample Size Calculation

3.4.4. Data Collection

After patients have been selected to participate in aim 2, they will also provide their UGAMail email address. Five days' post patient visit, the patient will receive an email notification

requesting their participation in a follow up survey. This follow up survey is being delivered through Google Docs; two patient pieces of patient identifying information are collected to match the survey record to the EHR from aims 1 and 2. The survey in its entirety is included in Appendix C. This survey will assess vaccination status, symptom development, self-rated stress score, health care decision-making strategies, and presence in public areas around campus.

Data collection will begin in December of 2016 and end in April of 2017 or when all PCR samples have been used. Ariella Perry will manage the email notifications daily in Qualtrics. Qualtrics is a subscription-based service which UGA currently provides to students free of charge. Informed consent will be collected in aim 1, as previously described. Therefore, only patients who receive a nasopharyngeal swab and a final PCR result of positive or negative will be included in this follow up procedure. Students who receive an invalid PCR result will not receive the follow up survey. Students will receive their first email notification the morning of the 5th day post diagnosis. The students will then receive 3 reminder emails; students who have already completed the survey will not receive a reminder email.

Participants are asked to provide their UGA myID, a unique username identifier used throughout the university, and date of birth as part of the survey. The UHC staff requires two identifying pieces of information to link the EHR to the survey data. The linking of these two data sets is required to know each student's PCR influenza result as tied to their behaviors.

3.4.5. Survey Response and Outcome Definitions

To address our objectives, we need clear definitions of our outcome and our survey responses. Our outcomes will be two composite variables developed from our survey responses. The variables used to create these composite variables are number of days of work or class missed, self-reported stress level, reliance on family for health care decisions, use of public transportation, and use of dining facilities. The exposure will be the Cobas Liat PCR influenza test result. A patient will be considered influenza positive if they had a positive rapid point of care PCR test. A patient will be considered influenza negative if they had a negative

rapid point of care PCR test. We will also assess potential covariates such as vaccination status and patient demographics.

The covariates are obtained from our survey, located in Appendix 3. All time-dependent variables are measured as within the last 5 days since UHC visit. We divide all the questions and corresponding covariates into two composite variables: emotional impact and social distancing. The emotional impact composite variable includes: self-rated stress level and reliance on a social network in relation to their health. Stress is reported on a five-point Likert scale, with 1 being less stressed than normal and 5 being a lot more stressed than normal. Health-related decision making will be reported as the number of times a parent, guardian or another family member was consulted from 0 to 5. Patients will also indicate their reliance on a social network of friends or significant others. Reliance on a social network is defined for the patient as driven to UHC, bought groceries or medicine on your behalf, and other situations that a patient deems as reliance. Patients will select one of the following options: a lot, occasionally, or not at all.

The second composite variable, social distancing, will include the following variables: number of days of class or work missed, use of public dining facilities, and use of public transportation. Patients will report the number of days of class or work missed as a continuous variable from 0 to 5. Patients will report use of public dining facilities as a categorical variable by indicating all from the following list that apply: Bolton, O-House, Snelling, Joe Frank Harris, Tate dining commons (i.e. Panda Express, Starbucks, etc.), or I did not eat at an on-campus food vendor in the past 5 days. Patients will report use of public transportation as a categorical variable by selecting one from the following options: University of Georgia Bus/Athens Transit Bus, rideshare (Uber, Lyft), carpool (with friends), or no use of public transportation.

Some important demographic information includes the vaccination status and residence type for the student. These variables are potential confounders or interactors with our survey responses. Students will indicate whether they received vaccination prior to diagnosis. We ask

students to indicate whether they received their influenza vaccine at least two weeks prior to diagnosis or not, as it takes two weeks for the influenza vaccination to be effective in the average human body. This vaccination variable will be collapsed into a dichotomous variable: those who received vaccination more than two weeks before diagnosis versus those who did not receive vaccination OR received vaccination less than two weeks before diagnosis. Residence type is a categorical variable and participants will select one of the following options: residence hall, apartment or house (alone), apartment or house (with roommates), I live at home with my family, or homeless.

3.4.6. Analysis

Each category of variables will be assessed as a separate model in our analyses. Therefore, we will build separates models through logistic regression as described by Hosmer, Lemeshow and Sturdivant for emotional impact and a model for the social distancing composite variable. The building of each model is described below. This process is similar between each category as only the outcome included in our model building change.

Data will be stored on the Google Drive account of UGA Flu Study (ugaflustudy@gmail.com). The responses will be password protected in an excel file; this password will only be accessible to Ariella Perry and Brian McKay, the dissertation committee, and any other approved data analyzers. A codebook will be created, and data cleaned by Ariella Perry. R will be used to perform the analysis.

3.4.7. Analysis: Emotional Impact

Exploratory data analysis will involve the examination of the data set. Next, an item analysis will be conducted for each variable individually to assess for missing data, lack of variability, and outliers. The composite variable emotional impact will be the outcome in our model building. The variables include in this composite variable are: self-rated stress level, reliance of family for health-related decision making, and reliance on a social network in relation to their health. The main exposure of this model will be PCR influenza diagnosis (positive vs.

negative). We will also include patient demographic variables. All categorical and dichotomous variables will be plotted using a stem and leaf plot to assess variability, while continuous variables will be plotted using histograms and line graphs.

Following the item analysis, correlation analysis will be used to assess relationship between the individual variables. All variables with a high correlation coefficient will be considered by the investigators for combination, exclusion, or inclusion based on the covariate relationship to the exposure-outcome pathway. All variables that will be included in the model building will be moved to a permanent data set. Recoding, for example a continuous to categorical variable, will be assessed on a case-by-case basis and transformed as necessary to satisfy model assumptions. All outcome and covariates will be assessed using univariate analysis to determine outcome-variable and variable-variable relationships.

We will then conduct bivariate analyses for the initial relationships between influenza diagnosis and each question of the survey. A chi-square test will be used to assess for significant differences between groups per variable. For continuous variables, we will use simple logistic regression. Through stratified analyses, we will identify confounders and effect modifiers. We recognize that many of the covariates could be confounders or effect modifiers, so this analysis is important prior to model building.

Finally, a logistic regression will be fitted to the data, using a manual forward selection process based on Aikake information criteria (AIC).[97] The change in AIC will be measured between the initial model with the addition of one covariate per model. Change in AIC is easy to interpret and allows a quick determination of strength of evidence when comparing a list of candidate models. The list of candidate models in each step will be compared to the best model selected in the previous step for a positive change in AIC. The model that gives the greatest change in AIC will be selected as the best model. Covariates continue to be added to this model until the change in AIC is less than 4.[97] If the change in AIC is less than 4, then no additional terms will be added to the model.

Analysis: Social Distancing

Exploratory data analysis will involve the examination of the data set. Next, an item analysis will be conducted for each variable individually to assess for missing data, lack of variability, and outliers. The covariates included in this model building are number of days of class or work missed, use of public dining facilities, and use of public transportation. The outcome of this model will be PCR influenza diagnosis (positive vs. negative).

All categorical and dichotomous variables will be plotted using a stem and leaf plot to assess variability, while continuous variables will be plotted using histograms and line graphs. Following the item analysis, correlation analysis will be used to assess relationship between the individual variables. All variables with a high correlation coefficient will be considered by the investigators for combination, exclusion, or inclusion based on the covariate relationship to the exposure-outcome pathway. All variables that will be included in the model building will be moved to a permanent data set. Recoding, for example a continuous to categorical variable, will be assessed on a case-by-case basis and transformed as necessary to satisfy model assumptions. All outcome and covariates will be assessed using univariate analysis to determine outcome-variable and variable-variable relationships.

We will then conduct bivariate analyses for the initial relationships between influenza diagnosis and each question of the survey. A chi-square test will be used to assess for significant differences between groups per variable. For continuous variables, we will use simple logistic regression. Through stratified analyses, we will identify confounders and effect modifiers. We recognize that many of the covariates could be confounders or effect modifiers, so this analysis is important prior to model building.

Finally, a logistic regression will be fitted to the data, using a manual forward addition process based on Aikake Information Criteria.[104] The model selection process has been described previously in section 3.4.7.

CHAPTER 4

RESULTS

Introduction

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

CHAPTER 5

CLINICAL DECISION RULES FOR THE DIAGNOSIS OF INFLUENZA: A SYSTEMATIC REVIEW, PROSPECTIVE VALIDATION, AND DEVELOPMENT OF A NOVEL PREDICTION MODEL IN A COLLEGE HEALTH POPULATION

Dale, A.P., Ebell, M. H., McKay, B., Handel, A., Forehand, R., Dobbin, K. To be submitted to *the Journal of the American Board of Family Medicine.*

ABSTRACT

Background: The diagnosis of influenza based on signs and symptoms alone can be difficult, given its overlap with many other acute respiratory infections. Clinical decision rules (CDRs) are prediction models that can be useful for disease diagnosis. We updated a previous systematic review that identified current CDRs for influenza diagnosis in outpatient care, externally validated these rules, and proposed novel CDRs for use in a college health population.

Methods: We conducted a systematic review of PubMed, DARE, Google Scholar, and the Cochrane library to identify CDRs for influenza diagnosis. Two authors independently reviewed articles for inclusion criteria and data abstraction. A meta-analysis was performed for CDRs with three or more studies. Each CDR was then externally validated in a college health population for classification accuracy and calibration. A rapid polymerase chain reaction (PCR) test was used as the reference standard. Finally, we developed novel CDRs by fitting a lasso logistic regression model and a fast and frugal tree.

Results: We identified 232 studies in our initial literature search. After full text review, we abstracted 16 studies including five types of heuristics, 12 multivariate models, four influenza-like-illness case definitions, four classification and regression trees (CARTs), and one-point score. Summary statistics were calculated for the “cough+fever” and “cough+fever+acute onset” CDRs (area under receiver operating characteristic curve [AUROCC]: 0.70 and 0.78, respectively). Twelve CDRs were externally validated in our population. Lasso logistic regression yielded a CDR including myalgia, chills, fever, and the absence of tonsillar exudate as predictors of influenza in college students (AUROCC: 0.77). Similarly, our fast and frugal tree yielded a CDR that includes myalgia, chills, fever, and acute onset of less than or equal to 48 hours (AUROCC: 0.69).

Conclusions: “Cough+fever” and “cough+fever+acute onset” heuristics remain good predictors of influenza diagnosis. Our external validation demonstrated that the Flu Score and a CART have fair accuracy in a college health population. The predictors of influenza diagnosis in a

college health population present in both of our internally validated CDRs include fever, myalgia, and chills. The possibility of using fever, myalgia, chills and/or acute onset of less than 48 hours is a simple heuristic should be externally validated in a new population.

5.1 *INTRODUCTION*

Influenza continues to have a significant annual burden in the United States. Influenza activity in the 2016-2017 season was rated “moderate” by the Centers for Disease Control and Prevention (CDC).[105] Previous epidemics have demonstrated a large morbidity and mortality from influenza worldwide, particularly in vulnerable populations.[106,107] The accurate and timely diagnosis of influenza is important to combating the consequences of poor vaccination coverage.[13] An evidence based solution to a dynamic and evolving disease such as influenza is a clinical decision rule.

Clinical decision rules (CDRs) are a type of prediction model that can be applied by clinicians to aid in diagnosis or prognosis.[58] A CDR for influenza would be particularly useful in the peak of an epidemic when outpatient care facilities may become overwhelmed, such as in 2009 of H1N1,[41] because clinical decisions can be made quickly and on limited information. Additionally, CDRs for influenza can also reduce overall costs by decreasing unnecessary tests and prescriptions ordered.[58]

A previous systematic review in 2010 identified 12 studies that included CDRs for the diagnosis of influenza.[5] Two CDRs demonstrated modest accuracy: “cough and fever” and “fever, cough, and acute onset”.[5] However, this systematic review has several limitations. It did not include influenza like illness (ILI) case definitions or any CDRs developed using modern multivariate techniques such as a classification and regression tree (CART) analysis, or perform split-sample or bootstrap validation.[5] Additionally, studies of hospitalized persons were included in the previous systematic review, but the largest burden from influenza is placed on ambulatory care, with over 11 million outpatient visits in the 2015-16 outbreak. [13] Finally, none were evaluated in a college health population.

Our systematic review will identify CDRs for the diagnosis of influenza in outpatient care. We will validate each CDR identified in our systematic review in a college health population seeking care at an on-campus outpatient clinic. In addition to external validation, we will also

develop novel CDRs for this population. For a detailed discussion of development and validation of CDRs, see chapter 3.

5.2 ***METHODS***

We performed a systematic review to identify prediction rules for influenza diagnosis in adults in PubMed, Google Scholar, Database of Abstract of Reviews of Effectiveness (DARE), and the Cochrane Library following the PRISMA guidelines.[68,108]

Search Strategy

The search strategy was developed based on published best practices for each of the databases.[68-73] The search strategy for each database is included in Table 5.1 in Appendix 1. We also reviewed any studies included in previous systematic reviews or meta-analyses, as well as those identified from the references lists of all included studies.

Inclusion and Exclusion Criteria

We included studies that reported the accuracy of a combination of signs, symptoms and/or point of care tests (i.e. a CDR) for the diagnosis of influenza in ambulatory care. We included all studies from any country and in any language. Studies were excluded if they were conducted in a specialized population (i.e. patients who did not represent the general population at risk), were exclusively in immunocompromised persons, or were not published within the last 30 years. Articles for influenza outbreaks that are not seasonal, such as the swine flu (H1N1) outbreak of 2009, were also excluded as these may not be comparable to seasonal influenza.

Data abstraction

Based on a review of the abstract, any study judged by either researcher to possibly report the accuracy of a combination of signs or symptoms or a CDR for the diagnosis of influenza was reviewed in full by both researchers. A CDR was defined as a point score or equation based on the history and physical examination. All articles included in previous systematic reviews of influenza diagnosis were also reviewed in full. Articles were screened for

the following information: clinical decision rule, measures of accuracy, type of care setting, age of patients, study design, influenza prevalence, country, years of data collection, and type of test used to confirm influenza diagnosis. A final list of included studies was developed, and all data were abstracted in parallel by two investigators (AD and BM). The reviewers also abstracted classification accuracy measures from the original studies including sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios. If possible, we calculated missing accuracy measures, such as positive and negative likelihood ratios, when sensitivity and specificity were provided. Any disagreements were resolved by a discussion between the two investigators. If an agreement could not be reached, a third investigator was contacted to make the final decision (ME).

Quality Assessment

Study quality was assessed using the Quality Assessment tool for Diagnostic Accuracy of Studies (QUADAS-2).[74] The full QUADAS-2 tool adapted to our study is shown in Appendix A of chapter 3, including specific definitions of low, high, and unclear risk of bias for each question.

Analysis

Meta-analysis of existing CDRs

Meta-analysis was performed for CDRs that have been evaluated in at least 3 or more studies. We used the “mada” and “metafor” packages in R v.3.4.3. The two investigators abstracted the true positive, false positive, false negative, and true negative information from each study. We then computed a summary positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio. Finally, we plotted the accuracy of each included study for a CDR on a summary receiver-operating characteristic curve.

External Validation of Existing CDRs in College Health Population

We recruited students at the University of Georgia Health Center (UHC) presenting with cough or at least two other suspected influenza symptoms: headache, cough, fever, chills,

sweats, fatigue, myalgia or arthralgia.[66],[67] At UHC, an electronic health record is maintained for each patient, and includes structured data (e.g. checkboxes and plus/minus indicators) to record individual signs and symptoms. During the study period, key signs and symptoms for patients with acute respiratory tract infection (ARTI) were required to be completed by clinicians. All patients received a Roche Cobas Liat Polymerase Chain Reaction (PCR) test for influenza as the reference standard for the diagnosis. Compared to reference laboratory PCR, it is 99% sensitive and specific for the diagnosis.[12] Each CDR was evaluated in this population for classification accuracy by calculating the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and area under the receiver operating characteristic curve. Calibration was assessed using the Hosmer-Lemeshow goodness of fit test.

Development of Novel Clinical Decision Rule using the LASSO Technique

We built a model for predicting influenza diagnosis in university students based on signs and symptoms. We used the least absolute shrinkage and selection operator (lasso) technique for logistic regression to build our model. The lasso technique is a type of penalized regression, which is a flexible shrinkage approach that works well when the expected number of events per variable could possibly be less than 10.[80] This is advantageous for our model building since we are developing a prediction model that needs to be memorable for clinicians.[80]

The lasso constrains the sums of the absolute values of the regression coefficients, meaning it can exclude parameters from a final model by shrinking their coefficient to 0.[81] We used the glmnet package in R v.3.4.3 to perform the lasso regression. The glmnet package built the logistic regression model using the lasso in relation to the tuning parameter, lambda. We also used cross validation to internally validate the model performance.

Development of a Fast and Frugal Tree for Influenza Diagnosis

We also fit a fast and frugal tree using the “FFTree” package in R version 3.4.3. For a detailed discussion of FFT see Chapter 3, page 43. A non-parametric method, a fast and frugal

tree has exactly two branches extending from each node where one of the branches will be an exit to a decision.[109] Speed is measured by the FFTree package by "mean cues used" (mcu).[82] Frugality measures the percent of information ignored by the algorithm when it is implemented on a dataset.[82] This is quantified by "percent cues ignored" (PCI).[82]

We split our data 60:40, training and testing data sets respectively. The package used the fan construction algorithms known as "ifan" and "dfan".[82] These algorithms explore virtual fans of fast and frugal trees with varying error tradeoffs and exit structures.[82] The algorithm ultimately selects the tree that maximizes the weighted accuracy and removes nodes that do not classify enough cases.[82] After construction in the training data set, the algorithm then applies the fast and frugal tree to the test data set and reports accuracy measures.[82] We will report mcu, pci, weighted accuracy (wacc), area under the receiver operating characteristic curve (AUROCC), sensitivity and specificity of the final selected fast and frugal tree.

5.3 RESULTS

Systematic Review

Our initial search and reference review yielded 232 studies, reduced to 199 studies after removal of duplicates. After review of the title and abstract, 27 appeared to meet our inclusion criteria. We excluded 11 articles after full text review because they did not gather original data, did not predict influenza diagnosis, did not include sufficient information on signs or symptoms of influenza, or the population of interest was hospitalized patients. No studies were excluded for being written in a language other than English (Figure 5.1). Study characteristics of the final 16 included studies are presented in Table 5.2. Two studies were conducted exclusively in children[110,111], one study in military trainees[112], and two studies in older adults.[113,114]

Studies were generally of good quality (Table 5.3). However, only three studies included split-sample validation of the proposed model.[115-117] One study exclusively validated the Flu Score[76], while 8 studies validated the commonly used "cough and fever" heuristic.[6,111-113,116,118-120] The most common source of bias was a failure to explain the reason for withdrawal. Four

studies did not use PCR or viral culture as their reference standard for all participants.[6,111,113,121] We chose to include these studies for our systematic review and external validation. However, the differences in diagnostic threshold, influenza prevalence, and the heterogeneity introduced by these four studies in particular led us to not calculate overall accuracy measures at this time. Studies reported 8 types of heuristics, 12 multivariate models, 4 ILI case definitions, 4 classification and regression trees (CARTs), and 1-point score (Table 5.4).

Meta-Analysis of "Cough+Fever" and "Cough+Fever+Acute Onset" CDRs

Only two CDRs have been used in 3 or more studies: "cough+fever"[6,111-113,116,118-120] and "cough+fever+acute onset".[6,113,116,119] We were unable to abstract true positive, false positive, false negative, and true negative data from one study that used the "cough+fever" CDR. [111] We abstracted data from 7 studies that reported the "cough+fever" rule and 4 studies that reported the "cough+fever+acute onset" rule. The "cough+fever" CDR had modest accuracy for a diagnosis of influenza (LR+: 3.3 95%CI: 1.4, 3.6; LR-0.54 95%CI: 0.5, 0.6), diagnostic odds (DOR:4.1, 95%CI: 2.7, 5.9), and an area under the receiver operating characteristic curve of 0.70 (Figure 5.2). The "cough+fever+acute onset" CDR was more accurate for the diagnosis of influenza (LR+: 4.6, 95%CI: 2.4, 8.4; LR: -0.6 95%CI: 0.4, 0.8), a higher diagnostic odd (DOR:8.5, 95%CI: 4.0, 16.1), and an AUROCC of 0.79 (Figure 5.3).

Validation of Existing CDRs in University Student Population

External validation was conducted for 15 CDRs identified in our systematic review, using data from 265 UGA health center patients who had a rapid PCR test and a complete medical record data regarding signs and symptoms. Five multivariate models failed to report the entire logistic regression model; typically the intercept was excluded from publication.[111,113,121-123] We contacted the authors of each multivariate model, but were unsuccessful in gaining access to the full models for validation. The accuracy and calibration of each included rule is summarized in Table 5.5.

Fever was defined as ≥37.8°C in order to be consistent with the recommended fever threshold in the United States.[124] The "cough+fever" CDR, where fever was objectively measured, had a sensitivity of 16% and a specificity of 95%. In contrast, when fever was measured either objectively or subjectively, the "cough+fever" CDR had a high sensitivity of 87% and a low specificity of 44%. The "cough+fever", "cough+fever+acute onset", "fever, cough and/or sore throat", and "fever + acute onset" CDRs when fever was measured only objectively performed poorly in regard to area under the receiver operating characteristic curve (range: 0.54-0.56). The "Cough+pharyngitis+ headache" CDR had a high sensitivity (89%) and low specificity (19%).

We validated three of the four case definitions for ILI in the UHC population. The case definition given by the Public Health Agency of Canada was excluded due to unclear definition of signs and symptoms, specifically fever, acute onset, and prostration likely due to influenza. All case definitions had low sensitivities and high specificities, indicating that they are most helpful for ruling in ILI rather than ruling ILI out. We were unable to validate one algorithm based on a CART[117] analysis because fatigue was not a required element of our electronic health record.

Our validation of the Flu Score[116] and 3 algorithms based on a CART analysis[115] is presented in Table 5.6. For the Flu Score, the proportion of patients with influenza in the high-risk group was 74% (LR:2.4) compared to 29% in the low risk group (LR:0.4). The AUROCC was 0.66 (95%CI: 0.60,0.71). A CDR is most useful when it classifies as few patients as possible in the moderate risk group, which usually requires additional diagnostic testing. Only 28% of patients were classified as moderate risk by the Flu Score, half as many patients as the 3 CART models (28% vs 70%, 63%, and 60%, respectively).[115]. To check calibration, each model was assessed using the Hosmer-Lemeshow test. All models had a p value less than 0.01, indicating a poor fit and calibration.

LASSO logistic regression

Accuracy of individual signs and symptoms in our college health population are presented in Table 5.7. Chills, headache, nasal discharge and sore throat were highly sensitive for influenza (>92%) but had low specificity (<25%). Patients who were negative for one of these four symptoms more than likely do not have disease, as reinforced by the mnemonic "SnNOut".[125] Using the lasso logistic regression approach with cross validation, we derived a multivariable model for influenza diagnosis listed in Table 5.8. The final prediction model included the presence of fever, myalgia, chills and absence of tonsillar exudate. The area under the receiver-operating characteristic curve was 0.77, indicating this model is a good test for influenza diagnosis in this population.

Fast and Frugal Tree

Our final fast and frugal tree for influenza diagnosis is displayed in Figure 5.4. Of all the potential signs and symptoms, 4 were selected by the "ifan" and "dfan" algorithms for use in the fast and frugal tree with the best weighted accuracy (wacc=69%). The first split identified patients that had no fever as more likely to not have influenza. The next node split according to whether the patient had myalgia; patients who reported no myalgia were more likely to not have influenza. The third node split according to duration of symptoms; patients reported symptoms for less than or equal to 48 hours were more likely to have flu. Finally, the terminal node split based on chills. Patients who had chills were more likely to have influenza and patients who did not have chills were more likely to not have influenza. This fast and frugal tree had a mean cue used (mcu) of 2.5 and a percent cues ignored (pci) of 90. These measures confirm that this model is fast and frugal. Finally, our weighted overall accuracy was 69%, with a sensitivity of 73% and a specificity of 64%. The ROC curve displaying all models fit using the FFTree package is in Figure 5.5; our fast and frugal tree is of fair accuracy (AUROCC: 0.69).

5.4 DISCUSSION

Systematic Review

Our systematic review yielded 40 CDRs from 16 studies. We were able to update the 2011 systematic review[5] of CDRs for influenza diagnosis and expand it by including ILI case definitions. Cough and fever were the most commonly used symptoms throughout the 14 CDRs we were able to validate. The most complex CDR was the Taiwanese ILI case definition, which required the exclusion of certain diagnoses (Table 5.4). "Cough+fever" and "cough+fever+acute onset" were the only CDRs to be reported in at least 3 studies. "Cough+fever+acute onset" CDR outperformed the "cough+fever" CDR in terms of discrimination and diagnostic odds ratios. This suggest that attendance to a clinic within 48 hours is important for distinguishing influenza from other acute respiratory infections. Overall, with the exception of these 2 CDRs, validation studies remain uncommon.

External Validation in College Health Population

Of all CDRs included, 5 of the 11 developed as a heuristic or ILI case definition were highly specific (≥95%) in our validation cohort. However, no CDR demonstrated good calibration (per Hosmer-Lemeshow test). "Cough+fever+myalgia" was the sole CDR to have good discrimination (AUROCC: 0.70). The discrimination of the heuristics increased from poor to fair when the definition of fever was expanded from an "objective fever" (measure temperature only) to "objective or subjective" measure (either measured or patient-reported fever). It is important to note that all 265 patients in our study had a cough. Of the 15 CDRs we validated, 14 included the presence or absence of a cough. This reduced the contribution of cough to differentiating influenza from other illnesses. Therefore, the overall accuracy of rules that included cough was decreased.

The 2nd CART and Flu Score demonstrated only fair discrimination in our UHC population as measured by the AUROCC (0.61 and 0.66, respectively). Interestingly, our external validation yielded likelihood ratios of similar magnitude for the low, medium, and high risks

groups of the original studies (Table 5.6). It is possible that the magnitude of the likelihood ratios are dampened because all patients in our population had a cough. Any CDR having cough as one of the diagnostic criteria would potentially be less accurate when validated in the UHC population since cough could not contribute to discriminating influenza from non-influenza.[115] For example, patients without a cough would not have been classified as "high risk" in CART 1; therefore the proportion of patients in the moderate risk group was decreased. Thus, it is not surprising that the proportion in each group does not mirror the original study.[115] A useful CDR will classify a smaller proportion of the population as intermediate or moderate risk, thus minimizing the number of patients that require testing for disease. CARTs 1, 2, and 3 had large moderate risk groups (70%, 60%, and 63% of the population, respectively) which is significantly more than previously reported (Table 5.4).[115] The fact that all of the college health population had cough therefore decreased the utility of the three CART CDRs since the moderate risk group is so large.

The Flu Score increased the likelihood of influenza in the high-risk group (LR: 2.4) and reduced the likelihood of disease in the low risk group (LR:0.4). These are similar associations compared to the original study (high risk LR: 2.7, moderate risk LR: 0.8, low risk LR: 0.2).[116] Our external validation has demonstrated that the Flu Score is successful in a third adult population.[76,116] It is important to continue to externally validate CDRs in order to avoid threats to generalizability[55,59] and reaffirms their utility.

Novel Clinical Decision Rules for Diagnosis of Influenza in a College Health Population

Lasso Logistic Regression

Our lasso logistic regression yielded a model that included fever, myalgia, chills, and the absence of tonsillar exudate. Fever, myalgia, and chills are included in at least one of the clinical decision rules abstracted in our systematic review. The absence of tonsillar exudate as a significant predictor of influenza diagnosis is particularly interesting since this variable is not included in any of the CDRs identified in our systematic review. A possible explanation is the

overlap of signs and symptoms of influenza with acute pharyngitis. Specifically, if a patient were to present rapidly (within 48 hours) to primary care, it is possible that the only distinguishing sign or symptom for their diagnosis of pharyngitis would be tonsillar exudate. Tonsillar exudate is a common sign of Group A and non-Group A beta-hemolytic streptococcus infection.[126] The presence or absence of tonsillar exudate in patients presenting with chills, fever, and myalgia could help distinguish between acute pharyngitis and influenza in a college health population.

Fast and Frugal Tree

In our fast and frugal tree, the following signs and symptoms were significantly associated with PCR confirmed influenza diagnosis: fever, myalgia, short duration of symptoms (less than or equal to 48 hours) and chills. All four of these symptoms and signs are commonly reported in patients with an influenza diagnosis.[66] Interestingly, patients who had fever, myalgia, and chills but did not present to the clinic within 48 hours were still more likely to have influenza. This suggests that fever, myalgia, and chills could be used as a CDR in patients with suspected influenza.

Limitations

Our analysis does have limitations. First, we were unable to do an external validation of all models identified in our systematic review. Second, a majority our data was collected during the peak of the influenza outbreak of 2016-17. We did not include an analysis that compared the week of influenza diagnosis as seen in one of the identified models.[122] However, seasonal influenza outbreak peak is unpredictable from year to year, therefore it would not be a useful predictor in a new CDR. Third, we did not have access to any demographic information. Several of the CDRs in this systematic review assessed demographic information such as age or sex as significant predictors.[111,112] Age does not vary greatly among the UGA college health population. Finally, we were unable to include cough as a potential indicator for influenza in our novel CDR development, as all patients in this cohort had a cough.

5.5 CONCLUSION

In our systematic review, we identified 40 models from 16 studies that predicted the diagnosis of influenza. Our meta-analysis of the “cough+fever” and “cough+fever+acute onset” CDRs revealed that these are fairly accurate rules for diagnosis of influenza when defining fever as either an objective or subjective measure. We externally validated 12 of these models in our 265 college health patients who received a rapid point of care PCR test. The Flu Score performed well in external validation with the best classification accuracy. We also identified a 2 new CDRs using fast and frugal tree analysis that require prospective validation.

Tables and Figures

Table 5.1 Search Strategies for the Six Databases Included in our Systematic Review

Database	Search Terms	Link to Database and Notes
PubMed	(influenza[Title/Abstract]) AND (diagnosis[Title/Abstract]) AND (multivariate[Title/Abstract] OR logistic[Title/Abstract] OR "prediction model"[Title/Abstract] OR "decision model"[Title/Abstract] OR "decision rule"[Title/Abstract] OR "clinical model"[Title/Abstract] OR "clinical rule"[Title/Abstract]) Filters: Abstract, Humans	https://www.ncbi.nlm.nih.gov/pubmed?otool=gaugalib
Google Scholar	“influenza clinical decision”	https://scholar.google.com/
DARE	(Influenza):TI AND (Decision Support Techniques)	https://www.crd.york.ac.uk/CRDWeb/
Cochrane Library	((mh, "influenza, human") OR "influenza") AND ((mh, "decision support techniques") OR "prediction rule" OR "decision rule" OR "decision model" OR "prediction model" OR ("diagnosis")	http://www.cochranelibrary.com/

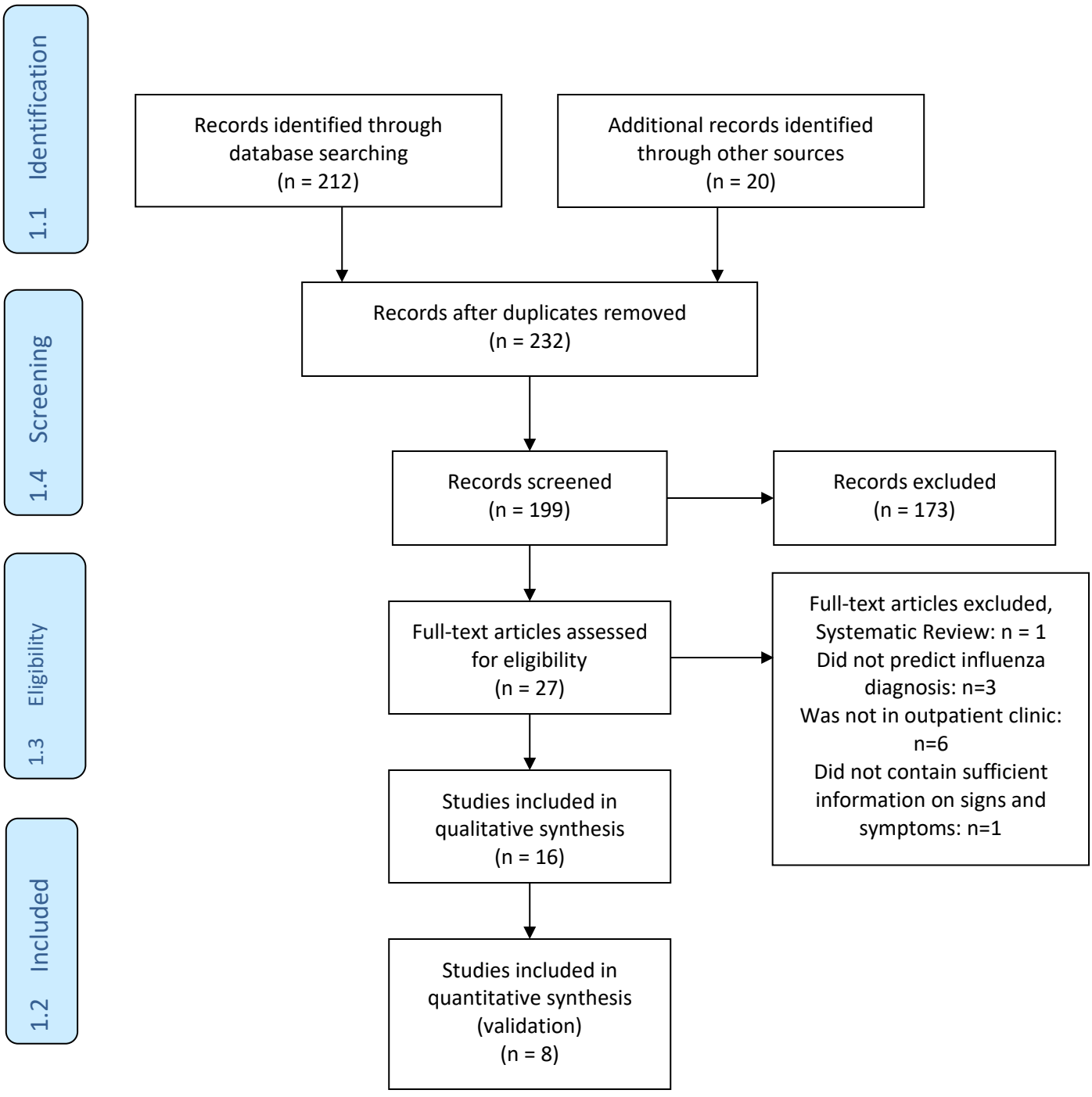

Figure 5.1 PRISMA[68,108] Diagram for Systematic Review of Clinical Decision Rules for Influenza Diagnosis in Outpatient Setting

Table 5.2 Study Characteristics of Included Clinical Decision Rules

Study, Year	Country	Setting	Year Conducted	Sample Size	Age range (mean)	Reference Standard
Afonso et al, 2012[115]	USA/Switzerland	Primary / Urgent / ER	1999-2000; 2002	201 and 258	17-90 (36.55)	Viral Culture and PCR*
Boivin et al, 2000[118]	Canada	Primary Care	1998-1999	100	(39.3)	PCR
Carrat et al, 1999[121]***	France	Primary Care	1995-1996	610	Not Reported	DIF+ and ELISA**
Ebell et al, 2012[116]	USA/Switzerland	Primary / Urgent / ER	1999-2000; 2002	201 and 258	17-90 (36.55)	Viral culture and PCR
Friedman et al, 2004[110]	USA	ER	2002	118	(6.2)	Viral culture
Govaert et al, 1998[113]	Netherlands	Primary Care	1991-1992	645	Not Reported	4xHIA++
Lam et al, 2016[114]	Canada	ER	2011-2013	1318	(77.4, median)	PCR
Monto et al, 2000[6]	North America, Europe, Southern Hemisphere	Outpatient	1994-1998	3744	(34.65)	Viral culture or 4xHIA
Ohmit and Monto, 2006[111]	USA / Europe / Southern Hemisphere	Outpatient / Urgent Care	Not Reported	952	Not Reported	Viral cultureulture or 4xHIA
Padin et al, 2014[112]	USA	Military medical clinic	2004-2009	21,570	(20.8)	PCR
Senn et al, 2005[122]	Switzerland	Outpatient / Urgent Care	1999-2000	201	(34.3)	Viral culture
Stein et al, 2005[119]	USA	ER / Urgent Care	2002	258	18-90 (34)	PCR

Van Elden et al, 2001[123]	Netherlands	Primary Care	1997-1998	81	Not Reported	PCR
Van Vugt et al, 2015[76]	Europe	Primary Care	2007-2010	1801	(48)	PCR
Yang et al, 2015[120]	Taiwan	Outpatient	2010-2012	158	(33, median)	Viral culture or PCR
Zimmerman et al, 2016[117]	USA	Outpatient / Urgent Care	2011-2012	4852	(34.15)	PCR

* PCR: Reverse transcriptase polymerase chain reaction test
+ DIF: Direct immunofluorescence
** ELISA: Enzyme linked immunosorbent assay (ELISA)
++ 4xHIA: fold or greater increase in influenza antibody titer vs active serum samples of hemagglutination inhibition
*** PCR and Culture for patients who's test results were uncertain

Table 5.3 Quality Assessment based on QUADAS-2 of Included Clinical Decision Rules

	Stein et al, 2005	Boivin et al, 2000	Monto et al, 2000	Govaert et al, 1998	Friedman et al, 2004	Carrat et al, 1999	Ohmit et al, 2006	Senn et al, 2005	Van Elden et al, 2001	Zimmerman et al, 2016	Afonso et al, 2012	Ebell et al, 2012	Padin et al, 2014	Yang et al, 2015	Lam et al, 2016	Van Vugt, 2015
Q1: Was the spectrum of patients representative of the patients who will receive test in practice?																
	L	L	L	L	L	L	L	L	L	L	L	L	H	L	H	L
Q2. Were selection criteria clearly described?																
	L	L	L	L	L	L	U	L	L	L	L	L	L	L	H	L
Q3. Is the reference standard likely to correctly classify the target condition?																
	L	L	L	L	L	H	L	L	L	L	L	L	L	L	L	L
Q4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?																
	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L
Q5. Did the whole sample or a random selection of the sample, receive verification using a reference standard?																
	L	L	L	L	L	H	L	L	L	L	L	L	L	L	L	L
Q6. Did patients receive the same reference standard regardless of the index test result?																
	L	L	L	L	L	H	H	L	L	L	L	L	L	L	L	L
Q7. Was the execution of the CDR described in sufficient detail to permit replication of the test?																
	H	H	H	L	H	H	H	L	H	L	L	L	L	L	H	L
Q8. Was the execution of the reference standard described in sufficient detail to permit its replication?																
	L	L	L	L	L	L	H	L	H	L	L	L	L	L	L	L
Q9. Was the clinical decision rule results interpreted without the knowledge of the results of the reference standard?																

	H	H	L	H	H	H	L	H	H	H	H	H	H	H	H	H
Q10. Were the reference standard results interpreted without knowledge of the results of the clinical decision rule?																
	L	L	L	L	U	L	L	L	L	L	L	L	L	L	U	L
Q11. Were the same clinical data available when test results were interpreted as would be available when test is used in practice?																
	L	L	L	L	H	L	L	L	L	L	L	L	L	L	U	L
Q12. Were uninterpretable/ intermediate test results reported?																
	L	L	L	U	L	L	U	L	L	U	U	U	U	L	U	U
Q13. Were withdrawals from the study explained?																
	U	H	U	U	L	H	U	H	H	U	H	U	U	L	L	U

*Judged as L(yes/low risk of bias), H(no/high risk of bias), or U (unclear if yes or no)

Table 5.4 Description of Included Clinical Decision Rules for Influenza Diagnosis and Accuracy Measures as reported in the original study

Study and Rule	Model	Flu Prevalence (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	LR+	LR-	LR
Cough+fever									
Stein et al, 2005	Fever (≥37.8°C) and cough	21	40	92	58	84	5.1	0.7	---
Boivin et al, 2000	Fever (>37.8°C) and cough	79	78	55	87	39	1.7	0.4	---
Monto et al, 2000	Fever (>37.8°C) and cough	66	64	67	79	49	1.9	0.5	---
Ebell et al, 2012	Fever (>38°C) and cough	33	61	80	61	80	3.1	0.5	---
Govaert et al, 1998	Fever (>38°C) and cough	6.6	30	94	26	95	5	0.7	---
Padin et al, 2014	Fever (>38°C) and cough	6.6	84	27	8	96	1.2	0.6	---
Ohmit et al, 2006	Fever (>38.2°C) and cough, in patients that received zanamivir	74	---	---	83	---	---	---	---
Ohmit et al, 2006	Fever (>38.2°C) and cough, in patients that received oseltamivir	67	---	---	71	---	---	---	---
Yang et al, 2015	Fever(subjective) and cough	45	86	58	62	83	2	0.2	---
Cough+fever+acute onset									
Stein et al, 2005	Fever (>37.8°C), cough, acute onset	21	75	89	65	93	6.5	0.3	---
Monto et al, 2000	Fever (>37.8°C), cough, acute onset	66	63	68	77	51	2	0.5	---
Govaert et al, 1998	Fever (>38°C), cough, acute onset	6.6	27	95	30	95	5.4	0.8	---
Ebell et al, 2012	Fever (>38°C), cough, acute onset	33	41	93	74	75	5.9	0.6	---
Cough+fever+headache									
Monto et al, 2000	Fever (>37.8°C), cough, headache	66	60	69	79	47	1.9	0.6	---
Cough+fever+nasal congestion									
Monto et al, 2000	Fever (>37.8°C), cough, nasal congestion	66	59	74	81	48	2.3	1.6	---
Cough+fever+myalgia									
Monto et al, 2000	Fever (>37.8°C), cough, myalgia	66	62	69	79	48	2	0.6	---

Cough+headache+pharyngitis									
Friedman et al 2004	Cough, headache, pharyngitis	35	80	78	77	81	3.7	0.3	---
Fever+Acute Onset									
Govaert et al, 1998	Fever (>38°C) and acute onset	6.6	---	---	24	---	---	---	---
Centers for Disease Control and Prevention Influenza Like Illness Case Definiton									
Lam et al, 2016	Fever (>37.8°C) and (cough and/or sore throat)	11	31	92	34	91	3.9	0.8	---
Yang et al, 2015	Fever (>37.8°C) and (cough and/or sore throat)	45	87	40	54	80	1.5	0.3	---
World Health Organization Influneza Like Illness Case Definition									
Yang et al, 2015	Fever (>38°C), cough, onset within last 10 days	45	85	63	65	83	2.3	0.3	---
Tawain Centers for Disease Control and Prevention Case Definition									
Yang et al, 2015	Must meet three criteria: sudden onset of disease with fever (ear temperature of ≥38°C [≥100.4°F]) and respiratory tract symptoms (including rhinorrhea, nasal congestion, sneezing, sore throat, cough, and dyspnea); (2) at least 1 of the following symptoms—muscle ache, headache, or extreme fatigue; and (3) exclusion for simple rhinorrhea, tonsillitis, or bronchitis	45	86	39	54	77	1.4	0.4	---
Public Health Agency of Canada Influenza Like Illness Case Definition									
Lam et al, 2016	acute onset of symptoms, fever and cough with sore throat, arthralgia, myalgia, or prostration	11	32	91	31	91	3.6	0.8	---
Multivariate Models									
Carrat et al, 1999	Any 3 of following: temperature >37.7°C, cough, chills, moderate or severe fatigue, pharyngitis, cervical or dorsal pain, and another case at home	26	---	---	27	91	---	---	---
	Respiratory signs, myalgia or stiffness, temperature >38.9°C	26	---	---	40	80	---	---	---
	Temperature >37.7°C and cough or sore throat	26	---	---	30	86	---	---	---

Govaert et al, 1998	Cough, fever, vaccination	6.6	---	---	---	---	---	---	---
Monto et al, 2000	Fever, cough, nasal congestion, age (>55 years), weakness, onset >36 hours, loss of appetite, male sex, sore throat	66	---	---	---	---	---	---	---
Ohmit et al, 2006	Zanamivir study: age, fever, cough, myalgia, sore throat	74	---	---	---	83	---	---	---
	Oseltamivir study (5-12 years of age): headache, cough	66	---	---	---	73	---	---	---
	Oseltamivir study (1-4 years of age): myalgia	67	---	---	---	73	---	---	---
Senn et al, 2005	Duration of symptoms (>48 hours versus ≤48 hours), temperature >37.8°C, cough, and week of consultation (49-50 vs ≥51)	52	80	59	67	73	2	0.3	---
Van Elden et al, 2001	Temperature (>38°C), abrupt onset (<5 days) and at least 1 of following: cough, coryza, headache, retrosternal pain, or myalgia. Must be during outbreak	52	---	---	52	---	---	---	---
	At least 4 of following during an outbreak: fever, cough, chills, malaise, myalgia, contact with influenza, hyperemic mucous membranes of nose and throat	52	---	---	54	85	---	---	---
	Cough, headache at onset, fever at onset, unvaccinated, period of increased influenza activity	52	---	---	75	80	---	---	---
Classification and Regression Trees									
Afonso et al, 2012		33							
Model 1	high risk: temperature >37.3°C, duration <2 days, cough	79	---	---	---	---	---	---	7.1
	moderate risk: temperature is not >37.3°C, positive for chills and sweats. OR temperature >37.3°C, duration > 2 days	32	---	---	---	---	---	---	0.9
	low risk: temperature is not >37.3°C, no chills or sweating	6	---	---	---	---	---	---	0.1

Model 2	high risk: temperature >37.3°C, duration <2 days	58	---	---	---	---	---	---	2.6
	moderate risk: temperature is not >37.3°C, positive for chills and sweats	18	---	---	---	---	---	---	0.4
	low risk: temperature is not >37.3°C, no chills or sweating	6	---	---	---	---	---	---	0.1
Model 3	high risk: temperature >38°C	63	---	---	---	---	---	---	3.4
	moderate risk: temperature is not >38°C, positive for myalgia	26	---	---	---	---	---	---	0.8
	low risk: temperature is not >38°C, no myalgia	8	---	---	---	---	---	---	0.1
Zimmerman et al	Fever, cough, fatigue	15	84	49	23	95	1.6	0.3	---
Score									
Ebell et al, 2012	Flu Score, sum of following: onset < 48 hours (1 pt), myalgia (2 pts), chills/sweats (1 pt), fever and cough (2 pts)	33							
	Low risk (0-2 points)	8	---	---	---	---	---	---	0.2
	Medium risk (3 points)	30	---	---	---	---	---	---	0.8
	High risk (4-6 points)	59	---	---	---	---	---	---	2.7
Van Vugt et al, 2015	Flu Score	15							
winter months, full cohort (n=1801)	Low risk (0-2 points)	10	---	---	---	---	---	---	0.6
	Medium risk (3 points)	21	---	---	---	---	---	---	1.5
	High risk (4-6 points)	32	---	---	---	---	---	---	2.7
Van Vugt et al, 2015	Flu Score	15							
peak influenza season (n=505)	Low risk (0-2 points)	14	---	---	---	---	---	---	0.5
	Medium risk (3 points)	32	---	---	---	---	---	---	1.5
	High risk (4-6 points)	50	---	---	---	---	---	---	3.2

Van Vugt et al, 2015	Flu Score	15							
onset of symptoms <2 days (n=299)	Low risk (0-2 points)	12	---	---	---	---	---	---	0.4
	Medium risk (3 points)	18	---	---	---	---	---	---	0.7
	High risk (4-6 points)	36	---	---	---	---	---	---	1.8

Sens= sensitivity; Spec= specificity; PPV= positive predictive value; NPV=negative predictive value; LR+= positive likelihood ratio; LR- = negative likelihood ratio; LR = likelihood ratio

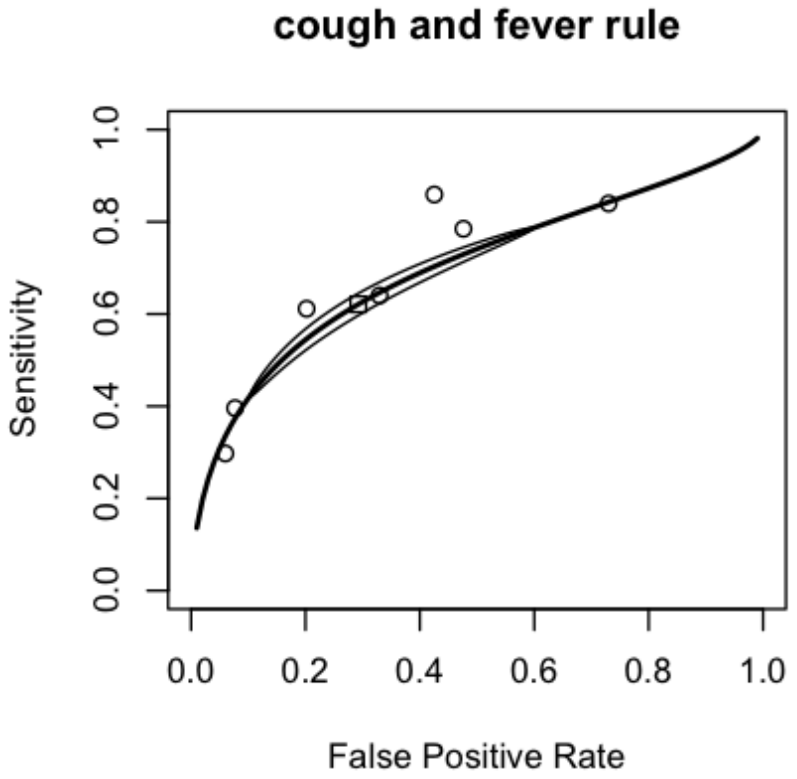

Figure 5.2 Summary Receiver Operating Characteristic Curve for the 7 Studies that Reported the “cough+fever” Clinical Decision Rule

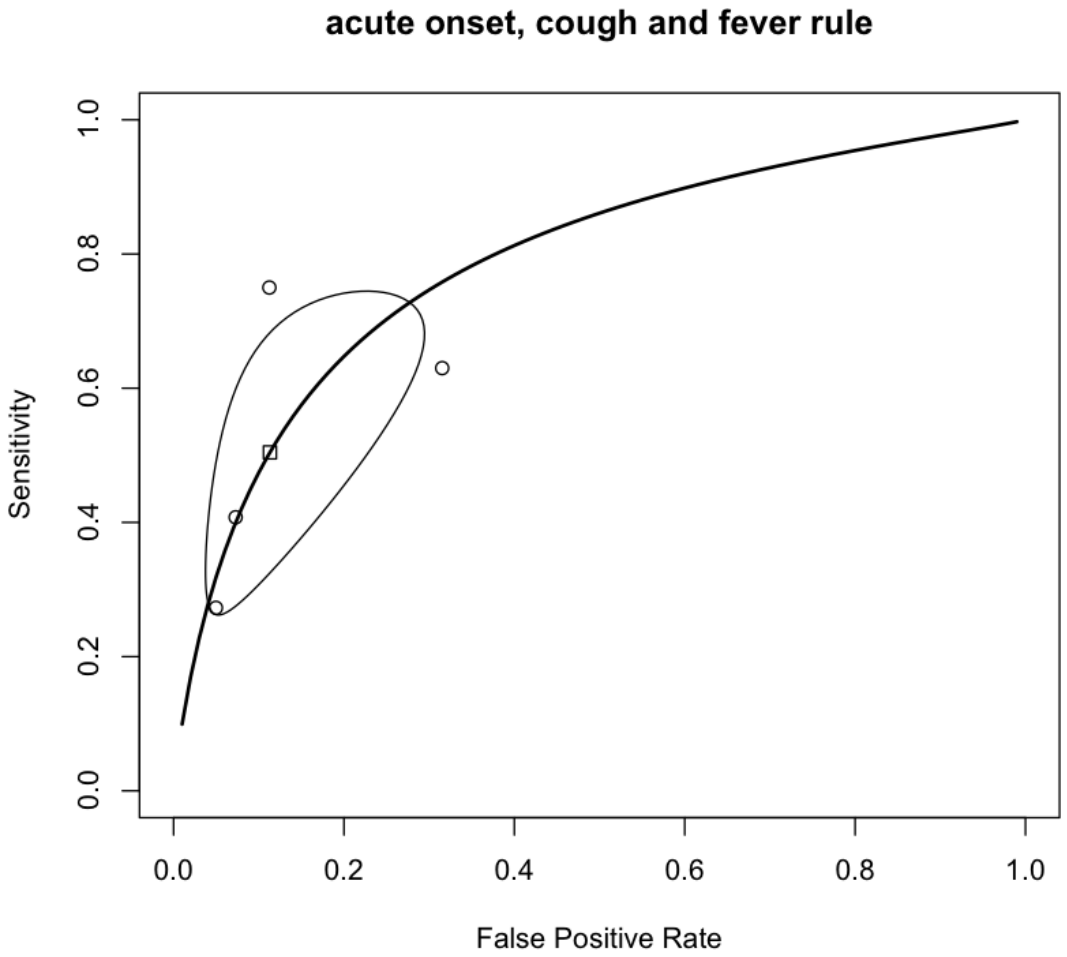

Figure 5.3 Summary Receiver Operating Characteristic Curve for the 4 Studies that Reported the “Cough+fever+acute onset” Clinical Decision Rule

Table 5.5 External Validation of Each Dichotomous Clinical Decision Rule in a College Health Population

CDR[1]	Influenza (#/total)	No influenza (#/total)	Sensitivity	Specificity	PPV	NPV	LR+	LR-	AUROCC
Cough+measured fever*	23/143	6/122	16%	95%	79%	49%	3.3	0.9	0.56
Cough+measured or subjective fever*[2]	124/143	68/122	87%	44%	65%	74%	1.6	0.3	0.67
Cough+ measured or subjective fever +headache	119/143	63/122	83%	48%	65%	71%	1.6	0.35	0.66
Cough+measured or subjective fever + nasal congestion	89/143	50/122	62%	59%	64%	57%	1.5	0.6	0.61
Cough+measured or subjective fever +myalgia	110/143	46/122	77%	62%	71%	70%	2.0	0.4	0.70
Cough+headache+ pharyngitis	127/143	99/122	89%	19%	56%	59%	1.1	0.6	0.54
Cough+measured or subjective fever*+acute onset	76/143	36/122	53%	70%	68%	56%	1.8	0.7	0.62
Fever (measured or subjective)** + acute onset	13/143	4/122	9%	97%	77%	48%	2.8	0.9	0.53
CDC: fever+cough and/or sore throat	22/143	6/122	15%	95%	79%	49%	3.1	0.9	0.55
WHO:	17/143	5/122	12%	96%	77%	48%	2.9	0.9	0.54
Taiwan CDC:	17/143	4/122	12%	97%	81%	48%	3.6	0.9	0.54

LR = likelihood ratio; AUROCC = area under the receiver operating characteristic curve.

*Fever is greater than or equal to 37.8 degrees Celsius

**Fever is greater than or equal to 38 degrees Celsius

[1]Hosmer-Lemeshow p value was <0.01 for all CDRs
[2]No difference between “cough+subjective fever” and “cough+measured or subjective fever”

Table 5.6 External Validation of the Three CART Clinical Decision Rules and Flu Score in a College Health Population

Rule	**Influenza/Total (%)**	**In Group (%)**	**LR**	**AUROCC (95% CI)**	Hosmer-Lemeshow p value
Flu Score					
High risk	78/106 (74%)	40	2.4	0.66 (0.60, 0.71)	**<0.01**
Medium risk	40/73 (55%)	28	1.0		
Low risk	25/86 (29%)	32	0.4		
CART 1					
High risk	35/44 (80%)	17	3.3	0.59 (0.54, 0.63)	**<0.01**
Medium risk	103/186 (55%)	70	1.1		
Low risk	5/35 (14%)	13	0.1		
CART 2					
High risk	48/62 (77%)	23	2.9	0.61 (0.56, 0.66)	**<0.01**
Medium risk	90/168 (54%)	63	1.0		
Low risk	5/35 (14%)	14	0.1		
CART 3					
High risk	17/22 (77%)	8	2.9	0.54 (0.51, 0.57)	**<0.01**
Medium risk	101/159 (64%)	60	1.5		
Low risk	25/84 (30%)	32	0.4		

LR = likelihood ratio; AUROCC = area under the receiver operating characteristic curve.

Table 5.7 Frequency, Sensitivity, Specificity, Positive Likelihood Ratio, Negative Likelihood Ratio, and Diagnostic Odds Ratio for each Clinical Sign and Symptom in Patients with Suspected Influenza that Received the Rapid Point of Care PCR test

	Patients that Received the Rapid PCR Test (n=265)						
Sign or Symptom	**Influenza (#/total)**	**No influenza (#/total)**	**Sensitivity**	**Specificity**	**+ LR**	**-LR**	**DOR**
Chills	138/143	91/122	97%	25%	1.3	0.1	13
Congestion	102/143	91/122	71%	25%	0.9	1.2	0.8
Diarrhea	14/143	9/122	10%	93%	1.4	1.0	1.4
Headache	132/143	102/122	92%	16%	1.1	0.5	2.2
Enlarged tonsils	9/143	20/122	6%	84%	0.4	1.1	0.4
Fever (>100.4*F)	124/143	68/122	87%	44%	0.3	0.3	1.0
Myalgia	118/143	61/122	83%	50%	1.7	0.3	5.7
Nasal discharge	136/143	108/122	95%	11%	1.1	0.5	2.2
Nausea	36/143	19/122	25%	85%	1.7	0.9	1.9
Pharynx erythema	92/143	62/122	64%	49%	1.3	0.7	1.9
Pharynx exudate	3/143	9/122	2%	93%	0.3	1.1	0.3
Rales	2/143	3/122	1%	98%	0.5	1.0	0.5
Sore throat	137/143	116/122	96%	5%	1.0	0.8	1.3
Symptom duration < 2 days	81/143	50/122	57%	59%	1.4	0.7	2.0
Tonsillar exudate	0/143	7/122	0%	94%	0	1.1	0
Unclear lungs	16/143	11/122	11%	91%	1.2	1.0	1.2
Vomit	18/143	9/122	13%	93%	1.9	0.9	2.1

LR = likelihood ratio; DOR = diagnostic odds ratio;

Table 5.8 Final Multivariate Logistic Regression via Lasso Technique for the Predictors of Influenza Diagnosis. Area under the receiver operating characteristic curve = 0.77.

Variable	β coefficient	Hazard Ratio
Myalgia	0.52	1.69
Chills	0.44	1.56
Fever	0.49	1.63
Tonsillar Exudate	-0.58	0.56
Intercept	-0.92	----

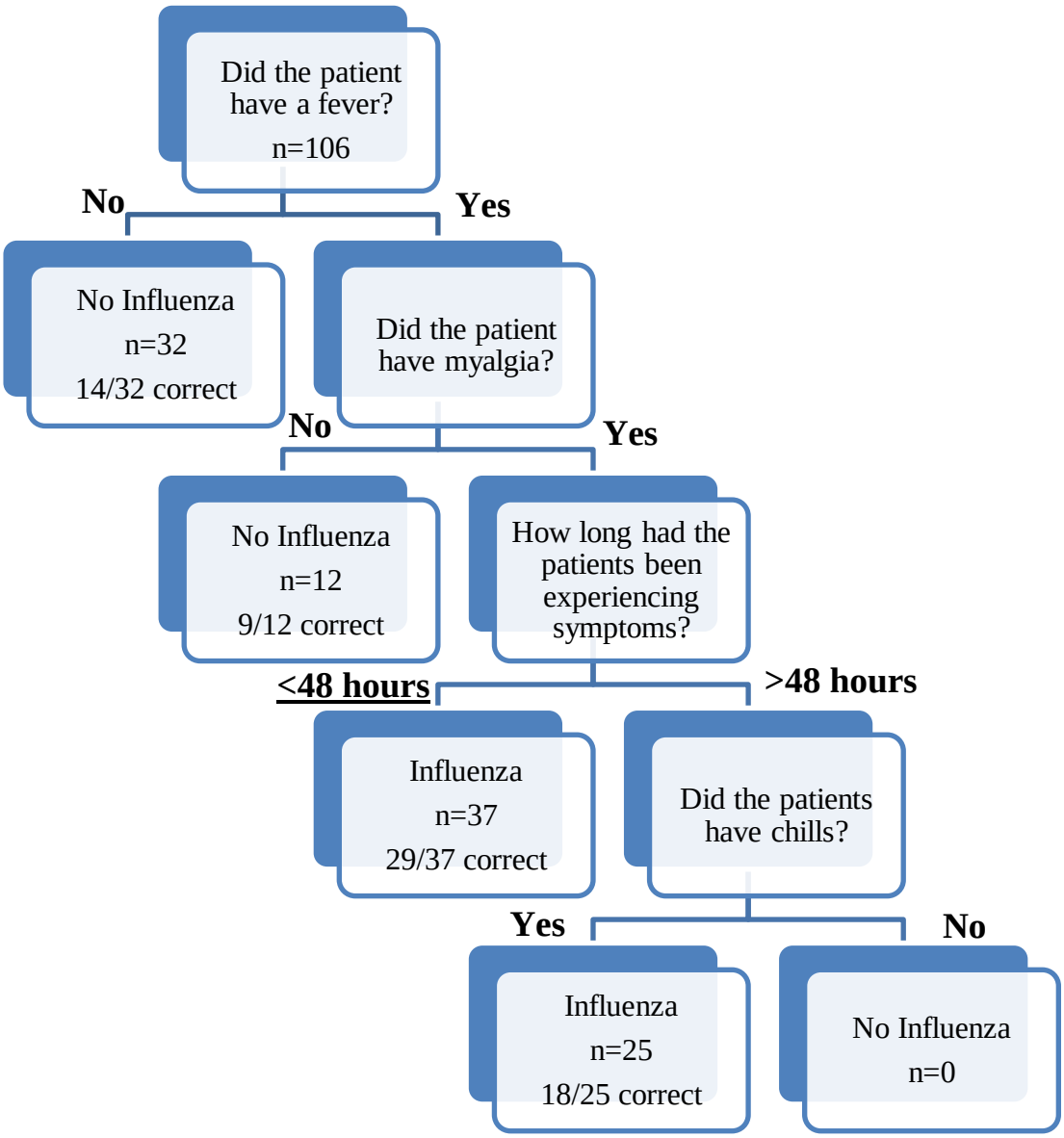

Figure 5.4 Fast and Frugal Tree for the Diagnosis of Influenza

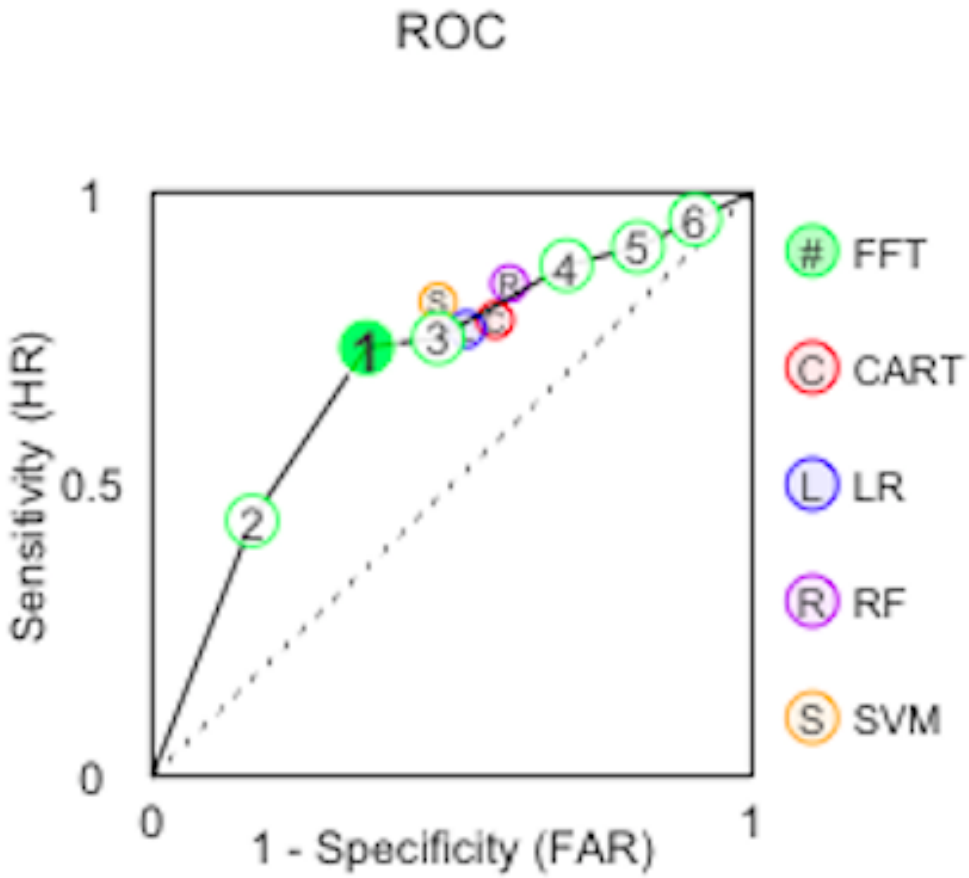

Figure 5.5 ROC Curve of all Models Created Using FFT Package

*FFT #: Fast and Frugal Tree, iteration number; CART = Classification and regression tree; LR = Logistic regression; RF + Random forest; SVM = Supported vector machine; FAR = false alarm rate; HR = hit rate.

CHAPTER 6

IDENTIFY WHETHER THE USE OF A RAPID POINT OF CARE POLYMERASE CHAIN REACTION TEST FOR THE DIAGNOSIS OF INFLUENZA A OR B INCREASES THE NUMBER OF PATIENTS WHO RECEIVE GUIDELINE CONSISTENT TREATMENT

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ABSTRACT

Background: The proper treatment of acute respiratory infections, including influenza, continues to be of concern for outpatient care. Patients still receive guideline inconsistent antibiotic or antiviral prescriptions. The rapid influenza test is currently used throughout the United States, but has poor sensitivity. The objective of this study was to identify if the use of a new highly accurate and rapid point of care test would significantly increase the likelihood of guideline consistent care. We also assessed the impact of the rapid point of care test on the likelihood of return visits within 2 weeks.

Methods: We prospectively recruited 300 students at a university health clinic who presented with cough or two influenza like illness symptoms between December 2016-February 2017 to receive a rapid polymerase chain reaction (PCR) test. These 300 patients were matched to at least one other patient who received usual care. We used five different strategies to build a logistic regression model to identify whether PCR-guided care increased the likelihood of US-guideline consistent care. We also assessed whether PCR guided care decreased the likelihood of return visits within two weeks by patients.

Results: Crude analysis revealed that the odds of guideline supported treatment was similar among patients who received care PCR-guided care compared to usual care (OR:1.24, 95% CI: 0.86-1.80). Our manual forward selection logistic regression model building revealed that the odds of receive guideline supported care did not significantly increase for patients who received PCR-guided care (aOR: 1.24, 95%CI: 0.83, 1.88). We also performed a 10x10 cross validation with 4 model selection strategies; the best fitting model built through a stepwise backward process also confirmed no significant association between PCR-guided care and guideline consistent care. Post-hoc analyses revealed that PCR-guided care significantly decreased the likelihood of an antibiotic prescription (aOR: 0.61, 95%CI: 0.40, 0.94) and increased the likelihood of an antiviral

prescription (aOR: 1.57, 95%ci: 1.09, 2.28). Additionally, PCR-guided care significantly decreased the likelihood of return visit within 2 weeks (aOR: 0.19, 95%CI: 0.04, 0.81). Conclusions: In a quasi-experimental study of PCR-guided versus usual care, there was a positive trend that PCR-guided care increased the likelihood of guideline consistent treatment. Patients who received PCR-guided care were significantly more likely to receive an antiviral and patients were significantly less likely to receive an antibiotic or have a return visit within two weeks.

6.1 Introduction

Influenza continues to be an important health problem in the United States, particularly for groups at increased risk of hospitalization and death. This includes the very young (<5 years of age), the old (>65 years of age), pregnant women, residents of long term health care facilities, and those with comorbidities such as chronic pulmonary disease and neurological disorders.[83] The annual burden of influenza in the United States is determined by several factors including the timing of the influenza season, the number of people vaccinated, the subtypes of influenza virus included in the vaccine, and the characteristics of the viruses that are circulating.[83] Recently, the 2009 influenza A (H1N1) epidemic in the United States affected approximately 10% of students on many college and university campuses.[15] The 2009 epidemic highlighted the need for further research about influenza in college and university students. These students tend to live in crowded dormitories or apartments, which may serve as a reservoir for diseases such as influenza to circulate.[84] While hospitalization rates are low, influenza can affect a student's academic performance, lead to unnecessary antibiotic and antiviral prescriptions, and increase the use of outpatient health care services. At the peak of the H1N1 influenza season, approximately 13% of primary care visits were for influenza-like illness (ILI) at college health services.[14] There are many challenges surrounding the prevention of influenza and its burden on the healthcare system.

Current treatment of influenza is primarily supportive care. Antiviral medications may also be used. In the United States, the only antiviral medication class currently recommended to treat or prevent influenza are neuraminidase inhibitors (NIs). NIs currently recommended by CDC guidelines include oseltamivir (Tamiflu) and zanamivir (Relenza).[27] Guideline consistent use of NIs reduces the mean duration of symptoms, and in observational studies appears to reduce the risk of complications that require antibiotics and may decrease hospitalization and mortality rates.[86]

In patients with influenza and a low risk for bacterial infections, antibiotics are not guideline consistent.[127] The use of antibiotics remains common for many viral acute respiratory infections, emphasizing the need for clinician and patient education regarding their ineffectiveness for these pathogens.[56] One reason for the over-prescription of antibiotics is the overlapping signs and symptoms between many respiratory infections. When a patient presents with cough and fever, it is important to be able to rule out pneumonia to eliminate the need for an antibiotic. Clinicians cite concern of a bacterial pneumonia infection as one of the leading reasons for prescribing an antibiotic in patients with influenza or lower respiratory tract infection.[89]

Another reason for the over-prescription of antibiotics is low confidence in the rapid influenza test. The use of rapid influenza tests for diagnosing patients is common in the US despite their poor sensitivity.[94] This lack of sensitivity in the rapid influenza test reduces its utility in clinical practice and can potentially lead to the overuse of antibiotics or NIs if physicians lack confidence in the test results. Polymerase chain reaction (PCR) tests are the gold standard in influenza diagnosis but until recently have taken 24 to 36 hours to yield results.[94] The recent introduction of a rapid point of care PCR test for influenza A and B combines the timeliness of the rapid flu test with the increased sensitivity and specificity of traditional PCR. Using a nasopharyngeal swab, the rapid point of care PCR test takes approximately 15 minutes to complete at the point of care. The result is a qualitative PCR result for the presence or absence of Influenza A or Influenza B. This test is 99.2% sensitive (95% CI: 95.1-99.9%) and 100% specific for influenza A virus (95%CI: not reported), and 100% sensitive (95%CI: 83.1-100%) and 100% specific for influenza B viruses (95%CI: not reported) when compared to a reference laboratory influenza A and B real-time PCR assay.[12] With the increased certainty in the results from a rapid point of care PCR test, the clinician can now have greater confidence in the final diagnosis.

The rapid point of care PCR test has the potential to be a useful test in the clinical care of patients with influenza-like illness but has yet to be independently evaluated for its impact on healthcare decision-making. We hypothesize that this may increase guideline consistent prescribing of antivirals and antibiotics in patients with acute respiratory infections. We also hypothesize that the use of PCR-guided care will decreased the likelihood of return visits within 2 weeks.

6.2 METHODS

We recruited 300 participants from December 2016-February 2017 at UHC. While patients were actively recruited for the PCR treatment group, the other clinic continued to treat patients using usual care practices. These patients, described as our usual care patients, received the standard care at UHC and were not offered the rapid PCR test. After data collection was completed, we then assessed whether a patient receive guideline consistent care or not.

Intervention and Outcome Variable Definitions

To address our objectives, we need clear definitions of our outcome and our intervention. Our intervention was the type of care a patient received (PCR vs. usual) and our outcome will be guideline consistent care. For patients who received PCR-guided care, the intervention and outcome definitions are as follows. A patient was considered influenza positive if they had a positive rapid point of care PCR test or a final clinical diagnosis of influenza. The definition of influenza positive must include both the test-based and final clinician diagnosis because not all patients received PCR-guided care. A patient was considered influenza negative if they had a negative rapid point of care PCR test and no final clinical diagnosis of influenza. Patients who received usual care was classified as influenza positive if they have a final diagnosis from their clinician of influenza. Patients who received usual care were considered influenza negative if influenza is not listed as one of their final diagnoses.

Defining treatment as guideline consistent or guideline inconsistent is more complex than defining final diagnosis, due to the overlapping symptom presentation of many respiratory diseases. We developed Table 6.1 to illustrate what would be guideline consistent and guideline inconsistent treatment depending on the diagnosis. Oseltamivir is only guideline consistent when administered within 48 hours of symptom onset in patients with influenza confirmed by PCR or clinician diagnosis per the Food and Drug Administration.[128] Antibiotics are guideline consistent in patients with a high risk of pneumonia or a final clinical diagnosis of a bacterial infection. For the purposes of this study, patients with a final diagnosis of acute otitis media or acute bacterial rhinosinusitis were excluded since antibiotic prescriptions are recommended for selected patients based on US treatment guidelines. [129,130]Patients who are diagnosed with influenza more than 48 hours after symptom onset, that do not have influenza, are at low risk for pneumonia, and do not have a bacterial infection as a clinical diagnosis should not receive oseltamivir or antibiotics.

Analysis: Primary Objective

Preliminary statistical analyses were performed in Stata. First, we stratified the EHR data accordng to our intervention: PCR tested, usual care, and not enrolled. Patients were classified as PCR tested if they were enrolled and received a nasopharyngeal swab. Usual care patients were not offered enrollment in the study and were selected from clinics that did not have active recruitment. Finally, patients were considered not enrolled in the study if they did not receive the PCR test when recruitment was active in their assigned clinic. Unenrolled patients were not included in our final analyses but we compared students enrolled in the study with those not enrolled to determine whether the enrolled students were typical of the population as a whole. Our intervention after their exclusion is binary: PCR-guided care or usual care. We described the data in Table 6.2 by sociodemographic factors, signs, symptoms, and laboratory test results. We used chi-square testing to determine any preliminary differences between treatment groups;

a p value less than 0.05 was considered statistically significant. We used several multivariate techniques to identify the association between PCR-guided care and the outcome of guideline consistent or inconsistent care while adjusting for potential covariates. Finally, propensity score matching was used to control for any differences between the intervention groups and assess for the magnitude of the association between intervention and outcome.

Multivariate Analysis

Strategy 1: Manual Forward Addition Based on AIC

After we identified our potential covariates, we first built a logistic regression model through a manual forward addition strategy. This technique involves beginning with the crude model and creating a model that adds characteristics. The AIC for each model was recorded and compared to the previous model. We then assessed the change in AIC between the two models; the model with the largest decrease in AIC was selected as the better fit.[97] This process was continued until the AIC change was no longer positive.

Strategy 2 Alternative Methods for Logistic Regression: Using MLR Package

We used R version 3.3.3 and its accompanying packages to perform cross validation with the MLR package. By using cross validation and repeating the model building, we increased the likelihood that our final model is a truly accurate representation of the relationship between PCR-guided care and guideline consistent care. We used stepwise forward addition, stepwise backward elimination, sequential floating forward addition, sequential floating backward elimination methods and a genetic algorithm.[131,132] A sequential floating method for feature selection builds in "floating" in conjunction with a stepwise method for selection of predictors by avoiding the nesting issue of features often seen in manual model building.[132] By combining the stepwise forward and stepwise backwards methods, this allows values of the features to "float" and remain unfixed as the model continues to grow with additional predictors.[132] A genetic algorithm uses a stochastic tool combined with a "survival of the fittest"

selection to propagate the solution model.[131] By combining these five methods with a 10-fold cross validation and 10 times repetition, we were more likely to find a repeatable result. These techniques were less likely to suffer from the inherent biases of manual model building by using the mlr package in R.

Strategy 3: Propensity Score Matching Analysis

We chose to use propensity score matching if the PCR-guided care and usual care groups appeared different in frequency of symptoms and signs. A propensity score represents the conditional probability that and individual will have received treatment, given the information available on covariates of interest.[133] We attempted 1:1, 1:2, 1:3 and 1:4 nearest neighbor matching.[134] We calculated the average treatment effect (ATE) and the average treatment effect in the treated (ATET). ATE represents the difference in expected outcomes between treatment and placebo groups.[134] The ATE quantifies the expected effect on our outcome of interest if the individuals in our population had been randomly assigned treatment; by using propensity score matching and measuring ATE we can simulate true randomization since this was not possible in our study.[134] ATET can be a more useful measure in that it directly quantifies the effect of treatment on the group intended.[134] However, for the purposes of our study, ATE was the most suitable measurement of interest.

Reconciliation of Multivariate Techniques

Given that we used 7 different techniques for assessing the relationship between PCR-guided care and guideline consistent care, a plan for selection of the best model is necessary. It is possible that these models would give different final interpretations since the inherent conditions of each technique are different. Foremost, the models that were built using cross-validation would be selected as the most “truthful”. These cross-validated models were repeated 100 times thereby increasing confidence in the final result. If all models reported a significant relationship between our intervention and outcome, the model that has the highest area under

the receiver operating curve in balance with parsimony was selected (AUROCC). If all the models reported a non-significant relationship between intervention and outcome, we reported the results of the cross-validated model that balances a high AUROCC and parsimony.

Analysis: Secondary Objective

We used Stata to perform all statistical analyses for the secondary objective. We used univariate and a manual multivariate analysis similar to what's described in the previous sections. We used these methods to assess the relationship between PCR-guided care versus usual care and the likelihood of a return visit within 2 weeks of their initial visit. We assessed all signs, symptoms, and other characteristics as potential explanatory variables.

6.3 RESULTS

Between December 2016 and February 2017, 3,095 patients with a chief complaint that generated a respiratory template were seen in the three UHC clinics. A total of 300 patients were enrolled to receive the rapid PCR test. Twelve of these patients were excluded from our final analysis due to an invalid PCR test result. Seven patients who received an invalid result agreed to be tested again, although several of these received another invalid result (n=5). Seven patients were missing all sign and symptom data and therefore were excluded from our analysis. The visit notes for these seven patients were reviewed but did not contain the information necessary to be included in the analysis. Some patients had both an invalid PCR result and no signs or symptoms data. Finally, we excluded 16 patients for having no reported cough. There are two explanations for this phenomenon. Our study recruitment staff included persons who had two suspected influenza symptoms instead of a cough plus one suspected influenza symptoms. Second, patients seeking enrollment into the study may have reported a cough verbally to the study enrollment staff but not to their clinician.

Therefore, 264 patients were included in the final PCR-guided care group for analysis. Patients were designated as receiving usual care if they presented with a respiratory infection

and met the inclusion criteria used by the PCR-guided care group, but to a clinic that was not currently enrolling patients to receive the PCR test at the time of visit. In the three clinics, 771 patients presented with the same inclusion criteria (described in section 1.3.2.3.1). and received usual care. Of these patients, 234 (30.4%) received a rapid flu test (not PCR). The recruitment of each group is presented in Figures 2.1 and 2.2. Table 6.2 presents the symptoms, signs, and location breakdown for each care group. We also did a count of the 7 most common influenza signs and symptoms for each patient and created Figure 6.3. The seven most common influenza signs and symptoms included in this count were: headache, cough, chills, myalgia, fever, nasal discharge and duration < 2 days. We chose these signs and symptoms based on our literature review and the CDC guidelines for NI use. This further illustrates that PCR-guided care patients tended to have more symptoms and signs than usual care patients.

Clinic 1 had 75 PCR treated patients, Clinic 2 had 134 PCR treated patients, and Clinic 3 had 55 PCR treated patients. Recruitment was nearly equivalent between Clinics 1 and 3 compared to Clinic 2, which is what we expected given our recruitment strategy. Patients in Clinics 1 and 3 were recruited nearly simultaneously and represent 49.3% of the final included participants, with an additional 10 days of recruitment taking place in Clinic 1 when the study first began.

We compared our final entire data set (PCR-guided care group and usual care group, n=1035) to the patients who met inclusion criteria in the clinic during PCR recruitment but were not enrolled, either because they refused (n=100), cited a lack of enough time to take the test (n=28), same day cancellation of appointment (n=56), decided they were either too sick or not sick enough to be swabbed (n=3), had appointment times past the designated recruitment and swab cut off time each day (n=33) or were not approached because the researcher was not present or was recruiting another participant (n = 90). The clinical characteristics of these patients are included in Table 6.2 as “unenrolled”. Patients that we unenrolled were significantly

different from PCR-guided care patients. PCR-guided care patients still tended to be sicker and have more symptoms, similarly to the usual care patients. The only symptom that significantly different between unenrolled patients and the PCR-guided care group that was not also different for PCR-guided care versus usual care was tonsillar exudate. Patients who were unenrolled were more likely to have tonsillar exudate.

Guideline Care: Consistent or Inconsistent

Overall, 193 of the 1,035 patients received guideline inconsistent care (18.7%) as defined in section 2.3.6. Table 6.3 and Table 6.4 illustrates selected differences between guideline consistent and guideline inconsistent care groups. Of all patients who received a NI, 27.5% had duration of symptoms greater than 48 hours. In the PCR-guided care group, 122 had a negative PCR test, of whom 27 (22.1%) were still given a final clinical diagnosis of influenza. Five of those 27 patients received an NI. In the usual care group, 537 of 772 (69.6%) did not receive a rapid influenza test, of whom 66 (21.2%) received an oseltamivir prescription. Finally, the PCR-guided care group had no significant difference in the odds of receiving guideline consistent care compared to the usual care group in the univariate logistic regression analysis (83.7% vs 80.5%, respectively, p=0.25, aOR:1.24, 95% CI: 0.86-1.80).

Strategy 1: Manual Forward Addition Logistic Regression

A multivariate logistic regression model using manual forward selection was selected to adjust for any signs, symptoms, or characteristics listed in Table 6.2. The final adjusted model is displayed in Table 6.5. Our manual forward addition strategy for logistic regression relied on a positive change in AIC of at least 2. Our model, fully adjusted for signs, symptoms, and clinic assignment found that the association between use of the PCR test and a greater likelihood of guideline supported care was not statistically significant (aOR 1.24, 95% CI 0.82 to 1.88), with a trend favoring guideline supported care in the PCR-guided care group. Our model included an adjustment for tonsillar exudate, clinic assignment, myalgia, pharynx erythema, pharynx

exudate, rales, enlarged tonsils, duration of symptoms, and unclear lungs. No other potentially confounding variables were statistically significant as shown in Table 6.5.

We then used a Hosmer-Lemeshow test to check for the goodness of fit of the final adjusted model. There were 10 distinct groups in our Hosmer-Lemeshow test because there were no ties. The Hosmer-Lemeshow chi square statistic was 10.9 with a p value of 0.21. The area under the receiver operating characteristic curve (AUROCC) was 0.77. Therefore, the model is a good fit for the data which is important since we want to determine whether PCR-guided-care is an independent predictor of outcome.

Strategy 2: 10x10 Cross Validation with Machine Learning

We chose to use R statistical software (v 1.0.136) to attempt 5 subset selection techniques, as described in section 2.3.6. We used a 10-fold cross validation, repeated 10 times. We used the MLR package to apply a stepwise forward addition, stepwise backward elimination, sequential floating forward addition, sequential floating backward elimination methods and a genetic algorithm. Each final model is listed in Table 6.6. Stepwise backward elimination and sequential floating backwards eliminated yielded models with 11 and 10 predictors. Area under the receiver operating curves (AUROCCs) were 0.75 and 0.749, respectively. Stepwise forward addition and sequential forward floating addition yielded 5 and 6 predictors. The AUROCCs were 0.721 and 0.728, respectively. The genetic algorithm yielded a model with 13 predictors and an AUROCC of 0.739. We selected the model produced by stepwise backwards elimination as our final model, since it included our intervention and had the highest AUROCC. This model had 11 predictors and is listed in Table 6.7. A Hosmer-Lemeshow test was used to assess the goodness of fit for the final fully adjusted model that did not include “care”. The Hosmer-Lemeshow chi-square statistics was 10.91, 8 degrees of freedom, and a p value of 0.21. Our intervention, PCR-guided care versus usual care, was only selected by the stepwise backward elimination and genetic algorithm. The stepwise backward

elimination model had the highest AUROCC and was more parsimonious that the final model built by the genetic algorithm.

Strategy 3: Propensity Score Adjustment

To account for differences between care groups, we performed propensity score matching for all signs and symptoms with greater than 10% difference as well as clinic assignment. We used a 1:1 matching followed by logistic regression to find the average treatment effect (ATE) and the average treatment effect in the treated (ATET). The ATE coefficient was 0.02 (95%CI: -0.07, 0.11; p value 0.664) and the ATET coefficient was 0.04 (95%CI: -0.01, 0.10; p value 0.125). Therefore, after propensity score matching followed by logistic regression, the type of care (PCR-guided vs usual care) was not a significant predictor of the likelihood that the patient received guideline consistent care.

Post Hoc Analyses: Prescription of Antibiotics or Antivirals

We also conducted post hoc multivariate analyses to predict the likelihood of antiviral prescription and a model to predict the likelihood of antibiotic prescription using manual AIC logistic regression model building. The results of these multivariate analyses are listed in tables 6.8 and 6.9 respectively. The relationship between the type of care received (PCR vs. usual) and likelihood of antiviral prescription was influenced by myalgia, duration of symptoms, fever, tonsillar exudate, unclear lungs, clinic assignment, nasal discharge, chills, and enlarged tonsils. Of note, patients who received PCR-guided care were significantly more likely to receive an oseltamivir prescription (aOR 1.58, 95% CI 1.09, 2.28) and significantly less likely to receive an antibiotic prescription (aOR 0.61, 95%CI 0.40, 0.94). The relationship between type of care received (PCR-guided vs. usual) and likelihood of antibiotic prescription was influenced by tonsillar exudate, pharynx erythema, pharynx exudate, duration of symptoms, sore throat, enlarged tonsils, unclear lungs, nasal discharge, and clinic assignment.

Likelihood of Return Visit

There were 28 return visits by patients within 2 weeks of their initial visit as listed in Table 6.10. We performed a chi-square test and a univariate logistic regression to determine if the relationship between PCR-guided care and a return visit were significantly associated. We found that the odds of a return visit for patients who received PCR-guided care were significantly lower than for patients who received usual care (aOR 0.22; 95%CI 0.05, 0.93). This represents an 78% decrease in the likelihood of a return visit among patients who received PCR-guided care. Adjusted multivariate analyses revealed that the relationship between PCR-guided care and likelihood of return visit was influenced by week day of visit and pharynx erythema (Table 6.11).

6.4 DISCUSSION

The use of a rapid PCR test was associated with a small but non-significant increase in the percentage of patients that received guideline supported care. In addition, patients receiving PCR-guided care were significantly more likely to receive an NI prescription and significantly less likely to receive an antibiotic prescription. Finally, patients were significantly less likely to return for a second visit within 2 weeks if they received PCR-guided care. Patients tested by PCR tended to be sicker; they had higher frequencies of symptoms and higher counts of seven common suspected influenza symptoms. The effect persisted after adjusting for both the number of symptoms and clinic site.

Discussion of Manually Adjusted Analysis

Our fully adjusted manually built model adjusted for the being assigned to clinic 3, presence of myalgia and duration of symptoms for 2 days or less. The final model adjusted for the absence of tonsillar exudate, pharynx erythema, pharynx exudate, rales, enlarged tonsils, and unclear lungs.

A possible explanation for why the presence of myalgia was an independent predictor of guideline consistent care points to the traditional presentation of influenza. Since influenza was

so common in our PCR-guided care group (50% prevalence), a typical influenza symptom like myalgia could influence the decision-making process. The absence of pharynx erythema, pharynx exudate, and tonsillar exudate may be explained by the high frequency of “acute pharyngitis-unspecified” diagnoses where bacterial cause was not clinically suspected.

Most episodes of influenza resolve within a week, therefore students who were unable to be seen rapidly at UHC due to becoming ill during the weekend may have sought care elsewhere. These students may also choose not to receive care, as treatment of influenza is primarily supportive. There are other reasons students may fail to seek care quickly. University students have many obligations including coursework, part time jobs, on-campus involvement, and more. Students, due to poor time management or other extraneous factors, may not have the time to be seen at UHC within the first two days of symptom onset. However, the UHC can see a student by the end of the next business day for an appointment, so appointment availability should not be a significant limitation.

The need to adjust for clinic assignment has several possible explanations. The clinics contain different clinicians who may have different practice patterns and serve different proportions of the university student population. Patients in Clinic 2 were less likely to receive guideline consistent care when adjusting for clinic assignment only (OR: 0.77, 95%CI: 0.49, 1.23). The varying experience and education levels of clinicians, such as a nurse practitioner (NP) or physician assistant (PA) compared to a medical doctor/physician can affect prescribing behaviors, as can the local culture and expectations of patients. It has been previously demonstrated that NPs/PAs are more likely to prescribe an antibiotic for an outpatient visit compared to physicians.[135]

Another reason for a guideline consistent care in Clinic 2 could be that clinicians did not accept or believe the PCR test results. If a clinician was highly confident in their diagnosis prior to the test result being shared, they could have chosen to accept their judgement over a test

result. This behavior was observed to occur in Clinic 2, but not in the other clinics. Our patient recruiters did receive complaints of anxiety and stress around the implementation of the PCR test, as many clinic assistants and clinicians were hesitant about the introduction of additional time into an appointment. At times, staff would not enroll a participant because they felt they wouldn't have tested the patient in the first place. After careful conversations regarding the implementation of the study, this was quickly remedied with the staff within the first week of recruitment in each clinic. Finally, limitations on recruitment times set by the clinic (8-11 am and 1-4 pm each day) eliminated some eligible participants.

The rapid PCR test used in this study is a realistic substitute for the rapid influenza test in primary care. The test takes approximately 15 minutes longer to complete and uses the same swab technique as current rapid influenza tests. Therefore, the amount of discomfort to the patient is equivalent. Overall in our study, an average of 20 minutes was added to appointment times of patients who received the PCR test as compared to usual care. Many organizations make efforts to minimize the amount of time a patient spends in total at a primary care practice. Minimizing time is also balanced with an assessment of quality of care. Further research into the cost effectiveness of this test as the standard in primary care practice is needed. The test currently reimburses at a maximum of $116.73 nationally and $71.18 in the state of Georgia.[136] Comparatively, the rapid influenza tests cost between $12-24 per test depending on brand.[137]

Other multivariate methods to predict guideline-consistent treatment

Among the 5 alternative methods used to create our final adjusted model for the likelihood of guideline consistent care, we chose the multivariate model that balanced parsimony and an increased AUROCC. for ease of memorization and due to the minimal increase in AUROCC between models. Therefore the stepwise backwards elimination methods is the best fit, given its fair AUROCC, our intervention being selected into the model, and a reasonable number of explanatory terms. In this model, we adjust for the myalgia, sore throat,

lung distress, unclear lungs, rales, pharynx exudate, tonsillar exudate, enlarged tonsils, PCR-guided care, clinic assignment, and duration of symptoms. It's positive beta estimate indicates that for patients with a duration of symptoms 48 hours or less, the participant was less more likely guideline consistent care. It is possible that the absence of enlarged tonsils, absence of pharynx exudate, and absence of tonsillar exudate is explained by the large number of diagnoses of acute pharyngitis with an unknown cause. These patients that received an antibiotic were considered guideline inconsistent, given that a large portion of acute pharyngitis cases are viral.[138]

Our intervention, PCR-guided care versus usual care, was selected as a feature in one of our models. Consistent with our manual analysis, it appears that there is not a statistically significant relationship between PCR-guided care and guideline supported care. Therefore, our final model from this technique using a 10-fold cross validation, repeated 10 times, for the stepwise forward selection of predictors is listed in Table 6.7. This model presents the best balance between parsimony and discrimination based on AUROCC. A Hosmer-Lemeshow test determined that this model is a good fit for the data and contains similar terms to our model built using a manual forward addition strategy.

Effect on NI Prescription

The likelihood of a prescription for a NI was significantly increased in patients who received PCR-guided care versus usual care (aOR 1.58, 95% CI: 1.09, 2.28; Table 6.8). This illustrates that with increasing clinician certainty, patients were more likely to receive a guideline consistent NI that aided in symptom reduction. This is useful for seasonal influenza outbreaks and even in future pandemic situations, increasing clinician likelihood in giving guideline consistent NI prescriptions. It is important for clinicians to consider the cost and potential side effects of oseltamivir prior to prescription, even in cases when the patient has been sick less than 48 hours.[29] Many clinicians noted throughout the study that they were surprised by patients

who did receive a positive rapid PCR test result, citing that many of them did not appear “sick enough” or follow “common symptoms” expected by the clinician. Some clinicians also did not believe the negative result.

Effect on Antibiotic Prescription

Interestingly, our study found that the use of PCR-guided care resulted in a 39% statistically significant decrease in antibiotic prescription when adjusting for several covariates (Table 6.9). This was an unexpected but important secondary consequence of our study. Antibiotic stewardship continues to be at the forefront of public health work. Therefore, the guideline consistent prescription of antibiotics and significant decrease in unnecessary antibiotic prescriptions to those with influenza is an important finding.

Likelihood of Return Visit

The likelihood of a return visit was significantly decreased in our unadjusted analysis. This trend held true even after adjusted analyses. The significant decrease in return visits within 2 weeks to the primary care clinic is important for pandemic influenza planning. A possible explanation for the significant decrease in return visits is the increased patient certainty in final diagnosis. By being presented a highly accurate test result, the patient feels secure in the discharge instructions. This is important for seasonal and pandemic influenza planning, as it decreases the number of influenza negative patients returning to the clinic. By returning to the clinic, they overwhelm the outpatient and emergency resources and put themselves at increased risk for influenza infection.[41]

Limitations

Our research does have limitations. First, due to logistical constraints at the clinic, we were unable to randomize the enrollment of patients in our study. A lack of randomization can decrease the generalizability of our results and dampen the effect of the intervention. Second,

not all our participants received a diagnostic test. Patients in usual care may have been treated empirically, meaning influenza diagnosis was never biologically confirmed.

Another limitation of our study was the baseline differences between patients in the PCR-guided and usual care groups. Patients who declined enrollment into the PCR-guided care group often told our recruiters that they did not feel they were “sick enough” or were very certain “I do not have the flu”. Based on our observations, many patients who declined to be enrolled during the study cited either a lack of severity of disease, a certainty in feeling they did not have influenza, or a lack of time as reasons for not participating. Therefore, it wasn’t surprising that students who were not recruited, but were eligible during the time of recruitment, appear less sick according to their recorded signs and symptoms in the EHR.

Overall, unenrolled patients had fewer reported signs and symptoms. Patients meeting inclusion criteria but not recruited were had similar symptom frequencies to the usual care groups, as seen in Table 6.2. There are several reasons that patients were eligible but did not get enrolled besides declining. Some patients were not approached because only one person was available to do recruitment in the clinics at a time, limiting the number of patients that could be offered recruitment. For approximately one week there was only one PCR machine available, due to an issue with the second machine, which also limited recruitment.

6.5 CONCLUSION

In a quasi-experimental study of PCR-guided versus usual care, there was a positive trend that PCR-guided care increased the likelihood of guideline consistent treatment. Patients who received PCR-guided care were significantly more likely to receive an antiviral and patients were significantly less likely to receive an antibiotic or have a return visit within two weeks. The future directions of this research are further discussed in the final chapter of this dissertation.

Tables and Figures

Table 6.1 Guide for Determining Guideline Consistency of Treatment.

Diagnosis	**Guideline Treatment**	
	Oseltamivir (n=312)	**Antibiotics (n=191)**
Influenza positive (PCR confirmed or final clinical diagnosis)	Consistent **(<48 hours onset)** 302	Inconsistent 27
No influenza, but high risk for pneumonia and/or bacterial infection diagnosis	Inconsistent 10	Consistent 24
No influenza, low risk for pneumonia and no bacterial infection diagnosis	Inconsistent 0	Inconsistent 140

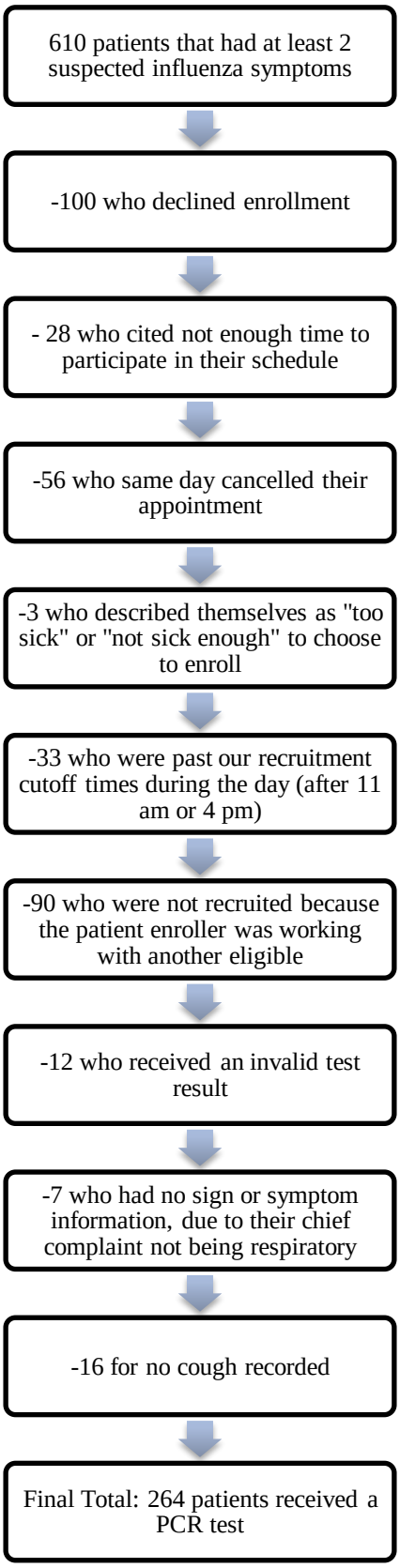

Figure 6.1 Recruitment of Patients to PCR Testing

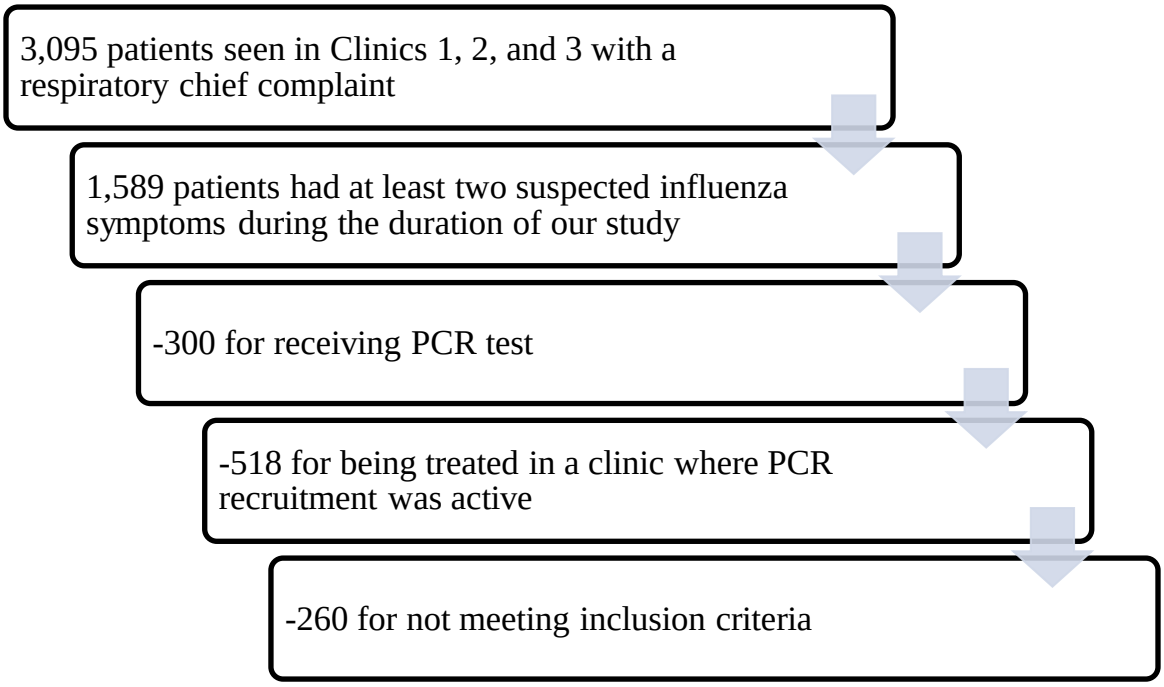

Figure 6.2 Selection from EHR of Patients Who Received Usual Care

Table 6.2 Signs, symptoms, and clinic assignments for PCR care and usual care

	PCR (n=264)		Usual Care (n=771)		Unenrolled (n=518)			
Characteristic	**N**	**Freq%**	**N**	**Freq %**	**N**	**Freq %**	**p value PCR vs Usual care**	**P value PCR vs unenrolled**
Cough	264	100.0%	771	100.0%	518	100.0%	**---**	**---**
Sore throat	253	95.8%	726	94.2%	495	95.6%	0.30	0.87
Nasal discharge	243	92.1%	670	86.9%	442	85.3%	**0.03**	**<0.01**
Headache	234	88.6%	620	80.4%	403	77.8%	**<0.01**	**<0.01**
Chills	229	86.7%	556	72.1%	345	66.6%	**<0.01**	**<0.01**
Fever	192	72.7%	428	55.5%	283	54.6%	**<0.01**	**<0.01**
Congestion	192	72.7%	534	69.3%	378	73.0%	0.29	0.92
Myalgia	179	67.8%	399	51.8%	241	46.5%	**<0.01**	**<0.01**
Pharynx erythema	154	58.3%	371	48.1%	241	46.5%	**<0.01**	**<0.01**
Nausea	55	20.8%	121	15.7%	82	15.8%	0.06	0.10
Enlarged tonsils	29	11.0%	81	10.5%	63	12.2%	0.83	0.64
Vomit	27	10.2%	60	7.8%	50	9.7%	0.22	0.92
Unclear lungs	27	10.2%	53	6.9%	42	8.1%	0.08	0.32
Diarrhea	23	8.7%	96	12.5%	75	14.5%	0.10	0.02
pharynx exudate	12	4.6%	25	3.2%	22	4.3%	0.33	0.84
tonsil exudate*	7	2.7%	35	4.5%	25	6.8%	0.18	**0.02**
Rales	5	1.9%	29	3.8%	13	2.5%	0.14	0.59
Lung distress	0	0.0%	3	0.4%	1	0.2%	0.31	0.48
Clinic 1	75	28.4%	238	30.9%	133	25.7%	**<0.01**	**0.64**
Clinic 2	134	50.8%	270	35.0%	279	53.9%	---	---
Clinic 3	55	20.8%	263	34.1%	106	20.5%	---	---
Duration $\leq$ 2 day	131	49.6%	296	38.4%	176	34.0%	**<0.01**	**<0.01**
$\geq$2 days	133	50.4%	475	61.6%	342	66.0%	---	---
Day of visit Friday	59	22.4%	205	18.7%	---	---	0.20**	---
Day of visit other weekday	205	77.6%	627	81.3%	---	---	---	---

**p value for chi-square testing between PCR-guided and usual care groups only.

Table 6.3 Final diagnosis and final prescriptions given to patients included in our study

	PCR	**Usual Care**	**Total**	**p value**
Influenza final diagnosis	64.0%	41.9%	47.5%	**<0.01**
Acute pharyngitis-unspecified diagnosis	8.3%	6.3%	0.7%	
Received NI	42.4%	25.9%	30.1%	**<0.01**
Received antibiotic	14.8%	19.7%	18.5%	0.07
Guideline supported	83.7%	80.5%	81.4%	0.25

Table 6.4 Stratification of guideline consistent and inconsistent care on variables of interest including PCR testing, rapid influenza testing, clinic assignment, and duration of illness

	Guideline Consistent care n=842 (81.3%)	**Guideline Inconsistent care n= 193 (18.7%)**	**p value**
PCR tested	221 (83.7%)	43 (16.3%)	-----
Rapid flu tested	207 (88.4%)	27 (11.6%)	-----
PCR positive	140 (97.9%)	3 (2.1%)	<0.01
PCR negative	82 (67.2%)	40 (32.8%)	-----
Clinic 1	258 (82.4%)	55 (17.6%)	<0.01
Clinic 2	306 (75.7%)	98 (24.3%)	-----
Clinic 3	278 (87.4%)	40 (12.6%)	-----
Duration <=2 days	367 (86.0%)	60 (14.0%)	<0.01
Duration >2 days	475 (78.1%)	133 (21.9%)	-----

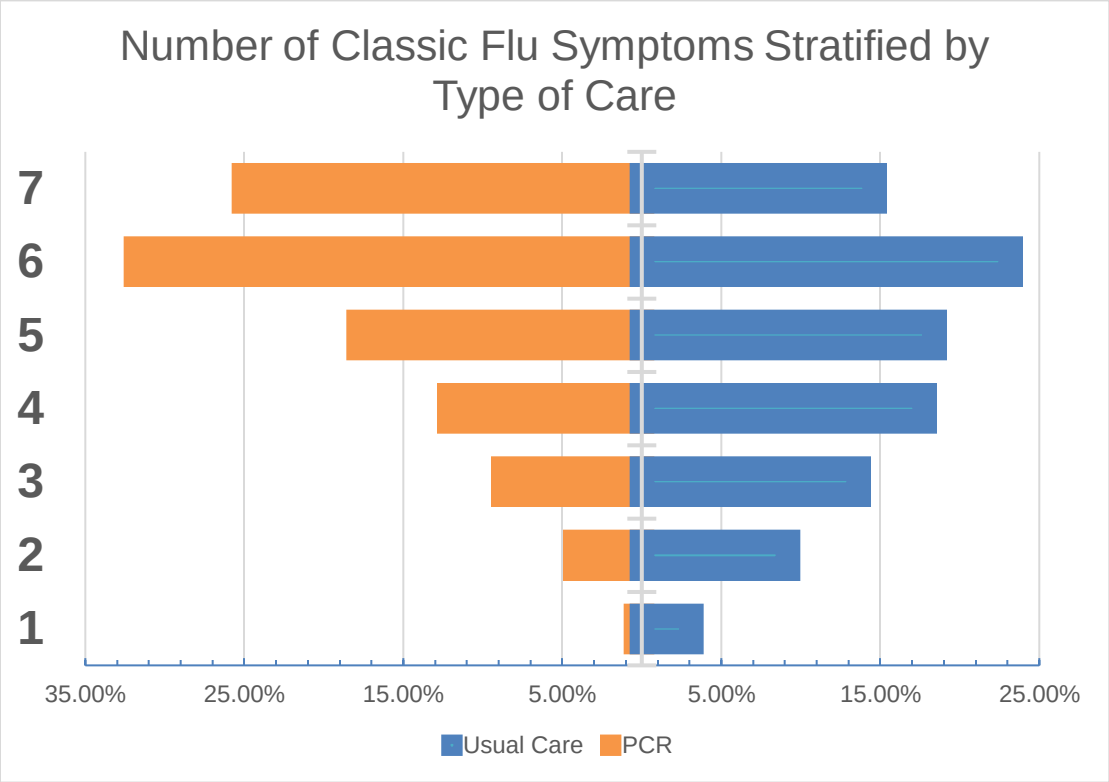

Figure 6.3 Influenza symptom count variable, stratified by type of diagnostic procedure used

Table 6.5 Final fully adjusted model for the relationship between PCR testing and guideline consistent care

Sign/Symptom	**Estimate (β coefficient)**	**Standard Error**	**p value**	**aOR (95% CI)**
PCR tested (y/n)	0.22	0.21	0.30	1.24 (0.83, 1.88)
Tonsillar exudate	-1.76	0.43	<0.01	0.17 (0.07, 0.39)
Clinic 2	-0.28	0.23	0.22	0.76 (0.48, 1.18)
Clinic 3	0.58	0.25	0.02	1.79 (1.09, 2.93)
Myalgia	0.85	0.19	<0.01	2.35 (1.61, 3.42)
Pharynx erythema	-0.60	0.21	<0.01	0.55 (0.37, 0.82)
Pharynx exudate	-1.25	0.40	<0.01	0.29 (0.13, 0.63)
Rales	-0.98	0.39	0.01	0.38 (0.17, 0.81)
Enlarged tonsils	-0.80	0.28	<0.01	0.45 (0.26, 0.78)
Duration of symptoms	0.55	0.20	<0.01	1.74 (1.17, 2.57)
Unclear lungs	-0.78	0.30	<0.01	0.46 (0.26, 0.82)
Intercept	1.49	0.19	<0.01	----------
H-L chi-square statistic= 10.9, p=0.21; AUROCC: 0.77				

Table 6.6 Final adjusted models for the prediction of guideline consistent treatment using five subset selection techniques using 10-fold cross validation, repeated 10 times using MLR package

Model building technique	Number of features selected	List of features	AUROCC
Stepwise backward	11	Myalgia, sore throat, lung distress, unclear lungs, rales, pharynx exudate, tonsillar exudate, enlarged tonsils, PCR-guided care, clinic assignment, duration of symptoms dichotomized	0.75
Sequential floating backwards elimination*	10	Myalgia, sore throat, lung distress, unclear lungs, rales, pharynx exudate, tonsillar exudate, enlarged tonsils, care, clinic assignment, duration of symptoms dichotomized	0.749
Stepwise forward addition*	5	Myalgia, pharynx erythema, pharynx exudate, enlarged tonsils, clinic assignment	0.721
Sequential floating forward addition*	6	Myalgia, rales, pharynx erythema, pharynx exudate, enlarged tonsils, clinic assignment	0.728
Genetic Algorithm	13	Myalgia, fever, sore throat, congestion, lung distress, unclear lungs, pharynx erythema, pharynx exudate, tonsillar exudate, enlarged tonsisl, PCR-guided care, clinic assignment, duration of symptoms dichotomized	0.739

*PCR-guided care was not selected as a feature.

Table 6.7 Final fully adjusted stepwise forward selection model selected from 5 subset selection techniques using 10-fold cross validation, 10 times repeated

Sign/Symptom	**Estimate (β coefficient)**	**Standard Error**	**p value**	**aOR**
Myalgia	0.76	0.19	<0.01	2.15
Sore throat	-0.74	0.49	<0.01	0.48
Lung distress	14.4	433.2	0.97	1.91 e06
Unclear lungs	-0.96	0.29	0.01	0.38
Rales	-1.13	0.40	<0.01	0.32
Pharynx exudate	-1.29	0.40	<0.01	0.27
Tonsillar exudate	-1.75	0.42	<0.01	0.17
Enlarged tonsils	-0.97	0.28	<0.01	0.38
PCR-guided care	0.20	0.94	0.35	1.22
Clinic 2	-0.49	0.21	0.02	0.62
Clinic 3	0.44	0.25	0.07	1.55
Duration of symptoms	0.55	0.20	<0.01	1.74
Intercept	2.09	0.51	<0.01	----------
Hosmer-Lemeshow chi-square statistic=10.91, df=8, p= 0.21 AUROCC= 0.75				

Table 6.8 Final fully adjusted model for likelihood of antiviral prescription: signs, symptoms, and clinic assignment

Sign/Symptom	**Estimate (β coefficient)**	**Standard Error**	**P value**	**aOR (95% CI)**
PCR tested (y/n)	0.46	0.19	0.02	1.57 (1.09, 2.28)
Myalgia	1.30	0.23	<0.01	3.65 (2.35, 5.68)
Duration of symptoms	1.77	0.17	<0.01	5.89 (4.18, 8.28)
Fever	0.93	0.24	<0.01	2.52 (1.57, 4.05)
Tonsillar exudate	-1.67	0.71	<0.01	0.19 (0.05, 0.77)
Unclear lungs	1.05	0.30	<0.01	2.86 (1.58, 5.17)
Clinic 2	0.13	0.21	0.55	1.13 (0.75, 1.72)
Clinic 3	0.74	0.23	<0.01	2.09 (1.34, 3.25)
Nasal discharge	0.80	0.32	0.01	2.24 (1.19, 4.19)
Chills	0.87	0.33	<0.01	2.38 (1.25, 4.53)
Enlarged tonsils	-0.71	0.34	0.03	0.49 (0.25, 0.95)
Intercept	-5.13	0.47	<0.01	----------
Hosmer-Lemeshow chi-square statistic= 3.16, df=10, p=0.92 Unadjusted OR: 2.10 (1.57, 2.82), AUROCC: 0.86				

Table 6.9 Final fully adjusted model for likelihood of antibiotic prescription: signs, symptoms, and clinic assignment

Sign/Symptom	**Estimate (β coefficient)**	**Standard Error**	**P value**	**aOR (95% CI)**
PCR tested (y/n)	-0.31	0.22	0.02	0.61 (0.40, 0.94)
Tonsil exudate	1.63	0.44	<0.01	5.10 (2.14, 12.1)
Pharynx erythema	0.96	0.21	<0.01	2.60 (1.73, 3.93)
Pharynx exudate	1.78	0.43	<0.01	5.94 (2.56, 13.8)
Duration of symptoms	-0.73	0.19	<0.01	0.48 (0.33, 0.71)
Sore throat	0.60	0.54	0.27	1.83 (0.63, 5.26)
Enlarged tonsils	0.89	0.27	<0.01	2.43 (1.42, 4.16)
Unclear lungs	0.79	0.29	<0.01	2.21 (1.26, 3.88)
Nasal discharge	-0.65	0.26	0.01	0.52 (0.31, 0.87)
Clinic 2	0.09	0.23	0.69	1.10 (0.70, 1.73)
Clinic 3	-0.44	0.25	0.08	0.64 (0.39, .05)
Intercept	-1.99	0.59	<0.01	----------
Hosmer-Lemeshow chi-square statistic= 6.32, df=8, p=0.61 Unadjusted OR: 0.71 (0.48, 1.04), AUROCC: 0.79				

Table 6.10 Signs, symptoms, and clinic assignments stratified by if a patient had a return visit within 2 weeks of their initial appointment

	Returned within 2 weeks (n=28)		**Did not Return within 2 weeks (n=1007)**		
Characteristic	**N**	**Freq%**	**N**	**Freq %**	**p value**
PCR-guided care	2	7.1%	262	26.0%	**0.02**
Cough	264	100.0%	771	100.0%	**-----**
Sore throat	25	95.8%	954	94.2%	0.21
Nasal discharge	27	92.1%	886	86.9%	0.17
Headache	22	88.6%	832	80.4%	0.58
Chills	19	86.7%	766	72.1%	0.32
Fever	15	72.7%	605	55.5%	0.49
Congestion	18	72.7%	708	69.3%	0.49
Myalgia	14	67.8%	564	51.8%	0.53
Pharynx erythema	20	58.3%	505	48.1%	**0.03**
Nausea	6	20.8%	170	15.7%	0.53
Enlarged tonsils	7	11.0%	103	10.5%	**0.01**
Vomit	4	10.2%	83	7.8%	0.26
Unclear lungs	5	10.2%	75	6.9%	**0.04**
Diarrhea	3	8.7%	116	12.5%	0.90
pharynx exudate	2	4.6%	35	3.2%	0.30
tonsil exudate*	3	2.7%	39	4.5%	0.07
Rales	2	1.9%	32	3.8%	0.25
Clinic 1	9	28.4%	304	30.9%	0.47
Clinic 2	8	50.8%	396	35.0%	---
Clinic 3	11	20.8%	307	34.1%	---
Duration > 2 days	9	32.1%	418	41.5%	0.32
< 2 days	19	67.9%	589	58.5%	---
Day of visit Friday	11	39.3%	192	19.1%	**<0.01**
Other Weekday	17	60.8%	815	80.9%	---

Table 6.11 Final fully adjusted model for likelihood of return visit: signs, symptoms, and clinic assignment

Sign/Symptom	**Estimate (β coefficient)**	**Standard Error**	**P value**	**aOR (95% CI)**
PCR tested (y/n)	-1.66	0.74	0.03	0.19 (0.04, 0.81)
Day of visit (Friday vs. other weekdays)	1.04	0.40	<0.01	2.83 (1.29, 6.19)
Pharynx erythema	0.97	0.43	0.02	2.65 (1.15, 6.10)
Intercept	-4.22	0.39	<0.01	----------
Hosmer-Lemeshow chi-square statistic= 2.56, p=0.63 AUROCC: 0.70				

CHAPTER 7

PCR- CONFIRMED INFLUENZA DIAGNOSIS AND STUDENT BEHAVIOR

Dale, A.P., Ebell, M. H., McKay, B., Handel, A., Forehand, R., Dobbin, K. To be submitted to *the Journal of the American Board of Family Medicine.*

ABSTRACT

Background: Influenza continues to be a concern for the college health population, especially following the 2009 epidemic of H1N1. University students lead active social lives that may be less affected by influenza diagnosis than in the general population. We hypothesize that use of a rapid PCR test to diagnose influenza will positively change student behavior. Specifically, students will report decreased stress levels and increase social distancing practices defined as absence from school or work, avoidance of public dining commons, and avoidance of public transportation.

Methods: We prospectively enrolled patients with clinically suspected influenza and cough to receive a rapid PCR test for influenza from December 2016 to February 2017 at a university health clinic. Patients then received a 10 question follow up survey assessing their behavior, vaccination status, and severity of symptoms after 5 days. We used logistic regression to assess the associations between influenza diagnosis and self-reported stress level and the three social distancing outcomes. Finally, we created a composite social distancing score using these three measures and performed a simple linear regression to evaluate the relationship.

Results: Of the 300 patients enrolled, 227 had a cough at their appointment, received a final rapid PCR test result, and completed the one week follow-up survey. Patients with PCR confirmed influenza were more likely to report a decrease in stress levels when adjusting for number of days of work or class missed (aOR: 0.68; 95%CI: 0.55, 0.85). Students with influenza were also more likely to report any absence from work or school (aOR: 3.86; 95% CI: 1.84,8.09). No difference was seen in the relationship between influenza diagnosis and attendance to dining commons or use of public transportation. Patients with PCR confirmed influenza were more likely to implement social distancing as defined by our social distancing score in simple linear regression (**β** : 1.65; 95%CI: 1.01, 2.29).

Conclusions: In a college health population, PCR-confirmed influenza diagnosis increased the number of days of absence from work or class. Students are willing to implement some social

distancing, but universities must consider plans for dining services for sick students to encourage isolation in a pandemic.

7.1 INTRODUCTION

Influenza creates a significant economic burden of over $87 billion per year in the United States.[99] Additionally, an average of 610,660 life-years lost, 3.1 million hospitalized days, and 31.4 million outpatient visits are attributed to seasonal influenza in the United States.[99] This represents a significant burden to the United States workforce, the elderly (>65 years of age), and the very young (<2 years of age).[99]

The impact of influenza is also significant for university and college students.[16] The burden of influenza like illness (ILI) in university students is greater compared to that associated with other upper respiratory infections.[16] Specifically, students with ILI miss more days of class, work, and social activities as compared to students with other upper respiratory infections.[16] These students also report a longer duration of illness, more days spent in bed, and more days with physical impairment as compared to an upper respiratory infection.[16]

There are many ways to reduce the burden of influenza including seasonal influenza vaccination and non-pharmaceutical interventions. Unvaccinated persons report missing more work hours and a decrease in work productivity.[100] As previously discussed in section 2.1.1, university students have beliefs about vaccine safety and efficacy that may decrease compliance.

Other preventive behaviors are available to university students during an influenza outbreak. These non-pharmaceutical interventions include: handwashing, face masks, cough covering, and self-isolation.[101] Students are more likely to participate in these behaviors as perceived personal risk increases.[48] Frequent handwashing and covering of the mouth when coughing have the highest compliance among university students.[48] A lack of self-perceived risk is the main contributor to low compliance with face masks and self-isolation.[48,49] Persons aged 16 to 24 years are the least likely to use a face mask compared to other adults unless the threat of pandemic influenza is high.[49]

University students lead active social lives. Therefore, the low rates of compliance to self-isolating behaviors is not surprising.[45,48] Students are unlikely to forgo social events such as Greek Week or parties when infected with influenza.[45] Additionally, university students live in crowded conditions, but fewer than 40% recognize this as a health risk.[54] Crowded living conditions and social events may be significant factors in the spread of influenza.[139] Even during a pandemic influenza outbreak, such as the H1N1 outbreak of 2009, student compliance with preventive behaviors and risk perception were low.[44] The lack of understanding of risk and low compliance with many preventive behaviors is troubling and requires a concentrated education effort by universities to overcome it.[16,44,48,101]

College students' lack of compliance with self-isolating behaviors may be linked to the social health and support system of the student. For most university students, influenza infection can represent the first time a student is making health-related decisions without consulting their family or guardians. Colleges and universities attempt to create strong social networks and ties to campus culture to support students to graduation. Many universities now institute a first year live on campus requirement for students, as it is demonstrated to have numerous social and educational benefits.[102] This requirement yields a strong social network in a university; however, this network can also be a substantial risk for infection.[140]

College students' understanding of risk as related to social networks and compliance with preventive behaviors is low.[15,35,44,54] However, these studies were conducted without the availability of a highly accurate test.[35] By introducing a highly accurate rapid PCR test it is possible that perceived risk will increase since a student will be more certain of their diagnosis. If perceived risk increases, the compliance with self-isolation may increase. Therefore, we hypothesize that students with PCR confirmed influenza will miss significantly more days of school/work, report a decreased use of public facilities, and a decrease in self-reported stress level.

7.2 METHODS

Setting

The University Health Center (UHC) at the University of Georgia (UGA) provides primary care, urgent care, and selected specialty services to the 35,000+ students enrolled at the university. The UHC has four primary care clinics with 20 primary care clinicians available to students for traditional business hours and Sunday urgent care hours. UHC is unique in that it is one of just two college health facilities in the nation that has been accredited by the Joint Commission for Ambulatory Care and Primary Care Medical Home. Students can make same day appointments, so this health care facility serves as an ideal location for a study of suspected influenza in young adults.

Population

In 2015, UGA enrolled 27,547 undergraduate students and 8,583 graduate students.[103] Further demographic information is included in Table 1.3 in Appendix 1. UHC serves currently enrolled UGA students who attend the Athens campus. These college students are ideal for study for several reasons. First, they are at an age that typically is not highly vaccinated against influenza. Second, they are assigned to a primary care clinician who oversees their care and is the first doctor available for scheduling. Third, these student's records are easy to follow throughout their four years, as UHC uses a comprehensive electronic health record (EHR). Finally, same or next day visits are usually available, and students do not have to pay for their visits, so there is no barrier to access.

Data Collection

After patients were selected to receive a rapid point of care PCR test as described in aim 2, they also provided their UGAMail email address. Five days' post patient visit, the patient received an email notification requesting their participation in a follow up survey. This follow up survey was delivered using Qualtrics, an online survey tool; two patient pieces of patient

identifying information were collected to match the survey record to the EHR from aims 1 and 2. The survey in its entirety is included in Appendix C. This survey assessed vaccination status, symptom development, self-rated stress score, health care decision-making strategies, and presence in public areas around campus. If necessary, students received up to 3 reminder emails.

Data collection began in December of 2016 and ended in February of 2017. Email notifications were managed daily using Qualtrics. The informed consent process has been described previously in Aim 1. Therefore, only patients who receive a nasopharyngeal swab and a final PCR result of positive or negative were included in this follow up survey. Students who received an invalid PCR result did not receive the follow up survey.

Survey Response and Outcome Definitions

Self-reported stress, the first outcome variable assessed, was reported on a five-point Likert scale, with 1 being “a lot less stressed than normal” and 5 being “a lot more stressed than normal”. We treated this outcome as an ordinal categorical variable. We then had 3 outcomes that captured social distancing by students: number of days of work or class missed, number of public dining facilities attended, and types of public transportation used. Patients reported the number of days of class or work missed in the week following the clinic visit as a continuous variable from 0 to 5. We dichotomized this variable to taking at least one day off versus no missed work or school. Patients reported use of public dining facilities as a categorical variable by indicating which, if any, of the 5 campus dining facilities they had attended during the week following their clinic visit. A binary outcome was created for attendance to any public dining commons versus no attendance to public dining commons. There were three types of public transportation that a patient could select: bus, rideshare, and carpool. We dichotomized use of public transportation to any versus none. We define “public transportation” as any transportation that involves at least one other person regardless of relationship to the patient.

We then created a continuous variable for “social distancing score” by subtracting the number of public dining facilities and number of public transportation modes used from the number of days of work or class missed. This created a social distancing categorical variable, with values from -8 (used all dining and transportation options and did not miss school) to 5 (stayed home for 5 days and did not use any public transportation or dining facilities). We assessed the normality of distribution using a histogram of the social distancing score and a Q-Q plot.[141] R version 3.3.1 was used to perform all analyses.

Univariate Analysis

Exploratory data analysis involved the examination of the data set. Next, an item analysis was conducted for each variable individually to assess for missing data, lack of variability, and outliers. All categorical and dichotomous variables were plotted using a stem and leaf plot to assess variability, while continuous variables were plotted using histograms and line graphs.

Following the item analysis, correlation analysis was used to assess the relationship between the individual variables. All variables with a high correlation coefficient were considered by the investigators for combination, exclusion, or inclusion based on the covariate relationship to the exposure-outcome pathway. Recoding, for example a continuous to categorical variable, was assessed on a case-by-case basis and transformed as necessary to satisfy model assumptions. We did not transform any covariates and chose to include all in our model building.

We then conducted bivariate analyses for the initial relationships between influenza diagnosis and each question of the survey. A chi-square test was used to assess for significant differences between groups per variable. For continuous variables, we used simple linear regression.

Multivariate Analysis

Finally, a logistic regression was fitted to the data using a manual forward addition technique based on Aikake Information Criteria.[104] We first manually cross validated our data using a 10 times repeated, 10 fold process. Each outcome variable was assessed as a separate model in our analyses. We built an ordinal logistic regression as described by Hosmer, Lemeshow and Sturdivant for self-reported stress level.[104] We then built 3 binary logistic regression models for each of the 3 social distancing score component variables: whether a patient missed class or work (yes vs no), whether a patient used any public dining commons (yes vs no) and whether the patient used any public transportation (yes vs no). The model building process was similar between each category as only the outcome included in our model building changed.

We used the following covariates in our model building: influenza vaccination status, days with a fever, severity of cough, residence type, reported reliance on family and friends, antibiotic prescription, antiviral prescription, clinic assignment, duration of symptoms, and the day of the visit. These covariates capture baseline illness severity, baseline symptom duration, prescriptions received, and follow up for 5 days post appointment.

We used a simple regression model building strategy using a manual forward addition technique for the analysis of the relationship between influenza diagnosis and the composite social distancing score variable.

7.3 RESULTS

Between December 2016 and February 2016, 300 students with ILI were enrolled in our study and tested for influenza using a rapid PCR test. Of the 300 patients, 242 completed the 9 questions follow up survey (81% response rate). Fifteen patients were excluded from analysis because they had an invalid PCR test (n=2) or did not have a cough at their initial visit (n=13). Therefore, 227 patients were included in our final analysis.

Responses to the follow-up survey are summarized in Table 7.1, stratified by influenza diagnosis. Patients with PCR confirmed influenza were less likely to report a dramatic improvement in their cough after 5 days, reported a longer duration of fever, and reported relying on their social network “a lot”. Persons without influenza were more likely to report having received an influenza vaccination (23.8% vs 4.9%, p=0.02).

Self-Reported Stress Level

The final adjusted ordinal regression model for the prediction of stress score is summarized in Table 7.2. The final model included the result of the PCR test for influenza, which was our exposure of interest, and the number of days of work or classed the patient reported missing. We used a Hosmer-Lemeshow goodness of fit test to examine the calibration of this explanatory model; the chi-square statistic was 25.2 and the p value was 0.67, indicating a good fit. In the multivariate analysis, there was a nonsignificant association between influenza diagnosis and increased self-reported stress level (aOR: 1.32; 95% CI: 0.79, 2.21). Patients who reported an increased number of days of work or class missed were significantly less likely to report increased levels of stress (aOR: 0.68; 95%CI: 0.55, 0.85).

Social Distancing: Univariate analysis

We first performed univariate analysis on our three binary outcomes for social distancing: missing any work or class, using any public transportation, and attending any public dining commons. Patients with PCR confirmed influenza were significantly more likely in the univariate analysis to miss days of work or class and to not use any public transportation (Table 7.1). However, there was no difference between influenza positive and negative patients regarding attendance to public dining commons (p=0.19). Patients were assigned a social distancing score based on their responses to number of days of classes missed, number of dining commons visited, and number of transportation services used. We first examined the social distancing score as a continuous variable. When plotted as a histogram in Figure 7.1, this

score appears to be skewed to the left in distribution. A Q-Q plot was generated, confirming an non-normal distribution in Figure 7.2. Of the 227 patients included in our analysis, 72 patients reported social distancing based on this definition. Finally, patients without influenza were more likely to report decreased social distancing per our composite score (83.8% vs 54.9%, $p<0.01$) in the univariate analysis.

Social distancing: Multivariate analysis

Separate binary logistic regression models were fit with the likelihood of missing class or work, eating in public dining commons, and using public transportation as the dependent variables. A Hosmer-Lemeshow test was used to assess goodness of fit for each model; the statistics are reported in Tables 3.3 to 3.6. All final adjusted explanatory models were deemed a good fit. Patients with PCR confirmed influenza were significantly more likely to miss days of class or work (aOR: 3.86; 95% CI: 1.84,8.09; Table 7.3). However, there was no association between having PCR confirmed influenza and any attendance of public dining commons or any use of public transportation (Tables 7.4 and 7.5). Patients with PCR confirmed influenza were more likely to implement social distancing as defined by our social distancing score in the linear regression (β : 1.65; 95%CI: 1.01, 2.29), Table 7.6.

7.4 DISCUSSION

Of the 227 patients who completed follow up surveys, 54% had PCR confirmed influenza. In the univariate analysis, patients with PCR confirmed influenza were significantly less likely to report improvement in their cough and reported more days with a fever. Influenza negative students were more likely to have received the influenza vaccination at least 2 weeks before their visit; 76% of influenza negative patients were still unvaccinated, demonstrating lack of compliance among college students and suggesting some vaccine efficacy despite a poor antigenic match during the 2017/2018 flu season.[14] Approximately 75% of patients reported missing at least one day of class due to their illness, regardless of the final diagnosis. Students

also shared similar responses to change in stress level regardless of their final influenza diagnosis. Students were evenly split amongst dining commons on campus, and typically lived with at least one other person. This suggests that students may view no difference in need for social isolation from public dining commons between an influenza final diagnosis and other respiratory diagnosis (pharyngitis, tonsillitis, bronchitis) since they already live in crowded conditions.

Self-reported Stress Levels

Stress is documented to affect illness behavior and recovery.[142] Patients with PCR-confirmed influenza diagnosis had no change in the likelihood of experiencing significant stress (aOR:1.32 , 95% CI: 0.79, 2.21), while students who reported missing class or work were more likely to report a decrease in stress (aOR: 0.68; 95% CI: 0.55, 0.85). One possible explanation for this relationship is that students can use their day or days to recover from illness and catch up on any missed classroom assignments. Not only are they receiving a physical reprieve from the classroom or workplace, they are receiving a mental break. These patients are also practicing an isolation technique and not spreading their illness to their coworkers and classmates. This demonstrates that students are willing to take advantage of the most basic of isolation techniques; skipping a day of class and work.

Social Distancing

It has been previously reported that students are unwilling to miss social gatherings or practice good isolation techniques when diagnosed with influenza.[45,48] Our analysis of social distancing through a composite variable revealed that improved knowledge of their diagnosis by using a highly accurate PCR test did not change attendance to public dining commons and use of public transportation in the adjusted analysis. On the other hand, students had nearly four times greater odds of missing days of class or work if they had PCR confirmed influenza (aOR 3.9, 95%CI: 1.8, 8.1). Additionally, the composite social distancing score variable analyses

revealed a statistically significant positive association with influenza diagnosis (**β**: 1.70, 95%CI: 1.05, 2.34). This suggests a need for universities to come up with an alternative dining plan for students who are sick, especially in the event of a pandemic. It is possible that use of public transportation types and public dining commons are linked; a majority of students who live in the residence halls participate in the meal plan. Therefore, despite missing class or work, students would still take advantage of transportation to the public dining commons.

Students were less likely to socially distance if they lived with at least one other person. In particular, students who lived in a residence hall were the least likely to practice social distancing. Considering the built environment of the residence hall, crowded conditions and lively company, it is not surprising that students would continue to interact with their residence hall mates.

Interestingly, students who reported any days with fever were significantly more likely to practice some measure of social distancing. This replicates the findings of a study in high school students during a pandemic influenza school closure.[143] Students were less likely to report doing outdoor activities, visiting friends, or working their job if they had a fever.[143] Previous studies have indicated that the amount of viral shedding and daily fever score are strongly correlated; increased viral shedding is associated with increased communicability of the influenza virus.[144,145] Most students would recognize fever as a sign of active infection. Even though number of days of reported fever did not different significantly between influenza positive and negative groups, this finding is important to emphasize in future public health campaigns. In a pandemic influenza (or other infectious respiratory disease outbreak), it will be important to educate the public to practice social distancing when they recognize certain signs and symptoms. A fever is easily recognizable, even without a thermometer, for most persons. Therefore, this would be a simple measure to reduce potential overcrowding of outpatient clinics.

Limitations

Our analysis is limited in that we are unable to assess whether a difference in university classification (first year, second year, third year, etc.) has an effect on students' response. Students who have been at the university longer or have previously experienced illness may have been more likely to socially distance. We also did not have an assessment of emotional status at appointment. This could have been useful in measuring student resilience to diagnosis of influenza during peak influenza season.

7.5 Conclusion

In our adjusted analysis, patients positive for influenza using a highly accurate rapid PCR test for influenza were more likely to report days of missed work or school and decreased self-reported stress levels than students negative for influenza. Patient attendance to public dining commons and use of public transportation did not vary according to influenza diagnosis. We identified several interesting trends, and future research with a larger sample size is warranted.

Tables and Figures

Table 7.1 Frequency of Responses to Follow Up Survey Questions for Patients Who Received Rapid Point of Care PCR Test

	Flu Positive by PCR (n=122)		**Flu negative by PCR (n=105)**		
	N	**%**	**N**	**%**	**p value ***
Flu vaccination					**0.02**
Unvaccinated	98	80.3%	68	64.8%	
Vaccinated in last two weeks	11	9.0%	12	11.4%	
Vaccinated more than two weeks ago	13	4.9%	25	23.8%	
Days of class or work missed during 5 days after clinic visit					**<0.01**
0 days	13	10.7%	41	39.0%	
1 day	30	24.6%	32	30.5%	
2 days	38	31.1%	25	23.8%	
3 days	29	23.8%	5	4.8%	
4 days	8	6.6%	0	0%	
5 days	4	3.3%	2	1.9%	
Dichotomous days of class or work missed					**<0.01**
Missed no days of class or work	13	10.7%	41	39.0%	
Missed at least 1 day of class or work	109	89.3%	64	61.0%	
Self-reported stress level during follow-up					0.31
A lot less stressed than normal	10	8.2%	11	10.5%	
Slightly less stressed than normal	20	16.4%	16	15.2%	
Average stress	48	39.3%	36	34.3%	
Slightly more stressed than normal	28	23.0%	35	33.3%	
A lot more stressed than normal	16	13.1%	7	6.7%	
Cough severity during follow-up					**0.01**
I did not have cough	2	1.6%	14	13.3%	
Improved dramatically	53	43.4%	39	37.1%	
Improve somewhat	57	46.7%	42	40.0%	
No Improvement	11	9.0%	10	9.6%	
Days with a fever during follow-up					**<0.01**

0 days	25	20.5%	46	43.8%	
1 day	30	24.6%	33	31.4%	
2 days	34	27.9%	17	16.2%	
3 days	25	20.5%	7	6.7%	
4 days	6	4.9%	0	0%	
5 days	2	1.6%	2	1.9%	
Dining facilities used during follow-up					0.77
I did not eat at an on-campus dining commons	71	60.2%	52	46.0%	
1 dining commons	19	16.1%	17	15.0%	
2 dining commons	12	10.2%	12	10.6%	
3 dining commons	12	10.2%	13	11.5%	
4 dining commons	5	4.2%	8	7.1%	
All on campus dining commons	3	2.5%	3	2.7%	
Dichotomous dining facilities used					0.19
I did not eat at an on-campus dining commons	71	58.7%	52	50.0%	
I ate at 1 or more dining commons	50	41.3%	52	50.0%	
Public transportation forms used during follow-up					0.07
I did not use public transportation	30	25.4%	14	12.4%	
1 form of public transportation	50	42.4%	46	40.7%	
2 forms of public transportation	24	20.3%	33	29.2%	
3 forms of public transportation	18	15.3%	12	10.6%	
Dichotomous public transportation use					**0.03**
I did not use public transportation	30	24.8%	14	13.5%	
I used at least 1 form of public transportation	91	75.2%	90	86.5%	
Residence type					0.32
Residence Hall	33	27.0%	32	30.5%	
Apartment or house	84	68.9%	65	61.9%	
Apartment or house, alone	4	3.3%	8	7.6%	
Live at home with family	1	0.8%	0	0.0%	
Homeless	0	0.0%	0	0.0%	
Reliance on social network					**0.03**
A Lot	32	26.2%	13	12.4%	

Occasionally	36	29.5%	40	38.1%	
Not at all	54	44.2%	52	49.5%	
Composite Social Distancing Score (-8 to 5)					**<0.01**
Score of 5	1	0.8%	0	0.0%	
Score of 4	6	4.9%	1	0.8%	
Score of 3	15	12.3%	4	3.8%	
Score of 2	15	12.3%	3	2.9%	
Score of 1	18	14.8%	9	7.4%	
Score of 0	15	12.3%	17	16.2%	
Score of -1	14	11.5%	19	18.1%	
Score of -2	14	11.5%	20	19.0%	
Score of -3	9	7.4%	12	11.4%	
Score of -4	5	4.1%	6	5.7%	
Score of -5	3	2.5%	4	3.8%	
Score of -6	6	4.9%	5	4.8%	
Score of -7	0	0.0%	4	3.8%	
Score of -8	0	0.0%	0	0.0%	

* Pearson Chi-Square test
**One student response missing

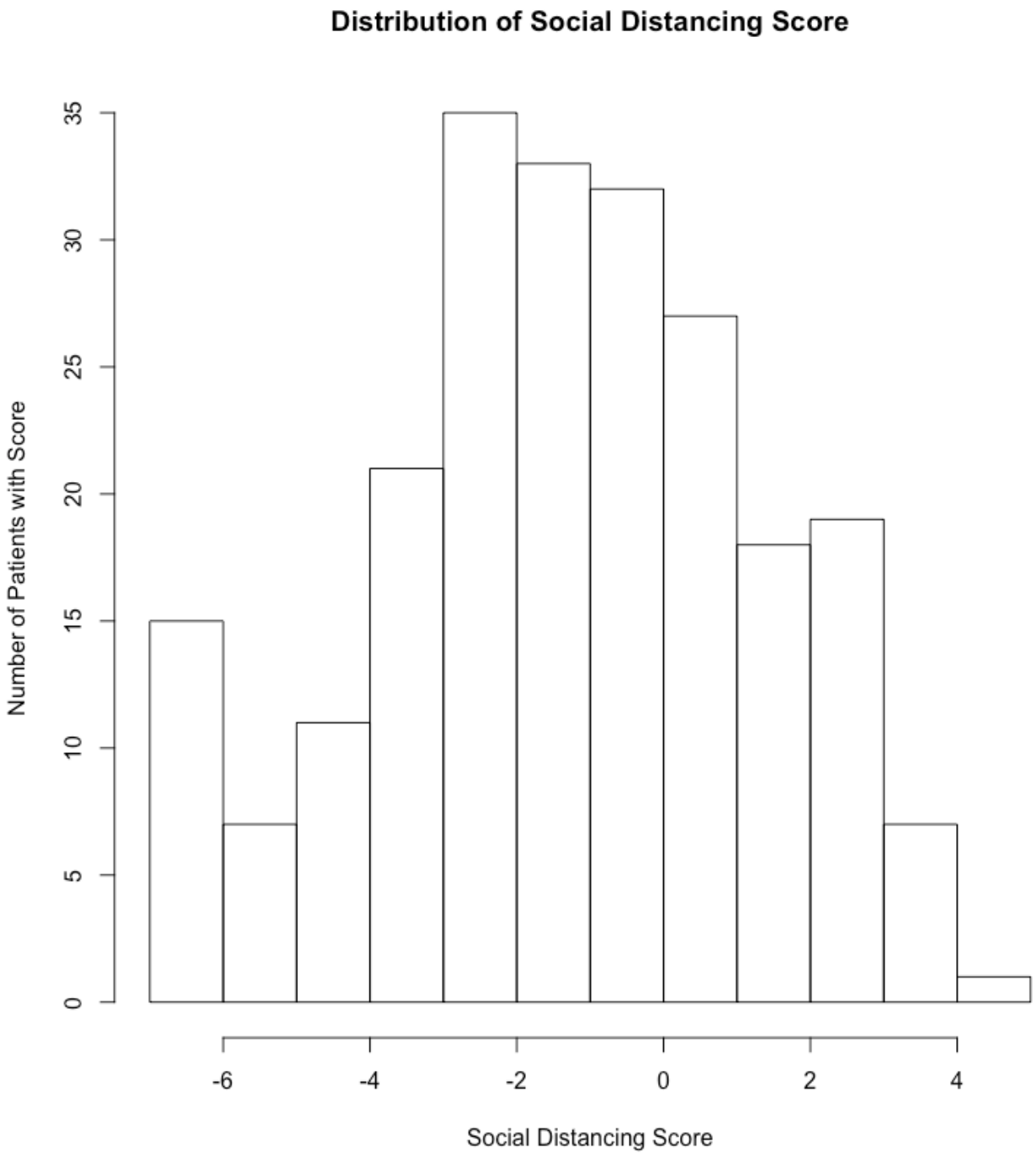

Figure 7.1 Histogram of Social Distancing Score

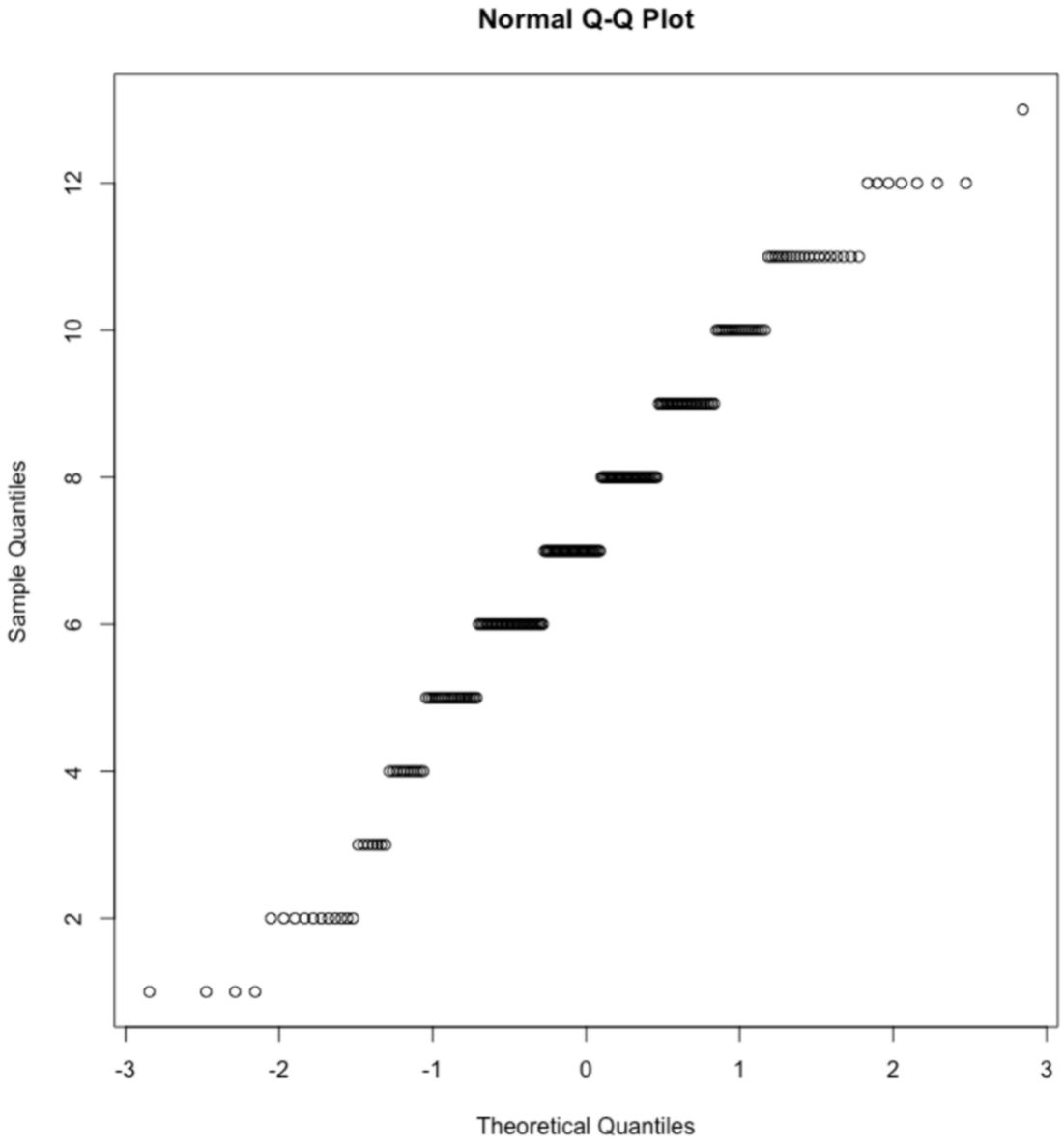

Figure 7.2 Q-Q Plot to Assess Normality of Social Distancing Score

Table 7.2 Final Ordinal Regression for the Impact of Influenza Diagnosis on Self-Reported Stress Level

Variable	β coefficient	Standard Error	p value	Hazard Ratio (95%CI)
Flu diagnosis using PCR	0.28	0.26	0.29	1.32 (0.79, 2.21)
Number of days of work or class missed	0.38	0.11	<0.01	0.68 (0.55, 0.85)
Hosmer-Lemeshow chi-square statistic= 25.2, p=0.67				

Table 7.3 Final Manual Forward Addition Selection Method for Logistic Regression for the Impact of Influenza Diagnosis on Number of Days of Work and Class Missed

Variable	β coefficient	Standard error	p value	Odds Ratio (95%CI)
Flu Diagnosis	1.32	0.37	<0.01	3.74 (1.80, 7.80)
Number of days with a fever	0.81	0.20	<0.01	2.24 (1.52, 3.32)
Intercept	-0.22	0.25	0.39	------
Hosmer-Lemeshow chi-square statistic=4.76, p=0.78 Area under the receive operating characteristic curve =0.79				

Table 7.4 Final Manual Forward Addition Selection Method for Logistic Regression for the Impact of Influenza Diagnosis on Attendance to Public Dining Commons

Variable	β coefficient	Standard Error	p value	Odds Ratio (95%CI)
Flu Diagnosis	0.65	0.22	0.19	0.65 (0.34, 1.24)
Living in Apartment/House	4.87	5.34	0.15	4.87 (0.57, 41.7)
Living in a Residence Hall	42.2	47.9	<0.01	42.2 (4.56, 390.6)
Clinic 2	3.17	1.23	<0.01	3.17 (1.48, 6.78)
Clinic 3	1.13	0.54	0.80	1.13 (0.45, 2.86)
Number of public transportation types used	1.63	0.30	<0.01	1.63 (1.14, 2.35)
Hosmer-Lemeshow chi-square statistic=48.6, p=0.26 Area under the receive operating characteristic curve: 0.82				

Table 7.5 Final Manual Forward Addition Selection Method for Logistic Regression for the Impact of Influenza Diagnosis on Use of Public Transportation

Variable	β coefficient	Standard Error	p value	Odds Ratio (95%CI)
Flu Diagnosis	-0.23	0.41	0.58	0.80 (0.35, 1.79)
Number of Public Dining Commons Attended	0.96	0.28	<0.01	2.60 (1.48, 4.58)
Number of Days of Work and Class Missed	-0.42	0.15	<0.01	0.67 (0.49, 0.89)
Intercept	1.78	0.39	<0.01	------
Hosmer-Lemeshow chi-square statistic=53.23, p=0.05 Area under the receive operating characteristic curve: 0.79				

Table 7.6 Final Stepwise Simple Linear Regression for the Impact of Influenza Diagnosis on Composite Variable Social Distancing

Variable	β coefficient (95% CI)	Standard Error	p value
Flu Diagnosis	1.70 (1.05, 2.34)	0.32	<0.01
Intercept	-1.60 (-2.06, -1.13)	0.24	<0.01
F Test statistic: 27.4, p <0.01			

Chapter 8

Conclusion

This concluding chapter serves as brief summary of the problems addressed by this dissertation, the methods and results of each of the three aims, and to discuss possible future directions for research. This chapter is meant to satisfy the requirements of the dissertation and will not present novel findings or conclusions.

The Issue: Influenza in a College Health Population

Influenza continues to have a significant burden in the United States, as seen in the ongoing 2017-2018 outbreak.[146] The rates of influenza like illness diagnosis and hospitalization have been the highest levels in recent years, underscoring the need for proper treatment and prevention.[146] Influenza related outpatient visits rose to 7.7% in early February, mirroring the peak activity of the 2009 influenza epidemic.[146] The 2009 epidemic greatly affected the college health population as emphasized in the literature review of this dissertation (chapter 2). Aside from the 2009 epidemic, college and university students are not the typical focus of influenza research as they do not represent a vulnerable population. Questions about diagnosis, treatment, and prognosis persist in a range of populations.

In an effort to identify how influenza affects a college health population, this dissertation examined the diagnosis, treatment, and follow up behavior of persons with and without influenza. We used a quasi-experimental design of 300 patients that received PCR-guided care to validate current clinical decision rules and develop two novel clinical decision rules. We then compared the PCR-guided care patients to 771 patients that received usual care to assess the likelihood of guideline supported care, antibiotic prescription, antiviral prescription, and return visit within 2 weeks. Finally, the 300 PCR-guided care patients received a follow up survey

assessing their symptom severity and behavior for the 5-days post appointment. By better understanding influenza in adults, particularly young adults, we hope to enable clinicians, public health practitioners, and researchers to better prepare for future pandemics.

Aim 1: A Systematic Review and External Validation of Existing Clinical Decision Rules for the Diagnosis of Influenza

In our first aim, we identified current clinical decision rules (CDRs) for the diagnosis of influenza through a systematic review of four online databases. Following our search, we calculated summary measures for CDRs with at least 3 reported studies. Each CDR was then externally validated in our college health population through classification accuracy and calibration tests. Finally, we fit two novel CDR using novel methods: lasso regression and a fast and frugal tree.

Our systematic review identified 16 studies that reported 8 types of heuristics, 12 multivariate models, 4 ILI case definitions, 4 classification and regression trees (CARTs), and 1 point score. We calculated summary statistics for the “cough+fever” and “cough+fever+acute onset” CDRs, since at least 3 studies reported their use in a validation population (7 studies and 4 studies, respectively). Meta-analysis of these two CDRs revealed good discrimination for influenza diagnosis (area under receiver operating characteristic curve [AUROCC]: 0.70 and 0.78, respectively). Twelve total CDRs were externally validated in our population, and were poor to fair in their discrimination with the exception of the “cough+fever+myalgia” CDR (AUROCC: 0.70). Lasso logistic regression yielded a CDR including myalgia, chills, fever, and the absence of tonsillar exudate as predictors of influenza in college students (AUROCC: 0.77). Similarly, our fast and frugal tree yielded a CDR that includes myalgia, chills, fever, and acute onset of less than or equal to 48 hours (AUROCC: 0.69).

We successfully updated a 2011 systematic review of CDRs for influenza diagnosis. “Cough+fever” and “cough+fever+acute onset” heuristics remain fair predictors of influenza

diagnosis. Our external validation of CDRs demonstrated that the Flu Score had the best classification accuracy. The predictors of influenza diagnosis in a college health population present in both of our internally validated CDRs include fever, myalgia, and chills. We have identified two new CDRs in need of external validation in the college health population, and possibly in other groups.

AIM 2: Identify whether the use of a rapid point of care PCR test for the diagnosis of influenza A or B increases the number of patients who receive guideline consistent treatment

We assessed the impact of PCR-guided care on guideline supported care and the likelihood of return visits in a quasi-experimental prospective study. Our adjusted analyses showed that PCR-guided care did not increase the likelihood of guideline supported care but did significantly affect prescriptions received and the likelihood of a return visit. Patients who received PCR-guided care were significantly more likely to receive an antiviral and to not receive an antibiotic. Adjusted analysis also revealed they were significantly less likely to return to clinic within 2 weeks. The over-prescription of antibiotics continues to be an issue in the treatment of acute respiratory infections; our finding suggests that the use of a highly sensitive and specific test assists in combating this public health issue. The reduction in likelihood of return visit is also important as outpatient care facilities may become overwhelmed during influenza outbreaks. Also, return visits medicalize illness behavior by reinforcing that every respiratory tract infection requires a physician visit or prescription.[147]

AIM 3: Influenza Diagnosis and Student Behavior

We prospectively enrolled patients to receive a rapid PCR test for influenza diagnosis from December 2016 to February 2017 at a university health clinic, as described in aim 2. Patients then received a 10 question follow up survey assessing their behavior, vaccination status, and severity of symptoms after 5 days. We used logistic regression to assess the relationship between influenza diagnosis to self-reported stress level and the three social

distancing outcomes. Finally, we created a composite social distancing score using these three measures and performed a simple linear regression to evaluate the relationship.

Of the 300 patients enrolled, 227 had a cough at their appointment, received a final rapid PCR test result, and completed the survey. Patients with an influenza diagnosis were more likely to report a decrease in stress levels when adjusting for number of days of work or class missed. Students with influenza were also more likely to report any absence from work or school. No difference was seen in the relationship between influenza diagnosis and attendance to dining commons or use of public transportation. Patients with PCR confirmed influenza were more likely to implement social distancing as defined by our social distancing score in simple linear regression. In a college health population, PCR-confirmed influenza diagnosis decreased reported stress and increased the number of days of absence from work or class. Students are willing to implement some social distancing, but universities must consider plans for dining services for sick students to encourage isolation in a pandemic.

Future Directions

Future studies should be conducted to replicate the findings of our studies. In particular, the external validation of our two novel CDRs presented in aim 1 in a new adult population would strengthen the generalizability of our results. A future CDR could incorporate surveillance data in the prediction of influenza diagnosis. In regard to the findings from our second aim, a randomized clinical trial addressing the use of the rapid PCR test for influenza diagnosis and the likelihood of guideline consistent care would ascertain the true relationship. Future work may focus on the use of other highly accurate diagnostic tests for common respiratory infections and their relationship to prescription of antibiotics or antivirals. Antibiotic stewardship remains an important issue in public health; this presents a potential new way to attack their over prescription. Student behavior after an influenza diagnosis did appear to follow previous findings[44], but we were able to build on this by categorizing the means by which a student

socially distanced. Examining a new cohort of a college health population may replicate our findings, and a direct comparison of the impact of more and less accurate diagnosis would be interesting. Finally, the consideration of vaccination status and implementation of other prevention methods such as social distancing could inform college and university administrators to best practices.

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Appendix A

Assessment of study quality using QUADAS criteria adapted to this clinical question

Definitions for QUADAS table items

1. Was the spectrum of patients representative of the patients who will receive the test in practice?

Yes: Consecutive patients presenting with cough, influenza like illness symptoms, or suspected influenza.

No: Other

2. Were selection criteria clearly described?

Yes: Inclusion and exclusion criteria were clearly described

No: Other

3. Is the reference standard likely to correctly classify the target condition?

Yes: Viral culture or RT-PCR was used to classify the target condition

No: Other

4.Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?

Yes: Clinical assessment obtained at the same time as reference standard test.

No: Other

5. Did the whole sample or a random selection of the sample, receive verification using a reference standard?

Yes: All patients received a reference standard test

No: Not all patients received the same reference standard test.

6. Did patients receive the same reference standard regardless of the index test result?

Yes: All patients received the same reference standard test

No: Different reference standard tests were used, depending on the results of the index test or other factors

7. Was the execution of the CDR described in sufficient detail to permit replication of the test?

Yes: The CDR was described in sufficient detail or represents a standard, widely used sign, symptom.

No: Other

8. Was the execution of the reference standard described in sufficient detail to permit its replication?

Yes: The reference standard test was described in sufficient detail or represents a standard, widely used test elsewhere described

No: Other

9. Was the clinical decision rule results interpreted without knowledge of the results of the reference standard?

Yes: CDR was used by personnel prior to results of the reference standard test, or this could be assumed based on the time needed to perform the reference standard test in relation to the CDR.

No: Other

10. Were the reference standard results interpreted without knowledge of the results of the clinical decision rule?

Yes: The reference standard test was interpreted by personnel masked to the CDR results, or this could be assumed based on usual reference laboratory practices.

No: Other

11. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice

Yes: The CDR was performed or interpreted by personnel who had access to clinical data about the patient.

No: Other

12. Were uninterpretable/ intermediate test results reported?

Yes: Uninterpretable or intermediate results were reported or numbers added up correctly

No: Uninterpretable or intermediate results were not reported or there appear to be missing data.

13. Were withdrawals from the study explained?

Yes: Withdrawals were adequately explained and accounted for by the researchers, or numbers add up (no missing data or patients).

No: Other

Table 1.3 Demographic characteristics of UGA student population

Strata	**Frequency**	**Percentage (%)***
Race		
American Indian	37	0.10
Asian	3549	9.83
African American/Black	2930	8.11
Hispanic or Latino	1769	4.90
Native Hawaiian or Pacific Islander	37	0.10
Unknown**	1630	4.51
2 or more races	1224	3.39
White	24954	69.07
Sex		
Male	15338	42.45
Female	20792	57.55
Enrollment Status		
Full Time	32553	90.10
Part Time	3577	9.90
TOTAL	**36130**	**100%**

*Percentages are rounded to nearest hundredth.
**Student with no declared race are listed as unknown.

Appendix B

Patient Recruitment Script

At the UGA Health Center, all patients are asked to provide a reason for their visit to the primary care clinic. Among the most common reasons are acute infections such as cough, sore throat, suspected influenza, sinus symptoms, and urinary tract infections. This information is taken by a medical assistant and entered in the electronic health record (EHR). He or she then selects a template appropriate for the problem, such as "Sore throat template" or "Respiratory tract infection template". We will program the EHR to identify patients presenting with cough or suspected influenza or self-diagnosed influenza during the study period. If a patient has one of those reasons for visit, a reminder will pop-up for the medical assistant, asking him or her to attempt to recruit the patient for the study. The script for the medical assistant is as follows:

Dr. Mark Ebell from the UGA College of Public Health is doing a research study on the diagnosis and treatment of influenza, and we'd like to ask you to participate. The purpose of the study is to see if more accurate tests for influenza can improve the quality of care.

We are inviting patients 18 years and older making a first visit to the doctor cough or suspected influenza to participate. Patients who are severely ill are not eligible.

It will take approximately 2 to 3 minutes to participate in the study. During this time, we will use a thin, flexible swab to get a sample of secretions from the back of your nose. This is the same kind of swab used for other kinds of rapid flu tests that you may have had in the past. Your doctor will receive the results of this new, highly accurate flu test.

The main incentive to you is that if you participate, you will receive a $25 gift card. We do not expect that you will have any direct benefit from participating. The only potential harm is mild, brief discomfort from the nasal swab. If you have any questions, you can contact Dr. Ebell at 706-542-1585.

Checklist for eligibility

Does the patient have a complaint of "cough", "cough and fever", "flu" or "suspected influenza"?	☐Yes ☐No
Is the patient interested in participating in the study?	☐Yes ☐No
Initial visit to a clinician for this episode of illness and onset within the past week?	☐Yes ☐No
Is patient at least 18 years of age?	☐Yes ☐No
Does the patient speak English?	☐Yes ☐No
Is the patient **not** severely ill or in distress?	☐Yes ☐No

If "Yes" to all, obtain informed consent (next page)

UNIVERSITY OF GEORGIA ADULT CONSENT FORM

Title of Study: Accuracy of signs and symptoms for diagnosis of influenza

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.

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

Principal Investigator: **Mark H. Ebell MD, MS**
Department of Epidemiology, College of Public Health
University of Georgia
706-542-1585 (l), 706-247-4953 (m), or ebell@uga.edu

Purpose of the Study

The purpose of this study is to evaluate the impact of a highly accurate PCR test for influenza on the appropriateness of prescribing and on the need for follow-up visits, as well as to evaluate accuracy of common signs and symptoms, alone and in combination, for the diagnosis of influenza. We will also track any treatments given, and whether you have to return to or call the clinic after this visit for the same problem. About 5 days from now, you will receive a text or email asking you to respond to a brief (2 minute) online survey about your symptoms and recovery.

Study Procedures

If you agree to participate, we will perform a test for influenza. The test involves taking a swab and inserting it into the back of the nose, near the back of the throat (the "nasopharynx") to get a sample of fluid secretions. The swab will be tested for influenza A and Influenza B (two strains of the virus) and the result will be given to your doctor. It takes about 20 minutes to run the test. In addition, about 5 days from now, you will receive a text or email asking you to respond to a brief (2 to 3 minute) online survey about your symptoms and recovery. Using the electronic health record, the research team will determine the signs and symptoms that were recorded,

any tests or treatments ordered, and whether you call or return to the clinic during the next two weeks. It is important that you know that all information will be kept confidential, and stored in secure servers without use of social security numbers.

Risks and discomforts

The test for influenza involves inserting a swab into the nasopharynx (back of the nose). This is the same procedure currently used for the current rapid flu test at the UGA Health Center. In both cases, there may be a few seconds of discomfort when the swab touches the tissue at the back of the hose. Otherwise there are no risks to the test.

Benefits

We expect that the information will provide important benefits for society and humankind by helping doctors take better care of patients with suspected influenza. This includes making sure the right patients get an antibiotic or Tamiflu. 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 a gift card for $15 today. If you respond to the brief follow-up survey in 5 days, you will receive an additional $10.

Clinical Trial Notification

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. You can search this Web site any time.

Privacy/Confidentiality

We will be using information from your health record about your visit today and any phone calls or return visits for the same problem during the next two weeks. The information will be retained in a secure manner on a password protected computer, and any paper files will be stored in a locked room. We will not download your name, address, or date of birth into the study dataset. The medical record number will be used to create a single data table for analysis, but that number will then be deleted. This study is funded by Roche Diagnostics, who makes the test, which has been approved by the FDA.

The project's research records may be reviewed by the 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. If you do not participate, you will receive usual care from your physician, which may or may not include a flu

test, depending on their usual decision-making. 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 706-542-1585. 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

Participant email address in order to send you your e-gift card at end of study:

UGA email: _____

UGA 81 number: 81_____

Compensation for Participation Record
This is a compensation record for participation in the "Accuracy of Signs and Symptoms for Diagnosis of Influenza" under the direction of
Dr. Mark Ebell at the UGA Health Center.

Participant Name:_____

Type of Compensation:

- ☐ Amazon Gift Card $15 Date: _____
- ☐ Amazon e-Gift Card $10 Date: _____

Signature of Participant: _____

Participant Address: _____

_____

_____

Name of Witness: _____

Signature of Witness: _____

Appendix C

Influenza Follow Up Survey

This survey should be completed 5 days after your appointment at the University Health Center. If you believe you have received this survey in error, please email Ariella Perry at ariella@uga.edu.All results will be stored in a secure location and no identifying information will be released in analysis.

Q1 What is your birthdate? Please enter as MM/DD/YY

1 When did you receive your flu vaccination? Select one response

- ❍ Within last 2 weeks (1)
- ❍ More than 2 weeks (2)
- ❍ I did not receive the flu vaccination in fall or winter of 2016 (3)

2 How many days of class or work did you miss since your University Health Center visit? Select one response.

	0 (1)	1 (2)	2 (3)	3 (4)	4 (5)	5 (6)
Number of days of class or work missed (1)	❍	❍	❍	❍	❍	❍

3 How much more stressed than usual have you felt in the last five days, above what you consider normal? Select one response.

	Less stressed than normal (1)	Click to write Scale point 2 (2)	Click to write Scale point 3 (3)	Click to write Scale point 4 (4)	A lot more stressed than normal (5)
My overall stress level (1)	❍	❍	❍	❍	❍

4 If you experience cough, has the severity of your cough decreased in the last 5 days? Select one response.

	No improvement (1)	Improved somewhat (2)	Improved dramatically (3)	I did not have a cough (4)
Cough improvement (1)	❍	❍	❍	❍

5 How many days have you experienced a fever in the last 5 days? Select one response.

	0 (1)	1 (2)	2 (3)	3 (4)	4 (5)	5 (6)
Number of days I had a fever. (1)	❍	❍	❍	❍	❍	❍

7 Did you eat in any of the following dining facilities in the last five days? Select all that apply.

- ❑ Bolton Dining Commons (1)
- ❑ O-House (Oglethorpe Dining Commons) (2)
- ❑ Snelling Dining Commons (3)
- ❑ ECV (Joe Frank Harris Dining Commons) (4)
- ❑ Tate Dining Commons or Cafes (Panda Express, Chickfila, Barberitos, etc) (5)
- ❑ I did not eat at an on-campus food vendor in the past 5 days. (6)

8 What kind of public transportation did you use in the last five days? Select all that apply.

- ❑ University of Georgia Bus/Athens Transit Bus (1)
- ❑ Rideshare (Uber, Lyft, Taxi) (2)
- ❑ Carpool (with friends or family) (3)
- ❑ I did not use public transportation (4)

9 What type of residence do you live in? Select one response.

- ❍ Residence Hall (1)
- ❍ Apartment or house (2)
- ❍ Alone in apartment or house (3)
- ❍ Live at home with family (4)
- ❍ Homeless (5)

10 Did you rely on a social network of friends or significant others in the past 5 days in relation t o your health? (I.e. drove you to the University Health Center, bought you groceries or medicine, etc) Select one response.

	A lot (1)	Occasionally (2)	Not at all (3)
I relied on friends and family in the last 5 days. (1)	❍	❍	❍

Q11 What is your UGA myID? (the first part of your email, before the @uga.edu)