The Relationship Between the Ordering of a Respiratory Viral Panel and the Presence of Acute Respiratory Illness and Influenza-like Illness Symptoms Reported in the Electronic Medical Record

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Sean Saul

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This thesis was presented

by

Sean Saul

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and approved by

Thesis Advisor: Linda Rose Frank, PhD, MSN, ACRN, FAAN, Professor of Public Health
Department of Infectious Diseases and Microbiology, Graduate School of Public Health
University of Pittsburgh

Mohamed Yassin, MD, PhD, Associate Professor of Medicine, School of Medicine
Associate Professor, Department of Infectious Diseases and Microbiology
Graduate School of Public Health, University of Pittsburgh

Mary Patricia Nowalk, PhD, RD, Professor of Family Medicine
Department of Family Medicine, School of Medicine
University of Pittsburgh

Linda R. Frank, PhD, MSN, ACRN, FAAN

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Sean Saul, MPH

University of Pittsburgh, 2019

Abstract

Background: Influenza causes a large burden of hospitalizations in the United States (U.S.) each year. Influenza can lead to viral or bacterial pneumonia, dehydration, ear infections, and sinus infections, while serious complications can include inflammation of the heart (myocarditis), brain (encephalitis) or muscle (myositis, rhabdomyolysis) tissues, and multi-organ failure (for example, respiratory and kidney failure). Efficient mechanisms to accurately and quickly identify Influenza are needed, especially with respect to those with more severe illness.

Methods: Chart reviews were conducted on a random sample of 1,029 patients appearing on a clinical informatics algorithm (CIA) generated list from 12/1/15 to 5/11/16. This list was used for recruitment in the HAIVEN study which is a Centers for Disease Control and Prevention (CDC)–funded, multicenter, test-negative, case-control study to determine the Influenza vaccine effectiveness (VE) against hospitalization. The CIA queried medical record databases of patients who were 18 years of age and older admitted to University of Pittsburgh Medical Center (UPMC) St. Margaret's Hospital in the previous 3 days using specified terms and diagnosis codes located in admission notes, emergency department notes, chief complaint upon registration, or presence of a respiratory viral panel charge (RVP). Using chart review data, each patient was deemed eligible for the study using 2 CDC descriptive eligibility boxes that aim to identify Acute

Respiratory Illness (ARI) and Influenza-like Illness (ILI) using specified symptom-based and diagnosis-based terms. A Kappa test determined agreement between having a term listed on these eligibility boxes and RVP status. Binary and multivariate logistic regression tests were used to characterize the clinical features of those missed by the clinical RVP approach but found by the CDC's screening criteria and to characterize the clinical features of those missed by the CDC's screening criteria but found by the clinical RVP approach.

Results: Of the 1,029 patients reviewed, 290 patients met the eligibility criteria and received an RVP ordered by a physician and 201 met the eligibility criteria but did not have an RVP ordered by a physician. A Kappa test resulted in a weak agreement between the 2 descriptive eligibly boxes and RVPs (kappa=.43). Both RVP status and the CDC's criteria were statistically significantly associated with fever, chest x-ray, and CT-scan.

Conclusion: The findings of this study suggest that physicians are ordering RVPs for ILI only moderately well and improvement through standardized ordering criteria may be needed. Using a CIA for recruitment for Influenza and other respiratory diseases studies was beneficial. The regression model further confirmed these findings. A hybrid case definition for inpatient Influenza may be needed.

Public Health Statement: The likelihood of being diagnosed with ARI or ILI by RVP was significantly higher if a patient had fever, chest x-ray, or CT-scan indicated. The likelihood of meeting the CDC's criteria was significantly higher if a patient had fever, chest x-ray, or lymphocyte count indicated in the EMR.

Table of Contents

List of Tables

List of Abbreviations

- acute respiratory illness (ARI)
- Advisory Committee on Immunization Practices (ACIP)
- anatomic pathology (AP)
- Centers for Disease Control and Prevention (CDC)
- clinical informatics algorithm (CIA)
- computed tomography scans (CT-scans)
- electronic medical record (EMR)
- emergency department (ED)
- European Centre for Disease Prevention and Control (ECDC)
- Food and Drug Administration (FDA)
- health care workers (HCW)
- history and physical (H&P)
- Influenza-like illness (ILI)
- length of stay (LOS)
- Rapid Reverse Transcription-Polymerase Chain Reaction Tests (Rapid-PCRs)
- respiratory viral panels (RVPs)
- Multi-Viral Reverse Transcription-Polymerase Chain Reaction (Multi-Viral-PCR)
- turnaround time (TAT)
- United States (U.S.)
- University Medical Center Hamburg-Eppendorf (UKE)

- University of Pittsburgh Medical Center (UPMC)
- Vaccine effectiveness (VE)
- white blood cell count (WBC)
- World Health Organization (WHO)

1.0 Introduction

Early detection of Influenza is critical to the course of treatment and subsequently the overall patient outcome for individuals presenting with acute respiratory illness (ARI) or Influenza-like illness (ILI) symptoms. Early detection is more important in inpatient settings because patients may already have had symptoms for a few a days before coming to the hospital. This shortens the window where certain treatments may be effective. The level of severity of Influenza for hospitalized patients can be life threatening in some cases. This risk has been addressed in some medical centers on a procedural level by the use of Rapid Reverse Transcription-Polymerase Chain Reaction (Rapid-PCR), attempting to shorten turnaround time (TAT) of respiratory viral panels (RVPs), and treatment with antivirals like oseltamivir. A rapid TAT is associated with fewer prescriptions for antibiotics. Influenza vaccination decreases the burden of ARI/ILI. The cost of an RVP is around $1,476 depending on the health care facility, which is a limiting factor for physicians deciding whether to order one for patients exhibiting respiratory symptoms (Mahoney, 2009). There have not been any substantial efforts to standardize the criteria or set of key symptoms or clinical indicators that physicians use as a best practice to assess whether or not to order an RVP for inpatients with suspected Influenza. Standardized criteria for ordering of RVPs across the United States (U.S.) specifically for Influenza may be needed.

The purpose of this study was to compare 2 methods for identifying ARI and/or ILI among hospitalized patients admitted with ARI and/or ILI. The first objective was to establish a relationship between clinically ordered RVPs and CDC's screening criteria for inpatient ARI and ILI. The second objective was to associate clinical indicators with the ordering of an RVP for Influenza or with the CDC's screening criteria in order to develop criteria for ordering RVPs.

2.0 Background

2.1 Clarification of Study Aims

The first aim of this study was to estimate the association between clinically ordered RVPs and the CDC's screening criteria for inpatient ARI and ILI. The study accomplished this aim by conducting manual chart reviews using numerous ARI and ILI symptoms from two descriptive eligibility boxes used for the HAIVEN research study. The manual chart review data were used to determine who screened positive for ARI and/or ILI. This was then compared to the patient's RVP status (yes/no). The purpose of this aim was to collect a vast amount of symptom-based and diagnosis-based data related to Influenza which could help in understanding why physicians order RVPs for suspected Influenza. It would also help in establishing a relationship between RVPs and the symptom-based/diagnosis-based data.

The second aim of this study was to characterize the clinical indicators missed by the clinical RVP approach but found by the CDC's screening criteria and vice versa. This will help the study determine if RVP status is an indicator of ARI/ILI in the electronic medical record (EMR) and if the CDC's screening criteria can be used by physicians when determining if their patients have Influenza or not. The study also sought to examine whether a hybrid screening criterion may be needed because the CDC's criteria use symptoms commonly associated with ARI and ILI. The study accomplished this by comparing the CDC's screening criteria for ARI/ILI to those with and without clinical RVPs.

2.2 The Epidemiology of Influenza

The impact of Influenza on Allegheny County and the U.S. for the 2018-2019 Influenza season was of concern for health care officials. There were 9,856 cases of Influenza from September 30, 2018 to September 28, 2019 in Allegheny County, Pennsylvania (Allegheny County Health Department, 2019). These cases are defined by testing positive using an antigen, culture, or Multi-viral Reverse Transcription-Polymerase Chain Reaction (Multi-Viral-PCR) test (Allegheny County Health Department, 2019). In addition, there were 288 hospitalizations due to Influenza and 29 deaths recorded as of September 28, 2019 (Allegheny County Health Department, 2019).

Nationally, 52.2% (42,303) of the outpatient and inpatient specimens tested in clinical laboratories tested positive for the Influenza virus (Centers for Disease Control and Prevention, 2019). Of the specimens tested during the described Influenza season of September 30, 2018–May 18, 2019, 47.8% tested negative for Influenza (Centers for Disease Control and Prevention, 2019). Of the positive specimens, 96% tested positive for Influenza A viruses (40,624) and 4% tested positive for Influenza B viruses (1,679) (Centers for Disease Control and Prevention, 2019). During the time period of October 1, 2018–April 30, 2019 there was a total of 18,847 laboratory-confirmed Influenza-related hospitalizations (Centers for Disease Control and Prevention, 2019). Over the course of this past Influenza season, the lives of 136 children and an estimated 61,200 adults were lost due to Influenza nationwide (Centers for Disease Control and Prevention, 2019). The CDC estimates that Influenza causes between 9 million and 45 million illnesses annually (Centers for Disease Control and Prevention, 2019).

In addition to the burden that Influenza causes locally and nationally the Influenza vaccine's effectiveness is also of concern. VE considers the direct, indirect, total, and overall

impact of the vaccine, meaning that both vaccinated and unvaccinated individuals are used for measurement (Centers for Disease Control and Prevention, 2019). The CDC determined that this past year's Influenza vaccine effectiveness (VE) was ~30% against Influenza illness and hospitalizations. These percentages are lower than average VEs (Belongia, 2016). A metanalysis conducted by researchers at the Center for Clinical Epidemiology and Population Health, Marshfield, Wisconsin found a pooled estimate of 33% for H3N2, 54% for type B, 61% for H1N1pdm09, and 67% for H1N1 (Belongia, 2016). They concluded that vaccine improvements are needed to increase effectiveness against H3N2 strain of the Influenza virus (Belongia, 2016). Data from the HAIVEN study were used in these estimates. The disease burden of Influenza and inconsistent VE of the vaccine each year pose challenges in prevention and treatment of this deadly illness.

2.3 Symptoms and Clinical Indicators of ARI/ILI/Influenza

The literature points to several different symptoms and clinical indicators that define ARI, ILI, and Influenza. Case definitions in use today include fever, cough, sore throat, presence of an ARI, feverishness, headache, malaise or myalgia, and shortness of breath. A 2015 study showed that cough was the number one predictor of Influenza with a Diagnostic Odds ratio (DOR) of 5.87 (Shah, 2015). Fever followed cough (DOR=4.49), followed by rhinorrhea (DOR=1.98), and myalgias (DOR=1.44) (Shah, 2015). They recommended a simplified case definition for all ages based on their findings using just fever and cough. A study performed in Israel found that fever was also the most predictive indicator of Influenza, when solely looking at the chief complaint (Shimoni, 2012). Additionally, a retrospective cohort study out of Hong Kong found that fever was more common in younger patients versus older patients who were diagnosed with severe acute respiratory syndrome (Chan, 2004). Another study found that fever, sore throat, runny nose, cough, shortness of breath, diarrhea, vomiting, headache, and body aches were all highly associated with death most likely resulting in some way from Influenza (Malhotra, 2016).

Radiographic scans such as computed tomography scans (CT-scans) have also been correlated with confirmed ARI (94%) and confirmed viral infection (10%) by researchers from the University of Pennsylvania (Shiley, 2010). Another study correlated these types of tests to laboratory confirmation of Influenza that looked at the H1N1strain, which was the predominant strain in the 2009 outbreak, characterized this strain by flu-like symptoms (88%), dyspnea (17%), and abnormal chest x-ray (7.1%), and abnormal CT-scan (73%) (Schoen, 2019).

A clinical informatics algorithm (CIA) has been used to determine which symptoms and clinical indicators are most highly related to Influenza. Swedish researchers found that the best predictor of Influenza specifically reviewing telenursing complaints was fever ($r=0.66$; $p<0.001$),

followed by syncope (Timpka, 2014). The chief complaint was the area of the EMR queried for this study. Another study that used a CIA and the same CDC eligibility criteria as this study showed that an RVP located in the EMR was the highest indictor of determining eligibility for their research study (65%-69%) (Silviera, 2019). This study found that symptoms for eligible patients were most often indicated in the EMR by the use of an ICD-10 code (55%), followed by RVP (36%), and admission note (25%) (Silviera, 2019).

In terms of Influenza vaccination status, a study from the University of Pittsburgh found that Influenza vaccination status was not a significant factor for physicians when ordering RVPs (Balasubramani, 2018). RVP testing was significantly higher in younger hospitalized patients who had an ARI/ILI as well as during the times of peak Influenza circulation.

Because this study focuses on the symptom and diagnosis-based data related to Influenza it is important to lay out literature in the area of recent case definitions and ones in use today. Notably, in 1999 the World Health Organization (WHO) defined Influenza as "a sudden onset of fever, a temperature >38°C and cough or sore throat in the absence of another diagnosis" (World Health Organization, 1999). This definition was used and data showed that the occurrence of ILI often correlated with high transmission levels of Influenza in the community (World Health Organization, 1999). The sensitivity of this definition was ~60% and its specificity ranged from 0% to a larger range of 60–90% when the virus was generally circulating, leaving room for improvement.

As of 2017 the European Centre for Disease Prevention and Control (ECDC) defines Influenza as the sudden onset of at least one of the following: fever, feverishness, headache, malaise or myalgia and at least one of the following: cough, sore throat, or shortness of breath. A French study completed in 2017 showed that sore throat could be removed from the ECDC and

CDC definitions because it was associated with decreased identification of Influenza (Casalegno, 2017).

In 2011 the WHO acknowledged that this definition could be improved. They proposed a change to this definition, which changed "sudden onset of fever" to "ARI, > 38 ˚C to ≥ 38 ˚C, and deleted sore throat (World Health Organization, 2011). The proposed new definition reads as follows "An ARI with a measured temperature of ≥ 38 ˚C and cough, with onset within the past 7 days" (World Health Organization, 2011).

Nationally, the U.S. CDC uses a case definition of fever >100°F which is measured orally or using an equivalent measure and cough and/or sore throat (Centers for Disease Control and Prevention, 2019). The CDC uses this definition for their Outpatient ILI Surveillance Network (ILINet). Healthcare providers report these symptoms/clinical indicators of ILI to the CDC weekly. Additionally, the CDC characterizes uncomplicated Influenza, which subsides within 3-7 days, by fever, chills, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis (Centers for Disease Control and Prevention, 2019).

2.4 EMR Documentation and Use for Treatment of Influenza

There is limited research that examines documentation of Influenza symptoms in the EMR, such as which disciplines of clinical workers are entering the data and their accuracy. These disciplines include, paramedics, medical assistants, nurses, residents, physicians, respiratory specialists, physician assistants, nurse practitioners, X-ray techs, and sonographers. However, there is some research that examines how often physicians use certain sections in the EMR when they are making a diagnosis. For example, an inpatient study evaluated the most important sections

of the EMR for physicians using regression analysis. The lab section was the second most frequently reviewed. (Kim, 2017). The investigation status and patient conditions sections of the EMR were positively associated with peak usage times.

Looking more at specific locations in the EMR, the chief complaint is an area that is used frequently by physicians who are overseeing admitted patients that have come from the ED (May, 2010). Researchers compared diagnostic investigations with chief complaint for pneumonia, viral illness, and upper respiratory infection. Their first analysis showed that 29% of the patients analyzed showed a different diagnosis for their chief complaint at admission from their chief complaint at discharge. Another study found that final ED EMR diagnosis has low sensitivity to Influenza (Dugas, 2015), which indicates that Influenza is not being detected well in the ED.

2.5 At Risk Populations

Influenza affects adults 65 years of age and older more so than any other age group primarily because they have weaker immune systems and a higher potential for underlying illness/chronic diseases. The CDC has estimated that between 70-80% of Influenza-related deaths during the flu season are among people in this age group (Centers for Disease Control and Prevention, 2019). There are high dose and adjuvanted Influenza vaccines available for this sub-population that create a stronger immune response to Influenza viruses. Other vulnerable populations include pregnant women, young children, people with asthma, heart disease, stroke, diabetes, HIV/AIDS, cancer, and children with neurologic conditions. Young children are more susceptible to Influenza and other viral respiratory infections. They are thought to play a large role in the initial spread of Influenza each season (Centers for Disease Control and Prevention, 2019).

In addition, health and age factors are associated with higher susceptibility to Influenza such as, neurodevelopmental conditions, blood disorders, chronic lung disease, endocrine disorders, kidney disorders, liver disorders, metabolic disorders, people who are obese, and people with weakened immune systems. Other more specific populations include children younger than 2 years old, American Indians, Alaska Natives, and people who live in nursing homes and other long-term care facilities.

2.6 RVP Tests

There are a several ways to test for the presence of Influenza in a clinical setting including Rapid-PCRs, Multi-Viral-PCR, and other nucleic acid amplification tests (Centers for Disease Control and Prevention, 2019). In more recent years Rapid-PCRs have been implemented in emergency rooms, inpatient settings, and outpatient settings, which have decreased the time that it takes to receive results. There are currently 11 different FDA approved rapid molecular assays on the market for use in the U.S. (Centers for Disease Control and Prevention, 2019). These tests use antigen detection assays and can detect Influenza viral antigens in as little as 10-15 minutes. They do this with a 50-70% sensitivity and high specificity (Centers for Disease Control and Prevention, 2019). The Food and Drug Administration (FDA) has recently published requirements to improve accuracy and sensitivity of rapid tests because these tests can produce some false negatives and more frequently false positives, which overestimate Influenza in the community during peak circulation (Centers for Disease Control and Prevention, 2019). The FDA recommends that physicians confirm negative results in severe presentations with Multi-Viral-PCR tests.

The second major type of test utilized to detect Influenza are Multi-Viral-PCR tests that test for Influenza viral RNA with a high sensitivity and specificity. Their sensitivity for Influenza A was calculated to be 98.3% and 98.6% for Influenza B by researchers at the University Medical Center Hamburg-Eppendorf (UKE) (Eigner, 2019). Thus, they are considered the gold standard for detecting Influenza. Unlike Rapid-PCRS, these tests can determine the subtype of Influenza A viruses. There are currently 42 FDA approved Multi-Viral-PCR tests on the U.S. market (Centers for Disease Control and Prevention, 2019). The disadvantage of Multi-Viral-PCR tests is the fact that results may not be in the hands of clinical professionals within a timeframe that is clinically relevant to affect treatment and cost. These tests cost around $1,476 depending on the health care facility (Mahoney, 2009). They are not always an option in outpatient or emergency department (ED) settings because respiratory specimens need to be transferred to a lab for testing. Additionally, they also cannot detect every circulating subtype of the Influenza A virus. In summary, Rapid-PCRs can quickly return a result to clinical staff, but their sensitivity does not compare to Multi-Viral-PCR tests which have a higher sensitivity. Their longer TAT means that treatment may be less beneficial and/or inappropriate by the time the result is known.

Early Influenza diagnosis affects patients' clinical outcome. Longer TAT for RVP could result in longer ICU length of stay, unnecessary antibiotic use and potentially worse outcome (Harris, 2013). The average TAT for the Luminex xTAG RVP (LxT) was 46.4 hours while the FilmArray RVP (BDFA) took an average of 3.6 hours (Jung, 2015). Locally in Pittsburgh some hospitals operated by the UPMC have implemented the use of Biofire tests, which are Rapid-PCRs that can produce results for 17 viruses in 1 hour (Linn, 2017). The exact percentage of health care systems in the U.S. that have implemented these rapid tests to reduce TAT is unknown. Another study found a similar TAT of 24 hours (Multi-viral-RVP) and 12 hours (Rapid-PCR) (Choi, 2017).

Shortening this time frame could help with early diagnosis of Influenza and subsequently faster treatment to improve clinical outcomes.

2.7 Current Practices in Treatment of Influenza

Antiviral medication should be started in critically symptomatic patients based on suspicion and should be discontinued if Influenza testing proves negative. The earlier the use of antivirals in relation to the onset of symptoms results in better outcomes. A few observational studies showed that the clinical benefit of oseltamivir is highest if started within 48 hours of symptom onset (Hsu, 2012; Louie, 2013; Muthuri, 2014). Shorter hospitalizations have also been reported (Katzen, 2018) if antiviral treatment is started within 6 hours of hospitalization. A study showed that the use of antivirals in pregnant women within 3 days of illness onset was beneficial (Siston, 2010). The CDC recommends that decisions regarding antiviral treatment should not wait until a laboratory confirmation of Influenza is known.

Neuraminidase inhibitors are the main class of antiviral in use for Influenza treatment. They act by blocking the viral neuraminidase enzyme and they are active against both Influenza A and B. These three drugs include oral oseltamivir phosphate, inhaled zanamivir, and intravenous peramivir. Oral oseltamivir can be used to treat any age and prevent Influenza in people 3 months and older (Centers for Disease Control and Prevention, 2019). The FDA approved oral baloxavir marboxil (Xofluza®) for treatment of patients 12 years and older and is not recommended for use in preventing Influenza (Centers for Disease Control and Prevention, 2019). Physicians are encouraged to use their clinical judgement when prescribing these medications using the severity

of illness, likelihood of Influenza, underlying medical conditions, time since their onset of symptoms, and age as the main factors (Centers for Disease Control and Prevention, 2019).

In hospitalized patients who present with symptoms or are confirmed to have Influenza, oral or enterically-administered oseltamivir is recommended to be administered as soon as possible (Centers for Disease Control and Prevention 2019).

A common public health issue arises when physicians do not have a laboratory confirmation of ARI, ILI, or Influenza is the over-utilization and unwarranted use of antibiotics and antivirals. As a precautionary measure, antibiotics are often prescribed to patients before test results come back, which is a contributing factor to the increased antibiotic resistance in the U.S. The Centers for Disease Control and Prevention issued a report stating that an estimated 2,049,442 illnesses and 23,000 deaths are caused annually due to antibiotic resistance (Centers for Disease Control and Prevention, 2018).

3.0 Methods

3.1 Clarification of Hypothesis

The hypothesis for the first objective of this study was that at least a moderate agreement (kappa > 0.5) would be seen between the CDC's screening criteria and an RVP ordered among those who meet qualifying entry criteria by manual chart during the time of Influenza circulation. The Influenza season was defined by the dates 12/1/15 to 5/11/16. In other words, the study speculated that a record of ARI/ILI/Influenza symptoms in the EMR would moderately correlate with a physician ordering an RVP. A kappa test was run to determine if the study's hypothesis would be rejected. The null hypothesis was that there will be no correspondence between the CDC's screening criteria and an RVP-based approach. The study did not speculate which clinical indicators would be associated with the ordering of an RVP for ARI/ILI/Influenza or with the CDC's screening criteria for the second objective.

3.2 Discussion of Statistical Analysis Tests for Hypothesis

This study utilized a several statistical tests to accomplish the aims that were developed during its planning. A kappa test was chosen to look at the first objective of this study which was to establish a relationship between clinically ordered RVPs and CDC's screening criteria for inpatient ARI and ILI. It is believed to be a stronger measure than a simple percent agreement calculation. This is because it looks at the possibility of the agreement occurring by chance and is

a statistical test that is used to measure inter-rater reliability and intra-rater reliability for qualitative data. They are commonly used when new techniques need to be compared like the RVP approach and whether patients met the CDC's criteria.

Standard statistical methods were used to compare variables. Independent samples t-tests were used to compare EMR indicated RVP status and the CDC's Screening Criteria for the continuous variables white blood cell count (WBC) at admission and Lymphocyte count at admission. They were chosen because they are additional clinical indicators that may be present in patients who present with an ARI, ILI or Influenza. Independent samples t-tests are commonly used to compare the means of continuous variables. Chi square tests were used to compare EMR indicated RVP status and the CDC's screening criteria to clinical indicators of ARI and ILI for the categorical variables fever, positive blood culture, positive chest X-ray, and CT scan. Chi square tests are commonly used to test relationships between categorical variables.

Lastly binary logistic regressions and multivariate logistic regressions were used to complete the second objective, which was to characterize who is missed by the RVP approach and by the CDC's screening criteria. These tests were chosen because they allowed for the comparison of the one dependent binary variable and the multiple clinical indications of ARI and ILI. They also allowed for the demographic variables race, sex, and age category to be added to the model. Significance was set at alpha ≤ 0.05 for all tests performed.

3.3 Target Population

The purpose of this study was to compare 2 methods for identifying ARI and/or ILI among hospitalized patients admitted with suspected ARI and/or ILI. The scope of this study affects the

1,223,348 people living in Allegheny County, who are all susceptible to the Influenza virus (United States Department of Commerce, 2018). Allegheny County is one of the oldest counties in the country with 17.1% of individuals aged over 65 and 3.1% aged 85 and older (United States Department of Commerce, 2018). Allegheny County has limited racial diversity with 89.03% White, 3.9% Black or African American, 3.11% Asian, 2.32% Hispanic, and 0.64% other (United States Department of Commerce, 2018). Allegheny County has a high aging population that serves as a challenge for health care systems, which makes this study more important, as they are disproportionality affected.

The sample that will be analyzed includes persons 18 years or older admitted to University of Pittsburgh Medical Center (UPMC) St. Margaret's Hospital which is a 248-bed acute care community/teaching hospital that is in Aspinwall, a small community outside the City of Pittsburgh (UPMC, 2019). It provides specialized diagnosis, treatment, rehabilitation, and education to its patients (UPMC, 2019). Some of the key specialties include orthopedic services, family medicine, general surgery, critical care, bariatric surgery, and emergency medicine (UPMC, 2019). The population that St. Margaret's serves has a higher percentage of individuals over 65 years of age than other comparable UPMC hospitals.

3.4 Data Collection, Organization, and Analysis

HAIVEN is a Centers for Disease Control and Prevention (CDC)–funded, multicenter, test-negative case-control study to determine the Influenza VE against hospitalization. HAIVEN developed a CIA that queries the UPMC inpatient EMR databases for patients who were ≥18 years of age admitted to UPMC St. Margaret in the previous 3 days. It queried patients that had an RVP

or at least one specified term or diagnosis code derived from the CDC's criteria in the admission notes, emergency department notes, or recorded chief complaint of patient upon registration. Locations where these terms were found are not mutually exclusive. When querying specified terms, the algorithm could not determine if the term queried was a symptom or clinical indicator.

A random sample of 1,099 patients was selected for manual chart review from a larger list of 2,198 potentially eligible patients that appeared on the CIA list from 12/1/15 to 5/11/16. This time period was defined as the Influenza season. After duplicates were removed, the sample consisted of 1,029. The number for the random sample was chosen because of the amount of time that the manual chart reviews took research assistants to complete.

HAIVEN did not retain data on why the CIA queried each patient because only a sub-set of patients from the CIA, ones who had RVPs completed, were approached for recruitment. Because of this, manual chart reviews were conducted on the random sample to determine why the CIA queried them. Manual chart reviews were conducted by 3 different research assistants. The following locations in the EMR were read and searched for both reviews: ED note, H&P note, clinical summary note, and discharge note. A second review was conducted for each of the 1,029 patients by a different research assistant. Logic from two descriptive eligibility boxes were used as a guideline for what specific terms were collected and to determine whether or not they met the CDC's criteria. The locations of ARI/ILI symptoms or diagnoses were retrieved from the HAIVEN CIA data set. Other clinical indicators for Influenza were collected such as, temperature on admission, positive blood culture, WBC count, neutrophil count, lymphocyte count, positive chest x-ray, CT scan positive, and RVP status.

The first and second reviews were then cross compared for accuracy, merged into one data set, and duplicate patients were removed. The data set was then cleaned, and missing values were investigated and confirmed.

A Kappa test with 95% confidence intervals was run to determine agreement between the CDC's screening criteria and the indication that an RVP was conducted. The agreement levels in the article by McHugh were used (McHugh, 2012). Independent samples t-tests were used for continuous variables and chi square tests were used for categorical variables to compare EMR indicated RVP status and the CDC's screening criteria to clinical indicators of ARI and ILI. Binary logistic regressions and multivariate logistic regressions were used to characterize who was missed by the RVP approach and by the CDC's screening criteria. Binary logistic regressions were run separately for each of the clinical indicators against the RVP approach and by the CDC's screening criteria. A model consisting of every clinical indicator collected and the 3 demographic variables was used in the multivariate logistic regression. Race was converted to "White" and Non-white" because of the low frequency of "Asian" (2), "American Indian/Alaskan Native" (2), and "Don't know" (15) in the data set. Regression models were run separately adjusting for race, sex, and age category. A P-value of <0.05 was used to test significance for all tests. Influenza/ILI/ARI diagnosis by the RVP approach and by the CDC's screening criteria were the dependent variables and the clinical indicators/demographic variables were the independent variables in the t-tests, chi square tests, and regressions. Table 1A in Appendix A lists and describes each variable used in the analyses. Table 1 lists different respiratory infections and their clinical description.

Table 1 Respiratory Infections and their Clinical Description

Diagnoses	Description of Diagnosis	Symptoms/clinical indicators	Description of Symptoms/clinical indicators
Influenza-like illness (ILI)	as fever (temperature of 100°F [37.8°C] or greater) and a cough and/or a sore throat in the absence of a known cause other than Influenza	**Cough**	expelling air from the lungs with a sudden sharp sound caused by bacteria or viruses
Influenza-like disease (ILD)	as fever (temperature of 100°F [37.8°C] or greater) and a cough and/or a sore throat in the absence of a known cause other than Influenza	**Fever**	A temperature >100.4 °F
Influenza	an acute respiratory disease caused by infection with Influenza viruses.	**Nasal Congestion**	blockage of the nasal passages usually due to membranes lining the nose becoming swollen from inflamed blood vessels.
Upper Respiratory Infection (URI)	caused by viral pathogens, such as Rhinovirus, ParaInfluenza, Adenovirus, RSV, and Influenza with no prominent symptom or sign	**Chest Congestion**	A buildup or excess of mucous in the lungs
Viral URI	caused by viral pathogens, such as rhinovirus, ParaInfluenza, Adenovirus, RSV, and Influenza with no prominent symptom or sign	**Sore throat**	a condition marked by pain in the throat, typically caused by inflammation due to a cold or other virus
Bronchitis	an acute respiratory infection with a normal chest radiograph that is manifested by cough with or without phlegm production that lasts for up to 3 weeks	**Chills**	feelings of coldness accompanied by shivering
Pneumonia	Pneumonia is an infection of the lungs that can cause mild to severe illness in people of all ages. Viruses, bacteria, and fungi can all cause pneumonia. Common signs of pneumonia can include cough, fever, and trouble breathing	**Body Aches**	a common symptom of many conditions like Influenza
Pneumonia (PNA)	same as Pneumonia	**Fatigue**	extreme tiredness resulting from mental or physical exertion or illness.
Bacterial Pneumonia	Pneumonia caused by bacteria	**Respiratory Distress**	labored breathing and is characterized by an inappropriate degree of effort to breathe based on rate, rhythm, and subjective evaluation
Community Acquired Pneumonia	Pneumonia acquired outside of a hospital setting	**Shortness of Breath (SOB)**	an intense tightening in the chest, air hunger, difficulty breathing, breathlessness or a feeling of suffocation

Table 1 Continued

Health-care Acquired Pneumonia	Pneumonia acquired while in a hospital	**Difficulty in Breathing (DIB)**	an intense tightening in the chest, air hunger, difficulty breathing, breathlessness or a feeling of suffocation
Aspiration Pneumonia	lung infection that develops after you aspirate (inhale) food, liquid, or vomit into your lungs	**Dyspnea**	an intense tightening in the chest, air hunger, difficulty breathing, breathlessness or a feeling of suffocation
Evaluate Pneumonia	when Pneumonia is the preliminary diagnosis/being diagnosed	**Positive Blood Culture**	Presence of pathogens like bacteria, yeast, and other microorganisms in blood
Bibasilar Pneumonia	Pneumonia characterized by abnormal lung sounds	**WBC count at admission**	White Blood cell count from a blood sample collected on the patient's day of admission
Asthma	a disease that affects your lungs. It causes repeated episodes of wheezing, breathlessness, chest tightness, and nighttime or early morning coughing.	**Lymphocyte count at admission**	Lymphocyte count from a blood sample collected on the patient's day of admission
COPD	a group of diseases that cause airflow blockage and breathing-related problems, includes emphysema and chronic bronchitis		
COPD Exacerbation	exacerbation caused by COPD	**Positive chest x-ray?**	
Asthma Exacerbation	exacerbation caused by asthma	**CT scan positive?**	
Status Asthmaticus	a severe condition in which asthma attacks follow one another without pause.	**RVP ordered**	
Asthmatic Bronchitis	the incidence of acute bronchitis in a person with asthma.		
Acute Respiratory Distress Syndrome	when fluid builds up in the tiny, elastic air sacs (alveoli) in your lungs. The fluid keeps your lungs from filling with enough air, which means less oxygen reaches your bloodstream. This deprives your organs of the oxygen they need to function		
Sepsis	Life-threatening organ dysfunction caused by dysregulated host response to infection		
Cystic Fibrosis Exacerbation (CF)	exacerbation caused by Cystic Fibrosis		
Respiratory Medical, Other	a respiratory issue that cannot be diagnosed		
Congestive Heart Failure (CHF)	when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs		
Idiopathic Pulmonary Fibrosis (IPF)	chronic and progressive lung disease without a known cause.		
Altered Mental Status (AMS)	a group of clinical symptoms rather than a specific diagnosis, and includes cognitive disorders, attention disorders, arousal disorders, and decreased level of consciousness		

4.0 Results

The demographics of the randomly selected 1,029-patient sample are summarized in Table 2. The largest age category was 65 years and older (65.4%) (Table 2). Females slightly outnumbered males (57.8%) (Table 2). The sample consisted of mostly white patients (90.7%) (Table 2). RVP was ordered on 36.9% (380) of the 1029 patients examined in this study (Table 2). 43% of Whites met the CDC's criteria and 23.8% had an RVP ordered (Table 2). Among those age 65+, 30.6% met the CDC's criteria and 15.1% had an RVP ordered (Table 2). Indicators of Influenza were also examined below (Table 2).

Table 2 Demographics of Randomly Sampled Patients (N=1,029)

Age category (n=1,029)	n (%)	RVP (yes, n (%))	CDC's Symptoms (yes, n (%))
18-64	356 (35)	111 (11)	178 (17)
65+	673 (65)	155 (15)	315 (31)
Male	435 (42)	110 (11)	198 (19)
Female	594 (58)	156 (15)	295 (29)
Race White	931 (91)	245 (24)	445 (43)
Non-white	98 (9)	21 (2)	48 (5)
Clinical Indicators			
Fever	93 (9)		
Positive Blood Culture	37 (4)		
Average WBC count	10.2		
Average lymphocyte count	14		
Positive chest x-ray	361 (35)		
Positive CT scan	238 (23)		
RVP ordered	380 (37)		

Table 3 shows the comparison between identification of ILI patients using RVPs and a symptom-based and diagnosis-based approach. Of the 380 patients that had an RVP ordered, 290 (76.3%) met the CDC's screening criteria, whereas among the 492 who met screening criteria only 290 (58.9%) had an RVP (Table 3). This resulted in a sensitivity of 76.3%, a specificity of 68.9%, and K= 0.43 (Table 3).

Table 3 Comparison of CDC's Screening Criteria and EMR Indicated RVP

	RVP		**Total**
CDC's Symptom Based Screening Criteria	**YES**	**NO**	
YES	290 (76)	202 (31)	492
NO	90 (24)	447 (69)	537
Total	380	649	1,029
Kappa (95% CI)	.43 (.37-.48)		
Sensitivity	76.3		
Specificity	68.9		

The locations of symptoms, clinical indicators, or diagnoses of ARI/ILI were found in the EMR and shown below in Table 4. An ICD-10 code in the H&P note was found to be the most common location (646) with a key word in the ED note being the second most prevalent location (438) (Table 4). Multiple locations and symptoms, clinical indicators, or diagnoses can be indicated for each patient (Table 4). Notably no ICD-10 codes were found in the ED note (Table 4).

Table 4 Location(s) of ARI/ILI Symptoms, Clinical Indicators, or Diagnoses

Location	N (%)
ICD10 code in H&P note	646 (63%)
Specified term found in ED note	438 (43%)
Specified term found in H&P note	330 (32%)
Specified term found in chief complaint	62 (6%)
ICD10 code in ED note	0

Table 5 shows the distribution of clinical indicators of ARI/ILI by the presence or absence of RVP and the presence or absence of CDC criteria. The likelihood of having an RVP was significantly higher when the patient had fever (p= <0.001), Chest X-ray (p= <0.001), CT-scan (p= <0.001), WBC count (p= 0.005), and lymphocyte count (p= 0.001) (Table 5). The likelihood of meeting the CDC's screening criteria was significantly higher when the patient had fever (*p*= 0.003), Chest X-ray (*p* = <0.001), and CT-scan (*p* = <0.001) (Table 5).

Table 5 Comparison of RVP Status and CDC's Screening Criteria to Clinical Indicators of ARI/ILI

	RVP N=266 (n (%))	No RVP N=754 (n (%))	P value	CDC's Symptoms Yes	CDC 's Symptoms No	P value
Fever (>100.4)	57 (21.5)	36 (4.8)	**<0.001**	64 (13.1)	29 (5.5)	**0.003**
Blood Culture	10 (3.8)	27 (3.6)	0.894	18 (3.7)	19 (3.6)	0.985
Chest X-ray	122 (45.9)	234 (31.0)	**<0.001**	224 (45.8)	130 (24.6)	**<0.001**
CT Scan	83 (31.2)	153 (20.3)	**<0.001**	140 (28.6)	94 (17.8)	**<0.001**
	(m (SD))	**(m (SD))**	**P value**	**(m (SD))**	**(m (SD))**	**P value**
WBC Count	11.9 (5.9)	9.8 (6.6)	0.005	10.4 (5.6)	9.8 (7.1)	0.189
Lymphocyte Count	12.3 (9.7)	14.7 (11.3)	**0.001**	13.4 (11.0)	14.6 (10.9)	0.072

Table 6 shows the relationship of clinical indicators of ARI/ILI to RVP status and the CDC's screening criteria from logistic regression. Fever (p= <0.001), Chest X-ray (p= <0.001), CT-scan (p= <0.001), WBC Count (p= 0.024), lymphocyte count (p= 0.003), and age category (p= 0.005) were positively corelated to RVP status (Table 6). The referent group for age category were patients 18-64 years old. Notably if a patient had a fever, they were 5.47 times more likely to have had an RVP ordered by a physician (Table 6). Fever (p= <0.001), Chest x-ray (p= <0.001), and CT-scan (p= <0.001) were positively correlated with the CDC's screening criteria (Table 6). Notably if a patient had a fever, they were 2.6 times more likely to have met the CDC's screening criteria (Table 6).

Table 6 Relationship of Clinical Indicators of ARI/ILI to RVP Status and CDC's Screening Criteria, (Unadjusted)

	RVP Status			CDC's Screening Criteria		
	Odds ratio	**95% CI**	**P value**	**Odds ratio**	**95% CI**	**P value**
Fever (>100.4)	5.47	3.51-8.54	**<0.001**	2.60	1.64-4.10	**<0.001**
Blood Culture	1.06	0.51-2.23	8.71	1.03	0.53-1.98	0.932
Chest X-ray	1.86	1.40-2.47	**<0.001**	2.61	2.00-3.40	**<0.001**
CT Scan	1.78	1.30-2.44	**<0.001**	1.85	1.38-2.49	**<0.001**
WBC Count	1.02	1.02-1.00	**0.024**	1.02	1.00-1.04	0.114
Lymphocyte Count	0.98	0.97-.99	**0.003**	0.99	0.98-1.00	0.070
Race						
White	Reference	N/A	N/A	Reference	N/A	N/A
Non-white	0.29	0.46-1.26	0.76	1.05	0.69-1.59	0.824
Sex						
Male	Reference	N/A	N/A	Reference	N/A	N/A
Female	0.95	0.72-1.26	0.724	0.85	0.66-1.09	0.189
Age Category						
18-64	Reference	N/A	N/A	Reference	N/A	N/A
65+	0.66	0.50-0.88	**0.005**	0.88	0.68-1.14	0.329

Table 7 shows the relationship of Clinical Indicators of ARI to RVP status and CDC's screening criteria adjusting for race, sex, and age category. Asian, American Indian/Alaska Native, and Don't Know were removed from the model because there were too few for analysis. Fever (p=

<0.001), chest x-ray (p= 0.0009), CT-scan (p= 0.018), lymphocyte count (p= 0.043), and older age (p= 0.001) (Table 7). Notably if a patient had a fever, they were 5.01 times more likely to have had an RVP ordered by a physician (Table 7). Fever (p= <0.001) and chest x-ray (p= <0.001) were positively corelated with the CDC's screening criteria adjusting for race, sex, and age category (Table 7). Notably if a patient had a fever, they were 2.35 times more likely to have met the CDC's screening criteria (Table 7).

Table 7 Relationship of Clinical Indicators of ARI/ILI to RVP Status and CDC's Screening Criteria, Adjusted for Race, Sex, Age Category

	RVP Status			**CDC's Screening Criteria**		
	Odds ratio	**95% CI**	**P value**	**Odds ratio**	**95% CI**	**P value**
Fever (>100.4)	5.01	3.16-7.95	**<0.001**	2.35	1.46-3.78	**<0.001**
Blood Culture	0.71	0.32-1.60	0.409	0.81	0.40-1.63	0.551
Chest X-ray	1.55	1.12-2.15	**0.009**	2.43	1.81-3.25	**<0.001**
CT Scan	1.53	1.08-2.19	**0.018**	1.36	0.98-1.89	0.063
WBC Count	1.02	0.99-1.04	0.161	1.00	0.98-1.02	0.852
Lymphocyte Count	0.99	0.97-1.00	**0.043**	1.00	0.98-1.01	0.391
Race						
White	Reference	N/A	N/A	Reference	N/A	N/A
Non-white	1.40	0.82-2.41	0.221	0.92	0.59-1.42	0.704
Sex						
Male	Reference	N/A	N/A	Reference	N/A	N/A
Female	1.24	0.91-1.68	0.167	0.03	1.33-1.73	1.026
Age Category						
18-64	Reference	N/A	N/A	Reference	N/A	N/A
65+	1.79	1.31-2.45	**<0.001**	0.06	1.31-1.73	0.994

5.0 Discussion

The first aim determined that there is room for improvement in the way that physicians order RVP tests for Influenza because of the moderate agreement seen from the Kappa test, and that standardized ordering criteria may be needed. In addition, these findings suggest that using a CIA for recruitment for Influenza and other respiratory diseases proves beneficial. The results of the kappa test point to the fact that the CDC's screening criteria can be used to complete an assessment for ARI, ILI, or Influenza and provide clear guidelines for treating Influenza. Compared with the WHO's and the CDC's case definition, the CDC's screening criteria is too broad to rapidly assess Influenza as it includes numerous ARI and ILI symptoms, indicators, and diagnoses. Interestingly, a study conducted at the University of Pittsburgh showed that an RVP indicated in the EMR was the highest indictor of determining eligibility for their research study (65%-69%) using a CART analysis (Silviera, 2019). Notably, this study used the same CDC screening criteria as this study.

A study indicated that diagnosis data for pneumonia, viral illnesses, and upper respiratory infections are more accurate than chief complaint data when referencing the discharge diagnoses as the final comparison (May, 2010). Based on this study's findings, physicians or other clinical employees at St. Margaret's Hospital are recording the most information related to ARI/ILI/Influenza in the H&P and ED notes, which are locations where diagnosis data is predominantly recorded. Additional studies may be needed to further analyze this finding and Influenza positivity.

The study indicated a significant association between an RVP order and the presence of a fever, positive chest x-ray, positive CT-scan, and lymphocyte count. Although no studies have

correlated an RVP order and these clinical indicators, numerous studies align a fever, positive chest x-ray, and a positive CT-scan to Influenza (Shimoni, 2012) (Chan, 2004) (Malhotra, 2016) (Shiley, 2010) (Schoen, 2019).This suggests that if a physician orders an RVP these criteria will be present or reported for the patient in question. These findings align with the WHO's case definition of "An ARI with a measured temperature of ≥ 38 ˚C and cough, with onset within the past 7 days" (WHO, 2019). No studies in the literature directly related RVP status to the presence of a fever, a positive chest x-ray, or a positive CT-scan. Additionally, lymphocyte count was not related to Influenza in any literature. This section of the study suggests that the use of an RVP when patients present with fever, a positive chest x-ray, or a positive CT-scan is warranted to confirm Influenza.

The study indicated that there is a significant association between a positive screening by the CDC's screening criteria and the presence of a fever, positive chest x-ray, and positive CT-scan. Again, numerous studies align with this portion of the study's findings (Shimoni, 2012) (Chan, 2004) (Malhotra, 2016) (Shiley, 2010) (Schoen, 2019). This indicates that the CDC's screening criteria can be used to complete an assessment for ARI, ILI, or Influenza and presumptively treat Influenza, which aligns with the literature. Four studies in the literature indicate a high statistical relationship between fever and Influenza (Shah, 2015), (Shimoni, 2012), (Chan, 2004), and (Timpka, 2014). The CDC's screening criteria includes fever, but not explicitly a positive chest x-ray or positive CT-scan, while it does include various ARI keywords and diagnosis codes. Influenza and chest x-rays/CT scans were shown to have a relationship in the literature (Schoen, 2019).

To further assess these variables, binary logistic regression tests were performed. They indicated fever, chest x-ray, and CT-scan were statistically related to both RVP status and the

CDC's screening criteria (Table 4). Again, no studies have correlated an RVP order and these clinical indicators, but numerous studies correlate a fever, positive chest x-ray, and a positive CT-scan to Influenza (Shimoni, 2012) (Chan, 2004) (Malhotra, 2016) (Shiley, 2010) (Schoen, 2019). WBC count at admission, lymphocyte count at admission, and age category were also significant when an RVP was ordered (Table 4). The findings from both the RVP approach and the CDC approach align very well with the WHO's case definition, which suggests that both can be used to identify Influenza.

5.1 Limitations

Our study addresses an important clinical question adequately. However, there are multiple limitations in this study. The first is the limitation related to patients' demographics. Our patients are mostly elderly white, which makes it hard to generalize results to other subgroups of the population. These demographics are representative of Allegheny County where the study was conducted. The second is that our study could not differentiate between what was a symptom or a clinical indicator in the H&P and ED notes for the specified terms that were queried for the manual chart reviews. This is because symptoms are self-reported by patients while clinical indicators are measured by a clinical worker. Interpreting a symptom versus a clinical indicator may not have been possible in some cases as some notes in the EMR simply list keywords that could align with a symptom or clinical indicator. Further research may be needed to assess whether symptoms or clinical indicators of Influenza are a more accurate representation of the patient's actual diagnosis.

5.2 Implications for the Development of a Set of "key Indicators" for RVP Testing

The study found that RVP status is positively related to fever, chest x-ray, and CT-scan (Table 5). Currently there is no standardized or adopted set of criteria or set of symptoms in use in the U.S. for hospitalized patients who are suspected to have Influenza. The CDC's case definition does not include ARI like the WHO's case definition, or the findings of this study indicated (Centers for Disease Control and Prevention, 2019). It is also aimed more towards outpatient settings as it uses the same definition as the ILINet network uses to screen for ILI (Centers for Disease Control and Prevention, 2019). Additionally, the definition of fever differs between the WHO's and the CDC as the WHO uses ≥ 38 ˚C (≥100.4 ˚F) and the CDC uses >100°F. This is because all other countries in the world use Celsius except the U.S. Additionally, the CDC defines fever clinically as ≥100.4 ˚F (Centers for Disease Control and Prevention, 2019). The data collected for our study used the guideline of ≥100.4 ˚F. Also, cough for the purposes of this study was defined as a symptom and not included in the analysis done with the clinical indicators. Although the kappa test is a better test for inter rater reliability, regression tests were run and showed significance in key clinical indicators that align closely with the WHO and CDC case definitions. A hybrid version of the WHO case definition and the CDC definition should be recommended based on the findings of this study. This also suggests physicians are not ordering enough RVPs for ILI/ARI.

5.3 Barriers to Adequate Influenza testing

As there is no specific case definition for the diagnosis of Influenza, physicians differ in their use of laboratory testing for Influenza. TAT represents a major problem for many hospitals and physicians. It prolongs length of stay (LOS) and is associated with increased antibiotic use (Lee, 2019) (Andrews, 2017). Certainly, the cost and availability of the testing in the facility have a major impact on physicians ordering Influenza testing. If the results of an RVP or other Influenza test are available more efficiently, physicians are more likely to utilize the results for accurate identification of Influenza and other respiratory viruses (Linn, 2017). This sample of patients had RVPs collected not Rapid-PCRs, which accounts for long TAT, so physicians were not ordering enough RVPs. A 2 to 3 day result TAT may result in the physician either already treating the patient or the patient may already be progressing and/or discharged without treatment. A decreased TAT is associated with better decision making for physicians when treating ARI/ILI (Lee, 2019). The implementation of Rapid-PCRs in emergency and inpatient settings is needed.

5.4 Hospital-based Quality Improvement

If physicians were to more freely utilize Influenza testing for patients with suspected Influenza LOS and antibiotic use would be positively affected (Lee, 2019). Accurate and timely test results are associated with better patient satisfaction (Walker, 2017). More importantly the spread of Influenza or other respiratory viral infections is a major threat to hospital safety and quality of care. Influenza and other respiratory viruses are highly contagious and capable of causing outbreaks in health care systems. The spread could be related to patients as well as health

care workers (HCW). Appropriate vaccination of HCW significantly helps to curb the spread of Influenza. However, this is not true for other viruses for which we do not have any protective vaccination. Contact and droplet precautions are initiated automatically once Influenza testing is ordered and the code is removed or modified based on the test results.

However, if physicians are not ordering RVPs, there is a much higher chance of missed diagnosis (Lee, 2019). This certainly could lead to an increased spread of Influenza within hospital settings. A study from Canada reviewed Influenza outbreaks in Ontario hospitals between 2012 and 2016 and found 256 outbreaks involving 1586 patients (Murti, 2018). In this study the definition of outbreak was two or more cases of Influenza (Murti, 2018). Additionally, there were 91cases of pneumonia and 40 deaths (Murti, 2018). Another study showed that Influenza in a hospital setting within the U.S. highlighted 12 outbreaks of Influenza with variable involvement of HCW (Dickinson, 2019). The burden of Influenza is quite real as far as patients' risks and a financial burden for both the patient and healthcare setting. An estimated cost of an outbreak in a Swiss hospital was over $120,000 (Sendi, 2019). This cost included diagnostics, medications and loss of productivity (sick days of HCW) (Sendi, 2019). Finally, in the peak of Influenza season, the risk of missed cases is even higher (Sendi, 2019). An average of 2-3 cases of ILI in a hospital is much easier to manage compared to 30-40 patients in a given day (Sendi, 2019). At the peak of the Influenza season, 40-50% of Influenza testing turns positive (Sendi, 2019). A suggestion of testing critically-ill patients with any respiratory illness was repeatedly entertained at the peak of the season as well as in any suspected transmission within a particular unit (Sendi, 2019). A major study showed a significant association between Influenza infection and acute myocardial infarction (Kwong, 2018). This study showed a risk interval of 6 for myocardial infarction in patients who had Influenza infection within 7 days. The list of medical conditions that are triggered by Influenza

infection is long and certainly adds more complexity to accurate diagnosis without laboratory testing for Influenza in suspected patients. This sample was collected during Influenza season, which means a high percentage of RVPs (upwards of 50%) could have been positive. Because of the severity and complexity of Influenza it is more beneficial for a physician to order an RVP or Rapid-PCR when only 1 or 2 of the predominant indicators are present versus the presence of all of the predominant indicators this study found.

5.5 Implications for Documentation of Other Team Members in the EMR

In order for physicians to truly order these tests more accurately the data that they are using from the EMR to make their diagnosis needs to be accurate. In the modern hospital system, a range of health care workers with differing backgrounds and training will be entering notes or data that could affect this proposed definition. Unfortunately, there is limited research in accurate EMR documentation. The study's proposed definition would read "confirmation of ARI by chest x-ray or CT-scan, fever ≥100.4 ˚F, and cough, with onset within the past 7 days". This definition would have health care workers entering data from an ambulance transport, emergency department visit, observation periods, or admission periods. Healthcare workers at these locations would include paramedics, medical assistants, nurses, residents, physicians, respiratory specialists, physician assistants, nurse practitioners, X-ray techs, and to sonographers. All of these clinical workers could be entering information into the EMR at any of the mentioned timepoints. Subsequently, there are multiple timepoints where information could either have been entered wrong or where it could have been misinterpreted in the EMR. The chief complaint, which could have been recorded by a number of different clinical workers is frequently used by physicians when making a clinical

diagnosis (May, 2010). The chief complaint is often recorded in the EMR. Notably a low sensitivity between the final ED EMR diagnosis and Influenza was found by researchers (Dugas, 2015). Another issue is the fact that patients report issues to a clinical worker or physician and then they record this information in the EMR i.e. self-reported data by the patient. Secondly, when x-ray techs, sonographers, or radiologists look at results of tests and there is room for misinterpretation. In most inpatient scenarios the physician who will be determining the course of treatment for the patient and subsequently whether or not to order an RVP will be using the notes of other clinical workers to make their decision. Table 4 evidenced that ARI/ILI symptoms can be found in numerous locations. When a physician is utilizing the EMR as a reference to make a diagnosis they may or may not know who or what clinical worker charted the information. Also, they may not know if the information is a clinical indicator or symptom when they are reading a note from another clinical worker in the EMR. This poses an issue for any standardized criteria for the ordering of an RVP specifically for Influenza.

6.0 Conclusion

The WHO Influenza annual burden reported approximately a half million deaths world-wide in 2018, which has increased from the previous season (WHO, 2017). The CDC reported 61,099 deaths in 2017-2018 which is also higher than previous seasons (Centers for Disease Control and Prevention, 2018). The burden of Influenza is unquestioned, but the best way to counter the presentation of Influenza symptoms/indicators in an inpatient setting is highly debated.

This study established a relationship between the ordering of an RVP and the presence of ARI/ILI/Influenza symptoms/clinical indicators reported in the EMR because accurate and timely testing of Influenza is paramount for inpatient settings especially because of the increased severity of illness in this vulnerable sub-population.

A hybrid version of the WHO case definition and the CDC definition should be recommended based on the findings of this study. Additionally, the study noted issues with TAT related to the use of RVPs, under use of Rapid-PCRs, the severity and complexity of Influenza in an inpatient setting, and issues with documentation of Influenza symptoms/indicators in the EMR. Because of these issues and severity of Influenza in an inpatient setting, the presence of 1 or 2 of the predominant clinical indicators is suggested for the ordering of an RVP when physicians suspect Influenza. Physicians are also not ordering enough RVPs for ILI/ARI/Influenza. The implementation of Rapid-PCRs in inpatient setting may also be warranted in order to decrease TAT and further complications from Influenza. The critical issue that this project's results highlighted is when and on what basis should physicians order an RVP for ILI/ARI/Influenza.

Appendix A Tables

Appendix Table 1 The Relationship of Clinical Indicators of Acute Respiratory Illness to RVP Status and CDC's Symptom Based Screening Criteria (adjusted for Race)

	RVP Status			CDC's Screening Criteria		
	Odds ratio	**95% CI**	**P value**	**Odds ratio**	**95% CI**	**P value**
Fever (>100.4)	5.20	3.29-8.24	**<0.001**	2.33	1.45-3.74	**<0.001**
Blood Culture	0.67	0.30-1.51	0.360	0.79	0.39-1.58	0.531
Chest X-ray	1.45	1.05-2.01	**0.027**	2.32	1.74-3.10	**<0.001**
CT Scan	1.49	1.05-2.12	**0.030**	1.32	0.95-1.83	0.079
WBC Count	1.02	0.99-1.04	0.147	1.00	0.98-1.02	0.896
Lymphocyte Count	0.99	0.96-1.00	0.144	1.00	0.99-1.01	0.627
Race						
White	Reference	N/A	N/A	Reference	N/A	N/A
Non-white	1.30	0.76-2.22	0.334	0.90	0.58-1.38	0.623

Appendix Table 2 The Relationship of Clinical Indicators of Acute Respiratory Illness to RVP Status and CDC's Symptom Based Screening Criteria (adjusted for Gender)

	RVP Status			CDC's Screening Criteria		
	Odds ratio	**95% CI**	**P value**	**Odds ratio**	**95% CI**	**P value**
Fever (>100.4)	5.09	3.22-8.04	**<0.001**	2.48	1.51-3.88	**<0.001**
Blood Culture	0.69	0.31-1.55	0.374	0.78	0.39-1.58	0.495
Chest X-ray	1.46	1.05-2.01	**0.023**	2.36	1.77-3.15	**<0.001**
CT Scan	1.50	1.05-2.13	**0.024**	1.34	0.97-1.86	0.077
WBC Count	1.02	0.99-1.04	0.153	1.00	0.98-1.02	0.848
Lymphocyte Count	0.99	0.97-1.00	0.113	0.98	0.99-1.01	0.579
Gender						
Male	Reference	N/A	N/A	Reference	N/A	N/A
Female	1.23	0.90-1.64	0.201	1.32	1.02-1.71	**0.038**

Appendix Table 3 The Relationship of Clinical Indicators of Acute Respiratory Illness to RVP Status and CDC's Symptom Based Screening Criteria (adjusted for Age Category)

	RVP Status			CDC's Symptoms		
	Odds ratio	**95% CI**	**P value**	**Odds ratio**	**95% CI**	**P value**
Fever (>100.4)	4.69	2.97-7.4	**<0.001**	2.26	1.41-3.62	**0.001**
Blood Culture	0.74	0.33-1.66	0.459	0.82	0.41-1.64	0.565
Chest X-ray	1.54	1.11-2.14	**0.010**	2.39	1.79-3.20	**<0.001**
CT Scan	1.51	1.06-2.15	**0.018**	1.34	0.97-1.86	0.077
WBC Count at Admission	1.02	0.99-1.04	0.145	1.00	0.98-1.02	0.842
Lymphocyte Count at Admission	0.99	0.97-1.00	**0.042**	1.00	0.98-1.01	0.474
Age Category						
18-64	Reference	N/A	N/A	Reference	N/A	N/A
65+	1.75	1.28-2.39	**<0.001**	1.30	0.99-1.71	0.060

Appendix Table 4 List of Variables

Variable	Description	Location in EMR	Labels	Type of Variable
CDC Screening Criteria Met	Did patient meet the CDC's screening criteria?	Determined by RA based on chart review	1= Yes, 0= No	Categorical
RVP Status	Was an RVP ordered?	Orders>general lab/anatomic pathology (AP), micro	1= Yes, 0= No	Categorical
Clinical Fever	>100.4°F	Vital signs	1= Yes, 0= No	Categorical
Blood Culture Status	Was the patient's blood culture positive?	Labs>Blood bank	1= Yes, 0= No	Categorical
Chest X-ray Status	Was the patient's Chest X-ray abnormal or positive for ARI?	Orders>Radiology	1= Yes, 0= No	Categorical
CT Scan Status	Was the patient's CT Scan abnormal or positive for ARI?	Orders>Radiology	1= Yes, 0= No	Categorical
WBC Count at Admission	Count from blood sample on day of admission	Lab>Hematology	N/A	Continuous
Lymphocyte Count at Admission	Count from blood sample on day of admission	Lab>Hematology	N/A	Continuous
Sex	Was the patient male or female?	Patient information	1= Male, 0=Female	Categorical
Age Category	Which age category did the patient fit into?	Patient information	1= 18-64, 0=65+	Categorical
Race	Was the patient white?	Patient information	1= White, 0= Non-white	Categorical
ICD10 code in H&P note	Did the CIA find an ICD10 code in the H&P note?	H&P note	1= Yes, 0= No	Categorical
Specified term in ED note	Did the CIA find a specified term in the ED note?	ED note	1= Yes, 0= No	Categorical
Specified term in H&P note	Did the CIA find a specified term in the H&P note?	H&P note	1= Yes, 0= No	Categorical
Specified term in chief complaint	Did the CIA find a specified term in the chief complaint?	Chief complaint	1= Yes, 0= No	Categorical
ICD10 code in ED note	Did the CIA find an ICD10 code in the ED note?	ED note	1= Yes, 0= No	Categorical

Appendix B IRB Approval

University of Pittsburgh
Institutional Review Board

3500 Fifth A
Pittsburgh, P
(412) 383-14
(412) 383-15
http://www.i

Memorandum

To: Richard Zimmerman, MD

From: IRB Office

Date: 2/27/2019

IRB#: REN19020073 / PRO15070634

Subject: Flu vaccine effectiveness in those hospitalized in a large diverse health system

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Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:

45 CFR 46.110.(5)
45 CFR 46.110.(7)

Please note the following information:

Approval Date: 2/27/2019
Expiration Date: 3/5/2020

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

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