EMERGENCY DEPARTMENT DIAGNOSIS AND MANGEMENT OF INFLUENZA

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Abstract

Introduction: Diagnosing influenza in the emergency department (ED) remains a challenge as physicians have no reliable tools to accurately and rapidly diagnose influenza; however, rapid diagnosis is crucial to begin antiviral therapy in patients with complications or at risk of complications from influenza. Centers for Disease Control and Prevention (CDC) Guidelines recommend prompt antiviral treatment for patients who are hospitalized, at extremes of age (<5 years old, >65 years old), or have a chronic disease or conditions putting them at increased risk of complications.

Methods: First, we determined compliance with CDC antiviral guidelines via a retrospective evaluation of ED patients with confirmed influenza. Then, we created a prospective cohort of ED patients who met CDC criteria for recommended antiviral treatment who were evaluated for influenza by 3 means: clinical diagnosis, a new molecular-based rapid test, and a Polymerase Chain Reaction (PCR) test. Comparing the clinical diagnosis and rapid influenza test to the standard PCR assay allowed for a performance evaluation of both clinician diagnosis, and the new molecular-based rapid test. Finally, a cost-effectiveness analysis was performed to compare influenza testing and treatment strategies.

Results: ED providers have poor compliance with CDC guidelines regarding antiviral treatment with only 41% of patients recommended to receive antiviral treatment being treated in the ED. Provider diagnosis for influenza has a poor sensitivity of 36%, especially compared to the molecular-based rapid influenza test which has 95% sensitivity in the same population. Finally, the most cost-effective testing and treatment strategy depends on influenza prevalence with rapid

testing as the most cost-effective treatment at low influenza prevalence, and treating all patients without testing as the most cost-effective strategy at high prevalence.

Conclusions: The challenges of making a clinical diagnosis of influenza in the ED, and current lack of a rapid sensitive influenza test, likely contribute to poor compliance with current CDC guidelines regarding antiviral administration. Integrating a new highly sensitive molecular-based rapid influenza test into ED clinical care, could improve compliance with CDC guidelines and is cost effective at low influenza prevalence.

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List of Acronyms

ED – Emergency Department
CDC – Centers for Disease Control and Prevention
PCR –Polymerase Chain Reaction
WHO – World Health Organization
IDSA – Infectious Disease Society of America
rt-PCR – Real-time Polymerase Chain Reaction
ICU – Intensive Care Unit
PCR –Polymerase Chain Reaction
DFA – Direct Immunofluorescence Assays
ILI – Influenza-like illness
FDA – Food and Drug Administration
PSI – Pneumonia Severity Index
IQR – Interquartile Range
CI – Confidence Interval
IRB – Institutional Review Board
ICER – Incremental Cost-effectiveness Ratio
QALY – Quality Adjusted Life Year

Introduction

Each year, influenza affects approximately 5-20% of the United States population causing over 200,000 hospitalizations and 3,000 – 49,000 deaths [1-3]. This substantial societal impact will further increase during severe epidemics with increased prevalence or virulence causing additional morbidity and mortality. As a key point of entry to the health care system, emergency departments (ED) are responsible for the initial management and treatment of a substantial proportion of these influenza patients, thus directly impacting overall public health. Fortunately, the past 15 years has brought both new antiviral medications and increasing evidence of their effectiveness in specific populations.

INFLUENZA ANTIVIRAL TREATMENT

Though of questionable benefit in healthy individuals, antiviral treatment for patients at increased risk or with existing complications is recommended by the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and the Infectious Disease Society of America (IDSA) [4-6]. Recent CDC guidelines recommend antiviral treatment specifically for patients with a severe or complicated course, hospitalization, or at high risk of influenza complications – including those younger than 5 years old, older than 65 years old, residing in a chronic-care facility, or with chronic medical conditions, immunosuppression, pregnancy, or morbid obesity [4].

Research involving antiviral use and clinical outcomes in these high-risk patients is extremely complex, limiting the availability of definitive randomized controlled studies. The majority of patients included in the clinical trials originally performed to demonstrate the effectiveness of antivirals did not have existing influenza-related complications or other characteristics placing

them at increased risk of complications [7,8]. These studies did show a decrease in the incidence of pneumonia and infectious complications in patients taking influenza antivirals, but were not properly powered to detect a potential impact on hospital admission or mortality due to the low event rate of these serious outcomes. One of the few randomized controlled trials for high risk patients was performed in children with asthma, and showed improved pulmonary function and fewer asthma exacerbations in children receiving antiviral medication [9].

In spite of the lack of randomized trials, a growing body of observational studies supports antiviral treatment in populations with or at increased risk of influenza related complications. The greatest evidence to date is in admitted patients, where numerous observational studies show a reduction in mortality, hospitalization, intensive care unit (ICU) admission and hospital length of stay associated with oseltamivir treatment [10-13]. Additional studies in specific at risk populations demonstrate reduction in hospitalization and death in patients with diabetes, pregnancy, and nursing home residence [14-17]. In their recommendations, both the WHO and CDC emphasize administering antiviral medications to patients with suspected, but not yet confirmed infections, as the time from symptom onset to antiviral treatment impacts patient outcomes [18-21].

Antiviral medications are currently recommended to be given within 48 hours of symptom onset, and appear to have increased effectiveness when given closer to the time of symptom onset. Several studies have demonstrated that further reducing the time between symptom onset and antiviral administration to 30 or even 24 hours, increases the beneficial effect of antivirals [18-21]. Although 48 hours from symptom onset is a common cut off in deciding to administer antivirals, this boundary is blurred by evidence that some populations, such as patients admitted to the hospital, may continue to receive benefit from antivirals when initiated beyond the 48 hour cut-off [11-13]. Despite the evidence that shortening the time between symptom onset and

antiviral administration results in improved outcomes, the practical ability to diagnose and treat influenza within this 48 hour time frame is difficult due to the lack of reliable rapid diagnostic tools.

RAPID DIAGNOSIS OF INFLUENZA

The current lack of reliable rapid influenza tests make diagnosis and timely treatment of influenza challenging, especially in fast-paced treatment settings such as the ED. There are currently no reliable methods to diagnose influenza in the timeframe of a typical ED visit, leaving emergency physicians to make diagnostic and treatment decisions with limited, insufficient information. The previous gold standard influenza test, viral culture, requires 3-10 days to perform, and is quickly being replaced by the more sensitive real-time polymerase chain reaction (rt-PCR), which typically requires several hours to result and is usually performed as batch testing, further lengthening time to result. Some laboratories utilize direct immunofluorescence assays (DFA), with moderate sensitivity of 50-80% for influenza and results in 30-60 minutes [22]. In an attempt to fill the need for rapid diagnosis, several rapid influenza tests have been developed; however, these antigen-based tests have sensitivities ranging from 10-70%, and current CDC guidelines require additional testing in the setting of a negative rapid influenza test due to their poor sensitivity [23].

Given the lack of reliable testing options which yield rapid results, emergency physicians often diagnose influenza based on symptoms. Many studies have attempted to validate the use of clinical symptoms to diagnose influenza overall showing poor sensitivity and specificity. One of the largest studies showed that a combination of fever and cough had a sensitivity 64% and specificity 67% [24]. Two subsequent meta-analyses confirmed that there are no symptoms or combination of symptoms which has adequate sensitivity to make informed clinical decisions regarding influenza treatment [25,26].

Cepheid's Xpert flu test is a new molecular-based rapid influenza test which yields a result in 80 minutes and has recently obtained Food and Drug Administration (FDA) approval for influenza testing. Previous validation studies performed in comparison to Luminex rt-PCR report a sensitivity of 91.2% and specificity of 99.4% giving an overall positive predictive value of 99.2% and negative predictive value of 93.1% [27]. Although promising, and with superior results compared to current antigen-based rapid influenza diagnostic tests, Xpert Flu has not been clinically validated or integrated into clinical practice.

CURRENT ED PRACTICE

Given the current difficulties of rapid diagnosis of influenza, and the evidence of improved antiviral efficacy when administered closer to the time of symptom onset, the CDC currently recommends that physicians treat patients who have an increased risk of influenza-related complications and suspected influenza with antivirals without waiting for confirmatory testing [4,28]. Despite the building evidence, and recommendations from expert organizations, patients remain under-treated with antivirals, and there continues to be a gap between recommendations and current clinical practice [29]. A survey of 1,055 ED clinicians during the 2006 -2007 influenza season revealed that only 56% of ED clinicians prescribed antiviral medications for some of their influenza patients that year [30]. Though this survey occurred before the current, more expansive CDC influenza treatment guidelines, the low number of prescribing ED clinicians is shocking considering the volume of influenza-like illness (ILI) and influenza patients treated in the ED, and the prevalence of high-risk criteria such as diabetes, cardiac disease, age greater than 65, and obesity in a typical ED population. This trend of under-treatment continues through the 2009 influenza season, where a retrospective evaluation of ED visits showed that only 50% of high-risk patients with a clinical diagnosis of influenza received antiviral treatment [31]. Despite the increased emphasis on rapid antibiotic administration in pneumonia and sepsis, antiviral use in the ED remains under-utilized. In an observational study of 327 patients admitted with

influenza, 89% received antibacterial therapy, whereas only 32% were prescribed antiviral medications despite the fact that the majority (59%) presented to the ED within 48 hours of onset of illness [11]. In fact, only 50% of these patients received influenza testing from the ED. The reticence of ED clinicians to prescribe antivirals has multiple possible explanations including difficulty confirming the diagnosis of influenza, as evidenced by numerous studies which have demonstrated the logical connection between increased influenza testing and increased antiviral use [30,32-34]. Other considerations contributing to the lack of influenza testing or treatment in the ED include economic concerns due to the high cost of oseltamivir treatment.

COST-EFFECTIVENESS ANALYSIS

Similar to the randomized controlled clinical effectiveness studies, the majority of the cost-effectiveness analyses of influenza treatment have focused on healthy adults. These studies often conclude that the most cost effective strategy is to treat all patients with antiviral medications, driven largely by a 1-2 day reduction in symptoms and decrease in lost work costs [35,36]. Cost-effectiveness studies examining patients at increased risk of influenza complications are more varied with some recommending influenza testing as the most cost-efficient method [37,38], and others continuing to recommend to treat all without testing [39]. When considering influenza testing, these studies have considered the accurate but expensive rt-PCR testing, or the less-expensive but inaccurate antigen-based rapid testing. New molecular-based rapid tests, with a more moderate price and improved accuracy could potentially shift the cost-effectiveness balance.

APPROACH

Despite growing evidence that influenza antivirals reduce morbidity and mortality in specific populations, and that antiviral medications are most effective when administered within 48 hours of symptom onset, ED physicians often do not prescribe them. There are several contributing

factors to this gap in current medical practice, including the current challenges with reliable rapid diagnosis, as demonstrated in Figure 1Figure 1. This work seeks to identify and quantify the current challenges of influenza diagnosis and treatment, and identify cost-effective solutions through the following four aims:

Aim 1: Determine compliance with CDC antiviral administration guidelines amongst patients with a positive influenza test sent from the ED. This aim will assess the current proportion of influenza patients either at risk of or with potential influenza related complications who receive antiviral treatment.

Aim 2: To determine the current rate of influenza misdiagnosis in the ED. Identifying the current rate of influenza misdiagnosis quantifies the current challenges of clinical influenza diagnosis.

Aim 3: To evaluate the clinical sensitivity and specificity of a novel molecular-based rapid influenza test (Cepheid Xpert Flu). This aim establishes the clinical validity of Cepheid Xpert Flu, and allows for comparison to other current diagnostic methods.

Aim 4: To determine the cost-effectiveness of influenza testing and treatment strategies for adults who present to the ED with an acute respiratory illness and meet CDC criteria for influenza treatment. Understanding the societal costs and benefits of these treatment strategies will help guide future clinical decision making and potential integration of new rapid influenza tests.

Aim 1 quantifies the essential problem of low administration of antivirals by retrospectively evaluating the proportion of patients with confirmed influenza who are recommended to receive

antivirals according to current CDC guidelines that receive antiviral treatment in the ED. Additionally, it will explore potential factors such as severity of illness or hospital admission that may be associated with antiviral treatment. This aim will be accomplished through a retrospective cohort of ED patients with confirmed influenza. One contributor to the lack of antiviral administration in the ED is the challenge of rapid influenza diagnosis due to the time constraints of current testing and inaccuracy of clinical signs and symptoms. **Aim 2** quantifies the current problems with influenza misdiagnosis in the ED through a prospective study comparing ED provider clinical diagnosis to rt-PCR testing. One potential solution to improve provider diagnosis is implementing a molecular-based rapid influenza test, such as Xpert Flu. **Aim 3** demonstrates the clinical validity of Xpert Flu by assessing the sensitivity and specificity of Xpert Flu, compared to rt-PCR, in the same prospective population used to evaluate the provider clinical diagnosis. This allows for direct comparison of the validity of these two potential diagnostic methods. Finally, **Aim 4** uses a cost utility analysis to identify the most cost effective approach to influenza management: rapid testing, clinical assessment, treat all, or treat none. Combined, these four aims provide a comprehensive approach to quantify and address the challenges of influenza diagnosis and management in the ED.

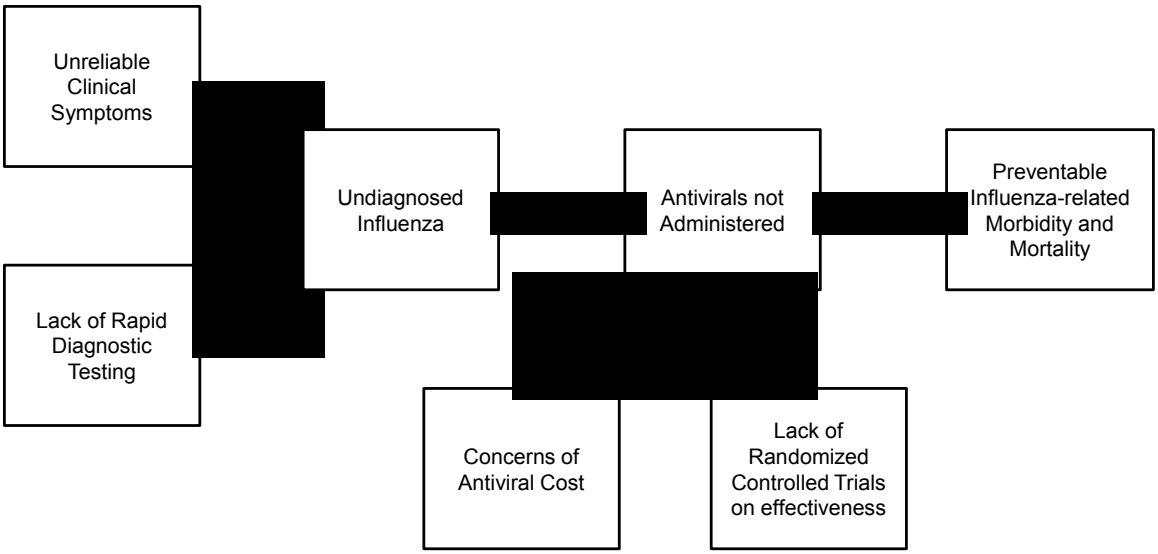

Figure 1: Proposed approach to evaluate influenza diagnosis and management in the Emergency Department

Aim 1: Compliance with Influenza Antiviral Recommendations

INTRODUCTION

Each year, influenza affects approximate 5-20% of the United States population causing over 200,000 hospitalizations and 3,000 – 49,000 deaths [1-3]. As one of the primary points of entry to the health care system, EDs are responsible for initial management and treatment of a substantial proportion of these influenza patients [40]. Antiviral treatment has been demonstrated to improve clinical outcomes for patients at increased risk for, or with existing complications, and is thus recommended by the CDC, WHO and IDSA [4-6]. Recent CDC guidelines provide specific recommendation for antiviral treatment including patients with a severe or complicated course, those requiring hospitalization, or those at high risk of influenza complications – including those younger than 2 years, older than 65 years, residing in a chronic-care facility, or with chronic medical conditions, immunosuppression, pregnancy, or morbid obesity [4].

Despite growing evidence that antiviral medications reduce influenza-related morbidity and mortality, and the release and dissemination of recommendations from multiple expert organizations, there continues to be a substantial gap between recommendations and current clinical practice [29]. One recent study which prospectively tested 1,657 ED patients for influenza between 2009 and 2011 demonstrated that more than 80% of patients with confirmed influenza in the ED did not receive antiviral treatment [41]. However over half of the patients in that study did not meet CDC criteria for recommended antiviral treatment, and the study did not fully evaluate adherence with CDC antiviral recommendations. Another single institution study evaluated ED adherence with CDC antiviral treatment recommendations and found that only 50% of patients with a final ED physician diagnosis of influenza, who met CDC criteria for treatment, actually received antiviral treatment [31]. However, the inclusion criteria used in this evaluation, a clinical diagnosis of influenza, has poor sensitivity for influenza [42]. Though previous

evaluations suggest that ED patients with influenza remain significantly undertreated, adherence to CDC guidelines amongst ED patients with confirmed influenza remains unknown.

Given the challenges of diagnosing influenza in the ED, and the importance of appropriately treating patients with existing or at increased risk of influenza-related complications, we sought to determine adherence with CDC antiviral recommendations amongst a cohort of ED patients with laboratory confirmed influenza. Understanding antiviral treatment patterns amongst this population could provide opportunities to improve ED care and potentially impact long term outcomes for patients with influenza who receive their initial diagnosis in the ED.

METHODS

Study design

We performed an observational cohort study of ED patients with laboratory confirmed influenza at an urban, university-affiliated tertiary care center with an ED volume of over 60,000 annual patient visits. This study was approved by the Johns Hopkins institutional review board with a waiver of consent.

Study Population

Adult subjects (18 years old or older) were included in the study if they had an ED visit between December 2008 and December 2012, and had a positive influenza test sent from the ED. Subjects were excluded if they left the ED prior to completion of their ED work up and treatment, defined as a recorded ED disposition of screened and left, left without being seen, or left against medical advice.

Study Protocol

Patient records of all ED patients with laboratory confirmed influenza were screened in duplicate to ensure all inclusion criteria, and no exclusion criteria were met. Two reviewers independently extracted data from the hospital's electronic medical record, which included both ED and inpatient documentation. We established the data points and data abstraction process prior to study initiation. Data were entered directly onto a standardized, closed entry, Microsoft Access (Microsoft Corporation, Redmond, Washington) database form. Data elements recorded include: subject demographics, current symptoms, past medical history, current medication use, initial ED vital signs, laboratory and culture data, ED management, disposition from the ED, and final ED diagnoses. Additionally, we collected information regarding the hospital course including influenza antiviral treatment while in the hospital.

Measurements

Using the abstracted information, subjects were categorized as either "recommended to receive antiviral treatment" or "not recommended to receive antiviral treatment" based on 2011 CDC guidelines [4]. Each subject was assigned to one of the 5 included influenza seasons (2008-2009, 2009-2010, 2010-2011, 2011-2012, 2012-2013) based upon the date of ED presentation, with each influenza season spanning from May 15th to May 14th of the following year. Duration of total symptoms was recorded and dichotomized as either 48 hours or less, or over 48 hours, based upon previous cut-offs for antiviral use in the literature [18]. Presence or absence of ILI was based upon the CDC criteria for ILI of a fever equal to or greater than 37.8 Celsius with either cough or sore throat [43]. Antibiotic and antiviral administration was recorded as either none, administered in the ED, or discharged with a prescription. If a subject was either administered an antiviral in the ED, or discharged from the ED with an antiviral prescription, they were considered to have received ED antiviral treatment. Similarly, if a subject was either administered an antibiotic in the ED or discharged from the ED with an antibiotic prescription,

they were considered to have received ED antibiotic treatment. Time variables were documented according to the medical record date and time stamp for critical events, including time of arrival (initial registration), time of antiviral administration, time the first positive influenza test resulted, and time the subject left the ED. If the time of the first positive influenza test result occurred prior to the time the subject left the ED, it was assumed that the influenza test result was available prior to disposition. For each subject, the Pneumonia Severity Index (PSI) was calculated as described previously as a marker of illness severity [44,45].

Data Analysis

Data were analyzed using Stata Statistical Software: Release 11 (StataCorp LP, 2009. College Station, TX). We used non-parametric statistics with results shown as medians and interquartile ranges (IQR) for continuous variables, and counts and percentages for dichotomous variables. Statistical comparisons were completed using chi-squared analysis. For all tests, the level of significance was set to $\alpha = 0.05$.

Subjects were initially divided into two groups, those recommended to receive antiviral medication and those not recommended to receive antiviral medication. The remainder of the analysis focused only on the group of subjects recommended to receive antiviral medication according to 2011 CDC guidelines, as this was the population of greatest interest. Subjects recommended to receive antiviral treatment were further divided into those who received ED antiviral treatment and those who did not. The primary outcome of this study is the proportion of subjects recommended to receive antiviral treatment who received ED antiviral treatment. With a sample size of 282 subjects recommended to receive antiviral treatment, and an *a priori* estimate of 50% receiving antiviral treatment, the resulting 95% confidence interval, (44-56%) is sufficiently narrow for clinical interpretation.

RESULTS

Between December 2008 and December 2012, 350 adults had influenza tests sent from the ED which were positive for influenza, of whom 8 left prior to completion of their ED work-up and treatment and were excluded from the study. Of the 342 subjects included in the analysis, 282 (82%) subjects met 2011 CDC criteria for antiviral treatment and 60 (18%) subjects did not. Characteristics of the study subjects and the 2011 CDC criteria are displayed in Table 1. Amongst all subjects, 130 (38%) received antiviral treatment from the ED. Of subjects recommended to receive antiviral treatment, 41% (95% CI 36-47%) received antiviral treatment in the ED. Subjects recommended to receive antiviral treatment were more likely to receive ED antiviral treatment compared to those who were not recommended to receive antiviral treatment (41% versus 23%, p=0.01). Only 60% of the population fit the CDC definition of ILI. Subjects recommended to receive antiviral treatment were less likely to meet CDC criteria for ILI than those who are not recommended to receive antiviral treatment (57% versus 75%, p=0.01).

Among individuals recommended to receive antiviral treatment, we compared those who were treated with an antiviral to those not treated with an antiviral as shown in Table 2. Antiviral treatment patterns were variable across influenza seasons as over half of the patients were treated during the largest (2009-2010) and smallest influenza seasons (2011-2012), but in the remaining seasons, less than half of the patients were treated. Treatment also varied with the type of influenza, as patients that were positive for influenza B positive were less likely to be treated. Consistent with previous evidence demonstrating that antivirals are more effective when given close to symptom onset, the duration of symptoms was associated with antiviral treatment as patients with symptoms less than 48 hours were more likely to receive antiviral treatment. In comparing patient presentation and diagnosis, patients with a clinical diagnosis of influenza were more likely to be treated with an antiviral and patients who had a positive influenza test result available prior to disposition were more likely to receive antiviral treatment. Patients with an

infiltrate on chest X-ray or those who received antibiotics in the ED were less likely to receive ED antiviral treatment for influenza. Using the Pneumonia Severity Index as a marker of severity of disease, there was no association between disease severity and antiviral treatment. Similarly, there was no association between hospital admission and antiviral treatment. Of the 111 patients admitted to the hospital without ED antiviral treatment, 55 (50%) received antiviral medication as an inpatient.

LIMITATIONS

This study is a retrospective evaluation of influenza testing at a single medical center. As with any retrospective evaluation there exists the potential for missing or false information in the medical record. The testing and treatment patterns at this single tertiary care medical center may not represent that of other facilities. As this study only evaluated patients who had a positive influenza, the results are influenced by the provider's decision to obtain influenza testing. Patients in whom providers did not test for influenza either because they did not suspect influenza or it would not change their management, are not included in this study and may represent a different patient population. However, as provider diagnosis of influenza and clinical signs and symptoms have low sensitivity for influenza, restricting the population to only those with a positive influenza test allows for evaluation of patients with confirmed disease.

Although CDC recommendations have remained largely the same over the timeframe of the study, some of the details have changed. The definition of the high risk population has remained fairly consistent with the exception the addition of Native American heritage and morbid obesity as risk factors in 2011 [4,46,47]. This study included no patients who were of Native American heritage. Of the 6 patients with morbid obesity, all had additional medical conditions which would include them in the high risk population. Hence, all subjects in this study identified as high risk according to the 2011 guidelines would have been considered high risk by previous

guidelines. Prior to 2009, the CDC recommended antiviral treatment for individuals with or at high risk of influenza-related complications if they had confirmed influenza and treatment was started within 48 hours of symptom onset [46]. As evidence demonstrating poor sensitivity of rapid influenza tests, and continued antiviral benefit even if started beyond 48 hours from symptom onset accumulated, these restrictions were removed in 2009 [47]. This may have contributed to the particularly low treatment rates seen in the 2008-2009 influenza season, but was consistent for the remaining 4 influenza seasons included in the study.

DISCUSSION

Despite a growing body of observational studies demonstrating the effectiveness of antiviral medications, ED providers do not follow CDC recommendations regarding influenza antiviral treatment. This study further confirms non-adherence with CDC recommendations as only 41% of patients with confirmed influenza who meet CDC criteria for recommended antiviral treatment received influenza antiviral treatment from the ED. The reticence of ED clinicians to prescribe antivirals has multiple possible explanations including difficulty in confirming the diagnosis of influenza, as evidenced by numerous studies which have demonstrated the logical connection between increased influenza testing and increased antiviral use [34,41,42].

The current lack of reliable rapid influenza tests make diagnosis and timely treatment of influenza challenging, especially in fast-paced treatment settings such as the ED. Though highly sensitive, traditional rt-PCR-based tests take several hours to result, reducing their clinical utility in the ED setting. Rapid antigen-based tests have a much faster turn-around time, but have lower sensitivity, ranging from 10-70%, and current CDC guidelines require additional testing in the setting of a negative rapid influenza test due to their poor sensitivity [23]. There are several emerging molecular-based tests with a more rapid turn-around time of approximately one hour; however, these test are not yet in widespread use, and are not available at most EDs. This study

confirms the challenge of obtaining sensitive laboratory results in the typical timeframe of an ED visit. Although all subjects in this analysis were tested for influenza in the ED, only 30% of patients recommended to receive treatment had a positive test which resulted while the patient was in the ED. Patients who had a positive test result while they were still in the ED were more likely to receive antiviral treatment (63%) than those who did not (46%). Increased availability of sensitive influenza tests which will result in the timeframe of a typical ED visit, could improve provider adherence with CDC guidelines.

Given the lack of reliable testing options which yield rapid results, emergency physicians often diagnose influenza based on symptoms. Many studies have attempted to validate the use of clinical symptoms to diagnose influenza overall showing poor sensitivity and specificity. One of the largest studies showed that a combination of fever and cough had a sensitivity 64% and specificity 67% [24]. Two subsequent meta-analyses confirmed that there are no symptoms or combination of symptoms which has adequate sensitivity to make informed clinical decisions regarding influenza treatment [25,26]. In this retrospective population, only 60% of subjects fulfill the CDC criteria for ILI, and patients who are recommended to receive treatment were less likely to have classic ILI symptoms than otherwise healthy individuals. Patients who may benefit the most from antiviral treatment (i.e. elderly or immunosuppressed patients), may not mount a fever or typical immune response to influenza, making the classic symptoms of ILI less useful in this critical population.

The lack of availability of highly-sensitive rapid laboratory tests, coupled with the non-specific symptoms with which influenza presents, creates a diagnostic challenge for providers. This uncertainty in the diagnosis of influenza may lead to decreased antiviral treatment. In this study, providers recorded a diagnosis of influenza in 20% of those recommended to receive antiviral treatment. Those with a diagnosis of influenza were more likely to receive antiviral treatment.

This uncertainty in diagnosis can be further complicated by the suspicion of an alternate diagnosis of bacterial infection. Though influenza is well known to cause lower respiratory tract disease, and the presence of influenza-related pneumonia is an indication for antiviral treatment, an infiltrate on a chest X-ray made a patient less likely to receive antiviral treatment. This suggests that the presence of an infiltrate on chest X-ray may have been interpreted as a bacterial pneumonia, thus misleading providers from diagnosing and treating influenza. This theory is supported by examining antibiotic use, where patients who received antibiotic treatment in the ED were less likely to receive antivirals.

Other factors such as concern for spreading antiviral resistance due to increased antiviral use, or belief that antivirals are not effective in preventing influenza-related complications may contribute to the lack of adherence with CDC guidelines regarding influenza antiviral treatment. The strongest evidence as to the effectiveness of antiviral medications is for admitted patients where observational studies show decreased mortality and length of stay associated with antiviral use [10,11]. Hence, potential provider concerns regarding antiviral resistance or lack of effectiveness should lead to greater treatment of admitted patients, where there is convincing evidence of effectiveness, and providers would not likely withhold medication in the name of preventing resistance. However, in this study, patients admitted the hospital were not more likely to receive antiviral treatment. As an additional evaluation of patients with more severe illness, we evaluated the relationship between antiviral treatment and the Pneumonia Severity Index, which was previously been shown to correlate with the severity of illness in influenza patients [45]. In this population, there was no association between antiviral treatment and the Pneumonia Severity Index, indicating that the sickest patients were not more likely to receive antiviral therapy.

CONCLUSION

In summary, there is poor adherence with CDC recommendations on influenza antiviral treatment amongst ED patients with laboratory confirmed influenza. Surprisingly, hospital admission and severity of illness are not associated with antiviral treatment. However, factors associated with making a clear influenza diagnosis such as a provider diagnosis of influenza, and a positive influenza test result during the ED visit are associated with antiviral treatment. These factors suggest that integrating a sensitive rapid influenza test in to ED care may improve adherence with CDC antiviral recommendations.

Table 1: Aim 1 Subject Characteristics

	All *n (column %)*	**Recommended to Treat*** *n (column %)*	**Not Recommended to Treat*** *n (column %)*
Number of Subjects	342	282	60
Age (Years)	37 (23-50)	42 (24-52)	25 (21-35)
Male Gender	141 (41%)	111 (39%)	30 (50%)
Race			
African American	237 (69%)	224 (79%)	49 (82%)
White	47 (14%)	39 (14%)	8 (13%)
Other	58 (17%)	19 (7%)	3 (5%)
Influenza Season			
2008-2009	40 (12%)	31 (11%)	9 (15%)
2009-2010	154 (45%)	128 (45%)	26 (43%)
2010-2011	78 (23%)	67 (24%)	11 (18%)
2011-2012	16 (5%)	56 (20%)	7 (12%)
2012-2013	54 (16%)	56 (20%)	7 (12%)
Type of influenza			
Influenza A	308 (90%)	261 (93%)	47 (78%)
Influenza B	33 (10%)	20 (7%)	13 (22%)
Diagnosis			
Influenza-like Illness	206 (60%)	161 (57%)	45 (75%)
ED diagnosis of influenza	72 (21%)	57 (20%)	15 (25%)
Treatment Criteria			
Hospital admission	177 (52%)	177 (63%)	NA
Complications/Pneumonia	54 (16%)	54 (19%)	NA
Age 65 or greater	19 (6%)	19 (7%)	NA
Chronic Disease			
Pulmonary	132 (39%)	132 (47%)	NA
Cardiovascular	84 (25%)	84 (30%)	NA
Renal	39 (11%)	39 (14%)	NA
Hematologic	26 (8%)	26 (9%)	NA
Metabolic	59 (17%)	59 (21%)	NA
Neurologic	32 (9%)	32 (11%)	NA
Immunosuppression	85 (25%)	85 (30%)	NA
Pregnancy	3 (1%)	3 (1%)	NA
Morbid Obesity	6 (2%)	6 (2%)	NA
Resides in Nursing Home	0 (0%)	0 (0%)	NA
Native American	0 (0%)	0 (0%)	NA
ED treatment			
Antiviral given in ED	106 (31%)	100 (35%)	6 (10%)
Antiviral prescription only	24 (15%)	16 (15%)	8 (13%)
Any antiviral treatment from ED	130 (38%)	116 (41%)	14 (23%)
Antibiotic given in ED	164 (48%)	152 (54%)	12 (20%)

* Recommendations based on 2011 Centers for Disease Control and Prevention criteria.

Table 2: Potential treatment factors of subjects recommended to receive antiviral treatment according to 2011 Centers for Disease Control and Prevention criteria.

	Recommend to receive antiviral treatment *n (column %)*	**Treated with Antiviral** *n (column %)*	**Not Treated with Antiviral** *n (column %)*	**p-value**
Number of Subjects	282	116	166	
Influenza Season				
2008-2009	31 (11%)	4 (3%)	27 (16%)	
2009-2010	128 (45%)	62 (53%)	66 (40%)	
2010-2011	67 (24%)	22 (19%)	45 (27%)	0.001
2011-2012	9 (3%)	6 (5%)	3 (2%)	
2012-2013	47 (17%)	22 (19%)	25 (15%)	
Type of influenza				
Influenza A	261 (93%)	113 (97%)	148 (89%)	0.009
Influenza B	20 (7%)	3 (3%)	17 (10%)	
Diagnosis				
Influenza-like Illness	161 (57%)	70 (60%)	91 (55%)	0.356
ED diagnosis of influenza	57 (20%)	42 (36%)	15 (9%)	< 0.001
Alternate Diagnosis				
Infiltrate on Chest X-ray	65 (23%)	17 (15%)	48 (29%)	0.005
ED diagnosis of pneumonia	54 (19%)	16 (14%)	38 (23%)	0.053
Antibiotic treatment in the ED	152 (54%)	49 (42%)	103 (62%)	0.001
Severity				
Hospital Admission	177 (63%)	66 (57%)	111 (67%)	0.088
Pneumonia Severity Index				
I	159 (56%)	66 (57%)	93 (56%)	
II	66 (23%)	22 (19%)	44 (27%)	
III	33 (12%)	18 (16%)	15 (9%)	0.518
IV	21 (7%)	9 (8%)	12 (7%)	
V	3 (1%)	1 (1%)	2 (1%)	
Positive influenza test result available before disposition	84 (30%)	55 (47%)	29 (17%)	< 0.001
Symptoms less than 48 hours	150 (53%)	73 (63%)	77 (46%)	0.007
Immunosuppressed	85 (30%)	46 (40%)	39 (23%)	0.004

Aim 2: Provider Diagnosis of Influenza

INTRODUCTION

Each year influenza causes significant morbidity and mortality including over 200,000 hospitalizations and 3,000-49,000 deaths in the United States alone [2,3]. Fortunately, timely antiviral treatment can decrease morbidity and mortality in patients at increased risk for, or with existing influenza-related complications, and is recommended in these populations by the CDC, WHO, and IDSA [4-6]. Specifically, the CDC recommends antiviral treatment for patients with a severe or complicated course, those requiring hospitalization, and those at high risk of complications, including patients at the extremes of age (<5 years old, >65 years old), residing in a chronic care facility, or with specific chronic medical conditions, immunosuppression, pregnancy, morbid obesity, or Native American heritage [4]. Antiviral therapy is most effective when given close to the time of symptom onset, therefore rapid diagnosis and treatment of individuals with influenza and existing or increased risk of complications is essential [18-21]. Moreover, given the limited number of effective antiviral options, and concerns of increasing antiviral resistance, antiviral treatment must also be targeted to those with influenza, who will benefit most from treatment. Hence, accurate diagnosis of influenza virus infections is key to providing targeted antiviral treatment.

Diagnosing influenza remains a challenge, especially in the ED where a substantial number of patients with influenza and other respiratory infections seek care. There are currently no reliable methods to diagnose influenza in the timeframe of a typical ED visit, leaving emergency clinicians to make diagnostic and treatment decisions with limited, insufficient information. The current gold standard influenza test, rt-PCR, typically requires several hours for results. In an attempt to fill the need for rapid diagnosis, several antigen-based rapid influenza tests are in use;

however these tests have poor to moderate sensitivity ranging from 10-70%, and current CDC guidelines require additional testing in the setting of a negative test [23]. Some laboratories utilize DFA, which result in as little as 30-60 minutes, but still have only moderate (50-80%) sensitivity [22]. Highly sensitive, molecular-based rapid tests are increasingly available but have not yet been widely adopted, particular in the ED setting [48].

Given the lack of access to highly accurate rapid tests, ED clinicians often diagnose influenza based on clinical signs and symptoms. Although many studies have attempted to validate the use of clinical signs and symptoms to diagnose influenza, findings indicate overall poor sensitivity and specificity. The CDC created the case definition of ILI as fever equal to or greater than 37.8 Celsius with either cough or sore throat; however, sensitivity of ILI for influenza is only 55-69% [43,49]. One of the largest studies showed that a combination of fever and cough had a sensitivity 64% and specificity 67% [24]. Further, two subsequent meta-analyses confirmed that there are no combination of signs and symptoms which have adequate sensitivity to make informed clinical decisions regarding influenza treatment [25,26]. Hence, in the current ED practice environment, accurate diagnosis of influenza remains a challenge.

Accurate diagnosis of influenza is particularly important in patients presenting with complications or conditions that increase the risk of influenza-related complications as diagnosis will impact decision-making regarding antiviral treatment. Although a previous ED-based study demonstrated that clinician judgment had a poor sensitivity of only 29% (95% CI 18-43%), it excluded this crucial population [42]. In this study, the sensitivity and specificity of clinician diagnosis and CDC's definition of ILI compared to PCR were determined in those recommended to receive antiviral treatment according to CDC guidelines. Additionally, appropriate use of antivirals was evaluated.

METHODS

Study design

This was a prospective observational cohort study to determine the sensitivity and specificity of clinician diagnosis and the CDC criteria for ILI compared to PCR testing for influenza in adult ED patients with an acute respiratory illness who met CDC criteria for recommended influenza antiviral treatment. The study was conducted at an urban, university-affiliated tertiary care ED with an ED volume of over 60,000 annual patient visits. It was approved by the Johns Hopkins Institutional Review Board.

Study Population

All adult patients presenting to the ED between December 2012 and March 2013 during study enrollment hours, with a chief complaint of fever or any respiratory-related symptom, were screened by trained, dedicated study coordinators. Study enrollment hours were Monday through Friday from 9am to 5pm during the month of December, and from 9am to 11pm during January, February, and March. Subjects were screened for the following inclusion criteria: 1) 18 years of age or older; 2) symptoms of an acute respiratory tract infection defined as new symptoms of cough, sinus pain, nasal congestion, rhinorrhea, sore throat, shortness of breath, or fever which developed over the previous 2 weeks; and 3) one or more of the following CDC indications for influenza treatment: hospital or observation admission, potential influenza related complications (i.e. pneumonia), age 65 years old or older, chronic pulmonary disease, cardiovascular disease (except hypertension alone), renal disease, hepatic disease, hematologic disease, metabolic disorders, neurologic and neurodevelopment conditions, immunosuppression (including that caused by medications or HIV infection), pregnant or less than two weeks postpartum, American Indians or Alaska natives, morbid obesity (body mass index ≥40), or resident of a chronic-care facility. Patients were excluded if they had prior diagnosis of influenza within the previous 2

weeks, did not speak English, were unable to provide informed consent, or were unable to provide follow-up contact information.

Study Protocol

Consenting subjects were asked to complete a written structured questionnaire regarding basic demographics, current symptoms, and past medical history. A nasopharyngeal swab was collected from each patient, placed in viral transport media (MicroTest M4RT, Remel, Lenexa, KS), aliquoted, frozen to minus 70 degrees, and stored for subsequent influenza testing with a PCR assay (Prodesse ProFlu+, Hologic Gen-probe Incorporated, San Diego, CA). ED providers were blinded from influenza PCR test results.

In order to obtain the clinician diagnosis, the ED provider for each subject was asked to respond "Yes" or "No" to the following question: "Do you think this patient has influenza?". Study coordinators were instructed to pose this question to providers as close to the time of subject disposition from the ED as possible but prior to the result of provider-requested rapid influenza testing (antigen detection by fluorescence microscopy).

Following the ED visit, data were extracted from the hospital's electronic medical record (EMR), which included both ED and inpatient documentation. Data were entered into a standardized, closed entry, Microsoft Excel (Microsoft Corporation, Redmond, Washington) database and included initial ED vital signs, ED laboratory and culture data, ED radiologic findings, ED management, disposition from the ED, and final (ICD 9) ED diagnoses.

Measurements

Presence or absence of ILI was based upon the CDC criteria for ILI of a fever equal to or greater than 37.8 Celsius with either cough or sore throat [43]. Antibiotic and antiviral administration

was recorded as either none, administered in the ED, or discharged with a prescription. A subject was considered to have received ED antiviral or antibiotic treatment if they were administered an antiviral or antibiotic in the ED, or discharged from the ED with an antiviral or antibiotic prescription.

Data Analysis

Data were analyzed using basic descriptive statistics including proportions and percentages for dichotomous variables, median and interquartile range for continuous data, sensitivity, specificity, and likelihood ratios. Data were analyzed using Stata Statistical Software: Release 11 (Stata Corp LP, 2009. College Station, TX).

RESULTS

Of the 303 subjects enrolled, 270 (89%) were included in the final analysis. Thirty-three patients who were initially enrolled but not included in the final analysis were: 1 patient found on detailed history not to meet all inclusion criteria; 11 who did not have PCR testing performed and; 21 who did not have a clinical provider diagnosis response completed prior to the return of provider-requested influenza testing, or prior to patient disposition from the ED.

Table 3 displays the basic demographics of the study subjects, as well as indications for potential antiviral treatment according to the CDC recommendations. The most common CDC indications for antiviral treatment were chronic pulmonary disease (64%), hospital admission (43%), chronic metabolic disease such as diabetes mellitus (30%), and immunosuppression (26%). Recent influenza vaccination was reported by 146 (54%) subjects, including 15 (36%) influenza positive patients. One third of the subjects (88) presented with symptoms for less than 48 hours.

Of the 270 subjects analyzed, 42 (16%, 95% CI 11%-20%) had influenza according to PCR testing. Of subjects with confirmed influenza, 27 (64%) had Influenza A and 15 (36%) had Influenza B. Clinicians correctly diagnosed 15/42 subjects found to have influenza by PCR, and incorrectly diagnosed influenza in 50/228 subjects who were negative for influenza by PCR (Table 4). Clinical diagnosis therefore had a sensitivity of 36% (95% CI 22-52%) and a specificity of 78% (95% CI 72-83%). For patients who presented within 48 hours of symptom onset, the sensitivity of clinician diagnosis was 39% (95%CI 14-69%). Similarly, the symptoms of ILI correctly identified 13/42 subjects with PCR confirmed influenza, and incorrectly identified 27/228 subjects who were negative for influenza by PCR (Table 4). Thus, ILI had an overall sensitivity of 31% (95%CI 18-47%), and a sensitivity of 46% (95%CI 19-75%) for patients presenting within 48 hours of symptom onset (Table 5). Only 18 patients had an EMR recorded diagnosis of influenza, which had a sensitivity of 26% (95% CI 14-42%) and specificity of 97% (95% CI 94-99%).

In this population of patients recommended to receive antiviral treatment according to CDC guidelines, only 15 (36%) subjects with PCR-confirmed influenza received antiviral treatment from the ED, with 11 (26%) starting the medication while still in the ED. Interestingly, 22 (52%) of subjects with PCR-confirmed influenza received antibiotic treatment from the ED, 4 of whom had an infiltrate on chest X-ray and a corresponding diagnosis of pneumonia. Among the 13 patients who had influenza and symptoms for less than 48 hours, only 6 (46%) received ED antiviral treatment, 3 (23%) of whom initiated treatment while still in the ED.

LIMITATIONS

This study was performed at a single academic medical center, thus potentially limiting its generalizability to other geographic areas and practices. Another potential limitation is the method of obtaining the clinician diagnosis. This study sought to determine the accuracy of

clinician diagnosis of influenza in the absence of ancillary influenza testing. ED clinicians were queried prior to the result of routine (i.e., provider requested) influenza testing if it was performed. We obtained ED clinician diagnosis as close as possible to final patient disposition so the clinician would have the full benefit of ancillary tests such as basic laboratory tests and diagnostic imaging. It is possible that the clinician obtained additional clinical information (e.g. new fever, and/or radiographic or other laboratory testing) after giving their study-related clinical diagnosis, which may have affected their diagnosis. However, the EMR diagnosis of influenza, which was recorded after clinicians had all available information, had similar or even lower sensitivity (26%; 95% CI 14-42%) than the reported clinician diagnosis (36%; 95% CI 22-52%).

DISCUSSION

This study evaluated the sensitivity and specificity of ED clinician diagnosis of influenza in adult ED patients who are recommended to receive antiviral treatment according to CDC guidelines. Overall, clinical diagnosis of influenza by ED clinicians had poor sensitivity and specificity. The low sensitivity (36%; 95% CI 22-52%) is similar to that reported previously by Stein et al (29%) [42]. Unlike Stein and colleagues however, the sensitivity of clinical diagnosis did not improve in the subset of patients who presented with less than 48 hours of symptoms. The specificity for clinician diagnosis in this study (78%; 95% CI 72-83%) was lower than that found in previous reports (92%; 95% CI 87-95%). The reduced specificity is likely related to the relatively higher level of medical complexity of our study population. The population in this study included those with current pneumonia or a history of pulmonary disease, which may have led to an increase in false positive influenza diagnoses.

Clinicians may rely on CDC's definition of ILI when considering the diagnosis of influenza in clinical practice. Although previous studies have demonstrated that the CDCs definition of ILI has a sensitivity of 55-69% in a broad population, our evaluation found a substantially lower

sensitivity (31%; 95% CI 18-47%) [49]. The decreased sensitivity of ILI is likely related to the patient population which included several patient groups that may not be able to mount an appropriate immune response or fever (e.g. immunosuppressed, elderly). This is consistent with previous findings that the sensitivity of symptoms such as cough and fever for diagnosing influenza are decreased in elderly patients (30%) compared to the larger population (64%) [24,25,50]. Thus, in those recommended to receive antiviral treatment in whom diagnosis is most essential, the classic symptoms of ILI are less reliable. This finding has important implications for clinical outcomes.

Previous work has demonstrated poor compliance with CDC recommendations regarding antiviral treatment. Hsieh et al. found that only 50% of ED patients with a final ED diagnosis of influenza, who met CDC criteria for recommended antiviral treatment, actually received it [31]. As this evaluation demonstrates, ED clinicians' diagnosis of influenza is a poor proxy for influenza. In our evaluation, the final ED diagnosis of influenza (as recorded in the electronic medical record) is only 26% sensitive for PCR-confirmed influenza. Thus, the actual compliance with CDC recommendations is likely to be even lower than previous estimates, because those estimates do not take into account patients who had influenza, but were not diagnosed due to the poor sensitivity of clinicians' diagnosis. This is confirmed by the current study, which demonstrates that only 36% of subjects with laboratory confirmed influenza, from a population of those recommended to receive antiviral treatment according to CDC guidelines, received antiviral treatment. In fact, a patient with influenza was more likely to receive antibiotic (52%) than antiviral (36%) treatment.

Previous literature has shown that antiviral treatment is most effective when administered closer to the time of symptom onset [18-21]. Previous recommendations to initiate antiviral treatment within 48 hours was recently extended in the CDC guidance, especially in patients with influenza

related complications, as multiple observational studies have shown that antiviral treatment up to 5 days from symptom onset decreased mortality in admitted patients [11-13]. Despite this change in recommendations, many providers consider treatment only if the patient has had under 48 hours of illness, especially in non-hospitalized patients. In our study population, 33% of the patients presented in less than 48 hours, of whom 31% had laboratory confirmed influenza. Of those patients, 46% received antiviral treatment.

In addition to undertreating subjects with influenza, this study demonstrated antiviral overtreatment in patients without influenza, which raises concerns of increasing antiviral resistance. Eleven percent of patients who did not have influenza received antiviral treatment. Of the 40 patients who received an antiviral, more of them had a negative influenza test (25) than a positive test (15). Due to the lack of rapid accurate influenza testing, the CDC recommends initiating antiviral treatment for all patients with existing or increased risk of influenza related complications in whom influenza suspected, regardless of influenza testing [4,28]. These recommendations are based on the assumption that the prolonged time to result of accurate conventional or batched molecular diagnostic tests will significantly delay antiviral treatment, which is most effective when given close to the time of symptom onset. Antigen-based rapid tests have poor sensitivity requiring additional testing if negative, also potentially increasing the time to antiviral treatment. Though these recommendations are well founded, they result in extensive overtreatment. Both over and under treatment could be substantially improved by integrating highly sensitive, molecular-based rapid tests into current clinical care.

CONCLUSION

Overall, this study evaluated the diagnosis and treatment of influenza in adult ED patients who met CDC criteria for recommended antiviral treatment. In this target population, both ED clinician diagnosis, and the classic CDC definition of ILI have poor sensitivity for influenza. ED

management of influenza demonstrates both under-treatment, in those with confirmed influenza (36%), and overtreatment in those without influenza (11%). Clinician's inability to appropriately administer antivirals is likely related to the underlying challenges of accurate diagnosis. Integrating new highly-sensitive rapid diagnostic tests for influenza could improve accuracy of both diagnosis and treatment of influenza in the ED.

Table 3: Aim 2 Subject Characteristics

	All *n (column %)*	Influenza Positive *n (column %)*	Influenza negative *n (column %)*
Number of Subjects	270	42	228
Age (Years)	50 (38-58)	43.5 (32-55)	50.5 (39.5-58)
Male Gender	110 (41%)	15 (36%)	95 (42%)
Race			
African American	220 (81%)	34 (81%)	186 (82%)
White	41 (15%)	5 (12%)	36 (16%)
Other	5 (1.9%)	1 (2.4%)	4 (1.8%)
CDC Guidelines (indication for antiviral treatment)			
Hospital admission	117 (43%)	16 (38%)	101 (44%)
Complications/Pneumonia	32 (12%)	4 (9.5%)	28 (12%)
Age 65 or greater	37 (14%)	5 (12%)	32 (14%)
Chronic Disease			
Pulmonary	172 (64%)	17 (40%)	155 (68%)
Cardiovascular	62 (23%)	5 (12%)	57 (25%)
Renal	31 (11%)	6 (14%)	25 (11%)
Hematologic	22 (8.1%)	4 (9.5%)	18 (7.9%)
Metabolic	82 (30%)	11 (26%)	71 (31%)
Neurologic	26 (9.6%)	7 (17%)	19 (8.3%)
Immunosuppression	71 (26%)	13 (31%)	58 (25%)
Pregnancy	1 (0.4%)	1 (2.4%)	0 (0%)
Morbid Obesity	23 (8.5%)	3 (7.1%)	20 (8.8%)
Resides in Nursing Home	6 (2.2%)	0 (0%)	6 (2.6%)
Native American	0 (0%)	0 (0%)	0 (0%)
Influenza Vaccination	146 (54%)	15 (36%)	131 (57%)
Symptoms less than 48 hours	88 (33%)	13 (31%)	75 (33%)

CDC – Centers for Disease Control and Prevention

Table 4: Emergency Department Influenza Diagnosis and Treatment

	All *n (column %)*	Influenza Positive *n (column %)*	Influenza Negative *n (column %)*
Number of Subjects	270	42	228
Diagnosis			
Clinician diagnosis of influenza	65 (24%)	15 (36%)	50 (22%)
Influenza-like Illness	40 (15%)	13 (31%)	27 (12%)
Final ED diagnosis of influenza	18 (6.6%)	11 (26%)	7 (3.1%)
ED treatment			
Antiviral given in ED	31 (11%)	11 (26%)	20 (8.8%)
Antiviral prescription only	9 (3.3%)	4 (9.5%)	5 (2.2%)
Any ED antiviral treatment	40 (15%)	15 (36%)	25 (11%)
Any ED antibiotic treatment	123 (46%)	22 (52%)	101 (44%)

Table 5: Test Characteristics of Emergency Department Clinician Diagnosis and Influenza-Like Illness

	Overall N=270	Symptom onset < 48 hours n=88	Symptom onset > 48 hours n=182
Influenza Prevalence	16% (11-20%)	15% (8-24%)	16% (11-22%)
Clinician Diagnosis			
Sensitivity	36% (22-52%)	39% (14-69%)	35% (18-54%)
Specificity	78% (72-83%)	83% (72-90%)	76% (68-82%)
Positive Likelihood Ratio	1.63 (1.01-2.62)	2.22 (0.95-5.17)	1.43 (0.80-2.53)
Negative Likelihood Ratio	0.82 (0.65-1.04)	0.74 (0.48-1.12)	0.86 (0.65-1.14)
Influenza-like Illness			
Sensitivity	31% (18-47%)	46% (19-75%)	24% (10-43%)
Specificity	88% (83-92%)	88% (78-94%)	88% (82-93%)
Positive Likelihood Ratio	2.61 (1.47-4.64)	3.85 (1.65-8.99)	2.05 (0.94-4.46)
Negative Likelihood Ratio	0.78 (0.64-0.96)	0.61 (0.37-1.02)	0.86 (0.70-1.06)

Aim 3: Performance of Rapid Molecular Influenza Testing

INTRODUCTION

Influenza is responsible for over 200,000 hospitalizations and 3,000-49,000 deaths in the United States each year [2,3]. However, morbidity and mortality associated with influenza infections could be decreased by timely antiviral treatment. The CDC, WHO and IDSA recommend antiviral treatment for patients with a severe or complicated course, namely those requiring hospitalization, as well as those at high risk of complications, including patients at the extremes of age (<5 years old, >65 years old), patients residing in a chronic care facility, and those with specific chronic medical conditions, immunosuppression, pregnancy, morbid obesity, or Native American heritage [4-6]. Unfortunately, compliance with these guidelines remains low, partially due to the challenge of timely and accurate diagnosis of influenza infection [28,31].

The majority of patients with influenza and other respiratory viruses seek care in episodic outpatient care settings such as EDs or other urgent and primary care settings, where rapid diagnosis and treatment is critical [40]. Due to non-specific symptoms, provider clinical diagnosis of influenza has low sensitivity, leading providers to rely on diagnostic testing for an accurate influenza diagnosis [42]. Most commercially available real-time polymerase chain reaction (rt-PCR) tests are typically run in batch, and require several hours to complete, delaying results. The current antigen detection tests are rapid, but have poor to moderate sensitivity, ranging from 10-70% [23]. Molecular-based rapid influenza tests, such as the GeneXpert Xpert Flu (Cepheid, Sunnyvale, CA, USA), may have clinical utility by filling this diagnostic gap, since it has a reported time to result of approximately 80 minutes and significantly higher sensitivity than rapid antigen detection tests [27].

The majority of previous performance evaluations of Xpert Flu demonstrate an overall high sensitivity (90-100%) and specificity (99-100%) for influenza A (5 out of 7 studies), Influenza A 2009 H1N1 (5 out of 8 studies), and Influenza B (4 out of 6 studies) [27,51-58]. Four notable exceptions include Popowich et al., who report moderate sensitivity (87%) for H1N1 [53]; Salez et al., who initially reported a lower sensitivity for influenza B (81%) [51], but later found improved sensitivity (95%) with a newer version of the assay [52]; Li et al., who reported lower sensitivity across all influenza types [A (79%), A 2009 H1N1 (75%) and B (77%)] [57]; and Pierro et al who found extremely low sensitivity for influenza A (38%) and moderate sensitivity for 2009 H1N1 (86%) [58]. Each of these previous reports, with the exception of Pierro et al., fails to clearly identify and define the test population in which the test was evaluated. Pierro et al, used samples from hospitalized patients, but demonstrated markedly different results from the previous evaluations and was limited by a small sample size (N=60). Thus the performance of rapid PCR-assays, such as Xpert Flu, in the recommended target population of patients with existing or at increased risk of influenza related complications and undifferentiated respiratory symptoms, remains unclear, particularly in the ED setting.

Prior to integration into routine clinical use, the clinical performance of Xpert Flu in the target population requires evaluation. Though clinicians in the outpatient episodic care setting may test an array of patients, accurate rapid influenza testing with Xpert Flu test would be most important in patients where the test result would impact clinical management, namely those who meet CDC criteria for antiviral therapy and are at risk for potential influenza related complications. Several of these conditions, such as advanced age and pneumonia, have been reported to be associated with decreased sensitivity of rapid antigen-based testing, highlighting the importance of evaluating Xpert Flu in this population [59]. In order to fully translate molecular-based rapid testing into clinical practice, we prospectively evaluated the sensitivity and specificity of Xpert

Flu in adult ED patients with an acute undifferentiated respiratory illness, who meet CDC criteria for recommended antiviral treatment.

METHODS

Study population and sample collection

Adult ED patients with an undifferentiated acute respiratory illness who met CDC criteria for recommended influenza antiviral treatment at an urban, university-affiliated tertiary care ED were prospectively enrolled between December 2012 and March 2013. Enrolled subjects met the following inclusion criteria: 1) 18 years of age or older; 2) symptoms of an acute respiratory tract infection, defined as new symptoms of cough, sinus pain, nasal congestion, rhinorrhea, sore throat, shortness of breath, or fever which developed over the previous 2 weeks; and 3) one or more of the following CDC indications for influenza treatment: hospital or observation admission, potential influenza related complications (i.e. pneumonia), age 65 years old or older, chronic pulmonary disease, cardiovascular disease (except hypertension alone), renal disease, hepatic disease, hematologic disease, metabolic disorders, neurologic and neurodevelopment conditions, immunosuppression (including that caused by medications or HIV infection), pregnant or less than two weeks postpartum, American Indians or Alaska natives, morbid obesity (body mass index ≥40), or resident of a chronic-care facility. Patients were excluded if they had prior diagnosis of influenza within the previous 2 weeks, did not speak English, were unable to provide informed consent, or were unable to provide follow-up contact information.

Following written consent, as approved by the Johns Hopkins University institutional review board (IRB), subjects completed a questionnaire detailing their current symptoms, past medical history, and basic demographics. A nasopharyngeal swab was collected and placed in viral

transport media (MicroTest M4RT, Remel, Lenexa, KS, USA). Following collection, viral transport media was aliquoted, and stored at -70°C for subsequent testing.

Molecular Testing

To eliminate the variable of elapsed time between sample collection and test performance, all samples were aliquoted into three tubes, stored frozen, and tested after a single freeze thaw. Testing by ProFlu+ (Hologic Gen-probe Incorporated, San Diego, CA, USA) and Xpert Flu (Cepheid, Sunnyvale, CA) was performed according to manufacturers' instructions (with the exception of samples with indeterminate Xpert Flu results) after enrollment was complete [60,61]. All testing was performed in a blinded fashion. Samples with indeterminate Xpert Flu results were not re-tested due to volume constraints; these samples were omitted from the final analysis. Discordant samples were evaluated using RT-PCR/ESI-MS via the PLEX-ID (Abbott Laboratories, Abbott Park, IL) per manufacturer instructions. Nucleic acid extraction was performed utilizing the Arrow Viral NA kit (Diasorin, Inc. Stillwater, MN), and extracted nasopharyngeal samples were amplified and analyzed utilizing the PLEX-ID RVS 2.5 kit as previously described [62]. Positive PLEX-ID detection were defined as reactions having a Q score >0.9.

Statistical Analysis

For the primary analysis, Prodesse ProFlu+ was considered the comparative standard. A similar subgroup analysis was performed evaluating patients with the highest acuity illness (those admitted to the hospital). In a secondary evaluation, discordant results were further evaluated with RT-PCR/ESI-MS with the two tests in agreement considered as the comparative standard. Data were analyzed utilizing basic descriptive statistics including proportions and percentages for dichotomous variables, median and interquartile range for continuous data, sensitivity, specificity,

and likelihood ratios. Data were analyzed using Stata Statistical Software: Release 11 (StataCorp LP, 2009. College Station, TX).

RESULTS

Of 303 subjects enrolled, 281 had sufficient data to be included in the final analysis. Of the 22 excluded subjects: 1 subject was found not to meet full inclusion criteria, 11 did not have ProFlu+ testing performed, 5 did not have Xpert Flu testing, and 5 had Xpert Flu tests which resulted in an error code. Among the 281 subjects included in the final analysis, 126 (44%) were admitted to the hospital. Additional details regarding the included subjects and the criteria for CDC recommended antiviral treatment are listed in Table 6.

Of 281 subjects, 43 (15%) were positive for influenza by ProFlu+, of which 28 were positive for Influenza A and 15 positive for Influenza B. Compared to ProFlu+, Xpert Flu had a sensitivity of 95.3% (95% CI 84.2-99.4) overall, 96.4% (95% CI 81.7-99.9%) for influenza A, and 93.3% (95% CI 68.1-99.8%) for influenza B (Table 7). Although Xpert Flu also detects 2009 H1N1, none of the samples were positive for influenza A, 2009 H1N1.

Two discordant results were obtained for influenza A and influenza B. For both viruses, one sample was positive by ProFlu+ but negative by Xpert Flu, and one sample was positive by Xpert Flu and negative by ProFlu+. Table 8 displays the concordant and discordant results. Discordant sample testing with RT-PCR/ESI-MS agreed with ProFlu+ testing with one exception; one sample was positive for influenza A by ProFlu+, negative for influenza A by Xpert Flu, and negative for influenza A by PLEX-ID. Using an operational gold standard definition of two tests in agreement, Xpert Flu had an overall sensitivity of 97.6% (95% CI 87.4-99.9%) and specificity of 99.2% (95% CI 97.0-99.9%). For Influenza A, the sensitivity of Xpert Flu was 100% (95% CI 87.2-100%) and specificity was 99.6% (95% CI 97.8-100%).

Restricting the comparison to the patients with the highest acuity of illness, the 126 subjects who were admitted to the hospital, Xpert Flu had 100% sensitivity and specificity for both influenza A [sensitivity 100%, 95%CI 76-100%; specificity 100%, 95% CI 97-100%] and influenza B [sensitivity 100%, 95%CI 57-100%; specificity 100%, 95% CI 97-100%]. That is, all 12 subjects with influenza A and 5 subjects with influenza B were verified as ProFlu+ and Xpert Flu with no discordant results.

LIMITATIONS

This evaluation of Xpert Flu was performed in a single, inner-city ED, and did not include otherwise healthy patients or children, thus potentially reducing the generalizability to all patients in various geographic locations. Additionally, of the 286 Xpert Flu tests performed, 5 (1.7%) resulted in an error code, leading to an indeterminate result. Manufacturer instructions state that these tests are to be repeated, which was not performed in this study due to inadequate sample volume. Although errors were low in this study (1.7%), delayed results can subsequently impact diagnosis and care.

DISCUSSION

We evaluated the clinical performance of Xpert Flu in adult ED patients with an acute undifferentiated respiratory illness, who met CDC criteria for recommended antiviral treatment. This is the first time this rapid diagnostic test has been evaluated in a high acuity ED population, where undifferentiated patients are evaluated and treated. In this high acuity target population, Xpert Flu had an overall sensitivity of 95.3% (95% CI 84.2-99.4) and specificity of 99.2% (95% CI 97.0-99.9%) when compared to ProFlu+. Similar high sensitivity and specificity was seen for both influenza A [sensitivity 96.4% (95% CI 81.7-99.9%)] and influenza B [sensitivity 93.3% (95% CI 68.1-99.8%)]. Using an operational gold standard of two tests in agreement, the sensitivity of Xpert Flu increased to 97.6% (95% CI 87.4-99.9%) overall and 100% (95% CI

87.2-100%) for influenza A. Integration of this rapid high sensitivity diagnostic test into ED practice for influenza could improve provider decision making and subsequent patient management.

The observed sensitivity and specificity of Xpert Flu in this high acuity ED population was similar to what has been reported by several previous studies performed in a more general patient population [27,51-56]. From a clinical viewpoint, diagnosing influenza and initiating antiviral treatment in the admitted population is most critical, as antivirals have shown substantial benefit in this population including a reduction in mortality [11-13]. One previous study demonstrated poor performance of Xpert Flu amongst hospitalized patients; however, our study showed excellent performance amongst the subpopulation of admitted patients with 100% sensitivity and specificity [58]. This previous evaluation used a PCR-based, laboratory developed test as a comparator, which may have been less accurate than the FDA approved Prodesse ProFlu+ assay used in this evaluation, resulting in the observed difference in sensitivities.

CONCLUSION

Overall, when prospectively evaluated in a population of undifferentiated ED patients with existing or at increased risk of influenza related complications, Xpert Flu demonstrated high sensitivity and specificity. Overall sensitivity compared to Prodesse ProFlu+ was 95.3% (95% CI 84.2-99.4) with similar high sensitivities for influenza A [96.4% (95% CI 81.7-99.9%)] and influenza B [93.3% (95% CI 68.1-99.8%)]. Specificity was 99-100% both overall, and for influenza A and influenza B individually. When evaluating a subpopulation of high acuity patients who were subsequently admitted for inpatient hospitalization, Xpert Flu had an overall sensitivity and specificity of 100%. With a demonstrated high level of sensitivity and specificity in a clinical ED population, and a rapid turn-around time of 80 minutes, Xpert Flu has significant

potential to aid clinicians working in episodic care settings such as EDs or urgent care centers where rapid influenza diagnosis and management can be challenging.

Table 6: Aim 3 Subject Characteristics

	n (column %)
Number of Subjects	281
Age (Years)	50 (38-58)
Male Gender	119 (42%)
Race	
African American	228 (81%)
White	44 (15%)
Other	9 (3.2%)
CDC Guidelines for antiviral treatment	
Hospital admission	123 (44%)
Complications/Pneumonia	19 (6.8%)
Age 65 or greater	39 (14%)
Chronic Disease	
Pulmonary	176 (63%)
Cardiovascular	64 (23%)
Renal	32 (11%)
Hematologic	23 (8.2%)
Metabolic	70 (25%)
Neurologic	25 (8.9%)
Immunosuppression	72 (26%)
Pregnancy	1 (0.4%)
Morbid Obesity	25 (8.9%)
Resides in Nursing Home	7 (2.5%)
Native American	0 (0%)

CDC – Centers for Disease Control and Prevention

Table 7: Test Characteristics of Xpert Flu compared to Prodesse ProFlu+

	All Influenza n=43	Influenza A n=28	Influenza B n=15
Influenza Prevalence	15% (11-20)	10% (6.7-14.1)	5.3% (3.2-8.7)
Test Characteristics			
Sensitivity	95.3 (84.2-99.4)	96.4 (81.7-99.9)	93.3 (68.1-99.8)
Specificity	99.2 (97.0-99.9)	99.6 (97.8-100)	99.6 (97.9-100)
Likelihood ratios			
Positive	113 (28.5-452)	244 (35-1727)	248 (35-1764)
Negative	0.05 (0.01-0.18)	0.04 (0.01-0.25)	0.07 (0.01-0.45)
Predictive Value			
Positive	95.3 (84.2-99.4)	96.4 (81.7-99.9)	93.3 (68.1-99.8)
Negative	99.2 (97.0-99.9)	99.6 (97.8-100)	99.6 (97.9-100)

Table 8: Concordance and discordance between Prodesse ProFlu+ and Xpert Flu

ProFlu+	**Xpert Flu**			Total
	Influenza A	Influenza B	Negative	
Influenza A	27	0	1*	28
Influenza B	0	14	1†	15
Negative	1*	1*	236	238
Total	28	15	238	281

* On discordant analysis, sample was negative for influenza by PLEX-ID

† On discordant analysis, sample was positive for influenza B by PLEX-ID

Aim 4: Cost Utility of Influenza Diagnosis and Management

INTRODUCTION

Each year, influenza affects approximate 5-20% of the United States population causing over 200,000 hospitalizations and 3,000 – 49,000 deaths [1-3]. Fortunately, the past 15 years has brought both new antiviral medications and increasing evidence of their effectiveness in specific populations. While the benefit of treatment is questionable in healthy individuals, evidence supports antiviral use for patients considered at increased risk for, or those with evidence of existing complications, and routine use in those populations is recommended by the CDC, the WHO and IDSA [4-6]. Recent CDC guidelines recommend antiviral treatment specifically for patients with a severe or complicated clinical course, requiring hospitalization, or considered at high risk for influenza complications – including those under 2 years old or 65 years of age or above, residing in a chronic care facility, with a chronic medical condition, pregnant or morbidly obese [4]. Antiviral medications are currently recommended to be given within 48 hours of symptom onset, and appear to have increased effectiveness when given closer to the time of symptom onset [18-21]. Despite the evidence that shortening the time between symptom onset and antiviral administration results in improved outcomes, practical ability to diagnose and treat influenza within this 48 hour time frame is difficult due to timing of patient presentation, medication costs, and lack of reliable rapid diagnostic tools.

In an attempt to fill the need for expediting definitive diagnosis, several rapid influenza tests have been developed. Previous antigen-based assays have been limited by moderate to poor sensitivities ranging from 10-70%, and current CDC guidelines accordingly require additional testing in the setting of a negative rapid influenza test [23]. Given the lack of high performance tests that yield rapid results, physicians frequently make a presumptive diagnosis of influenza

based on clinical presentation. Previous studies which have attempted to validate the use of clinical symptoms to diagnose influenza however, have demonstrated overall poor sensitivity and specificity. As example, one of the largest studies showed that a combination of fever and cough had a sensitivity of 64% and a specificity of 67% [24]. New molecular-based rapid influenza tests use PCR-based detection, yield results in 80 minutes, and have recently obtained FDA approval for use in clinical settings. Previous validation studies performed in comparison to a rt-PCR gold standard report a sensitivity of 91.2% (95% CI: 85.1-95.4) and specificity of 99.4% (95% CI: 96.7-100) [27]. Although promising, and with significantly improved performance relative to current rapid influenza diagnostic tests seen in clinical settings, molecular-based rapid tests have not yet been integrated into clinical practice, largely due to concerns over the clinical utility of testing relative to existing approaches, and the associated increased cost.

The majority of the cost-effectiveness analyses of influenza treatment have focused on healthy adults. These studies often conclude that the most cost effective strategy is to treat all patients with antiviral medications, driven largely by a 1-2 day reduction in symptoms and decrease in lost work costs [35,36]. Cost-effectiveness studies examining patients at increased risk of influenza complications have more varied outcomes which depend on influenza prevalence. When the prevalence of influenza is low, treating influenza based on the result of an influenza test is often the most cost effective method; however with increasing influenza prevalence, treating all patients with suspected influenza without testing becomes most cost effective [37,38]. When considering influenza testing, these studies have considered the accurate but expensive gold standard rt-PCR testing, or the less-expensive but inaccurate older antigen-based rapid testing. The emergence of new accurate molecular-based rapid tests, with a more moderate price and improved accuracy could potentially shift the cost-utility balance of influenza testing.

Previous cost-effectiveness studies evaluating influenza testing in high risk patients have restricted evaluation of those patients with ILI, most commonly defined as fever with cough or sore throat [35-38]. Limiting the population of included patients to those with ILI, which has been shown to have relatively poor sensitivity and specificity for influenza, provides an incomplete analysis as it does not accurately reflect the entire influenza population which may benefit from influenza testing and treatment in practice. A more comprehensive appreciation of the cost-effectiveness of influenza testing and treatment requires inclusion of a population with the broader criteria of acute onset respiratory or febrile illness, to ensure maximal inclusion of influenza patients and reflect the entire population that may benefit from testing and/or antivirals. Additionally, there remains limited evidence of the cost-effectiveness of influenza testing and treatment in more acute care settings such as the ED where the overall patient acuity mix is higher with increased rates of hospital admission, and hence increased rates of influenza-related complications and death, additionally impacting the balance between influenza testing and treatment.

We sought to determine the relative cost-effectiveness of influenza testing and treatment strategies for adults who present to the ED with an acute respiratory illness and meet 2011 CDC criteria for recommended influenza treatment. We performed an incremental evaluation of four separate influenza testing and antiviral treatment regimens using a cost-utility based approach: 1) Treat none, 2) Treat based on provider judgment, 3) Treat based on results of a molecular-based rapid diagnostic test, and 4) Treat all.

METHODS

Model Overview

We constructed a cost-utility decision analysis model using TreeAge Pro (TreeAge Software, Inc.) to make an incremental comparison among 4 influenza testing and antiviral treatment strategies: 1) Treat none, 2) Treat based on provider judgment, 3) Treat based on results of a molecular-based rapid diagnostic test, and 4) Treat all. This model considered patients presenting to the ED with symptoms of an acute respiratory infection who, if positive for influenza, would be recommended to receive antiviral treatment according to 2011 CDC guidelines; namely patients who are at risk or potentially have influenza-related complications. The analysis employed a societal perspective. To account for potential differences in mortality between treated and untreated influenza patients, we considered a lifetime horizon and discounted effects at 3% as recommended by the US Panel on Cost-Effectiveness in Health and Medicine [63].

Sensitivity analysis of the assumptions made in the base model were evaluated using a series of one-way sensitivity analyses displayed in a tornado diagram to highlight the relative impact of potential variation in each of these selected variables. In addition, we explored a range of influenza prevalence, as prevalence varies throughout the influenza season and has previously been shown to have a significant impact on cost-utility. Overall robustness of the conclusions based on the model was estimated via a probabilistic sensitivity analysis using a Monte Carlo simulation. This simulation used the stated variable ranges included in the one-way sensitivity analysis as well as 95% confidence intervals or inter-quartile ranges for the included variables as available. To interpret the results of the Incremental Cost-effectiveness Ratios (ICER) obtained from this analysis we adhered

to the generally accepted willingness to pay threshold of $50,000 per Quality Adjusted Life Year (QALY) [64].

Data and Assumptions

Influenza Prevalence

The decision analysis model, as shown in Figure 2, assumed the same influenza prevalence for each of the 4 potential treatment strategies. Although influenza prevalence varies throughout the season, the base prevalence of influenza used in this study (0.20), reflects the average prevalence of influenza amongst patients presenting to the ED with an acute respiratory infection between January and March [42]. Previous cost-effectiveness analyses have used the influenza prevalence in patients presenting with ILI (fever and cough or sore throat), a more rigorous criteria which increases prevalence, but also excludes one third of the patients with influenza [24,38]. Thus, a broader definition of acute respiratory virus is likely a more accurate definition of the desired testing population. In order to fully evaluate the cost-utility of the included testing and treatment options, we performed a secondary analysis over a large range of the potential prevalence of influenza: 0 to 0.6.

Patients who did not have influenza were not evaluated further as influenza testing or treatment would have no further impact on their care or outcomes. The only potential difference in the non-influenza patient's medical management would be due to side effects of the influenza antiviral medications. However, these medications have mild side effects which only very rarely would require additional medical evaluation or care and hence, would not increase costs [65].

Therefore, we did not consider side-effects of antiviral medication in treated patients, whether they have influenza or not.

This model assumed that all patients diagnosed with influenza, by either provider diagnosis or rapid test, were treated with antivirals. If patients received antiviral therapy, we assumed that therapy was initiated within 48 hours of symptom onset and continued at the dose and length of treatment recommended by the pharmaceutical manufacturer.

Influenza-related Complications

For all patients, it was also assumed that the proportion of patients admitted to the hospital from the ED is similar regardless of influenza diagnosis or treatment. For respiratory infections, ED clinician's decision-making regarding patient disposition is likely based on the patient's past medical history, appearance, physical examination, and laboratory and radiography results. We assumed that a rapid diagnostic confirmation of influenza would not impact the likelihood to admit a patient to the hospital, nor would administration of antivirals have sufficient time to act and affect the decision to admit to the hospital. As shown in Table 9, the proportion of influenza patients admitted to the hospital from the ED is estimated at 0.13 according to a retrospective evaluation of high risk patients presenting to the ED with influenza [31]. Alternate retrospective evaluations suggest the rate of admission in high risk patients could be as high as 0.57, which has been included as the peak range in the sensitivity analysis [66]. Subsequent complications after the decision of patient disposition from the ED are influenced by antiviral treatment and we thus evaluated for patients who have influenza but are not treated with antivirals compared to those with influenza who are treated with antivirals, as displayed in Table 9.

Hospitalized influenza patients can either die in the hospital or survive to discharge. Hospitalized influenza patients who are treated with an antiviral have a lower risk of death (4%) compared to those who are not treated with an antiviral (10%) [11]. The mortality benefit of antivirals was explored in the sensitivity analysis ranging from no benefit (0% difference in mortality between treated and not treated), to 12% difference in mortality between treated and non-treated individuals. After discharge from inpatient hospitalization, we assumed that the patient incurred no additional complications or expenses, and that influenza resolved without further effects.

Patients initially discharged from the ED either continued with no complications, had complications that required a repeat provider visit, or were subsequently hospitalized for influenza. Previous studies have shown that antivirals reduce the rates of complications [67,68]. It was thus assumed that patients with subsequent complications had a repeat provider visit to address the complication, and that no patients died at home. Several influenza complications require antibiotics, such as pneumonia, sinusitis, and otitis media, which have also been included in the analysis. Proportions of all complications and those requiring antibiotics are listed in Table 9 for treated and untreated influenza patients.

Quality Adjusted Life Years (QALYs)

Several studies have demonstrated that antiviral medications reduce the duration of symptoms by 1.5 – 2.5 days in both healthy and at-risk individuals [68]. One retrospective evaluation of the quality of life during a typical influenza illness using the EuroQol instrument found that influenza resulted in a 0.883 reduction in health-state compared to baseline, which was used to calculate the QALY's gained from reducing days of symptoms [69]. The QALYs gained from preventing a death depends upon the life expectancy. The adult population at high risk of influenza complications consists of a

wide array of risk variables including being over the age of 65 and having chronic or acute medical illness. It was assumed for the purposes of this analysis that the life expectancy of these patients is 15 years, an estimate based upon the age distribution of patients considered to be at high risk for influenza complications in previous studies [70]. However, a range of life expectancy from 10 years to 30 years is included in the sensitivity analysis to evaluate the effect of a range of potential values for this assumption. Using 3% discounting, 12.3 discounted QALYs are gained from preventing a death. The estimated QALY's used for this analysis are listed in Table 9.

Diagnostics

The clinical diagnosis of influenza is challenging to make despite numerous attempts to define a clear syndrome associated with influenza. The most commonly used set of symptoms are fever with cough or sore throat, which is only 64% sensitive [24]. In an undifferentiated population with an acute respiratory illness, provider decision making has a poor sensitivity (0.29) and specificity (0.92) [42]. During the initial two days of symptoms, when antivirals are most effective, provider sensitivity raises to 0.67. Thus, 0.67 was used as our base case sensitivity for provider decision making, but a range down to 0.29 was included in our sensitivity analysis. The new molecular-based rapid diagnostic tests have a far superior sensitivity (0.91) and specificity (1.00) [27].

Costs

Costs are estimated from a societal perspective and are in 2011 US dollars. Costs not initially found in 2011 US dollars were converted to 2011 US dollars using the Medical Care Consumer Price Index [71]. All costs occur within the first year of diagnosis and treatment as influenza is an acute disease, therefore no discounting was performed on costs. The cost of the initial ED visit was not included,

as this occurs before any specific treatment and testing, however the cost of testing and antiviral treatment was included for each patient receiving either.

It was assumed that patients treated with antivirals will receive a full treatment course with oseltamivir, which is estimated to cost $100.60 [72]. Oseltamivir is the most commonly used antiviral, however Zanamivir is slightly cheaper, and can also be used. Thus, these two prices included the sensitivity range for antiviral cost. We did not include costs for the amantadines as they are currently no longer recommended for influenza treatment due to high rates of resistance. Some patients require antibiotics and amoxicillin was selected as the representative antibiotic. The majority of subsequent infections include sinus infections, ear infections, and pneumonias, all of which can be treated with amoxicillin. Pneumonias in particular are often treated with more expensive antibiotics such as azithromycin or moxifloxacin for their added atypical bacterial coverage, and patients admitted to the hospital would likely require additional antibiotics to amoxicillin. These more expensive antibiotics were considered in the sensitivity analysis. Details on medication costs are listed in Table 9.

The expense associated with the rapid diagnostic test was estimated based on one of the new rapid influenza tests: Cepheid's Xpert Flu assay. The test is performed on a platform that is used for several other purposes in the hospital, and hence does not require specific purchasing for this purpose. This cost-utility analysis assumes an ED setting in a moderately-sized hospital which would therefore carry this platform. The overall price for the test includes 50$ for the test cartridge as stated by the manufacturer and $3 per test for labor based on an estimate from the hospital laboratory.

In the event of complications, the patient is likely to visit a medical professional either by returning to the ED, or seeing a primary care physician. If the patient was initially evaluated in the ED, they are likely to return to the ED for follow- up care for the same reasons they originally sought care in the ED; either they have no primary care physician, are unable to make an appointment to see their primary care physician, or feel that their illness requires the higher level of care available in the ED. Therefore, for the base case, the repeat visit was assumed to be in the ED. A cost of a repeat ED visit is estimated at $304 per a previously performed cost analysis study evaluating the cost of treating influenza patients in the ED which estimated the true cost of medical care including medications, supplies, and health professional fees. From this analyses we extracted the costs for patients over the age of 65 as a representative of our high risk patient population [66]. The cost of a primary care physicians visit, is substantially less, $72.11, as estimated by the American Medical association. To account for potential variability, we used these two figures in the sensitivity analysis.

Estimates of hospitalization costs were determined based on a previous cost analysis of the impact of seasonal influenza. This cost analysis used a probabilistic model to estimate costs [70]. To estimate hospitalization costs from this cost analysis, we used a weighted average of all medical care costs for all high risk adults who were hospitalized with influenza. This average was weighted by the number of cases in each age group who were hospitalized.

The population in question includes the elderly and those with chronic illnesses, so employment rates are likely to be lower than the general population. To that end, it is assumed that 50% of this population is employed and works 8 hours a day at the national mean hourly wage of $22.02 [73]. The actual proportion of employment and wage vary by location, so analysis was

performed with and without estimates of this indirect cost by allowing the sensitivity analysis range for this variable to decrease to 0. Days of missed work were estimated to be 10 days in patients without influenza treatment and 7 days in those who receive antivirals based on the time to return to normal activities previous studies [67].

RESULTS

Base Case Analysis

In the base case analysis, Treating None was clearly dominated by the other alternatives as it had the greatest cost ($1,260 95% CI 537-$4915) and least effectiveness (0 QALY saved by definition). Since there are other cheaper and more effective options, dominated alternatives, such as treating no patients, are not considered further as potentially cost-effective treatment options. Treatment based on provider judgment had the lowest cost ($1,153 95% CI $528-$4727) but also a low effectiveness (0.014 QALY saved 95% CI 0.009-0.209). This was followed by the treatment based on a molecular-based rapid diagnostic test with a slightly higher cost and effectiveness, and treating all patients, which had the highest cost, but also the highest effectiveness. As shown in Table 10, the results for each of these options are expressed as a cost-utility ratio, which demonstrates the cost to gain one QALY in that particular testing and treatment arm. Additionally, non-dominated alternatives are evaluated by the incremental cost-effectiveness ratio (ICER), which allows for comparison between two treatment arms, one of which has greater cost, but also greater effectiveness. The ICER demonstrates the additional cost for each additional QALY saved by moving from the lower cost to the higher cost option. The ICER between treatment based on provider judgment and treatment based on molecular-based rapid diagnostic testing was $1389/QALY saved, and the ICER between treatment based on molecular-based rapid diagnostic

testing and treating all, was $6249/QALY saved. Both of these ICERs are below the $50,000/QALY willingness-to-pay threshold generally accepted in the US.

Sensitivity Analysis

A one way sensitivity analysis of influenza prevalence demonstrated the significant impact of prevalence on cost-utility. At any potential prevalence greater than 0%, treating none was dominated by the other alternatives. At a prevalence above 23%, rapid diagnostic testing dominated provider judgment. At a prevalence above 26%, treating all dominated both provider judgment and rapid diagnostic testing. Thus, between 1% and 23% prevalence, provider judgment, rapid diagnostic testing, and treating all (in order of increasing cost) were potential options. Below a prevalence of approximately 3%, the ICER between provider judgment and molecular-based rapid diagnostic testing was greater than the $50,000/QALY threshold. Between 3% and 7% prevalence, the ICER between rapid diagnostic testing and treating all was greater than the $50,000/QALY threshold. Between 7% and 23% prevalence, the ICERs between provider judgment and molecular-based rapid diagnostic testing, and molecular-based rapid diagnostic testing and treating all, remained below the $50,000/QALY threshold. Adhering to the $50,000/QALY threshold, the most cost effective options are to treat based upon provider diagnosis from 0%-3% prevalence, treat based upon the results of molecular-based rapid testing from 3%-7% prevalence, and treat all above 7% prevalence. Figure 3 demonstrates the change in the ICER between treatment based on provider judgment and molecular-based rapid diagnostic testing and the ICER between treatment based on molecular-based rapid diagnostic testing and treat all, both compared to the willingness-to-pay threshold over the range of 1% prevalence until treat all dominates all alternatives at 26%.

Several one-way sensitivity analyses were performed to evaluate the impact of particular variables and assumptions on the ICER between treatment based on molecular-based rapid diagnostic testing and treating all. As seen in Figure 4, a tornado diagram was performed to evaluate sensitivity analysis of the remaining variables indicated in the methods section. A tornado diagram displays the results in order of potential impact on outcome with the variables with the greatest potential impact on the top and least impact on the bottom. The greatest effect came from the cost of antiviral treatment, where a cost of less than approximately $78 lead to the treat all option dominating over the treat based on a molecular-based rapid diagnostic test. Also with a significant impact on the outcome, if antiviral medications cause no improvement in mortality in admitted patients, then the ICER between rapid treatment and treating all is greater than the $50,000/QALY threshold indicating a potential benefit to treatment based on molecular-based rapid influenza testing. However, a mortality benefit of even 0.5% in admitted patients taking antiviral medications reduces the ICER to below the $50,000/QALY threshold. Notably, the remaining variables, probability of hospitalization, life expectancy, lost work costs, follow up visit costs, and cost of antibiotics did not have substantial impact on the most cost effective option.

The cost-effectiveness acceptability curve shown in Figure 5 summarizes the repeated Monte Carlo simulations. If a QALY had no economic value (willingness to pay equals zero), treatment based on provider judgment is the most economically preferred (saves the most money) in approximately 40 percent of repeated simulations, followed closely by treat all which is the most economically preferred in 38 percent of repeated simulations. This is followed by treatment based on molecular-based rapid diagnostic treating which is most efficient in 20 percent of the simulations. As the willingness-to-pay for QALYs increases to the commonly used $50,000/QALY, treating all is most economically preferred in almost all the simulations, while the remaining options are rarely most

economically preferred. Treating none is rarely the most cost-effective at any willingness-to-pay value

LIMITATIONS

True to any cost-effectiveness analysis, the results are limited by the assumptions used to create the model. This model only applies to patients are treated within 48 hours, as that is the commonly used time cut-off in much of the surrounding literature. This time limit thus decreases the generalizability of this analysis in patients who present or are potentially treated later in their disease course. Additionally, this analysis assumes that hospital admission and ED resource use is based upon the patient's clinical presentation and would not be impacted positively or negatively by a diagnosis of influenza, whether by clinical judgment or rapid test. Finally, this study utilizes a willingness to pay threshold of $50,000/QALY. The exact monetary value of a QALY is subjective, and while we use this standard threshold to aid in interpretation of the data, consideration of the actual monetary value of one QALY spent should be considered.

This analysis evaluates all adults at high risk of influenza-related complications, which is a varied group including those at risk due to age (age > 65), chronic illnesses, pregnancy, obesity, and those presenting with complications. It is likely that the cost-effectiveness of the 4 testing and treatment regimens examined here vary within the above-referenced risk groups based on age, past medical history and severity of illness. However, given the lack of literature describing influenza by specific subgroups, it is challenging to further reduce the population for specific sub-population calculations.

This study additionally assumes that any patient diagnosed with influenza – whether by rapid test or clinical evaluation – receives antiviral treatment as we only included patients who are recommended to receive treatment according to CDC guidelines. In reality this is not the case, as only 50% of high risk patients diagnosed with influenza in the ED receive antivirals [31]. Previous studies have shown that use of a rapid influenza test increases antiviral prescription rate, likely due to increased physician confidence in the diagnosis of influenza [74]. Hence the simplified assumption that all diagnosed patients will be treated, likely places rapid diagnostic testing at a disadvantage compared to how each of the testing and treatment arms would likely be implemented in a real clinical setting. Additional work is thus needed to evaluate the actual clinical utility of rapid testing and of provider diagnosis and the corresponding rates of antiviral prescription in high risk populations.

Finally, this model provides a cost-utility analysis to provide information on a population level; however, there are additional factors which may affect ultimate decision making. For example, this model does not attempt to model antiviral resistance patterns over time. Some of the considered treatment algorithms, such as treat all, would likely lead to increased selection for resistant variants, which may, along with other unmeasured factors, affect ultimate clinical decision making.

DISCUSSION

This incremental cost-utility analysis is the first ever evaluation of influenza testing and treatment in patients with a high risk of influenza complications presenting to the ED with an acute respiratory illness in the era of new highly sensitive rapid diagnostics. As demonstrated in previous analysis, the optimal method of influenza testing and treatment is highly dependent on

influenza prevalence, which changes rapidly throughout influenza season. Assuming a $50,000/QALY willingness-to-pay threshold, the most cost effective treatment option is treatment based on provider judgment from 0-3% prevalence, treatment based on a molecular-based rapid influenza test from 3-7% prevalence, and treating all at greater than 7% prevalence. These prevalences are based on a population presenting with a broadly defined respiratory illness, whereas previous studies have based their prevalence estimates on patients presenting with ILI, which is defined as fever and cough or sore throat [38]. While using the stricter criteria of ILI increases the prevalence of influenza in the testing population, it is also relatively insensitive, as it results in up to a third of influenza patients left untreated. Hence, the prevalence levels referenced in this analysis are likely to be lower than the corresponding influenza prevalence amongst a more select group of patients with ILI.

In considering the base case analysis, the three un-dominated treatment protocols, treat based on provider judgment, treat based on the results of a molecular-based rapid test, and treat all, do not differ substantial in terms of cost or effect, and are all superior to the treat none approach. Thus in patients with high risk or current influenza complications, who present to the ED in less than 48 hours, treatment with antivirals, whether based on provider judgment, rapid test, or treating all, results in decreased costs and increased benefit compared to not treating with antivirals. Which of the three treatment options is most cost effective depends on prevalence, and other individual and societal factors. In all but the lowest prevalences, treatment based on molecular-based rapid testing results in improved outcomes, compared to provider judgment, with a minimal additional cost of $1389/QALY in the base case scenario. The treatment based on molecular-based rapid testing option has the added benefit of influenza testing, and hence information regarding influenza prevalence to inform future decision making. From a strict cost-effectiveness perspective, the treat all option is similarly favorable at a prevalence above 7% with an ICER of

$6,246/QALY in the base case analysis. However, the treat all option raises some concerns regarding subsequent development of antiviral resistance due to heavy antiviral use. Although this analysis was taken from a societal perspective, we did not attempt to estimate how the rates of antiviral treatment would affect developing viral resistance for the two remaining effective antiviral medications, oseltamivir and zanamivir. The optimal method of administering antiviral treatment to high risk influenza patients is likely influenced by additional considerations not modelled in this analysis, such as antiviral resistance and individual patient evaluation and preferences.

CONCLUSION

Overall, the most cost effective method of influenza testing and treatment in high risk ED patients depends on local influenza prevalence; however, with any active influenza, antiviral treatment of any kind is superior to no treatment. Given the rapidly changing prevalence, the costs and effects of each treatment algorithm varies throughout the influenza season, and the most efficient ED policy may change throughout the influenza season. From a practical standpoint, providers in acute care settings would thus benefit from having real-time estimates of the prevalence of disease in their community or locale in order to make the most cost effective decisions for evaluating and treating patients who may have influenza. Although promising methods are being developed for real-time influenza monitoring, additional research combining surveillance with influenza treatment strategies is required in order to optimize an effective approach to clinical practice.

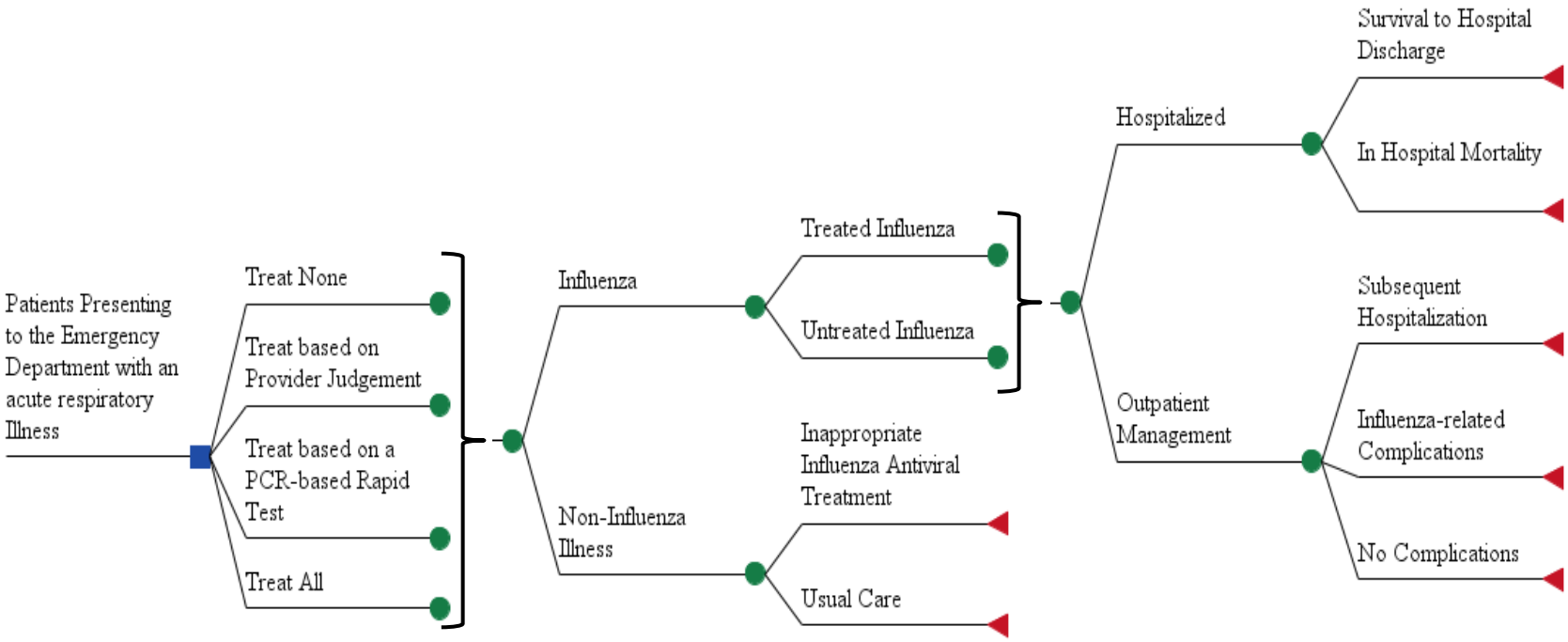

Figure 2: Overview of Decision Tree

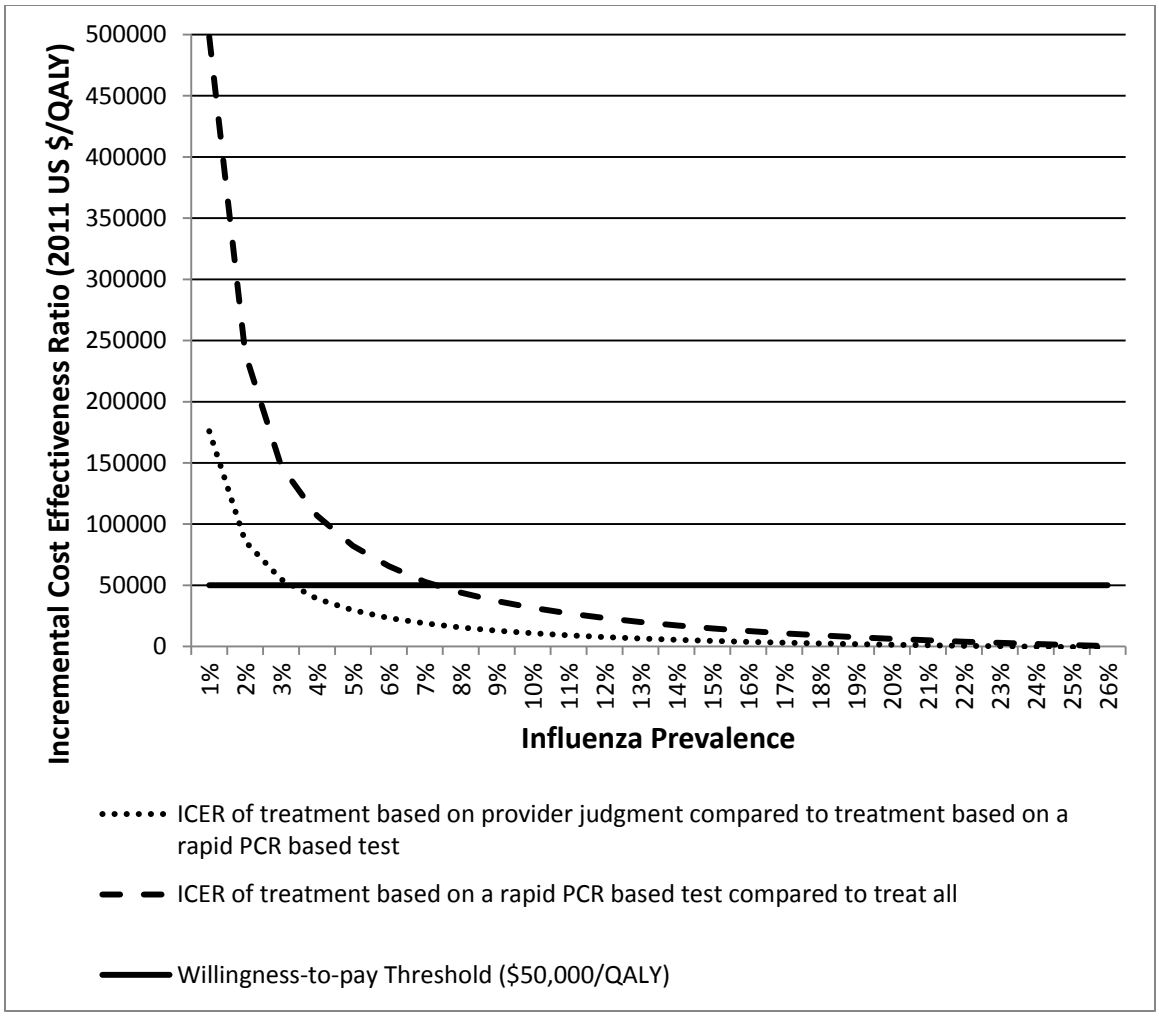

Figure 3: One-way Sensitivity Analysis of Influenza Prevalence: Incremental Cost Effectiveness Ratios (ICER) comparing treatment based on provider judgment to treatment based on a rapid PCR test (dotted line) and treatment based on provider judgment to treat all (dashed line), compared to the accepted willingness-to-pay threshold of $50,000/QALY (solid line).

QALY - Quality Adjusted Life Years

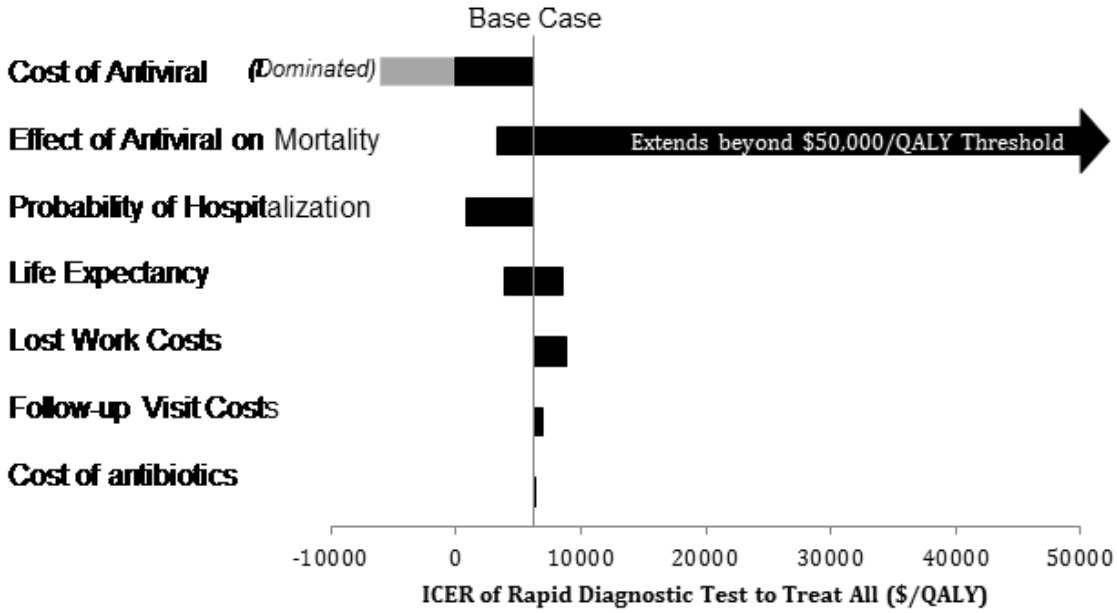

Figure 4: Tornado Diagram displaying Incremental Cost-effectiveness Ratio (ICER) between treatment based on molecular-based rapid Influenza Testing and Treat All algorithms

QALY = Quality Adjusted Life Year

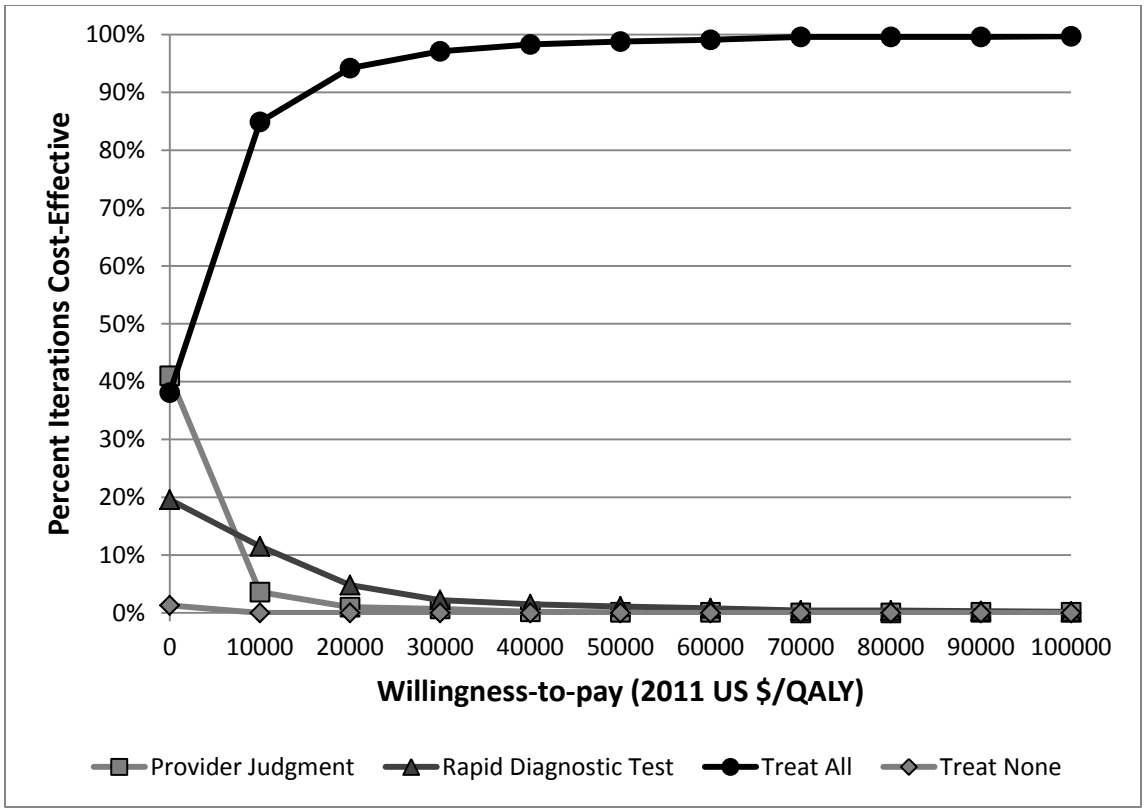

Figure 5: Cost-Effectiveness Acceptability Curve of Monte Carlo Simulation results across a range of Willingness-to-Pay Thresholds

QALY = Quality Adjusted Life Years

Table 9: Estimates of model Parameters

Variable	Baseline Value	Sensitivity Range	Source
Influenza Variables:			
Probability of Influenza in ED patient with acute respiratory illness	0.20	0.0 – 0.60	[42]
Proportion of ED patients admitted	0.13	0.13 - 0.57	[31,66]
Untreated Influenza:			
Probability of death in hospitalized patients	0.10	0.06 - 0.14	[11]
Proportion with complication requiring repeat PCP/ED Visit	0.46	0.30 - 0.62	[67,68]
Proportion with complication requiring antibiotics	0.38	0.23 - 0.53	[67,68]
Proportion re-hospitalized after discharge	0.032	0.015 - 0.049	[75]
Length of influenza illness, days	7.5	3.5 - 14.5	[67,68]
Missed work, days	10.0	5.5 - 20.5	[67]
Treated Influenza:			
Probability of death in hospitalized patients	0.039	0.002 - 0.078	[11]
Proportion with complication requiring repeat PCP/ED Visit	0.14	0.03 - 0.25	[67,68]
Proportion with complication requiring antibiotics	0.14	0.03 - 0.25	[67,68]
Proportion re-hospitalized after discharge	0.016	0.003 - 0.029	[75]
Length of influenza illness, days	5.0	3.0 - 9.0	[67,68]
Missed work, days	7.0	4.0 - 16.0	[67]
QALYs Gained by antiviral treatment:			
QALY gained for improvement of symptoms with antiviral use	0.006		
QALY gained per hospitalized patient due to decreased mortality	0.75	0.61 - 1.83	
Rapid influenza test characteristics:			
Sensitivity	0.91	0.85 - 0.95	[53]
Specificity	0.99	0.97 - 1.00	[53]
Provider Decision Making:			
Sensitivity	0.67	0.29 – 0.67	[42]
Specificity	0.92	0.92-0.96	[42]
Costs (In 2011 US dollars):			
Antiviral (full treatment course)	$100.60	$72.95 - $100.60	[72]
Antibiotic (full treatment course	$3.69	$3.69 - $68.91	[72]
Rapid diagnostic test	$53		Cepheid
Repeat Visit – ED or Primary Care physician	$303.87	$72.77 - $303.87	[66,76]
Hospitalization (with survival)	$31,970	$31,541 - $32,399	[70]
Hospitalization (with mortality)	$52,646	$50,572 - $54,717	[70]
Mean hourly Wage	$22.02		[73]

QALY: Quality Adjusted Life Years

Table 10: Base Case Cost-utility Ratios with *95% Confidence Intervals* of estimates based on probabilistic sensitivity analysis

Testing and Treatment Strategy	Cost (2011 US $)	QALY's Gained	Cost:Utility Ratio ($/QALY)	ICER ($/QALY)
Provider Judgment	$ 1,153 *($528-$4,727)*	0.014 *(0.009-0.209)*	84376	
Rapid Diagnostic Test	$ 1,160 *($558-$4,664)*	0.019 *(0.015-0.347)*	62490	1389
Treat All	$ 1,171 *($594-$4,653)*	0.020 *(0.017-0.382)*	57428	6246
Treat None	$ 1,260 *($537-$4,915)*	0.000	>100,000	Dominated

QALY: Quality Adjusted Life Years
ICER: Incremental Cost-effectiveness Ratio

Summary

Each year influenza affects 5-20% of the population, many of whom present to the ED for initial evaluation and treatment. Diagnosing influenza in the ED remains a challenge as physicians have no reliable tools to accurately and rapidly diagnose influenza; however, rapid diagnosis is crucial to begin antiviral therapy in patients with complications or at risk of complications from influenza as treatment is most effective when given within 48 hours of symptom onset. CDC Guidelines recommend antiviral treatment for patients who are hospitalized, at extremes of age (<5 years old, >65 years old), or have a chronic disease or conditions putting them at increased risk of complications. Given the lack of validated, sensitive, rapid testing, and the benefits of early treatment, the CDC currently recommends that providers initiate treatment in high-risk populations based on physician judgment and clinical signs and symptoms without waiting the extended period of time to confirm the diagnosis. However, clinical symptoms such as cough and fever have a sensitivity of only 64% and have been shown to be insufficient to diagnose or rule out influenza through numerous meta-analyses. As a result of the current diagnostic difficulties, providers often do not suspect, or are not confident in a diagnosis of influenza, resulting in misdiagnosis and under-treatment. Sensitive rapid testing is essential to improve diagnostic accuracy, allow for targeted antiviral therapy, and facilitate rapid antiviral administration which has been linked to improved patient outcomes in high risk populations.

New molecular-based rapid tests, such as Cepheid Xpert Flu, show greatly improved sensitivity compared to previous antigen-based rapid tests; however, they have yet to be validated in a generalized population. Integration of this rapid test into the ED environment is further complicated by the expense of molecular-based testing in a resource-limited environment, and lack of an easily identifiable testing population as classic ILI symptoms such as fever and cough have poor sensitivity. This study evaluated both current antiviral administration rates and clinical

influenza diagnostic accuracy in the ED. In addition, it characterized the clinical performance of Xpert Flu and evaluated the cost effectiveness of implementing molecular-based rapid testing in an applicable clinical setting.

There are several factors which may impact a clinician's decision to treat with antivirals including difficulty in diagnosing influenza, concern of the effectiveness of antivirals, antiviral cost, and increasing antiviral resistance. This work confirms that there is poor adherence with CDC recommendations for influenza antiviral treatment amongst ED patients. A retrospective cohort of patients with laboratory confirmed influenza from a clinically obtained influenza test sent from the ED demonstrated that only 41% of patients meeting CDC criteria for recommended treatment actually received antivirals. The most compelling evidence of the impact of antiviral treatment is in patients with severe disease, such as patients requiring hospital admission, where antivirals have been shown to reduce mortality. Thus, if concerns of antiviral effectiveness were the primary driver for clinician decision making, one would expect clinicians to prioritize treatment in this population with severe disease and greatest potential benefit. However, there was no association between antiviral treatment and markers of severity of illness such as hospital admission or the pneumonia severity index. This suggests that concern of antiviral effectiveness is not a primary factor in clinician decision making regarding antiviral treatment.

The retrospective cohort showing that 41% of patients recommended for antiviral treatment by the CDC actually received treatment was in a population where the patient received clinical influenza testing. Thus, in this population, a clinician considered influenza in the diagnosis as evidenced by the order of a clinical test. A subsequent prospective cohort, which systematically tested all patients with an acute respiratory illness who met CDC criteria for antiviral treatment, demonstrated a lower rate of compliance with CDC guidelines. In this broad population, which was unbiased by the clinician's clinical concern for influenza, only 26% of patients with

laboratory confirmed influenza received antiviral treatment from the ED. This difference demonstrates how physician diagnosis, or consideration of an influenza diagnosis, impacts treatment. Other factors indicating that the clinician was confident in a diagnosis of influenza, such as a diagnosis of influenza recorded in the electronic medical record, and a positive influenza test which resulted during the patient's ED visit were associated with antiviral treatment. Taken together, these factors suggest that difficulty in diagnosing influenza has a considerable impact on antiviral treatment.

Unfortunately, diagnosing influenza in the ED is a challenge as no sensitive tests are rapidly available and clinical signs and symptoms have poor sensitivity for influenza. To identify the sensitivity and specificity of clinician diagnosis, we systematically tested ED patients with an acute respiratory illness during influenza season, and obtained the clinician's diagnosis by asking the clinician: "Do you think this patient has influenza?". This study was restricted to an ED population of subjects who meet CDC criteria for recommended antiviral treatment as that is the population in which an accurate diagnosis of influenza is most critical as it would potentially impact clinical decision making regarding antiviral treatment. In this evaluation, we found that clinician diagnosis had a very low sensitivity of 36% and specificity of 78%.

Provider diagnosis is partially based on the patients presenting signs and symptoms. Numerous studies have demonstrated that signs and symptoms are not sensitive for influenza [24-26]. However, the majority of these studies are biased by the fact that fever is a mandatory inclusion criteria. Not surprisingly, these studies have found that fever is the most significant indicator of influenza [24-26]. In our prospective evaluation, patients were included if they had at least one symptom of an acute respiratory infection which included cough, sinus pain, nasal congestion, rhinorrhea, sore throat, shortness of breath, or fever. These broader inclusion criteria allowed for a more accurate evaluation of signs and symptoms in high risk patients with influenza. Among

patients with influenza, only 31% had the classic symptoms of ILI, according to the CDC definition of fever with couth or sore throat. This value is substantially lower than previous estimates, and was lower in patients with existing or at increased risk of complications compared to non-high risk individuals. This clearly demonstrates that classic symptoms such as ILI are not reliable to diagnose influenza in a high-risk population.

A new generation of molecular-based rapid influenza tests are currently available, but are not yet integrated into clinical practice. One of these tests, Cepheid Xpert Flu, yields results in 80 minutes, and has demonstrated high sensitivity in retrospective samples. To evaluate potential integration into clinical care, we evaluated the performance of this test in a target clinical population of high-risk ED patients with undifferentiated respiratory illness. In this population, the same used to evaluate the performance of clinician diagnosis, Xpert Flu had a sensitivity of 95% and specificity of 99%, vastly outperforming clinical diagnosis. This demonstrates that Xpert Flu is a viable solution to the challenges of influenza diagnosis in the acute care setting. Access to a reliable and timely diagnostic test, such as Xpert Flu, could improve compliance with CDC antiviral treatment guidelines. As with integrating any new test or technology, cost remains a concern.

In order to address cost concerns for both the expense of antivirals, and that of potentially integrating new rapid influenza testing, we performed a cost utility analysis comparing four influenza testing and treatment strategies: 1) Treat none, 2) Treat based on provider judgment, 3) Treat based on results of a molecular-based rapid diagnostic test, and 4) Treat all. Given concerns of the lack of sensitivity of clinical signs and symptoms as previously demonstrated, this analysis was performed using a societal perspective, and a broad population of ED patients recommended to receive antiviral treatment according to CDC guidelines with an acute undifferentiated respiratory illness. This analysis demonstrated that the most cost effective

method of managing influenza was directly related to prevalence of influenza. At a prevalence of less than seven percent, using a molecular-based rapid diagnostic test, such as Xpert Flu, was most cost effective. When the prevalence rose above seven percent, treating all was the most cost effective management option. The current method of treating according to clinical judgment was only cost effective at the absolute lowest prevalence.

This cost utility analysis did not take into account additional factors such as antiviral resistance, which is a continuing concern an often cited reason for not administering antivirals. Our prospective evaluation demonstrated significant antiviral overtreatment, with 11% of patients who were negative for influenza receiving antivirals. Though this concern may prevent clinicians from treating undifferentiated patients with an acute respiratory illness, integration of rapid influenza testing would allow for targeted antiviral testing and subsequently reduce this overtreatment in influenza negative patients.

Currently, there is poor compliance with current CDC guidelines for antiviral treatment amongst ED patients presenting with an acute respiratory illness. Part of this poor compliance is due to the challenges of influenza diagnosis in the ED. Clinical diagnosis, which is commonly used in many EDs, has very low sensitivity for influenza, likely contributing to the overall poor compliance with antiviral treatment guidelines. Improving diagnosis by integrating a molecular-based rapid influenza test into clinical care could result in improved compliance with current antiviral recommendations potentially leading to decreased influenza-related morbidity and mortality.

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Curriculum Vitae

DEMOGRAPHIC AND PERSONAL INFORMATION

Current appointment

2012 - Present Assistant Professor of Emergency Medicine

Personal Data

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Education and Training

Undergraduate:

1998 - 2002 Bachelor of Science in Chemistry, Yale University, New Haven CT

Doctoral:

2003 - 2007 Doctorate of Medicine, Vanderbilt University School of Medicine, Nashville, TN
2010 - 2014 Doctorate of Philosophy in Clinical Investigation
Johns Hopkins University School of Public Health, Baltimore, MD

Postdoctoral:

2007 - 2010 Harvard Affiliated Emergency Medicine Residency
Beth Israel Deaconess Medical Center, Boston, MA
2010 - 2012 Research Fellowship, Johns Hopkins Hospital, Baltimore, MD

Professional Experience

2002 – 2004 Researcher, Research and Development, Pfizer
2010 – 2012 Instructor, Department of Emergency Medicine, Johns Hopkins Hospital
Research Fellow – Emergency Medicine
PACER Fellow (Study of Preparedness and Catastrophic Event Response)

RESEARCH ACTIVITIES

Peer-reviewed Original Science Research Journal Articles

1. Damon BM, Ding Z, Anderson AW, **Freyer AS**, Gore JC. Validation of Diffusion Tensor MRI-based Muscle Fiber Tracking. Magn Reson Med. 2002;48(1):97-104. PMID: 12111936
2. Shinohara ET, Gonzalez A, Massion PP, Chen H, Li M**, Freyer AS**, Olson SJ, Andersen JJ, Shyr Y, Carbone DP, Johnson DH, Hallahan DE, Lu B. Nuclear Survivin Predicts Recurrence and Poor Survival in Patients with Resected Nonsmall Cell Lung Carcinoma. Cancer. 2005;103(8):1685-92. PMID: 15742356
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5. **Dugas A**, Lucas J, Edlow J. Diagnosis of Spinal Cord Compression in the Emergency Department. Acad Emerg Med. 2011;18(7):719-25. PMID: 21729189
6. **Dugas AF**, Rothman RE. Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza. Ann Emerg Med. 2011;58(3):303-4. PMID: 21871233
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11. Peterson S, **Dugas AF**, Rothman RE. Evaluation of 11 commercially available rapid influenza diagnostic tests—United States, 2011-2012. Ann Emerg Med. 2013;61(5):573-7. PMID: 23755399
12. **Dugas AF**, Jalalpour M, Gel Y, Levin S, Torcaso F, Igusa T, Rothman RE. Influenza forecasting with Google Flu Trends. PLoS One. 2013;8(2):e56176. PMCID: PMC3572967
13. **Dugas AF**, Morton M, Beard R, Pines JM, Bayram JD, Hsieh Y, Kelen G, Uscher-Pines L, Jeng K, Cole G, Rothman R. Interventions to Mitigate Emergency Department and Hospital Crowding During an Infectious Respiratory Disease Outbreak: Results from an Expert Panel. PLOS Currents Disasters. 2013;Edition 1. PMCID: PMC3644286
14. **Dugas AF**, Coleman S, Gaydos CA, Rothman RE, Frick KD. Cost-Utility of Rapid PCR-based Influenza Testing for High Risk Emergency Department Patients. Ann Emerg Med. 2013;62(1):80-8. PMID: 23522607

Extramural Funding

Current Grants:

1/2013 – 12/2015 Influenza Diagnosis, Treatment and Surveillance with Xpert Flu
BARDA/DHHS
Principal Investigators: Dugas and Rothman
Role: Co-Principal Investigator

7/2012 – 6/2017 Center for POC Technologies Research for Sexually Transmitted Diseases
NIH/NIBIB
Principal Investigator: Gaydos
Role Co-investigator

4/2014 – 3/2021 Johns Hopkins Center of Excellence for Influenza Research and Surveillance
NIH/NIAID
Principal Investigator: Rothman/Pekosz
Role Co-investigator

Previous Grants:

7/2011–7/2013 Diagnosis of influenza in the emergency department
5KL2RR025006
Johns Hopkins/NIH
Principal Investigator: Ford
Role: Clinical Research Scholar

1/2012-1/2013 An educational intervention to improve emergency providers' knowledge and attitudes towards patients with sickle cell disease pain crises
Blaustein Pain Treatment Center
Principal Investigator: Andrea Dugas
Role: Principal Investigator

7/2010 – 12/2013 The National Center for Preparedness and Catastrophic Event Response
2010-ST-061-PA0001
Department of Health and Human Services
Principal Investigator: Kelen
Role: PACER Fellow, Co-investigator

EDUCATIONAL ACTIVITIES

Educational Publications

Invited Editorials:

1. **Dugas AF**, Rothman RE. Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza. Ann Emerg Med. 2011;58(3):303-4.
2. Peterson S, **Dugas AF**, Rothman RE. Evaluation of 11 commercially available rapid influenza diagnostic tests—United States, 2011-2012. Ann Emerg Med. 2013;61(5):576-7.

Book Chapters:

1. **Dugas, A**. "Splenic Trauma." Essential Emergency Trauma. Ed. Shah K, Qaas J, Egan D. Lippincott, Williams and Wilkins, 2010.
2. **Dugas, A**. "In Suspected Tricyclic Antidepressant Overdose, Start Sodium Bicarbonate as Soon as the QRS Duration is Over 100 ms." Avoiding Common Emergency Medicine Errors. Ed. Mattu, A, et al. Lippincott, Williams, and Wilkins, 2010.
3. **Dugas, A**. "Spinal Cord and Cauda Equina Compression." Essential Emergency Imaging. Shah K, Lewis R, Turandot S. Lippincott, Williams & Wilkins, 2011.

Teaching

Classroom Instruction:

Emergency Medicine Resident Lectures

4/23/2008	"*STI's in the ED – Diagnosis and Counseling"*
6/16/2010	"*HIV Emergencies*"
7/15/2008	*"Missed Diagnosis - Cerebral Venous Thrombosis"*
7/1/2009	"*Literature Update - Pain Management in the ED"*
11/11/2009	"*Spinal Trauma"*
2/7/2014	*"Seizure"*

EMS Education

2008 Instructor to paramedics of Cataldo Ambulance Company

Clinical Instruction:

2010 – Current	Supervising Attending Physician, Johns Hopkins University, Department of Emergency Medicine, Johns Hopkins Hospital, Baltimore, MD
2013 – Current	Supervising Attending Physician, Johns Hopkins University, Department of Emergency Medicine, Johns Hopkins Bayview Medical Center, Baltimore, MD
2014 – Current	Undergraduate Mentor/Clinical Tutorial Johns Hopkins School of Medicine

CME Instruction:

2008 Emergency Medicine into the 21st Century
"Cerebral Venous Thrombosis"

2011 International Panel of Digital Disease Detection
"Harnessing the Internet for Health: Influenza Surveillance with Google Flu Trends"

CLINICAL ACTIVITIES

Certification

Medical Doctor Maryland, Department of Health and Mental Hygiene
License Number D0070380

Clinical Responsibilities

2010 – Current	Attending Physician, Johns Hopkins Hospital, Department of Emergency Medicine, Baltimore, MD
2013 – Current	Attending Physician, Johns Hopkins Bayview, Department of Emergency Medicine, Baltimore, MD

RECOGNITION

Awards

2010 PACER Scholar, Department of Homeland Security
2010 KL2 Clinical Research Scholar, Johns Hopkins University
2013 Fellow of the American College of Emergency Medicine

Invited Speaker

2008 Emergency Medicine into the 21st Century
Cerebral Venous Thrombosis
2011 International Panel of Digital Disease Detection, 1/2011
Harnessing the Internet for Health: Influenza Surveillance with Google Flu Trends
2012 Department of Defense, Chemical and Biological Defense Community of Interest, 7/2012
Influenza Surveillance and Prediction with Google Flu Trends

Professional Societies

2007 – 2010	Emergency Medicine Residents' Association *Regional Representative* *Health Policy Committee*
2007 – Present	Society for Academic Emergency Medicine *Research Committee*
2007 – Present	American College of Emergency Physicians