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Research Article

A Retrospective Analysis of the Impact of FilmArray Respiratory Panel Utilization on the Management of Pediatric Influenza

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ABSTRACT

This study was designed to examine whether use of a Nucleic Acid Amplification Testing, FilmArray, impacted the care of pediatric patients with influenza during a single season, June 2017 - May 2018. Sixty patients were stratified into two cohorts with 23 in the FilmArray cohort versus 37 in the rapid antigen testing cohort. Analysis included: age, sex, race, length of hospital stay (LOS), influenza subtype, and rapid antigen testing. Seven patients tested positive with FilmArray but negative on rapid antigen testing, which supports the higher sensitivity and specificity of FilmArray testing.

Patients receiving FilmArray testing had a longer LOS when compared to the rapid antigen cohort (median 46.7 hours vs 37.0 hours, respectively, p=0.04). No differences in LOS were noted when analyzed by influenza subtype. Results may indicate a difference in diagnostic practices between physicians or such testing may be independently associated with a high severity of illness.

Keywords: Pediatrics, Clinical pediatrics; FilmArray Respiratory Panel, Influenza, Polymerase chain reaction, Rapid antigen testing

Abbreviations: Digital Immunoassay (DIA), Institutional Review board (IRB), Length of Stay (LOS), Nucleic Acid Amplification Test (NAAT), Polymerase Chain Reaction (PCR), Pediatric Intensive Care Unit (PICU), Spartanburg Regional Healthcare System (SRHS), Structured Query Language (SQL)

INTRODUCTION

The influenza virus is an orthomyxovirus with strains classified as either A, B, or C. Influenza A and B causes the epidemic disease, whereas influenza C causes a milder form of the illness [1]. Influenza A can be sub classified according to its hemagglutinin (H) and neuraminidase (N), such as H1N1 [1]. In the United States, the highest rate of influenza infectivity occurs in the winter months. This virus is easily spread from person to person by respiratory droplets from individuals or surfaces. On average, 8% of the United States population is diagnosed with influenza each season and 9.3% of those are children between the ages of 0 and 17 years of age [2]. The highest incidence of influenza is in school-aged children and thus, it can easily spread to close contacts such as adults and other children [1].

Although most children recover from influenza within three to seven days, some may develop severe complications including dehydration, pneumonia, or bronchiolitis [1]. Children with chronic illnesses are at higher risk of developing such complications, especially those with a history of asthma, diabetes mellitus, sickle cell disease, hemodynamically significant cardiac disease, immunosuppression, and neurologic or neurodevelopmental disorders [1]. Of the children hospitalized with influenza during the 2017 - 2018 seasons, 57% had a comorbid condition [1]. Children less than two years of age are also at an increased risk of hospitalization secondary to influenza. Although rare, death may occur as a result of this virus. In the 2017 - 2018 seasons, The Centers for Disease Control and Prevention (CDC) recorded 185 deaths among children [2].

With these complications in mind, doctors' offices and emergency departments examine many children for concerns of influenza each season. Therefore, influenza is a significant contributor to pediatric healthcare costs annually. To diagnose influenza, a nasopharyngeal swab should be performed; optimally within four days of symptom onset [1]. Diagnostic options include rapid antigen detection, viral culture, or nucleic acid amplification tests (NAAT). Our institution utilizes the BD Veritor (Becton, Dickinson, Sparks, MD, USA), which is a form of the rapid antigen detection method, known

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as the digital immunoassay (DIA) [3]. This device can enhance the detection of viral antigens from a digital scan of the test strip [3]. A review of the available testing options performed by Azar et al. referenced a study that determined the DIA modality has a sensitivity of around 76.8% when detecting influenza B and 80% when detecting influenza A [3]. However, because the accuracy of these tests depends highly on the viral load, the CDC recommends against the use of rapid antigen detection in communities with low prevalence of influenza infectivity [3]. Additionally, during the peak period of the influenza season, rapid antigen detection tests can lead to an increased amount of false negative results [2]. To combat these downfalls, practitioners turn to a modality that has a higher sensitivity and specificity, such as NAAT. This becomes particularly important in hospitalized children who are at increased risk for complications associated with the virus.

The NAAT utilized in this study is the BioFire FilmArrayRespiratory Panel (BioFire Diagnostics, Salt Lake City, UT, USA). It is a polymerase chain reaction (PCR) - based test that detects 17 respiratory viruses (adenovirus, influenza A and B with subtyping, parainfluenza virus types 1-4, respiratory syncytial virus, coronaviruses 229E, HKU1, NL63, OC43, human metapneumovirus, and human rhinovirus/enterovirus) and three bacteria (*Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae*) with a one-hour processing time [4]. The overall sensitivity and specificity of this particular panel is 95% and 99%, respectively [4]. However, the FilmArray Respiratory Panel may be associated with significant hospital charges.

This study was designed to examine whether the use of the FilmArray Respiratory Panel impacted the care of pediatric patients with influenza in terms of length of stay during a single season.

METHODS

Approval to perform this study was obtained from the institutional review board (IRB) at Spartanburg Regional Healthcare System (SRHS). Due to the retrospective nature of this project, a waiver of the requirement to obtain written informed consent was granted by the IRB. Appropriate training was performed by all investigative parties before data collection began.

The study was a single-center, retrospective, observational study, conducted at a 540-bed community-based teaching hospital. Patients less than 18 years of age admitted to the general pediatric ward or Pediatric Intensive Care Unit (PICU) at SRHS with a diagnostic code of influenza between June 2017 through May 2018 were eligible for inclusion. Patient information was collected by querying electronic quality management system records and electronic lab records, using Structured Query Language (SQL). Chart reviews were performed to identify age, sex, race, length of hospital stay (LOS), pathogens identified on the FilmArray Respiratory Panel, and rapid antigen testing. Patients were stratified into two cohorts: Patients who received a FilmArray Respiratory Panel and those who did not. Of those patients that did not receive FilmArray testing, rapid antigen detection modalities were utilized. Discordance of test results from the FilmArray Respiratory Panel and rapid antigen testing were assessed. Patients who tested positive for influenza on the FilmArray Respiratory Panel were analyzed for any correlation between strain and length of hospitalization. Patients were excluded from the analysis if duplicate tests were conducted greater than seven days apart.

Data were de-identified after chart review was complete and stored in a password protected Excel document, with access given only to approve investigative parties. Information was then combined using Excel and SQL Server, directed to Excel for storage. Statistical analysis was performed using SAS JMP statistics software.

RESULTS

A total of 60 patients were included in this retrospective study. The study included 31 males and 29 females. FilmArray testing was utilized in 38% of patients while rapid antigen testing was used in the remaining 62% of patients. The FilmArray cohort was comprised of 35% females and 65% males. Of those, 57% were Caucasians, 26% were African Americans, 4% were Chinese, 4% were Asian, 4% were multiracial and 4% were of unknown ethnicity. The group that did not receive FilmArray testing included 57% females and 43% males. Of those, 68% of patients were Caucasian, 24% were African American, 5% were multiracial and 3% were of unknown ethnicity. Ages ranged from zero to six years of age with a median age of two for both groups. There were no statistically significant differences between groups with respect to gender (p=0.1), race (p= 0.6) or age (p=0.9) (Table 1).

The most common strain in both cohorts was influenza A accounting for 74% in the FilmArray cohort, and 86% in the rapid antigen cohort (p=0.24) (Figure 1). The FilmArray cohort subtypes were identified as 52% influenza A/H3, 17% influenza A/H1-2009, 4% influenza A-no subtype and 26% influenza B (Figure 2).

Table 1: Demographics of Patients with Influenza Admitted to the Pediatric Ward or PICU from June 2017 - May 2018 stratified into the FilmArray and Rapid Antigen Testing Groups.

FilmArray = No n=37		FilmArray = Yes n=23	p-value	Statistical Test
Age				Chi-Square
Median (IQR)	2 (0-5.5)	2 (0-6)	0.9	
Gender				Fisher's exact
Female	21 (57%)	8 (35%)		
Male	16 (43%)	15 (65%)	0.1	
Race				Chi-Square
Asian African American Chinese Multiracial	0	1 (4%)		
Unknown Caucasian	9 (24%)	6 (26%)		
	0	1 (4%)		
	2 (5%)	1 (4%)		
	1 (3%)	1 (4%)	0.6	
	25 (68%)	13 (57%)		

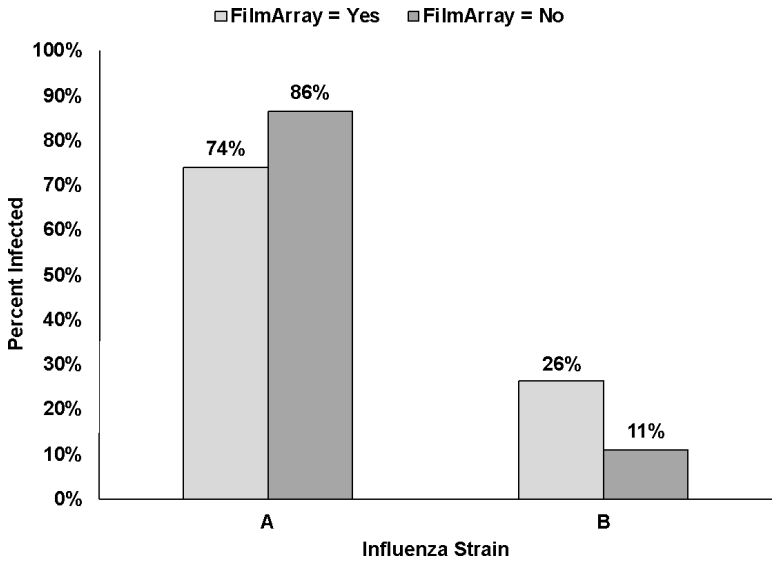

Figure 1: Influenza Strain Infectivity for the FilmArray and Rapid Antigen Testing Cohorts. Percentage of patients infected with influenza A or B in each group. Statistical analysis performed using Chi-Square.

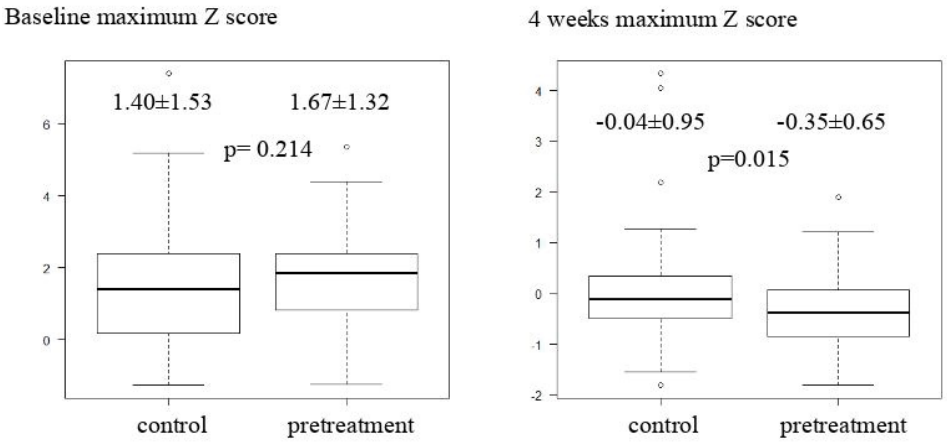

Figure 3: Length of Stay in hours for the FilmArray and Rapid Antigen Testing Cohorts. Box and whisker plot representation of length of stay for each group. Statistical analysis performed using Chi-Square. Statistically significant at the α=0.05 level.

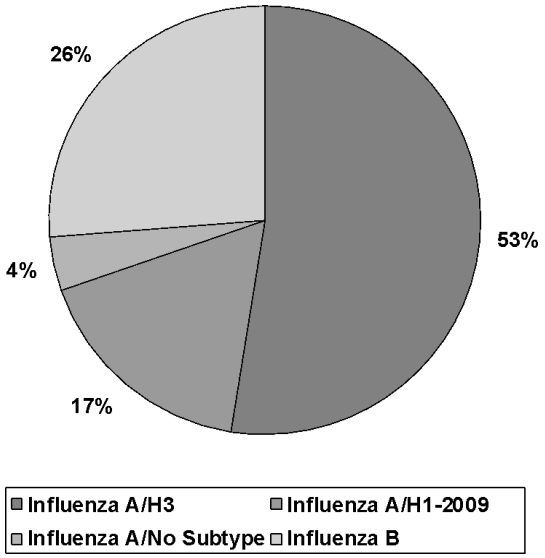

Figure 2: Influenza Subtype Infectivity in the FilmArray Cohort. Percentage of patients infected with each influenza subtype with FilmArray testing.

Those patients in the FilmArray respiratory cohort had a median hospital length of stay of 46.7 hours (29.1 - 73.5 hours), while those patients in the rapid antigen cohort averaged a median hospital length of stay of 37.0 hours (18.1 - 53.2 hours) (p=0.04, statistical significance at the α=0.05 level, Chi-square). Analysis of influenza subtypes and impact on length of stay did not yield any statistically significant associations. Discordance between the FilmArray Respiratory Panel and rapid antigen testing was noted in seven patients who tested positive with the FilmArray Respiratory Panel but negative on rapid antigen testing.

DISCUSSION

Our study found that FilmArray testing was associated with a longer length of stay for pediatric patients hospitalized with influenza by a difference of 9.7 hours. We also found no statistically significant associations between specific strains of influenza and length of stay. We were unable to delineate if the different influenza subtypes caused this association with hospital length of stay. It should be noted that we incorporated patients from the pediatric intensive care unit who may have been more severely ill and would have a longer length of stay regardless of the influenza diagnosis or use of FilmArray testing. As such, it is possible that the longer hospital stay outcome is due to physicians ordering FilmArray testing in patients deemed to have a greater severity of illness. Children in critical condition may lead physicians to rely on a test with a greater sensitivity and specificity due to the reassurance of a known diagnosis. A retrospective study by Rogers, et al. stated that healthcare providers may be more confident in discharge after they have identified a specific pathogen associated with the patient's illness [5]. This conclusion was made after they found a statistically significant decrease of six hours in the inpatient length of stay when children tested positive for a viral pathogen on FilmArray. Although our study showed an increased length of stay in our FilmArray cohort, a review of the literature discovered multiple research articles with conflicting reports on whether or not FilmArray testing decreases a patient's length of stay.

One such study by Andrews et al. performed in adult patients compared the BioFire FilmArray to routine laboratory-based PCR and serology tests and found no evidence of an association between FilmArray testing and length of hospital stay [6]. They attributed their length of stay results to a delay in initiation of the FilmArray nasal swab by clinical staff due to the lack of hospital procedures in place to optimize its utilization. Interestingly, they did find that use of the BioFire FilmArray produced faster results and subsequently physicians were able to administer time-sensitive antiviral medications for influenza significantly faster. Similarly, Brendish, et al. performed a study in adult patients that showed the use of FilmArray testing allowed for more cases of influenza to be diagnosed and therefore improved the time to initiation of antiviral medication [7]. In contrast, that study showed a decreased hospital length of stay when utilizing FilmArray testing. Regardless of hospital length of stay, both studies found a benefit in the use of the BioFire FilmArray due to faster results leading to prompt administration of treatment and therefore, its utility should be strongly considered for hospital-wide implementation. When comparing our results to the aforementioned studies, the inconsistencies in hospital length of stay may be attributed to discrepancies with its appropriate application.

Currently there is not a widely accepted algorithm in place that objectively determines when it is most appropriate to utilize the FilmArray Respiratory Panel. Implementing such a protocol would reduce physician biases and subjectivity. Gardiner et al. attempted to develop a two-stage testing algorithm to diagnose viral respiratory infections [8]. During the winter months, they incorporated an initial screen with Sofia® immunoassay, a DIA, then secondarily used the BioFire FilmArray on every patient with a negative immunoassay result. This practice was compared to the summer season when only FilmArray testing was utilized. The results showed that a two-step method prevented missing cases of influenza and saved time even during the peak of influenza season when more samples were tested. Our study also documented instances of missing cases of influenza as seen by the seven patients that were initially negative with rapid antigen testing and subsequently tested positive with FilmArray testing. This supports the idea that although the FilmArray Respiratory Panel may be associated with significant healthcare charges, its proven reliability makes it an advantageous testing modality that should be employed when most appropriate, such as in instances when rapid testing results are negative. Ultimately, healthcare providers may feel more comfortable ordering the test knowing that, by implementing it at opportune times, time and money will be saved for the patient and the hospital. Studies should continue to develop an evidence-based algorithm to optimize utilization in a cost-effective manner.

Further studies are also warranted to assist in identifying factors that may be predictive of a more significant burden of infection and subsequently longer hospital stays, especially in the pediatric population. Given that our study was restricted to inpatient management, we were unable to assess the impact of this test in alternate settings. Utilizing this test for studies in the emergency department and outpatient clinics may help to determine if there are any correlations between influenza subtype and admission status. By identifying which strains result in more severe complications, healthcare providers may be able to confidently determine the patient's disposition, such as discharging them home or admitting them to the pediatric ward or the pediatric intensive care unit. Due to our patient population only consisting of those that were already admitted, the major limitation of our study was our small sample size. Not only would a larger sample size increase the power of the study, but it would also help to generalize the results so that proper implementation could occur throughout multiple hospitals settings in a variety of communities.

A benefit of our study was the inclusion of pediatric intensive care unit patients, which enabled us to see if the use of FilmArray testing for all admitted pediatric patients with influenza had a benefit on their length of stay. However, with a variety of training backgrounds, different providers utilize alternate modalities to treat the same illness, thus there are multiple underlying factors that may have influenced our results. This supports the need for an algorithm to standardize the utilization of FilmArray testing for the diagnosis and treatment of influenza in pediatric patients across all inpatient wards. The other strength of our study was the inclusion of all pediatric patients admitted to the hospital throughout a single influenza season. This allowed us to include a full season's burden of illness, which reduced any confounding factors that would occur if one season's severity of illness was compared to another.

In conclusion, our study supports the notion that the FilmArray Respiratory Panel is more sensitive and specific than rapid antigen testing for the detection of influenza as demonstrated by those patients that would have been missed by rapid antigen testing. The longer length of stay noted in this study may be independently associated with the inclusion of patients with a high severity of illness or may simply indicate a difference in diagnostic practices between physicians.

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DECLARATION OF CONFLICTING INTEREST

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