ORIGINAL ARTICLE

CLINICAL PROFILE AND OUTCOME OF ADMITTED PEDIATRIC PATIENTS WITH INFLUENZA

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ABSTRACT

Background: Influenza is one of the most common illnesses pediatricians face. Children are especially at risk for contracting influenza. Aside from fever, cough and colds, the disease may present differently in children. Complications due to influenza are varied and anti-virals may be useful if given early in the course of illness.

Objectives: To determine the clinical profile of admitted pediatric patients with influenza based on rapid testing and determine its prevalence, outcome and complications.

Methods: Cross sectional study of pediatric patients who had nasopharyngeal swab for influenza by antigen rapid detection test were included. Retrospective chart review was done on patients with influenza-like illness admitted from 2013-2019.

Results: There were 244 patient charts reviewed, the mean age of patients was 5 – 9 years old and majority had no influenza vaccine during the year of admission. Patients presented with fever, cough, colds and non-specific symptoms. Ear pain, difficulty of breathing and myalgia were found to be associated with a positive influenza infection. Of the 244 suspected patients, 133 (54%) were positive for influenza rapid testing, 33% were influenza B positive and 21.3 % were influenza A positive. The most common clinical complication for influenza positive patients was pneumonia. 1 patient had respiratory failure, 5 had febrile convulsions and 7 developed viral myositis. 19% of the subjects had asthma as co-morbidity. Only 11% of the population had their annual influenza vaccine.

Conclusion: 54% of pediatric patients tested for influenza had positive tests for either Influenza A or B. Although generally a mild illness, it contributes to morbidity and mortality in children. Complications are not uncommon in the pediatric population as seen in this study. Vaccination remains an important preventive measure to curb influenza cases.

KEYWORDS: *Influenza, Seasonal Flu, Influenza A, B*

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INTRODUCTION

Influenza is one of the most common illnesses physicians face yearly. It is responsible for seasonal epidemics of pediatric respiratory diseases each year resulting in substantial morbidity, mortality and increased health care utilization. Children, especially those younger than two years of age have high rates of influenza cases, similar to the rates of hospitalization among the elderly.[1] Classic influenza infection is characterized by sudden onset of high fever, coryza, cough, headache, malaise and inflammation of the upper respiratory tree and trachea. Acute symptoms and fever often persist for 7 to 10 days. In younger children, croup, bronchiolitis and pneumonia are all possible clinical presentations of influenza. Gastrointestinal symptoms are uncommon in adults but can be the primary symptoms in children.[2] It may present immediately as a case of acute respiratory distress syndrome, acute myositis, encephalitis or viral myocarditis, most of which are not seen in adults. It is imperative that physicians be aware of these atypical presentations of influenza in children for rapid diagnosis and treatment. Common complications of influenza among children are well documented including bronchiolitis, otitis media, and pneumonia.[1] Laboratory diagnosis is the mainstay in the diagnosis of influenza infection. Clinical findings alone are insufficiently sensitive or specific to diagnose influenza, especially in younger children who less often have classic findings.[3] PCR remains the gold standard for testing. Rapid diagnostics tests have sensitivities of approximately 70% and specificities of 90%. Children may yield higher sensitivities than adults since children tend to harbor larger quantities of virus in their respiratory tracts making them easily detectable. Patients who may benefit the most from rapid influenza testing include children and adults with lower respiratory tract illness who have underlying medical conditions placing them at risk for secondary complications of influenza.[4]

Influenza disease presents differently in various populations. Most of the clinical signs and symptoms reported are based on Western population, where most journals or researches are published and where seasonal influenza is being monitored.[2] Currently there are still minimal local studies on clinical profile of influenza in the local population especially in children. A local study done by Lucero et al. monitored the circulating strains of influenza in the country from 2006 to 2012. This study focused on analyzing seasonality, and influenza strains for 5 years. The study was used by the World Health Organization (WHO) in predicting seasonal thresholds and epidemic curves.[5] Investigating clinical symptoms, complications and sequelae in the local pediatric population will help understand the impact and severity of the disease in the local setting.

Influenza is highly treatable and antiviral for influenza is most effective within 48 hours after the onset of signs and symptoms. Awareness of the clinical manifestation of influenza in pediatric patients would lead to early diagnosis, early treatment, shorter hospital stay, decreased antibiotics use, prevention of complications and hasten recovery. This study aims to determine the clinical profile of admitted pediatric patients in a tertiary hospital in Metro Manila who were suspected to have influenza and underwent rapid influenza testing.

MATERIALS AND METHOD

A. Study design and participants

This is a cross sectional study, using a retrospective chart review of pediatric patients admitted at a tertiary hospital in Metro Manila who were tested for influenza via rapid antigen detection kit from 2013 to 2019.

B. Inclusion and exclusion criteria for subject selection:

This study enrolled consecutive pediatrics patients (< 19 years old) admitted for suspected influenza and underwent influenza testing (with positive or negative results). Patients who were already undergoing treatment for influenza prior to rapid testing were excluded from the study.

C. Description of study procedure

Between 2013- 2019, records of pediatric patients who were tested for influenza using the *EZER*^{TM} Influenza A and B viral antigen rapid test device were included. The test kit was manufactured in Hangzhou China, sensitivity for influenza A is 94.7%, specificity of 94%, while sensitivity for influenza B is 91.7% and a test specificity of 97.5%. The test has no cross reactions with the following viruses: adenovirus, coxsackie, cytomegalovirus, echovirus, enterovirus, parainfluenza, poliovirus, respiratory syncytial virus, rhinovirus. Characteristics and variables such as age, sex, influenza vaccination status, clinical presentations, underlying medical conditions were collected. Outcome and complications of those who tested positive for influenza were likewise analyzed. The prevalence of influenza (A and B) and the signs and symptoms associated with either influenza A and B were studied.

D. Sample Size Estimation

Sample size was calculated based on the population proportion estimation. Sample size was calculated using signs and symptoms of nasal congestion symptom since it yielded the largest sample size. Assuming that the proportion of the patient is 52.7 with a maximum allowable error to 5%, and a reliability of 90%, sample size calculated is 269.

E. Mode of Data Analysis

Determination of the clinical profiles, clinical outcomes and prevalence of influenza A and B among participants were done using frequency and percentage for qualitative variables and mean and standard deviation for quantitative variables. Association of the different clinical profiles with the prevalence of influenza and with clinical outcomes were analyzed using univariate statistics. Chi square test were utilized for qualitative and quantitative clinical profiles respectively. Level of significance will be set at alpha = 0.05

F. Ethical considerations

This research upholds the highest ethical standard of confidentiality, transparency and integrity in processing personal information. The study abided by the principles of the Declaration of Helsinki (2013) and is conducted along the Guidelines of the International Conference on Harmonization – Good Clinical Practice (ICH-GCP). The Clinical Protocol and all relevant documents were approved by the Institutional Ethics Review Committee as well as the data privacy officer on July 9, 2019. Given that this research is dealing with vulnerable population (children), provisions were made to ensure their protection, anonymity and confidentiality of their medical information at all times. Patient confidentiality was respected by ensuring anonymity of patient records. Each patient document is coded and does not contain any identifying information in order to ensure confidentiality. The chart review was done by the author, and was done at the hospital premises. All study data were recorded and investigators are responsible for the integrity of the data i.e. accuracy, completeness, legibility, originality, timeliness and consistency. The manner of disseminating and communicating the study results guarantees the protection of the confidentiality of patient's data. All study- related documents such as the all versions of the protocol, ethical clearance, data collection forms, hard copies of source documents, is kept and stored by the principal investigator in strict confidentiality; after which they will be shredded**.** Data collections commenced upon approval of the research protocol by the Institutional Review Board and Institutional Ethics Review Committee. This paper was self-funded and the authors deny any conflict of interest.

RESULTS

A total of two hundred forty-four patient charts were reviewed for this study. Table 1 shows the characteristics of admitted patients suspected to have influenza and underwent influenza rapid test. The most common co-morbid condition seen was bronchial asthma followed by seizure disorder. Majority of suspected cases were female comprising

52.5% compared to males at 47.5%, and most of which are in the age group of 5- 9 years old. Eighty eight percent of influenza suspect patients did not receive their yearly influenza vaccine. Majority of suspected cases presented with symptoms of fever, cough and colds (Table 2).

Table 1. Characteristics of patients suspected to have Influenza

		N=244	Percentage
Sex	Female	128	52.5%
	Male	116	47.5%
Age group	0-5 months	4	1.6%
	6 -23 months	38	15.5%
	23-59 months	87	35.6%
	5- 9 years old	89	36.4%
	> 10 years old	36	14.7%
Vaccination status	With vaccine	28	11.5%
	Without vaccine	216	88.5%
Exposure to influenza	With exposure	53	21.7%
	Without exposure	191	78.3%
Comorbidities			
Asthma		47	19.3%
Congenital heart disease		2	0.8%
Seizure disorder		7	2.9%
Malignancy		0	0%

Table 2. Clinical Presentation of patients admitted for influenza-like illness

Symptoms	N=244	Percentage
Fever	239	98.4%
Cough	208	86%
Colds	185	75.8%
Sore throat	10	4.1%
Ear pain	6	2.5%
Abdominal Pain	22	9.0%
Loose stools	45	18.4%
Vomiting	53	21.7%
Myalgia	17	7.0%
Difficulty breathing	18	7.4%
Seizures	12	4.9%
Altered Consciousness	0	0%

Out of two hundred forty-four patients who underwent influenza testing one hundred thirty-three (54%) patients were positive for influenza. Eighty-one (33.2 %) patients were positive for influenza B, while 52 (21.3 %) were influenza A. Of these 133 patients who were confirmed influenza, 39 patients developed complications, the most common was pneumonia at 13.6%, other complications seen were myositis and benign febrile convulsion (Table 3, 4)

Table 3. Prevalence of Influenza

	N=244	**Percentage (%)**
Negative for Influenza	111	45.5%
(+) Influenza A	52	21.3%
(+) Influenza B	81	33.2%

Table 4. Clinical Complications of influenza positive patients

Clinical Complications	N = 39	%
Respiratory failure	1	1.5%
Pneumonia	18	13.6%
Secondary bacterial infection	8	6.1%
Encephalitis	0	0
Febrile convulsions	5	3.8%
Viral myositis	7	5.3%
Myocarditis	0	0

Majority of flu like symptoms such as fever, cough and colds were seen in both influenza positive and influenza negative patient. Non-specific systemic symptoms such as abdominal pain, loose stools, vomiting, myalgia and ear pain were likewise observed in patients either with influenza positive or negative results. A pearson chi-square showed the association of confirmed influenza positive patients with some signs and symptoms, setting the level of significance at 0.05. These signs and symptoms were ear pain, myalgia and difficulty of breathing had a p value < 0.05, making it statistically significant. (Table 5)

Table 5. Signs and Symptoms associated with positive and negative Influenza test

	Influenza A	%	Influenza B	%	Negative	%	Chi square (P < 0.05)
Fever	52	100%	80	98.8%	107	97.3%	0.417
Cough	47	90.4%	72	88.9%	89	81.7%	0.213
Colds	40	76.9%	62	76.5%	83	74.8%	0.94
Sore throat	3	5.8%	4	5.0%	3	2.%	0.583
Ear Pain	3	5.8%	3	3.7%	0	0%	**0.058**
Abdominal Pain	4	7.7%	9	11.1%	9	8.1%	0.72
Loose stools	11	21.1%	13	16%	21	18.9%	0.749
Vomiting	17	32.7%	16	19.8%	20	18.0%	0.093
Myalgia	2	3.9%	12	14.8%	3	2.7%	**0.003**
Difficulty breathing	1	1.9%	2	2.5%	15	13.5%	**0.004**
Seizures	4	7.7%	3	3.7%	5	4.5%	1.203
Altered consciousness	0	0%	0	0%	0	0%	0.548

Influenza A positive patients were shown to have higher rates of pneumonia, secondary bacterial infection and febrile convulsions, while patients who were influenza B positive were shown to develop viral myositis. (Table 6) All patients who were influenza positive were given oseltamivir. Eight patients were given parenteral antibiotics for concomitant bacterial infections, such as pneumonia and otitis media. All patients who were confirmed for influenza eventually recovered with an average hospital stay of four days. A patient who had cerebral palsy, seizure disorder, had concomitant bacterial and fungal infection stayed at the hospital for 52 days.

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Table 6. Clinical complications of patients positive for influenza A or B

	Influenza A	Influenza B
Respiratory failure	0%	1%
Pneumonia	17.30%	11.30%
Secondary bacterial infection	7.70%	5.00%
Encephalitis	0%	0%
Febrile convulsion	5.8%	2.5%
Viral myositis	3.8%	6.3%

DISCUSSION

Influenza has been a major cause of morbidity and mortality among children. Suspected patients typically present with symptoms such as fever, cough and colds. Other signs and symptoms include abdominal pain, loose stools, myalgia and ear pain. In this study, symptoms such as ear pain, difficulty of breathing and myalgia were found to be associated with a positive influenza result. Influenza in children ranges from subclinical illness to complicated disease. It is difficult to diagnose influenza in young children on the basis of clinical grounds because no specific signs or symptoms exist, and because other viral respiratory infections that present with fever also occur frequently during influenza season. In separate studies done by Machado et. al in Brazil,[6] Peltola et al in Finland[7] and Tran et al in Canada[8] they showed that there were no differences in clinical findings between influenza A positive and influenza B positive patients. Systemic symptoms such as myalgia, abdominal pain and loose stools were seen frequently in influenza B positive patients. According to the study done by Dilantika et al done in Indonesia, it is possible that the influenza B virus might bind to α 2, 6 sialic receptors in the human gastrointestinal tract and infect, actively replicate within the cells of the gastrointestinal tract causing abdominal pain and loose stools.[2]

The most common clinical complication of influenza seen in this study is pneumonia. Influenza A positive patients were prone to develop pneumonia. This is also seen in a similar study by Daley et. al, done in Sydney Australia where infection with influenza A was associated with severe pulmonary symptoms such as pneumonia or bronchitis.[9] However, one patient in this study developed respiratory failure secondary to influenza B infection and was subsequently intubated. Research done by Tran et. al concluded that mortality was greater for influenza B disease and were more likely to require ICU admission.[8] Our results also showed that influenza B positive patients were prone to develop viral myositis (6.3% vs 3.8%). A study done in Germany[10] showed a large outbreak of influenza B associated benign acute childhood myositis. It is an infrequently and poorly known complication of influenza and according to a research done in Taiwan a small glycoprotein unique in influenza B may render it to be more myotropic than influenza A, although further studies still need to be done to conclude on this hypothesis.[11]

Based on the WHO global influenza surveillance and response system, the predominant strain in the Philippines is influenza A.[12] This was also reported in the Global Influenza Initiative last 2017 where it was reported that influenza A remains to be the predominant strain in the Asia Pacific region, although there were sporadic outbreaks of influenza B during some weeks.[13] Out of two hundred forty-four admitted patients in the study seen to have influenza like illness, one hundred thirty-three (54%) were influenza positive. Thirty three percent (33%) were influenza B positive while only twenty one percent (21%) were influenza A positive. Traditionally, attention has been directed towards influenza A as a major source influenza infection. However the results of the Global influenza B study showed that influenza B represents roughly 20% of all cases reported to national influenza centers in 26 countries around the world, being the most common in the tropics and affecting younger age groups.[14] This was also similarly reported by Clotilde et al in a research on the epidemiology of influenza in the Asia Pacific region, that showed influenza B represented 31.4% of cases in Asia from 2010 to 2017 which was a

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higher proportion than reported elsewhere.[15] A study done by Kamigaki et al., in Baguio city showed similar reports where influenza B infections were higher among age groups 5-14 years. Influenza – related hospitalizations were higher for influenza B than influenza A.[16] This was similarly reported by Tran et al that one- third (1/3) of hospitalizations were due to influenza B.[8] Chia- Yu C et al, postulated that influenza B positive pediatric patients may have increased severity of the disease. This is because of the genetic differences between the Hemagglutinin receptor of the Yamagata lineage virus and Victoria lineage virus might alter the affinity of attachment to airway epithelium and along with young age and a naïve immune system, be responsible for the increased severity of the disease.[11] Another reason for a higher proportion of influenza B positive patients would be a possible vaccine mismatch. An influenza B vaccine mismatch is defined as a mismatch between the influenza lineage included in the vaccine and the linage that cause majority of cases in a season with significant circulation of influenza B. In a paper by Jennings et al (2018), that reviewed the epidemiology of influenza B in 15 countries in the Asia Pacific region (including the Philippines), significant or complete mismatch between the circulating and trivalent vaccine type B strain were observed on numerous occasions in countries. Influenza vaccine efficacy is reduced when there is a mismatch as is likely to be associated with a higher clinical disease burden. Evidence also suggests that younger age groups are frequently infected with influenza B. Extensive use of quadrivalent vaccines lagged until 2015 or later, and was mostly used in developed countries.[17] Although, it would be hard to conclude a vaccine mismatch based on the given data, and not within the scope of this paper.

Vaccines play a major role in the prevention of influenza. The recommended target population for influenza vaccination according to the WHO include pregnant women, healthcare workers, children aged 6-59 months, elderly and those with high risk conditions. [13] This study revealed that only 11.5% of patients received their yearly influenza vaccination. Among the twenty-eight patients (11.5%) who received their yearly vaccine, eleven were diagnosed to be influenza positive. The clinical effectiveness of influenza vaccines can vary by year and setting. This is driven by a number of factors such as virus dynamics, including vaccine match to circulating viruses and the overall influenza attack rate in the study population.[18] Vaccination is an important tool to reduce the burden of illness, especially in high risk groups. It is especially important in children as naïve immune systems respond less effectively, children are more likely than adults to become sick and to remain sick for longer periods of time. Children also have a higher viral load than adults and the period during which children can actively transmit infections to others is longer, thus increasing spread of disease. Because childhood transmission is a major driver of annual influenza epidemics, increasing vaccination uptake among children may therefore limit the widespread dissemination into the community.[19] According to the Global Influenza Initiative, disease burden in the Philippines is highest in young children, with the highest proportion of death in adults > 60 years and children aged < 5 years. Barriers to vaccination including geography, logistics, funding, lack of vaccine awareness and education. In the Philippines, insufficient or absent public funding are major barriers in doing mass influenza vaccinations. For the Philippines, influenza seasonality is from June to November, making the ideal time to administer influenza vaccine should be from April to May, with the quadrivalent vaccine having a more impact on influenza control.[13] Results of the study also showed that a proportion of admitted patients were influenza B positive. Since younger children have a higher probability of being infected with influenza B viruses, this group is more likely to benefit more from a quadrivalent vaccine containing B lineages.[17]

The genetic characteristics of influenza viruses facilitate the generation of novel strains with the potential to cause human disease. The influenza

virus contains its own RNA polymerase, which lacks proof reading functions leading to point mutations with regular frequency during genome replication. An accumulation of point mutations is known as antigenic drift and is responsible for seasonal variation of influenza A strains that cause annual epidemics. Antigenic shift is an abrupt, major change in the influenza virus proteins and enters the human population. A pandemic occurs if this newly generated strain causes disease in humans and can efficiently spread from person to person and throughout the world.[3] As the flu virus changes rapidly per year, surveillance schemes enables the WHO to evaluate the success of the yearly flu vaccine as well as recommend which influenza strains should be included in the yearly vaccine formulations. Surveillance is also important in monitoring pandemics and emerging anti-viral resistance.[20]

Influenza is an unrecognized burden in young children. In a study by Xin et al. on the global burden of respiratory infection associated with influenza in children under 5 years, in 2018 globally, there were an estimated 109.5 million influenza episodes, 10. 1 million influenza acute lower respiratory tract infection, 870, 000 influenza associated hospital admissions, and 15, 300 in hospital deaths. Research by Ruf and Knuf done in Germany showed that children age less than 5 years have greater rates of hospitalizations and complications than their older counterparts.[21] Influenza- associated complications contribute significantly to the disease burden. Common complications include otitis media, respiratory tract infections, the most important of which is pneumonia, encephalitis, and less commonly acute myositis- all these were seen in this study. Influenza illness causes children to lose school time, their parents to lose work, causing a socioeconomic as well as clinical burden.[22] In a study by Krow et al done in Utah, Salt lake City, 325 children were hospitalized for influenza for over 3 viral seasons, 16% had pneumonia and 15% were in the ICU, with 8% requiring mechanical ventilation. In the study, mortality rate was at 0.6% where 2 children died of influenza.[23] This was similarly seen in the study where complications included pneumonia, otitis media, acute myositis, and febrile convulsions. Although there was no reported mortality, the study had a patient who developed respiratory failure secondary to influenza related lower respiratory tract infection.

CONCLUSION AND RECOMMENDATION

In conclusion, majority of patients with influenza present with upper respiratory tract infections such as cough, colds and fever. This may be accompanied by other systemic symptoms such as myalgia, abdominal pain, loose stools and vomiting. Symptoms such as myalgia, difficulty of breathing and ear pain were significantly associated with a positive influenza result. Majority of cases admitted were influenza B positive. The most common clinical complication seen was pneumonia, and most of the patients did not receive yearly influenza vaccines.

The major limitation of this study is that it was done as a retrospective chart review and only included admitted patients. Suspected patients who were screened for influenza on an out-patient basis were not included in the study. Including these patients in a future study may give researchers a broader insight regarding influenza in children. This will also help track the trend of influenza in children within the community. Another limitation is the use of a rapid antigen detection kit and not the gold standard, PCR. Since the study revealed that majority of pediatric patients did not receive their yearly influenza vaccine, it is recommended that we re-educate parents regarding influenza and the benefits of yearly vaccination. Further research on influenza B in the Philippines, it's epidemiology and virologic characteristics are worthwhile. The study also recommends that influenza testing should be accessible to all patients, especially those with severe symptoms and in the high-risk group. Earlier testing, leads to earlier treatment,

decreasing morbidity and mortality among patients.

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