ORIGINAL ARTICLE

EFFECTS OF RAPID INFLUENZA ANTIGEN TEST ON ANTIMICROBIAL MANAGEMENT OF PEDIATRIC PATIENTS WITH INFLUENZA-LIKE ILLNESS IN THE EMERGENCY ROOM

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Background: Influenza is a commonly encountered respiratory tract infection and diagnosis remains to be a challenge. Use of a rapid antigen test may influence decisions on treatment in the emergency room (ER).

Objectives: This research aims to determine the effects of rapid influenza antigen test (RIAT) on antimicrobial management of influenza-like illness (ILI) in the ER, determine the clinical profile of pediatric patients with ILI and look into the relationship between RIAT result, symptomatology, and immunization status.

Methods: This is a cross-sectional study which involved review of charts of 195 pediatric patients with ILI who underwent RIAT (Klintec™) through a nasopharyngeal swab in the ER of a tertiary hospital from September 2019 to February 2020. Chi-square, Fischer exact test and likelihood ratio were used for data analysis.

Results: Most pediatric patients were 7–12 years old males. Majority presented with fever, cough, and colds and underwent RIAT at 2–4 days from onset of illness. About 73.33% of study participants did not receive their yearly influenza vaccine and 70.7% of patients with positive RIAT had no influenza vaccine. There is a lower percentage of vaccinated children who developed cough (86.5% vs. 89.5%) and colds (80.8% vs. 83.2%) when compared with unvaccinated children. RIAT result significantly affected management in terms of antimicrobial prescribing to patients with ILI.

Conclusion: Influenza presents with non-specific symptoms and vaccination remains a major preventive measure against the disease. The result of RIAT facilitates targeted treatment for influenza and decreases unnecessary antibacterial use, but this should be done with careful thought and interpretation.

KEYWORDS: *Influenza, Influenza-like illness, Rapid influenza antigen test*

INTRODUCTION

Influenza-like Illness (ILI) is defined by the World Health Organization (WHO) as an acute respiratory illness with fever of ≥38°C and cough with onset within the past 10 days.[1] Although not exclusively caused by the influenza virus, the rise in cases of ILI correlated well with the seasonal levels of transmission of influenza virus in the community. ILI affects millions of people worldwide and results in high morbidity and mortality in children. Symptoms shared by both ILI and influenza include myalgia, malaise, chills, headache, anorexia, coryza, pharyngitis, abdominal pain, vomiting and diarrhea but also present rarely as acute respiratory distress syndrome, encephalitis, and myocarditis.[2] These symptoms prompt parents to seek medical attention in the emergency room.[3] In the Philippines, influenza season starts from June to November but may extend during colder months.[4] According to the Department of Health Influenza/SARI Monthly Surveillance Reports, there were 68,091 ILI cases in the country from January 1 to June 29, 2019 and 48,329 belonged to the pediatric age group.[5] Also, out of 68,091 cases, only 4% were subjected to influenza diagnostic tests. Our locality reported 382 out of 3,664 ILI cases in our region in the first 6 months of 2019.[6] Influenza may be underreported because of the challenge in differentiating it from other viral and bacterial infections owing to the overlapping symptomatology. There are also respiratory tract infections with mixed bacterial and viral etiologies.[7] The diagnosis of influenza is difficult to ascertain based solely on clinical grounds and repercussions of misdiagnosis could result to irrational use of antimicrobial agents. Often times, clinicians start antibacterial treatment at the first instance they encounter patients with respiratory infections which may be caused by viruses. Overuse of antimicrobials can lead to resurgence of resistant organisms, surge of chronic infections, longer hospital stays if admitted, higher health care costs and even death.[8]

Diagnostic tools such as the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and viral culture for influenza are very costly, not readily accessible and require a longer turn-around time.[9,10] The use of Rapid Influenza Antigen Test (RIAT) is an alternative diagnostic modality that is relatively inexpensive, readily available and practical especially in fast-paced clinical settings like the emergency department.[9,10] RIAT is an immunoassay that can detect influenza A and B nucleoprotein antigens from respiratory specimens. On the average, the sensitivity and specificity of RIAT is 50-95% and 90-95%, respectively. One study showed that influenza diagnosed through RIAT led to a more guided treatment using antibacterial and antiviral agents.[11] Increased detection of influenza virus and timely availability of results from specimen collection resulted in lower antibacterial prescriptions and more directed use of antiviral agents.[11,12] The clinical benefits with the administration of the recommended first line antiviral agent Oseltamivir for suspected and confirmed influenza cases can also be maximized if given within 48 hours from symptom onset.[13]

RIAT became available in our institution last September 2019. The increased cases of influenza diagnosed through RIAT from children with ILI prompted the investigator to explore the effects of the said diagnostic test in the antimicrobial management of patients with ILI consulting in the emergency room; determine the clinical profile of pediatric patients presenting with ILI seen at the ER as to age and gender, signs and symptoms, history of influenza vaccination, and duration of signs and symptoms before testing; determine the association between history of influenza vaccination and RIAT result; determine the association between the symptomatology of ILI and vaccination history, and determine the association between RIAT and management in the emergency room in terms of antimicrobial prescriptions (antiviral alone, antiviral and antibacterial, and antibacterial alone). To the best of our knowledge, no similar study has been done and published locally.

MATERIALS AND METHODS

Study Design, Setting and Participants

This is a cross-sectional study that utilized total population sampling in a tertiary hospital. Data were collected from charts of pediatric patients seen in the emergency department from September 2019 to February 2020.

Inclusion and Exclusion Criteria

The study enrolled patients aged 0 to 18 years old diagnosed with ILI (as per WHO criteria) who were seen at the emergency department and underwent RIAT through a nasopharyngeal swab.

Excluded in the study were patients who did not undergo RIAT, patients with incomplete medical records, those requiring hospital admission, patients who were tested with RIAT ≥ 5 days from onset of symptoms, patients with Severe Acute Respiratory Infection (SARI) and those with other respiratory tract infections (pulmonary tuberculosis, pneumonia, empyema, pulmonary abscess) and comorbidities like chronic lung diseases.

Study Size

The sample size was computed using OpenEpi version 3 (2013) based on a prior local data on the prevalence of ILI which was 382. A total of 192 was derived at 95% confidence interval, and sets the minimum population required for the study. A total of 221 patient records were screened and from this, 195 were included in the final study.

Methods

Retrospective chart review and data extraction were done by two research assistants who were oriented on the inclusion and exclusion criteria. A standardized Data Collection Tool (DCT) was also utilized to ensure consistency. This study was conducted during the influenza season, between September 2019 to February 2020. Medical records of enrolled participants who met the eligibility criteria were examined. RIAT (Klintec^{TM}) was performed at the discretion of the ER physicians to patients with ILI during the study period. The test kit was manufactured by Zhejiang Orient Gene Biotech Co., LTD. It can indicate the type of influenza virus as either type A, B or both. It has a 92.6% sensitivity and 96.4% specificity for influenza A virus and 90% sensitivity and 95.8% specificity for influenza B virus for nasopharyngeal swab specimens. Its positive and negative predictive values were highly dependent on influenza prevalence. The test turn-around time is 10–15 minutes. There were no cross-reactions with adenovirus, coronavirus, Coxsackie virus, HHV, rhinovirus, measles, mumps, Sendai virus and parainfluenza virus.[14]

Through the DCT, the demographics and clinical profile were documented according to age group (divided according to age and stages, i.e., infancy, toddler, preschool, school age and adolescence), gender, influenza vaccination status, signs and symptoms, time of onset of signs and symptoms before RIAT, RIAT result, and the treatment prescribed.

All DCTs were submitted to the researcher who tallied each categorical data with their corresponding codes. The data was recorded using a password-protected Microsoft Excel sheet on a password-protected laptop. Double data entry was done to ensure data recording accuracy and frequencies were done to check for consistency.

Outcome Measures

The primary outcome measure is the effect of RIAT result in the management of pediatric patients with ILI in the emergency department in terms of antimicrobial prescription whether it be an antiviral alone, a combination of antiviral and antibacterial or an antibacterial alone.

Statistical Analysis

Demographics, clinical profile and the association between influenza vaccination history and RIAT result were presented as frequencies and percentages, and were analyzed using Chi-square test. The analysis of the association of the time of testing for RIAT from illness onset and RIAT result, the association of administration of antiviral and day of illness, and the association between RIAT result and the management of influenza with antimicrobials also made use of chi-square, Fisher exact test and likelihood ratio. Data were analyzed using SPSS Statistics version 21. The level of significance was set at $p < 0.05$.

Ethical Considerations

The study was approved by the institution's Research Ethics Committee (REC). The consent process was not applicable as this study utilized a retrospective chart review. However, permission was sought through informed and/or written consent from the attending pediatricians as recommended by the REC.

No data was divulged to comply with the Data Privacy Act of 2012. Chart review for data collection was only done at the Records Division of the hospital by the research assistants. Patient confidentiality was respected by ensuring the anonymity of patient records. All documents (electronic and printed copies) that were related to the study (i.e., data collection forms, consent forms, letters etc.) were kept and stored safely by the researcher.

RESULTS

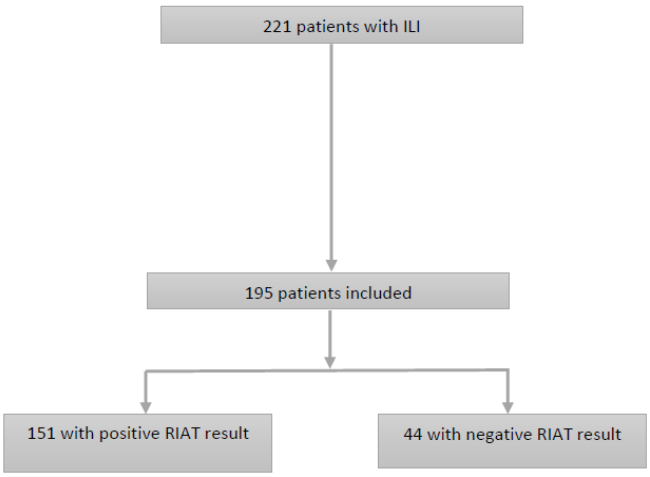

Figure 1: Schematic flowchart of patients included in the study; ILI, Influenza-like illness; RIAT, rapid influenza antigen test

A total of 221 patients with ILI were screened, 26 of whom were excluded for failing some of the eligibility criteria, reducing the total study population to 195 (Fig. 1). Among excluded patients, 7 were not tested for RIAT, 8 required hospital admission, 3 had co-morbidities, 3 were tested with RIAT ≥ 5 days from illness onset and 5 had incomplete medical records. Of 195 patients, 151 had a positive RIAT.

The demographic profile and vaccination status of 195 study participants are shown in Table 1. Majority are males (57.43%, n=112) and the modal age group is 7–12 years old (28.21%). About 73.33% (n=143) of the study population did not receive an influenza vaccine.

Table 1: Demographic and Influenza Vaccine Profile of Study Patients (N=195)

Age group	**With Vaccine (n=52)**	**Without Vaccine (n=143)**	**Chi-square (p <0.05)**
<12months	5 (2.56)	9 (4.62)	0.52
1-3 years	9 (4.62)	32 (16.41)	
4-6 years	8 (4.10)	34 (17.44)	
7-12 years	16 (8.21)	39 (20)	
13-18 years	14 (7.18)	29 (14.87)	
Chi-square value = 3.2275			
Gender	**With Vaccine (n=52)**	**Without Vaccine (n=143)**	**Chi-square (p <0.05)**
Male	33 (16.92)	79 (40.51)	0.30
Female	19 (9.74)	64 (32.82)	

Table 2 shows that the most common reported symptoms throughout all age groups were fever, cough, and colds. There is a higher proportion of patients belonging to the younger age group who manifested with loose bowel movement, vomiting, and seizures compared to older children. There is also a higher proportion of older children who presented with chills, body malaise, sore throat, ear pain, abdominal pain, headache, and anorexia (χ^2= 123.682, p value = 0.00001).

Table 2: Signs and Symptoms of Patients at the Emergency Room

Age Groups				Chi-Square (p <0.05)
0 – 3 years old (n=55)		4 – 18 years old (n=140)		
Symptom	**n (%)**	**Symptom**	**n (%)**	
Fever	55 (100)	Fever	140 (100)	0.00001
Cough	49 (89.1)	Cough	124 (88.6)	
Colds	49 (89.1)	Colds	112 (80.0)	
Loose bowel movement	19 (34.5)	Sore throat	55 (39.3)	
Vomiting	17 (30.9)	Vomiting	35 (25.0)	
Seizures	2 (3.6)	Body malaise	34 (24.3)	
Chills	0 (0)	Headache	32 (22.9)	
Body malaise	0 (0)	Abdominal pain	27 (19.3)	
Sore throat	0 (0)	Chills	23 (16.4)	
Ear pain	0 (0)	Ear pain	22 (15.7)	
Abdominal pain	0 (0)	Loose bowel movement	14 (10.0)	
Headache	0 (0)	Anorexia	12 (8.6)	
Anorexia	0 (0)	Seizures	0 (0)	

There is a significantly higher proportion of patients with positive RIAT who did not receive the influenza vaccine while 20% of patients with negative RIAT were vaccinated for influenza (χ^2 = 111.5832, p value = 0.00001) (Table 3).

Table 3: Influenza Vaccination History and RIAT result

Vaccination Status	Rapid Influenza Antigen Test Result		TOTAL n (%)	Chi-Square (p <0.05)
	RIAT Positive n (%)	RIAT Negative n (%)		
With influenza vaccine	13 (6.7)	39 (20)	52 (26.7)	0.00001
Without influenza vaccine	138 (70.7)	5 (2.6)	143 (73.3%)	
TOTAL	151 (77.4)	44 (22.6)		

RIAT: rapid influenza antigen test

Table 4 shows the difference in symptomatology of pediatric patients with ILI in relation to vaccination history. Irrespective of vaccination status, the top presenting symptoms are fever, cough, and colds and symptoms of ILI are independent of vaccination history (χ^2 = 5.208, p value = 0.970).

Table 4: Symptomatology of ILI and Vaccination History

Symptom	Without Vaccination n (%)	With Vaccination n (%)	TOTAL
Fever	143 (100)	52 (100)	195
Cough	128 (89.5)	45 (86.5)	173
Colds	119 (83.2)	42 (80.8)	161
Chills	16 (11.2)	7 (13.5)	23
Loose bowel movement	24 (16.8)	9 (17.3)	33
Vomiting	37 (25.9)	15 (28.8)	52
Seizures	2 (1.4)	0 (0)	2
Body malaise	23 (16.1)	11 (21.2)	34
Sore throat	41 (28.7)	14 (26.9)	55
Ear pain	19 (13.3)	3 (5.8)	22
Abdominal pain	20 (14.0)	7 (13.5)	27
Headache	24 (16.8)	8 (15.4)	32
Anorexia	10 (7.0)	2 (3.8)	12
TOTAL			195

Chi-square value = 5.208*; p value = 0.970
ILI: Influenza-like Illness
*Significant at 0.05 level

The duration of signs and symptoms of influenza prior to testing are shown in Table 5. There is a significantly higher proportion of patients who were positive for either influenza A or B or both antigens when RIAT was done at 2–4 days from illness onset (χ^2 = 8.043, p value = 0.039).

Table 5: Duration of Signs and Symptoms before RIAT

RIAT Positive (n=151)					RIAT Negative (n=44)	TOTAL n (%)
Onset of Symptoms	*Influenza A*	*Influenza B*	*Both*	*Total n (%)*		
≥ 12-24 hours	43	22	1	66 (33.85)	29 (14.87)	95 (48.72)
2-4 days	51	30	4	85 (43.59)	15 (7.69)	100 (51.28)
TOTAL	94	52	5	151 (77.44)	44 (22.56)	195

Chi-Square value = 8.043*; p value = 0.039
Fisher Exact Test value = 7.864; p value = 0.042
RIAT: rapid influenza antigen test
*Significant at 0.05 level

Table 6 shows a significantly higher proportion of patients with ILI who were prescribed by ER physicians with an antiviral alone (n=84) by the 2nd to 4th day of illness (χ^2 =5.677, p value = 0.059).

Table 6: Medications Administered and Day of Illness

Management	Day of Illness		TOTAL n (%)
	1st day, n (%)	2nd to 4th day, n (%)	
Antiviral Alone	73 (37.4)	84 (43.1)	157 (80.5)
Antiviral + Antibacterial	17 (8.7)	16 (8.2)	33 (16.9)
Antibacterial Alone	0 (0)	5 (2.6)	5 (2.6)
TOTAL	90 (46.1)	105 (53.9)	195

Chi-square value: 5.677*; p value = 0.059
Likelihood ratio: 7.605; p value = 0.022
*Significant at 0.05 level

There is a significantly higher proportion of patients who tested positive for influenza antigen and were prescribed with an antiviral agent alone (64.10%, n=125) while 13.33% were prescribed with both an antiviral and antibacterial. No patient with positive RIAT was given an antibacterial agent alone while 16.41% (n=32) of patients with negative RIAT were still prescribed with an antiviral (χ^2 = 17.621, p value = 0.001) (Table 7).

Table 7: Results of RIAT and Prescribed Antimicrobials

RIAT result	Antiviral Alone n (%)	Antiviral + Antibacterial n (%)	Antibacterial Alone n (%)	TOTAL n (%)
Positive	125 (64.10)	26 (13.33)	0 (0)	151 (77.44)
Negative	32 (16.41)	7 (3.59)	5 (2.56)	44 (22.56)
TOTAL	157 (80.51)	33 (16.92)	5 (2.56)	195 (100)

Chi-square value = 17.621*; p value = 0.001
Fisher Exact Test value = 13.567; p value = 0.001
RIAT: rapid influenza antigen test
*Significant at 0.05 level

DISCUSSION

Influenza is a common and highly contagious respiratory disease that causes a wide array of clinical symptoms in children. Features may vary with age, immunization status, and presence of co-morbidities.[2] The demographic data presented in this study varies from what was presented by Reyes et al. where majority of children with ILI were females with a mean age of 5–9 years old. Our findings of fever, cough, and colds were the most common presenting manifestation in patients with ILI in the pediatric population and were congruent with those of Reyes et al.[15] Our study also showed that loose bowel movement, vomiting, and seizures were commonly manifested by the younger age group which suggest that influenza may be less distinct in younger children.[2,16] Non-specific symptoms such as chills, body malaise, sore throat, ear pain, abdominal pain, headache, and anorexia were prominent in the older age group and are also consistent with the clinical manifestations of influenza infection.[2]

Children are more likely to be infected by influenza and have a higher viral load compared to adults thus harboring and actively transmitting the virus for a prolonged period.[17] About 73.33% (n=143) of our study patients did not receive their yearly influenza vaccine and 70.7% (n=138, p value = 0.00001) of patients with positive RIAT results were unvaccinated for influenza. Lack of vaccine coverage can be due to geographical factors, financial constraints, personal belief and lack of education on vaccination.[15] Our findings also indicate that there is

no relation in symptoms of pediatric patients with ILI with vaccination history (p value = 0.970). One hundred percent of vaccinated and unvaccinated children experienced fever. However, there is a lesser percentage of vaccinated children who experienced cough and colds as opposed to those who were unvaccinated. Children who do not receive the annual influenza vaccine are more likely to develop influenza-related illness.

During the 2009 influenza A (H1N1) pandemic, CDC reported that among the pediatric deaths registered, about 80% were unvaccinated.[18] Increasing vaccination coverage strengthens the control of viral spread in the community and confers a degree of protection against influenza.[17] Despite the findings that symptoms of ILI are independent of vaccination history, children who received the influenza vaccine have reduced influenza-related signs and symptoms. They have less severe infection and a shorter duration of illness compared to unimmunized children.[19] Moreover, vaccines are effective in decreasing flu-associated complications and healthcare burden.[17,19] At every opportunity, physicians should ensure the availability of vaccines, educate on the importance of vaccination, and actively encourage them to receive influenza vaccine yearly.

The diagnosis of influenza imposes a challenge to physicians because its presentation overlaps with other respiratory viruses and possible bacterial co-infections. Furthermore, clinical assessment alone may be insufficient especially in younger children who may not present with the classic findings of influenza.[20] The most definitive diagnostic tool for influenza requires a significant amount of time which is impractical in a fast-paced setting like the emergency department. An alternative diagnostic technique is RIAT which offers a fast and convenient evaluation of children with ILI.[21] The duration of signs and symptoms of ILI prior to testing can affect the results of RIAT.[10,22] Our study showed that RIAT was more likely to detect influenza viral antigen when the time of testing was done at 2–4 days from symptom onset (43.59%, p value = 0.039). The American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC) state that specimen collected and tested within 2–4 days from onset of illness will more likely yield a positive result.[9-10] The likelihood of an accurate diagnosis of influenza in conjunction with RIAT is further strengthened when the clinical symptoms are consistent with influenza and when its activity is high in a population.[9,10,22] Symptoms consistent with influenza increase the pre-test probability of an influenza viral infection, consequently increasing the reliability of a positive RIAT result.[10] Patients with ILI were tested with RIAT under the ER physician's discretion during the peak season of influenza. These findings suggest that ER physicians should subject patients to undergo RIAT during the influenza peak season within 2–4 days from onset of illness if the symptoms are consistent with influenza.

Patients on the 2nd to 4th day of illness were more likely prescribed with an antiviral alone (43.1%, p value = 0.059). Oseltamivir, one of the most commonly prescribed antiviral agents for influenza, is best started within 48 hours of illness onset. However, patients would still benefit from this antiviral if started by the 3rd and 4th day of illness if the clinical presentation is compatible with influenza.[13] ER physicians should not delay or defer prescribing an antiviral agent even after 48 hours of symptom onset especially if there is a high index of suspicion for influenza infection.

This study revealed that the results of RIAT affect decision-making of ER physicians in the management of ILI. Of 195 patients, 125 (64.10%) who tested positive were prescribed with an antiviral alone. Similar studies by Blaschke et al. and Jennings et al. stated that the most common antiviral agent prescribed was Oseltamivir when the diagnosis of influenza was confirmed through RIAT.[11,23] These findings suggest that the decision to initiate this antiviral by the physician was linked with a higher level of confidence and provided diagnostic certainty once influenza was confirmed through RIAT along with clinical assessment.[23] Likewise, RIAT facilitates the physician's decision-making for targeted treatment by prescribing an antiviral to patients with positive results. The physician's decision for use of

an antiviral may itself limit antibacterial prescriptions. About 13.33% (n=26) of study participants positive for influenza antigen test were prescribed with both an antiviral and antibacterial and no patient with positive RIAT was given an antibacterial alone. Jennings et al. and Bonner et al. observed that some physicians would prescribe both an antiviral and antibacterial to patients who have a positive influenza antigen test result.[23-24] On the other hand, both studies also stated that physicians were more willing to withhold antibacterial treatment once the diagnosis of influenza was supported by RIAT.[23] These decisions on treatment were made based on the physician's clinical evaluation, experience, and discretion that certain patients with influenza might have bacterial co-infections that warrant antibacterial use along with an antiviral.[11] Additionally, physicians would rarely start antibacterial treatment alone if the RIAT result is positive, limiting inappropriate antibacterial use.[23,25] About 16.41% (n=32) of our patients received an antiviral despite negative RIAT results. A negative RIAT result does not exclude influenza infection and nor should it affect the physician's decision in prescribing an antiviral especially when clinical suspicion for influenza is high. Physicians should not rely solely on RIAT results in their decision to initiate antiviral therapy.[21] ER physicians must take caution when interpreting results of RIAT. This diagnostic test has its advantages, but it should be interpreted in conjunction with careful clinical examination. In settings where RIAT or other means of testing for influenza are unavailable, physicians should still commence treatment with an antiviral especially if the patient's clinical manifestations are consistent with influenza infection to ensure timely treatment and avoidance of unnecessary antibacterial prescriptions which will help prevent the emergence of resistant bacteria.

CONCLUSION

In conclusion, this study showed that majority of pediatric patients with ILI belong to the 7–12 year old age group and were predominantly male. Fever, cough, and colds were the most common manifestations and majority were tested positive for RIAT at 2–4 days from symptom onset. A significant proportion of study participants did not receive an influenza vaccine and were positive for influenza antigen test. Vaccinated children have lesser probability of developing influenza-related symptoms compared to children who were unimmunized. RIAT in the diagnosis of influenza significantly affects decision making of ER physicians in terms of appropriate antimicrobial prescriptions. A positive influenza antigen test result led to a targeted treatment using the recommended antiviral thus preventing unnecessary antibacterial prescriptions.

LIMITATIONS AND RECOMMENDATIONS

This study was done in a single influenza season and in one tertiary hospital with a relatively few number of study patients. Furthermore, selection bias might be present in this study since it only included pediatric patients who underwent RIAT under the ER physician's discretion. Other factors such as physical examination and diagnostic tests (i.e., complete blood count, chest radiographs) that may also influence the ER physician's decision making for antimicrobial prescriptions were not investigated. Future studies may opt to explore other testing modalities for influenza and involve admitted patients or those seen in the outpatient department. A multi-center study done through multiple influenza seasons to make more conclusive findings is also suggested.

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