ORIGINAL ARTICLE

Comparative Demographics of Influenza A by Genetic Subtypes through Surveillance Approach for Severe Acute Respiratory Infection in Children: A Hospital-Based Study from 2019 to 2020

Asri Ludin Tambunan[1), Dwi Herawati Ritonga[2), Lydia[1), Muhammad Al Anas[1)

ABSTRACT

Severe acute respiratory infections (SARI) are diseases caused by transmittable agents, including Influenza A. SARI causes high morbidity and mortality of children under five in the world, including Indonesia, and is important to both health and socioeconomic concerns.

Objective: **This study assesses characteristics of influenza A, and its various subtypes, in a broad population at the point of care, across child's age groups, then evaluates the performance of clinical case definitions.**

Methods: **From January 2019 until December 2020, we take a sample from patients with SARI criteria hospitalized at the RSUD Drs H Amri Tambunan as one of the six sentinel SARI surveillance hospitals then sent it to the National Institute of Health Research and Development (NIHRD), Ministry of Health Indonesia for testing. We assess the associations between influenza A subtypes and demographic parameters.**

Results: **Of 28 subjects, 17 (60.7%) are male and 11 (39.3%) are female. 16 (57.1%) of them are young children (0-4 years) and 12 (42.9%) of them are older children (5-17 years). The most frequent diagnosis is Bronchopneumonia with 11 subjects (39.3%). 24 (85.7%) subjects have chief complaints of fever and cough, with diarrhea as second complaint in 5 patients (17.9%). We found H1pdm09 and H3 subtypes in 17 (60.7%) and 11 (39.3%) subjects, respectively. 15 (53.5%) are in a short period of care, and 13 (46.4%) are in a long period. We found a strong correlation between influenza A subtypes and length of stay (r = 0.937) with β-estimate and OR (95% CI) of 1.067 (0.233-4.885).**

Conclusions: **Young children are the age group most affected by influenza A by the risk of 1.067 times for a longer length of stay between subtypes. Many factors affect the probability of being infected with influenza and of being captured by national influenza surveillance.**

KEY WORDS

influenza A, genetic subtypes, surveillance, demographics

INTRODUCTION

Influenza virus is estimated to cause 3 to 5 million cases of severe illness and 250,000 to 500,000 deaths each year, while 5%-10% of adults and 20%-30% of children are infected with the influenza virus worldwide. In lower and middle-income countries, influenza could result in large economic burden encompassing direct costs to the health service and households, and indirect costs of productivity losses. Influenza has a high burden of disease and mortality worldwide, especially among groups at increased risk for complications, such as children under 5 years old, the elderly, pregnant women, and individuals with chronic medical conditions. Influenza prevention requires periodic vaccination campaigns designed according to the virological information gathered at different sentinel points[1)].

Severe Acute Respiratory Infection (SARI) is an important cause of morbidity and mortality worldwide. Increased uptake of the pneumococcal conjugate vaccine (PCV) and the Haemophilus influenzae type b (Hib) vaccine have led to declines in fatal outcomes due to lower respiratory infections, from 3.4 million deaths worldwide in 1990 to 2.8 million in 2010[2)]. However, SARI is associated with a large number of different viral and bacterial agents, notably influenza A and B viruses, parainfluenza viruses, coronaviruses, respiratory syncytial viruses (RSV), adenoviruses (AV), and rhinoviruses[3)].

The complex interrelationships between the prevalent pathogens that cause SARI are not well understood. Influenza, in particular, is a very common and sometimes serious infectious disease, with an epidemiological picture marked by seasonal peaks in winter months and antigenic drift and shift, which potentiate local and regional outbreaks and global pandemics[4)]. A community influenza burden assessment in England found that approximately 18% of the unvaccinated population became infected with influenza A or B viruses each season during 2006

Received on February 27, 2022 and accepted on March 11, 2022
1) Research and Development Division, RSUD Drs H Amri Tambunan Lubuk Pakam, Indonesia
2) Department of Pediatrics, RSUD Drs H Amri Tambunan Lubuk Pakam, Indonesia
Jl. Thamrin, Lubuk Pakam, North Sumatera, Indonesia
Correspondence to: Dwi Herawati Ritonga
(e-mail: dwiherawatiritonga@gmail.com)

Asri Ludin Tambunan: 0000-0001-6825-9818
Dwi Herawati Ritonga: 0000-0002-5050-1618
Lydia: 0000-0001-6514-6826
Muhammad Al Anas: 0000-0002-4521-5916

Table 1: General characteristics group of children patients admitted for influenza-associated severe acute respiratory infections (SARI) at RSUD Drs H Amri Tambunan, Lubuk Pakam, Deli Serdang 2019-2020 (n = 28)

Characteristics	Mean (min-max ± SD)	
Age	4.418 years (8 months-13 years ± 3.3032)	
Length of stay	5.39 days (2-12 days ± 2.455)	
Characteristics	No. of cases (percentages)	P-value
Gender		
Male	17 (60.7%)	< 0.001
Female	11 (39.3%)	< 0.001
Age category		
Younger children (0-4 years old)	16 (57.1%)	< 0.001
Older children (5-17 years old)	12 (42.9%)	< 0.001
Total	28 (100%)	

Table 3: Bivariate analysis of a group of children patients admitted for influenza-associated severe acute respiratory infections (SARI) at RSUD Drs H Amri Tambunan, Lubuk Pakam, Deli Serdang 2019-2020

Characteristics	Genetic Subtypes		p-value	r-value	β-estimate OR (95% CI)
	H1Pdm09	H3			
Age					
Young children	8	8	0.172[a]	0.253[c]	0.333
Older children	9	3			(0.065-1.707)
Gender					
Male	9	8	0.260[a]	0.313[c]	0.422
Female	8	3			(0.082-2.160)
Antibiotic treatment					
Yes	16	11	0.607[a]	0.432[c]	0.413
No	1	0			(0.061-2.045)
Length of stay					
Long period	11	2	**0.002[b]**	**0.937[c]**	**1.067**
Short period	6	9			**(0.233-4.885**
Total	**28 (100%)**				

[a]Fisher's exact test
[b]Chi-Square test
[c]Spearman correlation

Table 2: Clinical characteristics of a group of children patients admitted for influenza-associated severe acute respiratory infections (SARI) at RSUD Drs H Amri Tambunan, Lubuk Pakam, Deli Serdang 2019-2020 (n = 28)

Characteristics	No. of cases (percentages)	P-value
Primary Diagnosis		< 0.001
Acute Gastroenteritis	6 (21.4%)	
Acute Sinusitis	1 (3.6%)	
Bronchopneumonia	11 (39.3%)	
Complex Febrile Seizures	1 (3.6%)	
Dengue Fever	2 (7.1%)	
Simple Febrile Seizures	4 (14.3%)	
Thalassemia	1 (3.6%)	
Typhoid Fever	1 (3.6%)	
Upper Respiratory Tract Infection	1 (3.6%)	
Secondary Diagnosis		< 0.001
Absent	15 (53.6%)	
Bronchopneumonia	2 (7.1%)	
Creeping Eruption	1 (3.6%)	
Hepatitis	1 (3.6%)	
Malnutrition	1 (3.6%)	
Tuberculosis	1 (3.6%)	
Upper Respiratory Tract Infection	7 (25%)	
Chief Complaints		< 0.001
Fever and Cough	24 (85.7%)	
Seizures	4 (14.3%)	
Secondary Complaints		< 0.001
Absent	8 (28.6%)	
Anorexia	1 (3.6%)	
Cold	1 (3.6%)	
Diarrhea	5 (17.9%)	
Dyspnea	4 (14.3%)	
Fever and Cough	4 (14.3%)	
Pale	1 (3.6%)	
Seizures	1 (3.6%)	
Vomiting	3 (10.7%)	
Antibiotic treatment		< 0.001
Yes	27 (96.4%)	
No	1 (3.6%)	
Genetic subtypes		< 0.001
H1Pdm09	17 (60.7%)	
H3	11 (39.3%)	
Length of stay		< 0.001
Long period (< 5 days)	13 days (46.4%)	
Short period (> 6 days)	15 days (53.6%)	
Total	28 (100%)	

± 2011[5].

Although three-quarters of the infections in this population were asymptomatic, symptoms and complications are often more severe among well recognized high-risk groups. For example, the hospitalization rate due to respiratory illness during an influenza season in Japan was 4.3 times higher among pregnant women than among those who were not pregnant. Routine monitoring of influenza A/B virus activity is the foundation for preparedness and response to the virus and its pandemic potential[6]. Special studies are not sufficient to provide timely and actionable information to guide response. In 2006, WHO and other organizations evaluated the influenza A pandemic response and preparedness capacity in the country of Indonesia, among other countries. The review found deficiencies in the local epidemiological and laboratory capacity[7].

Recent understanding gained from pandemics in the past led to the development of the World Health Organization (WHO) Global Pandemics Preparedness Plan at the beginning of the 21st century. This plan was designed to help countries prepare for influenza virus pandemics like the ones experienced in 2009, when timely detection of the emergent virus failed, impeding the effectiveness of mitigation measures[8]. One result of this experience was the development of an active surveillance network to monitor admitted patients with severe acute respiratory infections (SARI) in sentinel hospitals that includes appropriate sampling, laboratory testing, and early online reporting[8,9].

The SARI surveillance network (SARInet) has been operating in various countries in the world and the South East Asia; in Indonesia, it includes six hospitals in different geographic regions (west, central, and east).

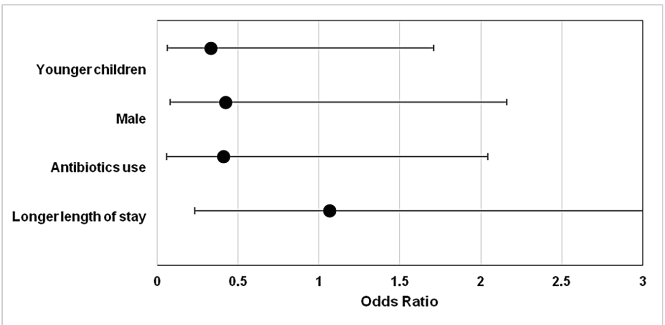

Figure 1. Forest plots for odds ratio towards genetic subtypes.

OBJECTIVE

Using the observational data collected through SARInet, this study aimed to 1) describe clinical characteristics of adult patients in RSUD Drs H Amri Tambunan Serdang Lubuk Pakam with influenza-associated SARI, and 2) analyze virus subtypes identified in specimens collected from those patients, hospital resources used in clinical management, clinical evolution, and risk factors associated with a fatal outcome.

METHODS

This descriptive observational study used data from the SARI surveillance network complemented by information obtained from reviews of individual medical records. The researchers identified adult patients hospitalized with influenza-associated SARI between January 2019 and December 2020 at RSUD Drs H Amri Tambunan, one of the six SARI sentinel surveillance hospitals in Lubuk Pakam, Deli Serdang, North Sumatera. SARI cases were identified using the following standard case definition: measured/reported fever plus respiratory symptoms associated with tachypnea (≥ 30 breaths/minute) and/or low pulse oximetry (blood oxygen saturation < 90% while breathing ambient air). However, fever was a conditional inclusion criterion, left to the discretion of the physician in charge of case recruitment, due to the older age of the study cohort, as described in more detail below.

Nasopharyngeal swab specimens collected from patients that met the SARI criteria were analyzed first by direct immunofluorescence (IF) for eight different viruses: influenza A and B, parainfluenza 1-3, respiratory syncytial virus, metapneumovirus, and adenovirus. Samples positive for influenza or negative for all respiratory viruses were processed further at the national reference laboratory in National Institute of Health Research and Development (NIHRD), Ministry of Health Indonesia, using reverse transcription polymerase chain reaction (RT-PCR) to detect influenza A or B and perform viral subtyping. All adult patients with SARI and influenza, based on molecular detection methods, were included in the study. Cases with incomplete information or readmissions were excluded.

For each case, demographic and other information, including age that we classified into young children (≤ 5 years old) and older children (≥ 6 years old) and gender; epidemiological week of admission; length of stay in long-term care facilities; comorbidities; symptoms and signs at admission (e.g., cough, sputum, obstructive symptoms, rhinorrhea, headache, myalgia); systolic (< 90 mmHg) or diastolic (< 60 mmHg) hypotension; initial laboratory evaluation (hemoglobin concentration; leukocyte, lymphocyte, and platelet count; erythrocyte sedimentation rate (ESR); plasmatic lactic dehydrogenase (LDH); albumin; blood urea nitrogen (BUN); serum creatinine concentration; and C-reactive protein (CRP) concentration); and presence or absence of pneumonia (as interpreted by the physician in charge or based on the radiologist report).

Pneumonia was classified as lobar or interstitial. Blood cultures were requested based on the discretion of attending physicians. Clinical presentation was classified in the following mutually exclusive groups: influenza-like illness (ILI) (no pneumonia, decompensated heart failure, or asthma); asthma (signs of obstruction without pneumonia or cardiovascular collapse); chronic bronchitis exacerbation (positive history, increased cough, sputum or dyspnea, and no pneumonia); pneumonia (as detected by chest x-ray); and cardiovascular decompensation (heart failure diagnosed by physical examination).

Data on variables associated with disease management (need for invasive or noninvasive mechanical ventilation; corticosteroid use (systemic or inhaled); vasoactive drugs; antiviral (oseltamivir); and antibiotic compounds prescription) were also obtained. Site of hospitalization (critical care or general ward beds) was also recorded, and outcome at discharge (deceased or alive).

Risk or protective factors associated with death or intensive care unit (ICU) admission were identified by odds ratio (OR) calculations. Continuous variables were transformed to categorical variables to facilitate OR estimations. Factors identified by univariate analysis were integrated in a multivariate analysis by binary logistic regression, and the correlations identified by Spearman if both of the variables were categorical, and Pearson if its numerical. This study was approved by the RSUD Drs H Amri Tambunan Lubuk Pakam and, as a retrospective analysis of the data, deemed exempt from the informed consent requirement. Patient anonymity was assured during the analysis.

RESULTS

From January 2019 to December 2020 (one year), 28 children patient with SARI were admitted to RSUD Drs H Amri Tambunan, Lubuk Pakam and were tested for influenza. In the general features, characteristics of the study included children with the mean age of 4.418 years ranging from 8 months to 13 years old with the mean length of stay is 5.39 days ranging from 2-12 days. We found 17 male (60.7%) and 11 female (39.3%) with the category of young children (0-4 years old) for 16 children (60.7%) and older children (5-17 years old) for 12 children (42.9%). All of the data were analyzed and we obtained the p-value for each variable of < 0.001 as can be seen in Table 1.

We obtain the clinical characteristics, with the most common primary diagnosis for the influenza-associated SARI is Bronchopneumonia for 11 samples (39.3%), followed by Acute Gastroenteritis for 6 samples (21.4%), Simple Febrile Seizures with 4 samples (14.3%), Dengue Fever for 2 samples (7.1%), and Acute Sinusitis, Complex Febrile Seizures, Thalassemia, Typhoid Fever and Upper Respiratory Tract Infection for 1 case each (3.6%), respectively. For the secondary diagnosis, most of the children are not having any secondary diagnosis for 15 samples (53.6%), followed by Upper Respiratory Tract Infection for 7 samples (25%), Bronchopneumonia for 2 samples (7.1%), and Creeping Eruption, Hepatitis, Malnutrition, and Tuberculosis for 1 case each (3.6%), respectively.

The most common chief complaints that came with influenza-associated SARI is fever and cough for 24 cases (85.7%), followed by seizures for 4 cases (14.3%). Again, most of the samples have no secondary complaints for 8 samples (28.6%), followed with diarrhea for 5 samples (17.9%), dyspnea, fever and cough for 4 samples each (14.3%), vomiting for 3 samples (10.7%) and anorexia, cold, pale, and seizures for 1 case each (3.6%).

For the history of treatment, nearly entire samples (27 cases, 96.4%) are having antibiotic treatments while one case has no history of antibiotic treatments (3.6%). For Influenza A genetic subtypes, we found 17 cases (60.7%) samples with H1Pdm09 subtypes and 11 cases (39.3%) for H3 subtypes. Through this, 15 samples are having short period of stay in the hospital for 15 days (53.6%) and 13 samples are having long period of stay (46.4%) as can be seen in Table 2.

In the table 3, we show the bivariate analysis between the variables and the genetic subtypes of Influenza A. For young children, 8 samples are having h1Pdm09 subtypes and 8 others are having H3 subtypes. While for older children, 9 samples are having H1Pdm09 subtypes while 3 samples are having H3 subtypes with the p-value of 0.172, r-value of 0.253 and B-estimate OR (95% CI) of 0.333 (0.065-1.707). 9 boys are having H1Pdm09 subtypes, and 8 of them are having H3 subtypes. While for the girls, 8 of them are having H1Pdm09 subtypes and 3 of them are having H3 subtypes with the p-value of 0.260, r-value of 0.313 and B-estimate OR of 0.422 (0.082-2.160). For the samples who received antibiotic treatments, 16 of them are having H1Pdm09 subtypes while 11 of them are having H3 subtypes. Only one samples who is not receiving any antibiotic treatments and having H1Pdm09 subtypes.

For the length of stay, 11 of samples are having long period of stay with H1Pdm09 subtypes, while 2 samples are having H3 subtypes. For short period of stay, we see the reverse result where most of the samples with H3 subtypes are dominantly having short period of care with 9 samples, compares to 6 H1Pdm09 who less likely for having short period of care with p-value of 0.002, r-value of 0.937 and B-estimate OR of 1.067 (0.233-4.885). This indicates that the length of stay and genetic subtypes are having significant and strong correlation. If the beta coefficient is positive, the interpretation is that for every 1-unit increase in the length of stay, the likelihood of H1Pdm09 will increase by the beta coefficient value of 1.067 times. For the rest of variables, no significant differences were detected between the age, gender and antibiotic treatment towards the genetic subtypes of Influenza A as in the Figure 1.

DISCUSSION

Sentinel surveillance of SARI at RSUD Drs H Amri Tambunan, Lubuk Pakam from 2019-2020 demonstrated that despite a seasonal distribution, influenza was a near-permanent cause of hospital admissions year-round, in Indonesia's temperate climate. This pattern reinforces the need for suspicion, diagnosis, and appropriate treatment of this viral infection beyond assumed timeframes (rain-dry)[9]. In this study, SARI affected mainly young children for the fact that in this group of age ≤ 5 years old are having slightly weak immune system due to low exposure of environment. Moreover, the length of stay was also prolonged in this group. These findings underscore the extent of the influenza disease burden and the need for additional public health efforts to prevent it[10].

Three factors appeared to have magnified the consequences of influenza in the study cohort: 1) low coverage of the influenza vaccine, 2) host characteristics, and 3) disease-associated conditions. Low coverage of the influenza vaccine (only 34.3%) decreased the preventive effect of seasonal vaccination—a strategy that has been shown to have a profound impact on vulnerable populations and reduce hospitalizations among elderly patients and those with diabetes mellitus, cancer, or dialysis[11]. Seasonal vaccination also reduces mortality in the same groups. More than 90% of the patients in this patient group had indications for influenza seasonal vaccination, but influenza vaccine uptake was low, and after multivariate analysis the vaccine turned out to be a significant protective factor for in-hospital mortality. Influenza vaccines are offered through the expanded program on immunization, and nationwide vaccination campaigns are carried out annually before the start of the influenza season[12]. To the best of the authors' knowledge, these results are the first to demonstrate a protective effect from influenza vaccine uptake in SARI patients admitted to hospitals in Lubuk Pakam, Deli Serdang. It seems clear that, based on these study results, Indonesia should continue to increase influenza vaccine coverage.

Host characteristics influenced severity and the need for intensive care unit or intermediate care beds and/or ventilatory assistance. This means that influenza affects hospitals by increasing not only the number of hospitalizations but also the demand for highly complex resources, amplifying its disease burden. Data on these factors have been previously reported, but the proportions of patients needing ventilatory support in this study were higher[13]. Disease-associated conditions affecting the influenza outcome in this study included antiviral use, which was reported in almost all of the identified SARI patients (although timeliness of use was suboptimal in nearly half of them). As shown consistently in large observational studies, early initiation of antiviral therapy (within 3-4 days of first symptoms) had a protective effect on hospital mortality. This same effect was observed in this study, in the univariate analysis. However, the fraction of patients in this study without antiviral therapy was low (<10%, and only two of them died), limiting the ability to draw statistical conclusions[14].

Another important finding in this study was that some SARI patients had no fever, which may have been related to the older age of the study cohort, as elderly people may not experience a rise in body temperature. This phenomenon has important implications for appropriate recognition of SARI-affected patients. The authors believe fever should not be a SARI criterion for surveillance purposes if other criteria are present to ensure appropriate recognition of every case and the disease burden associated with respiratory viruses[15].

In this study cohort, a wide array of clinical presentations was observed, including pneumonia, asthmatic crisis, ILI, chronic bronchitis exacerbation, decompensated heart failure, and other conditions, underscoring the broad spectrum in which influenza must be prevented, suspected, diagnosed, and treated. In addition, in this patient group, pneumonia presented with both consolidated and interstitial lung patterns, demonstrating once again that x-ray findings are not associated with specific etiologies[16]. For example, in a recent report, viral etiologies were associated with lung x-ray consolidation (59% of cases) as well as infiltrates (42%). On the other hand, bacterial-only events showed infiltrates in 31% of patients.

Lymphopenia (< 1000/μL) and increased CRP in plasma (> 10 times the upper-normal value) have been previously described in the literature, demonstrating the systemic involvement of influenza infection. In this study, altered renal function was frequently detected, but non-stringent criteria ("above normal values") were used. In addition to dehydration, several mechanisms have been identified in patients suffering from acute renal failure during influenza infection, including rhabdomyolysis, hemolytic uremic syndrome, acute glomerulonephritis, disseminated intravascular coagulation, and acute interstitial nephritis. In this study, two patients with renal failure (0.9% of the study cohort) presented with acute glomerulonephritis (reported elsewhere) and required renal replacement therapy[17,18].

Several in-hospital mortality risk factors for severe influenza requiring hospital admission have been described. They include delayed medical attention; lung, kidney, liver, or cardiovascular disease; cancer chemotherapy; increased BUN or creatinine concentration; a high Simplified Acute Physiology Score (SAPS) or Sequential Organ Failure Assessment (SOFA) score; age > 65 or > 80 years; admission to the intensive care unit (ICU); development of acute respiratory distress syndrome (ARDS); bilateral lung involvement; mechanical ventilation requirement; superinfection; corticosteroid use; and pregnancy[19]. The in-hospital risk factors found in this study cohort included admission to critical care beds; low Pa02/Fi02 ratio; and high creatinine concentration. Being bedridden was another identified risk factor and to some extent a proxy of older age and severe comorbidities; 28% of bedridden patients in the study cohort died. No association was found between influenza virus type and mortality, suggesting that viral type/subtype does not play a role in the final outcome of influenza-associated SARI in the elderly, frail population in Indonesia[20].

CONCLUSIONS

These study results indicate that influenza is a relevant cause of admissions for SARI, especially among elderly frail patients, and requires intensive care resources. Pneumonia is not the only form of clinical presentation, and influenza-related admissions, associated with every viral type and subtype, occur year-round. In this study, 1 out of 10 admitted patients had a fatal outcome related to host characteristics (being bedridden) and disease-associated conditions/variables (admission to CCU, low Pa02/Fi02 ratio, and increased serum creatinine concentration). A seasonal vaccine was protective, so efforts should be intensified to increase population coverage.

REFERENCES

1. Flerlage T, Boyd DF, Meliopoulos V, Thomas PG, Schultz-Cherry S. Influenza virus and SARS-CoV-2: pathogenesis and host responses in the respiratory tract. Vol. 19, Nature Reviews Microbiology. Nature Research; 2021. p. 425-41.
2. Troeger CE, Blacker BF, Khalil IA, Zimsen SRM, Albertson SB, Abate D, *et al*. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. The Lancet Respiratory Medicine. 2019 Jan 1; 7(1): 69-89.
3. Iha Y, Kinjo T, Parrott G, Higa F, Mori H, Fujita J. Comparative epidemiology of influenza A and B viral infection in a subtropical region: A 7-year surveillance in Okinawa, Japan. BMC Infectious Diseases. 2016 Nov 8; 16(1).
4. Wignjadiputro I, Susilarini NK, Praptiningsih CY, Sariwati E, Setiawaty V, Samaan G. Surveillance for Severe Acute Respiratory Infection as one approach to enhance Global Health Security in Indonesia. Health Science Journal of Indonesia. 2018 Oct 12; 9(1): 8-13.
5. Leung NHL. Transmissibility and transmission of respiratory viruses. Vol. 19, Nature Reviews Microbiology. Nature Research; 2021. p. 528-45.
6. Cheng W, Yu Z, Liu S, Zhang X, Wang X, Cai J, *et al*. Comparison of influenza epidemiological and virological characteristics between outpatients and inpatients in Zhejiang Province, China, March 2011-June 2015. International Journal of Environmental Research and Public Health. 2017 Feb 22; 14(2).
7. Lam TT, Tang JW, Lai FY, Zaraket H, Dbaibo G, Bialasiewicz S, *et al*. Comparative global epidemiology of influenza, respiratory syncytial and parainfluenza viruses, 2010-2015. Journal of Infection. 2019 Oct 1; 79(4): 373-82.
8. Nisar N, Aamir UB, Badar N, Mahmood MR, Yaqoob A, Tripathy JP, *et al*. Epidemiology of Influenza among patients with influenza-like illness and severe acute respiratory illness in Pakistan: A 10-year surveillance study 2008-17. Journal of Medical Virology. 2020 Dec 1; 92(12): 3028-37.
9. Fica A, Sotomayor V, Fasce R, Dabanch J, Soto A, Charpentier P, *et al*. Severe acute respiratory infections (SARI) from influenza in adult patients in Chile: The experience of a sentinel hospital. Revista Panamericana de Salud Publica/Pan American Journal of Public Health. 2019; 43.

10. Pangesti KNA, Susilarini NK, Pawestri HA, Setiawaty V. Influenza cases from Surveillance Acute Respiratory Infection in Indonesia, 2011. Health Science Indonesia. 2014; 5(1).
11. Chakhunashvili G, Wagner AL, Power LE, Janusz CB, Machablishvili A, Karseladze I, *et al*. Severe Acute Respiratory Infection (SARI) sentinel surveillance in the country of Georgia, 2015-2017. PLoS ONE. 2018 Jul 1; 13(7).
12. Elhakim MM, Kandil SK, Abd Elaziz KM, Anwar WA. Epidemiology of severe acute respiratory infection (SARI) cases at a sentinel site in Egypt, 2013-15. Vol. 42, Journal of Public Health (United Kingdom). Oxford University Press; 2020. p. 525-33.
13. King JP, McLean HQ, Belongia EA. Risk of symptomatic severe acute respiratory syndrome coronavirus 2 infection not associated with influenza vaccination in the 2019-2020 season. Influenza and other Respiratory Viruses. 2021;
14. Zhou L, Yang H, Kuang Y, Li T, Xu J, Li S, *et al*. Temporal patterns of influenza a subtypes and B lineages across age in a subtropical city, during pre-pandemic, pandemic, and post-pandemic seasons. BMC Infectious Diseases. 2019 Jan 25; 19(1).
15. Koutsakos M, Wheatley AK, Laurie K, Kent SJ, Rockman S. Influenza lineage extinction during the COVID-19 pandemic? Vol. 19, Nature Reviews Microbiology. Nature Research; 2021. p. 741-2.
16. Caini S, Kroneman M, Wiegers T, el Guerche-Séblain C, Paget J. Clinical characteristics and severity of influenza infections by virus type, subtype, and lineage: A systematic literature review. Influenza and other Respiratory Viruses. 2018 Nov 1; 12(6): 780-92.
17. Boniotti MB, Papetti A, Lavazza A, Alborali G, Sozzi E, Chiapponi C, *et al*. Porcine epidemic diarrhea virus and discovery of a recombinant swine enteric coronavirus, Italy. Emerging Infectious Diseases. 2016 Jan 1; 22(1): 83-7 .
18. Vilela VJ, Rosario A;, Gentile A, Giglio N, Kfouri R, Aurélio M, *et al*. Epidemiology and prevention of influenza in children in Argentina and Brazil. Rev Panam Salud Publica. 2017; 41.
19. Kalil AC, Thomas PG. Influenza virus-related critical illness: Pathophysiology and epidemiology. Vol. 23, Critical Care. BioMed Central Ltd.; 2019.
20. Murillo-Zamora E, Trujillo X, Huerta M, Ríos-Silva M, Guzmán-Esquivel J, Benites-Godínez V, *et al*. Survival in influenza virus-related pneumonia by viral subtype: 2016-2020. International Journal of Infectious Diseases. 2021 Nov 1; 112: 288-93.