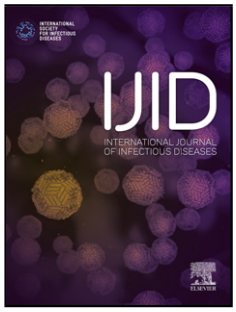
Journal Pre-proof



The “Timeless” use of Influenza-like Illness Criteria for influenza Detection in the Tropics

Aung H Aung, David C Lye, Lin Cui, Chee K Ooi, Angela LP Chow

PII: S1201-9712(21)00263-0

DOI: https://doi.org/10.1016/j.ijid.2021.03.045

Reference: IJID 5247

To appear in: *International Journal of Infectious Diseases*

Received Date: 27 November 2020

Revised Date: 9 March 2021

Accepted Date: 11 March 2021

Please cite this article as: Aung AH, Lye DC, Cui L, Ooi CK, Chow AL, The “Timeless” use of Influenza-like Illness Criteria for influenza Detection in the Tropics, *International Journal of Infectious Diseases* (2021), doi: https://doi.org/10.1016/j.ijid.2021.03.045

The "Timeless" use of Influenza-like Illness Criteria for influenza Detection in the Tropics

RUNNING TITLE: Use of influenza-like illness criteria in the tropics

Aung H Aung[1], David C Lye[2], Lin Cui[3], Chee K Ooi[4], Angela LP Chow [1, 5]

[1]Department of Clinical Epidemiology, Office of Clinical Epidemiology, Analytics, and Knowledge, Tan Tock Seng Hospital, Singapore

[2] Department of infectious disease, Tan Tock Seng Hospital, Singapore

[3] National public health laboratory, Ministry of health, Singapore

[4] Department of emergency medicine, Tan Tock Seng Hospital, Singapore

[5] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

HIGHLIGHTS

- Influenza, rhinovirus, and coronaviruses are key respiratory viruses in the tropics
- Influenza circulates year-round with bimodal surges in Apr-Jul and Nov-Feb
- Coronaviruses have unclear seasonality, rhinovirus is active in inter-flu seasons
- ILI criteria have moderate-to-high positive likelihood ratios to rule-in influenza
- CDC and WHO ILI case definitions can clinically diagnose influenza in the tropics

*CORRESPONDING AUTHOR: Angela Chow, Department of Clinical Epidemiology, Office of Clinical Epidemiology, Analytics, and Knowledge, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore.

E-mail: Angela_Chow@ttsh.com.sg; Tel: +65-6357 7477; Fax: +65-6357 7465

ABSTRACT

OBJECTIVE

We assessed the performance of influenza-like illness (ILI) case definitions by the Centers for Disease Control and Prevention (CDC), European Centers for Disease Control and Prevention (ECDC), and World Health Organization (WHO) in the tropics where the seasonal patterns of respiratory viruses in acute upper respiratory tract infections (AURTIs) are ill defined.

METHODS

Clinical data and samples for respiratory multiplex PCR test were collected from 717 consecutive patients attending for uncomplicated AURTI at a busy emergency department in Singapore, 2016-2018.

RESULTS

Influenza (20.6%), rhinoviruses (14.4%), and coronaviruses (3.6%) were the most common viral pathogens. Biannual peaks with year-round activity was identified for Influenza. Although higher rhinoviruses activity was observed in inter-influenza seasonal periods, rhinoviruses and coronaviruses circulated year-round without distinct seasonal patterns. During high influenza activity months, the CDC's and WHO's ILI case definitions had moderate-to-high positive likelihood ratios (LR+s) of 3.8-6.8 and 4.5-10.7 respectively for ruling in influenza. During other months, they had moderately high LR+s of 3.3-3.8 and 3.9-4.6 for clinically diagnosing influenza infection. The ILI case definitions had high specificities (77.2-85.4%) for rhinoviruses and coronaviruses.

CONCLUSION

The CDC and WHO ILI case definitions can be applied to clinically diagnose influenza in the tropics, regardless of the time of the year.

KEYWORDS: Influenza-like illness, Acute Upper Respiratory Tract Infection, Respiratory viruses, Seasonality, Tropics

INTRODUCTION

Acute upper respiratory tract infections (AURTIs) are common presenting medical conditions to primary care clinics and hospital emergency departments (EDs) (1). The majority of pathogens responsible for AURTIs are viruses (2). Respiratory viral pathogens usually follow recognizable seasonal patterns in temperate countries. However, respiratory viruses circulate all year round in the tropics and the identification of seasonal patterns is challenging (3, 4). Notably, influenza-associated mortality in the tropics was comparable to subtropical and temperate climates (5). Identification of the seasonal patterns of major respiratory viruses for a region is essential for the strategic planning of prevention and control efforts, including the timing of vaccination programs. Furthermore, understanding of the patterns would enable the early recognition of emerging epidemics with increases in viral circulation during non-seasonal periods.

AURTIs present with wide ranging symptoms, from mild nasal congestion to acute febrile respiratory illness. Differentiation of bacterial AURTIs requiring antibiotics from viral AURTIs remains a challenge for doctors. Although laboratory tests are helpful in the identification of causal organisms, point-of-care tests are inadequately sensitive and definitive tests often not timely enough for clinical decision making (6). Clinical criteria such as the influenza-like illness (ILI) criteria can be easily applied in different clinical settings for the identification of viral AURTI, with the benefit of reducing inappropriate antibiotics. ILI definitions by the Centers for Disease Control and Prevention (CDC), European Centers for Disease Control and Prevention (ECDC), and the World Health Organization (WHO) have been extensively applied for the identification of influenza infection in temperate regions (7), but to a much lesser extent

in the tropics (8). Furthermore, the application of ILI for the diagnosis of non-influenza viral AURTIs has not been well studied.

The circulatory patterns of non-influenza respiratory viruses in the tropics is also not well understood. Hence, in this study, we aim to assess for the seasonal variation of common respiratory viruses causing uncomplicated AURTI in tropical Singapore, and determine the performance of ILI definitions in the detection of the three most common respiratory viruses.

METHODS

We conducted a cross-sectional study on 717 consecutive consenting adults who visited the ED at Tan Tock Seng Hospital, for uncomplicated AURTI, from June 2016 to November 2018. The 1600-bed adult acute care hospital's ED attends to an average of 450 patients each day. Uncomplicated AURTI was identified by an ICD 10AM (International Classification of Diseases 10th edition) diagnosis code of J00 to J06 selected by the attending ED physician. An interviewer-administered questionnaire was used to obtain information on the presenting clinical symptoms and histories of vaccination, travel, and smoking. Data on socio-demographics, pre-existing medical conditions, clinical signs and vital parameters during the ED visit were extracted from the electronic health records. Charlson's Comorbid Index (CCI) was computed according to the weights assigned for 19 comorbid conditions by Charlson et al (9).

C reactive protein (CRP) levels were examined using a finger-prick point-of-care test (QuikRead go®). Participants were screened for major respiratory viruses using a multiplex PCR respiratory virus pathogen panel (Seeplex® RV15 ACE Detection) via nasal and throat swabs. The panel included influenza A & B, adenovirus, coronaviruses 229E/NL63 & OC43, parainfluenza viruses 1-4, rhinoviruses A, B & C, respiratory syncytial viruses A & B, bocaviruses 1-4, metapneumovirus and enterovirus.

The World Health Organization (WHO)'s case definition for ILI is an acute respiratory illness with a measured temperature of ≥38°C and cough within the past 10 days (10). The Centers for Disease Control and Prevention (CDC)'s case definition for ILI included fever (temperature of ≥37.8 °C) and cough and/or sore throat (11). The European Center for Disease Control and Prevention (ECDC)'s case definition for ILI is the sudden onset of symptoms and at least one of the following four systemic symptoms: fever or feverishness, malaise, headache, and myalgia, and at least one of the following three respiratory symptoms: cough, sore throat, and shortness of breath (12). ILI definitions from the CDC, ECDC, and WHO were compared for their sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio positive (LR+), likelihood ratio negative (LR-), and area under the curve (AUC) for specific viral infections (13). Furthermore, the performance of the ILI case definitions for the detection of influenza viruses were compared between high and low influenza activity months. Based on the monthly influenza positivity rates from the study data as well as from the publicly available national data provided by Singapore's Ministry of Health (14), high activity months were defined as the months with influenza positivity rates above one standard deviation of the average monthly influenza positivity rate derived from the study data and national data respectively for the study period.

Chi-square test was applied for comparison of differences in proportions for categorical variables. Student's t-test and Wilcoxon rank-sum test were used for comparison of differences in means and medians for ordinal and continuous variables. Univariate and multivariable logistic regression models were constructed to assess the association of factors with viral AURTI.Significant variables from backward stepwise regression using a p-value cutoff of 0.2 were selected for the . final multivariable multinomial logistic regression models to assess for the independent associations of ILI case definitions with AURTI from specific viruses. Multicolinearity in the data was identified using the variance inflation factor and tolerance. Statistical analyses were performed using STATA 13.0.

RESULTS

Of 717 participants, 343 (47.8%) had at least one respiratory virus identified. Among them, 15 (4.4%) had more than one virus detected (two viruses: 14; three viruses: 1). Influenza (148, 20.6%; influenza A: 102, influenza B: 46) were the most common viruses, followed by rhinoviruses (103, 14.4%), human coronaviruses (26, 3.6%; CoV-229E/CoV-NL63: 17, CoV-OC43: 9), parainfluenza viruses (24, 3.4%), and adenovirus (23, 3.2%).

Over the 30 months, respiratory viral activities were the lowest in December. Influenza activity was highest in February (30.8%), May (35.1 %), and June (36.2%) (P<0.001) (Figure 1). In contrast, rhinoviruses activity was the highest in August (23.1%), with increased activity in the inter-influenza high-activity months. Coronaviruses had higher activity in March (6%), September (6.3%) and November (6.3%), compared with other months.

The mean age of participants was 36 [IQR (28-51)] years, with a slight preponderance of male (n=439, 61.2%) and the majority (n=476, 66.4%) did not have any pre-existing co-morbidity (Table 1). Compared to those without a virus detected, patients who had a respiratory virus identified were similar socio-demographically, but more likely to present with fever, cough, runny nose, body ache and giddiness, and to have a documented temperature of >= 38^{o}C (p=0.001). Moreover, patients with viral infections were more likely to present with low oxygen saturation (SaO_2 less than 98%), and CRP levels of 5-20 mg/L. In contrast, half the patients without a virus detected had undetectable CRP levels (<5 mg/L).

More than half of those with a human coronavirus detected had a co-morbidity (CCI >= 1) (n=15, 57.7%) compared to less than one-third of those with an influenza infection (n=41, 27.7%). History of overseas travel (46.2%) was most common amongst patients with a coronavirus detected, whilst smoking (36.9%) was most prevalent in those with rhinoviruses identified. Only 10% of patients with an influenza infection reported receiving influenza vaccination within the past year, compared to 19.4-25.0% in patients with other viruses detected and 19.8% in those without any virus detected. Fever, cough, body

ache, and loss of appetite were the most common presenting symptoms among patients identified with influenza viruses (n=121, 81.8%; n=145, 98.0%; n=33, 22.3% and n=22, 14.9% respectively). Body ache was least common in those with rhinoviruses (n=6, 5.8%), whilst chest pain was most prominent in patients with a coronavirus infection (n=8, 30.8%).

After adjusting for age, gender, ethnicity, smoking habits and influenza vaccination histories, patients who presented in the month of June or August, had the onset of symptoms within four days, with presenting symptoms of cough or rhinorrhea, or a documented temperature >=38 degree Celsius, were 1.5 to 2.7 times more likely to have a respiratory virus detected (Table 2). Patients with CRP levels of 5-20 mg/L were twice more likely, whilst those with CRP >100 mg/L six times less likely to have a viral infection.

Patients fulfilling CDC's ILI case definition were six times as likely as those not fulfilling the definition to be infected with influenza viruses (aOR 5.95, 95%CI 3.29-10.76) (Table 3). In contrast, those who fulfilled WHO's ILI case definition were 8.8 and 2.5 times as likely as those who did not to be infected with influenza viruses (aOR 8.84, 95%CI 4.55-17.15) and other respiratory viruses (aOR 2.48, 95%CI 1.01-6.08) respectively. Both ILI case definitions were negatively associated with rhinoviral infection.

The CDC's and WHO's ILI case definitions had moderate sensitivities (38.5-49.3%), whilst the ECDC's ILI criteria had the highest sensitivity (78.4%) but lowest specificity (53.8%), for the detection of influenza viruses (Table 4A). During high influenza activity months based on the study data (June-2016, May-2017, June-2017, February-2018, July-2018 and November-2018), the CDC's and WHO's ILI case definitions had high PPVs of 71% and 75% and LR+s of 3.8 and 4.5 respectively (Table 4B). Furthermore, during high influenza activity months based on national data (June-2016, July-2016, May-2017, June-2017 and July-2017), the CDC's and WHO's ILI case definitions provided higher PPVs of 73% and 81%, and LR+s of 6.8

and 10.7 respectively (Table 4C). During low influenza activity months, the case definitions provided moderately high LR+s of 3.3-4.6

Both the CDC's and WHO's ILI case definitions had high specificities (77.2-85.4%), but poor sensitivities (3.9-19.2%), for the detection of rhinoviruses and coronaviruses,. In contrast, ECDC's ILI case definition was moderately sensitive (45.6-53.8%) and specific (47.2-45.9%) (Figure 2).

DISCUSSION

This study provided insights into the epidemiology of AURTI and the seasonal variation of common respiratory viruses over a 30-month period in tropical Singapore. Influenza predominated in the uncomplicated AURTI study population, with influenza positivity rates reaching 50% in high influenza activity months. Influenza is also one of the predominant viral etiologies of AURTI in temperate regions (15). We observed that although influenza was detected in the study population all year-round, influenza activity tended to increase in April-July and November-February albeit year-to-year variations. This is similarly observed in previous studies on hospitalized patients, military servicemen, and community-dwelling individuals conducted in Singapore (8, 16-18) as well as in other tropical regions (3). As such, biannual influenza vaccination with both northern and southern hemisphere seasonal vaccines is recommended for the tropics (19).

Rhinoviruses and human coronaviruses are the second and third most commonly detected viruses respectively in our study population, corroborating with observations in previous cohorts of community and inpatient acute respiratory infections (8). They circulated year-round without distinct seasonal patterns, although higher rhinoviruses activity was observed in inter-influenza seasonal periods. The possible interference between seasonal influenza epidemics and the activities of other respiratory viruses have been suggested in subtropical Hong Kong and temperate United States (20, 21). In temperate climates, whilst influenza epidemics tended to occur in winter, other viral respiratory

pathogens such as rhinoviruses activity surged in fall (22, 23). Our observation of higher activity of coronavirus in March and year-end, corresponded with the higher coronavirus circulation in neighbouring Southeast-Asian countries (24, 25) and the US (26).

During high influenza activity months, the CDC's and WHO's ILI case definitions had moderate-to-high LR+s of 3.8-6.8 and 4.5-10.7 respectively for ruling in influenza. During other months of the year, the CDC's and WHO's ILI criteria had moderately high LR+s of 3.3-3.8 and 3.9-4.6 for clinically diagnosing influenza infection. Our findings on the performance of CDC and WHO ILI case definitions are similar to that previously reported in community and inpatient cohorts in Singapore (27), and in an ED cohort in the US (28). These clinical definitions could guide the early administration of oseltamivir to prevent influenza-related complications in the patient and influenza transmission in the community. Notably, whilst prior influenza vaccination within the year reduced influenza infection by half (WHO ILI model: aOR 0.56, 95% CI 0.28-1.11; CDC ILI model: aOR 0.53, 95%CI 0.26 - 1.06), influenza vaccination uptake in the study population was reportedly low (18%). More needs to be done to promote influenza vaccination in the tropics especially for elderly population (29).

Furthermore, we observed that the CDC and WHO ILI case definitions had high specificities (77.2-85.4%) for the detection of rhinoviruses and coronaviruses, which would also serve well in ruling out these common viruses especially since they circulate year-round. Additionally, AURTI patients presenting with chest pain, particularly patients with pre-existing co-morbidities or on steroids or those who have had a recent travel history, coronaviruses infection should be considered. Chest pain in coronaviruses infection has been previously observed and thought to be due to the involvement of human angiotensin converting enzyme 2 (ACE2) receptor resulting in acute cardiovascular injury (30). The increase in coronaviruses activity corresponding to the seasonal increases in activity in neighboring countries support the observed association between travel and coronaviruses infection.

Strengths and limitations

Our study's strengths include the construction of a prospective cohort of uncomplicated AURTI presenting at one of the busiest ED in tropical Singapore over two northern- and two southern-hemisphere influenza seasons. Standardized protocols for sample collection, sample processing and testing were used, minimizing measurement error. Blinded virologic evaluation prevented any detection bias. The study could be limited by unknown and unmeasured potential confounding due to secondary bacterial infection although it was less likely to occur in the study population comprising of uncomplicated ARUTIs and unlikely in early illness presentation. Whilst the findings are generalizable to adult AURTIs in other tropical countries, they might not be applicable to children.

Conclusion

Influenza viruses, rhinoviruses, and coronaviruses are the most common causes of uncomplicated AURTI and circulate year-round in tropical Singapore. Influenza activity increases bi-annually in April-July and November-February, whilst higher rhinoviruses activity was observed in inter-influenza seasonal periods. The CDC and WHO ILI case definitions can be applied to clinically diagnose influenza in the tropics, regardless of the time of the year.

TRANSPARENCY DECLARATIONS

Ethics approval

The study was carried out with the approval from Domain Specific Review Board (DSRB), National Healthcare Group (NHG) (DRSB-2015/00248).

Funding

This work was supported by the National Healthcare Group Singapore's Clinician Scientist Career Scheme [NHG-CSCS/15005].

Conflict of interest

None to declare.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

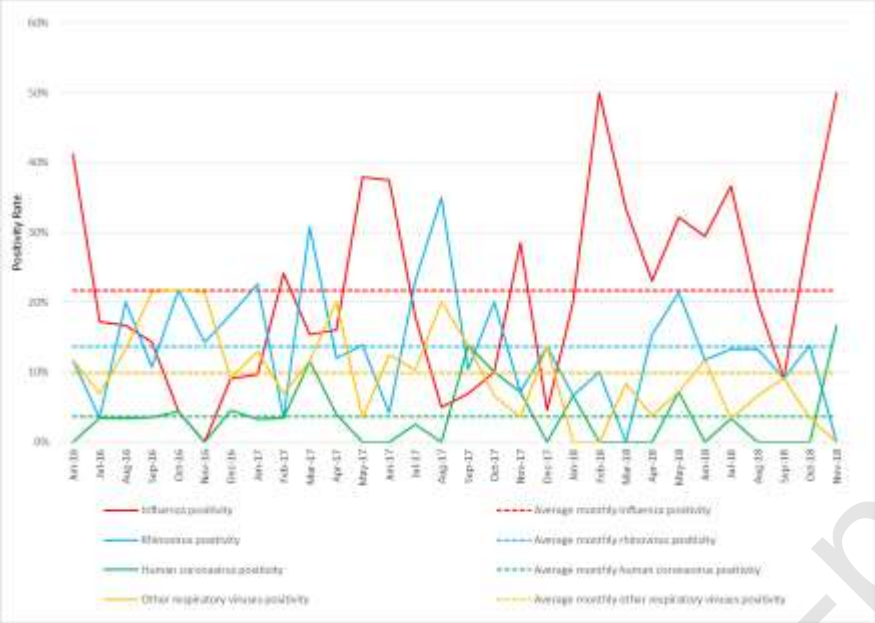
Ms Ong Lay See and Grace Tin for collecting the data, staff of TTSH ED who helped with study recruitment, and patients who participated in the study.

REFERENCES

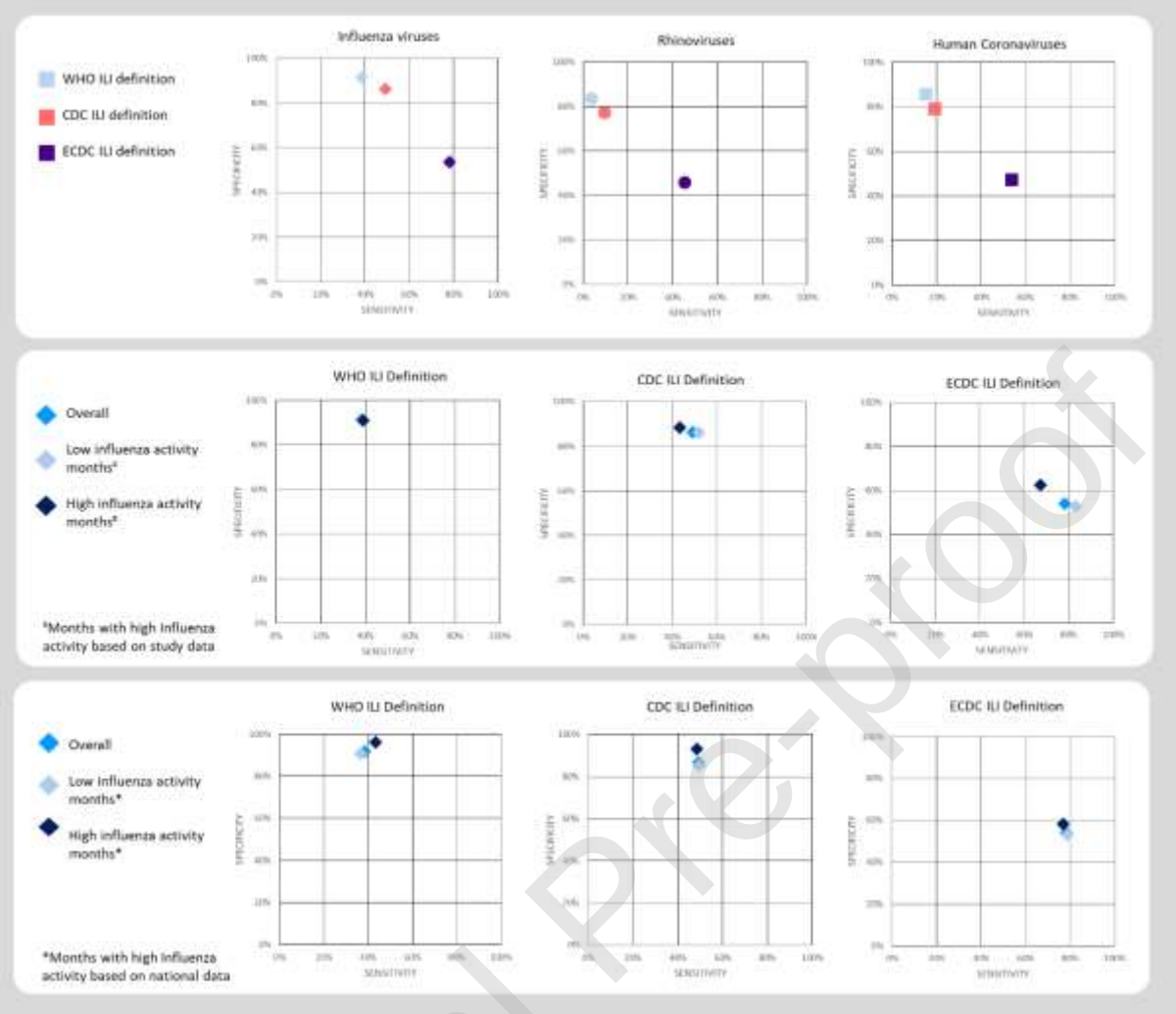
1. Lee WY. Antibiotic Prescribing for Patients with Upper Respiratory Tract Infections by Emergency Physicians in a Singapore Tertiary Hospital. Hong Kong Journal of Emergency Medicine. 2005;12(2):70-6.
2. Gonzales R, et al. Excessive antibiotic use for acute respiratory infections in the United States. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2001;33(6):757-62.
3. Lam TT, et al. Comparative global epidemiology of influenza, respiratory syncytial and parainfluenza viruses, 2010-2015. The Journal of infection. 2019;79(4):373-82.
4. Tamerius J, et al. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environmental health perspectives. 2011;119(4):439-45.
5. Chow A, et al. Influenza-associated deaths in tropical Singapore. Emerging infectious diseases. 2006;12(1):114-21.
6. Park JH, et al. Effect of rapid influenza diagnostic tests on patient management in an emergency department. Clinical and experimental emergency medicine. 2019;6(1):43-8.
7. Alchikh M, et al. Are we missing respiratory viral infections in infants and children? Comparison of a hospital-based quality management system with standard of care. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2019;25(3):380.e9-.e16.
8. Jiang L, et al. Detection of viral respiratory pathogens in mild and severe acute respiratory infections in Singapore. Scientific reports. 2017;7:42963.
9. Charlson ME, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83.
10. Organization WH. WHO surveillance case definitions for ILI and SARI: World Health Organization; 2018 [updated February 02, 2018; cited 2020 July 18, 2020]. Available from: https://www.who.int/influenza/surveillance_monitoring/ili_sari_surveillance_case_definition/en/.
11. Prevention CfDCa. U.S. Influenza Surveillance System: Purpose and Methods: US Centers for Disease Control and Prevention; 2020 [updated 08 July 2020; cited 2020 18 July 2020]. Available from: https://www.cdc.gov/flu/weekly/overview.htm
12. Control ECfDPa. EU case definitions: European Centre for Disease Prevention and Control; 2020 [updated April 28, 2020; cited 2020 18 July 2020]. Available from: https://www.ecdc.europa.eu/en/surveillance-and-disease-data/eu-case-definitions.
13. Casalegno J-S, et al. Performance of influenza case definitions for influenza community surveillance: based on the French influenza surveillance network GROG, 2009-2014. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2017;22(14):30504.
14. Singapore MoH. Weekly Infectious Disease Bulletin: Ministry of Health Singapore; 2018 [cited 2020 27 July 2020]. Available from: https://www-moh-gov-sg-admin.cwp.sg/resources-statistics/infectious-disease-statistics/2016/weekly-infectious-diseases-bulletin.
15. Zimmerman RK, et al. Influenza and other respiratory virus infections in outpatients with medically attended acute respiratory infection during the 2011-12 influenza season. Influenza and other respiratory viruses. 2014;8(4):397-405.
16. Lau YF, et al. Epidemiologic analysis of respiratory viral infections among Singapore military servicemen in 2016. BMC infectious diseases. 2018;18(1):123.

17. Pang J, et al. Risk factors for febrile respiratory illness and mono-viral infections in a semi-closed military environment: a case-control study. BMC infectious diseases. 2015;15:288.
18. Shek LP, Lee BW. Epidemiology and seasonality of respiratory tract virus infections in the tropics. Paediatric respiratory reviews. 2003;4(2):105-11.
19. Cowling BJ, et al. Influenza in the Asia-Pacific region: Findings and recommendations from the Global Influenza Initiative. Vaccine. 2017;35(6):856-64.
20. Zheng X, et al. Possible interference between seasonal epidemics of influenza and other respiratory viruses in Hong Kong, 2014-2017. BMC infectious diseases. 2017;17(1):772-.
21. Wu A, et al. Interference between rhinovirus and influenza A virus: a clinical data analysis and experimental infection study. The Lancet Microbe. 2020;1(6):e254-e62.
22. Price OH, et al. Using routine testing data to understand circulation patterns of influenza A, respiratory syncytial virus and other respiratory viruses in Victoria, Australia. Epidemiology and infection. 2019;147:e221.
23. Monto AS. The seasonality of rhinovirus infections and its implications for clinical recognition. Clinical therapeutics. 2002;24(12):1987-97.
24. Nguyen DNT, et al. Epidemiology and etiology of influenza-like-illness in households in Vietnam; it's not all about the kids! Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2016;82:126-32.
25. Dare RK, et al. Human coronavirus infections in rural Thailand: a comprehensive study using real-time reverse-transcription polymerase chain reaction assays. The Journal of infectious diseases. 2007;196(9):1321-8.
26. Killerby ME, et al. Human coronavirus circulation in the United States 2014-2017. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2018;101:52-6.
27. Jiang L, et al. Performance of case definitions for influenza surveillance. Eurosurveillance. 2015;20(22):21145.
28. Dugas AF, et al. Clinical diagnosis of influenza in the ED. Am J Emerg Med. 2015;33(6):770-5.
29. Ng Y, et al. Estimates of influenza-associated hospitalisations in tropical Singapore, 2010-2017: Higher burden estimated in more recent years. 2019;13(6):574-81.
30. Xiong T-Y, et al. Coronaviruses and the cardiovascular system: acute and long-term implications. European Heart Journal. 2020;41(19):1798-800.

(Fig. 1) Monthly positivity rate (%) of influenza, rhinovirus, human coronaviruses, and other respiratory viruses (n=717)



(Figure. 2) Performance influenza-like illness (ILI) case definitions in the detection of influenza viruses (high-activity and low-activity months), rhinoviruses and human coronaviruses (n=717).



Performance of the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the European Center for Disease Control and Prevention (ECDC) influenza-like illness (ILI) case definitions in the detection of influenza viruses (high-activity and low-activity months), rhinoviruses and human coronaviruses (n=717). (1st Row) Comparison of the performance of WHO, CDC, and ECDC ILI case definitions in the detection of influenza viruses, rhinoviruses, and human coronaviruses. (2nd Row) Comparison of the performance of WHO, CDC, and ECDC ILI case definitions in the detection of influenza viruses, during high and low influenza activity months classified using the study data. (3rd Row) Comparison of the performance of WHO, CDC, and ECDC ILI case definitions in the detection of influenza viruses, during high and low influenza activity months classified using national data.

(Table. 1) Characteristics and clinical presentation of patients, with and without respiratory viruses detected (n=717)

Factors	Virus not detected (n=374)	Virus Detected (n=343)	Specific Virus Detected			
			Influenza (n=148)	Rhinovirus (n=103)	Human coronavirus (n=26)	Other respiratory viruses (n=72)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age in years [median (IQR)]	35 (28-51)	37.5 (28-51)	37 (29-51)	32 (26-47)	44.5 (28-59)	34 (25-48.5)
Male Gender	234 (62.6)	205 (59.8)	88 (59.5)	63 (61.2)	16 (61.5)	42 (58.3)
Ethnicity						
Chinese	163 (43.6)	146 (42.6)	63 (42.6)	40 (38.8)	9 (34.6)	36 (50.0)
Indian	66 (17.6)	64 (18.7)	28 (18.9)	22 (21.4)	8 (30.8)	9 (12.5)
Malay	73 (19.5)	66 (19.2)	23 (15.5)	29 (28.2)	4 (15.4)	11 (15.3)
Others	72 (19.3)	67 (19.5)	34 (23.0)	12 (11.7)	5 (19.2)	16 (22.2)
Higher Educational level	206 (55.1)	193 (56.3)	78 (52.7)	65 (63.1)	13 (50)	39 (54.2)
Smoker	77 (20.6)	91 (26.5)	32 (21.6)	38 (36.9)	4 (15.4)	19 (26.4)
Recent Overseas Travel	95 (25.4)	96 (28.0)	34 (23.0)	28 (27.2)	12 (46.2)	24 (33.3)
Prior Influenza Vaccination within 1 year	74 (19.8)	58 (16.9)	15 (10.1)	20 (19.4)	6 (23.1)	18 (25.0)
Prior Pneumococcal Vaccination	25 (6.7)	24 (7.0)	8 (5.4)	7 (6.8)	5 (19.2)	5 (6.9)
<u>Pre-existing condition</u>						
Chronic Pulmonary Disease	77 (20.6)	79 (23.0)	19 (12.8)	34 (33.0)	9 (34.6)	17 (23.6)
Asthma	64 (17.1)	64 (18.7)	14 (9.5)	29 (28.2)	7 (26.9)	14 (19.4)

Chronic Obstructive Pulmonary Disease	13 (3.5)	15 (4.4)	5 (3.4)	5 (4.9)	2 (7.7)	3 (4.2)
Connective Tissue Disease	3 (0.8)	9 (2.6)	3 (2.0)	4 (3.9)	2 (7.7)	1 (1.4)
Myocardial Infarction	12 (3.2)	8 (2.3)	4 (2.7)	0 (0)	3 (11.5)	1 (1.4)
Ischaemic Heart Disease	13 (3.5)	13 (3.8)	6 (4.1)	1 (1.0)	4 (15.4)	2 (2.8)
Malignancy	12 (3.2)	10 (2.9)	4 (2.7)	2 (1.9)	1 (3.8)	3 (4.2)
Liver Disease	7 (1.9)	5 (1.5)	2 (1.4)	2 (1.9)	0 (0)	1 (1.4)
Renal Disease	5 (1.3)	1 (0.3)	1 (0.7)	0 (0)	0 (0)	0 (0)
Diabetes Mellitus	36 (9.6)	28 (8.2)	17 (11.5)	6 (5.8)	4 (15.4)	2 (2.8)
Charlson's Comorbid Index [median (IQR)]	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Charlson's Comorbid Index >= 1	121 (32.4)	120 (35.0)	41 (27.7)	40 (38.8)	15 (57.7)	25 (34.7)
Steroid Use	25 (6.7)	32 (9.3)	6 (4.1)	12 (11.7)	9 (34.6)	6 (8.3)
Systemic Corticosteroid Use	3 (0.8)	8 (2.3)	2 (1.4)	2 (1.9)	4 (15.4)	1 (1.4)
Inhaled Corticosteroid Use	23 (6.1)	26 (7.6)	4 (2.7)	10 (9.7)	6 (23.1)	6 (8.3)
Hypertension	65 (17.4)	49 (14.3)	24 (16.2)	12 (11.7)	5 (19.2)	9 (12.5)
<u>Month of Emergency Department Visit</u>						
Jan	26 (7.0)	20 (5.8)	6 (4.1)	8 (7.8)	2 (7.7)	4 (5.6)
Feb	23 (6.1)	16 (4.7)	12 (8.1)	2 (1.9)	1 (3.8)	2 (2.8)
Mar	23 (6.1)	27 (7.9)	12 (8.1)	8 (7.8)	3 (11.5)	5 (6.9)
Apr	27 (7.2)	24 (7.0)	10 (6.8)	7 (6.8)	1 (3.8)	6 (8.3)
May	24 (6.4)	34 (9.9)	20 (13.5)	10 (9.7)	2 (7.7)	3 (4.2)
Jun	24 (6.4)	33 (9.6)	21 (14.2)	5 (4.9)	0 (0)	7 (9.7)
Jul	52 (13.9)	46 (13.4)	23 (15.5)	14 (13.6)	3 (11.5)	7 (9.7)
Aug	31 (8.3)	34 (9.9)	9 (6.1)	15 (14.6)	1 (3.8)	9 (12.5)
Sep	46 (12.3)	33 (9.6)	8 (5.4)	8 (7.8)	5 (19.2)	12 (16.7)

Oct	44 (11.8)	38 (11.1)	13 (8.8)	15 (14.6)	4 (15.4)	8 (11.1)
Nov	26 (7.0)	22 (6.4)	11 (7.4)	4 (3.9)	3 (11.5)	4 (5.6)
Dec	28 (7.5)	16 (4.7)	3 (2.0)	7 (6.8)	1 (3.8)	5 (6.9)
Duration of illness						
>8 days	99 (26.5)	50 (14.6)	12 (8.1)	21 (20.4)	2 (7.7)	15 (20.8)
5-8 Days	119 (31.8)	86 (25.1)	37 (25.0)	23 (22.3)	7 (26.9)	22 (30.6)
1-4 days	156 (41.7)	207 (60.3)	99 (66.9)	59 (57.3)	17 (65.4)	35 (48.6)
Presenting Symptom						
Fever	180 (48.1)	244 (71.1)	121 (81.8)	58 (56.3)	15 (57.7)	52 (72.2)
Chills	22 (5.9)	20 (5.8)	12 (8.1)	4 (3.9)	1 (3.8)	3 (4.2)
Headache	33 (8.8)	32 (9.3)	17 (11.5)	7 (6.8)	2 (7.7)	6 (8.3)
Body Ache	43 (11.5)	57 (16.6)	33 (22.3)	6 (5.8)	4 (15.4)	14 (19.4)
Joint Pain	10 (2.7)	7 (2.0)	3 (2.0)	2 (1.9)	1 (3.8)	1 (1.4)
Any Musculoskeletal symptom (Joint pain/ body ache)	47 (12.6)	59 (17.2)	33 (22.3)	8 (7.8)	4 (15.4)	14 (19.4)
Tiredness	14 (3.7)	16 (4.7)	14 (9.5)	1 (1.0)	0 (0)	1 (1.4)
Giddiness	14 (3.7)	27 (7.9)	12 (8.1)	7 (6.8)	2 (7.7)	6 (8.3)
Cough	335 (89.6)	324 (94.5)	145 (98.0)	97 (94.2)	23 (88.5)	65 (90.3)
Rhinorrhea	160 (42.8)	178 (51.9)	76 (51.4)	57 (55.3)	13 (50.0)	34 (47.2)
Sore Throat	168 (44.9)	159 (46.4)	63 (42.6)	50 (48.5)	13 (50.0)	36 (50.0)
Any Nasal symptom (Runny nose/block nose/sneeze)	178 (47.6)	183 (53.4)	78 (52.7)	57 (55.3)	14 (53.8)	36 (50.0)
Shortness of Breath (SOB)	83 (22.2)	63 (18.4)	18 (12.2)	26 (25.2)	6 (23.1)	13 (18.1)
Chest Pain	54 (14.4)	43 (12.5)	15 (10.1)	17 (16.5)	8 (30.8)	5 (6.9)
Severe Chest symptoms (SOB/Chest pain)	116 (31.0)	89 (25.9)	29 (19.6)	35 (34.0)	11 (42.3)	16 (22.2)
Loss of appetite	25 (6.7)	33 (9.6)	22 (14.9)	5 (4.9)	1 (3.8)	5 (6.9)

Nausea	16 (4.3)	22 (6.4)	10 (6.8)	6 (5.8)	2 (7.7)	5 (6.9)
Vomiting	23 (6.1)	17 (5.0)	8 (5.4)	7 (6.8)	1 (3.8)	2 (2.8)
Abdominal Pain	17 (4.5)	13 (3.8)	6 (4.1)	2 (1.9)	2 (7.7)	4 (5.6)
Any Gastrointestinal Symptom (Nausea/Vomiting/Diarrhoea/Abdominal pain)	53 (14.2)	49 (14.3)	24 (16.2)	13 (12.6)	4 (15.4)	11 (15.3)
<u>Presenting Sign</u>						
Injected Pharynx	89 (23.8)	103 (30.0)	60 (40.5)	26 (25.2)	5 (19.2)	15 (20.8)
Abnormal lung findings	29 (7.8)	40 (11.7)	135 (91.2)	88 (85.4)	24 (92.3)	61 (84.7)
Temperature >= 38^{o}C	41 (11.0)	77 (22.4)	56 (37.8)	6 (5.8)	3 (11.5)	12 (16.7)
Hypotension (SBP<90 or DBP <=60)	87 (23.3)	91 (26.5)	45 (30.4)	27 (26.2)	6 (23.1)	14 (19.4)
Low oxygen saturation (SaO2 less than 98%)	120 (32.1)	140 (40.8)	71 (48.0)	38 (36.9)	8 (30.8)	26 (36.1)
Tachycardia (Heart Rate >100/min)	58 (15.5)	63 (18.4)	35 (23.6)	16 (15.5)	3 (11.5)	11 (15.3)
Tachypnoea (Respiration Rate >30/min)	5 (1.3)	3 (0.9)	0 (0)	2 (1.9)	0 (0)	1 (1.4)
C-reactive protein level (mg/L)						
<5	188 (50.3)	127 (37.0)	47 (31.8)	49 (47.6)	8 (30.8)	30 (41.7)
5 to 20	94 (25.1)	140 (40.8)	62 (41.9)	40 (38.8)	12 (46.2)	24 (33.3)
21 to 40	41 (11.0)	39 (11.4)	23 (15.5)	5 (4.9)	4 (15.4)	8 (11.1)
41 to 100	30 (8.0)	32 (9.3)	14 (9.5)	9 (8.7)	2 (7.7)	7 (9.7)
>100	20 (5.3)	4 (1.2)	1 (0.7)	0 (0)	0 (0)	3 (4.2)
CRP [Median (IQR) in mg/L]	<5 (<5-19)	8 (<5-19)	10 (<5-21)	6 (<5-12)	7.5 (<5-19)	8 (<5-19)

(Table. 2) Univariate and multivariable logistic regression analysis of factors associated with a respiratory viral infection (n=715*).

Factors	Univariable Analysis			Multivariable Analysis		
	OR	(95% CI)	p-value	aOR	(95% CI)	p-value
Age (Years)	1.00	(0.99 - 1.01)	0.609	1.00	(0.98 - 1.01)	0.394
Male Gender	0.89	(0.66 - 1.20)	0.442	0.78	(0.55 - 1.11)	0.172
Smoker	1.39	(0.98 - 1.97)	0.061	1.44	(0.95 - 2.18)	0.086
Recent Overseas Travel	1.14	(0.82 - 1.59)	0.434	1.23	(0.85 - 1.79)	0.280
Prior Influenza Vaccination within 1 year	0.83	(0.56 - 1.21)	0.321	0.74	(0.48 - 1.14)	0.174
Charlson's Comorbid Index >=1	1.13	(0.83 - 1.53)	0.456	1.11	(0.74 - 1.65)	0.629
Steroid Use	1.44	(0.83 - 2.48)	0.193	1.76	(0.90 - 3.43)	0.100
Systemic Corticosteroid Use	2.95	(0.78 - 11.22)	0.112			
Inhaled Corticosteroid Use	2.44	(0.70 - 2.24)	0.447			
<u>Month of Emergency Department Visit</u>						
Dec	3.44	(0.32 - 1.14)	0.119	Ref		
Jan	0.83	(0.45 - 1.51)	0.541	1.97	(0.77 - 5.01)	0.158
Feb	4.44	(0.39 - 1.44)	0.383	1.45	(0.55 - 3.83)	0.458
Mar	1.30	(0.73 - 2.32)	0.367	2.44	(0.96 - 6.14)	0.060
Apr	5.44	(0.55 - 1.71)	0.908	1.47	(0.59 - 3.65)	0.415
May	1.60	(0.93 - 2.77)	0.089	2.26	(0.93 - 5.51)	0.073
Jun	6.44	(0.90 - 2.68)	0.115	2.77	(1.11 - 6.84)	**0.028**
Jul	0.96	(0.63 - 1.47)	0.848	1.48	(0.65 - 3.37)	0.352
Aug	7.44	(0.73 - 2.03)	0.450	2.53	(1.04 - 6.15)	**0.041**
Sep	0.76	(0.47 - 1.22)	0.254	1.32	(0.57 - 3.04)	0.525

Oct	8.44	(0.59 - 1.48)	0.773	1.66	(0.72 - 3.85)	0.237
Nov	0.92	(0.51 - 1.65)	0.774	2.25	(0.90 - 5.62)	0.084
Duration of illness						
>8 days	0.47	(0.32 - 0.69)	**<0.001**	Ref		
5-8 Days	10.44	(0.52 - 0.99)	**0.046**	1.17	(0.72 - 1.90)	0.526
1-4 days	2.13	(1.58 - 2.87)	**<0.001**	2.14	(1.37 - 3.33)	**0.001**
<u>Presenting Symptoms</u>						
Fever	11.44	(1.95 - 3.62)	**<0.001**			
Chills	0.99	(0.53 - 1.85)	0.977	0.74	(0.35 - 1.56)	0.426
Headache	12.44	(0.64 - 1.77)	0.814	0.90	(0.49 - 1.64)	0.717
Body Ache	1.53	(1.00 - 2.35)	**0.049**	1.50	(0.87 - 2.58)	0.143
Joint Pain	13.44	(0.29 - 2.01)	0.579	0.70	(0.22 - 2.18)	0.536
Tiredness	1.26	(0.60 - 2.62)	0.539	1.12	(0.44 - 2.86)	0.817
Cough	14.44	(1.12 - 3.51)	**0.018**	2.51	(1.32 - 4.78)	**0.005**
Rhinorrhea	1.44	(1.07 - 1.94)	**0.015**	1.46	(1.05 - 2.03)	**0.026**
Sore Throat	15.44	(0.79 - 1.42)	0.700	1.02	(0.71 - 1.46)	0.921
Shortness of Breath	0.79	(0.55 - 1.14)	0.204	0.65	(0.40 - 1.05)	0.077
Chest Pain	16.44	(0.55 - 1.31)	0.457	1.02	(0.62 - 1.65)	0.952
Loss of appetite	1.49	(0.86 - 2.55)	0.152	1.68	(0.84 - 3.33)	0.142
Nausea	17.44	(0.79 - 2.97)	0.205	1.17	(0.53 - 2.56)	0.712
Vomiting	0.80	(0.42 - 1.52)	0.488	0.59	(0.27 - 1.27)	0.172
Abdominal Pain	18.44	(0.40 - 1.73)	0.614	1.06	(0.46 - 2.45)	0.892
<u>Presenting Sign</u>						
Injected Pharynx	1.37	(0.99 - 1.91)	0.060	1.38	(0.92 - 2.07)	0.119

Abnormal lung findings	19.44	(0.39 - 1.05)	0.078	0.59	(0.31 - 1.10)	0.097
Temperature >= 38°C	2.35	(1.56 - 3.55)	**<0.001**	2.72	(1.51 - 4.86)	**0.001**
Hypotension (SBP<90 or DBP <=60)	20.44	(0.85 - 1.67)	0.312	0.90	(0.60 - 1.35)	0.609
Tachycardia (>100/min)	21.44	(0.83 - 1.81)	0.308	0.75	(0.45 - 1.24)	0.263
Tachypnoea (<30/mins)	0.65	(0.15 - 2.75)	0.559	0.82	(0.17 - 3.99)	0.804
Low oxygen saturation (SaO2 less than 98%)	1.46	(1.08 - 1.98)	**0.015**	1.23	(0.84 - 1.80)	0.297
C-reactive protein level (mg/L)						
<5	0.58	(0.43 - 0.78)	**<0.001**	Ref		
5 to 20	23.44	(1.50 - 2.83)	**<0.001**	1.91	(1.29 - 2.80)	**0.001**
21 to 40	1.04	(0.65 - 1.66)	0.862	1.08	(0.61 - 1.89)	0.792
41 to 100	24.44	(0.70 - 1.99)	0.533	1.20	(0.64 - 2.25)	0.571
>100	0.21	(0.07 - 0.62)	**0.005**	0.17	(0.05 - 0.56)	**0.004**

(* two patients did not have a C-reactive protein test)

(Table. 3) Multivariable multinomial logistic regression models assessing the association of WHO ILI and CDC ILI case definitions and other factors with the detection of influenza viruses, rhinoviruses, human coronaviruses, and other respiratory viruses, with no virus detected as the reference category (n=717)

Model 1 : WHO ILI case definition	Influenza viruses			Rhinoviruses			Human coronaviruses			Other respiratory viruses		
Factors	aOR	(95% CI)	p value	aOR	(95% CI)	p value	aOR	(95% CI)	p value	aOR	(95% CI)	p value
Age (year)	1.01	(0.99 - 1.02)	0.766	0.99	(0.97 - 1.01)	0.080	1.02	(0.99 - 1.05)	0.356	0.99	(0.97 - 1.01)	0.190
Male Gender	0.65	(0.40 - 1.06)	0.083	0.80	(0.48 - 1.34)	0.390	1.64	(0.60 - 4.46)	0.337	0.78	(0.44 - 1.39)	0.392
Smoker	1.32	(0.75 - 2.34)	0.339	2.01	(1.18 - 3.42)	**0.011**	0.69	(0.20 - 2.41)	0.555	1.47	(0.77 - 2.81)	0.254
Recent Overseas Travel	0.81	(0.48 - 1.37)	0.417	1.07	(0.62 - 1.84)	0.818	4.14	(1.59 - 10.82)	**0.004**	1.39	(0.78 - 2.49)	0.273
Prior Influenza Vaccination within 1 year	0.56	(0.28 - 1.11)	0.095	0.81	(0.44 - 1.49)	0.495	0.74	(0.25 - 2.26)	0.593	1.23	(0.65 - 2.33)	0.538
Charlson's Comorbidity Index >=1	0.93	(0.54 - 1.61)	0.775	1.35	(0.77 - 2.40)	0.306	2.57	(0.85 - 7.77)	0.095	1.30	(0.68 - 2.51)	0.441
Steroid Use	0.61	(0.19 - 1.99)	0.411	1.65	(0.69 - 3.94)	0.262	15.04	(3.59 - 63.11)	**<0.001**	1.22	(0.41 - 3.61)	0.725
Month of Emergency Department Visit												

Dec	Ref			Ref			Ref			Ref		
Jan	2.72	(0.53 - 14.07)	0.234	1.51	(0.45 - 5.07)	0.506	5.83	(0.35 - 98.82)	0.222	0.99	(0.23 - 4.34)	0.984
Feb	5.04	(1.05 - 24.21)	**0.043**	0.38	(0.07 - 2.13)	0.267	3.47	(0.15 - 83.20)	0.444	0.56	(0.10 - 3.37)	0.525
Mar	6.01	(1.26 - 28.71)	**0.025**	1.39	(0.40 - 4.86)	0.612	14.75	(0.97 - 225.53)	0.053	1.14	(0.27 - 4.78)	0.864
Apr	3.78	(0.78 - 18.43)	0.101	1.09	(0.32 - 3.79)	0.898	1.67	(0.07 - 42.10)	0.757	1.07	(0.27 - 4.32)	0.928
May	9.13	(2.05 - 40.69)	**0.004**	1.43	(0.43 - 4.73)	0.565	9.51	(0.57 - 160.28)	0.118	0.70	(0.14 - 3.45)	0.654
Jun	10.9	(2.43 - 48.94)	**0.002**	0.83	(0.22 - 3.12)	0.775	NA			1.64	(0.43 - 6.29)	0.472
Jul	3.53	(0.83 - 15.14)	0.090	1.02	(0.35 - 3.03)	0.977	6.10	(0.43 - 87.36)	0.184	0.77	(0.21 - 2.85)	0.691
Aug	2.71	(0.57 - 12.98)	0.214	2.22	(0.73 - 6.82)	0.163	2.54	(0.10 - 64.31)	0.573	2.11	(0.58 - 7.71)	0.261
Sep	1.75	(0.37 - 8.24)	0.482	0.82	(0.26 - 2.66)	0.735	8.12	(0.63 - 105.14)	0.109	1.58	(0.47 - 5.32)	0.464
Oct	2.96	(0.66 - 13.38)	0.160	1.41	(0.47 - 4.27)	0.550	8.81	(0.62 - 125.00)	0.108	1.15	(0.31 - 4.21)	0.843
Nov	7.14	(1.50 - 34.13)	**0.014**	0.70	(0.18 - 2.84)	0.615	7.79	(0.52 - 117.80)	0.139	0.96	(0.22 - 4.21)	0.948
Fulfil WHO ILI case definition	8.84	(4.55 - 17.15)	**<0.001**	0.57	(0.18 - 1.81)	0.335	3.46	(0.80 - 15.07)	0.100	2.48	(1.01 - 6.08)	**0.048**
Headache	1.03	(0.48 - 2.22)	0.944	0.90	(0.36 - 2.29)	0.818	0.70	(0.12 - 4.09)	0.687	0.82	(0.30 - 2.25)	0.699
Body ache	1.67	(0.89 - 3.15)	0.116	0.58	(0.23 - 1.48)	0.249	2.23	(0.55 - 9.15)	0.267	2.11	(1.00 - 4.47)	0.053
Joint pain	0.50	(0.10 - 2.52)	0.396	1.08	(0.20 - 5.81)	0.931	0.89	(0.05 - 18.6)	0.937	0.36	(0.04 - 3.37)	0.365
Rhinorrhea	1.85	(1.17 - 2.93)	**0.009**	1.63	(1.01 - 2.62)	**0.047**	1.27	(0.50 - 3.23)	0.620	1.14	(0.66 - 1.96)	0.646
Sore throat	0.53	(0.32 - 0.87)	**0.012**	1.23	(0.73 - 2.06)	0.445	3.17	(1.07 - 9.07)	0.038	1.27	(0.71 - 2.25)	0.429
Shortness of breath	0.41	(0.20 - 0.85)	**0.015**	0.84	(0.45 - 1.58)	0.579	0.32	(0.08 - 1.22)	0.094	0.56	(0.24 - 1.28)	0.163
Chest pain	0.76	(0.37 - 1.55)	0.441	1.15	(0.60 - 2.22)	0.681	3.70	(1.24 - 11.08)	**0.019**	0.43	(0.16 - 1.17)	0.095
Loss of appetite	2.76	(1.27 - 5.97)	**0.010**	0.70	(0.24 - 2.04)	0.501	0.30	(0.03 - 3.45)	0.327	1.02	(0.33 - 3.15)	0.980
Nausea	1.08	(0.39 - 2.95)	0.895	1.24	(0.38 - 4.05)	0.728	3.59	(0.51 - 25.37)	0.200	2.15	(0.66 - 7.07)	0.210
Vomiting	0.25	(0.08 - 0.78)	**0.017**	1.24	(0.46 - 3.35)	0.671	0.34	(0.02 - 6.73)	0.474	0.33	(0.07 - 1.55)	0.157
Injected Pharynx	2.65	(1.56 - 4.51)	**<0.001**	1.02	(0.57 - 1.85)	0.955	0.50	(0.16 - 1.62)	0.245	0.72	(0.36 - 1.43)	0.334
Abnormal lung findings	0.45	(0.18 - 1.13)	0.086	0.53	(0.24 - 1.19)	0.123	2.14	(0.31 - 14.76)	0.441	0.26	(0.10 - 0.68)	**0.006**
Hypotension (SBP<90 or DBP <=60)	0.92	(0.53 - 1.59)	0.753	1.12	(0.65 - 1.95)	0.694	0.96	(0.32 - 2.90)	0.936	0.69	(0.34 - 1.40)	0.295
Tachycardia (>100/min)	0.89	(0.46 - 1.70)	0.702	0.80	(0.39 - 1.64)	0.535	0.38	(0.08 - 1.93)	0.243	0.74	(0.33 - 1.67)	0.458
Low oxygen saturation (SaO2 less than 98%)	1.27	(0.76 - 2.11)	0.377	1.35	(0.80 - 2.30)	0.273	0.69	(0.23 - 2.05)	0.493	1.10	(0.59 - 2.04)	0.776

Model 2 : CDC ILI case definition	Influenza viruses			Rhinoviruses			Human coronaviruses			Other respiratory viruses		
Factors	aOR	(95% CI)	p value	aOR	(95% CI)	p value	aOR	(95% CI)	p value	aOR	(95% CI)	p value
Age (year)	1.01	(0.99 - 1.02)	0.895	0.99	(0.97 - 1.01)	0.089	1.02	(0.99 - 1.05)	0.404	0.99	(0.97 - 1.01)	0.170

Male Gender	0.75	(0.46 - 1.22)	0.241	0.79	(0.48 - 1.32)	0.362	1.81	(0.65 - 5.01)	0.260	0.80	(0.45 - 1.41)	0.425
Smoker	1.08	(0.61 - 1.91)	0.816	1.91	(1.12 - 3.28)	**0.01 9**	0.47	(0.13 - 1.73)	0.254	1.38	(0.72 - 2.65)	0.339
Recent Overseas Travel	0.86	(0.50 - 1.46)	0.555	1.07	(0.62 - 1.84)	0.826	4.45	(1.69 - 11.71)	**0.003**	1.44	(0.81 - 2.57)	0.226
Prior Influenza Vaccination within 1 year	0.53	(0.26 - 1.06)	0.072	0.78	(0.42 - 1.44)	0.414	0.69	(0.23 - 2.14)	0.520	1.22	(0.64 - 2.31)	0.562
Charlson's Comorbidity Index >=1	0.94	(0.54 - 1.63)	0.814	1.26	(0.71 - 2.23)	0.444	1.92	(0.66 - 5.60)	0.235	1.26	(0.66 - 2.43)	0.494
Steroid Use	0.69	(0.21 - 2.31)	0.538	1.72	(0.72 - 4.11)	0.227	13.94	(3.57 - 54.53)	**<0.001**	1.30	(0.44 - 3.82)	0.642
Month of Emergency Department Visit												
Dec	Ref											
Jan	2.67	(0.51 - 14.08)	0.248	1.56	(0.47 - 5.24)	0.475	3.28	(0.22 - 50.43)	0.395	1.00	(0.23 - 4.37)	0.994
Feb	6.49	(1.32 - 31.86)	**0.021**	0.43	(0.08 - 2.43)	0.336	2.93	(0.14 - 65.80)	0.499	0.55	(0.09 - 3.27)	0.502
Mar	6.61	(1.36 - 32.34)	**0.020**	1.43	(0.41 - 5.02)	0.582	11.15	(0.80 - 156.75)	0.074	1.10	(0.27 - 4.62)	0.897
Apr	3.91	(0.79 - 19.44)	0.097	1.23	(0.36 - 4.29)	0.749	1.17	(0.05 - 32.39)	0.928	1.06	(0.27 - 4.23)	0.942
May	9.16	(2.01 - 41.90)	**0.004**	1.48	(0.45 - 4.94)	0.526	5.59	(0.37 - 85.79)	0.217	0.69	(0.14 - 3.41)	0.648
Jun	10.8	(2.36 - 49.46)	**0.002**	0.96	(0.26 - 3.63)	0.943	NA			1.73	(0.46 - 6.57)	0.423
Jul	3.66	(0.84 - 15.99)	0.085	1.10	(0.37 - 3.28)	0.871	4.83	(0.37 - 63.44)	0.231	0.77	(0.21 - 2.83)	0.690
Aug	2.34	(0.47 - 11.67)	0.303	2.48	(0.81 - 7.61)	0.115	2.42	(0.11 - 54.75)	0.580	2.09	(0.58 - 7.55)	0.261
Sep	1.66	(0.35 - 8.01)	0.530	0.84	(0.26 - 2.73)	0.767	6.24	(0.53 - 73.96)	0.143	1.60	(0.49 - 5.33)	0.444
Oct	2.11	(0.46 - 9.75)	0.340	1.55	(0.51 - 4.72)	0.441	6.58	(0.53 - 81.93)	0.142	1.09	(0.31 - 3.94)	0.897
Nov	6.23	(1.27 - 30.51)	**0.024**	0.84	(0.21 - 3.40)	0.801	6.93	(0.50 - 97.21)	0.151	0.95	(0.22 - 4.15)	0.941
Duration of illness												
>8 days	Ref											
5 - 8 Days	1.40	(0.65 - 3.03)	0.392	0.78	(0.38 - 1.57)	0.472	5.37	(0.87 - 33.30)	0.072	0.97	(0.46 - 2.05)	0.920
1 - 4 days	3.35	(1.63 - 6.90)	**0.001**	1.54	(0.83 - 2.83)	0.173	10.52	(1.88 - 59.05)	**0.008**	1.04	(0.51 - 2.12)	0.917
Fulfil CDC ILI case definition	5.95	(3.29 - 10.76)	**<0.001**	0.84	(0.37 - 1.93)	0.673	1.90	(0.53 - 6.84)	0.328	1.39	(0.62 - 3.14)	0.429
Headache	1.02	(0.48 - 2.18)	0.965	0.90	(0.35 - 2.33)	0.825	0.80	(0.14 - 4.58)	0.802	0.86	(0.32 - 2.32)	0.754
Body ache	1.25	(0.66 - 2.37)	0.508	0.57	(0.22 - 1.47)	0.240	1.87	(0.45 - 7.86)	0.398	2.13	(1.00 - 4.55)	0.053
Joint pain	0.62	(0.13 - 3.06)	0.554	1.21	(0.22 - 6.65)	0.829	0.61	(0.03 - 16.83)	0.761	0.36	(0.04 - 3.29)	0.361
Runny nose	1.65	(1.05 - 2.59)	**0.033**	1.72	(1.07 - 2.77)	**0.026**	1.49	(0.60 - 3.76)	0.396	1.14	(0.67 - 1.95)	0.647
Shortness of breath	0.42	(0.20 - 0.89)	**0.023**	0.84	(0.44 - 1.59)	0.579	0.40	(0.11 - 1.51)	0.175	0.53	(0.23 - 1.23)	0.135
Chest pain	0.91	(0.44 - 1.91)	0.796	1.21	(0.62 - 2.35)	0.583	4.64	(1.47 - 14.68)	**0.009**	0.42	(0.16 - 1.15)	0.089
Loss of appetite	3.17	(1.44 - 7.00)	**0.004**	0.77	(0.27 - 2.26)	0.628	0.58	(0.06 - 6.17)	0.646	1.15	(0.38 - 3.47)	0.808
Nausea	1.04	(0.38 - 2.82)	0.948	1.13	(0.34 - 3.72)	0.850	2.51	(0.38 - 16.6)	0.341	2.07	(0.64 - 6.75)	0.229
Vomiting	0.33	(0.11 - 0.98)	**0.045**	1.28	(0.48 - 3.44)	0.632	0.25	(0.01 - 6.93)	0.407	0.34	(0.07 - 1.58)	0.164

Injected Pharynx	1.91	(1.15 - 3.16)	**0.013**	1.11	(0.63 - 1.97)	0.738	0.74	(0.24 - 2.35)	0.606	0.77	(0.40 - 1.50)	0.439
Abnormal lung findings	0.41	(0.16 - 1.05)	0.061	0.51	(0.22 - 1.16)	0.104	1.83	(0.27 - 12.43)	0.537	0.27	(0.10 - 0.69)	**0.006**
Hypotension (SBP<90 or DBP <=60)	0.91	(0.53 - 1.56)	0.707	1.09	(0.63 - 1.91)	0.764	0.87	(0.29 - 2.59)	0.791	0.73	(0.36 - 1.46)	0.365
Tachycardia (>100/min)	0.81	(0.42 - 1.58)	0.536	0.81	(0.39 - 1.69)	0.565	0.50	(0.11 - 2.32)	0.372	0.83	(0.36 - 1.90)	0.650
Low oxygen saturation (SaO2 less than 98%)	1.28	(0.77 - 2.14)	0.354	1.25	(0.74 - 2.13)	0.417	0.58	(0.19 - 1.81)	0.344	1.16	(0.63 - 2.13)	0.654

(Table. 4) Performance of WHO, CDC, and ECDC ILI case definitions in the detection of influenza viruses (high - activity and low - activity months), rhinoviruses and human coronaviruses (n=717)

(Table 4A) Comparison of the performance of WHO, CDC, and ECDC ILI case definitions in the detection of influenza viruses, rhinoviruses, and human coronaviruses

	SENS	SPEC	PPV	NPV	LR+	LR -	AUC	95% CI of AUC	
Influenza									
WHO ILI definition	38.5%	91.6%	54.3%	85.1%	4.566	0.672	0.65	0.609	0.691
CDC ILI definition	49.3%	86.5%	48.7%	86.8%	3.645	0.586	0.679	0.636	0.722
ECDC ILI definition	78.4%	53.8%	30.6%	90.5%	1.696	0.402	0.661	0.622	0.700
Rhinovirus									
WHO ILI definition	3.9%	83.6%	3.8%	83.8%	0.236	1.150	0.437	0.413	0.461
CDC ILI definition	9.7%	77.2%	6.7%	83.6%	0.426	1.170	0.435	0.401	0.468
ECDC ILI definition	45.6%	45.9%	12.4%	83.4%	0.844	1.184	0.458	0.406	0.510
Human coronavirus									
WHO ILI definition	15.4%	85.4%	3.8%	96.4%	1.053	0.991	0.504	0.432	0.576
CDC ILI definition	19.2%	79.0%	3.3%	96.3%	0.916	1.022	0.491	0.413	0.570
ECDC ILI definition	53.8%	47.2%	3.7%	96.4%	1.019	0.978	0.505	0.406	0.605

(Table 4B) Comparison of the performance of WHO, CDC, and ECDC ILI case definitions in the detection of influenza viruses, during high and low influenza activity months[a] classified using the study data.

	SENS	SPEC	PPV	NPV	LR+	LR -	AUC	95% CI of AUC	
WHO ILI definition									
Overall	38.5%	91.6%	54.3%	85.1%	4.566	0.672	0.650	0.609	0.691
low influenza activity months	38.2%	91.6%	48.1%	87.9%	4.552	0.674	0.649	0.600	0.698
High influenza activity months	39.1%	91.3%	75.0%	69.2%	4.500	0.667	0.652	0.573	0.731
CDC ILI definition									
Overall	49.3%	86.5%	48.7%	86.8%	3.645	0.586	0.679	0.636	0.722
low influenza activity months	52.0%	86.2%	43.4%	89.8%	3.765	0.557	0.691	0.640	0.742
High influenza activity months	43.5%	88.4%	71.4%	70.1%	3.750	0.639	0.659	0.578	0.741
ECDC ILI definition									
Overall	78.4%	53.8%	30.6%	90.5%	1.696	0.402	0.661	0.622	0.700
low influenza activity months	83.3%	52.6%	26.4%	93.9%	1.758	0.317	0.680	0.637	0.722

High influenza activity months	67.4%	62.3%	54.4%	74.1%	1.788	0.523	0.649	0.559	0.738

(Table 4C) Comparison of the performance of WHO, CDC, and ECDC ILI case definitions in the detection of influenza viruses, during high and low influenza activity months[a] classified using national data.

	SENS	SPEC	PPV	NPV	LR+	LR -	AUC	95% CI of AUC	
WHO ILI definition									
Overall	38.5%	91.6%	54.3%	85.1%	4.566	0.672	0.650	0.609	0.691
low influenza activity months	36.7%	90.7%	47.6%	86.1%	3.928	0.698	0.637	0.589	0.684
High influenza activity months	43.6%	95.9%	81.0%	81.0%	10.679	0.588	0.698	0.616	0.779
CDC ILI definition									
Overall	49.3%	86.5%	48.7%	86.8%	3.645	0.586	0.679	0.636	0.722
low influenza activity months	49.5%	85.1%	43.5%	87.9%	3.333	0.593	0.673	0.624	0.723
High influenza activity months	48.7%	92.9%	73.1%	82.0%	6.821	0.552	0.708	0.624	0.791
ECDC ILI definition									
Overall	78.4%	53.8%	30.6%	90.5%	1.696	0.402	0.661	0.622	0.700
low influenza activity months	78.9%	52.9%	27.9%	91.5%	1.674	0.399	0.659	0.614	0.703
High influenza activity months	76.9%	58.2%	42.3%	86.4%	1.839	0.397	0.675	0.592	0.758

Abbreviations: SENS, sensitivity; SPEC, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive; LR -, likelihood ratio negative; AUC, area under the curve

The World Health Organization (WHO)'s case definition for influenza - like illness (ILI) is an acute respiratory illness with a measured temperature of ≥38°C and cough, with onset within the past 10 days.

The Centers for Disease Control and Prevention (CDC)'s case definition for Influenza - like illness (ILI) is fever (temperature of ≥37.8 °C) and cough and/or sore throat.

The European Center for Disease Control and Prevention (ECDC)'s case definition for Influenza - like illness (ILI) is the sudden onset of symptoms and at least one of the following four systemic symptoms: fever or feverishness, malaise, headache, and myalgia, and at least one of the following three respiratory symptoms: cough, sore throat, and shortness of breath.

[a]High influenza activity months were defined as calendar months with influenza positivity rates exceeding one standard deviation (>1SD) of the average monthly influenza positivity rate in the 30 - month study period using the study data (Table 4B) and national data published by Singapore's Ministry of Health (Table 4C). Low influenza activity months were the remaining calendar months during the study period.