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Burden and Seasonality of Viral Acute Respiratory Tract Infections among Outpatients in Southern Sri Lanka

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Abstract. In tropical and subtropical settings, the epidemiology of viral acute respiratory tract infections varies widely between countries. We determined the etiology, seasonality, and clinical presentation of viral acute respiratory tract infections among outpatients in southern Sri Lanka. From March 2013 to January 2015, we enrolled outpatients presenting with influenza-like illness (ILI). Nasal/nasopharyngeal samples were tested in duplicate using antigen-based rapid influenza testing and multiplex polymerase chain reaction (PCR) for respiratory viruses. Monthly proportion positive was calculated for each virus. Bivariable and multivariable logistic regression were used to identify associations between sociodemographic/clinical information and viral detection. Of 571 subjects, most (470, 82.3%) were ≥ 5 years of age and 53.1% were male. A respiratory virus was detected by PCR in 63.6% ($N = 363$). Common viral etiologies included influenza (223, 39%), human enterovirus/rhinovirus (HEV/HRV, 14.5%), respiratory syncytial virus (RSV, 4.2%), and human metapneumovirus (hMPV, 3.9%). Both ILI and influenza showed clear seasonal variation, with peaks from March to June each year. RSV and hMPV activity peaked from May to July, whereas HEV/HRV was seen year-round. Patients with respiratory viruses detected were more likely to report pain with breathing (odds ratio [OR] = 2.60, $P = 0.003$), anorexia (OR = 2.29, $P < 0.001$), and fatigue (OR = 2.00, $P = 0.002$) compared with patients with no respiratory viruses detected. ILI showed clear seasonal variation in southern Sri Lanka, with most activity during March to June; peak activity was largely due to influenza. Targeted infection prevention activities such as influenza vaccination in January–February may have a large public health impact in this region.

INTRODUCTION

Acute respiratory tract infections are a leading cause of morbidity and mortality worldwide and are most commonly caused by viruses.[1] Influenza is the most extensively studied of the respiratory viruses, causing infections in 10–20% of the world's population and accounting for substantial morbidity, mortality, and economic losses each year.[2,3] In addition to influenza, viruses such as respiratory syncytial virus (RSV), human enterovirus/rhinovirus (HEV/HRV), adenovirus, and parainfluenza are also associated with a significant burden of disease in patients with acute respiratory tract infections.[4–7]

The epidemiology of viral acute respiratory tract infections in the tropics, especially in low- and middle-income countries, is not as well described as in temperate, more developed countries. Influenza remains a common cause of illness, but the burden of other viruses is not well defined.[8,9] In addition, while influenza follows a clear seasonal pattern in temperate countries, in tropical and subtropical countries, seasonality appears to vary between countries and even within countries.[8,9] Perhaps due to limited data, less than half of tropical and subtropical countries, comprising 20% of the world's population, have a national vaccine policy for influenza.[10] For tropical and subtropical countries, local data regarding epidemiology of influenza and other respiratory viruses are needed to guide preventative public health measures such as vaccination.[11]

We examined the etiology, seasonal variation, and clinical manifestations of viral acute respiratory tract infections among outpatients presenting to an acute care facility in Sri Lanka, a tropical, lower middle-income nation. Sri Lanka does not currently have a national influenza immunization policy and influenza vaccines are not routinely administered through the public sector.[10]

METHODS

Study population and surveillance procedures. This was a cross-sectional study performed in the outpatient department (OPD) of the largest (1,500 bed) public, tertiary care hospital in the Southern Province of Sri Lanka. The OPD of this hospital serves over 1,000 patients daily between 8 AM and 7 PM.

Consecutive adults and children ≥ 1 year presenting to the OPD with acute respiratory tract infections were screened for enrollment by trained study physicians from March 2013 to January 2015. Patients were eligible for enrollment if they met criteria for influenza-like illness (ILI), as defined by the World Health Organization (WHO): tympanic temperature ≥ 38°C/100.4°F and acute onset of cough in the past 7 days without alternative diagnosis.[12] Consent was obtained from patients ≥ 18 years of age and the guardians of patients 1–17 years of age, and assent was obtained from patients 12–17 years of age.

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Enrolled patients were administered a standardized questionnaire in the local language of Sinhala and a physical examination was conducted. Two nasopharyngeal samples were collected from all patients for whom it was possible; patients unable to tolerate nasopharyngeal sample collection had a nasal sample collected instead. One sample was used immediately in rapid influenza testing, and the other was stored at –80°C for viral polymerase chain reaction (PCR) testing, as described below. Patients received standard clinical assessment and treatment including physical examination, additional diagnostic testing, and prescriptions from OPD physicians. Details regarding patients' clinical diagnoses and management were recorded. The result from the rapid influenza test was only released to patients and clinicians during the latter half of the study (January 2014–January 2015), with the result being released prior to any clinical decision-making. Details from this pre-post study have been reported previously.[13] Study physicians were not involved in clinical care or treatment, and OPD clinical personnel were not involved in study screening or enrollment procedures. Ethical approval for this study was obtained from the Ruhuna University Ethical Review Committee, Duke University Institutional Review Board, and Johns Hopkins Medicine Institutional Review Board.

Rapid influenza testing. All patients were tested with the Veritor Flu A+B rapid influenza kit (Becton Dickinson, and Company, Franklin Lakes, NJ) using a nasal/nasopharyngeal sample collected and run at the point of care. This rapid chromatographic immunoassay detects influenza A and B viral nucleoprotein antigens from nasal and nasopharyngeal swabs using a single processed sample.[14] The performance characteristics of the Veritor test were documented by Hassan and others, who showed that in pediatric patients, the sensitivity and specificity of the test when compared with PCR were 90.2% and 99.1%, respectively, for influenza A and 87.5% and 100%, respectively, for influenza B.[15]

Respiratory virus molecular testing. The second nasal/nasopharyngeal sample from each patient was placed in viral transport media and frozen at –80°C. These samples were later tested by real-time reverse transcription PCR (RT-PCR) with the Luminex xTAG respiratory virus panel (Luminex Molecular Diagnostics, Toronto, Canada). The platform detects influenza A, influenza B, HEV/HRV, RSV, human metapneumovirus (hMPV), parainfluenza viruses 1–4, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, bocavirus, and adenovirus.[16,17]

Statistical analysis. Seasonality of ILI, influenza, and the three other most common respiratory viruses was assessed using a modified definition from the Program for Appropriate Technology (PATH) for determining influenza seasonality.[11] The monthly proportion of positive cases for a specific virus out of all positive cases within a given calendar year was calculated. A "peak" in activity was defined as the monthly proportion being ≥10% during both years of the study.

Monthly weather data were obtained for the Galle region from the Sri Lanka Department of Meteorology (Colombo, Sri Lanka). Correlation between weather data (monthly rainfall, monthly minimum temperature, monthly maximum temperature, daily humidity, and nightly humidity) and the monthly proportion of subjects with ILI or influenza by PCR were determined using the Spearman correlation.[18]

Sociodemographic and clinical characteristics between patients with a positive versus negative respiratory viral test, and patients with a positive influenza versus positive other respiratory viral test, were compared using the Fisher's exact test for categorical variables and the Kruskall–Wallis test for continuous variables. Bivariable and multivariable logistic regression were carried out to determine the association (odds ratios [ORs] with 95% confidence intervals) between patients' sociodemographic characteristics/clinical symptoms and viral PCR test results.

For the multivariable analysis, adjusted models were constructed separately to determine features associated with respiratory virus positivity versus negativity and influenza positivity versus other virus positivity (all per PCR testing). Age ≥ 5 years (as a categorical variable) was included in all models. In addition, any sociodemographic characteristic or clinical symptom that was associated with the dependent variable in question at a P value < 0.05 on bivariable analysis was included in the individual multivariable model. Variables were checked for collinearity prior to inclusion in the models. To create more parsimonious models, variables were excluded in a stepwise fashion by decreasing P value until all P values were < 0.05 in the multivariable model. Each excluded variable was then added back sequentially to ensure that the variable was not significant in the final model.

Performance characteristics of the rapid test were calculated using the Luminex RT-PCR test result as a gold standard. Sensitivity, specificity, and positive and negative predictive values were determined. Patients with viral coinfections as identified by PCR were included in the analysis.

All analyses were performed using JMP PRO, Version 11 (SAS Institute Inc., Cary, NC) and STATA, version 11 (STATACorp, College Station, TX).

RESULTS

Sociodemographic and clinical description of study cohort. We enrolled 571 outpatients during the study period, with approximately half (53.1%) being male. The majority (82.3%) of subjects were ≥ 5 years of age and median age was 13.2 years (range = 1.1–74.8). Median days of both fever and cough were 2 days (interquartile range = 2–3 days for both). No subjects reported a prior history of influenza vaccination. A total of 441 (77.2%) subjects were prescribed an antibiotic at their OPD visit and none were admitted to the hospital for treatment with antivirals (physicians are not allowed to prescribe oseltamivir through the OPD).

Respiratory virus detection. Virus was detected by PCR in 63.6% (N = 363) of subjects, with 3.7% having more than one virus detected (Table 1). The most common viral etiology was influenza (223, 39.1%), with 163 (28.5%) influenza A and 60 (10.5%) influenza B. Other common viral etiologies included HEV/HRV (14.5%), RSV (4.2%), and hMPV (3.9%). The remainder of the viruses detected were parainfluenza virus (3.2%), coronavirus (1.4%), bocavirus (0.9%), and adenovirus (0.4%). Coinfections were present in 21 (3.7%), with the most common combination being

TABLE 1

Distribution of respiratory viruses isolated from outpatients presenting with acute respiratory tract infections to a tertiary care hospital in southern Sri Lanka, 2013–2015

Respiratory virus	Frequency (%) in all patients (N = 571)	Frequency (%) in patients < 5 years (N = 101)	Frequency (%) in patients ≥ 5 years (N = 470)	P value
Influenza	223 (39.1)	25 (24.8)	198 (42.1)	0.001
Influenza A	163 (28.5)	23 (22.8)	140 (29.8)	0.18
Influenza B	60 (10.5)	2 (2.0)	58 (12.3)	0.001
HEV/HRV	83 (14.5)	19 (18.8)	64 (13.6)	0.21
Respiratory syncytial virus	24 (4.2)	14 (13.9)	10 (2.1)	< 0.001
Human metapneumovirus	22 (3.9)	5 (5.0)	17 (3.6)	0.57
Parainfluenza virus	18 (3.2)	9 (8.9)	9 (1.9)	0.002
Parainfluenza 1	6 (1.1)	3 (3.0)	3 (0.6)	0.07
Parainfluenza 2	1 (0.2)	0 (0)	1 (0.2)	1.00
Parainfluenza 3	7 (1.2)	4 (4.0)	3 (0.6)	0.02
Parainfluenza 4	4 (0.7)	2 (2.0)	2 (0.4)	0.15
Coronovirus	8 (1.4)	2 (2.0)	6 (1.3)	0.63
Coronavirus 229E	0 (0)	0 (0)	0 (0)	N/A
Coronavirus HKU1	1 (0.2)	0 (0)	1 (0.2)	1.00
Coronavirus NL63	1 (0.2)	0 (0)	1 (0.2)	1.00
Coronavirus OC43	6 (1.1)	2 (2.0)	4 (0.9)	0.29
Bocavirus	5 (0.9)	4 (4.0)	1 (0.2)	0.004
Adenovirus	2 (0.4)	0 (0)	2 (0.4)	1.00
Negative	208 (36.4)	31 (30.7)	177 (37.7)	0.21
Coinfections*	21 (3.7)	8 (7.9)	13 (2.8)	0.02

HEV/HRV = human enterovirus/rhinovirus.

* Influenza (16), parainfluenza (seven), and HEV/HRV (six) were the most commonly identified viruses in coinfections.

influenza A and HEV/HRV (6, 1.0%). Influenza (16), parainfluenza (seven), and HEV/HRV (six) were the most commonly identified viruses in coinfections.

When examined by age group, influenza was more common in patients ≥ 5 years of age than among those < 5 years of age (42.1% versus 24.8%, P = 0.001; Table 1). Among patients < 5 years of age, the following viruses were more common than among those ≥ 5 years of age: RSV (13.9% versus 2.1%, P < 0.0001), parainfluenza (8.9% versus 1.9%, P = 0.002), and bocavirus (4% versus 0.2%, P = 0.004). Coinfections were also more common is those less than 5 years of age (7.9% versus 2.8%, P = 0.02).

Seasonality of ILI and respiratory viruses. ILI peaked from March to June during both years of the study period, with May having the highest activity (Figure 1A). Influenza also peaked during March–June in both years, with May again having the highest activity. During each influenza peak month, influenza A activity was > 10% in both years, whereas influenza B did not consistently show activity > 10% in both years. Among other respiratory viruses, RSV peaked during May–July and hMPV peaked in May and in July in both years (Figure 1B). HEV/HRV showed sporadic peak activity throughout the year including in March, May, July, and October.

Monthly rainfall, daily humidity, and nightly humidity did not show any correlation with ILI (P = 0.19, 0.63 and 0.54, respectively) or with influenza (P = 0.46, 0.96 and 0.17, respectively). ILI was positively associated with monthly maximum temperature (range = 28.5–32.5°C, P = 0.04). Influenza was positively associated with monthly minimum temperature (range = 23.5–26.3°C, P = 0.01).

Sociodemographic and clinical features associated with respiratory virus detection. On bivariable analysis, subjects who were male were more likely to have a respiratory virus detected (57.6% versus 45.2%, P = 0.005; Table 2). Having a sick contact in the past month was associated with a positive respiratory virus test (46.2% versus 35.1%, P = 0.01), whereas having longer durations of fever or cough were associated with a negative respiratory virus test (P = 0.02 and P < 0.001, respectively). In addition, the following clinical symptoms were associated with respiratory virus detection: pain with breathing (12.4% versus 6.3%, P = 0.02), anorexia (68.0% versus 50.0%, $P \leq 0.001$), fatigue/lethargy (73.3% versus 55.3%, P < 0.001), arthralgias (60.3% versus 47.6% P = 0.004), and myalgias (61.2% versus 48.6%, P = 0.004). Prior antibiotic use for the same illness was associated with having a negative respiratory viral test (5.2% versus 11.5%, P = 0.008). There was no association between respiratory virus positivity and receiving an antibiotic prescription at the OPD visit (P = 1.00).

On adjusted analysis, male sex (OR = 1.48, P = 0.04) and having a sick contact in the past month (OR = 1.86, P = 0.001) were positively associated with respiratory virus detection (Table 3). The symptoms of pain with breathing (OR = 2.60, P = 0.003), anorexia (OR = 2.29, P < 0.001), and fatigue (OR = 2.00, P = 0.002) were also associated with respiratory virus detection. Age < 5 years (OR = 0.45, P = 0.005) and greater days of cough (OR = 0.79, P < 0.001) were negatively associated with respiratory virus detection.

Features associated with detection of influenza versus other respiratory viruses by PCR. On bivariable analysis, age < 5 years was associated with a positive test for another respiratory virus compared with influenza (32.1% versus 11.2%, P < 0.001; Table 4). The following clinical symptoms were associated with detection of influenza versus other respiratory viruses: sick contact in the past month (51.8% versus 37.2%, P = 0.009), pain with breathing (17.9% versus 3.6%, P < 0.001), anorexia (75.8% versus 55.7%, P < 0.001), headache (82.1% versus 61.4%, $P \leq 0.001$), fatigue/lethargy (81.6% versus 60.0%, P < 0.001), arthralgias (71.3% versus 42.9%, $P \leq$ 0.001), and myalgias (71.7% versus 44.3%, P < 0.001). However, patients with influenza were less likely to report rhinitis (71.3% versus 83.6%, P = 0.008). Patients with influenza had a higher median temperature (101.2°F versus 100.9°F, P < 0.001)

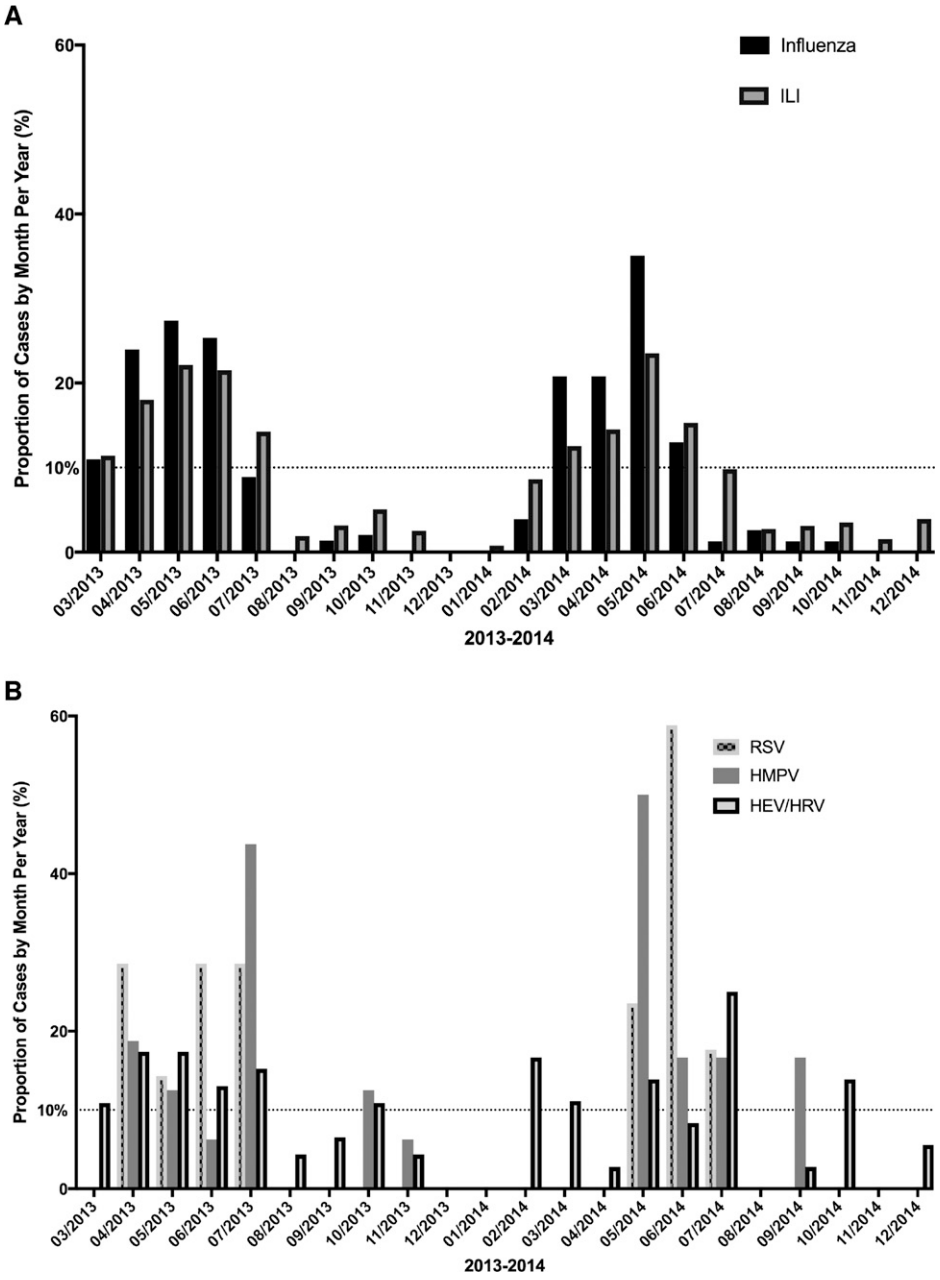

FIGURE 1. Variation in influenza-like illness (ILI) and respiratory viruses over time, shown as a percent of monthly positives divided by positives for the year, March 2013–January 2015. A peak in virus activity was defined as monthly proportion of virus greater than 10%.[11] (**A**) Variation in ILI and influenza (types A and B). (**B**) Variation in the three other most commonly isolated respiratory viruses: human enterovirus/rhinovirus (HEV/HRV), respiratory syncytial virus (RSV), and human metapneumovirus (hMPV).

and were more likely to have an additional diagnostic test such as a complete blood count ordered, when compared with patients with other respiratory viruses detected (19.7% versus 11.4%, $P = 0.04$).

On adjusted analysis, patients with influenza were more likely to report a sick contact within the past month (OR = 1.84, $P = 0.01$), pain with breathing (OR = 3.04, $P = 0.03$), anorexia (OR = 2.20, $P = 0.002$), and arthralgias (OR = 1.82, $P = 0.02$) compared with patients with other respiratory viruses detected (Table 3). Patients < 5 years of age were less likely to have influenza detected versus another respiratory virus detected (OR = 0.33, $P = 0.001$).

Rapid influenza test performance characteristics. The sensitivity and specificity of the Veritor Flu A+B rapid influenza test were 88.2% and 95.1%, respectively, when compared with the Luminex PCR test (Table 5). The rapid test performed better at detecting influenza A than influenza B, with sensitivity of 89.7% versus 84.5% ($P = 0.34$) and specificity of 97.8% versus 98.4% ($P = 0.47$), respectively. The test was more sensitive at detecting influenza when patients were 5 years of age or older (88.8% versus 84.0%, respectively; $P = 0.51$) and when monthly influenza prevalence was greater than 20% (88.6% versus 80.0%, respectively; $P = 0.13$). Having a nasal versus nasopharyngeal

TABLE 2

Sociodemographic and clinical characteristics of outpatients with acute respiratory tract infections who had a respiratory virus detected, southern Sri Lanka, 2013–2015

Characteristic	Frequency (%) or median (IQR)		OR (95% CI)	*P* value
	Respiratory virus positive *N* = 363 (%)	Respiratory virus negative *N* = 208 (%)		
Child (< 5 years)	70 (19.3%)	31 (14.9%)	1.36 (0.84–2.24)	0.21
Male	209 (57.6)	94 (45.2)	1.65 (1.16–2.32)	0.005
Sick contact in past month	165 (46.2)	73 (35.1)	1.59 (1.12–2.26)	0.01
Prior medical visit for same illness	95 (26.3)	62 (30.7)	0.81 (0.55–1.18)	0.28
Travel in past 4 weeks	55 (15.2)	32 (15.4)	0.99 (0.61–1.58)	1.00
Smoking (passive or active)	84 (23.1)	37 (17.8)	1.39 (0.90–2.14)	0.14
Prior antibiotic for same illness	19 (5.2)	24 (11.5)	0.43 (0.23–0.81)	0.008
Days of fever	2 (1–3)	2 (2–4)		0.02
Days of cough	2 (2–3)	3 (2–4)		< 0.001
Ear ache	18 (5.0)	11 (5.3)	0.93 (0.43–2.02)	0.85
Rhinitis	276 (76)	149 (71.6)	1.26 (0.85–1.85)	0.27
Sore throat	175 (48.2)	93 (44.7)	1.15 (0.82–1.62)	0.43
Dyspnea	64 (17.6)	25 (12.0)	1.57 (0.95–2.57)	0.09
Pain with breathing	45 (12.4)	13 (6.3)	2.12 (1.12–4.04)	0.02
Anorexia	247 (68.0)	104 (50.0)	2.13 (1.50–3.02)	< 0.001
Vomiting	67 (18.5)	31 (14.9)	1.29 (0.81–2.06)	0.30
Abdominal pain	26 (7.2)	11 (5.3)	1.38 (0.67–2.86)	0.48
Headache	269 (74.1)	145 (69.7)	1.24 (0.85–1.81)	0.28
Fatigue/lethargy	266 (73.3)	115 (55.3)	2.22 (1.55–3.17)	< 0.001
Arthralgias	219 (60.3)	99 (47.6)	1.67 (1.18–2.36)	0.004
Myalgias	222 (61.2)	101 (48.6)	1.67 (1.18–2.35)	0.004
Temperature (°F)	101.0 (100.6–101.7)	100.9 (100.5–101.7)		0.02
Wheezing	48 (13.3)	23 (11.1)	0.81 (0.48–1.37)	0.51
Antibiotic prescribed	280 (77.1)	161 (77.4)	0.98 (0.66–1.48)	1.00
Diagnostic tests ordered	60 (16.5)	52 (25.0)	0.59 (0.39–0.90)	0.02

CI = confidence interval; IQR = interquartile range; OR = odds ratio. Bivariable analysis was performed using the Fisher's exact test for categorical variables and the Kruskall–Wallis test for continuous variables.

sample did not impact test sensitivity greatly (86.7% versus 88.4%, respectively).

DISCUSSION

There are few studies that examine the viral etiology of acute respiratory tract infections in tropical, low- or middle-income countries. In our study in southern Sri Lanka, over 60% of outpatient subjects presenting with ILI were found to have a viral pathogen; influenza was the most common etiology, but other viruses such as HEV/HRV and RSV also contributed to disease burden. Distinct seasonality in ILI activity was noted from March to June during each year of the study period, which also corresponded to the months with highest influenza activity. However, no patients reported a prior history of influenza vaccination. Clinical symptoms such as anorexia and arthralgia were most frequently described with influenza, but were also common in patients with other respiratory viruses or no respiratory viruses detected. The Veritor Flu A+B rapid influenza test performed well in this setting, with an overall sensitivity and specificity of 88.2% and 95.1%, respectively.

In this study in southern Sri Lanka, ILI and influenza both had a clear seasonal pattern, with peak activity occurring from March to June of each year. RSV and hMPV accounted for a lower though important burden of disease during peak ILI period, whereas HEV/HRV showed sporadic activity throughout the year. The seasonality of respiratory viruses in tropical regions is not well understood, unlike in higher-income countries in temperate climates, where peak activity typically coincides with the winter months.[9,19,20] In tropical regions, RSV has been found to have different peaks such as March–August (Singapore) and April–September (Hong Kong), and in some countries has been associated with the rainy season

TABLE 3

Multivariable analysis of sociodemographic and clinical features associated with respiratory virus positivity or influenza positivity, southern Sri Lanka, 2013–2015

Characteristic	Respiratory virus positive vs. negative		Influenza positive vs. other respiratory virus positive	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male sex	1.48 (1.02–2.17)	0.04	–	–
Child (< 5 years)	0.45 (0.26–0.78)	0.005	0.33 (0.17–0.62)	0.001
Sick contact	1.86 (1.27–2.73)	0.001	1.84 (1.14–2.97)	0.01
Number of days of cough	0.79 (0.70–0.90)	< 0.001	–	–
Pain with breathing	2.60 (1.39–4.89)	0.003	3.04 (1.12–8.24)	0.03
Anorexia	2.29 (1.50–3.50)	< 0.001	2.20 (1.32–3.66)	0.002
Fatigue	2.00 (1.28–3.13)	0.002	–	–
Arthralgias	–	–	1.82 (1.09–3.05)	0.02

CI = confidence interval; OR = odds ratio. In each model, age (categorical variable) and sociodemographic characteristics and clinical symptoms associated with the dependent variable at a $P < 0.05$ on bivariable analysis were included.

TABLE 4

Sociodemographic and clinical characteristics of outpatients with influenza-like illness who had influenza vs. another respiratory virus isolated, southern Sri Lanka, 2013–2015

Characteristic	Frequency (%) or median (IQR)		OR (95% CI)	*P* value
	Influenza positive *N* = 223	Other virus positive *N* = 140		
Child < 5 years	25 (11.2)	45 (32.1)	0.27 (0.15–0.48)	< 0.001
Male	128 (57.4)	81 (57.9)	0.98 (0.64–1.50)	1.00
Sick contact in past month	114 (51.8)	51 (37.2)	1.81 (1.17–2.79)	0.009
Prior medical visit for same illness	60 (26.9)	35 (25.4)	1.08 (0.67–1.74)	0.81
Travel in past 4 weeks	33 (14.9)	22 (15.7)	0.94 (0.53–1.65)	0.88
Smoking (passive or active)	48 (21.5)	36 (26.5)	0.79 (0.48–1.30)	0.37
Prior antibiotic for same illness	11 (4.9)	8 (5.7)	0.86 (0.34–2.13)	0.81
Days of fever/chills	2 (1–3)	2 (2–3)		0.54
Days of cough	2 (1–3)	2 (2–3)		0.11
Ear ache	12 (5.4)	6 (4.3)	1.27 (0.48–3.39)	0.81
Rhinitis	159 (71.3)	117 (83.6)	0.49 (0.29–0.82)	0.008
Sore throat	108 (48.4)	67 (47.9)	1.02 (0.67–1.56)	1.00
Dyspnea	46 (20.6)	18 (12.9)	1.76 (0.98–3.24)	0.07
Pain with breathing	40 (17.9)	5 (3.6)	5.9 (2.43–14.1)	< 0.001
Anorexia	169 (75.8)	78 (55.7)	2.49 (1.59–3.95)	< 0.001
Vomiting	47 (21.1)	20 (14.3)	1.6 (0.92–2.81)	0.13
Abdominal pain	16 (7.2)	10 (7.1)	1.0 (0.43–2.22)	1.00
Headache	183 (82.1)	86 (61.4)	2.87 (1.78–4.58)	< 0.001
Fatigue/lethargy	182 (81.6)	84 (60)	2.96 (1.85–4.84)	< 0.001
Athralgias	159 (71.3)	60 (42.9)	3.31 (2.11–5.17)	< 0.001
Myalgias	160 (71.7)	62 (44.3)	3.2 (2.03–4.98)	< 0.001
Temperature (°F)	101.2 (100.8–102.0)	100.9 (100.6–101.3)		< 0.001
Wheezing	24 (10.9)	24 (17.1)	0.59 (0.33–1.09)	0.11
Antibiotic prescribed	168 (75.3)	112 (80)	0.76 (0.46–1.26)	0.37
Diagnostic tests ordered	44 (19.7)	16 (11.4)	1.91 (1.01–3.54)	0.04

CI = confidence interval; IQR = interquartile range; OR = odds ratio. Bivariable analysis was performed using the Fisher's exact test for categorical variables and the Kruskall–Wallis test for continuous variables. Coinfections with influenza were excluded.

(Papua New Guinea, Colombia, Kenya, and Gambia).[9,19] Other viruses such as HEV/HRV and parainfluenza do not appear to have a clear seasonal association, and may be endemic throughout the year, sporadic, or associated with epidemics.[9,19] In Sri Lanka, to our knowledge, only one other study has described the epidemiology of respiratory viruses other than influenza. Among hospitalized children ≤ 5 years of age in two regions of Sri Lanka, RSV accounted for > 50% of disease, with peak activity during May–July in the dry zone and during December–January and in April in the wet zone.[21] Our study was conducted in a wet region in the country, but peak RSV activity was during May–July. The reason for variation in seasonality within the country is not clear, but underscores the need for further studies on respiratory virus epidemiology in tropical and subtropical settings.

Influenza accounted for the largest burden of disease in our study, with peak activity between March and June each year. As with other respiratory viruses, influenza seasonality in the tropics is not well defined. Variable seasonality as well as year-round circulation have been observed, although influenza activity is not believed to be random.[20,22] In one study examining several countries in tropical and subtropical areas of southern and south-eastern Asia, peak influenza activity occurred during June–July or October–November. Countries closest to the equator had year-round circulation.[23] In Sri Lanka, the seasonality of influenza is debated. Two analyses based on FluNet data from the WHO have proposed peak influenza activity in October–December or in December.[11,24] One study examined influenza A activity among hospitalized patients in the Western Province of Sri Lanka and found peak activity from May to July, with a minor peak from October to December.[25] The Sri Lanka Ministry of Health identifies two peaks in influenza activity, with the first occurring during May-July and the

TABLE 5

Performance characteristics of the Veritor Flu A+B rapid influenza kit (Becton Dickinson), when compared with the gold standard of polymerase chain reaction by the xTAG Respiratory Viral Panel (Luminex Corporation)

Pathogen	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Influenza A and B	88.2% (83.2–92.2)	95.1% (92.3–97.1)	92.0% (87.5–95.3)	92.7% (89.5–95.2)
Influenza A	89.6% (83.8–93.8)	97.8% (95.8–99.0)	94.2% (89.3–97.3)	95.9% (93.5–97.6)
Influenza B	84.5% (72.6–92.7)	98.4% (96.9–99.3)	86.0% (74.2–93.7)	98.2% (96.7–99.2)
Age < 5 years	84.0% (65.4–93.6)	97.4% (91.0–99.5)	91.3% (73.2–98.5)	94.9% (87.5–98.0)
Age ≥ 5 years	88.8% (83.6–92.5)	94.4% (91.0–96.6)	92.1% (87.3–95.1)	92.1% (88.3–94.7)
Prevalence ≤ 20%*	80.0% (49.0–96.5)	98.3% (93.9–99.7)	80.0% (49.0–96.4)	98.3% (93.9–99.7)
Prevalence > 20%†	88.6% (83.6–92.2)	93.5% (89.6–96.0)	92.6% (88.1–95.5)	90.0% (85.6–93.2)
Nasal sample	86.7% (62.1–97.6)	97.4% (86.8–99.9)	92.9% (68.5–99.6)	95.0% (83.5–99.1)
Nasopharyngeal sample	88.4% (83.3–93.0)	94.8% (91.7–96.8)	91.9% (87.3–95.0)	92.4% (88.9–94.8)

CI = confidence interval. Overall performance characteristics for influenza A and B, as well as for specific subsets, are listed in the table.

* All months during study in which influenza prevalence was ≤ 20%.

† All months during study in which influenza prevalence was > 20%.

second occurring during November–January.[26] The results from our study overlap with the first peak period defined by the Ministry of Health. The reasons for variation in influenza peak activity between studies is unclear, but may be related to the specific region in Sri Lanka that was studied.[27,28] The lack of clear correlation between influenza and weather parameters in our study suggests that influenza seasonality is complex and likely affected by multiple factors, and again highlights the need for local epidemiological data.

The WHO's recommendations regarding the timing and composition of influenza vaccination are based on a country's location in the Northern or Southern hemisphere. However, studies suggest that such recommendations may not be applicable for more than half of countries in the tropical belt, given variable influenza activity.[24] Our data from 2013 to 2015 suggest that in southern Sri Lanka, influenza vaccination may need to be targeted to January–February, preceding peak influenza activity in March–June. Although Sri Lanka does not currently have a national influenza vaccine policy and the coverage rate with influenza vaccine is < 1%, the high burden of influenza in our study suggests that vaccination may provide benefit in this region.[10] We did not assess cost effectiveness of vaccination in our study, but studies from other low- or middle-income countries indicate that influenza vaccine is cost effective in the elderly, infants, and children and adults with high-risk conditions.[29–31] Influenza and ILI in low- or middle-income countries have a larger impact on indirect costs and productivity when compared with higher-income countries.[32] Knowledge of local epidemiology is a key component in developing and implementing public health measures such as vaccination. In Sri Lanka, further country and region-specific surveillance for respiratory viruses is needed.[20,23,24,33]

We identified several features such as having a sick contact within the last month, pain with breathing, anorexia, and fatigue as being associated with having a respiratory virus detected. These features are not dissimilar to clinical characteristics identified in other studies.[34–38] We also found clinical symptoms such as anorexia and arthralgias to be more common in patients with influenza versus other respiratory viruses. However, many of the symptoms associated with influenza were also commonly found in patients with other respiratory viruses or with no respiratory viruses, which speaks to the difficulty of clinical diagnosis in identifying patients with influenza.[34,38] While symptomatic treatment and public health measures in most cases are similar regardless of the type of respiratory virus, the implementation of vaccination and antiviral treatment of influenza makes accurate diagnosis an important consideration in this setting with substantial influenza disease burden.

The Veritor Flu A+B rapid influenza test performed well as a rapid point-of-care test in our study environment. Studies from higher-income settings have reported similar results with the Veritor test and there are data to suggest that the Veritor test has the ability to detect influenza at lower limits of detection when compared with other rapid tests.[15,39,40] The use of a rapid test with good performance characteristics in settings with limited laboratory infrastructure has the potential to individualize patient treatment and to add to local data on influenza epidemiology, which could influence public health decisions such as vaccination policy.[41] While the cost of rapid influenza testing (approximately $10–30 per test) may still prove prohibitive for resource-limited settings, the targeting of testing to patients with certain clinical characteristics such as anorexia and arthralgias, as found in our study, may prove to be more cost efficient.[42] In addition, over 70% of participants with ILI received an antibiotic prescription in our study. The use of rapid viral testing such as with the Veritor Flu A+B test may help reduce unnecessary antibiotic use in this setting.[13]

Some limitations to this study must be noted. ILI surveillance for the months of February and December was only performed during 1 year. However, the monthly proportion for ILI and the examined respiratory viruses was < 10% for each of these months, with the exception of HEV/HRV (> 10% in February 2014). By using a previously published definition by PATH and examining ILI epidemiology over a 2-year period, we attempted to define respiratory virus seasonality in a rigorous fashion. Our surveillance was only performed at one hospital in the Southern Province. However, this hospital serves as a tertiary care and referral center for the region, and our findings likely reflect broader disease patterns within the region. Finally, our surveillance activities were conducted over the period of two calendar years, and may not reflect seasonal patterns in other years. Further longitudinal studies on respiratory viral epidemiology are needed in this region.

To our knowledge, this is the first published description of respiratory virus epidemiology in southern Sri Lanka or among Sri Lankan outpatients. Influenza was the largest contributor to respiratory infections, with peak activity during March–June, although other viruses such as HEV/HRV and RSV also contributed to disease burden. The Veritor rapid influenza test performed well in our study population and may be a useful tool for describing local influenza epidemiology in resource-limited settings. Our study based on 2 years of surveillance data suggests that in southern Sri Lanka, targeting infection control and influenza vaccination efforts in January–February may have a large public health impact.

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