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Seasonal trends of viral respiratory tract infections in the tropics

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SUMMARY

To evaluate the seasonal trends of viral respiratory tract infections in a tropical environment, a retrospective survey of laboratory virus isolation, serology and immunofluorescence microscopy in two large general hospitals in Singapore between September 1990 and September 1994 was carried out. Respiratory tract viral outbreaks, particularly among infants who required hospitalization, were found to be associated mainly with respiratory syncytial (RSV) infections (72%), influenza (11%) and parainfluenza viruses (11%). Consistent seasonal variations in viral infections were observed only with RSV (March–August) and influenza A virus (peaks in June, December–January). The RSV trends were associated with higher environmental temperature, lower relative humidity and higher maximal day-to-day temperature variation. Although the influenza A outbreaks were not associated with meteorological factors, influenza B isolates were positively associated with rainfall. These data support the existence of seasonal trends of viral respiratory tract infections in the tropics.

INTRODUCTION

Upper respiratory tract infections and other respiratory diseases, such as asthma and bronchitis, are leading disease conditions seen at primary healthcare clinics in Singapore [1]. They make up more than 30% of the total 12–15 million outpatient cases seen annually and more than 50% of the 3–4 million childhood cases per annum. Additionally, these respiratory conditions account for approximately 15% of the total number of bed-days and discharges from hospitals among children in Singapore. The leading pathogens or triggers of these diseases are said to be viruses [2–4]. It is well known that seasonal outbreaks of respiratory viral infections, in particular, respiratory syncytial and influenza viruses, occur in the winter season in temperate regions [4–8]. These community outbreaks are associated with an increased risk of nosocomial transmission, thus putting at risk immunocompromised patients and children with cardiac and pulmonary disease, who are susceptible to severe complications. A knowledge of the trends and seasonality of respiratory viral infections in the community could provide the information necessary to alert health care providers on such viral outbreaks, facilitate the implementation of strategies to prevent and minimize transmission [9, 10], and introduce early therapeutic options such as ribavarin therapy in the high risk patient [11]. We studied the trends and seasonality of viral respiratory tract infections in a tropical environment and the association of these trends with meterological factors.

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MATERIAL AND METHODS

Positive results by viral isolation, serology and immunofluorescence microscopy for respiratory tract pathogens obtained from laboratory data of two large general hospitals in Singapore, the Singapore General and National University hospitals, between September 1990 and September 1994, were analysed retrospectively. These results were obtained mainly from specimens of inpatients (71%) and a smaller proportion of outpatient clinic cases (29%). In total, there were 12354 specimens analysed with an overall positivity (isolation, antigen detection or positive serology) of approximately 29%.

The collection, transportation, culture and identification of the viral specimens were carried out as previously described [12]. Viral isolation was performed for adenovirus, influenza viruses, parainfluenza viruses, respiratory syncytial virus and rhinovirus. Additionally, direct antigen detection via immunofluorescent techniques and serological methods (complement fixation tests) were also used for adenovirus, influenza and parainfluenza viruses, and respiratory syncytial virus.

The monthly percentages of positive samples were analysed. The time trends were estimated using a centred 12-month moving average. Each monthly positive rates was then divided by their corresponding trend values. The resulting values were averaged according to their respective months and expressed as percentage variation about the trend. Seasonality was evaluated by fitting the data to a series of Box–Jenkins regression-ARIMA (autoregressive integrated moving average) models [13]. These models are stochastic models which describe a univariate time-series as a function of its past values. The appropriate models were then selected based on a test statistic under the null hypothesis that the series was a sequence of random variables. To choose between equally fitted models and select the appropriate data transformation, the Akaike's information criterion was employed [14]. To test the null hypothesis that no seasonality was present, the likelihood ratio statistic was used. The likelihood ratio statistic is given as $n*\log(S_1/S_2)$, where S_1 and S_2 are the modified sum of squares for the regression-ARIMA model and the ARIMA model (with seasonal coefficients set to zero), respectively.

Data on daily meterological factors were obtained from the Meteorological Services of Singapore over the same period and correlated with the trends in viral respiratory tract infections. Initial bivariate associations were analysed via the Spearman's rank correlation test. Significant parameters were then analysed by time series methods using the PROC AUTOREG procedure of the SAS/ETS statistical program [15]. The AUTOREG procedure calculates the equivalent of the least square parameter estimates of a regression model when the data are time series and the error term is an autoregressive process. This was done as when time series data are used in a normal linear regression analysis, the error term is often not independent through time. The AUTOREG procedure overcomes this by using the two-step full transform estimation method [16] that produces better estimates. Nevertheless, separate models were used for the different meteorological factors and virus types to avoid problems with colinearity.

RESULTS

During the period of study, there were 3904 positive viral reports, giving an overall detection rate of approximately 29%. The profile of the viral pathogens detected, age and sex distribution, and diagnoses of the patients from whom the positive specimens were obtained are summarised in Table 1. RSV constituted the largest proportion of the viral pathogens detected (72% of total) chiefly by immunofluorescence on nasopharyngeal aspirates obtained mainly from infants and young children (median age 6 months) with diagnosis of lower respiratory tract infections. In contrast, influenza viruses (11% of total), which were detected by virus isolation and/or immunofluorescence microscopy, were well distributed among the different age groups. Parainfluenza viruses (11% of total) were detected mainly in young children below 10 years of age with bronchiolitis or laryngitis. Parainfluenza 3 virus caused more infections in infants under 6 months with bronchiolitis than parainfluenza 1 or 2. Adeno-, and rhinoviruses were detected sporadically, in small numbers and over a wide age range.

Figure 1 shows the pattern of viral isolations of the more commonly detected ones over the period of study. In terms of cyclical periodicity, there appeared to be annually recurring peaks for influenza A, parainfluenza type 3 and respiratory syncytial virus. In contrast, parainfluenza type 1 and 2 viruses (although number of cases were small), and to a certain extent influenza B, appeared to have a biennial pattern.

In terms of annual seasonality, influenza A viruses

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Table 1. *Age, male:female sex ratio and principal clinical diagnoses of patients compared with virus detected,* n (%)†

Virus*	Influ. A	Influ. B	Para. 1	Para. 2	Para. 3	RSV	Adeno.	Entero.	Rhino.	Total
n positive (%):	334 (8·6)	92 (2·4)	128 (3·3)	29 (0·7)	265 (6·8)	2818 (72·2)	201 (5·1)	25 (0·6)	12 (0·3)	3904 (100)
Age										
0–< 1 month	6 (1·9)	1 (1·2)	2 (1·7)	0 (0·0)	6 (2·4)	104 (4·0)	0 (0·0)	4 (23·5)	3 (27·3)	125 (3·5)
1–5 months	44 (14·1)	7 (8·1)	23 (19·2)	4 (14·3)	73 (28·5)	1153 (44·7)	17 (9·2)	5 (29·4)	3 (27·3)	1327 (37·0)
6–11 months	59 (18·8)	10 (11·7)	40 (33·3)	9 (32·2)	90 (35·2)	741 (28·8)	54 (29·1)	0 (0·0)	1 (9·1)	1003 (27·9)
1–< 2 years	56 (17·9)	13 (15·1)	39 (32·4)	8 (28·6)	68 (26·6)	423 (16·4)	49 (26·4)	0 (0·0)	0 (0·0)	656 (18·3)
2–< 5 years	36 (11·6)	8 (9·3)	14 (11·6)	5 (17·8)	18 (7·0)	144 (5·6)	28 (15·0)	1 (5·9)	1 (9·1)	258 (7·2)
5–< 10 years	16 (5·1)	9 (10·5)	2 (1·7)	2 (7·1)	1 (0·4)	6 (0·2)	15 (8·1)	2 (11·8)	0 (0·0)	55 (1·5)
10–< 20 years	14 (4·5)	7 (8·1)	0 (0·0)	0 (0·0)	0 (0·0)	3 (0·1)	12 (6·5)	1 (5·9)	0 (0·0)	35 (1·0)
⩾ 20 years	81 (26·0)	31 (36·1)	0 (0·0)	0 (0·0)	0 (0·0)	3 (0·1)	11 (5·9)	4 (23·5)	3 (27·3)	133 (3·7)
Not stated	22	6	8	1	9	242	15	8	1	312
Sex										
Male:female ratio	1·01	1·18	0·81	0·88	0·93	0·98	1·38	3·50	1·00	1·00
Principal clinical diagnosis‡										
Bronchitis	10 (3·6)	2 (2·5)	7 (6·2)	1 (3·9)	10 (4·4)	135 (5·5)	2 (1·2)	0 (0·0)	0 (0·0)	168 (5·0)
Bronchiolitis	26 (9·4)	9 (11·3)	22 (19·8)	3 (12·1)	65 (28·4)	1071 (43·9)	27 (15·5)	0 (0·0)	1 (12·5)	1226 (36·3)
Pneumonia	16 (5·8)	2 (2·5)	4 (3·6)	1 (3·9)	17 (7·4)	127 (5·2)	18 (10·4)	0 (0·0)	0 (0·0)	183 (5·4)
Laryngitis/LTB	13 (4·7)	3 (3·8)	38 (34·2)	11 (44·1)	29 (12·6)	31 (1·3)	2 (1·2)	0 (0·0)	0 (0·0)	129 (3·8)
URT/Flu	122 (43.9)	36 (45·0)	6 (5·4)	3 (12·1)	11 (5·0)	147 (6·0)	11 (6·4)	2 (11·8)	0 (0·0)	336 (10·0)
Asthma	5 (1·8)	3 (3·8)	6 (5·4)	1 (3·9)	20 (8·7)	113 (4·6)	3 (1·7)	0 (0·0)	0 (0·0)	152 (4·5)
Chest infection	49 (17·8)	16 (19·19)	16 (14·4)	4 (16·0)	42 (18·3)	620 (25·4)	39 (22·4)	0 (0·0)	0 (0·0)	785 (23·3)
Others	54 (19·5)	9 (11·3)	12 (10·8)	1 (3·9)	35 (15·3)	194 (8·0)	72 (41·4)	15 (88·2)	7 (87·5)	398 (11·8)
No diagnosis	56	12	17	4	36	380	27	8	4	531

* Virus: Influ, influenza; Para, parainfluenza; RSV, respiratory syncytial virus; Adeno, adenovirus; Entero, enterovirus; Rhino, rhinovirus.

† Percentage not including those with age 'not stated' and not including those with 'no diagnosis'.

‡ Principal clinical diagnosis: Bronchitis, bronchitis with or without wheezing; Bronchiolitis, bronchiolitis and asthmatic bronchitis; Pneumonia, bronchopneumonia and pneumonia; Laryngitis/LTB, laryngitis or laryngo-tracheo-bronchitis; URT1/flu; upper respiratory tract infection or flu; Others, mainly unspecified respiratory tract infection, but also include non-respiratory diagnoses.

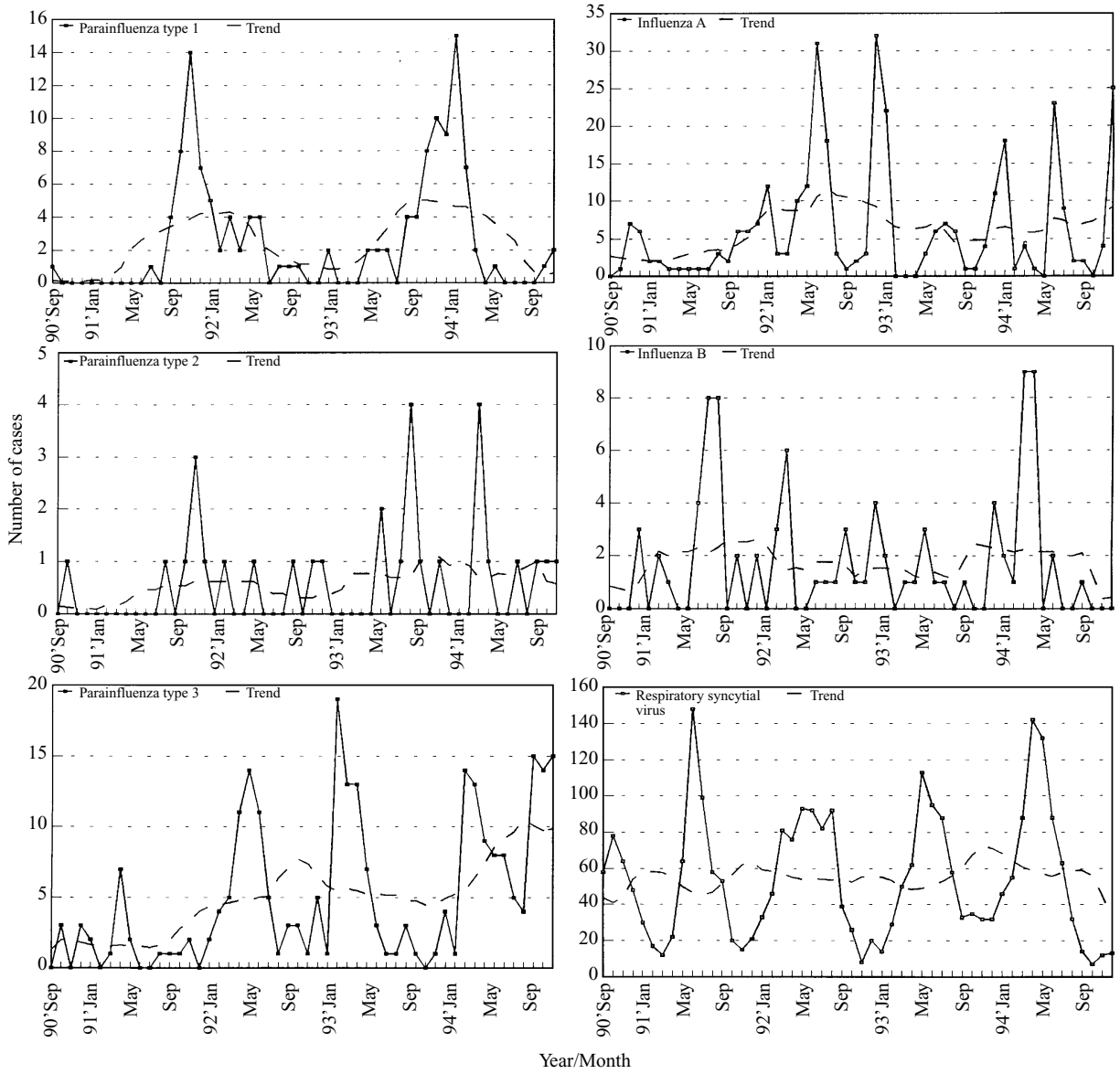

Fig. 1. Pattern of viral respiratory tract infections in Singapore: monthly distribution and time trends.

predominated between November–January and June–July over the period of analysis, while influenza B viruses appeared more between March–April, July and December. The test for seasonality was found to be significant for influenza A ($\chi^2 = 27{\cdot}42$, 11 D.F., $P < 0{\cdot}005$) but not significant for influenza B ($\chi^2 = 18{\cdot}85$, 11 D.F., $0{\cdot}05 < P < 0{\cdot}1$). The majority of influenza A virus isolated over the study period were of the H3N2 subtype with periodic appearance of the H1N1 subtype (April–September 1992). Additionally, over the period of analysis, the circulating H3 strains were heterogenous, being related to A/England/427/88, A/Beijing/353/89, A/Shanghai/6/90, A/England/261/91, A/Beijing/32/92, A/Shandong/9/93 and A/Guandong/25/93.

Parainfluenza virus trends did not show significant annual seasonality. Nevertheless, parainfluenza types 1 and 2 predominated mainly in the last quarter of the year while parainfluenza type 3 usually between February and May. RSV showed significant annual seasonal trends with increase in cases between the months of March and August with a peak in May–June ($\chi^2 = 31{\cdot}60$, 11 D.F., $P < 0{\cdot}0001$). In 1990, the season lasted longer, until November, and in 1992, it started earlier in February. The test for seasonality was not carried out for the other viruses due to low detection rates and sporadic isolations. It was however noted that a large outbreak of adenovirus type 7 infections occurred between May and September 1994.

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Table 2. Bivariate association between the daily viral detection rates and corresponding meterological parameters

Environmental parameters†: virus	Rainfall	Max. temp.	Max–min temp.	Avg. temp.‡	TWS	TSR	RH_{0900}‡	RH_{1500}
	Spearman's rank correlation coefficient§							
Meteorological data of the SAME day								
Influenza A								
Influenza B	0·08*			−0·08*				
Parainfluenza								
Type 1				−0·08*	0·08*		0·11**	
Type 2								
Type 3								
Respiratory Syncytial Virus		0·17***	0·27***	0·24***	−0·15***		−0·17***	−0·08*
Adenovirus	−0·08*		0·08*	0·07*			−0·10**	
Enterovirus								
Rhinovirus								
Total		0·13***	0·22***	0·18***	−0·09**		−0·16**	−0·06*
Meterological data LAGGED 1-day								
Influenza A								
Influenza B	0·06*							
Parainfluenza								
Type 1				−0·10**	0·09**		0·11**	
Type 2								
Type 3								
Respiratory Syncytial Virus		0·20***	0·29***	0·24***	−0·17***		−0·14***	−0·12***
Adenovirus			0·09**	0·09**			−0·06*	
Enterovirus								
Rhinovirus								
Total		0·16***	0·24***	0·19***	−0·10**		−0·13***	−0·12***
Meterological data LAGGED 2-days								
Influenza A								
Influenza B	0·07*							
Parainfluenza								
Type 1				−0·09**	0·13***		0·06*	
Type 2								
Type 3								
Respiratory Syncytial Virus		0·19***	0·27***	0·22***	−0·18***		−0·14***	−0·12***
Adenovirus		0·06*	0·09**	0·09**			−0·08*	−0·06*
Enterovirus								
Rhinovirus								
Total		0·17***	0·24***	0·19***	−0·11**		−0·14***	−0·13***

† Environmental parameters: Max. temp, maximum temperature; Max–min temp, daily maximal temperature variation (maximum–minimum temperature over a 24 h period); Avg. temp, average temperature; TWS, total wind speed; TSR, total solar radiation, RH_{0900}, relative humidity at 0900 h; RH_{1500}, relative humidity at 1500 h.

‡ During the period of analysis, the average daily temperature ranged between 25·2 and 30·9 °C and relative humidity at 0900 h ranged between 68 and 99%.

§ Spearman's rank correlation coefficients: not significant (blank column), * $P < 0{\cdot}05$, ** $P < 0{\cdot}01$, *** $P < 0{\cdot}001$.

Table 2 and Figure 2 show the association between the daily viral detection rates and meteorological factors. Influenza B virus trends were found to be positively associated with daily rainfall, whilst parainfluenza type 1 viruses were found to be more predominant during days with relatively low temperature and high relative humidity. The positive association with wind speed is likely related to its relationship with temperature and relative humidity (autocorrelated). RSV and adenovirus trends were found to be positively associated with daily temperature and negatively associated with relative humidity. Stronger positive associations were however observed between RSV trends and daily maximal

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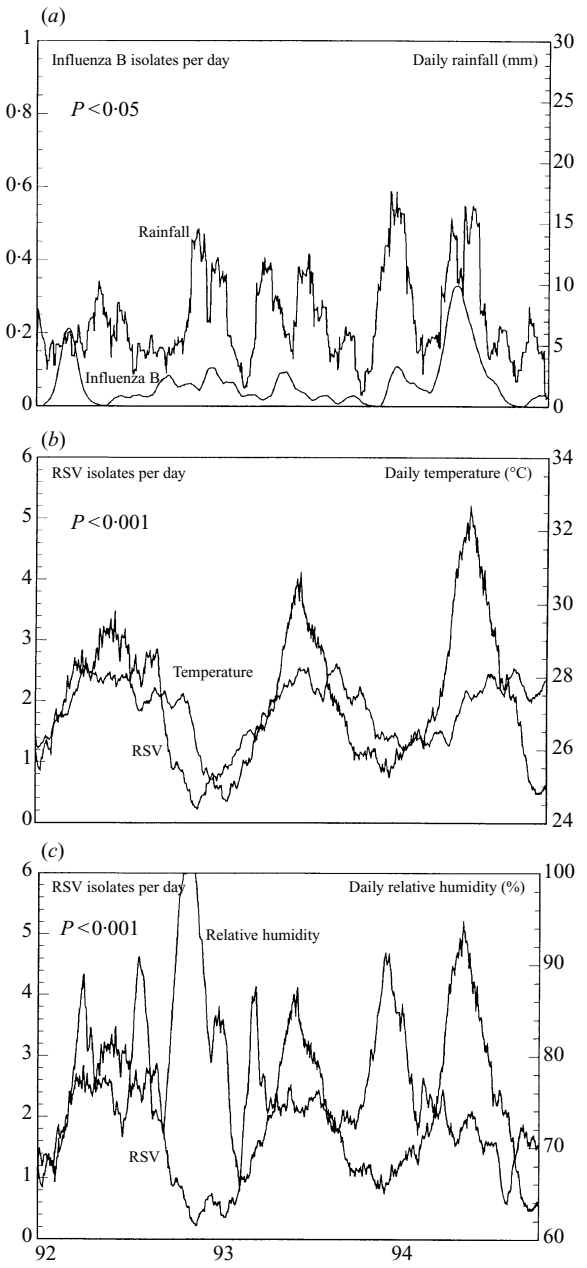

Fig. 2. Comparison between trends in viral respiratory tract infections and meteorological factors. (*a*) Trends in influenza B viral infections compared with average daily rainfall, (*b*) RSV compared with average daily temperature and (*c*) RSV compared with relative humidity in Singapore. The viral trends shown are daily 21-day moving averages.

temperature difference (maximum minus minimum temperature for the 24-h day) ($P < 0{\cdot}001$).

The positive association between RSV and daily temperature remained statistically significant ($P < 0{\cdot}01$) when analysed using time series models which controls for autocorrelation. In a different time series model, the association between RSV and daily maximal temperature difference was also significant ($P < 0{\cdot}01$). Similarly, the association between the trends for influenza B and rainfall also remained significant ($P < 0{\cdot}05$) via time series analysis. The other associations were not significant when analysed by time series models.

DISCUSSION

As with most parts of the world, viral respiratory tract infections form the most common cause of morbidity in Singapore. Approximately 3–5 million consultations with a general practitioner a year are for upper respiratory tract infections and other respiratory diseases [1], with children under the age of 14 years old making up more than half this number. Additionally, these respiratory conditions account for the utilization of more than 9000 discharges and approximately 35000 bed-days among children in Singapore (unpublished). Our data also showed that one of the main precipitating factors for acute asthma exacerbation requiring hospitalization among children in Singapore is viral respiratory infection [17].

The age distribution and clinical picture of viral infections associated with these respiratory viruses were similar to those previously described in Singapore [12] and elsewhere [4, 18–20]. The majority of the positive samples were obtained from children under the age of 2 years, in particular, with RSV and parainfluenza virus infections, while influenza viruses caused infection in all age groups. The age distribution for positive samples is likely a reflection of the greater likelihood of investigating young children and infants with more serious illness compared to adults in this study.

The distribution of viral respiratory agents seen in Singapore seemed to be similar to those in developing countries and other tropical regions, with RSV the predominant pathogen of respiratory tract infections in children [19–23]. It should be noted, however, that RSV is more easily detected in the laboratory, and that elsewhere, particularly in the temperate regions, rhinovirus, influenza and parainfluenza viruses were found more commonly than in this study [4, 24–26]. In our study, there were low rates of rhinovirus isolation. Although, the data in this study were based mainly on hospitalized patients and therefore may not pick up the milder cases of rhinovirus and parainfluenza infections, comparison of the types of viruses detected from both the out- and in-patients was similar (data not shown). Nevertheless, with more sensitive methods of RNA analysis and detection of

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rhinovirus [27], the profile of viral pathogens may change. Studies elsewhere have shown this virus may have an important role in infantile wheezing [28].

As in the temperate regions, this study clearly demonstrated periodicity, and in some cases, annual seasonality, of respiratory viral infections in the tropics. These observations contradict the reported trends in other tropical communities, such as Papua New Guinea [6] and Hawaii [29]. In these studies, RSV was found to occur year round with small peaks during the rainy season. In temperate communities, RSV peaks during the winter months, whether in the southern or northern hemisphere [5–7]. These winter outbreaks have been attributed to greater infectivity in the enclosed indoor environment of the winter season [7]. In stark contrast, our data indicate that the outbreaks of RSV were associated with high temperature and low humidity. The daily maximal variations or fluctuations in temperature appeared to be the most significant meteorological factor associated with the RSV trends. Similar association between the incidence of flu and daily maximal fluctuations in temperature was reported previously [30]. The reasons for this are not clear but it could be possible that greater fluctuations in temperature may act on the respiratory epithelium which then lead to changes in permeability and increase the susceptibility to infections [31]. Low relative humidity has also been shown to favour the survival of certain viruses while others have been shown to lose their infectivity after drying [32].

The observed association between influenza B virus and rainfall in this study was also reported in northeast Brazil [24]. But unlike the Brazilian study, we did not find a significant association between parainfluenza type 2 trends and rainfall. This was likely due to the low numbers of isolation in our study, as the pattern of parainfluenza type 2 isolation seem to resemble that of influenza B virus.

Although, this study analysed data over a relatively short period of 4 years, there was discernible cyclical periodicity in the more commonly detected viruses. We observed annual periodicity for RSV, influenza A and parainfluenza type 3, but a biennial periodicity for influenza B, parainfluenza type 1 and to some extent, type 2 (not very prominent because of small numbers). This cyclical periodicity mirrors those seen in UK (18) although the actual seasonal pattern differed slightly. This study has thus demonstrated the presence of seasonal variation in the occurrence of viral respiratory tract in a tropical environment.

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