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Climatic, temporal, and geographic characteristics of respiratory syncytial virus disease in a tropical island population

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SUMMARY

Respiratory syncytial virus (RSV) is an important cause of morbidity in children worldwide, although data from equatorial regions are limited. We analysed climatic, spatial, and temporal data for children presenting to hospitals in Lombok island, Indonesia with clinical pneumonia. During the study period, 2878 children presented and 741 RSV cases were identified. In multivariate analysis with an 8-day lag, occurrence of rain was associated with 64% higher incidence of RSV disease [incidence rate ratio (IRR) 1·64, 95% confidence interval (CI) 1·13–2·38]. A 1% rise in mean relative humidity and 1 °C increase in mean air temperature was associated with a 6% (IRR 1·06, 95% CI 1·03–1·10) and 44% (IRR 1·44, 95% CI 1·24–1·66) increase in RSV cases, respectively. Four statistically significant local clusters of RSV pneumonia were identified within the annual island-wide epidemics. This study demonstrates statistical association of monsoon-associated weather in equatorial Indonesia with RSV. Moreover, within the island-wide epidemics, localized RSV outbreaks suggest local factors influence RSV disease.

INTRODUCTION

Respiratory syncytial virus (RSV) is known to be an important cause of morbidity in infants and children in developed countries [1, 2]. Every year 91 000 infants are hospitalized with RSV infections in the United States [3]. Data from developing countries also point to a significant burden of lower respiratory illness associated with RSV [4–6] despite a larger contribution of bacterial pathogens in causing acute lower respiratory infection (ALRI) in several developing countries [7]. Moreover, disease caused by RSV in developing countries has fatality rates comparable to rates in high-risk children in developed countries [8–10].

The development of RSV vaccines makes it important to understand the epidemiology of RSV lower respiratory illness in order to develop a comprehensive disease control strategy. Seasonal, climatic, and spatial factors appear to influence the epidemiology of RSV infection [7, 8, 10, 11]. However, these factors have not been studied in detail, particularly in equatorial regions.

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RSV infection exhibits a clear seasonal pattern in most countries, with substantial variation from region to region. In temperate countries, both in northern and southern hemispheres, RSV outbreaks in children occur primarily during cold months [12–14]. For example, the RSV season in North America starts from the southern coastal areas in early autimn and moves northwards [10]. Between 1990 and 2000, the median onset for the United States was in week 51 (late December) with a median duration of 15 weeks [15]. During this period, the RSV season consistently started earlier and lasted longer in the South compared to the rest of the country [15]. Similarly, in subtropical countries RSV epidemics occur in winter [16, 17]. In the tropical belt, the epidemic cycle is often associated with rainfall, not temperature [18–21]. In equatorial countries with rainfall throughout the year, the association of outbreaks with precipitation has been less clear despite discernible seasonal variation of RSV transmission [7].

Associations of annual RSV epidemics with weather variables and description of spatial spread of RSV in populations are not available in many regions, and only limited data are available on these patterns from Indonesia. Data from Bandung in Java, Indonesia (elevation 750 m) suggest that a majority of cases occur in the rainy season – February to May [22]. Moreover, there is limited information available on RSV in island populations which may have unique disease dynamics, compared to non-island populations [23]. We utilized a disease surveillance dataset to describe the temporal and spatial aspects of childhood RSV disease and the association with climatic variables in a defined island population, at sea level in the tropical equatorial region.

MATERIALS AND METHODS

Study population

Lombok is part of the Indonesian archipelago in the province of Nusa Tenggara Barat and lies between 116° and 117° longitude and −8° and −9° latitude [24]. It has a total population of over 2 million in an area of about 4725 km² (1825 sq. miles) [25]. The study population is in an approximately 35 km × 64 km band south of Gunung Rinjani, Indonesia's highest volcano [4, 26]. The main roads of the island traverse this band.

Lombok has a typical tropical monsoon climate, with a dry and wet season, and short transitional periods. The dry season lasts from May to October and the wet season lasts from November to April [4, 26]. Official data from a single weather station for the years 1961–1990 show the average monthly rainfall in Lombok was estimated to range from 19 mm in August to 280 mm in January, with mean annual rainfall of 1514 mm and a mean total of 140 days of rain each year [27]. Temperatures ranged between 21 °C and 33 °C with little seasonal variability.

Basic curative care is delivered at village (*pustu*) level sub-health centres, staffed by a nurse and usually by a village midwife. Lombok is divided into four administrative regions; namely, Mataram, West, Central and East. Tertiary care is delivered at hospitals located in Mataram (which covers Mataram and the West regions), the Central region, the East region, and two smaller private hospitals. Most patients initially seek care at the sub-health centre because of the expense of using private providers [4].

The Lombok *Haemophilus influenzae* type b (Hib) project, described in detail elsewhere [4], collected data on respiratory and CNS illness patterns in hospitalized children aged <2 years from 1998 to 2003 in a defined island study population of 744 000 [4, 28] with about 15 000 infants enrolled each year [4]. The project was a randomized and blinded vaccine probe study with children receiving either routine immunization alone or with the addition of Hib conjugate vaccine. All study subjects received free hospital care for respiratory or CNS illness. The children were randomized by 818 hamlets, within 83 villages in 31 subdistricts in the four regions of the island. This study is based on the analysis of study hospitalization data for three calendar years from 1 January 2000 to 31 December 2002.

Study variables and data management

Selected data on the variables of pneumonia (RSV positive or negative) cases, date of admission, and village (*pustu*) of residence were obtained from the existing Hib study database. We used the daily number of RSV cases as the outcome variable. We obtained meteorological data including minimum, maximum, and mean temperature; minimum, maximum, and mean relative humidity; occurrence of rain on a particular day; and daily rain (in millimetres) from the Indonesian meteorological agency, Badan Metereologi dan Geofisika. The weather data were collected in Mataram at the western end of the island.

Using a hand-held GPS device, we collected geographical coordinates (single reading; degrees, minutes, and seconds converted to decimal degrees) for each *pustu*, and digitized and georeferenced a high-resolution map of Lombok. We used Microsoft Access 2000 for data management and preparation. Spatial and statistical analyses were performed using ArcView 8.1 (ESRI, Redlands, CA, USA) and Stata 8 (Stata Corporation, College Station, TX, USA) respectively.

Laboratory determination of RSV

Clinical nasopharyngeal specimens were collected from each hospital on five specified pick-up days (Monday, Tuesday, Wednesday, Thursday, Saturday). Samples from patients admitted on other days and on holidays were collected on the next routine pick-up morning. However, children admitted and discharged during non-pick-up days and children with severe illness and moribund condition were not sampled. All samples were transported to the laboratory at the main referral hospital in Lombok. A rapid test (RSV Testpak®, Abbott Laboratories, Abbott Park, IL, USA), with reported sensitivity and specificity of 92% and 93% respectively [29] was used for detection of RSV antigen.

Analytical methods

The case data were over-dispersed (mean > variance). We used negative binomial regression (which assumes Poisson variability on a given day, with daily rates following a gamma distribution) to regress the daily number of RSV cases on the daily meteorological variables. Separate unadjusted and combined multivariate models were run for occurrence of rain, amount of rain, mean relative humidity, and mean temperature. An incubation period of 5 days has been reported for RSV in the literature [30]. We did not have any data on the delay in seeking care after onset of symptoms. Therefore, we evaluated multivariate regression models with a lag of 5–9 days (i.e. 5 days incubation + 0–4 days delay in seeking care) for the weather variables. The lag period from the model with the highest value of pseudo-R^2 was chosen for the primary analysis. We evaluated interaction between variables that were statistically significant in the multivariate analysis.

We performed secondary analysis on association of climatic parameters with daily counts of RSV-negative ALRI, RSV cases in children aged <6 months, RSV cases with oxygen saturation <90%, and chest radiology-positive RSV cases. Radiologically confirmed pneumonia was defined as substantial alveolar consolidation or pleural effusion as agreed by a paediatric radiologist and a paediatrician during independent, masked readings of chest radiographs [28, 31].

Since the weather data were collected at the western end of the island, we performed analysis on data from sub-health centres at least 15 km from the data collection point to evaluate the robustness of associations.

We used Kulldorff's scan statistics to identify space–time clusters of RSV-positive cases [32]. Kulldorff's search protocol allows for the area of the moving scanning window to be variable. Monte Carlo methods are used to test the null hypothesis of no event clustering by comparing the event dataset to simulated random datasets [32]. We used retrospective space–time analysis to scan for clusters with high RSV rates using the space–time permutation model. Statistical significance of differences in proportions was assessed by exact test. All associations and candidate clusters were considered statistically significant at $\alpha < 0{\cdot}05$.

Ethical considerations

The Lombok Hib study was approved by Johns Hopkins Bloomberg School of Public Health Committee on Human Research and the Indonesia National Institute of Health Research and Development Ethical Commission, as well as by the local government.

RESULTS

Between 1 January 2000 and 31 December 2002; 2878 children presented with 5187 episodes of lower respiratory illness: 1653, 2126, and 1408 episodes in 2000, 2001, and 2002, respectively. For 3688 (71·1%) of these episodes, children were tested for RSV (72·0% in 2000, 70·7% in 2001, and 70·6% in 2002) and 741 (20·1%) were determined to be positive, including 246 (20·7%), 381 (25·3%) and 114 (11·5%), in 2000, 2001, and 2002, respectively ($P > 0{\cdot}05$). There were a total of 13 (1·8%) deaths among RSV-positive cases during hospitalization. However, 497 children died before a sample could be obtained indicating that the case-fatality ratio is probably underestimated.

Table 1. *Association of number of cases per day with occurrence of rain, amount of rainfall, mean relative humidity, and mean air temperature 8 days earlier*

	Bivariate (unadjusted) models		Multivariate models	
Meteorological parameter*	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
Occurrence of rain (yes)	2·07 (1·52–2·81)	<0·001	1·64 (1·13–2·38)	0·009
Amount of rain (mm)	1·01 (0·99–1·03)	0·22	0·99 (0·97–1·00)	0·16
Mean relative humidity (%)	1·06 (1·03–1·09)	<0·001	1·06 (1·03–1·10)	<0·001
Mean air temperature (°C)	1·39 (1·22–1·50)	<0·001	1·44 (1·24–1·66)	<0·001

IRR, Incidence rate ratio; CI, confidence interval.

* Measured over a 24-h period 8 days prior to the date for which the RSVcase counts were measured.

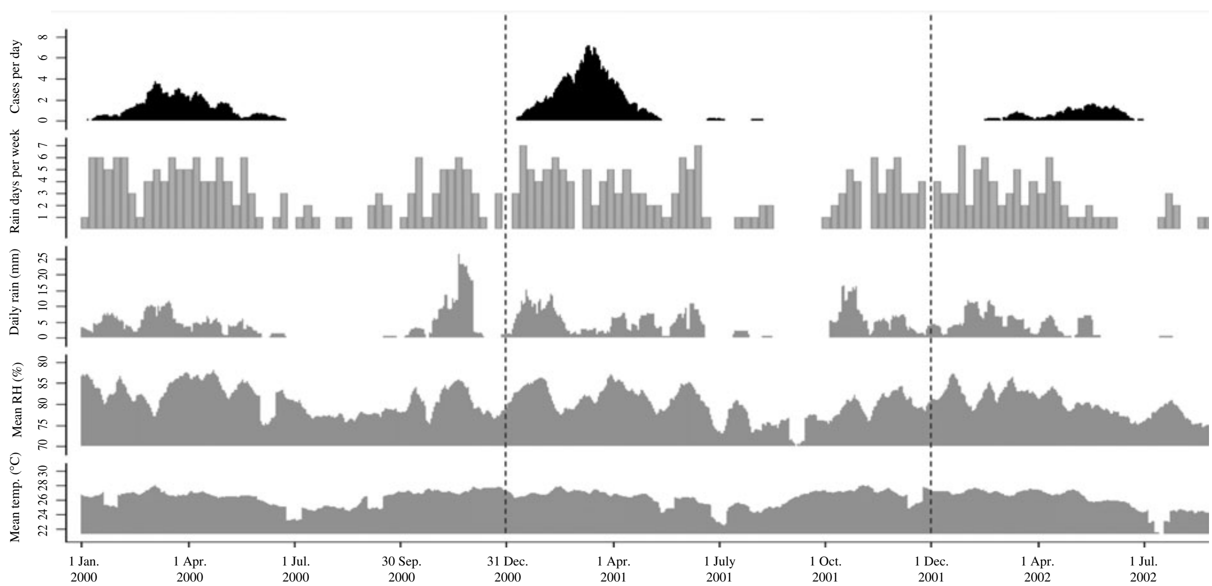

Fig. 1. Number of respiratory syncytial virus (RSV) cases per day, rain days in the corresponding week, daily amount of rain (mm), mean daily relative humidity (RH) (%), and mean daily air temperature (°C). Smoothing for RSV cases, daily amount of rain, mean daily RH, and mean daily air temperature performed by computing a moving average including 6 days before and 6 days after each day in the time series.

The rain data were missing at random for 112 (10·2%) days during the study period. Humidity and air temperature data were missing for all 30 (2·7%) days of September 2002. RSV count data were available throughout the study period.

Seasonality of RSV disease was evident from the distribution of RSV cases over time (Fig. 1). Although cases were reported in all months of the year, 656 cases (85%) in the 3-year study period were reported in just four calendar months: February–May (Fig. 1) which are usually the end of the rainy season. A total of 116, 102, and 104 days of rain and 1209, 1257, and 1453 mm of rain were documented in 2000, 2001, and 2002, respectively.

The model with a lag of 8 days had a pseudo-R^2 of 0·03 and was identified as the one predicting the highest amount of variability in the RSV count data. A pseudo-R^2 of 0·02 was associated with a lag of 5, 6, 7, and 9 days.

In the unadjusted models, occurrence of rain in a day was associated with a doubling of incidence of RSV disease 8 days later [incidence rate ratio (IRR) 2·07, 95% confidence interval (CI) 1·52–2·81] (Table 1). A 1% rise in mean relative humidity and 1 °C increase in mean air temperature was associated with a 6% (IRR 1·06, 95% CI 1·03–1·09) and 39% (IRR 1·39, 95% CI 1·22–1·50) increase in RSV cases, respectively, 8 days later (Table 1). The magnitude of association of humidity with RSV disease incidence was higher in days with no rain (IRR 1·10, 95% CI 1·06–1·16). Compared to the first quintiles of mean relative humidity and mean air temperature, the

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Table 2. *Association of number of cases per day with quintiles of mean relative humidity and mean air temperature 8 days earlier*

	Mean relative humidity*	Mean air temperature*
	IRR (95 % CI)	IRR (95 % CI)
1st Quintile	Reference	Reference
2nd Quintile	1·13 (0·72–1·77)	3·7 (2·29–5·99)
3rd Quintile	2·38 (1·55–3·64)	4·6 (2·85–7·43)
4th Quintile	2·34 (1·48–3·69)	4·21 (2·57–6·91)
5th Quintile	2·81 (1·80–4·36)	3·35 (2·05–5·49)

IRR, Incidence rate ratio; CI, confidence interval.
* Measured over a 24-h period 8 days prior to the date for which the RSV case counts were measured.

Table 3. *Association of climatic parameters with daily counts of RSV-negative acute lower respiratory infections, RSV cases in children younger than 6 months of age, RSV cases with oxygen saturation <90 %, and X-ray-positive RSV cases*

	RSV-negative ALRI	Age <6 months	O_2 saturation <90 %	X-ray positive
Meteorological parameter*	IRR (95 % CI)	IRR (95 % CI)	IRR (95 % CI)	IRR (95 % CI)
Rain (yes)	0·98 (0·86–1·11)	1·65 (1·14–1·60)	1·44 (1·24–1·66)	1·44 (1·13–2·38)
Amount of rain (mm)	1 (0·99–1·00)	0·99 (0·97–1·01)	0·99 (0·97–1·00)	0·99 (0·97–1·00)
Mean relative humidity (%)	1·01 (1·00–1·02)	1·06 (1·02–1·10)	1·07 (1·03–1·10)	1·07 (1·03–1·10)
Mean air temperature (°C)	0·99 (0·96–1·01)	1·35 (1·07–2·53)	1·64 (1·13–2·38)	1·64 (1·24–1·66)

RSV, Respiratory syvcytial virus; ALRI, acute lower respiratory infections IRR, Incidence rate ratio; CI, confidence interval.
* Measured over a 24-h period 8 days prior to the date for which the RSV case counts were measured.

incidence of RSV disease was higher in the other quintiles of these parameters with a relatively more pronounced dose–response relationship for mean relative humidity (Table 2).

Similarly, in multivariate analysis with an 8-day lag, occurrence of rain was associated with a 64 % higher incidence of RSV disease (IRR 1·64, 95 % CI 1·13–2·38). A 1 % rise in mean relative humidity and 1 °C increase in mean air temperature was associated with a 6 % (IRR 1·06, 95 % CI 1·03–1·10) and 44 % (IRR 1·44, 95 % CI 1·24–1·66) increase in RSV cases, respectively, 8 days later (Table 1). Among the interactions evaluated for combinations of the statistically significant weather variables, the interaction term for occurrence of rain and mean air temperature was statistically significant.

In secondary (multivariate) analyses of cases in children aged <6 months, cases with oxygen saturation <90 %, and chest radiology-positive cases; the associations of the climatic parameters with incidence of RSV disease were qualitatively similar to the associations observed in the primary analysis (Table 3). For ALRI cases negative for RSV, a 1 % increase in mean relative humidity was associated with a 1 % higher incidence of RSV disease. The other weather variables were not associated with RSV incidence (Table 3). Results from secondary analysis restricted to data from sub-health centres at least 15 km from the weather station were similar to the primary analysis in terms of magnitude and direction of the associations (analysis results available on request).

Four statistically significant space–time clusters of RSV disease comprising from 3 to 6 sub-health centres were identified during the study period (Fig. 2). The start and end dates and number of cases in each cluster are shown in Table 4. Two of the clusters were rural and two were in urban areas. The RSV cases occurring in space–time clusters did not have a significantly higher likelihood of having an oxygen saturation <90 % compared to cases occurring outside the clusters (IRR 1·14, 95 % CI 0·83–1·57). However, among RSV-positive cases there was a 23 %

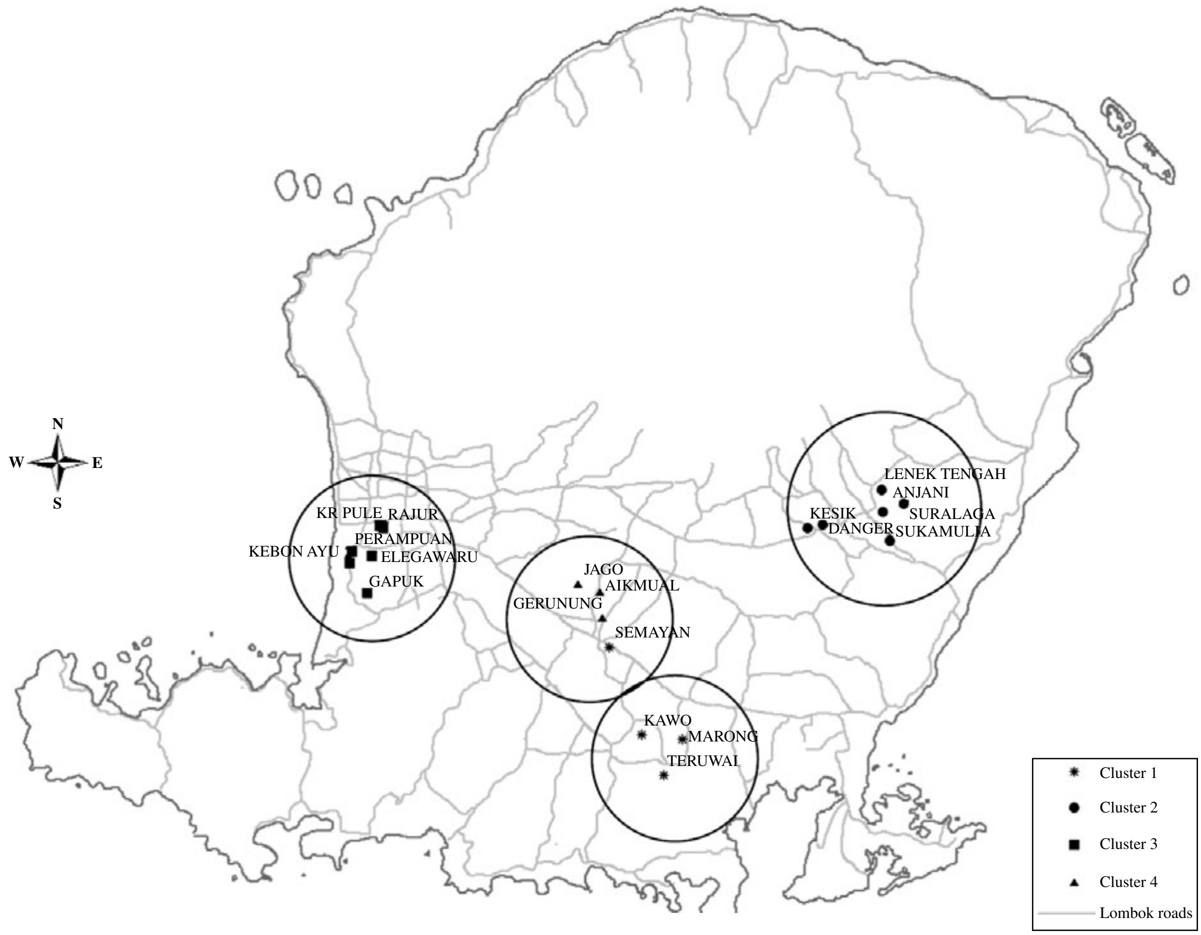

Fig. 2. Village (*pustu*) health centres included in statistically significant space–time clusters. Lombok, Indonesia, 1 January 2000 to 31 December 2002.

Table 4. *Characteristics of statistically significant clusters*

	Start date (2000)	End date (2000)	No. of cases
Cluster 1	1 Jan.	17 Mar.	27
Cluster 2	3 Mar.	3 May	34
Cluster 3	27 May	28 June	10
Cluster 4	9 Dec.	7 Feb.	11

higher incidence of alveolar consolidation on chest radiology inside the clusters compared to outside the clusters (IRR 1·23, 95% CI 1·07–1·41).

DISCUSSION

Djelantik *et al.* estimated the incidence of RSV-positive lower respiratory illness with hospitalization in Lombok to be 10–14/1000 child-years among children aged 2–23 months [4]. Moreover, findings from RSV surveillance in communities close to Bandung on the island of West Java, Indonesia – using a standardized WHO protocol – showed that the incidence of RSV determined at home visits was 34/1000 child-years, and was highest in the rainy season [22]. Our results confirm the reports of a significant burden of lower respiratory illness caused by RSV in Asia [4, 33] and add new evidence of seasonality and association of rain, humidity, and air temperature with RSV hospitalization. We also show evidence of localized space–time clustering of RSV hospitalization in Lombok; mostly during the 2000 season, and of substantial year-to-year variation.

The associations of RSV hospitalization incidence with climatic variables remained when restricting the analysis to young infants, those with severe disease, and those with alveolar consolidation on chest radiology. Even though the weather data were collected at a weather station on the west coast of the island, the overall associations remained consistent after restricting the analysis to regions at least 15 km from the weather data collection point. Non-RSV ALRI was mildly associated with mean relative humidity and not associated with other climatic variables.

Some studies in tropical and equatorial countries with high rainfall throughout the year show seasonality of RSV while others do not. In an analysis of hospitalization rates among children aged $\leqslant 15$ years in Hong Kong, transmission of RSV was documented during most of the year with an increase in the summer months [34]. Reese & Marchette analysed data from Hawaii and reported year-round transmission of RSV with peaks in October–April, the winter wet season [35]. The year-round transmission in Hawaii could be explained by high numbers of tourists travelling to Hawaii throughout the year [35]. In Singapore, rates of RSV disease were associated with higher temperature, lower relative humidity and higher maximal day-to-day temperature variation [36]. Weber *et al.* described a peak in RSV-associated ALRI during the rainy season in The Gambia [5]; however, earlier studies did not find such an association [37, 38]. Chan and colleagues reported RSV disease to be directly associated with number of days of rainfall in a month and inversely associated with monthly mean temperature in Malaysia [11]. The study, however, did not find an association between RSV disease and total monthly precipitation [11].

In the United States the RSV season has been documented to start in late December and end in late March with regional variability in median start time – ranging from late November and early January in the South and the Midwest, respectively [15].

Compared to several other respiratory viruses which are primarily spread by droplets, the mode of transmission for RSV is direct or indirect contact [39, 40]. It has been suggested that human social behaviour related to weather may increase person-to-person contact and may play a part in the seasonality of RSV epidemics [10, 11]. Crowding, large family size, multiple birth, and crowded homes are known risk factors for RSV infection [41]. Our findings of an association of RSV hospitalization with occurrence of rain but not the amount of rain are similar to the reported correlation in Malaysia [11] of RSV infection rates with number of days of rainfall rather than total precipitation. This may be a manifestation of increased exposure due to crowding and more time spent indoors. In other words, beyond the effect of making individuals stay indoors, the total amount of rainfall may be of less importance and since the duration of rain is not always proportional to the amount of rain in equatorial regions, we could not, therefore, find an association with total amount of rain.

The association of relative humidity and RSV incidence could partially be explained as a residual effect of rain. However, this association remained the same in the multivariate analysis. We did not find an interaction between relative humidity and other variables, and humidity remained associated with RSV incidence in the absence of rain – all suggesting an independent effect of humidity. Although the actual mechanism is unclear, presence of moisture might influence the viability and transmissibility of RSV. Our finding of an association between mean air temperature and RSV incidence is similar to that in the Singapore study [36]. However, the temperature-related results should be interpreted in the light of the relatively narrow range of temperature recorded during the study period (mean 26 °C, standard deviation 2·3 °C).

We found evidence of four distinct space–time clusters of RSV cases. One of the clusters appeared in the largest urban area and two of the clusters included the two trade ports on the island. Statistically significant space–time clusters of RSV did not appear every year and during the study period we could not discern any repeated or consistent sequence of emergence of these clusters. However, cases inside space–time clusters were more likely to have alveolar consolidation on chest radiology – indicating a higher probability of bacterial super-infection. This is the first analysis of RSV epidemiology using space–time clustering methods and our data show that there are geographically discrete micro-epidemics within the seasonal island-wide epidemic.

Our findings were limited by the availability of only 3 years of data. Even though few studies of tropical RSV disease have duration as long as our study, this study was not long enough to assess the impact of longer term climatic and geographical phenomena. Since this was a hospital-based study, the RSV case and rate data may be influenced by health-seeking behaviour. With the available study information, we cannot predict the direction of any estimation error or whether possible under- or over-estimation was differential with respect to the independent variables.

This study provides evidence of an association between hospitalized RSV illness and several climatic variables in an equatorial island setting. The local micro-epidemics suggest the effect of human behaviour within the annual epidemic. Prospective studies with more intense assessment of individual-level exposure are required to tease out the relative contributions of behaviour and biology in determining the seasonality of RSV disease incidence.

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DECLARATION OF INTEREST

None.

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