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Comparative Dynamics, Morbidity and Mortality Burden of Pediatric Viral Respiratory Infections in an Equatorial City

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Abstract

Background—Although acute respiratory infections (ARIs) are the global leading cause of pediatric morbidity and mortality, the relative impact of viral pathogens on pediatric ARIs is still poorly understood, especially in equatorial settings. Long-term studies of multiple viruses concurrently circulating in these regions are still lacking. Here we report the results of a systematic prospective surveillance of multiple respiratory viruses conducted every weekday for nearly a decade in an equatorial city in Brazil.

Methods—We analyze the relative burden of influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus and metapneumovirus, their seasonality and their association with climatic and demographic factors, ARI diagnosis and pediatric mortality.

Results and Conclusions—RSV was the primary driver of severe childhood respiratory infections, including pneumonia. RSV was also the virus most strongly associated with respiratory-associated deaths, with RSV circulation and pediatric mortality being in phase. Influenza was the second most common cause of childhood ARIs but, similarly to parainfluenza, adenovirus and metapneumovirus, it was mostly associated to upper tract infections, and peaked much earlier than mortality. The results also show that viral circulation can be strongly seasonal even in equatorial regions, which lack seasons with low temperatures: while parainfluenza predominantly circulated in the dry season, RSV and influenza were concentrated in the rainy season. The consistent epidemiological patterns observed can be used for an effective adjustment of the timing of therapeutic and prophylactic interventions in this and potentially other equatorial regions.

Keywords

influenza; RSV; pneumonia; tropics; ARI

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INTRODUCTION

Globally, acute respiratory infections (ARIs) are the leading cause of morbidity and mortality among children under five years of age ¹. The high burden of ARIs is disproportionate in developing countries, where it is estimated that over 1.5 million children die from acute respiratory infections, mainly pneumonia, every year ².

Although most acute respiratory infections have a viral etiology, the relative impact of the main respiratory viruses on childhood morbidity and mortality is still poorly understood, especially in tropical and equatorial regions. This is partially due to the uncertainties associated with the circulation patterns of respiratory viruses in these regions, which obey to different (and still largely unknown) drivers than in temperate regions. The difficulty also stems from a lack of rapid and proper diagnostic tools to differentiate between ARIs and their viral agents in many of these areas ³. Also, long-term, systematic studies involving prospective surveillance of multiple respiratory viruses concurrently circulating in the tropics are still lacking.

Accurate estimates of the relative contribution of viral pathogens to ARI deaths and the factors modulating their activity are essential for a timely and effective implementation of preventive interventions and optimal treatment routines, especially in light of recent efforts at vaccine development for other respiratory viruses ⁴ as well as the goal of reducing child mortality by two-thirds between 1990 and 2015 ⁵.

Here we compare the relative contribution of multiple respiratory viruses to childhood morbidity and mortality in Fortaleza (Brazil), an equatorial city with a climate similar to other regions (e.g., sub-Saharan Africa) where few studies of this kind have been performed. Clinical and viral surveillance of ARI cases was prospective and systematic, being conducted every weekday for nearly a decade. It targeted influenza and parainfluenza viruses, respiratory syncytial virus (RSV), adenovirus and metapneumovirus.

METHODS

Study location

Surveillance was undertaken at Fortaleza, the capital of Ceará (Brazil), located 4° south of the Equator (Fig.1). It has ~2.4 million inhabitants, a rainy season from January to June, and a dry season in the remaining months. Relative humidity is high (>70%) and temperature constant (~26–28 °C) throughout the year. Data collection was conducted at Hospital Infantil Albert Sabin (HIAS), a public teaching hospital that serves over 150 thousand children per year.

Laboratory-based Surveillance

Viral data were obtained from nasopharyngeal aspirates of children aged 1 month to 16 years with symptoms suggestive of ARI or ARI-related condition: cough, coryza, sore throat, earache, breathing difficulty, stridor, wheezing and fever (≥ 37.5 °C) within 7 days of onset. Aspirates were collected Monday to Friday, from January 2001 through December 2008. Samples were immediately taken to the laboratory, processed and screened for influenza A and B, adenovirus, RSV and parainfluenza viruses 1, 2, and 3 with an indirect immunofluorescence assay (IFA) conducted using the Respiratory Panel I Viral Screening and Identification (Light Diagnostic™, Chemicon, CA) as described previously ⁶. Screening of metapneumovirus was performed retrospectively for three years (2006–2008) using direct immunofluorescence (Human Metapneumovirus DFA reagent, Millipore). Data collection was approved by the Research Ethics Committee of HIAS. All samples were obtained with the written consent of parents or guardians of each child.

Age-Specific Mortality and Population Data

Age-specific mortality records were provided by the Brazilian Ministry of Health ⁷. We extracted all death records listing the following causes of death (ICD-10): influenza and/or influenza-like-illness (J10–J11), pneumonia (J12–J18), I20–25 (ischemic heart diseases) and diseases of pulmonary circulation (I26–28). Death rates per respiratory disease were obtained by dividing age-specific mortality by the annual population estimate (Brazilian Institute of Geography Statistics) for the corresponding age group.

Climatic data

Climatic variables were purchased from the Brazilian Institute of Meteorology (INMET) and downloaded from free climate maps generated by the interpolation of climatic information from ground-based meteorological stations (CRU TS 3.0 0.5°, Climatic Research Unit, University of East Anglia). The CRU monthly global datasets ⁸ include several climatic variables from 1901 until June 2006. We therefore used temperature and precipitation data from INMET (weekly aggregated records for the study period), and vapor pressure data from CRU. Since this latter variable was available with a monthly resolution, it was desegregated using linear interpolation. Climatic information was extracted and checked for consistency using scripts written in Matlab© for this purpose.

School Terms

We examined if the timing of any of the pathogens or ARIs was associated to the public primary school terms. Data was provided by the Secretary of Education of Fortaleza.

Data Analysis

To explore age-specific differences in the burden of viral respiratory infections and the association of respiratory viruses with ARIs we initially conducted contingency table analyses with post-hoc tests corrected for alpha inflation (Keppel's modified Bonferroni correction). ARIs were analyzed individually and categorized into upper and lower respiratory tract infections (URTI and LRTI, respectively), the latter being more severe and usually a complication of URTIs. Influenza A and B, and Parainfluenza 1, 2, 3 and 4 were grouped into one category (Influenza and Parainfluenza, respectively). Because we found an association of ARI diagnose with age and viral infection, we additionally used a generalized linear model that included a binomial outcome as the response variable (diagnosis: LRTI or URTI), a logit link function, virus as an independent categorical variable and age (in months) as a continuous covariate. Main terms and interactions were assessed by the Wald statistic.

An exploratory analysis was also conducted to identify putative associations between climatic factors, viral circulation, diagnosis and respiratory mortality. Pearson correlations between pairs of log-transformed time series were conducted with temporal lags from 0 to 11 weeks.

Seasonality

Although it is not our aim to describe the seasonality of individual viruses (previously described for some viruses ^{6, 9, 10}), here we conduct a detailed analyses of the viral seasonal signatures to determine their temporal association to ARIs, their severity and associated mortality. Wavelet analyses were used to investigate cycles and changes in seasonality. To further characterize seasonal patterns in the climatologic, viral and mortality data, we used Fourier analysis to extract the frequencies of the first, second and third harmonics in the data. By summing up these harmonics we obtained a model of the Periodic Annual Function (PAF), a seasonal signature of the original series where year-to-year variations are removed

but seasonal variations preserved. PAF was used to obtain the peak timings of each series. All analyses were conducted using Matlab (MathWorks) and SPSS v.19.0.

RESULTS

Impact and clinical burden of ARIs

At least one viral pathogen was identified in 1352 (30.7%) samples, with two simultaneous viruses identified in 2.9% of the positive samples. Most co-infections (67%) were RSV co-occurrences with other viruses, chiefly influenza (53% of RSV associations). Table 1 shows the results of all positive assays per age group (ungrouped results are available upon request to the authors). Overall, there was a strong association between age and the virus identified ($\chi^2_{16}=101.38$, $P<0.001$), with a marked drop in RSV cases among older children: while infants younger than 1 year accounted for over half of all RSV-confirmed cases, RSV detection dropped to 28.7% in children over 5.

Nearly the same percentage of children was diagnosed with upper and lower ARIs, the latter comprising mostly pneumonia (22%), bronchial hyperactivity (16.5%) and bronchiolitis (11.2%). Clinical diagnoses significantly depended on the infecting virus (diagnoses ungrouped or grouped into LRTI and URTI, respectively: $\chi^2_{16}=132.37$, $P<0.001$ and $\chi^2_4=91.01$, $P<0.001$). RSV was the viral cause of most LRTIs, among which pneumonia was prevalent, followed by bronchiolitis (Table 2). RSV accounted respectively for 63.4% and 76.4% of all pneumonia and bronchiolitis cases in children from all ages. Adenovirus and influenza were associated mostly to URTI cases (64% and 59% of cases, respectively).

The analysis exploring the simultaneous effect of viral agent and age on clinical outcome confirmed these results. Younger children were significantly prone to LRTIs (generalized linear model: $\chi^2_1=10.18$, $P<0.001$; Fig.2). Similarly, clinical diagnosis depended on the pathogen detected ($\chi^2_4=60.57$, $P<0.001$), with the probability of an URTI diagnosis being significantly different from that of an LRTI diagnosis for all viruses (GLM: $P<0.001$ for all viruses; individual viral patterns in Fig.2). The association of virus with a diagnosis of URTI or LRTI also depended on age (interaction between age and virus; $\chi^2_4=12.78$, $P<0.05$): for RSV, there was a higher frequency of LRTI than URTI only in children up to three years. Infection severity (LRTI or URTI) was not significantly higher in dual viral infections.

Seasonality in Viral Incidence

Approximately 87.8 (± 40.2) aspirates were obtained every week. Although sampling was constant, collection frequency was higher in the rainy season (Fig.3) due to the corresponding higher demand of treatment for respiratory complications. Mean viral detection was of 27.8% positive samples per week ($\pm 13.5\%$, Fig.3; the graphic analysis of the seasonal patterns of each virus is available upon request to the authors).

RSV was the most frequently detected virus (53.2% of positive samples; Table 1). Its activity was strongly seasonal (black bars in Fig.3), concentrating from mid-February to July, with a peak in mid-May. No RSV case was detected after week 36.

Influenza was the second most frequently identified virus (16.4% of positive samples). Influenza A was detected predominantly (and influenza B exclusively) in the first semester (dark grey bars in Fig.3), peaking in mid-April.

Parainfluenza (all types) was detected on 14.6% of the positive samples, predominating in the second semester and peaking in mid-September. Adenovirus represented only 5.5% of positive samples, but its detection pattern suggests that a marked seasonality is not expected.

Metapneumovirus (9.8% of positive samples) also showed a bimodal annual activity, with a major peak in the first semester.

Seasonality in the diagnosis of ARIs

The seasonal signatures of ARI diagnoses could be well established for bronchiolitis, pneumonia and, to a lesser extent, URTIs (the details of the seasonal analysis of each diagnosis is available upon requested to the authors). URTIs usually peaked earlier than pneumonia and bronchiolitis. There was a bimodal pattern where influenza and RSV underlie the first major peak in the diagnosis of URTIs, with parainfluenza and to a lesser extent adenovirus contributing to the second peak. Even when RSV occurrences were removed from this series, its seasonal features are not substantially affected (other than advancing the first peak by a few weeks, as RSV peaks slightly later than influenza).

Similarly to URTIs, the seasonal features of pneumonia mirrored the relative contribution of its underlying viruses. RSV is a major contributor, but influenza and parainfluenza alone could also determine the shape of the first and second peaks, respectively. The main seasonal component in the diagnoses of bronchiolitis and bronchial hyperactivity was solely determined by RSV.

Climatic Determinants of Viral Incidence

Precipitation had a marked seasonal pattern and was positively and most strongly correlated with RSV ($R > 0.44$ at all lags), and most intensively at a lag of 5 weeks ($R \pm 95\% \text{ CI} = 0.62 \pm 0.5$). For influenza, the strongest association with precipitation was at lag 2, but the association was weaker ($R = 0.36 \pm 0.07$). A strong correlation was also found between precipitation and LRTIs with a lag of 5 and 8 weeks (0.35 ± 0.08 and 0.37 ± 0.07 , respectively), with pneumonia at a lag between 4 and 10 weeks ($R > 0.35$, with a higher correlation at week 8, $R = 0.44 \pm 0.08$), and with bronchitis and bronchiolitis with a lag between 2 and 10 weeks ($R > 0.35$, with a higher correlation at week 8, $R = 0.43 \pm 0.08$). Vapor pressure parallels precipitation in the pattern of correlations obtained. With RSV it ranged from $R = 0.36 \pm 0.11$ to 0.61 ± 0.07 with a lag of 0 and 8 weeks, respectively. With influenza the correlation was only barely above 0.35 at weeks 0 and 1.

Average monthly temperatures ($25.7\text{--}28.3^\circ\text{C}$) were not strongly seasonal, and only weakly correlated with viral incidence and clinical diagnoses ($R < 0.35$), the only exception being with RSV incidence ($R = 0.44 \pm 0.08$ and $R = 0.44 \pm 0.08$ at lag 0 and 2, respectively). The highest average temperatures preceded the season of highest precipitation by only a few weeks, with temperature starting to drop immediately before the rainy season (Fig.1). Accordingly, all variables (but parainfluenza activity) were negatively correlated with temperature at lag 0, but after the beginning of the rainy season the relation is inverted. This suggests that precipitation and/or humidity, and not temperature, is the climatic driver of viral incidence and of the observed seasonality in the diagnoses.

Since the seasonal features of parainfluenza incidence were not explained by climate, we explored a putative association to diurnal temperature range. The highest correlations obtained were low (0.25–0.27), possibly due to the noise from the low detection rate of this virus.

School Terms

School terms were highly irregular in the period, but this variation was not associated with the timing of the ARIs or viruses studied (correlation coefficients lower than 0.2).

Mortality Burden

There were 3878 deaths with a respiratory or associated disease as the underlying cause (2001–2008), 787 of children in the age range focused here. As expected, young children and seniors were disproportionately affected. Pneumonia was the predominant cause of death both among children (85.4%) and the population as whole (87.6%), followed by chronic lower respiratory diseases.

RSV incidence had the strongest temporal association with childhood mortality ($R=0.34 \pm 0.08$ with lag 0), as expected based on the strong association of RSV with pneumonia. The correlation was however lower for all-age groups ($R=0.27 \pm 0.09$). The association of influenza with mortality was lower in both cases ($R=0.27 \pm 0.09$ at lag 3 and $R=0.18 \pm 0.10$ at lag 5 for children and all age groups, respectively). Importantly, influenza peaked 5–6 weeks earlier than mortality. Mortality was also in phase with the peak of LRTI cases, possibly reflecting the association of RSV and LRTI cases.

DISCUSSION

Our results show that in Fortaleza, an equatorial city, RSV is the primary viral driver of severe childhood respiratory infections, including pneumonia. RSV was also the viral pathogen most strongly associated with respiratory-associated deaths in young children, as indicated by the viral, clinical and mortality data. It was the predominant virus underlying lower respiratory tract infections in general, an indirect indication of its higher clinical severity. It was also the virus most frequently identified in specimens from patients diagnosed with pneumonia (63%), by far the major cause of respiratory deaths (85%). The annual distribution of RSV-confirmed cases was, additionally, the one which temporally better explained the independent dataset of childhood mortality, with the best observed agreement between the timing of their respective peaks and cycles. In fact, the highest level of association was obtained with a lag of 0 weeks, consistent with the observation that the peak in RSV circulation and pediatric mortality were in phase.

These results are in line with previous reports showing the respiratory syncytial virus as the most important and common viral pathogen causing lower respiratory tract infections in young children¹¹. Still, they suggest a contribution of RSV to childhood mortality in tropical regions higher than previously acknowledged. Our observation of RSV as the most likely and frequent viral cause of respiratory deaths, including pneumonia, among young children also conflicts in this sense with a recent suggestion¹² that influenza is a major source of childhood pneumonia in tropical settings, particularly where pneumonia is highly prevalent.

The lower correlation of RSV detection with mortality in all age groups, conversely, is in agreement with previous accounts of its lower impact on older age groups: younger children were not only disproportionately affected by ARIs in general (especially LRTI if younger than three years of age), but also proner to RSV infection than older age groups. The relative contribution of influenza to ARI cases, in turn, increased substantially with age, with influenza and RSV becoming equally represented among children older than 4 years. Our detection of 5.5% of influenza-confirmed cases among all patients is higher than the 1% rate found in Hong Kong¹³ and 0.1% in the US¹⁴. Nevertheless, it was mostly associated to upper than lower tract infections. The viral data also suggest that influenza circulation is out of phase with the mortality data, peaking 5 weeks earlier. Interestingly, the association of influenza circulation with mortality in all age groups was also low.

Although less prevalent than RSV and influenza, nearly 15% of all positive samples were associated to parainfluenza, predominantly parainfluenza 3. Different from RSV and

influenza, the proportion of LRTI diagnoses in parainfluenza-confirmed cases increased with age. The prevalence of metapneumovirus and adenovirus, although slightly higher in younger children, did not vary markedly among age classes. Both these viruses were also most strongly associated to URTI diagnoses. These results contrast with previous reports for São Paulo ¹⁵, where adenovirus was the predominant viral cause of pneumonia. The latter study, however, corroborates our findings on the leading role of RSV in bronchiolitis cases.

The consistent epidemiological patterns observed can be used for the adjustment of therapeutic and prophylactic strategies in this and potentially other equatorial regions. In the case of RSV, immunoprophylaxis with the monoclonal antibody palivizumab has been shown to reduce hospitalization rates and morbidity among premature and high-risk infants if initiated before the onset of the RSV epidemic season ¹⁶. Although palivizumab administration is generally recommended from May onwards ^{17,18}, our results show that RSV starts to circulate much earlier (mid-February) in Fortaleza and possibly other equatorial locations. Considering that palivizumab must be administered throughout the RSV season, the observation that RSV activity nearly ceases in August should be also taken into account to minimize wastage of what is a highly expensive treatment, especially in low income settings. The seasonality analyzes also shows that the timing of the peak in influenza activity among children occurs before the beginning of the scheduled vaccination against influenza in Brazil (initiated between mid-April and first week of May ¹⁹ and targeted at those older than 65 years of age). Assuming that there are no marked differences in the temporal circulation of influenza among age groups, our results support the recommendation for a change on the vaccination calendar in the equatorial region of Brazil ^{19,20}.

The present findings also show that the circulation of respiratory viruses can be strongly seasonal even in equatorial regions, which lack seasons with low temperatures. In Fortaleza, a city where rainfall has a strong seasonal signature and temperature is relatively constant, RSV and influenza activity was concentrated in the rainy season. While this is in concert with similar observations from studies in tropical and subtropical areas marked by seasonal rainfall ²¹, it contradicts trends reported in other tropical regions, where year-round RSV activity was observed ²². An important exception was parainfluenza, which predominantly circulated in the dry season ²³, a period marked by a high daily variation in temperature. Although sudden changes in temperature were connected to respiratory deaths among the elderly in temperate settings ²⁴, the much narrower and milder temperature ranges considered here restrain its putative role as an environmental driver of higher infection rates.

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Figure 1. Map of Fortaleza. Panels on the right show mean temperature and precipitation (2001–2008, INMET), and humidity (vapor pressure, 2001–2005, CRU).

Figure 2.

Age distribution of children diagnosed with ARIs by viral cause. Bars show the proportion of each virus associated to URTIs (left) and LRTIs (right) in each age class (from 0.5 to ≥ 4.5 years). Colors: black=RSV; dark grey=influenza; light grey=parainfluenza; white=adenovirus; patterned=metapneumovirus.

Figure 3.

Number of weekly viral isolation rates for each viral pathogen. Colors: black=RSV; dark grey=influenza; light grey=parainfluenza; white=adenovirus; patterned=metapneumovirus. The bars also show the number of samples yielding negative results (patterned white on top).

Table 1
Viruses identified in all positive immunofluorescence assays and general clinical diagnoses for each age group.

Age Class									
Viral Pathogen	y	1	1 < y	2	2 < y	3	3 < y	4	y > 4
RSV	409 _a		191 _b		92 _b		53 _b		43 _c
Influenza	65 _a		63 _b		46 _{b,c}		27 _{b,c}		50 _c
Parainfluenza	77 _a		62 _a		36 _a		14 _a		25 _a
Adenovirus	27 _a		24 _a		17 _a		6 _a		8 _a
Metapneumovirus	58 _a		29 _a		21 _a		11 _a		24 _a
General clinical diagnosis									
URTI	209 _a		166 _b		116 _{b,c}		61 _{b,c}		88 _c
LRTI	427 _a		203 _b		96 _{b,c}		50 _{b,c}		62 _c

The same subscript letters in different columns within a same row denote proportions that do not differ significantly at the 0.05 level.

Association of clinical diagnoses of ARIs and their underlying viral pathogens as identified in the immunofluorescence assays.

Table 2

Viral Pathogen	General Diagnosis		Specific Diagnosis				
	URTI	LRTI	Bronch. hyperact.	Bronchiol.	Bronchitis	Pneumonia	URTI
RSV	254 _a	543 _b	111 _a	185 _b	18 _{a,c}	220 _a	254 _c
Influenza	149 _a	102 _b	37 _{a,b}	16 _c	6 _{a,b,c}	43 _{b,c}	149 _a
Parainfluenza	108 _a	106 _a	39 _a	24 _a	3 _a	40 _a	108 _a
Adenovirus	53 _a	29 _b	3 _a	6 _a	3 _{a,b}	17 _{a,b}	53 _b
Metapneumov.	76 _a	67 _b	23 _{a,b}	11 _b	6 _a	27 _{a,b}	76 _a

The same subscript letters in different columns within a same row denote proportions that do not differ significantly at the 0.05 level.