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HEALTH SCIENCES

Respiratory syncytial virus causes more hospitalizations and deaths in equatorial Brazil than influenza (including during the 2009 pandemic)

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Abstract: Despite numerous studies evaluating influenza and Respiratory Syncytial Virus (RSV), there is still a lack of knowledge about them, especially in tropical countries. We compared the relative importance of respiratory viruses by examining their spatiotemporal patterns, age-specific hospitalization data and mortality data for 2007-2012 obtained from official sources. The data were aggregated into "respiratory infection seasonal zones" formed combining states that had similar seasonal patterns of pneumonia and influenza (P&I). Equatorial-North where P&I peaks in the middle of the year, Equatorial-South where P&I peaks in the first semester and coincides with the rainy-season, Subtropical where P&I peaks are clearly concentrated in the winter season, and Tropical Midwest and South-East where P&I peaks are a transition between the South-Equatorial and the Sub-tropical. Our analyses indicate that RSV has higher impact than influenza in equatorial region of Brazil, which was particularly evident during the circulation of the 2009pdm strain, and suggests that seasonal influenza may have a lower impact in Equatorial Brazil (and perhaps in other tropical regions of the world) than previously considered. Accordingly, we suggest that the broad assumption that influenza is the main cause of viral respiratory hospitalizations and death in equatorial regions be questioned with greater emphasis in future studies.

Key words: disease burden, influenza, RSV, seasonality, pandemic, 2009pdm.

INTRODUCTION

Influenza and Respiratory Syncytial Virus (RSV) are two important causes of respiratory infections related mortality (Fleming et al. 2015, Lafond et al. 2016). For example, studies suggest that influenza contributed to the deaths of 28,000 – 111,500 in children <5 years in 2008 (Nair et al. 2011); whereas RSV contributed to 66,000-200,000 deaths in children < 5 years of age in 2005 (Nair et al. 2010), with other recent studies showing similar results (Shi et al. 2017). The burden of both viruses varies strongly across populations, with 99% of related deaths in young children occur in developing countries (Nair et al. 2010, 2011). Influenza and RSV are also important causes of morbidity and mortality for other age groups, particularly older adults (Falsey et al. 2005, Jansen et al. 2007).

Nevertheless, despite all the research that has assessed the burden of influenza and RSV, there is still significant uncertainty regarding the relative contribution to morbidity and mortality. Discerning the relative burden between RSV and influenza is difficult since the viruses often circulate concomitantly. Clinical manifestations of these pathogens are indistinct and infections are typically not confirmed via testing (Fleming et

al. 2015, Jansen et al. 2007) not always available in health care settings, moreover the burden from these pathogens varies significantly from year-to-year (Nair et al. 2010, 2011, Thompson et al. 2003). Despite these obstacles, several studies attempted to determine the relative burden of these viruses but reported conflicting results.

A modeling study of mortality in England and Wales from 1999-2010 found that influenza has a higher mortality burden than RSV across all age groups (Hardelid et al. 2013). Other modeling studies using hospitalization and mortality data from the US (Thompson et al. 2003) and the Netherlands (Jansen et al. 2007) suggested that the burden of RSV was greater than influenza for children < 1 year, but influenza had a greater burden for all other age groups. However, each of these studies are at odds with a recent study comparing influenza and RSV burden in the UK which suggested that the impact of RSV was comparable, if not greater, for hospital admissions and deaths across nearly all ages (Fleming et al. 2015). Studies in Guatemala and Brazil demonstrate the importance of RSV as a cause of hospitalization and death in all age groups and suggest that it may be an important determinant of the seasonality of hospitalizations for respiratory infections (Mccracken et al. 2013, Raboni et al. 2018, Verani et al. 2013).

Little is known about the relative burden of influenza and RSV in the tropics. There are reasons to suspect that there may be differences in the relative importance of these viruses according to latitude. A recent study showed that the 2009 pandemic in Brazil caused significantly more morbidity and mortality in temperate regions than in tropical regions of Brazil, this difference was not explained by socioeconomic or age structures (Schuck-paim et al. 2012). We investigate whether the relative burden of RSV, influenza and other respiratory viruses vary spatially across Brazil. Brazil is an ideal country to investigate given it spans tropical and temperate regions, and it has relatively uniform viral surveillance and health care reporting systems. We compared the relative role of respiratory viruses in morbidity and mortality by examining spatiotemporal patterns of respiratory viruses, and age-specific hospitalization and mortality data for 2007-2012 (including the 2009 A/H1N1 influenza pandemic).

MATERIALS AND METHODS

Data sources

This study links three distinct datasets describing viral infections, and pnemonia and influenza (P&I) mortality and hospitalization in Brazil. Comparison of these three datasets across multiple years and age groups allowed us to assess the disease burden of respiratory viruses on these populations in terms of virus detection, hospitalization and mortality. Originally, the viral surveillance, mortality and hospitalization data were all aggregated to the monthly level by state (the Federal District, in the context of this paper, is considered a state for simplicity) for the period of January 2007 through December 2012. The mortality and hospitalization data were stratified by age due to the differential impact of the viruses across the different age groups.

Viral surveillance data were obtained from the program Sistema de Informação da Vigilância Epidemiológica da Gripe (Sivep-Gripe) of the Secretaria de Vigilância em Saúde, Ministério da Saúde do Brasil. The data include counts of positive tests by month and state for from 2007-2012 for virus influenza A, influenza B, respiratory syncytial virus (RSV), parainfluenza 1,

parainfluenza 2, parainfluenza 3, parainfluenza 4 and adenovirus (Table I).

Monthly mortality data for each state was obtained from the Sistema de Informação sobre Mortalidade (SIM) da Secretaria de Vigilância em Saúde do Ministério de Saúde do Brasil, which was established in 1975. These datasets were uniformly and systematically collected throughout the year and cover approximately 90% of the population. Regional differences in coverage ranged from 83.1% in the Northern Region to 96.7% in the Southeastern Region [data available for 2008; (DATASUS 2016)].

Finally, hospitalization data was obtained from the nationwide administrative database of the Unified Health System (Sistema Único de Saúde, SUS), which records all hospitalizations paid by the public sector. These data are published on the Ministério de Saúde do Brasil website for public access and include hospitalizations occurring in public hospitals at the federal, state and municipal levels and those occurring in private and non-profit hospitals under contract to the SUS. Visits and treatments occurring at outpatient settings (e.g., health clinics, medical offices and emergency wards) are not included in this database. These data span 2003-2015 and contain record-level information on cause of hospitalization (ICD-10 coded), patient age, gender and municipality of residence, admission and discharge dates, hospital type, specialty and hospital location. The records of Pneumonia and Influenza (P&I) attributed hospitalizations and P&I attributed death were filtered using the codes J10-18.9 of the ICD-10.

Data analyses

Visual inspection of the matrix of the incidence of P&I attributed hospitalizations and P&I attributed deaths by month and state (sorted by latitude) was achieved using the heat-grid graphic, displayed in Figure 2 (Alonso and Mccormick 2012) with the purpose of identifying patterns in regional time-series.

The state level data were aggregated into "respiratory infection seasonal zones" (RISZ) to increase our ability to identify differences in the effect of viral respiratory infections across populations in Brazil. Each zone was formed by combining states that had similar seasonal patterns of P&I hospitalization and mortality (Fig. 2). To infer the most prevalent viruses during respiratory infections season in the "yearly epidemic months" of each zone, we identify the four consecutive months where P&I hospitalizations were greatest each year (hospitalizations were chosen over mortality

TABLE I. Virus detection by the SIVEP-Gripe (Information System of Epidemiological Surveillance - Influenza) per age group for the period Brazil, 2007-2012.

	stillborn	0-4	05-14	15-29	30-49	50-59	60-69	70+	Total	
RSV	10	1,869	144	140	118	47	20	18	**2,366**	32%
Influenza A	7	457	342	576	397	78	44	35	**1,936**	26%
Influenza B	2	161	127	250	185	30	12	9	**776**	10%
Adenovirus	3	499	114	112	92	26	13	8	**867**	12%
Parainfluenza 1	1	146	36	40	39	15	4	6	**287**	4%
Parainfluenza 2	1	200	80	123	113	25	13	10	**565**	8%
Parainfluenza 3	4	405	49	76	69	24	11	7	**645**	9%
negative	*155*	*15,013*	*5,467*	*7,972*	*6,777*	*1,848*	*993*	*824*	**39,049**	
Viral detection	**28**	**3,737**	**892**	**1,317**	**1,013**	**245**	**117**	**93**	**7,442**	
(%)	0%	50%	12%	18%	14%	3%	2%	1%		

because they are more synchronous with viral activity and capture severe events, even when mortality is low or absent). In addition, we also included the signal of the overall viral detection using a Periodic Annual Function (PAF) (Alonso and Mccormick 2012) created with all years but 2009 (Schuck-paim et al. 2012), so a stationary reference model of respiratory viral activity could also be used for visual comparison.

Microsoft© Excel programs were used to archive data once it was aggregated from the original source. Data processing was conducted using scripts written in Matlab R2014a (MathWorks©). Finally, data analyses were performed and figures generated using the freely available software Epipoi (Alonso and Mccormick 2012).

RESULTS

Figure 1 shows the matrix of P&I cases by month and state sorted by latitude. Distinct seasonal patterns of P&I hospitalizations across latitudes are observed. In general, P&I increase early in the year in the North and Northeast of Brazil and then shift southwards along a "travelling wave" (Alonso et al. 2007). The impact of the 2009 pandemic on P&I hospitalizations and mortality in the southern most states (from Bahia south) is also clearly observed. In most of the remaining states (i.e., north of Bahia), an increase in P&I hospitalizations is evident but increases in P&I mortality is not as striking. It is important to observe that in this equatorial region the increase in hospitalizations and mortality occurred before the introduction of the influenza pandemic strain in Brazil.

Based on the P&I mortality and hospitalization data (Fig. 1), we distinguished 4 respiratory infection seasonal zones (RISZ) in Brazil (from North to South):

- "Equatorial-North": composed by the state of Roraima, where P&I peaks in the rainy-season which is in the middle of the year.
- "Equatorial-South": composed by the states of the North region of Brazil (but Roraima) and all the states of the Northeast region (but Bahia). P&I peaks in the first semester, coinciding with the rainy-season.
- "Tropical Midwest and South-East": composed by all the states of the Midwest region of Brazil, all the states of the Southeast region and Bahia. P&I peaks are a transition between the "South-Equatorial" and the "Sub-tropical" therefore with peaks in the rainy-season and in the middle of the year (winter).
- "Sub-tropical South": composed by the three states of the South region of Brazil, with P&I peaks clearly concentrated in the winter season.

In the "Equatorial-North", hospitalizations typically peak between May-/July and August-/October (Fig. 3a), which is consistent with viral detection in this zone (Fig. 3d). Mortality, on the other hand, does not have a clear seasonal pattern (Fig. 3b), only occasionally overlapping with hospitalizations. Viral detection (Fig. 3c) is dominated by RSV in this zone through the year, and a small proportion of influenza virus is detected without a regular pattern. We also observe that peaks in hospitalization often coincide with increased adenovirus activity. Although the number of influenza viruses detected was higher during the 2009 pandemic, it did not coincide with the year of maximum hospitalizations or mortality– in fact, the circulation of H1N1pdm in 2009 coincided with one of the periods with the lowest mortality during the study period.

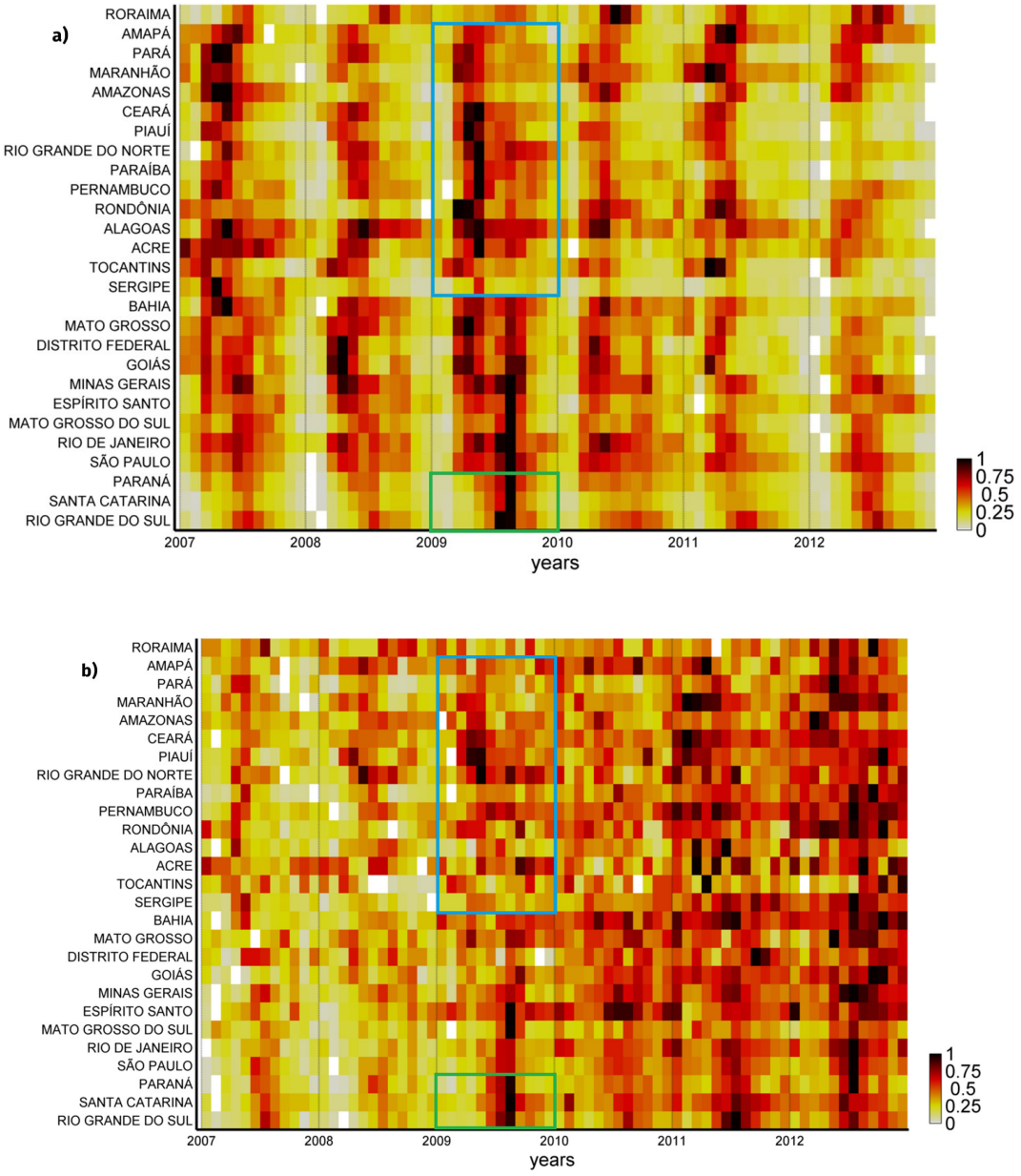

Figure 1. Heat-grids of monthly (a) hospitalization and (b) mortality in each state of Brazil as an ordinate from North (upper) to South (lower). Data are standardized to proportions with maximum of one per time series.

In the "Equatorial-South" zone, P&I attributed hospitalizations typically peak between March and June (Fig. 4a) and coincides with P&I attributed mortality, although the seasonality of mortality is less accentuated (Fig. 4b). The proportion overall of viral detection (Fig. 4d) is almost constant throughout the year, the virus species detected vary significantly throughout the year. The peak of RSV detection coincides with the peaks in hospitalizations and mortality. It should be noted that there was a large increase in the number of viral detections in 2009, but no significant increase in hospitalizations or deaths were observed

Figure 2. Map of Brazil with states classified within the four "respiratory infection seasonal zones" (RISZ) as defined in this study: "Equatorial-North" (red), "Equatorial-South" (green), "Tropical Midwest and South-East" (orange) and "Sub-tropical South" (blue).

(Schuck-paim et al. 2012). In fact, the higher incidence of hospitalizations and deaths in 2009 were in the months preceding the circulation of H1N1pdm. The only year where RSV was not the clearly predominant virus detected in the "peak window" was in 2012, and this corresponded to a combination of several viruses including RSV, influenza and adenoviruses.

In the "Tropical Midwest and Southeast" zone, P&I attributed hospitalizations typically peak between March/April and June/July, with a higher peak occurring in 2009 between June and September (Fig. 5a). Peaks in mortality (Fig. 5b) have a typical delay of one to two months from hospitalizations in this zone. Viral detection peaks in April and decays slowly through winter (Fig. 5d). The viruses that are predominant during the "peak windows" are mixed (Fig. 5c), with RSV clearly predominant in 2010 and 2011, influenza in 2009, while mix of different viruses characterizes the other years.

In the "Sub-tropical South" zone, P&I attributed hospitalizations typically peak between May and August, although they peaked a month later in 2009 (Fig. 6a). The peaks in mortality (Fig. 6b) align precisely with the hospitalizations (apart from 2011, where there is a delay of one month). Viral detection also starts to peak late spring to mid-winter (Fig. 6d). Influenza is clearly the predominant virus detected in the "peak windows" (Fig. 6c), presenting more than 50% of the detections, with the only exception being 2008 when parainfluenza 2 was prominent (similar to the "Tropical Midwest and Southeast").

DISCUSSION

We used viral detection, and P&I hospitalization and mortality data to present the first evidence of a differential impact of respiratory viruses on populations through different latitudes. Specifically, we demonstrated that influenza

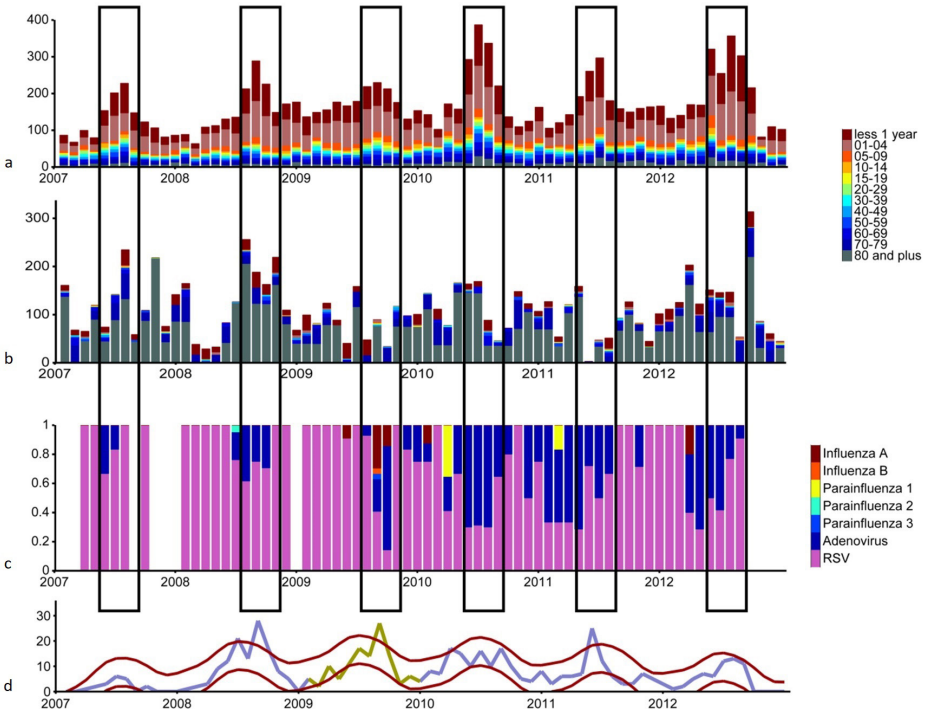

Figure 3. Epidemic monthly series of the "Equatorial-North" zone: (a) Hospitalizations in the public sector, (b) deaths, (c) proportion of respiratory viruses detected (d) total respiratory viruses detected and periodic annual function (PAF, when 2009 is excluded).

increases its role as the primary source of hospitalizations and deaths from viral respiratory causes in Brazil with distance from equatorial regions. Conversely, the impact of RSV increases with proximity to the equator.

We found that the Southern Zone of Brazil, which is situated in a subtropical region and presents relatively cold temperatures in the winter, is characterized by peaks in hospitalizations and deaths attributed to viral respiratory infections during the winter months. Viral detection is also concentrated in the beginning of those colder months, and influenza is indeed the most sampled virus during this period. In contrast, in the equatorial regions– which lacks a cold season and where respiratory infections are concentrated in the rainy season (Alonso et al. 2007, Freitas & Donalisio 2016, Moura et al. 2006, Moura 2010, Paynter et al. 2015, Tamerius et al. 2013, Yu et al. 2013)– the predominant virus is RSV during the periods when P&I attributed hospitalizations and deaths peak. Influenza, parainfluenza and adenoviruses are detected in those regions in the months of lower P&I attributed hospitalizations and deaths. The "Equatorial-North" zone is different, with detection of RSV high throughout the year with the peak of P&I hospitalizations sometimes coinciding with a peak of adenovirus, and influenza detection is sporadic. P&I mortality does not present a clear seasonal pattern.

The transition zone between the equatorial zones and the South Zone is composed by what we called "Tropical Midwest and Southeast" and present a epidemiological picture which can be considered a mixture of their northern and

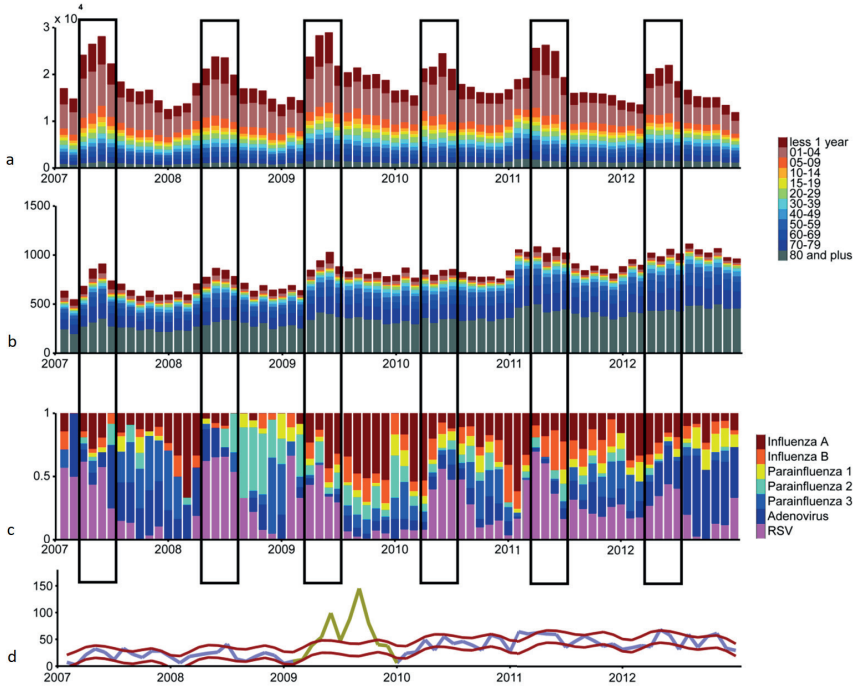

Figure 4. Epidemic monthly series of the "South-Equatorial" zone: (a) Hospitalizations in the public sector, (b) deaths, (c) proportion of respiratory viruses detected (d) total respiratory viruses detected and periodic annual function (PAF, when 2009 is excluded).

south neighboring zones: hospitalizations and deaths peak between the summer rainy season and the winter cold season, and the periods of higher P&I attributed hospitalizations and deaths are predominated by RSV in some years (as the "Equatorial-South" zone) and of influenza in others (as the "Sub-tropical South" zone).

It is particularly insightful to focus in the year when the emergence of the novel A/H1N1 pandemic influenza strain in 2009 occurred. That was a significant epidemiological event for several reasons: (a) it caused more hospitalizations and deaths than seasonal influenza worldwide (Simonsen et al. 2013), (b) in some regions its timing departed from the typical seasonal circulation and (c) it triggered a global intensification of surveillance systems of respiratory infections, particularly influenza. As a result, improved viral surveillance data since this time can assist to further our understanding of the role of influenza in respect with other respiratory viruses. It is remarkable that the strong increase in hospitalizations and deaths in the equatorial region during 2009 occurred prior to the introduction of the pandemic virus in Brazil (i.e., the first cases were confirmed in May (Oliveira et al. 2009), and coincided with a period when RSV was the predominant pathogen detected. This was in striking contrast to the "Tropical Midwest and Southeast" and "Sub-tropical South" zones where there was a marked increase in hospitalizations and deaths associated with A/H1N1 pandemic strain.

In summary, our analyses indicate that RSV is a virus with higher impact than influenza in the equatorial region of Brazil - which was particularly evident during the circulation of the 2009 H1N1pdm strain. Our analyses support not only the importance of RSV in general, but it raises the possibility that seasonal influenza

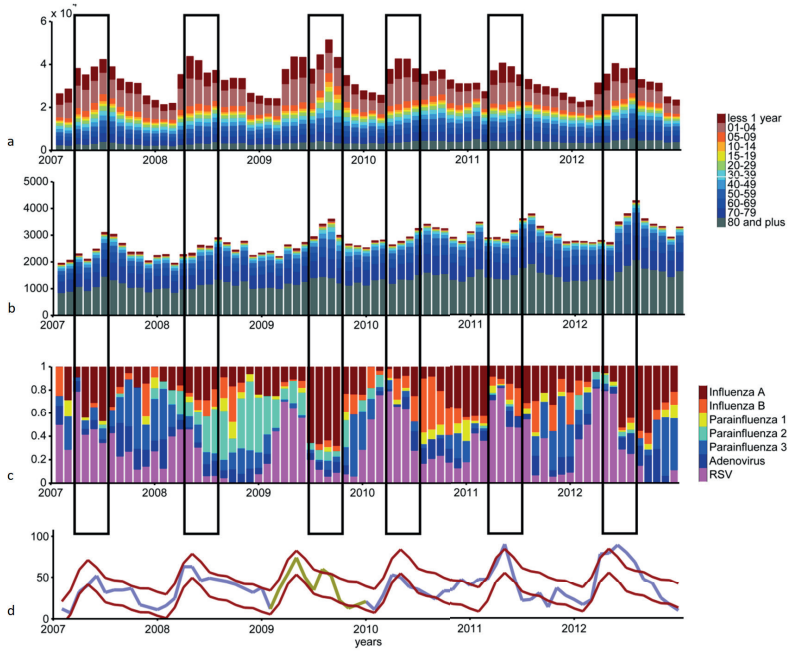

Figure 5. Epidemic monthly series of the "Tropical Midwest and Southeast" zone: (a) Hospitalizations in the public sector, (b) deaths, (c) proportion of respiratory viruses detected (d) total respiratory viruses detected and periodic annual function (PAF, when 2009 is excluded).

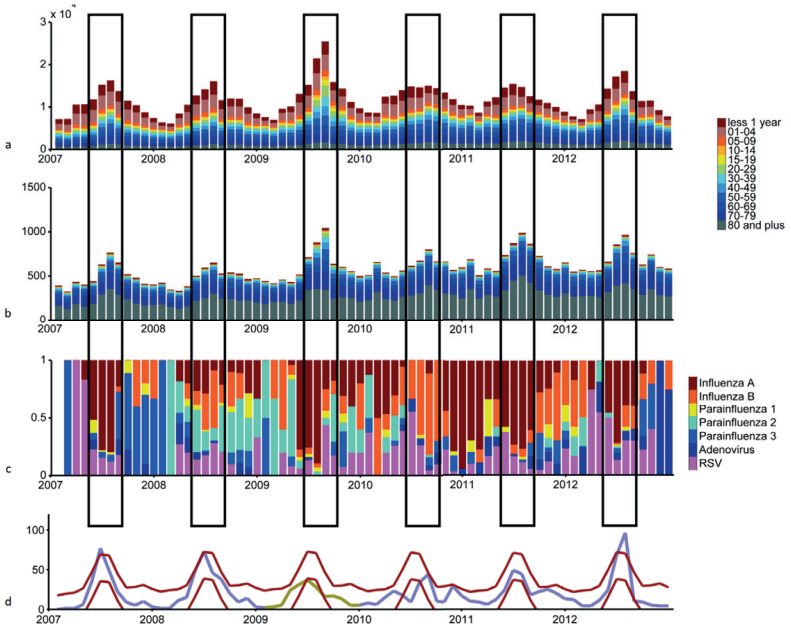

Figure 6. Epidemic monthly series of the "Sub-tropical South" zone: (a) Hospitalizations in the public sector, (b) deaths, (c) proportion of respiratory viruses detected (d) total respiratory viruses detected and periodic annual function (PAF, when 2009 is excluded).

has a lower impact in Equatorial Brazil (and perhaps in other regions of the world) than previously considered. This notion arises not only from normal seasonal years, but also from examination of hospitalization and deaths from the H1N1 2009pdm (with unquestionable higher burden globally). Accordingly, we recommend that the broad assumption that influenza is the main cause of viral respiratory hospitalizations and death in equatorial regions be critically analyzed in future studies. Recognition of the burden of each virus as a cause of illness and death is important for setting priorities in public policies for health. These aspects should be considered in view of the possibilities of offering new vaccines to the population, especially in countries with limited resources located in equatorial regions.

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Author contributions

Wladimir J. Alonso conceived, performed the analysis and write the manuscript. James Tamerius and André Ricardo Ribas Freitas contributed to the final version of the manuscript. All authors give final approval of the version to be submitted and any revised version.