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Original Contribution

# Seasonality of Influenza in Brazil: A Traveling Wave from the Amazon to the Subtropics

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Influenza circulation and mortality impact in tropical areas have not been well characterized. The authors studied the seasonality of influenza throughout Brazil, a geographically diverse country, by modeling influenza-related mortality and laboratory surveillance data. Monthly time series of pneumonia and influenza mortality were obtained from 1979 to 2001 for each of the 27 Brazilian states. Detrended time series were analyzed by Fourier decomposition to describe the amplitude and timing of annual and semiannual epidemic cycles, and the resulting seasonal parameters were compared across latitudes, ranging from the equator (+5°N) to the subtropics (−35°S). Seasonality in mortality was most pronounced in southern states (winter epidemics, June–July), gradually attenuated toward central states (15°S) ($p < 0.001$), and remained low near the equator. A seasonal southward traveling wave of influenza was identified across Brazil, originating from equatorial and low-population regions in March–April and moving toward temperate and highly populous regions over a 3-month period. Laboratory surveillance data from recent years provided independent confirmation that mortality peaks coincided with influenza virus activity. The direction of the traveling wave suggests that environmental forces (temperature, humidity) play a more important role than population factors (density, travel) in driving the timing of influenza epidemics across Brazil.

Brazil; climate; geographic locations; influenza, human; mortality; pneumonia; seasons

Influenza epidemics occur worldwide annually, resulting in considerable morbidity and mortality. The incidence of influenza displays a seasonal pattern in temperate areas, with marked peaks in the winter (typically December–April in the Northern Hemisphere and June–September in the Southern Hemisphere) (1, 2). Tropical and subtropical regions with mild winters are also subject to seasonal oscillations in influenza incidence, which have been linked to rainy seasons (3); however, the seasonal pattern is generally less pronounced than in temperate areas (1, 2). In particular, more than one period of viral activity may occur in any given year in tropical areas (4), suggesting a complex mechanism underlying observed seasonal patterns. Therefore, the reasons for the seasonality of influenza, as well as other viral respiratory diseases, remain elusive (5–8). Some authors have suggested the role of climate as a possible driving force of seasonality, where climate could have a direct influence on virus survival, transmission efficiency, or host susceptibility to infection or have an indirect influence through behavioral changes in human crowding (5, 9).

Because the influenza virus genome drifts gradually over time, and new viral strains spread globally, understanding the global patterns of influenza seasonality is paramount to designing effective control strategies and mitigating disease burden. Ideally, those strategies have to be tailored to epidemiologic and viral patterns in individual regions (1, 2). Only two recommendations for vaccine composition are established annually by World Health Organization

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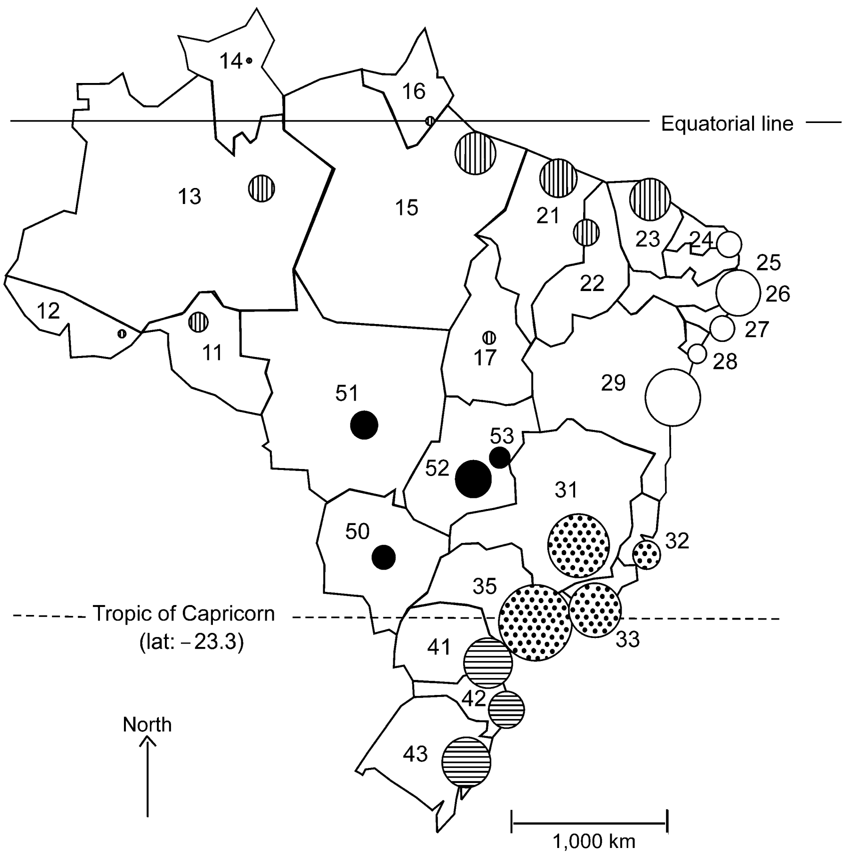

**FIGURE 1.** The 27 Brazilian "states" (26 administrative states plus the Capital District) used to analyze influenza seasonality. The location of each capital is represented by a circle, whose size is proportional to the population of each state ($\log_{10}$ scale). Numbers represent the official codes of the Brazilian states (refer to table 1 for the corresponding names), and the first digit of each number (and the line patterns) refers to one of the five Brazilian administrative regions: 1 = North, 2 = Northeast, 3 = Southeast, 4 = South, and 5 = Central-West. lat, latitude.

committees, corresponding to the Northern and Southern Hemispheres. Studies that quantify the differences in influenza seasonal patterns and impact between equatorial, tropical, and temperate environments can aid in optimizing local vaccine strain selection and timing for delivery (1, 2). Importantly, more research in this area can also shed light on the key factors responsible for the global persistence of influenza in the human population and the transhemispheric circulation of viruses.

In this paper, we compare influenza seasonal patterns in Brazil, a large country extending across more than 35 degrees of latitude in South America, encompassing the equatorial Amazon rain forest in the Northern Hemisphere to more temperate subtropical regions in the Southern Hemisphere (figure 1). We analyze spatial and temporal patterns in long-term time series of pneumonia and influenza mortality in 27 Brazilian states, as well as influenza laboratory-confirmed surveillance from recent years. We identify and characterize an annual "wave" of influenza epidemics traveling southward across Brazil and discuss the potential factors associated with this intriguing pattern of spread.

## MATERIALS AND METHODS

### Mortality and population data

Mortality records from 1979 to 2001 were provided by DATASUS, the national vital statistics agency of the Brazilian Ministry of Health (10). Coverage of the Brazilian vital statistics system has been steadily improving and was estimated to be approximately 82 percent in 1999 (ranging from 60.8 percent in the northeast region to 95.3 percent in the southern region) (11). Data collection is uniform throughout the year, therefore not affecting analyses of seasonal patterns. Individual death certificates were aggregated by month and 27 administrative units: 26 Brazilian states and the federal district (refer to the map in figure 1).

Several studies have shown that pneumonia and influenza deaths are the most specific endpoint for studying timing and amplitude of influenza-related mortality, on both the local and national scales (1, 12, 13). Deaths attributed to pneumonia and influenza as the underlying causes were extracted according to their *International Classification of Diseases* codes (refer to the supplementary table; this table, and other supplementary material so referenced in this

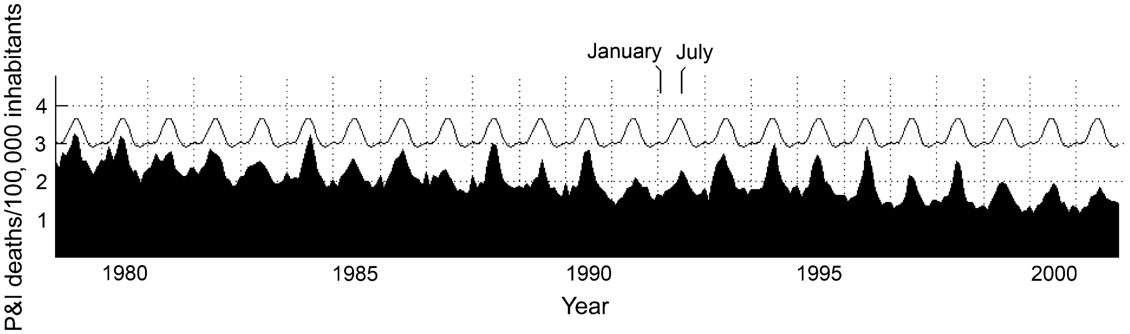

**FIGURE 2.** Monthly time series of deaths coded for pneumonia and influenza (P&I) per 100,000 inhabitants, Brazil, 1979–2001. Rates are not detrended. The black line (projected above its actual level for clarity) represents the periodic annual function obtained from summing the annual (first) and semiannual (second) harmonics of the Fourier decomposition of the P&I time series. The black line can be considered the seasonal signature of the original series—where year-to-year variations are removed but seasonal variations within the year are preserved. The location of January and July 1992 is indicated for reference.

paper, are posted on the *Journal*'s website (http://www.aje.oupjournals.org)). Annual population data were obtained from the same source and were aggregated to calculate monthly death rates per 100,000 inhabitants for each state (refer to figure 2 for national time series). The Brazilian population was 169.8 million in 2000 (14). The transition from *International Classification of Diseases*, Ninth Revision to *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision in 1995 was not accompanied by a visible change in annual pneumonia and influenza deaths (figure 2); therefore, no adjustment was needed (unlike in the United States (15)).

## Surveillance data

In 2000, the Brazilian Ministry of Health launched the national influenza surveillance system for outbreak detection to monitor virus circulation throughout the five Brazilian regions (figure 1) and to evaluate the effectiveness of control measures (16). The national influenza surveillance system is based on a network of general care facilities and emergency departments, which collect five clinical samples each week on average from patients with influenza-like illness and perform laboratory diagnosis via nasopharyngeal aspiration or combined oral and nasal swabs. Thus, these data collected systematically throughout the year represent an unbiased sample of the timing of influenza activity, appropriate for analyzing seasonal patterns. We obtained the monthly number of positive influenza isolates in each administrative region for 2000–2005 from the Secretariat of Health Surveillance of the Brazilian Ministry of Health (16) as an independent data set to establish an association with seasonal patterns of pneumonia and influenza mortality.

## Mortality data analysis

*Detrending.* Time series of monthly pneumonia and influenza death rates were detrended for each geographic unit. We estimated the annual trend by fitting a smooth spline curve to the annual average death rates. We then subtracted this trend from the time series of monthly pneumonia and influenza death rates and added a constant value equal to the mean monthly death rate for the entire study period.

*Seasonality analyses.* We used wavelet analyses (17, 18) to study time series of pneumonia and influenza mortality, in particular to detect changes in seasonality across the study period. These analyses showed that the predominant seasonal component in the series was the annual cycle for the entire period (supplementary figure 1). Since there was no obvious change in seasonal components over time at the national or state level (data not shown), we decided to focus on the stationary features in pneumonia and influenza mortality time series (i.e., constant from year to year) in subsequent analyses.

We used Fourier analyses to further characterize seasonal patterns of influenza (19, 20). With this frequency-domain method, the periodic variability of the monthly mortality time series is partitioned into harmonic functions. We extracted the amplitudes and phases (namely, timing) of the first and second harmonics (respectively, annual and semiannual component), each defined by their frequencies. By summing these harmonics, we obtained a model of the periodic annual function, which can be considered an average seasonal signature of the original series, in which year-to-year variations are removed but seasonal variations within the year are preserved. Once the periodic annual function was calculated, we obtained the relative amplitudes and timing of the two peaks of mortality (“major” (annual) peak and “minor” (semiannual) peak).

For each peak, we calculated the relative amplitudes by dividing the wave height (difference between the maximum and minimum value) by the absolute value of the peak of the periodic annual function (amplitude plus constant term, mean monthly death rate). Details on the significance tests for seasonal parameters are given in the online supplement.

Next, the seasonal parameters derived from the 27 state-specific pneumonia and influenza mortality time series were compared with the latitudes of the state capitals of Brazil, which correspond to the major population centers for each state. Since the timing and amplitude of the minor (semiannual) influenza seasonal component in state-specific time series were associated with large confidence intervals and did not show any consistent geographic patterns, we did not use them to characterize the seasonal patterns of influenza throughout Brazil.

## RESULTS

### National analyses of mortality data

Of the approximately 19 million registered deaths that occurred in Brazil from 1979 to 2001, 4.0 percent were attributed to pneumonia and 0.03 percent specifically to influenza. Figure 2 depicts the monthly time series of death from pneumonia and influenza for the whole country. Pneumonia and influenza death rates decreased on average 2.1 percent annually over the study period (test for linear trend, $p < 0.01$). In the Fourier analysis, the seasonality of influenza in Brazil was characterized by a semiannual pattern, peaking in the winter month of June (amplitude = 27 percent), with a second, smaller peak during the summer (January; amplitude = 13 percent; figure 2).

*Seasonal amplitude of major peaks in each state.* The seasonal amplitude of major peaks in pneumonia and influenza mortality, as derived by Fourier analysis, is indicated by state in table 1 and is plotted against the latitude of state capitals in figure 3A. Amplitude shows a steady and consistent decrease from the south (latitude 30°S) toward the latitude of about 15°S degrees. By contrast, northward from this latitude and closer to the equator, amplitudes remain low, with no systematic geographic variations (figure 3A). We estimated that latitude 15°S was the turning point of the best-fit piecewise relation between amplitude and latitude (refer to the supplementary material). On the basis of this result, we fitted a piecewise linear regression model between seasonal amplitude and latitude, separating the southern and northern regions of Brazil (figure 3A). To take into account the variability of amplitude estimates, we used a weighted regression, where weights are calculated as the inverse of the size of confidence intervals. This model gave a good fit in the south window ($R^2 = 0.88$, $p < 0.001$) but was not significant in the northern regions ($R^2 = 0.09$, $p = 0.14$). Thus, along the south-north axis, the amplitude of the seasonal component of influenza appears to decrease up to latitude 15.0°S, whereas, between latitude 15.0°S and the equator, seasonal amplitude is low and does not vary with latitude.

*Timing of epidemics in each state.* Surprisingly, we found that pneumonia and influenza mortality peaks traveled in a southward wave throughout Brazil, from the less populous north to the densely populated southern cities, including São Paulo (figure 3B). The major peak in pneumonia and influenza deaths occurred between April and May in states near the equatorial line. Southward, the peak was found progressively later in the year and occurred in the middle of July in the southernmost state. On the basis of a weighted linear regression of timing against latitude ($R^2 = 0.50$, $p < 0.0001$), we estimated that the approximately 33 degree latitude change from north to south Brazil corresponds to a 2.4-month lag in the timing of influenza epidemics (95 percent confidence interval: 1.5, 3.3 months), suggesting that the epidemic wave travels at the speed of about 1,500 km per month (95 percent confidence interval: 1,100, 2,500 km/month).

### Confirmation of seasonal mortality patterns with laboratory surveillance data

The monthly distribution of influenza isolates compiled by Brazil's laboratory surveillance system is presented by region in figure 4. Viral isolates in the north region were detected from November to May, with a major peak in March and a minor one in November, the latter suggesting the presence of an annual and semiannual epidemic cycle in those latitudes. In the northeast region, influenza was isolated in May and August only, in part because of low sampling. In the southeast region, influenza was isolated year-round, but 70 percent of the isolates were found between May and August, and a large peak occurred in May. Viral activity in the southernmost region spanned May to October, with most isolates (67 percent) found in June and July. Laboratory surveillance data therefore broadly confirm mortality patterns, despite the small sample size: Influenza viral activity starts early in equatorial zones and is found progressively later in tropical and subtropical zones of Brazil, with a 3-month lag in peak activity between north and south Brazil. Of note, peak activity occurred 0–1 months earlier in viral isolates than in mortality data, consistent with a few weeks' delay between primary viral infection and death, because of complications from bacterial pneumonia and exacerbation of underlying health conditions (12, 21).

## DISCUSSION

This quantitative analysis of the seasonal patterns in pneumonia and influenza mortality data in Brazilian states revealed an annual "wave" of influenza traveling southward across Brazil over an approximately 3-month period, starting in April in northern equatorial regions and reaching temperate regions of the south in July. Fourier decomposition offered a straightforward means to isolate the key seasonal components of influenza epidemic cycles, enabling us to quantify the amplitude and timing of the major annual peak in each state. Geographic variations in mortality data echoed patterns in laboratory surveillance data.

We also found that the amplitude of the seasonal cycles varied significantly along a latitudinal gradient: amplitude was strongest in southernmost subtropical zones and faded toward the tropics around latitude 15°S. We did not find evidence of further variations in amplitude between latitude 15°S and the northern equatorial zones, mostly represented by the Amazon forest and the coastal states of the northeast. These results are in line with the expected pattern of year-round influenza activity near the equator and increasing seasonal amplitude with (increasing) latitude away from the equator (2).

**TABLE 1. Seasonal components of the pneumonia and influenza monthly mortality time series in Brazilian states, sorted by the latitude of their capitals, 1979–2001***

| Administrative code | Administrative state | Latitude (degrees) | Amplitude (%) | 95% confidence interval on amplitude (%) | Phase (months) | 95% confidence interval on phase (months) |
|---|---|---|---|---|---|---|
| 14 | Roraima | 2.8 | 52.5 | 31.3, 88.0 | 7.9 | 6.6, 9.0 |
| 16 | Amapá | 0.1 | 37.3 | 24.1, 57.2 | 5.1 | 3.7, 6.6 |
| 15 | Pará | −1.5 | 21.6 | 15.3, 28.9 | 5.6 | 5.2, 6.3 |
| 21 | Maranhão | −2.6 | 22.3 | 10.0, 36.7 | 5.9 | 4.7, 6.9 |
| 13 | Amazonas | −3.1 | 17.6 | 6.4, 33.2 | 5.6 | 4.4, 7.5 |
| 23 | Ceará | −3.8 | 39.9 | 30.7, 48.9 | 5.2 | 4.8, 5.5 |
| 22 | Piauí | −5.2 | 30.3 | 18.9, 43.6 | 5.2 | 4.7, 5.7 |
| 24 | Rio Grande Do Norte | −5.8 | 30.6 | 21.8, 42.5 | 5.7 | 5.0, 6.7 |
| 25 | Paraíba | −7.1 | 18.8 | 8.2, 31.7 | 6.1 | 4.9, 7.5 |
| 26 | Pernambuco | −8.1 | 29.0 | 20.8, 38.3 | 5.5 | 5.0, 5.9 |
| 11 | Rondônia | −8.8 | 5.0 | 1.9, 25.7 | 9.6 | 1.6, 12.1 |
| 27 | Alagoas | −9.7 | 27.0 | 18.5, 36.8 | 6.3 | 5.6, 7.0 |
| 12 | Acre | −10.0 | 11.4 | 2.2, 33.8 | 5.2 | 1.5, 11.1 |
| 17 | Tocantins | −10.1 | 16.2 | 4.0, 47.1 | 3.8 | 1.0, 11.8 |
| 28 | Sergipe | −10.9 | 28.9 | 15.3, 45.6 | 6.1 | 5.4, 7.3 |
| 29 | Bahia | −13.0 | 24.3 | 17.8, 32.2 | 5.4 | 4.9, 5.8 |
| 51 | Mato Grosso | −15.5 | 3.7 | 2.0, 25.5 | 3.4 | 0.7, 12.3 |
| 53 | Distrito Federal | −15.8 | 10.5 | 3.1, 22.6 | 8.7 | 6.5, 11.0 |
| 52 | Goiás | −16.7 | 15.7 | 6.2, 29.8 | 7.2 | 5.4, 9.2 |
| 31 | Minas Gerais | −19.9 | 26.1 | 19.7, 32.6 | 7.1 | 6.7, 7.4 |
| 32 | Espírito Santo | −20.3 | 16.6 | 10.5, 24.2 | 6.3 | 5.3, 7.5 |
| 50 | Mato Grosso Do Sul | −20.4 | 24.4 | 15.5, 33.6 | 7.8 | 7.1, 8.4 |
| 33 | Rio De Janeiro | −22.9 | 18.5 | 13.7, 24.7 | 6.1 | 5.3, 6.7 |
| 35 | São Paulo | −23.6 | 29.6 | 25.5, 33.9 | 7.0 | 6.7, 7.3 |
| 41 | Paraná | −25.4 | 37.8 | 32.1, 44.1 | 7.1 | 6.7, 7.3 |
| 42 | Santa Catarina | −27.6 | 40.2 | 36.0, 45.0 | 7.6 | 7.3, 7.8 |
| 43 | Rio Grande Do Sul | −30.1 | 46.7 | 41.7, 52.4 | 7.6 | 7.4, 7.8 |
|  | All of Brazil | −15.8 | 29.0 | 28.1, 35.7 | 7.0 | 6.7, 7.2 |

* Phase (timing) and amplitude were derived from a Fourier analysis and correspond to the major annual peak of activity (first harmonic); refer to the online supplementary material for details on confidence intervals. Also refer to the map of states in figure 1, labeled by their administrative codes.

There are caveats relating to the use of pneumonia and influenza mortality data to study the timing and amplitude of influenza activity. Indeed, a fraction of the deaths modeled are not influenza related and may be caused by other respiratory pathogens. A number of studies support the use of pneumonia and influenza mortality data as a reliable proxy for studying the timing and amplitude of influenza activity in several countries (1, 12, 13, 22). Moreover, in this study, the timing of regional peaks in laboratory-confirmed influenza surveillance data coincided with peaks in mortality data, further supporting the finding that influenza drives the identified traveling wave. An additional limitation of this study is the use of administrative capitals as population centers of entire states. This choice is well justified, however, because most capitals occupy a central latitudinal position in each state, and approximately 20–25 percent of the population is concentrated in the state capitals (14). Additionally, the main study findings were robust to using state geographic centers instead of population centers (supplementary figure 2).

This study found a robust pattern in the timing of influenza epidemic peaks, ranging from equatorial ‘‘autumn’’ to subtropical winter along the north-south axis. While it has previously been reported that clinical cases of influenza peak between May and September in Brazil (23), we document here the interregional seasonal variations with latitude in this country. Moreover, this is the first known quantitative evidence of a traveling wave of influenza along

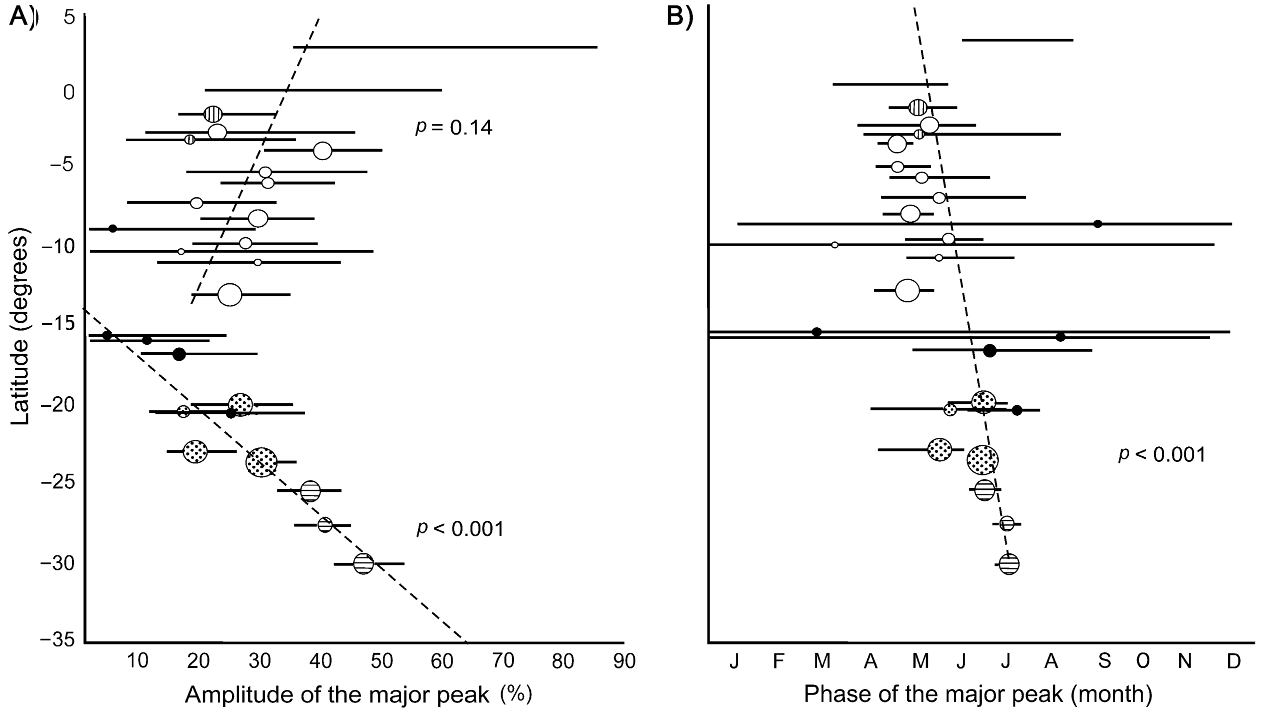

**FIGURE 3.** Variations in seasonal influenza patterns with latitude and the traveling wave across Brazilian states, 1979–2001. Latitudes of state capitals are plotted against characteristics of the annual peak of pneumonia and influenza monthly mortality time series in each state (based on the first harmonic obtained by Fourier decomposition): A) relative peak amplitude; B) peak timing. Circle sizes are proportional to the population size of each state ($\log_{10}$ scale). Dashed lines show the best-fit significant statistical relation (weighted regression) between seasonal parameters and latitudes; continuous lines are 95% confidence intervals on seasonal parameters. Line patterns represent different regions, as indicated in figure 1.

a north-south axis in a large contiguous region, spanning more than 35 degrees of latitude across equatorial and (sub)-tropical zones. It is important to note that our analysis focused on indicators of peak activity rather than epidemic onset or the entire period of disease activity. Crude pneumonia and influenza mortality peaks were found to be a good proxy for overall epidemic timing in US states (12) but could be less accurate in Brazil, where influenza activity lingers for several months. Hence, in this study, we did not use crude peaks but Fourier-processed peaks instead, because the Fourier approach can identify an average "center of mass" of epidemic activity in Brazilian states. The intriguing traveling wave of influenza in Brazil originates from equatorial and low-population regions in the north and moves toward temperate and highly populous regions in the south (figure 3). In Brazil, surface and air travel are associated with population patterns; people travel primarily between large population centers (as in the United States (13)). Hence, the southward traveling wave of influenza in Brazil goes against patterns in population sizes and movement of people. This finding is intriguing since a recent analysis of influenza in the United States revealed that population factors were key determinants of regional disease spread via rates of movement of people to and from work (13). We would have therefore expected influenza to spread from the most populous and well-connected urban centers, such as São Paulo and Rio de Janeiro, located in the south.

Two factors may explain the differences in influenza spread between Brazil and the United States. First, although Brazil is almost the same size as the United States, Brazil is less densely populated (24) and has a weaker transportation infrastructure—mainly in the sparely populated northern region—perhaps resulting in less population mixing. Second, the geographic situation in the two countries is different. Brazil extends across approximately 35 degrees of latitude in equatorial-tropical zones, whereas the continental United States extends across about 20 degrees of latitude in temperate zones. Hence, in well-mixed and temperate regions such as the United States, population factors drive the timing and spread of epidemics (13); in less-mixed and climatologically diverse regions such as Brazil, environmental factors may be the main driver of regional disease spread.

A variety of social, demographic, and environmental factors may contribute to geographic patterns of influenza in Brazil. Children are thought to play a key role in the local transmission of influenza in both families and schools (25, 26). However, school closure patterns are an unlikely explanation for the observed geographic differences in influenza seasonality, since Brazilian children have the same annual school cycle throughout the entire country. Although

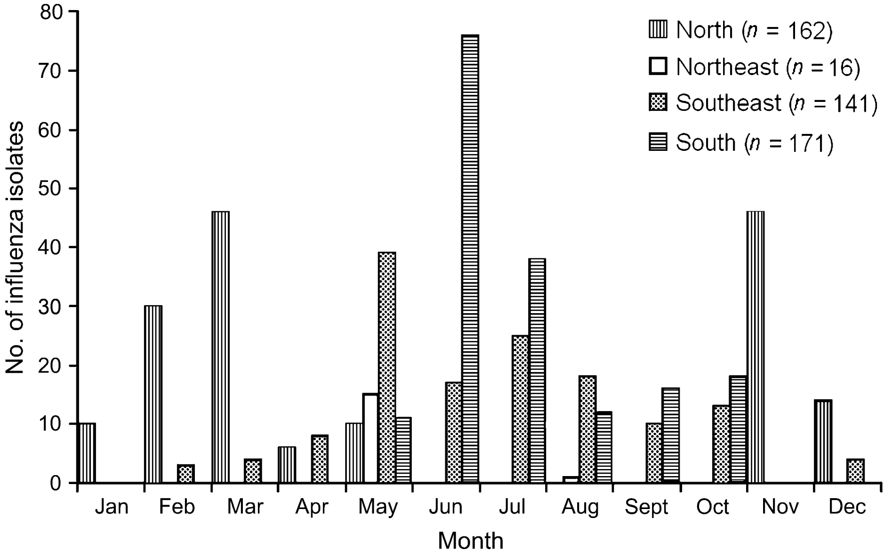

**FIGURE 4.** Monthly number of laboratory-confirmed influenza isolates during the period 2000–2005, as collected from sentinel units in four administrative regions of Brazil (refer to the map in figure 1). No data for the Central-West region. Line patterns represent different regions, as indicated in figure 1.

differences in birth rates between states could give rise to differences in disease dynamics (17), birth rates have declined nearly twofold over the study period in all states without noticeable changes in seasonal patterns of influenza (refer to DATASUS (10) and supplementary figure 1). Hence, we found no obvious variations in demographics to explain the observed patterns. It is also worth noting that variations in environmental factors are thought to have stronger effects on disease dynamics than variations in birth rates (5).

Geographic distances could possibly determine disease spread. The north of Brazil is geographically closer to the Northern Hemisphere, a more densely populated region from which influenza viruses could be reintroduced annually, earlier in the season than in the rest of Brazil. However, the importance of the international air transportation network in disseminating influenza between countries (27), and the intense passenger air traffic between the Northern Hemisphere and large cities in the southern regions of Brazil, mainly the southeastern megalopolis of São Paulo and Rio de Janeiro, considerably undermine this hypothesis.

If factors related to demographics, school calendars, population, geography, or the international air transportation network cannot explain the traveling wave of influenza in Brazil, we need to consider climatic triggers. The reasons for the marked seasonality of influenza in temperate areas of the world, and the less well defined seasonality in tropical and subtropical areas, remain unclear (28, 29). Physiologic and behavioral aspects have been hypothesized to explain the dramatic increase in cases of human influenza during colder months in temperate regions. Influenza viruses are released in droplets in the environment from nasopharyngeal secretions, and the virus survives longer in cold temperatures (30). Viral transmission is especially favored by certain conditions such as confinement in closed spaces and low humidity (30), while both excessive rain and low temperatures could stimulate human proximity (9).

Physiologic stress caused by extreme climate conditions could also affect the host response by increasing vulnerability to infection (6, 30). In low-latitude regions in which variations in temperature are not generally an important source of physiologic stress, heat and high humidity have been suggested to enhance virus survival and drive epidemic timing (31). Accordingly, in Brazil, high levels of humidity coincide with influenza activity near equatorial regions (north), while colder temperatures are associated with increased viral activity in winter months in subtropical regions (south). However, in Brazil as in other regions of the world, the association between influenza and climate or meteorology is prone to many confounding factors (32). Our favored hypothesis is that a combination of environmental and population determinants may together affect the traveling wave, where the climatology has to be right for a seeded virus to gain a foothold in a region and cause an epidemic. Clearly, further controlled experiments and epidemiologic studies are warranted to fully understand the seasonal triggers of influenza globally.

By linking temporal patterns in viral surveillance data with peaks in appropriately transformed mortality data for Brazil, this study has demonstrated that mortality data can be used to characterize seasonal patterns of influenza in the Tropics—even for countries with limited laboratory surveillance. Future studies could seek to quantify the mortality burden of tropical influenza for the whole population and for specific age groups. In temperate climates such as in the United States, excess mortality studies are commonly used to assess disease burden and evaluate the benefits of vaccination strategies (15). Aside from recent studies in a few places in southeast Asia (4), such evaluations have not been attempted in the Tropics because traditional excess mortality models cannot accommodate less well defined seasonal patterns in influenza activity unless there is intense virologic surveillance (2). In addition to demonstrating the existence of a mortality impact of influenza, a better understanding of seasonal drivers can also help toward efforts to control the disease, such as better guiding the timing and composition of influenza vaccine to be used in (sub)tropical regions (2). Vaccine recommendations for the Northern Hemisphere could be more appropriate for some countries in the Southern Hemisphere near the equator, which is becoming increasingly important as more tropical countries introduce and use substantial quantities of vaccine (33).

In conclusion, important insight into the regional circulation of influenza viruses can be deduced from studying mortality patterns (e.g., this study and those by Viboud et al. (13, 22)). We anticipate that large-scale sequencing of whole influenza genomes collected over several seasons in many countries will be a more powerful way to elucidate the spatiotemporal movements of viruses in the near future (34). The Tropics are a particularly important sampling location in this respect since year-round viral activity in this region could serve as a reservoir for human influenza, ensuring global persistence of the disease and early display of new virus variants.

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