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Influenza's Response to Climatic Variability in the Tropical Climate: Case Study Cuba

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Abstract

Background: Increase of climatic variability is influencing the behavior of influenza that causes acute respiratory infections.

Objective: To determine the mechanisms of influenza response to climate variability.

Methods: An ecological study with retrospective analysis of time series of Influenza and climatic, combined with the techniques of exploratory data analysis and correlation analysis with and without delay was performed. Influenza data (2010-2017) and climatic anomalies described by the Bultó climatic indexes were considered. For trend the Spearman and Kendall-Mannt coefficients were used. Cluster analysis of months and regions of Influenza was used. Kriging method combined with the inverse distance at 20 km^2 and weight matrix by the "queen" method of second order of contiguity was used, the spatial autocorrelation by the Moran's I, the Moran's correlograms and the Local Space Association Indicators were calculated.

Results: Influenza shows a circulation increase in the months of rainy season (May-October) with cycles of 2 years and a clear association with the climate variability. High humidity, temperature and precipitation predominated Influenza has a global tendency to decrease with a high persistence or serial correlation. It reaches a value of the Mann Statistician, 2.012 (0.0001) in the year 2010, however it decreases in time. Cumulative effect up to 2 months of the climate in the Influenza, with a correlation of 0.30 ($p<0.0043$) and 0.35 ($p<0.00051$) was evidenced. With a strong spatial correlation (Moran's $I>0.4136$ during July), the central region showed the higher circulation.

Conclusions: Influenza responds to climatic variability mainly during the rainy season (May-October), period in which high humidity, temperature combined with low pressures favor the viral circulation, condition the pH in the respiratory tract, leading to additional acidification of the local areas of the respiratory system.

Keywords: Climatic variability; Influenza seasonality; Response mechanisms; Respiratory infection; Tropical diseases

Introduction

Climatic variability, as a primary expression of the climate change, is the most significant environmental problem that humanity will face in the next years [1]. It is playing an important role in the increase of Influenza circulation, contributing to the burden of Acute Respiratory Infections (ARIs) [2]. ARIs are the main cause of morbidity and one of the leading causes of death at world level [3].

Influenza is considered the most contagious of the ARIs and the causative agent is influenza virus [4]. This infection affects people of all ages and spreads easily and in schools, community homes and workplaces with a negative social and economic impact by income loss though the size reduction of the workforce and the productivity, increases of the absenteeism, and interruption of the economic activity [5].

The clinical spectrum can range from Influenza like Illness (ILI) of mild course to a Severe Acute Respiratory Infection (SARIs) that usually requires hospitalization in Intensive Care Units and can lead to death. The World Health Organization (WHO) estimates that seasonal Influenza viruses cause approximately 3-5 million cases, 250,000-500,000 deaths and 200,000 hospitalizations annually [6]. In Americas Region 80000 deaths due to Influenza are estimated annually [7]. In the most serious Influenza pandemic occurred in 1918 caused by influenza A (H1N1) with an estimated of more than 20 million deaths in two years [8,9].

Influenza viruses are classified in: influenza type A, B and C. Being types A and B the most important in terms of human disease. [10]. Both show a similar genetic and structure, but differ in their biological, evolutionary and epidemiological characteristics [11,12]. The annual Influenza burden differs unpredictably from year to year, between age groups and from region to region [13-15]. There are several factors that can influence the seasonality of Influenza viruses such as the antigenic drift and antigenic change, the host immune response, social and climatic factors and solar radiation [16-18]. Information on seasonal

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patterns remains limited in the large regions of Central America [19]. Further studies should link the latitudinal gradients of the seasonality of influenza epidemics with the climatic elements [20].

Influenza viruses have a well-defined seasonal pattern [21,22] in countries with a temperate climate, with epidemics during the winter season (northern hemisphere: December-April and southern hemisphere: June-September) [23-26]. Humid and rainy conditions favor the viral activity in the tropical regions [23,27,28]. Three patterns have been observed: 1) Infections that occur throughout the year with peaks related to the rainy season, 2) Infections that occur throughout the year with biannual peaks associated with the rainy season, 3) Infections that occur without a clear seasonality [29-32].

In Cuba, influenza and pneumonia constitute the fourth cause of death and the first cause death by infectious diseases [33,34]. Since 2000, the Cuban Ministry of Public Health (MINSAP) has implemented a comprehensive ARI Care and Control Program, for the prevention and control of these infections [35]. The vaccination campaign is the main strategy to reduce the burden of influenza disease and vaccination is started before the seasonal months [36]. Therefore, the surveillance of climate variability that seasonal influenza can have as a prerequisite for pandemic preparedness and response is of vital importance. For this reason, knowing the epidemiology, the seasonal pattern of influenza viruses and the influence by climate is important in the planning of treatment and control strategies and allows defining when to vaccinate and which vaccine formulation to apply [22].

Besides the identification of the relationships between climatic variables and viruses, it is also necessary to understand and explain the mechanisms of biotropic responses of influenza viruses to several climatic conditions (interacting all climate-forming variables) described as climatic indexes of Bultó (BIs). Our study intends to understand the effects of climate changes and climatic conditions that favor the circulation of influenza in a tropical country such as Cuba, which allows anticipating their behavior, making maps of risk and formulate prediction models according climatic conditions. At the same time, the results may constitute valuable scientific information to update and refine the National Program for the Prevention and Control of ARI and regional and global influenza surveillance programs.

Materials and Methods

Climatic characteristics of cuba

Cuba is a tropical country located at the Caribbean Sea (Figure 1), with a rainy season in the summer (Aw, according to Köppen climate classification). The average of annual temperature ranges from 24°C to 26°C being higher in the lowlands and on the eastern coast, with temperatures lower than 20°C in the highest parts of the Sierra Maestra in Santiago de Cuba province. Despite its tropical condition, some seasonal characteristics are present in its thermal regime, with two well-known seasons: summer (rainy season) from May to October, being July and August the warmest months; and winter (less rainy season) from November to April, being January and February the coldest months. The national average rain record is 1335 mm; however, drought events recurrently occur, that can persist for several years [37]. The country has a population of 11,239,224 inhabitants [38].

Study design: An ecological study with retrospective analysis of time series, combined with techniques of exploratory data analysis (EDA) was conducted. Correlation analysis with and without delay, considered different indicators, was carried out:

Figure 1: Map of Cuba, provincial distribution.

Climatic data

The monthly series of climatic variables (2011-2017) to calculate the Bultó's indexes were obtained from the climate station network of the Meteorology Institute.

For the calculation of the incidence, data of the main climatic variables corresponding to the Casablanca station of the climatologic network of the Meteorology Institute were used. These include monthly series of: dissolved oxygen density in air (g/m^2), maximum and minimum mean air temperatures (°C), average thermal air oscillation (°C), average relative air humidity (%), (mm), mean atmospheric pressure at sea level (hpa), total precipitation (mm) and the number of days with precipitation 0.1 mm from which the two climatic indexes (BIt, 1, c), whose expression is generated from the analysis of time series of the climatic variables described above, applying techniques of multivariate analysis of main components to generate the weights or contributions of the variables to each index, obtaining the orthogonal functions whose expression is given by the equation:

$$BI_{r,t,p} = \sum_{1}^{n} \alpha_{\varepsilon}\left[\frac{\omega_{\varepsilon,t} - \varpi_{\varepsilon}}{\sigma_{\varepsilon}}\right] \qquad (1)$$

Where:

BI r, t, p: Bultó index, "r" is the index number of the index, "t" represents the months, and "p" is the country or area of study.

ε: Parameter describing the elements of the climate, which characterize the study region.

αε: Coefficients that define the weight for each element.

ω ε, t: It is the series of the climatic element ε at time t.

ϖ ε: Mean values of the elements of the climate.

σε: Standard deviation of the climatic element ωε,

Interpretation of Bultó complex climate indexes

BIt, 1, c describes inter-monthly and inter-seasonal variation; Includes maximum and minimum mean temperature, precipitation, atmospheric pressure, vapor pressure, and relative humidity.

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BIt, 2, c describe seasonal and inter-annual variation; Includes solar radiation and sunshine duration as factors that affect temperature and humidity. Positive values are associated with a high solar energy level.

Influenza microbiological data

Influenza data corresponds to the period of January/2010 to December/2017, with a total of 25,219 clinical samples (nasal and nasopharyngeal exudate, pharyngeal lavage) collected from several provinces during outbreaks reported in closed institutions. Samples following the criteria established by the program for virological surveillance were taken. Patient without age limit were included with acute infection of the upper or lower respiratory tract, with no more than ten days since onset of symptoms, and voluntariness for the sample taking with the purpose of performing virological diagnosis of influenza, severe acute respiratory infection, bronchiolitis and pertussis syndrome [39-42].

A total of 4315 (17%) positive samples Influenza A and B, by provinces and month were analyzed. Data source were obtained in the sentinel hospitals and ambulatory services from all provinces and sent to the National Reference Laboratory (NRL) at the "Pedro Kouri" Institute of Tropical Medicine, ARI diagnostic and surveillance of possible viral etiology. Real-Time Polymerase Chain Reaction assay (RT-PCR) for FLU detection was used, the rapid influenza type and subtype diagnostic, including H5N1 avian influenza virus and differential diagnosis with other respiratory viruses [43].

Statistical methods

Exploratory Data Analysis (EDA), for the description of statistical characteristics of the climatic and virological information was used, as well as to characterize the distribution by months (box plot); besides, the graphs of parallel profiles for identification of the viruses' responses to climate variations [44].

The analysis of trend and determination of change points was carried out with the nonparametric tests: Spearman coefficient and Kendall-Mannt. The Spearman coefficient test [45] determines whether or not there is a significant trend in a time series. The statistician test is:

$$r_s = 1 - \frac{6}{n\left(n^2-1\right)} \sum_{i=1}^{n} \left(y_i - 1\right)^2 \qquad (2)$$

The null hypothesis was: no trend existence. The null hypothesis is accepted or refused at a level α0 according to α1>α0 or α1<α0. In this study α0=0.05 was taken. The trend is increasing if rs>0 and is decreasing if rs<0.

The Kendall-Mann test [46] determines whether or not there is a global trend in a time series. The test statistician:

$$\mu(t) = \frac{[t-E(t)]}{\sqrt{\text{var } t}} \qquad (3)$$

Where,

$$\alpha_1 = P(P(|\mu|) > |\mu(t)|)$$

When the values μ (tn) are significant, it concludes with an increasing or decreasing tendency depending on μ (tn)>0 μ (tn)<0. The series μ(tn)'and μ(tn) are plotted and in the case of a significant trend the intersection of the curves locates approximately the beginning of this.

Cluster analysis for grouping the months and areas

Cluster method is a multivariate statistical procedure that begins with a set of data that is intended to reorganize into relatively homogeneous groups called clusters. The objective is to order observations in groups, in such way that the degree of natural association is high among members of the same group and low among members of different groups [46,47].

In this investigation the agglomerative hierarchical method for the determination of the groups was applied. The method of complete amalgamation as a criterion for formation of conglomerates was used [46]. At the same time the measure of association used were:

Distance (city block) Manhattan

D (i, j) = S| xki - xkj | (4)

Distance de Chebyshev

D (i, j) = Max| xki - xkj | (5)

One of the problems of this method is the representation of the natural structure of the data, when determining the ideal number of clusters. To solve this problem a heuristic procedure was used, where the melting value of each stage is compared with the average of the melting values added to product of a constant by the quasi-standard deviation of the melting values. When a fusion value exceeds this amount, it is concluded that the preceding level is the one that originates the optimal solution. The optimal value for this constant must be 1.25. The visual form of this analysis is through dendograms.

Spatial analysis

To address this analysis, the implementation of several spatial statistics techniques was carried out being, developed in three stages. The first one was to generate a grid with continuous information of 600 nodes (raster format), that is, transform the information of a finite number of samples into a continuous space that allow knowing the pattern of variation in the area and that is comparable with the observed in the sample, as well as to characterize areas where information is not available. For this, the Kriging method combined with the inverse distance method (IDW) [29,48,49] was implemented, with the aim of interpolating, with information in the entire study domain, at a resolution of 20 km^2.

Finally, in the second stage, through the concept of spatial autocorrelation, the use of exploratory analysis of spatial data, the calculation of the Moran´s I, the correlations of Moran and Local Indicators of Space Association (LISA) [50,51], allowed to identify the areas of hot and cold spots from the use of the weight matrix determined by the second-order contiguity "queen" method [52].

For the processing of the series trends and the generation of the different maps at spatial scale, the statistical software S-Plus 2000, GS-plus 10.0, Sigma Plot 10.0, Statistical 7 and GIS, ArcGIS 10.1 and WinStat.V1.0 were used.

Results

Positive samples of Influenza were significant with a pattern to decreasing over time.

The most significant month turned out was July, although it is valid to remember that the year 2010 was pandemic, resulting in an increase in April (Table 1).

The spatial distribution of virus positivity is also shown, resulting in the central provinces where it circulates with greater stability (Table 2).

Months/Year	2010	2011	2012	2013	2014	2015	2016	2017
1	0,46	0,49	0,23	0,6	0,49	0,63	0,32	0,23
2	0,70	0,37	0,09	1,02	0,35	0,56	0,46	0,32
3	2,20	0,35	0,42	0,65	0,23	0,37	0,32	0,21
4	7,93	0,25	0,16	1,9	0	0,3	0,23	0,25
5	4,98	0,05	0,86	3,36	0,02	0,3	0,72	0,28
6	2,13	0,72	2,32	4,89	0,05	1,23	0,81	0,67
7	1,74	2,41	1,65	3,15	0,12	3,43	0,63	0,83
8	3,04	2,9	1,37	1,81	0,16	1,92	0,63	0,14
9	2,90	0,3	0,76	1,3	0,93	1,48	1,55	0,00
10	1,65	0,05	0,63	1,46	1,21	1,37	1,27	0,09
11	1,02	0,16	0,63	1,27	1,88	1,48	0,51	0,07
12	0,49	0,16	0,3	0,65	0,97	0,74	0,12	0,21

Table 1: Percentage of positive Influenza samples by month and year, 2010–2017

Province/ Months	1	2	3	4	5	6	7	8	9	10	11	12
MAY	0,02	0,093	0,046	0,209	0,093	0,301	0,162	0,209	0,162	0,093	0,093	0,046
ART	0,14	0,07	0,116	0,116	0,046	0,255	0,371	0,324	0,44	0,185	0,232	0,232
CA	0,12	0,023	0,023	0,209	0,324	0,209	0,301	0,232	0,185	0,371	0,139	0,093
CF	0,21	0,348	0,232	0,232	0,51	0,185	0,394	0,603	1,182	0,348	0,324	0,093
CM	0,28	0,023	0,278	0,788	2,109	1,599	1,136	0,672	0,556	0,811	0,695	0,07
GM	0,02	0,093	0,185	0,718	0,904	1,089	0,927	1,136	0,695	0,093	0,209	0,046
GT	0,14	0,046	0,185	0,255	0,278	0,255	0,278	0,556	0,718	0,324	0,603	0,185
HG	0,23	0,394	0,209	0,742	1,159	2,781	1,205	1,437	0,997	1,228	0,579	0,209
IJ	0,12	0,07	0	0,07	0,185	0,162	0,023	0,046	0	0,023	0	0
LH	0,53	0,927	2,039	3,963	1,251	1,321	2,804	1,553	1,761	1,321	0,927	0,672
LT	0,14	0,07	0,046	0,348	0,649	0,417	0,463	0,417	0,695	0,255	0,185	0,185
MT	0,25	0,348	0,278	0,348	0,301	0,278	0,904	0,44	0,626	0,463	0,394	0,301
PR	0,07	0,07	0,324	0,973	1,275	0,742	0,417	0,927	0,834	0,162	0,07	0,139
SC	0,39	0,301	0,093	0,44	0,487	1,02	1,136	1,112	1,39	0,579	0,672	0,324
SS	0,09	0,371	0,209	0,603	0,417	0,579	0,811	0,649	0,255	0,278	0,139	0,185
VC	0,70	0,626	0,487	1,02	0,603	1,066	0,927	1,159	1,321	1,437	1645	0,834

Table 2: Percentage of positive Influenza samples by province and month

The pattern of influenza circulation, changes every year with cyclicity every 2 years, showing patterns of different behaviors, of the viral circulation, which is mainly concentrated in the months corresponding to the rainy period (Figure 2).

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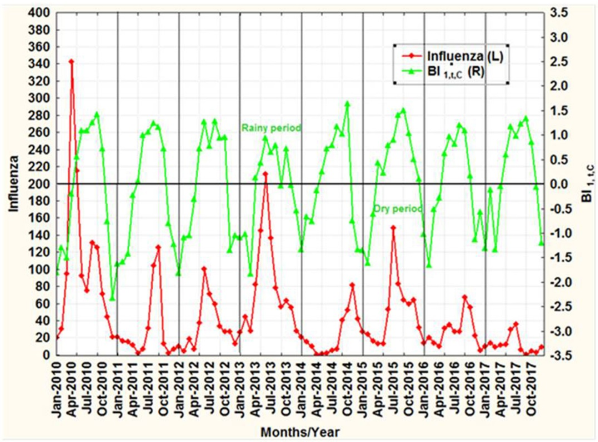

Figure 2: Temporal behavior of influenza in Cuba. Period January 2010-December 2017

The trend of influenza circulation is shown, with increasing level. This is a very important aspect when determining the epidemiological baseline to define the threshold and the seasonal pattern, in which influenza viruses present a global tendency to decrease with a high persistence or serial correlation (Table 3).

Identification of the months of viral circulation according to their seasonal variation (Figure 4).

There is a clear association between the seasonal climate pattern and influenza viruses circulation, characterized by an increase in circulation in the months corresponding to the rainy season, with a change in the transition months to a low circulation in dry season (Figure 5).

As well as, one can observe the considerable increase in the pandemic year 2010 and the tendency to decrease over time (Figure 3).

The high non-linear association between the seasonality of climatic variability and influenza viruses through climatic indices BI1, t, c and BI2, t, c is corroborated. The moments of greatest activity are the months corresponding to the rainy and warm periods (Figure 6).

Analysis of the spatial structure and its grouping

The results of the grouping by provinces are shown, which indicate us that distribution of viral circulation in the country is not at random, but behaves with an aggregation structure, observing that there is a spatial trend, because in all the zones or regions the Influenza does not circulate in the same way, having a greater preference towards the central region, with a marked heterogeneity and dispersion other regions (Figure 7).

Variable	Estadígrafos	Valor	p
Virus	Spearman	-1.83648	0.0000**
Influenza	Kendall – Mann	-1.94039	0.0000 **

Table 3: Values of Spearman and Kendall-Mann statisticians corresponding to the circulation of influenza viruses (** p< α= 0.01)

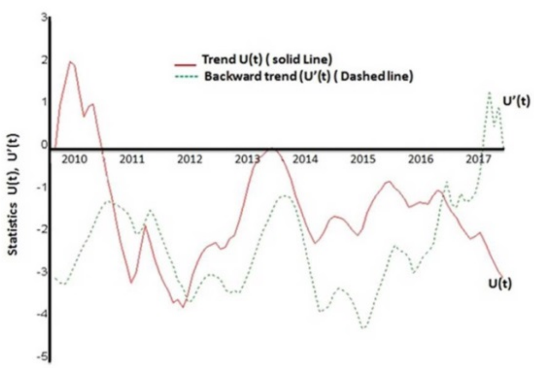

Figure 3: Direct series (continuous line) and retrograde (dashed line) of the Kendall-Mann (KM) statistician for the circulation of influenza viruses

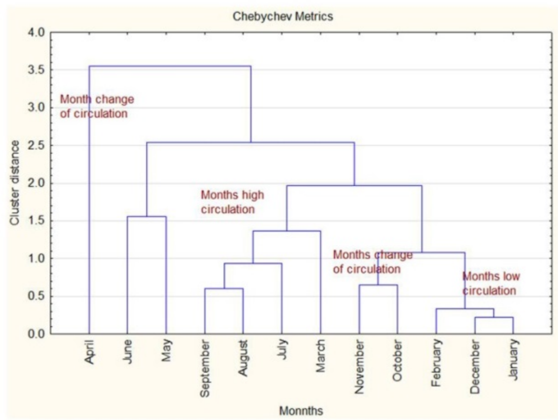

Figure 4: shows the pattern of influenza circulation by months. A preference of influenza circulation for some month's low circulations in other is observed.

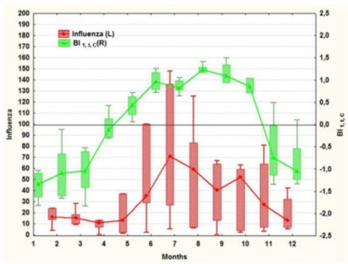

Figure 5: Seasonal pattern of influenza viruses according to the climatic variability described by BI1, t, c. (positive values: rainy period and negative values: dry period)

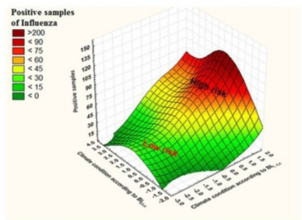

Figure 6: Response of influenza viruses to the climatic variability described by BI1, t, C (positive values: rainy period and negative values: dry period) and BI2, t, C

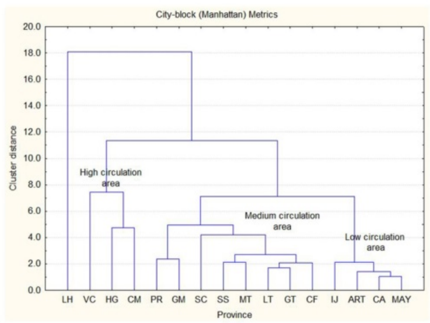

Figure 7: Dendrogram corresponding to the spatial variation according to the level influenza virus circulation in the country

Correlograms of Moran's I

The graphic representation and Moran's I values, for each of the different months, show evidence of a strong positive spatial autocorrelation, with delay distances ranging from 5 to 20 kilometers according to spatial resolution (Figure 8).

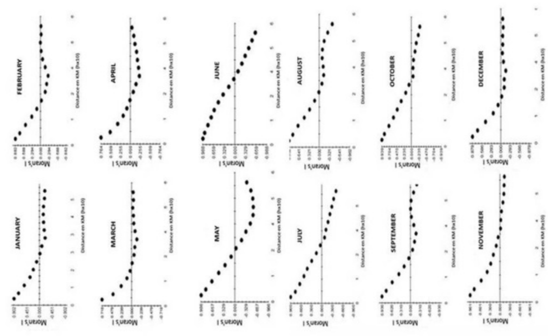

Figure 8: Temporal correlogram of the Moran index for the months of January to December

Influence of climatic variations described by BI 1, t, c on influenza viruses in a spatial scale

Table 4 shows the results of the multivariate Moran's I where, a strong positive spatial autocorrelation, between influenza and climate variations, given by BI, is observed. The influence of the climate on the formation of conglomerate or significant aggregation of high-low values (positive autocorrelation I>0) in the area with similar behaviors within the months of the same seasonal period, but slightly changing from one period to another is also shown.

A spatial structure of influence between the climatic conditions of each area and the response of the influenza virus's circulation is inferred. As the correlations are positive, this indicates that there is an association between the similar values of both indicators and nearby localities, resulting the month of July with the largest spatial association: Moran's I>0.41 (Table 4).

Spatial variation of the seasonal pattern of influenza viruses with climate variability

In the maps, the spatial distribution of the influenza viruses and the spatial responses to the climatic characteristics are shown, where the climate index (left of the graph) clearly describes the variation ranges of the climate pattern for Cuba, leaving defined the dry period (values negative of BI1, t, c, are lower than-0.75), the rainy period (positive values of BI1, t, c with a range greater than 0.75) and the transition months with ranges that range between -0.75 and 0.75. When analyzing the spatial behavior of influenza viruses, the areas of activity is observed both during the months of low and high circulation; despite circulation throughout the year is not present equally in all regions of the country. Viruses have a greater preference for the central region circulating throughout the year. However, the highest activity of viral circulation occurs in the provinces with the largest population (Havana and Santiago de Cuba) (Figure 9).

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Mechanisms of response between relationships

The relationships between climate variability and influenza viruses are not spurious, are justified, because the period of greatest viral circulation, coincides with the climatic period of higher humidity combined with high temperatures and low insolation because it increases the cloudiness, due to the marked influence of a low pressure center on the country leading to high climate variability, conditions that favor over saturation and condensation in the respiratory tract, aspects that coincide with other findings reported in the literature and that allow us to explain the mechanisms of response of the virus to climatic variability, and therefore explain the difference of the seasonal pattern of influenza in the tropics.

Meses	Valor de la I de Moran entre la Influenza/IB1,t,c	p*
E	0.2255	0.029
F	0.2295	0.014
M	0.2728	0.001
A	0.2018	0.045
M	0.3121	0.009
J	0.3743	0.003
J	0.4136	0.000
A	0.4028	0.000
S	0.4018	0.000
O	0.3878	0.000
N	0.3691	0.004
D	0.3732	0.001

Table 4: Spatial correlation given by the Multivariate Moran Index regarding to the effect of climatic variations described by BI1, t, c and influenza viruses (p*< α= 0.05)

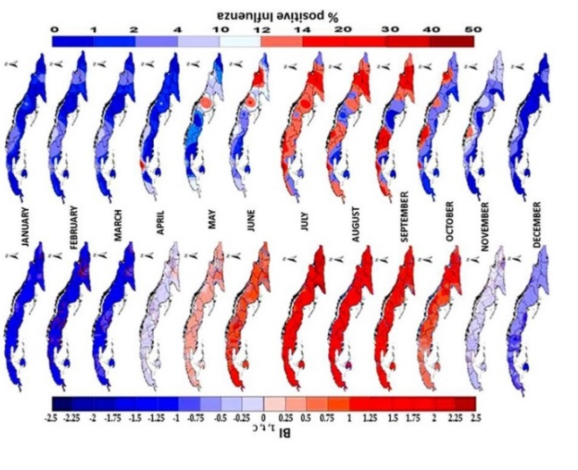

Figure 9: Spatial distribution of influenza viruses (right) in correspondence with the climatic variability for the months of January to December according to the climatic index BI 1, t, c (Left). Period 2010-2017

Discussion

Multi-year variation

The strong association of the temporal behavior pattern of Influenza and its association with climatic variability, where the conditions are warmer, wetter, and rainy, many cloudy days and less insolation or light hours with a predominance of low pressures has clearly evidenced. The increase in the Influenza virus circulation this means the pattern of behavior, has a preference for the months of May-September, although it does not manifest itself with the same intensity in all years. This suggests a dynamic seasonal pattern, with a change in tendency, this may favor these conditions to some process that leads to the increase of sensitivity in human beings. These coincide with the described by others, who identified many of these variables but with independent analyzes [53,54].

Analysis of the influenza virus series trend

We cannot confirm that in the studied period there was a clear global trend in the behavior of the influenza series, which is in accordance with the climatic trend that has remained oscillating. However, when analyzing the Mann statistician, some periods that increasing trend such as 2010 are observed, in which the statistician reached a value of 2012, highly significant, as well as in 2014, where it shows a new tendency to increase, but not significant. This pattern coincides with epidemic conditions in the country with a high report of respiratory infection cases associated with of influenza virus circulation. The rest of the period marked an oscillation and the trend to decrease predominated, being its minimum during 2012 and 2013 which a changed pattern with respect to previous years, when very significant epidemic conditions were found and which are within the pattern of behavior in the series. This aspect must be addressed when incorporating these behaviors in the prognostic models that are proposed.

A period of high circulation, followed by another period of low circulation was identified, confirming that viral activity manifests itself in the rainy season, with two change periods: April when it goes from low to high values and November-October when it transits from high to low values. It is confirmed that we are in the presence of a marked seasonality and that this could corresponds with the climate pattern that describes the Cuban climate.

The virus circulation showed a marked seasonality, circulating throughout the year, with a greater incidence in the months of May-September during 2011-2017 excluding the pandemic period of 2010, which agrees with is in agreement with those previously reported for Cuba [26].

It is evident that the affectations in the virus presence are due to the climatic variations described by the climatic indexes (BI1, t, c e BI2, t, c), corresponding to the months of the rainy period (May-October) and to transition months (April and October), combined with other environmental factors that favor the viruses circulation and multiplication.

The reason of a few months with low and others with high circulation is explained for the first case because the climatic conditions are not favorable for viral circulation. While in the months of high circulation, conditions are favorable to high humidity, increased precipitation which brings associated low insolation and greater number of cloudy days, due to the influence of low pressures on the country, which favor high levels of circulation as reported in other studies [2].

Aspects that are well reflected in the climatic indices (BI1, t, c and BI2, t, c) when taking ranges of values higher than 1,033. This shows that the climate has an effect on the pattern of the circulation, which has a cumulative influence on influenza viruses, which begins to manifest itself the following month and lasts up to two months later with a strong association for the first month with a correlation of 0.30 (0.0043) and for the second month of 0.35 (0.00051), both are statistically significant.

The seasonal and multiannual variations of the influenza viruses found in this study under tropical climate conditions confirm the findings reported by others, that viral activity is modified by seasonal and non-seasonal variations of the climatic elements [20,26].

The relationship between the seasonal pattern of influenza viruses and the seasonal climate pattern and their levels of significance were analyzed, which describe and corroborate the difference between both patterns. It is interesting to focus on the variation between months, something very important at the time of the modeling, because in the most classic approaches, what is done is to eliminate the pandemic year 2010, thus the MEM method proceeds, which considers the year 2010 as anomalous, affects the historical behavior of the series, which does not let to be true [55,56]. For this reason it is then eliminated, coinciding with the seasonal pattern of influenza viruses and the rainy period where climatic variability increases [26]. These variations are significant, even when climate of Cuba does not have the four typical seasons described for high latitudes but those observed at the tropical region with the traditional two large periods are observed [57].

Our results support that climate influences the seasonal pattern of influenza viruses and it has a high association with the pattern of climate variability. However we also observed that there is important to know the cumulative effect of climate on influenza that is an important element to raise a model. This was determined from when it begins to manifest and in what time the climate interacts with the viruses. It was evidenced that the climate has an effect on influenza viruses that begins to manifest itself the following month and lasts up to 2 months. This means that the viral response does not appear immediately after the climatic anomaly, but that its effects are observed the following month, having the climate a cumulative effect on the viruses.

The pattern of the influenza circulation responds to the climatic characteristics; with values of the climatic index of Bultó reflect the changes of the atmosphere circulation in Cuba where the index takes the positive values during the months of the rainy period associated with the establishment of the Azores-Bermuda anticyclone (bringing warmer and more humid air masses over the country). This favors a high frequency of cloudy days, with a reduction in the thermal amplitude and an increase in the frequency of rainy days, leading to a decrease in daylight hours. The index values that describe the variations of the transition months are not characterized in a similar way, or with the same intensity. The months corresponding to the dry season are associated to the influence of extra tropical phenomena and the greater or smaller influence of the continental anticyclone on Cuba. This defines the beginning of the flow of dry and cold air from the West that is characterized to the increase in drier, less warm days with a rise in thermal amplitude and a decrease in the frequency of rainy days [57]. The BI index describes a configuration that matches with has been described [57] and with the regionalization of the climate index [40].

Spatial analysis

There is also a clear seasonality on the spatial scale although it is not the same in all regions of the country. The central region reports more outbreaks; however, even though the virus remains circulating almost the whole year, those are not the provinces with the higher virus circulation. The central region is characterized by presenting the larger plain areas probably due to the physical-geographical position, high humidity; many consecutive days with precipitation associated with low pressure centers and more cloudiness causing low insolation that constitute favorable conditions for the viral circulation [58].

It is remarkable that particularly in the central provinces the viral circulation begins in the months of low circulation. It is also important to note that when the viral activity begins to increase in the peak months, the provinces with the highest population density (Havana, Camagüey and Holguín) reported greatest epidemic outbreaks during the months of May-June, and then spread to the different regions of the country, with July being the month of major spread of influenza viruses. In September, the circulation of influenza viruses begins to decrease to levels that are not dangerous. In the rest of the months it keeps circulating, but at low levels. This is clearly associated with the variations that the climate is experiencing in Cuba, going from very high warms and humid conditions to less favorable conditions for viral circulation.

This is a very important aspect when evaluating a possible spatial model; that is, the proposed model must, in some way, reflect that spatial variability and the groupings shown attending to the level of viral circulation and the favorable characteristics in each one of the country regions, which are not homogeneous and have a high heterogeneity, characterized by the climatic conditions.

Analysis of the moran´s I

The structure of the correlation indicates that there is a significant conglomerate or aggregation of high-low values (positive autocorrelation [I>0] in the area with similar patterns within the months of the same climate station, but slightly changing. The greatest variation of the index was observed in the transition months (April and October) and in those corresponding to the dry season, where the propagation distance of the virus decreases relatively. IT was different in the months of highest activity, starting from distances greater than 30 kilometers in which there is a change of sign (only occurs in the months of July and August, where the distance of propagation increases), which corresponds to a distribution of disaggregation or dispersion in the behavior of viruses, associated to the greater amplitude of climatic variability that does not favor the circulation; that is, it circulates at a very low frequency.

When there is a high circulation, the situation does not manifest itself in the same way, because, as the contagion effect increases, the climate does not determine the distribution and it is the dispersion of the virus's own dynamics that governs the pattern of circulation, such as in the months of July and August.

The spatial association given by the Multivariate Moran Index in relation to the effect of climatic variations described by the BI1, t, c and the influenza viruses shows the high viral activity in correspondence with the favorable climatic conditions in the region and in the neighboring, favoring the circulation of influenza viruses. This confirms that the spatial distribution of influenza viruses is not at random, but depends on the physical-geographic characteristics of the place, the climate variations and the characteristics of the virus´s behavior, which find more favorable conditions for their development in some regions than others.

Mechanisms of response that explain the relationships found between influenza and climate variability

Seasonal influenza viruses normally bind to cells in the upper respiratory tract, nose and throat, so they are easily transmitted and can infect cells deep in the lungs, precipitating severe viral pneumonia. Many previous studies have documented the dependence of influenza virus transmission on climatic and environmental elements, including temperature, humidity and atmospheric pressure [54], which are some of the variables that make up the BIs, with a strong temporal and spatial association.

To understand that high humidity favors the pH decrease (acidification) in the airways, we should take into account that the respiratory system is compound by organs that carry out diverse functions; but its capacity to exchange CO_2 and O_2 with the environment is the most important function, since the biological systems possess as main quality to be open systems that constantly exchange with the environment surrounding them.

It is well-known that lungs play an important role in the maintenance of a normal pH (5.5-6.5). The lungs allow the body to absorb the oxygen from the air and to eliminate the carbon dioxide (CO_2) from the body. CO_2 is a waste product, and when it accumulates too much in the body, pH fall. On the contrary, if there is not enough CO_2 expelled, the body pH level increases above the normal level.

In the rainy period a combination of high temperatures, decrease of atmospheric pressures and increase of the relative humidity (amount of water vapor at a given temperature) is observed with a decrease of the oxygenate density dissolved in the air with a hypoxia. That condition provokes a decrease of blood irrigation in the human being and then a vasoconstriction [59].

Another effect is the association with the super saturation due to high humidity in the inhaled air and the effect of the condensational growth in the upper airways, hindering the breathing and then increasing the CO_2 in the respiratory tract, liquefying very easily the water vapor [60]. The deposition of these droplets in the airways surface may lead to additional acidification of epithelial lining fluid in local areas of the airways. The pH reduction is a main feature of inflammatory respiratory diseases and plays a role in bronchoconstriction, impaired ciliary function and increased airways mucus viscosity, which raises the risk of deposition in the upper airways of infectious agents from the inhaled air.

Some relationship exists among the acidification of the respiratory tract mucous and the pH dependent conformation change of the flu hemaglutinin, as this is the major cover of the viral particle and recognize the Salic acid to allow the virus entering [61]. This action, in the case of the human being, requires to be activated by proteases of the host cell. These conditions are favored with the increasing of the airways acidification.

Changing seasonal and environmental factors, such as temperature, sunlight, rain, wind and humidity has a direct link with the increasing number of infectious diseases [62]. Environmental factors influence the host susceptibility to infection, as a result of seasonal changes on host humeral and cellular immune function, or due to direct environmental effects [18].

During the rainy season, people spent most of their time indoor and in crowded public places, which may increase its exposure to air-borne pathogens. Moreover, higher relative humidity may also affect the stability of air-borne droplets in which pathogens transmitted from person to person [63]. The transmission of Influenza viruses by droplets is enhanced in cooler, more humid seasons and during the rainy season in the tropics. During this weather, the exposure of the skin surface to sunlight is limited and can lead to vitamin D deficiency [64]. Epidemiological studies have demonstrated strong associations between seasonal variations in vitamin D levels and the incidence of various infectious diseases [65,66]. In the other hand, melatonin is a powerful natural hormone that is well known for its association with circadian and seasonal rhythms, and its synthesis is regulated by the environmental light/dark cycle [67].

The airborne antimicrobial potential of ultraviolet light (UV) has long been established; due to its strong absorbance in biological materials [68]. UV light limits the transmission and spread of airborne-mediated microbial diseases, such as influenza and tuberculosis [69]. Germicidal UV light can efficiently inactivate both drug-sensitive and multi-drug-resistant bacteria, as well as different strains of viruses [70]. Viruses are typically of micron or smaller dimensions, and then UV light can efficiently traverse and inactivate them [71].

In summary, the period of greatest viral circulation coincide with the presence of higher humidity, high temperatures, associated with the presence of a low atmospheric pressures center and variable climate conditions that favor super saturation and condensation in the respiratory tract, the change of pH in the airways, which can become acidic, leading to an additional acidification [60]. Additionally, destructive effects appear which may have a triggering role in a weakening of the respiratory defense mechanisms and, consequently, an increase in cough, bronchospasm and neurogenic inflammation [72,73], bronchoconstriction and deterioration of ciliary function, [74] Increased mucus viscosity of the airways [75-77]. Our results coincide with those identified by others, with a strong association with temperature, humidity and atmospheric pressure and identified it as possible meteorological warning factors for the incidence of Influenza infections [53,54]. That confirms our findings to explain the mechanisms of response of the virus and, the host as well as the rise of the diseases.

Conclusions and Futures Perspective

It was determined that influenza viruses respond to climate variability mainly during the months of May-October rainy season with a high association between the seasonality of Influenza and the climatic indexes on a temporal and spatial scale in Cuba. In the central region of the country the virus circulates the whole year coinciding with the areas where BIs presents favorable characteristics for viral circulation. This allowed us to show the response mechanism that explains the relationships found, since the predominant climatic characteristics favor the viral circulation, as well as the change of pH in the respiratory tract, which can become acid, leading to the additional acidification of the liquid epithelial lining in the local areas of the respiratory tract, which favor the presence of the influenza viruses.

The results obtained facilitate the formulation of the prediction models for the circulation of influenza viruses according to climatic conditions at a temporal and spatial scale, results that we will show in a second work.

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Conflicts of Interests

The authors declare that they have no conflict of interest.

Author's Contributions

All the authors participated in conceptualizing the design and coordination of the study, literature search and writing. LY contributed in the climatic data collection, worked in the statistical analysis, results interpretation and discussion, elaboration of maps, figures and writing of the first draft; OP worked in the statistical analysis, results interpretation and discussion; AB, VO contributed in the virological data collection, its analysis and interpretation; BS contributed in the epidemiological analyzes, made the final critical review and translation of the manuscript; AA, GG contributed in the virological data collection; and GM worked in the epidemiological and virological analysis. All authors read and approved the final manuscript.

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