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Detection of covid-19 epidemic waves and their interrelationships in the tri-border region between Brazil, Paraguay, and Argentina, 2020-2023: Covid-19 epidemic waves in the tri-border region

Larissa D P Luz, Jose Ueleres Braga, Elvira M G S Maciel

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Autores:

Larissa Djanilda Parra da Luz

Escola Nacional de Saúde Pública - Fundação Oswaldo Cruz, Rio de Janeiro, Rio de Janeiro, Brasil

E-mail: larissadpluz@gmail.com

ORCID: <https://orcid.org/0000-0002-1172-9492>

José Ueleres Braga

Escola Nacional de Saúde Pública - Fundação Oswaldo Cruz/Instituto de Medicina Social – Universidade Estadual do Rio de Janeiro, Rio de Janeiro, Brasil.

ORCID: <https://orcid.org/0000-0001-5247-007X>

Elvira Maria Godinho de Seixas Maciel

Escola Nacional de Saúde Pública - Fundação Oswaldo Cruz, Rio de Janeiro, Rio de Janeiro, Brasil.

ORCID: <https://orcid.org/0000-0002-9095-3141>

ABSTRACT

Introduction: The COVID-19 pandemic, caused by the SARS-CoV-2 virus, was declared a global public health emergency in 2020, profoundly impacting countries around the world. International border regions, such as the tri-border region between Brazil, Paraguay, and Argentina, faced unique challenges, such as high population mobility and the lack of regional integration in controlling the pandemic. Thus, this study aimed to identify and characterize the epidemic waves of COVID-19 in the three health regions of this tri-border region between 2020 and 2023.

Methods: Using secondary epidemiological data, confirmed cases of COVID-19 were analyzed in 9 municipalities in Brazil, 22 in Paraguay, and 13 in Argentina. Were used to smooth the epidemic curves and identify the waves, their peaks, and valleys based on the EpidemicKabu library, and the cross-correlation statistic function of the epidemic waves in the historical series of the countries.

Results: The study revealed five epidemic waves in total, five in Brazil, five in Paraguay and two in Argentina. The relation between the epidemic waves in Brazil and Paraguay was 0.74 and a lag -1, the correlation between Brazil and Argentina was 0.69 and lag max in 0 and the cross-correlation between Paraguay and Argentina resulted in 0.80 and lag max in 0, a strong correlation was observed of the three regions.

Conclusions: The results highlight the temporal heterogeneity of epidemic waves across the three countries and the importance of cross-border cooperation for infectious disease control. The study reinforces the need for integrated health policies and coordinated epidemiological surveillance in border regions, especially in areas with intense population mobility.

Keywords: COVID-19. Border Areas. Ecological Studies. Correlation of Data.

RESUMO

Introdução: A pandemia de COVID-19, causada pelo vírus SARS-CoV-2, foi declarada uma emergência global de saúde pública em 2020, impactando profundamente países ao redor do mundo. Regiões de fronteiras internacionais, como a tríplice fronteira entre Brasil, Paraguai e Argentina, enfrentaram desafios únicos, como alta mobilidade populacional e a falta de integração regional no controle da pandemia. Assim, este estudo teve como objetivo identificar e caracterizar as ondas epidêmicas de COVID-19 nas três regiões de saúde desta tríplice fronteira entre 2020 e 2023.

Métodos: Utilizando dados epidemiológicos secundários, foram analisados casos confirmados de COVID-19 em 9 municípios no Brasil, 22 no Paraguai e 13 na Argentina. Foram utilizados para suavizar as curvas epidêmicas e identificar as ondas, seus picos e vales com base na biblioteca EpidemicKabu e na função estatística de correlação cruzada das ondas epidêmicas nas séries históricas dos países.

Resultados: O estudo revelou cinco ondas epidêmicas no total, cinco no Brasil, cinco no Paraguai e duas na Argentina. A relação entre as ondas epidêmicas no Brasil e Paraguai foi de 0,74 e um lag -1, a correlação entre Brasil e Argentina foi de 0,69 e lag max em 0 e a

correlação cruzada entre Paraguai e Argentina resultou em 0,80 e lag max em 0, foi observada uma forte correlação das três regiões.

Conclusões: Os resultados destacam a heterogeneidade temporal das ondas epidêmicas nos três países e a importância da cooperação transfronteiriça para o controle de doenças infecciosas. O estudo reforça a necessidade de políticas de saúde integradas e vigilância epidemiológica coordenada em regiões de fronteira, especialmente em áreas com intensa mobilidade populacional.

INTRODUCTION

COVID-19 is a disease caused by the Coronavirus 2, related to Severe Acute Respiratory Syndrome (SARS-CoV-2), and was first reported in December 2019 in the province of Wuhan, China¹. The disease was classified by the World Health Organization (WHO) as a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and as a pandemic on March 11, 2020. It was the sixth time in history that the WHO declared a PHEIC².

Infected with SARS-CoV-2 presents a broad clinical spectrum, ranging from asymptomatic cases to those that may exhibit fever, fatigue, myalgia and more severe cases that may require medium to high-complexity support life and could progress to death^{3,4}.

In international border regions, the challenges in addressing COVID-19 were even more significant, considering that border towns faced divergences in migration control, cross-border flow, and, simultaneously, the lack of effective strategies for local and regional integration. Thus, in these territories, the transmission of infectious diseases is of great concern to health authorities due to the spatial diffusion processes characteristic of these areas^{5,6}.

In this context, the importance of coordination and integration of actions between countries to address PHEIC is highlighted. The towns in regions bordering between Brazil, Paraguay and Argentina required integration in coordinated health surveillance. This need is underscored by the daily crossing of over 100,000 people between Brazil and Paraguay on the *Ponte Internacional da Amizade* and around 10,000 people between Brazil and Argentina on the *Ponte Internacional da Fraternidade*, making this the busiest border in South America in movement of people⁷.

It is estimated that approximately 1.5 million people live in the tri-border region, which includes the towns along the border: Foz do Iguacu, located in the west of Paraná State, Brazil; Ciudad del Este, Alto Paraná Department; and, Puerto Iguazú, Iguazú Province, Argentina. The region is characterized by its ethnic and cultural diversity. In Foz do Iguacu, the population encompasses 95 nationalities and 29 ethnic groups, diverse in their colors, races, religions, social classes and other sociodemographic aspects⁸.

The diversity sociodemographic characteristics of the population highlight the need for region integration, However, in the context of health surveillance, studies have reported difficulties in accessing healthcare services in border towns, as well as inadequacies in health surveillance at towns and regions levels. This situations presents a timely and significant opportunity for study, particularly in the post-COVID-19 pandemic context^{7,9-11}.

During the COVID-19 pandemic, the implementation of pharmacological and non-pharmacological measures by health authorities – such as the provision of technological resources, supplies and vaccines – as well as the emergence and introduction of new variants of interest (VOI), occurred at different times and locations in border regions, this impacted the distribution of cases in the epidemic curves of Brazil, Paraguay and Argentina¹²⁻¹⁵.

Analyzing the temporal distribution patterns od COVID-19 epidemic waves in the three countries that make up the tri-border region is essential for planning and implementing surveillance, alert and response measures for public health emergencies. Thus, this study aimed to detected and characterized COVID-19 epidemic waves and their temporal cross-correlation n the three health regions of the border area between Brazil, Paraguay and Argentina from 2020 to 2023.

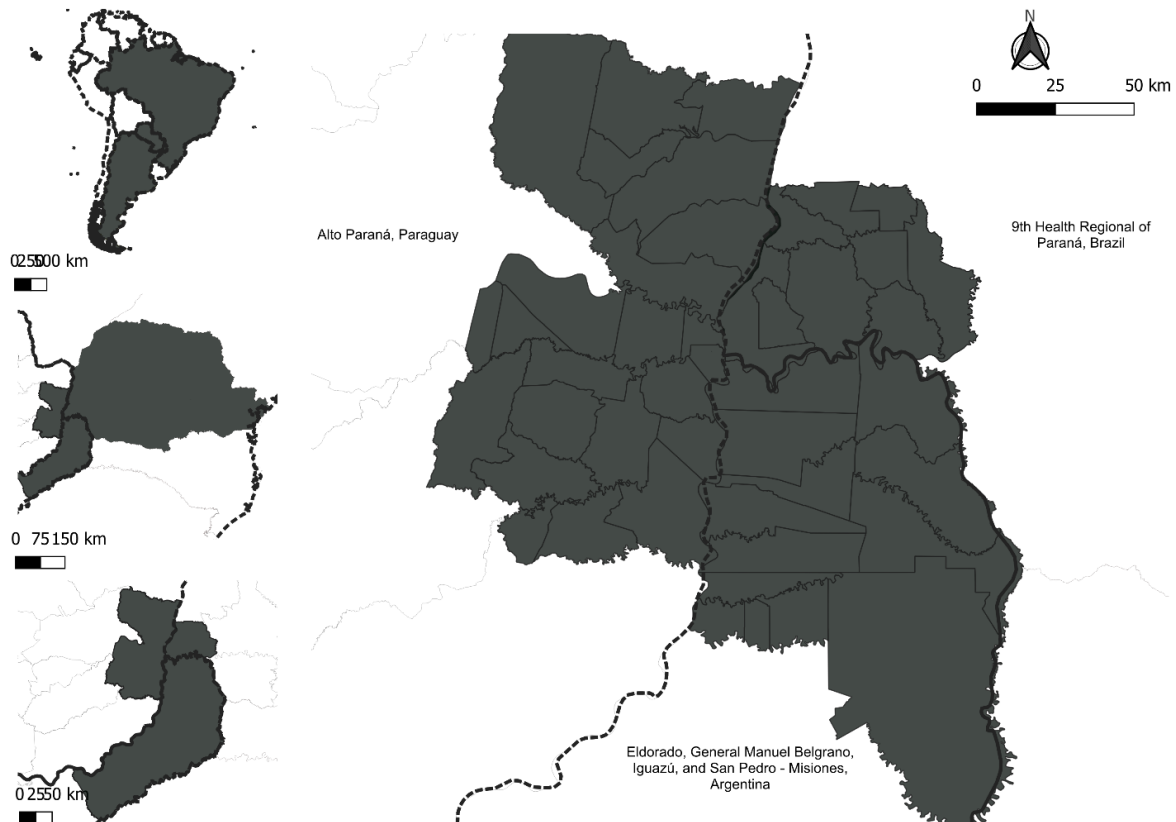
METHODS

This is an ecological temporal series study conducted with secondary public data on COVID-19, covering the towns that make up three health regions located along the border between Brazil, Paraguay and Argentina, in the South Border Arc of Brazil, in the west of State of Paraná, Brazil. The study included 9 cities from the 9th Health Region of State of

Paraná, Brazil; 22 cities from the Alto Paraná of Department, Paraguay; and 13 cities from the regions of Eldorado, General Manuel Belgrano, Iguazú and San Pedro, in the Misiones Province, Argentina (Figure 1).

In the 9th Health Region of the State of Paraná, Brazil, the population is estimated at 444,395 inhabitants distributed across the towns of Foz do Iguacu, Itaipulândia, Matelândia, Medianeira, Missal, Ramilândia, Santa Terezinha de Itaipu, São Miguel do Iguacu e Serranópolis do Iguacu¹⁶. In the Alto Paraná, Paraguay has a resident population of 853,613 habitantes distributed across the towns of Ciudad Del Este, Domingo Martinez De Irala, Doctor Juan León Mallorquín, Doctor Raúl Peña, Hernandarias, Itakyry, Iruña, Juan Oleary, Los Cedrales, Nacunday, Yguazú, Minga Guazú, Minga Porã, Mbaracayú, Presidente Franco, San Cristóbal, Santa Rita, Naranjal, Santa Rosa Del Monday, San Alberto, Santa Fe Del Paraná and Tavapy¹⁷. The regions of Eldorado, General Manuel Belgrano, Iguazú and San Pedro in the Province of Misiones, Argentina, have a population resident of 308,682 population distributed across the towns of 9 de Julio, Bernardo de Irigoyen, Colonia Delicia, Colonia Victoria, Colonia Wanda, Comandante Guacurary, Eldorado, Libertad, Puerto Esperanza, Puerto Iguazú, San Antonio, San Pedro and Santiago de Liniers¹⁸.

Figure 1. Study area map: Border region between the Brazil, Paraguay and Argentina



Source: 1) Territorial mesh of Brazil: IBGE Cartographic Base, 2022. 2) Territorial mesh of Paraguay INE Cartographic Base, 2022. 3) Territorial mesh of Argentina INDEC Cartographic, 2022.

The number of COVID-19 cases was obtained from three different databases: *Notifica COVID-19 Paraná*¹⁹, *Datos COVID-19 Paraguay*²⁰ and daily reports COVID-19, Misiones, Argentina²¹. Were included laboratory-confirmed cases between February 2020 and March 2023.

The databases were harmonized individually to consolidate a unified dataset of confirmed cases containing the same variables. The database consolidated was processed using EpidemicKabu²² library in Python 3.11²³. The epidemic curve of confirmed cases by Epidemiological Week (EW) was smoothed using the Gaussian Kernel function and the time series was replaced by the weighted average of its neighboring values, smoothing the curve by reducing abrupt fluctuations while preserving peaks and valleys. This process is necessary because the analysis of epidemic waves by allowing the precise identification of trend changes and infection points in peaks and valleys. Finally, were applied to cross-correlation

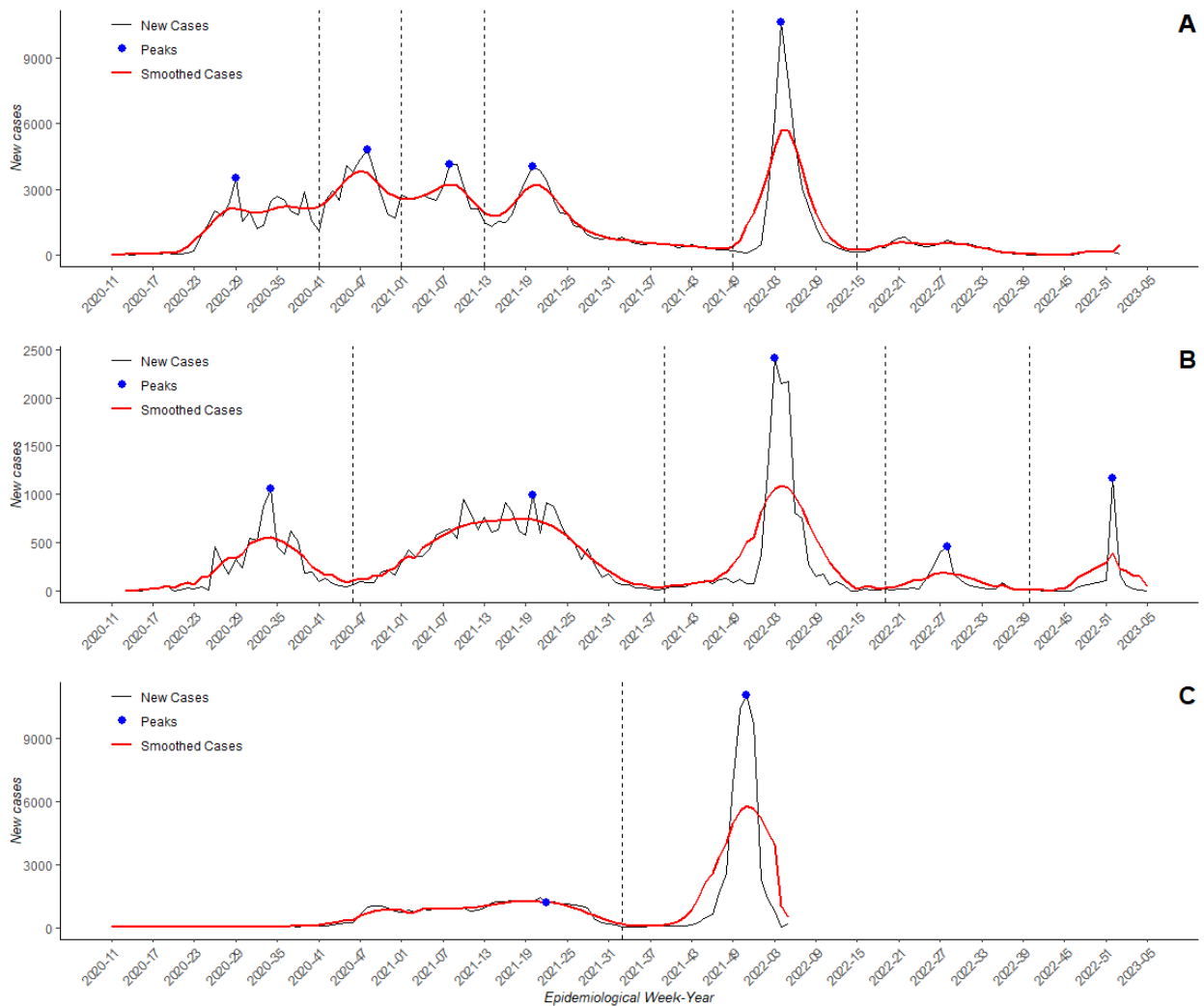
function (CCF) in R 4.3.0²⁴ to assess the analyses the nonlinear cross-correlation between the epidemic waves of Brazil and Paraguay, Brazil and Argentina and Paraguay and Argentina. For this study, was used a lag range of -40 to 40 EW, considering that one year can have 52 EW²⁵.

As it is an aggregated data in the public domain, this study received Declaration of Exemption from Ethical Analysis No. 18/2024 by the Ethics Committee for Research with Humans Beings of the Nacional School of Public Health of the Oswaldo Cruz Foundation.

RESULTS

From 2020 to 2023, there were recorded 300,882 cases de COVID-19 in the three study locations, distributed across five epidemic waves (Figure 2).

Figure 2. COVID-19 epidemic waves in Brazil, Paraguay and Argentina, 2020-2023



Note: (A) Confirmed cases, peaks, and smoothed cases of COVID-19 in cities of the 9th Health Region. (B) Confirmed cases, peaks, and smoothed cases of COVID-19 in cities of Alto Paraná, Paraguay. (C) Confirmed cases, peaks, and smoothed cases of COVID-19 in cities of Eldorado, General Manuel Belgrano, Iguazú, and San Pedro, Misiones/Argentina.

Figure 2A shows the epidemic curve of the 9th Health Region of the State of Paraná. Five epidemic waves were observed over time, with the most pronounced peak occurring in EW 49/2021. Before this peak, smaller waves of infection with COVID-19 occurred at regular intervals.

The epidemic curve of the Alto Paraná Department, Paraguay (Figure 1B), shows a similar standard to the epidemic curve of 9th Health Region of the State of Paraná, with five epidemic waves but with a lower intensity of cases. Differently, confirmed cases in the region

of Misiones Province, Argentina (Figure 1C), demonstrated a distribution with lower cases intensity, with more discreet variations in the number of new cases weekly. The biggest peak occurred at the end of 2021 although with lower absolute values compared to the Brazil and Paraguay.

It was found that all three health regions, shared a significant peak between EW 49/2021 and EW 04/2022, with approximately 10,000 confirmed cases per weekly. This situation shows the impacts of the reduction in restrictive measures, the increase in vaccination, and the transmissibility of the VOI Omicron (B.1.1.529).

In 9th Health Region of the State of Paraná highlighted significant differences in the number of cases and cumulative incidence when compared with Paraguay and Argentina (Table 1).

Table 1. Characteristics of the epidemic waves in the 9th Health Region, Paraná, Brazil, 2020 to 2023. N=202,855

Characteristics	Ondas epidemiológicas					
Start	First	Second	Third	Fourth	Fifth	Sixth
EpiWeek-Year	12-2020	42-2020	01-2021	13-2021	49-2021	14-2022
End						
EpiWeek-Year	41-2020	53-2020	08-2021	48-2021	13-2022	52-2022
Peak						
EpiWeek-Year	30-2020	49-2020	12-2021	20-2021	03-2022	21-2022
Number of cases in the wave	34607	36338	34568	45037	42050	10255
Number of cases at the peak	3532	4385	4140	4063	10643	789
Incidence rate per 100,000	7990,42	8390,09	7902,76	10296,12	9462,30	2307,63

Source: Notifica COVID-19, Paraná, Brazil.

The first wave started in EW 12/2020 and finish in EW 41/2020, with 34,607 cases and an incidence of 7,790.42/100,000 cases per residence population, peaking in EW 30/2020 with 3,532 cases. The second wave, between EW 42/2020 and EW 53/2020, recorded 36,338 cases, an incidence of 8,390.09/100,000 population, and peaking of 4,385 cases. The third and fourth waves showed similar numbers, with 45,037 and 42,050 cases, and incidence rates of 10,296.12 and 9,462.3/100,000 population, respectively, along with epidemic peaks of 781 and 747 cases in that week. The circulation of the Gamma variant (P.1), possibly influenced

by the fifth wave had the total number of cases 42,050, while the incidence rate of 9,462.3 cases per 100,000 population. The final wave (EW 14/2022) showed present the lowest number of cases (10,255) and the lowest cumulative incidence (2,307/100,000 cases per residence population), verifying a reduction in disease transmission of COVID-19 in the region.

Table 2 showed ed the characteristics of COVID-19 epidemic in Alto Paraná Department, Paraguay, the epidemic curve was distributed across five waves, with significances in duration, number of cases, and incidence rates. The first two waves occurred between 2020 and August 2021, both with similar peaks, though the second wave lasted longer. The second epidemic wave was the most intense, recording 19,590 cases and an incidence of 2,225.76 cases per 100,000 population. The highest peak was reached in EW 03/2022 with 2,407 cases reported that week, while the lowest occurred in fifth wave, with 455 cases in EW 28/2022. The third wave had the highest total od cases (11,830) and a peak of 2,407 cases in that week and the fourth epidemic wave had the lowest incidence with 227.9 cases per 100,000 population and the lowest peak (98 cases). The fifth wave, observed accumulated 1,740 cases, with the peak occurring in EW 25/2022, when 1,171 confirmed cases were reported in that week.

Table 2. Characteristics of the epidemic waves in the Alto Paraná region, Paraguay, 2020 to 2022. N=42,867

Characteristics	Waves				
	First	Second	Third	Fourth	Fifth
Start					
EpiWeek-Year	13-2020	46-2020	39-2021	19-2022	40-2022
End					
EpiWeek-Year	45-2020	38-2021	18-2022	38-2022	21-2023
Peak					
EpiWeek-Year	34-2020	20-2021	03-2022	28-2022	52-2022
Number of cases in the wave	7505	19590	12006	2026	1740
Number of cases at the peak	1062	990	2407	455	1171
Incidence rate per 100,000	903,19	2.325,76	1.406,49	237,34	203,84

Source: Datos COVID-19, Ministerio de la Salud y Bienestar Social, Paraguay. 2023

The border region of Departments of the Province Misiones (Table 3), Argentina reported a total of 85,160 cases distributed across two epidemic waves, differing from Brazil

and Paraguay. The first case was registered in Puerto Iguazú, Iguazú Department, on March 28, 2020. Following the first case, two epidemic waves were observed. The first epidemic wave occurred between EW 13/2020 and EW38/2021, with 36,313 cases and a peak of 1,405 cases in EW 27/2021. The second wave reported a higher incidence rate (15,852.38/100,000 population) and the second wave, recorded peak in EW 04/2022 with 11,066 cases, was significantly higher than the first epidemic wave, indicating faster and more intense transmission, despite the shorter duration.

Table 3. Characteristics of the epidemic waves in the Misiones region, Argentina, 2020 to 2022. N=85,160

Characteristics	Waves	
	First	Second
Start		
EpiWeek-Year	13-2020	39-2021
End		
EpiWeek-Year	38-2021	52-2022
Peak		
EpiWeek-Year	27-2021	04-2022
Number of cases in the wave	36313	48847
Number of cases at the peak	1405	11066
Incidence rate per 100,000	12326,08	15824,38

Source: Daily reports COVID-19 Misiones, Argentina. 2023.

A strong correlation was found between the countries (Table 4). The Brazil-Paraguay pair, showed a strong correlation, but the negative lag in -1 confirmed the influence of COVID-19 epidemic waves in Brazil on those in Paraguay, with one-week delay. The Brazil-Argentina pair is significant correlated, but without time lag (0), that is the epidemic waves were synchronized. Paraguay-Argentina pair have high correlation with synchronized times series (lag 0).

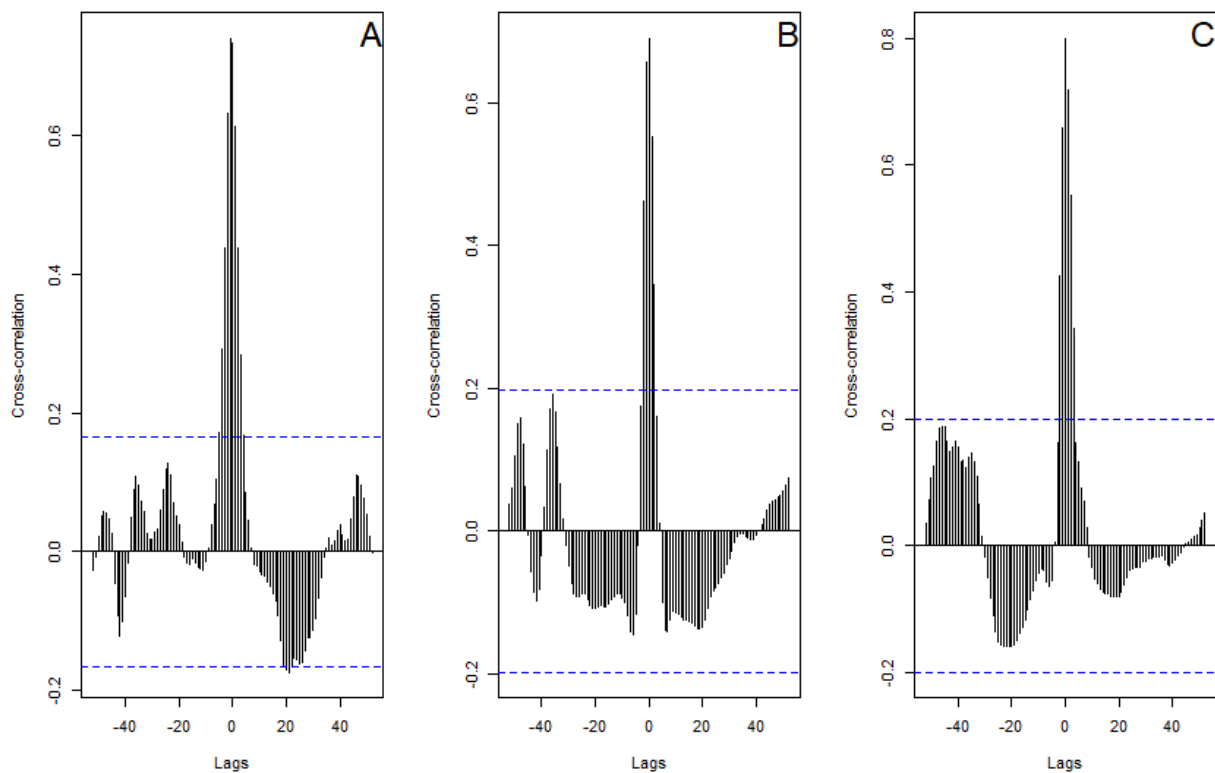
Table 4. Correlation between epidemic waves of Brazil, Paraguay and Argentina, 2022-2023

Country pair	Maximum correlation	Maximum lag
Brazil-Paraguay	0.7403063	-1
Brazil-Argentina	0.6899566	0
Paraguay-Argentina	0.7995550	0

Figure 3, shows the cross-correlation in the border regions. The cross-correlation between the epidemic waves in Brazil and Paraguay (Figure 3A) resulted in 0.74 and a

maximum was in lag of -1, a marked peak was in lag 0, these results confirm a strong and negative correlation between the time series of these two regions. However, the results shows that epidemics waves in Brazil were influenced the epidemic wave in Paraguay in one week. Others negatives and positives lags was observed, but they did not reach the same intensity as at lag 0.

Figure 3. Correlation of COVID-19 epidemic waves between Brazil-Paraguay, Brazil-Argentina, Paraguay-Argentina, 2022-2023



Note: (A) Cross-correlation between the time series of Brazil and Paraguay. (B) Cross-correlation between the time series of Brazil and Argentina. (C) Cross-correlation between the time series of Paraguay and Argentina.

The cross-correlation between the epidemic waves in Brazil and Argentina (Figure 3B) was 0.69 with the maximum lag of 0. A peak was observed at lag 0, although of smaller magnitude compared to the Brazil and Paraguay correlation. The correlation results confirmed a strong temporal of these border region. Variations were observed in the lags and that there was different temporal behavior between the two regions.

Figure 3C, shows the cross-correlation between Paraguay and Argentina. The results in 0.8 and a maximum lag of 0 was equal to the correlation between Brazil and Paraguay, and Brazil and Argentina. The peak was observed at lag 0. Moreover, as in the other cross-correlation, significant oscillation was constated at the lags, particularly for negative values.

Trough the CCF, a strong positive correlation was confirmed in the epidemic waves of border region in the Brazil, Paraguay, and Argentina, especially during the same period (lag 0), referring to the period from EW 53/2022 to EW 04/2023.

DISCUSSION

This study revealed that epidemic waves in the three-border area between Brazil, Paraguay, and Argentina were heterogenous, both in terms of the chronology of their occurrences and the responses of each country to the COVID-19 pandemic but have correlation between them. The dynamics of the epidemic waves were characterized by: 1) In 9th Health Region of the State of Paraná, Brazil, five epidemic waves were constated; In Alto Paraná Department, Paraguay, five epidemic waves too; While in Misiones Province, Argentina, two epidemic waves were observed during the period of transmission COVID-19; 2) The largest epidemic wave occurred simultaneously in all three regions, between the end of 2021 and the beginning of 2022, associated with the VOI BA 1.1.529 (Omicron), reported of WHO in December 2021²⁶. This event was the most significant in terms of the number of cases and the strain on local healthcare systems; 3) The peak of cases occurred on same weeks: first in region of Brazil, on EW 03/2022; followed by Paraguay, on EW 03/2022, and finally, in Argentina, on EW 04/2022. This result reflects the spread of the virus across borders and regional interconnectedness.

The identification and characterization of COVID-19 epidemic waves in border regions are necessary for supporting public health surveillance policies, especially in areas with high population mobility. The three-border area is a region of intense cross-border flow, which complicated implementation of uniform measures to contain the virus¹². In this context, the use of date analysis tools, such as the EpidemicKabu library, proved essential for

the accurate detection of epidemic waves, enabling a agile response from healthcare system in border region²².

In Brazil, the health system is decentralized to the states and towns, thus the State of Paraná adopted strict measures from the beginning of the pandemic. The first official guidance was issued on January 24, 2020, and on March 16, 2020, State Decree No. 4,230/2020 came into effect, establishing a series measure to curb the spread of the virus. These measure included increasing hospital eds and creating field hospitals, decentralizing diagnostic testing to towns, suspending non-essential services and activities, and restricting the consumption of alcoholic beverages during from 10 pm to 6 am²⁷. These actions contributed to the temporary containment of the COVID-19, but the country faced ongoing challenges due to its vast territorial extension and the heterogeneity od healthcare systems across different regions, according with recent findings on COVID-19 mitigation measures^{28,29}.

The health system in Paraguay is centralized, and the policies are decreed by the Ministry of Health, in Asunción. The first case of COVID-19 was recorded on February 3, 2020. Mitigation measures, which began to be implemented on March 10, 2020, included the suspension of public ad private events the closure of entertainment such as cinemas, theaters, and casinos, and the suspension of classes at all education levels. The closure of the border between Ciudad Del Este and Foz do Iguacu, 9th Region Health of the State of Parana, Brazil on March 18, 2020, shortly the first COVID-19 case was confirmed in Foz do Iguacu. This closure, initially, aimed at preventing the entry of cases from Brazil, was gradually flexibility, with a partial reopening for small and medium vehicles on July 29, 2020, and the full reopening on October 15, 2020, with a requirement for a negative PCR test to enter Paraguay. However, this requirement was not reciprocal for entry into Brazil, emphasizing the differences in policies between the two border regions³⁰.

The provinces of Argentina have administrative autonomy in public health and health systems, but the Ministry of Health remained in effect for an extended period, with the most significant being the closure of land borders with Brazil on March 24, 2020. These restrictions remained in place until October 2021³¹. The reopening of the borders and the

access the people other countries were conditioned on the presentation of a vaccination passport, which was a key strategy to prevent new outbreaks related to cross-border tourism³². This measure was very important in the three-border region, where tourism is a significant economic role.

The pandemic in this area was characterized by the circulation of multiple variants of SARS-CoV-2, with epidemic waves driven by different strains. Initially, the B.1.1.28 and B.1.1.33 VOI were predominant, but they were gradually replaced by VOI such as Gamma, Delta, and Omicron, which played a crucial role in the subsequent waves of the pandemic^{33–36}.

The countries of Latin America and Caribbean they were heavily affected by the COVID-19 pandemic, accounting for 15% of global cases and 28% of deaths by March 2022. This disproportionate impact was of the fragility of healthcare systems in the region, deep social inequalities, and a limited government support in many areas. Despite these challenges, Latin America became a global leader in vaccination, with 63% of its population fully vaccinated in March 2022³⁶.

It's was found that the confirmed cases were uneven across the three countries in the border region. While Argentina began its vaccination campaign on December 29, 2020, Foz do Iguaçu, in Brazil, started on January 20, 2021, and Paraguay on February 22, 2021^{37–39}. Despite advances in vaccination, the unequal distribution of vaccines and vaccine hesitancy remained significant challenges, particularly in Paraguay, in more rural and economically areas. However, vaccination uptake was of the main reasons for controlling the epidemic in 2022, specially during the circulation of the VOI Omicron, which resulted in a substantially lower cases, hospitalized and deaths^{36,40}.

Thus, this study had limitations. The available database in Paraguay was limited to confirmed cases by laboratory criteria, which may have underestimated the real number of infections. Additionally, no statistical associations were made between epidemic waves and the effects of pharmacological and non-pharmacological restrictive measures, especially the vaccination. In this way, other analyzes will be able to support the results of this study.

CONCLUSIONS

The analyzes of epidemic waves in cities in the triple border health regions between Brazil, Paraguay and Argentina showed heterogeneity in the distribution of time series with a strong and positive correlation for epidemic waves between Brazil and Argentina, and Paraguay and Argentina. However, a strong negative correlation was found between the epidemic waves in Brazil and Paraguay. Unilateral decisions between governments, associated with different responses from health systems and services in the region and vaccination capacity, were a determining factor in the dynamics of virus transmission in the region.

CONFLICT OF INTEREST

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

AUTHORSHIP CONTRIBUTION

Authors LDPS, JUB and EMGSM contributed to all stages of the research: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization and Writing.

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