HEALTH SCIENCES

Insights into the association of H1N1 seasonality with the COVID-19 pandemic in Brazil: an ecological time series analysis

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Abstract: During the COVID-19 pandemic, H1N1 seasonality disappeared worldwide. In Brazil, information on how coronavirus impacted this seasonality is scarce. In this study, we aimed to verify whether COVID-19 pandemic was associated with changes in the seasonality of H1N1, modeling the time series of H1N1 between pre-pandemic (2018 and 2019), pandemic (2020 and 2021) and post-pandemic (2022 and 2023) periods. For this purpose, we superimposed on this time series cases of COVID-19 from 2020 to 2023. Our findings highlighted that H1N1 exhibited a consistent seasonal pattern in the pre-pandemic period, with peaks mainly in months with the highest rainfall. However, this seasonality disappeared during the pandemic, with a significant decrease in the number of cases, in contrast with the predicted seasonality of H1N1 for the same period. In addition, the seasonal pattern of H1N1 in the post-pandemic showed a return to that observed in the pre-pandemic period, especially in 2023. We observed that the COVID-19 pandemic was consistently associated with changes in H1N1 seasonality in Brazil, underscoring the relative importance of monitoring patterns of respiratory syndromes to enhance our understanding of how coronavirus is associated with changes in seasonal diseases.

Key words: Influenza, coronavirus, respiratory syndromes, time series, underreports.

INTRODUCTION

Severe acute respiratory syndromes, including COVID-19 and H1N1, are of global concern (Soo et al. 2020). In particular, H1N1 presents a seasonal pattern in tropical and subtropical areas, with enhanced number of cases associated with low temperatures (Li et al. 2019, Sakamoto et al. 2020). Recently, with the COVID-19 pandemic, measures to prevent the spread of the virus were adopted (Soo et al. 2020). For example, wearing masks, working remotely, and canceling large events, helped to effectively control COVID-19 and other respiratory illnesses (Sunagawa et al. 2021). Large-scale testing for COVID-19 was an important factor in monitoring new cases (Soo et al. 2020). However, testing for other respiratory syndromes strongly declined in this period (Wagatsuma et al. 2021, Cellès et al. 2021). This is of great concern because the most common clinical symptoms of COVID-19 and H1N1 are similar, and include fever, cough, sore throat, and radiographic evidence of pneumonia (Miatech et al. 2020).

Brazil was strongly affected by the COVID-19 pandemic, with high number of confirmed cases and deaths (openDataSUS 2023). The first case of COVID-19 in Brazil was reported in late February 2020, with the virus quickly spreading across the country (openDataSUS 2023). However, information on how COVID-19 pandemic was associated with changes in H1N1 patterns (e.g. number of cases and seasonality) is scarce. In this study, we aimed to verify whether COVID-19

pandemic was associated with changes in H1N1 seasonality. For this purpose, we modeled H1N1 time series between pre-pandemic (2018 and 2019), pandemic (2020 and 2021) and post-pandemic (2022 and 2023) periods using a publicly available database. The application of time series analysis in health studies is important for the monitoring of infectious diseases across time periods (Spaeder et al. 2012), providing a good opportunity to promote disease control and prevention measures on local and large scales (Wagatsuma et al. 2021).

MATERIALS AND METHODS
Dataset

In this nationwide ecological time series study, we used positive cases of H1N1 between 2018 and 2023 to verify whether coronavirus pandemic was associated with changes in their seasonality. Generally, H1N1 has a seasonal pattern in Brazil (Li et al. 2019). Therefore, we superimposed on this time series positive cases of COVID-19 from 2020 to 2023. These data were obtained from openDataSUS (https://opendatasus.saude.gov.br/dataset), a public repository of the Brazilian Ministry of Health which provides information on Severe Acute Respiratory Syndromes since 2008, along 52 epidemiological weeks. For 2023, we used data up to epidemiological week 41 because the remaining weeks were not available. These anonymized data did not require ethical permissions. Recently, COVID-19 was included in the repository.

Statistical analysis

We carried out all analyses in GNU R 4.2.2 (R Core Team 2022). We initially examined the data distribution using boxplots and histograms and selected the Poisson distribution as the most appropriate model. We used a generalized linear model (*family=poisson(link="log")* for

the Poisson distribution) to formally test for differences in the cases of H1N1 between pre-pandemic, pandemic and post-pandemic periods. Whether significant, we carried out a post-hoc test for the generalized linear model for pairwise comparisons using medians. Assumptions of homogeneity of variances, normality and uniformity of residual distributions were checked using residual plots after modeling.

Afterwards, we used a Poisson regression model to smooth the H1N1 time series. With this model, we aimed to detect seasonal patterns for H1N1 and to verify whether coronavirus pandemic was associated with changes in H1N1 seasonality. We used a flexible cubic spline on the Poisson regression for controlling long-term trends. Finally, we predict the H1N1 time series pattern during the pandemic to verify how H1N1 would behave without the influence of the COVID-19.

RESULTS

We found that H1N1 number of cases differed between years, especially in pre- and post-pandemic periods that showed greater variability (Figure 1). However, this number was consistently and significantly lower in the pandemic period ($D_{5,252}$ = 13658; $p < 0.001$; see significant differences with the different letters in Figure 1). Along the time series (Figure 2a and b), we observed a consistent seasonal pattern for H1N1 in the pre-pandemic, with peaks occurring between epidemiological weeks 15 to 25 in 2018, and 20 to 30 in 2019. However, this pattern disappeared during the pandemic, remaining constant between 2020 and 2021 (Figure 2a and b). In addition, the first reported cases of COVID-19 were associated with changes in H1N1 seasonality, due to the abrupt decrease in the H1N1 number of cases (Figure 2c). These findings
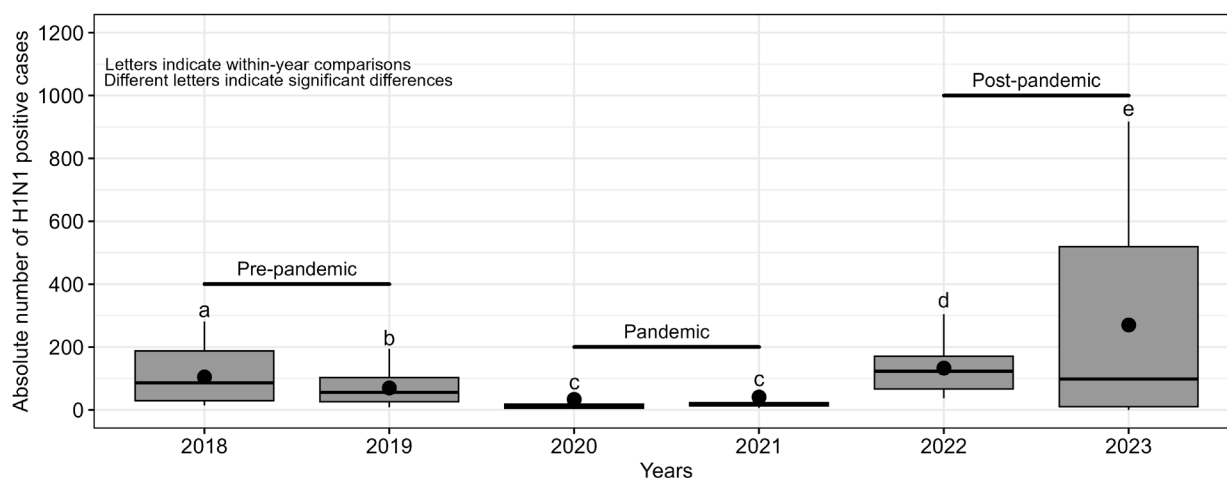
Figure 1. Box-plots showing the median for number of cases of H1N1 between pre-pandemic (2018 and 2019), pandemic (2020 and 2021), and post-pandemic (2022 and 2023) periods in Brazil. Letters indicate within-year comparisons. Different letters indicate significant differences.

contrast with the predicted H1N1 seasonality, which was similar with the pre-pandemic period (Figure 2a-c). Interestingly, the seasonal pattern of H1N1 in the post-pandemic showed a return to that observed in the pre-pandemic period, especially in 2023 (Figure 2a-b).

DISCUSSION

In this study, we assessed changes in H1N1 seasonality associated with the COVID-19 pandemic in Brazil. Overall, we observed a consistent seasonal pattern in the cases of H1N1 in the pre-pandemic period, with increases mainly in months with the highest rainfall. These results were similar to that found in other tropical regions for H1N1 (Li et al. 2019) and syncytial virus (Wagatsuma et al. 2021). However, during the pandemic this seasonal pattern disappeared, probably associated with increases in the COVID-19 number of cases, which was also observed worldwide (Sakamoto et al. 2020, Soo et al. 2020, Sunagawa et al. 2021, Wagatsuma et al. 2021). This finding is interesting, because it contrasts with the predicted pattern of H1N1 time series during the pandemic period, supporting our results. After the end of the pandemic,

we observed a return of the H1N1 seasonality, mainly in 2023. However, during 2022, this pattern was not consistent. This finding was probably associated with the peaks of COVID-19 in the same year, which also corroborated our results. Similar results were observed for malaria during the Ebola emergency in Sierra Leone, Africa (Magassouba et al. 2020). Currently, studies regarding H1N1 in the post-pandemic are still scarce worldwide. Therefore, our results may be used as a baseline for understanding how the COVID-19 pandemic may be associated with changes in the seasonality of H1N1, analyzing the pre- and post-pandemic periods.

We suggest that the disappearance of H1N1 seasonality during the pandemic may be linked to underreporting of cases. Similar patterns were identified for poliomyelitis, which showed a significant decrease in the number of notifications during the COVID-19 pandemic (Zomahoun et al. 2021). In addition, the number of malaria notifications significantly decreased in Africa during this period (Buonsenso et al. 2021). Furthermore, the same occurred for H1N1 in Japan (Sunagawa et al. 2021). Disease underreporting may be a factor observed during epidemics or pandemics (Araújo et al. 2023).
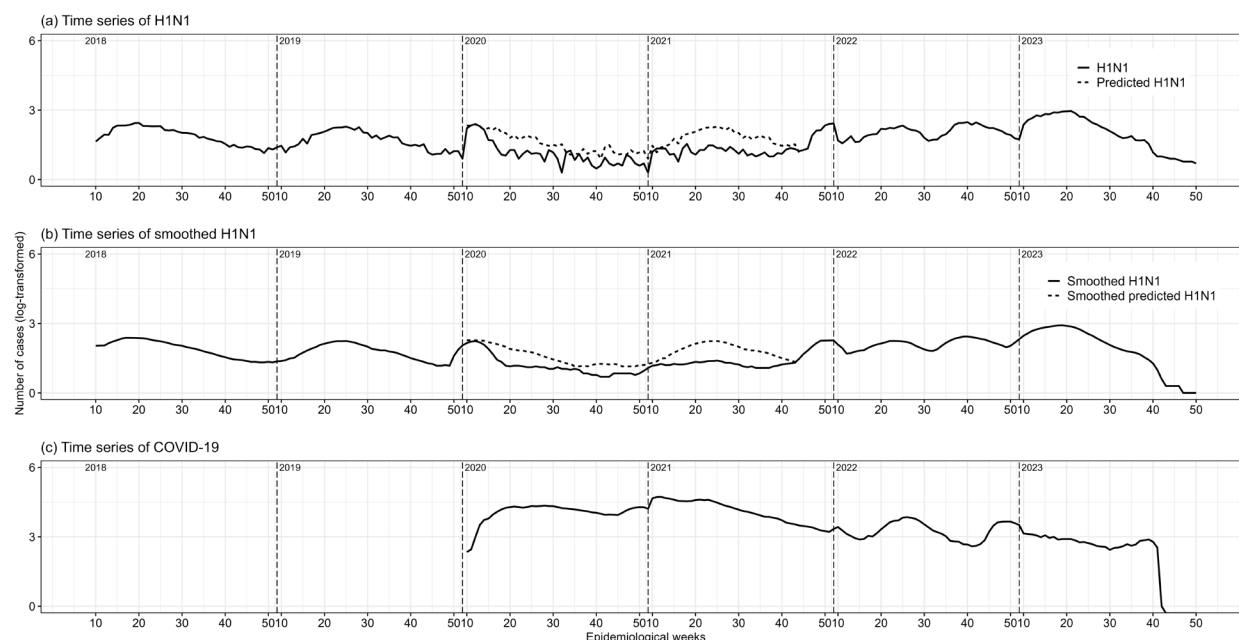
Figure 2. Time series of H1N1 number of cases from 2018 to 2023 in Brazil (a) along the 52 epidemiological weeks, with their smoothed pattern (b). The predicted pattern of H1N1 was showed with dashed lines. COVID-19 number of cases (c) was superimposed on this time series from 2020 to 2023. Number of cases was log-transformed for a better visualization.

For example, during the Ebola emergency in Sierra Leone, Africa, a decrease in the number of tuberculosis notifications was observed (Magassouba et al. 2020).

In addition to cases underreported during the pandemic, we may suggest other hypotheses linked to sanitary measures and travel restrictions established by health services. Firstly, the restrictions imposed during the COVID-19 pandemic, such as mask-wearing, travel restrictions, and social distancing, may decrease H1N1 number of cases due to less virus circulation (Soo et al. 2020). In Singapore, public health efforts to control COVID-19 likely reduced the transmission of influenza in February 2020 (Soo et al. 2020). In addition, these sanitary measures were also associated with low seasonal flu activity in Japan during the pandemic (Sakamoto et al. 2020, Sunagawa et al. 2021). Secondly, the closure of schools and the suspension of large events may contribute to a decrease in the spread of H1N1, since children

may be the main virus reservoirs (Maltezou & Drancourt 2003, Ratre et al. 2020). Thus, their absence from school and other events may probably reduce transmission rates (Cellès et al. 2021). This pattern was observed in Okinawa, Japan (Sunagawa et al. 2021).

Recently, co-infection with H1N1 and COVID-19 was reported (Miatech et al. 2020, Yue et al. 2020). We also suggest that co-infection may be associated with changes in H1N1 seasonality, since patients during the pandemic were primarily tested for COVID-19. As a result, the actual number of H1N1 positive cases may be underestimated (Yue et al. 2020), which may suggest the disappearance of H1N1 seasonality in this period.

In conclusion, COVID-19 pandemic may be associated with changes in H1N1 seasonality and likely led to underestimation of positive cases in Brazil. Although two years after the beginning of the pandemic, studies showing the impact of coronavirus on other respiratory

syndromes are important, mainly because these diseases have a high epidemic power (Li et al. 2019). The epidemic power of H1N1 was observed in the USA, when the virus re-emerged in 2010, after significant increases in the previous year (Spaeder et al. 2012). Thus, our findings underscore the relative importance of monitoring patterns of respiratory syndromes to enhance our understanding of how coronavirus is associated with changes in seasonal diseases.

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