REPORT

CORONAVIRUS

Spatiotemporal pattern of COVID-19 spread in Brazil

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Brazil has been severely hit by COVID-19, with rapid spatial spread of both cases and deaths. We used daily data on reported cases and deaths to understand, measure, and compare the spatiotemporal pattern of the spread across municipalities. Indicators of clustering, trajectories, speed, and intensity of the movement of COVID-19 to interior areas, combined with indices of policy measures, show that although no single narrative explains the diversity in the spread, an overall failure of implementing prompt, coordinated, and equitable responses in a context of stark local inequalities fueled disease spread. This resulted in high and unequal infection and mortality burdens. With a current surge in cases and deaths and several variants of concern in circulation, failure to mitigate the spread could further aggravate the burden.

Brazil is the only country with a population larger than 100 million that has a universal, comprehensive, free of charge health care system. Over three decades, this system contributed to reducing inequalities in access to health care and outcomes (*1*). It also facilitated the management of previous public health emergencies such as the HIV/AIDS pandemic (*2*). Despite recent cuts in the health budget (*3*), it was expected that Brazil's health system would place the country in a good position to mitigate the COVID-19 pandemic. With national coordination and through a vast network of community health agents, actions adapted to existing local inequalities (i.e., regional distribution of physicians and hospital beds) could have been implemented (*4*). However, Brazil is one of the countries most severely hit by COVID-19. As of 11 March 2021, 11,277,717 cases and 272,889 deaths have been reported. These numbers represent 9.5% and 10.4% of the worldwide cases and deaths, respectively, yet Brazil shares only 2.7% of the world's population. In late May 2020, Latin America was declared the epicenter of the COVID-19 pandemic, mainly because of Brazil. Since 7 June 2020, Brazil has ranked second in deaths worldwide.

In Brazil, the federal response has been a dangerous combination of inaction and wrongdoing, including the promotion of chloroquine as treatment despite a lack of evidence (*5*, *6*). Without a coordinated national strategy, local responses varied in form, intensity, duration, and start and end times, which to some extent were associated with political alignments (*7*, *8*). The country has seen very high attack rates (*9*) and disproportionally higher burden among the most vulnerable (*10*, *11*), illuminating local inequalities (*12*). After multiple introductions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Brazil had an initial epidemic phase (15 February to 18 March 2020) with restricted circulation (*13*), preceded by undetected virus circulation (*14*). Although the initial spread was determined by existing socioeconomic inequalities, the lack of a coordinated, effective, and equitable response likely fueled the widespread spatial propagation of SARS-CoV-2 (*12*). The goal of this study was to understand, measure, and compare the pattern of spread of COVID-19 cases and deaths in Brazil at fine spatial and temporal scales. We used daily data from state health offices covering the period from epidemiological week 9 (23 to 29 February 2020) to week 41 (4 to 10 October 2020).

In all states, it took <1 month between the first case and the first death; only 11 days in Amazonas and 21 in São Paulo (table S1). Epidemiological curves for Brazil (fig. S1) hide distinct patterns of initial reporting, propagation, and containment of SARS-CoV-2 across administrative units. As states and cities imposed and relaxed restrictive measures at different times, population mobility facilitated the circulation of the virus and acted as a trigger of disease spread (*15*). Figure 1, A and B, show that cumulative cases and deaths, respectively, per 100,000 people were not uniformly distributed across municipalities. We used the space-time scan statistic (*16*) to identify areas that recorded a significantly high number of cases (Fig. 1C and table S2) or deaths (Fig. 1D and table S3) over a defined period.

Deaths clustered ~1 month before cases. This likely reflects problems in surveillance, data reporting, and low testing capacity. The first significant cluster of COVID-19 deaths started on 18 May 2020 (Fig. 1D, #5) and was centered around Recife (the capital of Pernambuco). Five other clusters of deaths occurred before the first cluster of cases was observed on 16 June 2020 (Fig. 1C, #7). Among these were clusters around Fortaleza and Rio de Janeiro (the capitals of Ceará and Rio de Janeiro, respectively) and in a large area including Amazonas, Pará, and Amapá, states that have a disproportionally lower hospital capacity. Amazonas (the capital of which is Manaus) has the highest mortality per 100,000 people in the country, more than double the rate for Brazil. By October 2020, ~76% of its population was estimated to have been infected (*9*, *17*). Except for one cluster in August 2020 (Fig. 1D, #1), the duration of death clusters did not decrease over time, ranging from 10 to 13 days. This is different from what was observed in South Korea, where successful containment reduced the duration and the geographic extent of clusters over time (*18*). A similar pattern was observed for COVID-19 cases (Fig. 1C). In the central and southern areas, clusters occurred later (August and September 2020), corroborating a regional pattern of propagation of SARS-CoV-2 (*19*).

To understand and compare how COVID-19 cases and deaths spread across Brazil, we calculated the geographic center of the epidemic. Trajectories of the center by epidemiological week show that after the introduction in São Paulo, both cases (Fig. 2A and movie S1) and deaths (Fig. 2B and movie S2) progressively moved north until week 20 (starting 10 May 2020), when the epidemic started to recede in Amazonas and Ceará but gained force in Rio de Janeiro and São Paulo. Comparing trajectories in each state (fig. S2), we calculated a ratio of the distance that the center moved each week to the distance between the capital city and the most distant municipality (tables S4 and S5). In eight states, the median weekly ratio for deaths was larger than cases (Fig. 2C), suggesting a faster movement of the focus of deaths.

On average, it took 17.3 and 32.3 days to reach 50 cases and deaths, respectively. However, in four states, deaths accumulated to a 50 count first (Fig. 2D), and in Amazonas, Ceará, and Rio de Janeiro, the difference between the time it took for cases and deaths to reach a 50 count was 6, 1, and 3 days, respectively (table S1). This short interval suggests undetected (and thus unmitigated) introduction and propagation of the virus for some time. This was confirmed in Ceará (*20*), where a retrospective epidemiological investigation

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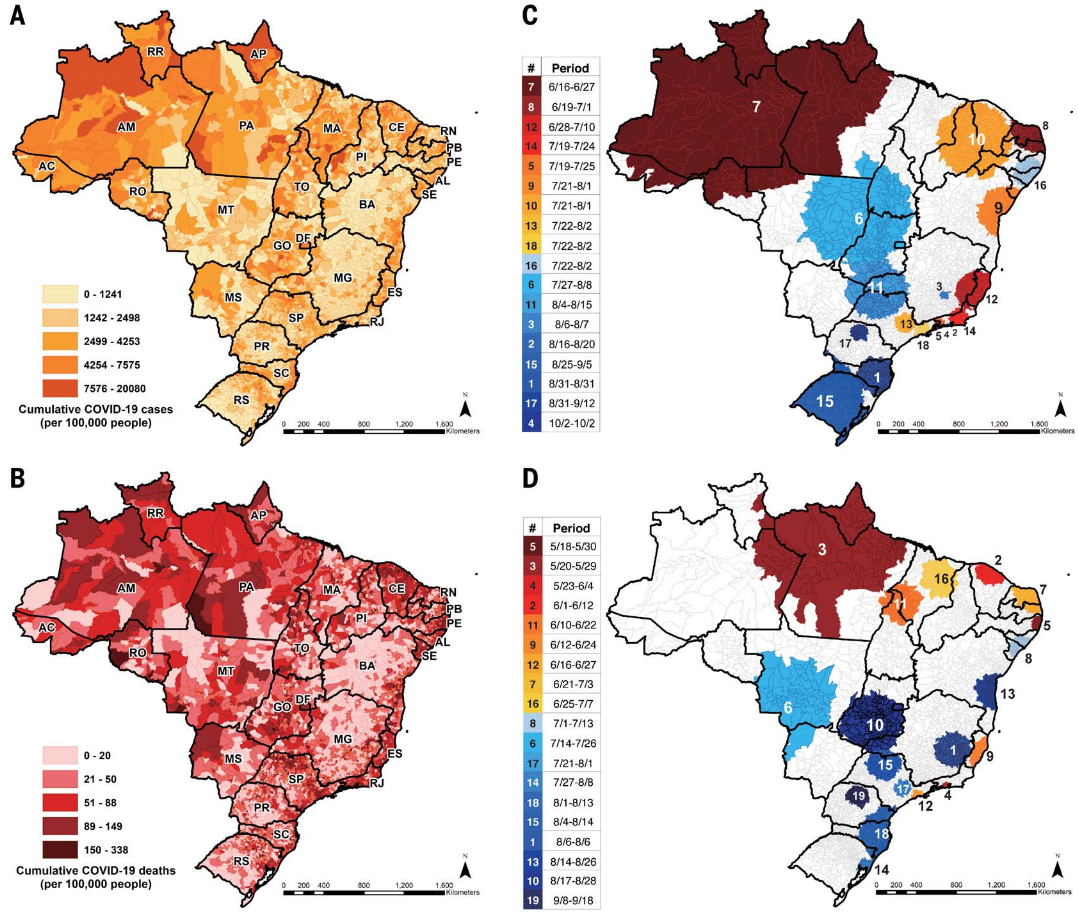

Fig. 1. Spatial distribution and clustering of reported COVID-19 cases and deaths. (**A** and **B**) Cumulative number of COVID-19 cases (A) and deaths (B) per 100,000 people by municipality. Dark lines on the maps show state boundaries. State acronyms by region are indicated as follows. North: AC, Acre; AP, Amapá; AM, Amazonas; PA, Pará; RO, Rondônia; RR, Roraima; TO, Tocantins. Northeast: AL, Alagoas; BA, Bahia; CE, Ceará; MA, Maranhão; PB, Paraíba; PE, Pernambuco; PI, Piauí; RN, Rio Grande do Norte; SE, Sergipe. Center west: DF, Distrito Federal; GO, Goiás; MT, Mato Grosso; MS, Mato Grosso do Sul. Southeast: ES, Espírito Santo; MG, Minas Gerais; RJ, Rio de Janeiro; SP, São Paulo. South: PR, Paraná; RS, Rio Grande do Sul; SC, Santa Catarina. (**C** and **D**) Spatiotemporal clustering of cases (C) and deaths (D) across Brazilian municipalities. Color and number codes in the clusters and the table on the left are the same, and the table indicates the interval during which each cluster was statistically significant. The color gradient (dark red to dark blue) indicates the temporal change based on the initial date of the cluster, and the cluster number indicates the rank of the relative risk for each cluster (tables S2 and S3). Clusters were assessed with the space-time scan statistic (see the supplementary materials).

revealed that the virus was already circulating in January. Also, if the initial cases occurred in high-income areas, it is possible that consultations in private practices were not reported into national systems of the Ministry of Health (*20*) and remained silent to the surveillance system. In addition, testing capacity in Brazil was limited, and the first diagnostic reverse transcription polymerase chain reaction test kits started to be produced in the country only in March. Although efforts of retrospective investigation were not scaled up in the country, a comparison of standardized rates of cases and deaths per 100,000 people (Fig. 2E) shows that in 11 states, including Amazonas, Ceará, and Rio de Janeiro, the death toll was larger than incidence.

To quantitatively measure the intensity of the spread of COVID-19 cases and deaths over time, we used the locational Hoover index (HI) (*21*, *22*). HI values closer to 100 indicate concentration in few municipalities, whereas those close to zero suggest more homogeneous spreading. If containment measures were effective, then we would expect the HI to decline slowly, remaining relatively high over time. Also, if measures were effective to avoid a collapse of the hospital system, then we would expect a higher HI for deaths compared with cases. Figure 3A shows the HI for Brazil and a clear trend toward extensive spread for both cases and deaths until about week 30 (19 to 25 July 2020). The pattern, however, varied across states. In the first week with reported events, Amazonas, Roraima, and Amapá had HI <50 for both cases and deaths. This suggests either undetected circulation of the virus before initial reports (i.e., when reporting started, there was already a large fraction of the population that had been infected) or fast and multiple introductions of the virus immediately followed by rapid spatial propagation (tables S6 and S7).

Overall, the spread of COVID-19 in Brazil was fast. By week 24 (7 to 13 June 2020) and 32 (2 to 8 August 2020), all states had HI <50 for cases and deaths, respectively. In nine states, including Amazonas, Amapá, Ceará, and Rio de Janeiro, the spread of deaths was faster than that of cases over several weeks (Fig. 3B), with some overlap with the time when clusters were observed in those areas (Fig. 1, C and D). Figure 3, C and D, show the first and last weekly HI for cases and deaths by states, and there are marked contrasts in HI trajectory (tables S6 and S7). By week 41 (4 to 10 October 2020), COVID-19 deaths in Amapá (HI = 31.3) had moved to the interior faster than cases (HI = 42.9). Rio de Janeiro had the most intense interiorization of both cases (HI = 14.9) and deaths (HI = 21.9), followed by Amazonas (cases HI = 20.2, deaths HI = 30.4). Both experienced a shortage of intensive care unit (ICU) beds, but Amazonas had smaller availability (~11 ICU beds per 100,000 people versus 23 in Rio de Janeiro), all concentrated in the capital city, Manaus. As the virus moved to the interior, a higher demand for scarce and distant resources intensified, not all of which were fulfilled in time to prevent fatalities (*23*). In Rio de Janeiro, political chaos compromised a prompt and effective response. Leaders were immersed in corruption accusations, the governor was removed from office and faces an impeachment trial, and the position of the Secretary of Health turned over three times between May and September, with one person who held that position arrested (*24*). By contrast, although Ceará also experienced a near collapse of the hospital system in late April to mid-May 2020 and had

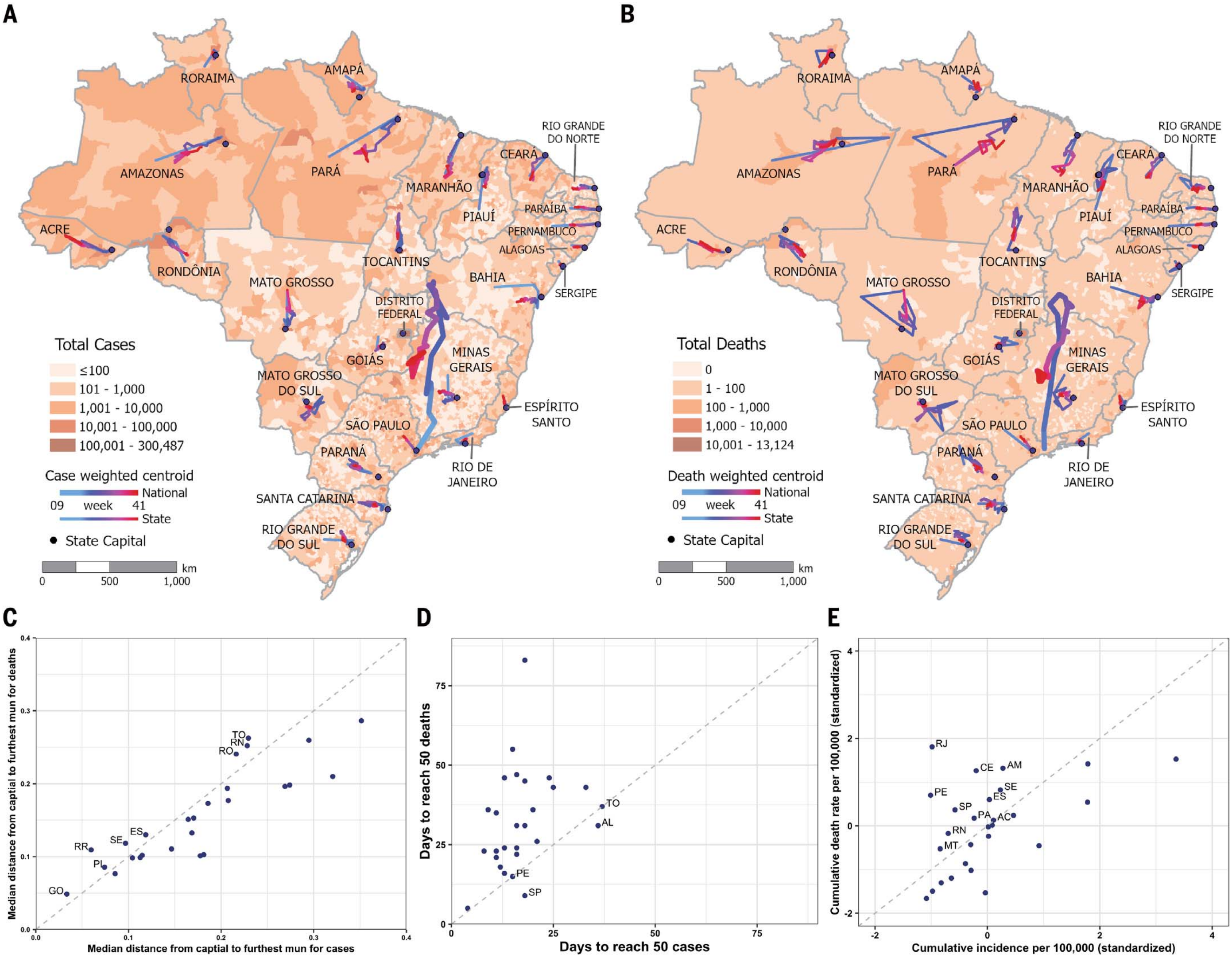

Fig. 2. Spatial and temporal spread of COVID-19 cases and deaths. (**A** and **B**) COVID-19 case-weighted (A) and death-weighted (B) geographic centers by epidemiological week. Thick lines show the geographic center for Brazil, thin lines show the trajectory of the center in each state, and the black dot indicates the state capital city (see the supplementary materials). The first case in each state was recorded in the capital city, except for Rio de Janeiro, Rondônia, Bahia, Minas Gerais, and Rio Grande do Sul, and thus the trajectory of the center starts in the interior. This was more common for deaths (14 states did not report the first death in the capital: Rio de Janeiro, Amazonas, Pará, Piauí, Rio Grande do Norte, Paraíba, Espírito Santo, Paraná, Santa Catarina, Mato Grosso do Sul, Mato Grosso, and Goiás). Figure S2 shows detailed maps for each state. (**C**) Scatterplot of the median distance that the geographical center of cases (*x*-axis) and deaths (*y*-axis) shifted weekly in each state (measured as the ratio of the distance that the geographical center of cases shifted weekly in each state to the distance between the capital city and the furthest municipality in the state). (**D**) Scatterplot of the number of days that it took for a state to reach 50 COVID-19 cases (*x*-axis) after the first case was reported and 50 deaths after the first confirmed COVID-19 death (*y*-axis). (**E**) Scatterplot of the standardized number of cases per 100,000 people (*x*-axis) and deaths per 100,000 people (*y*-axis) by state. The 45° lines in (C), (D), and (E) describe equal values for variables in the scatterplot.

silent circulation of the virus >1 month before the first case was officially reported (*20*), it ranked sixth in movement of cases (HI = 31.3) but was the antepenultimate in deaths (HI = 64.5). This suggests that even with the continued spread of the virus, local actions were successful in preventing fatality. No state had HI for cases >50 by week 41, revealing an extensive pattern of disease spread toward the interior.

Overall, a higher percentage of COVID-19 cases and deaths were observed outside of capital cities in weeks 20 (10 to 16 May 2020) and 22 (24 to 30 May 2020), respectively (Fig. 4A), with varied patterns across states (table S1). Rio Grande do Sul, Santa Catarina, and Paraná, all in the southern region, had earlier and concurrent shifts in cases and deaths (in March 2020), and this was the last region to show a major surge in COVID-19. In Rio de Janeiro and Amazonas, the shift in deaths was much later than cases: 10 and 8 weeks, respectively.

To better capture policies adopted at the national and local levels and their associations with movement of COVID-19 toward the interior of states, we used three indicators, the stringency index (STR), the containment index (CTN; all policies in STR except for the use of masks), and the social distancing index (SD; based on mobile devices). Because states introduced measures at different times and these were of various durations, national indices hide much variation (Fig. 4B). We observed the expected correlations (table S8) between policy indicators and HI for cases and deaths (Fig. 4C) but a positive correlation between HI and

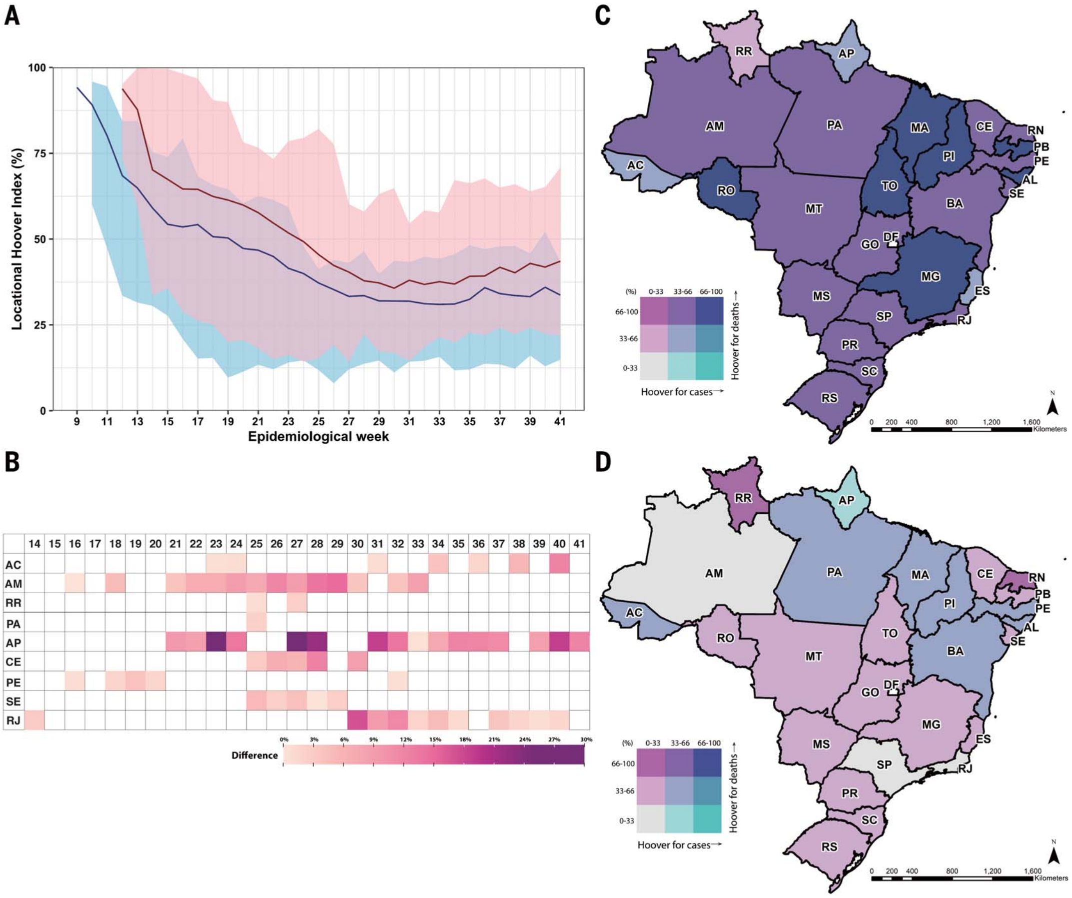

Fig. 3. Spread of COVID-19 cases and deaths. (**A**) Locational HI (see the supplementary materials) for cases (blue line) and deaths (red line) by epidemiological week. The area around each curve indicates the maximum and minimum index observed across states. (**B**) States and weeks when the locational HI for cases was bigger than that for deaths, indicating a faster spread of deaths. (**C** and **D**) Bivariate choropleth map of the locational HI for cases and deaths in epidemiological week 14 (29 March to 4 April 2020) (C) and epidemiological week 41 (4 to 10 October 2020) (D). Because SARS-CoV-2 reached states at different epidemiological weeks, (C) shows data from week 12 for RJ and SP; from week 13 for AM, PI, RN, PE, PR, SC, RS, and GO; from week 15 for AC; and from week 16 for TO. Similarly, (D) shows data for week 33 for MT and for week 39 for ES. State abbreviations are as in Fig. 1.

the distance by which the national geographical center of cases shifted weekly. This suggests a pattern of progressive concentration of cases and deaths in few but widespread areas. Considering each state (fig. S3), Amapá showed a negative correlation between STR and HI for deaths, indicating that policy measures failed to prevent the movement of deaths (this was the only state where deaths moved to the interior faster than cases by week 41; Fig. 3D).

We used hierarchical clustering analysis (*25*) in an attempt to group states into categories based on measures that captured the overall COVID-19 mortality burden, intensity of transmission, speed of COVID-19 deaths toward the interior of states, and adoption of distancing measures (Fig. 4D). Categories 3 and 4 include the top 10 states in deaths per 100,000 people, as well as those that observed the first spatiotemporal clustering of deaths and fast reporting and movement of deaths. Category 2 has the highest number of contiguous states and the lowest death burden by week 41. However, all categories combine states with different levels of inequality and distinct political alignment.

In summary, our results highlight the fast spread of both cases and deaths of COVID-19 in Brazil, with distinct patterns and burden by state. They demonstrate that no single narrative explains the propagation of the virus across states in Brazil. Instead, layers of complex scenarios interweave, resulting in varied and concurrent COVID-19 epidemics across the country. First, Brazil is large and unequal, with disparities in quantity and quality of health resources (e.g., hospital beds and physicians) and income (e.g., an emergency cash transfer program started only in June 2020, and by November 2020, 41% of the households were receiving it). Second, a dense urban network that connects and influences municipalities through transportation, services, and business (*26*) was not fully interrupted during peaks in cases or deaths. Third, political alignment between governors and the president had a role in the timing and intensity of distancing measures (*7*), and polarization politicized the pandemic with consequences to adherence to control actions (*27*). Fourth, SARS-CoV-2 was circulating undetected in Brazil for >1 month (*20*), a result of the lack of well-structured genomic surveillance (*28*). Fifth, cities imposed and relaxed measures at different moments based on distinct criteria facilitating propagation (*15*). Our findings speak to these issues but also show that some states, such as Ceará, were resilient, whereas others that had comparatively more resources, such as Rio de Janeiro, failed to contain the propagation of COVID-19.

In such a scenario, prompt and equitable responses, coordinated at the federal level, are imperative to avoid fast virus propagation and disparities in outcomes (*12*). However, the COVID-19 response in Brazil was neither prompt nor equitable. It still isn't. Brazil is currently facing the worst moment of the pandemic, with a record number of cases and deaths and near collapse of the hospital system. Vaccination has started but at a slow pace because of the limited availability of doses. A new variant of concern, which emerged in Manaus (P1) in December 2020, is estimated to be 1.4 to 2.2 times more transmissible and able to evade immunity from previous non-P1 infection (*29*). That variant is spreading across the country. It became the most prevalent in circulation in six of eight states where investigations were performed (*30*). As of 11 March 2021, Brazil had already reported deaths totaling 40% of the total COVID-19 deaths that occurred in all of 2020. In January 2021, Manaus witnessed a spike in cases and hospitalizations and a collapse of the hospital system, including a shortage of oxygen for patients (*31*). The death toll is horrific, as Manaus has already recorded 39.8% more COVID-19 deaths in 2021 than in 2020.

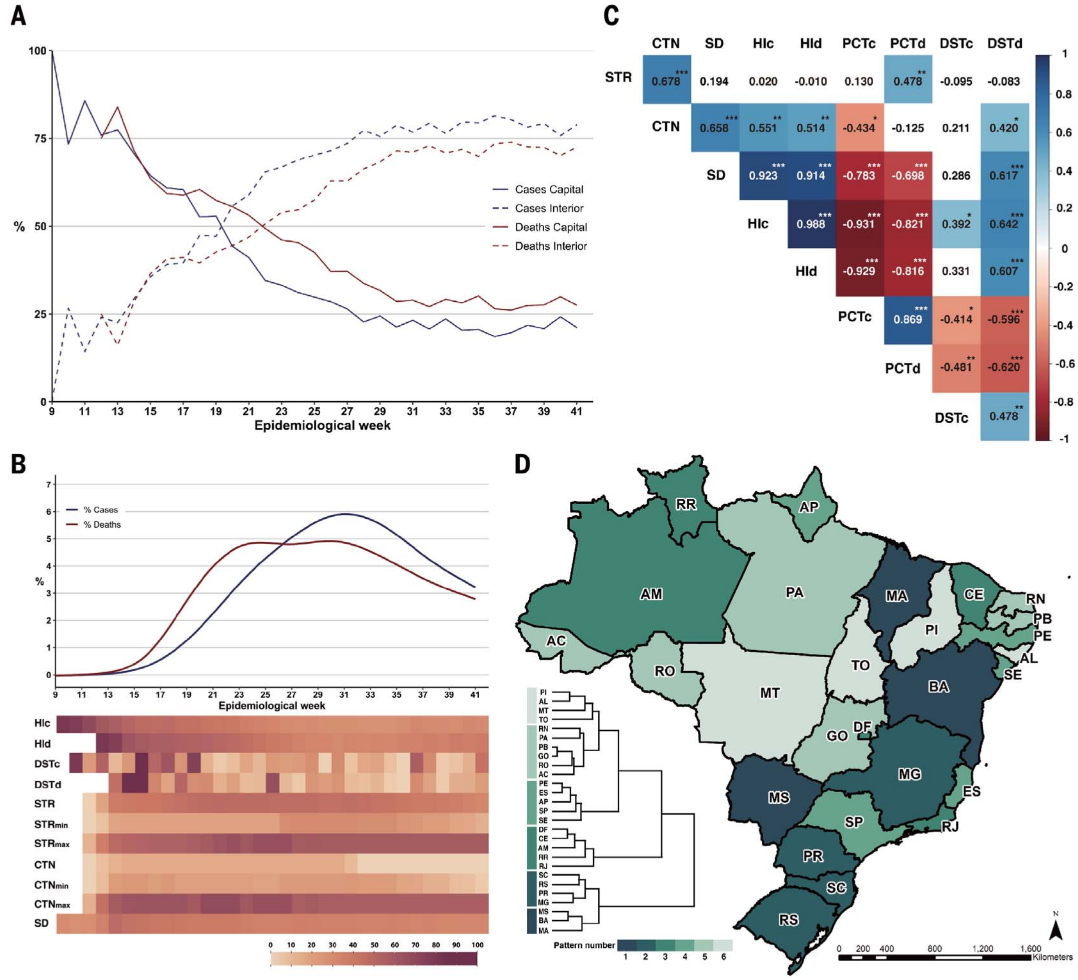

Fig. 4. Indicators of COVID-19 spread and response measures. (**A**) Percentage of cases (blue lines) and deaths (red lines) in the state capitals (solid lines) and the remaining municipalities (dashed lines) by epidemiological week. (**B**) Percentage of reported COVID-19 cases and deaths and selected variables by epidemiological week. Variables were as follows: STR, CTN, SD, HI for cases (HIc), HI for deaths (HId), percentage of cases in each epidemiological week (PCTc), percentage of deaths in each epidemiological week (PCTd), normalized distance by which the national geographical center of cases shifted in each week (DSTc), and normalized distance by which the national geographical center of deaths shifted in each week (DSTd). Distances were normalized to vary between 0 and 100. The subscript "min" indicates the minimum value of the index observed among all states in each week; the subscript "max" denotes the maximum value. (**C**) Correlation matrix (Pearson). Cells in shades of red or blue are statistically significant: $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$. (**D**) Hierarchical clustering dendrogram by state based on five variables: cumulative deaths per 100,000 people, maximum percentage of deaths in a week, maximum SD, epidemiological week when HId became <50, and maximum value of the effective reproduction number (R_t) over the study period (see the supplementary materials).

Without immediate action, this could be a preview of what is yet to happen in other localities in Brazil. Without immediate containment, coordinated epidemiological and genomic surveillance measures, and an effort to vaccinate the largest number of people in the shortest possible time, the propagation of P1 will likely resemble the patterns described here, leading to an unimaginable loss of lives. Failure to avoid this new round of propagation will facilitate the emergence of new variants of concern, isolate Brazil as a threat to global health security, and lead to a completely avoidable humanitarian crisis.

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SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/372/6544/821/suppl/DC1
Materials and Methods
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MDAR Reproducibility Checklist

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Science

Spatiotemporal pattern of COVID-19 spread in Brazil

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Unmitigated spread in Brazil
Despite an extensive network of primary care availability, Brazil has suffered profoundly during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Using daily data from state health offices, Castro *et al.* analyzed the pattern of spread of COVID-19 cases and deaths in the country from February to October 2020. Clusters of deaths before cases became apparent indicated unmitigated spread. SARS-CoV-2 circulated undetected in Brazil for more than a month as it spread north from Sã o Paulo. In Manaus, transmission reached unprecedented levels after a momentary respite in mid-2020. Faria *et al.* tracked the evolution of a new, more aggressive lineage called P.1, which has 17 mutations, including three (K417T, E484K, and N501Y) in the spike protein. After a period of accelerated evolution, this variant emerged in Brazil during November 2020. Coupled with the emergence of P.1, disease spread was accelerated by stark local inequalities and political upheaval, which compromised a prompt federal response.

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