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Global patterns and drivers of influenza decline during the COVID-19 pandemic

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ABSTRACT

Objectives: The influenza circulation reportedly declined during the COVID-19 pandemic in many countries. The occurrence of this change has not been studied worldwide nor its potential drivers.

Methods: The change in the proportion of positive influenza samples reported by country and trimester was computed relative to the 2014–2019 period using the FluNet database. Random forests were used to determine predictors of change from demographical, weather, pandemic preparedness, COVID-19 incidence, and pandemic response characteristics. Regression trees were used to classify observations according to these predictors.

Results: During the COVID-19 pandemic, the influenza decline relative to prepandemic levels was global but heterogeneous across space and time. It was more than 50% for 311 of 376 trimesters-countries and even more than 99% for 135. COVID-19 incidence and pandemic preparedness were the two most important predictors of the decline. Europe and North America initially showed limited decline despite high COVID-19 restrictions; however, there was a strong decline afterward in most temperate countries, where pandemic preparedness, COVID-19 incidence, and social restrictions were high; the decline was limited in countries where these factors were low. The “zero-COVID” countries experienced the greatest decline.

Conclusion: Our findings set the stage for interpreting the resurgence of influenza worldwide.

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Introduction

Starting with the worldwide spread of SARS-CoV-2, observations of a sharp decline in influenza circulation were reported. In the first months of 2020, the flu season was shortened in some northern hemisphere and tropical countries [1,2]. During the subsequent 18 months, influenza incidence showed an all-time low in New Zealand [3], Australia [4], the United States [5–7], and the WHO European Region [8]. The circulation was still low in 2021.

The measures adopted in response to the COVID-19 pandemic are likely to have hindered influenza transmission at the same time because the routes of transmission are identical. Indeed, the influenza decline, as well as that of other transmissible diseases,

coincided with nonpharmaceutical interventions against COVID-19 [2,6,7,9–11].

Understanding how this decline occurred may help interpret the current influenza trends and anticipate future viral circulation. Although the issue has been described for specific countries or regions [2–5,7,8,12–14], little work has been done at the global scale [15–17].

Here, we provide a global quantitative analysis of the influenza reduction based on the Global Influenza Surveillance and Response System FluNet database [18,19]. We considered the period between March 2020 and September 2021 and estimated the influenza reduction by country and trimester relative to a prepandemic period (2014–2019). We identified geographical, demographical, health preparedness, and COVID-19 status characteristics predictive of influenza decline using random forests and clustered observations with a similar decline in time and space using a regression tree.

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Material and methods

Overview of the methods

We used data from the FluNet influenza repository [18,19] to quantify the worldwide influenza change during the COVID-19 pandemic (March 2020 to September 2021) compared with the pre-pandemic period (December 2014 to December 2019). We mapped the influenza decline by trimester and country. We then used random forests to identify the most significant predictors of decline and a regression tree to classify trimesters-countries based on these predictors. Potential predictors included a wide range of covariates, among them, country factors (geographical, meteorological, demographic, and health preparedness factors), and variables associated with the COVID-19 pandemic, that were assembled from sources detailed hereafter.

Influenza data and definition of influenza reduction

The FluNet influenza repository [18,19] provides weekly counts of influenza specimens by country. For our analysis, we considered records from 2014 to 2021. To account for influenza seasonality, we defined 13-week-long “influenza trimesters” beginning on the first Monday after December 11, March 12, June 11, and September 11. These dates were chosen so that the middle of the December 11 trimester coincided with the peak of a typical influenza circulation in the northern hemisphere. We refer to these trimesters as December-March, March-June, June-September, and September-December, respectively.

Table 1
Definition, computation and source of the variables used as predictors of influenza change.

Variable	Description	Source	Min, max
Age	Median age of the country population	[20,21]	15.1, 48.2
Longitude	Population-weighted average of longitude for cities with more than 300K inhabitants by country or country capital longitude, from -180 (W) to 180 (E)	[22]	-100.7, 174.4
Latitude	Population-weighted average of latitude for cities with more than 300K inhabitants by country or country capital latitude, from -90 (S) to 90 (N)	[22]	-38.7, 60.4
T	Average temperature (in Celsius degrees) over the trimester-country	[23]	-8.8, 37.8
RH	Average relative humidity over the trimester-country	[23]	17.3, 93.5
IDVI	Infectious disease vulnerability index, country level indicator of the vulnerability to health emergencies from 0 (most vulnerable) to 1 (less vulnerable)	[24]	0.15, 1
COVID-19 daily cases	Average daily reported cases of COVID-19 per million inhabitants over the trimester-country	[25]	0, 553.5
Workplace presence reduction	Median percentage of reduction of daily presence in workplaces over the trimester-country. Reduction from the first 5 weeks in 2020 in the same location	[26]	-22.5%, 69.0%
Reduction of international flights	Average percentage of reduction in the inbound and outbound air passengers over the trimester-country with respect to the same trimester-country of 2019	[27]	-16.8%, 100%
nb days of school closure	For each country, number of days over the trimester where policies related to schools and universities closure were implemented	[28]	0, 91
nb days of workplace closure	For each country, number of days over the trimester where policies related to workplaces closure were implemented	[28]	0, 91
nb days of public event restrictions	For each country, number of days over the trimester where policies related to event restrictions were implemented	[28]	0, 91
nb days of gathering restrictions	For each country, number of days over the trimester where policies related to social gathering restrictions were implemented	[28]	0, 91
nb days of public transport restrictions	For each country, number of days over the trimester where policies related to public transport restrictions were implemented	[28]	0, 91
nb days of stay at home requirements	For each country, number of days over the trimester with "shelter-in-place" and otherwise confine to the home orders	[28]	0, 91
nb days of international travel restrictions	For each country, number of days over the trimester with airport screening, quarantine of arrival passengers or restrictions of international travels	[28]	0, 91
nb days of facial covering requirements	For each country, number of days over the trimester with policies on the use of facial coverings outside the home	[28]	0, 91
nb days of testing implementation	For each country, number of days over the trimester with government policy on who has access to testing for current infection (polymerase chain reaction tests)	[28]	0, 91
nb days of contact tracing implementation	For each country, number of days over the trimester with government policy on contact tracing after a positive diagnosis	[28]	0, 91
nb days of elderly shielding	For each country, number of days over the trimester with policies to protect older adults (as defined locally) in long-term care facilities and/or community and home-based settings	[28]	0, 91

IDVI, infectious disease vulnerability index; nb, number; RH, relative humidity; T, temperature;

Data from FluNet were aggregated by trimester-country. The 20 trimesters from December-March 2014-2015 to September-December 2019 defined the reference “pre-pandemic” period, and the six trimesters from March-June 2020 to June-September 2021 defined the “pandemic” period. The trimester from December 2019 to March 2020 was excluded because it overlapped with the period of COVID-19 emergence. We also discarded trimesters having less than 10 processed influenza specimens per week on average and those typically unaffected by influenza epidemics (i.e., having less than 5% of the annual positive cases on average during the pre-pandemic period, e.g., the summers in temperate regions).

We computed the percentage of influenza-positive cases as the ratio of positive to positive plus negative samples during the trimester (adding 0.5 to avoid division by zero issues). We computed the “log relative influenza level” as the base-10 logarithm of the ratio between the percentage of positive cases during a pandemic trimester and the average percentage of positive cases in the corresponding pre-pandemic trimesters [7,12]. Under the assumption that influenza surveillance was not substantially altered during the pandemic, this quantifies the reduction in influenza circulation. We also tested for secular trends that could potentially bias this indicator (Supplementary material).

Variables for prediction of influenza reduction

We collected the covariates described in Table 1 from public sources and IATA [20–28]. Additional details on covariate computation and their distributions are provided in the Supplementary material (section Definition of Covariates, Figure S1).

Clustering and regression tree analysis

We used the Variable Selection Using Random Forests (VSURF) algorithm to select the covariates that were highly predictive of influenza reduction [29]. Importance is defined as the increase in prediction error when the variable of interest is randomly reshuffled across observations. We discarded variables with close to zero importance in a univariable analysis. Then, we carried out a forward selection of predictors, including variables in their order of importance one at a time. Following the Breiman's rule [30], we retained the model with the least variables having prediction error less than the minimum prediction error plus one standard deviation.

Using the variables selected previously, we fit a regression tree to obtain an interpretable model [30]. The details of the approach are provided in the Supplementary material.

Analyses were performed with R version 4.2.1 [31] and packages *vsurf* [29] and *rpart* [32].

Robustness and sensitivity analyses

The details of the robustness checks and the sensitivity analyses are reported in the Supplementary material. In summary, we checked the robustness of the regression analysis to stochastic fluctuations in the dataset and to criteria for including the FluNet records in the analysis; we explored alternative definitions for covariates: COVID-19 daily deaths instead of COVID-19 daily cases, Oxford COVID-19 Government Response Tracker stringency index instead of governmental response [28], and alternative Google mobility reports instead of presence in workplaces. We also explored separate inclusion of age and infectious disease vulnerability index (IDVI) because these were highly correlated ($\rho_{\text{Spearman}} = 0.87$, $P_{\text{val}} < 0.01$).

Results

Decline of influenza in space and time

A total of 166 countries contributed data to FluNet between December 2014 and September 2021. Figure 1a shows the time course of the reports. In the prepandemic period, the percentage of positive tests varied seasonally between 4% and 33%, with major peaks during seasonal epidemics in northern countries and lower peaks for southern countries. The global number of tests for influenza remained within the range of historical levels throughout the whole COVID-19 pandemic period, but the percentage of influenza-positive tests dropped sharply to a minimum level of 0.04% during the months of July and August 2020.

A total of 112 countries remained for analysis, contributing 376 trimester-country observations (Table S1). During the pandemic, the percentage of influenza-positive tests varied across countries and trimesters over five orders of magnitude (from less than 0.002% to a maximum of 49%, as reported in Figure 1b) compared with only two orders of magnitude over the prepandemic period (between 1% and 95%). For 135 of the 376 observations, the percentage of positive influenza tests was more than 100 times smaller than expected. The reduction of influenza positivity could be dramatic, as shown by the zero positive tests of 26,114 processed tests reported in Japan during March–June 2021 compared with the average 75% expected in the prepandemic period. An increase in the percentage of positive tests was seen in 22 observations; this was, for example, the case of Haiti during December–March 2020–2021, where the percentage of positive tests was 15% compared with an expected 2.2% before the pandemic.

The spatial variation of the influenza decline is mapped in Figure 2 over the six pandemic trimesters. For the majority of

countries, the decline remained limited during March–June 2020, with 46 of 65 countries reporting less than 90% reduction from the prepandemic period (*i.e.*, log relative influenza level > -1). The decline became more pronounced in the subsequent trimesters, especially in North America, Europe, Mexico, and Japan during December–March 2020–2021 and March–June 2021. The decline was also strong in the majority of southern hemisphere countries during both June–September 2020 and June–September 2021. Conversely, a number of countries in South Asia (*e.g.*, Bangladesh, Afghanistan), Africa (*e.g.*, Mali, Senegal, Nigeria, Kenya, Zambia), and Central America (*e.g.*, Honduras, Haiti) showed limited influenza reduction throughout the whole COVID-19 pandemic period (log relative influenza levels > -1). The levels of reduction changed over the period. Interestingly, the log relative influenza level was as low as -2.4 during June–September 2020 in China but increased again starting September–December 2020. A similar increasing trend was observed also in a few other countries, such as in Kenya and Nigeria.

Clustering and regression tree analysis

The analysis was carried out on 93 countries, for which covariates were available, totaling 330 trimester-country observations (Table S1). Among the 20 covariates tested, 11 were selected as predictors of the log relative influenza level (Figure 3). Sociodemographic, preparedness, geographical, weather, and COVID-19 management aspects contributed all to explaining the changes, although, COVID-19 daily cases and IDVI were the most important.

The full regression tree built from the data accounted for 69% of the variance of the log relative influenza level ($R^2 = 0.69$; Figure S3, Table S2). To interpret the relationships between the selected variables and the trimesters–countries, we focus here on the first four splits based on IDVI, COVID-19 daily cases, longitude, and workplace mobility reduction (Figure 4a). The five groups identified by these splits (labeled 1–5, Figure 4a) showed a gradient in average log relative influenza level ranging from -3.03 (reduction by 99.9%) to -0.71 (reduction by 80%). How the observations in each group rank with respect to the whole dataset is shown in Figure 4b (see also Figure S2).

Group 1 included 109 trimesters–countries with high influenza decline, corresponding to the lower quartile of the whole dataset distribution. This group was characterized by high IDVI (median value corresponding to the 71th percentile (*pc.*) of the whole dataset), high COVID-19 daily cases (83rd *pc.*), old population (70th *pc.*), and low temperatures (25th *pc.*). The median reduction of workplace presence and median number of days with school closure were close to the whole population median but were higher than other groups, except for group 4 discussed hereafter. Population gathering restrictions were especially high (82nd *pc.*). The corresponding trimesters–countries included countries in Europe and North America during the 2020–21 influenza season, countries in temperate South America, and high IDVI countries in Central America and tropical Asia (Table S2 in the Supplementary material).

Group 2 was the smallest and had clustered observations with the largest influenza decline (median log relative influenza level corresponding to the least 8% of all data points). It gathered all observations from Australia, Japan, New Zealand, and South Korea. These trimesters–countries showed low COVID-19 daily cases (29th *pc.*), high IDVI (91st *pc.*), and high reduction of international flights (88th *pc.*). Reduction of workplace presence and number of days of school closure and gathering restrictions were comparatively low (23rd, 23rd, 13th *pc.*s., respectively).

Group 3 corresponded to 45 observations with intermediary log relative influenza level. Covariates were also close to the median of all data points. Singapore, from September–December 2020 to June–September 2021, was part of this group (larger tree in Fig-

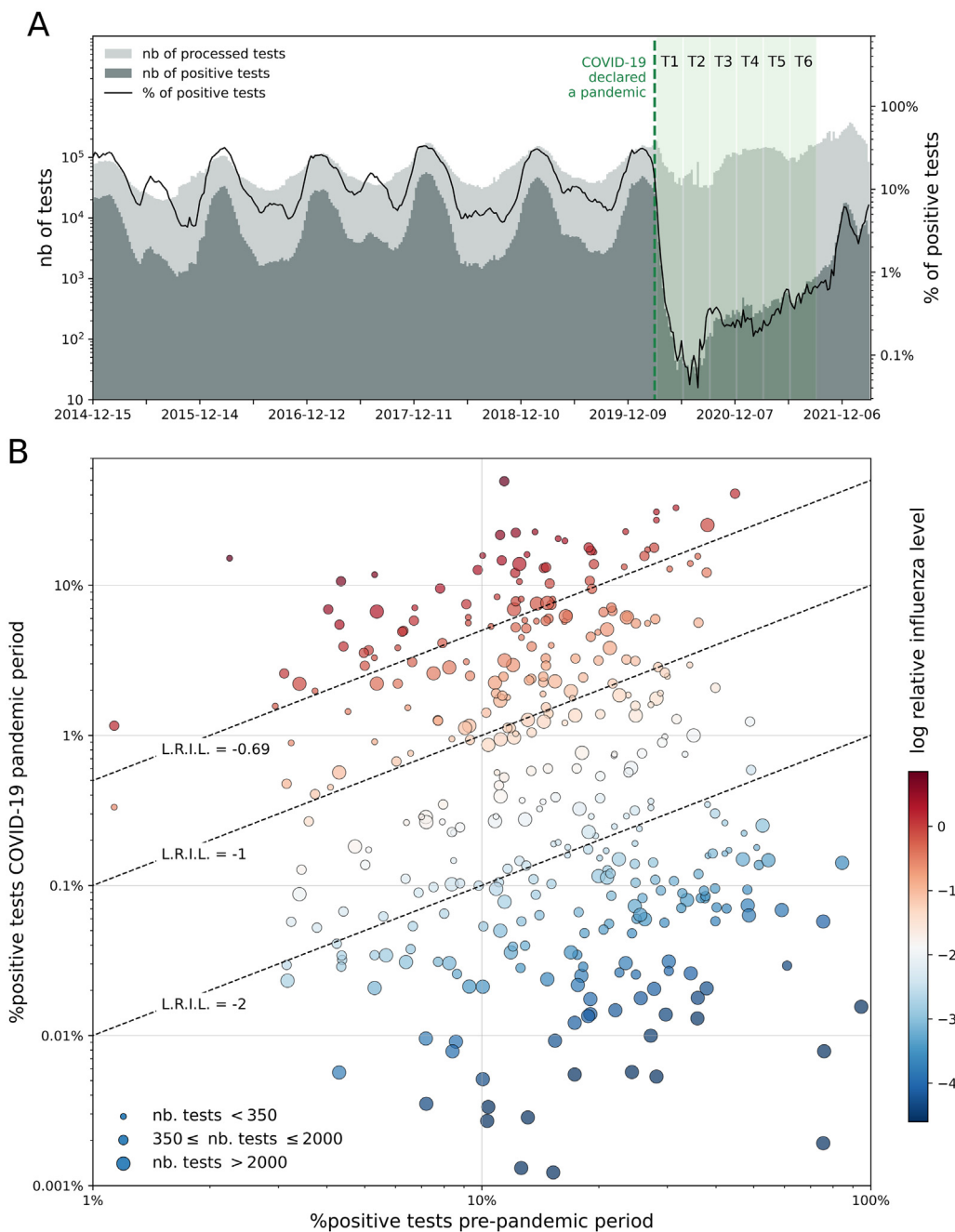


Figure 1. Change in influenza circulation during the COVID-19 pandemic relative to the prepandemic period. (a) Weekly counts of processed and positive tests of influenza reported to FluNet for all 166 countries included in the database from December 2014 to January 2022. The green shaded area indicates the COVID-19 pandemic period considered in the study. The six blocks indicate the trimesters. The week in which COVID-19 was declared a pandemic by World Health Organization is reported as reference. (b) Percentage of positive tests for the prepandemic and COVID-19 pandemic periods (December 2014–December 2019 and March 2020–September 2021, respectively), for all 376 countries and trimesters satisfying the filtering criteria on the FluNet data. For each trimester-country, the x coordinate is the average percentage of positive tests of the 5 years included in the prepandemic period, while the y coordinate is the percentage of positive tests during the COVID-19 pandemic period. The size of the dots is proportional to the number of samples found in FluNet for the pandemic period. Dots' color indicates the log relative influenza level. As guides to the eyes, the three dashed lines indicate the level curves of the L.R.I.L. equal to -2, -1 and -0.69, which correspond to flu reductions of 99%, 90% and 50%, respectively. L.R.I.L., log relative influenza level; nb, number.

ure S4). The covariates of these observations are close to the second group—high influenza reduction, low COVID-19 daily cases, and high reduction of international flights. Other observations of group 3 (e.g., Southeast Asia countries, such as Malaysia, Vietnam, Indonesia, and Thailand) were similar to Singapore but had lower population age and IDVI. They showed, however, a more limited influenza decline.

Group 4 had 39 observations corresponding to Europe and North America during the March–June 2020 trimester. At this period, influenza decline was limited (median log relative influenza level corresponding to the 68th pc. of all data points), but there was already a strong response to the COVID-19 pandemic as quantified, for instance by the reduction in the workplace presence (87th pc.) and number of days of school closure (83rd pc.).

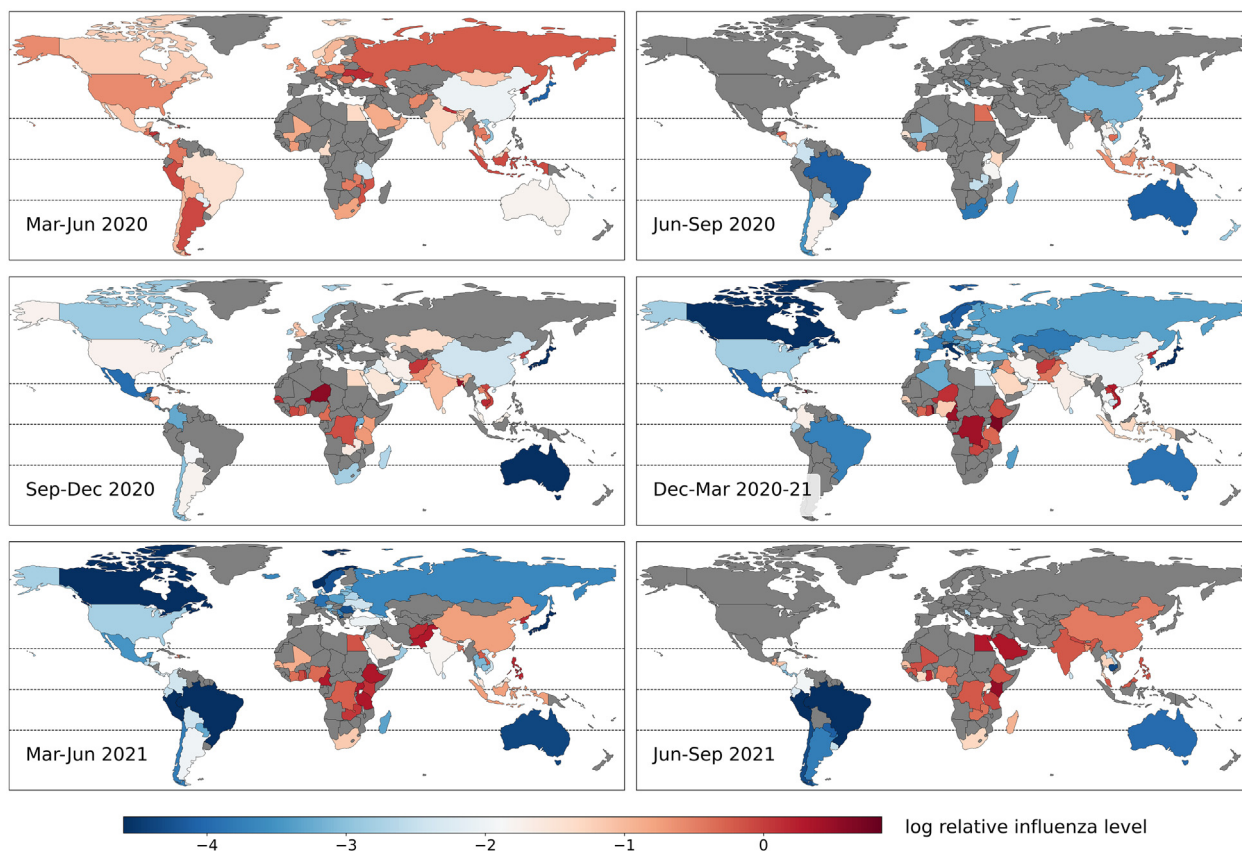


Figure 2. Influenza decline during the first 18 months of COVID-19 pandemic by trimesters-countries. Maps of the log relative influenza level for the six trimesters considered in the analysis. The gray color indicates trimesters-countries not included in the analysis.

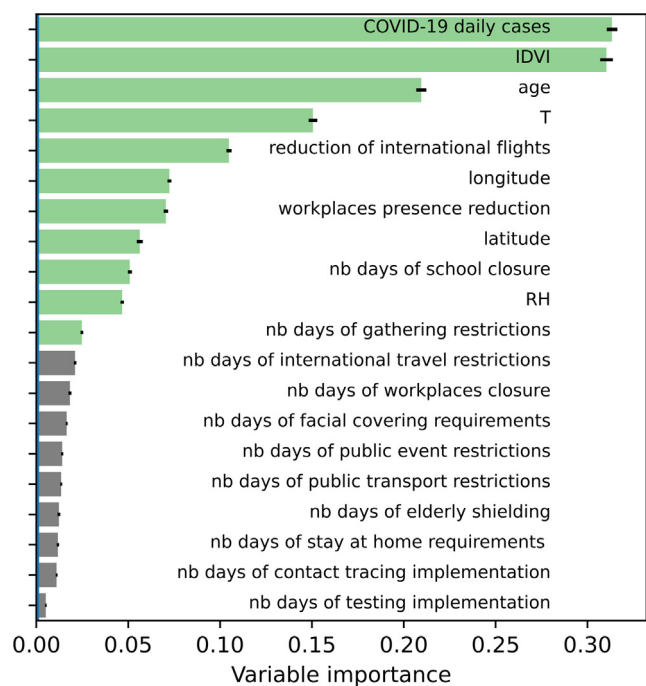


Figure 3. Importance of covariates predicting influenza decline in random forest analysis. Importance of covariates as predictors of the log relative influenza level. In green the 11 covariates selected as significant to build the model with the minimum prediction error following the Breiman's rule. Black segments show the standard deviations of the importance. IDVI, infectious disease vulnerability index; nb, number; RH, relative humidity; T, temperature.

Finally, group 5 included 123 trimesters-countries with the lowest decrease in influenza relative to the pre-pandemic period (log relative influenza level 76th pc.). In this group, there was a low number of COVID-19 cases (27th pc.), young population (19th pc.), low IDVI (19th pc.), and high temperatures (70th pc.). The response to the COVID-19 pandemic was mild, with limited reduction of international flights (28th pc.); the workplace presence reduction (34th pc.) and number of days of school closure (43rd pc.) were small compared with the whole population. This group was largely formed by tropical countries, such as in Africa, South and South-east Asia, Central America, and the Caribbean (Table S2 of the Supplementary material).

Robustness and sensitivity analyses

Variable selection and tree structure were robust to stochastic fluctuations. The five-group classification was robust to small perturbations in the data set, as was the selection of predictive variables. In some cases, for example with different inclusion criteria for FluNet data, observations in group 1 and group 2 tended to cluster together. More details are reported in the Supplementary material (section Robustness checks and sensitivity analyses, Table S3).

Discussion

The systematic analysis of influenza circulation across all continents and climatic regions shows that the influenza decline was global during the spread of the COVID-19 pandemic. This decrease was heterogeneous across countries and trimesters between March

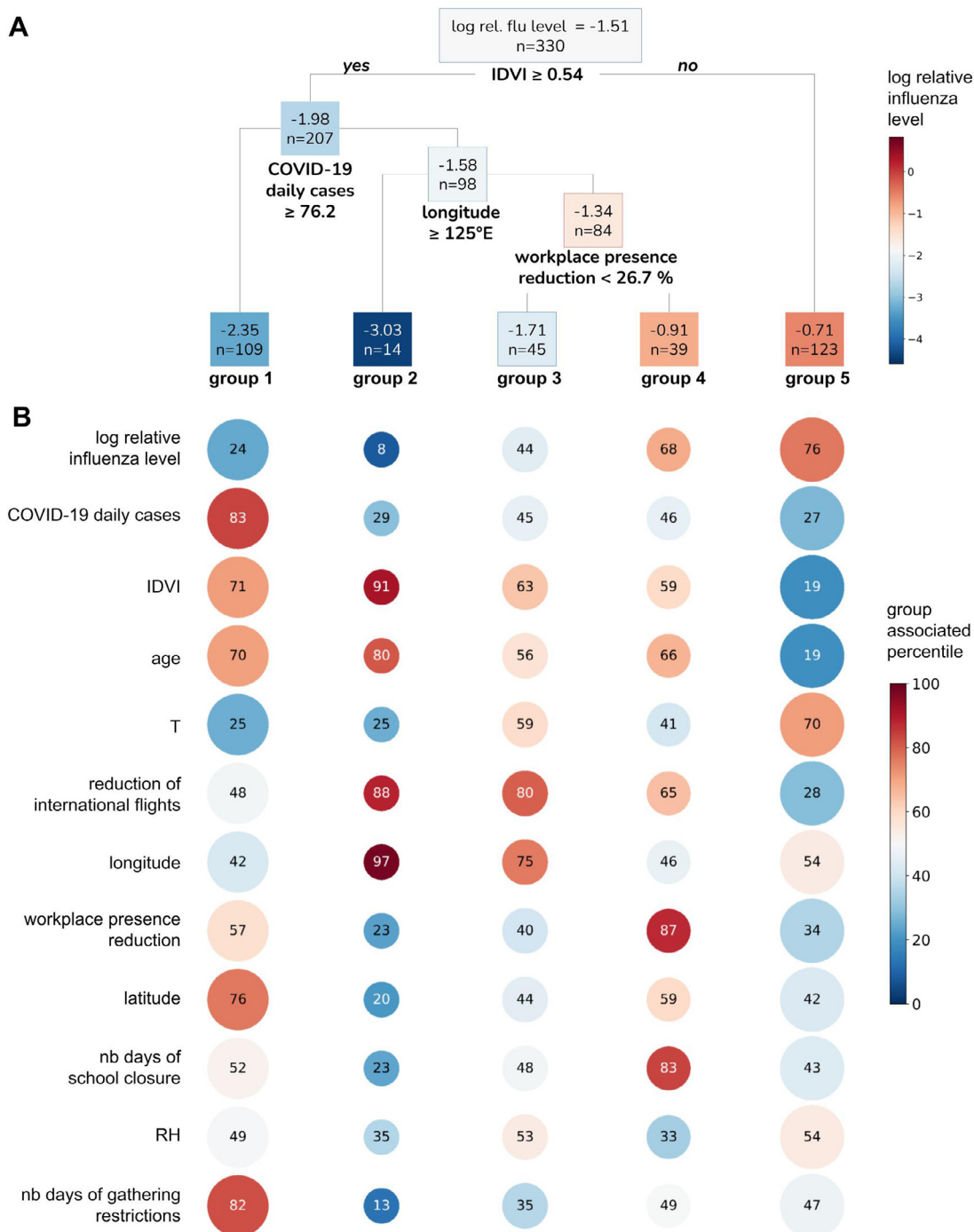


Figure 4. Regression tree analysis of influenza decline and characteristics of the identified subgroups. (a) Regression tree obtained with the variables selected in Figure 3. We report here the first four splits, which partition the observations in five groups. The full tree is reported in Figure S4 of the Supplementary material. For each node the average log relative influenza level and the number of observations are reported (the former is also indicated with a color scale). (b) Characteristics of each group. For each variable the color of the circle indicates the percentile of the whole dataset distribution the median of the group corresponds to. The percentile value is also indicated inside the circle. The size of the circle increases with the number of observations of the group. IDVI, infectious disease vulnerability index; nb, number; RH, relative humidity; T, temperature.

2020 and September 2021. Demographic, socioeconomic, weather, and COVID-19 characteristics explained a large part of this heterogeneity.

Influenza circulation is characterized by marked seasonal epidemics in temperate countries but a more complex annual pattern in the tropics [33]. Surveillance may be reinforced in epidemic times. The log relative influenza level allowed adjusting for such changes. We found that influenza declined nearly everywhere and

remained low compared with the prepandemic period during the 18 first months of the COVID-19 pandemic. Importantly, the worldwide number of influenza tests remained roughly the same in the prepandemic and pandemic period, ruling out a change in surveillance as the likely explanation. The largest reduction was between July and August 2020, and a progressive increase was seen again until September 2021. Temperate countries had the largest reduction, whereas it was limited in the tropics [14–16,34].

Influenza circulation could *a priori* change during the COVID-19 pandemic because of governmental measures, self-adapted behavioral changes, and direct interaction with SARS-CoV-2. We indeed found that reduction of international flights, presence at workplaces, school attendance, and mass gatherings explained part of the reduction; although, the impact was nonlinear. Initial strong restrictions against COVID-19 had to be relaxed in some low-resource countries [14,35,36], allowing renewed influenza circulation. Conversely, countries where a strong response against the COVID-19 pandemic could be maintained saw exceptionally low influenza circulation, except in March–June 2020, where strong local restrictions in Europe and the USA likely occurred at the end of the influenza season in the majority of cases [5]. For the rest of the time, temperate countries in Europe, North America, and South America that adopted a COVID-19 response centered over local restrictions by reducing workplace presence, school attendance, and gatherings had large reduction in influenza circulation, irrespective of the reduction of international flights. This was very different in four “zero-COVID” nations (Australia, New Zealand, Japan, and South Korea), where influenza dropped despite local restrictions were limited [37], suggesting a key role for border controls in preventing seeding from abroad. Reducing international flights by 94–97%, however, did not prevent influenza introduction in Vietnam from the neighboring country, Cambodia, [14] which is likely due to the difficulty of controlling land borders.

The limitation of gatherings or public events, imposed international travel restrictions, and school closure were previously found to be the main drivers in suppressing influenza [12,13]. However, actual behavior, such as the volume of flights rather than imposed international travel restrictions or percentage presence at the workplace rather than mandatory reduction, was more predictive of influenza reduction than governmental restrictions. Behavioral proxies may indeed capture adhesion to restrictions that depended on place and stage of the pandemic [38–40].

The reduction of influenza could also stem from direct viral interference with SARS-CoV-2, for example, through competition for cellular resources or interferon production [41,42]. Infection rates with influenza reportedly changed according to SARS-CoV-2 status and *vice versa* [42]. In this respect, we found a high influenza decline with high COVID-19 incidence in group 1 and low influenza decline with low COVID-19 incidence in group 5, as well as low levels for both in zero-COVID countries. Under-reporting of COVID-19 cases may be an alternative explanation to low COVID-19 reporting in the low-income countries of group 5 [35,36,43].

The characterization of influenza decline in space and time may come of use to analyze its resurgence over time. The loss of exposure to the influenza virus may lead to more severe waves or out of season waves [6,7] and may increase the susceptible pool, especially in children [44,45]. In the first half of 2022, influenza circulation was remarkably late in Europe [46] and early in the southern hemisphere, with a peak that was above average in Australia [47]. Other epidemiological changes could occur regarding the exposed population and the seeding from the tropics [33] as worldwide air transportation resumes. Deciding on the composition of the vaccine may also prove more difficult due to the change in the evolutionary dynamics of circulating strains [15]. Between March 2020 and August 2022, no B/Yamagata-lineage circulation was confirmed worldwide [15,48].

Our study is affected by limitations. We assumed that influenza surveillance was not substantially altered during the pandemic period. The number of samples in the FluNet database indeed did not change substantially over time because many countries maintained the influenza surveillance or quickly resumed it after initial disruption [3,4]. The influenza positivity rate may have been affected by changes in surveillance protocols due to the COVID-19 pandemic. We did not account for influenza vaccination due to limited infor-

mation at the global scale. Vaccination rates are highly heterogeneous among countries [49]. Although targeted recommendations increased coverage in the elderly during the 2020–21 season in nine northern hemisphere countries and Australia [49], the efficacy of the influenza vaccine during the study period remains unknown. Lineages circulating in southeast Asia during autumn 2020 were not included in the recommendations for the 2020–2021 Northern Hemisphere season [14]. Last, we relied on the FluNet database, which integrates worldwide influenza records, aggregating countries with highly diverse influenza surveillance quality and coverage. The results from the sensitivity analysis showed that the reported results were similar in varying exclusion criteria.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethical approval

Ethical approval or individual consent was not applicable.

Author contributions

FB, PYB, VC, OL, MT, and CP conceived and designed the study. FB, OL, MT, and CP designed the regression analysis. FB collected and analyzed the data and implemented the regression analysis. FB and CP accessed and verified the data and were responsible for the decision to submit for publication. FB and CP drafted the article. FB, PYB, VC, OL, MT, and CP interpreted the results and contributed to the writing of the final version of the article

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2022.12.042](https://doi.org/10.1016/j.ijid.2022.12.042).

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