Title: The impact of COVID-19 pandemic on influenza transmission: molecular and epidemiological evidence

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Abstract:

To quantify the impact of COVID-19-related control measures on the spread of human influenza virus, we analyzed case numbers, viral molecular sequences, personal behavior data, and policy stringency data from various countries, and found consistent evidence of decrease in influenza incidence after the emergence of COVID-19.
Keywords: COVID-19, influenza, case, effective population size, genetic diversity, epidemiology

Article Summary

We quantify a noticeable decrease in H1N1 and H3N2 cases and genetic diversity in selected countries since the onset of the COVID-19 pandemic.

Introduction

The emergence and spread of COVID-19 in 2020 led to a number of large-scale public health measures to limit international travel, reduce gatherings, and increase mask-wearing. While these preventative measures were implemented to curtail the COVID-19 pandemic, they seem to have also impacted the spread of other respiratory illnesses. There have been several reports on the decrease in case numbers during 2019-2020 influenza season in the northern hemisphere [6], and the lack of a 2020 influenza season in the southern hemisphere [8]. Here, we quantify the impact of the COVID-19 pandemic on the spread of influenza in terms of incidence and viral molecular diversity [1].

Method

Case count data

We analyzed weekly case count data of influenza available in FluNet [10] from various regions during the 2010-2020 influenza seasons. We defined $T_S$ and $T_E$ as the weeks during which the estimated number of cases reached 10% and 90% of the total case numbers in each influenza
season, respectively. Since the influenza outbreaks for most regions started before the COVID-19 outbreak, we compared $T_E$ and durations of influenza seasons pre- and post-COVID-19 pandemic. We defined the duration of an influenza season by the difference between $T_S$ and $T_E$, and standardized the duration in the 2019-2020 season by the average and standard deviation of the duration from previous 9 seasons.

**Viral molecular sequences**

We analyzed the HA segment of human influenza A H1N1 and H3N2 sequences available in the GISAID EpiFlu database on November 1st 2020. The collection dates of the sequences ranged from January 2016 to December 2020. We used BEAST [3] to estimate the effective population size ($N_e$) from 2016 to 2020 for each location. The numbers of sequences analyzed are indicated in Appendix Table 1.

**Results and Discussion**

To examine the indirect impact of COVID-19 on influenza dynamics, we compared the 2019-2020 influenza season with previous 9 seasons in 21 locations across 5 continents (Table 1). We found that for all locations in Asia, the outbreak in 2019-2020 both ended earlier and lasted for a shorter duration than previous years. In the Americas, Europe, and Africa, 12 locations out of 15 showed an earlier end of the flu season in the 2019-2020 season than previous years; the rest remained similar. For locations where influenza seasons usually end later in the year, such as Brazil, Guatemala, and South Africa, the difference in duration between the 2019-2020 season and previous seasons was larger than other locations. The flu season in the Southern Hemisphere, which usually starts much later in the year, disappeared in several countries in 2020 [6,8].
In addition to case count data, we analyzed molecular data to evidence our findings. For each location and each influenza type, we calculated the within-location genetic diversity, Watterson’s $\theta$ [9], for the first half of 2019 and for the first of 2020 (Appendix Table 2). We found that for 10 out of 11 locations we analyzed, $\theta$ decreased from 2019 to 2020 for H1N1, and 9 out of 11 locations for H3N2. On the other hand, we calculated between-region genetic diversity for each pair of regions once in 2019 and again in 2020; 9 out of 11 locations for H1N1 and 6 out of 11 locations for H3N2 had their between-region genetic diversity increase from 2019 to 2020 in at least 50% of pairs for which the location was involved, reflecting reduced travel between regions in 2020 (Appendix Table 3).

While Watterson’s $\theta$ measures overall viral diversity, the effective population size ($N_e$) quantifies genetic diversity over time [4]. We estimated $N_e$ for H1N1 in 11 countries and found a decrease in $N_e$ in 9 countries, including Italy and Taiwan (Figure 1; Appendix Figure 1; Appendix Table 1). For H3N2, we analyzed 5 countries, and found a decrease in $N_e$ in South Africa and Taiwan in 2020 (Figure 1; Appendix Figure 2; Appendix Table 1).

For personal measures and government policies against COVID-19, we also noticed that Asian countries tend to act earlier than countries in other continents, especially wearing masks (Appendix Table 4). Taken together, we observed earlier ends of flu seasons in Asia than in Europe and America, which could be explained by the earlier implementation of non-pharmaceutical interventions.
The decrease in influenza incidence after the emergence of COVID-19 was confirmed by both case count and molecular data, providing stronger support for a genuine decrease in influenza incidence, even when count data might be incomplete or imprecise due to potentially less flu surveillance in 2020.

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Dai-Wei Huang is an undergraduate student in the Interdisciplinary Program of Life Science, National Tsing Hua University, Hsinchu, Taiwan and is currently doing research related to epidemiology and biostatistics.
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Table and Figure

Table 1. Comparison of influenza outbreaks before and after the emergence of COVID-19

| Continent          | Country      | $T_E, 19-20$ | Median of $T_E$ in previous 9 seasons (range) | Difference in $T_E$ | Standardized duration in 2019-2020 season |
|--------------------|--------------|--------------|-----------------------------------------------|---------------------|------------------------------------------|
| Asia               | Singapore    | 4            | 27 (21, 29)                                   | -23                 | -2.12                                    |
|                    | Korea        | *4           | 15 (4, 17)                                    | -11                 | -1.20                                    |
|                    | China        | 4            | 20 (7, 29)                                    | -16                 | -1.42                                    |
|                    | Taiwan       | 15           | 24 (21, 27)                                   | -9                  | -2.47                                    |
|                    | Thailand     | 9            | 26 (11, 29)                                   | -17                 | -1.34                                    |
|                    | Japan        | *6           | 13 (10, 16)                                   | -7                  | -0.77                                    |
| North America      | Canada       | 11           | 14 (10, 17)                                   | -3                  | -0.07                                    |
|                    | USA          | 11           | 11 (8, 15)                                    | 0                   | 0.78                                     |
|                    | Mexico       | 11           | 11 (1, 24)                                    | 0                   | 0.10                                     |
| Central and south America | Brazil     | 12           | 27 (19, 28)                                   | -15                 | -0.26                                    |
|                    | Guatemala    | 13           | 23 (18, 27)                                   | -10                 | 0.12                                     |
| Europe             | Sweden       | 11           | 13 (9, 16)                                    | -2                  | 0.07                                     |
|                    | Norway       | 11           | 14 (5, 17)                                    | -3                  | 0.15                                     |
|                    | Denmark      | *11          | 11 (3, 15)                                    | 0                   | 0.65                                     |
|                    | Finland      | 8            | 11 (8, 12)                                    | -3                  | 1.10                                     |
|                    | Germany      | 10           | 12 (9, 13)                                    | -2                  | -0.49                                    |
|                    | France       | 10           | 11 (6, 14)                                    | -1                  | -0.04                                    |
|                    | UK           | 10           | 13 (4, 15)                                    | -3                  | 0.98                                     |
|                    | Spain        | 8            | 10 (5, 13)                                    | -2                  | -0.20                                    |
|                    | Italy        | 9            | 10 (6, 12)                                    | -1                  | 0.32                                     |
| Africa             | South Africa | 7            | 27 (26, 29)                                   | -20                 | -2.67                                    |

$\dagger$ Difference in $T_E$ is equal to $T_E, 19-20$ minus the median of $T_E$ in previous 9 seasons.

$\dagger$ Here, $n$ means the $n$th week in the second year of that season. For example, for 2019-2020 season, we expressed $T_E$ by the $n$th week in 2020.

$^\#$ Since there is no data for Taiwan on Flunet, we used the data of outpatient visits for influenza-like illness from Taiwan National Infectious Disease Statistics System (https://nidss.cdc.gov.tw/en/Home/Index).

* In 2019-2020 season, there was no processed specimen listed on Flunet since week 4 and week 6 in Korea and Japan, respectively.

$^\circ$ In Denmark, 2011-2012 season was excluded because there was no obvious influenza outbreak that year.
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Figure 1. Effective Population Size Trajectory of H1N1 in Italy and H3N2 in Taiwan
Appendix

Methods

**Personal measures and governmental policies against COVID-19**
We analyzed two personal measures taken against the spread of COVID-19 from YouGov [7]—wearing masks when in public places and improving personal hygiene, from February 21, 2020 to December 17, 2020. For governmental responses to COVID-19, we used the data from OxCGRT, the Oxford COVID-19 Government Response Tracker [5], from January 1, 2020 to May 31, 2020.

**Molecular Epidemiology**

We estimated a mutation rate of H3N2 for New York State of $4 \times 10^{-3}$ per base per year and $3.6 \times 10^{-3}$ for H1N1. We then fixed the corresponding global mutation rates for the rest of the locations. We assumed the HKY prior mutation model with empirical frequencies and Gamma+Invariant site heterogeneity with 4 Gamma categories and 3 partitions into codon positions and assumed the Bayesian Skyride Coalescent prior on effective population size trajectories. We examined convergence by the likelihood trace plot and the effective sample size for each location and type. To estimate $N_e$, we divided the output ($N_e \times G_t$) by the generation time ($G_t$) for H1N1 (2.3 days) and for H3N2 (3.1 days) [2]. We ran the MCMC for 10,000,000 iterations, thinning every 1000 iterations and with 10% of burnin. We removed any regions without convergence.

The within-region diversities were measured by Watterson’s $\theta$. The between-region diversities were measured as follows:

$$\text{Between-region diversity between region 1 and region 2} = \frac{\theta_{\text{region 1}} + \theta_{\text{region 2}}}{2} - \frac{\theta_{\text{pooled}}}{2}$$

where $\theta_{\text{pooled}}$ was Watterson’s $\theta$ when combining two regions together.
Appendix Table 1. Effective sample sizes of root age and number of sequences per country for influenza types H1N1 and H3N2. These effective sample size numbers were obtained with Tracer [3]. Effective sample sizes with N/A indicate lack of convergence and were omitted from the analysis.

| Country                | Genotype | Effective Sample Size | Sequences |
|------------------------|----------|-----------------------|-----------|
| Australia              | H1N1     | 7                     | 749       |
| Bangladesh             | H1N1     | 15                    | 407       |
| Brazil                 | H1N1     | N/A                   | 722       |
| California, USA        | H1N1     | N/A                   | 514       |
| Chile                  | H1N1     | 9                     | 741       |
| China                  | H1N1     | 6                     | 674       |
| England, UK            | H1N1     | N/A                   | 939       |
| France                 | H1N1     | 5                     | 905       |
| Guatemala              | H1N1     | 1546                  | 126       |
| Italy                  | H1N1     | 145                   | 250       |
| Japan                  | H1N1     | 19                    | 782       |
| New York, USA          | H1N1     | 2044                  | 186       |
| South Africa           | H1N1     | 3553                  | 180       |
| Taiwan                 | H1N1     | 3392                  | 115       |
| Australia              | H3N2     | N/A                   | 778       |
| Bangladesh             | H3N2     | 18                    | 503       |
| Brazil                 | H3N2     | N/A                   | 774       |
| California, USA        | H3N2     | N/A                   | 820       |
| Chile                  | H3N2     | N/A                   | 625       |
| China                  | H3N2     | N/A                   | 958       |
| England, UK            | H3N2     | N/A                   | 997       |
| France                 | H3N2     | N/A                   | 727       |
| Guatemala              | H3N2     | 2407                  | 145       |
| Italy                  | H3N2     | N/A                   | 513       |
| Japan                  | H3N2     | 4                     | 795       |
| New York, USA          | H3N2     | N/A                   | 625       |
| South Africa           | H3N2     | 220                   | 223       |
| Taiwan                 | H3N2     | 550                   | 331       |
### Appendix Table 2.

Within-region genetic diversity during the first half of 2019 compared to the first half of 2020, for influenza types H1N1 and H3N2. Diversity was measured by Watterson’s θ. The decrease column indicates whether genetic diversity decreased from the first half of 2019 to the first half of 2020. Sequences with more than 5% gaps were removed from the analysis. N/A indicates a lack of data.

| Country/Region       | Genotype | 2019      | 2020      | Decrease |
|----------------------|----------|-----------|-----------|----------|
| Australia            | H1N1     | 2.77E-02  | 2.20E-02  | Yes      |
| Bangladesh           | H1N1     | N/A       | N/A       | N/A      |
| Brazil               | H1N1     | 2.12E-02  | 1.38E-02  | Yes      |
| California, USA      | H1N1     | 2.55E-02  | 1.63E-02  | Yes      |
| Chile                | H1N1     | 2.22E-02  | 9.46E-03  | Yes      |
| China                | H1N1     | 3.46E-02  | 1.75E-02  | Yes      |
| England, UK          | H1N1     | 2.93E-02  | 2.03E-02  | Yes      |
| France               | H1N1     | 2.51E-02  | 2.08E-02  | Yes      |
| Italy                | H1N1     | 2.03E-02  | 1.28E-02  | Yes      |
| Japan                | H1N1     | 2.64E-02  | 1.88E-02  | Yes      |
| New York, USA        | H1N1     | 1.94E-02  | 1.68E-02  | Yes      |
| South Africa         | H1N1     | 6.44E-03  | 8.76E-03  | No       |
| Taiwan               | H1N1     | N/A       | N/A       | N/A      |
| Australia            | H3N2     | 2.97E-02  | 2.32E-02  | Yes      |
| Bangladesh           | H3N2     | N/A       | N/A       | N/A      |
| Brazil               | H3N2     | 2.65E-02  | 2.68E-02  | No       |
| California, USA      | H3N2     | 2.35E-02  | 4.58E-02  | No       |
| Chile                | H3N2     | 2.11E-02  | 1.35E-02  | Yes      |
| China                | H3N2     | 5.99E-02  | 1.45E-02  | Yes      |
| England, UK          | H3N2     | 2.77E-02  | 2.15E-02  | Yes      |
| France               | H3N2     | 3.28E-02  | 2.25E-02  | Yes      |
| Italy                | H3N2     | 2.66E-02  | 1.87E-02  | Yes      |
| Japan                | H3N2     | 3.02E-02  | 1.16E-02  | Yes      |
| New York, USA        | H3N2     | 1.70E-02  | 8.22E-03  | Yes      |
| South Africa         | H3N2     | 1.86E-02  | 3.21E-03  | Yes      |
| Taiwan               | H3N2     | N/A       | N/A       | N/A      |
**Appendix Table 3.** Between-region diversity during the first half of 2019 compared to the first half of 2020, for influenza types H1N1 and H3N2. For each pair of regions, we calculated the between-region diversity in the first half of 2019 and in the first half of 2020. The third column for each region denotes the number of pairs involving that region with an increase in between-region diversity from 2019 to 2020, divided by the total number of pairwise comparisons. Regions where this fraction is above 0.5 are marked in grey. N/A indicates that there was not enough data to calculate diversity.

| Country/Region         | Genotype | Increase in between-region theta |
|------------------------|----------|----------------------------------|
| Australia              | H1N1     | 8/10                             |
| Bangladesh             | H1N1     | N/A                              |
| Brazil                 | H1N1     | 4/10                             |
| California, USA        | H1N1     | 8/10                             |
| Chile                  | H1N1     | 9/10                             |
| China                  | H1N1     | 9/10                             |
| England, UK            | H1N1     | 9/10                             |
| France                 | H1N1     | 7/10                             |
| Italy                  | H1N1     | 8/10                             |
| Japan                  | H1N1     | 8/10                             |
| New York, USA          | H1N1     | 6/10                             |
| South Africa           | H1N1     | 0/10                             |
| Taiwan                 | H1N1     | N/A                              |
| Australia              | H3N2     | 2/10                             |
| Bangladesh             | H3N2     | N/A                              |
| Brazil                 | H3N2     | 6/10                             |
| California, USA        | H3N2     | 8/10                             |
| Chile                  | H3N2     | 5/10                             |
| China                  | H3N2     | 3/10                             |
| England, UK            | H3N2     | 7/10                             |
| France                 | H3N2     | 4/10                             |
| Italy                  | H3N2     | 5/10                             |
| Japan                  | H3N2     | 6/10                             |
| New York, USA          | H3N2     | 6/10                             |
| South Africa           | H3N2     | 10/10                            |
| Taiwan                 | H3N2     | N/A                              |
## Appendix Table 4. Comparison of personal measures and governmental policies against COVID-19

| Continent     | Country     | Mask     | Hygiene | Stringency index | Time to 0.5 |
|---------------|-------------|----------|---------|------------------|-------------|
|               |             | Median (range) | #Time to 70% | Median (range) | #Time to 70% | Median (range) | Time to 70% |
| Asia          | China       | 83 (79, 90) | 1       | 80 (74, 85)     | 1           | 75.46 (0, 81.94) | 3.7         |
|               | Japan       | 74.5 (62, 86) | 4       | 70.5 (65, 75)  | 5           | 40.74 (0, 47.22) | Inf         |
|               | Singapore   | 89 (21, 92) | 8       | 81 (74, 87)    | 1           | 36.11 (5.56, 76.85) | 14         |
|               | South Koreaa | NA       |         |         |             |             |             |             |
|               | Taiwan      | 85 (80, 89) | 1       | 80 (74, 87)    | 1           | 28.70 (2.78, 31.48) | Inf         |
|               | Thailand    | 83 (71, 90) | 1       | 79 (73, 88)    | 1           | 36.58 (0, 76.85) | 11.6        |
| North America | Canada      | 58 (6, 86)  | 19      | 72 (67, 82)    | 1           | 43.52 (0, 74.54) | 11.1        |
|               | USA         | 76 (5, 83)  | 17      | 61 (42, 72)    | 5           | 53.70 (0, 72.69) | 10.9        |
|               | Mexico      | 37 (17, 67) | ₹       | 78 (75, 82)    | 1           | 2.78 (0, 82.41)  | 12          |
| Central and South America | Brazil | NA       |         |         |             |             |             |             |
|               | Guatemala   | NA       |         |         |             |             |             |             |
| Europe        | Denmark     | 3 (1, 73)  | 35      | 70 (55, 83)    | 1           | 57.41 (0, 72.22) | 10.4        |
|               | Finland     | 6 (1, 56)  | Inf     | 69 (63, 82)    | 3           | 48.15 (0, 67.59) | 10.9        |
|               | Sweden      | 5.5 (1, 15) | Inf    | 64 (55, 72)    | 3           | 31.49 (0, 64.81) | 12.1        |
|               | Norway      | 6.5 (1, 47) | Inf    | 77 (61, 86)    | 1           | 58.33 (0, 79.63) | 10.7        |
|               | Germany     | 63 (1, 72) | 36      | 60 (56, 72)    | 3           | 42.13 (0, 76.85) | 11.1        |
|               | France      | 78.5 (5, 85) | 12      | 61 (55, 76)    | 3           | 65.97 (0, 87.96) | 10.9        |
|               | UK          | 33.5 (1, 76) | 25      | 61 (35, 77)    | 4           | 19.45 (0, 79.63) | 11.7        |
|               | Spain       | 87 (5, 90)  | 8       | 81.5 (73, 86)  | 1           | 68.06 (0, 85.19) | 10.6        |
|               | Italy       | 85 (26, 86) | 3       | 72 (68, 82)    | 1           | 63.89 (0, 93.52) | 7.7         |
| Africa        | South Africa | NA      |         |         |             |             |             |             |

# Time to 70% for mask and hygiene represents time to 70% of the interviewed people saying that they wore a face mask when in public places and washed hands frequently/used hand sanitizer, respectively. They are expressed as week numbers in 2020.

Inf means that 70% was never reached during our study period.
Appendix Figure 1. Estimated Effective Population Size Trajectory for H1N1 in selected regions.
Appendix Figure 2. Comparison of Effective Population Size Trajectory for H3N2 in selected regions.

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GISAID accession numbers for all sequences used can be found at https://github.com/leonkt/accession-numbers/.