Assessing the interactions between COVID-19 and influenza in the United States

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March 30, 2020

Abstract

The 2019-2020 influenza sentinel surveillance data exhibits unexpected trends. Typical influenza seasons have a small herald wave, followed by a decrease due to school closure during holidays, and then a main post-holiday peak that is significantly larger than the pre-holiday wave. During the 2019-2020 influenza season, influenza-like illness data in the United States appears to have a markedly lower main epidemic peak compared to what would be expected based on the pre-holiday peak. We hypothesize that the 2019-2020 influenza season does have a lower than expected burden and that this deflation is due to a behavioral or ecological interaction with COVID-19. We apply an intervention analysis to assess if this influenza season deviates from expectations, then we compare multiple hypothesized drivers of the decrease in influenza in a spatiotemporal regression model. Lastly, we develop a mechanistic metapopulation model, incorporating transmission reduction that scales with COVID-19 risk perception. We find that the 2019-2020 ILI season is smaller and decreases earlier than expected based on prior influenza seasons, and that the increase in COVID-19 risk perception is associated with this decrease. Additionally, we find that a 5% average reduction in transmission is sufficient to reproduce the observed flu dynamics. We propose that precautionary behaviors driven by COVID-19 risk perception or increased isolation driven by undetected COVID-19 spread dampened the influenza season. We suggest that when surveillance for a novel pathogen is limited, surveillance streams of co-circulating infections may provide a signal.

Introduction

In December 2019, a cluster of pneumonia cases caused by a novel coronavirus were identified in Wuhan, China. In the months since, the now-termed COVID-19 pandemic has rapidly spread around the world, leading to hundreds of thousands of cases in over 160 countries [1]. The first evidence of community spread of SARS-Cov-2, the virus which causes COVID-19, in the United States appeared in February 2020. Since then, there have been widespread workplace, school, and business closures to dampen transmission [2]. Preceding this widespread policy response, individuals, informed by massive media coverage, engaged in voluntary behaviors such as increased handwashing and social distancing [3]. Such non-pharmaceutical interventions (NPIs) are known to play a significant role in diminishing transmission, and are expected to be particularly important against SARS-Cov-2 as the virus appears to transmit for up to two weeks before symptoms appear [4]. Indeed, NPIs have been very effective in reducing the potential number of COVID-19 cases in China [5, 6]. As the COVID-19 outbreak unfolds, it is important to empirically understand the effects of NPIs on infection spread, and characterize the potential interaction between COVID-19 and other circulating respiratory infections. As the spread of COVID-19 in the United States has been temporally coincidental with the influenza season, and both infections share the same transmission pathways and NPIs, we focus on influenza as a case study.

Influenza dynamics are often evaluated through measuring influenza-like illness (ILI), which tracks cases of individuals with symptoms consistent with influenza, but where influenza is not laboratory confirmed. Typical ILI dynamics in an influenza season exhibit a small pre-holiday peak, followed by a larger post-holiday peak [7]. Recent ILI data for the United States show a markedly lower epidemic peak for the 2019-2020 influenza season compared to what would be expected based on the pre-holiday peak [8]. A similar phenomenon has been observed in other locations including Hong Kong and France [9, 10]. Understanding this uncharacteristic ILI behavior is important for understanding influenza epidemiology and optimizing influenza mitigation efforts. Assessing ILI dynamics in the US in the time of COVID-19 also provides a useful tool to understanding the ecological interaction between these two respiratory infections which share transmission pathways and interventions, as well as to gain a better understanding of COVID-19 dynamics and control.

Here we aim to: (1) identify whether ILI incidence in the US is lower than expected following the emergence of COVID-19; and (2) assess which factors explain the reduction in ILI levels among COVID-19 risk perception, changes in influenza risk perception, strain dynamics or environmental factors. Finally, (3) we propose mechanisms by which these factors act to result in the observed ILI dynamics.

Methods

We study spatial influenza-like illness (ILI) data for the United States, and use a combined statistical and mechanistic approach to address our aims.

Disease Data

Influenza case data was reported by the U.S. Center for Disease Control and Prevention's (CDC) Outpatient Influenza-like Illness Surveillance Network (ILINet) [11]. Physicians in this sentinel network of ILInet report weekly influenza-like illness based on a symptom profile: fever and a cough and/or sore throat. Visits with ILI cases are reported in addition to the total number of visits (all cause visits) seen by the physician. We obtained data for the 2019-2020 season at the time the study was conducted at the national and state level. We also obtained the ILI data for prior influenza seasons to use as controls. We selected control seasons with similar strain dynamics to the 2019-2020 influenza season, which has a combination of influenza A H1N1 and influenza B circulation: the 2015-2016, 2008-2009, and 2002-2003 seasons. The data were z-normalized and smoothed with a smoothing spline and forward filled for any missing values. No data were available for Florida.

Intervention Analysis

To assess whether ILI incidence during January-February 2020 deviated from expectations, we conducted an intervention analysis using the `CausalImpact` R package [12]. Briefly, this method uses data from control time series to construct structural models for a counterfactual time series, or what is projected to occur if a disruption ("intervention") had not occurred. In particular, we use past influenza seasons as controls to characterize counterfactual 2019-2020 influenza season dynamics if COVID-19 risk perception had not occurred; the comparison between this counterfactual influenza time series and the true influenza time series for 2019-2020 allow us to identify any deviations from expectations. We used three control time series of previous influenza seasons (the 2015-2016, 2008-2009, and 2002-2003 seasons) individually, and together. The disruption initiated by COVID-19 was modeled as an "intervention" starting February 3, 2020. Thus, we considered October 7, 2019 to February 3, 2020 as the pre-intervention period, and February 10, 2020 to March 2, 2020 as the post-intervention period.

Regression model

We used a regression-based approach to identify the factors that may explain the change identified in ILI dynamics above [13, 14]. The model structure is:

$$Y_{it} \sim Gaussian(\lambda_i, \theta)$$

where Y_{it} is the ILI cases normalized by total visits in US state i at week t. The mean of this distribution, λ_i, is modeled by:

$$log(\lambda_i) = \beta_0 + \sum_{1}^{j} \beta_j x_{i,j} + u_t + \mu_s$$

where β_0 is the intercept, β_j represents coefficient estimates for social and biological covariates, μ_s represents a state-level group effects, and u_t is a temporal autocorrelation random walk order 2 effect, with the structure $u_t - u_{t-2} \sim N(0, \tau_u)$. We also developed aspatial models for individual state data to identify if there is any spatial heterogeneity in the temporal processes.

The model covariates included COVID-19 risk perception, influenza risk perception, humidity (shown to be an important driver of influenza dynamics [15, 16]), and strain dynamics. To measure COVID-19 risk perception, we collected the weekly mean number of Google Trends searches of "coronavirus", "COVID", and "COVID-19" at the national and state level [17, 18]. To represent ILI risk perception, we collected the weekly mean number of Google Trends searches of "influenza" and "flu". To measure relative humidity, we collected data from the US Local Climatological Database, which provides summaries of climatological conditions from airport and other prominent weather stations managed by the National Weather Service, Federal Aviation Administration and Department of Defense [19]. For each state, we randomly chose a weather station that covered the appropriate time period, as a marker for humidity levels in that state. To measure strain dynamics, we used the National Respiratory and Enteric Virus Surveillance System (NREVSS) virological surveillance data to identify the proportion of respiratory specimens tested for influenza that tested positive for influenza A or influenza B [11].

Metapopulation model

To understand the process of respiratory disease transmission and mitigation, we developed a metapopulation model that represents age-specific contact between children and adults within metropolitan areas and is spatially divided into metropolitan areas linked through air traffic flows. The model is described in detail in [7]. We simulated a seasonal influenza epidemic in the US, including typical holiday school closure, and seasonality with the season ending at April 30, 2020. We then incorporated reduction in age-structured transmission by $(1-\delta\tau(t))$, where δ is the intensity of transmission decrease, which relates to the increase in risk perception level of $\tau(t)$. We parameterize $\tau(t)$ based on daily Google trends for COVID-19 and fit δ to assess the degree to which influenza transmission is reduced in the early stages of COVID-19 in the US. We consider two main possible mechanisms by which COVID-19 may have resulted in decreased transmission: 1) increased risk perception of respiratory transmitted disease resulting in precautionary behaviors, like increased handwashing, that reduce potentially transmissible contacts and 2) isolation of infected individuals, either due to undetected COVID-19 spread, or increased messaging surrounding remaining home if one is feeling ill for any reason.

Results

The 2019-2020 influenza season was smaller than expected

Comparing the 2019-2020 ILI dynamics to prior seasons with similar strain dynamics and trajectory of the first part of the influenza season, Figure 1 shows the smaller post-holiday peak compared to the pre-holiday peak. The intervention analysis further supports the conclusion that the influenza peak of the 2019-2020 season is lower and decreases sooner than expected (Figure 2). This decrease is temporally aligned with the increase in Google trends for COVID-19, which initially increases in early February. Our analysis demonstrates that influenza cases are significantly smaller than the projected portion of the season without COVID-19 considering both the absolute effect (95% confidence interval: -0.056, -0.025) and the relative effect (95% confidence interval: -57%,-25%).

COVID-19 risk perception is associated with a decrease in ILI

Our regression analysis of state-level ILI data allows us to assess which factors are predictive of the decline in ILI cases. We find that COVID-19 risk perception is negatively associated with ILI (Figure 3A), while influenza risk perception is positively associated. Additionally, we find that influenza B positive laboratory tests are positively associated with ILI dynamics, but influenza A and humidity are not significantly associated with ILI dynamics. At the state-level, 12 states have significant negative relationships between COVID-19 Google trends and ILI (Figure 3B). One state, South Carolina, has a strong positive association between COVID-19 Google trends and ILI, which reflects a delayed post-holiday peak (Appendix, Figure S1).

Modest transmission reduction in the early phase of COVID-19 results in observed influenza dynamics

Our age-structured metapopulation epidemiological model demonstrates that an average of 5% reduction in transmission due to increased COVID-19 risk perception results in a 19% decrease in total epidemic size, as observed in US ILI dynamics. This is based upon comparison of transmission with $\delta = 0.15$, which is consistent in dynamics with the observed 2019-2020 flu season, compared to baseline dynamics comparable to past influenza seasons.

Discussion

The 2019-2020 influenza season started earlier than most seasons and picked up momentum by the end of 2019, almost reaching the peak at the height of the severe 2017-18 flu season. By some accounts, after recovering from the routine winter holiday interruption, the epidemic was expected to be one of the worst we had seen in a while [20]. Instead, the epidemic trajectory was hampered in mid-February 2020, even before reaching the height of the pre-holiday peak. Based on statistical and mechanistic modeling approaches, our results suggest COVID-19 interaction as an explanation for the diminished ILI peak during the 2019-2020 influenza season.

We suggest that the link between increased risk perception and decreased disease transmission is heightened protective behaviors through non-pharmaceutical interventions (NPIs). This conjecture is supported by past studies that have shown that risk perception is a strong predictor of preventative health behaviors [21]. However, the timing of this effect (early to mid February) is important to consider. The decrease in the observed US ILI peak occurred before widespread closures of public spaces and implementation of social distancing to mitigate COVID-19 transmission. Our results could indicate that the use of personal NPIs such as handwashing and voluntary social distancing may have been occurring before policy changes took place in March 2020. In a survey conducted in early February 2020, US respondents rated their risk perception of COVID-19 as a median score of 5 out of 10, and more than 90% of participants were aware of infection prevention measures [22]. Our mechanistic model suggests that an average of 5% reduction in transmission likelihood could result in the ILI dynamics observed of the 2019-2020 season. Past studies have shown that frequent, effective handwashing can result in a comparable moderate reduction in infections [23, 24, 25]. A meta-analysis of the effects of NPIs in reducing influenza transmission demonstrated that hand hygiene was significant in reducing influenza transmission, with an odds ratio of 0.62 [26].

An alternative hypothesis is that of ecological interference between influenza and SARS-Cov2 [27]. Recent modeling studies [28] and genomic analyses [29] suggest that SARS-Cov-2 may have been circulating outside China since mid-January. If this is further substantiated with data, it may suggest that SARS-Cov-2 circulation created pressure for infected individuals to self-isolate, reducing the effective susceptible pool available to the influenza virus. Past work has shown isolation to be effective in reducing transmission [30, 31], and our mechanistic model results suggest that even a small reduction in the susceptible pool could result in the observed decline in influenza cases. One counterpoint to our expectation of widespread COVID-19 circulation since early February may be the lack of increased cases in respiratory disease hospital surveillance or in syndromic surveillance like ILINet (as the symptom profile for influenza and SARS-Cov-2 are overlapping) during this period. Additional data on COVID-19 prevalence from serological surveys will be necessary to further support these conclusions.

Alternative hypotheses to explain the diminished ILI peak independent of COVID-19 include changes in environmental factors, antigenic profiles, healthcare seeking, and vaccination patterns. We tested whether any changes in humidity, which is expected to be a significant driver of influenza dynamics, could explain the decline in ILI. However, our results identified no significant association, likely because there were no major shifts in humidity levels during the influenza season. We also tested whether a shift in the antigenic makeup of circulating influenza strains was explanatory. Early in the influenza season, influenza B was dominant, but since early February, influenza A H1N1 has been more prevalent. Influenza A H1N1 is expected to produce milder infections so this may explain the ILI reduction later in the season [32]. However, we found that influenza A dynamics were not significantly associated with ILI dynamics. We also considered whether there were changes in healthcare seeking that could have changed the apparent ILI dynamics, but we evaluated the number of total patients in ILINet, and found no increase in total patients within this timeframe (Appendix, Figure S2). Lastly, an increase in late vaccination may predict a smaller flu epidemic. However, CDC data from 2019-2020 shows that approximately 98% of the vaccine supply was distributed by January 1st 2020, and data from past seasons shows that over 90% of the cumulative flu vaccination coverage is reached by January 1st, 2020 [33, 34]. Thus we did not consider this hypothesis in our analysis.

Our study has several limitations. Our use of ILI data relies on healthcare-seeking behavior which is known to be heterogeneous spatially and across age groups [15]. Additionally, we selected seasons antigenically similar to the 2019-2020 season for comparison, but the current season displayed unusually high levels of influenza B activity. Our regression analysis is limited by known factors or available data. The humidity data assumes that each US state is represented by a random weather station. We use information seeking behavior measured by Google Trends as representative of COVID-19 and flu risk perception; while past work has shown such data to be a useful proxy [18], they are limited in aggregate and have not been fully validated. Lastly, our epidemiological model, while it captures local and global contact structures relevant to influenza transmission, models interventions and seasonality simplistically.

The US has had limited testing for COVID-19, and many who experience COVID-19-like symptoms have been unable to be tested, leaving a lack of information about the dynamics of COVID-19 [35]. The overlap in symptoms between influenza and mild cases of COVID-19 may lead SARS-Cov-2 cases to be identified as ILI. In fact, ILINet data since March 9, 2020 shows an uptick in ILI cases suggesting this misdiagnosis. In the absence of widespread testing, this effect shows promise for the syndromic surveillance of COVID-19 through ILI surveillance, but may be biased by an increase in "worried well" healthcare seeking.

Our results suggest that the dynamics of the 2019-2020 influenza season were impacted directly through transmission-reducing behaviors resulting from COVID-19 risk perception or indirectly through ecological interference between the two infections. While COVID-19 testing remains limited, researchers have advocated using existing sources of ILI tracking for COVID-19 surveillance. In addition to this strategy, we suggest that the interaction between a novel and circulating pathogen due to shared preventative behaviors or a shared susceptible pool can be leveraged to understand circulation of the former.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Research reported in this publication was supported by the National Institute Of General Medical Sciences of the National Institutes of Health under Award Number R01GM123007. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We also acknowledge support from the PhRMA Foundation. We thank Håvard Rue for his development of and assistance with the R-INLA package.

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Figures

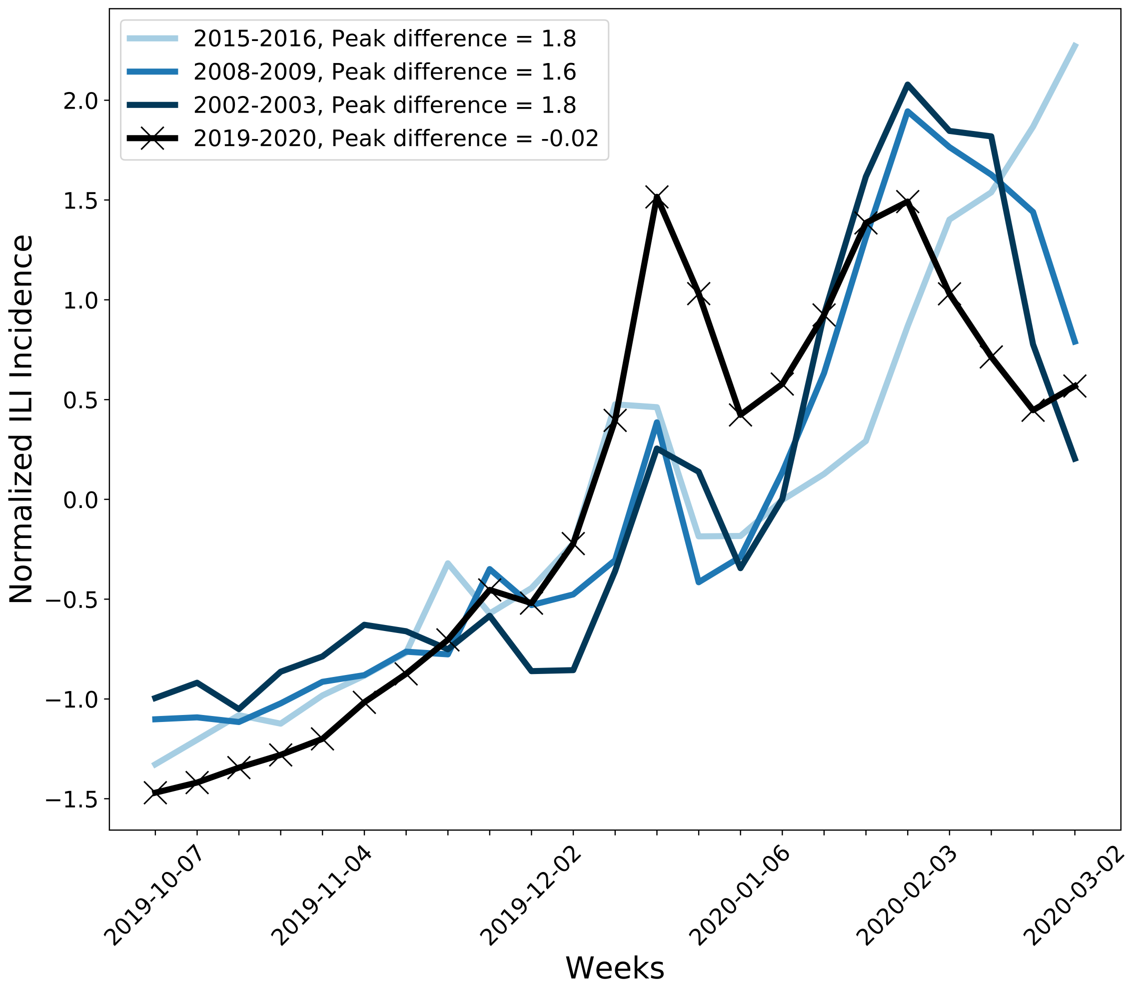

Figure 1: The z-normalized weekly time series of national ILI data from the CDC for the 2019-2020 season (black) compared with past antigenically-similar seasons (blue). The legend shows the pre-holiday peak size subtracted from the post-holiday peak size.

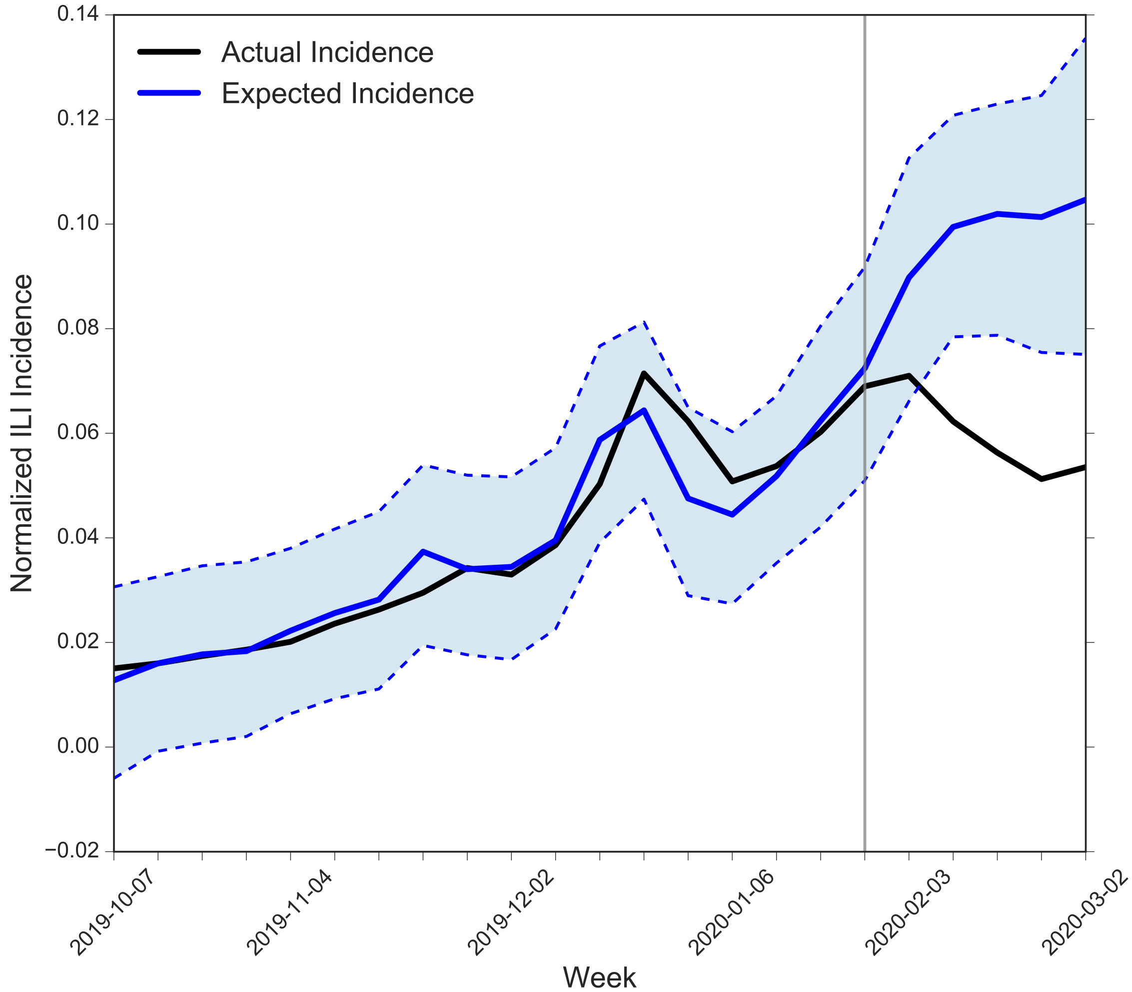

Figure 2: Comparing the observed 2019-2020 influenza season cases (black solid line) with a modeled influenza season based on past seasons (blue line with dashed confidence interval). The vertical gray line represents the initiation of the disruption brought about by COVID-19 circulation.

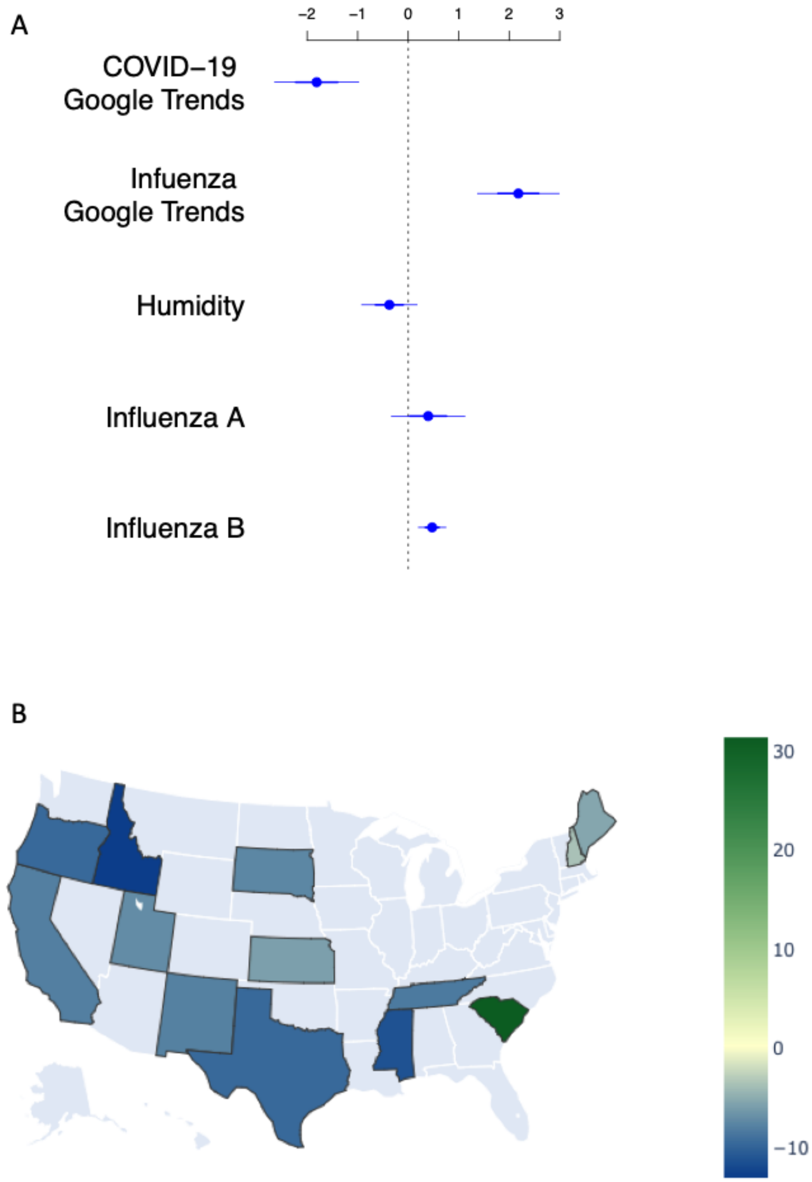

Figure 3: A) The coefficient estimates with 95% confidence interval for the national regression model. B) The significant coefficient estimates for COVID-19 Google trends in state-level regression models with individual state data. Blue states have a significant negative relationship between COVID-19 Google trends and ILI. Green states has a positive relationship. The remaining states have no significant relationship.

Appendix

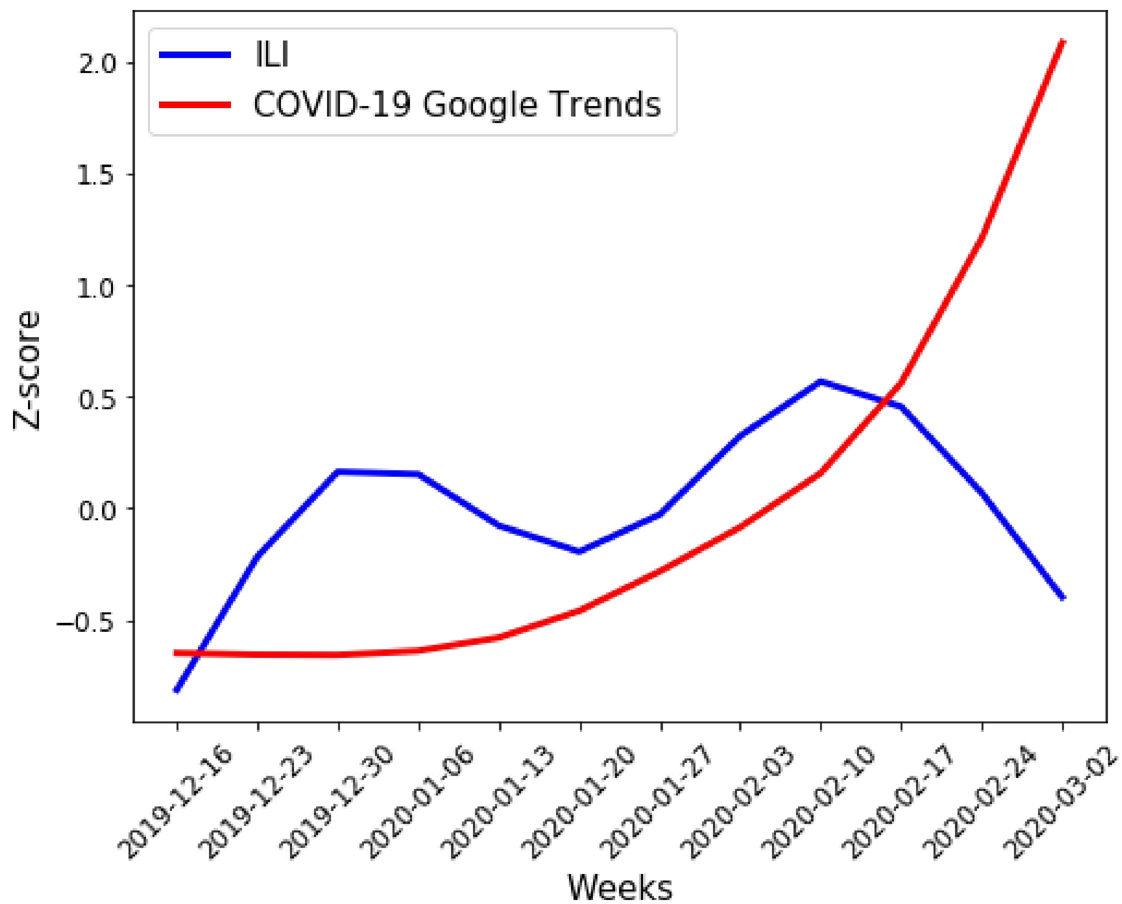

Figure S1: The z-normalized weekly time series of ILI data in South Carolina, compared to the COVID-19 Google trends in South Carolina.

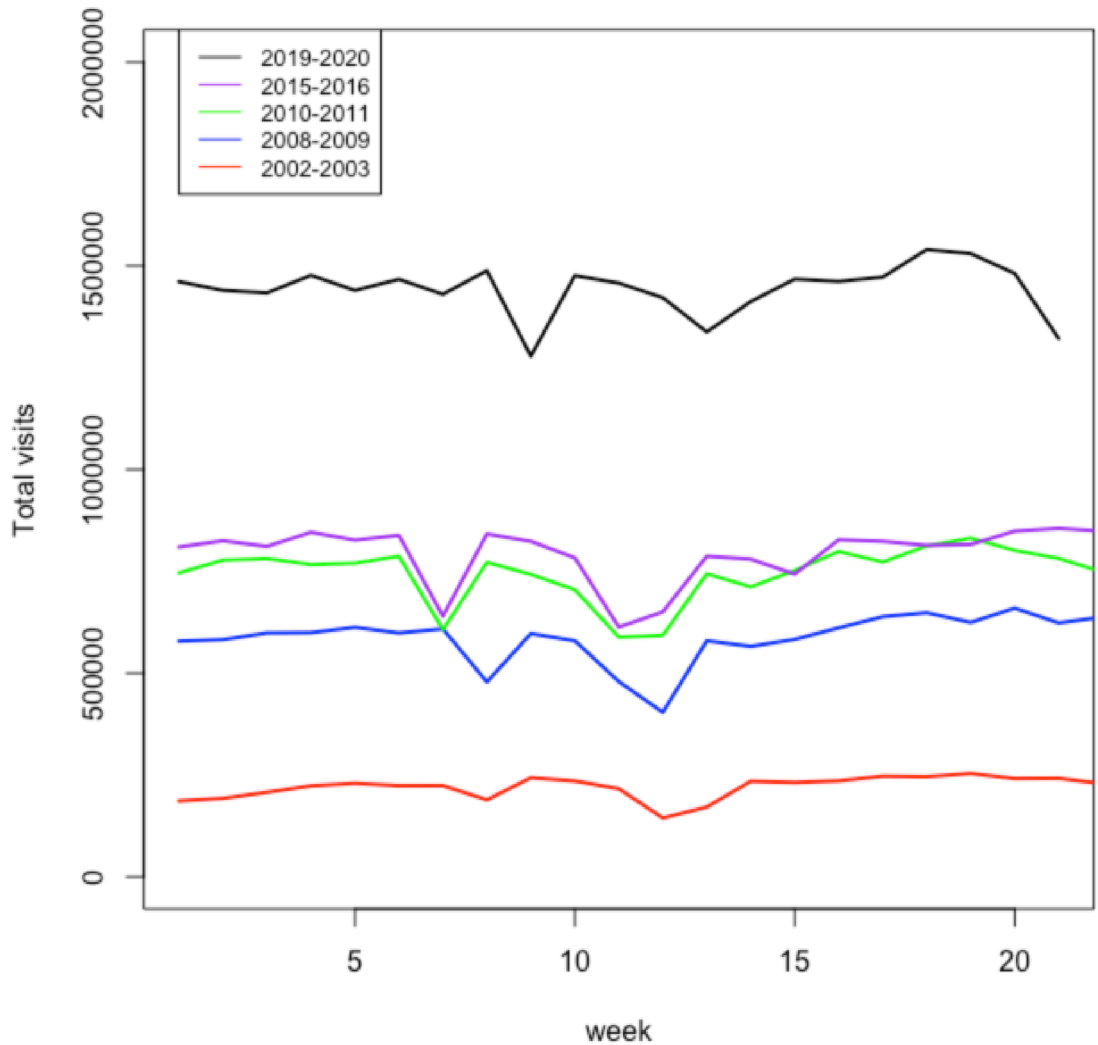

Figure S2: The weekly total visits for the 2019-2020 season, compared to control seasons. The overall levels of surveillance differ among the seasons, but the 2019-2020 does not exhibit an increase in total visits in the early stages of COVID-19.