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Demographics Of Hospitalized Covid-19 And Influenza Cases In Connecticut During The 2021-2022 Influenza Season: Is There Evidence Of Viral Interference?

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Abstract

Since the COVID pandemic began in March 2020, the epidemiology of influenza has changed dramatically in the United States. During the 2021-2022 influenza season in Connecticut, only 262 hospitalized influenza cases were recorded in New Haven and Middlesex Counties from October 2021-June 2022, while there are usually well over 1,000 cases in a single season. While the decline in influenza cases could be due to preventive measures adopted early in the pandemic, viral interference could also be to blame. Viral interference is the process by which infection with one virus transiently protects against infection by another virus via a generalized immune response. Numerous studies have provided evidence supporting this phenomenon in respiratory viruses. To date, however, no studies have investigated this at the population level in Connecticut. The aim of the current study was to investigate whether there was evidence of viral interference between influenza and SARS-CoV-2 during the 2021-2022 influenza season in Connecticut using demographic data collected from hospitalized influenza and COVID cases from the Connecticut Emerging Infections Program at Yale. To do so, chi-square tests comparing the proportion of hospitalized COVID and influenza cases in different demographic groups were performed both within and between three distinct time periods of the 2021-2022 flu season before, during and after the first Omicron wave from December 2021-January 2022. Overall, the results of the chi-square tests did not show strong evidence for viral interference within or between the time periods studied. The percentage of COVID and flu cases in each demographic group changed in similar directions for most groups over time. While this study did not find evidence of viral interference, the number of influenza and COVID cases may not have been high enough to see evidence of this at the population level. Future studies are needed to investigate the level of infection that is needed in the population to see evidence of viral interference if it does in fact occur.

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Introduction

Since the beginning of the coronavirus pandemic, the epidemiology of influenza has changed dramatically in the state of Connecticut. When the pandemic first hit in March 2020, cases of hospitalized influenza infections almost instantly dropped to near 0 in New Haven and Middlesex Counties where the Department of Public Health conducts surveillance.[1] As the pandemic progressed, only 6 hospitalized influenza cases were reported in New Haven and Middlesex Counties from October 2020-April 2021, when there are typically over a thousand cases in one season in these regions.[2] While hospitalized influenza cases started to bounce back during the next season, with a total of 262 cases recorded from October 2021-June 2022 in the counties under surveillance, this was still nowhere near the case count for a normal season.[3]

This trend in Connecticut was also reflected across the country and on a larger, global scale. According to Emerging Infections Program data from the CDC, influenza hospitalizations plummeted to historically low levels in California, New York, Georgia and several other states in March 2020.[1] Influenza infections were also reduced to abnormally low levels across the Northern and Southern Hemispheres during the early stages of the pandemic. While global influenza virus activity began to increase again in the 2021-2022 flu season, cases still remained well below the case count for a normal season.[4]

While many might suggest that it was preventive measures such as masking and social distancing that stopped influenza's spread, viral interference provides an alternative explanation. Heterologous viral interference is the process by which infection with one virus transiently restricts replication and infection by a second unrelated virus via a generalized immune response[5-7]. Since COVID was so widespread in the early days of the pandemic, perhaps flu cases dropped off in part because so many people were sick with COVID that they were protected from getting sick with the flu due to viral interference. If viral interference had occurred during the pandemic, we would expect that demographic groups with the highest proportion of COVID hospitalizations in a given time period also had the lowest proportion of influenza hospitalizations during that time period, and groups with the highest proportion of influenza hospitalizations had the lowest proportion of COVID hospitalizations. While viral interference has been proven at the cellular, molecular, and individual levels, to date, no studies in the state of Connecticut have investigated viral interference between SARS-CoV-2 and influenza at the population level.

Thus, the aim of the current study was to investigate whether viral interference could have occurred between influenza and SARS-CoV-2 in Connecticut using demographic data collected from hospitalized influenza and COVID cases from the Connecticut Emerging Infections Program at Yale from the 2021-2022 influenza season. To do so, hospitalized cases were compared between the two diseases within different demographic groups both within and between three distinct time periods before, during and after the first Omicron wave from December 2021-January 2022. Time periods were divided into distinct periods before, during and after the Omicron wave to determine if the changing fluctuation in COVID cases had an impact on the incidence of influenza cases over time.

Review of Literature

Human, animal, cellular and epidemiological models provide support for the theory of viral interference. In 2009, it was postulated that the influenza pandemic of influenza virus A was delayed by the annual autumn rhinovirus epidemic in several European countries. To test this, a study by Wu et al. (2020) found that infection of primary human airway epithelial cultures with rhinovirus, a respiratory virus with clinical effects similar to influenza and COVID-19, protected against influenza infection 3 days later due to increased expression of interferon stimulating gene

(ISG) mRNA (an important part of our immune defense against pathogens). This resulted in a 50,000-fold decrease in influenza RNA, whereas blocking the ISG response restored the proliferative activity of the influenza virus.[7] Further, Chan et al. (2018) found evidence of viral interference using a ferret model. Infection of ferrets with 2009 pandemic influenza A conferred protection against subsequent infection with respiratory syncytial virus (RSV), and infection with RSV reduced morbidity from influenza infection.[8]

Other laboratory and individual-level studies provide evidence for viral interference between SARS-CoV-2 and influenza. In a study of respiratory virus infections in a reconstituted human epithelial airway model, Fage et al. (2022) found that prior infection of airway epithelial cells with influenza or RSV infection significantly reduced gene copy levels of SARS-CoV-2 cells that subsequently infected the airways, even despite long infection times with SARS-CoV-2.[9] Further, a study by Stowe et al. (2021) found that influenza-positive individuals were 58% less likely to be infected with SARS-CoV-2 compared to those without influenza infection.[10] Finally, Essaidi-Laziosi et al. found that SARS-CoV-2 replication was inhibited over 1000-fold in cultures exposed to rhinovirus and influenza infection beforehand, while it replicated exponentially in cultures that were not exposed to prior respiratory virus infection. The authors found that this reduction in replication was mediated by interferon induction, an important part of the immune response against pathogens, suggesting that suppression of SARS-CoV-2 by rhinovirus and influenza is induced by an innate immune response.[11]

Studies have also been conducted using epidemiological methods and data to investigate viral interference between respiratory viruses at the population level. Price et al (2019) completed time-series analyses on over 58,000 clinical specimens collected from 2002-2017 from communities and hospitals in Australia and tested them for respiratory virus infections. Distinct temporal patterns in the circulation of respiratory viruses were found, providing evidence for viral interference on an epidemiological scale. RSV and influenza A had seasonal peaks at different times of year, with RSV circulating an average of six weeks prior to influenza. Specimens that were positive for influenza A were also significantly less likely to be infected with other respiratory viruses, suggesting that perhaps influenza infection protected against infection by other viruses.[12]

Further, Nickbakhsh et al. (2019) studied over 44,000 cases of respiratory illness from virological diagnostic data collected over a nine-year time period to determine if there was statistical evidence of interactions between heterologous viruses in the temporal patterns of infection at the population level.[13] The study found that the most dominant respiratory virus varied each month, due in part to seasonal fluctuations in the timing of individual virus peaks. They also found 26 significant virus-virus correlations in the monthly prevalence time series for different pairs of respiratory viruses, including a negative interaction between influenza B and rhinovirus and a negative interaction between influenza A and rhinovirus.

To determine the mechanism by which infection with one virus decreased the likelihood of infection by another, the authors also conducted epidemiological simulations of the co-circulatory transmission dynamics of a seasonal cold virus and influenza A. They found that host susceptibility to common cold-like viruses can be reduced following influenza infection, resulting in a decrease in the incidence of common-cold infections during peak influenza activity. This suggests that viral interference occurs as a result of a temporary protective immune response generated by influenza infection that decreases the probability of getting infected with the common cold.[13]

Further, Pinky and Dobrovolny (2022) used a compartmental epidemiological model to assess the impact of viral interference on the spread of SARS-CoV-2 and other respiratory viruses.[14] They found that influenza and rhinovirus epidemics were predicted to begin after a SARS-CoV-2 epidemic had burnt out, and that peak SARS-CoV-2 activity is delayed and decreased by RSV co-circulation, suggesting that viral interference can prevent respiratory viruses from reaching peak viral activity at the same time.

Finally, Takashita et al. (2023) studied influenza and COVID-19 activity each week for 45 weeks from 2019-2022 in 22 countries to determine if COVID-19 activity influenced influenza activity, and vice versa.[15] They found that peak influenza and COVID activity occurred in different regions in each country at different times, and increases in influenza activity were reported at different times than increases in COVID activity. Further, in France and Italy, increases in influenza activity were reported in several regions throughout the country, excluding regions with the highest level of COVID activity. The results of this analysis provide further evidence supporting viral interference at the population level between COVID and influenza.

There is abundant evidence suggesting that viral interference occurs between respiratory viruses, including SARS-CoV-2 and influenza. Thus, this study will contribute to the current literature with a novel method of investigating viral interference between SARS-CoV-2 and influenza viruses at the population level in Connecticut.

Methods

On behalf of the Connecticut Department of Public Health, the Emerging Infections Program (EIP) at the Yale School of Public Health conducts enhanced surveillance for hospitalizations with laboratory-confirmed influenza (FluSurv-NET) and laboratory-confirmed COVID-19 (COVID-NET) in New Haven and Middlesex Counties. Any person that lives in the catchment area and tests positive for influenza or COVID-19 by a laboratory test ordered by a healthcare provider up to 14 days before or during their hospitalization is considered a case.[16]

Using surveillance data from the Emerging Infections Program at Yale, an observational study was conducted on the demographics of hospitalized influenza and COVID cases from New Haven and Middlesex counties in the state of Connecticut from October 2021-June 2022. Data on race/ethnicity, sex, and age were analyzed from 262 hospitalized influenza cases and 6,335 hospitalized COVID cases reported to the Department of Public Health during this time period.

The incidence of hospitalized influenza and COVID cases was calculated and graphed each month from October 2021 to June 2022. Incidence was calculated per 100,000 persons using the combined population size of New Haven and Middlesex Counties, which was extracted from 2020 census data. Age, sex and race/ethnicity data were then extracted from each case and aggregated to draw comparisons between the demographics of hospitalized influenza and COVID cases. Age groups were broken down into the following: 0-4 year olds, 5-17 year olds, 18-49 year olds, 50-64 year olds, and individuals ages 65 and older. These age groups were chosen based on different exposure potential and risk of hospitalization. Race/ethnicity was categorized into non-Hispanic whites, non-Hispanic blacks, Hispanics, non-Hispanic Asian/Pacific Islanders, non-Hispanic American Indian/Alaska Natives, and non-Hispanic Multiracial individuals. These categories were chosen according to the classification scheme used for race and ethnicity at the EIP during the 2021-2022 influenza season. Sex was classified as either male or female.

Cases were then filtered by date of hospital admission and separated into three distinct time periods based on hospital admission date using Excel: October 2021-November 2021 (before the first Omicron wave hit), December 2021-February 2022 (during the first Omicron wave), and March 2022-June 2022 (immediately after the first Omicron wave). The total number of cases and the percentage of cases in each race/ethnic, gender and age group were then extracted and calculated in Excel for each disease within each time period.

Statistical analyses were then performed using chi-square tests to compare the percentage of cases in each demographic group between COVID and influenza *within* each time period, in order to determine if the demographics of those who were hospitalized with COVID were significantly different from those who were hospitalized with influenza. The percentage of cases in each demographic group was then compared between COVID and influenza *between* each time period using chi-square tests to determine if the demographics of influenza and COVID cases changed in similar or opposite directions before, during and after the initial Omicron wave from December 2021-January 2022.

R was used to perform all chi-square tests between influenza and COVID cases. P-values less than 0.05 were considered statistically significant.

Results

There were a total of 7 hospitalized influenza cases and 684 hospitalized COVID cases from October 2021-November 2021 before the first Omicron wave hit. Since the total number of influenza cases was too small to divide into subgroups to compare to COVID cases, no additional analyses were performed for this time period. From December 2021-February 2022 (denoted time period 2), there were a total of 46 hospitalized influenza cases and 4,091 hospitalized COVID cases. From March 2022-June 2022 (denoted time period 3), there were 212 hospitalized influenza cases and 1,560 hospitalized COVID cases. The case counts in each of these time periods were high enough for statistical analyses to be performed.

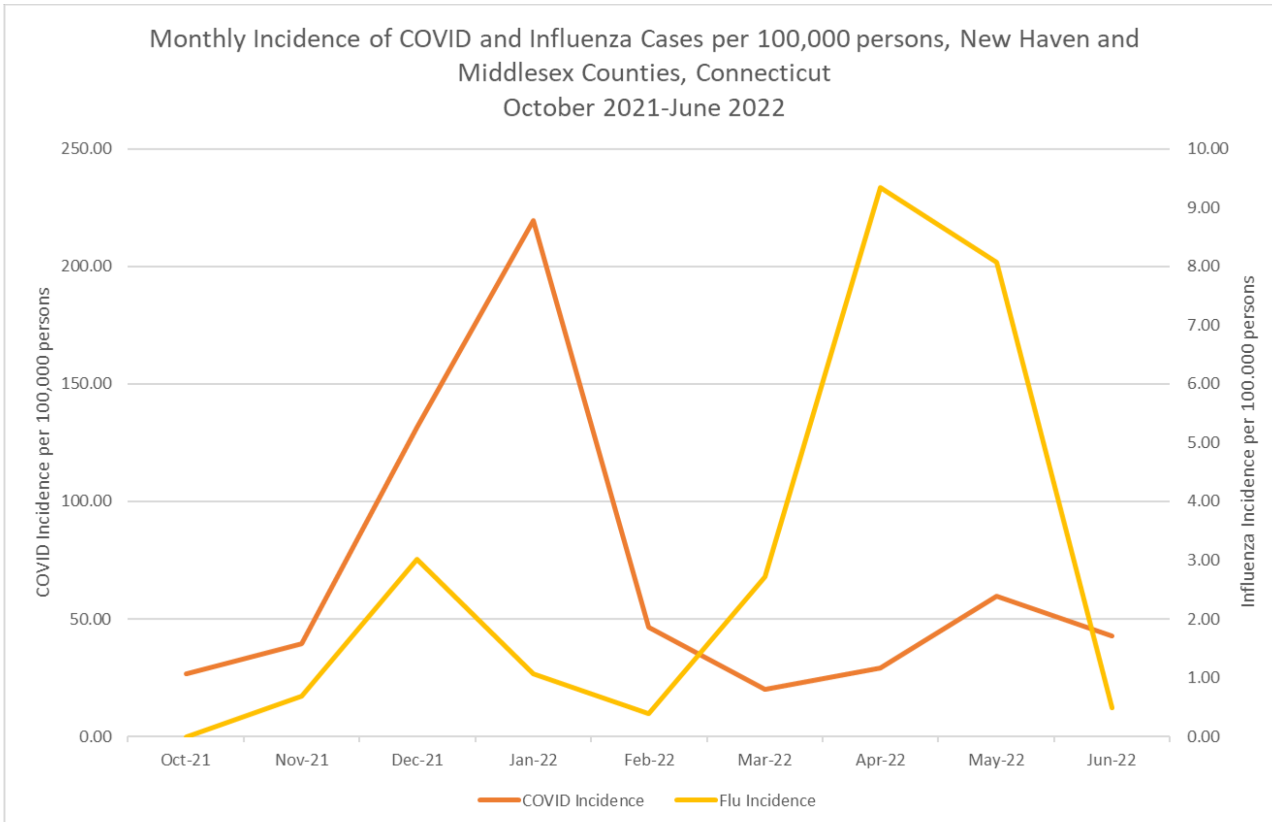

Figure 1: Monthly incidence of hospitalized COVID and influenza cases in New Haven and Middlesex Counties, October 2021-June 2022

Figure 1 shows the monthly incidence of hospitalized influenza and COVID cases in New Haven and Middlesex Counties from October 2021-June 2022. As shown in the graph, once COVID incidence dropped off to less than 50 cases per 100,000 people in early February, influenza cases began to increase sharply, reaching a peak in April while COVID incidence remained low. Further, as the graph clearly shows, influenza cases reached a peak in April, well after the peak in in COVID cases in December.

	INFLUENZA T2	COVID T2	p-value
Sex			
Male	23 (50.0%)	2022 (49.4%)	NS
Female	23 (50.0%)	2069 (50.6%)	NS
Race			
Non-Hispanic white	23 (50%)	2428 (59.4%)	NS
Non-Hispanic black	9 (19.6%)	808 (19.8%)	NS
Hispanic or Latino	11 (23.9%)	692 (16.9%)	NS
Asian/Pacific Islander	0	54 (1.3%)	NS
American Indian/ Alaska Native	0	8 (0.2%)	NS
Multiracial	1 (2.17%)	24 (0.6%)	NS
Age			
0-4 years old	1 (2.2%)	36 (0.9%)	NS
5-17 years old	2 (4.4%)	59 (1.4%)	NS
18-49 years old	10 (21.7%)	957 (23.4%)	NS
50-64 years old	8 (17.4%)	1046 (25.6%)	NS
65+ years old	25 (54.4%)	1993 (48.7%)	NS
Total number of cases	46	4091	

Table 1: Proportions of COVID-19 and Influenza Hospitalizations by Demographic features, Time period 2 (December 2021-February 2022), New Haven and Middlesex Counties

The demographic makeup of influenza and COVID cases in time period 2 from December 2021-February 2022 is given in Table 1. As noted above, there were 46 hospitalized influenza cases in this time period and 4,091 total hospitalized COVID cases. There were no statistically significant differences between the demographic makeup of hospitalized influenza and COVID cases for any of the demographic groups studied in time period 2. However, there were still some notable differences between the percentage of flu and COVID cases in several demographic groups.

For both pathogens, non-Hispanic whites were the most common racial/ethnic group to be hospitalized. However, non-Hispanic whites accounted for a higher percentage of COVID cases than flu cases, making up 59.4% of total COVID cases compared to 50.0% of total flu cases. Hispanics/Latinos were the second most common racial/ethnic group to be hospitalized with influenza, accounting for 23.9% of total flu cases and a much smaller percentage, 16.9%, of total COVID cases. The second most common racial/ethnic group to be hospitalized with COVID was non-Hispanic blacks, accounting for 19.8% of total COVID cases and a similar percentage, 19.6%, of total flu cases.

Individuals aged 65 and older were the most common age group to be hospitalized with both flu and COVID; however, this group comprised a higher percentage of total flu cases, making up 54.4% of total flu cases compared to 48.7% of total COVID cases. Further, 50-64 year olds were the second most common age group to be hospitalized with COVID, making up 25.6% of total cases, compared to 17.4% of total flu cases. The second most common age group to be hospitalized with flu was 18-49 year olds, making up 21.7% of total flu cases compared to 23.4% of total COVID cases.

Cases were evenly divided between males and females for both flu and COVID cases, with males and females making up about 50.0% of total cases for each disease.

Demographic Group	INFLUENZA T2	INFLUENZA T3	p-value
Sex			
Male	23 (50%)	83 (39.15%)	NS
Female	23 (50%)	129 (60.85%)	NS
Race			
Non-hispanic white	23 (50.0%)	130 (61.32%)	NS
Non-hispanic black	9 (19.56%)	37 (17.45%)	NS
Hispanic or Latino	11 (23.91%)	40 (18.87%)	NS
Asian/Pacific Islander	0	2 (0.943%)	NS
American Indian/ Alaska Native	0	1 (0.472%)	NS
Multiracial	1 (2.17%)	1 (0.472%)	NS
Age			
0-4 years old	1 (2.17%)	5 (2.36%)	NS
5-17 years old	2 (4.35%)	9 (4.25%)	NS
18-49 years old	10 (21.74%)	36 (16.98%)	NS
50-64 years old	8 (17.39%)	40 (18.87%)	NS
65+ years old	25 (54.35%)	122 (57.55%)	NS
Total number of cases	46	212	

Table 2: Proportions of influenza hospitalizations by demographic features and time periods 2 and 3 (Dec 2021-Feb 2022 and Mar 2022-June 2022), New Haven and Middlesex Counties.

Table 2 provides the demographic makeup of influenza cases in time periods 2 and 3. Overall, there were no statistically significant changes in the distribution of flu cases between time periods 2 and 3 in any of the demographic groups. However, there were still some sizable changes in the percentage of cases in some of the demographic groups over time.

Overall, flu cases increased from 46 cases in time period 2 to 212 cases in time period 3. The proportion of total influenza cases that were male decreased from 50.0% of total cases in time period 2 to 39.2% of total cases in time period 3, whereas the proportion of cases that were female increased from 50.0% of total cases in time period 2 to 60.1% of cases in time period 3. Further, the proportion of total flu cases that were non-Hispanic white increased from 50.0% of total cases in time period 2 to 61.0% of total cases in time period 3, and the proportion of cases that were Hispanic/Latino decreased from 23.9% of total cases in time period 2 to 18.9% of total cases in time period 3. Finally, 18-49 year olds made up 21.7% of total flu cases in time period 2 and 17.0% of total cases in time period 3.

Demographic Group	COVID T2	COVID T3	p-value
Sex			
Male	2022 (49.4%)	776 (49.7%)	NS
Female	2069 (50.6%)	784 (50.3%)	NS
Race			
Non-Hispanic white	2428 (59.4%)	1086 (69.6%)	<0.001
Non-Hispanic black	808 (19.8%)	202 (13.0%)	<0.001
Hispanic or Latino	692 (16.9%)	192 (12.3%)	<0.001
Asian/Pacific Islander	54 (1.3%)	25 (1.6%)	NS
American Indian/ Alaska Native	8 (0.2%)	5 (0.3%)	NS
Multiracial	24 (0.6%)	6 (0.4%)	NS
Age			
0-4 years old (group 1)	36 (0.9%)	27 (1.7%)	0.009
5-17 years old (group 2)	59 (1.4%)	38 (2.4%)	0.01
18-49 years old (group 3)	957 (23.4%)	284 (18.2%)	<0.001
50-64 years old (group 4)	1046 (25.6%)	335 (21.5%)	0.002
65+ years old (group 5)	1993 (48.7%)	904 (58.0%)	<0.001
Total number of cases	4091	1560	

Table 3. Proportions of COVID-19 hospitalizations by demographic features and time periods 2 and 3, New Haven and Middlesex Counties.

Table 3 provides the demographic makeup of COVID cases in time periods 2 and 3. Unlike flu, there were statistically significant changes in the distribution of cases between time periods 2 and 3 in most of the demographic groups that were hospitalized with COVID. There was a statistically significant increase in the proportion of total cases that were non-Hispanic white; the proportion of total cases in this group increased from 59.4% in time period 2 to 69.6% in time period 3. On the other hand, there was a statistically significant decrease in the proportion of total cases that were non-Hispanic black; this group accounted for 19.8% of total COVID cases in time period 2 and 13.0% of total COVID cases in time period 3. Further, there was also a statistically significant decrease in the proportion of total cases that were Hispanic/Latino; 16.9% of total cases were Hispanic/Latino in time period 2 compared to 12.3% in time period 3. The percentage of total cases in the 18-49 year old and 50-64 year old age groups changed significantly across time as well, decreasing from 23.4% to 18.2% and 25.6% to 21.5%, respectively. In the remaining age groups, there was a statistically significant increase in the percentage of cases across time. In the 0-4 year old age group, the percentage of total cases increased from 0.9% to 1.7%; in 5-17 year olds the percentage increased from 1.4% to 2.4%; and in the 65+ age group the percentage increased from 48.7% to 58.0%. Interestingly, unlike flu, the distribution of cases by sex did not change significantly across time for COVID; males and females made up about 50.0% of cases in both time periods.

	INFLUENZA T3	COVID T3	p-value
Sex			
Male	83 (39.2%)	776 (49.7%)	0.00470
Female	129 (60.9%)	784 (50.3%)	0.00470
Race			
Non-Hispanic white	130 (61.3%)	1086 (69.6%)	0.00363
Non-Hispanic black	37 (17.5%)	202 (13.0%)	NS
Hispanic or Latino	40 (18.9%)	192 (12.3%)	0.0162
Asian/Pacific Islander	2 (0.9%)	25 (1.6%)	NS
American Indian/ Alaska Native	1 (0.5%)	5 (0.3%)	NS
Multiracial	1 (0.5%)	6 (0.4%)	NS
Age			
0-4 years old	5 (2.4%)	27 (1.7%)	NS
5-17 years old	9 (4.3%)	38 (2.4%)	NS
18-49 years old	36 (17.0%)	284 (18.2%)	NS
50-64 years old	40 (18.9%)	335 (21.5%)	NS
65+ years old	122 (57.6%)	904 (58.0%)	NS
Total number of cases	212	1560	

Table 4: Proportions of COVID-19 and of Influenza Hospitalizations by demographic features, Time Period 3 (March 2022-June 2022), New Haven and Middlesex Counties.

Finally, the demographic makeup of flu and COVID cases in time period 3 from March 2022-June 2022 is given in Table 4. Unlike time period 2, there were some significant differences between the demographic makeup of flu and COVID cases during this time period. Males made up significantly fewer influenza cases compared to COVID cases, accounting for 39.2% of total influenza cases in this time period compared to 49.7% of total COVID cases. Females, conversely, made up a greater proportion of total influenza cases at 60.9% of total cases compared to 50.3% of total COVID cases. There was also a statistically significant difference in the proportion of influenza and COVID cases that were non-Hispanic white. Non-Hispanic whites made up a larger percentage of total COVID cases compared to influenza cases, accounting for 69.6% of total COVID cases compared to 61.3% of total flu cases. Conversely, while the difference did not reach statistical significance, non-Hispanic blacks accounted for a larger percentage of flu cases, making up 17.5% of total flu cases compared to 13.0% of total COVID cases. Hispanics/Latinos also comprised a significantly larger proportion of flu cases compared to COVID cases, accounting for 18.9% of total flu cases compared to 12.3% of total COVID cases. Finally, while none of the differences in age groups between influenza and COVID reached statistical significance, there were still some notable differences in the proportion of cases in some age groups between the two pathogens. Interestingly, individuals in the 5-17 year old age group accounted for a greater proportion of flu cases, at 4.3% of total cases compared to 2.4% of total COVID cases, and individuals in the 50-64 year old age group made up fewer flu cases, at 18.9% of total flu cases compared to 21.5% of total COVID cases.

Discussion

At first glance, the change in the incidence of influenza and COVID cases over time seems to suggest that viral interference could have occurred between the two pathogens during the 2021-2022 influenza season in Connecticut. Monthly flu incidence sharply increased and reached a peak only once the incidence of COVID reached a very low level starting in February 2022. This suggests that perhaps COVID incidence was high enough to suppress the incidence of influenza at the population level in the second time period from December 2021 to early February 2022. Only once COVID incidence dropped to less than 20 cases per 100,000 people beginning in February did influenza cases really begin to rise during the third time period, perhaps because the number of COVID cases was no longer high enough to suppress flu infections at the population level. Epidemiological studies of respiratory virus activity by Takashita et al. (2022)[15], Nickbaksh et al.

(2019)[13], Price at al (2019)[12], and Pinky and Dobrovolny (2022)[14] support these findings, as all reported similar results showing opposite trends in the circulation of different respiratory viruses in the same regions over the same time periods.

Despite this, when we compare the change in cases by demographic group, we no longer see evidence supporting the hypothesis of viral interference. If viral interference had occurred, we would expect to see an increase in the proportion of COVID cases between time periods 2 and 3 in demographic groups that experienced a decrease in the proportion of influenza cases, and an increase in the proportion of influenza cases between time periods 2 and 3 in demographic groups that experienced a decrease in the proportion of COVID cases. We would also expect to see significant differences between the percentage of flu cases and the percentage of COVID cases in each demographic group within each time period. These results would suggest that groups that were more likely to be hospitalized with COVID were less likely to be hospitalized with flu, and vice versa, suggesting that perhaps infection with one pathogen protects against infection by the other.

However, overall, the proportion of COVID and influenza cases changed in similar directions between the two time periods in most demographic groups, either increasing or decreasing for both pathogens over time. The percentage of total cases that were non-Hispanic white and 65+ increased from the second to the third time period for both influenza and COVID, whereas the percentage of total cases that were non-Hispanic black, Hispanic/Latino, and 18-49 years old decreased for both pathogens over time. Since the distribution of influenza and COVID cases changed in similar directions in these groups, we cannot conclude that viral interference occurred between the two pathogens, especially since the change in influenza cases over time was not significant. Further, comparing the percentage of influenza and COVID cases in each demographic group within each time period also yielded little evidence of viral interference. In time period 2, none of the differences in the demographic makeup of influenza and COVID cases reached statistical significance. While there were significant differences in the third time period, we still cannot conclude that viral interference occurred based on the trends in the distribution of cases over time

Interestingly, the percentage of total cases in the 18-49 year old and 50-64 year old age group decreased for COVID cases and increased for flu cases over time, which could suggest the possibility of viral interference. However, since this trend was not seen in all of the demographic groups (especially those with a higher proportion of cases such as non-Hispanic whites), and since the change in influenza cases over time was not significant, we still cannot conclude that viral interference occurred. This trend was also seen in the 0-4 year old age group, 5-17 year old age group, and the Asian/Pacific Islander, Multiracial and American Indian/Alaska Native groups, however the number of influenza cases (and COVID cases for the race/ethnic groups) in both time periods was too small in these groups to draw any conclusions.

Importantly, we might have failed to find sufficient evidence for viral interference due to the total number of hospitalizations within each demographic group. The total number of cases might have been too small to see sufficient evidence of interference at the population level. In fact, this was one of the major limitations of the study; we lacked precise infection data, especially for influenza, and thus used hospitalizations as a surrogate for infection. Since the total number of influenza and COVID infections were much higher than the number of hospitalized cases during the 2021-2022 influenza season, perhaps we would have seen stronger evidence of viral interference if the total number of infections had been analyzed instead. Further, the small number of hospitalized influenza cases limited the ability to detect statistically significant differences in comparisons of the distribution of cases involving influenza. Further analyses investigating the level of infection that is needed in the population to observe viral interference between SARS-CoV-2 and influenza are needed to determine if interference truly does occur. To date, no other studies have investigated this at the population level in Connecticut or elsewhere in the United States.

Despite the lack of evidence supporting viral interference, there were some distinctive differences in the distribution of cases over time in different demographic groups, which can likely be attributed to differences in socioeconomic status and preventive measures in different groups, and perhaps explains why we failed to find evidence of interference.

The outbreak of the highly infectious omicron variant of the coronavirus occurred during the winter of the second time period from December 2021-February 2022. Throughout the coronavirus pandemic in the United States, essential workers and individuals of lower socioeconomic status have consistently been at increased risk of coronavirus infection compared to the general population, due to factors such as lack of paid sick leave, overcrowded working and living conditions, and lack of proper personal protective equipment in the workplace.[17-19]

Non-Hispanic blacks and Hispanics/Latinos are more likely than non-Hispanic whites to occupy high-risk jobs and lower socioeconomic status in the United States.[19] Thus, these groups were likely at increased risk of exposure to the Omicron variant in the workplace and at home when the outbreak first occurred in the second time period, resulting in higher infection levels in these groups during time period 2 compared to time period 3. High infection levels in the second time period likely resulted in higher relative levels of immunity that protected members of these groups against further infection in the third time period, resulting in a relative drop in the percentage of cases in these groups over time. Since influenza is transmitted via the same respiratory route as COVID, perhaps non-Hispanic blacks and Hispanics/Latinos were also at increased risk of influenza infection due to the same working conditions and socioeconomic factors that increased their risk of COVID when Omicron first hit, leading to higher levels of flu infection in the second time period and lower levels of infection in the third time period.

Conversely, non-Hispanic whites were likely better able to protect themselves against the Omicron variant during the initial outbreak from December 2021-February 2022. Non-Hispanic whites are less likely to occupy high-risk jobs and more likely to have higher socioeconomic status, leading to fewer coronavirus infections in this group (due to less crowding in the household, for example) in the second time period. Relative lack of natural immunity from time period 2 likely created a larger pool of susceptible individuals in this group, leading to a higher number of cases in time period 3. Once again, since COVID and influenza are transmitted by the same respiratory route, perhaps the protective measures that prevented non-Hispanic whites from getting infected with COVID in the second time period also protected them against influenza infection, resulting in relatively lower levels of influenza immunity amongst non-Hispanic whites in the second time period that led to an increase in influenza cases in the third time period.

In fact, multiple studies have proven that protective measures against COVID-19 protected against influenza infections at the population level early in the coronavirus pandemic. An analysis by Cowling et al. (2020) found that prevention measures adopted by the Chinese government in early 2020 to contain the coronavirus also helped control influenza transmission. The authors found that there was a significant association between the decline in flu infections and the adoption of interventions such as masking, quarantine, and social lockdowns early on in the pandemic.[20] Another analysis of influenza and COVID activity following adoption of preventive measures at the outset of the COVID pandemic in three Scandinavian countries also found that influenza cases dramatically dropped off to less than 1% of tested cases when prevention measures for COVID were first adopted.[21] In the previous nine flu seasons, it took 10 weeks for the positive test rate to drop below 1%, suggesting that preventive measures successfully contained flu infections as well as COVID infections.

Different trends in the distribution of cases across time were also seen in different age groups. Older individuals, especially those aged 65+, have consistently suffered higher rates of morbidity, mortality and hospitalization from the coronavirus than younger people.[22-24] As a result, compared to younger people, older people may have taken greater precautions to protect themselves against Omicron during the initial outbreak, adopting masking and social distancing at a higher rate to protect against hospitalization and death.

Similar to the trends seen in racial/ethnic groups over time, increased adoption of protective measures by individuals in the 65+ age group likely protected them from experiencing high levels of COVID infections during the second time period when Omicron first hit, resulting in lower levels of population-level immunity in this group and subsequently higher levels of infection in time period 3. Protective measures adopted by this group against COVID likely also protected against infection by flu, which could explain why flu cases increased in this group over time as well. Conversely, since they are not at high risk of severe disease outcomes, younger individuals likely took fewer precautions against Omicron during the initial outbreak in time period 2, leading to a greater number of cases in this time period and a relative drop in the percentage of cases in this group over time.

In fact, multiple studies suggest that there are significant differences in coronavirus risk behavior by age group. A cross-sectional survey of adults in the United States in April 2020 about the use of protective measures against COVID-19 found that younger people were less likely to report wearing a face covering, and individuals ages 50 and older were more likely to report engaging in protective measures for COVID-19 than individuals ages 49 and younger.[25] Other observational studies of COVID risk-taking behaviors in different age groups also found that age was significantly related to risk behaviors. During the pandemic in 2020, younger people were more likely to engage in behavior that increased the risk of COVID infection compared to older people, and older people were more likely to adopt preventive measures such as social distancing and quarantining 1-2 months into the pandemic compared to younger people.[26-27]

Differences in COVID vaccination rates by age and race/ethnicity might also account for the differences in the distribution of cases in different demographic groups over time. According to data from the Connecticut Department of Public Health, a higher percentage of non-Hispanic whites, 31.6%, are fully vaccinated with a booster dose against COVID-19 compared to Hispanics and non-Hispanic blacks. Only 25.0% of Hispanics and 21.8% of non-Hispanic blacks in Connecticut are fully vaccinated and boosted.[28]

The discrepancy in booster coverage likely due to differences in socioeconomic status by race and ethnicity. As stated previously, non-Hispanic blacks and Hispanics are more likely to occupy lower socioeconomic status than non-Hispanic whites, which can impact vaccine access and acceptance. In fact, a study of COVID vaccine hesitancy in the United States found that people living in lower socioeconomic neighborhoods had lower rates of COVID-19 vaccination compared to neighborhoods of higher socioeconomic status.[29] Lower socioeconomic status impacts vaccine access in different ways. For example, people living in poverty are less likely to have health insurance that links them to a reliable primary care provider that can provide trusted vaccine information. Further, due to systemic mistreatment in the healthcare system, racial and ethnic minorities in the U.S. such as non-Hispanic blacks and Hispanics are more likely to mistrust the healthcare system and avoid vaccination.[30] As a result, non-Hispanic blacks and Hispanics likely received the booster later than non-Hispanic whites, resulting in a relative decrease in non-Hispanic black and Hispanic cases from time period 2 to time period 3 as more individuals got boosted later in time and received greater protection from the vaccine after the Omicron wave had largely subsided.

Differences in booster coverage by age group likely also impacted the distribution of cases in different demographic groups as well. Individuals over the age of 65 are more likely to be vaccinated and boosted against COVID-19 than younger age groups in Connecticut. More than 51% of those that are 65+ are fully vaccinated with a booster dose, compared to only 31% of 55-64 year olds, 20% of 45-54 year olds, and less than 20% of people between the ages of 5 and 44.[28]

Further, COVID boosters became available at different times in different age groups. Older people 65 and older were first eligible to receive a COVID booster in September 2021. Individuals ages 18 and older became eligible to get boosted in November 2021, followed by everyone over the age of 12 in January 2022. Vaccine-induced immunity against COVID begins to wane 3-6 months after immunization, and declines even further after 8 months.[31-32] Thus, since they were boosted in September, the 65+ age group likely had high levels of vaccine-induced immunity at the population level in time period 2 compared to time period 3, especially given that the majority, more than 51%, received a booster dose at some point. As population-level immunity began to wane by the third time period, more older individuals likely lost protection from the vaccine, resulting in an increase in cases in time period 3. Since less than half of younger people below the age of 65 got boosted, it is unlikely that the vaccine had any protective effect at the population level for any of the younger age groups.

Interestingly, the change in the percentage of male and female cases over time remained consistent for COVID, but changed significantly for flu. Male flu cases decreased by almost 10 percent, while female cases increased by 10% between time periods. While the exact cause of this change is unknown, a study by Tam et al. from 2014 investigating influenza-related hospitalization and female sex in New Haven County, Connecticut suggests a possible explanation for this trend. This study found that adult females were at a higher risk of hospitalization with influenza compared to adult males, especially women of childbearing age, suggesting that women might be at increased risk of flu hospitalization because they are at a higher risk of exposure to sick children.[33] In fact, a study of flu transmission in New York City households in 2009 found that women with a sick child at home were more likely to get infected with influenza compared to men in the same household, likely because women are more likely to stay home with sick children.[34] Perhaps, in the third time period, when flu cases began to increase in the population, as more children got sick with flu, more women of childbearing age were exposed and infected, thus accounting for the increase in the percentage of hospitalized flu cases in females over time.

Conclusions

While viral interference was not supported in this analysis, numerous other epidemiological and laboratory studies provide strong evidence suggesting that viral interference does occur between respiratory pathogens, including influenza and SARS-CoV-2. Future studies should continue to investigate this phenomenon at the population level in Connecticut to further investigate the results of this study. The current influenza season in Connecticut has already had over 1,000 cases, which is typical of a normal influenza season.[36] Perhaps, with such a high number of cases, viral interference would be evident at the population level. Since many are concerned by the threat of a "twin-demic" of COVID and influenza, it would be worthwhile to repeat this study in future influenza seasons and in more EIP sites to determine whether or not this is a real threat, as viral interference could possibly protect against such a dangerous phenomenon.

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