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Kimberlyn Roosa

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# Analysis of Seasonal Influenza Outbreak Trends in the United States from 2005-2015

by

Kimberlyn Marie Roosa

B.S., University of South Carolina

A Thesis Submitted to the Graduate Faculty  
of Georgia State University in Partial Fulfillment  
of the  
Requirements for the Degree

MASTER OF PUBLIC HEALTH

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30303

# Analysis of Seasonal Influenza Outbreak Trends in the United States from 2005-2015

by

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April 24, 2017

## Author's Statement Page

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Kimberlyn Marie Roosa

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## ABSTRACT

### **Background:**

Seasonal influenza epidemics occur annually in the United States (U.S.) and result in lost workforce productivity, strained healthcare services, and an annual economic burden of \$11 billion. While the U.S. has a comprehensive surveillance system, and the Centers for Disease Control and Prevention (CDC) publishes weekly updates on the outlook of seasonal influenza activity (FluView), there is a lack of literature analyzing seasonal influenza peak trends across and within regions of the country over multiple flu seasons. This study aimed to identify trends over time (2005-2015) in the timing and size of seasonal flu outbreak peaks, both across and within Health and Human Services regions.

### **Methods:**

Secondary data analysis was conducted on U.S. national influenza surveillance data compiled and provided by the CDC. The study includes all persons in the United States (all 50 states, District of Columbia, Puerto Rico, and the U.S. Virgin Islands) who sought healthcare for influenza-like illness (ILI) during the 2005-06 flu season through the 2014-15 season. Trends over time in peak timing and size were assessed overall (across all HHS regions) and within regions. The effect of the dominant subtype of influenza virus circulating on peak timing and size was also assessed.

### **Results:**

Trends in seasonal influenza outbreaks revealed peaks that occurred earlier over time ( $p < 0.0001$ ) and increased in size over time ( $p = 0.0012$ ). The median peak week did not vary significantly by region ( $p = 0.8541$ ). Also, peak week and peak size were negatively correlated showing that earlier epidemics result in higher ILI rates. The timing of the epidemic differed depending on the dominant subtype circulating ( $p = 0.0337$ ) with subtype 2009 H1N1 peaks occurring 3.5 weeks earlier than H1 peaks; however, subtype did not have a significant effect on the size of the epidemic peak ( $p = 0.1984$ ).

### **Conclusion:**

A significant decrease in peak week and a significant increase in peak size were observed over time, revealing a trend of earlier and more intense seasonal flu peaks. Since earlier epidemics are correlated with higher rates of ILI, anticipating earlier seasonal peaks highlights the importance of vaccination and other flu prevention strategies being utilized early in the flu season.

## **Introduction**

Influenza, commonly known as the 'flu', is a highly pathogenic disease caused by infection with an influenza virus, typically spread through contact with contaminated droplets in the air [1, 2]. The symptoms of influenza (fever, cough, headache, muscle and joint pain, sore throat, and runny nose) are common among other illnesses including meningitis, tuberculosis, and hepatitis A, but the seasonality of flu epidemics distinguishes influenza from these other clinically similar diseases [3]. Seasonal flu outbreaks are the results of small changes in strains of the virus already circulating among humans; these viruses typically result in epidemics with high number of infected persons, a generally low death rate, and few complications compared to epidemics of clinically similar diseases [3]. In temperate areas, large and intense outbreaks occur in winter months, followed by periods with little to no flu activity in warmer months [4]. In the United States (U.S.), seasonal flu epidemics cause 5-20% of the population to become ill with influenza each year, resulting in lost workforce productivity, strained healthcare services, and an annual economic burden of \$11 billion [1, 4].

The purpose of this study was to identify trends in timing and size of seasonal influenza epidemic peaks over a 10 year period (2005-2015) in the United States. National data was assessed as well as regional data by Health and Human Services (HHS) region. Peak timing was analyzed by HHS region to identify any variation in epidemic peak timing across regions of the United States. The dominant subtype (type A) of influenza virus circulating at epidemic peak was compared with peak timing and size to determine the effect of dominant subtype on these peak characteristics.



## **Literature Review**

### Overview of Influenza:

Influenza, or the ‘flu’, is a highly pathogenic disease caused by infection with an influenza virus. There are three types of influenza viruses: influenza type A infects humans and various animals, type B circulates only within humans, and type C can infect humans and pigs, but infections are typically mild and sporadic [3, 5, 6]. Influenza type A viruses are further categorized into subtypes distinguished by antigenic properties (refers to how the virus alters its surface proteins to evade a host immune response) of its surface glycoproteins, and type B viruses are divided into two main groups or lineages [3, 5, 6]. Despite common nomenclature of type A viruses circulating among humans and animals (H1N1: swine; H3N2: avian), the viruses are distinct; a human can be infected with an animal flu virus through direct contact with an infected animal, but the virus is not likely to spread far within a human population [5, 6]. While type A and type B viruses are responsible for seasonal flu epidemics, only type A viruses are known to have caused pandemics [1, 5, 6].

### Transmission and Risk Factors:

When a person infected with influenza coughs, sneezes, or talks, droplets containing viruses are dispersed into the air and can spread up to six feet from the host [1, 2]. Droplets can land in mouths or noses or possibly even be breathed into the lungs; influenza can also be spread by touching hands or other surfaces that are contaminated with the virus and then touching the nose or mouth [1, 2]. Those infected with influenza can transmit the disease up to one day before symptoms appear and remain infectious for five to seven days after becoming sick [2].

Influenza can affect all populations, but those at an increased risk for complications include: pregnant women, young children (aged 6-59 months), elderly persons, and those with weakened immune systems or underlying conditions [1, 6]. Underlying conditions that may increase the risk for complications include: HIV/AIDS, asthma, chronic heart or lung diseases, neurological or neurodevelopmental conditions, blood disorders, diabetes, kidney or liver disease, extreme obesity (BMI > 40), and metabolic disorders [1, 6, 7]. Influenza also spreads easily and rapidly in crowded areas like schools and nursing homes [1]. In addition, healthcare workers are at an increased risk, as their risk of exposure is high [7].

#### Symptoms, Complications, and Burden:

Influenza is characterized by the sudden onset of fever, cough, headache, muscle and joint pain, severe malaise, sore throat, and runny nose [1]. Most people recover from the symptoms within a week without medical attention; however, influenza can cause severe complications or death, especially in the high-risk populations previously mentioned [7]. Sinus and ear infections are moderate complications of influenza. More severe complications include: pneumonia, inflammation of the heart, brain, or muscle tissue, multi-organ failure, and sepsis [8]. Influenza can also worsen previous conditions like asthma and chronic heart disease [8].

In the United States, between 5-20% of the population becomes sick with influenza each year, and on average, 36,000 people die from flu-related complications [4]. Influenza epidemics can also take an economic toll on the country due to increased absenteeism in schools and workplaces, lost workforce productivity, and strained healthcare services [1]. Clinics and hospitals can be overwhelmed by the high volumes of patients during a flu epidemic. Overall, the economic burden of influenza in the United States is estimated at \$19 billion annually [4].

### Treatment and Vaccination:

Only two classes of agents have licensed products for treatment of the flu: influenza neuraminidase (NA) inhibitors and M2 proton channel blockers [9]. Viral resistance to the M2 blockers is frequently reported, which limits the effectiveness of the treatment, and only NA inhibitors are active against the currently circulating seasonal influenza viruses [1, 9]. The World Health Organization (WHO) recommends NA inhibitors as first-line treatment [1]. While the treatment options are limited, these antiviral drugs (available in some countries) can lessen symptoms, shorten sick time, and reduce the risk of severe complications and death, and should be administered ideally within 48 hours of symptom onset [1].

Vaccination is the most effective way to prevent disease from influenza; vaccines are safe and effective and have been used for over 60 years [1]. Vaccines are especially important for those populations at increased risk for flu complications and for people who live with or care for these high-risk persons [1, 10]. While flu vaccines are most effective when well-matched with the circulating viruses, among healthy adults, vaccination provides protection even when the viruses are not exactly matched [1].

The United States Centers for Disease Control and Prevention (CDC) provides vaccination recommendations each year regarding the strain, timing, and type of vaccine administered. On February 24, 2010, the CDC's Advisory Committee on Immunization Practices voted for "universal" flu vaccination in the United States to expand flu protection, so the CDC recommends that everyone six months or older should be vaccinated each flu season [10]. The CDC currently recommends the inactivated influenza vaccine (IIV) for all ages (over 6 months) or the recombinant influenza vaccine (RIV) for ages 18-49 years [11]. IIV is an intramuscular or intradermal injection of an inactive flu virus, and RIV is a new option (licensed January 2013)

that does not contain a flu virus [11, 12]. The live attenuated influenza vaccine (LAIV) is a nasal spray option (2-49 years), but the CDC is not recommending this option for the 2016-17 flu season due to the decreased effectiveness of the vaccine [11]. It is also important to note that it takes two weeks after vaccination for antibodies to develop and provide protection [12].

### Nonpharmaceutical Interventions:

Nonpharmaceutical interventions (NPIs) are actions that individuals and communities can take to slow the spread of infectious diseases like influenza. In 2007, the CDC collaborated with other federal agencies, educational institutions, businesses, healthcare providers, and private enterprises to develop an interim planning guide on the use of NPIs [13]. NPIs are some of the best ways of controlling influenza epidemics when vaccines have yet to be created and provide an extra layer of protection when vaccination is available [14].

Voluntary home quarantine, hand hygiene, face masks, and covering mouth with a tissue while coughing or sneezing are examples of personal NPIs [1, 13]. A study conducted in 2010 found that when compared with a non-masked control group, the use of face masks and hand hygiene significantly reduced the influenza-like illness (ILI) rates [13]. Surface cleaning is an environmental NPI that can be utilized to decrease risk of disease [14].

Community NPIs are used to slow the spread of disease once an epidemic is identified. Social distancing (increasing the distance between people) and closures are used in priority settings, such as child care centers, schools, workplaces, places of worship, events, concerts, meetings, and other events where people gather. While these are difficult to plan and execute, they can be the most effective ways to protect the community from the impact of the pandemic [14].

### Seasonal vs. Pandemic Influenza:

Certain influenza viruses (within type A and B) circulate seasonally and cause disease in humans each year. In temperate climates, seasonal epidemics tend to occur in the winter months [6]. In tropical regions, flu seasonality is less obvious and epidemics occur irregularly throughout the year [1]. These seasonal viruses evolve continuously through a process called ‘antigenic drift’ which results in small changes in genes over time as the virus replicates. This process produces viruses that are closely-related, so immune systems exposed to a similar virus can usually recognize the virus and respond (cross-protection); however, these small changes can accumulate over time, so immune systems may not recognize it [15]. For this reason, people can be infected with influenza multiple times throughout their lives, and components of seasonal flu vaccines must be reviewed frequently and updated periodically to ensure effectiveness [6, 15].

‘Antigenic shift’ is an abrupt, major change in an influenza type A virus that results in new proteins in flu viruses that infect humans [15]. These pandemics are typically zoonotic influenza viruses that adapt or acquire certain genes from human viruses that allow them to spread easily amongst a human population with little previous immunity, so the virus rapidly transmits and causes large outbreaks outside of the normal flu season [6]. Ongoing circulation of certain bird-flu types (A(H5), A(H7N9)) is a public health concern, as these commonly cause severe disease in humans and have the potential to mutate and become more transmissible [5].

### Surveillance in the United States:

Surveillance of influenza or ILI provides useful information concerning future effects of seasonal and pandemic influenza. The data can contribute to decisions regarding flu strains selected for annual vaccine production, use of antiviral treatment, and groups to recommend the

annual vaccine [16]. The CDC has a multi-component influenza surveillance system with the following goals: 1. Determine location and timing of influenza activity; 2. Determine which viruses are circulating; 3. Detect changes in circulating viruses; 4. Track influenza-related illness; 5. Measure impact on hospitalizations and deaths [17]. This comprehensive system has eight different surveillance components in five categories that cover all 50 states, District of Columbia (DC), Puerto Rico, and the U.S. Virgin Islands.

## **Manuscript**

### **Introduction**

Influenza, commonly known as the ‘flu’, is a highly pathogenic disease caused by infection with an influenza virus, typically spread through contact with contaminated droplets in the air [1, 2]. There are three types of influenza viruses: influenza type A infects humans and various animals, type B circulates only within humans, and type C can infect humans and pigs, but infections are typically mild and sporadic [3, 5, 6]. Pandemics of influenza occur when a virus strain not previously seen in humans emerges; the majority of persons do not have immunity, so the new strain has the ability to spread rapidly and easily through a human population [1]. Seasonal influenza outbreaks are the results of small changes in strains of the virus already circulating among humans [1]. While only type A is known to have caused pandemics, both type A and type B viruses circulate during the periodic, or seasonal, epidemics of influenza [1, 5, 6]. Once a pandemic virus has been established, it can begin circulating as a seasonal flu virus, for example: 2009 A(H1N1) [1].

The symptoms of influenza (fever, cough, headache, muscle and joint pain, sore throat, and runny nose) are common among other illnesses including meningitis, tuberculosis, and hepatitis A [3]. While influenza is clinically similar to other diseases, the characteristics of seasonal flu outbreaks are distinct. Seasonal flu viruses typically result in epidemics with high number of infected persons, a generally low death rate, and few complications compared to epidemics of clinically similar diseases [3]. In temperate areas, large and intense outbreaks occur in winter months, followed by periods with little to no flu activity in warmer months [4]. In the United States (U.S.), seasonal flu epidemics cause 5-20% of the population to become ill with

the flu each year, resulting in lost workforce productivity, strained healthcare services, and an annual economic burden of \$11 billion [1, 4].

The United States Centers for Disease Control and Prevention (CDC) gathers influenza-related data from public health and clinical laboratories in all 50 states, District of Columbia, Puerto Rico, and the U.S. Virgin Islands through a comprehensive surveillance system. The CDC compiles the data and disseminates the information through weekly influenza surveillance reports, or FluView [17]. Within the FluView reports, the CDC provides information regarding characteristics and trends of the current seasonal flu epidemic; however, they do not assess how these trends have changed over multiple flu seasons [17]. Since FluView data is reported with a lag, it is not ideal for in-season predictions, and so various other data sources using online information are being compared to FluView to assess correlation. Some of these sources include: Google Flu Trends, Twitter, and Wikipedia. The lag in FluView data was not an issue for this study, as we were assessing trends over multiple flu seasons.

The purpose of this study was to identify trends in timing and size of seasonal influenza epidemic peaks over a 10 year period (2005-2015) in the United States. National data were assessed as well as regional data by Health and Human Services (HHS) region. Peak timing was analyzed by HHS region to identify any variation in epidemic peak timing across regions of the United States. The dominant subtype (type A) of influenza virus circulating at epidemic peak was compared with peak timing and size to determine the effect of dominant subtype on these peak characteristics.



## **Methods**

### *Study Design*

This study was a cross-sectional, secondary analysis of existing U.S. national influenza surveillance data provided by the CDC (2005-2015).

### *Setting and Participants*

The study population for this analysis was the U.S. population (all 50 states, DC, Puerto Rico, and the U.S. Virgin Islands) who sought healthcare for ILI for flu seasons 2005-06 through 2014-15. Data were assessed on a national level as well as broken down by the ten Health and Human Services (HHS) regions (Figure 1).

The 2009-10 flu season was excluded from analysis as the exceptionally large peaks and early timing were due to the H1N1 pandemic, which occurred outside the regular flu season. Since the 2009 H1N1 strain was a new strain, not previously seen in humans, the 2009 epidemic was classified as pandemic rather than seasonal. Also, using Grubb's Test, it was found that the peak size in the 2009-10 season was an outlier in half of the regions (HHS regions 1, 5, 7, 8, 10) and peak timing was an outlier in four of the regions (1, 6, 7, 10), so this season was excluded from analysis.

### *Variables*

For each region, peak size was defined as the maximum ILI weekly total per flu season, and peak timing was defined as the week of the flu season that this maximum occurred. The CDC's definition of flu season was used: Week 40 through Week 39 of the following year. The peak week variable was coded as Week 1 of the flu season equating to Week 40 of the calendar year. The peak weeks were then categorized by the month in which they occurred (based on the

first day of the week – Sunday) to create the peak month variable. Both peak week and peak month were used. These variables were obtained from ILINet data.

For each region, data on the subtype (type A) circulating was recorded per peak week. The subtype with the highest percentage of positive tests was recorded as the dominant subtype circulating. Subtypes H1, H3, and 2009 H1N1 were included. This data was obtained from the virologic surveillance system.

#### *Data Source*

FluView is a weekly influenza surveillance report that contains information on year-round influenza activity in the United States. The Epidemiology and Prevention Branch in the Influenza division at the CDC collects, compiles, and analyzes the information provided by the collaborative surveillance system conducted by the CDC and its partners in state, local, and territorial health departments, public health and clinical laboratories, vital statistics offices, healthcare providers, clinics, and emergency departments. The comprehensive system contains five categories of influenza surveillance; information from virologic surveillance and outpatient illness surveillance categories were used for this analysis. [17]

The virologic surveillance category contains data from approximately 100 public health and over 300 clinical laboratories spanning all 50 states, Puerto Rico, and the District of Columbia (DC). The laboratories perform subtyping tests on respiratory samples from patients exhibiting ILI and report data regarding influenza virus type and subtype through either the U.S. WHO Collaborating Laboratories System or the National Respiratory and Enteric Virus Surveillance System (NREVSS). Influenza subtype data from this system were utilized for this analysis. [17]

The U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet) consists of over 2,800 enrolled outpatient healthcare providers in all 50 states, Puerto Rico, DC, and the U.S. Virgin Islands that report information on patient visits for influenza-like illness (ILI). For this surveillance system, ILI is defined as having a fever of 100° Fahrenheit (F) or higher, and cough and/or sore throat with no other known cause besides influenza. Data on reported number of ILI visits were used for this analysis. [17]

### *Statistical Methods*

Microsoft Excel was used to organize data. SAS 9.4 was used for recoding variables and performing statistical tests. An alpha level of 0.05 was used for all statistical tests.

The Shapiro-Wilk test for normality was used to determine if variables followed a normal distribution. Variables were tested across regions and within regions. Histograms and QQ-plots were also examined, as the sample size within regions (N=9) was small and could result in a non-significant result due to lack of statistical power. These tests and/or visuals revealed non-normality across all of the variables.

The following comparisons were tested across regions using the Kruskal-Wallis test (npar1way procedure in SAS): peak size by month, peak size by dominant subtype, peak week by subtype, and peak week by region (dependent by independent variable). Peak size was not tested across HHS regions, as there is high variation in population size, baseline ILI percentage, and other population factors that could affect the number of ILI visits, so the difference in median peak sizes across HHS regions would not provide any useful information for this study.

Dunn's test was used as a post-hoc test multiple comparisons test for associations that revealed statistical significance in the Kruskal-Wallis test. This was done using a Dunn macro in SAS provided by Cornell University [18].

The association between peak month and dominant subtype was assessed using Fisher's exact test of independence (proc freq procedure with Fisher option in SAS).

The following correlations were tested (proc corr with Spearman option in SAS) both across regions and within regions: peak size and flu season, peak size and peak week, and peak week and flu season.

## Results

This analysis contained data on 90 seasonal influenza epidemic peaks: 9 flu seasons and 10 HHS regions. Among the 90 peaks, 38 (42.22%) occurred in February, 24 (26.67%) in January, 15 (16.67%) in December, 12 (13.33%) in March, and 1 (1.11%) in April. H3 was the dominant subtype circulating for 57 (63.33%) of the seasonal flu peaks, H1 for 18 (20.00%), and the 2009 H1N1 subtype for 15 (16.67%).

Trends in epidemic peak timing (peak week) reveal that seasonal influenza outbreak peaks have been occurring earlier over time ( $p < 0.0001$ , Figure 2). While all HHS regions followed the trend, Regions 2, 9, and 10 showed little correlation to the downward trend in peak week. Peak timing was consistent across regions with a median peak week range of 18-21 weeks ( $p = 0.8541$ , Figure 3).

Seasonal epidemic peaks also revealed an upward trend in size of peaks over time across all regions ( $p = 0.012$ , Figure 4). Increasing peak size over time was less of a trend in Region 4. It was observed that the earlier the epidemic peak occurred, the larger the peak size was ( $p = 0.0005$ , Figure 5). Regions that strayed from this trend were 2, 4, and 10.

The dominant subtype of influenza virus circulating at the peak of the outbreak has an effect on the timing of the epidemic peak ( $p = 0.0396$ , Figure 6). Subtype H1 was heavily concentrated in February (66.67%) with little spread in other months, subtype H3 had the most peaks in February (38.6%) but had more peaks occur in earlier months (December and January), and the H1N1 subtype from the 2009 pandemic had the majority of its peaks (60.0%) in January (Table 6). Similarly, the median peak week of the 2009 H1N1 subtype occurred 3.5 weeks earlier than the median peak week of the H1 subtype ( $p = 0.0337$ , Figure 7).

While peak size appears to vary depending on the dominant subtype circulating, the differences in median peak size across subtypes were not significant ( $p=0.1984$ , Figure 8).

## **Discussion**

### *Timing of Seasonal Influenza Peaks*

The median peak week (week in which the highest incidence of ILI total occurred) across all of the HHS regions decreased significantly as the season increased (Figure 2), which indicates that seasonal flu epidemics have been peaking earlier over time. There is a lack of studies regarding temporality of seasonal flu epidemics in the United States, so anticipating earlier seasonal flu epidemics can be beneficial for earlier vaccination recommendations and preparation efforts. When seasonal flu epidemics occur, a strain is put on healthcare services, so insight on the timing of the seasonal peak could allow them to prepare adequately. Also, since vaccines provide protection for around six months, early flu vaccination should be recommended as the highest rates of ILI (peak) are being seen earlier in the season [10].

The timing of the seasonal flu peak (median peak week) did not vary significantly across HHS regions [Figure 3]. Ranging from week 18-21 of the flu season, the temporal spread of ILI peaks was small across the regions. A study of the 2009 H1N1 pandemic in Chile revealed a latitudinal gradient in which a temporal lag was seen from South to North [19]. This lag/gradient was not seen observed in the U.S, though this may be due to the regions in Chile having a greater difference in climactic conditions compared to the U.S. regions. Also since only median peak week was assessed, further comparison of peak week across regions by year may reveal a significant pattern.

The analysis revealed that timing of the seasonal flu peak is affected by the dominant subtype (Type A) circulating. Subtype H1-dominant peaks occurred most often in February (66.67%), and the 2009 H1N1 subtype occurred most often in January (60.00%). Subtype H3 was spread more evenly across peak months, but had the highest frequency in February [Table

6]. Dunn's test showed a significant difference of 3.5 weeks in median peak timing between subtypes H1 (Week 20.5) and 2009 H1N1 (Week 17) [Figure 7]. These results are again important for preparation and vaccination strategies. In seasons where the 2009 H1N1 strain is circulating, an earlier epidemic peak may be expected.

### *Size of Seasonal Influenza Peaks*

The size of seasonal flu epidemic peaks (maximum ILI total per flu season) is increasing over time. The majority of HHS regions (Regions 2, 3, 5, 6, 8, and 10) showed a strong correlation of increasing size over time (Figure 4); when assessed across all regions, a weak positive correlation was observed despite regional variation. The increase of ILI total over time does not necessarily indicate that the burden of influenza is increasing over time. Since the U.S. population, more specifically the population with access to healthcare, was increasing over this time period (2005-2015), the higher ILI totals may not be representative of the change in burden over time. However, the increasing size in peaks still represents the importance of universal vaccination coverage, as recommended by the CDC [10].

Based on this analysis, the dominant subtype circulating did not have an effect on the size of the seasonal epidemic peak, as the median peak size did not vary significantly across subtype (Figure 8). A study assessing seasonal flu characteristics by subtype in France found that seasons with subtype H3 dominating had higher incidence peaks [20]. The study in France, however, only compared subtypes H1 and H3 and did not include the 2009 H1N1 strain. The lack of significance in the Kruskal-Wallis test may be due to small sample sizes within subtypes (H1: 18, 2009 H1N1: 15).



The Spearman correlation coefficient between peak size and peak week (across all regions) indicates that there is a weak, but significant negative correlation between the two (Figure 5). As the peak week decreases, or occurs earlier in the year, the size of the epidemic peak increases. The median peak week was also found to differ significantly by peak month [Figure 9]. Dunn's test lacks statistical power, and thus did not provide additional information on which month pairs varied significantly by size, but it can be seen that as month goes from December to March (excluding the one peak in April), the median peak size and IQR are decreasing by month (Figure 9). These results indicate that flu seasons with earlier epidemic peaks will be more intense (larger), which continues to confirm the importance of vaccination early in the season.

### *Limitations*

The use of ILI data as an indicator for rates of influenza activity may over or underestimate the actual burden per region. Overestimation could be due to the general clinical definition of influenza that may encompass other respiratory diseases; however, the clinical specification of “no other known cause other than influenza” may help reduce this overestimation [17]. ILI data could also underestimate the burden of influenza, as the data only includes those who sought healthcare for their symptoms.

For this analysis, only the peak size (maximum ILI total) was recorded per season, per region, and the peak size may not be representative of the size of the season as a whole. However, since this study was focused on peak characteristics, the ILI total was sufficient as an indicator of size and timing of seasonal flu peaks.

The dominant subtype was only recorded at the peak week, and so may not be an accurate representation of the primary subtype circulating throughout the season. Also, not all positive influenza samples are subtyped. Future research assessing subtype prevalence throughout the flu season would be beneficial for determining the effect it has on characteristics of the season.

Sample sizes within regions were small (N=9), so statistical power was lacking for analysis within regions. Also, the use of nonparametric statistical tests (Kruskal-Wallis, Dunn's test, Spearman's rho) decreases the statistical power and contributes to a lack of significant results. Future studies analyzing trends over a greater period of time, or over various points of a season, may provide more significant results.

### *Conclusion*

While the U.S. has a comprehensive surveillance system, and the CDC publishes weekly updates on the outlook of seasonal influenza activity (FluView), there is a lack of literature analyzing seasonal influenza peak trends across and within regions of the country over multiple flu seasons. In this study, a significant decrease in peak week and a significant increase in peak size were observed over time, revealing a trend of earlier and more intense seasonal flu peaks. While subtype did not have an effect on the size of the epidemic peak, the median peak week varied based on the dominant circulating subtype. Trends in seasonal epidemic peak characteristics have important implications for predictive techniques, vaccination recommendations, and prevention strategies: trends of earlier and more intense epidemics should result in encouraging vaccination and personal protection methods earlier in the flu season.

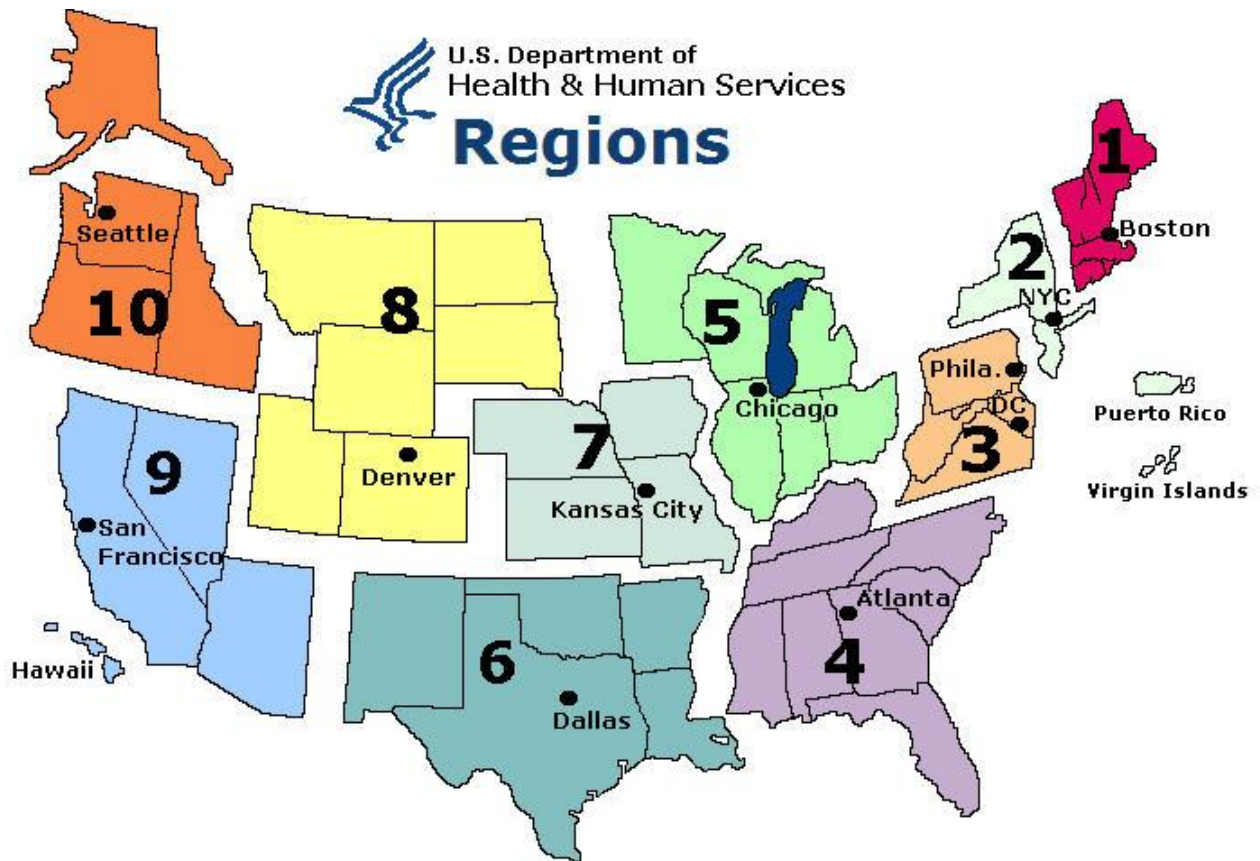
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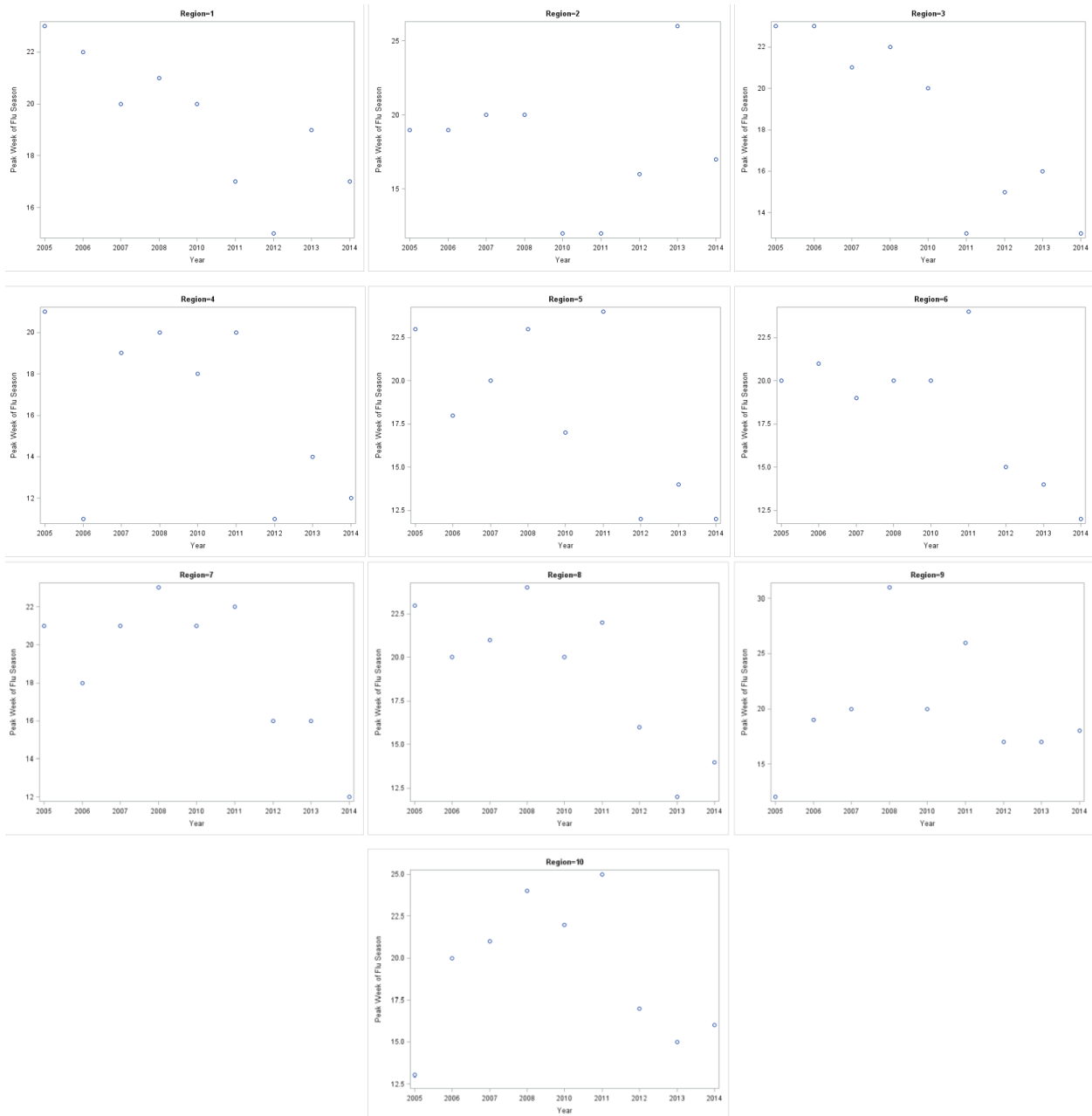
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Figures

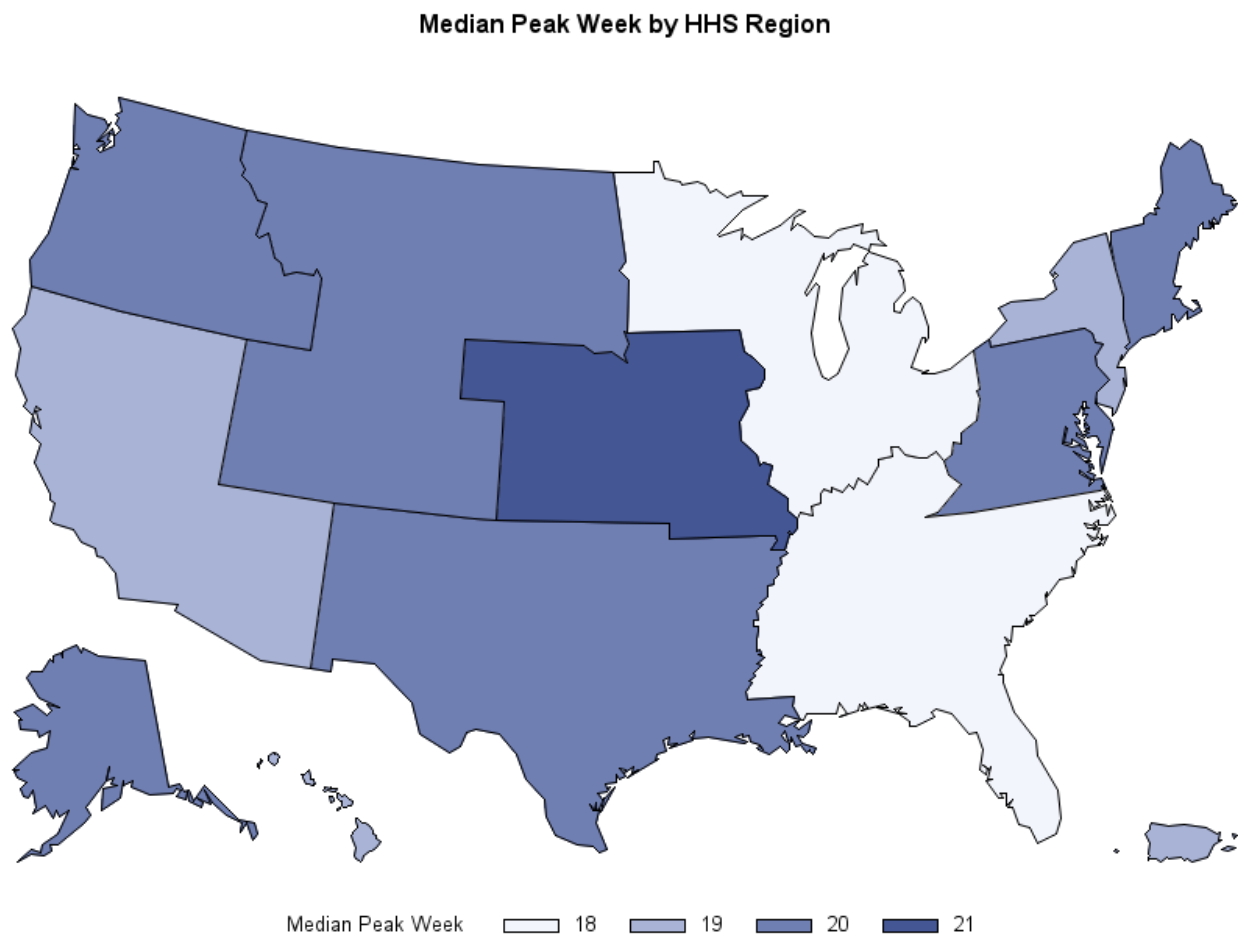
Figure 1. Health and Human Services Regions [21]



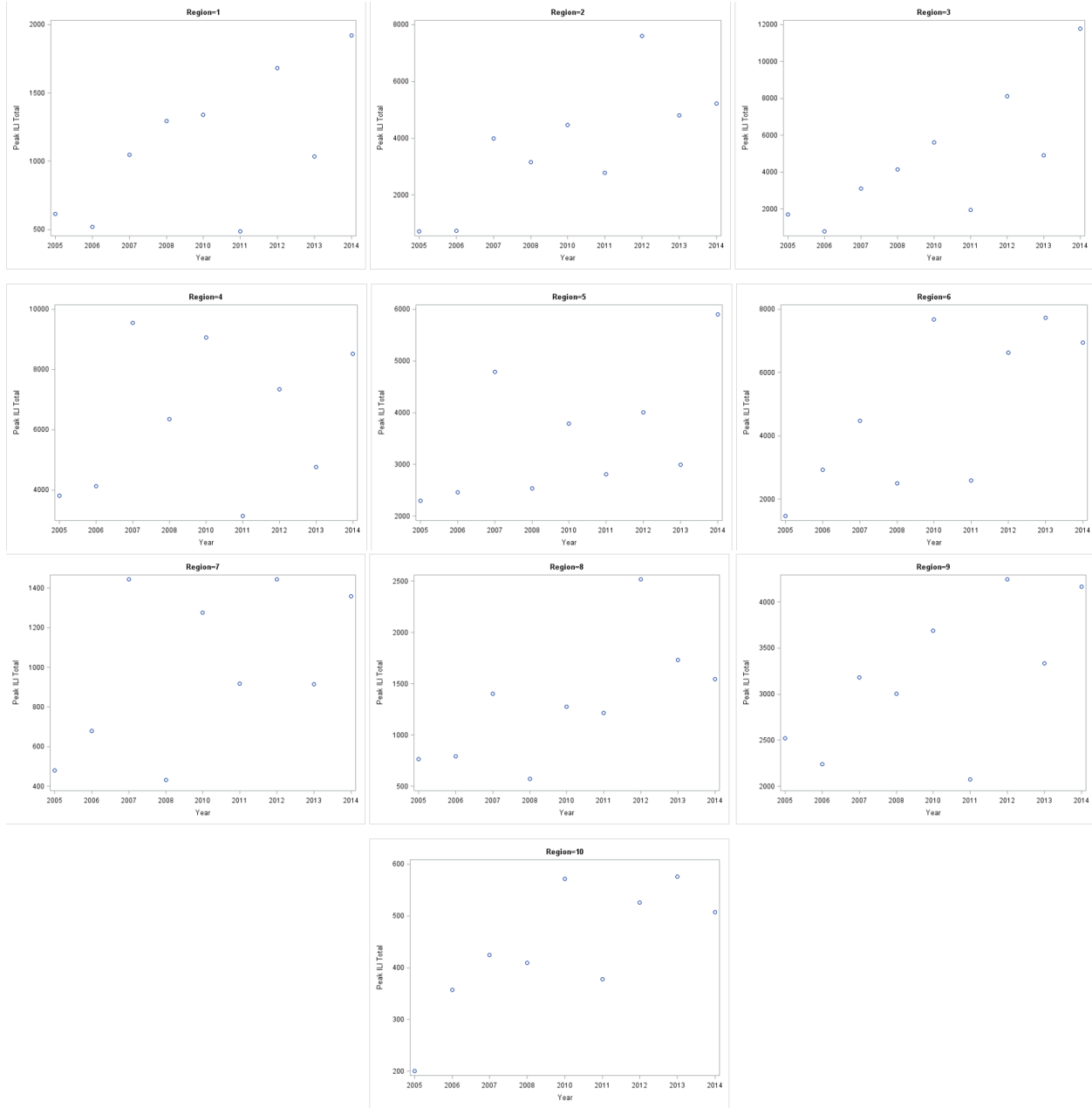
**Figure 2. Peak week over time (by year) per HHS Region (p<0.0001)**



**Figure 3. Peak timing (week) by Health and Human Services Region (p=0.8541)**

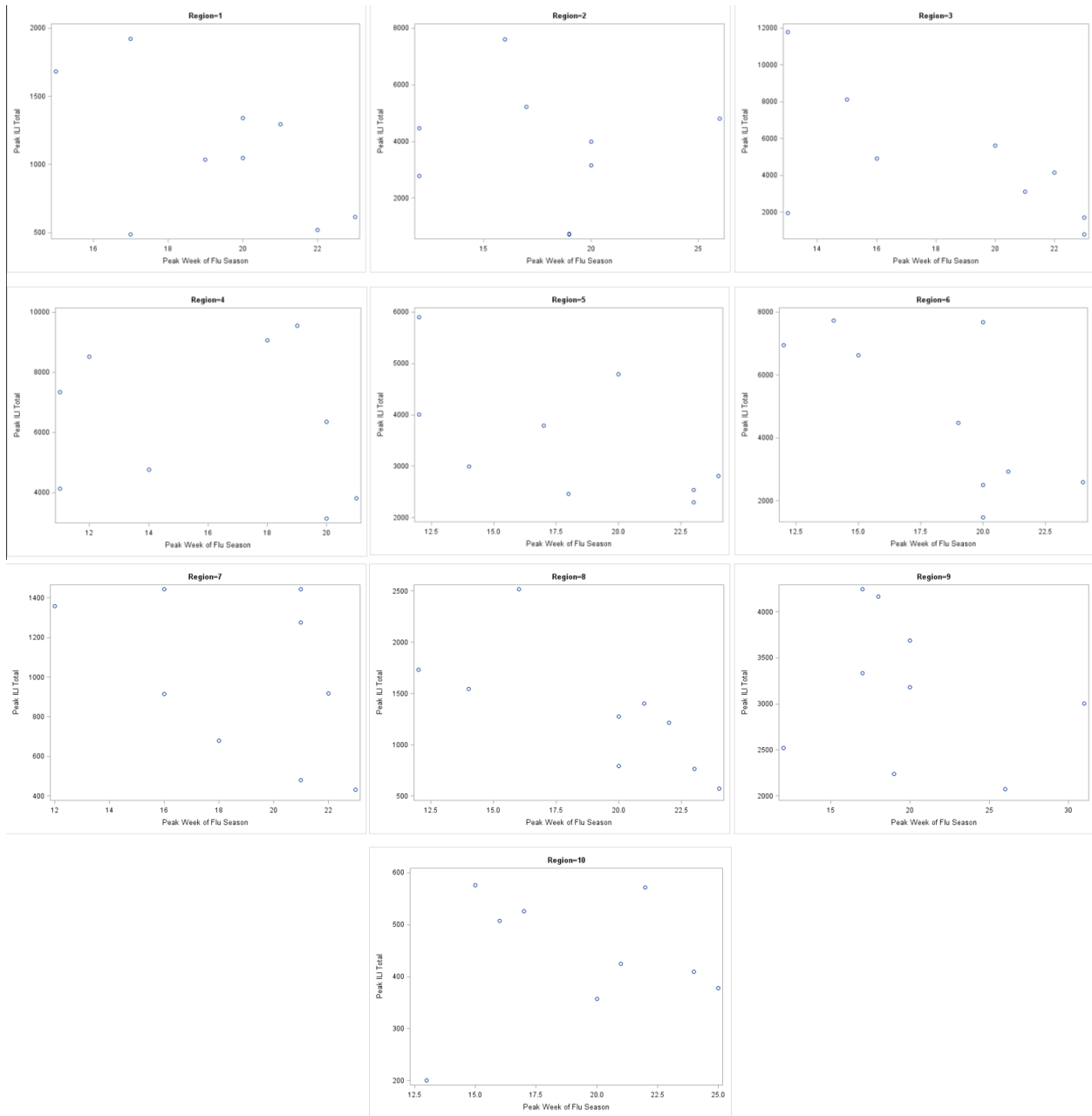


**Figure 4. Maximum ILI total (peak size) over time (year) per HHS region (p=0.012)**

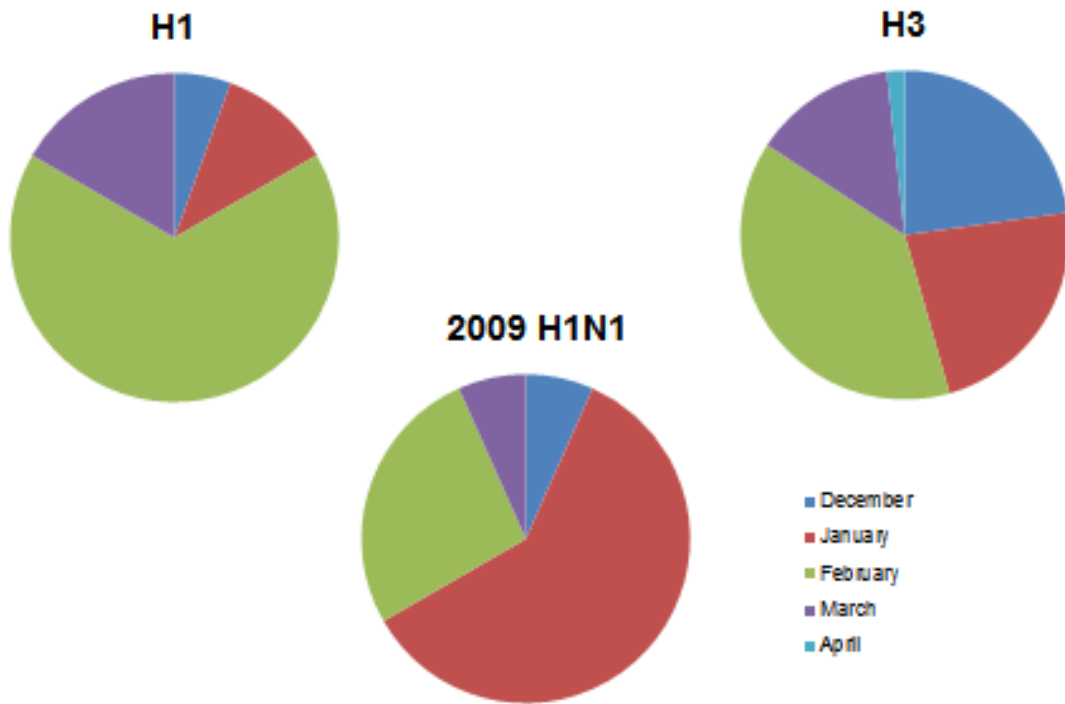




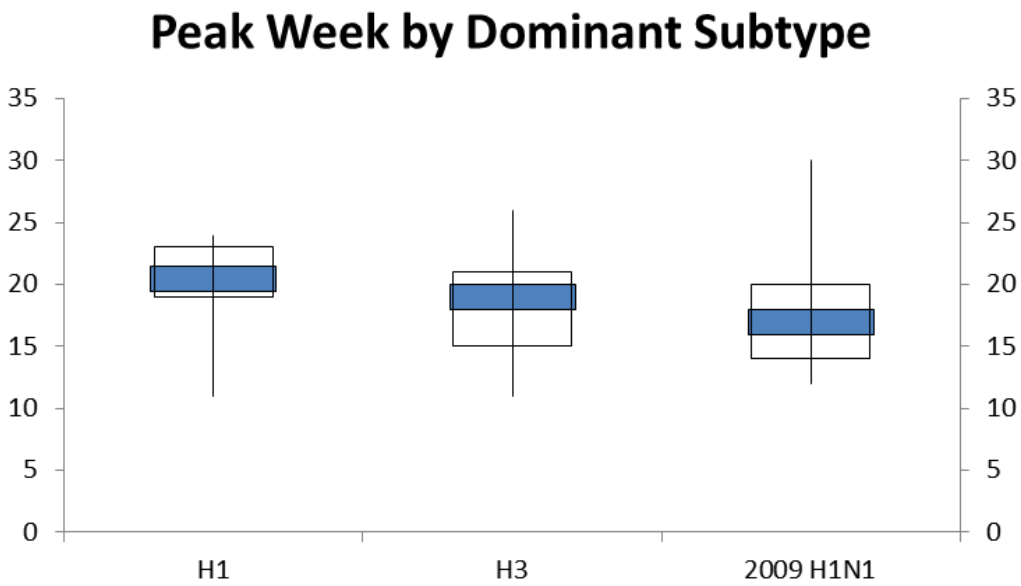
**Figure 5. Correlation of peak size by peak week (p=0.0005)**



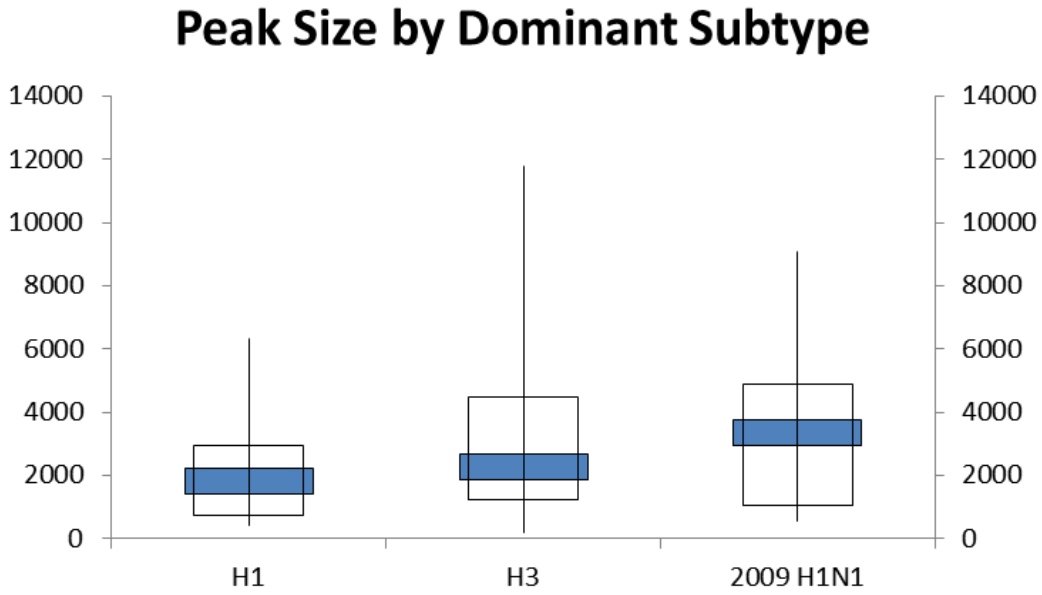
**Figure 6. Month in which the peak of the outbreak occurs by dominant subtype circulating (p=0.0396)**



**Figure 7. Peak timing (week, y-axis) by dominant subtype circulating (p=0.0337).**



**Figure 8. Peak influenza-like illness total (y-axis) by dominant subtype circulating (p=0.1984)**



**Figure 9. Peak influenza-like illness total (y-axis) by month in which the peak occurs (p=0.0494)**

