Applying Current Methods for Estimating Influenza Burden to an Academic Health Sciences Centre

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ABSTRACT

Public health planning for influenza is based on morbidity and mortality estimates derived from statistical models. Lower than anticipated 2009 H1N1 pandemic death estimates have raised questions about the method. Examining the statistical method is important for future policy and program development.

We compared the main methods of estimating influenza burden through a systematic literature review and by comparing statistical estimates of influenza-attributable burden at the Ottawa Hospital (TOH) to clinical estimates validated through chart review. We identified heterogeneity in methods used to estimate influenza-attributable mortality in the literature which resulted in within-season estimate variation by study. We found statistical estimates of influenza burden at TOH to be 4-8 times greater than clinically validated data. We also found no significant association between the outcomes examined and epidemic periods at TOH.

The findings of this study suggest discordance between model estimates by model approach and between model estimates and validated findings. Examining reasons for these discordances should be pursued.

1.0 INTRODUCTION

1.1 Influenza

Influenza is a single-stranded RNA respiratory pathogen. It causes a syndrome typically characterized by respiratory symptoms (including cough and sore throat), fever, and myalgia. Other symptoms can occur including gastro-intestinal, although these are less common. Occasionally, the infection can lead to a fulminant infection, with acute respiratory distress and a septic shock like syndrome (1). Influenza typically has the greatest morbidity and mortality impact in children, the elderly, and the immuno-compromised (2).

There are three types of the virus (A, B and C), with influenza type A being the most pathogenic and virulent of the three. Subtypes also exist composed of different combinations of the virus' HA and NA surface glycoproteins, for example subtype H1N1 or H5N1 (2, 3). The subtypes also have varying virulence.

Influenza viruses are transmitted via inhalation of virus-containing respiratory droplets from an infected person or by contact with virus present on environmental surfaces. The efficiency of influenza virus transmission depends on a number of factors including environmental, host and virus characteristics (4). For example, the efficiency of influenza transmission can be limited by the absence of specific amino acid sequences within the virus, conditions of high humidity, or pre-existing immunity within the host. Therefore, estimates of the number of cases caused by each infected person (also termed the reproductive number of the virus) can vary (5).

Once infected with influenza, individuals will mount an immune response, precluding future infections by the specific subtype. However, the major influenza antigens continue to

mutate. This leads to gaps in immunity. The frequency with which the virus genetically drifts renders the population continually vulnerable. As a result, localized influenza epidemics occur on an annual basis typically between November and April in temperate climates. The virus is also able to genetically *shift* causing dramatic changes in the HA and NA proteins and creating a novel virus for which the population has little to no immunity. This type of change is less frequent and can lead to an influenza pandemic, a rapid increase of influenza cases around the world (3). Over, the past century there have been several pandemics, which collectively have been estimated to result in millions of deaths worldwide.

In June 2009, the WHO declared that a pandemic was underway due to a new influenza A (H1N1) virus of swine origin. At the time this pandemic was recognized, governments put into place several actions to minimize its impact. These actions were justified on the basis of morbidity and mortality estimates extrapolated from recent influenza seasons.

1.2 Estimating Influenza Burden

For public health planning, it is necessary to estimate the impact of influenza under normal and pandemic conditions. This enables governments to calibrate future responses, which include the production and distribution of vaccines and antiviral agents and ensuring availability of appropriate health services. It also facilitates evaluations of the adequacy of responses. Current estimates of seasonal influenza deaths range from 2000-8000 (6).

In general, there are two basic approaches to assessing influenza mortality and morbidity. These include a clinical approach, in which only cases with a diagnosis of influenza are counted. This method ignores the fact that some patients with influenza are not diagnosed as such. The alternative method is a statistical approach, in which variations in seasonal mortality trends are

attributed to influenza activity. This method may be open to the ecological fallacy as it ignores the specific causes of death. The following sections describe these approaches in more detail.

1.2.1 Clinically Estimating Influenza Burden

Clinical estimates of influenza burden are the number of events coded as resulting from influenza. For example, counting the number influenza deaths in vital statistics, or summing discharge abstracts with a most responsible diagnosis of influenza.

Clinical estimates of seasonal influenza burden in Canada

Between 2000 and 2007, the number of seasonal influenza deaths recorded in vital statistics has ranged from 92 to 678 with a mean of approximately 300 deaths per year (7). These numbers are based on the WHO's International Classification of Disease (ICD-10) which allows for the distinction of those cases in which the virus was identified and those in which the influenza virus was not identified i.e. the diagnosis was made in the absence of laboratory confirmation. The majority of cases from 2000 to 2007 (~77% per year) did not have the virus identified.

Based on data from the Canadian Institute of Health Information (CIHI), Hospitalization Morbidity Database (HMDB), the annual mean number of hospitalizations with a most responsible diagnosis of influenza is approximately 800 hospitalizations per year (8, 9).

Limitations

Clinically quantifying the impact of influenza on human health is limited by the difficulty in identifying cases and causes of death. A number of different viruses can cause influenza-like-illness and laboratory confirmation of cases is not routinely conducted (2). Influenza is also known to lead to the development of pneumonia and exacerbate underlying cardiovascular and

respiratory conditions. As such, influenza cases can be missed if patients present to a physician with a secondary complication which is treated and documented without any reference to influenza (10, 11).

1.2.2 Statistically Estimating Influenza Burden

In the absence of reliable diagnosis data at the individual level, statistical approaches based on population data have been used to estimate the burden of the disease. These approaches were first proposed because of the similar seasonal patterns of mortality and influenza activity. Peaks in influenza activity have been shown to consistently overlap with peaks in all cause mortality data (10, 12, 13). Statistical methods are based on the assumption that influenza is an important driver of the peak elevations in mortality during influenza epidemics.

In general, the statistical approach involves estimating influenza-associated events as the difference between the event burden observed during an influenza epidemic and a statistically derived baseline burden that would have been expected in the absence of influenza (14). Three main statistical approaches are used to generate baseline mortality estimates: rate difference methods, regression, and time series analysis.

Rate difference methods use the average number of deaths during time periods associated with low or no influenza circulation to predict the baseline mortality such as peri-seasons (weeks during October to May when influenza circulation is uncommon but other respiratory viral pathogens are circulating) or summer months (periods when all respiratory virus circulation is uncommon) (15).

Regression methods, which include both linear and Poisson regression, model the expected baseline using a historical time series of mortality data and/or other indicators of influenza activity. Robert Serfling was the first to introduce a linear regression model that used a

linear term to describe secular trend and "cyclic" terms to describe seasonal trends, the latter of which was composed of sine and cosine terms with a full period in one year (16). The Serfling regression method involves taking a time series of mortality data over several years and excluding the mortality recorded during influenza epidemics. The regression model is then fit to the non-epidemic data to estimate a baseline for the subsequent season. The difference between the observed outcomes and the modeled baseline is then attributed to influenza (15). Poisson regression modeling involves fitting a model to the complete mortality time series and including model parameters that account for seasonality (e.g. monthly indicator variables), influenza activity (e.g. influenza certified deaths) and potential confounders such as activity of co-circulating viruses (e.g. laboratory specimens positive for respiratory syncitial virus). Poisson models estimate influenza-associated deaths by generating a predicted mortality value for the full-model for a given time period (e.g. week) and then subtracting a predicted value generated for that same time period when influenza activity model parameters are set to zero (10).

Time series models, like the linear regression models, use data from past non-epidemic weeks to predict mortality in the absence of an epidemic. In contrast, the time series model accounts for other factors affecting mortality by including a "random shock" component which represents all factors affecting mortality (e.g. weather, temperature, other respiratory pathogens etc.) and also accounts for the autocorrelation between observations (15). In addition, instead of deleting data entirely from epidemic weeks when developing the model, data from epidemic weeks are replaced by numbers forecasted using non-epidemic data (17).

Statistical estimates of seasonal influenza burden in Canada

Three Canadian studies have estimated influenza–attributable mortality at the national level in Canada (18-20). Shanzer et al estimated influenza-attributable mortality using a Poisson

regression model based on population mortality data from 1990-1999 in one study and 1994-2000 in the second study. In both studies, influenza was estimated to cause an average of 4000 deaths per year. Kwong et al used a Poisson regression model to estimate the impact of immunization on influenza mortality in Ontario based on population data from 1997-2004. Their study findings indicated that influenza can cause between approximately 2000 to 4500 deaths per year.

Schanzer et al also estimated the impact of influenza on hospital admissions in the adult population (>19 years of age) using a Poisson regression model and data from the CIHI HMDB for the period of 1994 to 2000 (8). They found that 8-10% of adult primary respiratory admissions could be attributed to influenza resulting in an average of 14,000 to 17,000 influenza hospital admissions per year.

Thus, the estimates from the statistical approaches are significantly higher than those using the clinical approach. For mortality, the number of patients estimated to die from influenza was, respectively, 300 patients versus 2000-4500 by the clinical versus statistical approaches. For hospitalizations, the number of patients admitted for influenza was, respectively, 800 versus 14,000 to 17,000, by the clinical versus statistical approaches.

Limitations

The main limitations of the statistical approach are the potential for ecological fallacy and seasonal confounding. As with any ecological study, an association between variables at a population level does not necessarily mean that an association at the individual level is occurring. In other words, even though peaks in influenza activity correspond to peaks in mortality it doesn't mean that each influenza-attributable death that is statistically estimated would in fact correspond to an individual with influenza. In addition, the association between

peaks in mortality and influenza activity could be confounded by other seasonal factors. For example, the circulation of respiratory syncitial virus (RSV) often overlaps with influenza. If not controlled for in the model, deaths resulting from this virus will be attributed to influenza (15). Researchers have also argued that other seasonal confounders such as cold weather distort the association (21).

1.3 The 2009 H1N1 Pandemic

As stated, in 2009 an influenza pandemic was identified by the WHO (termed the H1N1 pandemic). When it was first identified there were estimates of significant impact. However, analysis of pandemic H1N1 (pH1N1) cases in Canada has indicated that the disease was generally mild with complications occurring in atypical populations (e.g. young adults and pregnant women) (9). In total, Canada identified 8,678 pH1N1 hospitalizations and 428 deaths (9). These numbers were significantly lower than the 11 to 58 thousand deaths that were estimated to occur for a pandemic of mild to moderate severity during pre-pandemic planning (22).

The number of pH1N1 deaths was estimated clinically via a real-time national surveillance system in which each province and territory agreed to report to PHAC all pH1N1 deaths identified by their respective surveillance mechanisms. Deaths were classified based on a nationally agreed upon definition: a death occurring in any person with laboratory-confirmed pH1N1 influenza with no period of complete recovery between illness and death (J. Vachon, PHAC, personal communication, 2010).

Interestingly, the pH1N1 death count (428) is closer to the average clinical estimate of influenza deaths obtained from vital statistics (300) than to model estimates of seasonal or

pandemic mortality. Although the methodologies behind these two estimates are similar in the sense that they both involve counting deaths clinically classified as resulting from influenza, given that H1N1 was a novel virus that had severe outcomes and that response efforts generated heightened awareness, the number of pH1N1 deaths was expected to be much higher than vital statistic counts of seasonal influenza deaths. However, the pH1N1 death count was restricted to only those that were laboratory confirmed. As such, there is likely some mortality burden that is not captured in this estimate.

1.4 Examining Influenza Burden at a Single Hospital

There are three potential reasons why the current estimate of pH1N1 deaths in Canada might be lower than what was estimated at the outset of the pandemic. These include: there was actually more deaths, but these were not captured in the clinical surveillance program; the pH1N1 strain was less virulent than initially estimated; or, the forecasted estimates, which were based on statistical models from preceding influenza seasons were biased.

This study involved comparing the main methods of estimating influenza burden. I first compared estimates by modeling approach after systematically identifying all of the studies in the US and Canada that have statistically estimated national influenza mortality. I then examined the impact of the influenza at a single hospital level, where statistical estimates of burden could be validated against clinical estimates derived from hospital discharge data and confirmed through chart review. Furthermore, unlike any other study, I validated the clinical method for defining influenza cases and thus created a comparator for statistical estimates that served as an accurate picture of the true influenza burden.

By deriving and evaluating both clinical and statistical estimates of influenza burden in a single institution, I was able to examine the degree with which influenza activity is observable in a single hospital during both seasonal influenza epidemics and the pandemic using clinical information and to compare this with estimates of impact using statistical models. This provided me several opportunities. First, it allowed me to assess, at least at the hospital level, whether there were consistent numbers of deaths occurring over time. By looking at all deaths, this would allow me to determine whether a clinical surveillance program might underestimate influenza mortality, and if so by how much. Second, it enabled a comparison of health services utilization, patient characteristics, intensive care unit utilization, and mortality at a hospital level over several years. This allowed me an opportunity to get a sense as to whether the pH1N1 influenza strain was more virulent than previous seasonal influenza (i.e. I could determine whether there might be a hidden burden of influenza morbidity and mortality created by studying only clinically defined cases). More importantly, I was able to examine the third possibility referenced above, that is, whether statistical models produce biased estimates.

In summary, I performed this study to directly compare the statistical and clinical estimates. Therefore, if the estimates were comparable this would imply the models could be used in the future, if not, this would diminish our confidence that the models could be used for planning purposes.

2.0 OBJECTIVES

2.1 Primary Objective

The primary objective of this study was to determine whether a model-based assessment of influenza burden exceeded a clinically-based assessment when applied at a single hospital level, where influenza burden is measured in terms of influenza related in-hospital deaths, hospitalizations, and intensive care unit admissions.

2.2 Enabling Objectives

There were three enabling objectives in this study:

i. Identify and compare published statistical methods used to estimate influenza-attributable mortality;

ii. Apply one of the identified statistical methods to data from an urban teaching hospital to evaluate the impact of influenza on hospital mortality and utilization;

iii. Compare the model based assessment with clinically recorded events that are classified as resulting from influenza.

3.0 METHODS

3.1 Study Design & Paradigm

This study consisted of two distinct parts; a systematic literature review and a hospital-based analysis.

1. Systematic Literature Review

A systematic review of the literature was conducted to identify all of the studies which have estimated national influenza mortality in the US and Canada. From each study identified in the literature (Appendix A), I abstracted the following data: **1)** influenza seasons examined **2)** details of methodological approach (e.g., model type, model fitting procedure, definition of epidemic period, model parameters), **3)** type of mortality data used in model, and **4)** mortality estimates by year. I classified studies by the three most common types of mortality data used to derive an estimate (all-cause, circulatory/respiratory, and pneumonia/influenza). Within each mortality class, I converted predicted death counts for each influenza season to crude mortality rates by dividing the estimated number of deaths by the total population. Canadian and American population estimates were obtained from Statistics Canada and the US Census Bureau respectively (23, 24). I then compared mortality point estimates of all studies by influenza season over time. The complete summary of this preliminary study can be found in Appendix A.

The results of this study that directly involved comparing estimates by model approach are featured within the main body of this document because they are relevant to the findings of the hospital-based study.

2. Hospital-Based Analysis

The hospital-based analysis, herein referred to as the study, was the main study of my thesis project. It was a retrospective cohort study of all non-elective hospital admissions at the Ottawa Hospital (TOH) where the patient was admitted between September 1, 2002 and June 5, 2010 and was greater than one year of age. The study paradigm involved using a hospital cohort to compare the two main methods of evaluating the burden of influenza: clinical and statistical. Indicators of influenza burden were estimated clinically and statistically and inserted into the following equation.

x - y = z; where,
x = model-based estimate of an outcome
y = clinically-based estimate of an outcome
z = difference between x and y

If **z > 0**, it was indicative of an overestimate of influenza burden by statistical models.

If **z < 0**, it was indicative of an underestimate of influenza-attributable burden when using a model-based approach.

If **z=0,** it was indicative that model and clinically-based estimates are equal

3.2 Study Setting & Eligibility Criteria

The hospital study took place at TOH, which is composed of three campuses (the General, Civic and Riverside) with approximately 1,183 beds. TOH provides primary, secondary and tertiary care services to approximately 1.2 million people across Eastern Ontario.

The study population included only non-elective hospital admissions, including obstetrics, and was thus limited to the General and Civic campuses as the Riverside campus does

not provide in-patient services. The study included all patients admitted to TOH between September 1, 2002 and June 5, 2010 excluding those patients under the age of 1.

3.3 Study Outcomes

Primary

- Total number of deaths that occurred within the hospital as a result of influenza

Secondary

- Total number of non-elective hospital admissions that occurred as a result of influenza
- Total number of intensive care unit (ICU) admissions that occurred as a result of influenza

3.4 Data Sources

3.4.1 The Ottawa Hospital Data Warehouse (OHDW)

I created the study cohort from data stored in the Ottawa Hospital Data Warehouse (OHDW). The OHDW is a large relational database which connects clinical data from laboratory, pharmacy, and radiology information systems, with administrative data from patient registration and health records systems, over the multiple campuses of TOH. The database consists of five main data tables (Patient, Encounter, Service, Facility, and Reference tables) each with branching sub-tables that include more detailed data associated with a given main table. Each row in a particular data table has a unique warehouse identifier (WID) that identifies unique patients, encounters and/or services received during an encounter. The WIDS connect the data tables making it possible to extract all the data associated with one entire hospital encounter.

For the purpose of this study, I used data from two of the main tables (Encounter and Service) and seven of their associated sub-tables all of which are outlined in Appendix B and

described in Appendix C. Due to data availability of ICU data, I could only use ICU admissions that occurred after March 31, 2004 when examining the ICU cohort in this study.

3.4.2 FluWatch

I used data from Canada's FluWatch program to examine the timing of influenza epidemics in the Ottawa region. The Respiratory Virus Detection Surveillance System (RVDSS) is a component of FluWatch through which participating laboratories from across Canada submit weekly aggregate data on viral test results for a number of different respiratory viruses. The weekly aggregate data submitted by the two Ottawa-based labs (Children's Hospital of Eastern Ontario and the Ottawa Public Health Laboratory) between September 1, 2002 and June 5, 2010 was used as a reference for community level influenza activity.

3.5 Creation of Analytical Datasets

To create my analytical datasets I used Statistical Analysis Software (SAS) 9.1 to access, retrieve, transform and link data from the OHDW. I created one main dataset of all non-elective patient admissions in the time period of interest, and a subset of the main cohort which included all of the ICU admissions that occurred during those encounters. I then appended additional columns to each hospital admission to flag (via 1s or 0s) whether the patient had received an influenza antiviral prescription, had an influenza lab test, or had been assigned three diagnoses of interest during their hospital encounter. These steps are described in further detail below.

3.5.1 Main cohort

The principle unit of analysis was a hospital encounter. To identify encounters, I used the Health Records (HR) Abstracts table and obtained the patient ID, encounter ID, age, admission date, discharge date, gender, campus of stay, and length of stay for all non-elective patient admissions that occurred between September 1, 2002 and June 5, 2010. I also obtained the discharge disposition from the HR Discharge Abstracts Database (HR DAD) and the death indicator from the Encounter table for each of these admissions. I excluded patients with a discharge disposition code corresponding to cadavers and stillbirths as well as incomplete abstracts and patients under the age of 1.

Additional Information for Main Cohort

I accessed the Diagnosis table to retrieve all of the diagnosis data for each admission in the main cohort. I then flagged the admissions to identify whether they had been assigned each of three diagnoses of interest during the encounter: **1)** most responsible circulatory/respiratory diagnosis, **2)** most responsible influenza diagnosis, and **3)** any influenza diagnosis (i.e. admitting, secondary etc.). The ICD codes used to create these flags can be found in Appendix D.

I accessed the Service and Laboratory Service tables to identify the admissions in the main cohort that had an influenza laboratory test that was not cancelled or deleted at any point. I then accessed the Service Report and Service Report Text tables to retrieve the laboratory reports for these lab tests. I searched the text reports using text algorithms (Appendix E) to identify lab tests that were positive for influenza and then used this data to flag all admissions in the main cohort that had a positive influenza lab test.

I searched the Pharmacy Service and Pharmacy Service Ingredient tables using keywords and drug identification numbers (Appendix F) to identify and flag those admissions that included

an influenza antiviral prescription during the hospital encounter. Keywords were used in addition to Drug Identification Numbers (DINs) to bypass data quality issues resulting from variations in data entry across the different campuses and over time.

3.5.2 Intensive Care Unit Admissions

I created a sub-dataset comprised of all ICU admissions during the encounters in the main cohort that occurred after March 31, 2004. A sub-dataset was required as one patient encounter could have involved multiple ICU stays.

To create this dataset, I accessed the Inpatient Census History table to retrieve all of the transactions that occurred during each hospital encounter in the main cohort (e.g. bed transfers, changes in doctor etc.). From this, I took only those transactions that involved a change in nursing station and transformed the data to identify the length of stay at each nursing station. I subsequently limited this dataset to include only the intensive care unit nursing stations to generate the ICU dataset in which one row corresponded to one ICU admission that occurred during an encounter included in the main cohort. I also accessed the Nursing Unit and Nursing Unit Capacity sub-tables to examine the number of available ICU beds per week.

3.6 Derivation of Clinical Estimates

3.6.1 Description

I identified influenza cases in both my main cohort and ICU cohort using the following criteria: all hospital admissions with DAD-based influenza diagnosis OR a positive influenza lab test OR an antiviral prescription during the encounter. A priori, I did not define the specific combination of these criteria to define my clinical case. Rather, I used data through a validation process to

define the optimal combination of criteria to maximize the sensitivity and specificity of the approach. An overview of the steps used to derive my clinical estimates can be found in Appendix G.

3.6.2 Validation

To validate my algorithm, I used a data set which was compiled for a study investigating the accuracy of a clinical prediction tool designed to identify influenza during the 2009 pandemic (termed the Febrile Respiratory Illness screen). The dataset I obtained was created from a chart review of all patients greater than 18 years of age admitted to TOH via the emergency department from October 1, 2009 to January 31, 2010, that had received a Febrile Respiratory Illness (FRI) screen at initial presentation to the ER, and had subsequently been discharged with a respiratory, circulatory or infectious disease condition of interest (Appendix H). These diagnostic groups were selected to represent an appropriate 'at risk population'. An FRCPC-qualified internist reviewed 401 charts and classified whether cases represented clinical influenza based on what was documented in the medical record. The proportion of these cases in which influenza was deemed the clinical diagnosis based on this review in this sample was 13.6%.

I linked the chart review dataset to my main cohort by encounter WID, admission and discharge date. In total, three charts were not used. One chart was dropped because it was an elective admission and therefore did not meet inclusion criteria for the validation study. Two additional charts were dropped for data quality reasons. The first was a patient in the chart review dataset that had no November 2009 visit recorded in the data warehouse. I assumed that the medical record number had been entered incorrectly. The second was a patient in which the admission and discharge dates of the encounter in the chart review dataset did not match the data warehouse. As the patient had had multiple visits in November 2009, I was unsure which

encounter the entry corresponded to and thus decided not to use the encounter. After linking the data, I constructed 2*2 tables to compare my electronic algorithm with the criterion standard MD performed chart review. Using these tables, I calculated the sensitivity and specificity of my algorithm as a whole, as well as each algorithm component separately. I selected the optimal algorithm based on the results of the sensitivity and specificity analysis. I then applied this algorithm to the entire study period and flagged those encounters that met the algorithm.

3.6.3 Constructing Time Series of Influenza Cases

The encounters flagged for clinical influenza using my algorithm were aggregated by week based on date of admission to the hospital. The time period of interest in this study consisted of 405 weeks.

3.6.4 Defining Epidemic Periods

I used the time series of influenza cases to identify epidemic periods at TOH. Epidemic periods were defined as those weeks where the number of clinical influenza cases at TOH went above an estimated number 'expected' baseline influenza cases. To generate the 'expected' baseline, I applied a Serfling regression model to the weekly time series of influenza cases at TOH without those cases that occurred during high level of influenza virus circulation in Ottawa as identified via FluWatch data. An influenza epidemic period was deemed as starting when the number of influenza cases at TOH went above the upper 95% confidence interval for more than two consecutive weeks and ending when the count went below the 95% confidence interval for more than 2 consecutive weeks (25). Detailed steps on this approach can be found in Appendix I.

3.6.5 Estimating Clinical Influenza Cases

I used only the encounters flagged for clinical influenza during epidemic periods for the final clinical estimates. For each epidemic period, I summed the number of encounters that resulted in death and were flagged for clinical influenza, the number of encounters that were flagged for clinical influenza, and the number of ICU admissions which corresponded to a hospital encounter flagged for clinical influenza.

3.7 Comparing Cohort Characteristics by Epidemic Period

I compared cohort characteristics of non-elective hospital encounters between epidemic periods and non-epidemic periods, and between the pandemic and other epidemic periods. The one-way ANOVA test was used to compare the mean number of hospital and ICU admissions per day. The Kruskal-Wallis test was used to compare the median age at admission and length of stay in the entire cohort, the circulatory/respiratory sub-population, among clinical influenza cases and in the ICU cohort. The chi-square test was used to compare the case fatality among all hospital admissions, circulatory/respiratory sub-population and clinical influenza cases. The chi-square test was also used to compare the proportion of hospital encounters and ICU admissions that had a circulatory/respiratory most responsible diagnosis and the proportion that had clinical influenza. P values of <0.05 were considered statistically significant.

3.8 Derivation of Statistical Estimates

3.8.1 Description

To generate my statistical estimates of influenza-associated burden, I used the modeling approach described by Choi et al in 1981(25). In general, this approach involved using Fourier

analysis and Autoregressive Integrated Moving Average (ARIMA) models to forecast an expected baseline based on non-epidemic data. As ARIMA models require a reasonable number of data points (>100 observations), it is generally not recommended to use it until there are sufficient observations. Choi et al, and others, recommend using a Fourier analysis for time points preceding the 100 observations to generate a model for the initial period and then using an ARIMA model for the points thereafter. Regardless of the type of time series model, the general approach for estimating the influenza-attributable outcomes is as follows:

A) Develop a time series model to describe the observed pattern of outcomes during the first pre-epidemic period

B) Extend the model to forecast an estimated number of expected outcomes for each week during the first epidemic period

C) Develop a time series model (i.e. repeat step A) to describe the pattern of outcomes during the subsequent inter-epidemic period that uses information from the first pre-epidemic and epidemic periods. Specifically, the model uses weekly outcome events from the following eras:

- **a.** the observed number of outcomes during the first pre-epidemic period;
- **b.** the estimated number of outcomes during the first epidemic period;
- **c.** the observed number of outcomes during the first inter-epidemic period

D) Repeat step B to forecast an estimated pattern of expected outcomes during the second epidemic period

E) Repeat steps C and D until there is one model that predicts the estimated outcome events during all epidemic intervals

F) To calculate influenza-attributable events, difference the observed number of events and the model based estimated number of events during influenza epidemic periods.

3.8.2 Constructing Time Series of Outcomes

In order to build my model, I first needed to construct a time series for each of the outcomes for the weekly number of events observed: **1)** in-hospital deaths in non-elective hospital admissions; **2)** in-hospital deaths in those non-elective hospital admissions with a circulatory/respiratory most responsible diagnosis; **3)** non-elective hospital admissions; and **4)** ICU admissions. Outcomes were aggregated by week based on date of admission to the hospital or ICU.

3.8.3 Fourier Analysis

Fourier analytical models were used when there were less than 100 observations in the time series. Fourier analysis consists of linearly regressing cyclic terms on the number of weekly events in order to describe the wave-like patterns of the time series (25). The general form of this equation is as follows:

$$Y_t = a + b_t sin\left(\frac{k\pi t}{N}\right) + c_t cos\left(\frac{k\pi t}{N}\right) + dt$$

Where $\boldsymbol{Y_t}$ is the estimated number of events for week *t*; ***t*** is the index for week of event (1,2,3...); ***a*** is the intercept on the Y axis; $\boldsymbol{b_t}$ and $\boldsymbol{c_t}$ are the harmonic coefficients used to describe the pattern of the time series; ***k*** is the order of the harmonic coefficients (2, 4, 6, 8 etc..); ***N*** is the total number of data points; and $\boldsymbol{d_t}$ is the error.

I took the first set of the weekly outcome data that was classed as a non-epidemic period (i.e. N= 66 weeks) and calculated sine and cosine terms for each week using the following equations: S1=Sin(2πt/N) and C1=Cos(2πt/N); I calculated sine and cosine terms in multiples of 2 up to 12 (i.e. 4πt/N, 6πt/N etc.). I regressed the sine and cosine terms on the outcome of interest using PROC REG and determined which sine and cosine terms best fit with the data by

evaluating the significance of the parameters and the R-square value. The equation of the selected model was then used to forecast and replace the outcome data for the next epidemic period.

3.8.4 ARIMA Modeling

After completing modeling for the period up to 100 weeks with the Fourier analysis, I then had a time series of greater than 100 weeks composed of observed non-epidemic data points, as well as forecasted non-epidemic data points for the first epidemic period. At this point, I began to use ARIMA modeling.

ARIMA modeling involves describing the time series with (p, d, q) components, wherein p is the order of the autoregressive component, d is the order of the differencing component, and q is the order of the moving-average process. There are several steps in the constructing an ARIMA model. The first step in this analysis involved determining if an ARIMA model was appropriate for the outcomes of interest. This was performed by assessing the presence of autocorrelation in the error terms and determining if the autocorrelation of the series was significantly different from zero (i.e. the time series of the error terms was not white noise). The Durbin Watson statistic was used for the former, and the Ljung-Box Q statistic was used for the latter. Next, I examined the autocorrelation plots of the time series and conducted the Augmented Dickey-Fuller (ADF) unit root test to determine if the time series was stationary. If it was not stationary, I differenced the time series and re-examined the plots and ADF test results.

Once the time series was stationary, I modeled the outcome using a number of different ARIMA models with varying combinations of autoregressive (p) and moving average (q) terms to find a suitable model. A model was chosen based on the significance of the parameters, the Akaike's information criterion (AIC) value and insignificance of the autocorrelation of the

residuals. The chosen model was then used to forecast the outcome values of the set of weeks in the next epidemic period. Again, the forecasted data was incorporated into the 'non-epidemic' time series and the process repeated until the last epidemic forecast. After the last epidemic forecast replacement, I fit an ARIMA model one last time in the manner above to get the final model.

3.8.5 Estimating Influenza-Attributable Events

To generate the statistical estimate I summed the outcomes that went above the modeled baseline during each epidemic period. A detailed description of the modeling steps including SAS outputs can be found in Appendix J.

3.9 Comparing Clinical and Statistical Estimates of Influenza Burden

I compared the difference in magnitude of the clinical and statistical estimates of influenza deaths, hospital admissions and ICU admissions. I also visually examined and compared the trends in statistical and clinical estimates for all outcomes examined.

3.10 Assessing the Association between Outcomes and Epidemic Periods

I conducted an interrupted time series analysis using an ARIMA model to formally assess the association between the study outcomes (for example, weekly number of non-elective in-hospital deaths) and epidemics. I modeled epidemic periods using an indicator variable.

Using the same steps described in section 3.8.4, I determined the presence of autocorrelation in the error terms in the time series, verified that that the autocorrelation of the

series was significantly different from zero and ensured that the time series was stationary prior to estimating the parameters of my model.

Once the time series was stationary, I cross-correlated the stationary outcome time series with the epidemic indicator variable. To perform this step, I examined a number of different ARIMA models with varying combinations of autoregressive (p) and moving average (q) terms to find a suitable model. I determined the best model fit using the significance of the parameters, the AIC and the autocorrelation check of the residuals. The best model had the most significant parameters, the lowest AIC and insignificant autocorrelation of the residuals (i.e. the residuals were white noise). The modeling steps and SAS outputs used in this analysis can be found in Appendix K.

4.0 RESULTS

4.1 Systematic Literature Review

Search Results

The database search identified 2482 citations. After I removed duplicates (993) and applied my exclusion criteria (1425), 63 articles were selected for full review. I excluded a further 46 articles and identified 8 additional articles in references resulting in 21 studies for data abstraction and analysis (Exhibit 1). Four studies were based on Canadian data and 17 studies American data.

On visual inspection, trends in influenza mortality for studies examining the same influenza seasons appear to be consistent over time across different methods and across variations within the same method (Exhibit 2). Although consistent in trends over time, yearly point estimates for excess mortality varied considerably in magnitude by study (Exhibits 3 & 4). For example, for the 1979-80 influenza season in the US, Stroup et al (26) did not detect any excess mortality when using the univariate time series model but 9.9/100,000 with the multivariate model; Thompson et al (27) estimated 6.1 deaths/100,000 with the Serfling-Poisson model; Simonsen et al (12) estimated 7.7/100,000 with a Serfling model; and, Lui et al (28) estimated 16.2/100,000 with a Serfling model. Large variations in magnitude also occurred in point estimates produced by the same model type. For example, for the 1977-78 influenza season, three researchers used a Serfling model generating mortality rates that ranged from 13.9/100,000 to 25.5/100,000. Exhibit 4 outlines mortality estimates from 1988-2003 based on circulatory/respiratory mortality populations, some of which were provided with confidence intervals. The confidence intervals demonstrate that the variations in magnitude were not always

significantly different; however, there is still considerable variation. For example, in the 2001-02 influenza season, Thompson W.W. et al's Serfling model estimated a mortality rate of 4.9/100,000 while Thompson W.G. et al's Serfling-Poisson model generated a mortality estimate of 15.8/100,000 (29, 30).

4.2 Study Cohort Characteristics

4.2.1 Main Cohort

Between September 1, 2002 and June 5, 2010 there were 208,231 non-elective patient admissions (hereafter referred to as encounters) over the age of 1 at the General and Civic campuses of TOH (Exhibit 5). The median and inter-quartile range (IQR) in age at admission was 60 (42-75) and the median (IQR) length of stay in days was 5 (2-10). There were slightly more males (51.6%) than females (48.4%) and slightly more encounters at the Civic campus (52.5%) than the General campus (47.5%). A total of 24,303 (14.5 %) of all hospital encounters after April 4, 2004 resulted in one or more ICU admissions.

A most responsible circulatory or respiratory diagnosis was assigned to 29.2% of all hospital encounters, while only 0.1% of hospital encounters had a most responsible diagnosis of influenza. Overall, 6.3% of hospital encounters resulted in death. Of these deaths, 38.6% had a circulatory or respiratory most responsible diagnosis and 0.1% had an influenza most responsible diagnosis. Of all encounters with a circulatory or respiratory most responsible diagnosis, 8.3% resulted in death. Of all encounters with clinical influenza, 5.6% resulted in death.

4.2.2 ICU Admissions

From April 4, 2004 to June 5, 2010, there were 32,937 ICU admissions, of which 55% were one-time admissions and 45% were among patients admitted multiple times over the course

of their hospital stay. Approximately 14.5% of all hospital encounters had at least one ICU admission (n=24,302). The median age (IQR) of patients who experienced a requirement for ICU admission was 65 (54-76) and the median ICU length of stay (IQR) in days was 2 (1-5). Approximately 0.1% of ICU admissions had a most responsible diagnosis of influenza.

4.3 Clinical Influenza Estimates

Using the entire algorithm (which included the following components: a positive influenza lab or a influenza antiviral prescription or any influenza diagnosis), we identified 170 clinical influenza deaths, 1430 clinical influenza hospital encounters, and 527 ICU admissions that had clinical influenza (Exhibit 6). When using the 'positive influenza lab' component of the algorithm alone, we identified 45 influenza deaths, 454 influenza hospital encounters, and 132 ICU admissions. When using the 'antiviral' component alone we identified 146 deaths, 1156 hospital encounters, and 146 ICU admissions. When using the 'DAD-based influenza diagnosis' component alone we identified 41 deaths, 457 hospital encounters, and 127 ICU admissions.

4.3.1 Validation of Clinical Influenza Estimates

A total of 398 non-elective patient encounters were included in the validation cohort (Exhibit 5b). For this cohort, the median and inter-quartile range (IQR) in age at admission was 69 (53-81) and the median (IQR) length of stay in days was 6 (1-12). There were more females (53.3%) than males (46.7%) and more admissions at the General campus (55.5%) than the Civic campus (44.4%). A most responsible circulatory or respiratory diagnosis was assigned to 82.4% of the encounters and 10.6% had a most responsible diagnosis of influenza. Overall, 12.8% of the encounters resulted in death. A total of 77 (19.3 %) of the encounters had at least one ICU admission with a sum total of 106 distinct ICU admissions. Of all of the ICU admissions, 51.9%

were one-time admissions and 48.1% were among patients admitted multiple times over the course of their hospital stay.

The clinical influenza algorithm with all of the components was found to be highly sensitive (96.3%, 95% CI: 87.3-99.5%) but not specific (75.3%, 95% CI: 70.3-79.8%) based on comparison to the criterion standard – i.e. expert clinical review (Exhibit 7). In examining the sensitivity and specificity of the algorithm components, I found that the "positive influenza lab" component was more specific (98.0%, 95% CI: 95.9-99.2%) than sensitive (79.7%, 95% CI: 66.5-89.4%), while the opposite was true for the "antiviral" component which had a high sensitivity (94.4%, 95% CI: 84.6-98.8%) and a lower specificity (75.9%, 95% CI: 71.0-80.3%). Overall, the "DAD-based influenza diagnosis" had the best combined sensitivity and specificity, which were 90.7 % (95% CI: 79.7-96.9%) and 96.5% (95% CI: 94.0-98.2%) respectively (Exhibit 8).

4.3.2 Preliminary Estimates

Given the results of the sensitivity and specificity analysis, I based my clinical influenza estimates solely on the "DAD-based influenza diagnosis" component of the algorithm. Using this, I identified a total of 41 clinical influenza deaths, 457 clinical influenza hospital encounters, and 127 clinical influenza ICU admissions within the entire study period. Although we observed variation in the total number of influenza cases (i.e. hospital encounters) by the different algorithms, the timing of influenza activity was the same for both the complete algorithm and the "DAD-based influenza diagnosis" component (Exhibit 9).

4.3.3 Epidemic Periods

Using the time series of clinical influenza hospital encounters, I identified 7 epidemic periods which lasted a mean of 14 weeks and ranged from 9 to 34 weeks in duration (Exhibit

10). There was no epidemic period detected for the 2002-03 influenza season. The pandemic caused the longest epidemic period in the study.

4.3.4 Final Clinical Influenza Estimates

I identified a total of 38 clinical influenza deaths, 421 clinical influenza hospital encounters, and 118 clinical influenza ICU admissions within the 7 epidemic periods included in the study (Exhibit 11). During epidemic periods, clinical influenza deaths ranged from 0 to 19, hospital encounters ranged from 12 to 202 and ICU admissions ranged from 1 to 76. For all outcomes examined the highest clinical estimate was for the pandemic. The number of clinical influenza deaths, hospital encounters and ICU admissions that were recorded during the pandemic represented 50.0%, 48.0% and 64.4% of the total number of clinical counts respectively.

4.4 Comparing Cohort Characteristics by Epidemic Period

4.4.1 Epidemic Periods vs. Non-Epidemic Periods

When I statistically compared cohort characteristics between non-epidemic and epidemic periods I found that the proportion of all hospital encounters with clinical influenza was significantly higher during epidemic periods (P <0.001) and that these encounters had a significantly lower median age (P = 0.03) and shorter median length of stay (P<0.001) (Exhibit 12). I also found that the proportion of ICU admissions with clinical influenza was significantly greater during epidemic periods (P<0.001). However, I found no significant difference in the number of in-hospital deaths between epidemic weeks and non-epidemic weeks in any of the populations examined i.e. all hospital encounters (P = 0.265), encounters with a circulatory/respiratory most responsible diagnosis (P = 0.97) or encounters with clinical

influenza (P = 0.889). Although many of the other cohort characteristics were significantly different during epidemic weeks the differences in the point estimates were not meaningful. For example, the mean number of admissions per day was significantly greater during epidemic weeks but the point estimates were only different by 2 admissions per day; 73 in non-epidemic weeks and 75 in epidemic weeks.

4.4.2 Pandemic vs. Other Epidemic Periods

As with national descriptions of pandemic activity, TOH experienced two waves of pandemic influenza with the first peaking in mid-June 2009 and the second peaking at the beginning of November 2009 (Exhibit 13). Based on visual inspection, the number of influenza cases increased dramatically at TOH during the pandemic relative to other epidemic periods, with a peak of 48 cases during the second wave. The proportion of influenza cases with respect to all hospital encounters increased as well, with a peak of 8.2% during the second wave. The number of influenza deaths also increased during the pandemic with a peak of 6 deaths in the second week of November 2009; these deaths represented 12.7% of in-hospital mortality among non-elective hospital encounters for that week which was the peak of this measure (Exhibit 14).

Based on statistical tests, the only consistent differences between the pandemic and other epidemic periods were that the median age of clinical influenza cases during the pandemic was significantly lower than all other epidemic periods examined (range in P values: <0.0001 – 0.029) and the in-hospital mortality was not significantly different during the pandemic relative to any other epidemic period for any of the populations i.e. all encounters, circulatory/respiratory or influenza encounters (Exhibit 15).

I did not find any meaningful differences between the characteristics of all hospital encounters during the pandemic relative to other epidemic periods. I did find that the proportion

of encounters with a circulatory/respiratory most responsible diagnosis was significantly lower during the pandemic relative to all other epidemics ($P<0.001$) except the 2008-09 epidemic ($P = 0.368$). Also, the proportion of encounters with clinical influenza was significantly greater during the pandemic relative to the epidemic periods in 2003-04 ($P<0.001$), 2004-05 ($P<0.001$), 2005-06 ($P<0.001$) and 2008-09 ($P<0.001$) but not the 2006-07 ($P = 0.086$) or the 2007-08 ($P = 0.659$) epidemics.

The mean number of ICU admissions per day was significantly smaller during the 2004-05 ($P<0.001$) and the 2005-06 ($P<0.0001$) epidemics which was likely due to the increase in available beds previously discussed. The proportion of ICU admissions that had clinical influenza was significantly greater during the pandemic compared to the epidemic periods in 2004-05 ($P<0.001$), 2005-06 ($P<0.001$), 2006-07 ($P =0.003$) and 2008-09 ($P<0.001$) but not the 2007-08 epidemic period ($P =0.411$). The ICU admissions that had clinical influenza were significantly younger during the pandemic relative to the 2004-05 ($P = 0.003$), 2006-07 ($P = 0.001$) and the 2007-08 ($P<0.001$) epidemics but not the 2005-06 ($P = 0.192$) or the 2008-09 ($P = 0.088$) epidemics.

4.5 Statistical Estimates

4.5.1 Outcome Time Series

The mean number of weekly in-hospital deaths was 32 ± 5.9 in the entire cohort and 12 ± 3.5 in the circulatory/respiratory sub-population (Exhibit 16 & 17). There was a mean of 514 ± 28.9 (std. dev.) non-elective hospitalizations per week (Exhibit 18). There was a mean of 102 ± 20.2 (std. dev.) ICU admissions per week (Exhibit 19). Based on visual inspection, there did not appear to be an obvious relationship between epidemics and any of the outcomes used in the

study: deaths, non-elective hospital admissions, and ICU admissions. There was a notable increase in the number of ICU admissions per week over the course of the 2006 calendar year coincident with expansion in the number of ICU beds available. Based on hospital decision makers, this expansion was related to factors other than influenza activity.

4.5.2 Statistically Modeled Baselines

The predicted baselines of in-hospital mortality and hospital admissions were estimated based on 7 forecasts of non-epidemic data; one forecast with a Fourier model and 6 forecasts with ARIMA models of various forms. The predicted baseline of ICU admissions was estimated based on 6 forecasts as this time series was shorter in duration commencing in April 2004 (Appendix I).

All in-hospital deaths

The ARIMA predicted baseline had a mean of 32 ± 5.1 in-hospital deaths per week (Exhibit 20). A total of 314 influenza-attributable in-hospital deaths were identified in epidemic periods.

In-hospital deaths in circulatory/respiratory sub-population

The ARIMA predicted baseline had a mean of 12 ± 3.0 in-hospital deaths per week (Exhibit 21). Based on this, a total of 175 influenza-attributable in-hospital deaths were identified in epidemic periods using this population.

Non-elective hospital admissions

The ARIMA predicted baseline had a mean of 510 ± 24.7 hospitalizations per week (Exhibit 22). Based on this, there were a total of 1729 influenza-attributable hospital admissions were identified in epidemic periods.

ICU admissions

The ARIMA predicted baseline had a mean of 102 ± 19.5 admissions per week (Exhibit 23). Based on this there were a total of 502 influenza-attributable ICU admissions were identified in epidemic periods.

4.5.3 Final Statistical Estimates

Using statistical models, I identified a total of 314 influenza–attributable deaths based on all-cause mortality, 175 influenza-attributable deaths based on the circulatory/respiratory mortality sub-population, 1729 influenza-attributable hospital encounters, and 502 influenza-attributable ICU admissions within the 7 epidemic periods included in the study (Exhibit 11). Influenza-attributable deaths ranged from 17 to 121 with the all-cause model and 7 to 51 with the circulatory/respiratory model per epidemic period. The number of influenza-attributable hospital encounters ranged from 70 to 786 and the number influenza-attributable ICU admissions ranged from 36 to 120 per epidemic period. The highest statistical estimate was for the pandemic in all outcomes except influenza-attributable mortality based on the circulatory/respiratory sub-population. The number of influenza-attributable deaths based on all-cause and circulatory/respiratory mortality populations, influenza-attributable hospital encounters and ICU admissions that were recorded during the pandemic represented 38.5%, 24.6%, 45.5% and 23.9% of the total number of statistical estimates respectively.

4.6 Comparing Clinical and Statistical Estimates of Influenza Burden

4.6.1 Magnitude

The model estimates were higher than the clinical estimates in every epidemic period for every outcome examined (Exhibit 11). The total number of statistically estimated influenza-attributable deaths was 8 times greater than the clinical estimate when using all in-hospital deaths and 5 times greater when using the circulatory/respiratory subpopulation to derive the estimate. The total number of statistically estimated influenza-attributable hospital encounters and ICU admissions were 4 times greater than the clinical estimates for both outcomes. From one influenza season to the next the difference between the model and clinical estimates was not consistent. For example, the model estimate of influenza related hospitalizations was 11 times greater than the clinical estimate for the 2008-09 epidemic but only 2 times greater for the 2007-08 epidemic.

4.6.2 Trend

Based on visual inspection, the trends in statistically estimated influenza-attributable mortality were similar whether based on all in-hospital deaths or the circulatory/respiratory subpopulation (Exhibit 24). However, when compared to clinical estimates, statistical estimates increased from 2003-04 to 2004-05 while the clinical estimate decreased. The opposite is true for the estimates from 2006-07 to 2007-08. The trends in statistical and clinical estimates of influenza-attributable hospital encounters and ICU admissions were similar except for the fact that an increase in encounters was found between 2007-08 and 2008-09 for the statistical estimate of the encounters when it was a decrease in the clinical estimate. All outcomes

experienced a sharp increase in both statistically and clinically estimated influenza events from the 2008-09 epidemic period to the pandemic period.

4.7 Association between Outcomes and Epidemic Periods

The formal assessment of the association between each outcome time series with epidemic periods using ARIMA modeling techniques confirmed impressions based on visual inspection that the study outcomes were not associated with influenza epidemic periods.

4.7.1 All in-hospital deaths

The best model fit for the time series of weekly non-elective in-hospital deaths with the epidemic indicator variable was an ARIMA(1,0,1) model. Based on this model, epidemic periods were associated with a non-significant increase of approximately 1.1 in-hospital deaths per week ($P = 0.1594$).

4.7.2 In-hospital deaths in circulatory/respiratory sub-population

The best model fit for the time series of weekly non-elective in-hospital deaths in the circulatory/respiratory sub-population with the epidemic indicator variable was an ARIMA(1,0,1) model. Based on this model, epidemic periods were associated with a non-significant increase of approximately 0.7 in-hospital deaths per week in patients with a most responsible circulatory or respiratory diagnosis ($P = 0.1772$).

4.7.3 Non-elective hospital admissions

The best model fit for the time series of weekly non-elective hospital admissions with the epidemic indicator variable was an ARIMA(2,0,1) model. Based on this model, epidemic periods

were associated with a non-significant decrease of approximately 1.7 non-elective hospital admissions per week ($P = 0.6855$).

4.7.4 ICU admissions

Due to the upward shift in the weekly number of ICU admissions that occurred in August 2006, I examined the relationship between this outcome and epidemic periods in two distinct time series. The best model fit for the time series of the weekly ICU admissions from April 4, 2004 to August 5, 2006 was an ARIMA(1,0,1) model. Based on this model, epidemics were associated with a non-significant decrease of approximately 4.8 ICU admissions per week ($P = 0.1435$). The best model for the August 6, 2006 to June 5, 2010 was an ARIMA(6, 0, 6) model. Based on this model, epidemics were associated with a non-significant increase of approximately 2 ICU admissions per week ($P = 0.3687$).

5.0 DISCUSSION

5.1 Study Findings

In summary I have found that, in the literature, there is heterogeneity in the approach used to estimate excess influenza mortality at the national level which results in within-season variation in estimates of influenza mortality by study. When using one of the methods described in the literature on data from a single hospital, I found that the model estimates were much higher than validated clinical estimates for each epidemic period and each outcome examined. In addition, and perhaps most importantly, when I performed a simple cross-correlation analysis comparing variations in my study outcomes with epidemic periods, I did not find any statistically significant association.

Even when looking only at the population of influenza cases, I did not detect a significant difference in in-hospital mortality among influenza cases between epidemic weeks and non-epidemic weeks or the pandemic and other epidemic periods. However, I did find that during epidemic weeks the number of influenza cases increased and the proportion of all hospital encounters and ICU admissions with clinical influenza was significantly greater. In comparing the pandemic to other epidemic periods I found that while the number of influenza cases increased dramatically during the second wave and that these cases were significantly younger, the proportion of hospital encounters and ICU admissions with clinical influenza was comparable to some other epidemic periods.

5.1.1 Heterogeneity in Methods Used to Quantify National Excess Influenza Mortality

When examining mortality estimates by method I found that trends in mortality rates over time were similar across different methods but that there were differences in the magnitude of

estimates by study for the same influenza seasons e.g. one study indicating 14,000 people died while another indicating over 36,000 people died for the same influenza season. I also found that magnitudes varied, in some years, by over 20,000 deaths even when the same model approach was used which suggests that variations in individual modeling technique impact the magnitude of mortality estimates. For example, how researchers defined the epidemic period when using the Serfling model, or the indicators used to describe influenza activity when using the Poisson regression model.

Other studies have compared statistical methods with varying results. Newall et al found that Serfling and Serfling-Poisson models produced consistent trends in influenza mortality patterns but variation in the magnitude of mortality estimates with the Serfling-Poisson model generally producing higher estimates (31). In Thompson et al's comparison of rate difference, Serfling, Serfling-Poisson, and time series models, the authors concluded that the models produced estimates that were similar in both magnitude and trend across 31 influenza seasons (29). Choi et al compared time series and Serfling models and found the estimates produced by both models to be comparable overall but when comparing the forecasts of each model to observed non-epidemic data, they found the time series model provided more accurate forecasts (32).

Researchers have also looked the impact of changing the modeling approach used with the same model. Choi et al examined the impact of aggregating the data by month versus week and found that estimates based on weekly aggregated data were higher than monthly aggregated data for both the Serfling and ARIMA models in the all-cause mortality population (32). However, they observed less of a difference in the pneumonia and influenza mortality sub-population. Sandoval et al compared estimates of influenza-associated hospitalizations among

adults with congestive heart failure based on how the influenza season was defined and found that estimates of hospitalizations were higher when the definition used resulted in a larger amount of calendar time (33). Kwong et al also looked at the impact of widening epidemic period but unlike Sandoval et al did not find that this altered the findings of the study (20).

Overall, there appears to be a lack of consistency in the results generated when using this approach. As such, the ability of researchers to accurately evaluate mitigation efforts may be limited when using statistical estimates. If the reasons for variations in mortality estimates are not clear and we cannot validate national statistical estimates, it is difficult to know which estimate is correct from one season to the next. The difficulty in validating model estimates, that lack of consensus on which model is most accurate and large variations in point estimates within the same influenza seasons suggest that this method of estimating influenza mortality needs to be further explored.

5.1.2 Higher Model Estimates Compared to Validated Clinical Data

In total, the model estimates I derived for in-hospital mortality using an ARIMA model based on all-cause in-hospital mortality were 8 times greater than the clinically validated data. Even when estimating deaths using a smaller sub-population (circulatory/respiratory population) the model estimates were still 5 times greater than the clinical data. In addition, the total number of estimated hospital admissions and ICU admissions were also high at 4 times greater than the clinical estimates for both outcomes.

The ecological nature of statistically estimating influenza burden makes it difficult to validate, especially when estimates are made at the national level. I found only two other studies that have attempted to validate statistical estimates using smaller populations. Gilca et al compared 6 statistical methods for estimating paediatric virus-attributable hospitalizations

against data prospectively collected at admission (34). The authors found no one method provided accurate or consistent results relative to the prospectively collected virologic data. In addition, as in my systematic review, they found within-season and between-method variation in statistical estimates. However, unlike the results of our study, they found statistical estimates to be lower than the prospectively collected data. This may be because model estimates were based on admissions with a primary diagnosis of pneumonia, influenza or bronchiolitis, a smaller sub-population than that which was used in our study. Another important difference between our studies is that the populations they used to derive their clinical and statistical estimates were different: clinical estimates were derived from data collected at a single hospital in Quebec while model estimates were derived from an administrative database which records all acute care hospitalizations in Quebec.

Yang et al also used a paediatric population to validate model estimates but using the same data source for both estimates, two public hospitals in Hong Kong (35). Model estimates were derived using rate difference and Poisson regression models, and clinical estimates were derived from virologically confirmed cases. In this study, the rate difference method produced estimates that were much lower than observed data which was attributed to the different trends in influenza activity in the tropics i.e. the existence of significant influenza activity outside of the predominant season. The Poisson regression models produced estimates that were sometimes above and sometimes below the clinical estimates but were more comparable to the clinical data than in our study. At most, modeled influenza hospitalization rates were approximately twice the value of the clinical data for certain age groups. In their study model estimates were based on paediatric cases (<18) with a discharge diagnosis of acute respiratory disease (ICDCM9: 460-466 and 480-487). This population is larger than the one used by Gilca et al but smaller than the one

used in this study which may explain why their estimates are higher than the clinical estimates but not to the degree with which ours are. When using a larger population such as all-cause mortality versus pneumonia/influenza mortality, the model estimates will be higher regardless of modeling technique because one is attributing a variety of deaths to influenza instead of only pneumonia deaths i.e. deaths caused by all respiratory conditions, cardiac conditions etc. The populations I used were larger, therefore it makes sense that difference between my statistical and clinical estimates were also larger to a certain degree.

On face value, one might interpret our model estimates to infer that there is a large hidden burden of influenza-attributable events not captured in our clinical estimates. However, our clinical estimates were based on an algorithm which we validated through chart review and, although there may some cases that are missing (i.e. those outcomes that were caused by influenza prior to hospitalization and thus have no mention of influenza in their chart), it is unlikely we are missing significant numbers of cases such that it would refute our findings. Also, the lack of consistency in the difference between statistical estimates and clinical estimates from one season to the next suggests a lack of consistency in the model estimates.

Another important point for consideration was the absence of seasonal variation in the outcomes that I chose to examine which was apparent in the time series figures of the data. Estimating influenza-attributable burden is fundamentally based on the premise that seasonal fluctuations in the outcomes are apparent and coincided with influenza epidemics. The methodology was developed to statistically quantify the amount of excess burden that was attributable to influenza during these times. In my study, seasonal fluctuations in the outcomes I chose were not apparent graphically. As a result my modeled baselines for each outcome were ultimately smoothed time series with observed data points both above and below the modeled

baseline during both epidemic and non-epidemic periods. Consequently, model estimates may be overestimated especially given that the data points that went below the modeled baseline were not taken into consideration.

5.1.3 Lack of Association between Epidemic Periods and Hospital Outcomes

I found it interesting that the model estimates suggested either a hidden burden or an overestimation when the impact of influenza epidemics was not apparent on visual inspection of the data. As discussed, the association between outcomes and influenza activity is typically apparent graphically in published studies (12, 18, 34, 36-38). I therefore chose to formally assess the relationship and found that there was in fact no significant association between in-hospital mortality, hospital admissions and ICU admissions and influenza epidemic periods defined based on elevations influenza cases at TOH above a modeled baseline.

There are many studies on the impact of influenza on hospitalizations, most of which suggest that there is both a significant relationship between them and that influenza causes excess hospitalizations. Upshur et al found statistically significant correlations between circulating influenza and hospital admissions for pneumonia, congestive heart failure, and chronic respiratory diseases among the elderly in Ontario (38). In another study, Usphur et al also found that circulating influenza was consistently associated with elevated hospital admissions for chronic obstructive pulmonary disease, pneumonia and bronchiolitis among the elderly in Ontario (39). Sandoval et al found that there was a an 8-10% higher risk of hospitalization among adults with congestive heart failure regardless of how the influenza season was defined (33). Studies conducted at the national level, in both the US and Canada, suggest that influenza leads to thousands of excess hospitalizations for respiratory conditions each year with estimates of 10,000/year in Canada and over 90,000 in the US (8, 40).

In contrast, I was not able to find other studies that specifically examined the association between in-hospital mortality or ICU admissions and influenza. Using Cox regression analysis, Sandoval et al found that the risk of death during influenza seasons among individuals with congestive heart failure depended on how the influenza season was defined (33). A study by Dodek et al used Poisson regression analysis to examine whether the weekly number of ICU admissions for community acquired pneumonia (CAP) in three ICUs was associated with reports of influenza-like illness in the community (41). They found the presence of seasonal variation in the number of ICU admissions for CAP but no association between the admissions and the rate of ILI.

Again, I found that in all of the studies referenced above the populations that were used to examine the associations or derive model estimates of excess burden were more specific to respiratory conditions and thus more directly linked to influenza outcomes. In addition, many studies examined the impact by age group. Our study looked all ICU admissions and all non-elective hospital admissions which may have prevented us from seeing the relationship that is described in the literature. TOH typically functions at capacity; therefore, while the underlying population may change during influenza epidemics the overall number of hospital admissions or ICU admissions will remain the same. With respect to in-hospital mortality, the number of weekly deaths was low and the resulting instability of the time series may have prevented us from seeing a pattern that might emerge if the outcome was looked at from a higher level i.e. in-hospital mortality in Ontario. The same is true for the circulatory/respiratory in-hospital mortality for which the number of weekly deaths was even fewer. It may also be true that the inclusion of all age groups or circulatory-related events may cancel a pattern present in more specific sub-populations at the hospital.

Another potential reason for the lack of statistically significant association is power, particularly with respect to the mortality outcomes. The analysis for the mortality outcomes showed a non-significant trend in the appropriate direction. Given that I studied outcomes in a single hospital, it is possible that I did not have enough sample size to demonstrate an effect. However, the inability to demonstrate the effect could indicate that the association is not as strong as previously thought, and that while planners at the local level may need to adjust their activities by a small amount, influenza epidemics would not have a major impact on overall activity.

If all diagnoses other than influenza were removed from the weekly data, the impact of influenza was apparent at the Ottawa Hospital. During epidemic weeks influenza cases at the hospital and in the ICU were significantly greater than during non-epidemic weeks. Although influenza cases at the hospital represent a relatively small proportion of all hospital and ICU admissions, the proportions were over 30 times greater during epidemic weeks for both outcomes. However, even when looking strictly at influenza cases, I did not find a significant increase in in-hospital mortality among these cases during epidemics. Nor did I see a significant increase in case fatality in the hospital among all patients or patients with a circulatory/respiratory most responsible diagnosis. Given the size of the populations I was examining, even small difference between epidemic and non-epidemic weeks were statistically significant. Therefore, the insignificance of these findings is meaningful and supports the findings of my interrupted time series analysis.

In summary, I have found no detectable association between influenza epidemic periods defined based on elevations influenza cases at TOH above a modeled baseline, and the outcomes I chose to examine. This finding was further supported by the fact that I found no increased case

fatality among all hospital encounters, circulatory/respiratory hospital encounters or influenza cases during epidemic periods. However, I did find a significant increase in the proportion of influenza cases in the hospital and in the ICU during epidemic periods which suggests that sub-populations of outcomes more directly linked with influenza (e.g. respiratory conditions) may be more suitable for examining and modeling the impact of influenza on the hospital.

5.1.4 The Impact of H1N1 on the Ottawa Hospital

The H1N1 pandemic lead to a prolonged and dramatic increase of influenza cases at the Ottawa Hospital with an epidemic period that was approximately two times longer and resulted in 3-16 times more influenza cases relative to other epidemic periods. In addition, these cases were significantly younger with a median age 10-30 years younger than other epidemics. However, while the proportions of hospital and ICU admissions with influenza during the pandemic were significantly greater than some epidemics they were comparable to others.

Our findings are consistent with the literature. Many studies have found that cases of H1N1 were uncharacteristically young (9, 42-45). The report produced by the Canadian Institute of Health Information found that the influenza cases only accounted for 0.2% of total discharges outside of the peak pandemic period but that this was increased to 1.7% during the October-November wave of the pandemic (9). The report also indicated that while the overall number of ICU patients remained the same as in previous years, there were fewer admissions to patients with non-influenza related health problems. Shiley et al compared the epidemiological characteristics of pandemic influenza cases with those of seasonal influenza at two medical centres in Pennsylvania, US (45). They did not find a significant difference between deaths of hospitalized patients, or ICU admissions and based on all of their findings concluded that there were few clinically important differences between H1N1 and seasonal influenza. In contrast, Lee

et al looked compared pandemic and seasonal influenza cases in two hospitals in Hong Kong and found that the H1N1 cases had a higher rate of ICU admission and/or death (44). However, they only compared the H1N1 pandemic to one other influenza season while both our study and Shiley et al looked at multiple influenza seasons.

In summary, the pandemic impacted the hospital via an increase of influenza cases among younger adults but the degree with which the pandemic compares to other epidemics depends on which epidemic one compares it against.

5.2 Study Strengths & Limitations

Strengths

This is the first study to systematically identify studies in Canada and the US that have estimated influenza mortality, and compare mortality estimates by study. It is also the largest validation study examining the same adult population in a single hospital setting and the only validation study that also validated the clinical estimate through chart review. The impact of influenza was examined on multiple outcomes over multiple influenza epidemics using multiple methods. Lastly, the study findings were consistent in that clinically validated data did not agree with our modeled data and there was no association between the outcomes examined and epidemic periods identified in the interventions analysis. The impact of influenza on the hospital was also consistent across all epidemics when examining only influenza cases.

Limitations

Limitations of this study include limited modeling power, particularly with the mortality outcomes. The instability of these time series was interpreted as white noise in some of the iterations of the ARIMA modeling procedure which could translate into less reliable forecasts.

Another limitation of this study was a signal to noise issue. Looking at all-cause and circulatory/respiratory in-hospital deaths, all hospitalizations and all ICU admissions may have masked otherwise detectable patterns in sub-populations more closely related to influenza or age groups more vulnerable to influenza. The reliability of model estimates is also in question given that they were derived based on outcomes with no apparent association with influenza epidemics. Another potential limitation of this study is the impact of low prevalence of influenza in my population on the positive predictive value of the clinical influenza algorithm. Because the prevalence of influenza was low in my main cohort, I may have had an increased amount of false positives in my clinical influenza estimates.

5.3 Study Implications & Recommendations for Future Research

5.3.1. Statistically estimating influenza burden

The main objective of this study was to determine whether a model-based assessment of influenza exceeded a clinically based assessment when applied at a single hospital level. When taken at face value the model estimates derived in this study do suggest a large hidden burden in in-hospital mortality and hospital and ICU admissions due to the pandemic and influenza epidemics in general. However, the reliability of these estimates is in question given that this burden was not evident in clinically validated data and more importantly that the outcomes examined were not significantly associated with the influenza epidemics defined within the study. The discordances we have found between the model estimates and validated data suggest that the method may inherently overestimate influenza-attributable burden. The variation in statistically derived influenza mortality point estimates identified in the literature highlighted an additional inconsistency associated with this methodology.

The findings of this study suggest that there may be limitations to the current approach used for estimating point estimates of influenza burden. This has considerable implications for the development of influenza related policies and programs. On an annual basis the National Advisory Committee on Immunization makes recommendations on immunization for influenza. These recommendations are based in part on studies that have statistically estimated the impact of influenza on hospitalizations and mortality (46). Universal seasonal influenza immunization programs in the US have been deemed cost-effective based on models that incorporate statistical estimated influenza-attributable hospitalization and mortality as model parameters (47). The cost-effectiveness of treating influenza with antivirals has also been demonstrated using decision-analysis models that incorporate influenza-attributable estimates (48, 49). The economic impact of pandemic influenza has been forecasted using statistical estimates of influenza mortality and morbidity as model drivers (50). These types of studies have lead to major policy/program decisions such as the creation of national antiviral stockpiles, universal immunization programs, long-term contracts with pharmaceutical companies for pandemic vaccine development and the creation surveillance programs that monitor and report on influenza on a weekly basis; all of which require a substantial financial investment.

Given that statistical influenza morbidity and mortality estimates are used so frequently to inform seasonal and pandemic influenza management and preparedness a certain amount of investment should be made into further understanding the limitations of the method. Future studies should focus on identifying reasons for point estimate variation in the literature among studies estimating influenza mortality for the same season by examining which factors in modeling technique have the greatest impact. Future validation studies could include more hospitals in the Ottawa area to increase modeling power. It would also be useful to look at

outcomes by age group and in a strictly respiratory sub-population for comparison. Using multiple modeling methods would also strengthen the conclusions of the model findings. Lastly it might be beneficial to model outcomes with no known association to influenza; for example, a study that statistically estimates the influenza-attributable burden of a seasonal outcome with no known link to influenza (e.g. hip factures) and a non-seasonal outcome (e.g. appendicitis). If excess outcomes associated with influenza were identified in the seasonal outcomes this would suggest that the model was not controlling for seasonality. If excess outcomes associated with influenza were identified in the non-seasonal outcome this would suggest an inherent tendency for the modeling method to attribute outcomes to influenza.

5.3.2 Influenza at the Ottawa Hospital

I found that influenza epidemics, including the pandemic, did not lead to a greater number in-hospital deaths, hospital admissions or ICU admissions overall at the Ottawa Hospital but did lead to a significantly greater number of influenza cases within the hospital and within the ICU. This suggests that the Ottawa hospital should be prepared to deal with a surge of influenza cases on an annual basis by having respiratory-related expertise and treatment options available during these times. I also found that the influenza cases during the pandemic were younger than any other epidemic period which suggests that new influenza viruses impact the population in an atypical manner and that the hospital should be able to adapt to these changes. Future research should further examine and compare the characteristics of influenza patients at TOH across epidemic periods e.g. age, co-morbidities, treatments etc. It would also be helpful for hospital pandemic planning to look at the impact of epidemics on the emergency department given that this is often the front-line in an emergency situation such as a pandemic.

5.4 Conclusions

In conclusion I have found evidence to suggest that point estimates of influenza burden generated using statistical models may not be reliable and that more research is required to understand the limitations of this methodology. I also conclude that when examining the impact of influenza epidemics at the single hospital level populations more closely linked to the disease are required to detect the impact.

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7.0 EXHIBITS

Exhibit 1. Characteristics of studies included in the systematic review analysis

Study	Year	CA /US	Flu Year	Method	Epidemic Periods	Estimates Controlled for
Serfling(51)	1967	US	1957-63	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Housworth (13)	1974	US	1957-66	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Alling(52)	1981	US	1968-76	Multiple Linear Regression	Not defined	seasonality, trend, influenza activity
Choi(32)	1982	US	1967-78	Time Series	Observed deaths exceed the epidemic threshold† and there is widespread influenza activity as indicated by sentinel surveillance	seasonality, trend, autocorrelation of time points
				Serfling		seasonality, trend
Lui(28)	1987	US	1972-1985	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Stroup(26)	1988	US	1962-83	Time Series	Observed deaths exceed the epidemic threshold†	seasonality, trend, autocorrelation of time points
Simonsen(12)	1997	US	1972-92	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Simonsen(53)	1998	US	1968-72	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
			1972-95	Rate Difference	Months with documented influenza activity	trend,
Thompson W.W(27)	2003	US	1976-99	Serfling-Poisson	Not defined	seasonality, trend, influenza activity, RSV activity
Viboud(54)	2004	US	1972-97	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Dushoff(21)	2005	US	1979-2001	Annualized Regression	November – April	seasonality, trend
Viboud(55)	2006	CA	‘51, ‘57, ‘68	Serfling	Winter Months	seasonality, trend
Schanzer (18)	2006	CA	1989-99	Poisson	Not defined	seasonality, trend, influenza activity
Molinari(56)	2007	US	2003	Rate Difference	> 10% of specimens tested positive for influenza	trend
Kwong(20)	2008	CA	1997-2004	Serfling-Poisson	> 10% of lab tests positive for influenza for 2 consecutive weeks	seasonality, trend, sex, respiratory virus detections, predominance of H3N2, vaccine antigenic match
Schanzer(19)	2008	CA	1994-2000	Poisson	Not defined	seasonality, trend, x-mas, influenza activity, RSV, other respiratory viral activity, ILI
Foppa(57)	2008	US	1995-2005	Poisson	Not defined	seasonality, trend, influenza activity
Thompson W.W(29)	2009	US	1976-2002	Rate Difference	> 15% of viral isolates were positive for influenza	trend, seasonality (if using peri-season for baseline)
				Serfling-Poisson	Not defined	Seasonality, trend, influenza activity
			1972-2002	Serfling	Observed deaths exceed the epidemic threshold†	Seasonality, trend
				Time Series	Observed deaths exceed the epidemic threshold†	seasonality, trend, autocorrelation of time points
Thompson M.G(30)	2010	US	1976-2007	Serfling - Poisson	Not defined	Seasonality, trend, influenza activity
Viboud(58)	2010	US	2009 Pandemic	Extrapolation	May - December	N/A
Shrestha(59)	2010	US	2009 Pandemic	Extrapolation	April 2009 – April 2010	N/A

† > 1.64 standard deviations (std) or the 95% confidence interval (CI) above the baseline predicted by the model for ≥ 2 consecutive weeks

Exhibit 2. Influenza mortality rate estimates (per 100,000) by influenza for all studies using models based on all-cause mortality to estimate mortality for the influenza seasons of 1970-80.

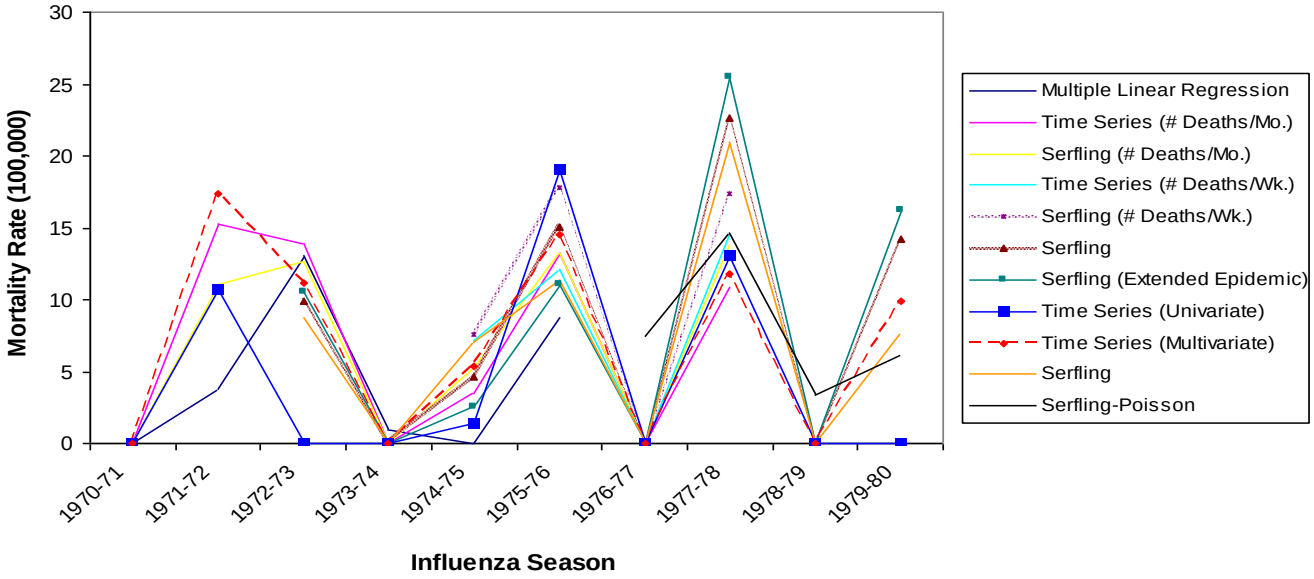


Exhibit 3. Estimates of Influenza mortality rate (per 100,000) based on all-cause mortality by method, 1968-88.

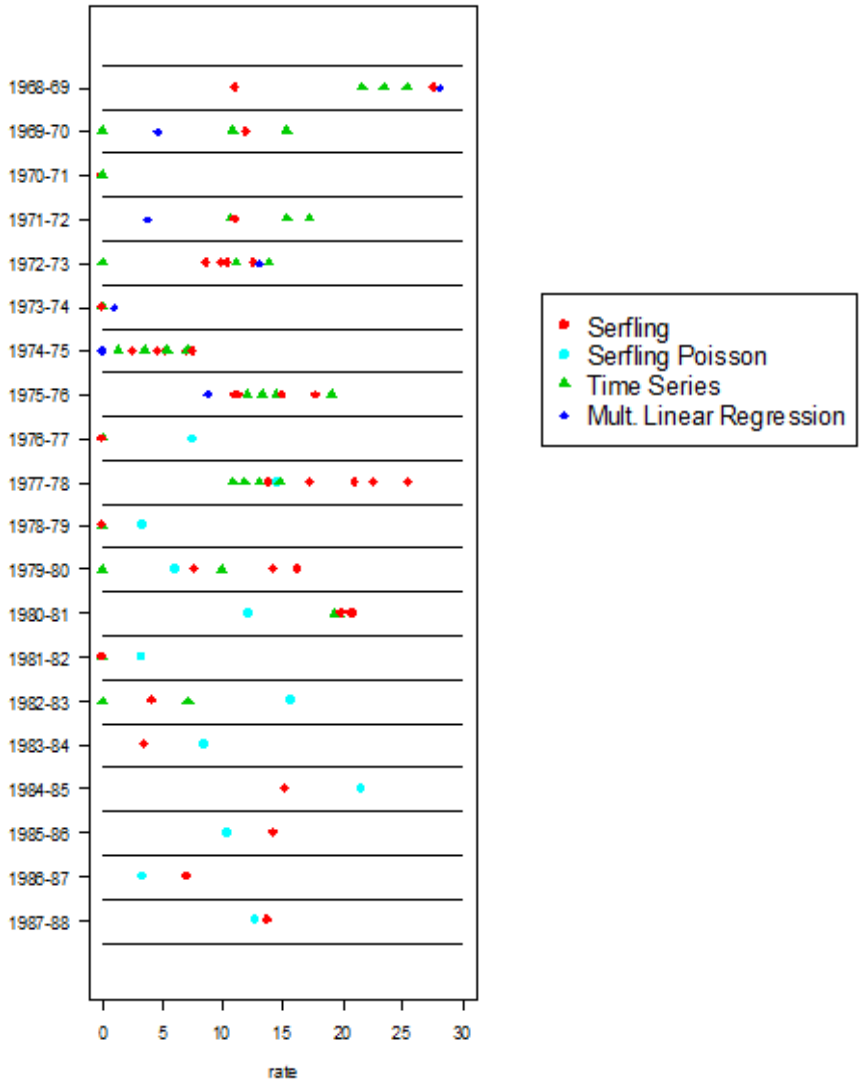


Exhibit 4. Estimates of influenza mortality rate (per 100,000) based on circulatory respiratory mortality by method, 1988-2003.

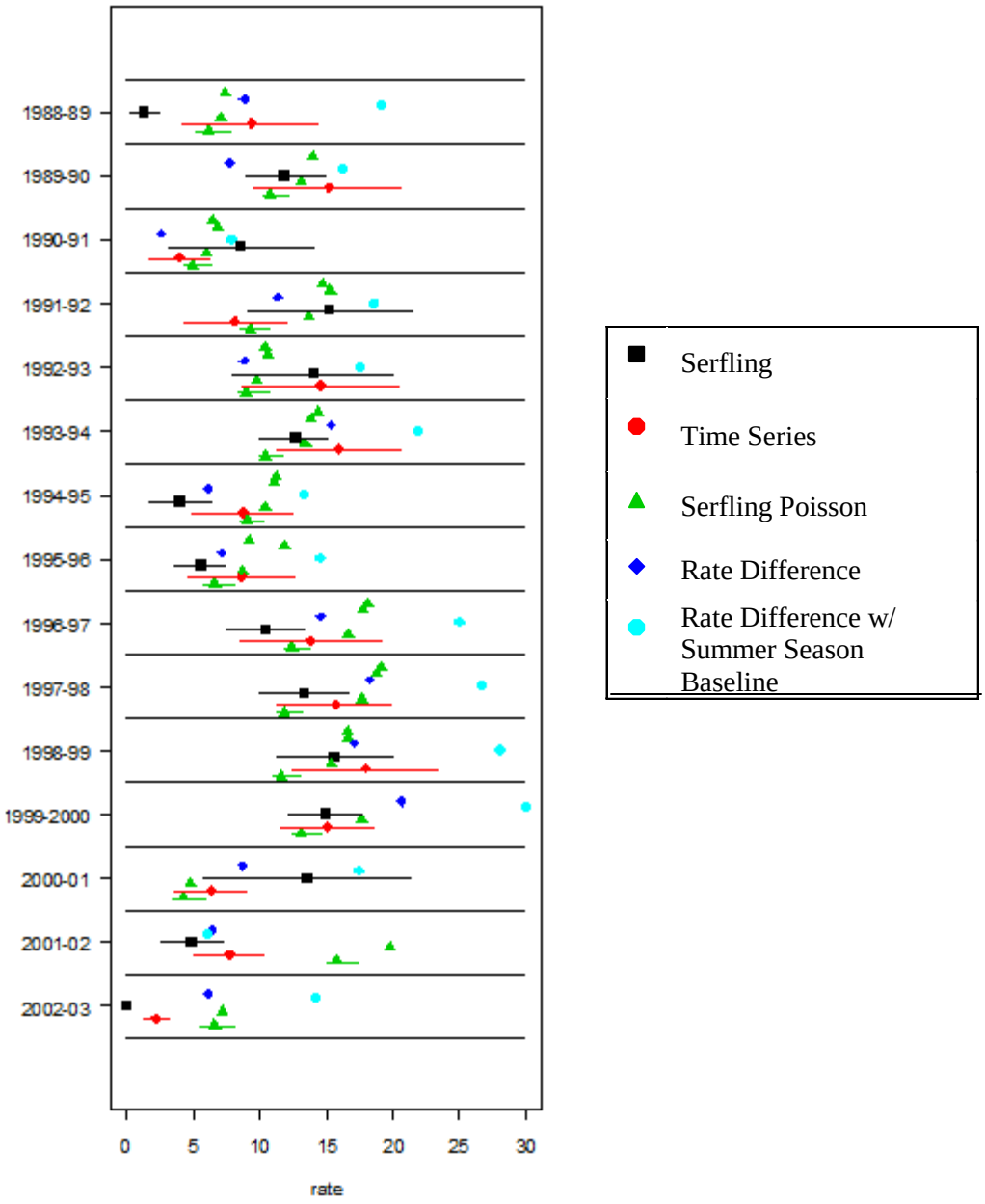


Exhibit 5. Characteristics of non-elective hospital encounters at the Ottawa Hospital, Sept. 1, 2002 to Jun. 5, 2010.

Characteristic	Value
Admissions, n*	208,231
Length of admission in days, median (IQR*)	5 (2-10)
Age at admission, median (IQR)	60 (42-75)
Gender, n (%)	
Male	100,759 (51.6)
Female	107,470 (48.4)
Campus, n (%)	
Civic	109,338 (52.5)
General	98,893 (47.5)
Most responsible diagnosis, n (%)	
Circulatory or Respiratory	60,715 (29.2)
Influenza	215 (0.1)
Deaths in-hospital, n (%)	
All	13,132 (6.3)
Circulatory/Respiratory	5,069 (2.4)
Influenza	12 (0.01)
Admission to ICU, n (%†)	
0	143,561 (85.5)
1	18,144 (10.8)
2	4,541 (2.7)
3+	1,618 (1.0)
ICU patient most responsible diagnosis, n (%††)	
Influenza	40 (0.1)

*n = number; IQR = inter-quartile range

†Proportion of all hospital admissions that occurred after April 4, 2004 (n= 167,864)

†† Proportion of all ICU admissions (n=32,897)

Exhibit 5b. Characteristics of the cohort used to validate the clinical influenza algorithm.

Characteristic	Value
Admissions, n*	398
Length of admission in days, median (IQR*)	6 (1-12)
Age at admission, median (IQR)	69 (53-81)
Gender, n (%)	
Male	186 (46.7)
Female	212 (53.3)
Campus, n (%)	
Civic	177 (44.5)
General	221 (55.5)
Most responsible diagnosis, n (%)	
Circulatory or Respiratory	328 (82.4)
Influenza	42 (10.6)
Deaths in-hospital, n (%)	
All	51 (12.8)
Circulatory/Respiratory	36 (9.1)
Influenza	2 (0.5)
Admission to ICU, n (%)	
0	321 (80.7)
1	55 (13.8)
2	17 (4.3)
3+	5 (1.3)
ICU patient most responsible diagnosis, n (%†)	
Influenza	8 (7.5)

*n = number; IQR = inter-quartile range

† Proportion of all ICU admissions (n=106)

Exhibit 6. The number of influenza deaths, hospital encounters and ICU admissions identified using the clinical influenza algorithm and each of its components.

Influenza	Algorithm Component(s)*			
	A or B or C	A	B	C
Deaths	170	45	146	41
Hospital Encounters	1430	454	1156	457
ICU Admissions	527	132	146	127

A=Positive influenza lab test; B=Antiviral prescription; C=DAD-based influenza diagnosis

Exhibit 7. Results of the sensitivity and specificity analysis of the algorithm used to identify influenza cases at the Ottawa Hospital.

	Chart Review		
Algorithm	**+**	**—**	**Total**
+	52	85	137
—	2	259	261
Total	54	344	398

Sensitivity = 96.3% (87.3 – 99.5)

Specificity = 75.3% (70.3 – 79.8)

Exhibit 8. Results of the sensitivity and specificity analysis of each algorithm component used to identify influenza cases at the Ottawa Hospital.

	Chart Review		
Positive Influenza Lab	**+**	**—**	**Total**
+	43	7	50
—	11	337	348
Total	54	344	398

Sensitivity = 79.7% (66.5 – 89.4)

Specificity = 98.0% (95.9 – 99.2)

	Chart Review		
Antiviral Rx	**+**	**—**	**Total**
+	51	83	134
—	3	261	264
Total	54	344	398

Sensitivity = 94.4% (84.6 – 98.8)

Specificity = 75.9% (71.0 – 80.3)

	Chart Review		
DAD-based influenza diagnosis	**+**	**—**	**Total**
+	49	12	61
—	5	332	337
Total	54	344	398

Sensitivity = 90.7% (79.7 – 96.9)

Specificity = 96.5% (94.0 – 98.2)

Exhibit 9. Time series of clinical influenza cases at the Ottawa Hospital using both the complete algorithm and the "DAD-based influenza diagnosis" component, September 1, 2002 to June 5, 2010**.**

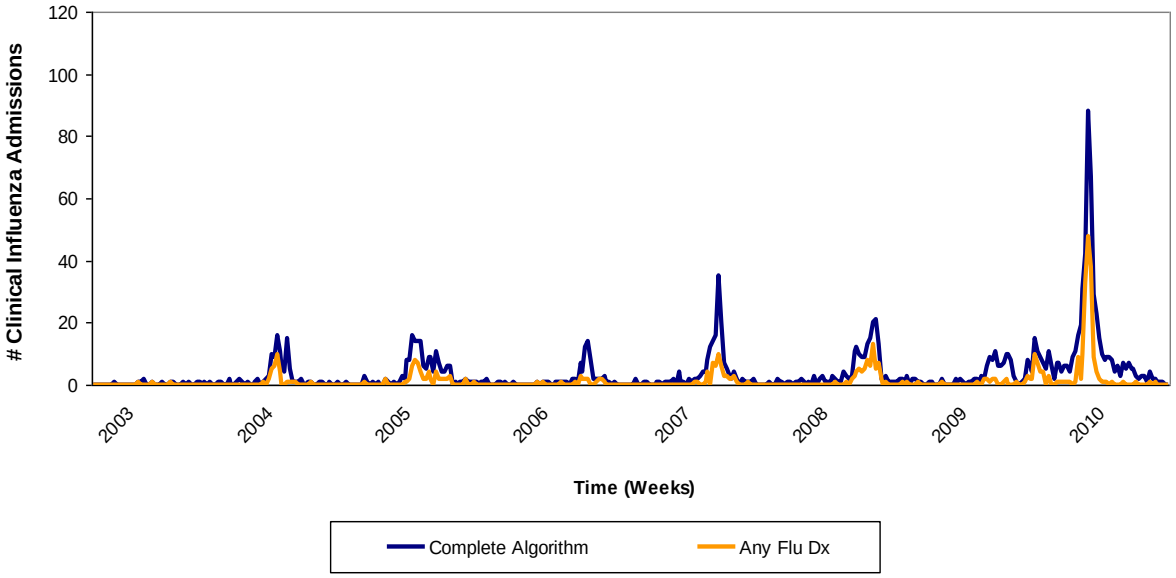


Exhibit 10. Timing and duration of epidemic periods at the Ottawa Hospital by influenza season, Sept. 1 2002 to Jun. 5 2010.

Influenza Season	Epidemic Period	Number of Weeks
2002-2003	No epidemic period	--
2003-2004	December 7 2003 to February 21 2004	11
2004-2005	November 28 2004 to Apr 2 2005	18
2005-2006	March 5 2006 to May 13 2006	10
2006-2007	February 18 2007 to April 28 2007	10
2007-2008	February 17 2008 to May 10 2008	12
2008-2009	February 1 2009 to Apr 4 2009	9
Pandemic	May 17 2009 to Jan 9 2010	34

Exhibit 11. The clinically and statistically estimated number of in-hospital deaths, hospital encounters and ICU admissions attributable to influenza, by epidemic period at the Ottawa Hospital.

Epidemic Period	In-Hospital Deaths			Hospital Encounters		ICU Admissions	
	Clinical	Statistical	Statistical* (Circ/Resp)	Clinical	Statistical	Clinical	Statistical
2003-04	5	18	27	31	70	--	--
2004-05	4	74	51	54	426	10	66
2005-06	0	17	7	15	85	1	36
2006-07	2	33	27	43	110	7	87
2007-08	7	26	18	64	121	22	96
2008-09	1	25	2	12	131	2	97
Pandemic	19	121	43	202	786	76	120
Total	38	314	175	421	1729	118	502

*Statistical estimate based on modeling of the circulatory/respiratory sub-population

Exhibit 12. Comparison of the characteristics of non-elective hospital encounters at the Ottawa Hospital between non-epidemic and epidemic periods, Sept.1, 2002 to Jun. 5, 2010.

Characteristic	Non Epidemic Periods	Epidemic Periods	*P* Value
All Admissions			
Mean admissions per day, n	73	75	0.003
Encounters resulting in death, %	6.3	6.4	0.265
Age at admission, median (IQR)	60 (41-75)	60 (42-75)	<0.001
LOS in days, median (IQR)	4.6 (2-10)	4.7 (2-10)	<0.001
Circulatory/Respiratory (CR) Encounters			
Encounters w/ CR MRDX, n (%)	44,487 (28.9)	16,228 (29.9)	<0.001
Deaths in CR Cases, n (%)	3,713 (8.3)	1,356 (8.4)	0.97
Age of CR cases, median (IQR)	68 (56-79)	69 (57-79)	<0.001
Influenza Cases			
Encounters w/ clinical influenza, n (%)	36 (0.02)	421 (0.8)	<0.001
Deaths in clinical influenza cases, n (%)	3 (8.3)	38 (9.0)	0.889
Age of clinical influenza cases, median (IQR)	68 (52-80)	60 (44-76)	0.033
LOS in days, median (IQR)	9 (5-22)	6 (3-12)	<0.001
ICU Admissions			
Admissions per day, n	14	15	<0.001
Admissions w/ CR MRDX, n (%)	15,336 (66.6)	6,711 (67.8)	0.023
Admissions w/ clinical influenza, n (%)	9 (0.04)	118 (1.2)	<0.001
Age at admission, median (IQR)	65 (54-76)	65 (54-76)	0.443
LOS in days , median (IQR)	2.0 (1-5)	2.1 (1-5)	<0.001

Exhibit 13. The weekly number and weekly proportion of non-elective hospital encounters with clinical influenza by admission date, Ottawa Hospital, Sept. 1, 2002 – Jun. 5, 2010.

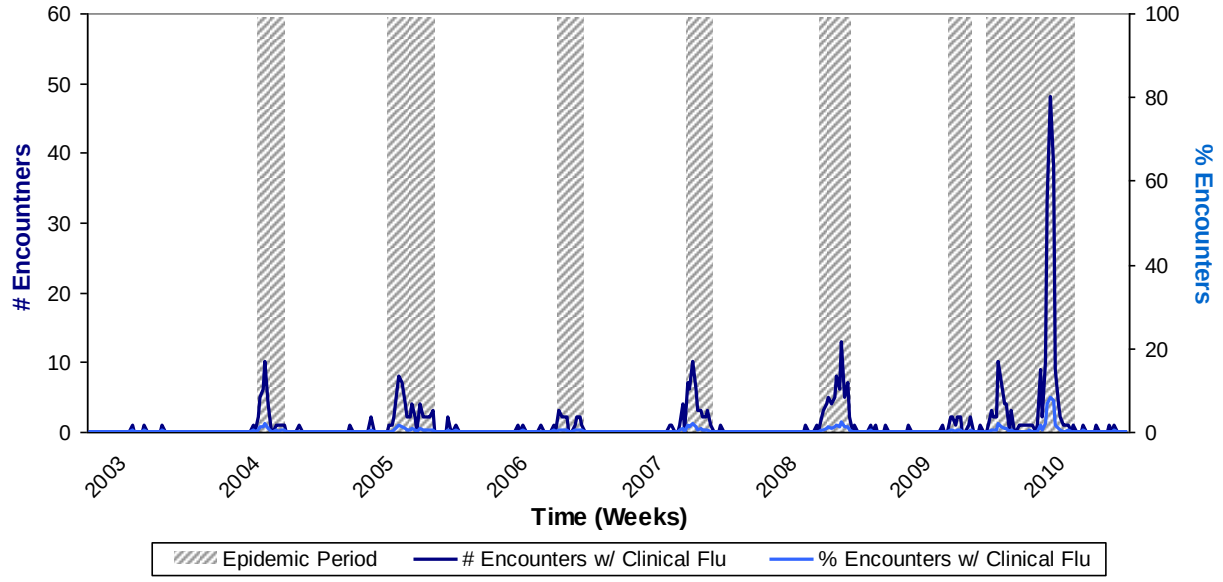


Exhibit 14. The weekly number and weekly proportion of non-elective in-hospital deaths with clinical influenza by admission date, Ottawa Hospital, Sept. 1, 2002 – Jun. 5, 2010.

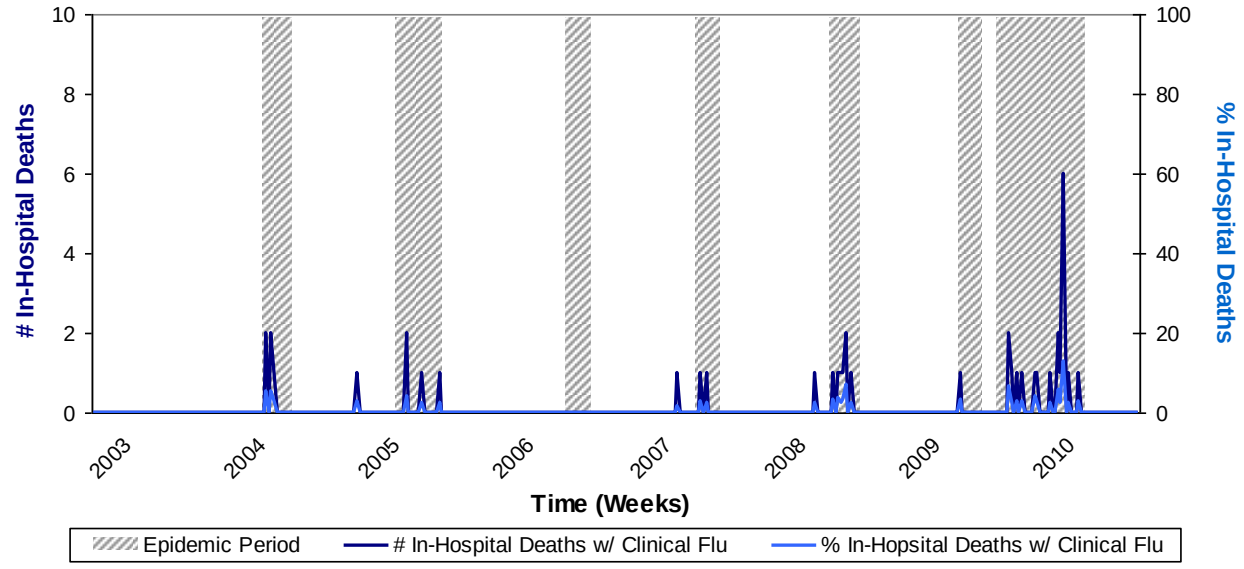


Exhibit 15. Comparison of the characteristics of non-elective hospital encounters at the Ottawa Hospital by epidemic period.

Characteristic	Epidemic Period						
	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09	Pandemic
All Encounters							
Number of encounters per day, mean	71	76	71	74	73	76	77
% of encounters resulting in death	6.5	6.6	6.2	6.6	6.3	6.0	6.4
Age at admission, median (IQR)	60 (41-74)	60 (43-75)	60 (43-75)	61 (42-76)	61 (42-76)	61 (44-75)	60 (41-75)
LOS in days, median (IQR)	5 (2-11)	5 (2-11)	4 (2-10)	4 (2-10)	5 (2-10)	5 (2-11)	4 (2-10)
Circulatory/Respiratory (CR) Encounters							
Number of encounters w/ CR MRDX* per day, mean	23	24	22	24	23	21	21
Deaths in CR Cases, %	9.3	8.7	7.0	8.7	8.4	6.9	8.5
Age at admission, median (IQR)	69 (57-79)	70 (57-79)	68 (56-78)	71 (57-80)	70 (58-80)	68 (57-79)	68 (56-79)
Clinical Influenza Encounters							
Number of encounters w/ clinical influenza per day, mean	0.4	0.4	0.2	0.6	0.8	0.2	0.8
Deaths in clinical influenza cases, %	16.1	7.4	0	4.7	10.9	8.3	9.4
Age at admission, median (IQR)	71 (60-82)	75 (65-82)	62 (45-74)	77 (66-84)	76 (61-86)	59 (48-75)	47 (30-60)
LOS in days, median (IQR)	7 (3-13)	7 (3-10)	5 (3-8)	9 (4-18)	7 (3-15)	7 (4-13)	5 (2-10)
ICU Admissions							
Number of admissions per day	--	12	11	16	17	18	17
Age at admission, median (IQR)	--	67 (54-76)	66 (54-75)	66 (53-76)	66 (55-77)	64 (53-75)	64 (53-75)
LOS in days , median (IQR)	--	2 (1-5)	2 (1-5)	2 (1-4)	2 (1-5)	2 (1-5)	2 (1-5)
Encounters w/ clinical influenza, n (%)	--	10 (0.7)	1 (0.1)	7 (0.6)	22 (1.6)	2 (0.2)	76 (1.9)
Age of clinical influenza encounters, median (IQR)	--	64 (52-73)	66 (66-66)	75 (72-82)	68 (57-86)	67 (58-75)	52 (32-59)

Exhibit 16. The weekly number of non-elective hospital encounters that resulted in death by admission date, Ottawa Hospital, Sept. 1, 2002 – Jun. 5, 2010.

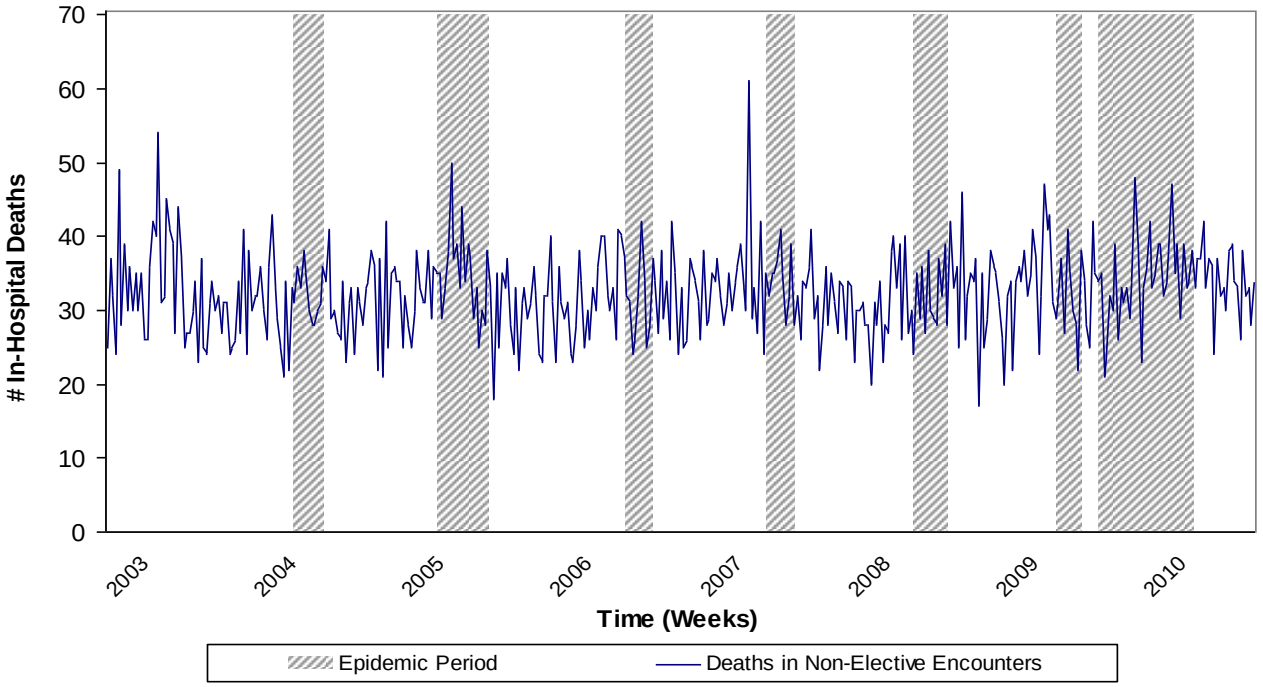


Exhibit 17. The weekly number of non-elective in-hospital deaths with a circulatory or respiratory most responsible diagnosis by admission date, Ottawa Hospital, Sept. 1, 2002 – Jun. 5, 2010.

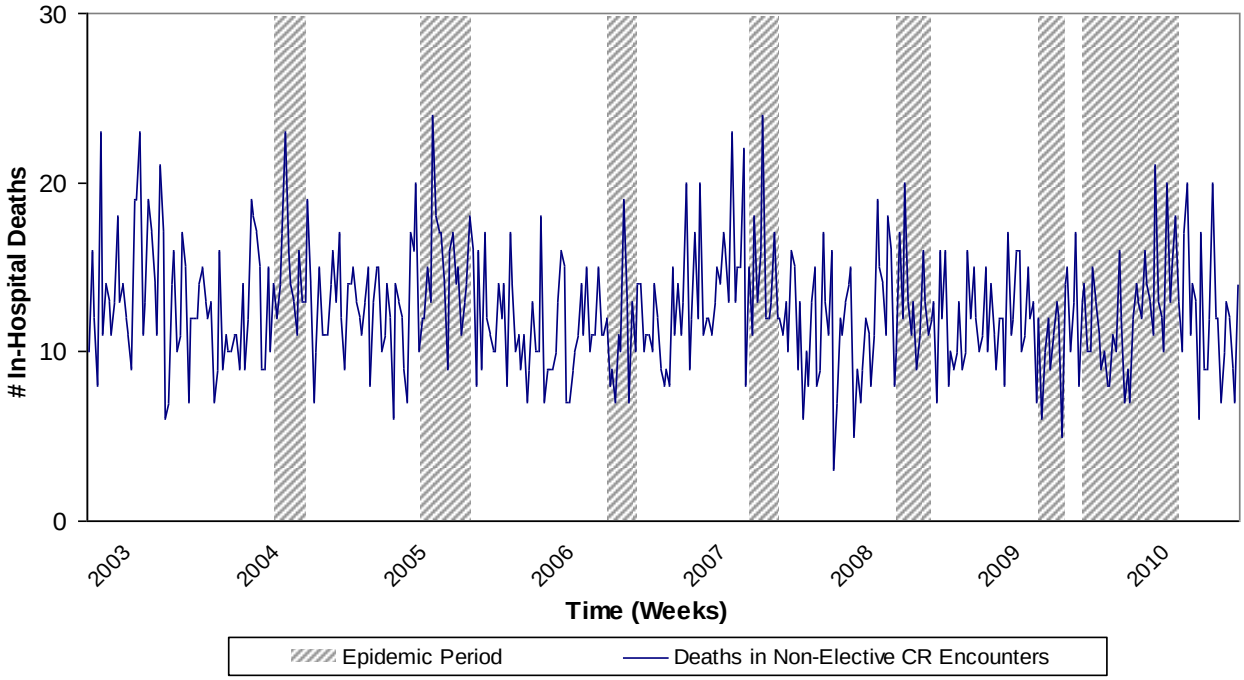


Exhibit 18. The weekly number of non-elective hospital admissions at the Ottawa Hospital, Sept 1, 2002 – Jun. 5, 2010

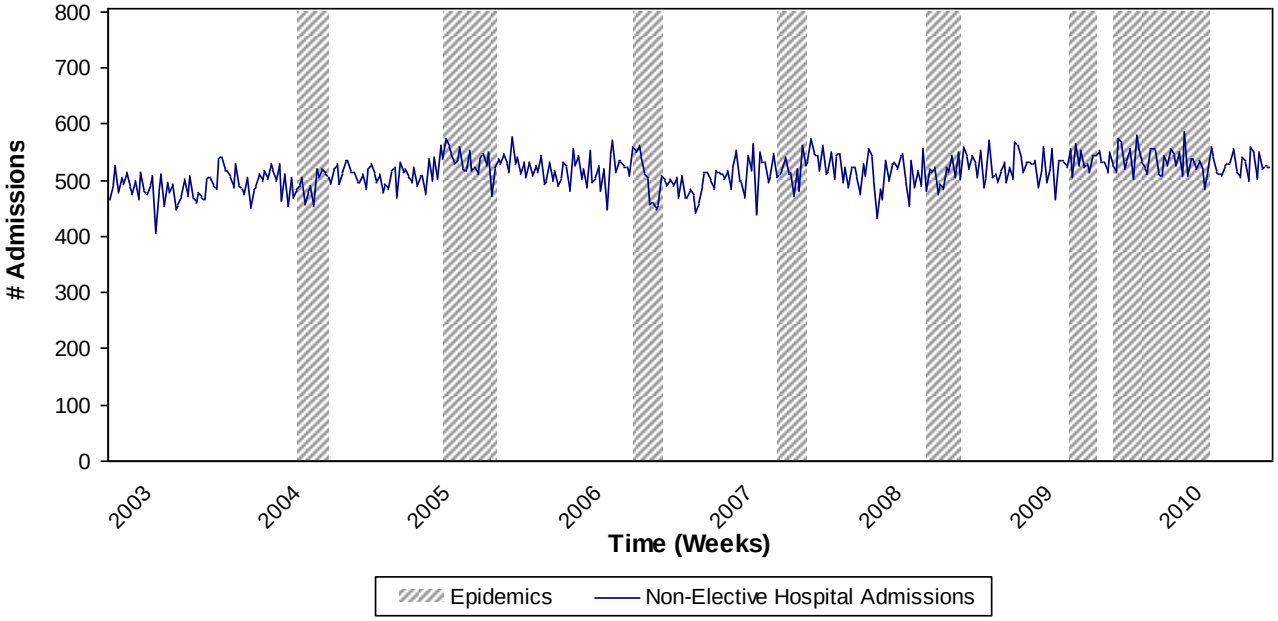


Exhibit 19. The weekly number of ICU admissions and weekly average number of available ICU beds by ICU admission date, Ottawa Hospital, Apr. 4, 2004 – Jun. 5, 2010.

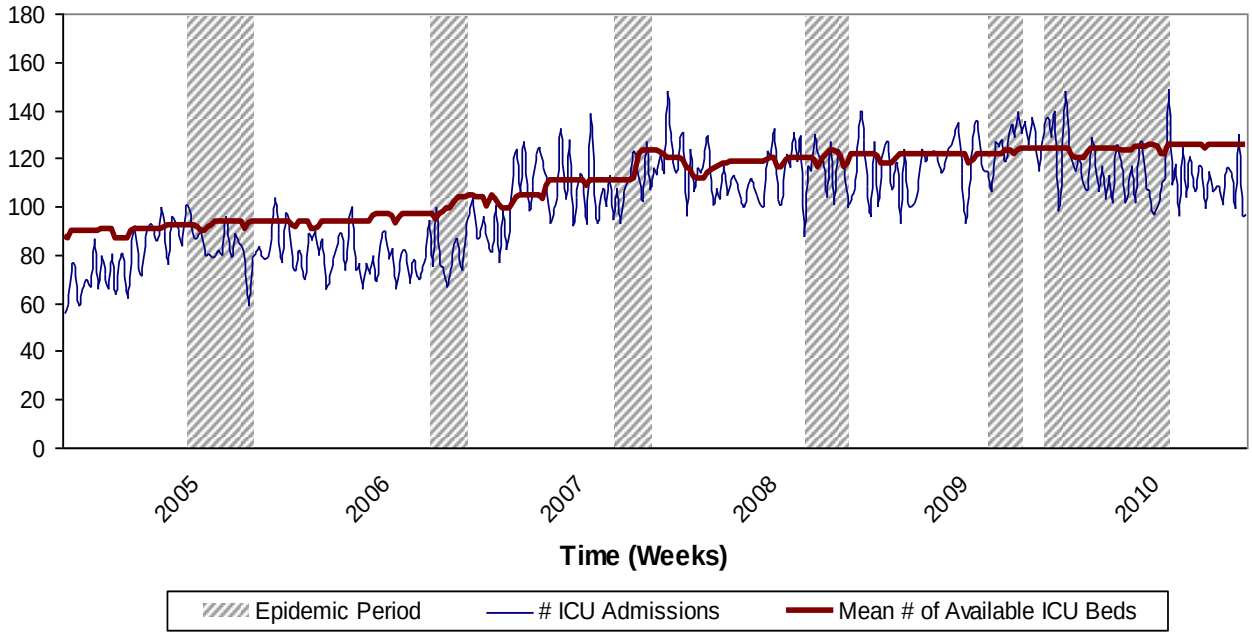


Exhibit 20. The modeled baseline and observed number of non-elective hospital encounters that resulted in death by admission date, Ottawa Hospital, Sept. 1, 2002 – Jun. 5, 2010**.**

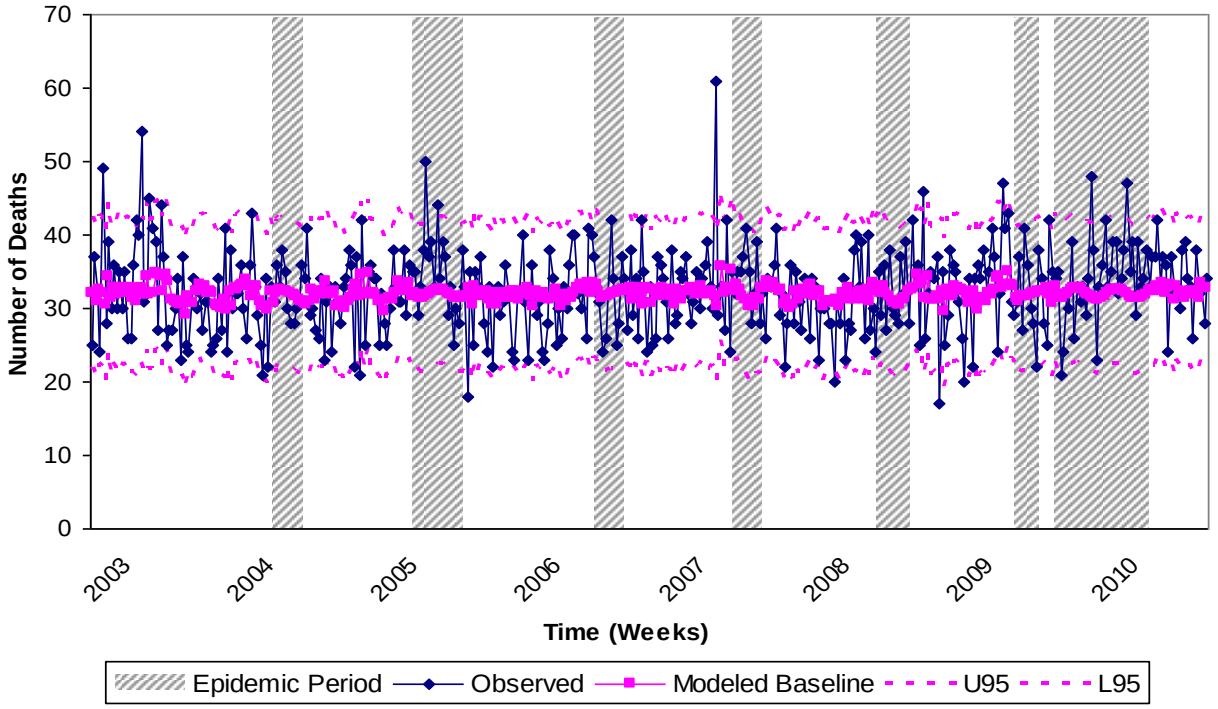


Exhibit 21. The modeled baseline and observed weekly number of non-elective in-hospital deaths with a circulatory or respiratory most responsible diagnosis by admission date, Ottawa Hospital, Sept. 1, 2002 – Jun. 5, 2010

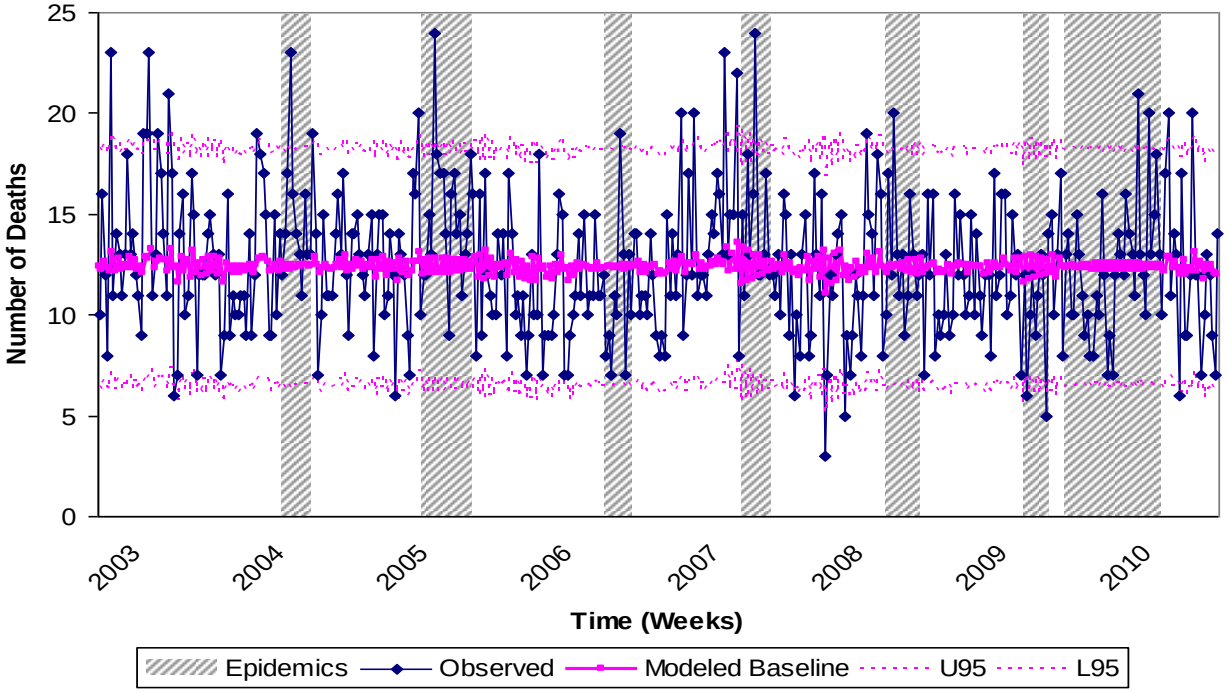


Exhibit 22. The modeled baseline and observed weekly number of non-elective hospital admissions at the Ottawa Hospital, Sept 1, 2002 – Jun. 5, 2010

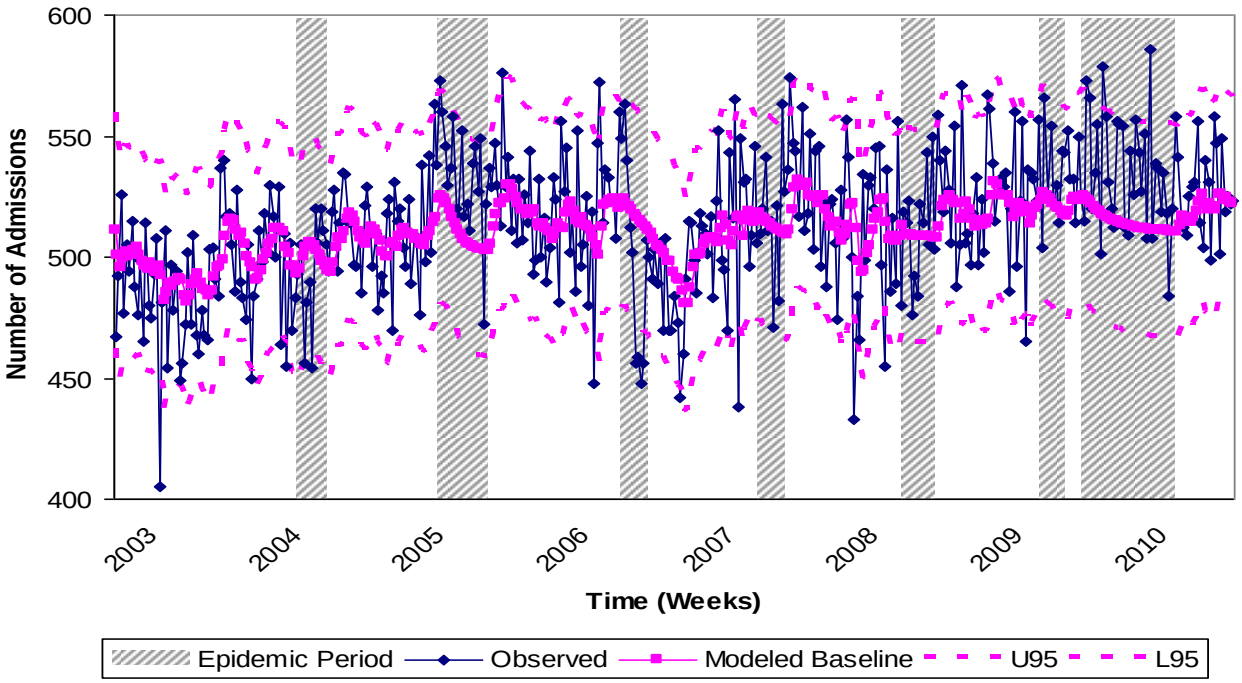


Exhibit 23. The modeled baseline and observed weekly number of ICU admissions by ICU admission date, Ottawa Hospital, Apr. 4, 2004 – Jun. 5, 2010.

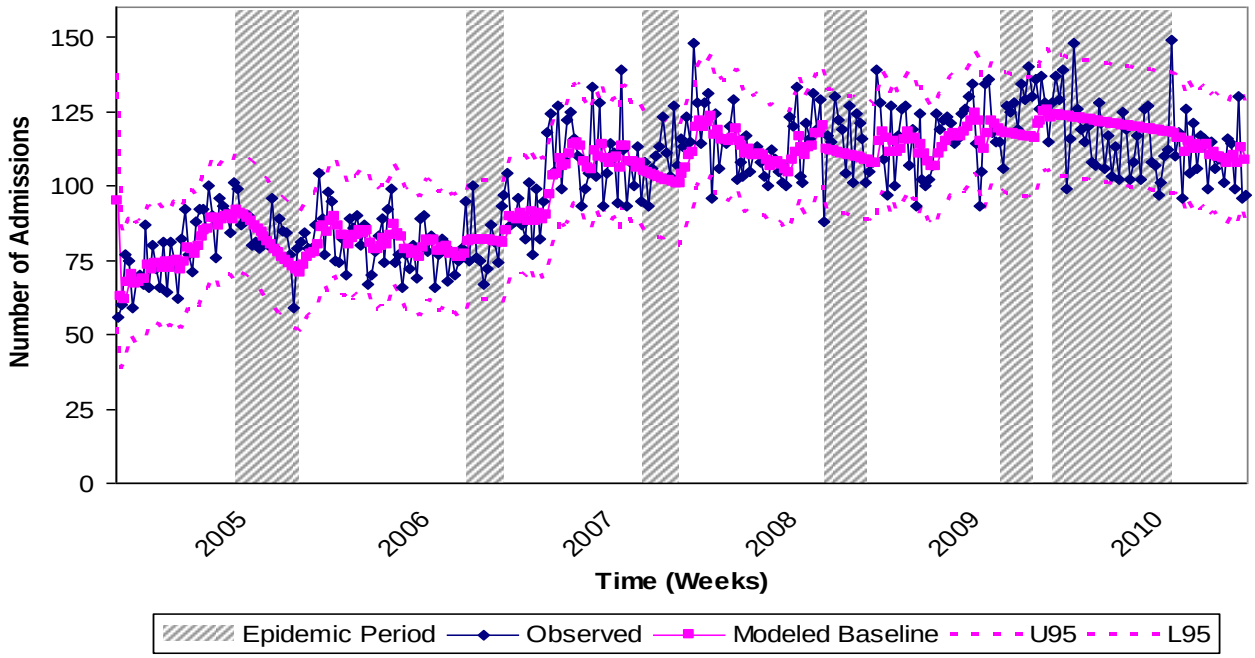
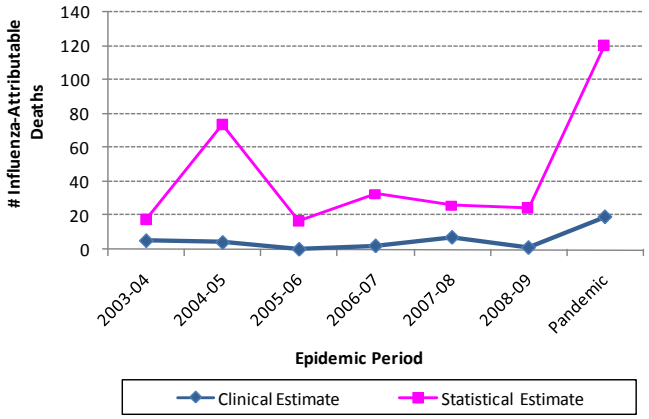
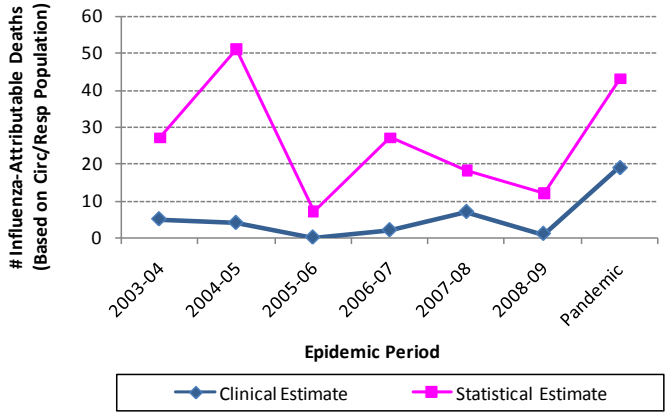
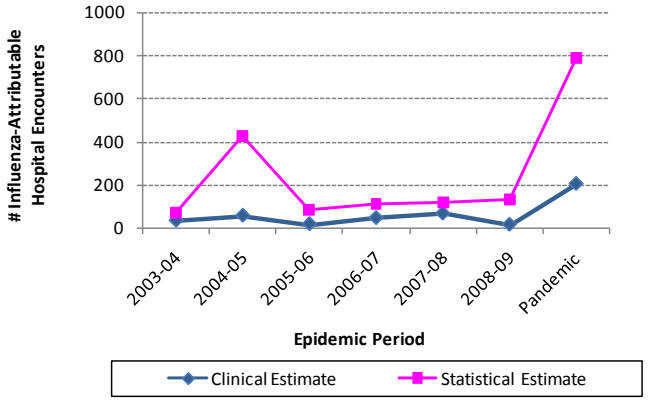
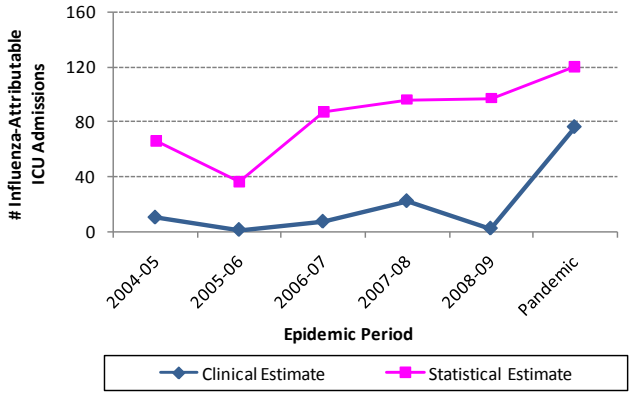


Exhibit 24. Trends in clinical and statistical estimates of influenza burden at the Ottawa Hospital, 2003-2010









APPENDICES

Appendix A: Systematic Review (Draft Publication)

Introduction

Every year influenza epidemics pose a threat to vulnerable populations. Quantifying the impact of these epidemics is important for the development and evaluation of public health policies and programs aimed at mitigating disease burden. However, the ability of public health officials to do so is complicated by challenges in identifying influenza cases. A number of different viruses can cause influenza-like illness and laboratory confirmation of cases is not routinely conducted (1). Influenza can also easily go undetected in cases that die or are hospitalized because of secondary complications such as pneumonia or exacerbation of existing cardiovascular/respiratory conditions. As a result, influenza is assumed to be largely under-reported on hospital discharge records and death certificates and thus under-estimated in databases that would typically be used to measure disease burden.

In the absence of reliable data at the individual level, statistical methods based on population-level data are used to estimate the impact of influenza. These methods estimate what mortality/morbidity would have been in the absence of influenza and then subtract the estimate from what was observed. Different model types have been used, including rate difference, regression models and time series analysis (4). No one method is currently universally accepted and modeling techniques have been debated in the literature. Researchers have also questioned the validity of estimates in light of the potential for ecological fallacy and seasonal confounding (27, 28, 29). We sought to systematically identify studies which have estimated influenza-related mortality in the United States and Canada in order to describe the variability of estimates by method.

Methods

Search Strategy

We conducted a systematic search of the following electronic databases from inception to April 2011: MedLine, Excerpta Medica (EMBASE), Cumulative Index to Nursing & Allied Health Literature (CINAHL), and Global Health. We used influenza, surveillance, statistical models and mortality as our key search terms and limited studies to those pertaining to humans (Appendix A). We also identified additional studies by reviewing the reference lists of key studies.

Inclusion and Exclusion Criteria

We included studies if they 1) involved primary research in which influenza mortality was estimated for one or more influenza seasons; 2) provided national mortality estimates for either the United States or Canada; or 3) were conducted after the introduction of the Serfling model in 19635 as it was from this point that statistical modeling techniques became the standard methodology. We included only studies based on Canadian and American data to ensure the consistency of influenza seasons with respect to circulating strains. We excluded studies if they 1) were guidelines, statements or commentary pieces (e.g. letters to the editor); 2) provided estimates exclusively for the 1918-19 pandemic; 3) used sentinel surveillance data to estimate mortality as an indicator of the relative severity of influenza seasons as opposed to mortality impact; and, 4) only provided sub-population mortality estimates (e.g. over 65 population).

Data Abstraction

We abstracted the following data from each study: 1) influenza seasons examined 2) details of methodological approach (e.g., model type, model fitting procedure, definition of epidemic period, model parameters), 3) type of mortality data used in model 4) mortality estimates by year.

Statistical Analysis
We classified studies by the three most common types of mortality data used to derive an estimate (all-cause, cardiovascular/respiratory, and pneumonia/influenza). Within each mortality class, we converted estimated influenza-associated death counts for each influenza season to crude mortality rates by dividing the estimated number of deaths by the total population. Canadian and American population estimates were obtained from Statistics Canada and the US Census Bureau respectively (websites to reference). We also calculated mean mortality rates by study for studies which provided estimates for the same influenza seasons.

Results

Search Results
The database search netted 2482 citations. After we removed duplicates (993) and applied our exclusion criteria (1425), 63 articles were selected for full review. We excluded a further 46 articles and identified 8 additional articles in references resulting in 21 studies for data abstraction and analysis (Table 1.). Four studies were based on Canadian data and 17 studies American data.

Study Characteristics
We identified eight main methods: extrapolation, rate difference, time series analysis, Serfling model, Serfling-Poisson model, Poisson regression, multiple linear regression and annualized regression. The most commonly used method was the Serfling model, having been used in 9 studies since 1967, followed by the Serfling-Poisson model which was introduced in 2003 and has been used in four studies since. Seven of the eight methods were based on the derivation of baseline mortality which was then subtracted from the observed mortality (Table 2.). Extrapolation methods were not based on the derivation of baseline mortality but instead extrapolated a national mortality estimate from sentinel surveillance data. This type of method was only used in the two studies seeking to estimate mortality for the 2009 pandemic in advance of the availability of vital statistics mortality data (25, 26). As outlined in Table 1, studies exhibited heterogeneity in the definition of epidemic period and what parameters were included in the model even when the same method was used.

The most common mortality data used to derive mortality estimates were all-cause, circulatory/respiratory and pneumonia/influenza, which were used in twelve[7,8,9,10,11,12,14,17,18,20,21,22], five[14,16,19,23,24] and ten[6,9,10,11,12,13,14,15,16,24] studies respectively. Some studies used more than one type of mortality data and/or more than one method. Two studies compared different methods within the article. Choi et al compared time series analysis to the Serfling model (9) and Thompson et al compared rate difference, Serfling, Serfling-Poisson and time series methods (23). Five studies examined how variations within the same method impacted mortality estimates (9, 10, 11, 14, 21). Within method variation included the difference between modeling the weekly number of deaths versus monthly number of deaths (9); widening the epidemic period (10); comparing a univariate to a multivariate time series model (11); including a model parameter adjusting for RSV (14); and, lagging indicators of influenza activity backward and forward in time (21).

Analysis

Trend
Crude mortality rates ranged from 0 to 34.1/100,000 in Canada and 0 to 30.1/100,000 in the US. On visual inspection, trends in influenza mortality appear to be consistent over time across different methods and across variations within the same method (Figure 1.) Consistency in trend was observed despite large differences in the magnitude of mortality estimates (Figure 2.). For the most part, no one method consistently produced higher or lower estimates (Table 3). As a result, average mortality rates were similar for studies examining the same influenza seasons (Table 4). Exceptions to this trend were seen in

certain studies using the rate difference method and Poisson regression. The rate difference method that used the summer season for the baseline produced the highest estimate for 20 of the 27 influenza seasons examined (23). The Poisson regression model used by Foppa et al22 consistently produced lower estimates than the Serfling-Poisson models used by Thompson et al14 from 1995-1999.

Magnitude

Although consistent in trends over time, yearly point estimates for excess mortality varied considerably in magnitude by study (Figures 3 and 4). For example, for the 1979-80 influenza season in the US Stroup et al11 did not detect any excess mortality when using the univariate time series model but 9.9/100,000 with the multivariate model, Thompson et al14 estimated 6.1 deaths/100,000 with the Serfling-Poisson model and, using a Serfling model, Simonsen et al estimated 7.7/100,000 while Lui et al estimated 16.2/100,000. Large variations in magnitude also occurred in point estimates produced by the same model type. For example, for the 1977-78 influenza season, three researchers used a Serfling model generating mortality rates that ranged from 13.9/100,000 to 25.5/100,000.

Figure 4 outlines mortality estimates from 1988-2003 based on circulatory/respiratory mortality populations, some of which were provided with confidence intervals. The confidence intervals demonstrate that the variations in magnitude were not always significantly different; however, there is still considerable variation. For example, in the 2001-02 influenza season, Thompson W.W. et al's23 Serfling model estimated a mortality rate of 4.9/100,000 while Thompson W.G. et al's24 Serfling-Poisson model generated a mortality estimate of 15.8/100,000.

Discussion

When examining mortality estimates by method we found that trends in mortality rates over time were similar across different methods but that there were differences in the magnitude of mortality estimates by study within the same influenza seasons. We also found that variations in magnitude occurred even when the same model approach was used which suggests that the variations in individual modeling technique impact the magnitude of mortality estimates. For example, how researchers defined the epidemic period when using the Serfling model, and the indicators used to describe influenza activity when using the Poisson regression model varied by study.

Other studies have compared different statistical methods with varying results. Newall et al found that Serfling and Serfling-Poisson models produced consistent trends in influenza mortality patterns but variation in the magnitude of mortality estimates with the Serfling-Poisson model generally produced higher estimates (31). Choi et al compared the accuracy of the time series and Serfling models by comparing the observed and forecasted non-epidemic data (9). They found the time series model using weekly data to be the most accurate but that when using monthly data there was no difference between the models. In Thompson et al's recent comparison of rate difference, Serfling, Serfling-Poisson, and time series models, the authors concluded that the models produced estimates that were similar in both magnitude and trend across 31 influenza seasons. A recent study by Gilca et al compared 6 commonly used statistical methods for estimating paediatric virus-attributable hospitalizations against a prospective study using virologic data collected at admission (30). The authors found no one method provided accurate or consistent results and they emphasized the need for careful validation of these methods to better inform public health policy.

The variation in mortality estimates produced using statistical methods does not change the fact that influenza circulates every year imposing a mortality burden that is likely underestimated using non-statistical methods due to the difficulty in identifying cases. It does, however, suggest that the ability of researchers to accurately evaluate mitigation efforts may be limited. If the reasons for variations in

mortality estimates are not clear and we cannot validate statistical estimates, it is difficult to know which estimate is correct from one season to the next.

To our knowledge this is the first study to systematically identify studies in Canada and the US that have estimated influenza mortality to compare mortality estimates by study. Limitations of this study include the use of only one reviewer which may have resulted in missed studies. We may have also missed studies by not searching unpublished literature. In addition, there may be other explanations for variability that we were unable to ascertain. Future studies could focus on identifying reasons for point estimate variation by examining which factors in modeling technique have the greatest impact. Studies could also look at ways of validating mortality estimates by using populations that contain enough individual level data to compare statistical estimates against reliable clinical estimates.

The statistical techniques used to estimate influenza mortality continue to enhance our knowledge of the influenza virus by providing an indication of the relative severity of influenza epidemics, demonstrating variations in virulence by virus type and strain, and providing estimates that affirm the need to remain vigilant. However, the difficulty in validating statistical mortality estimates, that lack of consensus on which model is most accurate and large variations in point estimates within the same influenza seasons suggest that this method of estimating influenza mortality needs to be further explored.

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27. Fleming DM, Cross KW, Watson JM et al. Excess winter mortality (letter to the Editor). BMJ. 2002; 324.7349: 1337. (1 June).

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31. Newall AT, Viboud C, Wood JG. Influenza-attributable mortality in Australians aged more than 50 years: a comparison of different modeling approaches. Epidemiol. Infect. 2010;138(6):836–842.

Table 1. Characteristics of 21 studies included in analysis.

Study	Year	CA/ US	Flu Year	Method	Epidemic Periods	Estimates Controlled for
Serfling[6]	1967	US	1957-63	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Housworth[7]	1974	US	1957-66	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Alling[8]	1981	US	1968-76	Multiple Linear Regression	Not defined	seasonality, trend, influenza activity
Choi[9]	1982	US	1967-78	Time Series	Observed deaths exceed the epidemic threshold† and there is widespread influenza activity as indicated by sentinel surveillance	seasonality, trend, autocorrelation of time points
				Serfling		seasonality, trend
Lui[10]	1987	US	1972-1985	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Stroup[11]	1988	US	1962-83	Time Series	Observed deaths exceed the epidemic threshold†	seasonality, trend, autocorrelation of time points
Simonsen[12]	1997	US	1972-92	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Simonsen[13]	1998	US	1968-72	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
			1972-95	Rate Difference	Months with documented influenza activity	trend,
Thompson W.W[14]	2003	US	1976-99	Serfling-Poisson	Not defined	seasonality, trend, influenza activity, RSV activity
Viboud[15]	2004	US	1972-97	Serfling	Observed deaths exceed the epidemic threshold†	seasonality, trend
Dushoff[16]	2005	US	1979-2001	Annualized Regression	November – April	seasonality, trend
Viboud[17]	2006	CA	‘51, ‘57, ‘68	Serfling	Winter Months	seasonality, trend
Schanzer[18]	2006	CA	1989-99	Poisson	Not defined	seasonality, trend, influenza activity
Molinari[19]	2007	US	2003	Rate Difference	> 10% of specimens tested positive for influenza	trend
Kwong[20]	2008	CA	1997-2004	Serfling-Poisson	> 10% of lab tests positive for influenza for 2 consecutive weeks	seasonality, trend, sex, respiratory virus detections, predominance of H3N2, vaccine antigenic match
Schanzer[21]	2008	CA	1994-2000	Poisson	Not defined	seasonality, trend, x-mas, influenza activity, RSV, other respiratory viral activity, ILI
Foppa[22]	2008	US	1995-2005	Poisson	Not defined	seasonality, trend, influenza activity
Thompson W.W[23]	2009	US	1976-2002	Rate Difference	> 15% of viral isolates were positive for influenza	trend, seasonality (if using peri-season for baseline)
				Serfling-Poisson	Not defined	Seasonality, trend, influenza activity
			1972-2002	Serfling	Observed deaths exceed the epidemic threshold†	Seasonality, trend
				Time Series	Observed deaths exceed the epidemic threshold†	seasonality, trend, autocorrelation of time points
Thompson M.G[24]	2010	US	1976-2007	Serfling - Poisson	Not defined	Seasonality, trend, influenza activity
Viboud[25]	2010	US	2009 Pandemic	Extrapolation	May - December	N/A
Strestha[26]	2010	US	2009 Pandemic	Extrapolation	April 2009 – April 2010	N/A

† > 1.64 standard deviations (std) or the 95% confidence interval (CI) above the baseline predicted by the model for ≥ 2 consecutive weeks

Table 2. Summary of approach used by methods based on the derivation of a baseline mortality which is subtracted from the observed mortality

Method	First Used*	Derivation of Baseline
Serfling Model[6,7,9,10,12,13,15,17,23]	1967	Forecasted by model fitted to historical non-epidemic mortality data
Multiple Linear Regression[8]	1981	Calculated from the regression equation based on the observed values of the indicator for influenza activity in the year with the least amount of influenza deaths for the period being examined
Time Series[9,11,23]	1982	Fit primary model to historical non-epidemic mortality data and use model to replace historical epidemic data points. Fit secondary model to composite historical mortality data to forecast baseline.
Serfling-Poisson Model[14,21,23,24]	2003	Model fit to all mortality data; baseline estimate derived by setting influenza-related model parameters to zero.
Annualized Regression[16]	2005	Mortality time series detrended using least squares quadratic model; mortality in May to October used as baseline months
Poisson Regression[18,20,22]	2006	Model fit to all mortality data; baseline estimate derived by setting influenza-related model parameters to zero.
Rate Difference[19,23]	2007	Use mortality data from non-epidemic time periods (i.e. summer or peri-seasonal periods)

*In the studies that met the inclusion and exclusion criteria

Table 3. Methods with the highest mortality rate estimate by mortality population for influenza seasons where more than one method was used

Method	Number of Seasons with Highest Mortality Estimate*†		
	AC	CR	PI
Serfling Model	8	7	9
Multiple Linear Regression	2		
Time Series	4	11	7
Serfling-Poisson Model	14	10	13
Poisson Regression	0		
Rate Difference		2	

*AC=all-cause CR=circulatory/respiratory PI=pneumonia/influenza
†Rate difference with summer baseline not included

Table 4. Comparison of mean mortality rates (per 100,000) for studies providing mortality estimates for the same influenza seasons.

Study	Model Type	Mean Rate [95% CI]
1969-76 (All-Cause Mortality)		
Alling	Multiple Linear Regression	4.5 [-0.1, 9.0]
Choi	Time Series Analysis	8.8 [2.1, 15.4]
Choi	Serfling Model	7.8 [2.3, 13.2]
Stroup	Time Series Analysis	8.5 [2.1, 14.8]
1976-92 (All-Cause Mortality)		
Simonsen	Serfling Model	9.7 [5.7, 13.6]
Thompson W.W.	Serfling-Poisson Model	11.1 [8.0, 14.2]
1989-1999 (All-Cause Mortality)		
Schanzer	Poisson Regression	13.0
Thompson W.W.	Serfling-Poisson	18.6 [14.7, 22.6]
1979-2001 (Circulatory & Respiratory Mortality)		
Thompson W.W.	Serfling-Poisson Model	10.7 [8.3, 13.0]
Thompson W.W.	Serfling-Poisson Model (Incl. RSV)	13.6 [10.7, 16.6]
Thompson W.W.	Peri-Season Rate Difference	9.0 [6.6, 11.5]
Thompson W.W.	Summer-Season Rate Difference	16.6 [13.2, 19.9]
Thompson W.W.	Serfling Model	9.5 [7.3, 11.7]
Thompson W.W.	Serfling-Poisson Model	10.1 [7.9, 12.3]
Thompson W.W	Time Series Analysis	11.4 [9.3, 13.4]
Thompson M.G	Serfling-Poisson Model	8.4 [6.8, 9.9]
1976-92 (Pneumonia & Influenza Mortality)		
Simonsen	Serfling Model	2.3 [1.5, 3.0]
Thompson W.W.	Serfling-Poisson Model	1.9 [1.3, 2.4]
Viboud	Serfling Model	1.9 [1.0, 2.7]
Thompson M.G	Serfling-Poisson Model	1.6 [1.2, 2.1]

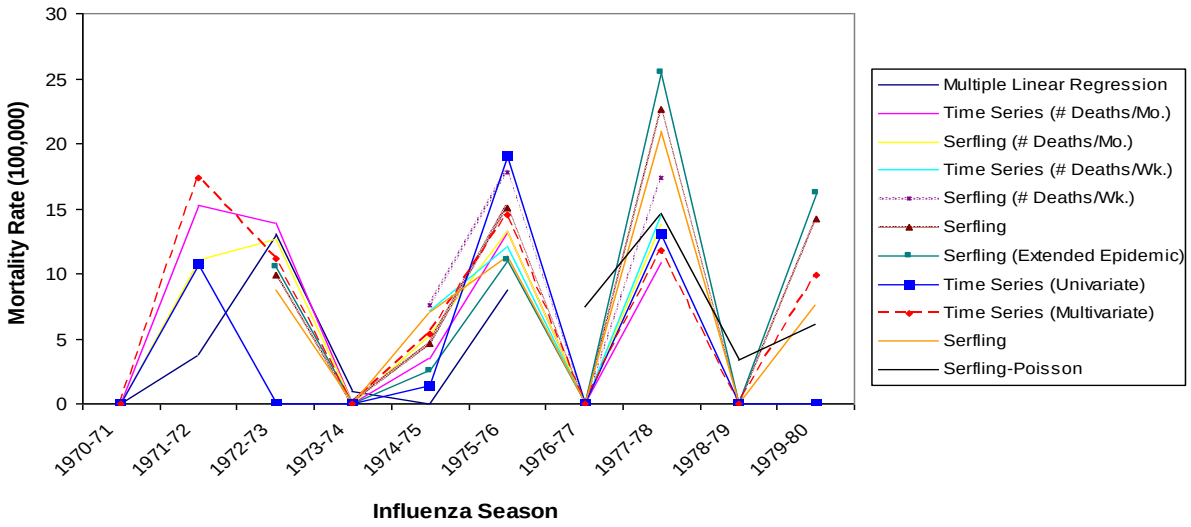


Figure 1. Influenza mortality rate estimates (per 100,000) by influenza season for all studies using models based on all-cause mortality to estimate mortality for the influenza seasons of 1970-80.

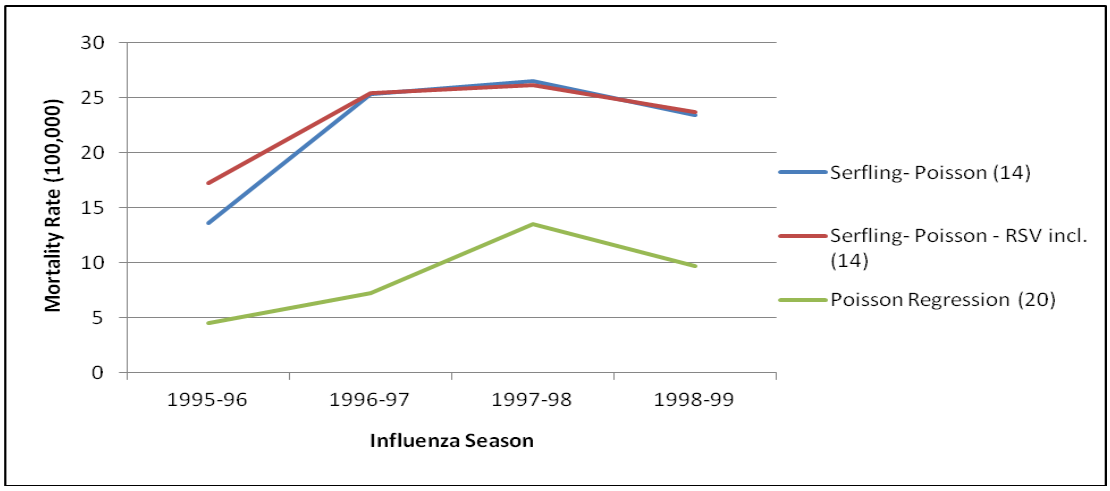


Figure 2. Influenza mortality rate estimates (per 100,000) by influenza season for studies using models based on all-cause mortality from 1995-1999

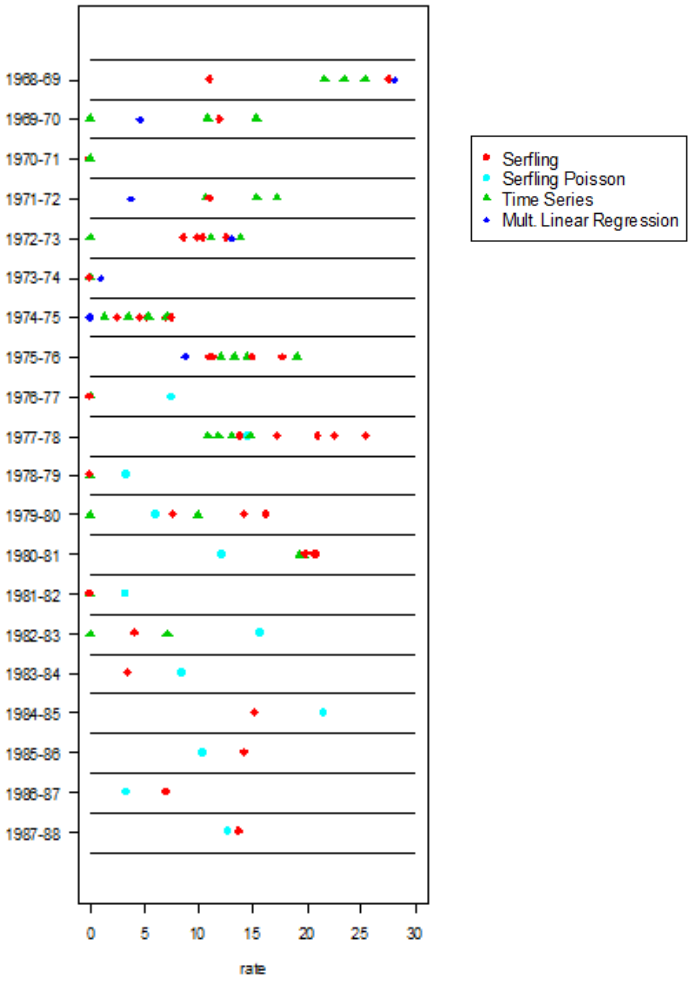


Figure 3. Estimates of Influenza mortality rate (per 100,000) based on all-cause mortality by method, 1968-88.

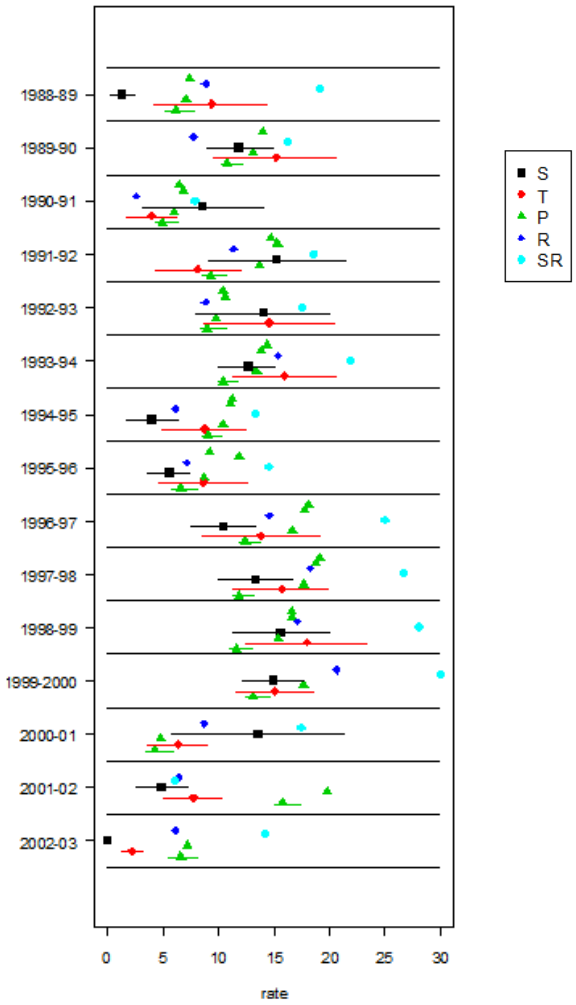


Figure 4. Estimates of influenza mortality rate (per 100,000) based on circulatory/respiratory mortality by method, 1988-2003; S=Serfling, T=time series, P=Serfling-Poisson, R=rate difference and SR=rate difference using summer season as the baseline.

Appendix 1 - Search Strategies

MEDLINE:

1. Influenza, Human/
2. exp Influenza A virus/ or Influenza B virus/
3. influenza.tw.
4. or/1-3
5. exp population surveillance/
6. surveillance.tw.
7. models, statistical/ or exp regression analysis/ or stochastic processes/
8. (statistical adj (model$ or method$)).tw.
9. regression.tw.
10. (time adj2 series).tw.
11. poisson distribution/
12. or/5-11
13. exp Mortality/
14. mortality.tw.
15. death$.tw.
16. r/13-15
17. 4 and 12 and 16
18. animals/ not humans/
19. 17 not 18

EMBASE:

1. influenza/ or exp influenza virus B/ or exp influenza virus A/
2. influenza.tw.
3. or/1-2
4. health survey/
5. surveillance.tw.
6. statistical model/
7. (statistical adj (model$ or method$)).tw.
8. regression.tw.
9. "regression analysis"/
10. poisson distribution/
11. (time adj2 series).tw.
12. "time series analysis"/
13. or/4-12
14. exp mortality/
15. mortality.tw.
16. death/ or "cause of death"/
17. death$.tw.
18. or/14-17
19. 3 and 13 and 18
20. animals/ not humans/
21. 19 not 20

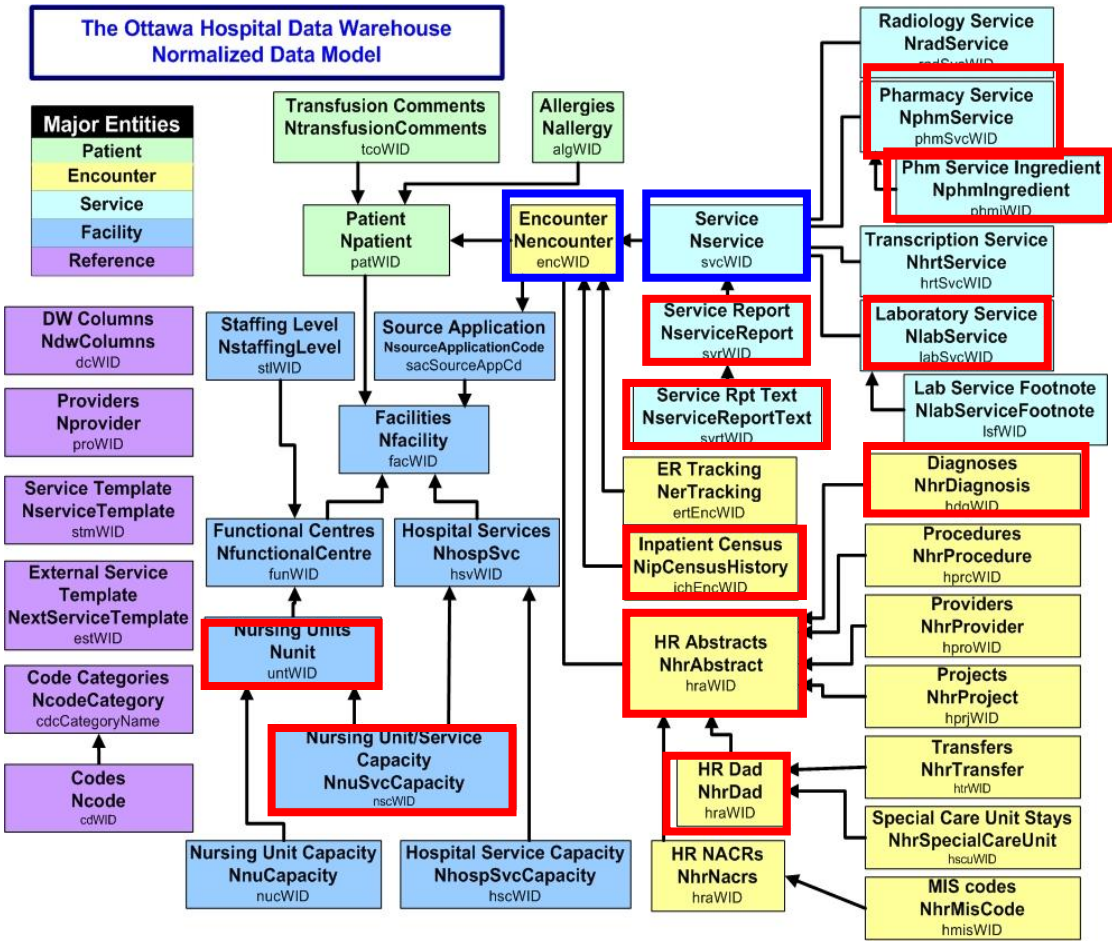
CINAHL:

S1 (MH "influenza")
S2 (MH "Influenza A Virus+")
S3 (MH "Influenza B Virus)
S4 TI influenza
S5 AB influenza
S6 S1 or S2 or S3 or S4 or S5
S7 (MH "Models, Statistical")
S8 (MH "Regression")
S9 (MH "Poisson Distribution")
S10 (MH "time series") or AB "time series" or TI "time series"
S11 TI regression or AB regression
S12 TI surveillance or AB surveillance
S13 (MH "mortality+") or TI mortality or AB mortality
S14 (MH "death+") or TI death or AB death
S15 S13 or S14
S16 (MH "Population Surveillance")
S17 S7 or S8 or S9 or S10 or S11 or S12 or S16
S18 S6 and S15 and S17

Global Health:

S1. SU "influenza" OR DE "Influenza A virus" OR DE "Influenza B virus"
S2. AB influenza or TI influenza
S3. S1 or S2
S4. DE "mortality"
S5. AB mortality or TI mortality
S6. DE "death" OR DE "causes of death"
S7. AB death$ or TI death$
S8. S4 or S5 or S6 or S7
S9. DE "regression analysis"
S10. AB regression or TI regression
S11. DE "time series"
S12. AB (time N2 series) or TI (time N2 series)
S13. AB poisson or TI poisson
S14. AB statistical model$ or TI statistical model$
S15. (ZU "statistical methods") or (ZU "statistical models")
S16. (ZU "surveillance systems")
S17. AB surveillance or TI surveillance
S18. S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S19. S3 and S8 and S18

Appendix B: Map of the Ottawa Hospital Data Warehouse (OHDW)



The nine data warehouse tables I used in this study with main tables outlined in blue and sub-tables outlined in red.

Appendix C: Description of OHDW Tables Used in Study

Table	Type	Unit of Analysis	Availability*	Study Use
Encounter	Main	One encounter per row (e.g. inpatient, ED, outpatient)	January 1999	Encounter WID used to extract data from Encounter sub-tables and to link to other main tables; Encounter Death Indicator used to identify deaths
HR Abstracts	Sub-table	One encounter per row corresponding to a record from the Discharge Abstract Database (DAD) or National Ambulatory Care Reporting System (NACRS)	April 1995	Obtain age, gender, admission date, discharge date, campus of stay, and length of stay of encounters in main cohort
HR DAD	Sub-table	One inpatient discharge per row (e.g. inpatient, rehab, day surgery)	April 1995	Obtain discharge disposition of encounters in main cohort
Inpatient Census	Sub-table	One inpatient transaction per row (e.g. transfer to ICU)	April 2004	Identify ICU admissions for encounters in main cohort
Diagnosis	Sub-table	One patient diagnosis per row corresponding to an encounter in HR Abstract (e.g. the admitting, most responsible and other diagnoses of a patient during one encounter)	April 1995	Obtain diagnosis data in order to identify those encounters with diagnoses of interest (circulatory/respiratory, influenza)
Service	Main	One service per row which is then further classified as radiology, pharmacy etc.	July 2002	Identify influenza laboratory tests conducted for the encounters in main cohort; Service WID used to extract data from Service sub-tables;
Pharmacy Service	Sub-table	One pharmacy order per row	June 2004	Identify encounters that were prescribed influenza antiviral medication
Phm Service Ingredient	Sub-table	One ingredient of a pharmacy order per row	June 2004	Identify encounters that were prescribed influenza antiviral medication
Laboratory Service	Sub-table	One lab order per row	July 2002	Obtain status of laboratory services conducted for encounters in main cohort
Service Report	Sub-table	One service report per row	July 2002	Obtain lab reports of influenza tests conducted for encounters in main cohort
Service Report Text	Sub-table	One line of text from a service report per row	July 2002	Identify positive influenza lab tests
Nursing Units	Sub-table	One nursing unit per row	April 2004	Identify nursing units for which I wanted to examine capacity
Nursing Units Capacity	Sub-table	Capacity information for one nursing unit on one day per row	April 2004	Examine the number of available ICU beds over time

*Date when data was available from both the General and Civic Campuses

Appendix D: ICD Codes Used to Apply Diagnosis Flags

Disease	ICD-9	ICD-10
Diseases of the Circulatory System	390-459	I00-I99
Diseases of the Respiratory System	460-519	J00-J99
Influenza	487-488	J09-J11

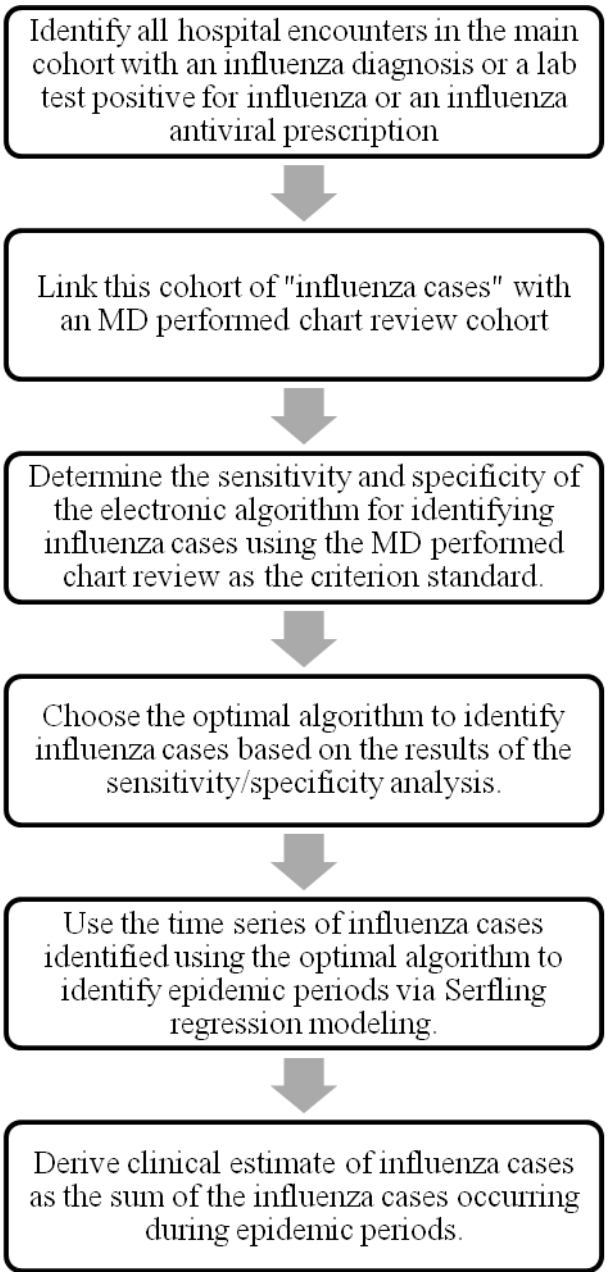
Appendix E: Text Algorithms Used to Identify Positive Influenza Lab Tests

```
data classified;
      set wrapped;
      year = year(datepart(labSpecimenDtm));
      if    find(upcase(report), 'INFLUENZA VIRUS TYPE A') > 0 or
            find(upcase(report), 'INFLUENZA A VIRUS') > 0 or
            find(upcase(report), 'INFLUENZA VIRUS TYPE B') > 0 or
            find(upcase(report), 'INFLUENZA B VIRUS') > 0
      then influenza = 1;
      else influenza = 0;

      if    find(upcase(report), 'INFLUENZA A VIRUS DETECTED') > 0 or
            find(upcase(report), 'INFLUENZA A VIRUS RNA DETECTED') > 0 or
            find(upcase(report), 'INFLUENZA VIRUS TYPE A DETECTED') > 0 or
            find(upcase(report), 'INFLUENZA VIRUS TYPE A RNA DETECTED') >0 or
            find(upcase(report), 'INFLUENZA B VIRUS DETECTED') > 0 or
            find(upcase(report), 'INFLUENZA B VIRUS RNA DETECTED') > 0 OR
            find(upcase(report), 'INFLUENZA VIRUS TYPE B DETECTED') > 0 or
            find(upcase(report), 'INFLUENZA VIRUS TYPE B RNA DETECTED') > 0
      then detected = 1;
      else detected = 0;

      if    find(upcase(report), 'INFLUENZA A VIRUS PRESENT') > 0 or
            find(upcase(report), 'INFLUENZA A VIRUS RNA PRESENT') > 0 or
            find(upcase(report), 'INFLUENZA VIRUS TYPE A PRESENT') > 0 or
            find(upcase(report), 'INFLUENZA VIRUS TYPE A RNA PRESENT') > 0 or
            find(upcase(report), 'INFLUENZA B VIRUS PRESENT') > 0 or
            find(upcase(report), 'INFLUENZA B VIRUS RNA PRESENT') > 0 OR
            find(upcase(report), 'INFLUENZA VIRUS TYPE B PRESENT') > 0 or
            find(upcase(report), 'INFLUENZA VIRUS TYPE B RNA PRESENT') > 0
      then PRESENT = 1;
      else PRESENT = 0;
```

Appendix F: The DINs and Keywords Used to Identify Antiviral Prescriptions

Drug Identification Number (DIN)	
DIN	**Drug**
01913999	Amantadine
01914006	Amantadine
01919288	Amantadine
01990403	Amantadine
02022826	Amantadine
02034468	Amantadine
02130963	Amantadine
02139200	Amantadine
02199289	Amantadine
02238306	Amantadine
02262649	Amantadine
02241472	Oseltamivir
02245549	Oseltamivir
02304848	Oseltamivir
02304856	Oseltamivir
02240863	Zanamivir
Keywords	
Adamantanes	
Amantadine	
Amantidine	
Oseltamivir	
Relenza	
Tamiflu	
Zanamivir	

Appendix G: Overview of Steps Used to Derive Clinical Estimates



Appendix H: Discharge Diagnoses Used to Screen Patients in the Chart Review

ICD-10 Code	Disease
J (all)	Diseases of the respiratory system (Chapter X)
A15-A19	Tuberculosis
A37	Whooping cough
A40	Streptococcal septicaemia
A41	Other septicaemia
A49	Bacterial infection of unspecified site
I26	Pulmonary embolism
I28	Other diseases of pulmonary vessels
I50	Heart failure
I51.4	Myocarditis, unspecified
R57	Shock not elsewhere classified

Appendix I: Modeling Steps – Defining Epidemic Periods

1) Create weekly "non-epidemic" time series of influenza activity indicator

I created a weekly time series of the number of influenza cases at TOH and then omitted the cases that occurred during peak periods of influenza virus circulation in the Ottawa region chosen via visual inspection of the FluWatch data.

2) Append sine and cosine terms to each week

$S1_t = SIN(2\pi t/52.167)$
$C1_t = COS(2\pi t/52.167)$

3) Fit Serfling regression equation to the "non-epidemic" time series

$Y_t = SIN(2\pi t/52.167) + COS(2\pi t/52.167)$

Where

Y_t = the number of influenza cases in week t

```
proc genmod data=tdat.flucases;
model y = S1 C1/  dist = normal;
output out=SerfPred p=predi resdev=devi lower=lowere upper=uppere;
run;
```

Model Information

Data Set	TDAT.FLUCASES
Distribution	Normal
Link Function	Identity
Dependent Variable	Y Y

Number of Observations Read	405
Number of Observations Used	284
Missing Values	121

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	281	193.0799	0.6871
Scaled Deviance	281	284.0000	1.0107
Pearson Chi-Square	281	193.0799	0.6871
Scaled Pearson X2	281	284.0000	1.0107
Log Likelihood		-348.1850	

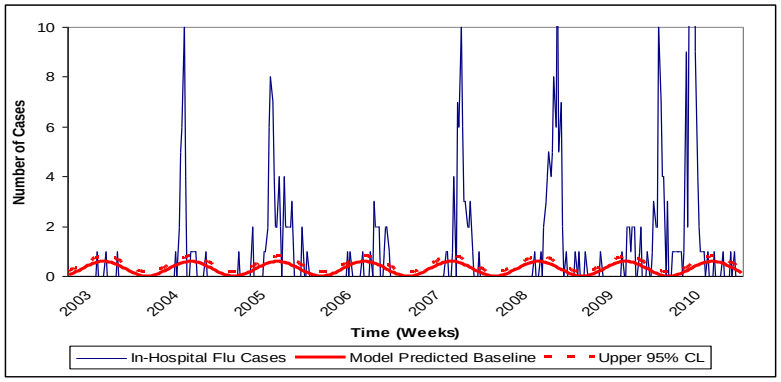
Analysis Of Parameter Estimates

Parameter	DF	Standard Estimate	Wald Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	0.2920	0.0520	0.1902	0.3938	31.58	<.0001
S1	1	0.1344	0.0669	0.0033	0.2656	4.04	0.0445
C1	1	-0.2623	0.0763	-0.4118	-0.1128	11.82	0.0006
Scale	1	0.8245	0.0346	0.7594	0.8952		

NOTE: The scale parameter was estimated by maximum likelihood.

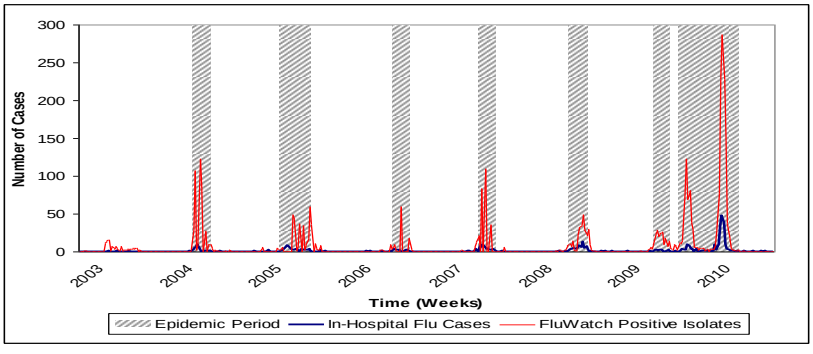
4) Use the predicted baseline to identify epidemic periods

I identified epidemic periods as starting when the number of influenza cases at TOH went above the 95% confidence interval of the predicted baseline for greater than 2 consecutive weeks and ending when they went below for the 95% confidence interval for greater than 2 consecutive weeks.



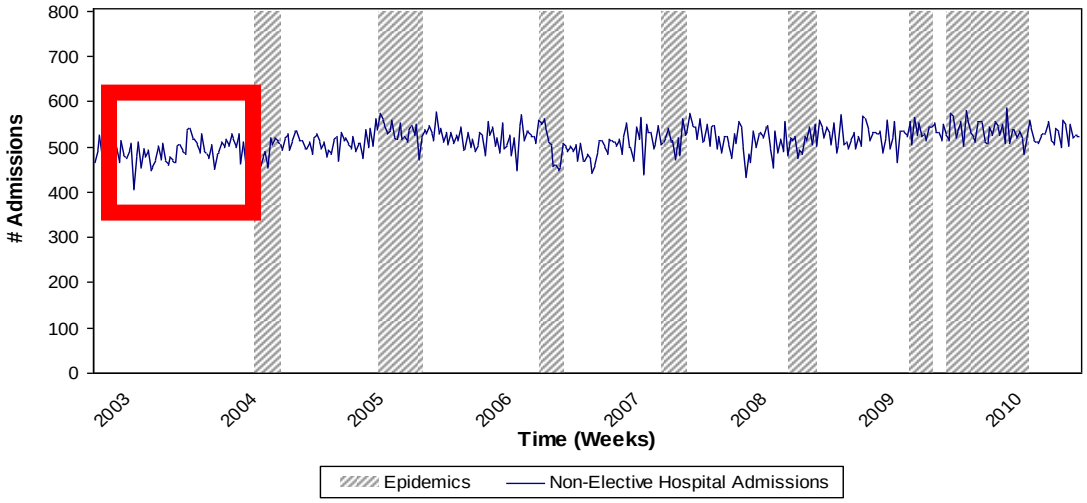
5) Examine new epidemic periods relative to indicators of influenza activity

Although the parameters in the Serfling model were significant, the fit of the model was not optimal (deviance statistic < 1). However, the epidemic periods defined using this method are consistent with influenza activity demonstrated via both the influenza cases at TOH and FluWatch data. I therefore felt confident using these epidemic periods in my analysis.



Appendix J: Modeling Steps – Derivation of Statistical Estimates

1) Take time series of first non-epidemic period Sept 1, 2002 to Dec 6, 2003 which consisted of 66 data points.



2) Append sine and cosine columns

```
data tdat.ModelAH;
      set tdat.ModelAllHosps;
S1=SIN(2*3.1415926*t/66);C1=COS(2*3.1415926*t/66);
S2=SIN(4*3.1415926*t/66);C2=COS(4*3.1415926*t/66);
S3=SIN(6*3.1415926*t/66);C3=COS (6*3.1415926*t/66);
S4=SIN(8*3.1415926*t/66);C4=COS (8*3.1415926*t/66);
S5=SIN(10*3.1415926*t/66);C5=COS (10*3.1415926*t/66);
S6=SIN(12*3.1415926*t/66);C6=COS (12*3.1415926*t/66);
t2=t*t;
run;
quit;
```

3) Run Proc Reg to regress the sine and cosine terms on the number of admissions. Start with all of the terms and determine which model fits best using R-square and the significance of the parameters.

```
proc reg data=tdat.fourier8;
model CRAdm = S1 C1 S2 C2 etc.  / SS1;
output out=out1 Predicted=P Residual=R;
run;
quit;
```

Model	Parameters Included	R-Square	Significant Parameters
1	S1 C1 S2 C2 S3 C3 S4 C4 S5 C5 S6 C6	0.35	I* S1 C4
2	S1 C1 S2 C2 S3 C3 S4 C4 S5 C5	0.35	I* S1 C4
3	S1 C1 S2 C2 S3 C3 S4 C4	0.32	I* S1 C4
4	S1 C1 S2 C2 S3 C3	0.18	I* S1
5	S1 C1 S2 C2	0.15	I* S1
6	S1 C1	0.12	I* S1
7	S1 C1 S4 C4	0.25	I* S1 C4

*I=Intercept

I chose to use model 7. Below is the output for 7 to show how I derived the model.

The REG Procedure
Model: MODEL7
Dependent Variable: Hosps Hosps

Number of Observations Read 66
Number of Observations Used 66

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	10088	2521.90644	5.20	0.0011
Error	61	29591	485.09232		
Corrected Total	65	39678			

Root MSE	22.02481	R-Square	0.2542
Dependent Mean	490.56061	Adj R-Sq	0.2053
Coeff Var	4.48972		

Parameter Estimates

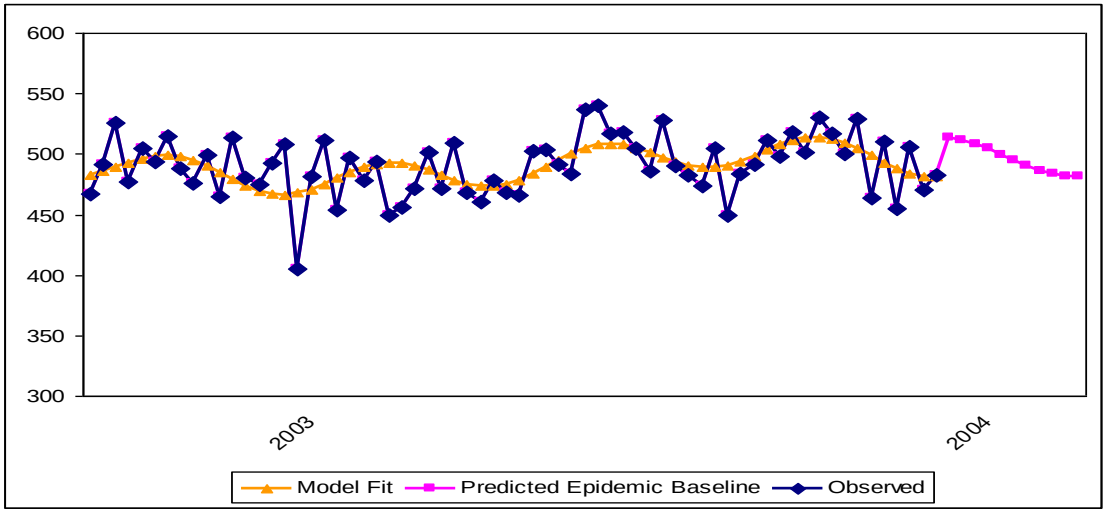
Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	490.56061	2.71107	180.95	<.0001
S1		1	-11.32345	3.83403	-2.95	0.0045
C1		1	3.25950	3.83403	0.85	0.3986
S4		1	4.09888	3.83403	1.07	0.2892
C4		1	-12.24908	3.83403	-3.19	0.0022

MODEL

HospAdm = 490.56061-11.32345SIN((2*3.14*t)/N)+ 3.25950COS((2*3.14*t)/N)
+4.09888SIN((8*3.14*t)/N)-12.24908COS((8*3.14*t)/N)

t= Observation Number (week)
N= Total # of Observations (weeks)

4) Use this model to predict the number of admissions for the first epidemic period of 11 weeks (Dec 7, 2003 to Feb 15, 2004).



5) Apply an ARIMA model to the new time series of 117 weeks which runs from Sep 1 2002 to Nov 1, 2004 as follows:

- **66 weeks observed non-epidemic data**
- **11 weeks model 7 predicted data from step 4**
- **40 weeks of real non-epidemic data**

STEP1: Determine if ARIMA model is appropriate

```
proc autoreg data=tdat.ARIMA_AH;
 model Hosps = /dw=5 dwprob;
run;
```

Durbin-Watson Statistics

Order	DW	Pr < DW	Pr > DW
1	1.6058	0.0155	0.9845
2	1.2986	<.0001	0.9999
3	1.4119	0.0011	0.9989
4	1.4913	0.0059	0.9941
5	1.7354	0.1435	0.8565

Significant at fist four lags (Pr<DW testing for positive autocorrelation) which provides evidence of autocorrelation in the error terms

```
proc arima data=tdat.ARIMA_AH;
 identify var=Hosps;
run;
```

```
Autocorrelation Check for White Noise

 To      Chi-          Pr >
Lag     Square   DF   ChiSq    ---------Autocorrelations-------

  6     25.91     6   0.0002   0.178   0.300   0.237   0.180   0.057   0.002
 12     30.72    12   0.0022   0.109   0.023   0.069   0.055   0.087   0.096
 18     45.62    18   0.0003   0.249   0.106   0.079   0.144   0.096  -0.024
 24     47.76    24   0.0027  -0.005   0.056  -0.015  -0.009   0.021   0.103
```

The null hypothesis of this test is that the series is white noise. The ChiSq statistic (aka the Ljung-Box statistic) is significant at all lags indicating that the series is not white noise.

STEP2: Check to see if time series is stationary

```
proc arima data=tdat.ARIMA_AH;
 identify var=Hosps stationarity = (adf = (1))outcov=ADF;
run;
```

```
Augmented Dickey-Fuller Unit Root Tests

Type          Lags    Rho      Pr < Rho    Tau     Pr < Tau     F      Pr > F

Zero Mean      1     0.0793     0.6995     0.24    0.7534
Single Mean    1    -48.6812    0.0010    -4.61    0.0003     10.72    0.0010
Trend          1    -70.9501    0.0004    -5.67    <.0001     16.14    0.0010
```

The null hypothesis of the Tau test is that the series has a trend (is non-stationary); the p-value for trend is less than 0.05 therefore we can reject the null hypothesis i.e. this time series does NOT have a trend and we do not need to difference.

STEP3: Try different models to determine what AR MA processes to use

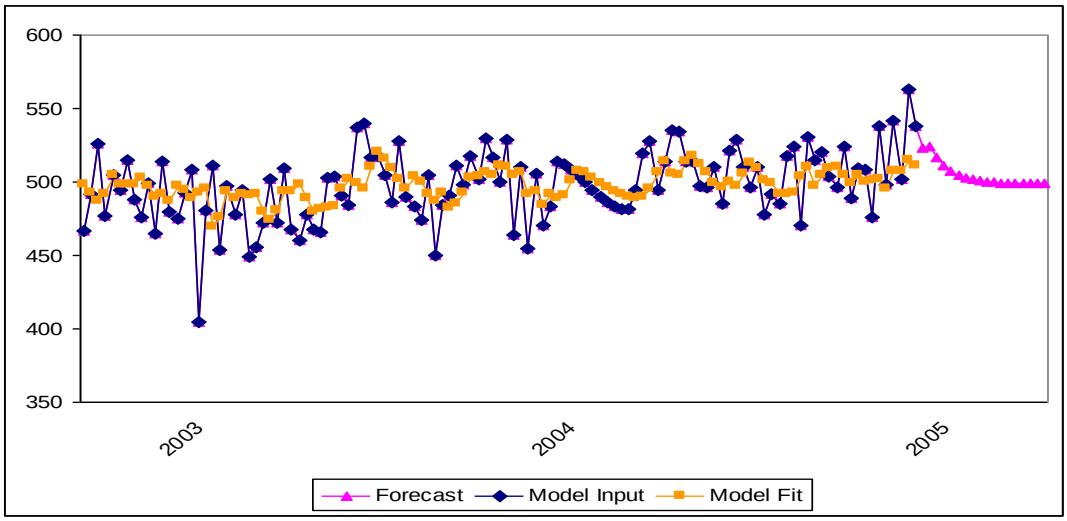
Model	Processes Incl.	Significant Parameters	AIC	LBQ* Stat: P > 0.05
8	AR(1)	ALL	1075	Not all lags
9	AR(2)	MU; AR2	1066	All lags
10	MA(1)	MU	1076	Not all lags
11	MA(2)	MU; MA2	1071	Not all lags
12	AR(1) MA(1)	ALL	1066	All lags
13	AR(2) MA(1)	MU; AR1; AR2	1065	All lags
14	AR(1) MA(2)	ALL	1063	All lags

* LBQ statistic for the 'autocorrelation check of the residuals'; all lags should be Insignificant i.e. residuals=white noise.

Based on the significance of the parameters, the AIC and the autocorrelation check of the residuals model 14 is the best fit.

STEP4: Forecast forward with model 14

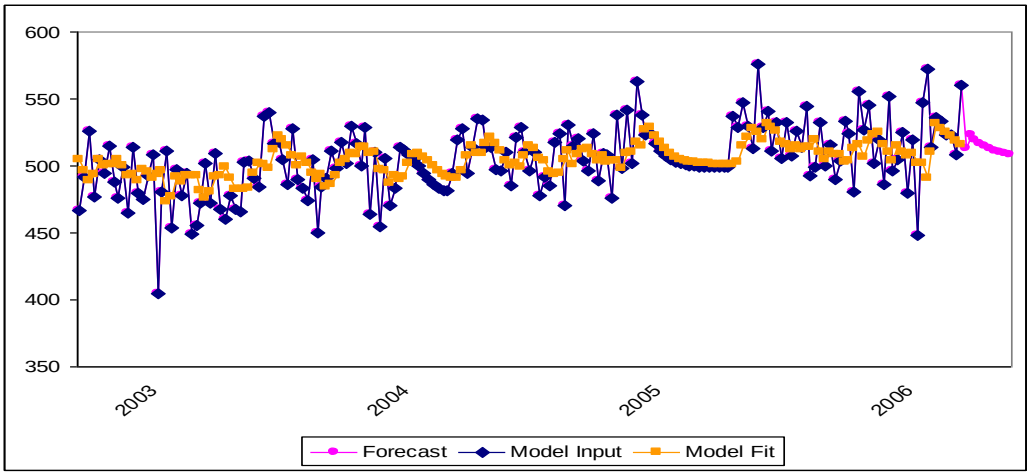
```
proc arima data=tdat.ARIMA_AH2;
 identify var=hosps noprint;
 estimate p=1 q=2 method=ml noprint;
 Forecast lead=10 out=AH_Forecast;
run;
quit;
```



8) Take new time series with model 12 predicted data points added and the next non-epidemic period and apply ARIMA model for next forecast. Steps 1 & 2 omitted for simplicity.

Model	Processes Incl.	Significant Parameters	AIC	LBQ* Stat: P > 0.05
15	AR(1)	ALL	1693	Not all lags
16	AR(2)	ALL	1670	Not all lags
17	MA(1)	MU	1697	Not all lags
18	MA(2)	MU; MA2	1683	Not all lags
19	AR(1) MA(1)	ALL	1668	Not all lags
20	AR(1) MA(2)	ALL	1663	All lags

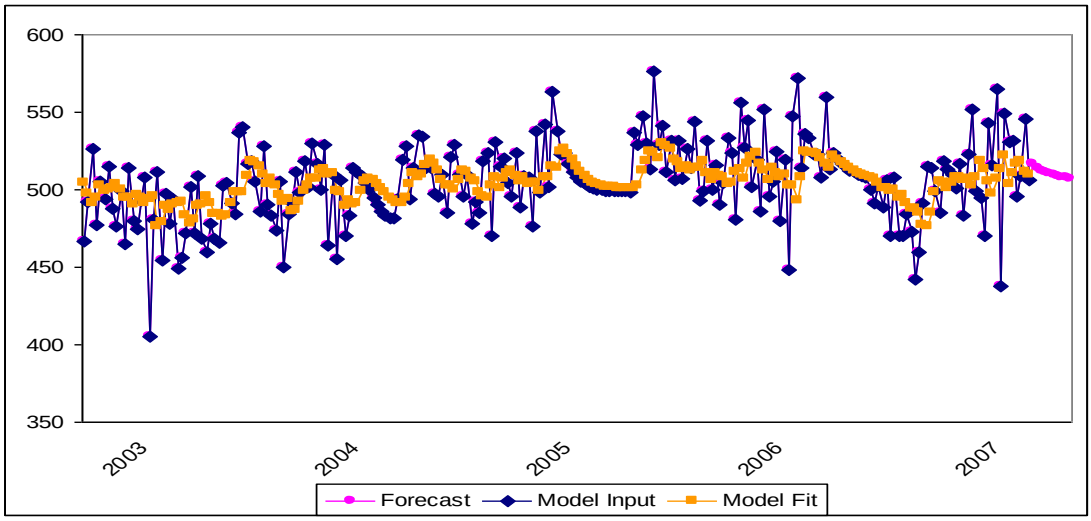
```
proc arima data=tdat.ARIMA_AH2;
 identify var=hosps noprint;
 estimate p=1 q=2 method=ml noprint;
 Forecast lead=18 out=AH_Forecast;
run;
quit;
```



9) Take new time series with model 20 predicted data points and the next non-epidemic period and apply ARIMA model for next forecast

Model	Processes Incl.	Significant Parameters	AIC	LBQ* Stat: P > 0.05
21	AR(1) MA(1)	ALL	2131	Not all lags
22	AR(1) MA(2)	ALL	2125.2	All lags
23	AR(2) MA(1)	ALL	2125.4	All lags
24	AR(2) MA(2)	MU	2127	Not all lags

```
proc arima data=tdat.ARIMA_AH3;
 identify var=hosps noprint;
 estimate p=1 q=2 method=ml noprint;
 Forecast lead=10 out=AH_Forecast3;
run;
quit;
```

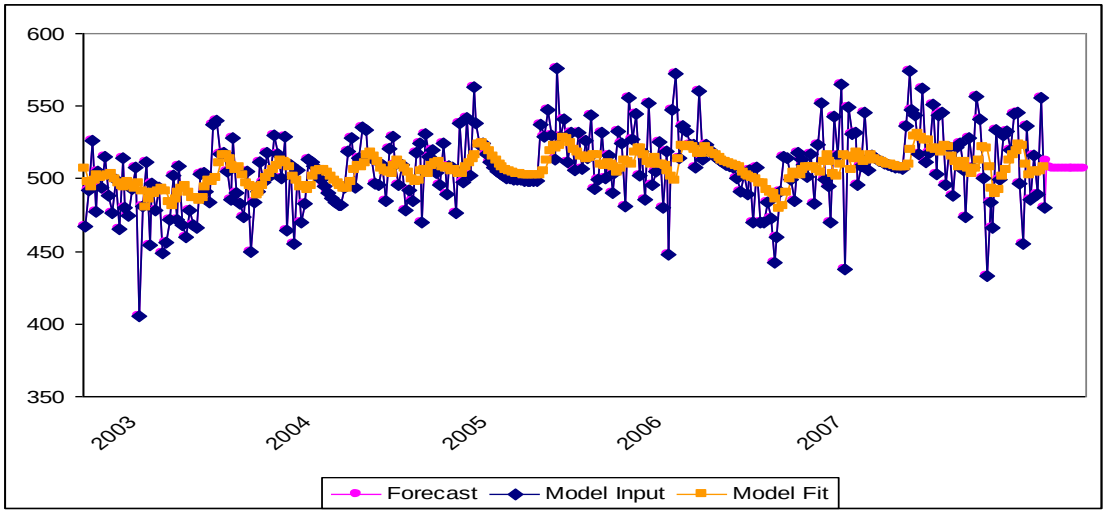


9) Take new time series with model 22 predicted data points and the next non-epidemic period and apply ARIMA model for next forecast

Model	Processes Incl.	Significant Parameters	AIC	LBQ* Stat: P > 0.05
25	AR(1) MA(1)	All	2628	Not all lags
26	AR(1) MA(2)	All	2626	All lags
27	AR(2) MA(1)	All	2625	All lags
28	AR(2) MA(2)	MU; AR2	2625	All lags

Model 26 chosen here because the values of the chi square statistic were higher.

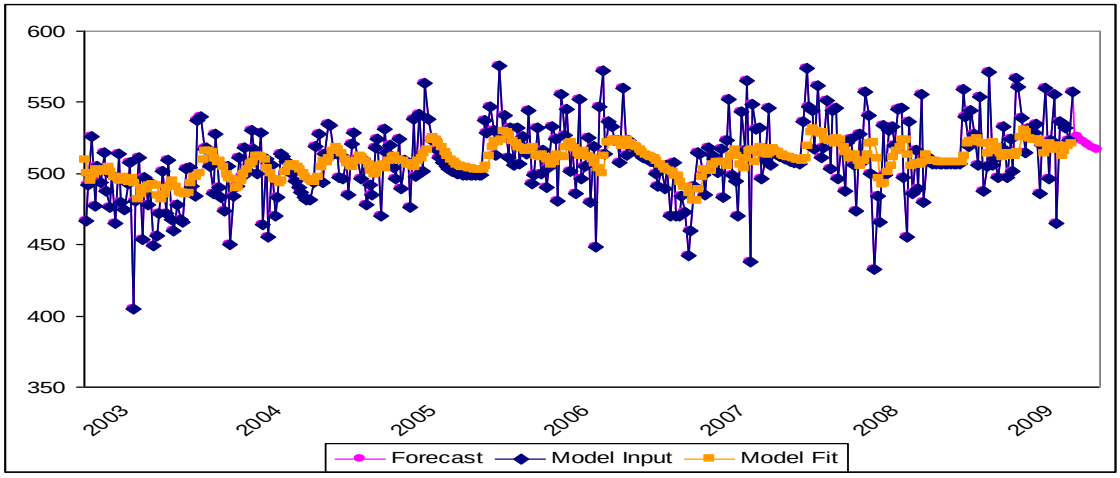
```
proc arima data=tdat.ARIMA_AH4;
 identify var=hosps noprint;
 estimate p=1 q=2 plot method=ml;
run;
quit;
```



10) Take new time series with model 26 predicted data points and the next non-epidemic period and apply ARIMA model for next forecast

Model	Processes Incl.	Significant Parameters	AIC	LBQ* Stat: P > 0.05
29	AR(1) MA(1)	ALL	3087	All lags
30	AR(1) MA(2)	ALL	3085	All lags
31	AR(2) MA(1)	ALL	3085	All lags
32	AR(2) MA(2)	MU	3086	All lags

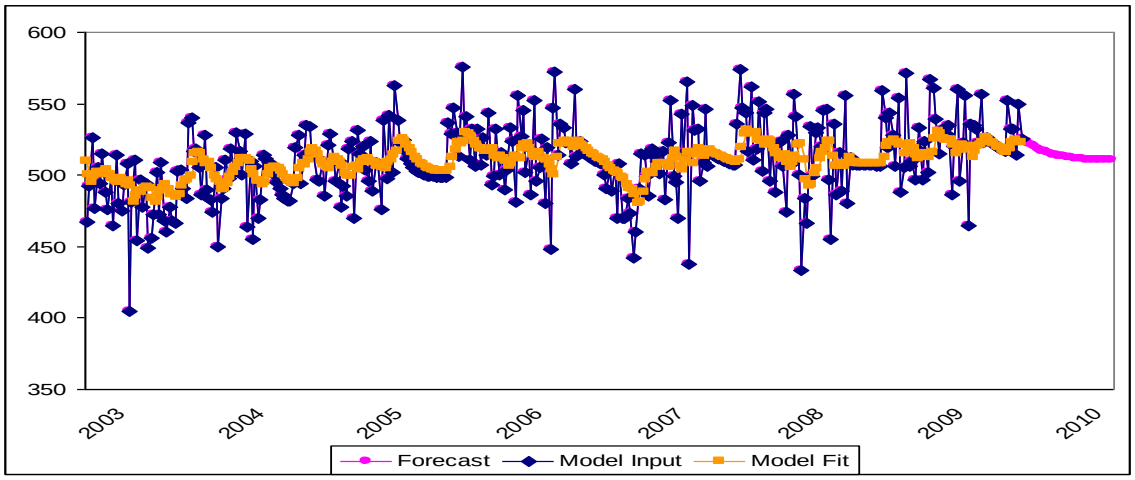
```
proc arima data=tdat.ARIMA_AH5;
 identify var=hosps noprint;
 estimate p=1 q=2 method=ml noprint;
 Forecast lead=9 out=AH_Forecast5;
run;
quit;
```



11) Take new time series with model 30 predicted data points and the next non-epidemic period and apply ARIMA model for next forecast

Model	Processes Incl.	Significant Parameters	AIC	LBQ* Stat: P > 0.05
33	AR(1) MA(1)	ALL	3214	ALL
34	AR(1) MA(2)	ALL	3212	ALL
35	AR(2) MA(1)	ALL	3212	ALL
36	AR(2) MA(2)	MU	3213	ALL

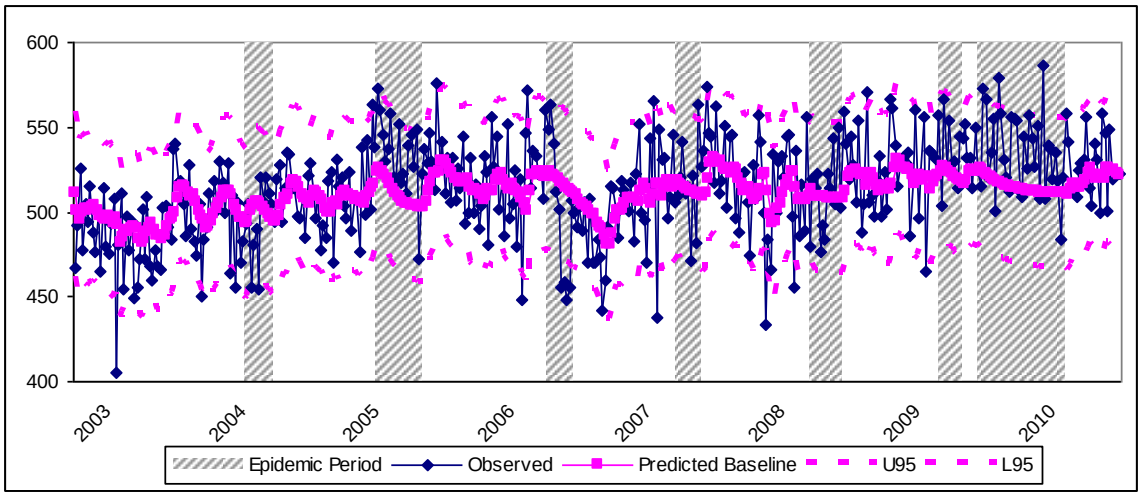
```
proc arima data=tdat.ARIMA_AH6;
 identify var=hosps noprint;
 estimate p=1 q=2 method=ml noprint;
 Forecast lead=34 out=AH_Forecast6;
run;
quit;
```



12) Model the complete non-epidemic time series to get the final model

Model	Processes Incl.	Significant Parameters	AIC	LBQ* Stat: P > 0.05
33	AR(1) MA(1)	ALL	3675	ALL
34	AR(1) MA(2)	ALL	3673	ALL
35	AR(2) MA(1)	ALL	3672	ALL
36	AR(2) MA(2)	MU	3694	ALL

```
proc arima data=tdat.ARIMA_AH7;
 identify var=hosps;
 estimate p=1 q=2 method=ml noprint;
 forecast out=AH_final;
run;
quit;
```



Appendix K: Modeling Steps – Association between Outcomes and Epidemics

```
/*****************************************************************
CROSSCOR CHECK: HOSPITAL ADMISSIONS AGAINST EPIDEMICS;
ADMISSIONS = # of non-elective admissions/week;
EPIDEMIC = 0 or 1 based on examination of indicator of influenza
activity
*****************************************************************/

proc autoreg data=tdat.crosscorcheck;
 model ADM = /dw=5 dwprob;
run;
```

```
Durbin-Watson Statistics

Order            DW     Pr < DW     Pr > DW

  1          1.4354      <.0001      1.0000
  2          1.2102      <.0001      1.0000
  3          1.3993      <.0001      1.0000
  4          1.3770      <.0001      1.0000
  5          1.4835      <.0001      1.0000
NOTE: Pr<DW is the p-value for testing positive autocorrelation, and Pr>DW is the p-value
for testing negative autocorrelation.
```

H_0: The error terms are not auto-correlated

Significant at all lags (Pr<DW testing for positive autocorrelation); therefore, there is some autocorrelation present in the error terms

```
proc arima data=tdat.crosscorcheck;
 identify var=ADM nlag=12;
run;
quit;
```

```
The ARIMA Procedure

      Name of Variable = ADM

Mean of Working Series    514.1506
Standard Deviation        28.89999
Number of Observations         405


                                    Autocorrelations

Lag    Covariance    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1      Std
Error

  0       835.209        1.00000    |                    |********************|
0
  1       232.951        0.27891    |                  . |******              |
0.049690
```

```
  2       326.306        0.39069    |                   . |********           |
0.053416
  3       247.001        0.29574    |                   . |******             |
0.060059
  4       254.601        0.30484    |                   .  |******            |
0.063553
  5       208.527        0.24967    |                   .  |*****             |
0.067066
  6       237.073        0.28385    |                   .  |******            |
0.069323
  7       174.431        0.20885    |                   .  |****              |
0.072136
  8       188.964        0.22625    |                   .  |*****             |
0.073613
  9       206.457        0.24719    |                   .  |*****             |
0.075311
 10       197.831        0.23686    |                   .  |*****             |
0.077288
 11       183.785        0.22005    |                   .  |****              |
0.079060
 12       170.063        0.20362    |                   .  |****              |
0.080558

"." marks two standard errors

                    Inverse Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1       -0.01972    |                  . | .                  |
  2       -0.18481    |                ****| .                  |
  3       -0.07134    |                  .*| .                  |
  4       -0.05253    |                  .*| .                  |
  5       -0.01567    |                  . | .                  |
  6       -0.05531    |                  .*| .                  |
  7        0.04423    |                  . |*.                  |
  8        0.02014    |                  . | .                  |
  9       -0.05495    |                  .*| .                  |
 10       -0.05054    |                  .*| .                  |
 11       -0.02809    |                  .*| .                  |
 12       -0.00676    |                  . | .                  |

Partial Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1        0.27891    |                  . |******              |
  2        0.33929    |                  . |*******             |
  3        0.15821    |                  . |***                 |
  4        0.12684    |                  . |***                 |
  5        0.05771    |                  . |*.                  |
  6        0.09945    |                  . |**                  |
  7        0.01273    |                  . | .                  |
  8        0.03084    |                  . |*.                  |
  9        0.08858    |                  . |**                  |
 10        0.06466    |                  . |*.                  |
 11        0.03216    |                  . |*.                  |
```

```
 12        0.00744     |                  . | .                  |
```

Autocorrelation Check for White Noise

To Lag	Chi-Square	DF	Pr > ChiSq	Autocorrelations				
6	227.20	6	<.0001	0.279	0.391	0.296	0.305	0.250
0.284								
12	353.01	12	<.0001	0.209	0.226	0.247	0.237	0.220
0.204								

H_0: none of the autocorrelation of the series up to a given lag is significantly different from 0

We can reject the white noise hypothesis.

```
proc arima data=tdat.crosscorcheck;
 identify var=ADM stationarity = (adf = (1))outcov=ADF;
run;
```

Augmented Dickey-Fuller Unit Root Tests

Type	Lags	Rho	Pr < Rho	Tau	Pr < Tau	F	Pr > F
Zero Mean	1	-0.1693	0.6441	-0.24	0.5992		
Single Mean	1	-143.659	0.0001	-8.48	<.0001	35.98	0.0010
Trend	1	-197.452	0.0001	-9.89	<.0001	48.91	0.0010

H_0 (Tau test): the series has a trend (is non-stationary).

The first p-value is greater than 0.05 indicating that we may need to difference the data. However, this is for a model that assumes a zero mean. My data visually don't show a trend and the ACF and PACF don't indicate a need to difference.

```
proc arima data=tdat.crosscorcheck;
 identify var=ADM crosscor=(epidemic) noprint;
 estimate input=(epidemic) p=2 q=1 plot method=ml;
run;
quit;
```

Maximum Likelihood Estimation

Parameter	Estimate	Standard Error	t Value	Approx Pr > |t|	Lag	Variable	Shift
MU	514.14050	5.59614	91.87	<.0001	0	ADM	0
MA1,1	0.74086	0.06013	12.32	<.0001	1	ADM	0
AR1,1	0.81473	0.07449	10.94	<.0001	1	ADM	0
AR1,2	0.12770	0.06067	2.10	0.0353	2	ADM	0

```
NUM1           -1.72321       4.25544       -0.40       0.6855        0    Epidemic         0

Constant Estimate      29.59872
Variance Estimate      649.7838
Std Error Estimate     25.49086
AIC                    3777.996
SBC                    3798.015
Number of Residuals         405


                Correlations of Parameter Estimates

Variable                ADM       ADM       ADM       ADM   Epidemic
Parameter                MU     MA1,1     AR1,1     AR1,2      NUM1

ADM            MU     1.000     0.030     0.026    -0.000    -0.188
ADM         MA1,1     0.030     1.000     0.748    -0.574    -0.008
ADM         AR1,1     0.026     0.748     1.000    -0.938     0.001
ADM         AR1,2    -0.000    -0.574    -0.938     1.000    -0.044
Epidemic     NUM1    -0.188    -0.008     0.001    -0.044     1.000



Autocorrelation Check of Residuals

 To        Chi-             Pr >
Lag      Square     DF     ChiSq    --------------------Autocorrelations-----------------
---

  6        3.01      3    0.3895     0.007     0.055    -0.033    -0.011    -0.055
0.006
 12        6.37      9    0.7029    -0.077    -0.036     0.018     0.019     0.002    -
0.013
 18       13.22     15    0.5853     0.004    -0.060     0.034    -0.014     0.104    -
0.021
 24       18.77     21    0.6001     0.055     0.017     0.090    -0.032    -0.021
0.000
 30       26.43     27    0.4947    -0.012    -0.098     0.048    -0.064    -0.031    -
0.022
 36       29.32     33    0.6509     0.030     0.012     0.064    -0.015     0.023
0.024
 42       31.98     39    0.7798    -0.015     0.019     0.010     0.030    -0.013
0.064
 48       35.94     45    0.8306    -0.047     0.013    -0.005     0.074     0.028
0.003
```

Here the AR(2) MA(1) is the best model fit given the significance of the AR and MA terms and the insignificance of the Chi-square statistic in the autocorrelation check of the residuals. The P(1) and MA(1) also showed signs of being a good fit but the AIC was slightly better for the AR(2) MA(1) model (3779 vs. 3778) and the chi-square statistics in the AC check of the residuals were larger with the AR(2) MA(1) model as well. Based on this model fit, epidemics were associated with a decrease of approximately 1.7 hospital admissions per week but this association was not significant.

```
/*************************************************************
CROSSCOR CHECK: ALL IN-HOSPITAL DEATHS AGAINST EPIDEMICS;
DEATHS = # of deaths/week;
EPIDEMIC = 0 or 1 based on examination of indicator of influenza
activity
*************************************************************/

proc autoreg data=tdat.crosscorcheck;
 model Death = /dw=5 dwprob;
run;
```

```
      Durbin-Watson Statistics

Order             DW     Pr < DW     Pr > DW

  1           1.9676      0.3720      0.6280
  2           1.7442      0.0056      0.9944
  3           2.0562      0.7472      0.2528
  4           1.7957      0.0279      0.9721
  5           1.8525      0.0990      0.9010
```

Significant autocorrelation of the error terms present

```
proc arima data=tdat.crosscorcheck;
 identify var=death nlag=10;
run;
quit;
```

```
Name of Variable = Death

Mean of Working Series    32.42469
Standard Deviation        5.858191
Number of Observations         405


Autocorrelations

Lag    Covariance    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1      Std
Error

  0     34.318403        1.00000    |                    |********************|
0
  1      0.485554        0.01415    |                    . | .                  |
0.049690
  2      4.268873        0.12439    |                    . |**                  |
0.049700
  3     -1.086079        -.03165    |                   .*| .                  |
0.050463
  4      3.295210        0.09602    |                    . |**                  |
0.050512
  5      1.943574        0.05663    |                    . |*.                  |
0.050961
  6      1.214124        0.03538    |                    . |*.                  |
0.051116
```

```
  7      3.696142        0.10770    |                  . |**                  |
0.051176
  8      2.754956        0.08028    |                  . |**                  |
0.051733
  9      1.603082        0.04671    |                  . |*.                  |
0.052040
 10     -0.398107        -.01160    |                  . | .                  |
0.052143
 11      0.419780        0.01223    |                  . | .                  |
0.052150
 12      2.042978        0.05953    |                  . |*.                  |
0.052157

Inverse Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1       -0.00209    |                  . | .                  |
  2       -0.09759    |                 **| .                  |
  3        0.06400    |                  . |*.                  |
  4       -0.06875    |                 .*| .                  |
  5       -0.03869    |                 .*| .                  |
  6       -0.00039    |                  . | .                  |
  7       -0.08731    |                 **| .                  |
  8       -0.06747    |                 .*| .                  |
  9       -0.01972    |                  . | .                  |
 10        0.03572    |                  . |*.                  |
 11        0.00808    |                  . | .                  |
 12       -0.04219    |                 .*| .                  |

Partial Autocorrelations
Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1        0.01415    |                  . | .                  |
  2        0.12421    |                  . |**                  |
  3       -0.03550    |                 .*| .                  |
  4        0.08295    |                  . |**                  |
  5        0.06327    |                  . |*.                  |
  6        0.01121    |                  . | .                  |
  7        0.10221    |                  . |**                  |
  8        0.07150    |                  . |*.                  |
  9        0.01385    |                  . | .                  |
 10       -0.02761    |                 .*| .                  |
 11       -0.00800    |                  . | .                  |
 12        0.04392    |                  . |*.                  |
```

```
                          Autocorrelation Check for White Noise

 To        Chi-              Pr >
Lag      Square     DF     ChiSq    --------------------Autocorrelations-----------------
---

  6       12.45      6    0.0527     0.014     0.124    -0.032     0.096     0.057
0.035
 12       22.44     12    0.0328     0.108     0.080     0.047    -0.012     0.012
0.060
```

The series is not white noise and the autocorrelation plots do not suggest the need to difference.

```
proc arima data=tdat.crosscorcheck;
 identify var=Death stationarity = (adf = (1))outcov=ADF;
run;
```

```
Augmented Dickey-Fuller Unit Root Tests

Type         Lags     Rho     Pr < Rho     Tau     Pr < Tau    F     Pr > F

Zero Mean      1    -3.6842    0.1869    -1.36    0.1620
Single Mean    1    -308.531   0.0001    -12.38   <.0001     76.59  0.0010
Trend          1    -314.267   0.0001    -12.47    <.0001    77.79  0.0010
```

No differencing required here based on ADF TAU test results.

```
proc arima data=tdat.crosscorcheck;
 identify var=death crosscor=(epidemic) noprint;
 estimate input=(epidemic) p=1 q=1 plot method=ml;
run;
quit;
```

```
Maximum Likelihood Estimation

                            Standard                 Approx
Parameter      Estimate         Error    t Value    Pr > |t|     Lag    Variable     Shift

MU             32.15270       0.44011      73.06      <.0001       0    Death            0
MA1,1           0.84038       0.16835       4.99      <.0001       1    Death            0
AR1,1           0.88304       0.14649       6.03      <.0001       1    Death            0
NUM1            1.08479       0.77097       1.41      0.1594       0    Epidemic         0


Constant Estimate      3.760622
Variance Estimate      34.00692
Std Error Estimate     5.831545
AIC                    2581.607
SBC                    2597.622
Number of Residuals         405



Correlations of Parameter Estimates

Variable              Death     Death     Death  Epidemic
Parameter                MU     MA1,1     AR1,1      NUM1

Death          MU      1.000     0.057     0.069    -0.448
Death       MA1,1      0.057     1.000     0.987    -0.066
Death       AR1,1      0.069     0.987     1.000    -0.089
Epidemic     NUM1     -0.448    -0.066    -0.089     1.000
```

Autocorrelation Check of Residuals

To Lag	Chi-Square	DF	Pr > ChiSq	Autocorrelations					
6	7.88	4	0.0961	-0.050	0.074	-0.094	0.048	0.011	-0.007
12	12.25	10	0.2684	0.070	0.042	0.013	-0.044	-0.010	0.042
18	15.91	16	0.4591	-0.005	-0.069	0.012	-0.055	0.027	-0.004
24	17.36	22	0.7432	0.020	-0.016	-0.010	-0.009	-0.049	-0.011
30	28.99	28	0.4128	0.013	-0.032	0.083	-0.121	-0.005	-0.062
36	32.39	34	0.5466	-0.009	0.055	0.050	-0.024	0.033	-0.020
42	34.96	40	0.6963	-0.062	-0.024	-0.026	-0.021	0.008	0.008
48	43.72	46	0.5682	-0.074	0.012	-0.020	0.058	-0.087	0.046

I picked the AR(1) MA(1) as the best model fit given the significance of the AR and MA terms and the insignificance of the Chi-square statistic in the autocorrelation check of the residuals. Based on this model fit, epidemics were associated with an increase of approximately 1 death per week but this association was not significant.

```
/*****************************************************************
CROSSCOR CHECK: CR DEATHS AGAINST EPIDEMICS;
CR DEATHS = # of deaths/week in those with a circ/resp MRDX
EPIDEMIC = 0 or 1 based on examination of indicator of influenza
activity
*****************************************************************/

proc autoreg data=tdat.crosscorcheck;
 model CRDeath = /dw=5 dwprob;
run;
```

Durbin-Watson Statistics

Order	DW	Pr < DW	Pr > DW
1	1.7603	0.0077	0.9923
2	1.9120	0.2014	0.7986
3	1.7892	0.0212	0.9788

```
  4          1.7968      0.0286      0.9714
  5          1.8685      0.1302      0.8698
```

Significant autocorrelation present at the first, third and fourth lags

```
proc arima data=tdat.crosscorcheck;
 identify var=crdeath nlag=12;
run;
```

```
Name of Variable = CRDeath

Mean of Working Series    12.51605
Standard Deviation        3.510529
Number of Observations         405


                                    Autocorrelations

Lag    Covariance    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1      Std
Error

  0     12.323816        1.00000    |                   |********************|
0
  1      1.466369        0.11899    |                   . |**                  |
0.049690
  2      0.479252        0.03889    |                   . |*.                  |
0.050389
  3      1.220451        0.09903    |                   . |**                  |
0.050463
  4      1.148030        0.09316    |                   . |**                  |
0.050941
  5      0.570070        0.04626    |                   . |*.                  |
0.051360
  6      1.605096        0.13024    |                   . |***                 |
0.051462
  7      1.504320        0.12207    |                   . |**                  |
0.052270
  8      1.238270        0.10048    |                   . |**                  |
0.052969
  9      1.241276        0.10072    |                   . |**                  |
0.053438
 10      0.061963        0.00503    |                   . | .                  |
0.053904
 11      0.794876        0.06450    |                   . |*.                  |
0.053905
 12      0.349695        0.02838    |                   . |*.                  |
0.054096

"." marks two standard errors

Inverse Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1       -0.07165    |                  .*| .                  |
  2        0.03285    |                  . |*.                  |
  3       -0.04175    |                  .*| .                  |
  4       -0.05355    |                  .*| .                  |
```

```
  5        0.01666    |                    . | .                    |
  6       -0.09577    |                   **| .                    |
  7       -0.07189    |                   .*| .                    |
  8       -0.05091    |                   .*| .                    |
  9       -0.07075    |                   .*| .                    |
 10        0.05178    |                    . |*.                   |
 11       -0.03902    |                   .*| .                    |
 12        0.02147    |                    . | .                   |

Partial Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1        0.11899    |                    . |**                   |
  2        0.02509    |                    . |*.                   |
  3        0.09291    |                    . |**                   |
  4        0.07196    |                    . |*.                   |
  5        0.02379    |                    . | .                   |
  6        0.11372    |                    . |**                   |
  7        0.08434    |                    . |**                   |
  8        0.06788    |                    . |*.                   |
  9        0.06211    |                    . |*.                   |
 10       -0.04712    |                   .*| .                    |
 11        0.03686    |                    . |*.                   |
 12       -0.02246    |                    . | .                   |


                          Autocorrelation Check for White Noise

 To        Chi-              Pr >
Lag      Square     DF     ChiSq    --------------------Autocorrelations-----------------
---

  6       21.87      6    0.0013     0.119     0.039     0.099     0.093     0.046
0.130
 12       38.55     12    0.0001     0.122     0.100     0.101     0.005     0.064
0.028
```

```
proc arima data=tdat.crosscorcheck;
 identify var=CRDeath stationarity = (adf = (1))outcov=ADF;
run;
```

```
Augmented Dickey-Fuller Unit Root Tests

Type           Lags         Rho    Pr < Rho        Tau    Pr < Tau          F    Pr > F

Zero Mean         1    -10.3361      0.0251      -2.29      0.0215
Single Mean       1    -337.093      0.0001     -12.93      <.0001      83.63    0.0010
Trend             1    -349.181      0.0001     -13.15      <.0001      86.40    0.0010
```

Similar to the death time series; doesn't appear to be a need to difference and the series is not white noise.

```
proc arima data=tdat.crosscorcheck;
 identify var=crdeath crosscor=(epidemic) noprint;
 estimate input=(epidemic) p=1 q=1 plot method=ml;
```

```
run;
quit;
```

Maximum Likelihood Estimation

Parameter	Estimate	Standard Error	t Value	Approx Pr > |t|	Lag	Variable	Shift
MU	12.34348	0.35142	35.12	<.0001	0	CRDeath	0
MA1,1	0.85336	0.07884	10.82	<.0001	1	CRDeath	0
AR1,1	0.92455	0.05764	16.04	<.0001	1	CRDeath	0
NUM1	0.66886	0.49569	1.35	0.1772	0	Epidemic	0

Constant Estimate	0.931289
Variance Estimate	11.92945
Std Error Estimate	3.453903
AIC	2157.44
SBC	2173.456
Number of Residuals	405

Correlations of Parameter Estimates

Variable	Parameter	CRDeath MU	CRDeath MA1,1	CRDeath AR1,1	Epidemic NUM1
CRDeath	MU	1.000	-0.077	-0.079	-0.355
CRDeath	MA1,1	-0.077	1.000	0.944	0.158
CRDeath	AR1,1	-0.079	0.944	1.000	0.151
Epidemic	NUM1	-0.355	0.158	0.151	1.000

Autocorrelation Check of Residuals

To Lag	Chi-Square	DF	Pr > ChiSq	Autocorrelations				
6	4.21	4	0.3790	0.010	-0.068	0.003	0.004	-0.040	0.062
12	8.72	10	0.5589	0.059	0.038	0.047	-0.056	0.019	-0.016
18	13.32	16	0.6491	0.060	0.020	-0.073	0.028	0.023	-0.016
24	18.93	22	0.6497	-0.027	0.049	0.005	-0.003	-0.082	0.056
30	31.66	28	0.2886	-0.123	-0.052	0.003	-0.043	0.071	-0.066
36	36.56	34	0.3508	-0.045	0.040	0.007	-0.061	0.056	-0.023
42	44.42	40	0.2906	-0.069	0.048	-0.080	-0.009	-0.059	0.020
48	50.61	46	0.2964	-0.066	0.050	0.051	-0.035	-0.023	0.048

Again, I picked the AR(1) MA(1) as the best model fit given the significance of the AR and MA terms and the insignificance of the Chi-square statistic in the autocorrelation check of the residuals. Based on this model fit, epidemics were associated with an increase of approximately 0.7 deaths per week but this association was not significant.

```
/*****************************************************************
CROSSCOR CHECK: ICU ADMISSIONS AGAINST EPIDEMICS;
ICU ADMISSIONS = # of ICU admissions/week;
EPIDEMIC = 0 or 1 based on examination of indicator of influenza
activity
*****************************************************************/
proc autoreg data=tdat.ICUcrosscor;
 model ICU_ADM = /dw=5 dwprob;
run;
```

```
        Durbin-Watson Statistics

Order            DW     Pr < DW     Pr > DW

  1          0.5537      <.0001      1.0000
  2          0.5534      <.0001      1.0000
  3          0.6255      <.0001      1.0000
  4          0.5785      <.0001      1.0000
  5          0.6038      <.0001      1.0000
```

Significant autocorrelation of the error terms present

```
proc arima data=tdat.ICUcrosscor;
 identify var=ICU_ADM nlag=12;
run;
quit;
```

```
The ARIMA Procedure

    Name of Variable = ICU_ADM

Mean of Working Series    102.2888
Standard Deviation         19.9851
Number of Observations         322


                                  Autocorrelations

Lag    Covariance    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1      Std
Error

  0       399.404        1.00000    |                   |********************|
0
  1       285.451        0.71469    |                 . |**************      |
0.055728
  2       282.688        0.70777    |                 .  |**************      |
0.079235
  3       266.100        0.66624    |                .   |*************       |
0.096900
```

```
  4       274.303        0.68678    |                .   |**************      |
0.110212
  5       266.129        0.66631    |                .   |*************       |
0.122785
  6       281.750        0.70543    |                .   |**************      |
0.133543
  7       266.543        0.66735    |                .   |*************       |
0.144654
  8       266.440        0.66709    |                .   |*************       |
0.153918
  9       244.268        0.61158    |                .   |************        |
0.162650
 10       249.879        0.62563    |                .   |*************       |
0.169641
 11       248.361        0.62183    |                .   |************        |
0.176661
 12       258.564        0.64738    |                .   |*************       |
0.183333

"." marks two standard errors

Inverse Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1       -0.12878    |                ***| .                 |
  2       -0.10189    |                 **| .                 |
  3       -0.02089    |                  . | .                 |
  4       -0.05053    |                 .*| .                 |
  5        0.00664    |                  . | .                 |
  6       -0.11887    |                 **| .                 |
  7       -0.04060    |                 .*| .                 |
  8       -0.06258    |                 .*| .                 |
  9        0.07619    |                  . |**                 |
 10        0.02526    |                  . |*.                 |
 11       -0.00421    |                  . | .                 |
 12       -0.07836    |                 **| .                 |
Partial Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1        0.71469    |                  . |**************      |
  2        0.40266    |                  . |********            |
  3        0.18616    |                  . |****                |
  4        0.22872    |                  . |*****               |
  5        0.13206    |                  . |***                 |
  6        0.22253    |                  . |****                |
  7        0.07012    |                  . |*.                  |
  8        0.06688    |                  . |*.                  |
  9       -0.06232    |                 .*| .                  |
 10        0.02018    |                  . | .                  |
 11        0.04683    |                  . |*.                  |
 12        0.09049    |                  . |**                  |


                          Autocorrelation Check for White Noise
```

```
 To        Chi-             Pr >
Lag      Square     DF     ChiSq    --------------------Autocorrelations----------------
---

  6      939.65      6    <.0001     0.715     0.708     0.666     0.687     0.666
0.705
 12     1761.32     12    <.0001     0.667     0.667     0.612     0.626     0.622
0.647
```

```
proc arima data=tdat.ICUcrosscor;
 identify var=ICU_ADM stationarity = (adf = (1))outcov=ADF;
run;
```

```
Augmented Dickey-Fuller Unit Root Tests

Type           Lags         Rho    Pr < Rho        Tau    Pr < Tau          F    Pr > F

Zero Mean         1     -0.8239      0.5041      -0.55      0.4759
Single Mean       1    -39.5823      0.0016      -4.62      0.0002      10.69    0.0010
Trend             1    -100.656      0.0001      -6.95      <.0001      24.30    0.0010
```

The ACF decays very slowly indicating the differencing may be required but the ADF test indicates that no trend is present. Looking at the graph I can see that there is an increase in the number of ICU Admissions per week from 2006 to 2007 so I am going to difference by 1.

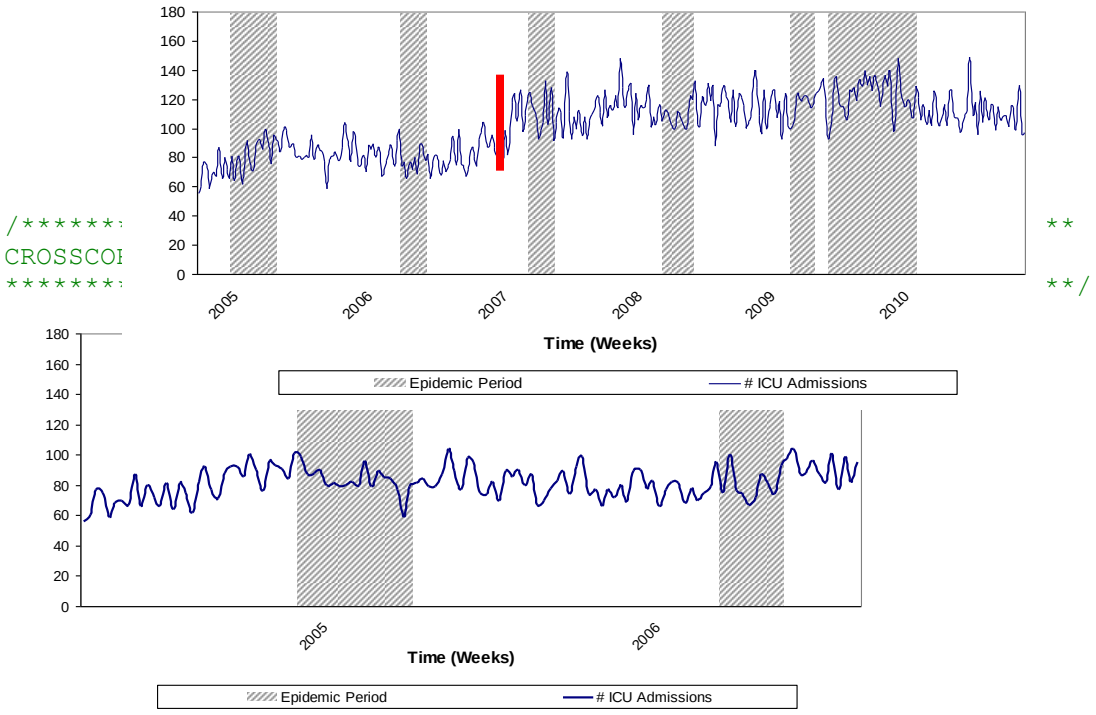
```
proc arima data=tdat.ICUcrosscor;
 identify var=ICU_ADM (1) nlag=12;
run;
quit;
```

```
Name of Variable = ICU_ADM

Period(s) of Differencing                          1
Mean of Working Series                      0.127726
Standard Deviation                           14.8942
Number of Observations                           321
Observation(s) eliminated by differencing          1


                                  Autocorrelations

Lag    Covariance    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1      Std
Error

  0       221.837        1.00000    |                    |********************|
0
  1      -110.989        -.50032    |          **********| .                  |
0.055815
  2     16.857314        0.07599    |                .   |**.                 |
0.068373
  3    -25.676369        -.11574    |                .**|  .                 |
0.068636
  4     14.345513        0.06467    |                .   |* .                 |
0.069241
  5    -22.558294        -.10169    |                .**|  .                 |
0.069429
```

```
  6     30.953092        0.13953    |                .  |***               |
0.069891
  7    -15.468781        -.06973    |                . *|  .               |
0.070754
  8     25.012646        0.11275    |                .  |**.               |
0.070968
  9    -30.963414        -.13958    |                ***|  .               |
0.071524
 10      9.303322        0.04194    |                .  |* .               |
0.072367
 11    -13.185757        -.05944    |                . *|  .               |
0.072443
 12     23.914075        0.10780    |                .  |**.               |
0.072595

"." marks two standard errors

                    Inverse Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1        0.80341    |                 . |****************    |
  2        0.64494    |                 . |*************       |
  3        0.52468    |                 . |**********          |
  4        0.41010    |                 . |********            |
  5        0.30783    |                 . |******              |
  6        0.20440    |                 . |****                |
  7        0.14858    |                 . |***                 |
  8        0.11424    |                 . |**                  |
  9        0.11164    |                 . |**                  |
 10        0.07834    |                 . |**                  |
 11        0.03869    |                 . |*.                  |
 12        0.00285    |                 . | .                  |

Partial Autocorrelations

Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

  1       -0.50032    |          **********| .                  |
  2       -0.23254    |               *****| .                  |
  3       -0.26120    |               *****| .                  |
  4       -0.17330    |                 ***| .                  |
  5       -0.25955    |               *****| .                  |
  6       -0.10446    |                  **| .                  |
  7       -0.09981    |                  **| .                  |
  8        0.05635    |                  . |*.                  |
  9       -0.03411    |                  .*| .                  |
 10       -0.05317    |                  .*| .                  |
 11       -0.09980    |                  **| .                  |
 12       -0.00835    |                  . | .                  |

                          Autocorrelation Check for White Noise

 To        Chi-             Pr >
Lag      Square     DF     ChiSq    --------------------Autocorrelations-----------------
---
```

```
  6        98.52       6     <.0001     -0.500      0.076     -0.116      0.065     -0.102
0.140
 12       116.48      12     <.0001     -0.070      0.113     -0.140      0.042     -0.059
0.108

Augmented Dickey-Fuller Unit Root Tests

Type           Lags          Rho     Pr < Rho        Tau     Pr < Tau           F    Pr > F

Zero Mean         1     -777.383       0.0001     -19.57       <.0001
Single Mean       1     -777.968       0.0001     -19.54       <.0001      190.88    0.0010
Trend             1     -778.997       0.0001     -19.52       <.0001      190.54    0.0010
```

I tried many different models but couldn't get the AC check of the residuals to be insignificant. It was the same when I tried to model the non-differenced time series. In re-examining the time series, we came to the conclusion that it is not working because there are really two distinct time series here. In August 2006, there was an upward shift in the weekly number of ICU admissions which is most likely due to the increase in available ICU beds. Therefore, I did a cross correlation check on this outcome as two distinct time series. The first part runs from April 4, 2004 to August 5, 2006 and the second runs from August 6, 2006 to June 5, 2010.




```
proc autoreg data=tdat.ICUcrosscor1;
 model ICU_ADM = /dw=5 dwprob;
run;
```

```
Durbin-Watson Statistics

 Order            DW     Pr < DW     Pr > DW
```

```
   1          1.3231      <.0001      0.9999
   2          1.3678      0.0002      0.9998
   3          1.3809      0.0004      0.9996
   4          1.3917      0.0008      0.9992
   5          1.5479      0.0151      0.9849
```

Significant autocorrelation of the error terms present

```
proc arima data=tdat.ICUcrosscor1;
 identify var=ICU_ADM nlag=12;
run;
quit;
```

```
Autocorrelations

 Lag    Covariance    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1      Std
Error

   0       110.427        1.00000    |                   |********************|
0
   1     33.956201        0.30750    |                .  |******              |
0.090536
   2     29.583593        0.26790    |                .  |*****               |
0.098726
   3     27.530254        0.24931    |                .  |*****               |
0.104515
   4     26.670545        0.24152    |                .  |*****               |
0.109281
   5     14.412960        0.13052    |                .  |***  .              |
0.113572
   6      5.085097        0.04605    |                .  |*    .              |
0.114795
   7     11.502331        0.10416    |                .  |**   .              |
0.114946
   8     18.938779        0.17150    |                .  |***  .              |
0.115717
   9     16.954642        0.15354    |                .  |***  .              |
0.117782
  10     20.460157        0.18528    |                .  |****.               |
0.119412
  11     15.754843        0.14267    |                .  |***  .              |
0.121745
  12      6.800671        0.06159    |                .  |*    .              |
0.123108
                  Inverse Autocorrelations

               Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

                 1       -0.07665    |                . **|   .                |
                 2       -0.13328    |                .***|   .                |
                 3       -0.14723    |                .***|   .                |
                 4       -0.16294    |                .***|   .                |
                 5        0.02503    |                .   |*  .                |
                 6        0.18067    |                .   |****                |
                 7        0.06175    |                .   |*  .                |
                 8       -0.07700    |                . **|   .                |
                 9       -0.06283    |                .  *|   .                |
```

```
                10       -0.11791    |               . **|   .               |
                11       -0.03215    |               .  *|   .               |
                12        0.09663    |               .   |** .               |


                    Partial Autocorrelations

              Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

                1        0.30750    |               .   |******             |
                2        0.19145    |               .   |****               |
                3        0.14196    |               .   |***.               |
                4        0.11797    |               .   |** .               |
                5       -0.02440    |               .   |   .               |
                6       -0.08328    |               . **|   .               |
                7        0.04515    |               .   |*  .               |
                8        0.13172    |               .   |***.               |
                9        0.08705    |               .   |** .               |
               10        0.10517    |               .   |** .               |
               11       -0.00374    |               .   |   .               |
               12       -0.11315    |               . **|   .               |


                          Autocorrelation Check for White Noise

   To        Chi-              Pr >
  Lag      Square     DF     ChiSq    --------------------Autocorrelations---------------
-----

    6       38.73      6    <.0001     0.307     0.268     0.249     0.242     0.131
0.046
   12       55.15     12    <.0001     0.104     0.172     0.154     0.185     0.143
0.062
```

Not white noise. ACF seems to decays relatively quick.

```
proc arima data=tdat.ICUcrosscor1;
 identify var=ICU_ADM  stationarity = (adf = (1))outcov=ADF;
run;
quit;
```

```
    Augmented Dickey-Fuller Unit Root Tests

    Type           Lags         Rho    Pr < Rho        Tau    Pr < Tau          F    Pr >
F

    Zero Mean         1     -0.1071      0.6570      -0.11      0.6443
    Single Mean       1    -57.6511      0.0011      -5.56      <.0001      15.57
0.0010
    Trend             1    -60.9336      0.0004      -5.64      <.0001      15.98
0.0010
```

The ADF test doesn't indicate a need to difference. Visual inspection of the time series doesn't suggest a need to difference so will try without differencing.

```
proc arima data=tdat.ICUcrosscor1;
```

```
 identify var=ICU_ADM crosscor=(epidemic) noprint;
 estimate input=(epidemic)p=1 q=1 plot method=ml;
run;
quit;
```

Maximum Likelihood Estimation

Parameter	Estimate	Standard Error	t Value	Approx Pr > |t|	Lag	Variable	Shift
MU	81.60725	4.24680	19.22	<.0001	0	ICU_ADM	0
MA1,1	0.74983	0.08933	8.39	<.0001	1	ICU_ADM	0
AR1,1	0.95216	0.03947	24.13	<.0001	1	ICU_ADM	0
NUM1	-4.76073	3.25451	-1.46	0.1435	0	Epidemic	0

Constant Estimate	3.904239
Variance Estimate	92.50314
Std Error Estimate	9.617855
AIC	903.1713
SBC	914.3874
Number of Residuals	122

Correlations of Parameter Estimates

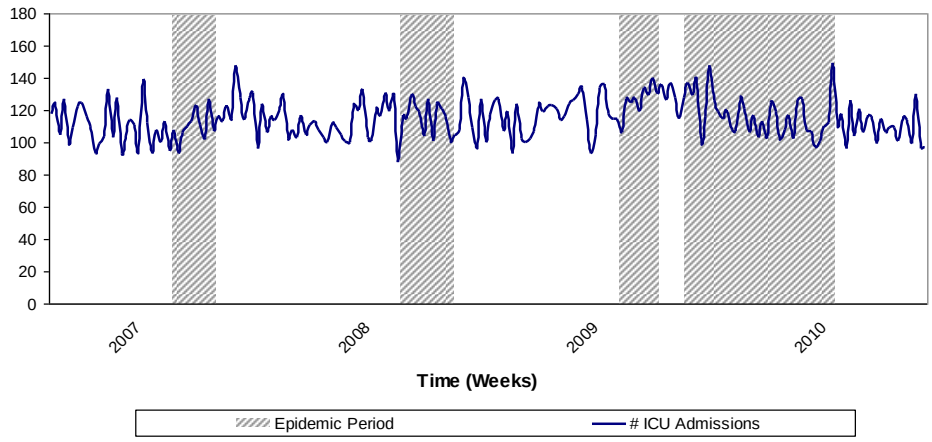
Variable	Parameter	ICU_ADM MU	ICU_ADM MA1,1	ICU_ADM AR1,1	Epidemic NUM1
ICU_ADM	MU	1.000	0.142	0.264	-0.163
ICU_ADM	MA1,1	0.142	1.000	0.765	0.091
ICU_ADM	AR1,1	0.264	0.765	1.000	-0.041
Epidemic	NUM1	-0.163	0.091	-0.041	1.000

Autocorrelation Check of Residuals

To Lag	Chi-Square	DF	Pr > ChiSq	Autocorrelations				
6	4.63	4	0.3278	-0.018	-0.024	-0.003	0.011	-0.078	-0.169
12	11.55	10	0.3162	-0.048	0.086	0.070	0.152	0.111	0.034
18	14.73	16	0.5445	0.022	0.065	-0.095	-0.085	-0.036	0.018
24	19.33	22	0.6251	-0.155	0.001	0.035	0.057	0.034	0.038

Here the AR(1) MA(1) is the best model fit given the significance of the AR and MA terms and the insignificance of the Chi-square statistic in the autocorrelation check of the residuals. The AR(2) model showed signs of being a good fit but the AIC was slightly better for the AR(1) MA(1) model (909 vs. 903) and the chi-square statistics in the AC check of the residuals were larger with the AR(1) MA(1) model as well. Based on this model fit, epidemics were associated with a decrease of approximately 4.7 ICU admissions per week but this association was not significant.

```
/*************************************************************
CROSSCORCHECK: ICU ADMISSIONS PART 2
*************************************************************/
```




```
proc autoreg data=tdat.ICUcrosscor2;
 model ICU_ADM = /dw=5 dwprob;
run;
```

Durbin-Watson Statistics

Order	DW	Pr < DW	Pr > DW
1	1.7210	0.0235	0.9765
2	1.6474	0.0073	0.9927

```
3          1.9408      0.3911      0.6089
4          1.6863      0.0217      0.9783
5          1.7004      0.0323      0.9677
```

Significant positive autocorrelation of the error terms present

```
proc arima data=tdat.ICUcrosscor2;
 identify var=ICU_ADM nlag=12;
run;
quit;
```

```
    The ARIMA Procedure

                                Name of Variable = ICU_ADM

                             Mean of Working Series     114.935
                             Standard Deviation        12.3927
 Number of Observations         200



Autocorrelations


 Lag    Covariance    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1      Std
Error

   0       153.581        1.00000    |                   |********************|
0
   1     20.600629        0.13414    |                   .  |***                 |
0.070711
   2     25.143858        0.16372    |                   .  |***                 |
0.071972
   3      1.802212        0.01173    |                   .  |  .                  |
0.073810
   4     20.348491        0.13249    |                   .  |***                 |
0.073820
   5     18.628994        0.12130    |                   .  |**.                 |
0.074999
   6     50.585598        0.32937    |                   .  |*******             |
0.075974
   7     30.832852        0.20076    |                   .  |****                |
0.082806
   8     26.571531        0.17301    |                   .  |***                 |
0.085205
   9     -3.141865        -.02046    |                   .  |  .                  |
0.086944
  10      7.372664        0.04801    |                   .  |* .                 |
0.086968
  11      4.819793        0.03138    |                   .  |* .                 |
0.087101
  12     25.995172        0.16926    |                   .  |***                 |
0.087157

                                  "." marks two standard errors
```

```
                          Inverse Autocorrelations

               Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

                 1        0.02746    |                .  |* .                |
                 2       -0.04161    |                . *|  .                |
                 3        0.00512    |                .  |  .                |
                 4       -0.06059    |                . *|  .                |
                 5       -0.05874    |                . *|  .                |
                 6       -0.21469    |               ****|  .                |
                 7       -0.12658    |                ***|  .                |
                 8       -0.07235    |                . *|  .                |
                 9        0.06905    |                .  |* .                |
                10        0.03378    |                .  |* .                |
                11        0.03841    |                .  |* .                |
                12       -0.03169    |                . *|  .                |

Partial Autocorrelations

               Lag    Correlation    -1 9 8 7 6 5 4 3 2 1 0 1 2 3 4 5 6 7 8 9 1

                 1        0.13414    |                .  |***                |
                 2        0.14840    |                .  |***                |
                 3       -0.02798    |                . *|  .                |
                 4        0.11467    |                .  |**.                |
                 5        0.10035    |                .  |**.                |
                 6        0.28598    |                .  |******             |
                 7        0.13424    |                .  |***                |
                 8        0.07640    |                .  |**.                |
                 9       -0.08924    |                .**|  .                |
                10       -0.03456    |                . *|  .                |
                11       -0.04064    |                . *|  .                |
                12        0.03563    |                .  |* .                |


Autocorrelation Check for White Noise

   To        Chi-             Pr >
  Lag      Square     DF     ChiSq    --------------------Autocorrelations---------------
-----

    6       38.41      6    <.0001     0.134     0.164     0.012     0.132     0.121
0.329
   12       60.09     12    <.0001     0.201     0.173    -0.020     0.048     0.031
0.169
```

```
proc arima data=tdat.ICUcrosscor2;
 identify var=ICU_ADM  stationarity = (adf = (1))outcov=ADF;
run;
quit;
```

```
Augmented Dickey-Fuller Unit Root Tests
```

Type	Lags	Rho	Pr < Rho	Tau	Pr < Tau	F	Pr > F
Zero Mean	1	-0.8330	0.5019	-0.74	0.3951		
Single Mean	1	-125.588	0.0001	-7.77	<.0001	30.18	0.0010
Trend	1	-129.184	0.0001	-7.84	<.0001	30.72	0.0010

Not white noise. ACF seems to decays relatively quick although there is a bit of a spike at lag 6. The ADF test doesn't indicate a need to difference. Visual inspection of the time series doesn't suggest a need to difference.

```
proc arima data=tdat.ICUcrosscor2;
 identify var=ICU_ADM crosscor=(epidemic) noprint;
 estimate input=(epidemic)p=6 q=6 plot method=ml;
run;
quit;
```

Maximum Likelihood Estimation

Parameter	Estimate	Standard Error	t Value	Approx Pr > |t|	Lag	Variable	Shift
MU	114.25828	1.71773	66.52	<.0001	0	ICU_ADM	0
MA1,1	0.75633	0.07857	9.63	<.0001	1	ICU_ADM	0
MA1,2	0.82696	0.08942	9.25	<.0001	2	ICU_ADM	0
MA1,3	-1.79405	0.11690	-15.35	<.0001	3	ICU_ADM	0
MA1,4	0.59277	0.14488	4.09	<.0001	4	ICU_ADM	0
MA1,5	0.92499	0.08257	11.20	<.0001	5	ICU_ADM	0
MA1,6	-0.76089	0.08583	-8.86	<.0001	6	ICU_ADM	0
AR1,1	0.77297	0.04298	17.98	<.0001	1	ICU_ADM	0
AR1,2	0.89149	0.02518	35.40	<.0001	2	ICU_ADM	0
AR1,3	-1.77770	0.01541	-115.37	<.0001	3	ICU_ADM	0
AR1,4	0.62457	0.04476	13.96	<.0001	4	ICU_ADM	0
AR1,5	0.97565	0.02281	42.78	<.0001	5	ICU_ADM	0
AR1,6	-0.70798	0.0083010	-85.29	<.0001	6	ICU_ADM	0
NUM1	1.97101	2.19264	0.90	0.3687	0	Epidemic	0

Constant Estimate 25.25052

Variance Estimate	124.1306
Std Error Estimate	11.14139
AIC	1552.316
SBC	1598.492
Number of Residuals	200

The ARIMA Procedure

Autocorrelation Check of Residuals

To Lag	Chi-Square	DF	Pr > ChiSq	Autocorrelations					
6	.	0	.	0.018	0.012	-0.019	-0.040	-0.034	0.043
12	.	0	.	0.061	0.028	0.017	-0.001	-0.003	-0.015
18	6.86	6	0.3337	-0.058	-0.039	0.075	-0.003	0.016	0.103
24	12.62	12	0.3971	-0.038	0.014	0.044	-0.100	-0.025	0.105
30	14.30	18	0.7094	0.028	-0.069	-0.012	-0.006	0.035	-0.017
36	18.79	24	0.7630	-0.066	-0.016	0.030	-0.067	0.072	0.057

Here the AR(6) MA(6) is the best model fit given the significance of the AR and MA terms and the insignificance of the Chi-square statistic in the autocorrelation check of the residuals. Based on this model fit, epidemics were associated with an increase of approximately 2 ICU admissions per week but this association was not significant.