More Than Just the "Flu"?: Measuring the Impact of Influenza on Hospitalizations of the Elderly in Ontario 1988-1993

By

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A thesis in conformity with the requirements for the Degree of Master of Science
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Abstract

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This thesis examined the relationship between circulating influenza virus and admissions to hospital among elderly persons in the province of Ontario for four targeted conditions: pneumonia, congestive heart failure, chronic lung disease and acute respiratory disease for five influenza seasons from 1988-1993. Using administrative data, age and sex adjusted and age and sex specific rates and time series analysis found consistent strong relationships between influenza virus and admissions for pneumonia and congestive heart failure. The relationship was less strong for congestive heart failure and acute bronchitis. A structured chart audit indicated that pneumonia is accurately coded in a large administrative data base. The study concludes that influenza is a major cause of morbidity and hospital utilization in the elderly population and that administrative data is an excellent means of measuring the extent to which the goals of influenza control are being achieved.
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# Table of Contents

**Introduction** .................................................................................................................................................................................. 1

**Review of Literature** ........................................................................................................................................................................ 3

  Virological Considerations................................................................................................................................................................. 3
  Molecular Biology and Viral Ecology.................................................................................................................................................... 3
  Clinical Features....................................................................................................................................................................................... 4
  Overview of the Epidemiology of Influenza............................................................................................................................................ 6
  Mortality and Morbidity Studies............................................................................................................................................................. 6
  Temporal Aspects: Trends and Time Series........................................................................................................................................... 12
  Bacterial Pneumonia in the Elderly: Epidemiologic and Diagnostic Issues.......................................................................................... 16
  Prospective Studies of Community Acquired Pneumonia.................................................................................................................... 17
  Epidemiologic Studies Using Administrative Data Bases................................................................................................................... 19
  Diagnostic Considerations................................................................................................................................................................. 21
  Summary and Conclusions.................................................................................................................................................................... 23

**Objectives** ....................................................................................................................................................................................... 26

**Methods and Approach** ...................................................................................................................................................................... 27

  Data Sources............................................................................................................................................................................................ 27
  Chart Audit.............................................................................................................................................................................................. 27
  Ontario Influenza Surveillance Data.................................................................................................................................................... 28
  HMRI/CIHI............................................................................................................................................................................................. 30
  Extraction of Study Files......................................................................................................................................................................... 30
  Population Data..................................................................................................................................................................................... 31

**Methods of Analysis** ........................................................................................................................................................................ 33

  Chart Audit.............................................................................................................................................................................................. 33
  Calculation of Rates.................................................................................................................................................................................. 34
  Time Series Analysis.............................................................................................................................................................................. 34

**Results** .................................................................................................................................................................................................. 36

  Objective 1.......................................................................................................................................................................................... 36
  Objective 2.......................................................................................................................................................................................... 38
  Objective 3......................................................................................................................................................................................... 55
  Figures.................................................................................................................................................................................................. 61
Introduction

The control of influenza is a stated priority of public health efforts in Canada. Despite improvements in medical care in the past three decades, influenza continues to cause considerable morbidity and mortality in the entire Canadian population. Influenza related illness contributes significantly to health service utilization in terms of visits for physician services, emergency rooms and hospitalizations. Influenza is a major source of lost productivity and absenteeism for both schools and work-places (La Force, 1985; Sullivan et al., 1993; Nichol et al., 1995; Dixon, 1985). Therefore, the health and economic consequences of influenza are considerable.

The elderly bear a disproportionate burden of the serious morbidity and mortality from influenza. For this reason, provincial public health departments and national advisory committees have placed the strongest emphasis and devoted the most resources to the control of influenza in the elderly. The annual recommendations from the Canadian National Advisory Committee on Immunization have advocated universal immunization of all persons over the age of 65 (National Advisory Committee on Immunization, 1993). Despite this recommendation, influenza vaccination rates for the elderly in Ontario in 1993 averaged only 53 percent (Duclos & Hatcher, 1993).

Although it is known that the elderly are the most likely to suffer from complications arising from influenza infections, the quantification of this burden has not been the subject of much research. The Canadian Consensus Conference on Influenza, held in 1993, called for increased research to assess the morbidity caused by influenza (Anon., 1993). One of the areas
recommended for increased attention was the use of hospital separation data bases to assess influenza morbidity.

It is the intention of this thesis to contribute to the understanding of the effects of influenza on the hospitalization patterns of the elderly in Ontario. In particular, the relationship between the circulation of influenza viruses in Ontario and the effect this has on admission rates for pneumonia, acute and chronic respiratory diseases and congestive heart failure will be studied utilizing two complimentary analytic techniques: rate standardization and time series analysis. Issues in the reliability of administrative data bases will be examined by means of a hospital chart audit.

The relationship between influenza and the morbidity experience of the elderly is complex. Consideration of the virology and molecular biology of influenza and the epidemiology of respiratory illness in the elderly must be undertaken to set the ground for understanding the specific hypothesis to be tested in this thesis. To this end, the virology, molecular biology, and clinical manifestations of influenza will first be reviewed. Following this, the epidemiology of influenza and pneumonia in the elderly will be reviewed. An argument for the utility of time series analysis will be advanced. As pneumonia is the most important recognized complication related to influenza, special attention will be devoted to issues in the epidemiology and clinical management of pneumonia. Issues related to the hospital coding of pneumonia will be reviewed.
Virological Considerations

A respiratory virus of the family orthomyxoviridae, influenza has a long and notable history as a human pathogen. Influenza-like epidemics have plagued humans since the beginning of recorded history (Langmuir et al., 1985; Gregg et al., 1978; Shortridge, 1995). The influenza pandemic of 1918-19 was responsible for an estimated 20-50 million deaths world-wide (Patterson & Pyle, 1991). The late 20th Century has seen three major global pandemics in 1957-8, 1968 and 1977 (Wiselka, 1994). Influenza viruses have been isolated in Ontario each year since 1983 as documented by the influenza surveillance conducted by the Public Health Branch of the Ministry of Health in Ontario (Naus & Offner, 1993).

Molecular Biology and Viral Ecology

Influenza viruses have three main types: A, B and C. Influenza A has a genome that consists of 8 separate strands of RNA. Two of these strands code for the surface antigens haemagglutinin and neuraminidase by which influenza A viruses are classified into subtypes. Currently there are 13 known haemagglutinin subtypes and 9 neuraminidase subtypes (Webster et al., 1992). Influenza B has no known subtypes. Influenza C is only rarely pathogenic in humans and will not be discussed further. Since 1933, three pathogenic strains of influenza A have been isolated in man: H1N1, H2N2, and H3N2. Two subtypes of influenza A have been circulating in Ontario since 1977: H1N1 and H3N2. Within each haemagglutinin/neuraminidase sub-type a wide range of variations occur. It is these annual variations that provide the information for the constitution of the annual influenza vaccine.

Influenza viruses should be regarded as constantly evolving entities with well
documented ability for rapid and unpredictable mutation. The capacity for mutation occurs through a variety of mechanisms. Webster and colleagues (Webster et al., 1992) have enumerated the major mechanisms of mutation: a) point mutation (antigenic drift) b) gene reassortment (genetic shift) c) defective interfering particles and d) RNA recombination.

Point mutations accounting for antigenic drift are explained in part by the replicating process of RNA viruses. As viruses lack ‘proof-reading’ enzymes to ensure fidelity of the replication process, error rates for viral replication can be as high as 1 in 1,000 bases. This combined with the rapid replication of viruses results in the production of a large quantity of genetic variants, not all of which have survival advantage.

The host reservoir for influenza viruses appears to be found in aquatic birds (Schafer et al., 1993). The viruses appear to be adapted to the avian host and are not pathogenic to them. Influenza viruses are capable of causing disease in a wide variety of mammalian and avian species. The current theory for genetic shifts holds that genetic reassortment occurs through interspecies transfer, with pigs being an important link between avian reservoirs and humans (Schafer et al., 1993). As pigs are capable of accepting influenza genes from both aquatic birds and humans the theory holds that pigs act as mixing vessels for the reassortment of the viral genome. Supporting evidence for this theory comes from the fact that most genetically shifted influenza subtypes have emerged geographically from areas where integrated porcine/avian agriculture is practised (Schafer et al., 1993). It is postulated that genetic shift was responsible for the unprecedented virulence of the 1919 pandemic.

**Clinical Features**

Influenza causes an acute, moderate to severe illness with characteristic signs and
symptoms: malaise, fever, sore throat, cough, myalgia and arthralgia. Prostration is not uncommon. The incubation period of the virus is 2-3 days. Acute symptoms can last from 2-7 days. Cough may persist for weeks. The infected person is capable of transmitting the virus for 3-6 days with droplets spread by aerosol (Benenson, 1985). As cough is prominent and persistent, influenza is efficiently spread from person to person.

Complications from influenza are numerous. Pneumonia, both bacterial and viral are well documented (Foy et al., 1979; Glezen, 1983; Glezen et al., 1987; Ghendon, 1992; Connolly et al., 1993). Bronchitis, bronchiolitis, otitis media and sinusitis are commonly reported complications. (Connolly et al., 1993) Less frequent complications include myositis, myocarditis, pericarditis, Reye's syndrome, Goodpasture's syndrome, encephalopathy and transverse myelitis (Benenson, 1985). The circulation of influenza A viruses has been clearly linked to outbreaks of meningococcemia (Cartwright et al., 1991; Hubert et al., 1992). Influenza A is more severe in pregnant women (Glezen, 1993). Several observational studies have implicated maternal influenza infections with the development of schizophrenia though the issue of causation remains unresolved (Sham et al., 1993).

Influenza A and B are potentially preventable with the use of influenza vaccine. Randomized clinical control trials have established the efficacy of influenza vaccine for healthy adults (Nichol et al., 1995). The efficacy of influenza vaccine in the elderly has been controversial. Because of declining immune function and co-morbidity, the efficacy of influenza vaccine has remained debateable in the mind of many clinicians (Nicholson et al., 1987; Coles et al., 1992). Recent evidence from a large cohort study in the United States (Nichol et al., 1994), and a randomized control trial in the Netherlands (Govaert et al., 1994) indicate that the vaccine is effective in preventing both clinical infection and serious complications in the elderly from
influenza. Cost effectiveness studies in both the United States (Maucher & Gambert, 1990; Riddiough et al., 1983) and Canada (Helliwell & Drummond, 1988) have supported the cost effectiveness of annual influenza vaccination of the elderly.

Influenza A infections can be treated with amantadine and rimantadine. If the drug is started within 48 hours of the onset of symptoms, viral shedding is reduced and the duration of clinical symptoms is shortened (Benenson, 1985). Amantadine can also be used prophylactically in outbreak situations (Atkinson et al., 1986). The use of amantadine is recommended by NACI in outbreak situations in long-term care facilities (National Advisory Committee on Immunization, 1993). Side effects are common in the elderly if care is not exercised in titrating the dose to renal function. Resistance of influenza A strains to amantadine has been reported, but the clinical significance of this has yet to be established (Patriarca et al., 1987).

Overview of the epidemiology of influenza

Mortality and Morbidity Studies

The epidemiology of influenza remains incompletely understood. As a virus with a demonstrated capacity to cause high morbidity and mortality in populations world-wide, there is considerable interest in understanding the underlying epidemiology. Influenza epidemics are characterized by sudden and explosive spread through communities. Attack rates can be high, particularly in years when population immunity is low; there can be considerable variation of attack rates between age groups within a defined year. Stuart-Harris (Stuart-Harris, 1982) estimated the rates of influenza A in Britain for the 1973-74 influenza season. The rate for acute respiratory illness during this season ranged from 62,400 per 100,000 persons in the age group of 0 to four years to 11,100 per 100,000 in those over the age of 65. Glezen (Glezen, 1982) estimated that annual attack rates range from 30-50,000 per 100,000 in children and 7-25,000
per 100,000 in adults. Younger age groups are more likely to be infected as they lack antibodies to a variety of sub-type variants. The Laboratory Centre for Disease Control in Ottawa estimates that 70-75,000 hospitalizations and 6,700 deaths are attributed to influenza and pneumonia in Canada annually (Anon., 1993).

Although the younger age groups are more likely to be infected, the vast majority of complications and mortality are experienced by the elderly. Nicholson (Nicholson, 1990) estimates that 80-90% of the excess mortality due to influenza occurs in those over the age of 65. In Britain, those over the age of 75 experienced rates of death 765 times greater than the lowest mortality group (children aged 5-14.) A study in the Netherlands (Sprenger et al., 1993), examining data from the 1989-1990 influenza season, found the mortality rate associated with influenza in those over the age of 80 to be 207 per 100,000. This was 6.6 times higher than the age group 70-79 and 11.5 times higher than the 60-69 year age group.

The risk of death increases significantly in the presence of co-morbidity. Louria et al. (Louria et al., 1959), in a classic study conducted during the 1957 pandemic demonstrated the high mortality associated with influenza infections in those suffering from chronic cardiac and respiratory disease. Barker and Mullooly (Barker & Mullooly, 1980) in a mortality study of influenza outbreaks noted that the risk of death increases with the number of co-morbidities. They found that cardiovascular, pulmonary, and combined cardiovascular and pulmonary disease are associated with 104 percent, 240 percent and 870 percent increase in mortality rates compared to the group with no co-morbidities.

The Influenza Research Centre at Baylor College of Medicine has conducted community surveillance studies of influenza infections in Houston since 1974 (Glezen, 1982). These studies have formed the basis for understanding the effects of influenza and other respiratory viruses on
the mortality and morbidity experiences of a population. The sampling frame includes all socio-economic strata. The surveillance system includes volunteer families as well as primary care practitioners and pediatricians who collect viral specimens from individuals suffering from acute respiratory tract infections who seek medical attention on a year round basis.

The Houston data indicates that a wide variety of respiratory viruses circulate throughout the year (Perrotta et al., 1985; Glezen et al., 1987). In the Houston studies, viruses tend to occupy seasonal niches, and as one virus achieves peak circulation other viruses are relatively dormant. From the patterns of viral circulation, they are able to correlate morbidity and mortality from respiratory tract infections with specific respiratory viruses.

Glezen (Glezen, 1982), in a review article summarizing 7 years of surveillance, points out that 39.3% of respiratory illness occurred in the 11 week period defined by the circulation of influenza viruses. Influenza seasons were also responsible for at least 20% of all medically attended acute respiratory illnesses during the years of surveillance. The results of the Houston studies show that influenza viruses characteristically appear on an annual basis, and that utilization for visits to emergency rooms, physicians offices and hospitalizations for acute respiratory tract infections usually peak with the presence of circulating influenza virus. Attack rates were highest in the younger age groups, but hospitalizations and deaths were highest in the elderly. They calculated average acute respiratory tract infection hospitalization rates of 725 per 100,000 in the greater than age 65 category and pneumonia and influenza mortality rates of 103.5 per 100,000.

Barker (Barker, 1986), in a study using the National Hospital Discharge Survey, compared admissions for pneumonia and influenza, other respiratory disease in the absence of pneumonia and influenza, and acute cardiac conditions during eight influenza seasons from
1970-1978. In this analysis, admission rates for the above conditions were compared for defined epidemic and non-epidemic seasons. Barker quantified the excess hospitalization associated with epidemics rather than the seasonal increase associated with influenza circulation. Rates were also calculated for average hospitalizations in the quarter immediately following influenza circulation. The study found higher rates of admission for pneumonia and influenza in epidemic years in the 65 and over age group. However, no significant increase was found for other respiratory conditions or acute cardiac conditions. Barker concluded that: "... virtually all increased hospitalization during influenza epidemics involve clinically significant lower respiratory tract infections. There is accordingly little reason to suspect an important effect of influenza virus directly on the cardiovascular system..." (Barker, 1986 p. 786).

Two limitations mark this study. By focusing on quarterly statistics commencing in January, relevant admissions will be missed from epidemics that commence in November or December. Consequently the data may underestimate the true extent of utilization. Secondly, as the work of the Houston surveillance study indicates, reliance upon an arbitrarily defined epidemic year obscures morbidity associated with non-epidemic years. The appropriate comparison, then, is not epidemic influenza seasons to non-epidemic seasons, but rather influenza seasons to comparable periods in the year when influenza viruses are known not to be circulating.

Another limitation of the above studies is that for the most part, the elderly are aggregated together as a homogenous group. It is well recognized in the geriatric literature that there are significant heterogeneities in the elderly population (Norman & Toledo, 1992). As the more detailed mortality studies indicate, the experience of the very old differs from that of the 'young' old. Consequently the aggregation of the elderly into one group likely obscures
significant differences in age groups that may have implications for health planning.

McBean (McBean et al., 1993) examined the annualized age-sex and race adjusted rates of hospitalization for pneumonia and influenza and other conditions deemed to be susceptible to pneumonia in Medicare beneficiaries in the United States. Two influenza seasons, one predominant influenza A (1989-1990) and one predominant influenza B season (1990-1991), were examined and compared to an equivalent time period in the interim. Influenza periods, rather than being defined by quarter, were defined on the basis of viral isolation periods reported to the Centre for Disease Control in Atlanta. They calculated rates for age groups from 65-74, 75-84 and 85 and over and calculated the relative risk for each influenza season to the interim.

The results from this study show that pneumonia and influenza rates for admission are higher during influenza seasons than in the interim periods. The influenza A season had higher rates than the influenza B season. The admission rates with pneumonia and influenza as the primary diagnosis were 27.97 per 1,000 Medicare beneficiaries for the influenza A season, and 20.60 per 1,000 for the influenza B season. Significant relative risks were reported for the following diagnosis: influenza and pneumonia as primary diagnosis, when influenza and pneumonia appears in any diagnosis, acute bronchitis, chronic respiratory disease, and congestive heart failure. The highest relative risk was found for acute bronchitis during the influenza A season (RR 2.17 C.I. 2.10-2.24). No significant increases were found for acute and chronic cardiac disease, arrhythmia, stroke, cancer or diabetes.

The results indicate that influenza seasons are associated with a 16-117% increase in admissions for a variety of conditions in the elderly. In the influenza B season, a defined non-epidemic season, statistically significant increases in admissions were found that would have
been missed had one compared influenza seasons to each other, or focused only on epidemic seasons.

Nichol (Nichol et al., 1994) in a cohort study examining the efficacy and cost-effectiveness of influenza vaccine conducted over the same seasons as the McBean study, found statistically significant increases in admissions for pneumonia and influenza, all acute and chronic respiratory conditions and congestive heart failure among the unvaccinated cohort. The findings in the unvaccinated cohort act as a natural history study of the effects of influenza.

The results of the Nicol and McBean studies contradict that of Barker's in that admission rates are found to be higher for congestive heart failure during influenza seasons. Part of this could be attributed to the fact that both the Nicol and McBean study do not differentiate between non-epidemic and epidemic seasons. As well the rates in these studies were calculated on the basis of the duration of isolation of influenza virus, not by fiscal quarter. McBean and colleagues discount the possibility of changes of diagnosis, or coding differences to account for this change. They suggest that future studies include chronic respiratory disease and congestive heart failure in the analysis of the impact of influenza.

Consequently, following the results of the McBean study, this thesis will examine the relationship between circulating influenza virus and hospital admissions by the elderly for pneumonia, acute upper respiratory disease, congestive heart failure and chronic obstructive pulmonary disease. The study will seek to replicate McBean's finding of increased rates of admission for congestive heart failure and chronic obstructive pulmonary disease during influenza seasons and quantify the extent of the burden imposed by pneumonia morbidity in the elderly of Ontario.
Temporal Aspects: Trends and Time Series

The above studies have been concerned with annualized rates, or rates calculated over time. Another way of assessing the impact of influenza is to look at the temporal dimensions of each influenza season. Rather than averaging all seasons, one can look at the relationship between the presence of influenza and the occurrence of the outcome of interest as it has occurred in each particular season. One can then assess the inter-season variability of influenza as well as estimate the duration of effect for each influenza season.

Influenza circulation has a seemingly regular recurrence pattern in that it occurs on an annual basis, but not in a predictable fashion. In temperate climates, influenza can make its appearance anywhere from the early fall to the late spring (Shortridge, 1995). A typical influenza season lasts from 10-15 weeks, although there is variability in this owing to the fact that two or more virus types can circulate in a given season. Consequently, although there are identifiable regularities in the occurrence of influenza epidemics, no satisfactory predictive models for influenza have been developed.

Historically, the first models related to influenza focussed upon all cause mortality during influenza seasons. This approach harkens back to the mid 18th century when it was noticed that mortality rates increased seasonally. The work of William Farr established the concept of excess mortality attributable to influenza epidemics, following the 1847 epidemic (Fine, 1982). Mortality data on all cause mortality and pneumonia and influenza has been kept on a weekly basis in the United States since 1918 (Baron et al., 1988).

This approach was modified over time and formed the basis of the development of a regression model by Serfling (Fine, 1982) used to calculate excess pneumonia and influenza mortality. Serfling's method, used by the Centre for Disease Control in Atlanta for over 20 years
fits a regression model by least squares method, with sin and cosine terms in the regression equation, to weekly mortality data for the previous five years, exclusive of weeks with epidemic influenza. From this an estimated baseline was created for deaths for the next twelve months. If mortality rates exceed 1.64 standard deviations from the regression line, then the epidemic threshold has been crossed and excess mortality can be inferred.

The Serfling model, despite its utility has several drawbacks. There are concerns that the estimates, by relying on death certificate data, may not always result in the proper attribution of death. Furthermore the estimates may be biased too low because the regression equation is fitted on non-epidemic weeks. Artifacts have occurred because the data is reported by the date on which the death certificate is filled rather than the date of death. The model has been found to show artifactual increases and decreases around holiday times. This is particularly important as influenza activity can be intense in the Christmas holiday time frame. Choi and Thacker (Choi & Thacker, 1981) have argued for the modification of the Sherfling model using a Box-Jenkins time series methodology which improved time-series forecasts.

Time-series methodology has a long history of application in econometrics, particularly in the domain of forecasting. It has only recently captured the attention of epidemiologists (Bowie & Prothero, 1981; Helfenstein, 1986, 1991; Catalano & Serxner, 1987). As influenza has a significant seasonal component it can be modelled in a manner that controls for the effect of seasonality. As well, time series analysis allows for the comparison of multiple time series. One can estimate the extent to which two time series are correlated over time. Cross-correlation functions can be calculated for time-series data to investigate the relationship between two sets of data collected over the same time periods. Consequently time-series analysis provides another perspective with which to analyse the impact of influenza.
Time-series analysis is suited to data that is collected over time and that feature seasonal traits. The methodology can be used for descriptive or analytical uses. It is also more appropriate than other regression techniques when the data indicates a degree of autocorrelation, such as admissions to hospital during influenza epidemics.

Of the many time-series methods developed, the most thoroughly studied and used is the Box-Jenkins ARIMA methodology (Box & Jenkins, 1970). ARIMA stands for autoregressive integrated moving average. The autoregressive component assumes that each observation is directly dependent on past observations, and that the value of these autocorrelations are determined by the preceding values for a certain number of lags. An integration process is used to remove a trend from the data, or to remove other forms of non-stationarity. A non-stationary series occurs when the mean value of the series varies over time. This occurs when a time series has an upward or downward trend. The moving average process examines the value of a current value on the basis of immediately adjacent values. A more detailed description of time series methodology is found in Appendix 1.

There are few studies that utilize time series methods to study influenza. Time-series studies have focussed upon mortality due to influenza and pneumonia for the purpose of forecasting mortality or calculating excess mortality (Carrat & Valleron, 1995). Time series methods have also been used to study the effects of air-pollution on mortality controlling for influenza effects and for examining the relationship between the seasonal patterns of influenza and meningococcemia (Kunst et al. 1993, Hubert et al., 1992).

There have been no full scale time-series analysis looking at the relationship between circulating influenza viruses and hospital admissions in the elderly. Perotta (Perrotta et al., 1985) reported a strong correlation between virological circulation and increases in hospital
admissions in adults. The correlation coefficient of .74 is impressive and has been quoted widely. However, this estimate is likely specific to the jurisdiction where it was made. Further compromising the generalizability of the estimate is the noted season to season variability of the effects of influenza in populations. It is likely that the strength of this correlation varies from year to year as well as from place to place. No published studies exist to test this hypothesis.

A further limitation to Perotta’s study is that it does not indicate the method by which the cross-correlations were calculated. The tabular data presented in the article indicates a number of strongly positive correlations at different lags. This gives rise to the suspicion that the series were simply cross-correlated. As Helfenstein (Helfenstein, 1991), and Bowie and Prothero (Bowie & Prothero, 1981) have both noted, simple cross-correlations between two seasonally related variables will result in artifactually elevated cross-correlation coefficients. The high correlations are likely attributable to a common seasonal effect. The effect of seasonality must be controlled for in order to calculate an unbiased correlation coefficient. The appropriate method to use would be a transfer function model in which the two series are “pre-whitened” in order to eliminate the inflation of the variance of the two series due to the common seasonal structure.

As has been demonstrated above, there is a strong association between influenza and hospitalizations of the elderly for a variety of conditions. Another way of examining this association would be to examine the seasonal increase of admissions in the time domain and to examine how closely the seasonal rise of admissions for conditions purported to be sensitive to influenza, parallel the circulation of influenza viruses. The demonstration of increased hospitalization for congestive heart failure during an influenza season should be evident in the time series analysis as well. Given that some dispute exists in the literature about the relationship between influenza virus and admissions for congestive heart failure in the elderly, time series
analysis would provide additional evidence on the purported association.

Consequently, this thesis will employ time series methodology, in particular, transfer function models, to elaborate further the relationship between circulating influenza viruses and hospitalizations in the elderly population of Ontario. The use of transfer function models will permit a more precise estimate of the strength of the correlation between the presence of influenza and hospital admissions as well as rendering an accurate estimate of the temporal relationship between the two series. The study will attempt to replicate the findings of Perotta and extend the use of time series methodology to the study of congestive heart failure and chronic obstructive pulmonary disease. There are no published studies utilizing time series methodology to study these conditions.

**Bacterial Pneumonia in the Elderly: Epidemiologic and Diagnostic Issues**

Pneumonia is one of the leading causes of death in the elderly. The elderly, defined as those over the age of 65, are hospitalized at a greater rate for pneumonia than other age groups, and are more likely to experience complications from their illness (Marrie, 1992; Granton & Grossman, 1993). Pneumonia in the elderly presents complex issues in both diagnosis and therapy. The presenting signs and symptoms of pneumonia in the elderly are protean, and often do not correspond to established classic presentations (Marrie, 1992; Norman & Toledo, 1992; Granton & Grossman, 1993). Host factors such as co-morbidities and alterations in mental status often complicate the diagnostic process. Pneumonia in the elderly can be mistaken for other conditions such as congestive heart failure and vice versa. As well, factors such as expected death or advance directives may mitigate the degree of aggressiveness with which a definitive diagnosis is pursued (though these issues have not been systematically assessed). Agent factors also contribute to the complexity of diagnosis and treatment. A vast array of
bacteria, viruses and other microorganisms are capable of causing pneumonia. However, despite this variety, the clinical manifestations are, for the most part indistinguishable.

**Prospective Studies of Community Acquired Pneumonia**

The epidemiology of community acquired pneumonia in the elderly is a subject of ongoing research. Several studies have been conducted over the last fifteen years seeking to determine the etiology of community acquired pneumonia (Garb et al., 1978; Garabaldi, 1985; British Thoracic Society, 1987; Fang et al., 1990; Granton & Grosman, 1993; Bartlett & Mundy, 1995; Chow et al., 1995). The utility of these studies is evident; a clear understanding of the causes of pneumonia is imperative for selecting appropriate therapy. The utilization of diagnostic services is contingent upon the expected yield from diagnostic strategies. Prospective studies of the etiology of community acquired pneumonia in the elderly have been summarized by Granton and Grossman (Granton & Grossman, 1993). In the best of circumstances, with well defined protocols and exemplary laboratory services, causative organisms have not been isolated from 21-49% of patients enrolled in the studies. When a bacterial pathogen is isolated, *streptococcus pneumoniae* was the most frequent cause in 9 of 12 studies identified. *Streptococcus pneumoniae* was identified as the causative agent in 9-76% of the patients enrolled in theses studies. Influenza A was the third most common cause of pneumonia in 4 of 12 studies, with causation attributed for 5-9% of the cases. Influenza B, with 7% of the cases, is the third most common pathogen in one study. The degree to which viruses are identified as causative agents depends on whether or not viral studies are included in the protocol, the method of detection used and the time of the collection of the specimen relative to the duration of viral replication and shedding. Furthermore, the extent to which a pathogenic strain of influenza is in circulation on any given year directly effects the extent to which influenza is likely
to be isolated. Studies of short duration, or that are conducted in years that influenza is not circulating will not capture the effects of influenza.

The studies mentioned above are also unable to capture the extent to which a serious viral illness, such as influenza, may predispose an elderly person to develop pneumonia. Given the fact that in each study a large proportion of cases do not have a microbiological diagnosis, it is possible that viral infections may be a contributing or a direct cause of lower respiratory disease. Influenza infections are known to predispose vulnerable persons to the development of pneumonia through several mechanisms. In general, there is destruction and impairment of lower respiratory function and increased inflammation and permeability of immune barriers in the upper respiratory tract and complex interactions between bacterial and viral proteases (Sweet and Smith 1980; Cesario and Yousefi 1992; Greenberg 1992; Schebauer et al., 1992). Consequently, a proportion of pneumonia in the elderly that is attributed to unknown bacterial causes may in fact have a viral origin.

Marrie (Marrie et al., 1989) conducted a large five year study of 1269 cases of community acquired pneumonia in Nova Scotia with 672 of those being elderly. Of these cases, 57% were of unknown etiology. Streptococcus pneumoniae accounted for 7% of the cases and Influenza A for 5%.

Epidemiologic studies using administrative data bases.

The use of administrative data bases for the analysis of health services has been well established for surgical procedures (Naylor et al., 1994). As surgical procedures are well defined events they tend to be properly classified and coded on hospital separation data bases. However, the reliability of coding for certain medical conditions has been less thoroughly researched. Williams and Young (Williams and Young, 1996) recently reviewed the reliability of diagnostic
coding for a set of medical conditions. Specifically, they reviewed the literature concerning agreement between coded principal diagnoses and published or developed explicit criteria. In eight studies analysed they found variability in the rate of agreement between hospital records and expert criteria. The greatest disagreement between coded diagnosis and expert opinion occurred for conditions where diagnostic uncertainty is highest among practising clinicians. The rates of agreement were highest for conditions in which diagnostic uncertainty is less, such as myocardial infarction and fractures. In order to use administrative data bases for the epidemiological analysis of medical conditions it is necessary to ensure that the coding adequately reflects a true diagnosis.

Few studies have been published examining the reliability of diagnostic coding for pneumonia. Marrie and colleagues (Marrie et al., 1987) compared the coding of pneumonia found on discharge separations with the findings of a prospective cohort study they had conducted on the etiology of community acquired pneumonia. The authors were chiefly interested in determining whether the medical records data, coded using ICD-9, were adequate for the examination of the epidemiology of pneumonia on the basis of specific etiologies.

They reported that the medical records data base listed 127 discharges with ICD-9 codes for pneumonia compared to 105 identified by their prospective study; of these, 73 were found in both data sources. There was agreement on the etiologic diagnosis of pneumonia for 38/72 (52%) of the records. Of note, diagnoses that require serology, such as mycoplasma pneumoniae and viral pneumonia, were not classified by the appropriate ICD-9 coding on discharge. This is not surprising as there is a time lag in the return of serology results and consequently this information may not have been available to coders at the time of abstraction.

Marrie concludes that medical records data be used with caution for studying the
epidemiology of the etiology of pneumonia. They state: "Pneumonia is an especially difficult diagnosis to use for the assessment of the quality of medical records data, because the only circumstances in which one is sure of the etiologic diagnosis are blood-culture positive pneumonia and lung tissue or pleural fluid culture-positive pneumonia." (Marrie et al., 1987 p.23-24).

Gray (Gray et al., 1994) conducted a large scale epidemiologic study of the etiology of pneumonia in active duty Navy and Marine corps personnel. The study covered the years from 1981-1991 and included 6,522 admissions. The study sample was drawn from a centralized computer database of all admissions for active duty personnel. Inclusion criteria included all persons 17-65 years old who were on active duty or cadets. They also conducted a small chart audit to determine the method by which the etiologic diagnosis was made. ICD-9 codes for pneumonia (480-487) were used in the study.

The results of Gray's study indicate 65% of the pneumonia admissions had no causative organism identified when ICD-9 code 485 and 486 are combined. The data was used to calculate the mean annual rate of admission on the basis of etiology. The median age of the population was 22 years. The most common pathogens identified were *streptococcus pneumoniae* 12.3 % (ICD-9 code 481) and *mycoplasma pneumoniae* 10.8% (ICD-9 code 483). Influenza accounted for only 0.45% of the admissions. This is not surprising as military personnel are required to receive influenza vaccinations annually and the efficacy of the vaccine is highest amongst young and healthy adults.

The analysis of the chart audit is only mentioned briefly with no tabular data provided. The authors allude to the study in a paragraph: “Our record review confirmed that few admissions diagnosis were based on specific tests, which supports our observation that most
diagnoses and treatment were empiric and non-specific. Unfortunately, our record review questionnaire was not well suited to determine which diagnostic tests were run when specific diagnoses were not made. However, assuming that Navy clinicians did order the appropriate tests, these data emphasize the need to improve routinely available diagnostic tests for agents that cause lower respiratory tract disease.” (Gray et al., 1994 p.798).

The lack of numerical data to support the above assertions, together with the findings of Marrie’s study, indicate that caution is necessary when using administrative data bases for examining the epidemiology of the etiology of pneumonia. It leaves open the question of how accurately the codes reflect the diagnosis of pneumonia per se. The results, however, do not vitiate aggregating pneumonia codes in order to study temporal trends for pneumonia admissions or as an index of acute respiratory disease morbidity.

In order to proceed with aggregating codes it is necessary to determine the accuracy of coding in the data base under investigation. Consequently, this thesis will attempt to assess the validity of the coding of pneumonia in the HMRI/CIHI database by means of a structured chart audit. Pneumonia will be the chief focus of the chart audit as it is the most important clinical outcome associated with influenza. The International Classification of Diseases, 9th revision, includes a separate code for each possible microbiologic etiology of pneumonia. Other target conditions, such as congestive heart failure and acute bronchitis, have less extensive codes associated with them, and consequently there is less difficulty in using them in aggregate form. Nonetheless, as there exists possible misclassification, charts from the other diagnostic categories of interest will be examined.

Diagnostic Considerations

The diagnosis of pneumonia usually requires a clinical history compatible with a lower
respiratory tract infection: cough, fever, malaise and the development of sputum production. Chest radiographs and laboratory tests are ordered to confirm the clinical suspicion of pneumonia, and ideally identify the causative organism so that appropriate therapy is selected.

In the elderly, diagnosis of pneumonia is complicated by the fact that clinical signs and symptoms suggestive of pneumonia may not be present (Marrie, 1992; Granton & Grossman, 1993). A febrile response to pathogens may be blunted; cough may be absent or minimal. The only overt sign of illness may be an alteration in activity level or mental status. With increased age, and the presence of co-morbid conditions, the manifestations of pneumonia depart from the well described classic pattern and assume a plurality of presentations.

The yield of diagnostic tests vary considerably. Chest radiographs are the gold standard for the diagnosis of pneumonia. However, despite the existence of diagnostic pearls for the pattern recognition of specific etiologies, etiologic diagnosis cannot be reliably ascertained from radiographs (Scanlon & Unger, 1973; Young & Marrie, 1994). Indeed, viral and bacterial pneumonia cannot be reliably distinguished radiographically (Scanlon & Unger, 1973). As well, there is considerable inter-observer variability in the interpretation of the presence of pneumonia. Young and Marrie (Young & Marrie, 1994) conducted a study on the inter-observer variability in the interpretation of chest radiographs of pneumonia patients. They found that agreement on the diagnosis of pneumonia was most likely when lobar consolidation or segmental opacities were present. However, patchy infiltrates were most likely to be interpreted as non-pneumonia.

Laboratory tests include blood-cultures, sputum culture, and serology. Blood cultures are highly sensitive, but are positive in only 6-7% of cases (Woodhead et al., 1991). Sputum examination is frequently ordered but often not obtainable from elderly patients (Granton & Grossman, 1993; Hodder, 1994). Even when produced it may not be of sufficient quality for
diagnostic purposes. When samples are produced, the rate of false positive gram stains approaches 50 percent (Woodhead et al., 1991). More invasive methods for obtaining specimens such as transtracheal aspiration and bronchoscopy are excellent for obtaining high quality specimens but are seldom used in the routine investigation of pneumonia in the elderly.

Serological methods exist for the diagnosis of a variety of bacterial and viral pathogens. Serology requires the collection of acute and convalescent sera, usually one specimen at the onset of illness and the other 3-4 weeks later. This delay makes serology of limited diagnostic utility as treatment decisions must be made early and cannot wait on the precise etiology to be determined. Many new rapid antigen detection techniques have been developed for viral and bacterial agents, but none has achieved wide-spread acceptance or proven their clinical utility (Bartlett & Mundy, 1995). The difficulty surrounding the diagnosis of pneumonia with current techniques have prompted some to question the use of routine testing (Woodhead et al., 1991; Antoniou & Grossman, 1995). At present, most therapy is based on empirical considerations with precise etiology playing only a limited role in therapeutic decisions.

Summary and Conclusions

The above considerations make it evident that influenza is a major cause of morbidity and mortality in the elderly. Traditional approaches that emphasize epidemic versus non-epidemic years, or that seek to calculate excess only during epidemics obscure the measurement of the annual predictable morbidity associated with influenza in the elderly. Studies that aggregate the elderly into one age-group likely obscure important differences between age-groups. Limiting the consideration of the impact of influenza to pneumonia mortality and hospitalizations may also miss significant increases in morbidity associated with other conditions. Time-series analysis can complement information derived from age and sex standardized rates
and help to generate a more robust and thorough appreciation of the impact of influenza on the elderly population of Ontario.

The focus on the existence of excess mortality, which, although of great importance, may not be the only important indicator of the serious health impacts of influenza on a population. Consequently, seasons labelled non-epidemic in terms of mortality, may have been significant in terms of morbidity. This can occur when influenza periods are not intense, but long and protracted. Analysis of the mortality patterns of the 1978 H1N1 epidemic failed to show excess mortality, though subsequent analysis indicated considerable morbidity (Barker, 1986). The focus upon identifying epidemic years of influenza or of seeking excess from projected baselines using mortality can therefore obscure the annual increases in morbidity caused by influenza. From the point of view of health services and planning, it is likely that estimates of morbidity caused by influenza will yield more important information.

The Nicol and McBean studies demonstrate the power and utility of large administrative data bases for retrospectively assessing the effects of influenza on a population. The existence of a large administrative data base of all discharge separations from Ontario allows the opportunity to perform similar studies. The utility of this would be to quantify the extent to which influenza contributes to health service utilization by the elderly. It can thus serve as a marker for determining how well the public health objectives of influenza control are being met, as well as providing the grounds for the estimation of the costs incurred by influenza and may contribute to the foundation of rational health services planning.

This thesis will seek to confirm the work of McBean et al., by employing a similar methodology to estimate the impact of influenza on the admission rates for targeted conditions. It will extend their work by examining in detail the age and sex specific admission rates for these
targeted conditions. A detailed analysis of the differences between age groups and sexes has not been published using Ontario data.

The thesis will also seek to corroborate the findings of Perotta et al. This study will extend the use of time series models to examine congestive heart failure, chronic respiratory disease and acute bronchitis. The explicit focus on admissions in the elderly for these conditions constitutes an original contribution to the literature.
Objectives

Chart Audit:

1) To examine the validity for the coding of pneumonia in the HMRI/CIHI database

Comparison of Influenza Seasons:

1.) To calculate the age and sex specific and adjusted rates of admission for pneumonia, acute bronchitis, chronic respiratory disease, and congestive heart failure for five influenza seasons from 1988-1993.

2.) To estimate the impact of influenza on the risk of admission for the same conditions by comparing influenza seasons to interim periods when influenza is not circulating. This estimate can be regarded as the seasonal excess attributable to influenza.

The a priori hypothesis to be tested is that influenza seasons are associated with increased hospital admission rates for each defined diagnostic group.

Time Series Analysis:

1.) To estimate the strength of the correlation between the circulation of influenza virus and admissions for pneumonia, acute bronchitis, chronic respiratory disease and congestive heart failure for each influenza season.

The a priori hypothesis to be tested is whether there is a significant positive correlation between the circulation of influenza viruses and increases in hospital admissions for each defined diagnosis group.

2) To estimate the lag time between the peak circulation of influenza virus and the admissions for the same conditions.
Methods and Approach

Data Sources

A) Chart Audit

Three hospitals were selected from which to collect chart information. The Chesley and District Memorial Hospital, a small 20 bed hospital that serves a rural community with a catchment population of approximately 10,000 persons; The County of Bruce Hospital, a 100 bed hospital serving the southern portion of Bruce County; and The Sunnybrook Health Sciences Centre, a 1024 bed teaching hospital in Metropolitan Toronto. Permission for access to charts was granted by each institution for the purposes of collecting information regarding the utilization of diagnostic tests and the coding for the diagnosis of pneumonia. No personal identifiers were taken from the charts. Charts were requested from the diagnostic codes for pneumonia, as well as congestive heart failure, acute bronchitis and chronic obstructive pulmonary disorders.

A form was developed for data collection. (Appendix 2) Demographic variables, place of residence prior to admission, place discharged to and vital status were recorded. Information on diagnostic test utilization was abstracted from the chart. Information on the following tests were collected: haemoglobin, white blood cell count, electrolytes, blood urea nitrogen, creatinine, and arterial blood gases; microbiological studies included sputum cultures, blood cultures, serology, urinary antigen studies and throat washings or nasopharyngeal aspirates; chest radiographs and their interpretation by the radiologist was recorded. The diagnostic coding was recorded from the discharge separation sheet that is submitted to HMRI/CIHI.

Values collected for the blood tests consisted of the first recorded value and therefore
represented the admission value. Results from microbiology and radiology referred to all tests ordered during the first week of admission. For example, if three sets of blood cultures were ordered, and all were negative, the results were recorded negative. If however, any reported microbiological specimen was ordered during the first week and found to be positive, it was recorded as positive. For radiological reports, all reports extant on the chart that were ordered during the hospital admission were examined. If the report was consistent with pneumonia, and the radiograph was ordered less than one week after admission it was recorded as positive. This was to screen out nosocomial pneumonia contracted during prolonged admissions.

The chart audit data were entered into a data base using Epi-Info version 6.02. All data were abstracted by the student.

A sample of 225 charts form the years 1990-1993 were drawn: 50 each from the Chesley and District Memorial Hospital and the County of Bruce General Hospital and 125 from the Sunny brook Health Sciences Centre. The hospitals were chosen on the basis of administrative ease of access to the charts. Inclusion criteria were: age greater than 65 years old on admission, admission with a diagnosis of pneumonia, chronic obstructive pulmonary disease, acute bronchitis or congestive heart failure. It was requested that 66% of the charts be for patients with a diagnosis of pneumonia, and that 75% of the charts be from a period during which influenza circulated. Charts were excluded if the patient was less than 65 years old, was transferred from a different institution, or contracted pneumonia during the admission.

B) Ontario Influenza Surveillance Data

Influenza surveillance is conducted annually by the Public Health Branch of the Ministry of Health in Ontario. Surveillance commences in October and continues until the end of April.
Influenza is a reportable disease under Ontario regulation 559/91 of the Health Protection and Promotion Act. The data includes laboratory surveillance, reports of influenza through the reportable disease information system (RDIS), reports of institutional outbreaks and through absenteeism and illness surveillance at selected schools.

As a reportable disease, influenza must be reported to medical officers of health in Ontario. Laboratories that isolate influenza virus follow a protocol to forward information to the medical officer of health in the health unit where the case resides. The data are entered into the RDIS data base. As well, 10 laboratories in Ontario participate in influenza surveillance. The Laboratory Centre for Disease Control (LCDC) in Ottawa contacts the laboratories weekly during the influenza season. LCDC forwards the results of the weekly influenza totals to the Disease Control Service of the Public Health Branch where they are tabulated and published in the Public Health Epidemiology Report of Ontario (PHERO) in an annual report on the influenza season.

Laboratory confirmation consists of either isolation of virus from nasal or pharyngeal secretions, direct antigen detection from nasal or pharyngeal secretions or a demonstrated four-fold rise in hemagglutination titres to influenza virus from serological specimens collected at the onset of illness and four weeks later. The majority of laboratory confirmed influenza infections are either virus isolation or antigen detection.

For the purposes of this study, influenza seasons were defined on the basis of reported laboratory confirmed cases from Ontario. An influenza season was defined as commencing with the isolation of influenza virus on consecutive weeks and ending when no further isolations were made.

Weekly totals for the influenza seasons were obtained from the Laboratory Centre for
Disease Control in Ottawa.

HMRI/CIHI

The Hospital Medical Records Institute, renamed the Canadian Institute for Health Information, is a federally chartered non-profit non-governmental organization that collects and analyses health information derived from a standardized discharge separation abstract. The Institute for Clinical Evaluative Sciences, sited at the Sunnybrook Health Sciences Centre, has been granted permission to use the data base for research purposes.

On discharge each chart has administrative and clinical variables abstracted by a medical records clerk. Data are collected on a fiscal year basis from April 1-March 31. The database provides information on demographic variables such as age and sex, residence, admission date, discharge date, length of stay, diagnosis and procedures. Diagnosis codes can accommodate up to sixteen diagnoses. Discharge diagnoses are classified according to the International Classification of Diseases (ICD-9) classification. A physician field is included that identifies the specialty of the physician rendering services to the hospitalized patient.

Uniform standards are set by the institute. Compulsory fields include a principal diagnosis (most responsible diagnosis). Abstracts that fail to include compulsory fields are returned to the hospital of origin. Data quality issues have been addressed in a study sponsored jointly by the Ontario Ministry of Health, the Ontario Hospital Association and the Hospital Medical Records Institute (Anon., 1991) The report indicated that of all the diagnosis codes, the most responsible diagnosis had the highest agreement. Coding for other conditions besides the most responsible diagnosis was found to be discretionary and subject to individual interpretation.

Extraction of Study Files

Data from standard files were abstracted from fiscal years April 1 to March 31 1988-
1993. Extracted variables were age, sex, birth date, health care number, diagnosis codes 1-8, admission date, discharge date, length of stay, hospital, hospital region, and vital status on separation date. The following ICD-9 codes were included: Pneumonia and Influenza: 480.0-487.0; Acute Bronchitis: 466.0-466.1; Chronic Respiratory Disease: 490.0-492.0 and Congestive Heart Failure: 428.0-428.9.

All records were included if the age was 65 years old or greater and a resident of Ontario. A hierarchical rule was used to create data sets for each diagnosis group. Each diagnosis group was constructed by extracting records for the target condition when it appeared in the first or second diagnosis code, exclusive of the presence of the other diagnosis groups in any diagnosis code.

The records were sorted by admission date and sex. Age groupings were created as follows: 65-74, 75-84 and 85+. ICD-9 codes were then aggregated into four groups: pneumonia and influenza, acute bronchitis, chronic respiratory disease, and congestive heart failure. Weekly data files were created for each diagnosis group overall and by age group and sex using the SAS program PROC EXPAND which can be used to convert data recorded by day to weekly aggregates. The weekly series extends from April 8 1988 to March 31 1994. With this series it is possible to examine 5 influenza seasons: 1988-89, 1989-90, 1990-91, 1991-92, 1992-93.

Population Data

Population data were obtained for Ontario for the years 1988-1991 on the basis of intercensal estimates published by census Canada. 1991 was a census year, so census data were used. 1992-1993 populations were drawn from extrapolations from Census Canada. These estimates were used to calculate the age specific rates of admission for each influenza season.
For standardization, the 1986 population from Statistics Canada was used.
Methods of Analysis

Chart Audit

All variables extracted in the chart audit were examined for their distributions. The distributions of the diagnosis codes were tabulated as were all diagnostic procedures. Percentages of diagnostic testing for each diagnosis code for pneumonia were calculated.

A decision rule was created to determine whether the chart data supported a diagnosis of pneumonia as follows. Definite pneumonia: two or more of the clinical symptoms: malaise, cough, dyspnea and sputum production; radiographic evidence of pneumonia defined as a radiologist’s interpretation of a film being consistent with pneumonia and blood culture or pleural fluid culture of a causative organism. Probable pneumonia consisted of two or more clinical signs and symptoms; radiographic evidence consistent with pneumonia and sputum isolation or serological evidence of a causative organism. Possible pneumonia consisted of two or more clinical signs and symptoms and radiographic evidence consistent with pneumonia. Pneumonia, diagnosis uncertain consisted of two or more clinical signs and symptoms; no causative organism isolated and chest radiograph reported as negative. All ICD-9 codes for pneumonia as the principal diagnosis were classified according to these criteria and percentages of records meeting these criteria were calculated. Principal diagnoses other than pneumonia were examined to determine if pneumonia existed in these categories but was incorrectly coded.
Calculation of Rates

Age specific annualized rates were calculated for each age and sex group for each influenza and interim series for five years. Age and sex adjusted standardized annualized admission rates were calculated. Weekly counts were aggregated for each diagnosis group according to age and sex and summed for each of the five influenza seasons in order to create numerators. Interim period rates were calculated by the same method on the basis of a comparable number of weeks commencing June 1. This was necessary as influenza can be isolated as late as May in some seasons. Denominators for each season were constructed from the census estimate for the year in which the influenza season ended. Therefore, the denominator for both the influenza season and the interim period were for the same year. The ratios were calculated by dividing the influenza season by the interim period for both age specific rates and age and sex adjusted rates. 95% confidence intervals for the age specific rates were calculated following the method of Chiang (Chiang, 1984).

Time Series Analysis

Time plots were created for each diagnosis group and for influenza isolates by aggregating the weekly totals for each diagnosis group. Each season was analysed from the onset of consecutive weeks of reported isolations until the end of the season.

Time series models were fit to the data using Eviews software. Models were constructed following the method established by Box and Jenkins. The process entails three steps: identification, estimation and diagnosis. For identification one examines the autocorrelation function and partial autocorrelation function. Identification of the input series, influenza, indicated that fitting AR(1) models was appropriate. Coefficients were then estimated using ordinary least squares. Co-efficients must be statistically significant to remain in the model. The
adequacy of this model is assessed by the Q statistic which indicates whether the input series has any residual autocorrelation structure remaining. The Q statistic tests the hypothesis that all the lags of the residual series are uncorrelated. After the same AR(1) term was imposed on the output series (pneumonia, congestive heart failure, chronic obstructive pulmonary disease, and acute upper respiratory disease) cross correlations were calculated on the residuals of each series. Significant correlations are defined as those that exceed twice the standard error. As yet, there is no method to place confidence intervals on estimated cross-correlations. Time series methodology is discussed in detail in Appendix 1.
Results

In this chapter, tables will be incorporated into the text and figures will be found at the end of the chapter. The results will be presented sequentially according to the objectives of the thesis. Consequently, the results of the chart audit will be presented first, followed by the detailed examination of annualized admission rates and finally the time series analysis.

Objective 1

225 charts were selected by the participating institutions. 183 met the inclusion criteria. 20 were excluded because the patient was transferred from another institution, 12 were excluded because the chart was from a patient less than 65 years old, and 10 were excluded because of nosocomial pneumonia.

102 of 183 charts that met the inclusion criteria for analysis were from the diagnostic codes for pneumonia, 28 were from the diagnostic codes for congestive heart failure, 33 for chronic obstructive lung disease and 20 from acute upper respiratory disease. The mean age of the chart audit sample was 79.6 years old. There were 102 males and 81 females.

Table 1 shows the breakdown of pneumonia codes according to the a priori classification protocol. 81 of 102 (79.4%) charts coded for pneumonia were found to be either definite (3) probable (11) or possible (67). The other 21 were classified as uncertain.

In the uncertain category, 12 were reported as having no radiographic evidence of pneumonia, and would likely be more accurately coded as acute upper respiratory disease; 4 had congestive heart failure or pleural effusions thought to be secondary to congestive heart failure and 5 charts lacked sufficient data to properly classify according to the decision protocol.

Of the 81 charts drawn from the non-pneumonia codes, no charts had evidence that
supported a primary diagnosis of pneumonia according to the classification protocol.

For the 91 charts classified as ICD-9 codes 485.0 and 486.0, 87 had chest radiographs. Of these, 70 (77.7 %) were interpreted by radiologists as consistent with pneumonia. 12 (13.3 %) were reported negative, 3 had pleural effusions, 1 was reported as congestive heart failure. 1 had no report available on the chart.

Of the twelve reported negative chest radiographs, 10 had clinical signs and symptoms consistent with pneumonia, but no microbiological evidence of a causative organism. For the other two, no clinical data were recorded. However, one of these cases had a blood culture positive for *Escherichia coli*.

Of the 70 cases coded for no specific etiology and with radiographic evidence of pneumonia, 1 case had a positive blood culture for Group A streptococcus (ICD-9 code 482.3) and signs and symptoms compatible with pneumonia. 6 had positive sputum samples: one case each of *streptococcus pneumoniae*, *hemophilus influenza*, *pseudomonas aeruginosa* and *branhamella catarrhalis* and two cases with mixed growth: one with *klebsiella* and *e-coli* and one with *streptococcus pneumoniae* and *staphylococcus aureus*. This would represent a possible 10% misclassification rate on the basis of etiology.

Of the 11 cases with etiologies identified, all met clinical criteria and 10 had radiographic evidence of pneumonia. Etiologic diagnosis was made on the basis of blood culture for two cases, and by sputum culture for four cases and urine culture for one case. No causal organism could be determined for 4 cases. No cases were diagnosed on the basis of serology, pleural fluid culture or trans-tracheal aspirates. Consequently, 36% of the charts with etiologic diagnosis listed had no supporting evidence for the etiology.

Of the 81 charts drawn from ICD-9 codes 466.0, 428.0-428.1, and 490.0-496.0, no
cases were found in which radiographic evidence of pneumonia was reported by the radiologist.

Table 1: Classification of Pneumonia by Decision Rule

<table>
<thead>
<tr>
<th>Pneumonia Code</th>
<th>Number</th>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>480.00-480.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>481.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Bacterial</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>482.00-484.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia Unspecified</td>
<td>91</td>
<td>1</td>
<td>8</td>
<td>63</td>
<td>19</td>
</tr>
<tr>
<td>485.00-486.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>102</td>
<td>3</td>
<td>11</td>
<td>67</td>
<td>21</td>
</tr>
</tbody>
</table>

**Diagnostic Utilization**

Although the primary intention of the audit was not to enumerate the total number of laboratory tests ordered for each patient, a secondary objective was to determine whether serological or viral isolation studies were used in the diagnosis of pneumonia. The order sheets and laboratory results section of each chart that was coded from ICD-9 480-487 was examined for a record of viral serology, throat or nasopharyngeal washings, or viral culture. Two charts contained viral studies. One set of tissue cultures was ordered by a pathologist post mortem, and one set of culture was ordered for a patient suffering from pneumonia secondary to a herpes virus infection. Contrarily, 77.6% of patients with pneumonia had blood cultures and 62.1% had sputum examinations ordered. As well, it is of interest to note that the influenza immunization status was not noted on any patient chart.

**Objective 2**

In this section the results for each diagnostic group will be presented in detail. The general format will be to present the age and sex adjusted annualized rates first, followed by the
age specific annualized rates for males and then females. A table summarizing the salient results will be found at the conclusion of this section.

**Rates of Admission:**

Table 2 shows the characteristics of the predominant influenza strains, the defined influenza seasons and interim periods for the study.

Table 2: Influenza Isolates and Characteristics: 1988-1993

<table>
<thead>
<tr>
<th>Year</th>
<th>Predominant Influenza Isolates</th>
<th>Dates of Influenza Season</th>
<th>Dates of Interim Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-93</td>
<td>A/Beijing H3N2 (48%)  B/Panama (52%)</td>
<td>12/11/92-05/07/93</td>
<td>06/06/93-10/24/93</td>
</tr>
<tr>
<td>1991-92</td>
<td>A/Beijing H3N2 (96%)</td>
<td>10/26/91-07/02/92</td>
<td>06/07/91-09/13/91</td>
</tr>
<tr>
<td>1990-91</td>
<td>B/Yamagata (98%)</td>
<td>11/23/90-04/05/91</td>
<td>06/02/91-10/06/91</td>
</tr>
<tr>
<td>1989-90</td>
<td>A/Shanghai H3N2 (94%)</td>
<td>10/29/89-03/25/90</td>
<td>06/03/90-10/28/90</td>
</tr>
<tr>
<td>1988-89</td>
<td>A/Taiwan H1N1 (88%)</td>
<td>12/11/88-04/16/89</td>
<td>06/04/89-10/01/89</td>
</tr>
</tbody>
</table>

**Pneumonia**

**Age and sex adjusted annualized rates:**

The age and sex adjusted annualized admission rates per 100,000 population varied from year to year. Table 3 shows the annualized age and sex adjusted admission rates per 100,000 persons for each influenza season and interim period. The highest age and sex adjusted annualized admission rate was associated with the 1990-1991 influenza season: 17,668 per 100,000. The lowest age and sex adjusted annualized admission rate was associated with the 1988-1989 influenza season: 11,867 admissions per 100,000 persons. The percentage increase in comparison to the interim period ranged from a low of 33% for the 1988-1989 season to a high of 62% for the influenza season of 1992-1993.

Table 3: Age and Sex Adjusted Annualized Admission Rates: Pneumonia
Age Specific Rates:

The annualized age specific rates of admission for pneumonia were higher in each age group in each influenza season for males compared to females. In the oldest age group, the male admission rate ranged from 57% to 90% higher than the female rate. The range in percentage difference between males and females in the 75-84 age group was 52 to 73%. For the 65-74 age group the range in percentage difference was 9 to 54%.

Pneumonia

Males

Each influenza season showed non-overlapping confidence intervals in annualized age specific rates for each age group in comparison with the interim period. Tables 4-6 show the estimates of the annualized admission rates for both the influenza season and interim period and the 95% confidence intervals for males and pneumonia. For the 85+ age group, the percentage increase rate of admission ranged from 27-47% compared to the interim. For the 75-84 age group the percentage increase ranged from 43-55%. For the 65-74 age group the percentage increase ranged from 21-36%.

The annualized age-specific admission rates for pneumonia were 1.85 to 2.24 times higher in the 85+ category compared to the age 75-84 age group for each comparable influenza season and 6.2 to 9.9 times higher compared to the 65-74 age group for each comparable

<table>
<thead>
<tr>
<th>Year</th>
<th>Influenza Season</th>
<th>Interim Period</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>11867</td>
<td>8964</td>
<td>1.33</td>
</tr>
<tr>
<td>1989-1990</td>
<td>13991</td>
<td>9186</td>
<td>1.52</td>
</tr>
<tr>
<td>1990-1991</td>
<td>12114</td>
<td>9018</td>
<td>1.34</td>
</tr>
<tr>
<td>1991-1992</td>
<td>17688</td>
<td>11569</td>
<td>1.53</td>
</tr>
<tr>
<td>1992-1993</td>
<td>14623</td>
<td>8836</td>
<td>1.62</td>
</tr>
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</table>
influenza season. Figure 1 shows the comparison of the annualized age specific admission rates for the influenza seasons 1988-1989 to 1992-1993.

**Table 4: Annualized Admission Rates per 100,000: Males 85+ Pneumonia**

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non Overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>5037</td>
<td>4635</td>
<td>4232</td>
<td>4009</td>
<td>3651</td>
<td>3294</td>
<td>1.27</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>5927</td>
<td>5498</td>
<td>5069</td>
<td>4265</td>
<td>3904</td>
<td>3542</td>
<td>1.4</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>5800</td>
<td>5381</td>
<td>4963</td>
<td>4226</td>
<td>3871</td>
<td>3518</td>
<td>1.39</td>
<td>Yes</td>
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<td>1991-92</td>
<td>7533</td>
<td>6977</td>
<td>6423</td>
<td>5810</td>
<td>5325</td>
<td>4841</td>
<td>1.31</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td>5556</td>
<td>5171</td>
<td>4787</td>
<td>3847</td>
<td>3529</td>
<td>3212</td>
<td>1.47</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Table 5: Annualized Admission Rates per 100,000: Males 75-84**

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non Overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>2447</td>
<td>2316</td>
<td>2184</td>
<td>1813</td>
<td>1700</td>
<td>1587</td>
<td>1.36</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>2868</td>
<td>2729</td>
<td>2589</td>
<td>1868</td>
<td>1758</td>
<td>1645</td>
<td>1.55</td>
<td>Yes</td>
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<tr>
<td>1990-91</td>
<td>2529</td>
<td>2400</td>
<td>2271</td>
<td>1908</td>
<td>1797</td>
<td>1684</td>
<td>1.39</td>
<td>Yes</td>
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<td>1991-92</td>
<td>3952</td>
<td>3759</td>
<td>3567</td>
<td>2789</td>
<td>2630</td>
<td>2470</td>
<td>1.43</td>
<td>Yes</td>
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<td>1992-93</td>
<td>2780</td>
<td>2650</td>
<td>2520</td>
<td>1963</td>
<td>1855</td>
<td>1748</td>
<td>1.43</td>
<td>Yes</td>
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</table>

**Table 6: Annualized Admission Rates per 100,000: Males 65-74**

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>795</td>
<td>745</td>
<td>695</td>
<td>608</td>
<td>566</td>
<td>521</td>
<td>1.32</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>903</td>
<td>850</td>
<td>800</td>
<td>750</td>
<td>703</td>
<td>655</td>
<td>1.21</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>863</td>
<td>816</td>
<td>766</td>
<td>642</td>
<td>600</td>
<td>555</td>
<td>1.36</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>920</td>
<td>863</td>
<td>811</td>
<td>702</td>
<td>653</td>
<td>607</td>
<td>1.32</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td>880</td>
<td>830</td>
<td>783</td>
<td>665</td>
<td>625</td>
<td>585</td>
<td>1.32</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Females:**

Similar to the males, each influenza season was associated with non-overlapping confidence intervals in comparison to the interim period. Tables 7-9 show the estimated
annualized admission rates per 100,000 and the 95% confidence intervals for females and pneumonia. The range of percentage increase for females 85+ was 47 to 65%; for the 75-84 age group: 48 to 79% and for the 65-74 age group: 24 to 70%.

The annualized admission rates for the oldest female age group were 1.7 to 2.1 times higher than the 75-84 age group for each influenza season and 4.7 to 5.5 times higher than the 65-74 age group for each comparable influenza season. Figure 2 shows the age specific annualized admission rates for each influenza season from 1988 to 1993.

Table 7: Annualized Admission Rates per 100,000: Females 85+ Pneumonia

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>3145</td>
<td>2937</td>
<td>2726</td>
<td>2176</td>
<td>2003</td>
<td>1829</td>
<td>1.47</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>3292</td>
<td>3087</td>
<td>2884</td>
<td>2021</td>
<td>1863</td>
<td>1705</td>
<td>1.65</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>3013</td>
<td>2818</td>
<td>2629</td>
<td>2053</td>
<td>1895</td>
<td>1740</td>
<td>1.49</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>3963</td>
<td>3707</td>
<td>3452</td>
<td>2548</td>
<td>2344</td>
<td>2141</td>
<td>1.58</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td>3040</td>
<td>2855</td>
<td>2675</td>
<td>1845</td>
<td>1705</td>
<td>1563</td>
<td>1.7</td>
<td>Yes</td>
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</table>

Table 8: Annualized Admission Rates per 100,000: Females 75-84 Pneumonia

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>1471</td>
<td>1389</td>
<td>1308</td>
<td>1003</td>
<td>934</td>
<td>868</td>
<td>1.48</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>1782</td>
<td>1695</td>
<td>1605</td>
<td>1018</td>
<td>950</td>
<td>884</td>
<td>1.78</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>1660</td>
<td>1576</td>
<td>1492</td>
<td>1026</td>
<td>960</td>
<td>895</td>
<td>1.64</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>2285</td>
<td>2170</td>
<td>2052</td>
<td>1300</td>
<td>1215</td>
<td>1126</td>
<td>1.79</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td>1730</td>
<td>1650</td>
<td>1568</td>
<td>1040</td>
<td>978</td>
<td>915</td>
<td>1.69</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 9: Annualized admission Rates per 100,000: Females 65-74 Pneumonia

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>576</td>
<td>537</td>
<td>497</td>
<td>468</td>
<td>434</td>
<td>400</td>
<td>1.24</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Congestive Heart Failure:
Age and Sex Adjusted Annualized Rates:

The age and sex adjusted annualized admission rates varied from year to year. The rates ranged from a high of 21,763 per 100,000 for the 1991-1992 influenza season to a low of 14,928 per 100,000 for the 1989-1990 influenza season. The percentage difference to the interim period ranged from a low of 3% for the 1991-1992 influenza season to a high 17% for the 1990-1991 influenza season. Table 10 shows the annualized age and sex adjusted admission rates per 100,000 for each influenza season and interim period.

Table 10: Age and Sex Adjusted Annualized Admission Rates: Congestive Heart Failure

<table>
<thead>
<tr>
<th>Year</th>
<th>Influenza Season</th>
<th>Interim Period</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989-90</td>
<td>611</td>
<td>571</td>
<td>532</td>
</tr>
<tr>
<td>1990-91</td>
<td>568</td>
<td>529</td>
<td>495</td>
</tr>
<tr>
<td>1991-92</td>
<td>844</td>
<td>793</td>
<td>741</td>
</tr>
<tr>
<td>1992-93</td>
<td>595</td>
<td>560</td>
<td>523</td>
</tr>
</tbody>
</table>

Age Specific Rates

The annualized age specific rates of admission for congestive heart failure were higher in each age group in each influenza season for males compared to females. In the oldest age group, the male admission rate ranged from 5% to 24% higher than the female rate. The range in percentage difference between males and females in the 75-84 age group was 22 to 34%. For
the 65-74 age group the range in percentage difference was 41 to 88% higher.

Males:

For the 85+ age group non-overlapping confidence intervals of annualized admission rates were found in the 1989-1990, 1990-1991, and 1992-1993 influenza seasons. For the 75-85 age group, statistically significant increases were found in each influenza season except 1991-1992. For the 65-75 age group, non-overlapping confidence intervals for admission rates were found for the 1988-89 and 1992-93 seasons only. The range of percentage increase for the non-overlapping years ranged from 22 to 33% for the 85+ age group, 11 to 15% for the 75-84 age group and 17 to 24% for the 65-74 age group. Tables 11-13 shows the estimated annualized age specific admission rates and 95% confidence intervals for males and congestive heart failure.

The annualized age specific admission rates were 1.32 to 1.55 times higher in the 85+ age group compared to the 75-84 age group and 3.68 to 4.40 times higher than the 65-74 age group. Figure 3 shows the comparison of the annualized age specific admission rates for the influenza seasons from 1988 to 1993.

**Table 11: Annualized Admission Rates per 100,000: Males 85+ Congestive Heart Failure**

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>4352</td>
<td>3980</td>
<td>3606</td>
<td>3865</td>
<td>3515</td>
<td>3164</td>
<td>1.13</td>
<td>Yes</td>
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<tr>
<td>1989-90</td>
<td>4511</td>
<td>4139</td>
<td>3767</td>
<td>3717</td>
<td>3381</td>
<td>3044</td>
<td>1.22</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>4884</td>
<td>4502</td>
<td>4121</td>
<td>3713</td>
<td>3381</td>
<td>3050</td>
<td>1.33</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>5786</td>
<td>5302</td>
<td>4819</td>
<td>5438</td>
<td>4969</td>
<td>4501</td>
<td>1.07</td>
<td>No</td>
</tr>
<tr>
<td>1992-93</td>
<td>4508</td>
<td>4324</td>
<td>4141</td>
<td>3601</td>
<td>3284</td>
<td>2967</td>
<td>1.31</td>
<td>Yes</td>
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</tbody>
</table>
Table 12: Annualized Admission Rates per 100,000: Males 75-84 Congestive Heart Failure

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>2918</td>
<td>2774</td>
<td>2629</td>
<td>2576</td>
<td>2439</td>
<td>2305</td>
<td>1.13</td>
<td>Yes</td>
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<tr>
<td>1989-90</td>
<td>2868</td>
<td>2729</td>
<td>2587</td>
<td>2584</td>
<td>2450</td>
<td>2318</td>
<td>1.11</td>
<td>Yes</td>
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<tr>
<td>1990-91</td>
<td>3047</td>
<td>2903</td>
<td>2760</td>
<td>2653</td>
<td>2518</td>
<td>2387</td>
<td>1.15</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>3952</td>
<td>3759</td>
<td>3567</td>
<td>4078</td>
<td>3915</td>
<td>3756</td>
<td>0.96</td>
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<td>1992-93</td>
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<td>3253</td>
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<td>3005</td>
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<td>2738</td>
<td>1.13</td>
<td>Yes</td>
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</table>

Table 13: Annualized Admission Rates per 100,000: Males 65-74 Congestive Heart Failure

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>1110</td>
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<td>990</td>
<td>897</td>
<td>845</td>
<td>792</td>
<td>1.24</td>
<td>Yes</td>
</tr>
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<td>1989-90</td>
<td>992</td>
<td>939</td>
<td>884</td>
<td>966</td>
<td>910</td>
<td>858</td>
<td>1.03</td>
<td>No</td>
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<td>1990-91</td>
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<td>974</td>
<td>976</td>
<td>921</td>
<td>842</td>
<td>1.12</td>
<td>No</td>
</tr>
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<td>1991-92</td>
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<td>1441</td>
<td>1363</td>
<td>1556</td>
<td>1474</td>
<td>1396</td>
<td>0.98</td>
<td>No</td>
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<td>1992-93</td>
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<td>1173</td>
<td>1118</td>
<td>1055</td>
<td>1003</td>
<td>950</td>
<td>1.17</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Females:

Non-overlapping confidence intervals for annualized age specific admission rates in comparison to the interim period were associated with the 1988-1989, 1990-1991, 1991-1992 and 1992-1993 influenza seasons in the 85+ age group. For the 75-84 and 65-74 age groups non-overlapping confidence intervals for annualized age specific admission rates were found for the 1988-1989 and 1990-1991 influenza seasons only. The range of percentage increase for the influenza seasons was 14 to 30% for the 85+ age group, 8-15% for the 75-84 age group, and 17-18% for the 65-74 age group. Tables 14-16 shows the estimated annualized age specific admission rates and 95% confidence intervals for each influenza season in comparison to the interim period for females and congestive heart failure.

The annualized age specific admission rates were 1.6 to 1.65 times higher in the 85+ age group compared to the 75-84 age group and 5.45 to 5.98 times higher than the 65-74 age
group. Figure 4 shows the comparison of the annualized age specific admission rates for each age group for females and congestive heart failure.

Table 14: Annualized Admission Rates per 100,000: Females 85+ Congestive Heart Failure

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>3837</td>
<td>3603</td>
<td>3371</td>
<td>2976</td>
<td>2771</td>
<td>2568</td>
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<td>1989-90</td>
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<td>3384</td>
<td>3171</td>
<td>3234</td>
<td>3034</td>
<td>2831</td>
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<td>1990-91</td>
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<td>3418</td>
<td>3279</td>
<td>3081</td>
<td>2879</td>
<td>1.17</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>5337</td>
<td>5037</td>
<td>4737</td>
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<td>4430</td>
<td>4152</td>
<td>1.14</td>
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<td>1992-93</td>
<td>4183</td>
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<td>3753</td>
<td>3265</td>
<td>3078</td>
<td>2888</td>
<td>1.29</td>
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</table>

Table 15: Annualized Admission Rates per 100,000: Females 75-84 Congestive Heart Failure

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>2274</td>
<td>2171</td>
<td>2071</td>
<td>1974</td>
<td>1876</td>
<td>1782</td>
<td>1.15</td>
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<td>2150</td>
<td>2053</td>
<td>1955</td>
<td>2032</td>
<td>1937</td>
<td>1842</td>
<td>1.06</td>
<td>No</td>
</tr>
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<td>1990-91</td>
<td>2376</td>
<td>2276</td>
<td>2174</td>
<td>2060</td>
<td>1966</td>
<td>1871</td>
<td>1.16</td>
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<td>3222</td>
<td>3081</td>
<td>2944</td>
<td>2996</td>
<td>2863</td>
<td>2730</td>
<td>1.08</td>
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<tr>
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<td>2305</td>
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<td>1.1</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 16: Annualized Admission Rates per 100,000: Females 65-74 Congestive Heart Failure

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>691</td>
<td>655</td>
<td>613</td>
<td>597</td>
<td>558</td>
<td>521</td>
<td>1.17</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>661</td>
<td>621</td>
<td>582</td>
<td>613</td>
<td>574</td>
<td>537</td>
<td>1.08</td>
<td>No</td>
</tr>
<tr>
<td>1990-91</td>
<td>734</td>
<td>692</td>
<td>653</td>
<td>621</td>
<td>584</td>
<td>545</td>
<td>1.18</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>967</td>
<td>911</td>
<td>856</td>
<td>956</td>
<td>896</td>
<td>841</td>
<td>1.02</td>
<td>No</td>
</tr>
<tr>
<td>1992-93</td>
<td>703</td>
<td>663</td>
<td>625</td>
<td>725</td>
<td>685</td>
<td>645</td>
<td>0.97</td>
<td>No</td>
</tr>
</tbody>
</table>

Chronic Respiratory Disease
Age and sex adjusted annualized rates:

The age and sex adjusted annualized admission rates per 100,000 population varied from
year to year. The highest age and sex adjusted annualized admission rate was associated with the 1991-1992 influenza season: 12,049 per 100,000. The lowest age and sex adjusted annualized admission rate was associated with the 1988-1989 influenza season: 9,227 admissions per 100,000 persons. The percentage increase in comparison to the interim period ranged from a low of 21% for the 1988-1989 season to a high of 43% for the influenza season of 1992-1993.

Table 17 shows the annualized age and sex adjusted admission rates per 100,000 persons for each influenza season and interim period.

**Table 17: Annualized Age and Sex Adjusted Admission Rates: Chronic Obstructive Pulmonary Disease**

<table>
<thead>
<tr>
<th>Year</th>
<th>Influenza Season</th>
<th>Interim Period</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>9227</td>
<td>7527</td>
<td>1.21</td>
</tr>
<tr>
<td>1989-1990</td>
<td>9713</td>
<td>7992</td>
<td>1.25</td>
</tr>
<tr>
<td>1990-1991</td>
<td>9851</td>
<td>8057</td>
<td>1.22</td>
</tr>
<tr>
<td>1991-1992</td>
<td>12049</td>
<td>9030</td>
<td>1.33</td>
</tr>
<tr>
<td>1992-1993</td>
<td>9296</td>
<td>6508</td>
<td>1.43</td>
</tr>
</tbody>
</table>

**Age Specific Rates**

The annualized age specific rates of admission for chronic obstructive pulmonary disease were higher in each age group in each influenza season for males compared to females. In the oldest age group, the male admission rate ranged from 175 to 240% higher than the female rate. The range in percentage difference between males and females in the 75-84 age group was 91 to 156% higher. For the 65-74 age group the range in percentage difference was 65 to 93% higher in females compared to males.
Males

For the 85+ age group, there were no non-overlapping confidence intervals for the annualized age specific admission rates for the influenza period compared to the interim period.

For the 75-84 and 65-74 age groups, all influenza seasons were associated non-overlapping confidence intervals in comparison to the interim. The range of percentage increase was 17 to 32% for the 75-84 age group and 24-69% for the 65-74 age group. Tables 18-20 show the estimated annualized age specific admission rates per 100,000 and 95% confidence intervals for influenza seasons and interim periods from 1988-1993 for males and chronic lung disease.

The annualized age specific admission rates were 1.18 to 1.20 times higher in the 85+ age group compared to the 75-84 age group and 2.6 to 2.9 times higher in comparison to the 65-74 age group. Figure 5 shows the comparison of the annualized age specific admission rates for each age group for males and chronic lung disease for the influenza seasons 1988 to 1993.

Table 18: Annualized Admission Rates per 100,000: Males 85+ COPD

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>2713</td>
<td>2421</td>
<td>2132</td>
<td>2500</td>
<td>2221</td>
<td>1942</td>
<td>1.09</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>2888</td>
<td>2516</td>
<td>2226</td>
<td>2392</td>
<td>2124</td>
<td>1860</td>
<td>1.18</td>
<td>No</td>
</tr>
<tr>
<td>1990-91</td>
<td>3013</td>
<td>2697</td>
<td>2382</td>
<td>2658</td>
<td>2363</td>
<td>2068</td>
<td>1.14</td>
<td>No</td>
</tr>
<tr>
<td>1991-92</td>
<td>3456</td>
<td>3085</td>
<td>2715</td>
<td>3163</td>
<td>2811</td>
<td>2459</td>
<td>1.09</td>
<td>No</td>
</tr>
<tr>
<td>1992-93</td>
<td>2535</td>
<td>2280</td>
<td>2025</td>
<td>2063</td>
<td>1835</td>
<td>1605</td>
<td>1.24</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 19: Annualized Admission Rates per 100,000: Males 75-84 COPD

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>2150</td>
<td>2026</td>
<td>1903</td>
<td>1724</td>
<td>1613</td>
<td>1503</td>
<td>1.26</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>2218</td>
<td>2095</td>
<td>1971</td>
<td>1784</td>
<td>1676</td>
<td>1563</td>
<td>1.25</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>2355</td>
<td>2224</td>
<td>2092</td>
<td>2029</td>
<td>1908</td>
<td>1787</td>
<td>1.17</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 20: Annualized Admission Rates per 100,000: Males 65-74 COPD

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>984</td>
<td>929</td>
<td>874</td>
<td>755</td>
<td>705</td>
<td>658</td>
<td>1.32</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>1021</td>
<td>963</td>
<td>910</td>
<td>750</td>
<td>703</td>
<td>655</td>
<td>1.38</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>963</td>
<td>910</td>
<td>858</td>
<td>779</td>
<td>732</td>
<td>684</td>
<td>1.24</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>1181</td>
<td>1115</td>
<td>1044</td>
<td>733</td>
<td>663</td>
<td>589</td>
<td>1.68</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td>903</td>
<td>855</td>
<td>808</td>
<td>543</td>
<td>505</td>
<td>468</td>
<td>1.69</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Females

For the 85+ age group, only the 1989-1990 influenza season was associated with non-overlapping confidence intervals between the influenza season and the interim period (34%). For the 75-84 age group each influenza season was associated with non-overlapping confidence intervals. For the 65-74 age group, each influenza season except 1989-1990 was associated with non-overlapping confidence intervals between the two periods. The range of percentage increase between the influenza season and interim was 20 to 49% for the 75-84 age group and 15 to 41% for the 65-74 age group. Tables 21-23 show the estimated annualized age specific admission rates and 95% confidence intervals for each influenza season and interim period for females and chronic lung disease.

The annualized age specific admission rates ranged from 17% lower to 3% higher for the 85+ age group in comparison to the 75-84 age group and were 1.6 to 1.82 times higher in the 85+ age group compared to the 65-74 age group. Figure 6 shows the comparison of the annualized age specific admission rates for the age groups for the influenza seasons 1988 to 1993.
Table 21: Annualized Admission Rates per 100,000: Females 85+ COPD

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>926</td>
<td>816</td>
<td>705</td>
<td>937</td>
<td>826</td>
<td>716</td>
<td>0.98</td>
<td>No</td>
</tr>
<tr>
<td>1989-90</td>
<td>1013</td>
<td>905</td>
<td>795</td>
<td>766</td>
<td>673</td>
<td>576</td>
<td>1.34</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>963</td>
<td>858</td>
<td>753</td>
<td>763</td>
<td>671</td>
<td>579</td>
<td>1.27</td>
<td>No</td>
</tr>
<tr>
<td>1991-92</td>
<td>1233</td>
<td>1093</td>
<td>956</td>
<td>1167</td>
<td>1030</td>
<td>896</td>
<td>1.06</td>
<td>No</td>
</tr>
<tr>
<td>1992-93</td>
<td>930</td>
<td>830</td>
<td>732.5</td>
<td>855</td>
<td>763</td>
<td>668</td>
<td>1.08</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 22: Annualized Admission Rates per 100,000: Females 75-84 COPD

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>855</td>
<td>792</td>
<td>732</td>
<td>713</td>
<td>658</td>
<td>603</td>
<td>1.2</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>1008</td>
<td>942</td>
<td>876</td>
<td>739</td>
<td>684</td>
<td>626</td>
<td>1.38</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>1032</td>
<td>966</td>
<td>900</td>
<td>755</td>
<td>700</td>
<td>645</td>
<td>1.38</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>1311</td>
<td>1226</td>
<td>1141</td>
<td>937</td>
<td>863</td>
<td>793</td>
<td>1.42</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td>1078</td>
<td>1013</td>
<td>948</td>
<td>735</td>
<td>680</td>
<td>630</td>
<td>1.5</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 23: Annualized Admission Rates per 100,000: Females 65-74 COPD

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>551</td>
<td>512</td>
<td>476</td>
<td>465</td>
<td>431</td>
<td>397</td>
<td>1.19</td>
<td>Yes</td>
</tr>
<tr>
<td>1989-90</td>
<td>534</td>
<td>497</td>
<td>461</td>
<td>474</td>
<td>439</td>
<td>405</td>
<td>1.12</td>
<td>No</td>
</tr>
<tr>
<td>1990-91</td>
<td>553</td>
<td>516</td>
<td>482</td>
<td>479</td>
<td>445</td>
<td>413</td>
<td>1.15</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>722</td>
<td>674</td>
<td>626</td>
<td>559</td>
<td>519</td>
<td>474</td>
<td>1.29</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td>538</td>
<td>505</td>
<td>473</td>
<td>380</td>
<td>353</td>
<td>325</td>
<td>1.41</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Acute Upper Respiratory Disease
Age and sex adjusted annualized rates:

The age and sex adjusted annualized admission rates per 100,000 population varied from year to year. The highest age and sex adjusted annualized admission rate was associated with the 1991-1992 influenza season: 3,383 per 100,000. The lowest age and sex adjusted annualized
admission rate was associated with the 1992-1993 influenza season: 2362 admissions per 100,000 persons. The percentage increase in comparison to the interim period ranged from a low of -10% for the 1992-1993 season to a high of 32% for the influenza season of 1990-1991.

Table 24 shows the annualized age and sex adjusted admission rates per 100,000 persons for each influenza season and interim period.

Table 24: Age and Sex Adjusted Annualized Admission Rates Acute Upper Respiratory Disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Influenza Season</th>
<th>Interim Period</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>2655</td>
<td>2252</td>
<td>1.18</td>
</tr>
<tr>
<td>1989-1990</td>
<td>3031</td>
<td>2343</td>
<td>1.29</td>
</tr>
<tr>
<td>1990-1991</td>
<td>2907</td>
<td>2200</td>
<td>1.32</td>
</tr>
<tr>
<td>1991-1992</td>
<td>3384</td>
<td>2976</td>
<td>1.14</td>
</tr>
<tr>
<td>1992-1993</td>
<td>2362</td>
<td>2604</td>
<td>0.91</td>
</tr>
</tbody>
</table>

**Acute Upper Respiratory Disease**

**Age Specific Rates**

The annualized age specific rates of admission for acute upper respiratory disease were higher in the 85+ and 75-84 age group in each influenza season for males compared to females. In the oldest age group, the male admission rate ranged from 99 to 169% higher than the female rate. The range in percentage difference between males and females in the 75-84 age group was 24 to 53%. For the 65-74 age group the range in percentage difference was 0 to 37%.
Males

For the 85+ age group, all confidence intervals for influenza seasons overlapped with the interim period. The estimated annualized admission rate for the 1992-1993 influenza season was lower than the interim period. For the 75-84 age group, only the 1991-1992 influenza season was associated with non-overlapping confidence intervals. (41%) For the 65-74 age group, only the 1992-1993 influenza season was associated with non-overlapping confidence intervals (41%). Tables 25-27 show the estimated annualized age specific admission rates and 95% confidence intervals for influenza seasons and interim periods for acute respiratory disease and males.

The admission rates ranged from 3.56 to 3.94 times higher in the 85+ age group in comparison to the 75-84 age group and 7.6 to 10.5 times higher in the 85+ age group in comparison to the 65-74 age group. Figure 7 shows the comparison of the annualized age specific admission rates per 100,000 for each age group and each influenza season for males and acute respiratory disease.

Table 25: Annualized Admission Rates per 100,000: Males 85+ AURI

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>1710</td>
<td>1484</td>
<td>1255</td>
<td>1632</td>
<td>1410</td>
<td>1134</td>
<td>1.05</td>
<td>No</td>
</tr>
<tr>
<td>1898-90</td>
<td>1871</td>
<td>1637</td>
<td>1405</td>
<td>2039</td>
<td>1795</td>
<td>1547</td>
<td>0.91</td>
<td>No</td>
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<tr>
<td>1990-91</td>
<td>1889</td>
<td>1645</td>
<td>1400</td>
<td>2271</td>
<td>2000</td>
<td>1729</td>
<td>0.82</td>
<td>No</td>
</tr>
<tr>
<td>1991-92</td>
<td>2229</td>
<td>1941</td>
<td>1644</td>
<td>2315</td>
<td>2019</td>
<td>1719</td>
<td>0.96</td>
<td>No</td>
</tr>
<tr>
<td>1992-93</td>
<td>1365</td>
<td>1180</td>
<td>998</td>
<td>3985</td>
<td>3665</td>
<td>3338</td>
<td>0.32</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 26: Annualized Admission Rates per 100,000: Males 75-84 AURI

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>445</td>
<td>390</td>
<td>337</td>
<td>382</td>
<td>334</td>
<td>282</td>
<td>1.17</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 27: Annualized Admission Rates per 100,000: Males 65-74 AURI

<table>
<thead>
<tr>
<th>Year</th>
<th>Males 75-84</th>
<th>1989-90</th>
<th>468</th>
<th>361</th>
<th>389</th>
<th>339</th>
<th>290</th>
<th>1.22</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-91</td>
<td></td>
<td></td>
<td>503</td>
<td>389</td>
<td>442</td>
<td>387</td>
<td>332</td>
<td>1.16</td>
<td>No</td>
</tr>
<tr>
<td>1991-92</td>
<td></td>
<td></td>
<td>604</td>
<td>463</td>
<td>433</td>
<td>378</td>
<td>315</td>
<td>1.41</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td></td>
<td></td>
<td>378</td>
<td>285</td>
<td>318</td>
<td>278</td>
<td>235</td>
<td>1.19</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 28 shows the estimated annualized age specific admission rates for each influenza season and the interim period for males and acute respiratory disease.

Females

For the 85+ age group, non-overlapping confidence intervals of admission rates were found for the 1989-1990 (68%) and 1990-1991 (55%) influenza seasons in comparison to the interim period. For the 75-84 age groups, non-overlapping confidence intervals for admission rates were found for the 1989-1990, 1990-1991 and 1992-1993 seasons. The range of percentage increase was 37-46%. For the 65-74 age group, non-overlapping confidence intervals for admission rates were found for the 1989-1990 influenza season (37%) and the 1991-1992 influenza season (40%). Tables 28-30 show the estimated annualized age specific admission rates for each influenza season and the interim period for males and acute respiratory disease.

The annualized age specific admission rates for the 85+ age group were 2.07 to 2.03 times higher than the 75-84 age group and 3.7 to 5.3 times higher than the 65-74 age group. Figure 8 shows the comparison of the annualized age specific admission rates for each age group and each influenza season for females and acute respiratory disease.
### Table 28: Annualized Admission Rates per 100,000: Females 85+ AURI

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>713</td>
<td>616</td>
<td>521</td>
<td>645</td>
<td>555</td>
<td>463</td>
<td>1.1</td>
<td>No</td>
</tr>
<tr>
<td>1989-90</td>
<td>811</td>
<td>716</td>
<td>618</td>
<td>503</td>
<td>426</td>
<td>350</td>
<td>1.68</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>771</td>
<td>679</td>
<td>613</td>
<td>511</td>
<td>437</td>
<td>361</td>
<td>1.55</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>833</td>
<td>722</td>
<td>607</td>
<td>719</td>
<td>615</td>
<td>511</td>
<td>1.17</td>
<td>No</td>
</tr>
<tr>
<td>1992-93</td>
<td>675</td>
<td>593</td>
<td>510</td>
<td>663</td>
<td>580</td>
<td>500</td>
<td>1.02</td>
<td>No</td>
</tr>
</tbody>
</table>

### Table 29: Annualized Admission Rates per 100,000: Females 75-84 AURI

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>305</td>
<td>268</td>
<td>232</td>
<td>232</td>
<td>200</td>
<td>168</td>
<td>1.34</td>
<td>No</td>
</tr>
<tr>
<td>1989-90</td>
<td>353</td>
<td>316</td>
<td>279</td>
<td>245</td>
<td>216</td>
<td>182</td>
<td>1.46</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>339</td>
<td>303</td>
<td>266</td>
<td>255</td>
<td>221</td>
<td>189</td>
<td>1.37</td>
<td>Yes</td>
</tr>
<tr>
<td>1991-92</td>
<td>396</td>
<td>348</td>
<td>304</td>
<td>333</td>
<td>293</td>
<td>248</td>
<td>1.19</td>
<td>No</td>
</tr>
<tr>
<td>1992-93</td>
<td>295</td>
<td>265</td>
<td>230</td>
<td>223</td>
<td>193</td>
<td>165</td>
<td>1.38</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Table 30: Annualized Admission Rates per 100,000: Females 65-74 AURI

<table>
<thead>
<tr>
<th>Year</th>
<th>U95</th>
<th>Influenza</th>
<th>L95</th>
<th>U95</th>
<th>Interim</th>
<th>L95</th>
<th>Ratio</th>
<th>Non-overlapping C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-89</td>
<td>171</td>
<td>150</td>
<td>129</td>
<td>145</td>
<td>126</td>
<td>108</td>
<td>1.18</td>
<td>No</td>
</tr>
<tr>
<td>1989-90</td>
<td>174</td>
<td>155</td>
<td>134</td>
<td>132</td>
<td>113</td>
<td>97</td>
<td>1.37</td>
<td>Yes</td>
</tr>
<tr>
<td>1990-91</td>
<td>155</td>
<td>137</td>
<td>116</td>
<td>134</td>
<td>116</td>
<td>97</td>
<td>1.18</td>
<td>No</td>
</tr>
<tr>
<td>1991-92</td>
<td>215</td>
<td>193</td>
<td>167</td>
<td>159</td>
<td>137</td>
<td>115</td>
<td>1.4</td>
<td>Yes</td>
</tr>
<tr>
<td>1992-93</td>
<td>128</td>
<td>113</td>
<td>98</td>
<td>113</td>
<td>98</td>
<td>83</td>
<td>1.15</td>
<td>No</td>
</tr>
</tbody>
</table>
Summary

Table 31 summarizes the results of the admission rate analysis.

Table 31: Summary of salient results from admission rate analysis

<table>
<thead>
<tr>
<th>Diagnosis Group</th>
<th>Male rates higher than female rates in each season</th>
<th>Oldest age group higher than younger age groups in each season</th>
<th>Number of non-overlapping confidence intervals: Males</th>
<th>Number non-overlapping confidence intervals: Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Yes</td>
<td>Yes</td>
<td>15/15</td>
<td>15/15</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>Yes</td>
<td>Yes</td>
<td>10/15</td>
<td>8/15</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>Yes</td>
<td>No</td>
<td>10/15</td>
<td>10/15</td>
</tr>
<tr>
<td>Acute Upper Respiratory Disease</td>
<td>No</td>
<td>Yes</td>
<td>4/15</td>
<td>7/15</td>
</tr>
</tbody>
</table>

Objective 3

Time-Series Analysis

In this section, the descriptive statistics and time plots for the influenza seasons analysed will be first presented followed by the analysis of the time series models. The graphic depiction of the time series data for the overall series and for each specific influenza season can be found in the figures immediately following this section.

Descriptive Statistics

Table 32 shows the descriptive statistics for the time series for each aggregated diagnosis group.
TABLE 32: Descriptive Statistics for Diagnosis Groups

<table>
<thead>
<tr>
<th>Diagnosis Group</th>
<th>Mean Weekly Admissions</th>
<th>Standard Deviation</th>
<th>Median</th>
<th>Range</th>
<th>Total Number of Admissions in Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>248.93</td>
<td>81.6</td>
<td>235</td>
<td>118-689</td>
<td>77,418</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>347.18</td>
<td>51.13</td>
<td>345</td>
<td>225-489</td>
<td>107,972</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>178.77</td>
<td>37.14</td>
<td>173</td>
<td>173-359</td>
<td>55,598</td>
</tr>
<tr>
<td>Acute Upper Respiratory Disease</td>
<td>22.78</td>
<td>10.21</td>
<td>21</td>
<td>7-74</td>
<td>7,084</td>
</tr>
</tbody>
</table>

1.) Description of weekly series

Figure 9 shows the overall series of admissions aggregated by diagnosis group and the influenza isolates for the period from 1988-1994. Visual inspection of the graph shows conspicuous spikes on an almost annual basis particularly for the pneumonia and chronic respiratory disease groups. Visual inspection also shows the seasonal variation of the admissions and their relationship to influenza. The cyclic increases in the number of admissions correspond to the presence of influenza virus. Significant peaks occur for pneumonia and chronic respiratory disease in 1990, 1992, 1993 and 1994. Neither of these series demonstrate a conspicuous overall trend, as interim periods are comparable. For pneumonia and chronic respiratory disease, the lowest weekly totals correspond to the summer months.

The series representing congestive heart failure admissions lacks the striking seasonal peaks displayed by pneumonia and chronic respiratory disease. The overall trend is upward over the six years. Only in 1989-1990 is there a perceptible concomitant rise in the number of admissions for congestive heart failure during the circulation of influenza viruses.

The 1990-1991 season does not demonstrate equally as dramatic increases. A small but appreciable increase from the baseline is visible for both pneumonia and chronic respiratory disease. No evident increase is demonstrated for congestive heart failure. The 1992-1993 season differs from the others in that it has two distinct peaks: an early spike at the beginning of the influenza season and a latter peak at the height of the influenza season. The latter peak seems to have a modest parallel in the congestive heart failure series.

**Time Series Models:**

**Input Series and Transfer Function Models**

ARIMA models were fit to the influenza series for each influenza season from 1988 to 1993. Table 33 shows the regression co-efficients and Q statistics for each season. A first order autoregressive model (AR(1)) was found to adequately fit each season, as the residual series could be shown to be white noise by the Q statistic criteria. Each AR(1) model was imposed on the aggregate output series for pneumonia, congestive heart failure, acute upper respiratory disease and chronic obstructive pulmonary disease for each influenza season. The residuals of the input series were cross-correlated to the residuals of the output series and the correlation coefficients and lags were calculated.
Table 33: Regression Models for Influenza Input Series

<table>
<thead>
<tr>
<th>Year</th>
<th>Model</th>
<th>Regression Co-Efficient</th>
<th>P. Value Q Statistic (12 th Lag)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>AR(1)</td>
<td>0.909</td>
<td>.752</td>
</tr>
<tr>
<td>1989-1990</td>
<td>AR(1)</td>
<td>0.889</td>
<td>.884</td>
</tr>
<tr>
<td>1990-1991</td>
<td>AR(1)</td>
<td>0.902</td>
<td>.489</td>
</tr>
<tr>
<td>1991-1992</td>
<td>AR(1)</td>
<td>0.889</td>
<td>.695</td>
</tr>
<tr>
<td>1992-1993</td>
<td>AR(1)</td>
<td>0.905</td>
<td>.578</td>
</tr>
</tbody>
</table>

Pneumonia:

Table 34 shows the correlation coefficients and lag times for each season. Statistically significant positive correlations were found for each season. The lags, however, varied from season to season. For the 1989-1990, 1990-1991 and 1991-1992 seasons, the series were instantaneously related. For these three seasons, there was no lag time between increased influenza circulation and increased admissions for elderly Ontarians. The Pearson R ranged from 0.4176 to 0.6438. For the 1992-1993 series, pneumonia admissions were significantly correlated at -1 (0.4722) and -3(0.48) weeks. The 1988-1989 season had a significant correlation at lag +2 weeks (0.5479) indicating an increase in admissions before an increase in influenza isolations.

Table 34: Cross-Correlations between Influenza and Pneumonia Admissions

<table>
<thead>
<tr>
<th>Year</th>
<th>Lag/Lead (Week)</th>
<th>R</th>
<th>Simple R at 0 lag</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>+2</td>
<td>0.55</td>
<td>0.79</td>
</tr>
<tr>
<td>1989-1990</td>
<td>0</td>
<td>0.5</td>
<td>0.69</td>
</tr>
<tr>
<td>1990-1991</td>
<td>0</td>
<td>0.42</td>
<td>0.59</td>
</tr>
<tr>
<td>1991-1992</td>
<td>0</td>
<td>0.64</td>
<td>0.69</td>
</tr>
<tr>
<td>1992-1993</td>
<td>-1</td>
<td>0.48</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>-3</td>
<td>0.49</td>
<td></td>
</tr>
</tbody>
</table>
Congestive Heart Failure:

Table 35 shows the correlation co-efficients and lag times for each season. The influenza and congestive heart failure series were found to have no significant relationship for the 1988-1989 and 1990-1991 influenza seasons. For the 1989-1990 and 1990-1991 influenza seasons, admissions were significantly negatively correlated with influenza circulation at +2 and +10 weeks (R -0.44 and -0.46). For the 1992-1993 season there was a significant positive correlation at lag-3 weeks (R 0.54)

Table 35: Cross-Correlations between Influenza and CHF Admissions

<table>
<thead>
<tr>
<th>Year</th>
<th>Lag/Lead (Week)</th>
<th>R</th>
<th>Simple R at 0 lag</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>No Significant Correlation</td>
<td>N/A</td>
<td>-0.38</td>
</tr>
<tr>
<td>1989-1990</td>
<td>+2</td>
<td>-0.46</td>
<td>0.55</td>
</tr>
<tr>
<td>1990-1991</td>
<td>+10</td>
<td>-0.44</td>
<td>0.23</td>
</tr>
<tr>
<td>1991-1992</td>
<td>No Significant Correlation</td>
<td>N/A</td>
<td>-0.23</td>
</tr>
<tr>
<td>1992-1993</td>
<td>-3</td>
<td>0.54</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Chronic Obstructive Pulmonary Disease.

Table 36 shows the correlation co-efficients and lag times for each season. There was no significant relationship for the 1992-1993 season. The other four influenza seasons had significant positive correlations with R values ranging from 0.39 to 0.67. The lag times varied from -3 to +1.

Table 36: Cross-Correlations between Influenza and COPD Admissions

<table>
<thead>
<tr>
<th>Year</th>
<th>Lag/Lead (Week)</th>
<th>R</th>
<th>Simple R at lag 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>+1</td>
<td>0.67</td>
<td>0.53</td>
</tr>
<tr>
<td>1989-1990</td>
<td>0</td>
<td>0.61</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Acute Respiratory Disease:

Table 37 shows the correlation co-efficients and lag time for each season. For the 1988-1989 and 1991-1992 seasons there were no significant correlations. For the 1989-1990 and 1992-1993 influenza seasons, the series were significantly positively correlated at lag 0 (R 0.71 and 0.44). For the 1992-1993 season there was also a significant negative correlation at lag +7 (R -0.52). For the 1990-1991 season, the series were positively correlated at lag +5 (R 0.47).

**Table 37: Cross-Correlations between Influenza and AURI Admissions**

<table>
<thead>
<tr>
<th>Year</th>
<th>Lag/Lead (Week)</th>
<th>R</th>
<th>Simple R at 0 lag</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>No Significant Correlation</td>
<td>N/A</td>
<td>0.36</td>
</tr>
<tr>
<td>1989-1990</td>
<td>0</td>
<td>0.71</td>
<td>0.74</td>
</tr>
<tr>
<td>1990-1991</td>
<td>+5</td>
<td>0.47</td>
<td>0.53</td>
</tr>
<tr>
<td>1991-1992</td>
<td>No Significant Correlation</td>
<td>N/A</td>
<td>0.65</td>
</tr>
<tr>
<td>1992-1993</td>
<td>0</td>
<td>0.44</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>+7</td>
<td>-0.52</td>
<td></td>
</tr>
</tbody>
</table>

In summary, consistent correlations were found in each season for pneumonia and for four of five seasons for chronic obstructive pulmonary disease. The relationship was less consistent or innapparent for congestive heart failure and acute upper respiratory disease.
Figure 1: Age Specific Admission Rates
Males Pneumonia

Figure 2: Age Specific Admission Rates
Females Pneumonia
Figure 3: Age Specific Admission Rates
Males CHF

Figure 4: Age Specific Admission Rates
Females CHF
Figure 5: Age Specific Admission Rates
Males COPD

![Graph showing age-specific admission rates for males with COPD across different influenza seasons.

Figure 6: Age Specific Admission Rates
Females COPD

![Graph showing age-specific admission rates for females with COPD across different influenza seasons.]
Figure 7: Age Specific Admission Rates
Males AURI

Figure 8: Age Specific Admission Rates
Females AURI
Figure 9: Overall Series
All Diagnosis Groups

Figure 10: 1988-1989 Influenza Season
All Diagnosis Groups
Figure 11: 1989-1990 Influenza Season
All Diagnosis Groups

Figure 12: 1990-1991 Influenza Season
All Diagnosis Groups
Figure 13: 1991-1992 Influenza Season
All Diagnosis Groups

Figure 14: 1992-1993 Influenza Season
All Diagnosis Groups
Discussion

Objective 1

This study is unique in that it focuses exclusively on community acquired pneumonia in persons over the age of 65. As well, no other published studies have sought to look for misclassification error in the coding of pneumonia by examining diagnostic groups for which pneumonia can easily be clinically confused.

The results of the chart audit indicate that pneumonia is reliably coded in the HMRI/CIHI data base. The absence of pneumonia in any of the potential categories of misclassification is reassuring. However, the reliability must be seen as limited to the presence of pneumonia and not specific etiologies. There was possible misclassification of pneumonia in that some charts indicated the presence of an organism but were coded as no specific etiology, whereas in some charts, etiologic diagnosis was recorded in the absence of any isolated organism. The other source of misclassification error occurred in those charts that lacked radiographic evidence of pneumonia. These cases may be more appropriately coded as acute upper respiratory disease. Consequently, pneumonia admissions are a good indicator of respiratory morbidity. An explanation of the misclassification may relate to the fact that hospital chart abstracters do not look for corroborating evidence of etiology, but rather code according to the discharge diagnosis indicated by the most responsible physician. As well, the isolation of an organism in sputum does not necessarily guarantee etiology.

The results of this chart audit are similar to those reported by Marrie and colleagues (Marrie et al., 1987) which compared administrative data to a prospective study of pneumonia. In their study, they found that administrative data bases were reliable for the presence of pneumonia. They report a sensitivity of 69.5% when comparing the administrative data to the
gold standard of the prospective study. The authors note, however, that administrative data bases are unreliable in terms of the specific etiology. The authors caution against the use of administrative data for the epidemiology of specific organisms and recommend alterations to the ICD-9 coding system to produce more accurate information on the etiology of pneumonia for epidemiologic purposes.

This chart audit can be compared to the study by Gray and colleagues (Gray et al., 1994), the only other large study examining pneumonia on the basis of ICD-9 codes. In their cohort, consisting of young healthy military recruits, etiologic diagnosis was not found in 64.9% of hospital admissions. No attempt was made to determine the reliability of diagnosis or search for misclassification in other codes. Given the general good health of the cohort, it is unlikely that chronic lung diseases or congestive heart failure would be prevalent. As well, given the concern for the health of military personnel, it is likely that a more concerted effort was made for etiologic information to inform therapeutic choice.

The results of the chart audit are consonant with the ongoing clinical controversy over the appropriate diagnostic strategy for pneumonia. Several authors have advanced the argument that aggressive and extensive searches for etiology are not cost-effective (Woodhead et al., 1991; Antoniou & Grossman, 1995; Bartlett & Mundy, 1995). They argue for an empirical approach to the management of pneumonia and recommend minimal utilization of diagnostic testing and therapy designed to cover the most common community pathogens. Others have argued the need to tailor therapy to etiology in order to reduce the spread of antibiotic resistance and garner more accurate information on the etiology of community acquired pneumonia (Bartlett, 1996). The dispute between the “empiricists” and the “etiologic purists” is not likely to be resolved soon, but underscores the necessity for developing diagnostic utilization protocols in
persons hospitalized with pneumonia. Guideline development could optimize the tradeoffs between diagnostic over-utilization and fears of antibiotic resistance.

As well, the need for better epidemiologic studies in the etiology of community acquired pneumonia in the elderly is clear. The precise role of several agents is likely underestimated due to the lack of utility of diagnostic testing. Etiologies that can only be ascertained by the use of convalescent sera are of little value in the management of an acutely ill patient. No clinical signs and symptoms, radiologic patterns or constellations of presenting biochemistry reliably distinguish viral from bacterial pneumonia, or differing bacteriologic etiologies.

Although a small sample, the evidence indicates that while viruses are recognized important pathogens, diagnostic strategies for hospitalized elderly patients are directed toward the discovery of bacterial pathogens. This may be justifiable in that there are no specific therapies for most forms of viral pneumonia and diagnostic techniques for viral illness are rarely available in a timely enough manner to influence therapeutic decisions.

The chart audit study is subject to several limitations. There was a relatively small sample from three hospitals. The comparison of the distribution of the ICD-9 codes from the chart audit to the HMRI/CIHI data base indicates comparability. However, the sample was too small to assess variability in the coding by institution. As well, given the well documented variations of practice and hospitalization in Ontario, significant differences could be obscured in both diagnostic styles and coding practices (Naylor et al., 1994, Goel et al., 1996). Consequently biases derived from coding practices and physician styles could not be assessed. As well, the quality of the chart data are limited by the extent to which data are recorded. If data are not recorded in the chart then it will not be available for analysis.

Another limitation of the small sample size was the lack of representation of all ICD-9
codes for pneumonia which is inevitable in a small sample. As well, the charts were chosen on the basis of convenience sampling determined on the basis of administrative access. The representativeness of such a strategy can be questioned. However, the distribution of the ICD-9 codes from the chart audit were commensurate with the distribution found in the HMRI/CIHI data base. The choice of a large teaching hospital and two community hospitals is likely indicative of Ontario coding practice.

The absence of pneumonia in any of the possible categories of misclassification, though reassuring, is likely a chance finding. It is likely that a larger sample would eventually find evidence of misclassification. As well, no attempt was made to assess the accuracy of the coding of congestive heart failure, acute upper respiratory tract infection or chronic lung disease. As argued above, pneumonia is recognized as the most important complication of influenza. As there is a greater number of ICD-9 codes for pneumonia, some justification for their aggregation must be made. The chart audit demonstrates that the etiologic coding of pneumonia is not optimally accurate. Consequently it is justifiable to aggregate these codes for the purposes of rate estimation and time series analysis. The reliability of the coding for the other diagnostic groups should be assessed according to a set of specified criteria. This would form the basis for future research.

**Objective 2**

The results of the admission rate analysis indicate that influenza seasons are associated with increased hospital utilization in the elderly. This study indicates that the association is consistent and strong for pneumonia admissions. The results are less consistent for the other three aggregated diagnosis groups. Given the variability found in the results, each diagnostic group will be discussed individually. However, it would be prudent to first discuss the
implications of the chart audit for the admission rate analysis.

Relationship of chart audit to rate analysis:

The chart audit demonstrated that pneumonia is reliably coded for the presence of pneumonia, but not optimally accurate with respect to specific etiologies. The results of the chart audit have implications for the interpretation of the admission rate analysis. The chart audit showed the accuracy of coding to be 79% in comparison to preset criteria. The chief source of misclassification appeared to be congestive heart failure and acute bronchitis. Although the sample size of the audit was small, it allows for a sensitivity analysis of the results.

It is likely that the relationship between pneumonia and influenza is robust. Even if one reduces the estimates by 20%, the elevation of rates of admission during influenza seasons would remain in comparison to the interim period. The age and sex specific rates would diminish somewhat, but the relative relationships between the sexes, age groups and the ratios between influenza seasons and the interim periods would also hold unless it could be demonstrated that coding practices varied from season to season and that misclassification was less likely in the interim period or that misclassification was more likely on the basis of age group or sex. There is no evidence to support these claims. As well, given the small sample size, and as argued above, it is likely that some misclassification of pneumonia exists in other codes. This is likely small, but could plausibly be set at 5%. The net effect would be to reduce the estimates of the total number of pneumonia admissions, but would not diminish the significance of the rate elevations in comparison to the interim period or between the sexes and across age groups.

The chart audit indicates that acute bronchitis is likely underestimated. 12% of charts
coded as pneumonia should have been classified as acute bronchitis. As a consequence, the rate analysis likely underestimates the relationship between acute bronchitis and influenza. The same argument applies, though to a lesser extent, for congestive heart failure. 4% of the charts classified as pneumonia could have been classified as congestive heart failure. If the misclassification is equally likely in both influenza and interim periods, then the relationships demonstrated above remain the same, but the magnitude of the effect may be greater.

**Pneumonia**

Each influenza season was associated with increased rates of admission in comparison to the comparable interim period. The results were consistent from year to year. There was some variability in that the 1991-1992 season was associated with the highest annualized admission rates. The relationship between age groups for each sex was also consistent from year to year. The oldest age group for males had the highest admission rates in each of the influenza seasons studied. The magnitude of this effect is quite substantial, ranging from 600 to 900% higher than males in younger age groups and 7 to 90% higher than females in the same age group in the same years. Consequently, the impact of influenza seasons on pneumonia admissions in the elderly can be regarded as substantial.

The admission rate analysis followed the methodology established by McBean et al. (McBean et al., 1993). As the McBean study included two of the influenza seasons analysed in this study, a comparison between these results is possible. In the McBean study, pneumonia and influenza admissions were substantially increased in the 1989-1990 and 1990-1991 season. The percentage increases compared to interim that they report are higher than the rates reported here, ranging from 89 to 91% for the H3N2 influenza A season of 1989-1990 and 45 to 48% for the 1990-1991 influenza B season.
The calculated age specific rates are also higher in the McBean study. They did not report age and sex specific rates, but rather aggregated sexes for the age specific rates. Consequently, the higher morbidity associated with older men is not commented upon and the results are not directly comparable.

This study differs from most other studies in that it calculates age and sex specific rates for different age groups and thus allows for the comparison of the impact of influenza on older age groups. Most studies have defined the elderly as over age 65 and thus are unable to demonstrate the significant impact influenza has on the oldest age groups, particularly in males.

**Congestive Heart Failure**

Unlike the pneumonia series, the relationship between circulating influenza viruses and admissions for congestive heart failure seems to be variable. Four of the five influenza seasons were associated with increased rates of admission in the two oldest age groups for males, as compared to four of five for the oldest female age group, and three of five for the second oldest. For the youngest age group, two seasons were associated with increased admissions in comparison to the interim period.

However, the non-overlapping years were not consistent across sexes and age groups. The 1988-1989 season was the only season that was associated with increased admissions in both sexes and all age groups for congestive heart failure. Contrarily, for the 1991-1992 season, only the oldest age group for females had an increased admission rate in comparison to the interim.

The McBean study documented a 20% increase in admissions for congestive heart failure for the 1989-1990 influenza A season and 16% increase in admissions for the 1990-1991 influenza B season. The McBean study did not calculate age and sex specific admission rates,
but relied solely on the aggregate. The percentage increases in this study are comparable to the McBean study and indicate that there may be a relationship between admissions for congestive heart failure and influenza. This would support the conclusions of McBean et al. against the claims of Barker (Barker, 1986) that there is no relationship between influenza and admissions for congestive heart failure. Certainly, the results of this analysis support the inclusion of the measurement of congestive heart failure morbidity in the analysis of the impact of influenza.

**Acute Upper Respiratory Disease**

The results of the analysis of the impact of influenza on acute upper respiratory diseases fail to replicate the McBean study and do not support the *a priori* hypothesis of a strong relationship. McBean reported 116% increase in acute upper respiratory disease for the 1989-1990 influenza A season and 68% increase for the 1990-1991 influenza B season. In their study, females were admitted at a higher rate than males in comparison to the interim period for both seasons.

For males in particular, rates were not consistently elevated. Only four non-overlapping confidence intervals were found for males, and in one case, the rates were higher in the interim period for the oldest age group (1992-1993). In comparison to the McBean study, neither the 1989-1990 nor the 1990-1991 season has increases in admission rates for males in any age group. An interesting finding in the males was a higher admission rates for the 85+ age group for the interim period of 1992-1993. Inspection of the crude data reveals a 6 week elevation of rates in the summer of the interim period. This could represent a chance finding or may be evidence of other factors influencing admissions. Summer respiratory admissions can be related to air quality problems such as increased ozone or other particulate matter, as well as other respiratory pathogens (Burnett et al., 1994, 1995).
For females, the 1989-1990 season was the only season associated with an increase in admission rates in all age groups, but the percentage increase in comparison to the interim does not exceed 68%. The 1990-1991 season has increases for the oldest two age groups, but not the youngest. The percentage difference in comparison to the interim does not exceed 55%.

There are several possible interpretations for the reported differences. If the results of the chart audit can be generalized, approximately 12% of pneumonia admissions may, in fact, be for acute respiratory disease. As noted above, given the proportionately higher rates of admission for pneumonia during influenza seasons, the results of this analysis would underestimate the relationship between circulating influenza virus and admission for acute upper respiratory disease. As well, coding practices may vary between the United States and Canada. With the utilization of Diagnosis Related Groups for the payment of Medicare benefits, it may be that coding is more accurate and less reliant on physician judgement than is the case in Ontario.

**Chronic Obstructive Pulmonary Disease**

Consistent with the findings of the McBean study, the rates of admission for chronic pulmonary disease were elevated in comparison to the interim period. The McBean study reported a 37% increase for the 1989-1990 influenza season and 28% increase for the 1990-1991 influenza season. The results of this study are consistent with these findings. However, a striking finding in the admission rate analysis for chronic obstructive pulmonary disease was a lack in consistent elevation of admission rates for the oldest age groups for both females and males. For the youngest two age groups consistent increases in admission rates were detected.

This phenomenon has not been previously reported. In the McBean analysis, age and sex specific admission rates were not calculated for chronic pulmonary diseases. McBean notes that increases in chronic pulmonary disorders had not been previously documented in admission
studies examining the impact of influenza. The results of this study indicate that chronic respiratory diseases are significantly impacted by the presence of circulating influenza virus. The reasons for the lack of increase in the oldest age group are unclear. Perhaps the oldest age group is more likely to be diagnosed with, or coded as pneumonia. If co-morbidities are not recorded appropriately, then the presence of chronic pulmonary disorders would be obscured.

An alternative explanation is that chronic pulmonary disorders are not consistent with longevity. Most individuals suffering from chronic respiratory disorders do not have prolonged life spans, and consequently the numbers in the oldest age category are low in comparison to the younger age categories. The age distribution is likely skewed towards the younger end. The morbidity associated with chronic obstructive pulmonary disease may be similar between the categories, but this would not explain the lack of increase in comparison to the interim period.

Certainly, though, one would expect gradient in age specific rates for chronic pulmonary disease similar to that found in pneumonia and the other diagnosis groups.

**Objective 3**

**Time Series Analysis**

This study is unique in that it applies transfer function methodology to five independent influenza seasons for four different diagnosis groups. Time series methodology has been applied to pneumonia and acute upper respiratory admissions, but no published studies exist examining congestive heart failure and chronic obstructive pulmonary disease.

**Pneumonia**

The time series analysis indicates a moderately strong correlation between circulating influenza virus and hospitalizations for pneumonia in the elderly. The explained variance between the two series varies from year to year. The range of R-squared values from 23 to 41%
indicates that the presence of circulating influenza virus explains some but not all of the variance related to hospitalizations. In three of the five years the series were instantaneously related and no lag between influenza circulation and hospital admissions for pneumonia occurred. The influenza season of 1992-1993 was the only season associated with a lag of hospital admissions and circulating influenza strains. For the 1988-1989 season, influenza isolate peaked 2 weeks after admissions began to rise.

The correlation coefficients are lower and lag times different than those reported by Perotta (Perrotta et al., 1985). Perotta’s study reported a correlation coefficient of .74 at -1 week between adult acute respiratory admissions and circulating influenza strains. There are several potential reasons for the differences in findings.

Perotta’s study utilized data from a series of randomly collected isolates from a stratified sample of community physicians. This method of surveillance is more likely to capture the onset and peak of viral circulation than the Ontario system that relies largely on passive reporting from a select set of participating laboratories. The majority of Ontario isolates derive from pediatric hospitals and nursing home outbreaks (Naus & Offner, 1993). In years that have substantial nursing home outbreaks, it is likely that the peak circulation of influenza will correspond more closely to hospitalizations in the elderly as it is a reasonable supposition to believe that the two events would be closely related. Therefore, because Ontario surveillance relies substantially more on isolations from the elderly than does a stratified community sample, it is possible that the reported lags may be at variance from the true relationship. Only a study utilizing data collected from random samples by surveillance physicians could verify the relationship between lag times for admission and circulating influenza in the community.

It is also likely that the variability of time lags and explained variance from year to year
depends on other plausible causes, such as co-morbidities in the persons acquiring influenza, temperature and ambient air-quality as well as the circulation of other respiratory viruses. The moderate correlation coefficients for each influenza season indicate that such factors play a role. As well, Perotta’s study does not indicate the method by which the correlation was calculated. If the two series were simply cross-correlated, then it is likely that this estimate is biased and inflated.

Recent studies have demonstrated that respiratory syncytial virus is likely a substantial contributor to morbidity and mortality in the elderly. Studies by Fleming (Fleming & Cross, 1993), Nicholson (Nicholson, 1996) and Falsey (Falsey et al., 1995) have demonstrated the importance of RSV as a contributing factor to morbidity and mortality in the elderly. The Nicholson and Falsey studies indicate that morbidity and mortality may be greater for RSV than for influenza and likely is not restricted to the institutionalized elderly, though further research is required to clarify this relationship. If the relationship between RSV and morbidity and mortality in the elderly is as significant as these studies suggest, then the exact role that influenza plays as the major contributor to respiratory morbidity and mortality in the elderly will have to be reconsidered. Certainly, the magnitude of preventable hospitalization and mortality may be less than what was previously believed.

Unlike Houston, where Glezen’s studies have taken place, RSV co-circulates on an annual basis with influenza in Ontario. Given that RSV and influenza are clinically indistinguishable in the elderly, and may in fact be present simultaneously in the same person (Kimball et al., 1983; Wald et al., 1995) further studies are required to separate the effects of RSV and influenza and clarify their impact on hospital admissions. As RSV isolates are now routinely collected on a weekly basis, such a study will be feasible.
The Nicholson study also indicated that temperature variables are significantly associated with winter mortality. Temperature, humidity, and air quality variables such as sulphur dioxide and ozone are plausibly linked to respiratory morbidity and mortality (Kunst et al., 1997; Schwartz & Marcus, 1990; Burnett et al., 1994, 1995; Ostro, 1995; Anderson et al., 1996). It is likely that these variables exert an influence on hospitalizations for pneumonia in the elderly. As temperature and air quality data are also systematically collected, a future study including these variables is recommended.

**Congestive Heart Failure**

There are no published studies using time series analysis to link circulating influenza strains to admissions for congestive heart failure. The results of the correlation study indicate that there is no consistently strong relationship between the two. In only the 1992-1993 influenza season is a plausible significant relationship found. For two of the seasons, there are negative correlations and for two of the seasons (1991-1992 and 1988-1989) there are no significant correlations.

The time series analysis is at variance with the admission rates analysis. The difference between the two may be accounted for by the fact that the time series analysis looks at simple correlations between weekly admission totals and influenza circulation. The numbers of admissions on a crude basis are higher in the younger age groups and the relationship between congestive heart failure and influenza is strongest in the older age groups. Hence, it is possible that the relationship is obscured in the time series analysis. A time series analysis congestive heart failure admissions classified by sex and age group may illuminate the association further.

**Acute Upper Respiratory Disease.**

As with congestive heart failure, an inconsistent picture emerges from the time series
analysis. No significant relationships were found for the 1991-1992 and 1988-1989 seasons. A strong positive correlation was found for the 1989-1990 season. The positive correlation at lag +5 for 1990-1991 must be regarded as implausible and therefore unrelated. It is unlikely that meaningful effects would be lagged more than a month apart. The negative correlation at lag +7 for the 1992-1993 season should also be similarly interpreted.

The lack of a consistent strong association between influenza and acute upper respiratory disease is surprising as one would expect a strong correlation a priori. As noted in the admission rate analysis, the relationship was not strong and consistent. The reasoning outlined in the admission rate analysis obtains here as well: it is possible that admissions for acute upper respiratory disease are misclassified, and in fact show up in the pneumonia categories. Given this possibility, the effects of circulating influenza on acute upper respiratory disease are underestimated in this study, and consequently the time series analysis does not adequately model the true relationship of the impact of influenza on admissions for acute upper respiratory diseases.

**Chronic Obstructive Pulmonary Diseases**

As with pneumonia, the time series study indicates a significant relationship between circulating influenza strains and admissions for chronic obstructive pulmonary disease. In each of the years, with the exception of the 1992-1993 influenza season a significant plausible correlation exists. The Pearson R values for the correlation tend to be slightly higher for the chronic obstructive pulmonary disease series than for the pneumonia series. As with the pneumonia series, the presence of influenza explains some, but not all the variance in the admissions. The same arguments advanced for pneumonia hold here: further studies with a more complete and exhaustive set of explanatory variables are required.
Visual inspection of the 1992-1993 chronic obstructive pulmonary disease series indicates a spike in admissions prior to the commencement of influenza circulation. This spike no doubt is responsible for the non-significant relationship between influenza and hospital admissions for this season. The spike may be due to other viral or bacterial pathogens, some other factor such as environmental influences or may be just a random spike. Further analysis of this season could illuminate the reason for the increase of chronic obstructive pulmonary diseases in these weeks.

Taken in conjunction with the admission rate analysis, the time series study provides evidence of a strong relationship between circulating influenza and admissions for chronic obstructive pulmonary disease. Future studies of the impact of influenza should include measurement of chronic obstructive pulmonary disease morbidity.

**Comparison of raw correlations with ARIMA modeled crosscorrelations:**

For four of the five pneumonia series the raw correlation coefficient would overestimate the relationship. The range of r value inflation is from 0.05 to 0.24. For the three seasons in which the relationship between the influenza series and the pneumonia series were instantaneously related, only the 1991-1992 season had comparable r values. For congestive heart failure the pattern is inconsistent. In two seasons negative correlations become positive, and two seasons with no significant correlation by ARIMA modelling become significantly negatively correlated. For the COPD series, the r values are comparable, with the ARIMA modelled values being slightly higher save for the 1991-1992 season in which they are 0.16 lower. In the non-significant 1992-1993 season, a correlation of 0.38 was found on simple correlation. The most dramatically affected series was the AURI series. Each simple correlation was significant ranging from 0.36 to 0.74. For comparable years the values are similar.
It is important to note that the raw correlations at lag 0 are not the highest correlation coefficients. When one crosscorrelates at various lags one finds higher values at different lags. For example, the 1991-1992 influenza season had correlation coefficients as high as 0.88 at lag +3. The Perotta study reported the highest correlation coefficient at lag -1. When one examines the tabular data, it is evident that they chose the highest of a series of lagged correlation coefficients. This indicates that simple crosscorrelations will miss relationships at different lags, and that simply crosscorrelating lagged series results in a multitude of difficult to interpret significant correlations.

**Limitations of the Study:**

This analysis is subject to a number of limitations. The limitations can be classified in three broad categories: data limitations, methodological and analytic limitations and confounders.

**Data Limitations.**

The admission rate and time series analyses rely on two primary data sources: influenza surveillance data and CIHI hospital separation abstracts. Each data source is subject to limitations.

The Ontario influenza surveillance data relies on passive reporting. Although surveillance is carried out on an annual basis, the collection of specimens relies on physician judgement. The majority of specimens derive from pediatric hospitals and institutional outbreaks. Community physicians rarely order diagnostic tests for influenza in either a practice or hospital setting. As a consequence, the number of isolations on an annual basis must be regarded as an underestimation of the true extent of influenza circulation. In the 1989-1990 season, the highest number of isolations was 50. In contrast, the time plot for that season shows a marked peak to
the highest weekly recorded totals for pneumonia in the study. International reports of this season indicate it to be one of the more severe influenza seasons in the past decade (Ahmed et al., 1995). The results of undercounting, of which the 1989-1990 season is the most prominent example, would be to underestimate the true correlation coefficients. A more accurate estimate of the number of isolations would add more information to the input series for the calculation of cross-correlations.

The second limitation of passive reporting is that it may miss the true onset of circulating influenza virus. A study by Quenel (Quenel et al., 1994), utilizing data from a large sentinel surveillance system, examined the relationship between health service based indicators and influenza viruses. They found that health service indicators increased earlier than virological isolations. In other words, only after an index of suspicion was raised were isolations for virus obtained. Pediatric health services indicators were the least sensitive measure as RSV dominated the data. The pattern of health services utilization they discovered during influenza seasons was that emergency room visits were consistently the first indicator to rise, followed by general practitioner visits, sick leave prescriptions and then drug consumption. The study did not specifically look at hospitalizations for the elderly. The implications of this study relate specifically to the time series analysis. The lag time reported in this study may be biased because of the manner in which the isolates are collected. A delay of one week between peak isolations and the true peak of community viral circulation would effect the calculated lags. Consequently, the lags reported in this study may not represent the true lags. However, if the majority of admissions for pneumonia arise through the emergency department, then hospitalizations for the elderly could be a sensitive indicator of the presence of circulating influenza viruses and the lag times an accurate representation.
The use of large administrative data bases is now considered to be appropriate for research (Naylor et al., 1994, Goel et al., 1996). However, administrative data are subject to limitations. The data are not collected specifically for the purposes of research, and coding practices, historically, have not been uniform across the province. Nonetheless, as the chart audit demonstrates, coding is reliable. Other data quality studies indicate that the most responsible diagnosis is reliably coded (Anon., 1991). Some discretion and variability of coding still exists. The fields used for this study are all mandatory fields and are reliably coded. Other limitations of administrative data bases are multiple re-admissions, which increase the numerator; and the possibility of misclassification to other diagnostic codes. If the target condition is not listed by the physician or the abstractor, then it would not be included in the study.

Methodologic and Analytic Limitations:

The admission rate analysis relies on the calculation of age and sex specific rates for defined influenza seasons. The definition of an influenza season as consisting of the total number of weeks in which influenza is isolated is well established in the literature. However, this method of analysis may underestimate the impact of influenza. The time plots, and all other epidemiologic analysis of influenza indicate that, although an influenza season characteristically lasts for 12 to 20 weeks, peak activity rarely exceeds 6 weeks. By including all admissions for the duration of the season, the impact is diminished. A more appropriate analysis would be to examine rates for the peak only. This would necessitate a smaller data set to analyse and would consequently add uncertainty to the estimates. However, it may be a more accurate indicator of the impact of influenza.

The study also uses an ecological approach. The study frame is data collected from all Ontario. Given the geographical and climatological heterogeneity of the province, local variation
of the impact of influenza is obscured. It is likely that different areas of the province are affected differently. Some areas may be more or less severely affected. Sentinel surveillance data from France indicates that this is likely the case\(^1\) (Chauvin, 1994). Small area analysis and graphical depiction of the evolution of influenza circulation could grant insight into the nature of influenza transmission.

A further limitation to the analysis is that there is no verification of the presence of influenza in those admitted to hospital. As the chart audit makes clear, viral studies are rarely employed as part of the diagnostic work up for pneumonia and would be even less likely to be ordered for those admitted for congestive heart failure.

Time series analysis is also subject to limitations. In this study, transfer function models were fit to influenza seasons only. The duration of these seasons ranged from 16 to 22 weeks. Many time series analysts caution that 30 to 50 data points are required to adequately calculate the auto-correlation and partial auto-correlation functions necessary to specify an appropriate model (Crabtree et al., 1990). The concern with small samples is that the Q-statistic may be biased and indicate a residual series that is white noise when in fact it is not. However, these constraints should not be regarded as absolute. In this analysis, to get 30 to 50 data points would entail adding zero values to the input series. This has the effect of reducing the mean value of the series and biases the model. Certainly, evolving influenza seasons have the hallmark features of an AR(1) process. All data were collected on the same unit of measure (week). It makes biologic sense to model admissions as an output only in the presence of influenza circulation. By looking at each season independently, the presence of other cyclic influences is

\(^1\) This is illustrated by the incidence maps for influenza created by the sentinel surveillance system in France. They can be viewed on the World Wide Web at http://www.b3e.jussieu.fr:80/sentiweb
removed, as is the need for seasonal differencing. Consequently, the use of a smaller set of data points is justified.

Confounders

The ecologic nature of the study does not control for potential confounders (Kelsey et al., 1986). There are other explanatory variables that may also have an influence on hospital admissions. Co-morbidities and vaccination status likely play a large role in the vulnerability of the elderly to influenza (Barker & Mullooly, 1980; Bently, 1992; Fedson et al., 1993; Nichol et al., 1994; Ahmed et al., 1995). As this study is concerned chiefly with the relationship between influenza circulation and hospital admissions, no analysis of co-morbidities is possible.

Influenza vaccination may also influence admission rates. The vaccination status of those admitted was unknown. If unique identifiers were available for vaccinnees then a linkage study could be performed. Two such studies have been reported. Nichol (Nichol et al., 1994) and Fedson (Fedson et al., 1993) both report lower admission rates for the recipients of vaccine for the target conditions discussed in this thesis. In Ontario, only the number of doses delivered is reported, not who has received the vaccine (Tamblyn, 1994). As well, given the consistent annual increase in admission rates for both pneumonia and chronic obstructive pulmonary disease, it would appear that further analysis of who receives the vaccine is needed. The similarity of results from year to year indicate that influenza control remains illusive. Given the disproportionately high burden of pneumonia morbidity experienced by the oldest age group, and the documented reduced vaccine efficacy with advanced age, vaccination policy may need to be reconsidered.

The match between circulating influenza strain and vaccine strain varies from year to year (National Advisory Committee on Immunization, 1993). Again, the consistency of the
results indicate that yearly variation of influenza virus or vaccine strain do not alter dramatically the rates of hospital admission in the five years under study particularly for pneumonia and chronic respiratory diseases. The highest annualized admission rates were associated with the 1991-1992 season in which an excellent match between strains was reported. Further study on the number of elderly influenza vaccine recipients and their hospitalization experience would help to illuminate this problem.

This thesis did not examine mortality. Influenza vaccine has also been demonstrated to reduce mortality in the elderly (Barker & Mullooly, 1980; Gross et al., 1988; Webster et al., 1992; Anon., 1993; Ahmed et al., 1995; Carrat & Valleron, 1995; Mims, 1995). However, morbidity and mortality are not always linked in influenza seasons (Barker, 1986). Further analysis of hospital mortality during influenza seasons is necessary to explore this phenomenon.

The possible role of RSV and environmental variables has been discussed above. The co-circulation with influenza confounds the relationship of which is the more important pathogen with respect to hospitalization. Influenza circulation is characterized by variability in its onset and peak circulation from year to year. The correlations for pneumonia and chronic respiratory diseases seem to be tightly linked to the circulation of influenza. Examining the correlations with RSV would clarify the issue considerably, and no studies using transfer function models and RSV have been published. The two studies that are germane to the point have used either linear regression or weighted moving averages (Fleming & Cross, 1993; Nicholson, 1996). Using the crosscorrelation co-efficient is arguably a superior method.

Environmental variables may be independent or synergistic with respiratory morbidity. Certainly it is plausible to implicate them as co-factors in admission. However, for pneumonia and chronic respiratory diseases, the associations were strong and consistent from year to year.
The addition of environmental variables would likely help to explain some of the variance in the time series analysis. The addition of mean weekly temperature and humidity variables is feasible, but would necessitate decomposing the data into regions as one could not plausibly assume the same weather patterns for southern and northern Ontario. The same argument would hold for the use of the air quality index as an indicator of ambient air quality. This would make for a smaller sample and less stable estimates.
Conclusions

The results of this study indicate a strong and consistent relationship between the presence of circulating influenza virus and hospital admissions for the elderly for pneumonia and chronic respiratory diseases in the elderly population of Ontario. This occurs on an annual basis and is not related exclusively to the presence of epidemic years. The effect seems most pronounced on the oldest segment of the population and males are more severely affected than females. The study indicates that this relationship is less strong and inconsistent for congestive heart failure and acute respiratory diseases. The study also indicates that coding for pneumonia is a reliable indicator of respiratory morbidity in the elderly. The results indicate that influenza is still a significant public health problem and that control of influenza requires ongoing attention.

The results support the findings of McBean et al. and add additional support to their recommendations that congestive heart failure and chronic respiratory disease be included in any analysis of the impact of influenza on the elderly. The results of this study show that the impact of influenza is apparent annually, and that analysis of seasons regarded as “epidemics” likely will underestimate the annual impact of influenza on hospital utilization.

The results also demonstrate the potential utility of time series methodology for the epidemiologic study of health services utilization. Understanding the relationship between circulating respiratory pathogens and hospital admissions would be an important component of health services planning.

Furthermore, the results of the study indicate the usefulness of administrative data bases for the assessment of the degree to which influenza control is being achieved.
Key implications of the study:

The results of this study have implications for health services planning, communicable disease control, primary care practice and public education.

In the current climate of fiscal restraint and hospital and bed closings, health services planners would be well advised to prepare for an annual increase in demand for hospital services during influenza seasons. A failure to recognize the need for increased beds or community resources for the elderly during influenza seasons could lead to increased morbidity and mortality. Certainly, community resources will be strained if a large number of acutely ill seniors are not adequately attended. Planning for increased community care during influenza seasons could help to reduce the complications associated with influenza by helping to secure access to medical care when needed.

The results also indicate that circulating influenza virus is associated with increased costs to the health care system. While this study was not concerned with health care expenditures, McBean et al. estimated an excess cost of over 1 billion dollars for the 1989-1990 influenza season and 750 million dollars for the 1990-1991 season. The indirect costs of influenza are estimated to be four times as great as the direct costs (McBean et al., 1993). The analysis here provides the basis for an economic analysis of the cost implications of influenza in Ontario. Although not an objective of the thesis, a simple example can illustrate this point. If the number of admissions for the diagnosis groups studied are aggregated for the 1991-1992 influenza season and the aggregated totals for the interim subtracted, an excess of 5,148 hospitalizations occurred. Assuming, for the purpose of illustration, using an average length of stay of 8 days (derived form the benchmark length of stay for pneumonia from Naylor et al., 1994) and hospital costs of $400 a day, the excess cost for the 1991-1992 influenza season would be $16,500,000
for care of the elderly alone.\textsuperscript{2}

Health services planning could be aided by better surveillance and prompt dissemination of results. The presence of a sophisticated surveillance system such as that found in France could be established in Ontario. In this manner, practitioners and planners could be made aware of the commencement of influenza seasons and plan their activities and resources appropriately. Disease control objectives could be better served by the presence of such a surveillance system.

Practising physicians can benefit from this study by being aware of the impact influenza has on the elderly. The results support the importance of offering influenza vaccine as a means of protecting against the complications of influenza. As well, with the aid of sentinel surveillance, physicians could approach prescribing more rationally. No studies have been done analysing the relationship between antibiotic prescriptions and the presence of influenza or other respiratory pathogens.

For the public, the results would help to better inform the public of the severity of influenza. The perception of influenza as just the "flu" minimizes the serious morbidity and mortality associated with influenza. Clarifying the relationship with RSV could also better inform the public on what to expect from influenza vaccine. The impression that the vaccine is not effective could be related in part to the newly recognized severity of RSV infections in the elderly. Those protected from influenza but afflicted with severe RSV may conclude that the vaccine does not work. Practitioners could inform patients of the limitations of influenza vaccine and the importance of RSV as a pathogen.

\textsuperscript{2} It should be noted that this is a rough indication of costs. Using benchmark averages, and estimated costs likely underestimates the costs as lengths of stay for the elderly tend to be longer. The calculation is meant only to give an indication of the utility of this form of analysis for the purposes of economic analysis.
Further research is necessary to examine the role that environmental variables and RSV play in the increases in hospital admissions in the elderly. Such research could lead to a more complete understanding of the determinants and causes of an important public health problem and lead to better interventions to reduce morbidity and mortality in the elderly.
References


Atkinson, WL; Arden, NH; Patriarca, P; et al. (1986): Amantadine prophylaxis during an institutional outbreak of type A (H1N1) influenza. Arch Intern Med 146, 1751-1756.


Barker, W; Mullooly, J (1980): Influenza Vaccination for Elderly Persons: Reduction in Pneumonia and Influenza Hospitalizations and Deaths. JAMA 244, 2547-2549.


Burnett, R et al. (1994): Effects of low ambient levels of ozone and sulphates on the frequency of respiratory admissions to Ontario hospitals. Environmental Research 65, 172-194.


Coles, FB; Balzano, GJ; Morse, DM (1992): An outbreak of Influenza A (H3N2) in a well immunized nursing home population. JAGS 40, 589-592.
Connolly, AM; Salmon, RL; Lervy, B; Williams, DH (1993): What are the complications of influenza and can they be prevented? Experience from the 1989 epidemic of H3N2 influenza A in general practice. BMJ 304, 1452-1454.


Falsey, A; Cunningham, C; Barker, W; et al. (1995): Respiratory syncitial virus and influenza A in the hospitalized elderly. The Journal of Infectious Diseases 172, 389-394.

Fang, GD; Fine, M; Orloff, J; Arisumi, D; Yu, V (1990): New and Emerging Etiologies for Community-Acquired Pneumonia with Implications for Therapy: A Prospective Multicentre Study of 359 Cases. Medicine 69, 307-316.


Fleming, DM; Cross, KW (1993): Respiratory syncytial virus or influenza? The Lancet 342, 1507-1510.


Garb, J; Brown, R; Garb, JR; Tuthill, R (1978): Differences in etiology of pneumonias in nursing home and community patients. JAMA 240, 2169-2172.


Govaert,ME; Thijs,CT; Masurel,N; et al. (1994): The efficacy of influenza vaccination in elderly individuals: A randomized double-blind placebo control trial. JAMA 272, 1661-1665.


Hannoun, C; Kendal, AP; Klenk, HD; Ruben, FL (Eds.) (1993): Options for the Control of Influenza. Excerpta Medica, Amsterdam.


Howells, C; Vesselinova-Jenkins, C; Evans, A; James, J (1975): Influenza vaccination and mortality from bronchopneumonia in the elderly. The Lancet, 381-383.

Hubert, B; Watier, L; Garnerin, P; Richardson, S (1992): Meningococcal disease and influenza-like syndrome: A new approach to an old question. The Journal of Infectious Diseases 166, 542-545.


Kimball, A; Foy, H; Cooney, M; Allan, I; Matlock, M; Plorde, J (1983): Isolation of respiratory syncytial and influenza viruses from the sputum of patients hospitalized with pneumonia. The Journal of Infectious Diseases 147, 181-184.


Langmuir, A D; Worthen, T D; Solomon, J; Ray, C G; Petersen, E (1985): The Thucydides syndrome: A new hypothesis for the cause of the plague of Athens. NEJM 313, 1027-1030.


Age 13, 81-85.


Nicol, KL; Lind, A; Margolis, K; Murdoch, M; McFadden, R; et al. (1995): The effectiveness of vaccination against influenza in healthy, working adults. NEJM 333, 889-893.

Nichol, KL; Margolis, KL; Wuorenma, J (1994): The efficacy and cost-effectiveness of vaccination against influenza among elderly persons living in the community. NEJM 331, 778-784.


Olive, KE; Berk, SL (1992): Infections in the nursing home. Clinics in Geriatric Medicine 8, 821-


Saah, A J; Neufeld, R; Rodstein, M; La Montagne, J (1986): Influenza Vaccine and pneumonia mortality in a nursing home population. Arch Intern Med 146, 2353-2357.


Shwarzman, S W; Adler, J L; Sullivan, R J; Marine, W M (1971): Bacterial pneumonia during the


Srasberg, MA; Greenland, S; Sorvillo, F; et al. (1986): Influenza in the elderly: report of an outbreak and a review of vaccine effectiveness reports. Vaccine 4, 38-44.


Webster, RG; Bean, WJ; Gorman, OT; Chambers, TM; Kawaoka, Y (1992): Evolution and ecology of influenza A viruses. Microbiological Reviews 56, 152-179.


Appendix 1

Assumptions of Time Series Analysis

In epidemiology estimates of the measure of association between two variables often use regression methods. The assumptions of traditional regression methods hold that the observed data are realizations of independent random variables. Consequently, the unexplained variation in the regression equation (error terms) are assumed to be independent and normally distributed.

If, however, the observations are realized in a manner in which the temporal sequence exerts an influence, then the observations may not necessarily be regarded as independent in time, but may be auto-correlated. The concept of auto-correlation holds that any value of a variable may be dependant on the previous value (or values) of that variable. This is exemplified in daily temperature readings, where a high daily temperature is more likely to be followed the next day by a similar high value (positive auto-correlation) and low daily temperatures are more likely to be followed by a low daily value. Likewise, the number of admissions for pneumonia is serially auto-correlated on the hypothesis that influences such as circulating influenza viruses may effect the number of admissions for targeted diagnosis on successive weeks.

The precise definition of the time period considered affects the degree of manifest auto-correlation. If one defines the temporal frame to include longer time periods, the degree of auto-correlation is likely to diminish somewhat. Consequently monthly values for variables such as hospital admissions will not display the auto-correlations of their values as readily as weekly data. Consequently to examine the effects of influenza on hospital admissions using time series methodology, the optimal time frame is weekly or daily, rather than monthly or quarterly.

When the variables of interest both share a common seasonal pattern or are serially auto-
correlated, the correlations between the two series can be spuriously inflated if the common structure of seasonality is not taken into account (Helfenstein, 1991). The simple fact of seasonality may confound the relationship or obscure a common factor. For example, Bowie and Prothero (Bowie and Prothero, 1981) criticized studies examining the correlations between daily or weekly mortality and daily or weekly temperature that showed strong and statistically significant correlation coefficients between the two series. The high correlations were interpreted as indicating a strong causal relationship between the two variables. Bowie and Prothero, however, demonstrated that another variable, orange importation into Great Britain, that does not share a plausible causal link to mortality (unless the oranges are poisoned), was also strongly correlated to mortality. When methods are used to control for the seasonal pattern, the significance of the correlation disappears.

A variety of techniques exist to analyse time-series data. The most commonly used and best studied techniques are the family of autoregressive integrated moving average models (ARIMA). In this technique it is assumed that any data aggregated as a time series can be represented as a regression parameter (or set of parameters) and an error term that is modelled as an ARIMA process. An autoregressive parameter is estimated when a variable is regressed on a previous value for the same variable. Let $Y_{t-1}, Y_t, Y_{t+1}, \ldots$ represent observations at times $t-1, t, t+1$ and $A_{t-1}, A_n, A_{t+1}$ represent a white noise sequence with a mean of zero and a variance $\sigma^2$. If one assumes that $Z_t$ is linearly dependent on the previous observation $Z_{t-1}$ and on the random shock $A_n$, then one can construct an autoregressive model of the first order, called an AR(1) model as follows:

$$Z_t = \varphi Z_{t-1} + A_n,$$

where $\varphi$ is a parameter.

ARIMA models are identified by examining the autocorrelation (ACF) and partial
autocorrelation (PACF) functions. The autocorrelation function determines the correlation between $Z_t$ and $Z_{t-k}$, where $k$ represents the number of time lags. For the proper identification of an ARIMA model one uses an iterative procedure that commences by the examination of the ACF and PACF. Various patterns of the ACF and PACF are associated with identifiable ARIMA models (McCleary and Hay, 1980). Figure 1 shows the ACF and PACF correlogram for the input series used for influenza for the 1989-1990 season. The symmetrical manner in which the ACF attenuates towards zero, and the significant spike at lag 1 of the PACF identify it as an AR (1) process.

Using the principle of parsimony, one attempts to identify the simplest model to represent the time series. Parameters fit must be statistically significant on the basis of T-tests to be included in the model. As well a goodness of fit test examines the residuals of the fitted series. If the residual series behaves like a white noise series, that is there is no conspicuous pattern to the residuals, then the model is deemed to fit. A statistic called the Ljung-Box Q statistic is employed to test the residual series. The Q statistic is calculated as follows:

$$Q_{LB} = T(T+2) \sum_{j=1}^{p} \frac{r_j^2}{(T-j)}$$

To compute the Q-statistic at lag $p$, $r_j$ is the jth autocorrelation. $T$ is the number of observations. The Q statistic tests the hypothesis that all of the calculated auto-correlations are 0. If all the autocorrelations are not significantly different from zero, then the series of residuals can be regarded as a white noise process. The statistic has a chi-squared distribution, and when the series has an ARIMA process imposed on it the degrees of freedom are equal to the number of autocorrelations calculated after one has subtracted the number of estimated autoregressive
and moving average terms.

A species of ARIMA models that allows for the direct assessment of the effects of the independent variable on the dependant variable is the transfer function model. It allows for the calculation of the cross-correlation between two time series at a number of different time lags. Crucial to the transfer function model is the concept of pre-whitening. As noted above, if one cross-correlates two series that share a common seasonal pattern, the magnitude of the cross-correlations is likely to be inflated because of an inflation in the variance of each series, particularly in the presence of auto-correlation in each series. The transfer function prevents this overinflation by modelling the input series, for example, influenza isolates, as a regression coefficient and a noise term. Once the appropriate ARIMA model has been chosen for the input variable, the same structure is imposed on the output series. The cross correlations of the residual series gives a more accurate estimate of the correlation between the two series. The formula for the cross-correlation coefficient between two series \( y \) and \( x \) at lag \( \tau \) is calculated as follows:

\[
z_{\tau} = \frac{\sum_{t=1}^{T-\tau} (y_t - \overline{y})(x_{t-\tau} - \overline{x})}{\sum_{t=1}^{T} (y_t - \overline{y})(x_t - \overline{x})^2}
\]

The model is explicitly causal and seeks to estimate the direct effect of the input variable on the output variable. Consequently, shared attributes of the two series, such as seasonality and auto-correlation are adjusted for and what is estimated is the direct effect of the input series on the output series.
In this study, AR(1) models were found to fit the input series influenza. This is biologically plausible in that influenza seasons are similar in nature to common source epidemics. As such an evolving influenza season is characterized by an increase and then decrease in the number of isolates. Consequently, each weekly total is related to the previous weeks total and are auto-correlated. Table 1 shows the regression models for each influenza season. Q-statistics for each season showed that an AR(1) model would create a white noise residual series. The residual series from each influenza season was cross-correlated to the residual series for each diagnosis group for each influenza season after an AR(1) model was imposed on the output series.

Table 1: Regression Models for Influenza Input Series

<table>
<thead>
<tr>
<th>Year</th>
<th>Model</th>
<th>Regression Co-Efficient</th>
<th>P. Value Q Statistic (12 th Lag)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1989</td>
<td>AR(1)</td>
<td>0.909</td>
<td>.752</td>
</tr>
<tr>
<td>1989-1990</td>
<td>AR(1)</td>
<td>0.889</td>
<td>.884</td>
</tr>
<tr>
<td>1990-1991</td>
<td>AR(1)</td>
<td>0.902</td>
<td>.489</td>
</tr>
<tr>
<td>1991-1992</td>
<td>AR(1)</td>
<td>0.889</td>
<td>.695</td>
</tr>
<tr>
<td>1992-1993</td>
<td>AR(1)</td>
<td>0.905</td>
<td>.578</td>
</tr>
</tbody>
</table>
Appendix 2

DATA ABSTRACTION SHEET

STUDY NUMBER

AGE

SEX

ADMISSION DATE

DISCHARGE DATE

ADMITTED FROM: Community/ Long term care facility

Vital signs on presentation to E.R.

Temperature
Pulse
Respiratory Rate
Blood Pressure
Mental Status

Clinical signs and symptoms

Cough
Dyspnea
Change in mentation
Fever
Sputum Production

Investigations in E.R.

Haemoglobin
White Blood Count
Sodium
B.U.N.
Creatinine
Arterial Blood Gases:
O2
CO2
02 Sat

Chest Xray
Yes  No  New Infiltrate

Co-morbidity Noted:

Yes  No  Type  Number

Influenza Vaccination Status Noted:  Yes  No  
Readmission for same diagnosis within 6 weeks:  Yes  No

Investigations in Hospital

Sputum  Y  N  Results
Blood Cultures  Y  N  Results
Viral Titres  Y  N  Results
Throat Swab  Y  N  Results
Chest Xray  #

Treatment in Hospital

I.V. Antibiotics  Yes  No  Type:
Amantadine  Yes  No
Chest Physiotherapy  Yes  No

Discharge Status

Alive: Home/ Long Term Care Facility

Dead

Discharge Coding

ICD-9 Codes used for discharge diagnosis.