Epidemiol. Infect. (2007), **135**, 574–582. © 2006 Cambridge University Press
doi:10.1017/S095026880600714X Printed in the United Kingdom

Risk of hospitalization during influenza season among a cohort of patients with congestive heart failure

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(*Accepted 27 June 2006; first published online 29 August 2006*)

SUMMARY

It is uncertain whether hospitalization among patients with congestive heart failure (CHF) increases during the influenza season. This retrospective cohort study used influenza surveillance data from the United States (1986–1987 to 1990–1991), clinical information from the Studies of Left Ventricular Dysfunction (SOLVD) database, and daily temperature data from the National Climatic Data Center to assess the effect of influenza season on hospitalizations in this cohort of patients. The overall hospitalization rate was higher during influenza seasons compared to non-influenza seasons [relative risk (RR) 1·08, 95% confidence interval (CI) 1·01–1·16]. Multivariable Cox modelling revealed an adjusted hazard ratio (HR) of 1·11 for hospitalization during the influenza season (95% CI 1·03–1·20, $P=0·005$). Overall death rates were also higher during influenza seasons than non-influenza seasons (RR 1·09, 95% CI 0·97–1·21), but the corresponding adjusted HR for death was not significant (HR 1·01, 95% CI 0·98–1·24, $P=0·11$). Patients with CHF have a greater risk of hospitalization during the influenza season than in the non-influenza season, supporting the current belief that patients with CHF should be regarded as a high-risk group.

INTRODUCTION

Influenza is a major cause of morbidity and mortality in both the United States and Canada [1, 2]. Individuals with chronic medical conditions, such as lung or heart disease, are identified as being at higher risk for complications of influenza [3, 4]. Although there is evidence to suggest that respiratory infections lead to worse outcomes in patients with chronic lung disease [5], less is known about the impact of the influenza season on excess hospitalization and death in patients with congestive heart failure (CHF).

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Higher rates of hospital admissions for CHF have been reported during influenza epidemic periods compared to non-epidemic periods [6–8], but the findings have been inconsistent. Previous studies have also been limited by use of population-based analyses without access to patient-level comorbidities. Since patients with CHF may be hospitalized for other causes that are related to influenza, but which are not listed on the discharge certificate as the primary or secondary cause, the impact of influenza on patients with CHF has not, to our knowledge, previously been determined. About five million people in the United States and 350 000 in Canada have CHF [9, 10]. Therefore, obtaining estimates of risk of complications associated with influenza season in this population is of major public health importance.

To test the hypothesis that there is increased hospitalization during influenza seasons in adults with CHF, we conducted a retrospective cohort study from 1986 to 1990 using a large clinical database and US national influenza surveillance data. This database allowed us to conduct an analysis that included two influenza seasons (1987–1988, 1989–1990) that were remarkable for an increased severity of illness due to H3N2, the predominant influenza subtype that was circulating [11]. We conducted a separate analysis to examine the secondary outcome of all-cause mortality.

METHODS

Overview

All-cause hospitalization and death rates during the 1986–1990 influenza and non-influenza seasons were compared to provide crude estimates of the overall risk of hospitalization and death associated with circulating influenza among patients with CHF. Cox regression models were constructed to assess these same risks while adjusting for potential confounding variables.

Study population

Data collected for the Studies of Left Ventricular Dysfunction (SOLVD) trials were used as the clinical database. SOLVD consisted of two double-blind, placebo-controlled randomized trials that examined the effect of the angiotensin-converting-enzyme (ACE) inhibitor enalapril on morbidity and mortality in moderately severe CHF patients [12, 13]. Participants with CHF and left ventricular ejection fractions $\leqslant 35\%$ who were already taking drugs other than an ACE inhibitor were eligible. Participants were ineligible if they were aged >80 years or if they had any of the following: haemodynamically serious valvular disease requiring surgery, unstable angina, angina thought to be serious enough to require revascularization procedures, myocardial infarction in the previous month, severe pulmonary disease, serum creatinine $>177\,\mu$mol/l, or any other disease that might substantially shorten survival or impede participation in a long-term trial. Asymptomatic CHF patients, defined as those with no clinical symptoms of CHF, were enrolled in the SOLVD Prevention trial, while symptomatic CHF patients were enrolled in the SOLVD Treatment trial. Participants were followed prospectively from 1986 to 1991. During this period, 39 924 patients with ejection fractions $\leqslant 35\%$ were identified. Of these 6·4% ($n=2569$) were enrolled in the Treatment trial and 7·4% ($n=4228$) were enrolled in the Prevention trial. The reasons for exclusion included the following: use of an ACE inhibitor (28%), cardiovascular problems (12%), contraindications to use of an ACE inhibitor (11%), lack of consent (11%), administrative reasons (21%), cancer or other life-threatening disease (12%), other reasons (5%). There were 24 study sites of which 21 were located throughout the continental United States, two in Canada, and one in Belgium [14]. Each was comprised of 1–8 hospitals [14]. Only participants from the 21 US sites were included in our analysis, since weekly influenza isolate data were available. A small number (<1%) of the participants were excluded because the exact date of their first hospitalization post-randomization could not be determined, leaving 5448 people in the study population. Individual-level longitudinal clinical and medical data, including demographics, medication history, comorbidities, and records of hospitalizations and deaths, were ascertained. To control for comorbidity, we used the Charlson Index to calculate a comorbidity score for each participant [15].

The influenza season

National influenza surveillance data from 1986–1987 to 1990–1991 were obtained from the Influenza Branch of the Centers for Disease Control and Prevention. The weekly number of isolates submitted for testing each year and the weekly number of positive tests obtained during each year (by virus type and subtype) were used to calculate 3-week moving averages of positive influenza isolates. Study years were defined to begin on 1 July and end on the following 30 June. The start of the influenza season was defined as the first week in which the moving average of positive influenza isolates was at least 5% of all respiratory isolates submitted, and the end of the season was defined as the last week in which it was at least 5%. Two additional weeks were added to the end of each influenza season to capture cases associated with any lagged effect of influenza [16, 17]. Isolate data and SOLVD study sites were classified into four regions: Central, Northeast, West, and South. The influenza season for each study year was used as a proxy for exposure to circulating influenza at that time. These seasons were specific to each

region. All events that occurred during an influenza season for a given study year were considered as influenza-season events. All weeks not included in the influenza season for a particular study year were defined as the non-influenza season.

Study outcomes

The primary outcome of interest was first-time hospitalization during the entire study period. For this analysis, each SOLVD participant was considered to be at risk of an event until his/her first hospitalization occurred. If a patient died, was lost to follow-up, or if the study follow-up period ended, the last SOLVD follow-up visit was taken as that person's last day at risk. All patient-days at risk during the influenza season and non-influenza seasons for each year and for all-years combined were calculated based on date of randomization, dates of the beginning and end of each influenza season, and the date of hospitalization, death or last SOLVD visit.

A separate analysis examined the secondary outcome of all-cause mortality. In this case, each SOLVD participant was defined to be at risk until the date of death or until the end of the study follow-up period. State and national records were consulted to confirm all reports of death [14]. If a patient was lost to follow-up or the study ended, the last SOLVD follow-up visit was taken as the last day at risk of death for that individual.

Statistical analysis

Incidence rates of first-time hospitalization during each of the five study years (1986–1987, 1987–1988, 1988–1989, 1989–1990, 1990–1991) and all-years combined were determined by dividing the number of events during a given time period by the total days at risk for eligible individuals during the same period. Days at risk were calculated from the date of enrolment into the study until the date of the first hospitalization or, if no hospitalization occurred, until the date of the final follow-up visit. We calculated the rate ratio [relative risk (RR)] and 95% confidence intervals (CI) for hospitalization and mortality during the combined influenza seasons compared to combined non-influenza seasons. Subgroup analyses were performed to determine the effect of influenza on hospitalization and death for the following groups, which were specified *a priori*: trial, age group, geographic region, and study drug.

A Cox regression model with time-dependent effects [18] was used to estimate the effect of influenza season on hospitalization when adjusted for the following variables: symptomatic CHF (i.e. trial), age, Charlson Comorbidity Index score, New York Heart Association (NYHA) CHF classification [19], ejection fraction, therapy with enalapril, study site, and maximum daily temperature. The influenza season for each individual was defined as a time-dependent variable [20] based on the randomization date and follow-up time of each participant and the dates of the influenza season of his/her region during each study year. The cumulative risk of hospitalization over the entire study period was calculated based on the number of days that each person contributed to the five influenza seasons under study. The cumulative risk of hospitalization during the non-influenza season was also determined similarly. Given that winter has been associated with increased cardiovascular morbidity and mortality, we adjusted the analysis for ambient temperature [21–25]. We obtained temperature readings for each day of the 5 years of the study from the National Climatic Data Center, for each of the study sites. We defined days as 'cold' if the maximum daily temperature was $\leqslant 5\ ^{\circ}C$ [21]; this variable was used as a time-dependent factor in the Cox model, referring to the temperature on the day of the event being considered.

The adjusted hazard ratio (HR) associated with the influenza season compared to the non-influenza season and a 95% CI was calculated. A similar analysis was adopted with death as the outcome. The effect of changing the lag period for cold temperature was done for hospitalization and death analyses.

RESULTS

A total of 5448 patients were followed until first-time hospitalization, death, or loss to follow-up over a median time of 485 days. The mean follow-up times of patients who were asymptomatic for CHF (i.e. in the Prevention trial) and symptomatic for CHF (i.e. in the Treatment trial) were significantly different (617 days and 506 days respectively, $P<0{\cdot}001$). Sixty-two per cent of the study population was hospitalized during the study period. Patients were followed until death (or loss to follow-up) for a median time of 961 days. In the mortality analysis, the mean follow-up times for the patients in the two trials were also significantly different (951 days and 927 days respectively,

Table 1. *Overall incidence of hospitalization among patients with congestive heart failure during the influenza season vs. non-influenza season and their relative risk, 1986–1987 to 1990–1991*

Group	Subgroup	Influenza season*	Non-influenza season*	RR (95% CI)
Entire population	($n=5448$)	113·9	105·2	1·08 (1·01–1·16)†
By trial	Prevention ($n=3322$)	94·0	87·4	1·07 (0·97–1·18)
	Treatment ($n=2126$)	155·3	137·6	1·13 (1·01–1·25)†
By age group (yr)	<50 ($n=905$)	91·4	85·4	1·07 (0·87–1·27)
	50–64 ($n=2847$)	111·2	101·0	1·10 (0·99–1·21)
	$\geqslant 65$ ($n=1686$)	130·7	122·7	1·07 (0·96–1·18)
By geographic region	Central ($n=1358$)	114·7	100·1	1·15 (0·98–1·31)
	Northeast ($n=2395$)	108·8	106·2	1·02 (0·92–1·13)
	West ($n=475$)	105·7	93·2	1·13 (0·82–1·45)
	South ($n=1220$)	125·3	116·0	1·08 (0·93–1·24)
By treatment arm	Placebo ($n=2719$)	137·4	112·2	1·22 (1·11–1·34)†
	Enalapril ($n=2729$)	105·9	98·7	1·07 (0·96–1·18)

RR, Relative risk; CI, confidence interval.
* Ratesare per 100 000 patient-days.
† Statistically significant at 95% confidence level.

$P=0·03$). Twenty-four per cent of the population died during the study; <3% were lost to follow-up.

Risk of hospitalization during the influenza season compared to the non-influenza season

Overall hospitalization rates during the influenza and non-influenza seasons and the relative risk for the entire population and subgroups are summarized in Table 1. The hospitalization rate during the combined influenza season was significantly higher than the combined non-influenza season (113·9 and 105·2 hospitalizations per 100 000 patient-days respectively; RR 1·08, 95% CI 1·01–1·16). In the subgroup analyses, significant season effects were seen among the Treatment trial patients and in patients on placebo (Table 1). No significant season effects were seen in any of the other subgroups. Patients with overt CHF symptoms, patients on placebo, and patients aged $\geqslant 65$ years had the highest hospitalization rates during the combined influenza season (155·3, 137·4 and 130·7 per 100 000 patient-days respectively).

Risk of death during the influenza season compared to the non-influenza season

The corresponding analyses of overall death rates are summarized in Table 2. Mortality during the influenza season was higher than during the non-influenza season, but the difference was not statistically significant (27·1 and 24·9 deaths per 100 000 patient-days respectively; RR 1·09, 95% CI 0·97–1·21). However, among Treatment trial patients (i.e. those who had overt heart failure), the difference was statistically significant (RR 1·19, 95% CI 1·02–1·36).

Adjusted risk of hospitalization and death during influenza season

The multivariable Cox model revealed a higher risk of hospitalization during the influenza season than the non-influenza season (adjusted HR 1·11, 95% CI 1·03–1·20, $P=0·005$, when adjusted for trial, age group, Charlson Comorbidity Index score, NYHA CHF class, ejection fraction, enalapril, cold temperature, and study site). The HRs for each independent predictor in the model for hospitalization are shown in Table 3. Factors associated with an increased risk of hospitalization included: participation in the Treatment trial, age $\geqslant 50$, Charlson score >2, and NYHA CHF class $>$I. The adjusted risk of death associated with the influenza season was 1·01 (95% CI 0·98–1·24, $P=0·11$, when adjusted for trial, age group, Charlson Comorbidity Index score, NYHA CHF class, ejection fraction, enalapril, cold temperature, and study site). The HRs obtained for each independent predictor in the model for death are shown in Table 4. The same factors associated with an increased risk of hospitalization were significantly associated with death. Analyses run with cold temperature 1, 7, and 14 days prior to hospitalization or

Table 2. *Overall incidence of death among patients with congestive heart failure during the influenza season vs. non-influenza season and their relative risk, 1986–87 to 1990–91*

Group	Subgroup	Influenza season*	Non-influenza season*	RR (95% CI)
Entire population	($n=5448$)	27·1	24·9	1·09 (0·97–1·21)
By trial	Prevention ($n=3322$)	16·6	15·7	1·06 (0·87–1·25)
	Treatment ($n=2126$)	46·1	38·8	1·19 (1·02–1·36)†
By age group (yr)	<50 ($n=905$)	19·7	16·9	1·17 (0·79–1·54)
	50–64 ($n=2847$)	27·0	24·1	1·12 (0·94–1·30)
	$\geqslant 65$ ($n=1686$)	31·3	30·1	1·04 (0·85–1·72)
By geographic region	Central ($n=1358$)	28·1	22·2	1·26 (1·01–1·52)†
	Northeast ($n=2395$)	29·0	26·9	1·08 (0·91–1·25)
	West ($n=475$)	20·0	20·1	1·00 (0·49–1·50)
	South ($n=1220$)	24·1	26·4	0·91 (0·69–1·13)
By treatment arm	Placebo ($n=2719$)	28·1	26·8	1·05 (0·88–1·21)
	Enalapril ($n=2729$)	26·2	23·0	1·14 (0·95–1·32)

RR, Relative risk; CI, confidence interval.
* Rates are per 100 000 patient-days.
† Statistically significant at 95% confidence level.

Table 3. *Hazard ratios for all cause hospitalization in patients with congestive heart failure associated with each risk factor adjusted for the other variables in the table, 1986–1987 to 1990–1991*

Variable	Levels	Adjusted HR* (95% CI)	*P*
Influenza season	Non-influenza season	1·00	
	Influenza season	1·11 (1·03–1·20)	0·005
Temperature (daily max.)	$\geqslant 5{\cdot}0$ °C	1·00	
	$<5{\cdot}0$ °C	0·957 (0·86–1·06)	0·40
Trial	Prevention	1·00	
	Treatment	1·14 (1·03–1·26)	0·01
Age (yr)	<50	1·00	
	50–64	1·13 (1·02–1·25)	0·02
	$\geqslant 65$	1·33 (1·19–1·48)	$<0{\cdot}0001$
Charlson Comorbidity Index score	1–2	1·00	
	3–5	1·14 (1·04–1·25)	0·004
NYHA CHF classification	I	1·00	
	II	1·28 (1·17–1·39)	$<0{\cdot}0001$
	III or IV	1·78 (1·57–2·02)	$<0{\cdot}0001$
ACE inhibitor therapy	Placebo	1·00	
	Enalapril	0·862 (0·805–0·922)	$<0{\cdot}0001$
Ejection fraction	1% change	0·992 (0·986–0·997)	0·003

HR, Hazard ratio; CI, confidence interval; NYHA, New York Heart Association; CHF, congestive heart failure; ACE, angiotensin-converting enzyme.
* Adjusted for influenza season, trial, age, Charlson Comorbidity Index score, NYHA class, enalapril therapy, ejection fraction, and study site.

death yielded results similar to those presented above (data not shown).

The adjusted HR for hospitalization during the influenza season without cold temperature in the model was similar to forcing cold temperature into the model (HR 1·11, 95% CI 1·04–1·19, $P=0{\cdot}003$). In contrast, the adjusted HR for death during the influenza season without cold temperature in the model

Table 4. *Hazard ratios for all cause death in patients with congestive heart failure associated with each risk factor adjusted for the other variables in the table, 1986–1987 to 1990–1991*

Variable	Levels	Adjusted HR* (95% CI)	*P*
Influenza season	Non-influenza season	1	
	Influenza season	1·01 (0·98–1·24)	0·11
Temperature (daily max.)	⩾5·0 °C	1	
	<5·0 °C	1·07 (0·90–1·26)	0·39
Trial	Prevention	1	
	Treatment	1·61(1·37–1·89)	<0·0001
Age (yr)	<50	1	
	50–64	1·32 (1·10–1·57)	0·02
	⩾65	1·66 (1·38–1·99)	<0·0001
Charlson Comorbidity Index score	1–2	1	
	3–5	1·21 (1·06–1·38)	0·006
NYHA CHF classification	I	1	
	II	1·24 (1·07–1·43)	0·0004
	III or IV	1·75 (1·45–2·11)	<0·0001
ACE inhibitor therapy	Placebo	1	
	Enalapril	0·865 (0·776–0·964)	0·0009
Ejection fraction	1% change	0·963 (0·955–0·971)	<0·0001

HR, Hazard ratio; CI, confidence interval; NYHA, New York Heart Association; CHF, congestive heart failure; ACE, angiotensin-converting enzyme.

* Adjusted for influenza season, trial, age, Charlson Comorbidity Index score, NYHA class, enalapril therapy, ejection fraction, and study site.

showed a substantial effect and was highly significant (HR 1·16, 95% CI 1·04–1·29, $P=0·009$).

DISCUSSION

We found an increased risk of overall hospitalization among patients with CHF, rather than an increase in risk of CHF admissions during the influenza season as in some previous studies [6, 7]. Our study adds to previous work by assessing all-cause hospitalization in a well-defined cohort. Using a random sample of 5% of elderly hospitalized Medicare recipients, McBean and colleagues showed that the risk of hospitalizations for CHF during a circulating influenza A period was higher than during the non-circulating period (RR 1·20, 95% CI 1·18–1·22) [6]. Barker examined national hospital discharge data and found a slight excess in hospitalization due to CHF during epidemic periods among older adults [7]. Upshur *et al.* performed a time-series analysis using national discharge data and reported an inconsistent relationship between hospital admissions (including for CHF) and circulating influenza viruses among older people in Ontario [8]. An important strength of our study is that patient-level covariates were included. Since there is evidence that hospital admissions and deaths due to cardiac-related causes are higher during winter months compared to summer months [22–26], we adjusted for cold temperature.

Our data reveal that patients with more comorbidity, less functional ability, overt symptoms for CHF, and greater age had higher risk of hospitalization during the influenza season. These latter findings were not unexpected given the known increased morbidity with older people during influenza epidemics [3]. Other investigations have indicated that people aged ⩾80 years may be at greatest risk for complications due to influenza [17, 20].

Although the risk of death associated with influenza season was increased when we did not adjust for the effect of temperature, after adjustment we could not demonstrate an effect independent of temperature (HR 1·01, 95% CI 0·98–1·24). It is possible that there were too few deaths in our dataset to be able to detect an effect. However, the upper limit of the confidence limit does not rule out the possibility of an important effect. A recent report provides strong support for influenza as the cause of increase risk of winter mortality [27].

The diagnosis of influenza virus infection is usually not confirmed in the laboratory, and influenza

Table 5. *Regional distribution of predominant influenza type and subtype in the United States*, 1986–1987 to 1990–1991*

Study year	Time period	Region	Predominant influenza type/subtype	% total positive isolates submitted
1	1986–1987	Overall	A(H1N1)	n.a.
		Central	A(H1N1)	100
		Northeast	A(H1N1)	99·8
		South	A(H1N1)	98·9
		West	A(H1N1)	99·4
2	1987–1988	Overall	A(H3N2)	n.a.
		Central	A(H3N2)	89·4
		Northeast	A(H3N2)	59·6
		South	A(H3N2)	89·8
		West	A(H3N2)	76·4
3	1988–1989	Overall	A(H1N1) & B	n.a.
		Central	B	42·4
		Northeast	A(H1N1)	42·5
		South	B	55
		West	B	51·8
4	1989–1990	Overall	A(H3N2)	n.a.
		Central	A(H3N2)	87·5
		Northeast	A(H3N2)	94·5
		South	A(H3N2)	77·2
		West	A(H3N2)	70·4
5	1990–1991	Overall	B	n.a.
		Central	B	87·9
		Northeast	B	90·7
		South	B	88·6
		West	B	68·8

n.a., Data not available.
* Regional data obtained from National Surveillance Influenza data from the Influenza Branch of the Centers for Disease Control and Prevention. Overall data obtained from *Morbidity and Mortality Weekly Reports*.

Table 6. *Overall incidence of hospitalization among patients with congestive heart failure during the influenza season vs. non-influenza season and their relative risk, by year, per 100 000 population*

Group	Influenza season	Non-influenza season	RR (95% CI)
1986–1987	19·72	15·97	1·23
1987–1988	12·62	13·20	0·96
1988–1989	12·29	10·30	1·19
1989–1990	8·77	9·54	0·92
1990–1991	8·97	7·48	1·20

RR, Relative risk; CI, confidence interval.

Table 7. *Overall incidence of death among patients with congestive heart failure during the influenza season vs. non-influenza season and their relative risk, by year, per 100 000 population*

Group	Influenza season	Non-influenza season	RR (95% CI)
1986–1987	4·59	3·03	1·51
1987–1988	3·07	3·00	1·02
1988–1989	3·08	2·52	1·22
1989–1990	2·37	2·26	1·05
1990–1991	1·81	2·50	0·72

RR, Relative risk; CI, confidence interval.

infection is often cleared before the onset of secondary complications that might result in hospitalization or death [28, 29]. The lack of individual-level data on exposure to and infection with influenza may have led to an underestimation of risks associated with influenza in patients with CHF. We acknowledge that lack of information on influenza vaccination status may also have led to an underestimation of risk. However, only 43% of people with chronic pulmonary and cardiac conditions in the United States were

vaccinated against influenza in 1998, and it is probable that vaccination coverage was even lower during the study period used in this analysis [30]. An assumption of determining cumulative risk in this study was that the risks of hospitalization and death were similar during each year. In our study period, year 1 involved mostly A(H1N1), years 2 and 4 predominantly A(H3N2), and years 3 and 5 predominantly influenza B (Table 5). Influenza A(H3N2) is associated with more serious morbidity and mortality than the other two strains [31]. The predominant strain, however, was usually the same across regions in a given year (Table 5). The relative risks of hospitalization or death by season were highest in years 1 and 3 where A(H1N1) predominated (Tables 6 and 7). Since respiratory syncytial virus (RSV) often co-circulates with influenza, the results could have been due to both RSV and influenza [32]. We acknowledge that the cohort studied was highly selective and it is likely that they had fewer co-existing comorbidities than the general population of patients with CHF. Furthermore, the medical attention paid to these clinical participants may have led to interventions to prevent hospitalization and death that would not have been in place for patients with CHF who did not participate in the clinical trial. These factors may have led to an underestimate of the effect of influenza on hospitalization and death.

In summary, we conclude that all-cause hospitalizations are increased during influenza season in patients with CHF. These findings support the current belief that patients with CHF should be regarded as a high-risk group [3, 4].

ACKNOWLEDGEMENTS

We gratefully acknowledge the assistance of Keiji Fukuda, Lynette Brammer, and Alicia Postema from the Influenza Branch of the Centers for Disease Control and Prevention.

DECLARATION OF INTEREST

None.

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