Response to reviewer 1:

1. The reviewer states that a major problem is that there is no gold standard for influenza morbidity and mortality to judge which definition may give more accurate results and that we do not control for other winter respiratory viruses such as RSV.

We agree with the reviewer that a gold standard for influenza morbidity and mortality would have been helpful in validating the definitions. However, given that we defined exposure based on retrospective U.S national influenza surveillance conducted throughout the United States, it was not possible to obtain any individual-level influenza variables that might have permitted sensitivity analyses using alternative definitions. The reviewer raises the important point that controlling for winter respiratory viruses such as RSV is a limitation. This is a challenge for studies that make use of surveillance data to define start and stop date of influenza. Because symptoms of influenza and RSV are indistinguishable, individual-level laboratory confirmation is needed. We addressed the diagnostic limitations in our discussion by stating

“It could be that while all influenza-attributable events were identified, hospitalizations and deaths not related to influenza (but due to co-circulating viruses such as respiratory syncitial virus) may have been incorrectly attributed to influenza” (Page 11, Para 2).

We also acknowledged the limitation of lack of individual data in the following sections:

“Attributing a particular influenza type to each participant was not possible since there was no individual level data available that could identify the exact influenza subtype that each person was exposed to and for how long” (Page 12, Para 2).

“As well, there was no individual-level data on exposure to and infection with influenza. Our assumption is that study patients living in a particular geographic region were exposed to the virus during the circulating period and that this exposure increased the probability of hospitalization or death.” (Page 12, Para 1)

2. The reviewer states that it should not be surprising that changing the length of the influenza season changes the hazard ratio.

We agree that changing the length of the influenza season would be expected to change the hazard ratio. Indeed, our objective was to demonstrate what the size of this effect could be.

3. The reviewer states that we do not discuss that by changing the definitions we also change the reference (non-influenza) period i.e the longer the influenza season, the more likely the comparison will be dominated by summer months.
We agree with the reviewer that we were not explicit about this point. To address this, we have inserted the following text as an explanation of the higher hazard ratios seen with death for the 5% moving average and the first/last isolate in the discussion:

“One possible explanation for this is that by increasing the length of the influenza season, the 5% moving average and the first/last isolate definitions meant that a higher proportion of the reference period would be summer months, at which time there is less likely to have circulating respiratory viruses.’ (Page 11, Para 1).

4. *The reviewer states that it would make more sense to compare to other winter months when influenza is not circulating.*

We agree with the reviewer that using different winter months may have helped reduce the effect of other winter viruses. We acknowledge this as a limitation in both the current paper and in our previous paper where the objective was to assess the effect of influenza on season using a single definition (Sandoval C, Walter SD, Krueger P, Smieja M, Smith A, Yusuf S, Loeb M. Risk of hospitalization during influenza season among a cohort of patients with congestive heart failure. 1986-1991. Epidemiology and Infection 2006; 29:1-9).

However, the purpose of the present study was a comparative assessment of the effect of changing commonly used definitions of the influenza season in a carefully defined cohort of patients. The approach suggested by the reviewer, although otherwise of potential interest, would not have allowed us to assess the effect of commonly used definitions of the influenza season. In this context, we believe that our analysis satisfactorily addressed the study question as formulated and stated.

5. *The reviewer suggests that we calculate the actual hospitalization or death rate attributable to influenza.*

We agree with the reviewer that hospitalization or death rates attributable to influenza are of interest. We did this by using the formula \((HR - 1)/HR\) to determine the fraction of hospitalizations and deaths attributable to influenza and then multiplying this value by the total number of hospitalizations and deaths that occurred over the influenza season (as defined in one of four different ways). This method takes into account both the hazard and the duration of the influenza season.

We have therefore added the following text to the methods (Page 7, Para 3):

“To compare the effects of the hazard ratio and time of exposure to influenza season of the difference definitions of the influenza season, we calculated the proportion of hospitalizations and deaths attributable to influenza (hazard ratio – 1/hazard ratio) and multiplied this by the number of events (hospitalizations or deaths) within the influenza season however defined.”
The results are shown in Tables 3 and 4.

We have added the following text to the discussion (Page 11, Para 1):

By having a combination of high hazard ratio and long season (larger number of events), the 5% moving average and the first/last isolate definitions showed the greatest number of hospitalizations (109/1204 and 132/1777) and deaths (66/475 and 114/713) respectively attributable to influenza.

6. The reviewer comments that we allude to expectations that hospitalizations and deaths should be higher in years of circulating influenza A but do not provide supporting data.

We have added the following reference to support this statement (Page 12, Para 2):


7. The reviewer suggests that we provide a figure that shows the influenza seasons (number of weeks) for each definition.

We agree and have inserted this information in the form of a table (Table 5). We attempted to construct a figure but the result, given the large amount of data, was unwieldy. The table shows the first and last week of the influenza season based on the various definitions for the study years and stratified by geographic region. We now clarify [in the paper] that the isolate data and SOLVD study sites were stratified by U.S geographic region (Page 6, Para 1) “Isolate data and SOLVD study sites were classified into four regions: Central, Northeast, West, and South.” CDC surveillance begins at about week 40 and ends at about week 20 of the following year. The table provides the reader with a detailed breakdown of the influenza season weeks.

8. The reviewer suggests that we describe the study population and comment on varying flu seasons for participants.

We agree and have added the following text to describe the study population (Page 5, Para 1):

“Participants with CHF and left ventricular ejection fractions ≤ 35% who were already taking drugs other than an angiotensin-converting-enzyme inhibitor were eligible. Participants were ineligible if they were over the age of 80 years or if they had any of the following: hemodynamically 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 higher than 177 umol per litre, 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 ≤ 35% were identified. Of these 6.4% or 2,569 were enrolled in the treatment trial and 7.4% or 4,228 were enrolled in the prevention trial. The reasons for exclusion included the following: use of an angiotensin-converting-enzyme inhibitor (28%), cardiovascular problems (12%), contraindications to use of an angiotensin-converting-enzyme 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 US, two in Canada, and one in Belgium (12, 13). Each was comprised of one to eight hospitals. 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 5,448 people in the study population.”

We address the effect of varying influenza seasons for participants with the following text in the comment section:

“Influenza A(H3N2) is associated with more serious morbidity and mortality than influenza A(H1N1) and influenza B [21]. In our analysis, the cumulative risk was determined by assuming that the risks of hospitalization and death was similar across years (otherwise sounds like risk of hosp is similar to risk of death…), but the predominant influenza type differed by study year. During our study period, years 2 and 4 were predominantly A(H3N2), year 1 was mostly A(H1N1) and years 3 and 5 were mostly influenza B. Furthermore, the predominant influenza subtype may not be the same in all regions, thus potentially affecting risk geographically. In our case, however, the predominant type was the same in all regions for most years.

Attributing a particular influenza type to each participant was not possible since there was no individual level data available that could identify the exact influenza subtype that each person was exposed to and for how long.”

**Response to reviewer 2:**

1. *The reviewer states that there are no descriptive statistics for the influenza seasons defined by the four methods and that these should be included.*

We have now included a table (Table 1) showing the influenza weeks (first and last week) in response to a comment from reviewer 1. Table 1 includes event rates (number of hospitalizations and deaths) and denominators (number of patient-days).
2. *The reviewer comments that Tables 2 and 3 are misplaced and should be interchanged.*

We thank the reviewer for alerting us about this error and have correctly placed the Tables.

3. *The reviewer asks that we clarify whether influenza seasons were considered time-dependent or time-independent covariates.*

We have now addressed the fact that the influenza seasons were considered time-dependent and have added the following text to the methods (Page 7, Para 2):

“The influenza season for each participant was defined as a time-dependent variable based on his/her randomization date and follow-up time, and on the dates of the influenza season of his/her region during each study year.”

4. *The reviewer suggests that weekly influenza isolation rates be plotted so that readers can observe when the first and last isolates occur.*

Reviewer 1 requested a figure of the weeks included in the influenza seasons using the various definitions. We have now included this information (which indicates the weeks corresponding to the first and last isolate) as a table (Table 5).

5. *The reviewer comments that it is not clear how the incidence rates for hospitalization and mortality were defined.*

The incidence rates during the influenza season were defined according to the patient-days of observation during the influenza season. To clarify this, we have inserted the following text into the methods (Page 7, Para 2):

“All patient-days at risk during the influenza season and non-influenza seasons 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. Incidence rates of first hospitalization were determined by dividing the number of events during a given time period (influenza or non-influenza season) 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 ratios (relative risks) and 95% confidence intervals (CI) for hospitalization and mortality during the combined influenza seasons when compared to combined non-influenza seasons.”

6. *The reviewer asks that we control by season because influenza seasons are often confounded by cool and warm seasons.*

We agree with the reviewer that influenza seasons can be confounded by temperature. In fact, using the 5% moving average definition, we obtained temperature readings for each day of
the five 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 \( \leq 5 \) degrees Celsius; 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. However, because this showed no effect in the multivariable model, HR 0.957 (95% CI 0.86, 1.060) for hospitalization (Sandoval C et al., Epidemiology and Infection 2006; 29:1-9) we decided not to include it in the models where definition of season varied.

7. *The reviewer suggests that we use different cut-off points to define influenza season and plot ROC curves to demonstrate the errors incurred at different cut-off points.*

We agree with the reviewer such an approach could potentially be helpful in determining the optimal definition of influenza season. However, as discussed by the first reviewer, the challenge with this particular data set is that there is no gold standard. That is, we do not have individual-level influenza isolate data on participants to assess errors. Moreover, different definitions will not necessarily produce monotonic changes in accuracy. Although results could be plotted in ROC type space, we are not certain that we could actually fit the ROC curve.