

# Intensity of Influenza-Like Illness (ILI) and Congestive Heart Failure (CHF) Deaths: A Correlation Study in Louisiana, 2000-2012

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**Influenza infection has been linked to significant morbidity and mortality, especially in vulnerable populations including the elderly and those with chronic disease, such as congestive heart failure (CHF). This correlation analysis used influenza surveillance data and vital statistics mortality data to assess the correlation between influenza-like illness (ILI) and CHF deaths in Louisiana from 2000-2012 on a weekly level and at the seasonal level. The correlation between ILI proportion and mean number of deaths for the entire study period was 0.23 (significant at  $p < 0.0001$ ). The comparisons made at the seasonal level showed some association between season's intensity and CHF mortality. The clinical implication of this study is that ILI surveillance can be used to issue alert to clinicians who treat CHF patient in order to stress measures aimed at preventing deaths from CHF.**

## INTRODUCTION

In Louisiana, it is estimated that 450,000 to 900,000 individuals are infected with influenza annually, although precise numbers are not known for several reasons.<sup>2</sup> For example, many infected individuals will not seek medical care and of those who do, only a small percentage may be tested for influenza infection. As a result, Louisiana and other states, cities, and even insurance companies rely on sentinel surveillance programs to track influenza activity and viral characteristics with funding and reporting requirements from the Centers for Disease Control and Prevention (CDC).<sup>2,4,9</sup> A voluntary outpatient surveillance program is one component of the CDC's nationwide surveillance system which also includes virologic, mortality, hospitalization and geographic surveillance.

Influenza infection contributes to thousands of deaths in the US and hundreds of deaths in Louisiana each year.<sup>1,2,4,10,11</sup> However, the precise number of individuals who die as a result of influenza infection are not known. Rather, the CDC relies on statistical models to provide estimates of influenza-associated mortality, i.e. those deaths which it is thought that influenza was a likely contributor to the cause of death, but not necessarily the primary cause.<sup>11</sup> Estimates of influenza-associated mortality have historically been based on underlying deaths coded for pneumonia and influenza. It has been recognized since the middle of the 20th century that death certificate data listing influenza as the cause of death grossly underestimates, and sometimes, overestimates influenza-associated mortality.<sup>1,11</sup> However, more recent models also include estimates based on underlying respiratory and circulatory deaths, including pneumonia and influenza, which have been proven to provide more accurate estimates of influenza-associated mortality.<sup>10,11</sup> The most recent data from the CDC estimates an annual average of 23, 607 influenza-associated deaths from 1976-2007.<sup>10,11</sup> Estimates from the CDC based on data from 1990-1999 are higher at

36,000 annual flu-associated deaths, 545 of which are estimated to occur in Louisiana each year.<sup>1,2,4</sup>

It is well-recognized that the most vulnerable population to influenza infection and complications including death are those individuals  $\geq 65$  years old. This group accounts for a significant majority of influenza-associated deaths each year (approximately 90 percent).<sup>1,4,10</sup> Possibly due to higher rates of chronic disease among this group and decreased immunologic capacity to fight infection.<sup>3</sup> Individuals with underlying cardiovascular disease, including CHF, represent one population at increased risk of influenza-associated mortality<sup>1,3,4</sup> and is believed to be related to cardiac decompensation as a result of respiratory compromise.<sup>3</sup> Studies indicate a decreased risk of hospitalization secondary to CHF and improved all-cause mortality in elderly individuals vaccinated against influenza, suggesting an underlying correlation between influenza infection and CHF-associated morbidity.<sup>12,13,14</sup> The purpose of this study was to investigate the correlation between ILI and CHF mortality in a population based cohort.

## METHODS

ILI surveillance data from the Infectious Disease Epidemiology Section and CHF mortality data from the Louisiana Vital Records Registry were used in this analysis.

### Influenza Seasons

The study period comprised 472 weeks from October 1, 2000 (CDC week 40) through May 25, 2012 (CDC week 20). Analyses were performed by influenza season, defined as the period from week 40 (usually at the beginning of October) through week 20 of the subsequent year (usually at the end of May). Eleven influenza seasons (2000- 2001 season to the 2011-2012 season) were included in this analysis. The 2005-2006 season

**Table 1.** Comparison of means of CHF Deaths, between Mild and High-Intensity ILI Seasons

1	2	3	4	5	6	7	8	9	10	11	12
Mild Season	Mean CHF deaths /week	High Season	Mean CHF deaths /week	Mean difference	T test for equality of means	Df	Significant (2 tailed)	95% Confidence Interval of the difference	High season mortality higher with significant difference	High season mortality lower with significant difference	No significant difference
2000-01	22.12	2006-07	21.93	-0.19	0.09*	44	0.92	4.48 to 4.10			N
		<b>2007-08</b>	<b>25.18</b>	<b>3.06</b>	<b>2.28</b>	<b>64</b>	<b>0.03</b>	<b>0.38 to 5.74</b>	<b>Y</b>		
		<b>2008-09</b>	<b>26.18</b>	<b>4.06</b>	<b>2.58</b>	<b>64</b>	<b>0.01</b>	<b>0.92 to 7.20</b>	<b>Y</b>		
		<b>2009-10</b>	<b>29.18</b>	<b>7.06</b>	<b>4.95</b>	<b>64</b>	<b>0.0001</b>	<b>4.21 to 9.91</b>	<b>Y</b>		
		<b>2010-11</b>	<b>27.21</b>	<b>5.09</b>	<b>3.21</b>	<b>64</b>	<b>0.0021</b>	<b>1.92 to 8.26</b>	<b>Y</b>		
2004-05	28.42	<b>2006-07</b>	21.93	-6.49	<b>3.03</b>	<b>44</b>	<b>0.004</b>	-10.81 to 2.18		<b>Y</b>	
		<b>2007-08</b>	25.18	-3.24	<b>2.38</b>	<b>64</b>	<b>0.024</b>	-5.97 to -0.52		<b>Y</b>	
		2008-09	26.18	-2.24	1.41	64	0.162	-5.41 to 0.93			N
		2009-10	29.18	0.76	0.53	64	0.602	2.43 to 3.65			N
		2010-11	27.21	-1.21	0.76	64	0.45	-4.42 to 1.99			N
2011-12	24.06	2006-07	21.93	-2.13	1.06*s	37	0.29	6.90 to 1.94			N
		2007-08	25.18	1.12	0.98	64	0.33	-1.17 to 3.41			N
		2008-09	26.18	2.12	1.51	54	0.13	-0.70 to 4.94			N
		<b>2009-10</b>	<b>29.18</b>	<b>5.12</b>	<b>4.12</b>	<b>64</b>	<b>0.0001</b>	<b>2.60 to 7.60</b>	<b>Y</b>		
		<b>2010-11</b>	<b>27.21</b>	<b>3.15</b>	<b>2.21</b>	<b>53</b>	<b>0.03</b>	<b>0.30 to 6.01</b>	<b>Y</b>		

**Column 1** shows the mild seasons and **column 2** show the mean (average) number of deaths during these seasons, **Columns 3** shows the high seasons and **column 4** show the mean (average) number of deaths during these seasons, **Column 5** shows the difference between the means of the high season and the low season. A positive number indicates that the high season mean was the highest, a negative number shows the opposite, **Column 6, 7, 8 and 9** shows the result of the statistical comparison of these two means. **Column 8** shows the probability of such a result due to chance alone. A probability less than 0.05 is considered significant. **Column 9** shows the confidence interval of the difference between the two means, **Column 11, 12 and 13** shows a summary of these results.

was excluded as data from this year were thought to be inaccurate and inconsistent in the immediate post-Hurricane Katrina period. In summary, data included five consecutive seasons from 2000 through 2005 and six consecutive seasons from 2006 through 2012. CHF mortality and ILI data were not available for one week during the 2003-04 season (CDC week 40) and CHF mortality data were not available for four weeks during the 2006-07 season (CDC weeks 48-51).

#### Weekly Correlation Analysis

In a first step a correlation analysis was performed at the week level to examine the correlation of the number of CHF deaths from Vital Records with the Infectious Disease Epidemiology Section weekly ILI surveillance data using Microsoft Excel software and Epi Info, version.<sup>7</sup> Two correlation analyses were performed using ILI and CHF mortality data: the entirety of the data from the 2000-01 season through the 2011-12 season, and

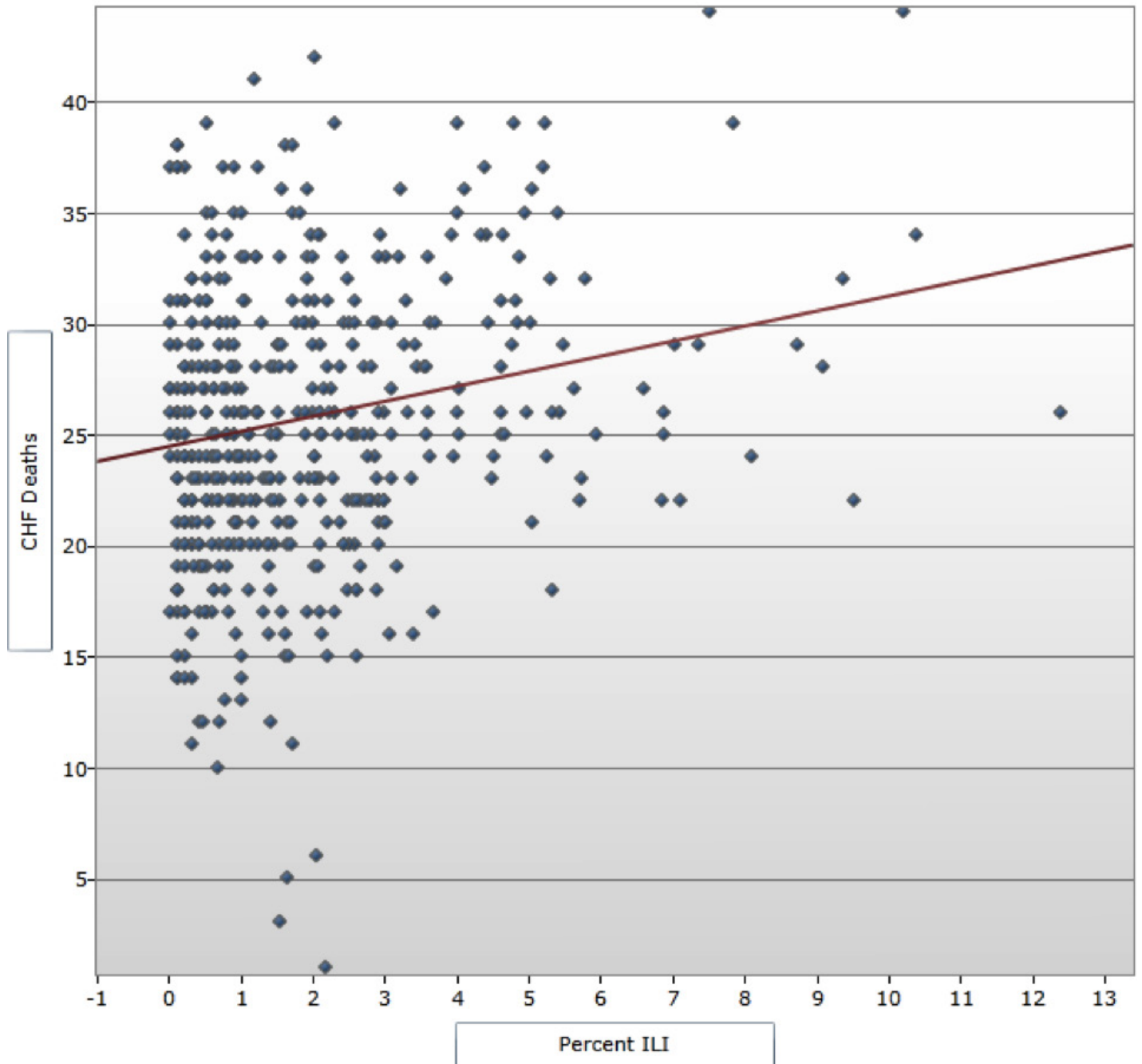


Figure 1. CHF Deaths and ILI Correlation Analysis, 2000-2012 (\*Slope of the straight line fit using the least squares method = 0.79)

the data from the 2006-07 season through the 2011-12 season, the period in which more robust influenza surveillance has taken place in Louisiana.

#### Seasonal Univariate Analysis

In a second step an analysis was carried out at the influenza seasonal level (October of one year to September of the next year). Mean ILI was calculated for each influenza season and used to quantify mild and high intensity seasons. For the purpose of this analysis, mild-intensity seasons (2000-01, 2004-05, and 2011-12) were defined as those seasons without any weeks

with ILI activity greater than five percent and the lowest mean ILI during the entire influenza season. High-intensity seasons (2006-07, 2007-08, 2008-09, 2009-10, and 2010-11) were defined as those seasons with at least two weeks of ILI greater than or equal to five percent. For each season a univariate analysis was carried out comparing mean number of CHF deaths in each high-intensity season with the mean number of CHF deaths in each mild-intensity season. The equality of the means was assessed using t tests for continuous variables. Variances were compared to use the most appropriate statistical test. Significance was set at  $p < 0.05$ .

## RESULTS

### Correlation Coefficient between Weekly CHF Death and ILI Activity

The correlation coefficient between CHF deaths and ILI activity for the overall study period was 0.23 ( $p < 0.0001$ ). The correlation between CHF deaths and ILI activity for data specifically from 2006-2012 was 0.33 ( $p < 0.0001$ ). Both sets of data (2000-2012) and (2006-2012) had statistically significant results,  $p < 0.05$ . The relationship between CHF deaths and ILI activity for these two sets is also shown in Figures 1 and 2. Each point on the graphs represents a matched pair (CHF deaths on the y-axis and percent ILI on the x-axis).

### Comparison of Means between Seasons

While the weekly correlations are very significant, communicating the results to alert physicians is anticipated to be more difficult. Therefore it became interesting to explore the possibility of characterizing the seasonal intensity. Outreach for that single piece of information would be easier to achieve than a weekly message. Hence the seasonal comparison was undertaken.

The equality of means between mild and high-ILI seasons was compared for eight influenza seasons. The mean of each high-intensity season was compared to the mean of each mild-ILI season. The mean number of deaths due to CHF for each season used in this analysis is shown in Table 1. The explanation for the content of the columns is displayed at the bottom of the table. Comparisons between mild and high-ILI seasons resulted in mean differences ranging from -6.49 ( $p < 0.01$ ) to 7.06 ( $p < 0.0001$ ) (Table 1). Of the fifteen individual comparisons conducted, six statistically significant differences showed a higher mean for the high season and only two showed the opposite. Other comparison 6 showed non significant results. Therefore the assumption that at the year level, a high season was associated with a higher mean of CHF deaths was only verified in 6 out of the 15 comparisons.

## DISCUSSION

### Limitations of the Study

**Weekly correlation:** This study demonstrates a positive correlation between weekly ILI activity and weekly count of CHF deaths in Louisiana. The correlation is not strong but is statistically significant suggesting that influenza activity and CHF mortality are associated. When using more robust surveillance data from the 2006-07 through 2011-12 influenza seasons, the correlation is stronger providing additional evidence of a link between these two variables.

**Seasonal correlations:** The relationship between CHF mortality and mild and high-activity influenza seasons is less clear. There were significant positive mean differences in 6 of the 15 comparisons suggesting the possibility that there are more

CHF deaths in a high-ILI season, a result that is to be expected if there is a positive correlation between ILI and CHF mortality. This result is not observed, however, by the finding of two significant negative mean differences, i.e. two high-ILI seasons had lower mean numbers of CHF deaths when compared to a mild-ILI season. This may be related to the lack of robust surveillance data in Louisiana prior to 2006. The ILI data for the 2004-2005 influenza season (the mild-ILI season with a larger mean number of deaths than two high-ILI seasons) may underestimate the true burden of influenza as a result of inadequate surveillance.

The correlation analysis used in this study limits inferences regarding the causal direction of the association between CHF mortality and ILI activity. Despite the strongly positive slopes fit to the data using the method of least squares, correlation should never be confused with causation. For example, it is possible that ILI activity is influenced by CHF mortality or that other unknown variables influence both ILI and CHF mortality. Furthermore, this analysis does not take into account other comorbidities that may contribute to a patient's death.

Despite this caveats, this study provides additional evidence of the link between chronic disease and influenza activity. More than five million Americans live with CHF and it is important from both a public health and clinical perspective to further elucidate the relationship between this vulnerable population and influenza infection.<sup>15</sup> Influenza infection is typically not confirmed with a laboratory diagnosis and infection is often cleared before the onset of complications that might lead to hospitalization and death. Therefore, it is critical to more fully understand the effect of influenza infection on patients with CHF, so that appropriate population-based interventions can take place. This study demonstrates a positive correlation between CHF mortality and ILI activity. These findings lend additional support to the current view that patients with CHF represent a high-risk group.<sup>15</sup>

### Observations from the Literature

Prior studies have examined the relationship between influenza vaccination and risk of hospitalization due to CHF. Nichol and colleagues examined influenza vaccination and risk of hospitalization in a large cohort of patients in managed care organizations over two influenza seasons and found a decreased risk of hospitalization due to CHF in elderly patients over 65 years old who were vaccinated.<sup>12</sup> In a retrospective, controlled study Seo et al. demonstrated a statistically significant reduction in risk of hospitalization due to new onset or acute exacerbation of CHF in vaccinated patients greater than 65 years old (OR 0.274,  $p < 0.004$ ).<sup>13</sup> Using data from the Studies of Left Ventricular Dysfunction (SOLVD) database, Sandoval et al. found higher rates of hospitalization and mortality due to CHF during influenza seasons when compared to non-influenza periods (RR 1.08 and 1.09).<sup>15</sup>

ILI is not all caused by influenza, it also includes other viral respiratory infection. The role of influenza increases as the proportion of ILI increases. Random samples of naso-pharyngeal swab tested by polymerase chain reaction (PCR) for influenza



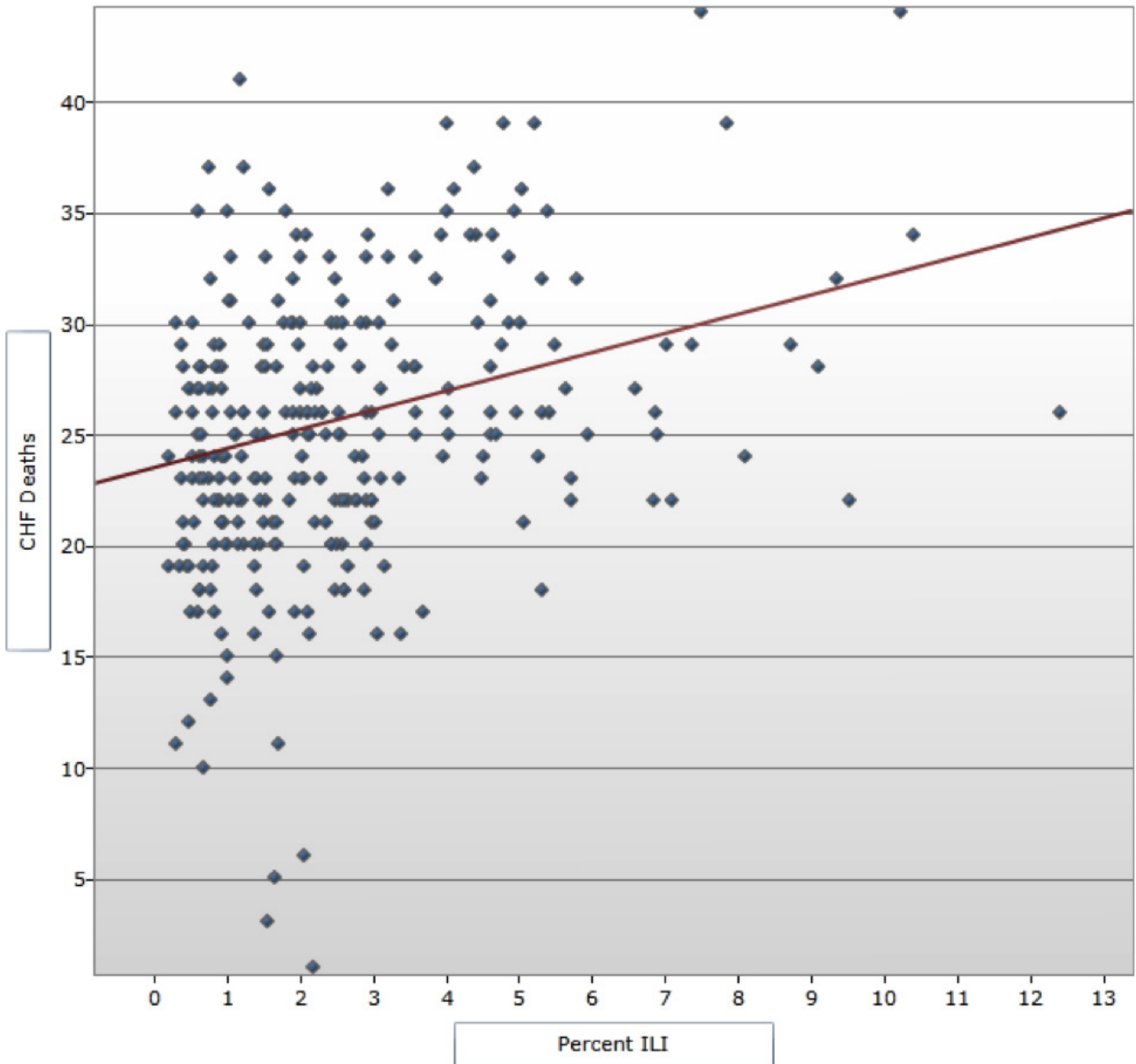


Figure 2. CHF Deaths and ILI Correlation Analysis, 2006-2012 (\*Slope of the straight line fit using the least squares method, 1.01).

virus show a good correlation between proportion of ILI and proportion of specimen with positive PCR (Correlation coefficient = 0.841  $P = 0.000$ , 95% C.I. = 0.701 to 0.919). Therefore in the weeks with high proportion of ILI, the proportion of positive influenza PCR is also elevated.

#### Clinical Implications of this Study

The weekly status of influenza intensity (estimated from the proportion of ILI among outpatients) is widely publicized throughout the height of the influenza season through health

alerts from the health department, e-mails to emergency departments, infectious disease physicians, pulmonologists, health care facility infection preventionists, health department website and the media. Health care providers could use this information to:

1. Encourage their CHF patient to get vaccinated against influenza,
2. Warn them about the need to consult whenever they experience flu-like symptoms, whether they are severe or not,
3. Consider early treatment if influenza is suspected

#### 4. Monitor their patient with CHF more closely.

Although the ILI seasonal intensity association with CHF mortality is weaker than the weekly intensity, being a single indicator for a season, it is easier to communicate to clinicians. Practically as soon as ILI is above five percent for two consecutive weeks, an alert will be sent through the usual channels to remind clinicians about the mortality risks.

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