Excess Deaths Attributable to Influenza-Like Illness in the ESRD Population

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ABSTRACT

Background Morbidity and mortality vary seasonally. Timing and severity of influenza seasons contribute to those patterns, especially among vulnerable populations such as patients with ESRD. However, the extent to which influenza-like illness (ILI), a syndrome comprising a range of potentially serious respiratory tract infections, contributes to mortality in patients with ESRD has not been quantified.

Methods We used data from the Centers for Disease Control and Prevention (CDC) Outpatient Influenza-like Illness Surveillance Network and Centers for Medicare and Medicaid Services ESRD death data from 2000 to 2013. After addressing the increasing trend in deaths due to the growing prevalent ESRD population, we calculated quarterly relative mortality compared with average third-quarter (summer) death counts. We used linear regression models to assess the relationship between ILI data and mortality, separately for quarters 4 and 1 for each influenza season, and model parameter estimates to predict seasonal mortality counts and calculate excess ILI-associated deaths.

Results An estimated 1% absolute increase in quarterly ILI was associated with a 1.5% increase in relative mortality for quarter 4 and a 2.0% increase for quarter 1. The average number of annual deaths potentially attributable to ILI was substantial, about 1100 deaths per year.

Conclusions We found an association between community ILI activity and seasonal variation in all-cause mortality in patients with ESRD, with ILI likely contributing to >1000 deaths annually. Surveillance efforts, such as timely reporting to the CDC of ILI activity within dialysis units during influenza season, may help focus attention on high-risk periods for this vulnerable population.


Seasonal variation in morbidity and mortality has long been a subject of scientific investigation, with some studies reported almost a century ago.1–4 In the 1960s and 1970s, the seasonal pattern in mortality from cardiovascular causes was a particular focus of study.3,5 Because cardiovascular-related and other deaths were more frequent during winter, ambient temperature was initially proposed as the putative mechanism,5 but investigators soon hypothesized a link between the seasonal incidence of respiratory diseases and certain causes of mortality.3 In the ensuing decades, a wealth of reports suggested that influenza, the archetypal seasonal respiratory infectious disease, was associated with morbidity and mortality.6–10 Changes in the inflammatory milieu may be partly responsible for a putative link between influenza and mortality,11 but this remains insufficiently understood.

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Influenza is not the only infectious agent responsible for serious respiratory tract infections. A syndrome known as influenza-like illness (ILI), defined by the US Centers for Disease Control and Prevention (CDC) as a fever higher than 37.8°C plus a cough and/or sore throat, can develop in response to infection with a wide range of agents, including influenza, respiratory syncytial virus, rhinovirus, coronavirus, adenovirus, parainfluenza, and many others. ILI is of sufficient public-health importance that the CDC closely monitors its epidemiology. Seasonal variation in mortality in patients receiving hemodialysis was recently described, but the underlying mechanism for these patterns has not been elucidated. Seasonal variation in mortality in patients with ESRD could be linked to the seasonality of ILI activity, but to our knowledge has never been examined explicitly. We hypothesized that seasonal fluctuations in ILI activity would be reflected in corresponding changes in the patterns of death in patients with ESRD treated with dialysis or kidney transplant.

METHODS

Data Sources and Study Population

We used data from the US Outpatient Influenza-like Illness Surveillance Network (ILINet), a mechanism by which the CDC monitors influenza and ILI activity. This network comprises over 2700 health care providers in the United States, encompassing over 30 million patient visits each year. Weekly data on physician visits and ILI activity in the community (defined as the percentage of patient visits to health care providers for ILI) are reported to the CDC, including numbers of patients, by age. These data result in estimates of the percentage of visits to health care providers because of ILI, and are reported nationally and locally.

We used the Centers for Medicare & Medicaid Services (CMS) ESRD data from 2000 to 2013 to calculate total numbers of deaths among patients with ESRD by quarter, from the fourth quarter (Q4) of 2000 to Q4 of 2012. Death information was obtained from the ESRD Death Notification (form CMS-2746), which is submitted to the CMS within 30 days of a death. These data were supplemented with information from the CMS enrollment database, inpatient claims, and the Social Security Death Master File.

Statistical Analyses

Assessing the association between ILI incidence and mortality required the following: (1) addressing secular changes in the size of the ESRD population between 2000 and 2012, and selecting a reference standard against which we could compare seasonal mortality counts; (2) addressing comparability of time intervals in the CDC and ESRD data; (3) assessing the relation between the CDC ILI data and mortality; (4) predicting seasonal mortality counts; and (5) estimating the number of deaths potentially associated with changes in ILI. Below we outline how we handled each of these problems.

To address secular changes in the size of the prevalent ESRD population (the “denominator population”), which increased by 62% over the study period, and the associated change in the death rates over this period, we fit a cubic smoothing spline to the yearly death counts for the third quarter (Q3) of each year from 2000 to 2012. The “smoothness” of the resulting line is determined by a smoothing parameter ranging from 0 (linear fit between each point) to 1 (least squares linear fit through all points); a value of 0.6 was chosen by visual inspection to allow for minor nonlinearity. We chose Q3 as our reference standard because the lowest number of deaths typically occur over the summer, and it is a period when relatively less ILI circulates in the community. Next, we divided each quarter’s deaths by the estimated number of deaths from the smoothed spline function, resulting in a series of values that measured the relative discrepancy from the underlying time trend across Q3 of each year from 2000 to 2012. We then subtracted 1 from each value and multiplied by 100. The resulting values represent quarterly relative mortality, expressed as percent increase (or decrease) compared with the average Q3 death counts, after removal of the death trend due to the annual increase in the prevalent ESRD population.

Second, we aggregated the weekly ILI data into quarters. An average quarterly ILI burden was estimated by averaging the national weekly ILI estimates derived from the CDC from 2000 to 2012. ILI estimates during July to September were not collected from 2000 to 2002, so values were imputed from the average of the remaining nonmissing Q3s.

Third, to assess the relationship between the CDC ILI data and mortality, we used Q4 of each year and the first quarter (Q1) of the following year (the influenza season) to create regression models to predict Q4 and Q1 deaths using Q4 and Q1 ILI estimates. We then used these models to predict seasonal mortality counts and calculate excess deaths associated with ILI for each influenza season. To do so, we estimated two linear regression models: (1) a regression of Q4 relative mortality on Q4 ILI, and (2) a corresponding regression of Q1 relative mortality on Q1 ILI. These models generated predicted change in relative mortality (as a
percentage of average Q3 mortality) for a one-unit absolute (as opposed to relative) percentage point change in ILI incidence, separately for Q4 and Q1. Predicted death counts for Q4 and Q1 were obtained by multiplying the estimated number of deaths from the smoothed spline function (representing average Q3 mortality counts after removing trend) by 1 plus the regression-predicted percent change in relative mortality. Finally, we estimated the number of deaths associated with an increase (or decrease) in ILI values each year, by first subtracting the average summer (Q3) ILI percentage from each Q4 and Q1 ILI percentage. We then multiplied each resulting Q4 and Q1 ILI value by the appropriate parameter estimates from the regression models and, in the final step, multiplied these estimates by the smoothed spline values (representing average number of Q3 deaths) to give an estimate of the number of “excess” deaths associated with ILI for each season.

To test the robustness of our findings, we performed two separate sensitivity analyses. First, we assessed the effect of adding estimates of the percentage of patients with ESRD who received the influenza vaccination from 2000 to 2012 (US Renal Data System reference tables 2012, 2013, and 2014; https://www.usrd.org/archive.aspx). Second, we assessed the effect of adding estimates of influenza vaccine effectiveness (https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm) to our regression models for Q4 and Q1. Because estimates of vaccine effectiveness were available only beginning in 2004, we limited the vaccine effectiveness models to 2004–2012.

RESULTS

The pattern of ILI activity over time is shown in Figure 1, illustrating the known strong seasonality. The overall trend in quarterly deaths among patients with ESRD, 2000–2012, is shown in Figure 2. The annual increase in the number of deaths is largely due to the overall increase of the ESRD population, from 390,158 in 2000 to 678,383 in 2014.18 Figure 2 also illustrates how death counts vary by season, with the highest death counts in Q1 and the lowest in Q3.

Relative seasonal mortality, or the mortality in a given calendar quarter relative to the referent group (in this case, the Q3 average after removing the underlying increasing trend), is shown in Figure 3. Each quarter’s value can be considered the relative mortality compared with the average summer (Q3) mortality, expressed as a percentage. Q4 (Q4year blue) and Q1 (Q1year+1, black) correspond to each influenza season, and demonstrate higher relative mortality than for quarter 2 and Q3 for each year examined. In most cases, relative mortality was highest in Q1. In some years, relative mortality was similar for Q4year and Q1year+1. Regression models for Q4 and Q1 estimated that a 1% absolute increase in Q4 ILI was associated with a 1.5% (95% confidence interval, 0.6% to 2.4%) increase in Q4 relative mortality (relative to the average Q3 death count), and that a 1% absolute increase in Q1 ILI was associated with a 2.0% (95% confidence interval, 0.2% to 3.9%) increase in Q1 relative mortality.

Observed versus predicted death counts for Q4 and Q1 for each year (Figure 4) indicated relatively good prediction of the death counts from the ILI values. The mean absolute difference between observed and predicted counts was 211 and 306 deaths for Q4 and Q1, respectively.

Annual deaths potentially attributable to ILI (Table 1) averaged >1000 (average Q4 deaths, 341; average Q1 deaths, 711; total, 1052), and ranged from a minimum of 633 (2011–2012) to a maximum of 1604 (2009–2010). Notable influenza seasons with respect to distribution of deaths in Q1 versus Q4 were 2003–2004 and 2009–2010, when most ILI activity occurred in Q4, with resulting low ratios of 0.26 and 0.34, respectively. Regarding total number of excess deaths, the highest seasons were, in decreasing order, 2009–2010 (1604 total deaths), 2007–2008 (1441 total deaths), and 2010–2011 (1348 total deaths).

When the percentage of patients with ESRD vaccinated and vaccine effectiveness were added, separately, to the Q4 and Q1 models, the ILI parameter estimates changed little (<10% and <5%, respectively); corresponding P values for percentage vaccinated and vaccine effectiveness were nonsignificant.

DISCUSSION

Seasonal variability of health events and outcomes has long been established in the general population and is increasingly recognized as an important phenomenon in patients with kidney disease, including those receiving dialysis.15–17 The duration and intensity of influenza seasons have been identified as contributors to this seasonal increase in health risks6–8,19–23 especially among vulnerable populations, such as patients with ESRD, in whom the effectiveness of influenza vaccinations is reduced.24–27 However, the contribution of ILI to mortality in the ESRD population has not specifically been quantified. Given that viral infections are likely associated with hospitalizations and death attributed to ostensibly noninfectious causes, we hypothesized that seasonal patterns in ILI might be associated with mortality in patients with ESRD. Using detailed information collected by the CDC on ILI combined with quarterly mortality data for patients with ESRD, we found an association between severity and timing of ILI activity and mortality. The estimated excess mortality was substantial, averaging approximately 1100 deaths, or approximately 2.4% of all deaths per influenza season. These findings suggest that protection against, surveillance of, and, where possible, treatment of infections due to influenza and related viral respiratory illnesses may constitute an opportunity to reduce deaths in patients with ESRD.

Influenza and, more generally, ILI-related mortality disproportionately affect vulnerable populations such as the elderly, those with chronic diseases, and those characterized by immunocompromised states.28–30 Patients with ESRD constitute
just such an at-risk population for a variety of reasons. First, they often have multiple high-risk comorbid conditions, including diabetes mellitus, cardiac diseases, and pulmonary diseases, reducing “physiologic reserve” in the setting of acute medical stressors. Second, they generally have reduced immunologic function, in the form of impaired T cell–mediated immunity, B cell (humoral) immunity, antigen presentation by dendritic cells, and impaired phagocytic

Figure 1. The intensity and timing of outpatient visits for influenza-like illness vary year to year. CDC percentage of outpatient visits for influenza-like illness. OP, outpatient.

Figure 2. Death counts among patients with ESRD are seasonal, with higher counts during colder months. Quarterly death counts among patients with ESRD, 2000–2013.
and function in cells of mononuclear origin. An additional contribution to impaired immunologic function is the state of chronic inflammation that characterizes patients receiving maintenance dialysis. Third, close proximity to others who have viral illnesses for prolonged periods of time, as typically occurs in thrice-weekly in-center maintenance hemodialysis, is a risk factor for diseases transmitted via respiratory droplets.

If ILI meaningfully contributes to excess deaths in the ESRD population, as this study suggests, greater emphasis

Figure 3. After standardizing death counts to “average summer,” the intensity and timing of death counts among patients with ESRD become apparent. Relative quarterly mortality, by quarter, compared with Q3, after accounting for death trends over time.

Figure 4. Predicted death counts among patients with ESRD are relatively close to observed death counts. Observed versus predicted death counts in the fall (Q4) and winter (Q1) among patients with ESRD, 2000–2013.
Table 1. Quarterly ILI percent and relative mortality percent, and estimated excess deaths, by influenza season

<table>
<thead>
<tr>
<th>Influenza Season</th>
<th>Q4 Relative Mortality</th>
<th>Q1 Relative Mortality</th>
<th>Total Relative Mortality</th>
<th>Q1/Q4 Excess Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ILI Percent</td>
<td>Percent</td>
<td>Excess Deaths</td>
<td>ILI Percent</td>
</tr>
<tr>
<td>2000–2001</td>
<td>1.76</td>
<td>5.12</td>
<td>221</td>
<td>2.84</td>
</tr>
<tr>
<td>2001–2002</td>
<td>1.75</td>
<td>4.75</td>
<td>226</td>
<td>2.93</td>
</tr>
<tr>
<td>2002–2003</td>
<td>1.60</td>
<td>5.94</td>
<td>190</td>
<td>2.39</td>
</tr>
<tr>
<td>2003–2004</td>
<td>3.57</td>
<td>11.11</td>
<td>770</td>
<td>1.43</td>
</tr>
<tr>
<td>2004–2005</td>
<td>1.58</td>
<td>5.61</td>
<td>194</td>
<td>3.47</td>
</tr>
<tr>
<td>2005–2006</td>
<td>1.85</td>
<td>6.42</td>
<td>279</td>
<td>2.67</td>
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<tr>
<td>2006–2007</td>
<td>1.78</td>
<td>7.00</td>
<td>262</td>
<td>2.69</td>
</tr>
<tr>
<td>2007–2008</td>
<td>1.59</td>
<td>5.25</td>
<td>206</td>
<td>3.84</td>
</tr>
<tr>
<td>2008–2009</td>
<td>1.24</td>
<td>4.47</td>
<td>98</td>
<td>2.51</td>
</tr>
<tr>
<td>2009–2010</td>
<td>4.67</td>
<td>8.24</td>
<td>1196</td>
<td>1.87</td>
</tr>
<tr>
<td>2010–2011</td>
<td>1.80</td>
<td>7.24</td>
<td>281</td>
<td>3.36</td>
</tr>
<tr>
<td>2011–2012</td>
<td>1.47</td>
<td>3.58</td>
<td>176</td>
<td>1.96</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval.
*Ratio of Q1 excess deaths to Q4 excess deaths.

on monitoring, prevention (when possible), and treatment may be warranted. The CDC ILINet36 tracks and provides timely reports of ILI incidence in the general population. ILIs reflect a set of symptoms that may be caused by a wide array of viruses, including rhinovirus, adenovirus, respiratory syncytial virus, parainfluenza virus, and human metapneumovirus, as well as influenza (which could account for 10%–50% of all ILI).28 Any or all of these viruses may be associated with poor outcomes in chronically ill populations, such as the ESRD population. The nephrology community should consider the potential merits of tracking ILI within individual dialysis units, in a fashion analogous to that undertaken by the CDC in primary care practices nationwide. This type of surveillance initiative might provide dialysis unit–specific data on ILI incidence, which could be used to conduct epidemiologic studies, guide quality improvement efforts (e.g., isolating patients with suspected ILI within dialysis units), and ultimately, inform disease-management strategies.

Prevention is a challenging issue because most ILI is not influenza. Even in the case of influenza, only about two thirds of patients on dialysis receive the vaccination annually,40,41 and further, the vaccine appears to be substantially less effective in this population.40 Unfortunately, although the CDC recommends influenza vaccinations for patients with CKD,42 the optimal vaccination strategy is unknown.43 For example, immunity resulting from single-dose vaccines may wane before the end of an influenza season, leading to suggestions that patients on dialysis should receive high-dose or adjuvanted influenza vaccines.44,45 Given that vaccines have not been developed for the majority of viruses responsible for ILI, the nephrology community should expect at most a modest benefit from any dialysis population–wide influenza vaccination program, as well as supporting future efforts to explore the immune response to vaccinations in such patients.

Treatment and containment approaches could entail, first, on-site rapid detection and identification of influenza and other ILIs in patients receiving maintenance dialysis, followed by physical isolation of the affected patient within the dialysis unit. In addition to potentially hastening treatment for ILI among those affected, use of protective barriers (e.g., masks) and greater discipline in comprehensive disinfection of the dialysis station might prevent the spread of viral upper respiratory infections. Such interventions, if successfully implemented, might confer benefits well beyond those associated solely with mortality. Reduction in community-wide ILI burden might reduce morbidity and hospitalizations, especially for patients at risk for cardiopulmonary events such as acute myocardial infarction or exacerbations of chronic obstructive pulmonary disease or asthma.7,46–48

These findings have potential implications for epidemiologic and health services studies designed to evaluate clinical outcomes over time. The variability in timing and severity of each influenza season (and resulting ILI incidence) can affect morbidity and mortality events, and investigators should consider accounting for ILI in their analyses.49

This study should be evaluated in light of the following limitations. We used an ecologic study design owing to the sources of exposure (CDC ILINet) and death (ESRD) data included in the analysis. As such, the opportunity for residual confounding cannot be ruled out. Our measure of mortality was on the basis of total quarterly death counts and did not take into consideration cause of death. Possibly, some causes of death that may occur more frequently in colder months could be unrelated to ILI; for example, falls resulting in severe fractures that lead to death or other trauma-related deaths. We elected to perform an analysis using quarters because of uncertainty in the temporal relationship between ILI infection and various causes of death. As a result, our aggregation of ILI data and mortality data into quarterly measurements lacks fine granularity. Finally, although these data may be the best source of ILI information available, they may not accurately reflect
actual ILI incidence, particularly at local or regional levels. Because behavior and activity patterns of patients with ESRD likely vary somewhat from those of the general population, patterns of exposure to ILI might differ in patients with ESRD relative to community-dwelling individuals with intact kidney function.

In summary, we found evidence that community ILI activity is associated with seasonal variation in all-cause mortality in patients with ESRD. Surveillance efforts, such as near real-time reporting of ILI activity to the CDC, may be useful in focusing attention on periods of high risk for this vulnerable population.

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DISCLOSURES

K.J.R. is employed by Research Triangle Institute. G.M.C. has received a research grant and consulting fees from Amgen. B.D.B. owns stock in, and is employed by Amgen. M.A.B. has received research grants from Amgen and AstraZeneca, has ownership or partnership in NoviSci, and has received consulting fees from AbbVie, Amgen, Merck, RxAnte, CERobs, Genentech, Outcomes Insight, and TargetPharma. J.L. has received consulting fees from Fibrogen. W.C.W. has received consulting fees from Akebia, Amgen, AstraZeneca, Bayer, Daichii-Sankyo, Fibrogen, Relpysa, Vifor FMC Renal Pharma, and ZS Pharma. T.S. has received research grants (National Institute on Aging: R01/R56 AG023178, AG056479); owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk; and is involved in the Center for Pharmacoeconomics, whose current members are GlaxoSmithKline, UCB Biosciences, Merck, and Shire. K.L.M. owns stock in, and is employed by Amgen. C.A.H. has received a research grant from Amgen and consulting fees from AstraZeneca and Fibrogen. A.J.C. has received consulting fees from Fibrogen and is employed by NxStage. D.T.G., A.A., and J.B.W. declare no conflicts of interest.

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