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Benefit of Early Initiation of Influenza Antiviral Treatment to Pregnant Women Hospitalized With Laboratory-Confirmed Influenza

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(See the editorial commentary by Tita and Andrews on pages 505–6.)

Background. We describe the impact of early initiation of influenza antiviral treatment among pregnant women hospitalized with laboratory-confirmed influenza during the 2010–2014 influenza seasons.

Methods. Severe influenza was defined as illness with ≥1 of the following: intensive care unit admission, need for mechanical ventilation, respiratory failure, pulmonary embolism, sepsis, or death. Within severity stratum, we used parametric survival analysis to compare length of stay by timing of antiviral treatment, adjusting for underlying conditions, influenza vaccination, and pregnancy trimester.

Results. Among 865 pregnant women, the median age was 27 years (interquartile range [IQR], 23–31 years). Most (68%) were healthy, and 85% received antiviral treatment. Sixty-three women (7%) had severe influenza, and 4 died. Severity was associated with preterm delivery and fetal loss. Women with severe influenza were less likely to be vaccinated than those without severe influenza (14% vs 26%; $P = .03$). Among women treated with antivirals ≤2 days versus those treated >2 days from illness onset, the median length of stay was 2.2 days (interquartile range [IQR], 0.9–5.8 days; n = 8) versus 7.8 days (IQR, 3.0–20.6 days; n = 7), respectively, for severe influenza ($P = .03$) and 2.4 days (IQR, 2.3–2.5 days; n = 153) versus 3.1 days (IQR, 2.8–3.5 days; n = 62), respectively, for nonsevere influenza ($P < .01$).

Conclusions. Early initiation of influenza antiviral treatment to pregnant women hospitalized with influenza may reduce the length of stay, especially among those with severe influenza. Influenza during pregnancy is associated with maternal and infant morbidity, and annual influenza vaccination is warranted.

Keywords. influenza; pregnancy; influenza antiviral treatment; length of stay; early antiviral treatment.

Pregnant women are at increased risk for seasonal and pandemic influenza-related complications [1–6]. During the 2009 influenza A(H1N1) pandemic, pregnant women represented 1% of the US population and yet accounted for 6% of hospitalizations and 5% of deaths associated with infection due to the pandemic strain (influenza A[H1N1]pdm09) [2]. Complications described during this period included intensive care unit (ICU) admission, respiratory failure, and preterm delivery [2–4, 7]. Since then, limited data have been published describing pregnant women with influenza [8–10].

To reduce influenza-associated morbidity and mortality, the American College of Obstetrics and Gynecology and the Advisory Committee on Immunization Practices recommend annual influenza vaccination for pregnant women at any time during pregnancy [11–13]. However, current estimates of vaccination coverage among pregnant women are around 50% [14]. Considering the suboptimal influenza vaccine uptake in this group, antiviral medications are an important adjunct to managing treatment in pregnant women with suspected influenza [12]. The objectives of this study were to describe the epidemiology and clinical outcomes associated with hospitalizations for laboratory-confirmed influenza among pregnant women during recent influenza seasons in the United States and to assess the impact of early initiation of influenza antiviral treatment in this population.

METHODS

Setting and Population

We used data from the Influenza Hospitalization Surveillance Network (FluSurv-NET). FluSurv-NET conducts population-based

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surveillance in selected counties in California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Rhode Island, Tennessee, and Utah. The network includes >240 hospitals covering approximately 27 million people (about 9% of the US population). Data collection was determined by the Centers for Disease Control and Prevention to be for routine public health surveillance purposes and thus was not subject to institutional review board (IRB) approval for human research protections. Participating sites submitted the study to their state and local IRBs for review as required.

Data Collection and Definitions

In this analysis, we included pregnant women aged 15–44 years residing in the surveillance area who were hospitalized within 2 days of an influenza virus–positive test result. All were enrolled during 4 consecutive influenza seasons, beginning in 2010–2011, with a season defined as the interval from 1 October through 30 April. Hospitalization was defined as an admission to an inpatient ward of the hospital; an overnight stay was not required. Laboratory testing for influenza virus was performed at the discretion of the clinicians providing medical care, and confirmation included a positive result of reverse transcription polymerase chain reaction analysis, rapid antigen testing, direct or indirect fluorescent antibody staining, or viral culture.

Patients were identified through hospital laboratory and admission databases, infection control logs, and hospital discharge data. For patients with a positive result of an influenza virus test, medical records were reviewed using a standardized case report form to collect information on demographic characteristics, pregnancy status, medical history, and clinical course of illness during hospital stay, including certain complications (eg, encephalitis and pneumonia), admission to the intensive care unit (ICU), need for mechanical ventilation, and mortality. Data abstraction also captured the first 9 hospital discharge codes, using the *International Classification of Diseases, Ninth Revision (ICD-9)*.

We used data abstracted from medical records and *ICD-9* codes to categorize complications as follows: pneumonia (*ICD-9* codes 089, 480–487, and 488.11), respiratory failure (*ICD-9* codes 799.1, 518.81, 518.84, and V46.1), acute respiratory distress syndrome (ARDS; *ICD-9* codes 518.5 and 518.82), pulmonary embolism (*ICD-9* codes 415.1 and 673), asthma exacerbation (*ICD-9* codes 493.01–02, 493.11–12, 493.21–22, and 493.91–92), chronic obstructive pulmonary disease (COPD) exacerbation (*ICD-9* codes 491.21–22), sepsis (*ICD-9* codes 286.6, 036.3, 040.82, 785.5, and 995.91–92), diabetic ketoacidosis (*ICD-9* codes 249.1 and 250.1), acute renal failure (*ICD-9* codes 584, 572.4, and 404.02–03), and dehydration (*ICD-9* codes 276.50–276.52). Fetal loss was identified based on *ICD-9* codes for missed abortion and spontaneous abortion (*ICD-9* codes 632 and 634).

Underlying medical conditions were classified into the following categories: asthma, chronic pulmonary disease (apart from asthma), metabolic disease, cardiovascular disease (excluding hypertension), blood disorders/hemoglobinopathy, neurologic/neuromuscular disease, renal disease, and liver disease. Pregnant women were stratified into the first (≤13 weeks gestation), second (14–28 weeks gestation), and third (≥29 weeks gestation) trimesters of pregnancy. Delivery at <37 weeks gestation was considered before term. A patient was considered vaccinated if receipt of influenza vaccine occurred at least 14 days prior to hospitalization, considering the relevant influenza season. When the date of a patient's influenza vaccination was not available in the medical record, a vaccination registry or the patient's primary care provider was consulted or the patient was interviewed to obtain vaccination history [15]. Severe influenza was defined by ICU admission, need for mechanical ventilation, respiratory failure (including ARDS), pulmonary embolism, sepsis, or death. Hospital length of stay (LOS) was calculated as the discharge date minus the admission date. Treatment was considered as receipt of influenza antiviral medication at any time during the course of illness (including receipt up to 2 days before hospitalization, if treatment was continued after admission). The time from illness onset to antiviral treatment initiation was stratified into early treatment (if antiviral medication was initiated ≤2 days from illness onset) and late treatment (if antiviral medication was initiated >2 days from illness onset).

Statistical Analysis

We used χ^2 or Fisher exact tests to compare clinical characteristics among pregnant women and frequencies of outcomes and complications, by severity, for categorical variables. Kruskal–Wallis test was performed to assess differences in the distribution of nonnormally distributed continuous variables. When examining the impact of early initiation of antiviral treatment, we only included treated patients in our models, to avoid any potential treatment bias introduced by physicians' inclination to treat more severe cases [16]. Assuming that treatment would need to be initiated for a full day before it could be beneficial, we excluded patients hospitalized for ≤1 day from our models. Among patients hospitalized for >1 day, within each severity stratum we used parametric survival analysis to compare hospital LOS by the timing of antiviral treatment, adjusting for the presence of underlying medical conditions, influenza vaccination status, and pregnancy trimester. We limited the model to pregnant women who did not deliver during hospitalization, to remove the potential confounding effect of delivery on LOS. We chose a parametric survival analysis because of the approximately normal distribution of our data, and we wanted to estimate the adjusted median hospital LOS and difference by the timing of antiviral treatment [17]. Women with unknown dates of illness onset and antiviral initiation and women who

died during hospitalization were excluded from the parametric analysis. We characterized the distribution of LOS, using exponential, Weibull, log-logistic and log-normal models. For each severity stratum, we chose the model with the best fit, based on plots of transformed survival probabilities against log-days, which produce straight lines and tight data scatter when used for the appropriate survival model [17]. For all predictors and associations between variables, differences were considered significant at a P value of $< .05$. All analyses were performed using SAS software, version 9.3 (Cary, North Carolina).

Table 1. General Characteristics of Pregnant Women Hospitalized With Laboratory-Confirmed Influenza During the 2010–2014 Influenza Seasons, Overall and by Disease Severity

Characteristic	Overall (n = 865)	Severe[a] (n = 63)	Nonsevere (n = 802)	*P* Value[b]
Age group, y				.88
15–24	315 (36)	24 (38)	291(36)	
25–34	451 (52)	31 (49)	420 (52)	
35–44	99 (11)	8 (13)	91 (11)	
Race/ethnicity[c]				.26
Non-Hispanic white	314 (42)	28 (53)	286 (41)	
Non-Hispanic black	240 (32)	15 (28)	225 (33)	
Hispanic	188 (25)	10 (19)	178 (26)	
Pregnancy trimester on admission, wks[d]				**.04**
First, ≤13	88 (11)	9 (15)	79 (10)	
Second, 14–28	266 (32)	25 (43)	241 (31)	
Third, ≥29	478 (57)	24 (41)	454 (59)	
Underlying medical condition				
Any	278 (32)	28 (44)	250 (31)	**.03**
Asthma	182 (21)	21 (33)	161 (20)	**.01**
Metabolic disease	64 (7)	7 (11)	57 (7)	.20
Cardiovascular disease (excluding hypertension)	31 (4)	5 (8)	23 (3)	.05
Immunocompromised condition	28 (3)	4 (6)	27 (3)	.30
Blood disorder/hemoglobinopathy	20 (2)	2 (3)	18 (2)	.60
Neurologic/neuromuscular disease	18 (2)	2 (3)	16 (2)	.40
Renal disease	10 (1)	1 (2)	9 (1)	.50
Chronic pulmonary disease (excluding asthma)	7 (1)	0 (0)	7 (1)	>.99
Liver disease	4 (0)	0 (0)	4 (0)	>.99
Other characteristics				
Influenza vaccination	221 (26)	9 (14)	212 (26)	**.03**
Antiviral treatment	731 (85)	53 (84)	678 (85)	.90
Influenza virus type/subtype[e]				
Influenza A virus	739 (85)	57 (91)	682 (85)	. . .
H1N1pdm09	197 (23)	27 (42)	170 (21)	**.01**[f]
H3N2	173 (20)	7 (11)	166 (21)	
Not subtyped	494 (57)	29 (46)	465 (58)	. . .
Influenza B virus	125 (15)	6 (10)	119 (15)	. . .
Time from illness onset to hospitalization, d[g]	1 (0–2)	1(1–3)	1 (0–2)	.08
Time from hospitalization to antiviral treatment, d	0 (0–1)	0 (0–1)	0 (0–1)	.90
Time from illness onset to antiviral treatment[h]				
Overall, d	2 (1–3)	2 (1–4)	2 (1–3)	.05
Early[i], proportion (%)	353/500 (71)	14/27 (52)	339/473 (72)	**.03**
Late[j], proportion (%)	147/500 (29)	13/27 (48)	134/473 (28)	

Data are no. (%) of women or median value (interquartile range), unless otherwise indicated, and were obtained from the Influenza Hospitalization Surveillance Network.

Abbreviations: d, days; H1N1pdm09, 2009 pandemic influenza A(H1N1) virus; wks, weeks; y, years.

[a] Defined by intensive care unit admission, need for mechanical ventilation, death, respiratory failure, acute respiratory disease syndrome, pulmonary embolism, or sepsis.

[b] Calculated using χ^2 analysis or the Fisher exact test, for categorical variables, and the Kruskal–Wallis test, for continuous variables.

[c] Data are for 742 women.

[d] A total of 832 women had information on trimester; 58 had severe influenza, and 774 had nonsevere influenza.

[e] For 1 woman, the influenza virus type was not distinguished.

[f] For comparison of H1N1pdm09 and H3N2.

[g] A total of 588 women had a known date of illness onset or hospitalization date.

[h] A total of 500 women had a known date of illness onset and antiviral initiation.

[i] Defined as ≤2 days from illness onset.

[j] Defined as >2 days from illness onset.

RESULTS

General Characteristics and Influenza-Associated Complications

During the influenza seasons from 2010–2011 through 2013–2014, 865 of 3169 women (27%) aged 15–44 years hospitalized with laboratory-confirmed influenza were pregnant. Over half (52%) were aged 25–34 years, and 57% were in the third trimester of pregnancy (Table 1). The most commonly reported racial/ethnic groups in our study were non-Hispanic white (42%), followed by non-Hispanic black (32%) and Hispanic (25%). The majority (68%) had no underlying medical conditions other than pregnancy, but among those who did, the most common condition was asthma (21%). Most women (85%) were treated with antivirals, and all treated women received oseltamivir (Tamiflu). Only 26% of hospitalized pregnant women had received influenza vaccine for the season. The median time from illness onset to hospitalization was 1 day (interquartile range [IQR], 0–2 days). The median time from hospitalization to antiviral treatment was 0 days (IQR, 0–1 days), with the majority of women (71%) treated ≤2 days from illness onset (Table 1). The median LOS was 2 days (IQR, 1–3 days) for all pregnant women. The most common complications were pneumonia (13%), dehydration (9%), asthma exacerbation (6%), respiratory failure (3%), and sepsis (3%; Table 2).

Characteristics, by Severity

Sixty-three women (7%) met criteria for severe influenza, of whom 4 (6%) died. Women with severe influenza were more likely to be in an earlier stage of pregnancy and to have underlying medical conditions, compared with pregnant women with nonsevere influenza (44% vs 31%; $P = .03$; Table 1). Women with severe influenza were less likely to have received influenza vaccination than women with nonsevere influenza (14% vs 26%; $P = .03$; Table 1). The presence of influenza A(H1N1)pdm09 was more likely among women with severe influenza (42% vs 21%; $P = .01$). Of the 4 women who died, all were treated with antivirals; 3 were treated >2 days after illness onset, including one who was admitted within 2 days of illness onset (the date of illness onset was unknown for 1 patient); and only 1 had received influenza vaccine for the season. Three of the deaths involved women <35 years of age with no underlying medical conditions. The frequency of influenza antiviral treatment did not differ by disease severity. The median times from illness onset to hospitalization and from illness onset to antiviral treatment also did not differ by severity (Table 1).

Table 2. Influenza-Associated Complications Among Pregnant Women Hospitalized With Laboratory-Confirmed Influenza During the 2010–2014 Influenza Seasons, Overall and by Disease Severity

Complication	Overall, No. (%) (n = 865)	Severe, No. (%)[a] (n = 63)	Nonsevere, No. (%) (n = 802)	*P* Value[b]
Pneumonia	112 (13)	35 (56)	77 (10)	**<.01**
Dehydration	79 (9)	6 (10)	73 (9)	.91
Asthma exacerbation	50 (6)	12 (19)	38 (5)	**<.01**
Sepsis/shock	26 (3)	26 (41)	NA[c]	
Respiratory failure	25 (3)	25 (40)	NA[c]	
ARDS	9 (1)	9 (14)	NA[c]	
Acute renal failure	7 (1)	7 (11)	0 (0)	**<.01**
Diabetic ketoacidosis	4 (1)	0 (0)	4 (<1)	**<.01**
Pulmonary embolism	4 (<1)	4 (6)	NA[c]	
COPD exacerbation	2 (<1)	0 (0)	2 (<1)	**<.01**

Data were obtained from the Influenza Hospitalization Surveillance Network.

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease.

[a] Defined by intensive care unit admission, need for mechanical ventilation, death, respiratory failure, ARDS, pulmonary embolism, or sepsis.

[b] Calculated using χ^2 analysis or the Fisher exact test, for categorical variables.

[c] Not applicable (NA) because these complications were limited to severe influenza.

Table 3. Clinical Outcomes Among Pregnant Women Hospitalized With Laboratory-Confirmed Influenza During the 2010–2014 Influenza Seasons, Overall and by Disease Severity

Characteristic	Overall (n = 865)	Severe[a] (n = 63)	Nonsevere (n = 802)	*P* Value[b]
Live birth	188 (22)	7 (11)	181 (23)	**.03**
Preterm delivery, proportion (%)[c]	41/188 (22)	5/7 (71)	36/181 (20)	**<.01**
Fetal loss	4 (0.4)	3 (5)	1 (0.1)	**<.01**
LOS, d, median (IQR)	2 (1–3)	5 (2–7)	2 (1–3)	**<.01**
ICU admission	38 (4)	38 (60)	NA[d]	
Mechanical ventilation	16 (2)	16 (25)	NA[d]	
Death	4 (<1)	4 (6)	NA[d]	

Data were obtained from the Influenza Hospitalization Surveillance Network.

Abbreviations: d, days; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

[a] Defined by ICU admission, need for mechanical ventilation, death, respiratory failure, acute respiratory disease syndrome, pulmonary embolism, or sepsis.

[b] Calculated using χ^2 analysis or the Fisher exact test, for categorical variables, and the Kruskal–Wallis test, for continuous variables.

[c] Preterm delivery calculated among number of live births.

[d] Not applicable (NA) because these complications were limited to severe influenza.

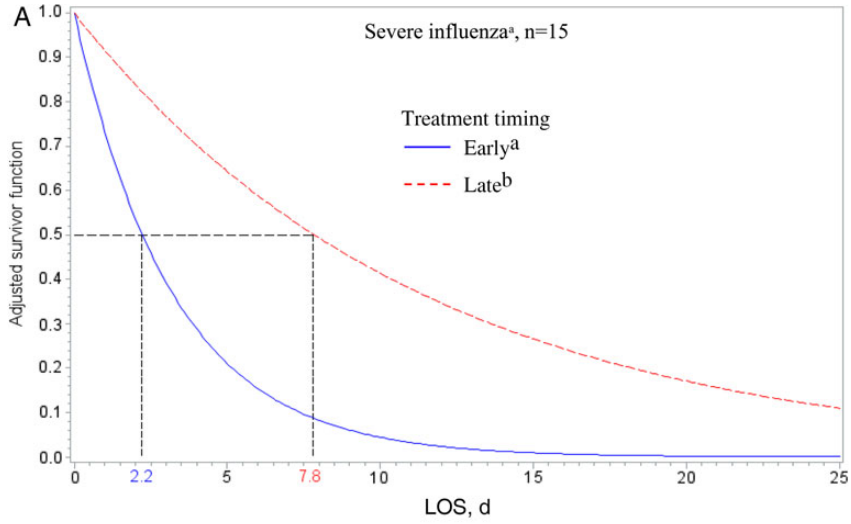
Pregnancy-Related Complications and Outcomes

One hundred eighty-eight women (22%) had a live birth while hospitalized with influenza, of whom 41 (22%) delivered before term (Table 3). Among women with live births, preterm delivery was more common among those with severe influenza, compared with those with nonsevere influenza (5 of 7 [71%] vs 36 of 181 [20%]; $P < .01$). A total of 4 of 865 women (0.4%) experienced a fetal loss during hospitalization; 3 (5%) were among the 63 with severe influenza, compared with 1 (0.1%) among the 802 with nonsevere influenza ($P < .01$). Women with severe influenza had a longer median hospital LOS than women with nonsevere influenza (5 days [IQR, 2–7 days] vs 2 days [IQR, 1–3 days]; $P < .01$; Table 3).

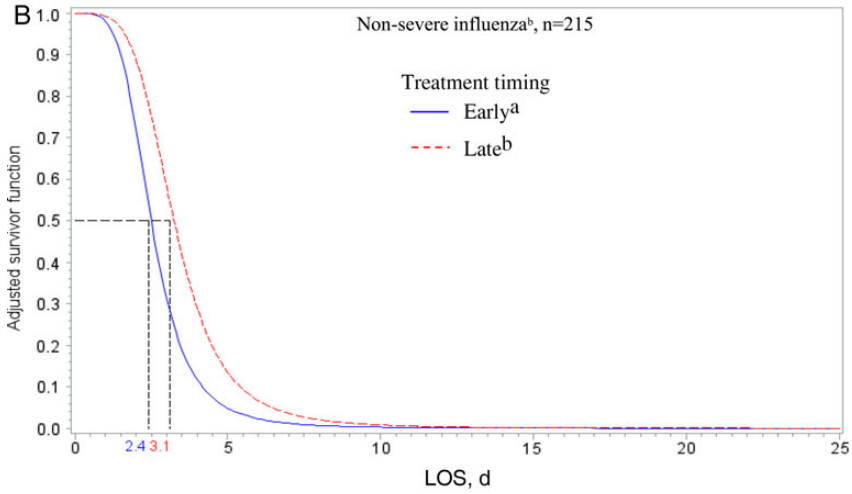
Parametric Survival Analysis

There were 15 of 63 women (23.8%) with severe influenza and 215 of 802 (26.8%) with nonsevere influenza who were included in the model. They all had available information on timing of

illness onset and antiviral treatment, did not deliver during hospitalization, were admitted for >1 day, and did not die during their hospitalization (Figure 1). We examined 4 models to determine the best fit for the data. The best fit was the exponential model for women with severe influenza (Figure 2) and the log-logistic model for those with nonsevere influenza (Figure 3). Using these best-fit models, we found that, after adjustment for the presence of any underlying medical condition, influenza vaccination status, and pregnancy trimester, early initiation of antiviral treatment (ie, ≤2 days from illness onset) was associated with a shorter LOS. Among women with severe influenza who were treated early, the median LOS was 2.2 days (IQR, 0.9–5.8 days), compared with 7.8 days (IQR, 3.0–20.6 days; $P = .03$) among those treated later (Figure 1*A*). Among women with



Treatment Timing	Women, No.	LOS, d, Median (IQR)	*P*
Early[a]	8	2.2 (0.9–5.8)	.03
Late[b]	7	7.8 (3.0–20.6)	



Treatment Timing	Women, No.	LOS, d, Median (IQR)	*P*
Early[a]	153	2.4 (2.3–2.5)	<.01
Late[b]	62	3.1 (2.8–3.5)	

Figure 1. Length of stay (LOS), by timing of treatment from illness onset, for 15 pregnant women with severe (*A*) and 215 with nonsevere (*B*) laboratory-confirmed influenza during the 2010–2014 influenza season who were hospitalized for >1 day and did not deliver or die during hospital stay. Data were obtained from the Influenza Hospitalization Surveillance Network. An exponential model was used for analysis of women with severe influenza, and a log-logistic model was used for analysis of women with nonsevere influenza. [a]≤2 days from illness onset; [b]>2 days from illness onset; [c]*P* values for LOS comparisons were calculated using the χ^2 test in a model adjusted for underlying medical condition, influenza vaccination status, and pregnancy trimester. Abbreviations: d, days; IQR, interquartile range.

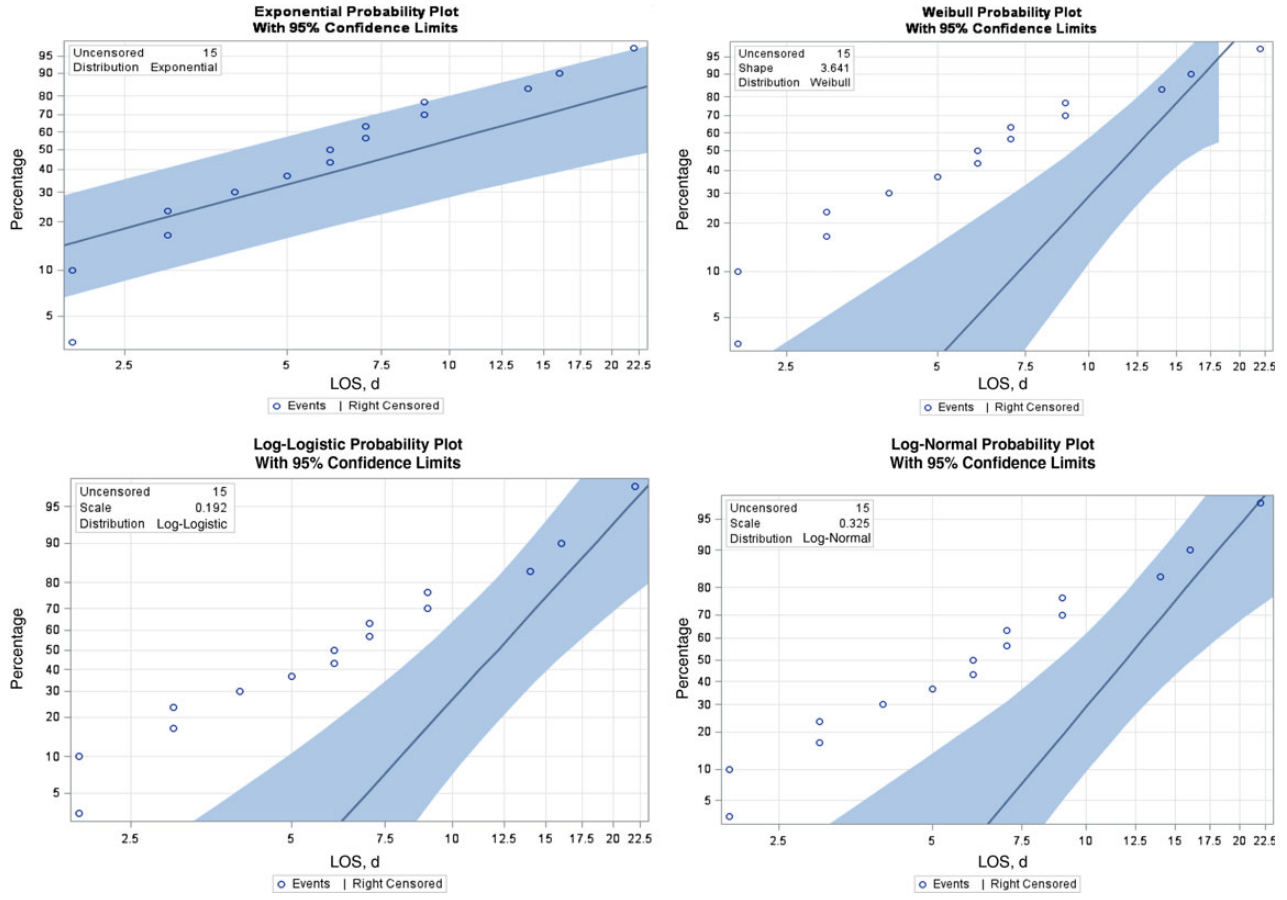


Figure 2. Diagnostic probability plot for pregnant women with severe laboratory-confirmed influenza during the 2010–2014 influenza season who were hospitalized for >1 day and did not deliver or die during hospital stay. Data were obtained from the Influenza Hospitalization Surveillance Network and were adjusted for underlying medical condition, influenza vaccination status, and pregnancy trimester. The Akaike information criterion values for the probability plots were as follows: exponential, 43.56; Weibull, 22.74; log logistic, 23.82; and log normal, 22.86. The exponential model was chosen because it yielded the best-fitting probability plot. Abbreviations: d, days; LOS, length of stay.

nonsevere influenza, those treated early also had a shorter median LOS (2.4 days [IQR, 2.3–2.5 days]) than those treated later (3.1 days [IQR, 2.8–3.5 days]; $P < .01$; Figure 1*B*).

DISCUSSION

This is the first and largest study to report on the clinical characteristics and outcomes of pregnant women hospitalized with laboratory-confirmed influenza since the 2009 influenza pandemic. In this study, most hospitalized pregnant women had no underlying medical conditions and were admitted to the hospital for a median of 2 days; approximately 60% were in their third trimester of pregnancy at time of hospitalization. Although influenza in most women was relatively uncomplicated medically, 7% had severe influenza, 4 died, and 4 experienced fetal loss. Women with severe influenza were more likely to be earlier in gestation, to have underlying medical conditions, and to experience preterm delivery and fetal loss than women with nonsevere influenza. After adjustment for any medical condition, vaccination status, and pregnancy trimester, antiviral treatment given ≤2 days from illness onset reduced hospital LOS among women who neither delivered nor died during hospitalization. This was more pronounced among women with severe influenza, who had a reduction in median LOS of approximately 5 days.

The high antiviral coverage (85%) in our study population, suggests that providers have continued to use influenza antiviral agents to treat hospitalized pregnant women with laboratory-confirmed influenza since the 2009 pandemic [2, 3, 16, 18]. Furthermore, during the 2009 pandemic, 24%–50% of pregnant women were treated early (ie, ≤2 days from illness onset) [2, 3, 7]. In contrast, we found that, among pregnant women who received antivirals in our study, 71% were treated early, perhaps demonstrating patients' awareness of the importance of seeking care early and physicians' adherence to influenza antiviral treatment recommendations [12].

Previous studies have shown that early initiation influenza-associated antiviral treatment reduces the duration and severity of influenza and decreases the frequency of associated complications [19–22]. However, our study is the first to assess the

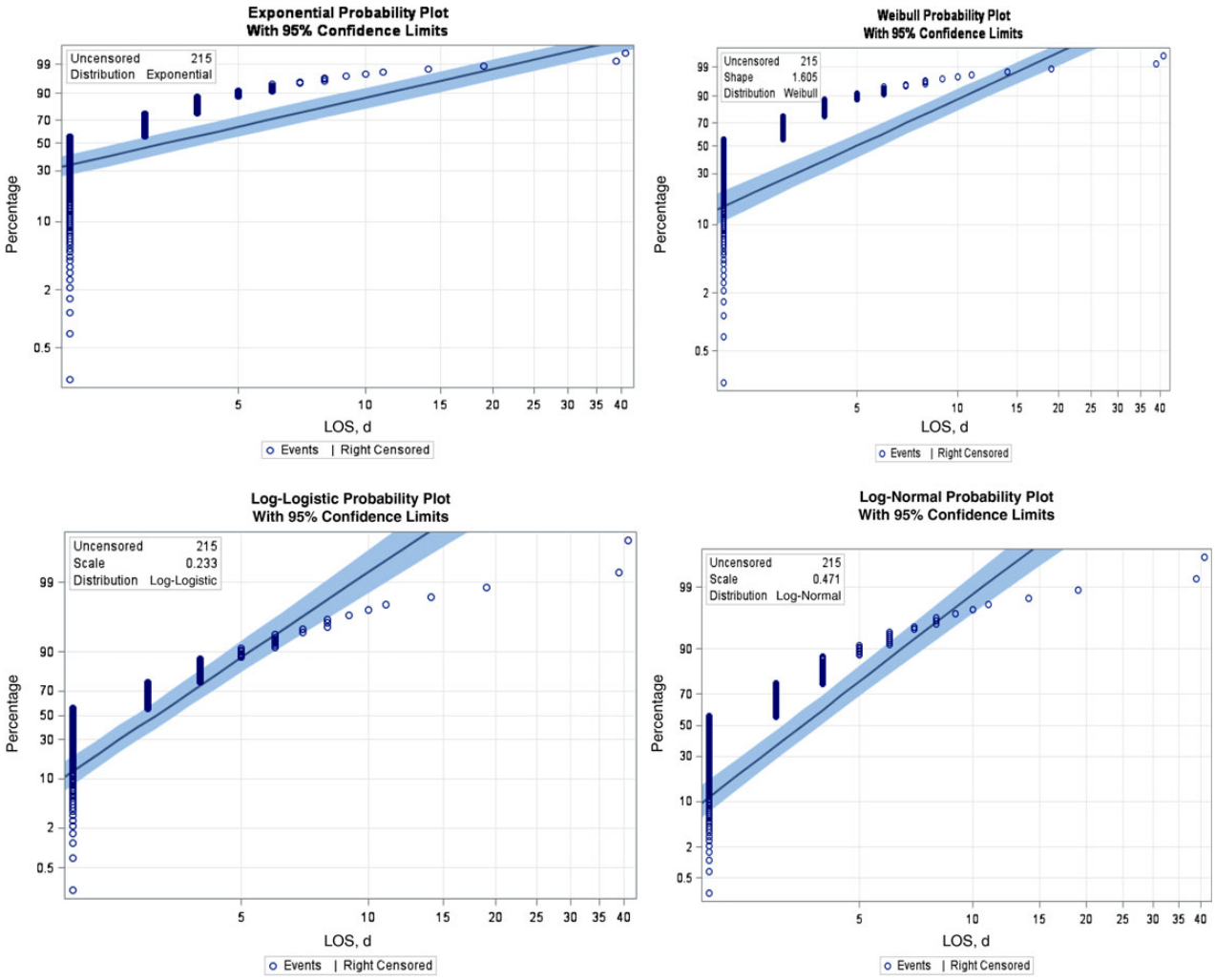


Figure 3. Diagnostic probability plot for pregnant women with nonsevere laboratory-confirmed influenza during the 2010–2014 influenza season who were hospitalized for >1 day and did not deliver or die during hospital stay. Data were obtained from the Influenza Hospitalization Surveillance Network and were adjusted for underlying medical condition, influenza vaccination status, and pregnancy trimester. The Akaike information criterion values for the probability plots were as follows: exponential, 506.93; Weibull, 431.31; log logistic, 259.29; and log normal, 300.18. The log-logistic model was chosen because it yielded the best-fitting probability plot. Abbreviations: d, days; LOS, length of stay.

impact of early versus late initiation of antiviral treatment on LOS among pregnant women hospitalized with severe and nonsevere influenza. We found that influenza antiviral treatment initiated ≤2 days from illness onset was associated with a reduction in LOS of approximately 5 days among women with severe influenza. The magnitude of the effect of antiviral treatment was less pronounced among women with nonsevere influenza, with a significant reduction in LOS of <1 day. The impact of early initiation of influenza antiviral treatment on LOS may reflect the effect of antiviral medications on attenuating other outcomes that influence LOS. The timing of antiviral initiation has been shown to have an important effect on clinical outcomes among critically ill patients with influenza [23, 24]. Antiviral therapy may have a more substantial impact on severe influenza, owing to more active and prolonged viral replication [25–27]. Our data demonstrate findings similar to those of Louie et al, who noted that the relative risk of ICU admission among pregnant women treated >2 days after symptom onset was 4 times that among women treated earlier during the 2009 pandemic [7].

The most common complications associated with hospitalization in our patient-population were pneumonia, asthma exacerbation, dehydration, and sepsis. These complications were less common among pregnant women, compared to nonpregnant women, aged 15–44 years in FluSurv-NET (Table 4). In addition, ICU admission, need for mechanical ventilation, and death accounted for a smaller proportion of hospitalizations in this study, compared with reports from the 2009 pandemic. During the 2009 pandemic, the percentages of hospitalized pregnant women who required ICU admission (12%–19%), needed mechanical ventilation (6%–14%), and died (1%–6%) [2, 7, 18] were almost 2-fold higher than those seen in our

Table 4. General Characteristics of Pregnant and Nonpregnant Women Hospitalized With Laboratory-Confirmed Influenza During the 2010–2014 Influenza Seasons

Characteristic	Pregnant (n = 865)	Nonpregnant (n = 2304)	*P* Value[a]
Age group, y			**<.01**
15–24	315 (36)	503 (22)	
25–34	451 (52)	746 (32)	
35–44	99 (11)	1055 (46)	
Race/ethnicity			**<.01**
Non-Hispanic white	314 (42)	1021 (51)	
Non-Hispanic black	240 (32)	673 (34)	
Hispanic	188 (25)	311 (16)	
Underlying medical condition			
Any	278 (32)	1668 (74)	**<.01**
Asthma	182 (21)	881 (38)	**<.01**
Metabolic disease	64 (7)	513 (22)	**<.01**
Cardiovascular disease (excluding hypertension)	31 (4)	225 (10)	**<.01**
Immunocompromised condition	28 (3)	419 (18)	**<.01**
Blood disorders/hemoglobinopathy	20 (2)	117 (5)	**<.01**
Neurologic/neuromuscular disease	18 (2)	315 (14)	**<.01**
Renal disease	10 (1)	157 (7)	**<.01**
Chronic pulmonary disease (excluding asthma)	7 (1)	114 (5)	**<.01**
Liver disease	4 (0)	39 (2)	**<.01**
Other characteristics			
Influenza vaccination	221 (26)	580 (25)	.83
Antiviral treatment	731 (85)	1856 (81)	**.01**
Time from symptom onset to hospitalization, d	1 (0–2)	2 (1–3)	**<.01**
Time from hospitalization to antiviral treatment, d	0 (0–1)	0 (0–1)	**<.01**
Time from symptom onset to antiviral treatment			
Overall, d	2 (1–3)	2 (1–4)	**<.01**
Early[b]	584 (80)	1326 (71)	**<.01**
Late[c]	147 (20)	530 (29)	
Complications			
Pneumonia	112 (13)	788 (34)	**<.01**
Dehydration	79 (9)	280 (12)	**.02**
Asthma exacerbation	50 (6)	495 (21)	**<.01**
Sepsis/shock	26 (3)	319 (14)	**<.01**
Respiratory failure	25 (3)	315 (14)	**<.01**
ARDS	9 (1)	93 (4)	**<.01**
Acute renal failure	7 (1)	153 (7)	**<.01**
Diabetic ketoacidosis	4 (1)	76 (3)	**<.01**
Pulmonary embolism	4 (<1)	14 (<1)	.63
COPD exacerbation	2 (<1)	36 (2)	**<.01**
Death	4 (<1)	40 (2)	**<.01**

Data are no. (%) of women or median value (interquartile range) and were obtained from the Influenza Hospitalization Surveillance Network.

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; d, days; y, years.

[a] Calculated using χ^2 analysis or the Fisher exact test, for categorical variables, and the Kruskal–Wallis test, for continuous variables.

[b] Defined as ≤2 days from illness onset.

[c] Defined as >2 days from illness onset.

study population. Our findings may reflect a lower threshold for pregnant women to be hospitalized, owing to increased physician awareness of influenza-associated complications in pregnant women, as well as the impact of early initiation of antiviral treatment.

Few women (26%) in our study had received influenza vaccination. Studies have reported low vaccination coverage (15%) among pregnant women prior to the 2009 pandemic [28]. Vaccination coverage has increased since, but it is still suboptimal (50%) [14]. It should be noted that in our study, pregnant women with severe influenza were almost half as likely to be vaccinated as pregnant women with nonsevere influenza, which could suggest that unvaccinated pregnant women may have an increased risk for severe outcomes. Although we did not explore this association in our analysis, influenza vaccination has been shown to be effective among pregnant women, reducing the risk of laboratory-confirmed influenza by approximately 50% [29]. The protection afforded by vaccination may also extend to infants, principally in their first 6 months of life, when they are not eligible for vaccination [30–33]. Annual influenza vaccination should be offered to pregnant women at any gestational age, to prevent complications in mother and infant [13, 34].

Influenza virus infection of pregnant women influenced infant morbidity during the 2009 pandemic [2, 7, 18]. Similarly during the subsequent nonpandemic period, we found that 22% of deliveries among women who gave birth during their influenza-associated hospitalization were before term, which is higher than the percentage of preterm births (11%–12%) reported nationally in the United States for all births during 2011–2013 [35]. During influenza pandemics, studies have reported preterm birth frequencies of 8%–30% among women who delivered during their influenza-associated hospitalization [2, 18, 36]. The proportion of births occurring before term and the proportion of pregnancies resulting in fetal loss noted in our study were even higher among those with severe influenza, consistent with another study from the 2009 pandemic, which described higher frequencies of pregnancies resulting in preterm delivery and fetal death among women admitted to the ICU [18]. The frequency of pregnancies resulting in preterm births and fetal loss seen in pregnant women underscores the adverse consequences of influenza among pregnant women even during nonpandemic periods.

Our study is subject to several limitations. First, the decision to hospitalize pregnant women is complex, and there may be unaccounted factors that influenced this decision, since substantial differences existed between pregnant and nonpregnant women aged 15–44 years with influenza (Table 4). Hospitalized pregnant women in FluSurv-NET were tested at the discretion of treating clinicians. Thus, those with milder or atypical influenza symptoms could have been missed. Alternatively, physicians may be more inclined to test pregnant women than nonpregnant women for influenza and to hospitalize pregnant women with mild influenza. Therefore, we likely captured a broad spectrum of influenza presentations in this population. Second, we did not collect information on type of delivery; thus, we were unable to adjust for it. Because cesarean delivery

could be associated with a prolonged hospital stay, we avoided this potential bias by restricting our analysis to women who did not deliver during hospitalization. Finally, pneumonia diagnosis at the time of admission could confound the association between the timing of treatment and LOS, because those with pneumonia could require lengthy hospitalization. However, we believe that any potential confounding effect was mitigated by building separate models for women with severe and those with nonsevere influenza and by the fact that only a small percentage (13%) of women with radiographic information at admission had a diagnosis of pneumonia (Table 2).

In conclusion, pregnant women are at risk of influenza complications during seasonal influenza. Influenza virus infection during pregnancy continues to be associated with maternal and infant morbidity, including ICU admission, preterm birth, fetal loss, and maternal death. All pregnant women should receive annual influenza vaccination to prevent influenza and associated complications for themselves and their infants. Early initiation of antiviral treatment may reduce hospital LOS, particularly among women who have a more severe influenza presentation. When influenza is suspected among pregnant women, physicians should initiate antiviral treatment early, without waiting for laboratory test results.

Notes

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