Influenza-Associated Cystic Fibrosis Pulmonary Exacerbations

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Background: Although cystic fibrosis (CF) is the most common inherited respiratory disease, the burden of influenza among individuals with CF is not well characterized.
Methods: We used the CF Foundation Patient Registry to determine the relationship between pulmonary exacerbation incidence rate and influenza virus season from July 2003 through June 2007. The outcome of interest, pulmonary exacerbation, was defined as treatment of a respiratory illness with IV antibiotics. Each influenza season was defined as all months during which ≥ 15% of laboratory tests for influenza virus were positive in the US influenza virologic surveillance system. We calculated incidence rates of pulmonary exacerbation during the influenza and summertime seasons as well as relative rates with 95% CIs. A multivariate regression model adjusted for demographic and clinical predictors.
Results: In 2003, the patient cohort size was 21,506 patients, and 7,727 patients experienced at least one pulmonary exacerbation. The overall pulmonary exacerbation incidence rate in the influenza season was 595.0 per 10,000 person-months compared with a summertime baseline of 549.6 per 10,000 person-months. The incidence rate ratio was 1.08 (95% CI: 1.06, 1.10). Multivariate analysis did not change our estimate of risk (adjusted odds ratio: 1.07; 95% CI: 1.05, 1.10). An estimated annual excess of 147.6 per 10,000 person-months or an excess 2.1% of total exacerbations occur during the influenza season.
Conclusion: Our data demonstrate a substantial contribution of the influenza season to CF morbidity. Further studies to determine any causal link between influenza infection and CF pulmonary exacerbations are necessary.   *CHEST 2010; 137(4):852–860*

Abbreviations: aOR = adjusted odds ratio; CF = cystic fibrosis; CF Registry = Cystic Fibrosis Foundation Patient Registry; RSV = respiratory syncytial virus

An estimated 30,000 people in the United States have cystic fibrosis (CF).[1] CF is an autosomal recessive disease that affects multiple organ systems; however, respiratory complications account for nearly 85% of CF mortality.[1] Exacerbations of CF pulmonary disease are common and are characterized by cough, increased sputum production, dyspnea, decreased energy level and appetite, weight loss, and decreases in spirometric parameters.[2] Over the last 2 decades, the quality of life and median survival among persons with CF have improved substantially.[1] Nevertheless, increasing age in CF is associated with worsening nutritional status, declining lung function,

and increased pulmonary exacerbations.[1] Given that the rate of pulmonary exacerbations is associated with increased mortality,[3-6] it is important to identify pulmonary exacerbations that may be preventable.

CF pulmonary exacerbations represent decreased host defenses within the lungs leading to alterations in airway microbiology, increased sputum production, and ventilatory obstruction.[2] Pulmonary exacerbations are associated with the acquisition of new organisms and increased concentrations of airway flora.[7-12] The presence of some organisms in the airways, including *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and methicillin-resistant *Staphylococcus aureus* are associated with clinical deterioration.[8-10,13-15] Furthermore, nearly two-thirds of all initial infections with *P aeruginosa* have been found to occur during winter months, suggesting that winter respiratory virus season may affect pulmonary host defenses.[16] Although evidence of influenza and other respiratory virus infections has also been observed during pulmonary exacerbations,[17-20] studies to date have not addressed the role of respiratory viruses in the etiology of the exacerbations.

We undertook this study to determine whether CF exacerbation rates were temporally associated with the influenza season and to determine the proportion of CF exacerbations that were attributable to the influenza season. We hypothesized that CF exacerbations would be seasonal and that a portion of these clinical events would be attributable to the influenza season.

MATERIALS AND METHODS

Study Population

This was a cohort study of individuals followed in the CF Foundation Patient Registry (CF Registry) from January 1, 2003, through December 31, 2007. The CF Registry tracks the health of people with CF in the United States. Approximately 80% of an estimated 30,000 people with CF seen in >115 CF Foundation-accredited care centers are included. Generally, patients enter the CF Registry at the time of diagnosis, which usually occurs during infancy. Little is known about persons with CF who are not included in the CF Registry. A full description of the registry is available.[1] Demographic and clinical data are recorded at each clinic visit, during outpatient antibiotic therapy, during hospitalizations, and at year-end reviews. The reasons for individual hospitalizations and outpatient antibiotic therapy are recorded for each event. Baseline descriptive statistics were calculated for CF Registry patients from the 2003 year-end review.

Outcome of Interest

All persons in the CF Registry were included for analysis. The outcome of interest was a documented CF pulmonary exacerbation requiring hospitalization or home IV antibiotic therapy. Duplicate recorded pulmonary exacerbations in a single calendar month were excluded. Patients with a year-end review were considered present within the cohort for the entire calendar year for the purpose of patient-time follow-up. The institutional review board at the University of Washington approved this study.

Assessment of Exposure

The surveillance year was defined as July 1 through June 30 of the subsequent calendar year. As had been done in prior influenza modeling studies,[21] the influenza season was defined as all months during which ≥ 15% of laboratory tests for influenza virus were positive in the US influenza virologic surveillance system.[22] Three periods in the surveillance year were defined based on laboratory-confirmed influenza activity. The "influenza season" was October through December in 2003-2004, December through March in 2004-2005, January through March in 2005-2006, and January through March in 2006-2007. Because CF pulmonary exacerbation data were available by month, influenza epidemic activity was defined by month; however, epidemic influenza activity occurred in only partial months during these periods. The "peri-influenza season" was defined as the time from October through April in which nationwide laboratory tests for influenza were < 15%. The "summer season" was the remaining months in the surveillance year.

Statistical Analysis

Patients were categorized into two age groups for analyses (< 18 years and ≥ 18 years). Exacerbation incidence rates were calculated by dividing the number of exacerbations per selected period by the total person-time of follow-up during that period. To include an entire influenza season per 12-month period, incidence rate data were assessed by surveillance year. The influenza season-attributable risk was calculated by subtracting the rates during the summer period from rates during the influenza season. Analyses were based on incidence rate-difference models, which have been used to estimate influenza-associated deaths and hospitalizations.[21,23-27]

Multivariate logistic regression with robust standard errors was then used to assess the effect of demographic and clinical predictors on the odds of a pulmonary exacerbation during influenza activity periods. Covariates for the model were determined *a priori* based on a review of the literature for factors associated with pulmonary exacerbations. These covariates included age, gender, insurance status, race, median income of zip code in which patients lived, pancreatic insufficiency, FEV_1, and whether height-weight measures met CF Foundation goals.[1] To account for exacerbations by the same individual per surveillance year, marginal general estimation equations were used to calculate standard errors using the clustered sandwich estimator. *P* values < .05 were considered statistically significant. Analyses were performed with STATA statistical software (version 10.1; STATACorp; College Station, TX).

RESULTS

Baseline Characteristics

In the 2003 calendar year, the CF Registry had a total of 21,506 patients (Table 1). Of these, 8,625 (40.1%) were adults and 12,881 (59.9%) were children. The majority of adults and children were non-Hispanic, white (92.8% and 86.1%), male (53.1% and 51.3%), and had private/health maintenance organization insurance (55.3% and 50.1%). The median household income by zip code of residence was $44,323.5 for adults and $42,998.0 for children.

Baseline Clinical Description

Adults and children with CF had a median of four outpatient clinic visits and zero hospital admissions

Table 1—Baseline Characteristics of Patients Seen at Cystic Fibrosis Foundation-Accredited US Care Centers, 2003

Characteristic	Adults (≥ 18 y)	Children (< 18 y)
Demographic data		
Person-years	8,625	12,881
Sex, % female	4,044 (46.9)	6,275 (48.7)
Insurance status		
Private/HMO	4,767 (55.3)	6,456 (50.1)
Public	3,402 (39.4)	6,161 (47.8)
No insurance	287 (3.3)	161 (1.3)
Other/unknown	169 (2.0)	103 (0.8)
Median zip code income (IQR)	44,323.5 (35,609-56,393)	42,998 (34,750-56,408)
Race/ethnicity		
Non-Hispanic white	8,000 (92.8)	11,094 (86.1)
Non-Hispanic black	224 (2.6)	575 (4.5)
Hispanic	313 (3.6)	1,042 (8.1)
Other/unknown	88 (1.0)	170 (1.3)
Health care use		
Total outpatient visits, median (IQR)	4 (1-7)	4 (2-6)
Total hospital admissions, median (IQR)	0 (0-1)	0 (0-1)
Clinical data		
FEV_1, L, mean (SD)	2.3 (1.0)	1.9 (0.8)
FEV_1, % predicted, mean (SD)	60.8 (23.9)	86.8 (20.8)
FVC, L, mean (SD)	3.3 (1.1)	2.3 (1.0)
FVC, % predicted, mean (SD)	74.6 (20.7)	93.6 (18.2)
$FEV_1 > 50\%$ predicted	5,153 (63.7)	8,242 (93.7)
Height-weight above US mean	414 (5.0)	5,242 (44.8)
Pancreatic insufficiency	7,460 (86.5)	12,018 (93.3)
Pseudomonas aeruginosa culture positive	5,903 (77.8)	5,455 (44.6)
Burkholderia cepacia culture positive	398 (5.3)	211 (1.7)
Staphylococcus aureus culture positive	3,041 (40.1)	7,106 (58.2)

Baseline data are for the 2003 calendar year. Data are presented as No. (%) unless otherwise specified. CF = cystic fibrosis; HMO = health maintenance organization; IQR = interquartile range.

for any cause in the 2003 calendar year (Table 1). On average, adults had worse lung function than children (FEV_1% predicted: 60.8% vs 86.8%), lower percent height-weight measures above US average (5.0% vs 44.8%), and lower rates of pancreatic insufficiency (86.5% vs 93.3%). Adults also had higher rates of *P aeruginosa* infection (77.8% vs 44.6%) and *B cepacia* infection (5.3% vs 1.7%), but lower rates of *S aureus* infection (40.1% vs 58.2%).

Pulmonary Exacerbations Seasonality

During the 2003-2004 surveillance year, CF Registry patients were followed for 264,234 person-months. A total of 7,727 unique patients experienced a pulmonary exacerbation requiring hospitalization or home IV therapy (Table 2). Pulmonary exacerbations included 6,748 unique patients who were hospitalized for treatment and 2,262 unique patients who received home IV therapy. There were 14,903 recorded pulmonary exacerbations, and the overall rate of pulmonary exacerbations in 2003-2004 was 564.0 per 10,000 person-months. Adults had nearly twice the exacerbation incidence rate of children (788.1 per 10,000 person-months vs 411.9 per 10,000 person-months).

During the study period, there was an annual increase in the incidence rate of pulmonary exacerba-

tions during the winter months (Fig 1). Further, incidence rates for adults and children were temporally associated with increases in influenza activity nationwide.

Pulmonary Exacerbations Attributable to the Influenza Season

The mean duration of influenza season during the study was 3.25 months per year. Over the entire influenza season, crude exacerbation incidence rates were 825.4 per 10,000 person-months among adults and 433.7 per 10,000 person-months among children. Exacerbations during the influenza season contributed to an excess of pulmonary exacerbations of 45.4 per 10,000 person-months (Table 3). Assuming a 3.25-month influenza season annually, we estimate that there are 147.6 pulmonary exacerbations per 10,000 people with CF that are attributable to influenza every year. Applied to the 2003 CF Registry census, this would equal 317 pulmonary exacerbations or 2.1% of the total number of pulmonary exacerbations observed in the registry that year. Estimated annual excess exacerbations attributable to the influenza season for adults and children are 55.9 per 10,000 people and 39.9 per 10,000 people.

Exacerbations	Persons Hospitalized[a]	Persons with Home IV Therapy[b]	Persons Hospitalized or Receiving Home IV Therapy[b]
1	4,052	1,660	4,134
2	1,508	416	1,866
3	607	113	812
4	295	51	446
5	151	16	213
6	79	3	133
7	26	0	75
8	14	3	24
9	7	0	8
10	8	0	12
11	1	0	3
12	0	0	1
Total persons with exacerbations	6,748	2,262	7,727
Mean (SD)	0.5 (1.0)	0.1 (0.5)	0.6 (1.2)
Median (IQR)	0 (0-1)	0 (0-0)	0 (0-1)

The influenza surveillance year was defined as July 1 through June 30 of the subsequent calendar year. See Table 1 for expansion of abbreviations.
[a]During the 2003-2004 surveillance year, persons in the Cystic Fibrosis Foundation Patient Registry were followed for 264,234 person-months.
[b]The analysis was of monthly CF pulmonary exacerbations. Duplicate exacerbations in a single calendar month were excluded. Multiple exacerbations in one calendar month that included hospitalizations and home IV therapy were recorded as a single hospitalization. Because the same individual could be hospitalized and receive home IV therapy for multiple exacerbations in a year, the sum of persons hospitalized and persons receiving home IV therapy does not equal the total number of persons with exacerbations.

Multivariate Model of Exacerbation

Crude incidence rates of pulmonary exacerbations were 7% to 10% greater during the influenza season compared with summertime baselines among both age categories (Table 4). A multivariate logistic regression model was constructed to estimate the probability of influenza season exacerbations when adjusted for patient demographic, socioeconomic, and clinical status. The multivariate risk estimates were comparable to the crude incidence rate ratios. Adjusted odds ratios (aORs) comparing exacerbations in the influenza season to the summer season baseline were 1.07 (95% CI: 1.05, 1.10) in adults and 1.08 (95% CI: 1.05, 1.12) in children.

Sensitivity Analyses

To account for some of the activity by other, cocirculating respiratory viruses in the winter, we conducted a sensitivity analysis comparing incidence rates from the influenza season and peri-influenza season. Relative risk estimates were lower for the entire cohort (1.05), adults (1.06), and children (1.04) when the influenza season was compared with the peri-influenza season. Estimates of excess annual CF pulmonary exacerbations attributable to the influenza season (the difference between influenza and peri-influenza incidence rates) were 26.6 per 10,000 persons among the entire cohort, 44.9 per 10,000 persons among adults, and 16.8 per 10,000 persons among children. Although the primary analysis has demonstrated that exacerbations during the influenza season are elevated when compared with a summer baseline with little to no respiratory virus activity, this sensitivity analysis demonstrates that influenza season exacerbations are also elevated when compared with other periods during the winter season when other respiratory viruses circulate.

Because the distribution of individuals in the cohort with pulmonary exacerbations was so highly skewed, we investigated the effect outliers with multiple exacerbations had on our model. In another sensitivity analysis, we excluded all individuals with more than one pulmonary exacerbation (Fig 2). The overall exacerbation incidence rate during the influenza season was decreased to 205.8 per 10,000 person-months, whereas the summertime baseline was 169.7 per 10,000 person-months (Table 5). The relative risk of exacerbation between the two seasons was 1.21 (95% CI: 1.17, 1.26), which demonstrates a substantial increase in risk compared with the entire cohort. Of note, persons with < 2 pulmonary exacerbations per year represent roughly 84% of the entire CF Registry. When the multivariate logistic regression model was applied to this subset of patients, effect size was decreased (aOR, 1.12; 95% CI: 1.09, 1.16).

In a subsequent analysis, we investigated the effect of the influenza season on individuals with ≥ 4 pulmonary exacerbations. The overall influenza season incidence rate was 4,329.2 per 10,000 person-months, nearly an order of magnitude greater than the full cohort. Summertime baseline rates also increased, resulting in an overall relative risk of 1.06 (95% CI: 1.02, 1.10), similar to the estimate for the entire cohort. Although this subset represents only a small proportion of the overall patient registry, they experience an estimated annual excess of 778.4 exacerbations per 10,000 people that are attributable to the influenza season. The probability of exacerbation among this subset of patients was also similar when applied to a similar logistic regression model as described above (aOR, 1.08; 95% CI: 1.04, 1.13).

Discussion

Our analysis suggests that a substantial proportion of morbidity in CF is associated with the influenza season.
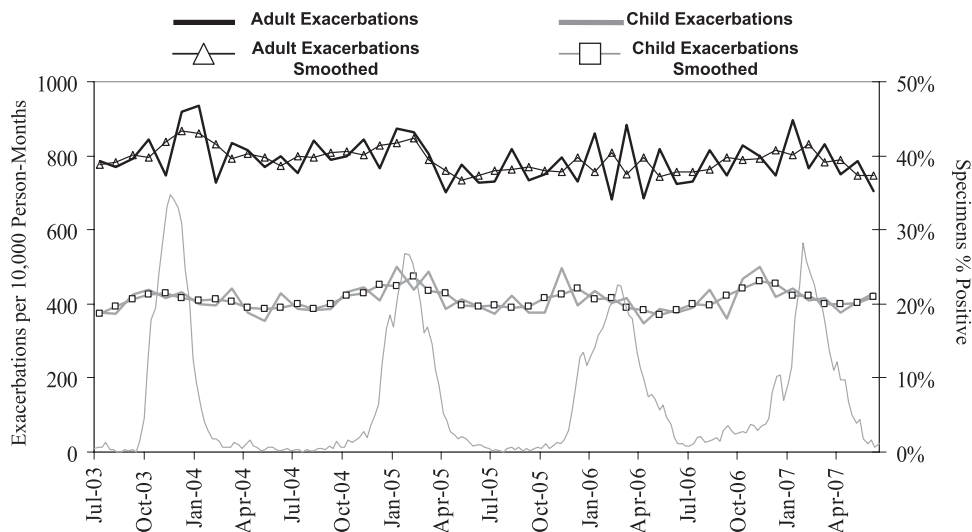
FIGURE 1. Cystic fibrosis (CF) pulmonary exacerbation incidence rates per 10,000 person-months by age group and US influenzalike illness rates, July 2003 through June 2007. Weekly influenzalike illness rates are from US influenza surveillance data.[21,22] Influenzalike illness rates are plotted on the Wednesday of each week. CF exacerbation incidence rates are plotted on the 15th day of each calendar month.

Influenza is a substantial public health threat, and it is estimated to be associated with >36,000 deaths and 220,000 hospitalizations in the United States annually.[28,29] With the recent emergence of novel 2009 influenza A(H1N1) in the United States and Mexico,[30] high rates of community transmission have been seen. However, rates of hospitalization are well below pandemic planning estimates.[31,32] Nevertheless, early data indicate that individuals with comorbidities, including chronic lung disease, are at increased risk of influenza-associated hospitalization and death.[31,33]

Persons with chronic lung disease are also at increased risk of seasonal influenza-associated compli-cations.[34] A study of health care use by patients with chronic lung disease found an influenza-attributable excess of antibiotic courses (IV and po) were near 1,000 prescriptions per 10,000 patients.[25] The study also determined the highest incidence of influenza-associated cardiopulmonary hospitalizations was approximately 6,500 per 10,000 person-months for persons >65 years of age. Incidence rates of younger patients with chronic lung disease ranged from approximately 500 per 10,000 person-months for children 5 to 14 years of age and 3,500 per 10,000 person-months for adults 50 to 64 years of age. In our study, pulmonary exacerbation rates were found to be intermediate to these rates of outpatient and inpatient

Table 3—Seasonal Incidence Rates of CF Pulmonary Exacerbations and Estimated Annual Excess Events, July 2003 Through June 2007

Age Group	Season[a]	Incidence Rate per 10,000 Person-Mo	Event Frequency	Person-Mo	Influenza-Attributable Risk per 10,000 Person-Mo[b] (95% CI)	Estimated Excess Annual Events per 10,000 People[c]
Total	Influenza	595.0	18,049.0	303,368.0	45.4 (34.3, 56.3)	147.6
	Peri-influenza	568.4	19,861.0	349,449.0	…	…
	Summer	549.6	25,473.0	463,453.0	…	…
Adults (18+ y)	Influenza	825.4	10,311.0	124,928.0	55.9 (35.6, 76.0)	181.7
	Peri-influenza	780.5	11,362.0	145,579.0	…	…
	Summer	769.5	14,792.0	192,220.0	…	…
Children (0-17 y)	Influenza	433.7	7,738.0	178,440.0	39.9 (27.6, 52.1)	129.7
	Peri-influenza	416.9	8,499.0	203,870.0	…	…
	Summer	393.8	10,681.0	271,233.0	…	…

See Table 1 for an expansion of abbreviations.

[a]Three influenza activity periods were defined by review of US influenza surveillance data.[21,22] The influenza season was all months during which ≥15% of laboratory tests for influenza virus were positive in the US influenza virologic surveillance system. The peri-influenza season was all months during October through April during which influenzalike illness activity was below epidemic thresholds. The summer season was all months from April through September.

[b]Rates during the summer season were used as the baseline rates for calculation of the influenza season-attributable risk.

[c]Estimates are based on average influenza season of 3.25 mo.

Table 4—*Multivariate Model of the Association Between CF Pulmonary Exacerbations and the Influenza Season, July 2003 Through June 2007*

|	Statistic	Influenza Season	Peri-influenza Season	Summer Season
All ages	Incidence rate per 10,000 person-months	595.0	568.4	549.6
	Incidence rate ratio (95% CI)	1.08 (1.06, 1.10)	1.03 (1.01, 1.05)	Referent
	Adjusted OR (95% CI)	1.07 (1.05, 1.10)	1.03 (1.00, 1.05)	Referent
Adults (18+ y)	Incidence rate per 10,000 person-months	825.4	780.5	769.5
	Incidence rate ratio (95% CI)	1.07 (1.05, 1.10)	1.01 (0.99, 1.04)	Referent
	Adjusted OR (95% CI)	1.07 (1.05, 1.10)	1.02 (0.90, 1.04)	Referent
Children (0-17 y)	Incidence rate per 10,000 person-months	433.7	416.9	393.8
	Incidence rate ratio (95% CI)	1.10 (1.07, 1.13)	1.06 (1.03, 1.09)	Referent
	Adjusted OR (95% CI)	1.08 (1.05, 1.12)	1.04 (1.00, 1.07)	Referent

Adjusted for age, gender, insurance status, race, median income of zip code, pancreatic insufficiency, FEV_1 percent, whether height-weight measures met CF Foundation goals, and repeated outcomes for some individuals. OR = odds ratio. See Table 1 for expansion of other abbreviations.

therapy during the influenza season. The outcome of interest in our study was pulmonary exacerbations treated with either home IV antibiotic therapy or inpatient hospitalization. The decision regarding the setting to treat the patient is based on disease severity and physician practice patterns not solely related to disease severity. Milder exacerbations are often treated with inhaled or oral antibiotics; these clinical events were not captured in our definition of pulmonary exacerbation, likely resulting in an underestimate of influenza-associated risk.

Although CF practitioners have long been aware of the seasonality of pulmonary exacerbations, this study is the first of which we are aware that has been able to demonstrate significant increases in event rates during the influenza season. Arguably the healthiest 84% of the patient registry have a 12% to 21% increased odds of an influenza season exacerbation, whereas the sick-

est minority with ≥4 exacerbations annually have an influenza season-attributable risk that is >10 times the rest of the patient cohort. Although children generally have the highest influenza attack rates, individuals with chronic comorbid conditions and the elderly have the highest rates of death and hospitalizations. Given the progressive decline in lung function and overall health among patients with CF, it is possible that children experience higher influenza attack rates but experience more self-limited disease and less progression to pulmonary exacerbation.

CF pulmonary exacerbations are believed to be a result of decreased host defenses and colonizing bacterial overgrowth; however, moderate or severe, primary influenza infection may be indistinguishable from a pulmonary exacerbation in CF. Furthermore, influenza viral infection can alter host defense equilibrium, increase airway resistance and mucus production,
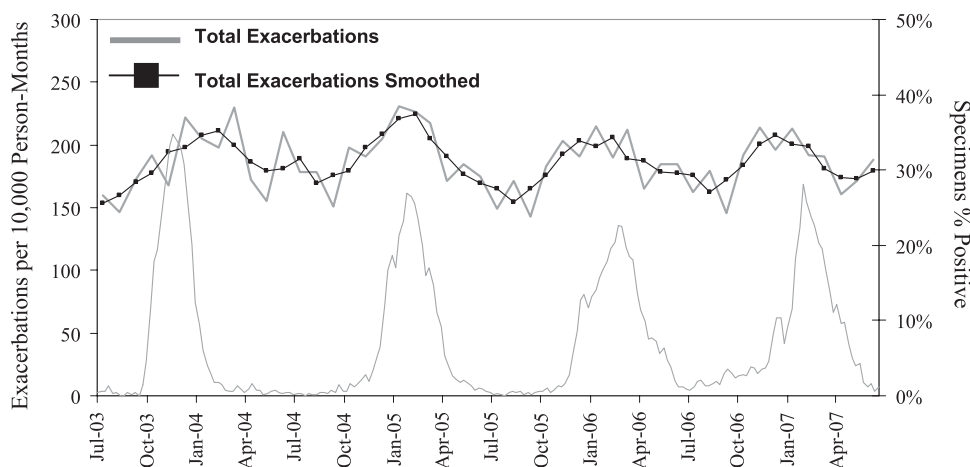
FIGURE 2. CF pulmonary exacerbation incidence rates per 10,000 person-months and US influenzalike illness rates among patients with <2 pulmonary exacerbations, July 2003 through June 2007. Y-axis changed from Figure 1 to demonstrate seasonal variation. Smoothed function is a moving average of five data points: the two previous, the current, and the two subsequent incidence rates. See Figure 1 legend for expansion of abbreviation.

Table 5—*Seasonal Incidence Rates of CF Pulmonary Exacerbations Among Persons With Fewer Than Two Annual Exacerbations and More Than Four Annual Exacerbations, July 2003 Through June 2007*

	Statistic	Influenza Season	Peri-influenza Season	Summer Season
Persons with fewer than two exacerbations				
All ages	Incidence rate per 10,000 person-months	205.8	191.1	169.7
	Incidence rate ratio (95% CI)	1.21 (1.17, 1.26)	1.13 (1.09, 1.17)	Referent
Adults (18+ y)	Incidence rate per 10,000 person-months	266.1	240.6	217.4
	Incidence rate ratio (95% CI)	1.22 (1.16, 1.29)	1.11 (1.05, 1.17)	Referent
Children (0-17 y)	Incidence rate per 10,000 person-months	169.3	160.4	140.4
	Incidence rate ratio (95% CI)	1.21 (1.15, 1.27)	1.14 (1.09, 1.20)	Referent
Persons with more than four exacerbations				
All ages	Incidence rate per 10,000 person-months	4,329.2	4,156.3	4,089.7
	Incidence rate ratio (95% CI)	1.06 (1.02, 1.10)	1.02 (0.98, 1.05)	Referent
Adults (18+ y)	Incidence rate per 10,000 person-months	4,337.4	4,179.0	4,159.7
	Incidence rate ratio (95% CI)	1.04 (1.00, 1.09)	1.00 (0.96, 1.05)	Referent
Children (0-17 y)	Incidence rate per 10,000 person-months	4,314.3	4,115.2	3,965.2
	Incidence rate ratio (95% CI)	1.09 (1.03, 1.15)	1.04 (0.99, 1.09)	Referent

See Table 1 for expansion of abbreviations.

and promote colonizing bacterial overgrowth and secondary bacterial infections.[2,7-12] The relationship between influenza infection and subsequent bacterial pneumonia is long established.[35] Other respiratory viruses can exacerbate chronic lung disease, and some, most notably respiratory syncytial virus (RSV), may also circulate during the winter months. Of note, RSV activity occurred 1 to 2 months after the 2003-2004 influenza peak, but coincided with subsequent influenza seasons. Nevertheless, both the primary analysis and sensitivity analysis demonstrate exacerbation increases during the influenza season when compared with peri-influenza baselines, periods during which other wintertime, respiratory viruses circulate. Further studies are underway to evaluate the risk of CF exacerbations in regions and times when influenza and RSV activity are not coincident, which may better distinguish their relative contribution to CF morbidity. Furthermore, although respiratory viruses have been isolated from individuals during pulmonary exacerbations,[17-20] further studies are needed to determine the causal link between laboratory-confirmed influenza infection and CF morbidity.

Both trivalent inactivated influenza vaccine and intranasal live cold-adapted influenza vaccine are safe and immunogenic in persons with CF;[36] however, there is some evidence that antibody response may be lower in children at high risk for influenza infection compared with healthy children.[37-39] Nevertheless, influenza vaccine effectiveness has been demonstrated among children and adults with other chronic respiratory diseases.[40-43] Additionally, a small, retrospective study among individuals with CF found significantly fewer laboratory-confirmed influenza virus infections in those who had received the influenza vaccine.[44]

Our study is subject to limitations. Laboratory test results for influenza were not available; therefore we could demonstrate that pulmonary exacerbations were associated with the influenza season but not influenza infection. We were unable to include influenza vaccination into our model for two reasons: first, the CF Registry began recording influenza vaccination three influenza seasons into the study period in 2006; and, second, date of receipt is not recorded in the registry so timing with regard to the influenza season is impossible. Nevertheless, it is likely that this is a highly vaccinated cohort. In 2006, among those for whom vaccine receipt/nonreceipt was documented, 91.0% of age-eligible children and 87.9% of adults received influenza vaccine. However, 26.9% of age-eligible children and 38.0% of adults did not have vaccine receipt/nonreceipt documented. One might expect higher morbidity in a cohort of patients with CF who had lower vaccination rates. Furthermore, our time-series analysis used only the month of pulmonary exacerbation and excluded duplicate exacerbations in the calendar month. This could lead to miscoded events as a hospitalization at the end of a month followed by discharge to home to complete a course of IV antibiotics at the beginning of the next month could be recorded as two separate events. This double counting of events, if they occur randomly throughout the course of the year, would bias our results toward a null given that the influenza season averaged less than one-third of the year.

Original Research

This study demonstrated for the first time to our knowledge that CF pulmonary exacerbations increase significantly during the winter and that they are highly associated with the influenza season. These findings suggest that a substantial proportion of CF morbidity may be preventable by influenza vaccination or chemoprophylaxis. Although all patients with CF are recommended to receive influenza vaccination, CF Registry vaccination rates appear to be below these goals.[1] Adults and persons with multiple annual pulmonary exacerbations have elevated rates of influenza season exacerbations, and they should be targeted for vaccination. Nevertheless, the risk of exacerbation during the influenza season as compared with summertime baselines was consistently elevated among all subgroups analyzed in the study and supports universal vaccination. Furthermore, vaccination against influenza of caregivers and close contacts of patients with CF is highly recommended, as it may decrease influenza transmission. Although further studies to determine any causal link between influenza and CF pulmonary exacerbations are necessary, influenza vaccination is the best way to avoid infection and its complications.

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Original Research