Clinical Infectious Diseases

MAJOR ARTICLE

Changing Rates of Chronic *Pseudomonas aeruginosa* Infections in Cystic Fibrosis: A Population-Based Cohort Study

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Background. Chronic *Pseudomonas aeruginosa* lung infection is associated with significant morbidity and mortality in cystic fibrosis (CF). It is not known whether recent advances in care have affected the rates of chronic infection. We aimed to determine if the rates of developing new chronic *P. aeruginosa* infection among adolescents and adults with CF significantly changed over time.

Methods. The cohort consisted of individuals with CF followed in the Cystic Fibrosis Foundation Patient Registry aged ≥13 years without chronic *P. aeruginosa* at baseline. Multivariable regression models accounting for within-patient correlation were used to assess the change in rate of developing chronic *P. aeruginosa* infection between 2003 and 2012.

Results. A total of 15 504 individuals were followed for a median of 5 (interquartile range, 2–9) years. The annual rates of developing new chronic *P. aeruginosa* decreased from 14.3% in 2003 to 6.4% in 2012. After adjusting for potential confounders, relative risk (RR) of developing chronic *P. aeruginosa* infection decreased significantly over time compared to 2003 (*P* value test of trend < .001). Compared with 2003, the RR of developing chronic *P. aeruginosa* infection in 2012 was 0.33 (95% confidence interval, 0.30–0.37). No significant increases in risk of chronic infections with other major CF bacterial pathogens relative to 2003 were identified.

Conclusions. Among individuals with CF, a significant decrease in the risk and rates of developing chronic *P. aeruginosa* infection between 2003 and 2012 was observed. Whether this decline results in changes in clinical outcomes warrants further exploration.

Keywords. cystic fibrosis; epidemiology; *Pseudomonas aeruginosa*; population-based study; airway infections.

Pseudomonas aeruginosa is considered the archetypal pathogen and results in chronic airway infections in up to 60%–70% of adults with cystic fibrosis (CF) [1–7]. Upon infection with *P. aeruginosa,* the clinical course typically consists of conversion to a mucoid phenotype (occurring at a median duration of 1–3 years) [8, 9], leading to greater frequency of exacerbations, increased treatment burden, and worsening clinical status [10–15]. Chronic *P. aeruginosa* infection in CF is associated with greater morbidity and mortality irrespective of lung function [13, 16]. *Pseudomonas aeruginosa* can be eradicated in early infection but, once established, can rarely be eliminated from the airway [17]. This feature of infection is likely due to the inherent abnormalities of airway clearance and the organism's ability to form bacterial communities largely resistant to antibiotics [18, 19].

Advances in the diagnosis and management of CF are leading to significant improvements in survival, with increasing proportions of individuals living well into adulthood, including those with severe lung disease [5, 20]. Notably, 2015 US registry reports demonstrate that more than 50% of individuals with CF are aged >18 years [5]. In parallel, mortality decreased by 1.8% per year between 2000 and 2010. If this observed rate continues, individuals born with CF in 2010 are predicted to have life spans greater than 50 years [20]. This benchmark has already been surpassed in other countries such as Canada [1]. With these marked demographic shifts in CF, we have yet to understand the effects that these advances in care have had in the older CF population on the rate of developing chronic *P. aeruginosa* infections. A single-center study showed that the prevalence of chronic and mucoid *P. aeruginosa* decreased significantly between 2002 and 2012, but this effect was no longer significant after adjusting for confounders [21]. Thus, we aimed to determine if there has been a significant change in the rates of developing chronic *P. aeruginosa* infection among adolescents and adults in the United States over this same time period. We hypothesized that the rates of developing chronic *P. aeruginosa* infection have decreased in the CF populations over time.

Received 22 September 2017; editorial decision 5 March 2018; accepted 8 March 2018; published online March 9, 2018.

Presented in part: North American Cystic Fibrosis Conference. Phoenix, AZ, October 2015. *Pediatr Pulmonol*; 50(S41):385.

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Clinical Infectious Diseases® 2018;67(7):1089–95

DOI: 10.1093/cid/ciy215

METHODS

Study Population

The Cystic Fibrosis Foundation Patient Registry (CFFPR), first developed in the 1960s, contains prospectively collected demographic and clinical data on consenting individuals with CF who are receiving care at CF Foundation–accredited centers (>120) in the United States [5, 22]. In 2012, more than 27 000 individuals provided data to the registry, representing approximately 81%–84% of the US CF population [5, 22]. We accessed data from the CFFPR for the period from January 2001 to December 2012 for purposes of this study. All individuals aged ≥13 years were considered for inclusion as this reflects the median acquisition age of mucoid *P. aeruginosa* and has been highly associated with chronic *P. aeruginosa* infection [11]. The population was dynamic in that individuals could enter the cohort throughout the study period if they reached age-inclusion criteria and/or had a new diagnosis of CF at ≥13 years. Alternatively, individuals could leave the population due to death, leaving the registry, or meeting exclusion criteria. Individuals were excluded from further observation after meeting the definition of chronic *P. aeruginosa* infection or following bilateral lung transplantation. Additionally, those with no clinical encounters in the study period were excluded. The study was approved by the University of Washington Institutional Review Board (45798).

Study Design

A retrospective, cohort study was conducted between 2003 through 2012 to examine the annual rate of developing chronic *P. aeruginosa* infection. The primary predictor of interest was time designated and categorized by calendar year. CFFPR encounter data were summarized quarterly for each calendar year. In quarters with more than 1 clinical encounter, the quarter was considered positive for *P. aeruginosa* if any single encounter had a positive respiratory culture (sputum, oropharyngeal, or bronchoalveolar lavage) for the organism. Microbiologic testing was performed locally for patients in accordance with Cystic Fibrosis Foundation consensus guidelines [23].

The primary outcome of interest was the development of chronic *P. aeruginosa* infection. Each individual entering the cohort was assigned an initial status of *P. aeruginosa* infection on the basis of data using a 2-year roll-in screening period (ie, for 2003, data from 2001 to 2003 were used). Initial *P. aeruginosa* infection status was classified as never (no positive cultures), intermittent (at least 1 positive culture but not meeting chronic definition), or chronic infection (>50% positive cultures requiring a minimum of 3 cultures in 8 quarters) using a modified definition of chronic infection originally proposed by Lee et al [24]. As culture frequency is variable and low in the CFFPR, to decrease the risk of misclassification, a modified definition that was previously developed and since tested was used [21, 25]. Individuals who met the definition for chronic *P. aeruginosa* infection in the screening period were excluded from the analysis cohort. Those who met the never or intermittent status initially were followed with *P. aeruginosa* status assessment at each subsequent quarter during the observational period to identify the development of chronic infection using the same definitions.

As a secondary outcome, we assessed the development of mucoid *P. aeruginosa* infection over the study period as mucoidy has been previously demonstrated to be correlated with chronicity [26]. Mucoidy was defined as having at least 1 positive respiratory culture with a mucoid *P. aeruginosa* phenotype in a calendar year. We also assessed for the development of new chronic infection with other CF bacterial pathogens using the primary definition as for *P. aeruginosa*. The organisms examined included *Burkholderia cepacia* complex, *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia*, and methicillin-resistant *Staphylococcus aureus* (MRSA).

Statistical Analyses

Baseline demographics and clinical status were defined as the time of entry into the observed cohort. Descriptive statistics were used to summarize the cohort data. Continuous variables were reported as medians with interquartile ranges (IQR). Discrete variables were reported as proportions. The development of chronic *P. aeruginosa* infection was summarized by year; once an individual developed chronic infection (first event), he/she was excluded from further follow-up in a given analysis. Time-independent variables included age at diagnosis (years), age at entry, sex (male/female), pancreatic insufficiency (PI; yes/no), cystic fibrosis transmembrane conductance regulator (CFTR) functional class (I-III/IV-V/unclassified/unknown) [27], baseline lung function (forced expiratory volume in 1 second predicted [FEV_1%]), and CF-related diabetes (CFRD). CFRD was defined as being present if an individual with CF was prescribed insulin; we used this conservative definition given the complexities in CFRD diagnosis. PI was defined as present by receipt of pancreatic enzyme replacement therapy. Multivariable generalized estimating equations (GEEs) using a Poisson distribution with log link, an independent working correlation structure, and robust variance estimation were constructed for each of the primary and secondary outcomes to account for repeated measures within a longitudinal dataset [18]. The GEE model was assumed to afford a valid inference for the outcomes as the population sample size to be used was large and annual event rates were expected to be low (approximately 10% or less) [28]. The multivariable models incorporated a priori confounders as above to determine the relative risk (RR) of developing chronic infection by calendar year relative to 2003. Additionally, for the primary outcome, we constructed 2 additional multivariable GEE models stratified by age (13–18/19–35/>35 years) and by CFTR functional class given their association with differential clinical status [29] (I-III/IV-V/unclassified/unknown), respectively, to determine if there were distinct changes in chronic *P. aeruginosa* infection risk over time.

As a sensitivity analysis to the primary outcome, a separate multivariable GEE model was developed to determine the RR of developing chronic *P. aeruginosa* infection in a cohort restricted to individuals who aged into the cohort at 13 years (less likely to have chronic infection at entry). All hypotheses and outcomes were predetermined, and a 2-tailed *P* value < .05 was considered statistically significant.

RESULTS

Patient Population

A total of 15 504 individuals aged ≥13 years were analyzed for development of chronic *P. aeruginosa* infection over the study period (Figure 1). The median period of observation was 5 (IQR, 2–9) years. Baseline demographics for this cohort are summarized in Table 1. Compared to the 9192 (37%) individuals excluded from the observation group due to meeting the definition of chronic *P. aeruginosa* during the screening period, individuals free of chronic infection at the start of the observation period were younger, had better lung function, and a greater proportion had residual CFTR function (classes IV–VI). Changes within the cohort between 2003 and 2012 are summarized in Supplementary Table 1. Comparing the 2003 to 2012 analytic cohorts, mean lung function (FEV_1%) improved from 73.2% to 81.5% and CFRD prevalence increased from 10.5% to 19.6%, respectively.

Primary Outcome—Development of Chronic *P. aeruginosa* Infection

The annual rate of developing chronic *P. aeruginosa* infection among the cohort was 14.3% (N = 1347) in 2003 and decreased to 6.4% (N = 522) in 2012. There was a significant decrease in the development of chronic *P. aeruginosa* infection throughout the observation period (*P* value test of trend < .001). Compared to 2003, the relative risk of developing chronic *P. aeruginosa* infection in 2012 was 0.45 (95% confidence interval [CI], 0.41–0.49), with the intervening years also having a significant decrease in incidence (Table 2). After adjusting for age, age at diagnosis, sex, CFTR functional class, baseline FEV_1%, CFRD, and PI, the decrease in RR of developing chronic *P. aeruginosa* infection remained significant (*P* value test of trend < .001; Table 2). The decrease in development of new chronic *P. aeruginosa* infection was comparable among age groups (13–18, 19–35, >35) and CFTR functional groups (I-III, IV-V, other) (Supplementary Figures 1 and 2).

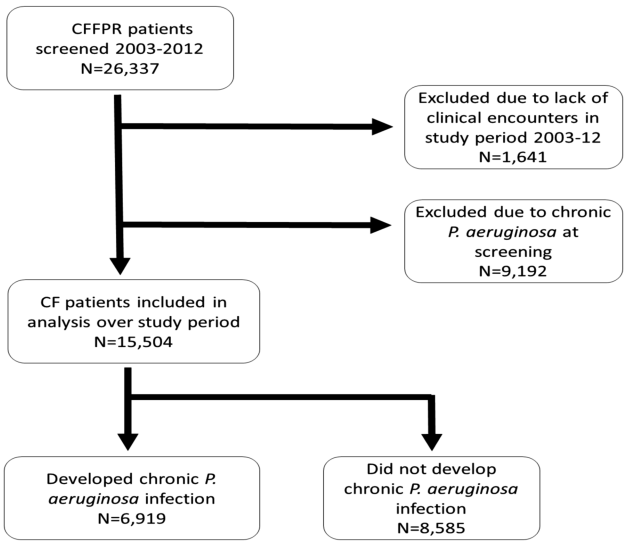

Figure 1. CONSORT flow diagram. Abbreviations: CF, cystic fibrosis; CFFPR, Cystic Fibrosis Foundation Patient Registry.

Secondary Outcomes

Using the mucoidy definition for chronic *P. aeruginosa*, the annual rate was 10.3% in 2003 (N = 786) and decreased to 6.5% (N = 505), in keeping with the primary outcome. This was a significant trend even after adjusting for confounders as with the primary outcome (*P* value test of trend < .001). When other CF bacterial pathogens of *B. cepacia* complex, *A. xylosoxidans*, *S. maltophilia*, and MRSA were examined for RR of new chronic infection compared to 2003, an increase in parallel to the decrease observed with *P. aeruginosa* was not observed. Conversely, all organisms with the exception of MRSA had an overall decreased RR of developing new chronic infections over time (Figure 2).

Sensitivity Analysis

As a sensitivity analysis, the change in rates of developing chronic *P. aeruginosa* during the observation period was compared only among individuals who aged into the cohort at 13 years (n = 6789). Over the 10-year observation period, there was a significant decrease in the rate of developing chronic *P. aeruginosa* infection (*P* value test of trend < .001) (Figure 3).

DISCUSSION

Among a large cohort of adolescents and adults with CF, we demonstrated a significant decrease in the risk of developing chronic *P. aeruginosa* infection between 2003 through 2012, even with adjustment for potential confounders. When we used an alternate definition of mucoidy for *P. aeruginosa* chronic infection, we demonstrated a similar significant decrease over time. There appeared to be no concurrent increase in other CF bacterial pathogens over the same period, but this warrants further study.

Recent observational studies have suggested that the prevalence of *P. aeruginosa* infection is decreasing in both adolescents and adults [7, 30, 31]. Both chronic infection and the mucoid phenotype of *P. aeruginosa* are associated with increased morbidity and mortality when compared to those without *P. aeruginosa* infection or those with nonchronic or nonmucoid infections [10]. Our study is one of the first contemporary evaluations of new chronic infections (as a more sensitive measure

Table 1. Comparison of Baseline Characteristics Between Individuals With and Without Chronic *Pseudomonas aeruginosa* Infection

	Free of Chronic Infection		Chronic Infection at Baseline	
Demographics	N = 15504		N = 9192	
Median age, years (IQR)	15.6	(13.6–24.5)	20.0	(13.0–29.0)
Median age of diagnosis, years (IQR)	0.86	(0.21–7.17)	0.59	(0.17–3.39)
Gender, female N (%)	7096	(45.8)	4588	(49.9)
Race, white N (%)	14513	(93.6)	8784	(95.6)
Ethnicity, Hispanic N (%)	843	(5.4)	487	(5.3)
f508del[a] status				
Homozygous, N (%)	6166	(39.8)	4207	(50.8)
Heterozygous, N (%)	5876	(37.9)	3133	(37.8)
Other/Unknown, N (%)	3462	(22.3)	1635	(10.3)
CFTR Functional classification[b]				
Minimal, N (%)	9301	(60.0)	6207	(67.5)
Residual, N (%)	1964	(12.7)	418	(4.6)
Other/Unknown, N (%)	4239	(27.3)	2567	(27.9)
Forced expiratory volume in 1 second, % predicted, mean (standard deviation)	81.9	(24.1)	67.8	(25.7)
Comorbidities				
Cystic fibrosis–related diabetes,[c] N (%)	1165	(10.2)	1741	(19.3)
Pancreatic insufficiency,[d] N (%)	10018	(92.8)	8227	(89.5)
Microbiology				
Pseudomonas aeruginosa, N (%)	4392	(41.9)	7229	(91.3)
Mucoid *Pseudomonas* phenotype, N (%)	2474	(56.3)	5797	(80.2)
Staphylococcus aureus, N (%)	7455	(71.2)	4207	(53.0)
Methicillin-resistant *Staphylococcus aureus*, N (%)	6264	(84.0)	3199	(76.0)
Methicillin-resistant *Staphylococcus aureus*, N (%)	1947	(26.1)	1422	(33.8)
Haemophilus influenzae, N (%)	1656	(15.8)	592	(7.5)
Burkholderia sp.,[e] N (%)	422	(4.0)	237	(3.0)
Alcaligenes xylosoxidans,[e] N (%)	747	(7.1)	562	(7.1)
Stenotrophomonas,[e] N (%)	1628	(15.5)	859	(10.8)

Abbreviation: CFTR, cystic fibrosis transmembrane conductance regulator; IQR, interquartile range.

[a]Homozygous: both alleles containing the delta F508 mutation; Heterozygous: one allele containing the delta F508 mutation; other/unknown: alleles containing mutations that are different or unknown.

[b]Minimal: both alleles containing mutations resulting in minimal CFTR function (class 1, 2, or 3); residual: at least 1 allele containing mutation resulting in partial CFTR function (class 4 or 5); unclassified: at least 1 allele with unknown CFTR function and if other allele function known, mutation resulting in minimal CFTR function.

[c]Cystic fibrosis–related diabetes: use of insulin.

[d]Pancreatic insufficiency: use of pancreatic enzymes.

[e]Burkholderia: Burkholderia species, Achromobacter: Alcaligenes xylosoxidans, Stenotrophomonas: Stenotrophomonas Maltophilia.

compared to prevalent infections) of *P. aeruginosa* in a large CF population while accounting for within-person correlations and confounders. In a prior study in which a small cohort of adults from a single center was used, we identified a trend toward decreasing prevalence of chronic *P. aeruginosa* infection, although it did not reach our predetermined significance level [21]. Other regional and national studies have also demonstrated a decline in the frequency of chronic *P. aeruginosa* infection over time, though these were both in earlier cohorts and applied alternative definitions of chronic infection [32, 33].

The observed decreased incidence in *P. aeruginosa* infections may be attributable to several changes. As noted, the study period occurred when inhaled antibiotics were frequently used. In the setting of newly acquired *P. aeruginosa* infection, inhaled anti-pseudomonal antibiotics can eradicate it from the subsequent respiratory culture about 75% of the time [24, 25, 28, 34–36], and those with successful eradication have delayed reacquisition [37, 38]. In the study by Mayer-Hamblett et al, those who remained free of *P. aeruginosa* for more than 12 months after eradication therapy had a significantly reduced risk of developing chronic *P. aeruginosa* infection (hazard ratio, 0.26; 95% CI, 0.17–0.40) [37]. Although the majority of *P. aeruginosa* eradication studies targeted the pediatric CF population, a recent study demonstrated that eradication was successful in adults [39]. Concordantly, we noted that a significant decrease in the incidence of developing chronic *P. aeruginosa* occurred during the observation period for both the 18–35 and >35 age groups.

During this study period, an increased proportion of individuals with residual function CFTR mutations were diagnosed and included in the registry data. This likely occurred because of advances in CF diagnostics resulting in more individuals being diagnosed as adults and may have contributed to lower incidence of chronic *P. aeruginosa* infection [40]. Further, the introduction of CFTR modulator agents, such as ivacaftor (not

Table 2. Unadjusted and Adjusted Relative Risk of Developing Chronic *Pseudomonas aeruginosa* Infection Compared to 2003

	Unadjusted		Adjusted[a]	
Year	RR[b]	(95% CI)	RR[c]	(95% CI)
2003	-	-	-	-
2004	0.68	(0.63–0.74)	0.70	(0.65–0.76)
2005	0.65	(0.60–0.70)	0.62	(0.58–0.68)
2006	0.56	(0.52–0.62)	0.51	(0.46–0.56)
2007	0.56	(0.51–0.61)	0.50	(0.45–0.55)
2008	0.56	(0.51–0.61)	0.49	(0.45–0.55)
2009	0.50	(0.45–0.55)	0.41	(0.37–0.46)
2010	0.47	(0.43–0.51)	0.41	(0.37–0.45)
2011	0.45	(0.41–0.50)	0.38	(0.34–0.43)
2012	0.45	(0.41–0.49)	0.35	(0.31–0.39)

Abbreviations: CI, confidence interval; RR, relative risk.

[a]Adjusted for age at entry, age at diagnosis, gender, cystic fibrosis transmembrane conductance regulator functional class, baseline forced expiratory volume in 1 second, cystic fibrosis–related diabetes at entry, and pancreatic insufficiency at entry.

[b]Trend test $P < .001$.

[c]Trend test $P < .001$.

used during the study period), which improves CFTR function, may have a similar result. Using recent data from the G551D observational cohort, Heltshe et al demonstrated significantly reduced odds of isolating *P. aeruginosa* from the airways and a 23% reduction in mucoid *P. aeruginosa* following ivacaftor therapy compared to culture data prior to initiation (odds ratio, 0.65; $P < .001$) [41]. However, when we assessed new chronic *P. aeruginosa* infection among the CFTR functional groups in our study cohort, similar decreases were noted across groups, arguing against the theory that changes in the CF genetic composition over time significantly affected our results.

Although we conducted a large population-based study of incident chronic *P. aeruginosa* infection in CF, we have several limitations to consider. A number of definitions for chronic *P. aeruginosa* infection have been evaluated in the literature [24, 42, 43], most using the original or modified form of the Leeds criteria. As the average number of months with available culture data vastly differed in our CFFPR-based cohort (Supplementary Table 2) compared to the initial validation study for the Leeds criteria, strict application of this score to our study may have resulted in frequent misclassification. Thus, we applied a modified version of the Leeds criteria to our cohort [24] and have successfully used it for *P. aeruginosa* classification in CF in the past [21]; it has since been demonstrated to perform similarly to the original score, including in relation to clinical outcomes [25]. As the frequency of quarterly cultures in our cohort was low, even if misclassification occurred, it would have biased results toward the null. In regard to the other bacterial pathogens assessed, we used a conservative definition of chronic infection as applied to *P. aeruginosa*, and it is possible that the incidence of other bacterial pathogens was underestimated by this approach. Next, as we observed a marked drop in incidence of chronic *P. aeruginosa* infections between 2003 and 2004, this may have been due to left censoring of the cohort with individuals either aging into the cohort at 13 years or entering at a later age following a new diagnosis. In our restricted cohort sensitivity analysis that was based on the probability of increasing chronic infection risk with age, the initial drop in incident chronic *P. aeruginosa* was no longer observed; however, the significant decrease over the study period persisted. Third, as the definition of chronic infection is dependent on number of cultures over time, there was potential for individuals with worsened lung function to undergo more

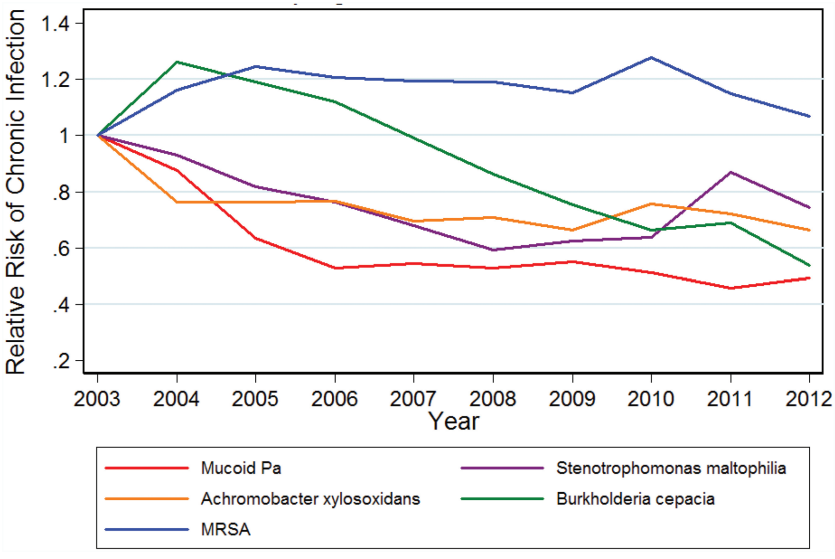

Figure 2. Development of chronic infections with other cystic fibrosis pathogens compared to 2003 in study period. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*.

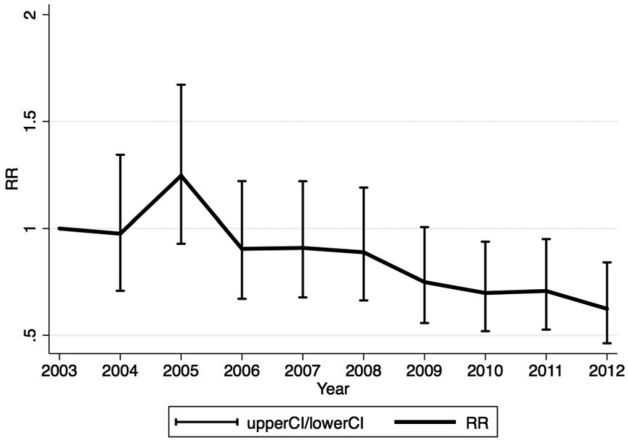

Figure 3. Risk of chronic *Pseudomonas aeruginosa* among individuals entering the cohort at age 13 years by year relative to 2003 adjusting for age, age at diagnosis, gender, cystic fibrosis transmembrane conductance regulator functional class, baseline forced expiratory volume in 1 second, predicted, cystic fibrosis–related diabetes, and pancreatic insufficiency. Abbreviations: CI, confidence interval; RR, relative risk.

respiratory cultures. We summarized culture data quarterly to minimize this effect. Further, the number of total cultures increased over time, which may have resulted in increasing incidence of *P. aeruginosa* infection captured and thus would have again biased the results toward the null. Last, with use of the registry data, we captured approximately 84% of the CF population in the United States; such a subset, albeit large, could be different from the entire CF population in the United States. However, patients are more likely to be seen in specialty CF centers captured in the CFFPR as they get sicker and require more specialized care. We also acknowledge that given the use of registry data, missingness and loss to follow-up may impact the results in an unpredictable manner. Regardless, this was a large CF population–based study to robustly examine incident chronic *P. aeruginosa* infections over a 10-year period and improves our understanding of the epidemiologic trends of this organism.

In conclusion, our large registry-based study in the United States demonstrated a significant decline in incident chronic *P. aeruginosa* infections in adolescents and adults with CF between 2003 through 2012. We did not observe a parallel increase in other characteristic bacterial airway pathogens over the same period. Additional studies are needed to determine whether these changes in chronic *P. aeruginosa* infection continue and how they correlate with future clinical outcomes in CF.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. E. C. and M. C. were primarily responsible for data management and analysis. M. C., R. S., and K. R. were responsible for the creation of the manuscript. C. H. G., A. R., N. M. H., and M. C. were responsible for the project's inception and supervision. All authors contributed to development of the final manuscript. C. H. G. serves as guarantor of the work.

Acknowledgments. We thank the Cystic Fibrosis Foundation (CFF) for use of The Cystic Fibrosis Foundation Patient Registry (CFFPR) data to conduct this study. Additionally, we thank the patients, care providers, and clinic coordinators at CF centers throughout the United States for their contributions to the CFFPR.

Financial support. C. H. G. receives funding from the CFF, the National Institutes of Health (NIH; grantsR01HL103965, R01HL113382, R01AI101307, UM1HL119073, P30DK089507), and the US Food and Drug Administration (grant R01FD003704). N. M. H. reports grants from the NIH and CFF. R. S. is supported by fellowship funding from Cystic Fibrosis Canada, the Canadian Institutes of Health Research, and Alberta Innovates-Health Solutions. K. J. R. is supported by fellowship funding from the CFF.

Potential conflicts of interest. C. H. G. has consulted for Vertex Pharmaceuticals and has participated on the boards of Transave Inc, KalBios Pharmaceuticals, and Boehringer Ingelheim Pharm GmbH & Co outside of the submitted work. In her role as co-director of the Therapeutics Development Network Coordinating Center, N. M. H.'s institution receives other funding from AbbVie Inc. Achaogen AlgiPharma AS Aridis Pharmaceuticals LLC Bayer HealthCare AG Catabasis Celtaxsys Corbus Pharmaceuticals Covance, Inc. CURx Pharmaceuticals, Inc. Flatley Discovery Lab LLV Gilead Sciences, Inc. Horizon Pharma KaloBios La Jolla Pharmaceutical Laurent Pharmaceuticals Life Science Strategies Mylene Gencey Nivalis Therapeutics, Inc. Novartis Pharmaceuticals Corp. ProQR Therapeutics B.V. Protalix Ltd. Proteostasis Therapeutics, Inc. Pulmatrix Quintiles, Inc. Sanofi Savara Pharmaceuticals Synedgen, Inc. Teva Branded Pharmaceutical Products R&D Vertex Pharmaceuticals Incorporated, outside the submitted work. All remaining authors: no reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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