CHEST

# Changing Epidemiology of the Respiratory Bacteriology of Patients With Cystic Fibrosis

*Elizabeth L. Salsgiver, MPH; Aliza K. Fink, DSc; Emily A. Knapp, BA; John J. LiPuma, MD; Kenneth N. Olivier, MD; Bruce C. Marshall, MD; and Lisa Saiman, MD, MPH*

**BACKGROUND:** Monitoring potential changes in the epidemiology of cystic fibrosis (CF) pathogens furthers our understanding of the potential impact of interventions.

**METHODS:** We performed a retrospective analysis using data reported to the Cystic Fibrosis Foundation Patient Registry (CFFPR) from 2006 to 2012 to determine the annual percent changes in the prevalence and incidence of selected CF pathogens. Pathogens included *Pseudomonas aeruginosa*, methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S aureus* (MRSA), *Haemophilus influenzae*, *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*. Changes in nontuberculous mycobacteria (NTM) prevalence were assessed from 2010 to 2012, when the CFFPR collected NTM species.

**RESULTS:** In 2012, the pathogens of highest prevalence and incidence were MSSA and *P aeruginosa*, followed by MRSA. The prevalence of *A xylosoxidans* and *B cepacia* complex were relatively low. From 2006 to 2012, the annual percent change in overall (as well as in most age strata) prevalence and incidence significantly decreased for *P aeruginosa* and *B cepacia* complex, but significantly increased for MRSA. From 2010 to 2012, the annual percent change in overall prevalence of NTM and *Mycobaterium avium* complex increased.

**CONCLUSIONS:** The epidemiology of CF pathogens continues to change. The causes of these observations are most likely multifactorial and include improvements in clinical care and infection prevention and control. Data from this study will be useful to evaluate the impact of new therapies on CF microbiology. CHEST 2016; 149(2):390-400

**KEY WORDS:** cystic fibrosis; *Pseudomonas aeruginosa*; registry; *Staphylococcus aureus*

**ABBREVIATIONS:** CA = community-associated; CF = cystic fibrosis; CFF = Cystic Fibrosis Foundation; CFFPR = Cystic Fibrosis Foundation Patient Registry; CFTR = cystic fibrosis transmembrane conductance regulator; IRB = institutional review board; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; NTM = nontuberculous mycobacteria

**AFFILIATIONS:** From the Columbia University Medical Center (Ms Salsgiver and Dr Saiman), New York, NY; Cystic Fibrosis Foundation (Drs Fink and Marshall, and Ms Knapp), Bethesda, MD; University of Michigan (Dr LiPuma), Ann Arbor, MI; and the National Heart, Lung, and Blood Institute (Dr Olivier), National Institutes of Health, Bethesda, MD.

Ms Salsgiver is currently at the Weill Cornell Medical Center (New York, NY).

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**CORRESPONDENCE TO:** Lisa Saiman, MD, MPH, Columbia University Medical Center, Department of Pediatrics, 650 W 168th St, PH 4 W Room 470, New York, NY 10032; e-mail: LS5@cumc.columbia.edu



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Recent advances in clinical care and disease-specific therapies have increased the life expectancy and quality of life among people with cystic fibrosis (CF).[1,2] However, progressive lung disease associated with chronic respiratory infections and inflammation remains the most common cause of morbidity and mortality in CF.[3] Monitoring changes in the epidemiology of CF pathogens is essential to optimally manage CF lung disease and to understand the potential impact of therapeutic interventions on CF microbiology.

We previously evaluated the epidemiology of CF pathogens using data reported to the Cystic Fibrosis Foundation Patient Registry (CFFPR) from 1995 to 2005.[4] We found that the annual prevalence and incidence of *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex significantly declined during the study period. In contrast, the prevalence and incidence of methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S aureus* (MRSA), *Haemophilus influenzae, Stenotrophomonas maltophilia,* and *Achromobacter xylosoxidans* increased. Others have also reported changing trends in CF microbiology. The most common *Burkholderia* species has changed from *B cenocepacia* to *B multivorans* in both the United States [5] and the United Kingdom.[6] Increases in MRSA,[7-9] *A xylosoxidans*,[8,10,11] and *S maltophilia*[8,9,12] have also been reported. The prevalence of nontuberculous mycobacteria (NTM) varies by age and by country, but has been increasing[13-16] particularly for *Mycobacterium abscessus*.[17,18] However, determining epidemiologic trends in CF microbiology can be challenging because of lack of reliable historical data for some pathogens; changes in reporting strategies; variations in sampling methods, microbiologic techniques, and culture frequency; and the patient population studied.

Thus, we wanted to determine if the epidemiology of CF pathogens has continued to evolve since our previous analysis.[4] To do so, we used data reported to the CFFPR from 2006 to 2012, as recommendations for microbiologic culturing and processing of CF respiratory tract specimens and for reporting results were consistent during this period. The objectives of the current study were to examine longitudinal trends in the incidence and prevalence of CF pathogens, including age-specific annual estimates, from 2006 to 2012. We also analyzed the epidemiology of specific *Burkholderia* species and NTM species reported from 2010 to 2012 following the addition of enhanced microbiology reporting options in the CFFPR. Findings from the current study have potential implications for clinical care, new therapeutic strategies, and implementation of infection prevention and control recommendations.

## Materials and Methods

### CF Foundation Patient Registry

The CFFPR is deployed throughout the CFF-accredited care center network as an institutional review board (IRB)-approved observational study with consent from patients/parents/guardians to participate, which includes allowing the submission of their data to the CFFPR for research purposes. Based on the responses to a specific question required on annual progress reports from all care centers, approximately 95% of patients in the CFF care center network have provided consent to allow data submission to CFFPR (Bruce C. Marshall, MD, unpublished data, June 2013). The CFFPR database contains the demographic, diagnostic, and clinical characteristics of approximately 27,000 individuals with CF cared for at approximately 120 accredited CF care centers and 50 affiliate programs.[19]

CFF guidelines recommend that patients have respiratory cultures each quarter. Cultures can be reported as negative or positive for pathogen(s) of interest, or reported as "normal flora" and can be obtained from throat swabs, sputum, or BAL. Since 2003, data entry guidelines have requested entry of all culture results into the CFFPR. Prior to 2010, positive *Burkholderia* cultures were reported as either as *B cepacia* complex or as "other gram-negative species." Since 2010, data entry options for 19 *Burkholderia* species have been available (e-Fig 1). Prior to 2010, NTM-positive cultures were recorded as nontuberculous mycobacteria. Since 2010, the options of recording *M avium* complex (MAC), *M abscessus*, *M fortuitum* group, *M gordonae, M kansasii, M marinum, M terrae,* and "other" have been available.

### Study Population

The study population included patients with CF who had at least one respiratory tract culture result in the CFFPR from January 2006 through December 2012. Patients who underwent solid organ transplantation were included in the analysis until the year of their transplant. Patients who died during the study period were included until the year of death. The Columbia University Medical Center IRB considered this study exempt from additional IRB review.

### Case Definitions

An incident case was defined as the first time a patient was reported to have a positive culture for the pathogen of interest. Culture results for the 10 previous years were reviewed, as available, for each incident case to confirm that no previous cultures had been positive for that pathogen. For example, a patient with a positive culture for *P aeruginosa* in 2006 and no positive cultures for *P aeruginosa* between 1996 and 2005 would be considered an incident case in 2006. Once a patient was an incident case for a specific pathogen, they were excluded from the denominator for subsequent calculations of incidence. Only patients with one or more cultures reported in a given study year contributed to the denominator (as appropriate) for incidence in that year.

A prevalent case was defined as a patient with one or more positive respiratory tract cultures for the pathogen of interest. For example, if a patient had a first positive culture for *P aeruginosa* in 2006 and then positive cultures for *P aeruginosa* each year from 2007 to 2012, the patient would be considered an incident case in 2006 and a

prevalent case in 2006 to 2012. Patients with one or more cultures reported in a given study year contributed to the denominator for prevalence in that year. Patients with negative cultures or normal flora were considered neither incident nor prevalent cases.

### Data Analysis

The age-specific prevalence and incidence rates for CF pathogens reported to the CFFPR were determined for 2012.[7] Trends in the prevalence and incidence of *P aeruginosa,* MRSA, MSSA, *H influenzae, B cepacia* complex, *S maltophilia,* and *A xylosoxidans* were calculated from 2006 to 2012. Due to the changes in the data collection fields implemented in 2010 described above, only the annual, age-specific percent changes in prevalence were determined from 2010 to 2012 for specific *Burkholderia* and NTM species, as incidence for these pathogens could not be determined because of the short surveillance period. NTM cultures from sputum, induced sputum, or BAL from patients ≥ 12 years of age were analyzed, as younger children have inconsistent production of sputum, and throat swabs are unreliable to detect NTM.[20]

Trends in incidence and prevalence were assessed by estimating the average, annual age-specific percent change, using Poisson regression models, accounting for repeated measures. Separate models were developed for each pathogen and parameter estimates were obtained for the whole population and stratified by age group. The age strata were those used in the annual CFFPR reports and included the following age ranges: 0-1, 2-5, 6-10, 11-17, 18-25, and ≥26 years.[7] Age-specific incidence rates were calculated using age at the time of the first positive culture. Age-specific prevalence rates were calculated using age on December 31 of the relevant study year. All analyses were conducted using SAS version 9.3 (SAS Institute Inc).

Our analyses were based on two assumptions. The first assumption was that to be an incident case, a patient had tested negative for that pathogen for 10 years. We conducted an analysis to determine the sensitivity of our incidence trend estimates and compared the results of the 10-year look-back interval with results using 5- and 2-year look-back intervals to assess changes in the overall incidence of each pathogen. The second assumption was that one positive culture was sufficient to meet criteria for an incident or prevalent case for a given year. Thus, to determine the impact of potentially false-positive cases in our analysis, we compared the overall trend estimates to assess changes in incidence and prevalence using one positive culture with results using two positive cultures. Both sensitivity analyses used data from 2006 to 2012 for *P aeruginosa*, MRSA, MSSA, *H influenzae, B cepacia* complex, *S maltophilia,* and *A xylosoxidans.*

## Results

### Study Population

During the study period, of the 33,653 unique patients who had data reported to the CFFPR, 31,915 (94.8%) were eligible for inclusion (21,146-25,530 patients per year), as shown in Figure 1. Overall, 42.9% of patients had at least one culture reported to the CFFPR during all 7 years of the study, while 8.7% were included for only 1 year. An increasing proportion of patients had four or more cultures per year reported in 2012 vs 2006 (48% vs 35%, respectively; $P < .001$).

### Age-Specific Prevalence and Incidence Rates of CF Pathogens, 2012

In 2012, 25,530 of 27,804 patients (92%) had at least one culture recorded in the CFFPR. Of these, 12%, 15%, 21%, and 52% had one, two, three, or four or more cultures reported, respectively. The age-specific prevalence and incidence rates for CF pathogens in 2012 are shown in Table 1. The pathogens of highest prevalence were MSSA and *P aeruginosa*, with prevalence rates of 52.3% and 49.6%, respectively, followed by MRSA (26.5%), *H influenzae* (15.6%), *S maltophilia* (13.4%), and NTM species (12.0%). The lowest prevalence rates were noted for *A xylosoxidans*

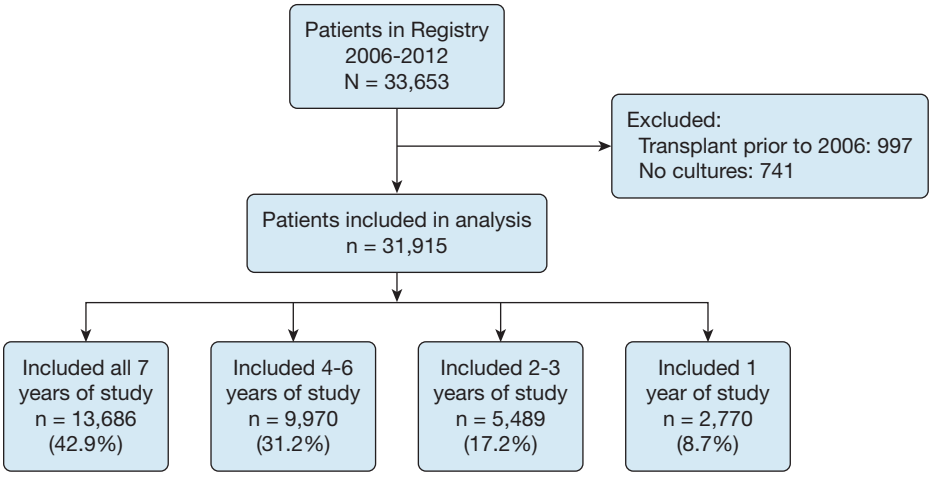


Figure 1 – *Flow diagram of eligible patients. Patients in the Cystic Fibrosis Foundation Patient Registry eligible for current study and number of years of participation.*

**TABLE 1** ] Age-Specific Prevalence and Incidence Rates for Cystic Fibrosis-Associated Pathogens, 2012

| Age Strata | PA | MRSA | MSSA | HI | SM | AX | All BCC[a] | BC | BM | BG | All NTM[b] | MAC | MAB | Other NTM[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Overall | | | | | | | | | | | | | | |
| Prevalence | 49.56 | 26.47 | 52.29 | 15.57 | 13.40 | 6.36 | 2.57 | 0.38 | 0.68 | 0.45 | 12.04 | 6.94 | 5.03 | 0.82 |
| Incidence | 16.20 | 7.67 | 27.51 | 7.35 | 6.16 | 2.13 | 0.70 | … | … | … | … | … | … | … |
| 0-1 y | | | | | | | | | | | | | | |
| Prevalence | 22.02 | 11.74 | 51.42 | 21.54 | 12.63 | 1.38 | FD[d] | FD[d] | FD[d] | FD[d] | NRM[e] | NRM[e] | NRM[e] | NRM[e] |
| Incidence | 21.04 | 9.60 | 45.41 | 19.19 | 12.22 | 1.38 | FD[d] | FD[d] | FD[d] | FD[d] | NRM[e] | NRM[e] | NRM[e] | NRM[e] |
| 2-5 y | | | | | | | | | | | | | | |
| Prevalence | 21.35 | 17.18 | 58.50 | 32.46 | 9.05 | 1.85 | FD[d] | FD[d] | FD[d] | FD[d] | NRM[e] | NRM[e] | NRM[e] | NRM[e] |
| Incidence | 15.89 | 8.04 | 33.92 | 15.52 | 6.40 | 1.58 | FD[d] | FD[d] | FD[d] | FD[d] | NRM[e] | NRM[e] | NRM[e] | NRM[e] |
| 6-10 y | | | | | | | | | | | | | | |
| Prevalence | 29.75 | 26.21 | 63.22 | 26.53 | 12.76 | 4.15 | 1.37 | FD[d] | 0.34 | FD[d] | NRM[e] | NRM[e] | NRM[e] | NRM[e] |
| Incidence | 12.22 | 8.48 | 31.00 | 11.39 | 6.39 | 2.18 | 0.59 | … | … | … | NRM[e] | NRM[e] | NRM[e] | NRM[e] |
| 11-17 y | | | | | | | | | | | | | | FD[d] |
| Prevalence | 43.82 | 32.01 | 60.71 | 14.54 | 18.22 | 7.64 | 2.24 | 0.25 | 0.69 | 0.34 | 11.18 | 5.85 | 5.61 | FD[d] |
| Incidence | 13.15 | 7.88 | 26.21 | 4.15 | 6.86 | 2.70 | 0.73 | … | … | … | 5.52 | … | … | FD[d] |
| 18-25 y | | | | | | | | | | | | | | |
| Prevalence | 63.58 | 32.40 | 49.49 | 9.04 | 14.47 | 9.08 | 3.96 | 0.62 | 1.31 | 0.58 | 12.79 | 7.05 | 5.77 | 0.89 |
| Incidence | 15.78 | 8.44 | 19.56 | 4.01 | 5.69 | 2.31 | 1.10 | … | … | … | 6.06 | … | … | … |
| 26+ y | | | | | | | | | | | | | | |
| Prevalence | 74.13 | 24.28 | 37.76 | 5.79 | 10.97 | 7.50 | 4.05 | 0.67 | 0.77 | 0.91 | 11.89 | 7.40 | 4.15 | 1.04 |
| Incidence | 20.16 | 5.68 | 14.01 | 3.25 | 4.09 | 1.98 | 0.77 | … | … | … | 5.86 | … | … | … |

AX = *Achromobacter xylosoxidans*; BC = *Burkholderia cenocepacia*; BCC = *B cepacia* complex; BG = *B gladioli*; BM = *B multivorans*; FD = few data; HI = *Haemophilus influenzae*; MAB = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex; MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-resistant *S aureus*; NRM = without reliable mycobacteria cultures; NTM = all nontuberculous mycobacteria species; other BCC = other *B cepacia* complex; other NTM = other nontuberculous mycobacteria species; PA = *Pseudomonas aeruginosa*; SM = *Stenotrophomonas maltophilia*.

[a]*Burkolderia cepacia* complex includes *B cepacia, B multivorans, B cenocepacia, B stabiliz, B vietnamiensis, B dolosa, B ambifaria, B anthina, B pyrrocinia, B ubonensis, B latens, B diffusa, B arboris, B seminalis, B metallica, B contaminans, and B lata*.

[b]Only incidence for "All NTM" could be determined.

[c]Other NTM include the *Mycobacterium fortuitum* group, *M gordonae, M kansasii, M marinum*, and *M terrae*.

[d]Data are not provided, as there are < 10 patients contributing to the numerator.

[e]Patients with CF < 12 y without reliable mycobacteria cultures.

(6.4%) and *B cepacia* complex (2.6%). Similar patterns were noted for incidence; incidence was highest for MSSA (27.5%), followed by *P aeruginosa* (16.2%), and lowest for *B cepacia* complex (0.70%).

### Changes in Overall Prevalence and Incidence of CF Pathogens, 2006-2012

The average annual percent change in overall prevalence and incidence significantly decreased for *P aeruginosa*, *H influenzae,* and *B cepacia* complex (Table 2). For MSSA and *A xylosoxidans,* the overall annual percent change in incidence significantly decreased, but prevalence did not significantly change. In contrast, the overall annual percent change in the prevalence and incidence of MRSA increased, as did the prevalence of *S maltophilia*.

### Changes in Age-Specific Prevalence and Incidence of CF Pathogens, 2006-2012

Among the pathogens studied, the largest absolute changes in incidence and prevalence, and the most pronounced differences by age groups were demonstrated for *P aeruginosa* and MRSA (Figs 2A, 2B). For *P aeruginosa*, the average annual percent change in incidence and prevalence significantly decreased in all age strata, except for a nonsignificant decrease in incidence among adults 18-25 years old (Table 2). For MRSA, the annual incidence increased among those 2-5, 11-17, and 18-25 years old, and prevalence increased in all age strata. For MSSA, prevalence remained stable in children and adolescents, but significantly increased in adults. MSSA incidence remained stable in all age strata, except children 2-5 years old, in whom incidence significantly decreased. For *H influenzae*, prevalence remained stable in most strata, but decreased in children 2-5 years old, and *H influenzae* incidence declined in children and adolescents 2-17 years old. For *S maltophilia*, prevalence increased in adolescents and adults. For *A xylosoxidans*, prevalence decreased in children 2-5 years old, while incidence decreased in children 2-10 years old and adults aged $\geq$ 26 years. For *B cepacia* complex, prevalence decreased in those 2-5, 11-17, and $\geq$ 26 years old, while incidence decreased in children 2-5 years old.

### Changes in Prevalence of Burkholderia and NTM Species, 2010-2012

The average annual percent change in prevalence of different *Burkholderia* species from 2010 to 2012 by age strata is shown (Table 3). Neither the overall nor age group strata average annual percent change in prevalence significantly changed from 2010 to 2012.

From 2010 to 2012, 13,169 culture results for NTM were reported to the CFFPR. The proportion of patients who had one or more cultures sent for NTM increased from 45% in 2010 to 54% in 2012 ($P < .001$). For all NTM and for MAC, the annual percent change in prevalence significantly increased from 2010 to 2012, but remained stable for *M abscessus* complex and other NTM species (Table 4).

### Sensitivity Analyses

The first sensitivity analysis examined the impact of using 10-, 5-, and 2-year look-back intervals on the incidence of CF pathogens. As expected, incidence rates were slightly higher when using the shorter look-back time interval (e-Table 1), but there were no significant differences in annual percent change in incidence for the 10-year look-back interval compared with the shorter look-back intervals (e-Table 2). The second sensitivity analysis examined the impact of using one vs two positive cultures per year to assess the annual percent change in incidence and prevalence estimates; the percent change was similar for one vs two positive cultures (e-Table 3).

## Discussion

This study demonstrated that the epidemiology of CF pathogens in the United States has continued to change in recent years. We found that the overall incidence and prevalence of *P aeruginosa* and *B cepacia* complex significantly decreased during the 7-year study period while the overall incidence and prevalence of MRSA increased. These trends are a continuation of our previous findings[4]; from 1995 to 2012, the prevalence of *P aeruginosa* decreased from 60.4% to 49.6%, the prevalence of *Burkholderia* species decreased from 3.6% to 3.0%, while the prevalence of MRSA increased from 0.1% to 26.5%.

In an observational cohort study, causality cannot be assessed, but we speculate that several practice changes in the CF population could have reduced the incidence of *P aeruginosa,* MSSA, *H influenzae*, *A xylosoxidans,* and *B cepacia* complex. CFFPR data demonstrate that more recent cohorts have better lung function than previously reported age-matched cohorts, thanks to numerous advances in CF-specific therapies, suggesting that children and adolescents have less structural lung disease and, therefore, less risk for infection.[2] The

**TABLE 2** ] Average Annual Percent Change in the Prevalence and Incidence of Cystic Fibrosis-Associated Pathogens by Age Strata, 2006-2012

| | PA | | MRSA | | MSSA | | HI | | SM | | AX | | BCC[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age Strata | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value |
| Overall | | | | | | | | | | | | | | |
| Prevalence | −1.7 | < .001 | 5.3 | < .001 | 0.1 | .276 | −1.3 | < .001 | 1.4 | < .001 | 0.6 | .225 | −2.6 | < .001 |
| Incidence | −3.3 | < .001 | 2.3 | < .001 | −1.2 | < .05 | −3.8 | < .001 | −0.2 | .784 | −3.3 | < .001 | −3.3 | < .05 |
| 0-1 y | | | | | | | | | | | | | | |
| Prevalence | −4.3 | < .001 | 4.5 | < .05 | 0.5 | .419 | −1.2 | .285 | 0.8 | .627 | −4.3 | .418 | 12.5 | .459 |
| Incidence | −4.6 | < .001 | 3.5 | .077 | 0.0 | .972 | −1.8 | .117 | −0.1 | .956 | −4.3 | .416 | 12.5 | .459 |
| 2-5 y | | | | | | | | | | | | | | |
| Prevalence | −3.3 | < .001 | 4.3 | < .001 | −0.1 | .689 | −1.3 | < .05 | −0.6 | .594 | −8.8 | < .05 | −15.6 | < .05 |
| Incidence | −2.9 | < .05 | 4.4 | < .05 | −2.7 | < .05 | −4.1 | < .001 | −0.2 | .875 | −9.4 | .002 | −12.3 | < .05 |
| 6-10 y | | | | | | | | | | | | | | |
| Prevalence | −2.2 | < .001 | 5.1 | < .001 | 0.1 | .780 | −0.9 | .100 | −0.1 | .939 | −2.8 | .102 | 0.2 | .956 |
| Incidence | −3.7 | < .05 | 2.2 | .061 | −1.6 | .200 | −4.4 | < .05 | 0.2 | .908 | −4.4 | < .05 | −1.5 | .708 |
| 11-17 y | | | | | | | | | | | | | | |
| Prevalence | −3.3 | < .001 | 5.3 | < .001 | 0.4 | .096 | −0.1 | .931 | 2.6 | < .001 | 1.8 | .093 | −6.4 | < .05 |
| Incidence | −3.1 | < .05 | 2.2 | < .05 | −1.0 | .509 | −5.9 | < .05 | 0.2 | .870 | 1.2 | .498 | −5.3 | .105 |
| 18-25 y | | | | | | | | | | | | | | |
| Prevalence | −2.5 | < .001 | 6.5 | < .001 | 1.0 | < .05 | −0.5 | .596 | 3.5 | < .001 | 1.7 | .091 | −1.0 | .528 |
| Incidence | −2.7 | .113 | 3.3 | < .05 | 2.0 | .244 | −3.3 | .067 | 0.0 | .870 | −2.7 | .144 | 1.7 | .572 |
| 26+ y | | | | | | | | | | | | | | |
| Prevalence | −0.9 | < .001 | 5.8 | < .001 | 1.7 | < .001 | 0.8 | .470 | 1.6 | < .05 | 1.1 | .260 | −3.4 | < .05 |
| Incidence | −4.2 | < .05 | 1.3 | .281 | −1.0 | .445 | −2.0 | .228 | −0.1 | .949 | −4.2 | < .05 | −5.8 | .114 |

See Table 1 legend for expansion of abbreviations.

[a]*Burkholderia cepacia* complex includes *B cepacia, B multivorans, B cenocepacia, B stabiliz, B vietnamiensis, B dolosa, B ambifaria, B anthina, B pyrrocinia, B ubonensis, B latens, B diffusa, B arboris, B seminalis, B metallica, B contaminans, and B lata*.

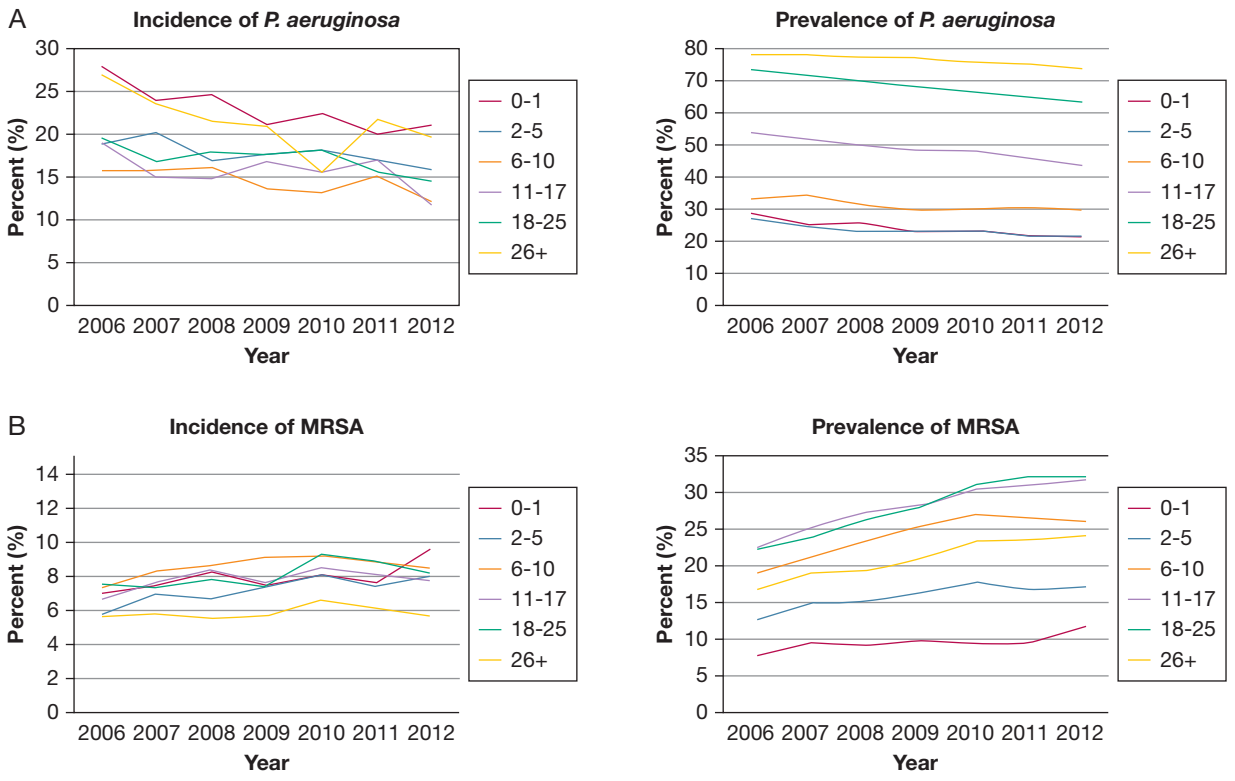


Figure 2 – *A, Overall incidence and prevalence of Pseudomonas aeruginosa in patients with CF from 2006 to 2012. The overall incidence and prevalence of* P *aeruginosa among these patients is shown by age strata. B, Overall incidence and prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in patients with cystic fibrosis from 2006 to 2012. The overall incidence and prevalence of MRSA among these patients is shown by age strata. These data reflect an analysis of the US Cystic Fibrosis Foundation Patient Registry.*

proportion of patients identified by newborn screening increased during the study period from about 21.5% in 2006 to about 60.0% in 2012,[21] which may also improve overall lung health. For over a decade, CF centers have been progressively implementing more rigorous infection prevention and control strategies to reduce the risk for patient-to-patient transmission of CF pathogens and acquisition from the natural and/or health-care environment.[22,23] Furthermore, the prevalence of *B cepacia* complex, *H influenzae*, and *P aeruginosa* also decreased. While successful early eradication strategies for *P aeruginosa* have been well studied,[24,25] eradication studies have not been performed for *B cepacia* complex and *H influenzae*. However, it is possible that caregivers

**TABLE 3** ] Average Annual Percent Change in Prevalence of *Burkholderia* species by Age Strata, 2010-2012[1]

| | All *Burkholderia* species[a] | | *B cenocepacia* | | *B multivorans* | | *B gladioli* | |
|---|---|---|---|---|---|---|---|---|
| Age Strata, y | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value |
| Overall | 1.1 | .520 | −8.2 | .132 | 0.7 | .865 | 0.0 | .996 |
| 0-1 | FD[b] | FD[b] | FD[b] | FD[b] | FD[b] | FD[b] | FD[b] | FD[b] |
| 2-5 | −41.4 | .094 | FD[b] | FD[b] | FD[b] | FD[b] | FD[b] | FD[b] |
| 6-10 | 1.0 | .902 | FD[b] | FD[b] | −11.4 | .530 | −13.0 | .525 |
| 11-17 | 3.8 | .454 | −1.2 | .932 | 6.7 | .463 | −11.7 | .248 |
| 18-25 | −0.3 | .927 | −11.9 | .253 | 6.4 | .379 | 5.4 | .614 |
| 26+ | 0.6 | .819 | −1.4 | .190 | −8.9 | .170 | 4.4 | .512 |

See Table 1 legend for expansion of abbreviation.

[a]Burkholderia cepacia spp. includes *B cepacia, B multivorans, B cenocepacia, B stabiliz, B vietnamiensis, B dolosa, B ambifaria, B anthina, B pyrrocinia, B ubonensis, B latens, B diffusa, B arboris, B seminalis, B metallica, B contaminans, and B lata.*

[b]Data are not provided, as there are < 10 patients contributing to the numerator.

**TABLE 4** ] Average Annual Percent Change in Prevalence of Nontuberculous *Mycobacterium* species by Age Strata, 2010-2012[a]

| | All NTM | | MAC | | *M abscessus* | | Other NTM[b] | |
|---|---|---|---|---|---|---|---|---|
| Age Strata, y | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value | % Change | *P* Value |
| Overall (12+) | 3.9 | < .05 | 7.4 | < .05 | −1.6 | .540 | 2.3 | .757 |
| 12-17 | −1.1 | .782 | 3.0 | .605 | −3.6 | .510 | −26.8 | .184 |
| 18-25 | 6.7 | < .05 | 11.3 | .014 | 1.7 | .711 | −1.0 | .934 |
| 26+ | 4.3 | .121 | 6.4 | .094 | −3.0 | .493 | 12.2 | .273 |

See Table 1 legend for expansion of abbreviations.
[a]Average annual percent change in prevalence only reported for patients with CF who are ≥12 y old.
[b]Other NTM include the *Mycobacterium fortuitum* group, *M gordonae, M kansasii, M marinum, and M terrae.*

are implementing eradication strategies for pathogens other than *P aeruginosa.* Reduced prevalence may also reflect decreased incidence, as well.

Both the incidence and prevalence of MRSA increased during the study period. These trends are concordant with observations in people without CF. Previously, MRSA infections were limited to specific risk groups, such as hospitalized patients, patients on dialysis, and those in nursing homes. In the 1990s, community-onset infections among otherwise healthy individuals began to occur. While progress has been made to decrease hospital-associated infections caused by MRSA in patients without CF over the past several years, community-associated (CA) MRSA infections have continued to increase.[26] Thus, it is likely that patients with CF acquire MRSA in both health-care and nonhealth-care settings. Support for this can be derived from molecular-typing studies that have demonstrated that approximately 65% to 70% of patients with CF harbor health-care-associated clones and about one-third of patients with CF harbor CA clones.[27-29] Furthermore, older patients with CF are more likely to harbor hospital-associated clones, suggesting acquisition prior to the widespread onset of CA MRSA.[30] Support for acquisition of MRSA in health-care settings is provided by a report that found that more stringent infection prevention and control strategies, which included universal contact precautions, significantly reduced MRSA in a pediatric CF clinic.[31] Studies to find effective therapeutic approaches to eradication are ongoing.[32,33]

We found that the prevalence of *S maltophilia* increased. This multidrug-resistant gram-negative pathogen has been increasing in health-care and CA infections in patients without CF and most commonly causes respiratory tract infections.[34] *S maltophilia* can be found in water sources in both health-care and nonhealth-care settings, including sink drains, sponges, and faucets.[35] These observations suggest that, like MRSA, the epidemiology of *S maltophilia* in people with CF is similar to that of those without CF.

Over the past 2 decades, the CF community has had increasing concern about infections with NTM, because of increased morbidity and mortality associated with these pathogens. Recent evidence of patient-to-patient transmission including the role of airborne transmission has heightened this concern.[36,37] From 2010 to 2012, when robust data in the CFFPR were available, the prevalence of all species of NTM and of MAC increased. The CFF recommends at least annual screening for NTM,[20] but as evidenced in this study, many patients are screened several times per year, presumably because of providers' clinical concerns. The increased frequency of culturing may have contributed to the increased prevalence, although the frequency is still less than recommended by the CFF.[38] Future studies should continue to evaluate the incidence and prevalence of specific species over a longer time, as well as the frequency of and risk factors for patient-to-patient transmission.

The CFF has made great efforts to accurately capture CF microbiology and minimize data entry errors (e-Fig 1). A recent audit conducted by the CFF suggested relatively little missing data and few data entry errors. Findings from MRSA or *P aeruginosa* cultures recorded in the electronic medical record were missing in the CFFPR for 1.2% of CF clinic visits. Among 5,203 CF clinic visits with microbiology data reported in both the electronic medical record and CFFPR, 57 (1.1% [95% CI, 0.8%-1.4%]) and 70 (1.3% [95% CI, 1.0%-1.7%]) discrepancies were noted for *P aeruginosa* and MRSA, respectively (E. Knapp, MPH, and A. Fink, DSc, unpublished data, September 2014). Furthermore, changing taxonomy for gram-negative pathogens may result in data entry errors and/or epidemiologic changes in CF pathogens. For

example, *B pseudomultivorans* was named as another member of the *B cepacia* complex in 2013 and, retrospectively, has been detected in individuals with CF since 1999.[39] Adding this species to the CFFPR will alter the epidemiology of other common *Burkholderia* species (J. J. LiPuma, MD, unpublished data, October 2013). Among 341 isolates identified as *A xylosoxidans*, only 42% were confirmed as such, while 24% were identified as *A ruhlandii* and 17% as *A dolans*.[40] As clinical microbiology laboratories identify these species correctly and as they are added to the CFFPR, a decrease in the incidence of *A xylosoxidans* and an increase in the two other *Achromobacter* species would be expected.

The two sensitivity analyses performed could inform future studies. While using a longer 10-year look-back interval was a more conservative approach to estimating incidence and prevalence, the same trends were found using the shorter 5- and 2-year look-back intervals. This suggests that our results were not sensitive to the length of the look-back interval. However, the analysis of the shorter intervals was likely confounded by increasing both the number of eligible cases and the number of individuals eligible for the denominator. We also found that the results using two positive cultures, rather than one positive culture, to define incidence and prevalence were similar. Thus, both sensitivity analyses suggested minimal impact of data entry errors and that our findings are robust.

This study had limitations. This observational study cannot determine causality and may be subject to reporting bias, laboratory misidentification of CF pathogens, and data entry errors. Finally, the frequency of culturing for bacteria and for mycobacteria increased throughout the study period, which would be expected to increase incidence and prevalence rates.

In summary, the epidemiology of CF pathogens continues to change. The pathogens of highest prevalence and incidence in 2012 were MSSA and *P aeruginosa*, followed by MRSA. The incidence and prevalence of *A xylosoxidans* and *B cepacia* complex were relatively low. From 2006 to 2012, the annual percent change in overall (as well as in most age strata) prevalence and incidence significantly decreased for *P aeruginosa* and *B cepacia* complex, but significantly increased for MRSA. Furthermore the prevalence of NTM and MAC increased from 2010 to 2012. Such data will be useful to evaluate the impact of newer therapies, including CF transmembrane conductance regulator (CFTR) correctors and potentiators, the effectiveness of the new infection prevention and control guideline,[23] and eradication strategies. For example, the first US Food and Drug Administration-approved CFTR corrector, ivacaftor, developed for individuals with CF harboring the G551D CFTR mutation, significantly reduced the prevalence of *P aeruginosa* culture positivity by 35% during the median 12.5 months of treatment.[41] Finally, evidence-based eradication guidelines for *P aeruginosa* have been published and promise to standardize the treatment of first acquisition of this pathogen.[42]

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