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Changing Epidemiology of the Respiratory Bacteriology of Patients with Cystic Fibrosis

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Abbreviations List

CA	community-acquired
CF	Cystic Fibrosis
CFF	Cystic Fibrosis Foundation
CFFPR	Cystic Fibrosis Foundation Patient Registry
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NTM	nontuberculous mycobacteria
spp.	species

ABSTRACT

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 CF Foundation Patient Registry (CFFPR) from 2006-2012 to determine the annual percent changes in the prevalence and incidence of selected CF pathogens. Pathogens included *P. aeruginosa*, methicillin-susceptible *S. aureus* (MSSA), MRSA, *Haemophilus influenzae*, *B. cepacia* complex, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*. Changes in nontuberculous mycobacteria (NTM) prevalence were assessed from 2010-2012 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 2006-2012, 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 2010-2012, the annual percent change in overall prevalence of NTM and *M. 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.

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Key Words
Cystic fibrosis, registry, *Pseudomonas aeruginosa, Staphylococcus aureus, Burkholderia,* MRSA, NTM

INTRODUCTION

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 *Burkholderia cenocepacia* to *Burkholderia multivorans* in both the U. S.[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 *M. abscessus.*[17,18] However, determining epidemiologic trends in CF microbiology can be challenging due to 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* spp. and NTM spp. 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.

METHODS

CF Foundation Patient Registry

The CFFPR is deployed throughout the CF Foundation accredited care center network as an 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 CF Foundation care center network have provided consent to allow data submission to CFFPR (Bruce C. Marshall, unpublished observations). 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]

CF Foundation 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 bronchoalveolar lavage (BAL). Since 2003, data entry guidelines request entry of all culture results into the CFFPR. Prior to 2010, positive *Burkholderia* cultures were reported as either as *B. cepacia* complex or 'other gram negative species'. Since 2010, data entry options for 19 different *Burkholderia* spp. have been available (e-Figure). Prior to 2010, NTM

positive cultures were recorded as 'nontuberculous mycobacteria'. Since 2010, *M. avium* complex, *M. abscessus*, *M. fortuitum* group*, M. gordonae, M. kansasii, M. marinum, M. terrae* and 'other' have been available.

Study Population

The study population included CF patients with at least one respiratory tract culture result in the CFFPR from January 2006 to 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 Institutional Review Board 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* spp. and for specific NTM spp. as incidence for these pathogens could not be determined due to the short surveillance period. NTM cultures from sputum, induced sputum or BAL from patients 12 years of age and older 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: 0-1, 2-5, 6-10, 11-17, 18-25 and 26 years of age and older.[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 31st of the relevant study year. All analyses were conducted using SAS version 9.3.

Our analyses were based on two assumptions. The first assumption was that to be an incident case a patient had been 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 2006-2012 for *P. aeruginosa*, MRSA, MSSA, *H. influenzae, B. cepacia* complex, *S. maltophilia,* and *A. xylosoxidans*.

RESULTS

Study population

During the study period, 33,653 unique patients had data reported to the CFFPR of whom 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 seven years of the study, while 8.7% were included for only one year. An increasing proportion of patients had 4 or more cultures per year reported in 2012 versus 2006 (48% vs. 35%, respectively, $p < 0.001$).

Age-specific prevalence and incidence rates of CF pathogens, 2012

In 2012, 25,530 (92%) of 27,804 patients had at least one culture recorded in the CFFPR of whom 12%, 15%, 21%, and 52% had 1, 2, 3, or 4 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 spp. (12.0%). The lowest prevalence rates were noted for *A. xylosoxidans* (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 (Figure 2A and 2B). For *P. aeruginosa*, the average annual percent change in incidence and prevalence significantly decreased in all age strata, except for a non-significant decrease in incidence among 18-25 year olds (Table 2). For MRSA, the annual incidence increased among 2-5, 11-17 and 18-25 year olds 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 2-5 year olds in whom incidence significantly decreased. For *H. influenzae*, prevalence remained stable in most strata, but decreased in 2-5 year olds 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 26 years and older. For *B. cepacia* complex, prevalence decreased in those 2-5, 11-17 and 26 years and older while incidence decreased in 2-5 year olds.

Changes in prevalence of *Burkholderia* and Nontuberculous mycobacteria spp., 2010-2012

The average annual percent change in prevalence of different *Burkholderia* spp. 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 ($p<0.001$). 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 spp. (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 U.S. 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 seven 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* spp. 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 of infection.[2] The proportion of patients identified by newborn screening increased during the study period from ~21.5% in 2006 to ~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 of patient-to-patient transmission of CF pathogens and acquisition from the natural and/or healthcare 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 care givers 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 non-CF individuals. Previously, MRSA infections were limited to specific risk groups such as hospitalized patients, dialysis patients, and nursing home residents. In the 1990's, community-onset infections among otherwise healthy individuals began to occur. While progress has been made to decrease hospital-associated infections caused by MRSA in non-CF patients during the past several years, community-associated MRSA infections have continued to increase.[26] Thus, it is likely that CF patients acquire MRSA in both healthcare and non-healthcare settings. Support for this can be

derived from molecular typing studies that have demonstrated that approximately 65% to 70% of CF patients harbor healthcare-associated clones and about one-third of CF patients harbor community-associated clones.[27-29] Furthermore, older CF patients are more likely to harbor hospital-associated clones suggesting acquisition prior to the widespread onset of community-associated MRSA.[30] Support for acquisition of MRSA in healthcare settings is provided by a recent 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 healthcare and community-associated infections in non-CF patients and most commonly causes respiratory tract infections.[34] *S. maltophilia* can be found in water sources in both healthcare and non-healthcare settings including sink drains, sponges, and faucets.[35] These observations suggest that, like MRSA, the epidemiology of *S. maltophilia* in individuals with CF is similar to that of individuals without CF.

Over the past two decades, the CF community has had increasing concern about infections with NTM due to 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 CF Foundation recommends at least annual screening for NTM[20], but as evidenced in this study, many patients are screened several times per year, presumably due to 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 period 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-Figure). A recent audit conducted by the CFF suggested relatively little missing data and few data entry errors. MRSA or *P. aeruginosa* cultures recorded in the electronic medical record (EMR) was missing in the CFFPR for 1.2% of CF clinic visits. Among 5,203 CF clinic visits with microbiology data reported in both the EMR 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 and A. Fink, unpublished observations). 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* spp. (J.J. LiPuma, unpublished observations). Among 341 isolates identified as "*A. xylosoxidans*", only 42% were confirmed as *A. xylosoxidans* while 24% were *A. ruhlandii* and 17% were *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* spp. 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 2006-2012 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 2010-2012. 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 FDA-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 12.5 months (median) of treatment.[41] Finally, evidence-based eradication guidelines for *P. aeruginosa* have recently been published and promise to standardize the treatment of first acquisition of this pathogen.[42]

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Table 1: Age-specific prevalence and incidence rates for CF Pathogens, 2012[1, 2]

Age Strata (years)	PA	MRSA	MSSA	HI	SM	AX	All BCC[3]	BC	BM	BG	All NTM[4]	MAC	MAB	Other NTM[5]
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														
Prevalence	22.02	11.74	51.42	21.54	12.63	1.38								
Incidence	21.04	9.60	45.41	19.19	12.22	1.38								
2-5														
Prevalence	21.35	17.18	58.50	32.46	9.05	1.85								
Incidence	15.89	8.04	33.92	15.52	6.40	1.58								
6-10														
Prevalence	29.75	26.21	63.22	26.53	12.76	4.15	1.37		0.34					
Incidence	12.22	8.48	31.00	11.39	6.39	2.18	0.59	-	-	-				
11-17														
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	
Incidence	13.15	7.88	26.21	4.15	6.86	2.70	0.73	-	-	-	5.52	-	-	
18-25														
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+														
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	-	-	-

[1] Abbreviations used in Table: PA – *Pseudomonas aeruginosa*, MRSA – methicillin-resistant *Staphylococcus aureus*, MSSA – methicillin-resistant *Staphylococcus aureus*, HI – *Haemophilus influenzae*, SM – *Stenotrophomonas maltophilia*, AX – *Achromobacter xylosoxidans*, All BCC – all *Burkholderia cepacia* complex, BC – *Burkholderia cenocepacia*, BM – *Bulkholderia multivorans*, Other BCC – Other *Burkholderia cepacia* complex, BG – *Burkholderia gladioli*, All NTM – all nontuberculous mycobacteria spp., MAC – *Mycobacterium avium* complex, MAB – *Mycobacterium abscessus*, Other NTM – Other nontuberculous mycobacteria spp.

[2] Data are not provided for gray cells as there are fewer than 10 patients contributing to the numerator. Patterned cells represent CF patients under 12 years of age without reliable mycobacteria cultures.

[3] All BCC includes: *B. cepacia*, *B. multivorans*, *B. cenocepacia*, *B. stabilis*, *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.*

[4] Only incidence for 'All NTM' could be determined.

[5] Other NTM includes: *Mycobacterium fortuitum* group, *Mycobacterium gordonae*, *Mycobacterium kansasii*, *Mycobacterium marinum*, and *Mycobacterium terrae*.

Table 2. Average Annual Percent Change in the Prevalence and Incidence of CF Pathogens by Age Strata, 2006-2012

Age Strata (years)	*Pseudomonas aeruginosa*		Methicillin-resistant *Staphylococcus aureus*		Methicillin-sensitive *Staphylococcus aureus*		*Haemophilus influenzae*		*Stenotrophomonas maltophilia*		*Achromobacter xylosoxidans*		*Burkholderia cepacia* complex[1]	
	% 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	<0.001	5.3	<0.001	0.1	0.276	-1.3	<0.001	1.4	<0.001	0.6	0.225	-2.6	<0.001
Incidence	-3.3	<0.001	2.3	<0.001	-1.2	<0.05	-3.8	<0.001	-0.2	0.784	-3.3	<0.001	-3.3	<0.05
0-1														
Prevalence	-4.3	<0.001	4.5	<0.05	0.5	0.419	-1.2	0.285	0.8	0.627	-4.3	0.418	12.5	0.459
Incidence	-4.6	<0.001	3.5	0.077	0.0	0.972	-1.8	0.117	-0.1	0.956	-4.3	0.416	12.5	0.459
2-5														
Prevalence	-3.3	<0.001	4.3	<0.001	-0.1	0.689	-1.3	<0.05	-0.6	0.594	-8.8	<0.05	-15.6	<0.05
Incidence	-2.9	<0.05	4.4	<0.05	-2.7	<0.05	-4.1	<0.001	-0.2	0.875	-9.4	0.002*	-12.3	<0.05
6-10														
Prevalence	-2.2	<0.001	5.1	<0.001	0.1	0.780	-0.9	0.100	-0.1	0.939	-2.8	0.102	0.2	0.956
Incidence	-3.7	<0.05	2.2	0.061	-1.6	0.200	-4.4	<0.05	0.2	0.908	-4.4	<0.05	-1.5	0.708
11-17														
Prevalence	-3.3	<0.001	5.3	<0.001	0.4	0.096	-0.1	0.931	2.6	<0.001	1.8	0.093	-6.4	<0.05
Incidence	-3.1	<0.05	2.2	<0.05	-1.0	0.509	-5.9	<0.05	0.2	0.870	1.2	0.498	-5.3	0.105
18-25														
Prevalence	-2.5	<0.001	6.5	<0.001	1.0	<0.05	-0.5	0.596	3.5	<0.001	1.7	0.091	-1.0	0.528
Incidence	-2.7	0.113	3.3	<0.05	2.0	0.244	-3.3	0.067	0.0	0.870	-2.7	0.144	1.7	0.572
26+														
Prevalence	-0.9	<0.001	5.8	<0.001	1.7	<0.001	0.8	0.470	1.6	<0.05	1.1	0.260	-3.4	<0.05
Incidence	-4.2	<0.05	1.3	0.281	-1.0	0.445	-2.0	0.228	-0.1	0.949	-4.2	<0.05	-5.8	0.114

[1] *Burkholderia cepacia* complex includes: *B. cepacia*, *B. multivorans*, *B. cenocepacia*, *B. stabilis*, *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*.

Table 3: Average Annual Percent Change in Prevalence of *Burkholderia* spp. by Age Strata, 2010-2012[1]

Age Strata (years)	All *Burkholderia* spp.[2]		*Burkholderia cenocepacia*		*Burkholderia multivorans*		*Burkholderia gladioli*	
	% change	P-value	% change	P-value	% change	P-value	% change	P-value
Overall	1.1	0.520	-8.2	0.132	0.7	0.865	0.0	0.996
0-1								
2-5	-41.4	0.094						
6-10	1.0	0.902			-11.4	0.530	-13.0	0.525
11-17	3.8	0.454	-1.2	0.932	6.7	0.463	-11.7	0.248
18-25	-0.3	0.927	-11.9	0.253	6.4	0.379	5.4	0.614
26+	0.6	0.819	-10.4	0.190	-8.9	0.170	4.4	0.512

[1] Data are not provided for gray cells as there are fewer than 10 patients contributing to the numerator

[2] *Burkholderia cepacia* spp. includes: *B. cepacia*, *B. multivorans*, *B. cenocepacia*, *B. stabilis*, *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*.

Table 4: Average Annual Percent Change in Prevalence of Nontuberculous *Mycobacteria* spp. by Age Strata, 2010-2012[1]

Age Strata (years)	All nontuberculous mycobacteria		*Mycobacterium avium* complex		*Mycobacterium abscessus*		Other nontuberculous mycobacteria[2]	
	% change	P-value	% change	P-value	% change	P-value	% change	P-value
Overall (12+)	3.9	<0.05	7.4	<0.05	-1.6	0.540	2.3	0.757
12-17	-1.1	0.782	3.0	0.605	-3.6	0.510	-26.8	0.184
18-25	6.7	<0.05	11.3	0.014	1.7	0.711	-1.0	0.934
26+	4.3	0.121	6.4	0.094	-3.0	0.493	12.2	0.273

[1] Average annual percent change in prevalence only reported for CF patients 12 years of age and older.

[2] Other nontuberculous mycobacteria includes: *Mycobacterium fortuitum* group, *Mycobacterium gordonae*, *Mycobacterium kansasii*, *Mycobacterium marinum*, and *Mycobacterium terrae*.

Figure 1. Flow diagram of eligible patients. Patients in CF Foundation Patient Registry eligible for current study and number of years of participation.

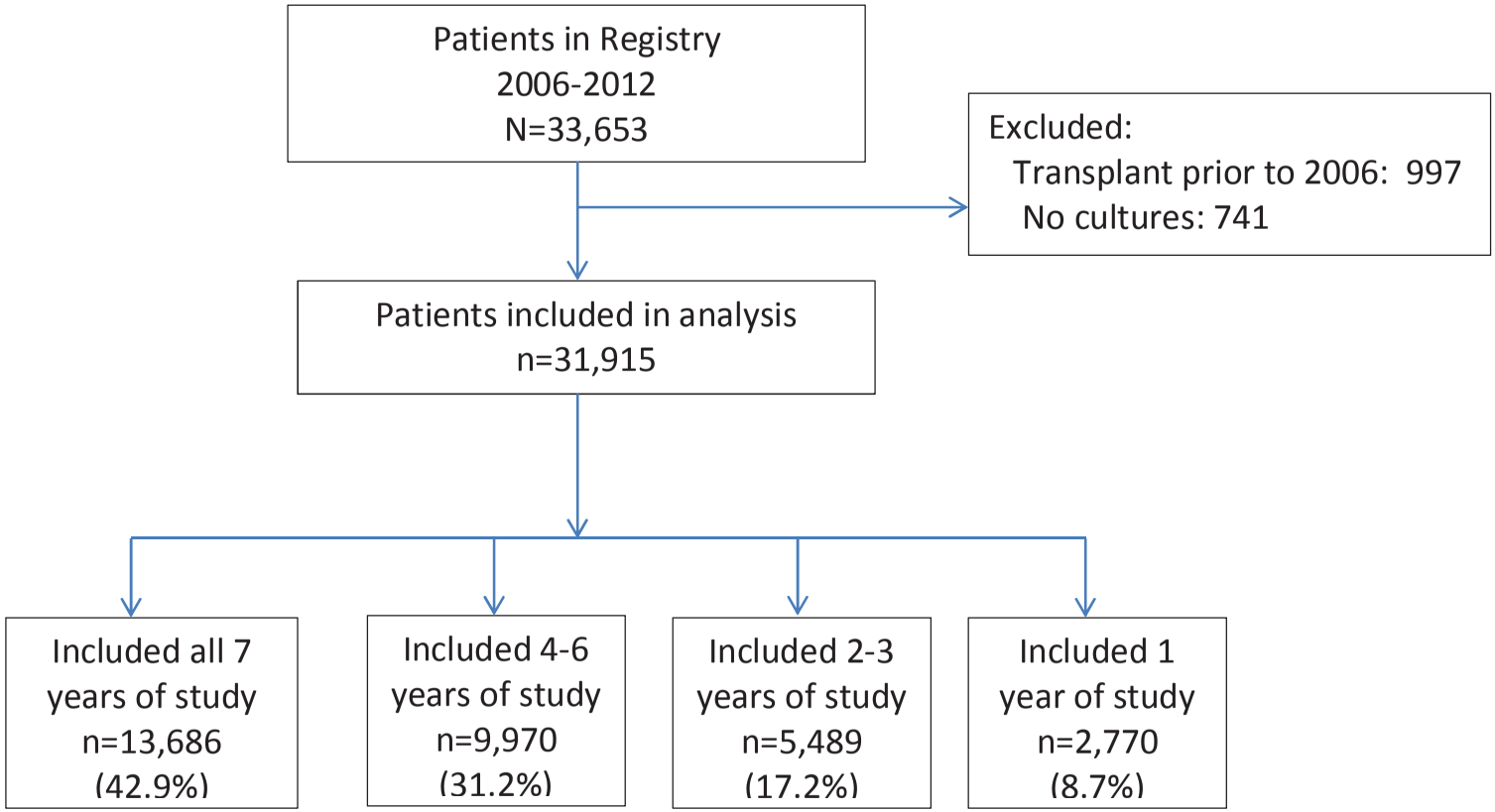
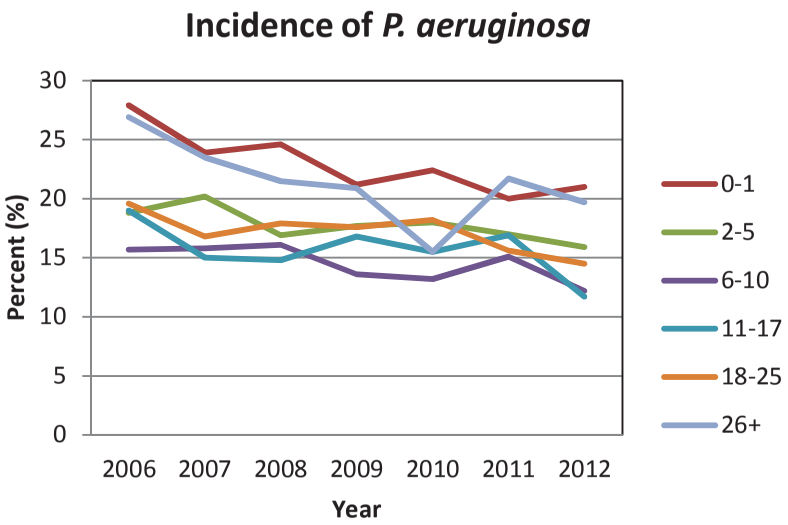
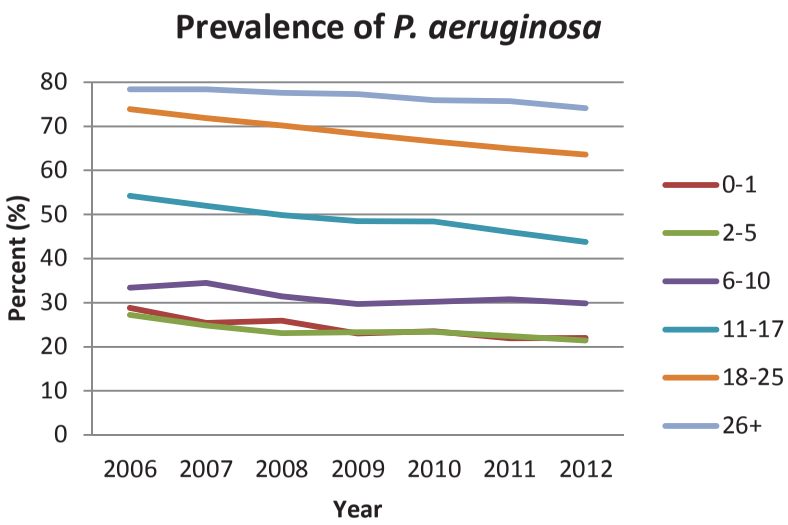


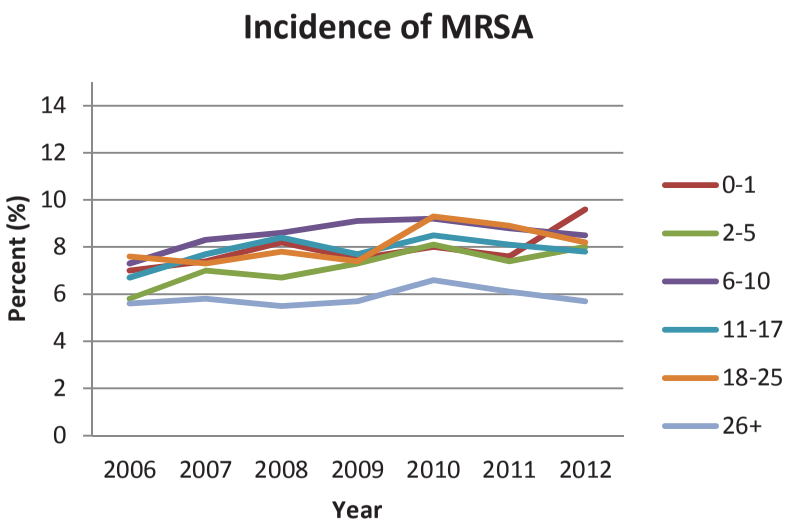
Figure 2.

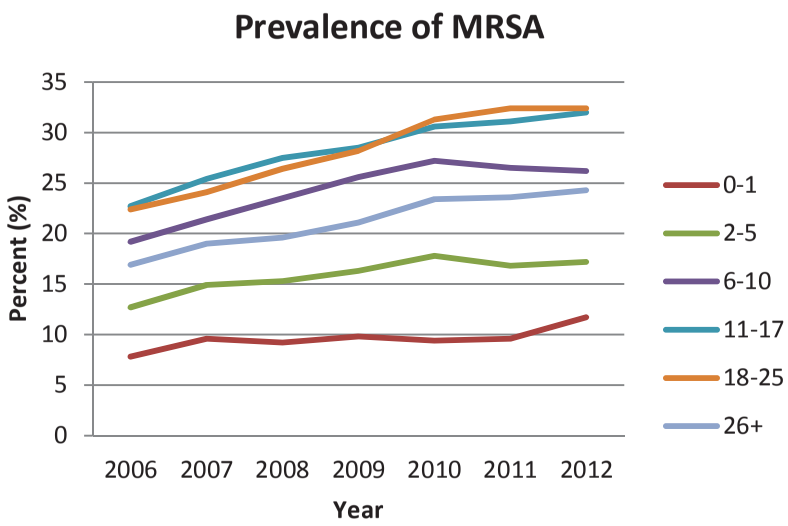
A. Overall Incidence and Prevalence of *Pseudomonas aeruginosa* in patients with CF from 2006 to 2012. The overall incidence and prevalence of *Pseudomonas aeruginosa* among patients with CF is shown by age strata.





B. Overall Incidence and Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with CF from 2006 to 2012. The overall incidence and prevalence of MRSA among patients with CF is shown by age strata. These data reflect an analysis of the United States Cystic Fibrosis Foundation Patient Registry.





eTable 1: Sensitivity Analysis 1: Annual Incidence of CF Pathogens by 10-, 5-, and 2-year Look-back Intervals, 2006-2012[1]

Year	Look-back Interval (years)	*P. aeruginosa*	MRSA	MSSA	*H. influenzae*	*S. maltophilia*	*A. xylosoxidans*	*B. cepacia* complex[2]
2006	10	20.58	6.65	29.63	9.71	6.43	2.60	0.68
	5	20.88	6.70	27.08	8.99	6.55	2.67	0.68
	2	23.57	7.22	27.21	10.19	7.17	2.94	0.84
2007	10	19.11	7.22	28.84	9.11	6.45	2.33	0.71
	5	20.52	7.29	25.70	8.55	6.55	2.39	0.73
	2	23.64	7.87	26.30	9.74	7.15	2.67	0.81
2008	10	18.58	7.41	28.89	8.72	6.27	2.39	0.60
	5	19.95	7.44	25.62	8.45	6.32	2.47	0.65
	2	22.52	8.01	25.78	9.50	6.93	2.76	0.77
2009	10	17.88	7.34	27.85	8.09	6.09	1.971	0.65
	5	18.19	7.44	24.67	7.82	6.26	2.03	0.70
	2	20.43	8.21	25.81	8.95	7.11	2.37	0.78
2010	10	17.55	8.21	28.17	8.91	6.71	2.10	0.51
	5	18.19	8.40	24.75	8.48	6.93	2.20	0.53
	2	20.92	9.11	26.19	9.55	7.84	2.48	0.63
2011	10	17.76	7.73	27.67	8.06	6.49	2.10	0.58
	5	18.48	7.92	24.57	7.88	6.78	2.18	0.60
	2	20.67	8.64	25.35	9.13	7.59	2.50	0.70
2012	10	16.20	7.67	27.51	7.35	6.16	2.13	0.60
	5	16.63	7.81	25.05	7.12	6.40	2.20	0.61
	2	19.01	8.66	25.89	8.16	7.13	2.46	0.70

[1]Abbreviations used in Table: MRSA – methicillin-resistant *Staphylococcus aureus*, MSSA – methicillin-resistant *Staphylococcus aureus*

[2] *B. cepacia* complex includes: *B. cepacia*, *B. multivorans*, *B. cenocepacia*, *B. stabilis*, *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* and excludes *B. gladioli* and *B. pseudomallei*

eTable 2. Sensitivity Analysis 1: Annual Percent Change in Incidence of CF Pathogens Comparing 10-, 5-, and 2-year Look-Back Intervals, 2006-2012[1]

Look-back interval (years)	*P. aeruginosa*		MRSA		MSSA		*H. influenzae*		*S. maltophilia*		*A. xylosoxidans*		*B. cepacia* complex[2]	
	% change	P-value[3]	% change	% change	% change	% change	% change	P-value	% change	P-value	% change	P-value	% change	P-value
10	-3.3	<0.001	2.3	<0.001	-1.2	<0.05	-3.8	<0.001	-0.2	0.784	-3.3	<0.001	-3.3	<0.05
5	-3.5	<0.001	2.6	<0.001	-1.2	<0.05	-3.0	<0.001	0.4	0.513	-3.1	<0.001	-3.1	<0.05
2	-3.5	<0.001	3.0	<0.001	-0.7	<0.05	-2.8	<0.001	0.8	0.087	-2.8	<0.001	-3.6	<0.05

[1] Abbreviations used in Table: MRSA – methicillin-resistant *Staphylococcus aureus*, MSSA – methicillin-resistant *Staphylococcus aureus*

[2] *B. cepacia* complex includes: *B. cepacia*, *B. multivorans*, *B. cenocepacia*, *B. stabilis*, *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* and excludes *B. gladioli* and *B. pseudomallei*

[3] The p-values reported in this table demonstrate similar annual percent changes in incidence when comparing the 10 year look-back interval with the 5 and 2 year look-back intervals.

eTable 3. Sensitivity Analysis 2: Annual Percent Change in Prevalence and Incidence of CF Pathogens Comparing One vs. Two Positive Cultures per Year, 2006-2012[1]

Number of positive cultures	*P. aeruginosa*		MRSA		MSSA		*H. influenzae*		*S. maltophilia*		*A. xylosoxidans*		*B. cepacia* complex[2]	
	% change	P-value	% change	P-value	% change	P-value	% change	P-value	% change	P-value	% change	P-value	% change	P-value
One culture														
Prevalence	-1.7	<0.001	5.3	<0.001	0.1	0.276	-1.3	<0.001	1.4	<0.001	0.6	0.225	-2.6	<0.001
Incidence	-3.3	<0.001	2.3	<0.001	-1.2	<0.05	-3.8	<0.001	-0.2	0.784	-3.3	<0.001	-3.3	<0.05
Two cultures														
Prevalence	-1.8	<0.001	4.6	<0.001	-0.1	0.297	-1.9	<0.001	0.7	<0.05	-0.2	0.632	-3.5	<0.001
Incidence	-3.9	<0.001	1.8	<0.05	-1.7	<0.001	-4.5	<0.001	-0.8	0.185	-4.1	<0.001	-4.2	<0.05

[1] Abbreviations used in Table: MRSA – methicillin-resistant *Staphylococcus aureus*, MSSA – methicillin-resistant *Staphylococcus aureus*

[2] *B. cepacia* complex includes: *B. cepacia*, *B. multivorans*, *B. cenocepacia*, *B. stabilis*, *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* and excludes *B. gladioli* and *B. pseudomallei*

eFigure 1: CF Foundation Patient Registry, Data Collection Form, implemented 2010

Respiratory Microbiology

Bacterial Culture

Bacterial culture done? ☐

Date of Culture: (MM/DD/YYYY)

Type of Specimen:

○sputum ○ induced sputum

○throat/nasal ○bronchoscopy

Culture Results:

○Microorganisms ○Normal flora

○No growth/sterile culture

Staphylococcus aureus: ☐

○ MRSA (methicillin resistant Staph aureus)

○MSSA (methicillin sensitive Staph aureus)

Haemophilius influenzae (any species): ☐

Pseudomonas aeruginosa: ☐

☐mucoid ☐ non mucoid ☐mucoid status unknown

Susceptibility Testing*(Please use the most resistant PA strain. If multiple PA strains are resistant to the same number of classes of antibiotics then use the following schema: Beta lactams> Quinolones>Aminoglycosides).*

Resistant to All Aminoglycosides Tested (e.g., tobramycin, gentamicin, amikacin):

○Yes ○No ○Testing not done

Resistant to All Quinolones Tested (e.g., ciprofloxacin, levofloxacin, moxifloxacin):

○Yes ○No ○Testing not done

Resistant to All Beta Lactams Tested (e.g., ceftazidime, imipenem, meropenem, piperacillin/tazobactam (Zosyn), ticarcillin/clavulanic acid (Timentin), aztreonam):

○Yes ○No ○Testing not done

Burkholderia species: ☐

☐ B. gladioli

☐ B. cenocepacia

☐ B. multivorans

☐ Burkholderia– other

☐ B. cepacia ☐ B. stabilis ☐ B. vietnamiensis

☐ B. dolosa ☐ B. anthina ☐ B. ambifaria

☐ B. pyrrocinia ☐ B. ubonensis ☐ B. arboris

☐ B. latens ☐ B. lata ☐ B. metallica

☐ B. seminalis ☐ B. contaminans

☐ B. diffusa ☐ B. pseudomallei

Was the identification of the Burkholderia species confirmed at the CFF reference lab? ○Yes ○No ○Unknown

Other microorganisms:

☐ Alcaligenes (Achromobacter) xylosoxidans

☐ Stenotrophomonas (Xanthomonas)/Maltophilia

☐Other types:

☐ Acinetobacterbaumannii ☐Acinetobacter species -other*

☐ Agrobacterium species ☐Bordetella species

☐Brevundimonas species

☐Chryseobacterium species

☐Cupriadidusmetallidurans

☐Cupriaviduspauculus

☐Cupriavidusrespiraculi

☐Delftiaacidivordans

☐Delftia species - other* ☐Enterobacter species

☐Exophiliadermatitidis

☐Herbaspirillumfrisingense

☐Herbaspirillumseropedicae

☐Inquilinuslimosus

☐Klebsiellapneumoniae ☐Klebsiella species - other*

☐Ochrobacterum species

☐Pandoraeaapista

☐Pandoraeanorimbergensis

☐Pandoraeapulmonicola

☐Pandoraeasputorum ☐Pandoraea species - other*

☐ Pseudomonas mendocina

☐ Pseudomonas pseudoalcaligenes

☐ Pseudomonas putida ☐ Pseudomonas stutzeri

☐ Pseudomonas species - other*

☐Ralstoniainsidiosa

☐Ralstoniapickettii

☐Ralstonia species - other*

☐Serratiamarcescens

☐ Streptococcus milleri

Fungal/Yeast:

☐ Aspergillus (any species) ☐ Candida (any species)

☐ Scedosporium species

Other bacterial or fungal species:☐

Specify: _____

Mycobacterial culture