1 **Supplemental Text**

2 **Detailed Statistical Analysis**

3 We calculated summary statistics for patients observed in each calendar year (2003-2011). We calculated

4 weight-for-age z-scores as done previously (1). We normalized forced expiratory volume in one second (FEV_1)

5 to percent predicted FEV_1 ($FEV_1\%$) using National Health and Nutrition Evaluation Survey (NHANES) III (2)

6 and Global Lung Initiative equations (3). We tabulated the prevalence for each of the studied infections for each

7 calendar year (2003-2011) and used univariable logistic regression (4) to evaluate associations between every

8 pair of infections to understand the extent of cross correlation during each year of the study. We repeated the

9 evaluation of between-organism associations by using multivariable logistic regression models of every

10 organism for each other organism adjusted by clinical variables including age, sex, late diagnosis of cystic

11 fibrosis (CF), $FEV_1\%$, number of acute pulmonary exacerbations (APE), pancreatic sufficiency and diabetes

12 statuses, and nutritional status using weight-for-age z-scores for each calendar year of the study. We examined

13 late diagnosis of CF in two ways, by including an adjustment for either the actual age at the time of diagnosis or

14 as a binary variable for diagnosis before or after the age of 6 months.

15   To examine relationships between culture results from any one year t to the respective next calendar year,

16 $t+1$, we pursued a strategy of building increasingly complex models. In our earliest efforts, we created and

17 inspected two by two tables of each organism showing absence or presence in every possible two consecutive

18 year period during 2003-2011. For selected pairs of organisms, for example methicillin-sensitive

19 *Staphylococcus aureus* (MSSA) and *Pseudomonas aeruginosa,* we created and inspected four by four tables for

20 the four combinations of absence or presence of each organism for each two consecutive year period.

21   For each year of the study period (2003-2011), we examined cross-sectional associations by fitting

22 univariable logistic regression models for each of the eight studied organisms with the remaining 7 organisms.

23 Based on the 504 resulting models, we performed multivariable models for each of the eight organisms for each

24 year adjusted for the presence of the 6 remaining organisms and repeated multivariable models with additional

25 adjustments for variables for clinical characteristics. Because we adjusted for age of CF diagnosis in two ways,

26 using actual age at diagnosis or diagnosis before or after age 6 months, we fitted an additional 1,512 models. We

27 inspected the results selectively and graphically as illustrated, in part, by Figure S1.

28   For each period of two consecutive years, designated as year *t* (years 2003-2010) and year *t+1* (2004-

29 2011)*,* we fitted 64 multivariable logistic regression models to examine the presence of each of the eight studied

30 infections in year *t+1* as the dependent variables using the presence of all eight studied organisms in year *t* as

31 explanatory variables. After inspection of these models, we adjusted each model using clinical covariates from

32 each year *t* and compared the coefficients with the respective unadjusted multivariable models. Because we

33 adjusted for age of CF diagnosis in two ways, using actual age at diagnosis or diagnosis before or after age 6

34 months, we fitted an additional 1,152 models. After evaluation of these models by selective comparison of

35 specific cells from extensive tables, as shown in part by Tables S3-S4 and graphically as shown in part by main

36 text Figures 2 and 3, we used generalized estimating equations to fit generalized linear regression models

37 (GEEGLM) using an independence working correlation matrix (5, 6) to take into account multiple observations

38 per individual in order to use the data set as a whole as shown in main text Figure 4 and Figures S2 and S3,

39 generating an additional 32 models.

40   We compared results with GEEGLM using an auto-regressive correlation matrix because of the nature of

41 data collection over time. We proceeded to build candidate multivariable models of each cultured organism in

42 year *t+1* with all eight organisms in year *t* as independent covariates and incrementally adjusted for other

43 clinical variables measured in year *t*, generating an additional 32 models. Clinical variables included age, sex,

44 late diagnosis of CF, best $FEV_1\%$ in each year, annual number of APE, pancreatic sufficiency and diabetes

45 status and weight-for-age *z*-score in year *t*. We used the age and the weight-for-age *z*-score on the date of the

46 best $FEV_1\%$ during each year *t*. We defined patients as pancreatic sufficient if they were noted to be sufficient

47 for all encounters during a year, and we defined patients as diabetic if the condition was present at any time

48 during year *t*. Results of GEEGLM modeling using both independence and auto-regressive working correlations

49 matrices were compared graphically (not shown).

50   To better understand the sensitivity of our multivariable models of each organism in year $t+1$ to

51   antimicrobial or other pulmonary treatments, we examined the effect of adding each covariable, how it changed

52   the model coefficients for organism interaction and clinical variable adjustment. We tested oral azithromycin,

53   inhaled aztreonam, recombinant human DNase (DNase), hypertonic saline, and tobramycin and days per year of

54   therapy with home intravenous (IV) antibiotics and hospitalization days for pulmonary exacerbation treatment

55   in year t. We used a single forward selection step with each treatment. Over an extended period, we selectively

56   examined changes in maximum likelihood for all other covariable coefficients for the resulting 21,824 models.

57   We examined changes in effects related to studied organisms graphically by adding additional clusters of forest

58   plots in a manner similar to main text Figures 2, 3 and 4 and Figure S1 to extensive additional figures that are

59   not shown.

60   The CFFPR does not identify the specific IV antibiotics used during home IV antibiotic or

61   hospitalization days and does not present reasoning or details of matching of specific antibiotics to organisms or

62   their antibiotic resistance patterns precluding more specific analyses. We included a consideration of lung

63   transplantation as a treatment by comparing additional GEEGLM models using data from patients without or

64   prior to lung transplantation compared to models using data obtained post-lung transplantation. Finally, we

65   examined the extent and patterns of missingness among the bacterial infection variables and patients due to

66   differences in age, sex, pancreatic sufficiency and diabetes statuses, weight for age z-score, FEV_1%, or APE (1).

67   We assessed and compared clinical characteristics between included and excluded patient using t and χ^2 tests.

68   All analyses were performed using the R statistical system (7).

69 Supplemental Text References

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Supplemental Tables

70 **Table S1. Selected Characteristics of Pediatric Study Patients**

Patient Characteristics	Year								
	2003	2004	2005	2006	2007	2008	2009	2010	2011
n	8735	8965	9067	9055	9278	9283	9378	9354	9414
Number of cultures[a]	24363 (0.982)	27156 (0.997)	29785 (0.999)	31507 (0.999)	34177 (1.000)	35386 (1.000)	36622 (0.999)	36886 (0.999)	38259 (1.000)
Cultures per Patient[b]	2 (1 - 4)	3 (2 - 4)	3 (2 - 4)	3 (2 - 4)	3 (2 - 5)	4 (3 - 5)	4 (3 - 5)	4 (3 - 5)	4 (3 - 5)
Age[b]	12.0 (9.02 - 14.9)	12.1 (9.09 - 15.0)	12.2 (9.06 - 15.0)	12.2 (9.16 - 15.1)	12.1 (9.13 - 15.1)	12.2 (9.09 - 15.2)	12.2 (9.05 - 15.2)	12.2 (9.12 - 15.1)	12.2 (9.15 - 15.1)
Female[b]	4211 (48.2)	4302 (48.0)	4350 (48.0)	4355 (48.1)	4523 (48.7)	4580 (49.3)	4660 (49.7)	4661 (49.8)	4679 (49.7)
Pancreatic Sufficiency[b]	378 (4.33)	449 (5.01)	432 (4.77)	491 (5.42)	530 (5.71)	610 (6.57)	669 (7.13)	848 (9.07)	818 (8.69)
Diabetes[b]	370 (4.24)	387 (4.32)	460 (5.07)	547 (6.04)	598 (6.45)	671 (7.23)	681 (7.26)	702 (7.50)	781 (8.30)
FEV_1%[b,c]	91.0 (76.6 - 104)	91.5 (77.7 - 104)	92.4 (78.6 - 105)	92.7 (79.3 - 105)	93.9 (80.0 - 105)	94.5 (81.1 - 106)	94.5 (81.4 - 107)	95.4 (82.5 - 107)	95.4 (82.4 - 107)
Acute Pulmonary Exacerbations[b]	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)	0 (0 - 1)
Weight-for-Age *z*-score[b]	-0.58 (-1.25 - 0.12)	-0.54 (-1.22 - 0.15)	-0.51 (-1.19 - 0.16)	-0.48 (-1.14 - 0.18)	-0.45 (-1.12 - 0.21)	-0.40 (-1.07 - 0.24)	-0.38 (-1.05 - 0.25)	-0.35 (-1.04 - 0.28)	-0.32 (-1.02 - 0.30)
MSSA[c,d]	5191 (59.4)	5418 (60.4)	5496 (60.6)	5411 (59.8)	5623 (60.6)	5577 (60.1)	5628 (60.0)	5604 (59.9)	5636 (59.9)
P aeruginosa[d]	4565 (52.3)	4622 (51.6)	4498 (49.6)	4280 (47.3)	4291 (46.2)	4063 (43.8)	3978 (42.4)	3967 (42.4)	3843 (40.8)
MRSA[c,d]	1145 (13.1)	1440 (16.1)	1763 (19.4)	1961 (21.7)	2221 (23.9)	2418 (26.0)	2599 (27.7)	2744 (29.3)	2788 (29.6)
B cepacia Complex[d]	224 (2.56)	224 (2.50)	224 (2.47)	224 (2.47)	227 (2.45)	204 (2.20)	209 (2.23)	219 (2.34)	236 (2.51)
S maltophilia[d]	1189 (13.6)	1314 (14.7)	1397 (15.4)	1391 (15.4)	1443 (15.6)	1421 (15.3)	1485 (15.8)	1603 (17.1)	1638 (17.4)
A xylosoxidans[d]	517 (5.92)	534 (5.96)	562 (6.20)	570 (6.29)	560 (6.04)	622 (6.70)	582 (6.21)	603 (6.45)	610 (6.48)
Candida species[d]	719 (8.23)	681 (7.60)	800 (8.82)	727 (8.03)	709 (7.64)	775 (8.35)	687 (7.33)	1233 (13.2)	1355 (14.4)
Aspergillus species[d]	1163 (13.3)	1312 (14.6)	1326 (14.6)	1355 (15.0)	1366 (14.7)	1369 (14.7)	1355 (14.4)	1406 (15.0)	1440 (15.3)

[a] Number (fraction of study participants with usable culture data)

[b] Median (1st and 3rd quartiles)

[c] FEV_1%: Percent predicted forced expiratory volume in 1 second; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *S aureus*

[d] Number of patients infected (percent of enrolled patients)

71 **Table S2: Selected Characteristics of Adult Study Patients**

Patient Characteristics	Year								
	2003	2004	2005	2006	2007	2008	2009	2010	2011
n	6891	7463	7866	8428	9027	9503	10006	10464	11120
Number of cultures[a]	18119 (0.988)	20220 (0.994)	21965 (0.997)	24361 (0.997)	27215 (0.998)	29880 (0.998)	31623 (0.998)	33360 (0.998)	36150 (1.000)
Cultures per Patient[b]	2 (1 - 3)	2 (1 - 4)	2 (1 - 4)	2 (1 - 4)	3 (2 - 4)	3 (2 - 4)	3 (2 - 4)	3 (2 - 4)	3 (2 - 4)
Age[b]	25.6 (21.0 - 33.5)	25.7 (21.1 - 33.9)	25.7 (21.1 - 34.1)	25.8 (21.3 - 34.2)	26.0 (21.4 - 34.4)	26.2 (21.5 - 34.5)	26.6 (21.8 - 34.8)	26.7 (21.8 - 35.1)	27.0 (21.9 - 35.3)
Female[b]	3235 (46.9)	3509 (47.0)	3700 (47.0)	3964 (47.0)	4241 (47.0)	4480 (47.1)	4733 (47.3)	4957 (47.4)	5270 (47.4)
Pancreatic Sufficiency[b]	640 (9.32)	749 (10.1)	757 (9.64)	874 (10.4)	927 (10.3)	1044 (11.0)	1161 (11.6)	1571 (15.0)	1482 (13.3)
Diabetes[b]	1133 (16.4)	1357 (18.2)	1459 (18.5)	1863 (22.1)	2066 (22.9)	2174 (22.9)	2341 (23.4)	2568 (24.5)	2820 (25.4)
$FEV_1\%$[b,c]	62.5 (43.4 - 81.8)	63.6 (44.3 - 83.2)	64.8 (45.4 - 83.8)	66.1 (46.3 - 85.0)	66.9 (46.4 - 85.4)	67.2 (47.3 - 86.0)	68.0 (47.9 - 86.8)	68.9 (48.4 - 87.1)	69.1 (49.0 - 87.40)
Acute Pulmonary Exacerbations[b]	0 (0 - 1)	1 (0 - 1)	0 (0 - 1)	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)	0 (0 - 2)	0 (0 - 1)	0 (0 - 1)
Weight-for-Age z-score[b]	-0.43 (-1.19 - 0.25)	-0.38 (-1.16 - 0.28)	-0.37 (-1.14 - 0.28)	-0.32 (-1.10 - 0.33)	-0.28 (-1.09 - 0.34)	-0.25 (-1.04 - 0.37)	-0.20 (-1.03 - 0.41)	-0.19 (-1.04 - 0.41)	-0.19 (-1.04 - 0.41)
MSSA[c,d]	2661 (38.6)	2874 (38.5)	3001 (38.2)	3293 (39.1)	3517 (39.0)	3722 (39.2)	3946 (39.4)	4155 (39.7)	4468 (40.2)
P aeruginosa[d]	5404 (78.4)	5847 (78.3)	6158 (78.3)	6449 (76.5)	6809 (75.4)	7060 (74.3)	7345 (73.4)	7515 (71.8)	7924 (71.3)
MRSA[c,d]	889 (12.9)	1202 (16.1)	1392 (17.7)	1627 (19.3)	1929 (21.4)	2158 (22.7)	2406 (24.0)	2770 (26.5)	3013 (27.1)
B cepacia Complex[d]	360 (5.22)	356 (4.77)	398 (5.06)	383 (4.54)	395 (4.38)	414 (4.36)	410 (4.10)	478 (4.57)	520 (4.68)
S maltophilia[d]	679 (9.85)	750 (10.0)	846 (10.8)	929 (11.0)	997 (11.0)	1036 (10.9)	1131 (11.3)	1278 (12.2)	1372 (12.3)
A xylosoxidans[d]	511 (7.42)	561 (7.52)	604 (7.68)	670 (7.95)	676 (7.49)	733 (7.71)	761 (7.61)	865 (8.27)	891 (8.01)
Candida species[d]	576 (8.36)	496 (6.65)	565 (7.18)	643 (7.63)	682 (7.56)	834 (8.78)	974 (9.73)	1896 (18.1)	2204 (19.8)
Aspergillus species[d]	1295 (18.8)	1365 (18.3)	1398 (17.8)	1558 (18.5)	1630 (18.1)	1821 (19.2)	1786 (17.8)	2003 (19.1)	2238 (20.1)

[a] Number (fraction of study participants with usable culture data)

[b] Median (1st and 3rd quartiles)

[c] $FEV_1\%$: Percent predicted forced expiratory volume in 1 second; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *S aureus*

[d] Number of patients infected (percent of enrolled patients)

72 **Table S3. Estimated Odds Ratios (standard error, *p* value) from GEEGLM Models using an**
73 **Independence Correlation Matrix for Organisms in Year *t* Adjusted for the Remaining 6 Organisms in**
74 **Each Year *t*.**

Organism Cultured in Year *t+1*	Organisms Cultured in Year *t*[a]							
	MSSA[b]	*P aeruginosa*	MRSA[b]	*B cepacia* Complex	*S maltophilia*	*A xylosoxidans*	*Candida* Species	*Aspergillus* Species
MSSA[b]	**2.28 (0.0172, <0.001)**	**-0.764 (0.0147, <0.001)**	**-0.467 (0.0172, <0.001)**	**-0.329 (0.0397, <0.001)**	0.0506 (0.0205, 0.0134)	**-0.109 (0.0271, <0.001)**	**-0.106 (0.0241, <0.001)**	-0.033 (0.0189, 0.0806)
P aeruginosa	**-0.568 (0.0155, <0.001)**	**3.01 (0.0207, <0.001)**	**-0.19 (0.019, <0.001)**	**-0.539 (0.043, <0.001)**	**-0.142 (0.0235, <0.001)**	**-0.148 (0.0305, <0.001)**	**0.0973 (0.0271, <0.001)**	**0.209 (0.0218, <0.001)**
MRSA[b]	**-0.0903 (0.0185, <0.001)**	0.0104 (0.0195, 0.594)	**3.81 (0.0245, <0.001)**	**-0.214 (0.0541, <0.001)**	**0.097 (0.0263, <0.001)**	0.0406 (0.0345, 0.239)	-0.0116 (0.0314, 0.711)	-0.00269 (0.0246, 0.913)
B cepacia Complex	-0.0672 (0.0447, 0.133)	**-0.369 (0.0455, <0.001)**	-0.101 (0.0549, 0.0645)	**5.79 (0.0626, <0.001)**	-0.0586 (0.0714, 0.412)	**-0.344 (0.103, <0.001)**	0.131 (0.0693, 0.0581)	-0.103 (0.0658, 0.119)
S maltophilia	**0.138 (0.02, <0.001)**	**-0.236 (0.0201, <0.001)**	0.0448 (0.0231, 0.0521)	**-0.328 (0.0553, <0.001)**	**2.5 (0.025, <0.001)**	-0.0125 (0.0345, 0.717)	**0.175 (0.0303, <0.001)**	**0.441 (0.0228, <0.001)**
A xylosoxidans	0.00616 (0.0277, 0.824)	-0.0526 (0.0289, 0.0681)	0.0365 (0.0331, 0.27)	**-0.43 (0.0874, <0.001)**	0.102 (0.0381, 0.00749)	**3.8 (0.0375, <0.001)**	0.0505 (0.0435, 0.246)	**0.189 (0.0345, <0.001)**
Candida Species	**-0.0824 (0.0212, <0.001)**	**0.157 (0.0223, <0.001)**	**0.135 (0.0245, <0.001)**	**0.191 (0.0559, <0.001)**	**0.174 (0.0281, <0.001)**	**0.175 (0.0364, <0.001)**	**2.49 (0.0263, <0.001)**	**0.0959 (0.0261, <0.001)**
Aspergillus Species	0.0488 (0.0179, 0.00646)	**0.243 (0.0191, <0.001)**	**0.0864 (0.0209, <0.001)**	**-0.225 (0.0511, <0.001)**	**0.484 (0.0225, <0.001)**	**0.157 (0.0316, <0.001)**	**0.178 (0.0272, <0.001)**	**2.23 (0.0224, <0.001)**

[a] **Bold** characters show strong statistical associations ($p < 0.01$), plain shows weaker associations ($0.01 \leq p < 0.05$), gray shows non-significant associations. Each cell in the table gives the effect estimate for each variable in year *t* (standard error, *p* value). Intercepts are not shown.

[b] MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *S aureus*

Table S4. Estimated Odds Ratios (standard error, *p* value) from Multivariable GEEGLM Model using an Independence Correlation Matrix for Organisms in Year *t* Adjusted for Other Organisms and Clinical Variables in Year *t*.

Organism Cultured in Year *t+1*	Organisms Cultured in Year *t*[a]							
	MSSA[b]	*P aeruginosa*	MRSA[b]	*B cepacia* Complex	*S maltophilia*	*A xylosoxidans*	*Candida* Species	*Aspergillus* Species
MSSA[b]	**2.21 (0.0174, <0.001)**	**-0.565 (0.0158, <0.001)**	**-0.449 (0.0179, <0.001)**	**-0.144 (0.0401, <0.001)**	**0.0567 (0.0208, 0.0065)**	0.00292 (0.0279, 0.917)	-0.0495 (0.0246, 0.0444)	0.0436 (0.0195, 0.0256)
P aeruginosa	**-0.436 (0.0164, <0.001)**	**2.79 (0.0214, <0.001)**	**-0.255 (0.0204, <0.001)**	**-0.891 (0.0457, <0.001)**	**-0.175 (0.0243, <0.001)**	**-0.369 (0.0322, <0.001)**	0.0327 (0.0281, 0.245)	**0.102 (0.0229, <0.001)**
MRSA[b]	**-0.11 (0.0191, <0.001)**	-0.00814 (0.0211, 0.7)	**3.76 (0.0247, <0.001)**	**-0.264 (0.0548, <0.001)**	0.0621 (0.0267, 0.0201)	-0.0119 (0.0352, 0.735)	-0.0379 (0.032, 0.236)	-0.0206 (0.0253, 0.416)
B cepacia Complex	0.042 (0.0462, 0.364)	**-0.569 (0.0494, <0.001)**	**-0.155 (0.0567, 0.00622)**	**5.63 (0.0624, <0.001)**	-0.0748 (0.0705, 0.289)	**-0.48 (0.101, <0.001)**	0.0513 (0.0701, 0.464)	-0.142 (0.0645, 0.0276)
S maltophilia	**0.091 (0.0204, <0.001)**	**-0.256 (0.0222, <0.001)**	-0.0291 (0.0237, 0.218)	**-0.367 (0.0565, <0.001)**	**2.45 (0.0253, <0.001)**	**-0.0691 (0.0354, 0.051)**	**0.125 (0.0309, <0.001)**	**0.395 (0.0234, <0.001)**
A xylosoxidans	0.0479 (0.0286, 0.0943)	**-0.216 (0.0311, <0.001)**	-0.06 (0.0338, 0.0761)	**-0.599 (0.087, <0.001)**	0.0723 (0.0384, 0.0593)	**3.69 (0.0372, <0.001)**	-0.0321 (0.0442, 0.468)	**0.122 (0.0352, <0.001)**
Candida Species	-0.0511 (0.0218, 0.019)	0.034 (0.0241, 0.158)	**0.0808 (0.0251, 0.0013)**	0.0593 (0.0555, 0.286)	**0.139 (0.0286, <0.001)**	0.0762 (0.0366, 0.0373)	**2.45 (0.0271, <0.001)**	0.0277 (0.0267, 0.3)
Aspergillus Species	**0.0554 (0.0185, 0.00271)**	**0.144 (0.0204, <0.001)**	0.0304 (0.0213, 0.154)	**-0.317 (0.0526, <0.001)**	**0.44 (0.0229, <0.001)**	0.0774 (0.0319, 0.0152)	**0.114 (0.0278, <0.001)**	**2.16 (0.0226, <0.001)**

[a] **Bold** characters show strong statistical associations ($p < 0.01$), plain shows weaker associations ($0.01 \leq p < 0.05$), gray shows non-significant associations. Each cell in the table gives the effect estimate for each variable in year *t* (standard error, *p* value). Intercepts are not shown.

[b] MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *S aureus*

Table S4 (Continued). Odds Ratios (standard error, *p* value) for Adjustment Variables in Year *t* for associations with organisms in Year *t+1* from Multivariable GEEGLM Model using an Independence Correlation Matrix for Organisms in Year *t* shown just above.

Organism Cultured in Year *t+1*	Clinical Adjustment Variables Measured in Year *t*[a]								
	Age	Sex	Pancreatic Sufficiency Status	Diabetes	FEV$_1$%[b]	APE[b]	Weight for *z*-score	Cultures Done	Late Diagnosis
MSSA[b]	**-0.0196 (0.000949, <0.001)**	**-0.066 (0.0154, <0.001)**	-0.00241 (0.0295, 0.935)	-0.0439 (0.0234, 0.0604)	**0.00272 (0.000388, <0.001)**	**-0.105 (0.00761, <0.001)**	0.00727 (0.00787, 0.356)	-0.0079 (0.00402, 0.0497)	**-0.0443 (0.0159, 0.00531)**
P aeruginosa	**0.0188 (0.00119, <0.001)**	0.0417 (0.0172, 0.0152)	**-0.557 (0.0318, <0.001)**	**0.0742 (0.0279, 0.00791)**	**-0.0106 (0.000449, <0.001)**	**0.132 (0.009, <0.001)**	**-0.0375 (0.00849, <0.001)**	**-0.0247 (0.00458, <0.001)**	**-0.108 (0.0176, <0.001)**
MRSA[b]	**-0.0113 (0.00122, <0.001)**	0.0439 (0.0193, 0.0229)	**-0.285 (0.0406, <0.001)**	0.0431 (0.0285, 0.131)	-0.00106 (0.000496, 0.032)	**0.102 (0.00909, <0.001)**	-0.0238 (0.00989, 0.0159)	-0.0119 (0.00499, 0.0173)	**-0.11 (0.0198, <0.001)**
B cepacia Complex	**0.00894 (0.00246, <0.001)**	-0.0804 (0.0451, 0.0749)	**-0.622 (0.102, <0.001)**	0.0747 (0.0612, 0.222)	**-0.00847 (0.0011, <0.001)**	**0.0879 (0.0196, <0.001)**	-0.018 (0.023, 0.434)	0.00884 (0.011, 0.422)	**-0.144 (0.0471, 0.00225)**
S maltophilia	**-0.0098 (0.0014, <0.001)**	**0.0694 (0.0207, <0.001)**	**-0.2 (0.0443, <0.001)**	**-0.145 (0.0313, <0.001)**	**-0.00319 (0.000534, <0.001)**	0.00299 (0.00963, 0.756)	0.000702 (0.0102, 0.945)	**0.051 (0.00473, <0.001)**	-0.0331 (0.0213, 0.121)
A xylosoxidans	-0.00357 (0.00171, 0.0373)	**0.11 (0.0297, <0.001)**	**-0.165 (0.0607, 0.00647)**	0.0245 (0.0407, 0.547)	**-0.00787 (0.00074, <0.001)**	**0.0881 (0.0124, <0.001)**	**-0.0656 (0.0147, <0.001)**	**0.0231 (0.00674, <0.001)**	-0.0244 (0.0305, 0.423)
Candida Species	**0.00358 (0.00125, 0.00428)**	0.0148 (0.0222, 0.505)	-0.0463 (0.0434, 0.286)	**0.0935 (0.0301, 0.00191)**	**-0.00383 (0.000542, <0.001)**	**0.0372 (0.00956, <0.001)**	-0.0141 (0.0108, 0.192)	**0.0365 (0.00504, <0.001)**	-0.0133 (0.0229, 0.561)
Aspergillus Species	**0.00724 (0.00109, <0.001)**	0.0237 (0.0191, 0.214)	**-0.28 (0.0395, <0.001)**	-0.0576 (0.027, 0.033)	**-0.00139 (0.000471, 0.00313)**	0.00942 (0.00838, 0.261)	**-0.0536 (0.00918, <0.001)**	**0.0564 (0.0045, <0.001)**	-0.00654 (0.0198, 0.741)

[a] **Bold** characters show strong statistical associations ($p < 0.01$), plain shows weaker associations ($0.01 \leq p < 0.05$), gray shows non-significant associations. Each cell in the table gives the effect estimate for each variable in year *t* (standard error, *p* value). Intercepts are not shown.

[b] FEV$_1$%: Percent predicted forced expiratory volume in 1 second; APE: acute pulmonary exacerbation; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *S aureus*

Table S5. Enrollment of Two-Year Study Cohorts

		Study Cohorts							
		2003-4	2004-5	2005-6	2006-7	2007-8	2008-9	2009-10	2010-11
Number of CFFPR Patients in Year t		20981	22138	22473	22951	23704	24316	25034	25661
Patients with Age < 6 Years in Year t		4260	4376	4283	4367	4390	4530	4699	4880
Older Patients, Age >=6[a]		16721	17762	18190	18584	19314	19786	20335	20781
Patients Missing Culture Data in Year t or $t+1$ (Fraction of Older Patients)[a]		1095 (0.065)	1334 (0.075)	1257 (0.069)	1101 (0.059)	1009 (0.052)	1000 (0.051)	951 (0.047)	963 (0.046)
Patients Enrolled in Cohort		15626	16428	16933	17483	18305	18786	19384	19818
Number Missing Clinical Data in Year t (fraction of enrolled)[b]	Age	0	0	0	0	0	0	0	0
	Female	0	0	0	0	0	0	0	0
	Pancreatic Sufficiency	37 (0.0024)	27 (0.0016)	23 (0.0014)	6 (<0.001)	0 (<0.001)	0 (<0.001)	1 (<0.001)	2 (<0.001)
	Diabetes	0	0	0	0	0	0	0	0
	$FEV_1\%$[c]	195 (0.012)	203 (0.012)	205 (0.012)	247 (0.014)	253 (0.014)	272 (0.014)	288 (0.015)	324 (0.016)
	APE[c]	0	0	0	0	0	0	0	0
	Weight-for-Age z-score	55 (0.0035)	73 (0.0044)	94 (0.0056)	100 (0.0057)	119 (0.0065)	161 (0.0086)	116 (0.006)	291 (0.015)
	Microbial Culture	0	0	0	0	0	0	0	0
	Missing Any Clinical Data	281 (0.018)	300 (0.018)	320 (0.019)	350 (0.02)	369 (0.02)	431 (0.023)	404 (0.021)	596 (0.03)

[a] Patients older than 6 are usually able to produce sputum for culture making these patients eligible for study. Patients unable to produce sputum or had missing culture information for any other reason could not be included in our main analyses.

[b] Patients missing data for disease characteristics routinely measured at patient encounters were not included in analyses that adjusted for clinical variables.

[c] $FEV_1\%$: Percent predicted forced expiratory volume in 1 second; APE: acute pulmonary exacerbation

Table S6. Comparison of Patients with Culture Data to Patients Excluded Because of Missing Cultures[a]

Study Cohort	Mean Age, years (SD)			Proportion Male			Proportion with Pancreatic Sufficiency			Proportion with CF-Related Diabetes		
	Excluded	Study	p^b	Excluded	Study	p^c	Excluded	Study	p^c	Excluded	Study	p^c
2003-4	24.2 (11.9)	19.1 (10.5)	<0.001	0.454	0.476	0.342	0.100	0.0648	<0.001	0.108	0.0963	0.195
2004-5	24.3 (11.8)	19.5 (10.7)	<0.001	0.449	0.475	0.0752	0.116	0.0725	<0.001	0.134	0.106	0.002
2005-6	25.9 (12.0)	19.7 (10.8)	<0.001	0.446	0.476	0.0495	0.111	0.0703	<0.001	0.14	0.113	0.004
2006-7	27.7 (12.1)	20.1 (11.0)	<0.001	0.471	0.475	0.844	0.127	0.0769	<0.001	0.218	0.138	<0.001
2007-8	29.2 (12.5)	20.4 (11.3)	<0.001	0.474	0.479	0.78	0.156	0.0787	<0.001	0.241	0.146	<0.001
2008-9	30.3 (12.3)	20.8 (11.4)	<0.001	0.456	0.482	0.099	0.140	0.0875	<0.001	0.279	0.152	<0.001
2009-10	30.6 (12.2)	21.1 (11.6)	<0.001	0.453	0.484	0.0548	0.148	0.0934	<0.001	0.315	0.156	<0.001
2010-11	31.8 (12.6)	21.4 (11.8)	<0.001	0.450	0.485	0.0522	0.195	0.120	<0.001	0.305	0.166	<0.001

[a] Means or Fractions are based on data for patients in the first year of each cohort.

[b] *t*-test.

[c] χ^2 test.

83 **Table S6 (Continued). Comparison of Patients with Culture Data to Patients Excluded Because of**
84 **Missing Cultures[a]**

Study Cohort	Mean FEV$_1$%[b] (SD)			Mean APE[b] truncated at 5 (SD)			Mean Weight-for-age z-score		
	Excluded	Study	p[c]	Excluded	Study	p[c]	Excluded	Study	p[c]
2003-4	77.6 (25.1)	77.8 (26.6)	0.78	0.230 (0.654)	0.704 (1.15)	<0.001	-0.317 (1.17)	-0.506 (1.07)	<0.001
2004-5	75.2 (25.9)	78.2 (26.6)	<0.001	0.314 (0.802)	0.736 (1.16)	<0.001	-0.390 (1.14)	-0.470 (1.05)	0.006
2005-6	74.9 (24.9)	78.7 (26.4)	<0.001	0.251 (0.706)	0.743 (1.17)	<0.001	-0.322 (1.15)	-0.444 (1.08)	<0.001
2006-7	76.7 (25.0)	79.0 (26.1)	0.008	0.194 (0.569)	0.779 (1.19)	<0.001	-0.271 (1.17)	-0.402 (1.10)	<0.001
2007-8	75.2 (24.7)	79.4 (26.3)	<0.001	0.277 (0.800)	0.787 (1.20)	<0.001	-0.279 (1.20)	-0.377 (1.07)	0.009
2008-9	76.8 (24.8)	79.7 (26.5)	<0.001	0.223 (0.711)	0.816 (1.22)	<0.001	-0.248 (1.13)	-0.341 (1.09)	0.006
2009-10	76.8 (25.3)	79.8 (26.6)	<0.001	0.263 (0.743)	0.808 (1.22)	<0.001	-0.189 (1.17)	-0.309 (1.11)	0.003
2010-11	76.7 (24.8)	80.2 (26.5)	<0.001	0.187 (0.573)	0.759 (1.18)	<0.001	-0.201 (1.22)	-0.298 (1.14)	0.016

[a] Means or Fractions are based on data for patients in the first year of each cohort.

[b] FEV$_1$%: Percent predicted forced expiratory volume in 1 second; APE: acute pulmonary exacerbation

[c] t-test.

85 **Table S7. Patients Age >6 in the CFFPR During the Study but Excluded from All Study Cohorts[a]**

	2003	2004	2005	2006	2007	2008	2009	2010	2011
Patients in each CFFPR year with no culture data for any study year, 2003-2011	143	112	77	76	63	59	59	65	100[b]
Deaths Among Completely Excluded Patients[c]	36	23	10	12	<10[d]	<10[d]	<10[d]	<10[d]	<10[d]

[a] Does not include patients excluded solely for Age < 6 Years.

[b] Number of patients without culture data in any study year is increased in the last year of the study due to patients entering the CFFPR for the first time in that year.

[c] The later during the study that a death occurred, the more likely the patient had a 2 year period with data able to be included earlier in the study.

[d] Exact number suppressed to reduce the chance of disclosing exact identities.

Table S8. Characteristics of Patients Never Included in the Study[a]

Year	Age, Years (SD, p^b)	Proportion Male (p^c)	Proportion with Pancreatic Sufficiency (p^c)	Proportion with CF-Related Diabetes (p^c)	FEV$_1$%[d] (SD, p^b)	APE[d] truncated at 5 (SD, p^b)	Weight-for-age z-score (SD, p^b)
2003	28.2 (12.1, <0.001)	0.46 (0.54)	0.091 (<0.001)	0.167 (0.01)	80.0 (26.1, 0.33)	0.17 (0.48, <0.001)	-0.254 (1.42, 0.03)
2004	30.2 (11.0, <0.001)	0.39 (0.28)	0.112 (<0.001)	0.224 (<0.001)	81.3 (27.1, 0.15)	0.11 (0.38, <0.001)	-0.346 (1.40, 0.14)
2005	30.9 (13.1, <0.001)	0.38 (0.16)	0.174 (<0.001)	0.174 (0.32)	85.6 (23.2, 0.01)	0.12 (0.56, <0.001)	-0.181 (1.43, 0.04)
2006	32.8 (11.5, <0.001)	0.43 (0.54)	0.250 (<0.001)	0.279 (0.01)	84.1 (25.6, 0.04)	0.03 (0.17, <0.001)	-0.178 (1.39, 0.13)
2007	35.1 (11.5, <0.001)	0.36 (0.03)	0.220 (<0.001)	0.322 (<0.001)	88.9 (22.0, 0.001)	0.05 (0.29, <0.001)	-0.215 (1.28, 0.42)
2008	39.0 (9.57, <0.001)	0.46 (0.61)	0.200 (0.0039)	0.327 (0.001)	92.5 (21.2, <0.001)	0.05 (0.23, <0.001)	-0.235 (1.19, 0.23)
2009	36.0 (12.1, <0.001)	0.46 (0.59)	0.218 (<0.001)	0.345 (<0.001)	86.5 (23.9, 0.02)	0.02 (0.14, <0.001)	-0.160 (1.38, 0.26)
2010	38.6 (13.3, <0.001)	0.44 (0.45)	0.279 (<0.001)	0.23 (0.21)	86.8 (26.3, 0.04)	0.02 (0.123, <0.001)	0.062 (1.34, 0.03)
2011	39.0 (16.3, <0.001)	0.47 (0.85)	0.293 (<0.001)	0.261 (0.07)	85.1 (24.7, 0.07)	0.08 (0.34, <0.001)	0.135 (1.11, <0.001)

[a] Does not include patients excluded solely for Age < 6 Years

[b] t-test p-value from comparison with study patients analyzed in each year (data summarized in Table S6)

[c] χ^2 test p-value from comparison with study patients analyzed in each year (data summarized in Table S6)

[d] FEV$_1$%: Percent predicted forced expiratory volume in 1 second; APE: acute pulmonary exacerbation

Supplemental Figure Legends

Figure S1. Comparison of univariable cross-sectional associations with adjusted cross-sectional

associations between airway infections. As in Figure 2 in the main text, forest plots show the odds ratio

(circles) and 99% confidence intervals (bars) of having positive cultures for each of the eight studied organisms

within each study year comparing presence versus absence of a positive culture for each of the other seven

organisms in the same year. This supplemental figure adds an additional cluster of forest plots for each cross-

sectional relationship to show the results of univariable relationships. The outcomes parallel those shown in

Figure 2: (A) MSSA: methicillin sensitive *Staphylococcus aureus*, (B) PA: *Pseudomonas aeruginosa*, (C)

MRSA: methicillin resistant *S aureus*, (D) BCC: *Burkholderia cepacia* complex, (E) SM: *Stenotrophomonas*

maltophilia, (F) AX: *Achromobacter xylosoxidans*, (G) CS: *Candida* species, (H) AS: *Aspergillus* species. Utah

Red results show univariable relationships unadjusted by the presence of other organisms or clinical

characteristics. Purple results are from models adjusted by the presence of the remaining six other organisms.

Turquoise results are from models additionally adjusted for clinical characteristics: age, sex, late diagnosis of

CF, best FEV_1% in each year, annual number of APE, pancreatic sufficiency and diabetes status and weight-for-

age *z*-score.

Figure S2. Adjusted associations between each airway infection in years 2003-2010 with itself in years

2004-2011. Forest plots show the log odds (circles) and 99% confidence intervals (bars) by logistic regression

of having positive cultures in years *t+1* for each of the eight studied organisms when the same organism was

present in respective years *t* where *t=2003-2010*. The outcomes for years *t+1* were (A) MSSA: methicillin-

sensitive *Staphylococcus aureus*, (B) PA: *Pseudomonas aeruginosa*, (C) MRSA: methicillin-resistant *S aureus*,

(D) BCC: *Burkholderia cepacia* complex, (E) SM: *Stenotrophomonas maltophilia,* (F) AX: *Achromobacter*

xylosoxidans, (G) CS: *Candida* species, (H) AS: *Aspergillus* species. Utah Red results are from models adjusted

by the presence of the other seven organisms. Green results are from models additionally adjusted for clinical

110   characteristics in years t: age, sex, late diagnosis of CF, best FEV$_1$% in each year, annual number of APE,

111   pancreatic sufficiency and diabetes status and weight-for-age z-score.

112   **Figure S3. Adjusted associations between each airway infection in year t with itself In year $t+1$.** Each

113   forest plot show the log odds (circles) and 99% confidence intervals (bars) by GEEGLM utilizing the entire

114   2003-2011 CFFPR data set for each of the eight studied organisms in year $t+1$ when the same organism was

115   present in respective years t where t=2003-2010. The outcomes from years $t+1$ were*:* (A) MSSA: methicillin-

116   sensitive *Staphylococcus aureus*, (B) PA: *Pseudomonas aeruginosa*, (C) MRSA: methicillin-resistant *S aureus*,

117   (D) BCC: *Burkholderia cepacia* complex, (E) SM: *Stenotrophomonas maltophilia,* (F) AX: *Achromobacter*

118   *xylosoxidans*, (G) CS: *Candida* species, (H) AS: *Aspergillus* species when the same organism was present in

119   culture for year t. Utah Red results are from models adjusted by the presence of the other seven organisms.

120   Green results are from models additionally adjusted for clinical characteristics in years t: age, sex, late diagnosis

121   of CF, best FEV$_1$% in each year, annual number of APE, pancreatic sufficiency and diabetes status and weight-

122   for-age z-score.