

Pulmonary Exacerbations



Table of Contents

- What defines a pulmonary exacerbation?
- What association is there between pulmonary exacerbations and airway microbiota and inflammation?
- How are pulmonary exacerbations treated?
- How is the patient impacted by a pulmonary exacerbation?



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- **What defines a pulmonary exacerbation?**
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What Is a Pulmonary Exacerbation?

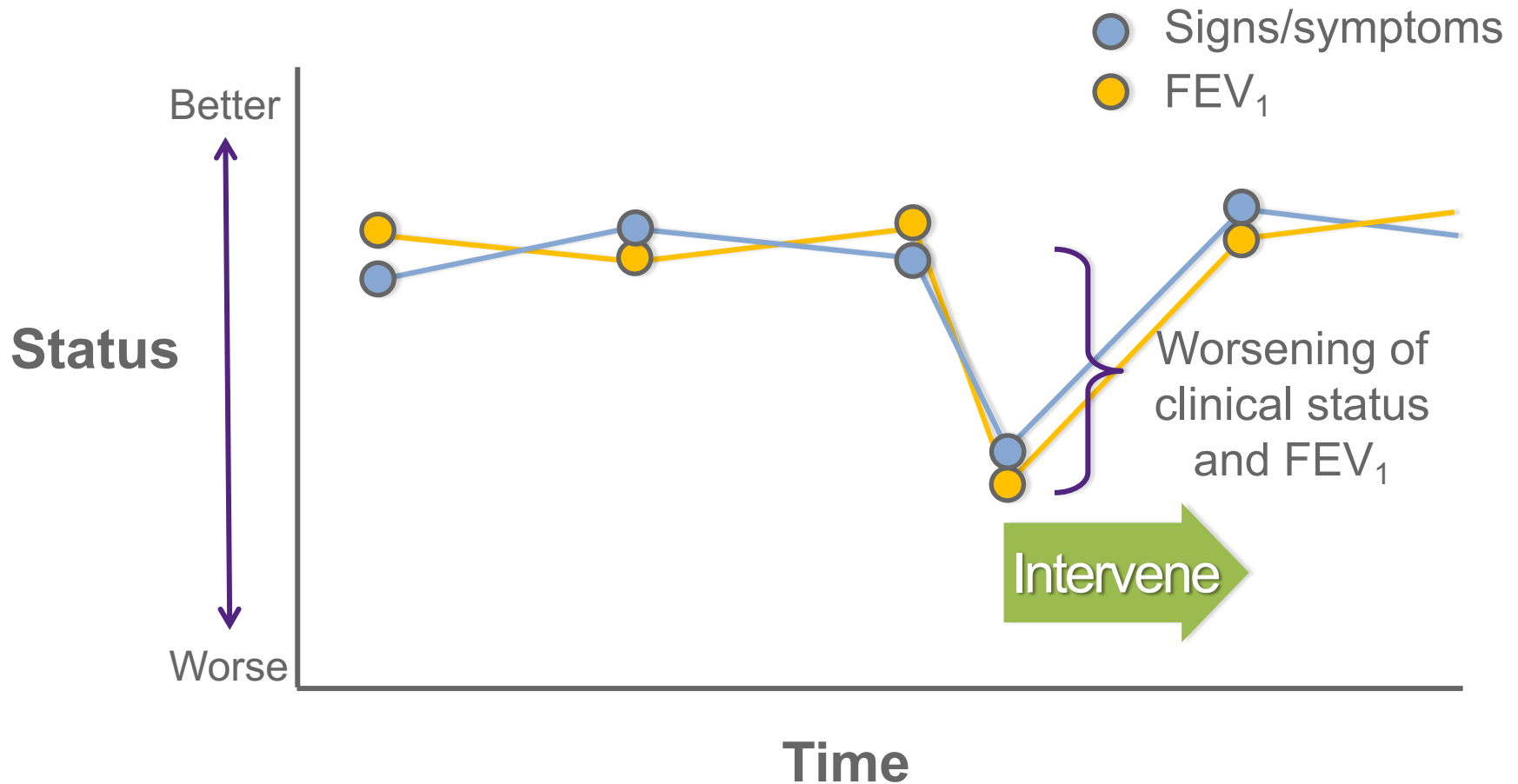
While there is no consensus definition on what constitutes a pulmonary exacerbation, there are clinical features common to the various definitions

- An *acute* worsening of respiratory symptoms
 - cough, increased sputum, hemoptysis
- Weight loss, malaise

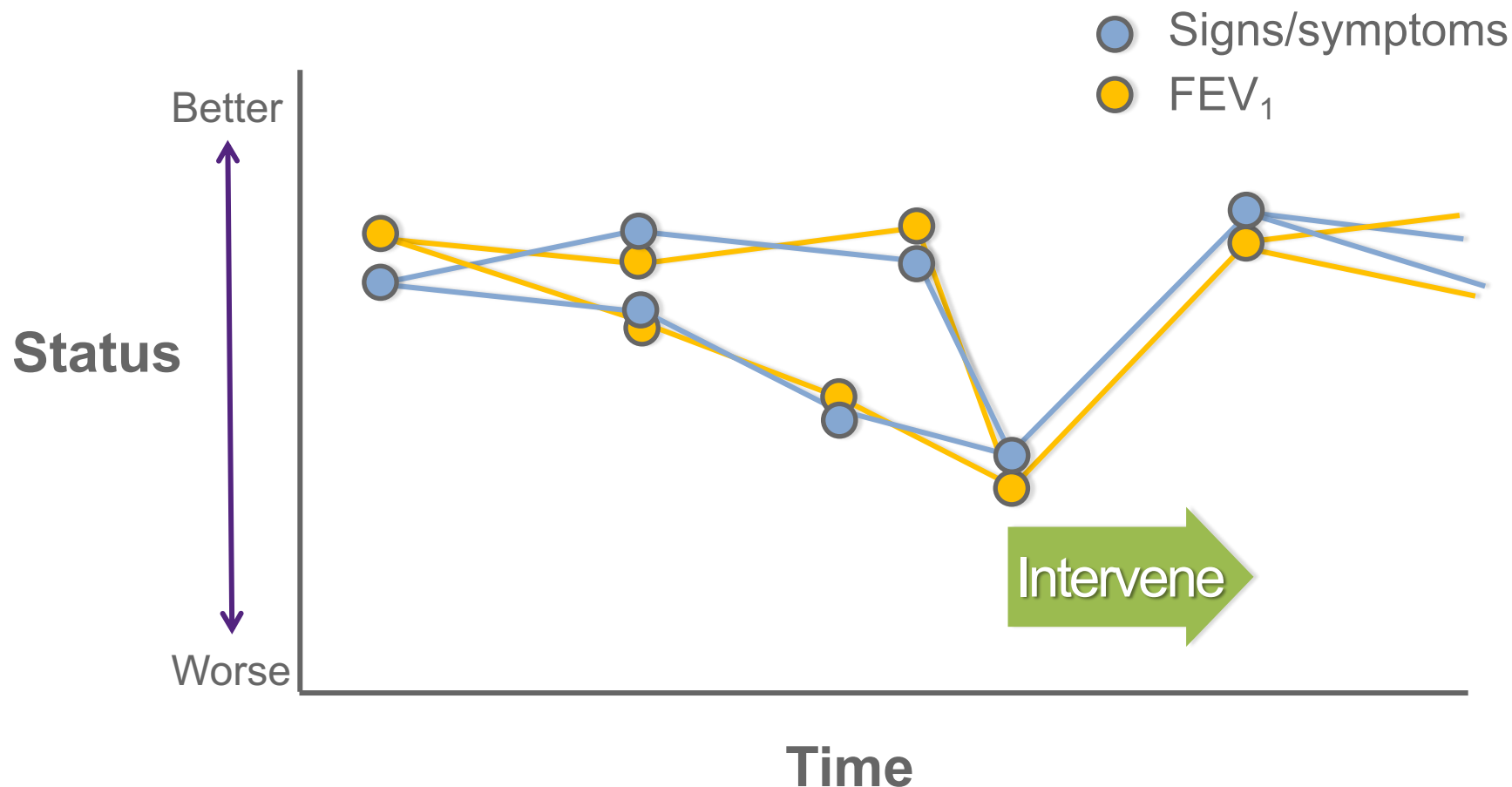
...accompanied by...

- An *acute* decrease in lung function (ie, FEV₁)

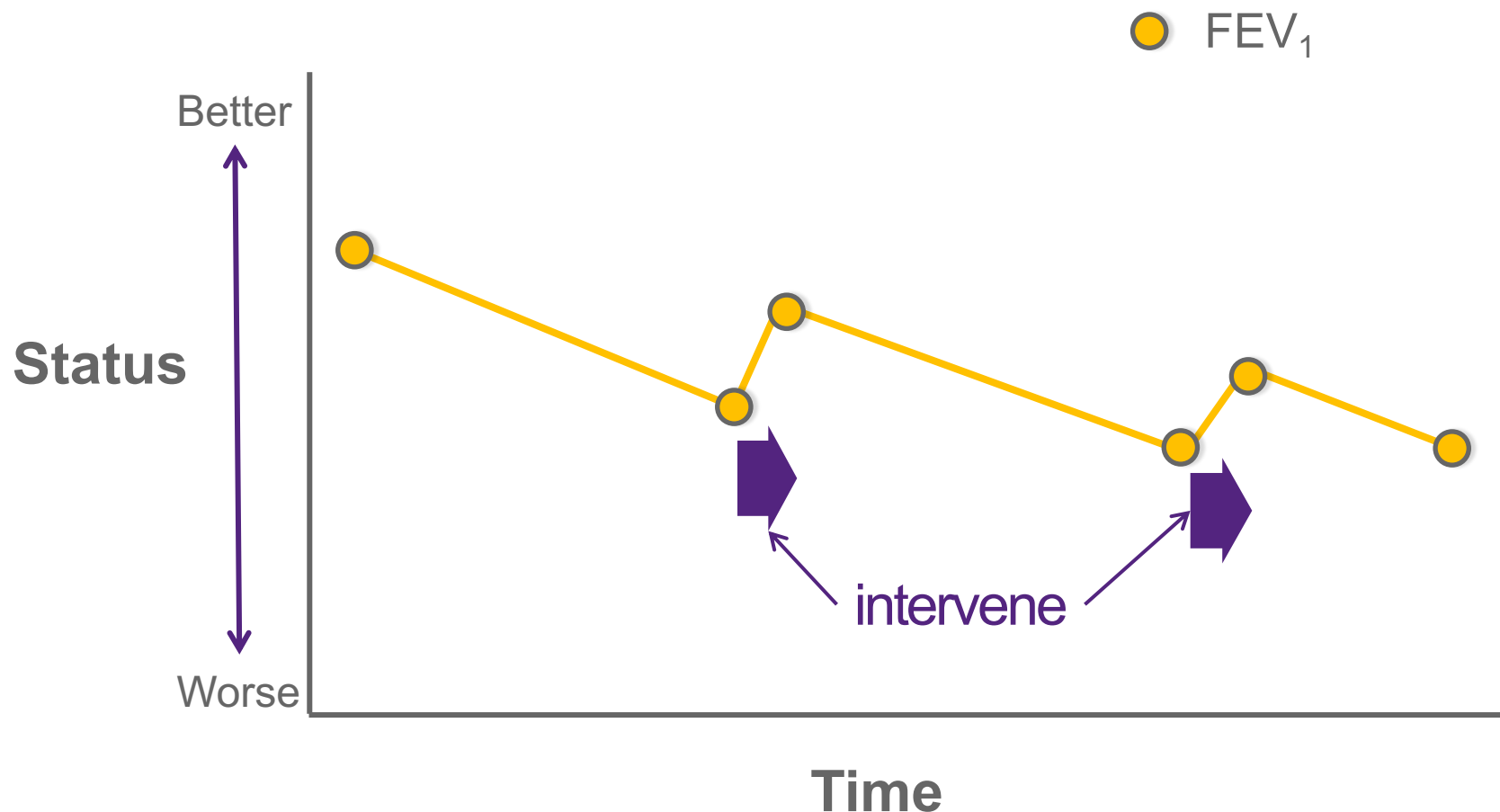
A Typical Course of a Cystic Fibrosis Pulmonary Exacerbation Is...



But, Are All Exacerbations Acute Events?



...and Recovery May Be Incomplete, Leading to Cumulative Worsening



Pulmonary Exacerbation Signs and Symptoms Are Many

Clinical or Lab Characteristic	Rosenfeld et al (OR) ^a	Dakin et al (%) ^b			Rabin et al (OR) ^d			
		Age <5 Years	Well Child	Advanced Disease ^c	Age <6 Years	Age 6-12 Years	Age 13-17 Years	Age ≥18 Years
Increased cough	24.5	100	98	93	3.9	4.4	2.3	2.8
Exercise intolerance	22.4	–	91	98	–	–	–	–
Increase in sputum production	24.5	–	91	88	2.2	1.5	3.0	1.8
Change in activity	15.2 ^e	91	86	98	–	–	–	–
Hemoptysis	–	–	79	91	3.2	2.0	2.3	2.4
Change in appetite or weight	15.2 (appetite) 2.1 (weight) ^f	91	93	91	2.2 ^g	1.4 ^g	2.0 ^g	1.7 ^g
School or work absenteeism	5.6	–	–	–	–	–	–	–
Retractions or use of accessory muscles	12.9	–	–	–	–	–	–	–
Change in chest sounds	4.3	74	70	56	7.8 ^h	2.8 ^h	2.7 ^h	2.5 ^h
Change in respiratory rate	14.1	74	62	65	–	–	–	–
Fever	5.9	40	35	49	–	–	–	–
Change in spirometry	2.7 ⁱ	–	95	93	–	4.1	3.7	3.8
Oxygen saturation	–	37	30	53	–	–	–	–
Chest X-ray changes	–	58	58	49	–	–	–	–

^aOdds ratios (OR) for association of characteristics with the presence of a pulmonary exacerbation from univariate logistic models; ^bPercentage of questionnaire respondents managing children and adolescents rating item “helpful” or “very helpful” (among 43 respondents); ^cScenario involved a patient with established bronchiectasis and chronic sputum production; ^dOR for the presence (vs absence) of a pulmonary exacerbation with mutual adjustment for all variables; ^eIncreased fatigue; ^fWeight loss ≥1 kg over past month; ^gRelative decline in weight-for-age percentile; ^hNew crackles; ⁱDecline in FEV₁ ≥10% during the past month. Rosenfeld M et al. *J Pediatr.* 2001;139(3):359-365. Dakin C et al. *Pediatr Pulmonol.* 2001;31(6):436-442. Rabin HR et al. *Pediatr Pulmonol.* 2004;37(5):400-406.



Defining Pulmonary Exacerbations: One Example of a Proposed Model Based on Clinical Features

Clinical Feature	Odds Ratio	95% CI	Coefficient
Decreased exercise tolerance	5.8	2.7-12.3	1.8
Increased cough	4.3	1.9-9.7	1.5
Increased sputum	4.3	1.8-10.5	1.5
Absence from work or school	5.0	2.1-11.7	1.6
Increased adventitial sounds on lung examination	3.2	1.7-6.0	1.2
Decreased appetite	3.0	1.3-6.8	1.1

- Score = sum of coefficients for features present in the individual patient
- Critical value: 2.6
- Scores >2.6 are classified as having pulmonary exacerbation

Pulmonary Exacerbation Definition: No Consensus

Item	Items defining an exacerbation						Items used in clinical scores		
	Wohl	Homnick	Smith	Wilmott	Blumer	Fuchs	Blumer	Mastella	Beaudry*
Change in sputum production: volume, appearance or color	X	X	X	X	X	X	X	X	X
New or increased hemoptysis	X			X		X			
Increased cough	X	X	X	X	X	X		X	X
Decreased activity			X					X	
Malaise, fatigue, or lethargy		X		X		X			
Decreased exercise tolerance			X		X		X	X	
Increased dyspnea		X	X	X	X	X			
Increased chest discomfort		X		X					
Increasing respiratory rate			X		X		X	X	X
Work of breathing								X	X
Fever >38 ° C orally		X		X	X	X	X	X	X
Anorexia or weight loss	X	X	X	X	X	X	X		
Changes in chest sounds	X		X	X	X	X	X	X	
Decrease in FEV ₁ or FVC	X	X	X	X	X	X	X	X	
Radiographic changes indicative of an exacerbation		X	X	X	X	X			
Sinus pain or tenderness						X			
Change in sinus discharge						X			
Sputum microbiology	X			X					
Oxygen desaturation		X					X	X	X
Resting pulse rate								X	X
ESR, CRP, WCC								X	

*Pediatric subjects only; all other trials included pediatric and adult subjects. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WCC, white cell count. Dakin C et al. *Pediatr Pulmonol.* 2001;31(6):436-442.



Proposed Definitions for Pulmonary Exacerbations

Fuchs et al¹

IV antibiotics for any 4

- Change in sputum
- New or Increased hemoptysis
- Increased cough
- Increased dyspnea
- Increased malaise, fatigue or lethargy
- Temperature over 38°C
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in chest physical examination
- Pulmonary function decreased by 10%
- Radiographic changes indicative of lung infection

European Consensus group modified Fuchs criteria²

Need for additional antibiotic for any 2:

- Change in sputum volume or color
- Increased cough
- Increased malaise, fatigue or lethargy
- Anorexia or weight loss
- Decrease in pulmonary function by 10% or more/Radiographic changes
- Increased dyspnea

Defining Pulmonary Exacerbations: Patient and HCP Differ in Their Perspectives

Top Indicators in Adult CF Patient Survey

Statement	Mean Score (out of 10)
A large decrease in lung function (greater than 10% FEV ₁)	9.33
Feeling more short of breath than usual	8.52
Trouble breathing	8.52
Feeling the need to do more airway clearance than usual	8.37
An increase in symptoms at night	8.22
Producing more sputum	8.19
Finding it harder than normal to do your usual exercise	7.96
Finding it harder than normal to do your usual activities	7.93
Feeling more exhausted than usual	7.85
More coughing than usual	7.85

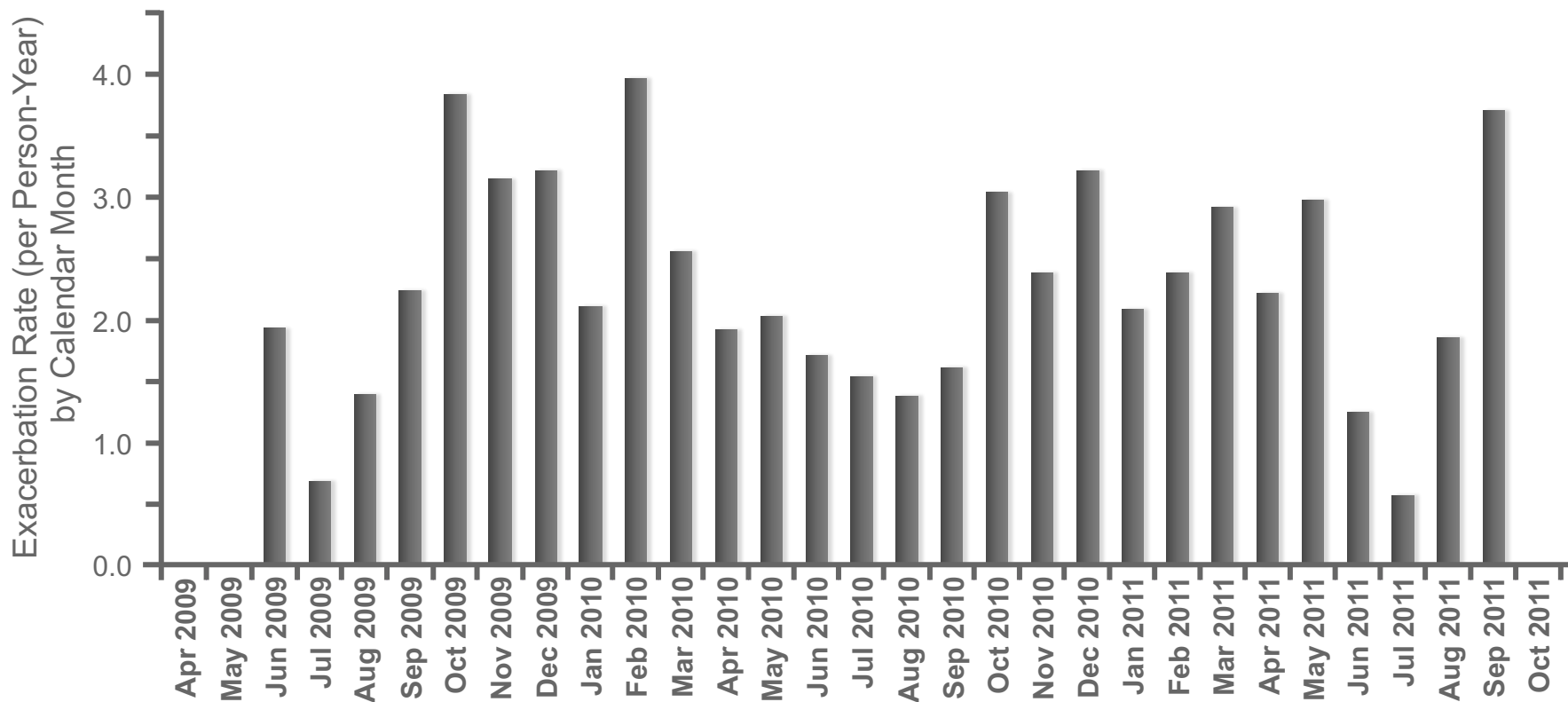
Top Indicators in Health Care Professional Survey

Statement	Mean Score (out of 10)
Increased sputum	8.84
A large decrease in lung function (greater than 10% FEV ₁)	8.84
More shortness of breath than usual	8.32
Increased inflammatory markers (for example CRP and white cell count)	7.92
Fever or increased temperature	7.89
Increased respiratory rate at rest	7.82
Decreased oxygen saturation	7.79
Hypoxia/hypoxemia	7.76
Change in the colour of sputum	7.61
New changes on chest X-ray	7.47
Increased coughing	7.47

CRP, C-reactive protein.
 McCourt F et al. *J Cyst Fibros.* 2015;14(1):90-96.



Seasonal Nature of Pulmonary Exacerbations



Adapted from Brumback LC et al. *Pediatr Pulmonol.* 2014 Apr 29. doi: 10.1002/ppul.23056. [Epub ahead of print]



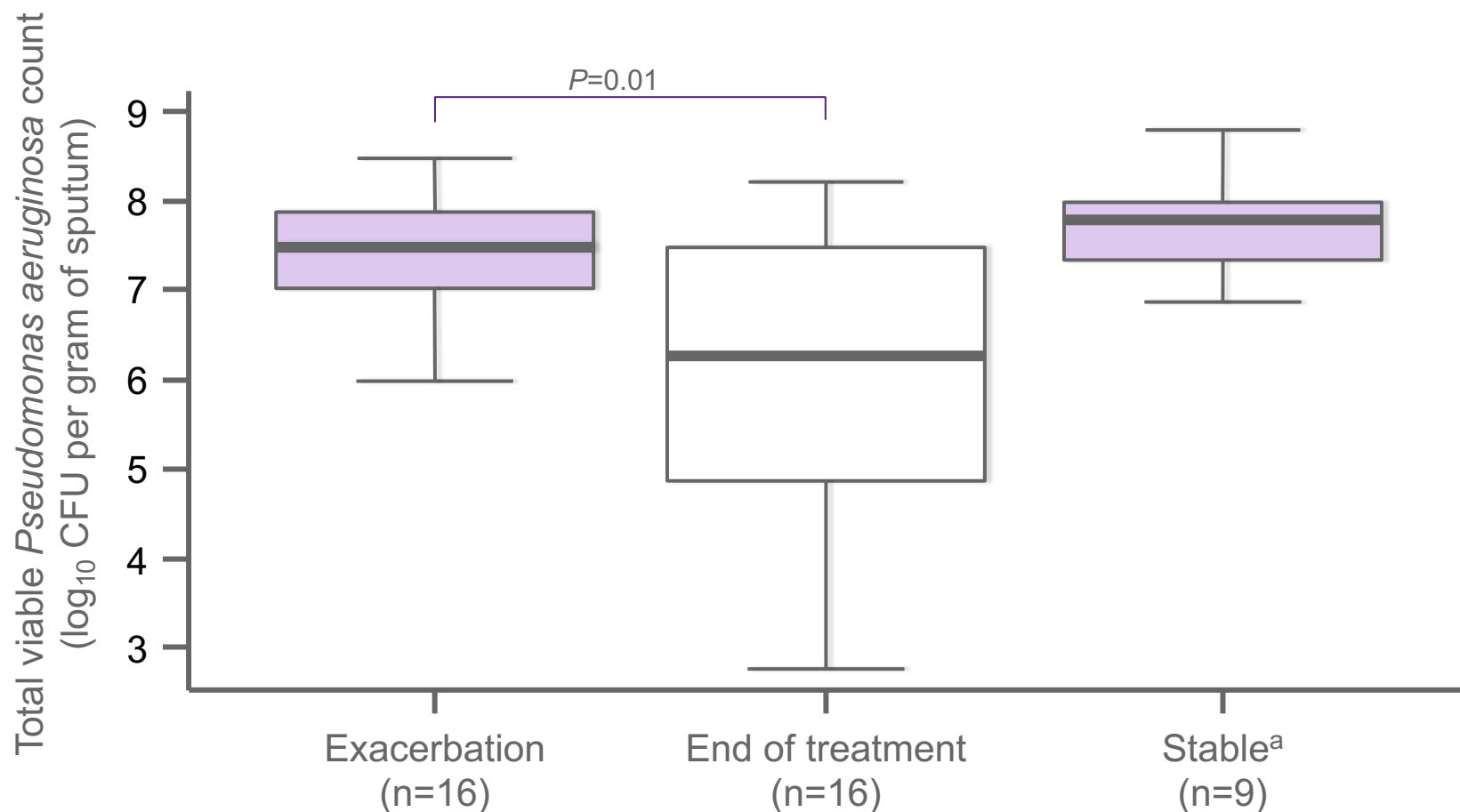
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Pseudomonas Count Does Not Predict Exacerbation

- Total number of viable bacteria does not necessarily predict that a patient will have an exacerbation*



Adapted from Tunney MM et al. *Thorax*. 2011;66(7):579-584.

CFU, colony-forming unit.

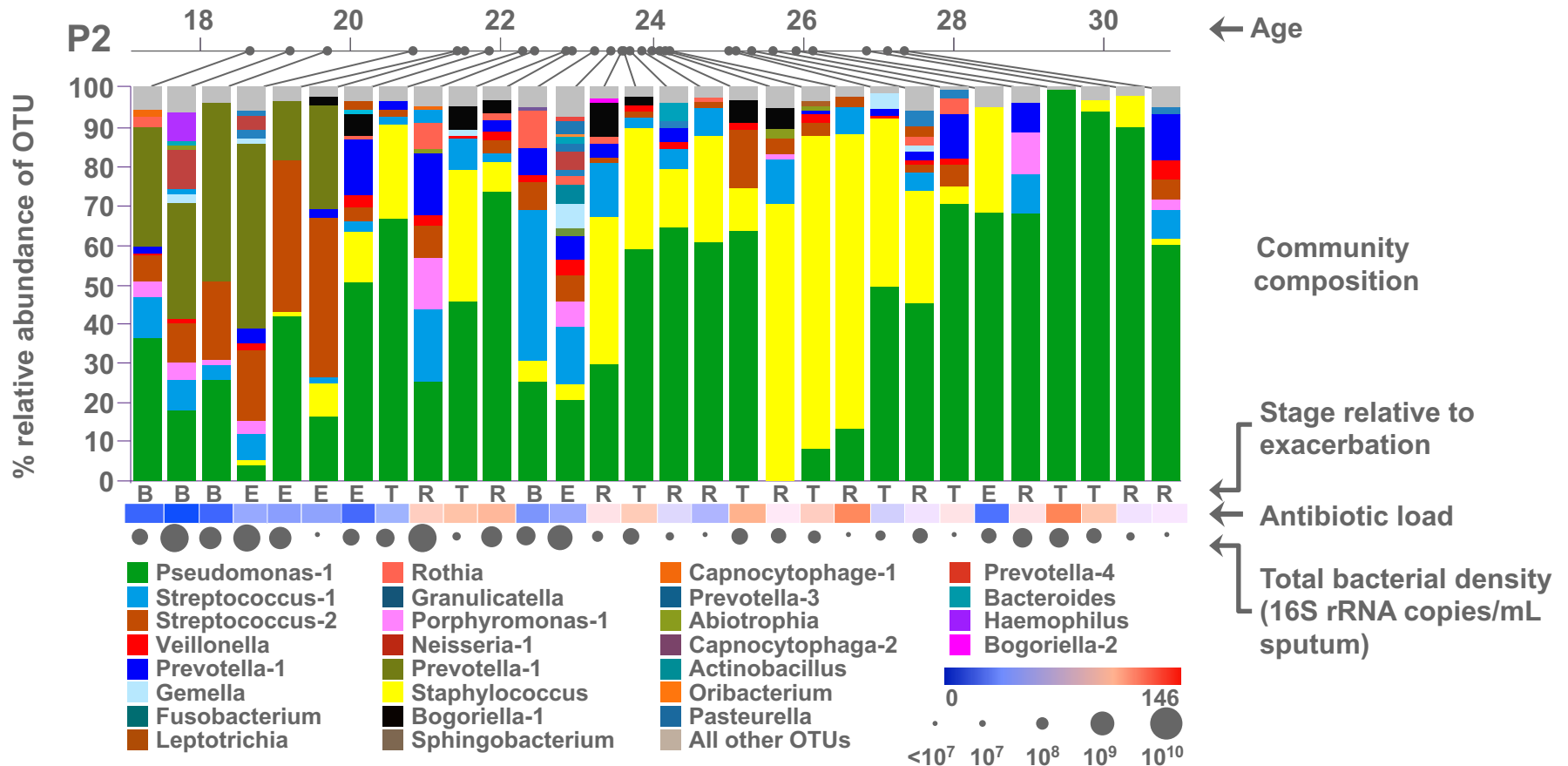
^aSamples collected before or after exacerbation.

Sputum samples were cultured from patients who had an exacerbation in the prior year, and at their next visit or exacerbation (prior to and after completion of antibiotic treatment).



Bacterial Community Diversity Is Not an Indicator of Pulmonary Exacerbation

Relative abundance of OTUs in a patient with CF and declining lung function



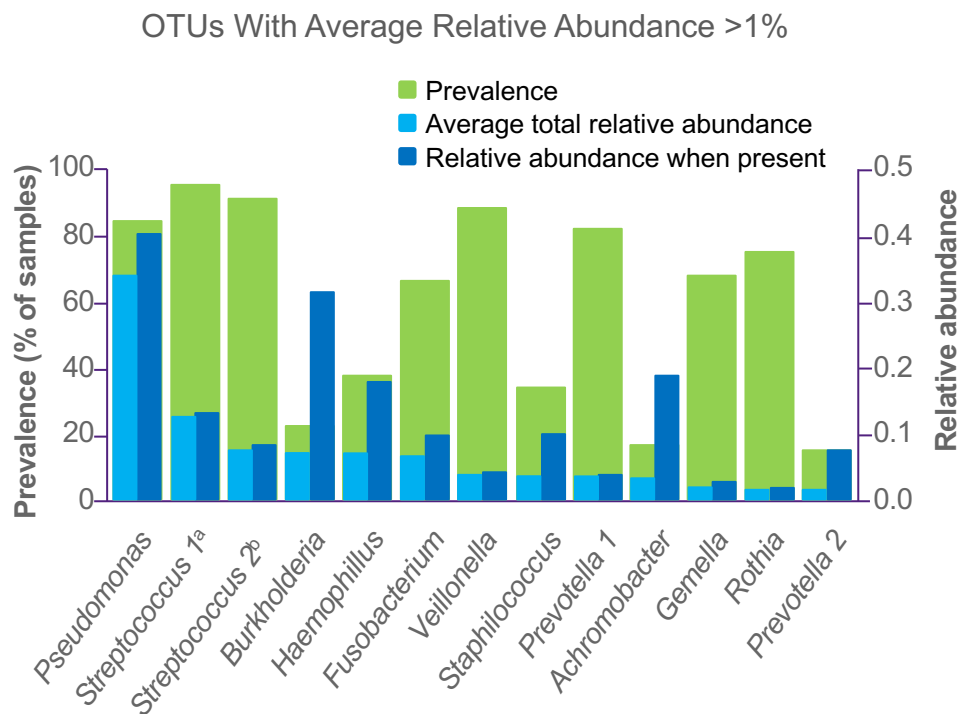
Adapted from Zhao J et al. *Proc Natl Acad Sci U S A*. 2012;109(15):5809-5814.

B, baseline; E, exacerbation; OTU, operational taxonomic unit; R, recovering; T, antibiotic treatment.

This study characterized the bacterial communities in 126 sputum samples representing serial collections spanning 8 to 9 years from 6 age-matched male patients With CF. Sputum DNA was analyzed by barcoded pyrosequencing of the V3-V5 hypervariable region of the 16S rRNA gene, defining 662 OTUs from >633,000 sequences



Bacterial Load or Diversity and Pulmonary Exacerbations



Baseline vs exacerbation samples

- Overall no significant differences in bacterial load or diversity
- Changes in community structure (membership and relative abundance) varied greatly across patients
 - Greater diversity at baseline predicted greater difference between baseline and exacerbation samples
 - *Pseudomonas*-dominated communities showed greater dissimilarity than communities without a dominant OTU
- *Gemella* was the most discriminative OTU for baseline vs exacerbation samples

Adapted from Carmody LA et al. *Ann Am Thorac Soc.* 2013;10(3):179-187.

^a*S. mitis* group.

^b*S. salivarius* group.

OTU, operational taxonomic unit.

DNA prepared from 68 paired baseline and exacerbation sputum samples collected from 28 patients with CF were subjected to barcoded 16S rRNA gene pyrosequencing. Bacterial density was calculated by quantitative polymerase chain reaction.



Number of *Burkholderia cepacia* Infection and Acute Exacerbations Increase Risk of Death

Covariate (X_{0-10})	Coefficient		Odds Ratio
	β_{0-10}	SE	
Age (per year)	0.011	0.0049	1.011
Gender (male=0, female=1)	0.15	0.074	1.16
FEV ₁ % (per %)	-0.042	0.0025	0.96
Weight-for-age z score	-0.28	0.041	0.75
Pancreatic sufficiency (0 or 1)	-0.14	0.23	0.87
Diabetes mellitus (0 or 1)	0.44	0.098	1.55
<i>Staphylococcus aureus</i> (0 or 1)	-0.25	0.09	0.78
<i>B. cepacia</i> (0 or 1)	1.41	0.19	4.12
No. of acute exacerbations (0–5)	0.25	0.024	1.42
No. of acute exacerbations x <i>B. cepacia</i>	-0.28	0.06	0.75

Inflammation Associated With Pulmonary Exacerbations Improves With Treatment

Parameters	Day 1 Median (range)	Day 8 Median (range)	Day 15 Median (range)
CRP (mg/L)	22 (1–123)	4 ^a (1–4.7)	4 ^a (1–3.1)
WBC (10 ³ cells/μL)	11.61 (6.12–32.83)	9.42 ^a (4.93–14.80)	9.41 ^a (4.02–14.45)
ESR (mm/h)	27 (4–62)	23 (2–70)	20 ^a (2–62)
FVC (%)	70 (29–99)	77 ^a (39–117)	80 ^a (37–113)
FEV ₁ (%)	44 (0.16–0.82)	53 ^a (0.19–1.03)	55 ^a (0.19–1.00)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; WBC, white blood cells.

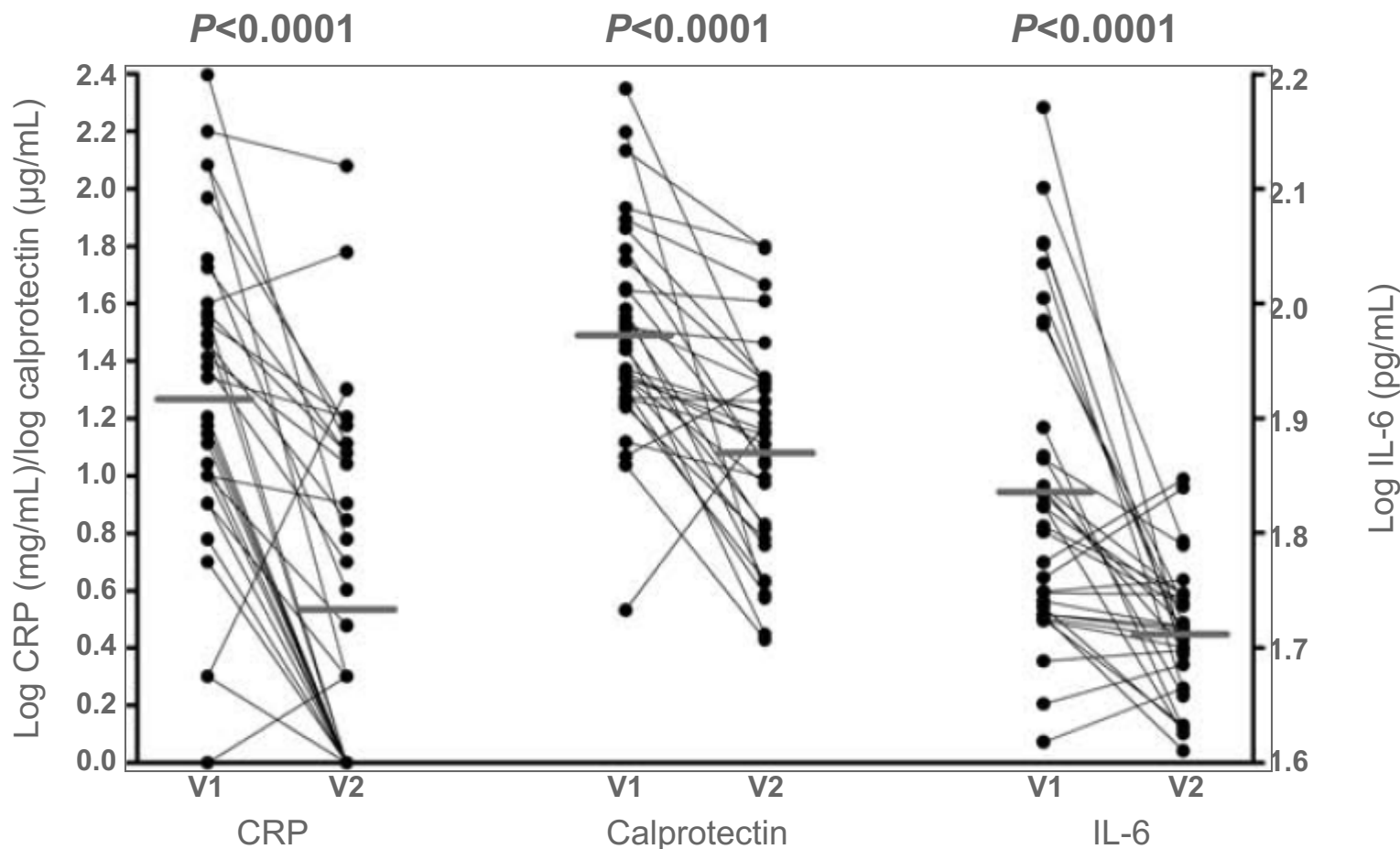
^aSignificant change in comparison with Day 1 of hospitalization, $P < 0.05$ (Wilcoxon).

Sputum and blood samples were collected from 18 patients (all chronically colonized with *P. aeruginosa*) at Day 1 (prior to the start of the antibiotic treatment on the same day), Day 8, and Day 15 of treatment for a total of 27 hospitalization periods, and inflammation parameters (CRP, WBC, ESR) and lung function (FEV₁ and FVC) were determined.

Deschaght P et al. *PLoS One*. 2013;8(11):e79010.



Changes in Inflammatory Mediators During Treatment for Pulmonary Exacerbations Vary by Patient



- White cell count was also highly variable between patients but significantly improved with treatment ($P=0.022$)

Pulmonary Exacerbations

- What defines a pulmonary exacerbation?
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- **How are pulmonary exacerbations treated?**
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Why Is it Important to Treat Pulmonary Exacerbations?

- Important resource utilization: frequent hospitalizations and IV antibiotic courses^{1,2}
- Negative impact on quality of life^{2,3}
- Impact on lung function: 25% of patients do not return to baseline ppFEV₁ after a pulmonary exacerbation⁴
- Correlated with lower survival⁵⁻⁷

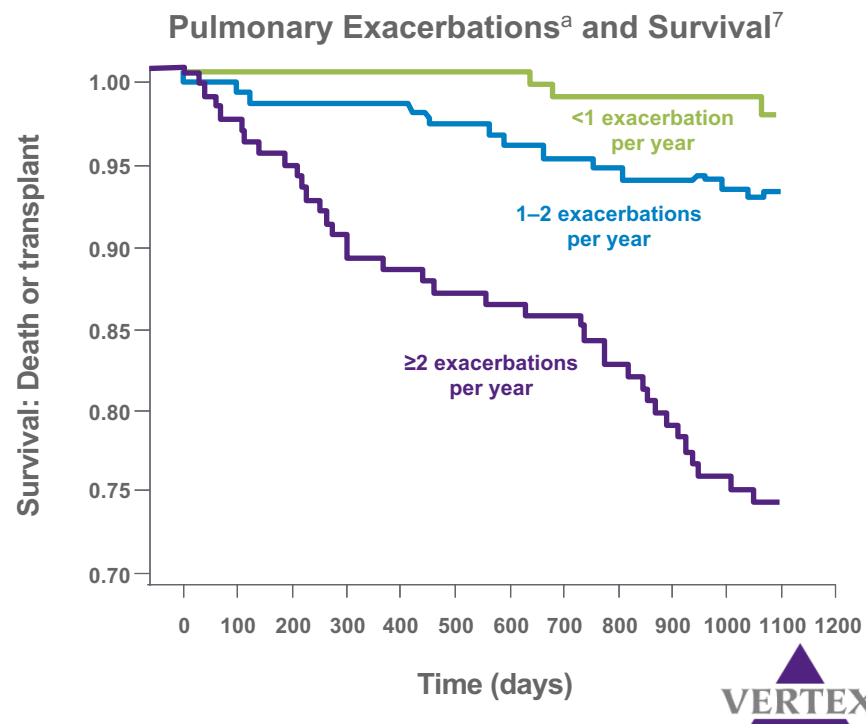


Figure Adapted from de Boer K, et al. *Thorax*. 2011;66(8):680-685.

^aPulmonary exacerbations requiring oral or IV antibiotics

1. Collaco JM et al. *Am J Respir Crit Care Med*. 2010;182(9):1137-1143.

2. Bradley J et al. *Eur Respir J*. 2013;4:571-577.

3. Britto MT et al. *Chest*. 2002;121(1):64-72.

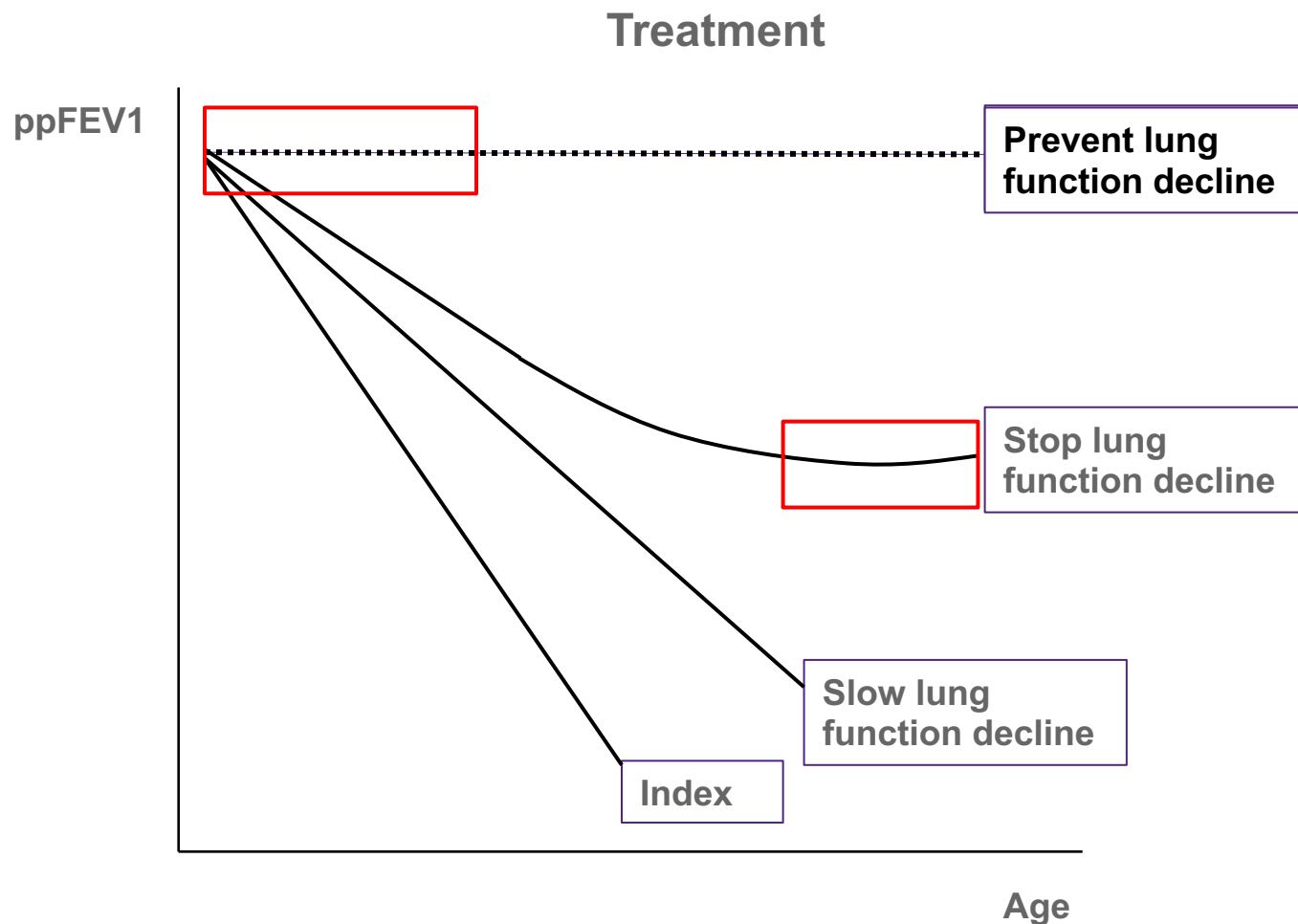
4. Sanders DB et al. *Am J Respir Crit Care Med*. 2010;182(5):627-632.

5. Liou et al., *Am J Epidemiol*. 2001;153:345-52

6. Stephenson et al. *Eur Respir J*. 2015;45(3):670-679.

7. de Boer K, et al. *Thorax*. 2011;66(8):680-685.

Ideally, the Goal of Pulmonary Exacerbation Treatment Is to Prevent Lung Function Decline



Cystic Fibrosis Pulmonary Guidelines for Treatment of Pulmonary Exacerbations

Recommendation	Grade
Site of treatment (home vs hospital)	I
Chronic medications	B
Inhaled plus IV tobramycin	I
Airway clearance	B
1 vs 2 antibiotics for <i>Pseudomonas</i>	I
Aminoglycosides: Once daily vs multidose	C
Continuous infusion β -lactam antibiotics	I
Duration of antibiotics	I
Routine synergy testing	D
Systemic corticosteroids	I

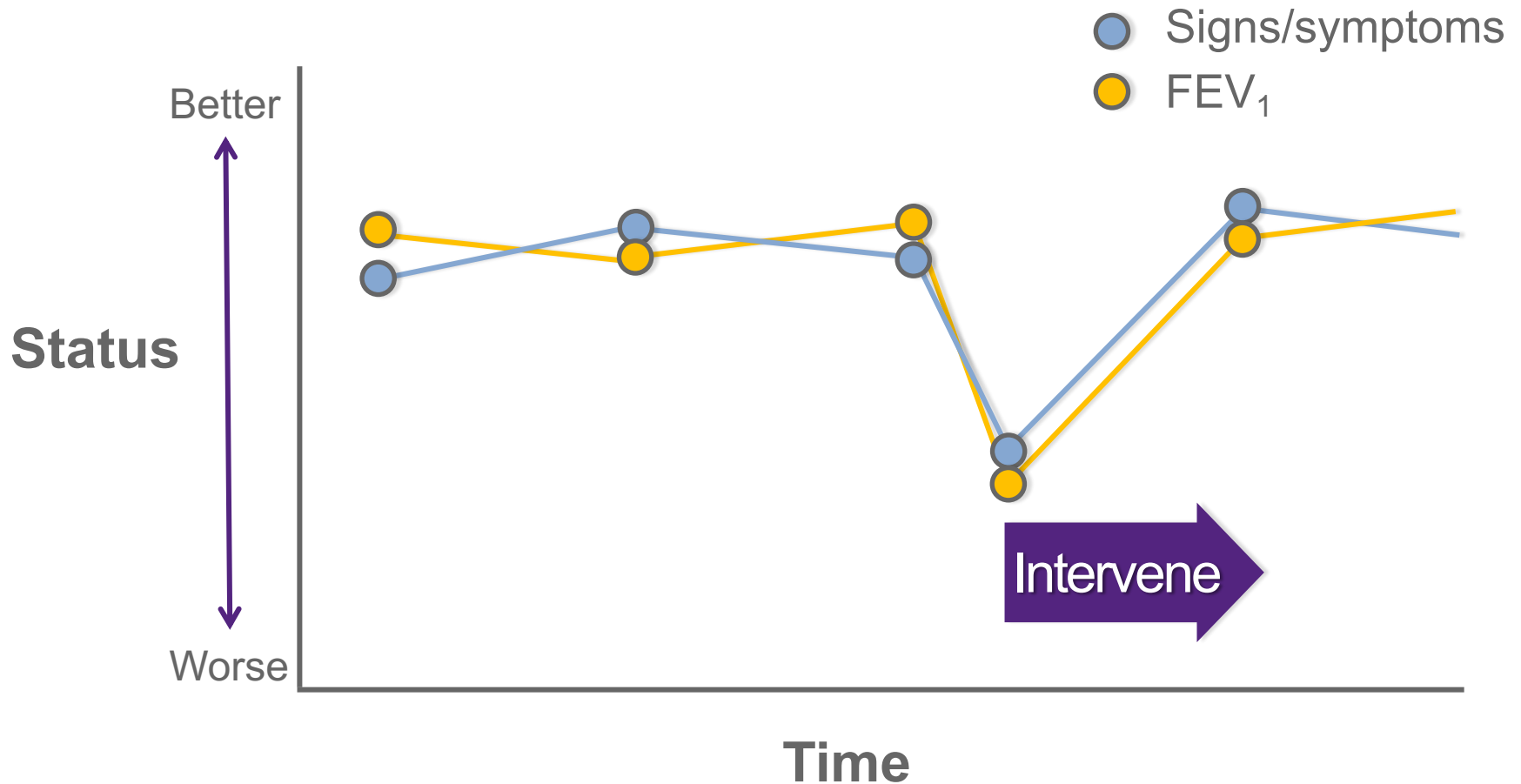
About antibiotics

B, committee recommends based on potential moderate/substantial benefit; C, recommends against routine use; D, recommends against use; I, insufficient evidence on balance of benefit and harm.

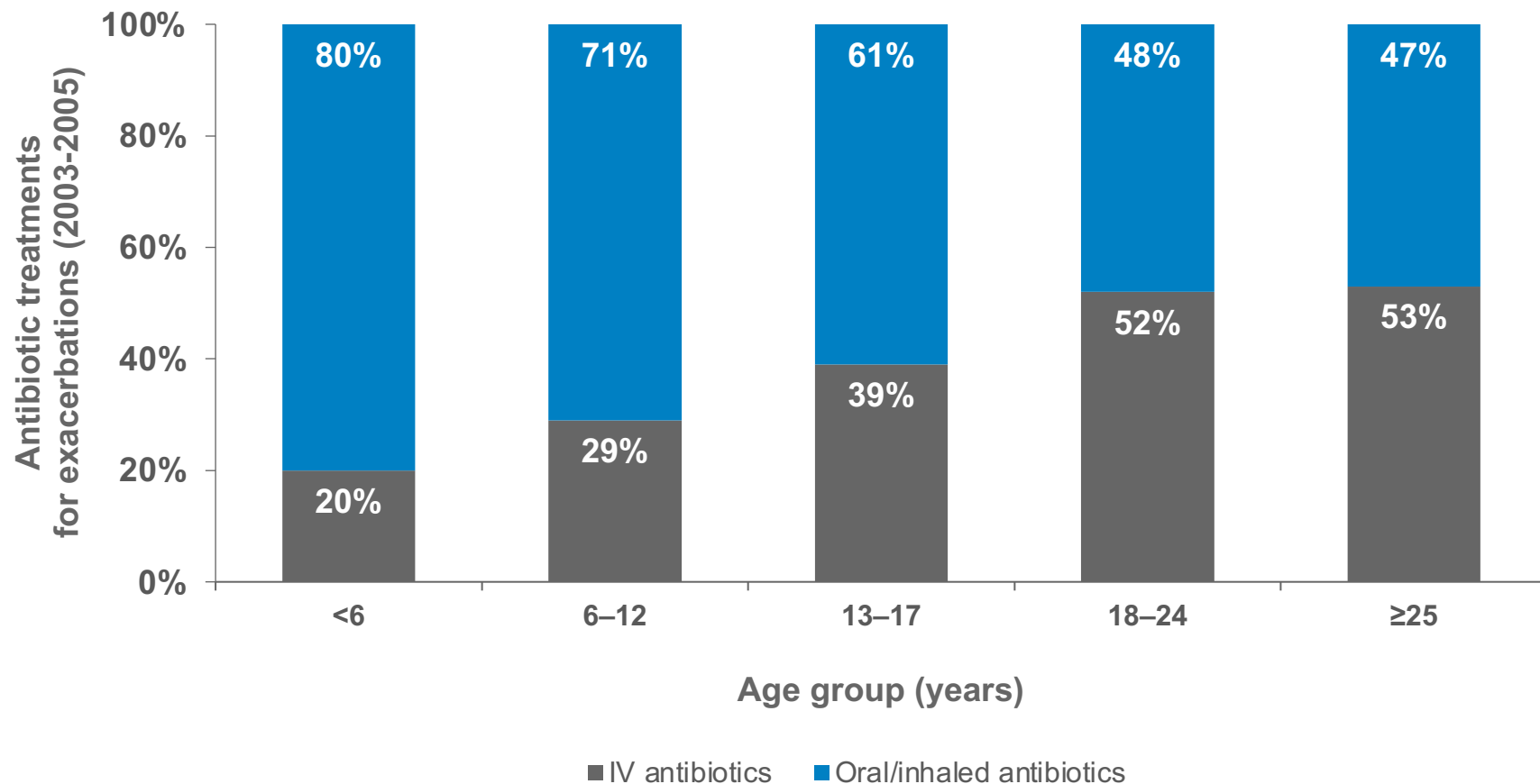
Flume PA et al. *Am J Respir Crit Care Med.* 2009;180(9):802-808.



Antibiotics Are a Common Treatment for an Exacerbation



Children Are More Likely to Receive Oral or Inhaled Antibiotic Treatments for Pulmonary Exacerbations



Has Our Collective Vision Changed?

If exacerbation incidence inversely correlates with
FEV₁ % predicted¹...

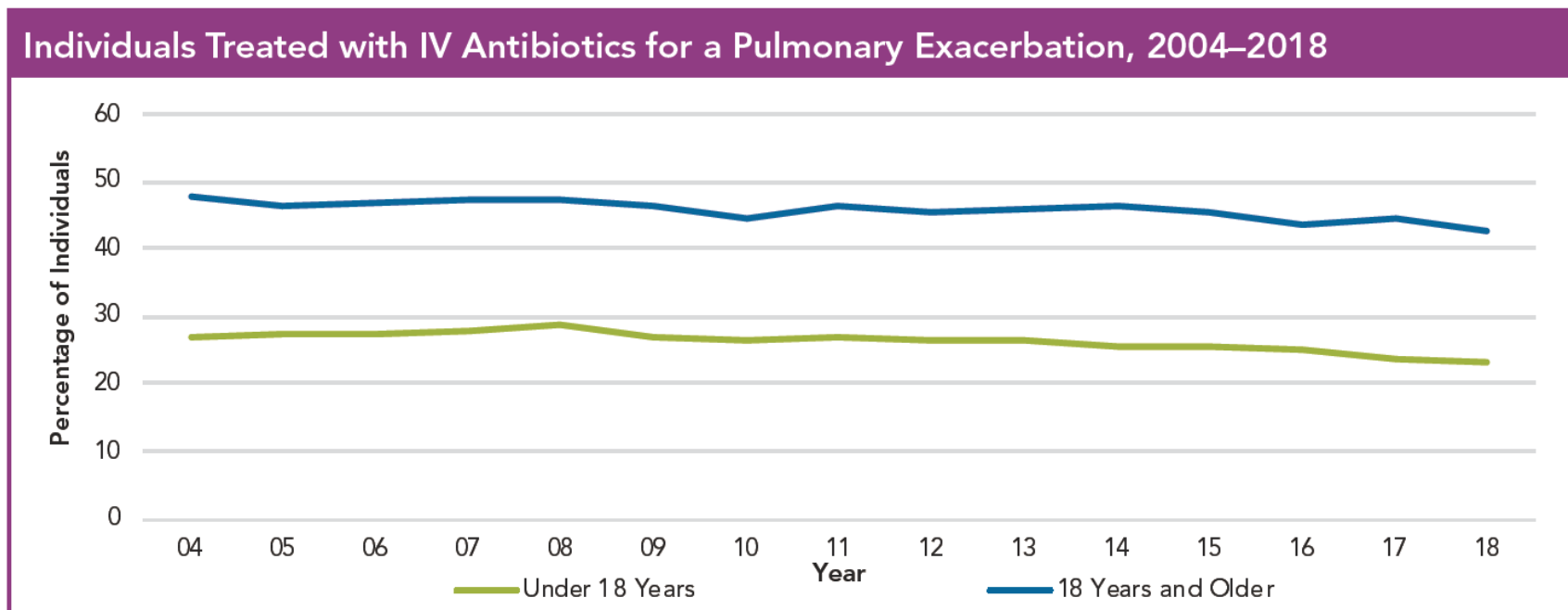
...and...

mean FEV₁ for the US CF cohort has generally improved
over the past decade²...

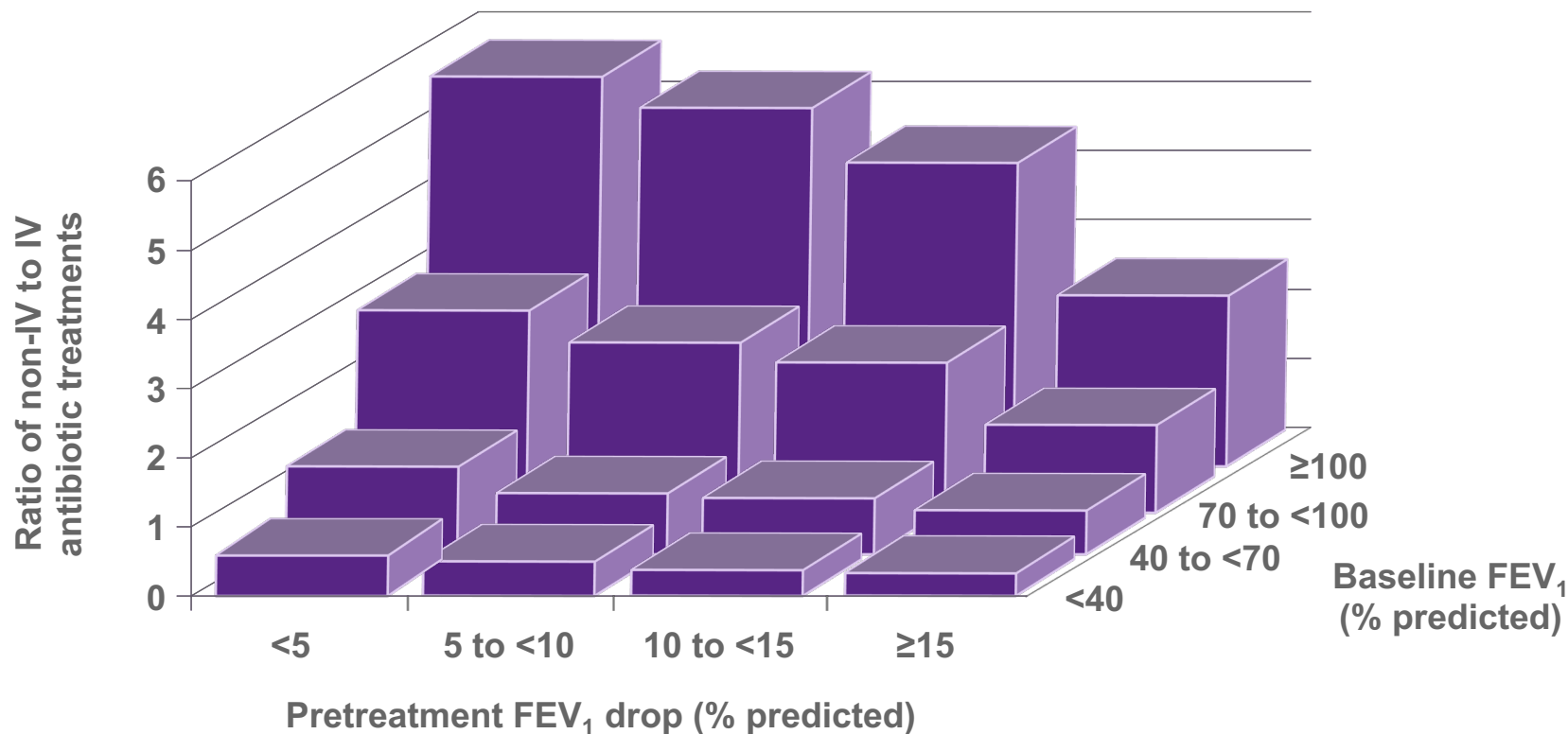
...then...

shouldn't the mean rate of IV treatment for exacerbations
be falling?

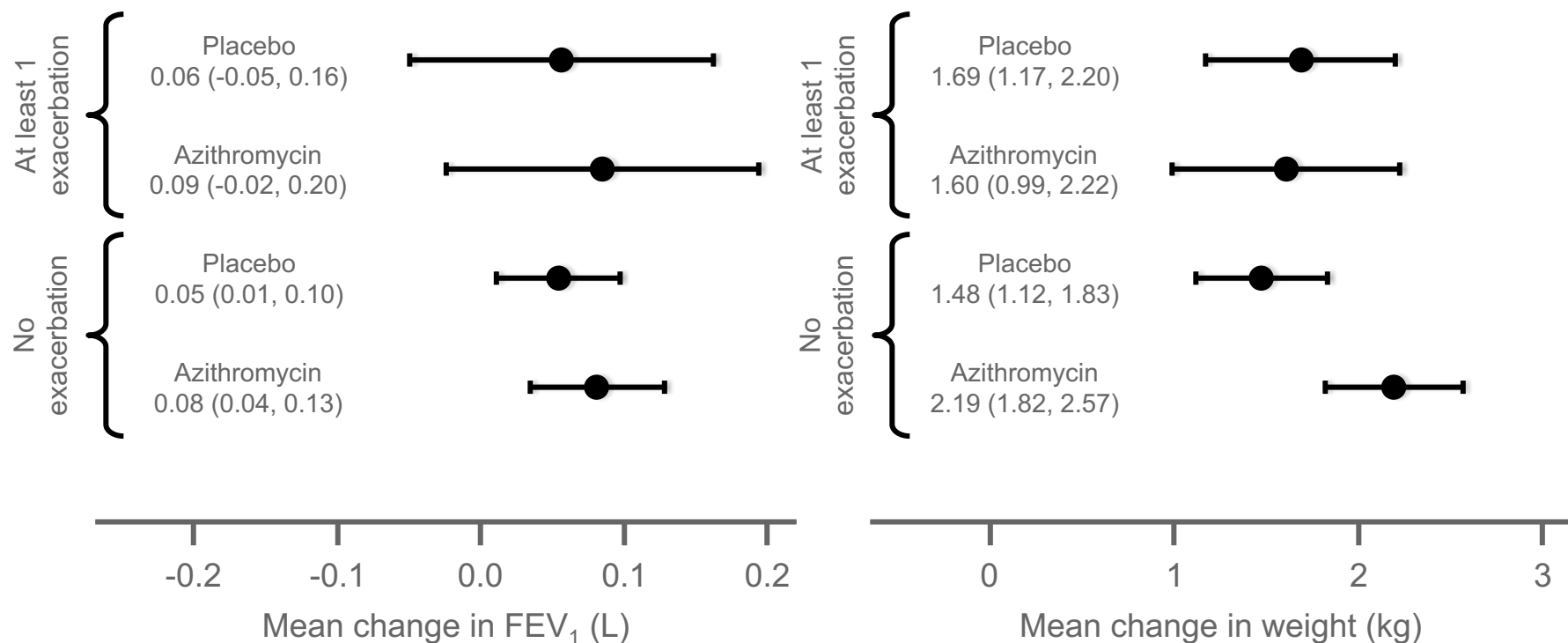
Annual IV Antibiotic Treatment for Pulmonary Exacerbation: US CF Cohort 2004-2018



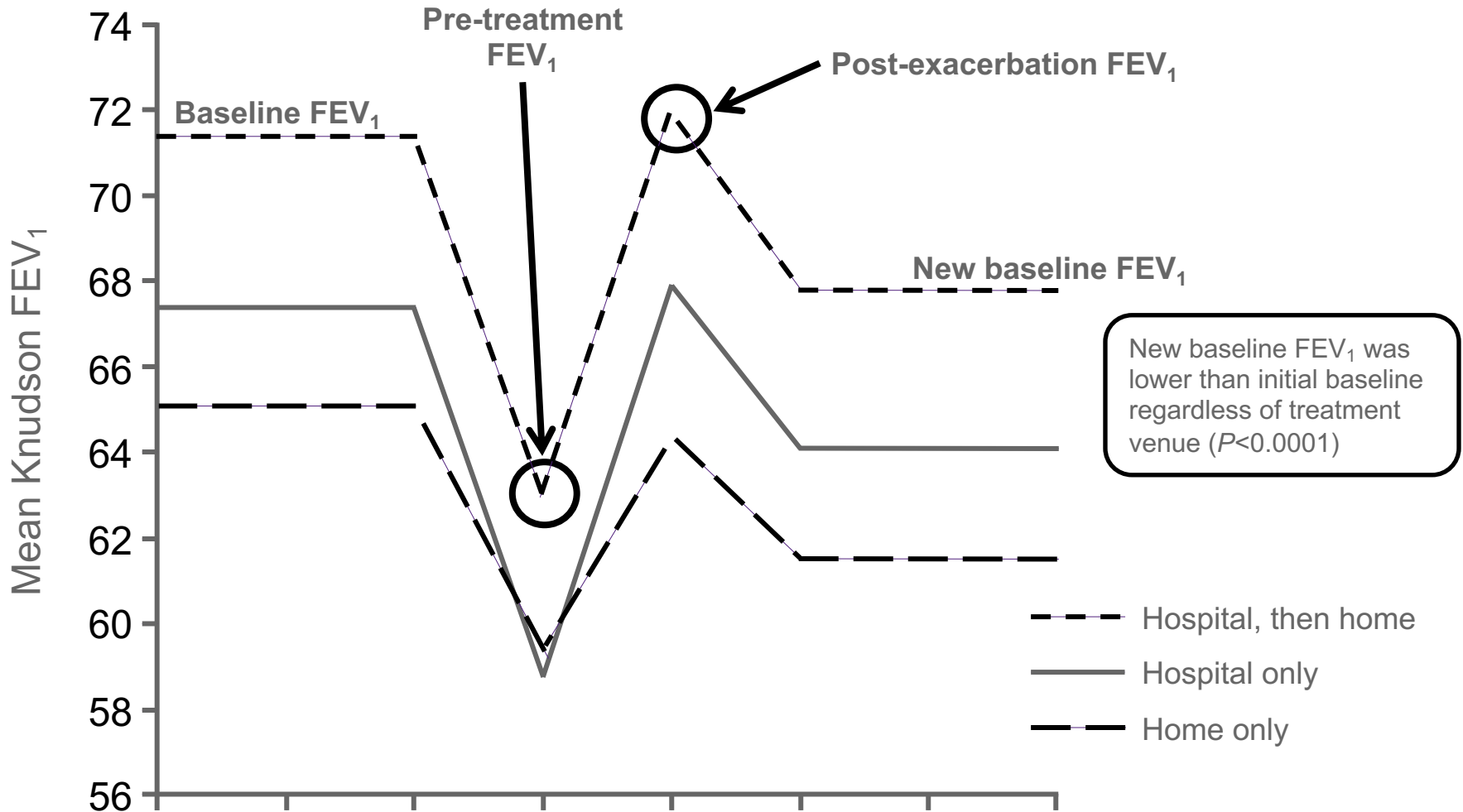
Non-IV to IV Ratio of Antibiotic Treatment Based on Baseline FEV₁ and Drop in FEV₁



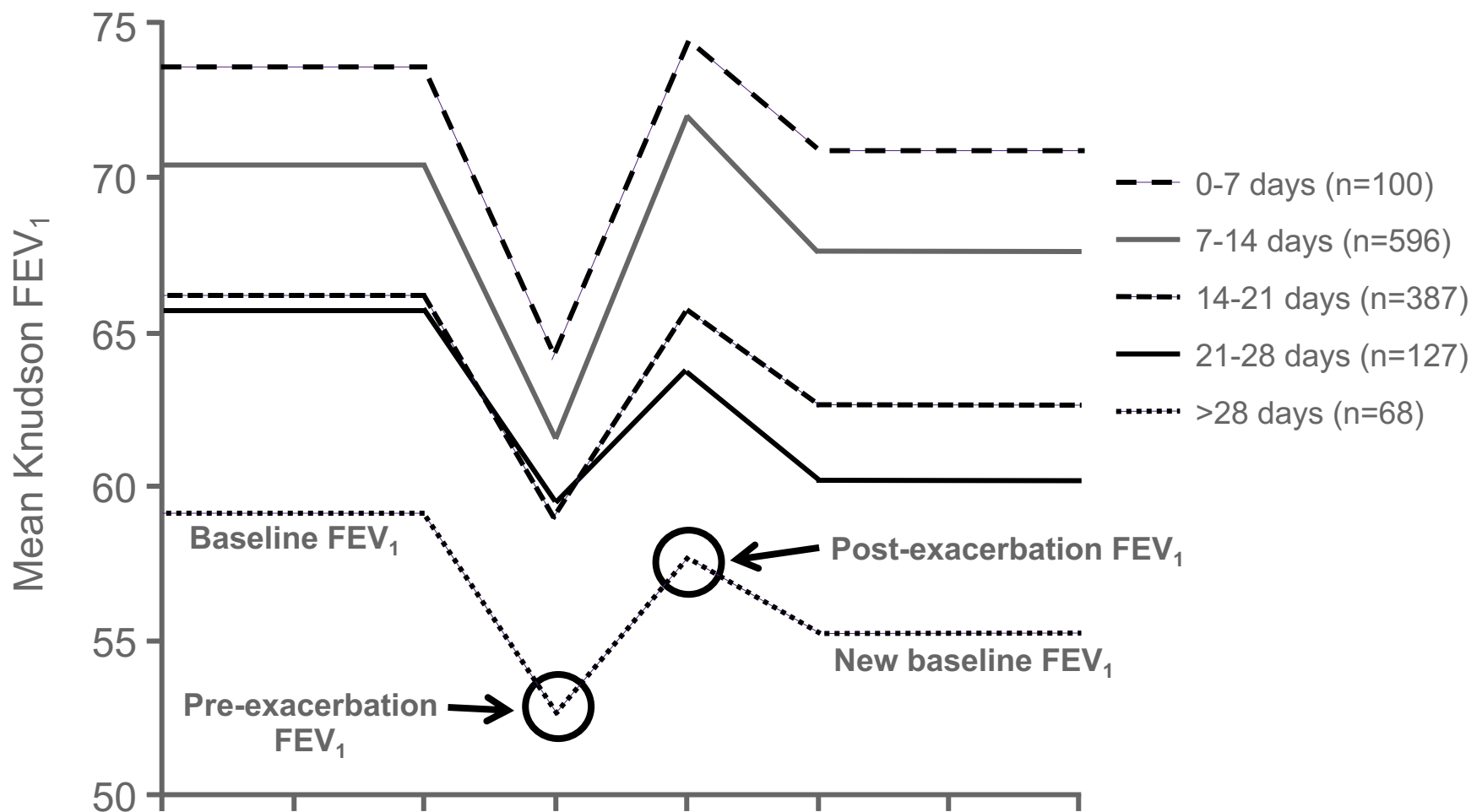
Chronic Oral Antibiotic Treatment Has No Impact on Lung Function or Body Weight in *P. aeruginosa*-Negative Patients With Pulmonary Exacerbations



FEV₁ Baseline Is Lower Post-exacerbation Regardless of IV Antibiotic Venue (Home vs Hospital)



FEV₁ Baseline Is Lower Post-exacerbation Regardless of IV Antibiotic Duration



Pulmonary Exacerbations

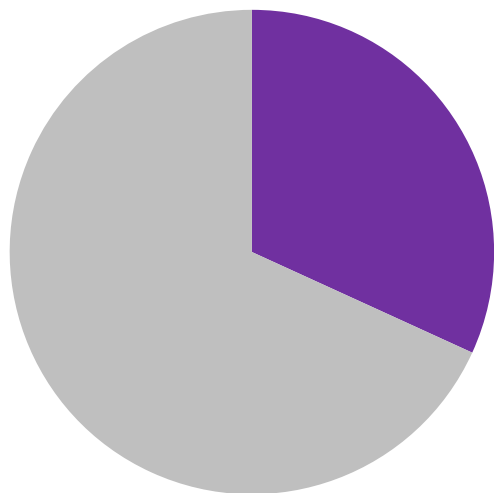
- What defines a pulmonary exacerbation?
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Pulmonary Exacerbations Are Frequent

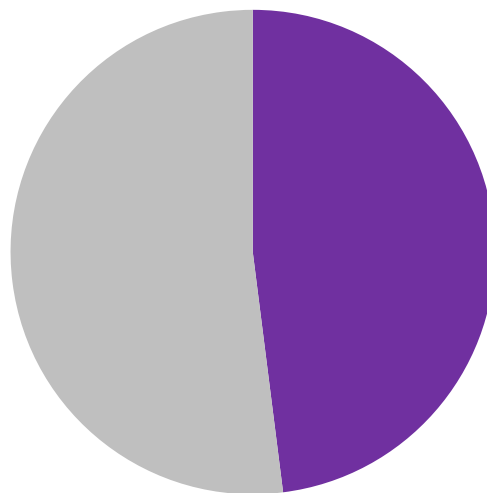
Based on Requirement for IV Antibiotics

33.3% (10,248 patients)



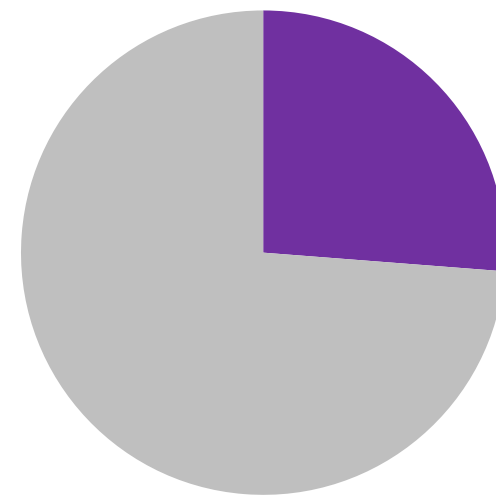
Among 30,775 patients in the 2018 CFF Registry¹

44.7% (4400 patients)



Among 9,847 patients in the 2018 UK CF Registry²

28.8% (357 patients)

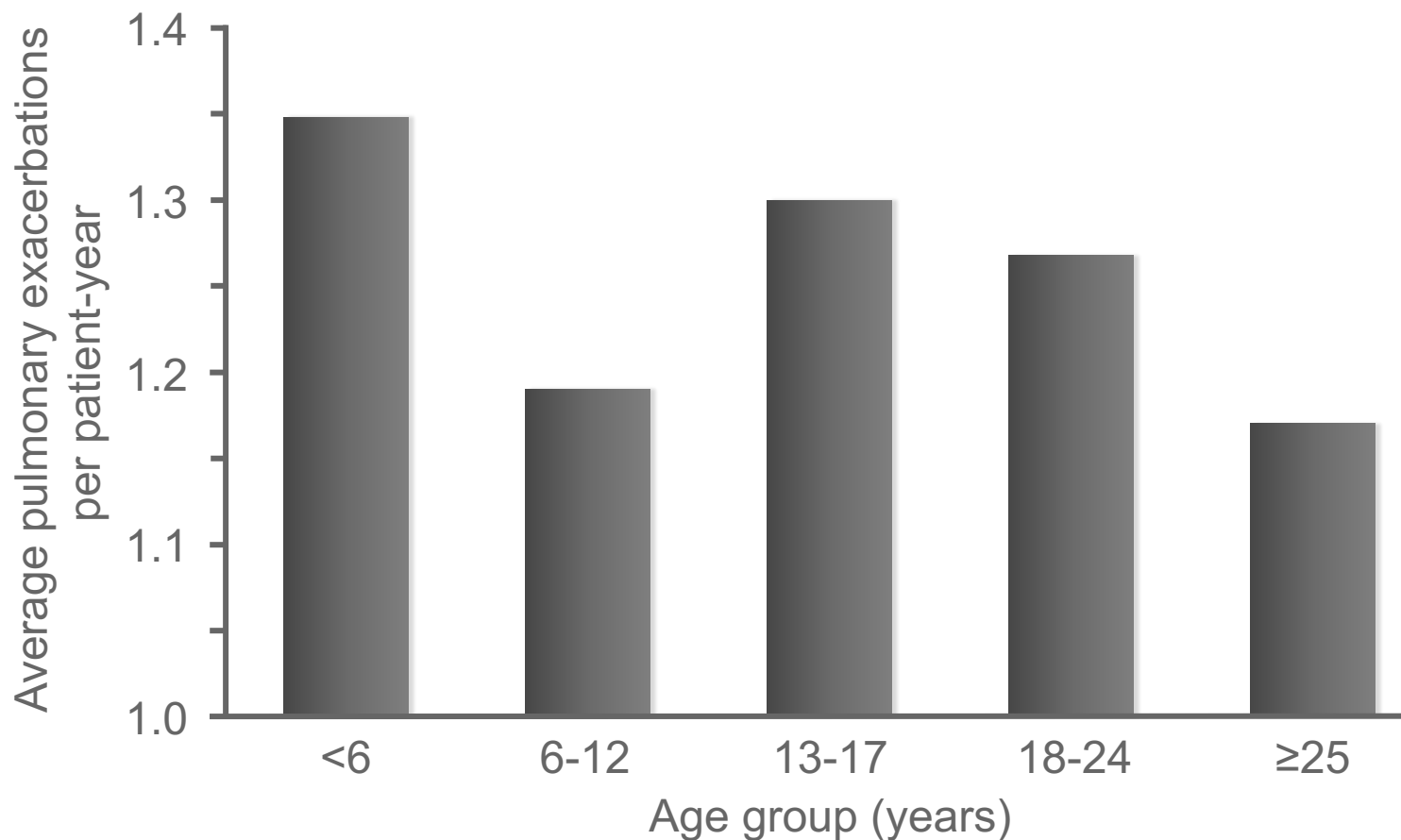


Among 1,239 patients in the 2018 Ireland CF Registry³

1. Cystic Fibrosis Foundation (CFF) Patient Registry. 2018 Annual Data Report. Bethesda, MD: CFF; 2019. 2. United Kingdom Cystic Fibrosis Patient Registry. 2018 Annual Data Report. Available at: [cysticfibrosis.org.uk](http://www.cysticfibrosis.org.uk). 3. Cystic Fibrosis Registry of Ireland. 2018 Annual Report. Available at: http://www.cfri.ie/docs/annual_reports/CFRI2018.pdf. Accessed April 2020.



Frequency of Clinician-Diagnosed Pulmonary Exacerbations by Age

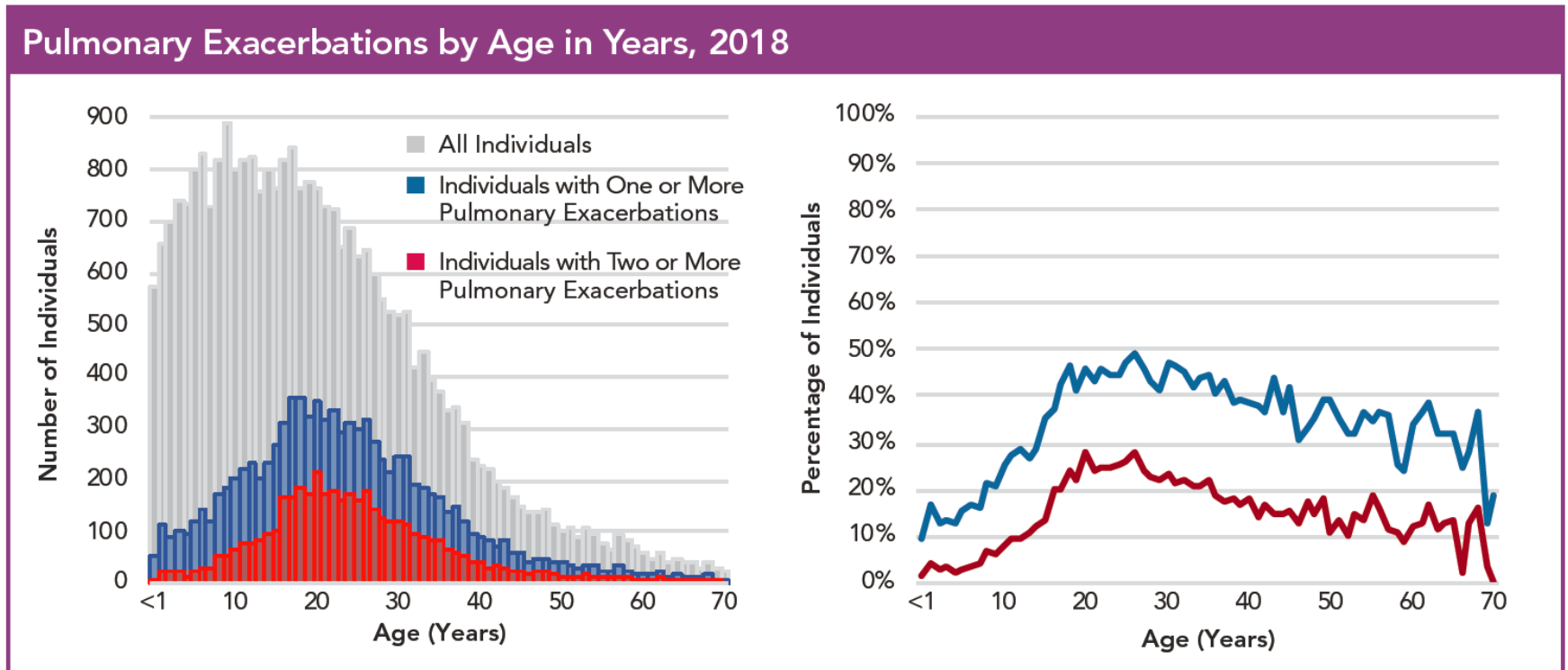


Adapted from Wagener JS et al. *Pediatr Pulmonol.* 2013;48(7):666-673.

Pulmonary exacerbations were defined prospectively as any new or increased respiratory symptoms or any clinical worsening in pulmonary status for which the clinician decided to initiate new antibiotic therapy.

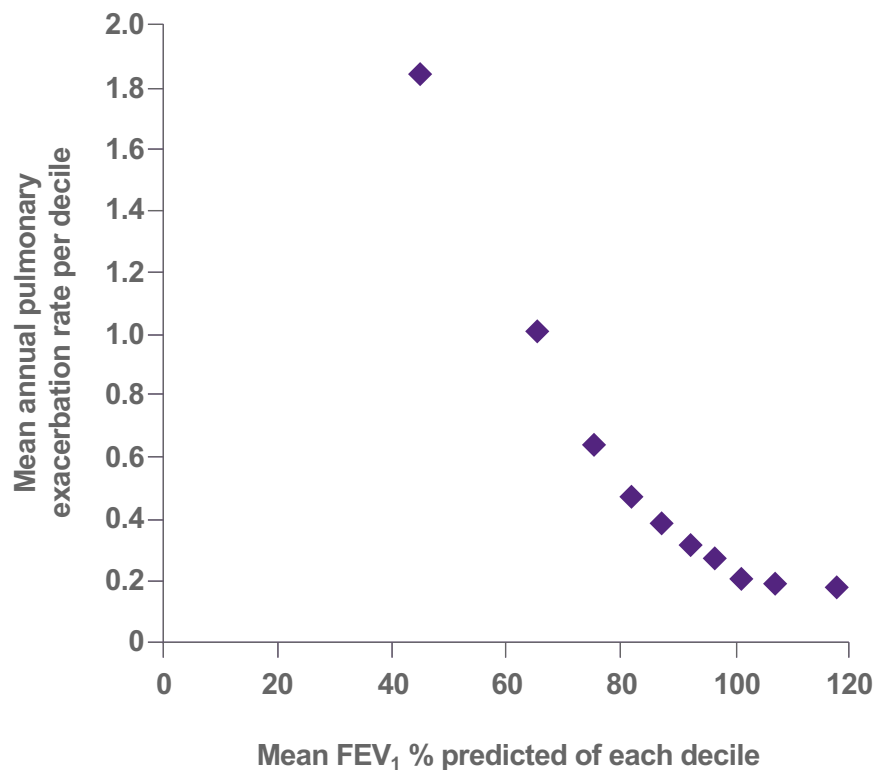


Pulmonary Exacerbations Generally Increase With Increasing Age (US Data)

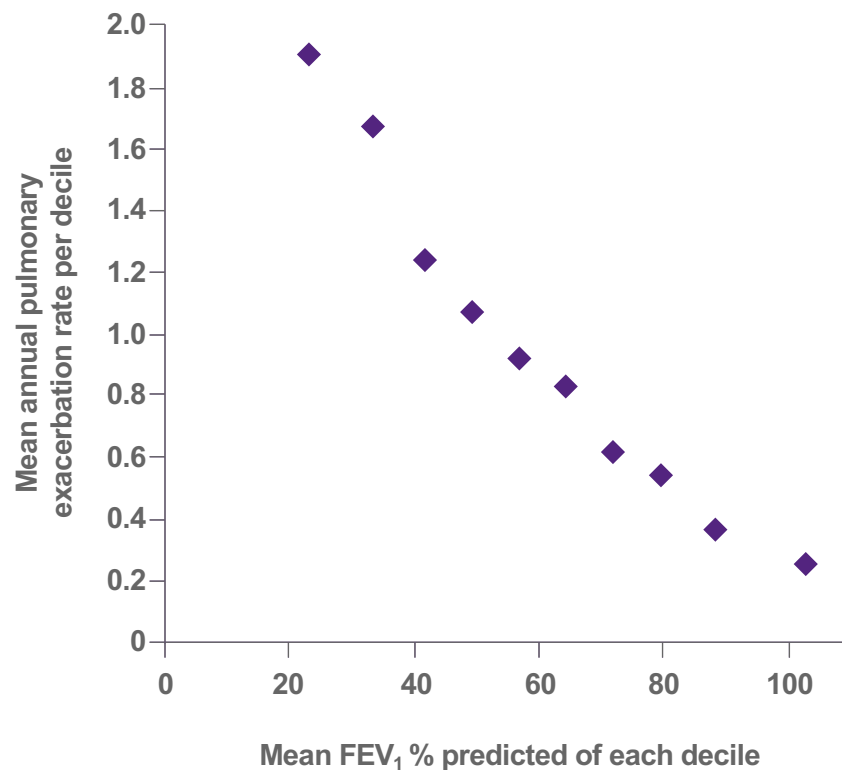


Risk of Pulmonary Exacerbation Is Higher With Lower FEV₁

Patients <18 years of age



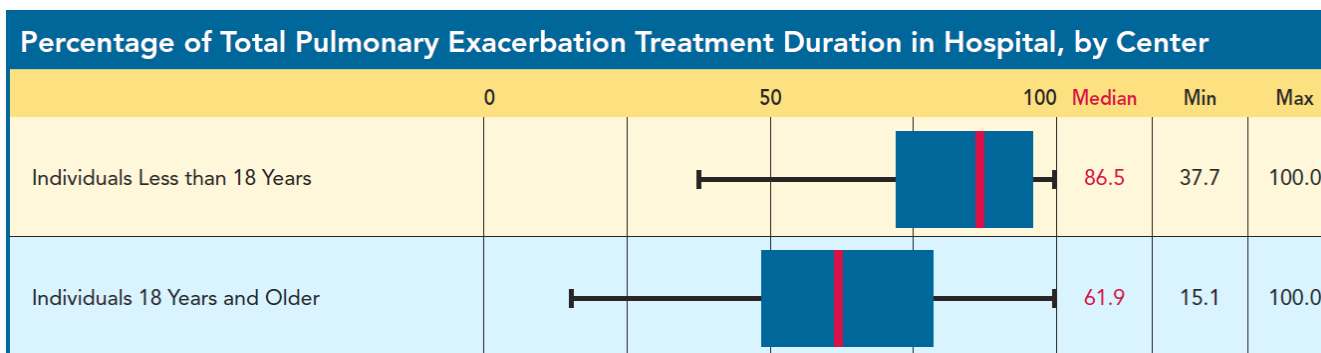
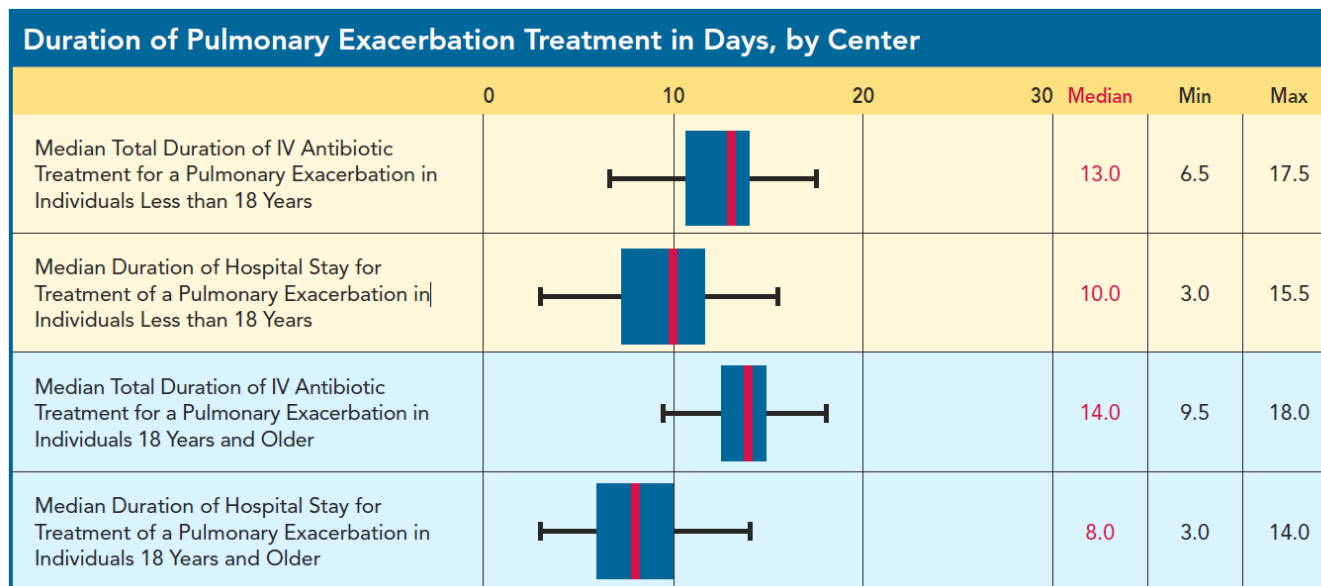
Patients ≥18 years of age



Impact of Pulmonary Exacerbations on Patients and/or Caregivers

- Days of work or school lost to hospitalization and IV antibiotic therapy^{1,2}
 - IV antibiotic therapy ranged from 13 hospital days to 19 at-home days per course in the US Twin Sibling Study¹
 - In a UK study, a mean of 1.5 exacerbations per patient per year required hospitalization with a mean length of stay of 9.2 days²
- Negative effect on patient physical and psychosocial health-related quality of life (HRQoL)^{2,3}
 - Increasing number of pulmonary exacerbations was the only significant predictor of poorer HRQoL physical and psychosocial scores in multivariable analyses³
 - HRQoL (based on CFQ-R and EQ-5D) was poorer with worsening pulmonary exacerbation status (none, mild, or severe)²
 - Mild exacerbations were managed without hospitalization; severe exacerbations required hospitalization

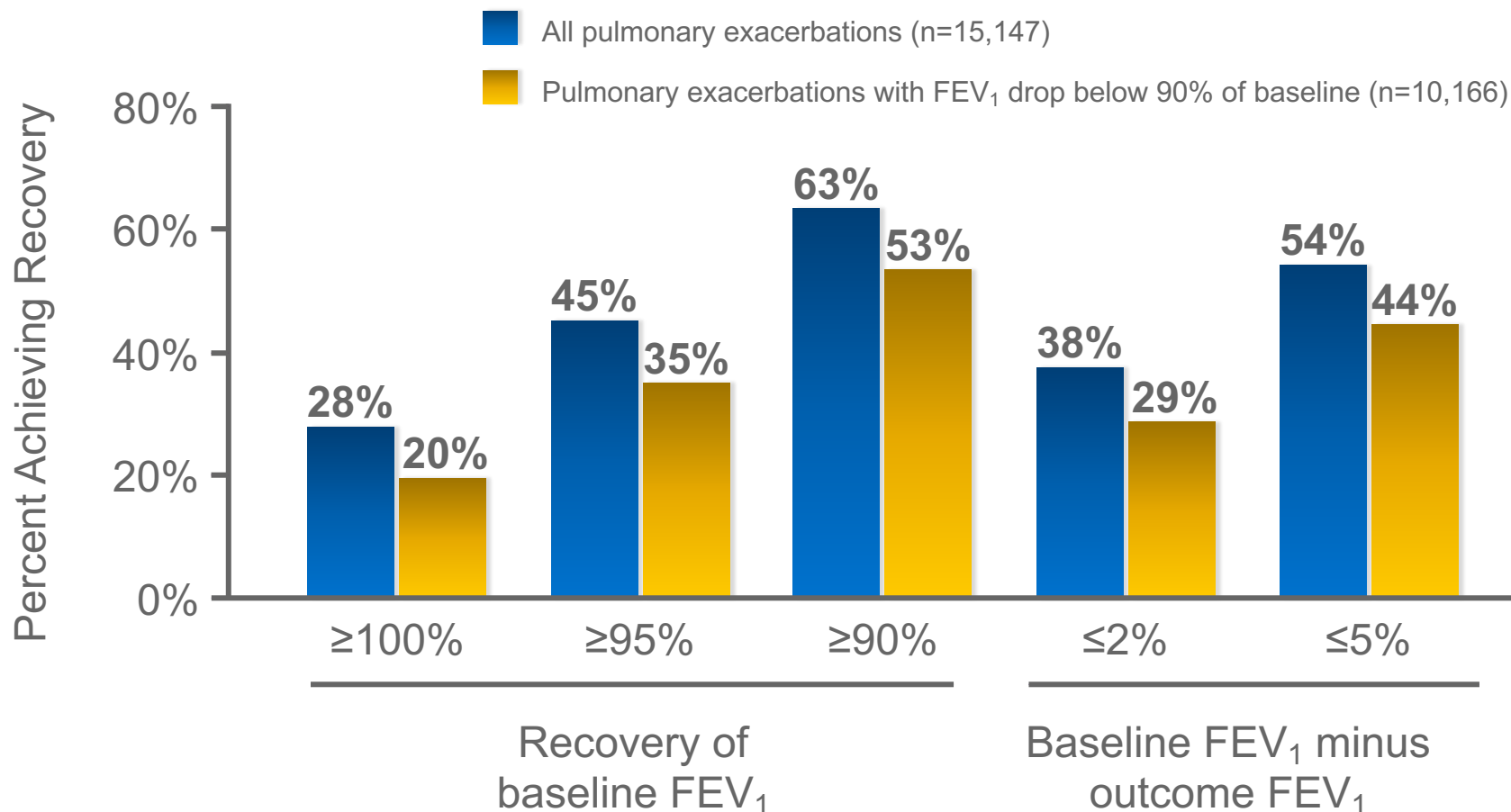
Pulmonary Exacerbation Treatment Involves Hospitalization and IV Antibiotics for >1 to 2 Weeks, With Variability by Center (US Data)



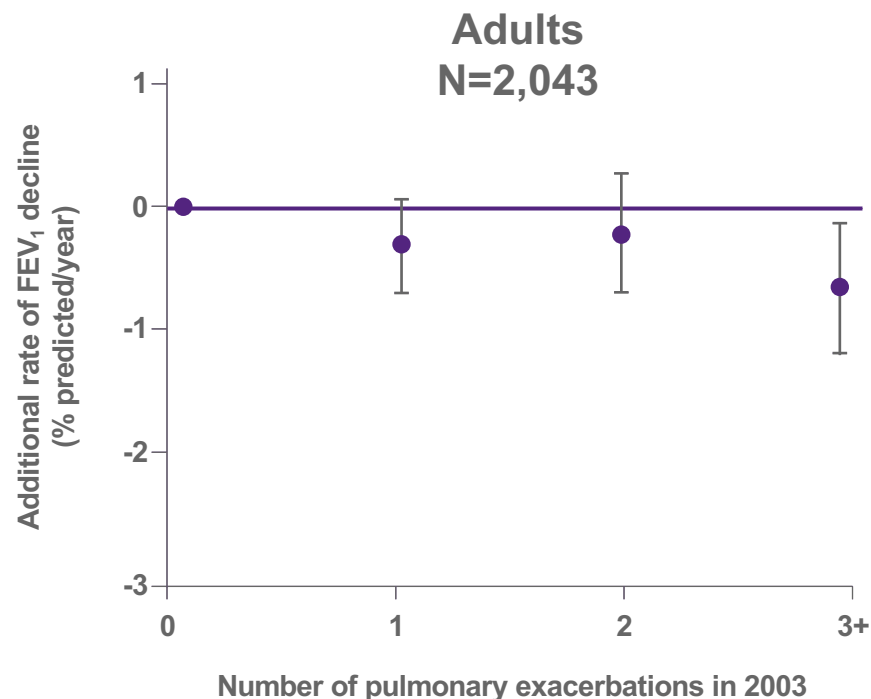
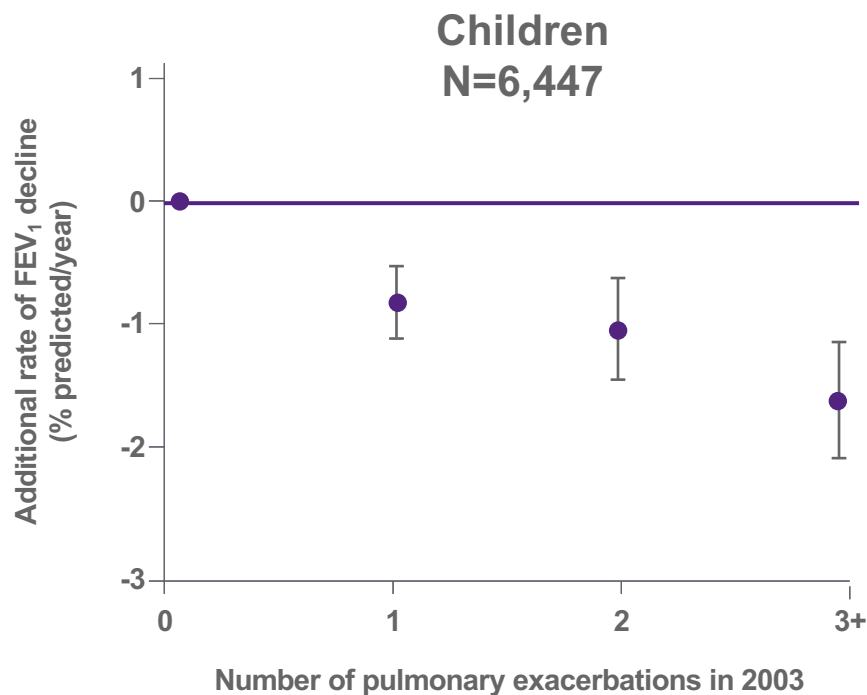
Pulmonary Exacerbation Associated With More Rapid, Permanent Decreases in FEV₁

- Baseline lung function (FEV₁) fails to recover in approximately 25% of exacerbations¹
- Even when there is initial FEV₁ recovery, a new lower baseline is often established²
- Pulmonary exacerbations are associated with permanent reduction in lung function and a fast subsequent rate of decline in FEV₁²⁻⁴

Full FEV₁ Recovery Following Treatment Does Not Occur in Many Patients



Annual FEV₁ Decline Related to Exacerbations

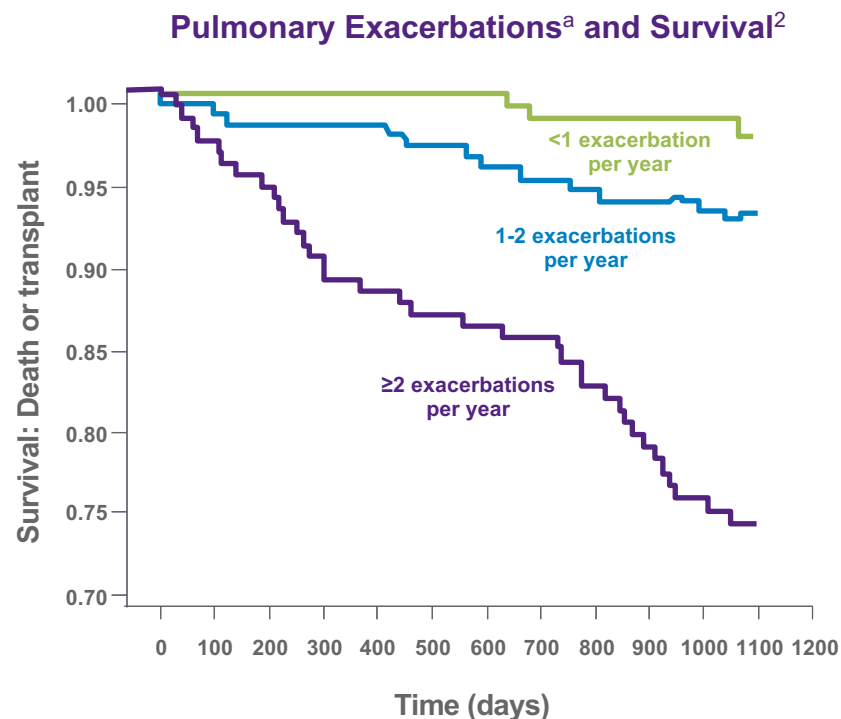


Average Annual Rate of FEV₁ Decline Versus Patients With No Exacerbations in 2003

Number of PEs in year	1	2	3+
Children (age 6-20)	-0.83 (<i>P</i> <0.001)	-1.06 (<i>P</i> <0.001)	-1.63 (<i>P</i> <0.001)
Adults (age ≥21)	-0.33 (<i>P</i> =0.09)	-0.23 (<i>P</i> =0.36)	-0.67 (<i>P</i> =0.01)

Pulmonary Exacerbations Have a Cumulative Effect on Loss of Lung Function and Risk of Death

- 1-2 exacerbations/year increases risk of death 3-fold¹
 - ≥ 3 exacerbations/year increases risk of death 4.5-fold¹
- ≥ 2 exacerbations/year leads to a >4-fold increased risk of death or lung transplant vs 0 exacerbations²
- Each acute pulmonary exacerbation within the year had an unexpectedly large, negative impact on 5-year survival equal to subtracting 12% from the measured FEV1% value³



^aPulmonary exacerbations requiring oral or IV antibiotics
Figure Adapted from de Boer K, et al. *Thorax*. 2011;66(8):680-685.

1. Stephenson et al. *Eur Respir J*. 2015;45(3):670-679.

2. de Boer K, et al. *Thorax*. 2011;66(8):680-685.

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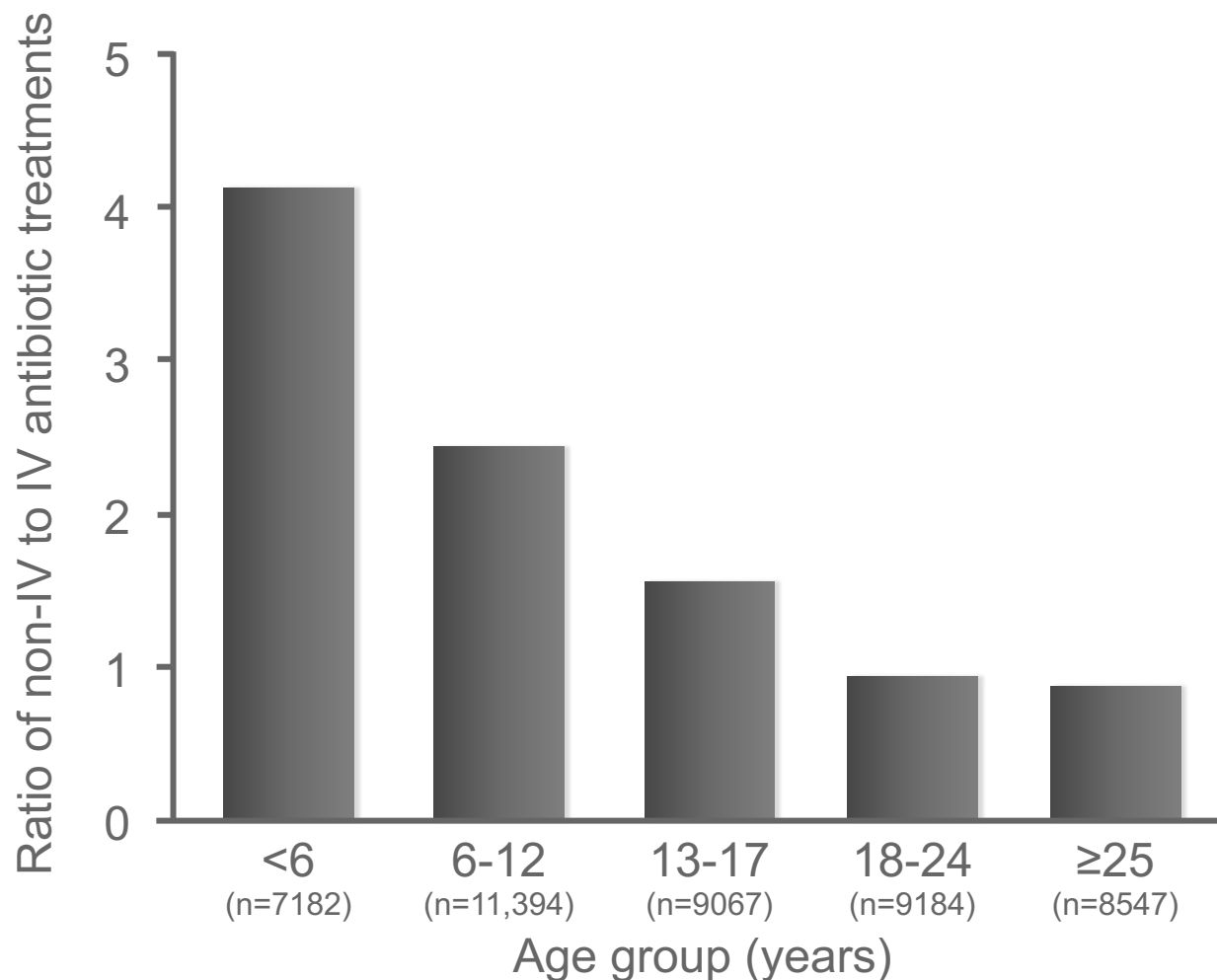
Conclusions

- No specific consensus definition for what constitutes a pulmonary exacerbation but agreement on clinical significance
- Bacteria are only 1 factor in the generation of a pulmonary exacerbation
- Exacerbations may begin early in life and become more frequent as lung disease progresses
- Patients experience a significant medical burden from pulmonary exacerbations and trying to prevent these exacerbations is important
- Frequent exacerbations can result in rapid lung function decline and earlier death

MORE INFORMATION



Non-IV to IV Ratio of Antibiotic Treatment for a Pulmonary Exacerbation by Age



Adapted from Wagener JS et al. *Pediatr Pulmonol.* 2013;48(7):666-673.

