in this age group is likely underestimated by less interventional methods of microbiological screening (2). It also aligns with the accumulating evidence that increasing prevalence is associated with increasingly aggressive use of antibiotics in this cohort, and we would support the call for further work to explore the clinical implications of fungal airway infection. We are, however, concerned that the data may not represent the full picture of cystic fibrosis airway microbiology in early childhood, most notably for the omission of microbiology results from airway samples obtained during pulmonary exacerbations.

We acknowledge that previously reported data from the same group report the sensitivity of oropharyngeal (OP) cultures for the detection of *Pseudomonas aeruginosa* to be low (23%) when compared against BAL performed at times of clinical stability (3). However, during pulmonary exacerbations, substantially higher sensitivity (76%) is reported for OP cultures compared with BAL for the detection of *P. aeruginosa* (4), and no benefit has been found for a strategy of bronchoscopic airway sampling over noninvasive sampling to guide treatment of pulmonary exacerbations in young children (5). Although imperfect, noninvasive airway sampling, with reduced exposure to general anesthesia risk and a significantly reduced cost, continues to form a routine part of clinical care in many cystic fibrosis centers worldwide. Sputum induction has also been shown to act as a credible alternative to BAL in symptomatic children (6).

In the current study (1), routine treatment of pulmonary exacerbations at one of the two study sites was guided by previous cultures (including OP samples), thereby inferring that OP cultures were considered to reflect lower airway microbiology. Yet the results of noninvasive (OP or other) cultures collected between surveillance bronchoscopies, and in particular during pulmonary exacerbations, are not reported. The omission of microbiological samples collected during symptomatic periods risks potential underreporting of the prevalence of bacterial airway infection, particularly if infection is then cleared after targeted antibiotic therapy. ■

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Lower Airway Infection in Preschool Children with Cystic Fibrosis: An International Comparison

To the Editor:

We read with interest the paper by Breuer and colleagues published in the *Journal* in September 2019, which demonstrated a declining prevalence of *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Staphylococcus aureus* lower airway infection in children with cystic fibrosis (CF) over an 18-year period (1). Like the authors, we have been conducting BAL surveillance in preschool children with CF at three of the six specialist CF centers in Ireland, as part of SHIELD CF (The Study of Host Immunity and Early Lung Disease in Cystic Fibrosis). Here, we present data on 335 BAL samples from 110 children with CF that were collected from 2010 to 2018. We also find a reassuring reduction in the prevalence of *P. aeruginosa* infection in BAL from Irish children over time.

There are, however, two clear differences between our data and those published by Breuer and colleagues that warrant discussion. Although the prevalence of infection with *P. aeruginosa* we observe does not differ significantly from that reported by Breuer and colleagues, *S. aureus* and *H. influenzae* prevalence is significantly higher and *Aspergillus* prevalence is significantly lower in our cohort (Table 1). A closer look at the data (Table 2) reveals striking differences in the prevalence of *S. aureus* and *H. influenzae* in the first 2 years that decreases with age, and an increasing difference in the rates of infection with *Aspergillus*, which only becomes significant in the older cohort.

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Table 1. Prevalence of Pathogenic Organisms in the Lower Airways of Preschool Children with Cystic Fibrosis in Irish Cystic Fibrosis Centers, 2010–2018

	2010–2012 (*n* = 87)	2013–2015 (*n* = 149)	2016–2018 (*n* = 99)	2012–2018 (*n* = 285)	Breuer *et al.* (1) 2012–2018 (*n* = 866)	*P* Value
P. aeruginosa	3 (3.4)	8 (5.4)	1 (1)	10 (3.5)	51 (5.9)	0.11
P. aeruginosa PCR	4/65 (6.2)	16/101 (15.8)	2/80 (2.5)	19 (8.9)	NA	NA
S. aureus	14 (16.1)	35 (23.5)	24 (24.2)	66 (23.2)	78 (9.1)	<0.001
H. influenzae	30 (34.5)	40 (26.8)	25 (25.3)	74 (26)	72 (8.3)	<0.001
Aspergillus sp.	5 (5.7)	4 (2.7)	4 (4)	9 (3.2)	97 (11.2)	<0.001

Definition of abbreviations: *H. influenzae* = *Haemophilus influenzae*; NA = not available; *P. aeruginosa* = *Pseudomonas aeruginosa*; *S. aureus* = *Staphylococcus aureus*.
Comparison is made with data from Breuer and colleagues (1). Data are shown as *n* (%).

These data are somewhat surprising at first sight given the seemingly homogeneous approach to treatment of young children with CF and, indeed, the processing of airway specimens in the clinical laboratories of specialist centers in the developed world. Like our Australian colleagues, we approach airway clearance and treatment of intercurrent infection aggressively in this young cohort. We also routinely treat our patients <2 years of age with antistaphylococcal prophylaxis—in our case, flucloxacillin as opposed to co-amoxiclav. We routinely use co-amoxiclav for treatment of low-grade exacerbations throughout childhood and also use azithromycin prophylaxis in selected children in this age group. We use 28 days of inhaled tobramycin for eradication of *P. aeruginosa* and only use oral or intravenous antipseudomonal therapy if this fails on more than one occasion.

The Australian data show much lower rates of infection with *S. aureus* and *H. influenzae* in the first 2 years of life. The fact that this difference decreases with age suggests that it may decline as a result of antibiotic prophylaxis and that co-amoxiclav is more effective than flucloxacillin in this regard. The difference in prevalence of *Aspergillus* species between the two datasets is the opposite of what is seen with *S. aureus* and *H. influenzae*, where an increasing difference is evident over time. This may be related to cumulative antibiotic exposure, and although direct comparisons of total antibiotic exposures are not possible, the description of antibiotic use in the paper by Breuer and colleagues would suggest that more antibiotics are used overall in Australian children than in Irish children.

Another potential factor in the differing prevalence of airway pathogens is the local environment. Airway *P. aeruginosa* infection was previously shown to be linked to environmental conditions (2). It is possible that different environmental conditions in Ireland and Australia have an effect on the prevalence of *Aspergillus* and that treatment of suspected airway *P. aeruginosa* infection might contribute to this (3), particularly as this seems to be more aggressive in the Australian cohort.

Independently of the etiology of the significant differences in lower airway infection between our countries, these data raise the question of which is the greater evil, a higher prevalence of bacteria or a higher prevalence of *Aspergillus?* This can only be understood with further clinical research and underlines the importance of structured longitudinal clinical research programs and international comparisons and collaboration in CF. ■

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Table 2. Prevalence of Pathogenic Organisms in Irish and Australian Cohorts (2012–2018) according to Age at the Time of Sampling

	0–2 Years			3–4 Years			5–6 Years		
	Ireland (*n* = 122)	Australia (*n* = 304)	*P* value	Ireland (*n* = 117)	Australia (*n* = 236)	*P* value	Ireland (*n* = 96)	Australia (*n* = 326)	*P* value
P. aeruginosa	4 (3.3)	13 (4.3)	0.63	3 (2.6)	14 (5.9)	0.16	5 (5.2)	24 (7.4)	0.06
S. aureus	20 (16.4)	13 (4.3)	<0.001	24 (20.5)	25 (10.6)	0.01	29 (30.2)	40 (12.3)	0.08
H. influenzae	32 (26.2)	4 (1.3)	<0.001	38 (32.5)	23 (9.7)	<0.001	25 (26.0)	45 (13.8)	0.6
Aspergillus sp.	1 (0.8)	11 (3.6)	0.14	5 (4.3)	26 (11.0)	0.03	7 (7.3)	60 (18.4)	<0.001

Definition of abbreviations: *H. influenzae* = *Haemophilus influenzae*; *P. aeruginosa* = *Pseudomonas aeruginosa*; *S. aureus* = *Staphylococcus aureus*.
Comparison is made with data from Breuer and colleagues (1). Data are shown as *n* (%).

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Reply to Turnbull *et al.* and to Hulme *et al.*

From the Authors:

In a recent issue of the *Journal*, we reported a change in infection prevalence observed over the 18 years of the AREST CF (Australian Respiratory Early Surveillance Team for Cystic Fibrosis) prospective study, specifically, a reduction in the prevalence of bacterial infections (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Haemophilus influenzae*), which resulted in *Aspergillus* species becoming the most prevalent lower respiratory infection cultured in recent years (1).

In a letter to the editor, Hulme and colleagues present infection prevalence data from a 6-year BAL surveillance program (SHIELD CF [The Study of Host Immunity and Early Lung Disease in Cystic Fibrosis]) in preschool-aged children with cystic fibrosis (CF) conducted at three specialist CF centers in Ireland. Differences in the prevalence of lower respiratory infections between their cohort and our Australian cohort, as well as possible explanations for these differences, are discussed in the letter. The Irish data show a much higher prevalence of lower respiratory *S. aureus* and *H. influenzae* infections and a much lower prevalence of *Aspergillus* species infections. These differences are striking, especially in the younger age group (0–2 yr).

Differences in the prevalence of bacterial infections between CF centers are not surprising. Even within the AREST CF cohort, significant differences between the two participating centers were reported (2). There could be numerous reasons for such differences, including antibiotic stewardship, practices involving antibiotic prophylaxis, varying protocols for the treatment of pulmonary exacerbations and environmental factors (as discussed by Hulme and colleagues), and patient adherence to treatment, infection control, and airway clearance routines.

The decrease in the prevalence of *S. aureus* and *H. influenzae* infections over the 18 years of the AREST CF study coincided with an overall more aggressive treatment approach. Specifically, use of chronic antibiotics increased considerably. Between 2004 and 2018, the percentage of preschool patients treated with long-term azithromycin and any use of inhaled tobramycin increased from 0% to 30% and 4.7% to 44%, respectively, possibly influencing the prevalence of bacterial infections. Interestingly, prophylactic treatment with amoxicillin–clavulanate did not change over the study period. In their letter, Hulme and colleagues do not provide specific information regarding antibiotic use in their patients, which makes it difficult to compare treatment effects on bacterial infection prevalence between the cohorts.

In a different letter, Turnbull and colleagues raise concern that infection prevalence in our study does not represent the full picture of CF airway microbiology in preschool children owing to a lack of report on samples obtained during pulmonary exacerbations, such as oropharyngeal swabs and induced sputum. We agree that it is possible that samples obtained during exacerbations might have increased the *incidence* of positive bacterial cultures. However, we aimed to report lower airway infection *prevalence*. Including upper airway samples, which have been shown to have a low positive predictive value for detecting lower airway infection during both exacerbations and clinical stability (3–5) (regardless of the test's sensitivity), would lead to an overestimation of the prevalence of lower airway infection. Furthermore, including samples obtained during exacerbations would introduce a selection bias, which would also cause an overestimation of infection. Thus, although we do agree that it is important to understand exacerbation microbiology, it's questionable whether such data should be included in an epidemiological study describing lower airway infection prevalence trends in relatively well preschool children with CF. In addition, and most importantly, exacerbation microbiology would not change the significant prevalence of lower respiratory *Aspergillus* species infections reported in our study.

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