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Association of meteorological and geographical factors and risk of initial *Pseudomonas aeruginosa* acquisition in young children with cystic fibrosis

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SUMMARY

Initial infection with the sentinel respiratory pathogen in children with cystic fibrosis (CF), *Pseudomonas aeruginosa* (*Pa*), is generally with environmental strains of this ubiquitous organism. The purpose of this study was to evaluate the associations between meteorological and geographical factors and risk of initial *Pa* acquisition in young children with CF. Using the U.S. Cystic Fibrosis Foundation Patient Registry from 2003 to 2009, 3463 patients met inclusion criteria, of which 48% ($n = 1659$) acquired *Pa* during follow-up. From multivariable Weibull regression, increased risk of *Pa* acquisition was associated with increasing temperature [hazard ratio (HR) per 1 °C: 1·13; 95% confidence interval (CI) 1·08–1·13], dew point (HR per 1 °C: 1·10, 95% CI 1·07–1·13), rainfall (HR per cm: 1·10, 95% CI 1·07–1·12), latitude (HR per 1 °C northing: 1·15, 95% CI 1·11–1·20), longitude (HR per 1 °C easting: 1·01, 95% CI 1·01–1·02) and elevation (HR per 100 m: 1·05, 95% CI 1·03–1·07). These results suggest that environmental factors may play a previously unrecognized role in the aetiology of initial *Pa* acquisition.

Key words: Cystic fibrosis, epidemiology, paediatrics, *Pseudomonas*, respiratory infections.

INTRODUCTION

Cystic fibrosis (CF), an autosomal recessive disorder, is characterized by chronic endobronchial bacterial infection causing progressive pulmonary function decline and structural airway damage ultimately resulting in premature death. *Pseudomonas aeruginosa* (*Pa*), an environmentally ubiquitous Gram-negative bacterium, is the sentinel respiratory pathogen in CF patients. Chronic infection with this organism is seen in ~80% of US CF patients [1–4], and earlier *Pa* acquisition is associated with increased morbidity and mortality [2]. Initial *Pa* acquisition typically occurs in the first few

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years of life [4]; these initial *Pa* clinical isolates typically resemble those found in the natural environment in that they are non-mucoid and antibiotic susceptible [5]. Subsequently, chronic *Pa* infection occurs through adaptation of *Pa* strains to the individual respiratory milieu [6–8] and is generally characterized by mucoid and antibiotic-resistant communities [5, 9]. Therefore, early aggressive *Pa* eradication is recommended following initial infection [10].

Development of effective *Pa* prevention strategies outside of infection control guidelines in the clinical care setting [11, 12] have been limited due to an incomplete understanding of both the aetiology of and risk factors for initial *Pa* acquisition. The basic defect in the cystic fibrosis transmembrane conductance regulator (CFTR) is clearly implicated in the pathophysiology of *Pa* infection [13]; however, the numerous studies that have investigated demographic [14–16] and home environmental [17] factors, genetic modifiers [18, 19], as well as newborn screening [20, 21] have yet to identify individual-level modifiable or non-modifiable risk factors that are highly predictive of *Pa* acquisition.

Recognition that the natural environment is the likely source of initial *Pa* acquisition has resulted in recent efforts to identify macroenvironmental factors that could potentially influence *Pa* acquisition [22–24], as these factors may influence incidence of infectious diseases by affecting the propagation and virulence of the microorganism in the environment, the host's immunity, and the interaction of the host with the natural environment [25]. For young children with CF, previous studies have reported that seasonal differences for incident *Pa* acquisition vary by climatic zone [24] and temperature is associated with prevalent *Pa* infection [22], while geographical differences in time of initial *Pa* acquisition differ between urban and rural environments [23] and within the United States [26]. To date, no study has performed a comprehensive analysis of both meteorological and geographical variables and time to initial *Pa* acquisition.

In line with this research direction and to fill a current gap in our understanding of initial *Pa* acquisition, the objective of this study was to evaluate the association between specific meteorological, and geographical factors and the risk of initial *Pa* acquisition in young children with CF in the United States. Identification of meteorological and geographical factors associated with *Pa* acquisition could potentially contribute to our understanding of the aetiology of infection, as well as guide future *Pa* prevention strategies.

METHODS

Study population and design

We conducted a retrospective cohort study to evaluate the association of selected meteorological and geographical variables with time to initial *Pa* acquisition in young children with CF using data from the U.S. Cystic Fibrosis Foundation National Patient Registry from 2003 to 2009. The Registry contains detailed encounter based data on individual-level demographic and disease characteristics for approximately 80% of CF patients in the United States [27].

The study population included all children residing in the contiguous 48 states born after 31 December 2002 (all children were aged <7 years at study completion) with at least one respiratory culture recorded in the Registry prior to age 2 years. Additionally, to investigate incident *Pa* infection, children were excluded from the study population if *Pa* was isolated from the first recorded respiratory culture. This study was approved by the Institutional Review Board of the University of Washington and the Cystic Fibrosis Foundation Registry Committee.

Pa acquisition

The primary outcome of interest was time to initial *Pa* acquisition, defined as the date of first *Pa*-positive respiratory culture recorded in the Registry. Current clinical recommendations include quarterly (i.e. four times per year) respiratory culturing [28], which in this young population is usually performed by oropharyngeal swab. In children who acquired *Pa*, the exact date of *Pa* acquisition was unknown. Rather, *Pa* acquisition was only observed to have occurred within the time interval between the date of previous negative *Pa* culture (left-hand endpoint of acquisition interval) and the date of positive *Pa* culture (right-hand endpoint of acquisition interval).

Exposure variables

Using individual-level zip code data from the Registry, subjects were spatially referenced to the corresponding zip code centroid using ArcGIS version 10·1 (ESRI, USA). Individual zip code was taken as that recorded in the year in which *Pa* was acquired (for those children who acquired *Pa*) or year of last clinical visit (for those who remained *Pa* free). Data for the *meteorological* variables temperature (°C), dew point (a measure for absolute humidity; °C), and rainfall (mm) were

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obtained from the National Oceanic and Atmospheric Administration (NOAA) National Climate Data Center (NCDC) Cooperative Summary of the Day. This database includes location and daily summary measures of selected meteorological variables from a network of climate monitoring stations located throughout the United States. Daily summary measures were extracted for each day during the study period, from 1 January 2003 to 31 December 2009. Each monitoring station was then geocoded using ArcGIS; individual exposures were assigned based on data of the nearest monitor from the individual's zip code centroid, which was based on the shortest (linear) distance from zip code centroid to monitoring station. Data were limited to those stations with complete daily data over the time period.

Individual-level exposure was based on the mean daily average for each of the meteorological variables over the 365-day period prior to date of *Pa* acquisition, the left-hand endpoint of the acquisition interval (or last recorded negative culture). For those children who were observed for less than a 1-year period, either due to censoring or *Pa* acquisition, exposure included only those days for which the child was at risk for *Pa* acquisition.

For each zip code centroid the following residential *geographical* variables were collected: latitude, longitude, elevation (using the National Elevation Dataset; http://ned.usgs.gov) and distance to a freshwater body (defined as the shortest straight-line distance from zip code centroid to the nearest freshwater body using the National Hydrographic Dataset; http://nhd.usgs.gov). We evaluated several definitions of freshwater body: (1) river/stream, (2) lake, (3) wetland, and (4) any freshwater body. Urban/rural status was also determined using the Rural Urban Commuting Area Codes (RUCA, version 2.0) and categorized as urban, large rural, small rural, or isolated area [29].

Statistical analysis

Demographic and disease characteristics were compared between children who acquired *Pa* and those that remained *Pa* free during follow-up. Group comparisons were made using Student's t tests with unequal variances and χ^2 tests for continuous and categorical variables, respectively.

Time to *Pa* acquisition was analysed using Weibull regression with interval-censored outcomes, as previously described [26]. Children entered risk sets upon first encounter recorded in the Registry. Patients who remained *Pa* free at last encounter recorded prior to 1 January 2010 were right-censored; censoring time was based on the date of last encounter. Initially, univariate analyses were performed to examine associations between each exposure variable of interest and time to *Pa* acquisition. Multivariable regression was then used to evaluate the association of each of the exposure variables after adjustment for individual-level demographic and disease characteristics. Each of these models was adjusted for *a priori*-identified variables that could potentially be associated with *Pa* acquisition including, sex, race [white *vs.* non-white (95% of US CF patients are white)], ethnicity (Hispanic *vs.* non-Hispanic), insurance status (any private *vs.* no private), CFTR gene functional class [high risk: CFTR mutations on both alleles resulting in minimal CFTR function (class 1, 2, or 3, including ΔF508); low risk: at least one allele with a mutation resulting in residual CFTR function (class 4 or 5); and unclassified: both alleles with unknown functional class, or one allele with minimal CFTR function and the second with unknown functional class] [30–32], identified by CF newborn screening (yes/no), year of birth, and culture frequency (number of cultures performed divided by number of days under observation to censoring or *Pa* acquisition). Next, two separate multivariable regression models evaluated the associations between each set of predictor variables: (1) meteorological and (2) geographical and time to *Pa* acquisition, adjusting for the previously described individual characteristics and either meteorological or geographical factors; these will be referred to as the meteorological-only and geographical-only models. Finally, a fully adjusted analysis incorporating all meteorological and geographical predictors, as well as individual-level demographic and disease characteristics, was performed.

Results of regression models are presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). For these analyses, we report HRs for a 1 °C increase in temperature and dew point, and a 1 mm increase in rainfall, 1° increase in latitude (northing) and longitude (easting), a 100 m increase in elevation, and a 10 km increase in distance to a water body. A two-sided P value <0·05 was considered statistically significant for all analyses. All analyses were conducted using R version 3.0.1 [33].

RESULTS

A total of 3463 children met the eligibility criteria and were included in the final study population. Patients

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Table 1. *Distribution of demographic and disease characteristics in young children with cystic fibrosis from 2003 to 2009, by* Pseudomonas aeruginosa *acquisition status*

	Remained *Pa* free ($N = 1804$)	Acquired *Pa* during follow-up ($N = 1659$)	*P* value*
Female, %	875 (49)	862 (52)	0·04
White, %	1651 (92)	1540 (93)	0·2
Hispanic, %	176 (10)	169 (10)	0·7
Insurance, %			0·5
Any private	1023 (57)	911 (55)	
No private	765 (42)	736 (44)	
None	16 (1)	12 (1)	
Identified by newborn screening, %	927 (51)	600 (36)	<0·01
Mean age at diagnosis, months (S.D.)	2·2 (4·0)	2·1 (4·0)	0·7
ΔF508 mutation category, %			<0·01
Homozygous	749 (42)	878 (53)	
Heterozygous	808 (45)	613 (37)	
Other	247 (14)	168 (10)	
CFTR mutation functional class, %†			<0·01
High risk	1119 (62)	1260 (76)	
Low risk	230 (13)	97 (6)	
Unclassified	455 (25)	302 (18)	

Pa, Pseudomonas aeruginosa; S.D., standard deviation; CFTR, cystic fibrosis transmembrane conductance regulator.
* Based on χ^2 tests for categorical variables or *t* test with unequal variances for continuous variables.
† CFTR mutation class is defined as follows: High risk, includes children in which CFTR mutations on both alleles result in minimal CFTR function (class 1, 2, or 3), including ΔF508. Low risk, at least one allele with a mutation resulting in partial CFTR function (class 4 or 5). Unclassified, both alleles with unknown functional class, or one allele with high risk CFTR function and the second with unknown functional class.

were followed for a median of 2·2 years (25th–75th percentiles: 1·1–3·8), during which time 1659 (48%) acquired *Pa*. The mean age of *Pa* acquisition in those that acquired *Pa* was 1·3 years (S.D. = 0·4 years). The demographic and disease characteristics of the study population by *Pa* acquisition status are presented in Table 1. Compared to those who remained *Pa* free during follow-up, children acquiring *Pa* were more likely to be female (52 *vs.* 49%), have a high risk CFTR genotype (76 *vs.* 62%) and not be identified with CF by newborn screening (36 *vs.* 51%).

Overall, the median distance of subjects to the nearest meteorological monitoring station was 5·8 km (95% CI 5·5–6·1 km). Table 2 compares the average daily meteorological and geographical characteristics between children who acquired *Pa* during follow-up and those that remained *Pa* free. Compared to children who remained *Pa* free, those acquiring *Pa* during follow-up were more likely to reside at locations with higher average daily temperature (13·8 *vs.* 12·9 °C), dew point (6·8 *vs.* 5·7 °C) and rainfall (0·14 *vs.* 0·12 mm). Children who acquired *Pa* during follow-up, on average, resided at lower latitudes and higher longitudes, resided at a closer distance to a water body and at a lower elevation.

Results of the regression analyses evaluating the associations between meteorological and geographical variables and time to initial *Pa* acquisition are presented in Table 3. In univariate analyses ('unadjusted'), increased temperature (HR 1·04, 95% CI 1·03–1·05), dew point (HR 1·05, 95% CI 1·04–1·06) and rainfall (HR 1·11, 95% CI 1·09–1·14) were associated with increased risk of *Pa*, while increasing latitude (HR 0·97, 95% CI 0·96–0·98) and elevation (HR 0·98, 95% CI 0·96–0·99) were found to be protective for *Pa* acquisition. Distance to freshwater body was not associated with time to initial *Pa* acquisition. After adjustment for potential confounding demographic and clinical variables ('adjusted'), similar magnitudes of association for these factors and *Pa* acquisition were found. Comparable results were also obtained in the multivariable meteorological- and geographical-group-adjusted regression models. In the meteorological-only group-adjusted model, inclusion of both temperature and dew point in the model resulted in a substantially attenuated risk

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Table 2. *Distribution of meteorological and geographical variables for young children with cystic fibrosis from 2003 to 2009, overall and by* Pseudomonas aeruginosa *acquisition status*

	Overall		Remained *Pa* free		Acquired *Pa* during follow-up	
	Mean (S.D.)	Median (25th-75th percentiles)	Mean (S.D.)	Median (25th-75th percentiles)	Mean (S.D.)	Median (25th-75th percentiles)
Meteorological variables (average daily)						
Temperature (° C)	13·4 (4·4)	12·5 (10·0 to 16·5)	12·9 (4·3)	12·1 (9·6 to 16·1)	13·8 (4·4)	13·0* (10·4 to 17·0)
Dew point (° C)	6·3 (4·3)	5·7 (3·5 to 8·8)	5·7 (4·3)	5·2 (3·0 to 8·4)	6·8 (4·3)	6·2* (4·0 to 9·4)
Rainfall (mm)	0·14 (0·33)	0·12 (0·08 to 0·14)	0·13 (0·33)	0·12 (0·08 to 0·14)	0·14 (0·33)	0·12 (0·09 to 0·14)
Geographical variables						
Latitude (° northing)	38·5 (4·6)	39·6 (35·2 to 41·8)	38·8 (4·5)	39·8 (35·5 to 42·1)	38·2 (4·7)	39·2* (34·3 to 41·7)
Longitude (° easting)	−89·7 (14·2)	−85·9 (−79·9 to −95·5)	−90·1 (14·8)	−86·2 (−79·8 to −96·0)	−89·2 (13·4)	−85·7 (−80·1 to −95·1)
Elevation (m)	287 (375)	205 (81 to 303)	301 (399)	208 (81 to 307)	273 (346)	203* (81 to 301)
Distance to water body (km)	15·7 (13·3)	12·22 (5·9 to 22·2)	15·9 (13·2)	12·4 (6·1 to 22·4)	15·5 (13·3)	12·1 (5·6 to 21·6)

* Reflects a statistically significant ($P<0·05$) difference between children remaining *Pa* free and those acquiring *Pa* during follow-up, based on a two-sided *t* test with unequal variances.

estimate for temperature (HR 1·00, 95% CI 0·98–1·02) and minimal change for the point estimate of the dew point variable (HR 1·05, 95% CI 1·02–1·07). Temperature and dew point were highly correlated variables ($\rho = 0·81$). In the geographical-only group-adjusted model, a 1 unit (northing) increase in latitude was associated with a 2% decreased risk for *Pa* acquisition (95% CI 1·0–4·0), and there was a similar association per 100 m gain in elevation (HR 0·98, 95% CI 0·97–0·99). In this model, distance to any freshwater body was selected as the distance to water body variable and was not associated with *Pa* acquisition; results for distance to each specific water body type (river/stream, lake, wetland) were evaluated and resulted in nearly identical risk estimates. As distance to any or each individual water body type (river/stream, lake, wetland) resulted in similar, non-statistically significant risk estimates in models, we present results for distance to any freshwater body for this and the fully adjusted model, as this represents the shortest distance to a water body for each individual.

The fully adjusted regression model included both meteorological and geographical variables, as well as patient demographic and disease characteristics. After adjustment for geographical variables, the association of time to *Pa* acquisition and temperature (HR 1·13, 95% CI 1·08–1·17) and dew point (HR 1·10, 95% CI 1·07–1·13) were more prominent. Independent inclusion of temperature or dew point in this final model resulted in similar point estimates for these variables, 1·14 (95% CI 1·10–1·18) and 1·13 (95% CI 1·10–1·16), respectively, with no corresponding change in inference for other covariates. By contrast, in this model, increases in geographical variables (latitude and longitude) were found to be associated with increased risk of *Pa* acquisition.

DISCUSSION

In this study both meteorological factors, including increased temperature, dew point and rainfall and the residential geographical variables of latitude, longitude, and elevation, were associated with increased risk of initial *Pa* acquisition in a large cohort of young children with CF in the United States. These results suggest that meteorological and geographical factors, some previously unreported, may play a role in initial *Pa* infection in CF patients. Although these reported associations do not provide specific guidance for the development of *Pa* prevention strategies, they

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Table 3. *Results of univariate and multivariable Weibull regression analyses evaluating the association between selected meteorological and geographical risk factors and time to initial* Pseudomonas aeruginosa *acquisition in young children with cystic fibrosis, 2003–2009*

	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Meteorological-only† HR (95% CI)	Geographical-only† HR (95% CI)	Fully adjusted‡ HR (95% CI)
Meteorological variables					
Temperature (1 °C)	1·04 (1·03–1·05)	1·04 (1·03–1·05)	1·00 (0·98–1·02)		1·13 (1·08–1·17)
Dew point (1 °C)	1·05 (1·04–1·06)	1·05 (1·03–1·06)	1·05 (1·02–1·07)		1·10 (1·07–1·13)
Rainfall (1 mm)	1·11 (1·09–1·14)	1·12 (1·10–1·15)	1·11 (1·08–1·13)		1·10 (1·07–1·12)
Geographical variables					
Latitude (1° northing)	0·97 (0·96–0·98)	0·97 (0·96–0·98)		0·98 (0·96–0·99)	1·15 (1·11–1·20)
Longitude (1° easting)	1·00 (0·99–1·00)	1·00 (1·00–1·01)		1·00 (1·00–1·01)	1·01 (1·01–1·02)
Elevation (100 m)	0·98 (0·96–0·99)	0·97 (0·96–0·99)		0·98 (0·97–0·99)	1·05 (1·03–1·07)
Distance to water body (10 km)					
Any	0·98 (0·95–1·02)	0·98 (0·94–1·01)		0·98 (0·95–1·02)	1·00 (0·96–1·03)
River/stream	0·94 (0·84–1·05)	0·94 (0·84–1·05)			
Lake	1·00 (1·00–1·01)	1·00 (0·99–1·00)			
Wetland	0·98 (0·95–1·02)	0·98 (0·95–1·01)			
RUCA classification					
Urban	1·0	1·0		1·0	1·0
Large rural city/town	1·08 (0·93–1·24)	1·06 (0·92–1·22)		1·09 (0·95–1·26)	1·13 (0·98–1·31)
Small rural town	1·11 (0·92–1·23)	1·12 (0·92–1·36)		1·16 (0·96–1·41)	1·21 (0·99–1·47)
Isolated small rural town	1·00 (0·82–1·23)	1·00 (0·81–1·23)		1·06 (0·86–1·31)	1·04 (0·84–1·29)

HR, Hazard ratio; CI, confidence interval; RUCA, Rural Urban Commuting Area Codes.
* Adjusted for individual-level demographic and disease characteristics, including sex, race, ethnicity, insurance status, CFTR functional class, identification by newborn screening, year of birth, and culture frequency.
† Meteorological and geographical predictors analysed in separate models ('meteorological-only' and 'geographical-only'), adjusted for individual-level characteristics, and either meteorological or geographical factors.
‡ Meteorological and geographical predictors analysed in the same model, adjusted for individual-level, and both meteorological and geographical factors.

may guide future research focused on understanding the role of environmental factors in the aetiology of *Pa* infection. Strengths of the present study include a large national study population of *Pa*-negative children and data for meteorological and geographical exposure variables from a time period shortly preceding initial acquisition of *Pa*.

Comparison of the results obtained in this study to others is limited. Collaco *et al.* [22], while focusing on *Pa* prevalence rather than incidence, found similar risk factors; they reported an association between increased ambient temperature and prevalence of *Pa* in young CF patients in both the United States and Australia. They used a 30-year (1961–1990) long-term monthly and annual summary for temperature and relative humidity. In the present study *Pa* incidence was evaluated in relation to short-term summary measures for temperature, dew point, and rainfall in the year preceding initial *Pa* acquisition, allowing for a more clear characterization of the temporality of these associations. Additionally, we have reported the associations for each of the meteorological and geographical factors after adjustment for both demographic and disease characteristics. The median age of initial *Pa* in the current study is younger than that reported in previous investigations [17, 34–36] and likely reflects the eligibility criteria for the current cohort. Children were only included in our study population if they were diagnosed with CF prior to age 2 years, whereas children in the prior cohorts were not required to be diagnosed in infancy.

Ranganathan *et al.* [23] explored the geographical variation of initial *Pa* acquisition in 105 young children with CF in the Australian state of Victoria. In that study, the odds of *Pa* acquisition was increased in children residing outside Melbourne compared to those living in Melbourne (odds ratio 4·08, 95% CI 1·55–11·30), although the age of acquisition between these two groups did not significantly differ. Results obtained from an environmental questionnaire identified only one factor associated with increased odds of acquisition, i.e. water sprinkling system use. In the present

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study, we adjusted for urban/rural status, although no statistically significant associations were found for rural/urban status and risk of *Pa* acquisition. Kopp and colleagues [37] have described a higher prevalence of *Pa* in CF patients in the CF National Patient Registry residing in the southern United States compared to other regions, concordant with our findings of earlier age at *Pa* acquisition in lower latitudes.

We have previously reported increased *Pa* acquisition in summer [incidence rate ratio (IRR): 1·22, 95% CI 1·07–1·40] and autumn (IRR 1·34, 95% CI 1·18–1·52) months compared to winter months in patients in the US CF Registry [24]. These seasonal differences were also found to differ between climatic zones, suggesting that climatic factors may contribute to risk of initial *Pa* acquisition. Subsequently, we found that the risk of initial *Pa* acquisition differed geographically in US CF patients, with spatial variation accounting for approximately 45% of the residual risk for *Pa* acquisition [26], further strengthening the hypothesis that environmental factors are implicated in initial *Pa* acquisition.

The present analysis accounted for geographical variability through adjustment for both latitude and longitude. Interestingly, when both meteorological and geographical variables were considered in the same model, larger effect sizes for meteorological variables were observed while point estimates for several of the geographical variables changed direction, indicating that both geographical and meteorological variables should be incorporated into models when evaluating the effects of other environmental factors on *Pa* acquisition. Although interpretation of the fully adjusted model becomes more difficult with the inclusion of additional variables, the association of geographical factors and the risk of *Pa* acquisition were influenced by inclusion of meteorological variables. These findings are likely due to the complex relationships between climate and geography. For example, in the geographical-only model, increasing elevation was found to be protective for *Pa* acquisition; however, this observed association may reflect a temperature effect as temperature generally increases with increasing elevation. After adjusting for temperature, the protective effect associated with increased elevation was no longer observed. Accordingly, when conditioning on all predictors, it is possible that other potential pathways of association were not captured by the included variables.

The importance of environmental conditions for understanding the epidemiology of many infectious disease processes has been well described [25, 38], and includes impacts associated with both the host behaviours and susceptibility, as well as the pathogen proliferation within the environment [39–41]. Although *Pa* is ubiquitous in the environment, little is known about the biogeography of *Pa* in the United States and elsewhere. Further, the geoepidemiology of *Pa* infections has not been well described, primarily due to infrequent infections in immunocompetent individuals.

There are several limitations of the present study. First, precise timing of *Pa* acquisition in the study population was unknown due to the non-acute, subclinical nature of *Pa* infection. However, US CF patients typically have respiratory cultures performed every 3 months and we used interval-censored outcomes to account for the uncertainty of acquisition date. Second, the observed effect size estimates for several of the meteorological and geographical risk factors were relatively modest and may reflect unmeasured confounding such as host behaviour (e.g. outdoor activity time). Third, zip code centroid was used as a proxy variable for residence location for the study population. This variable may have introduced misclassification of several of our exposures. However, this misclassification would likely be non-differential by outcome status. Fourth, this study only explored select meteorological and geographical risk factors and their association with initial *Pa* acquisition. Exposures in the home environment may also influence initial *Pa* acquisition and future studies may consider a comprehensive analysis of such factors. Similarly, while strains of *Pa* isolated at the time of initial infection of young CF patients are generally similar to those found in the natural environment [42], cross-infection or nosocomial acquisition cannot be ruled out. Finally, the current results reflect upper airway (oropharyngeal) rather than lower airway culture results. Rosenfeld *et al.* [43] evaluated the diagnostic accuracy of oropharyngeal cultures compared to simultaneous bronchoalveolar lavage and found better specificity (95%) than sensitivity (44%) for detection of lower airway *Pa*. Nonetheless, oropharyngeal swabs are standard of care for assessment of respiratory cultures in pre-expectorating patients in the United States, and acquisition of *Pa* in the upper airway is generally considered an important clinical outcome.

In conclusion, meteorological and geographical factors, particularly increased temperature, dew point and rainfall were found to be associated with time to initial *Pa* acquisition in young children with CF. Future research

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to evaluate the manner in which these factors contribute to *Pa* acquisition may inform our understanding of the aetiology of initial *Pa* acquisition and provide insight for preventive strategies in this population.

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DECLARATION OF INTEREST

None.

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