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REVIEW

Infection in cystic fibrosis: impact of the environment and climate

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ABSTRACT

In many countries numbers of adults with cystic fibrosis (CF) exceed that of children, with median survival predicted to surpass 50 years. Increasing longevity is, in part, due to intensive therapies including eradication of early infection and suppressive therapies and pulmonary exacerbations. Initial infections with common CF pathogens are thought to arise from the natural environment. We review the impact of climate and environment on infection in CF. Specifically, several studies indicate that higher ambient temperatures, proximity to the equator and the summer season may be linked to the increased prevalence of *Pseudomonas aeruginosa* in people with CF. The environment may also play an important role in the acquisition of Gram negative organisms other than *P. aeruginosa*. There is emerging data suggesting that climatic and environmental factors are likely to impact on the risk of infection with NTM and fungi in people which are found extensively throughout the natural environment.

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Introduction

Cystic fibrosis (CF) is the most common life-limiting hereditary disease in Caucasian populations [1,2]. Advances in CF care have seen a dramatic change in disease and the number of CF patients reaching adulthood. Indeed, in many parts of the world > 50% of the CF population are adults with a growing population of patients who are aged 40 and above [3–8]. Based on currently available therapies, this is predicted to increase further over the next 20 years [7,9,10]. However, the evolving demographics of the CF population have been met with new challenges for management.

Increased longevity in the CF population has seen an increase in the occurrence of disease-related complications such as massive hemoptysis, pneumothoraces, and severe pulmonary exacerbations [11–14]. In parallel, complications such as CF-related diabetes, metabolic bone disease of CF, psychological comorbidities, drug reactions, and toxicity, as well as infection with a broader range of emergent microbial pathogens have arisen [15,16]. On the other hand, longer life span and better quality of life for young adults with CF has resulted in greater opportunities for pursuing tertiary education and careers, long-term personal relationships, and having children [13,15,17]. Together these observations suggest that the demographics, behavior, and disease sequelae of the CF population are in flux.

Improvements in health outcomes and quality of life in the CF population have occurred in parallel with increasing globalization and opportunities for travel. This has seen many more individuals with CF participating in national and international travel, and consequently, greater exposure to a novel array of environmental microbiota. Characterizing how these interacting factors drive acquisition of pathogens and changing microbial epidemiology in CF is of major clinical importance.

The purpose of this review is to provide a comprehensive summary of recent literature documenting the evidence of the impact of the environment and climate on infection in people with CF. In addition to highlighting current evidence, we also underscore areas in which additional knowledge is required to completely understand the relationship between climatic and environmental conditions on the person with CF. Finally, we apply current evidence to address complex clinical dilemmas faced in the CF clinic. Importantly, patients and their families will be increasingly keen to understand risk factors for infection acquisition including geographical location of home, specific behavioral risk factors (e.g. swimming location, showering, traveling to specific locations). Therefore, we also provide a series of recommendations for people with CF, including advice on preparation for travel and consider specific risks associated with specific regions.

Microbiology of the CF airway

Infection of the CF airway is classically associated with an ensemble of microbial species including *Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenzae, Stenotrophomonas maltophilia, Achromobacter spp., Burkholderia*

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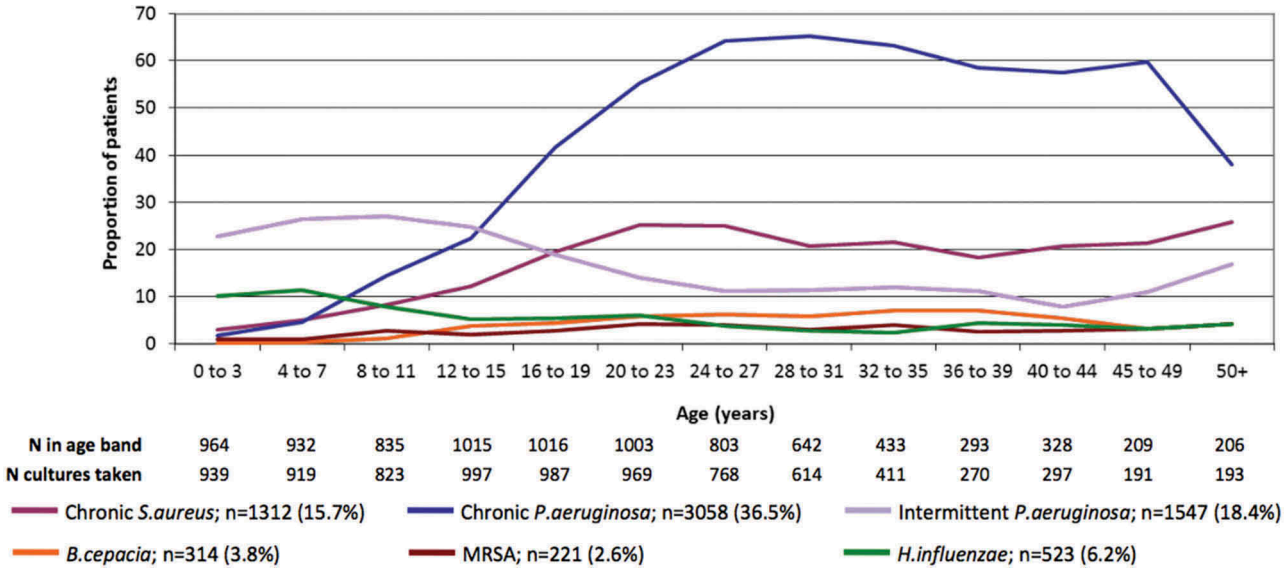

Figure 1. Prevalence of recognised respiratory pathogens among pediatric and adult CF patients living in the UK. Chronic *Staphylococcus aureus* and *Pseudomonas aeruginosa* infection data excludes patients with CF that were intermittently infected with these pathogens. MRSA, methicillin-resistant *Staphylococcus aureus*. Reproduced with permission from the UK Cystic Fibrosis Trust; UK Cystic Fibrosis Registry Annual Data Report 2013. Cystic Fibrosis Trust, 2014. Available at: www.cysticfibrosis.org.uk/research-care/uk-cf-registry/cf-registry-reports [Last accessed 28 August 2015].

cepacia complex, and *Aspergillus spp.* [18] (Figure 1). The composition of lung microbiota evolves with age, such that, while young children are commonly infected with *S. aureus* and *H. influenzae*, adults often host increasingly resistant bacteria, including *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA). These resistant bacteria can cause chronic lung infection and are associated with adverse clinical outcomes. Infections with other less common pathogens including a range of non-fermenting Gram-negative bacilli (e.g. *S. maltophilia, Achromobacter spp.*, *B. cepacia* complex, *Inquilinus limosus, Pandoraea spp.*, and *Ralstonia spp.*), fungal, and non-tuberculous mycobacteria (NTM) species have also emerged in the CF population in recent years [16,19,20].

Recent work has demonstrated that many of the pathogens that inhabit the CF airway are naturally occurring in a variety of environmental reservoirs. Such a finding has led to an upsurge of interest in characterizing the role of climate and environmental conditions in the acquisition of bacterial pathogens among persons with CF.

P. aeruginosa

P. aeruginosa is a versatile organism which has minimal nutritional requirements and an enhanced capacity to survive in a variety of ecological niches including reduced oxygenation and increased temperature [21]. It is commonly isolated from moist environments such as swimming pools, bathrooms, water-based and antiseptic solutions [22–26] (Table 1).

General population (non-CF) impact

Population studies of *P. aeruginosa* suggest a non-clonal epidemic structure and a limited association between genotype and ecological setting indicating that most environmental strains are capable of causing infection in humans and animals [23,27] (Figure 2). Within this population framework, it is conceivable that environmental factors including climate may also play an important role in the epidemiology of this organism in susceptible hosts. Earlier studies of community-acquired infections indicate a relationship between climate and prevalence. Incidence of acute *P. aeruginosa* otitis media peaks during summer [28] and several studies confirm that cases of bacterial keratitis caused by *P. aeruginosa* occur more frequently in tropical climates than that of *S. aureus* [29,30]. Similarly, rates of hospital acquired *P. aeruginosa* infections are higher in warmer climates and during hotter periods. In a 7-year investigation, it was shown that for every 10°F increase in the outside temperature the incidence of *P. aeruginosa* infection rose by 17% [31].

The underlying mechanisms contributing to this increase in warmer climates remain unknown, though it is possible to speculate that several factors may be involved. First, warmer climates are associated with increased outdoor activity and recreational water use [32], which in turn may increase exposure among susceptible individuals. Elevated bacterial loads and enhancement of adhesion may also occur with increased temperature. In support of this hypothesis, when Pirnay and colleagues assessed total bacterial load, including Pseudomonas species, isolated from a Belgian river they observed an overall increase in bacterial load and *P. aeruginosa* concentration during summer [25]. There is also some *in vitro* evidence to suggest that incubation of *P. aeruginosa* at elevated temperatures may improve adhesion to some substrates [33]. However, these findings are not supported by other studies which demonstrate that growth temperature has no impact upon biomass volume and adhesion capabilities under increased temperature [34,35]. Discordance between the findings of these *in vitro* investigations may reflect differences in experimental procedures and bacterial strains, though it is clear that each of these studies demonstrate the versatility of *P. aeruginosa* through its capacity to grow under a diverse range of environmental conditions.

Table 1. Bacterial niches, infections, and acquisition routes.

Bacteria	Natural habitat	Human infection	Cystic fibrosis pathogen	Proposed mode of acquisition in cystic fibrosis	Impact of the environment and climate
Pseudomonas aeruginosa	Aqueous environments Aqueous solutions Domestic & hospital settings Vegetation	Opportunistic pathogen Specific host susceptibility Nosocomial infections	Highest prevalence ↑Age = ↑prevalence ↑Mortality & morbidity Chronic infections	Direct contact Aerosol/inhalation Natural environment Person to person spread	↑Risk: • Closer to equator • Hot weather • Fresh water exposure • Rural residency
Burkholderia species	Soil Aqueous environments Vegetation Pharmaceutical products	Opportunistic pathogen Specific host susceptibility Travel to endemic regions	Low prevalence Significant pathogen ↑Mortality & morbidity Contra-indicator for lung transplantation	Aerosol/inhalation Natural environment Person-to-person spread	↑Risk: • Tropical environment • Close to equator • Extreme weather • Monsoonal rainfall
Achromobacter species	Soil Aqueous environments Aqueous solutions Hospital settings	Acute infections Nosocomial infections	↑Prevalence in adults 'Emerging' pathogen Uncertain clinical impact	Not well established Direct contact Person-to-person spread	Unknown
Stenotrophomonas maltophilia	Aqueous environments	Opportunistic pathogen Specific host susceptibility	↑Prevalence in adults 'Emerging' pathogen Evidence of ↑morbidity	Not well established Direct contact Aerosol/inhalation Person-to-person spread	↑ Risk: • Warm weather • Geographic location • ↑Population density
Haemophilus influenzae	Nil Human commensal	Respiratory infections Young and elderly patients Specific host susceptibility	↑Prevalence in children	Aerosol/inhalation	Unknown ↑Risk in winter for respiratory infections
Staphylococcus aureus	Nil Human commensal	Acute infections Chronic infections Nosocomial infections	2nd highest prevalence Often acquired in childhood Chronic infections	Poor hygiene Direct contact	Limited ↑prevalence of community acquired infections in tropics & during warmer weather

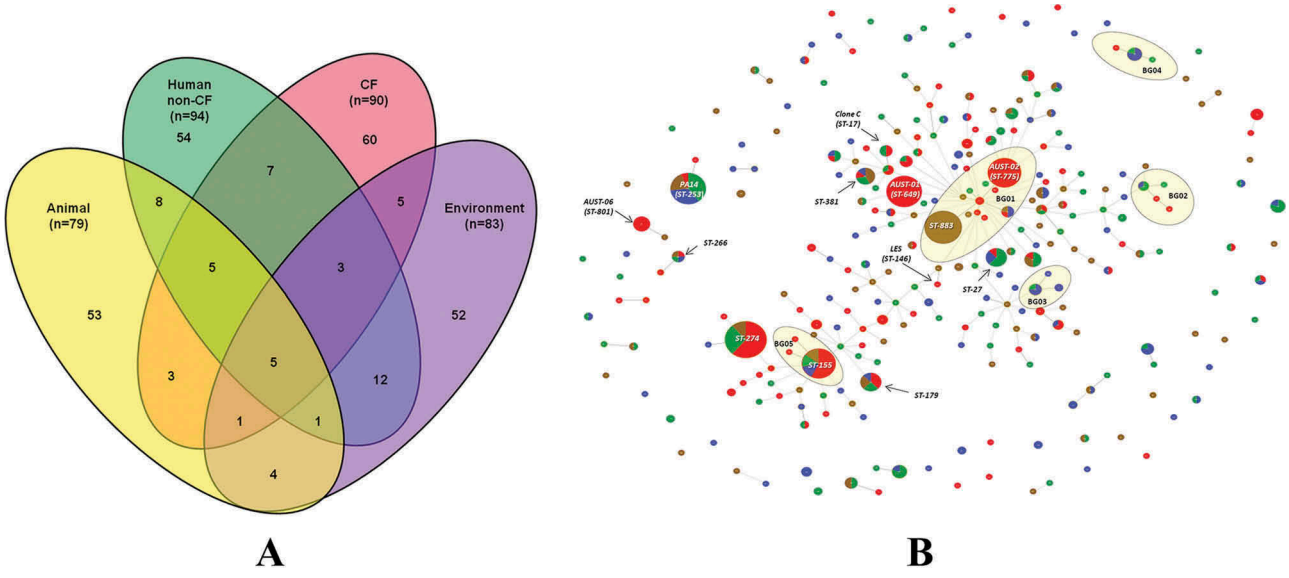

Figure 2. Population structure and overlap of *Pseudomonas aeruginosa* strains isolated from different ecological niches. (A) Venn diagram showing the biodiversity of 272 *P. aeruginosa* genotypes detected among 499 isolates cultured from patients with cystic fibrosis (CF), patients without CF (Human non-CF), animals and the environment. Overall, 53 (19%) genotypes were shared between different ecological settings, with five STs detected in all four ecological settings. Reproduced with permission from PLOS ONE; Kidd TJ, SR Ritchie, KA Ramsay, et al. *Pseudomonas aeruginosa* exhibits frequent recombination, but only a limited association between genotype and ecological setting. PLoS One 2012;7(9),e44199. (B) goeBURST Minimal Spanning Tree of 499 typeable *P. aeruginosa* isolates (n = 272 genotypes) grouped up to the triple-multilocus sequence type variant level. Each circle corresponds to an individual genotype and the dimensions of each circle are relative to the number of isolates belonging to that genotype. Red, green, brown and blue circles represent isolates collected from patients with cystic fibrosis (CF), non-CF patients, animals and environmental samples, respectively. The 53 genotypes shared between different ecological settings are represented by multi-coloured circles. Reproduced with permission from PLOS ONE; Kidd TJ, SR Ritchie, KA Ramsay, et al. *Pseudomonas aeruginosa* exhibits frequent recombination, but only a limited association between genotype and ecological setting. PLoS One 2012;7(9),e44199.

P. aeruginosa is an opportunistic pathogen causing acute and chronic infection in humans and animals [23]. Exogenous acquisition is considered the most common route of infection. Community acquired infections include keratitis, skin infections, and otitis media and externa. Nosocomial sources are also important contributors to infection [36]. *P. aeruginosa* has high levels of intrinsic resistance and the capacity to acquire resistance to most antibiotic classes [37]. *P. aeruginosa*

can also develop and grow within biofilm structures protecting itself from antibiotics, host defense mechanisms, desiccation, UV light, and disinfectants [38].

Impact on people with CF

In people with CF, *P. aeruginosa* is the most common bacterial species isolated from respiratory secretions and is associated with accelerated pulmonary decline, reduced quality of life, and decreased life expectancy [39,40]. The prevalence of *P. aeruginosa* increases with age, with the highest rates observed in adults [3–6,8,41]. Acquisition of *P. aeruginosa* in CF frequently occurs in early life and, if untreated, can establish long-term chronic infection. Important adaptive changes to facilitate chronic respiratory infection include loss of motility and establishment of complex biofilm communities [38]. Many of these changes enhance the capacity of *P. aeruginosa* to withstand host immunity and antibiotic therapy. One strategy to combat the establishment of chronic infection has been aggressive eradication regimens upon acquisition of the pathogen [40,42].

Earlier studies supported by less sophisticated bacterial genotyping methodologies indicated that most initial respiratory infections with *P. aeruginosa* in children with CF may arise from the environment [9]. More recently, these data were confirmed using modern genotyping techniques. Two infant cohort studies demonstrated that commonly encountered environmental genotypes were most frequently associated with *P. aeruginosa* infection [43,44]. Furthermore, it has been postulated that patients may acquire genotypically indistinguishable (or shared) *P. aeruginosa* strains by person-to-person transmission [45,46]. Different shared strains have been isolated from patients throughout Europe, North America, and Australia, some of which are associated with increased hospitalization and worse clinical outcomes [45,46]. Despite extensive sampling of hospital, home, and natural environmental settings, no environmental reservoirs have been found for these shared strains of *P. aeruginosa* [23,47]. Alternative routes of transmission have been explored, with airborne transmission of cough aerosols demonstrating the potential to result in cross-infection [48].

Influence of climate

Until recently, the impact of season and climate upon the acquisition of *P. aeruginosa* infection in CF has received limited attention. One of the earliest studies assessing seasonality and acquisition of *P. aeruginosa* was conducted by the Danish group [49]. In this single-center study, most acquisitions occurred during winter months with the lowest incidence rate occurring during summer months. However, several more recent investigations using larger data sets derived from much broader geographic regions suggest that *P. aeruginosa* prevalence and acquisition may be associated with warmer seasons and/or elevated temperatures. Psoter and colleagues showed that the highest incidence rates in young children from North America occurred during summer and autumn (Figure 3(A)), whereas there were no seasonal differences noted in the rate of *S. aureus* (a non-environmental organism) acquisition (Figure 3(B)). This study also demonstrated that these seasonal effects varied according to geographically-defined climate zones [50]. Collaco and colleagues utilized data from two cohort-based studies from the USA and Australia, as well as national registry data to demonstrate that increases in *P. aeruginosa* prevalence and acquisition occur at an earlier age in patients residing in regions with higher ambient temperatures [51]. Utilizing CF Foundation Patient Registry data from the USA between 2003 and 2009, a recent analysis also evaluated the association between various meteorological and geographical factors with the risk of *P. aeruginosa* acquisition in young children with CF [52]. This analysis demonstrated that an increased risk of *P. aeruginosa* acquisition was associated with increasing temperature, rainfall, and the dew point. Relationships to other environmental characteristics were also examined revealing an association between latitude, longitude, and elevation with *P. aeruginosa* acquisition [52].

When analyzing regions of the USA, using data from the USA Patient Registry (2007–2012), the prevalence of *P. aeruginosa* infection demonstrated significant differences. Dividing the USA into West, Midwest, Northeast, and South categories, the prevalence of positive cultures was higher in the south and mid-western states compared to west and northeast regions [53]. These results were similar to a study analyzing time to first acquisition (incidence cases) among the pediatric CF population in the USA, with patients residing in the southern regions having an elevated risk of acquiring *P. aeruginosa* at an earlier age, whereas in the western states the age of acquisition was found to be older [54].

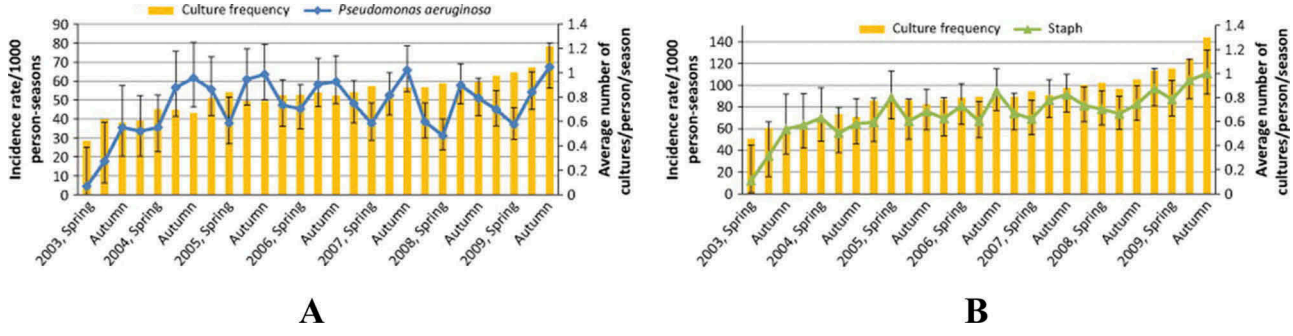

Figure 3. Seasonal incidence rates for *Pseudomonas aeruginosa* (A) and *Staphylococcus aureus* (B) acquisition among young children with cystic fibrosis in the USA from 2003 to 2009. Whiskers represent 95% confidence intervals. Reproduced with permission from Elsevier (License No. 3695510746702); Psoter KJ, AJ De Roos, J Wakefield, et al. Season is associated with *Pseudomonas aeruginosa* acquisition in young children with cystic fibrosis. Clin Microbiol Infect 2013;19(11),E4839.

Environmental conditions (other than climate and season)

Beyond climatic conditions and seasons, other environmental conditions including rurality and proximity to natural water sources have been examined for linkages with infection in people with CF. An Australian study concluded that children from rural areas had a significantly greater risk of acquiring *P. aeruginosa* compared to their metropolitan counterparts. Disparity in the number of non-Caucasians residing in metropolitan versus rural areas may in part explain these findings. Other potential confounders including age, gender, outpatient visits, hospitalization, sampling frequency, and methodology were all accounted for and did not influence the final findings. Here there was little climatic variation between the rural and metropolitan areas, raising the possibility that children from rural areas are exposed to a greater environmental burden of *P. aeruginosa* compared to those patients residing in metropolitan areas [44]. These data support the findings of an earlier pediatric study from Wisconsin in the USA suggesting that living in an urbanized area with a high population density was protective of *P. aeruginosa* infection [55]. Although one possible interpretation of this data is that rural areas experience greater pathogen burden [44], it is also possible that these results could be explained by proximity to a CF facility [55]. Further research is needed to better understand such observations.

Water is often associated with environmental *P. aeruginosa* acquisition. Indeed, recent studies indicate that rather than showing a ubiquitous association with household environments, *P. aeruginosa* is most commonly found in moist areas, in particular drains [26,56]. Recent work from our group also shows that *P. aeruginosa* can be readily isolated from municipal swimming pools, tap water, and riverine systems [23]. Despite these data, Rosenfeld and colleagues concluded that hot tub use was not associated with *P. aeruginosa* acquisition while swimming pool use showed a protective effect; the latter of which was possibly confounded by improved levels of fitness and health among pool users [57].

Recent data also suggest an association between *P. aeruginosa* infection and residential proximity to surface water sources. Although limited by a relatively small population size, a recent analysis conducted by a Belgian group showed that compared to uninfected patients, those with chronic *P. aeruginosa* infection resided closer to water sources [58]. Likewise, a registry-based study involving young children from the USA found that *P. aeruginosa* acquisition on average occurred more frequently in those residing closer to freshwater bodies [52]. However, time to initial *P. aeruginosa* infection in these patients was not associated with the distance to freshwater bodies; though, this latter finding may have been influenced by the fact that zip code centroid was used as a proxy variable for residence location.

Other studies indicate that variables such as pollution, exposure to cigarette smoke, residential location, population density, and clinical status have no additional impact on acquisition [44,50,51,53,54,57,58]. While it remains difficult to determine mechanisms of *P. aeruginosa* acquisition in people with CF, a growing body of evidence has suggested that local environmental and geographic location/climate in which people are residing can play a role. Seasonal effects, ambient temperature, and the proximity to water all impact on exposure to *P. aeruginosa* and subsequent infection in people with CF. While it is incumbent on clinicians and other CF care providers to be aware of the potential infection risk, a common sense approach is needed when discussing infection risks with patients.

Burkholderia *species*

The genus Burkholderia contains more than 80 different species which have been isolated from a diverse range of ecological niches [18,59] (Table 1). Many Burkholderia species are capable of metabolizing a variety of substrates and have the potential for agricultural applications [60]. Several species including, *B. cepacia* complex, *Burkholderia gladioli, Burkholderia fungorum*, and *Burkholderia pseudomallei* have been reported in patients with CF [18,61–64].

B. cepacia *complex*

The *B. cepacia* complex comprises > 20 closely related species that demonstrate resistance to numerous antimicrobial agents. While these organisms infrequently cause infection in the healthy population (non-CF) [18,65], the prevalence of *B. cepacia* complex organisms in CF ranges from 2% to 10% [3–6,8,41,66]. In CF, the acquisition of some *B. cepacia* complex species is associated with increased lung function decline and mortality and is considered a contraindication for lung transplantation in many centers [18,67].

Person-to-person transmission of *B. cepacia* complex organisms, in particular *Burkholderia cenocepacia,* has been reported widely in people with CF [18]. Strict cohort segregation has been associated with a decrease in the incidence of new cases of epidemic strains of *B. cenocepacia* [63]. However, recent data also demonstrate that non-epidemic cases of *B. cepacia* complex continue to occur suggesting that the environment is major source of acquisition [63,66]. Currently, there are few studies that have assessed relationships between geographical and climatic conditions with the risk of *B. cepacia* complex infection [51,52]. In earlier work from our group, we observed increased rates of *B. cepacia* infections in CF patients living in subtropical Australia [68]. Similarly, analysis of the USA CF Data Registry revealed regional variation in the prevalence of Burkholderia species infections, though the distribution of individual species other than for *B. cenocepacia* and *Burkholderia multivorans* was not assessed [53]. Interestingly, annual incidence of non-epidemic *B. cepacia* complex infections also correlates with increased rainfall in subtropical and tropical areas of Australia [66]. Taken together, these studies indicate that non-sporadic *B. cepacia* complex infections in CF may be associated with geography and climate. Further investigations including adequate numbers of subjects and a focused study design are now needed to substantiate these findings.

Other Burkholderia *species*

B. pseudomallei, the causative agent of meliodosis, is endemic in tropical regions where it can be isolated from soil and water

[69–71]. In the general population (non-CF), most cases of meliodosis occur in the immunocompromised host [69,71]. *B. pseudomallei* infection has also been reported among persons with CF [62,64]. Direct contact with contaminated soil or water and inhalation of aerosolized bacteria are thought to represent the primary sources of acquisition [69–71], with most cases of *B. pseudomallei* occurring during extreme weather events (e.g. monsoonal rainfall, typhoons, tsunamis) [71]. *B. gladioli* and *B. fungorum* are each distinct saprophytic species and have been isolated from persons with CF [59,61]. The precise source of these infections remains unclear; however, both have been isolated from soil with *B. fungorum* biofilms also detectable in drinking water distribution systems [61,72].

Achromobacter *and* Stenotrophomonas *species*

Achromobacter species are environmental organisms culturable from a range of natural habitats and are opportunist pathogens, which display increased resistance to a broad spectrum of antibiotics [73–75] (Table 1). *S. maltophilia* is found widely in the natural environment including clinical and domestic settings and is capable of causing a range of community and hospital infections in the general population (non-CF) [76] (Table 1). *S. maltophilia* has a strong affinity for water and damp locations and is able to survive under minimal-nutrient conditions [76,77].

Achromobacter and Stenotrophomonas species are often referred to as 'emerging' pathogens in CF, with a prevalence ranging from 8% to 20% [3–6,8,16,41]. The clinical impact of *Achromobacter spp.* infection is presently unclear with some studies indicating an association with increased requirement for intravenous antibiotics, lower lung function, and elevated inflammatory markers, and yet others report no difference in clinical status [78–80].

S. maltophilia is more likely to cause infection in older patients with evidence of structural lung disease and is now considered an independent risk factor for pulmonary exacerbation in CF [81–83].

The modes of acquisition of these organisms are not well understood. Exposure to contaminated surfaces or fluids in community and hospital environments has been implicated in new cases of *Achromobacter spp.* infection. One study showed that *Achromobacter spp.* was more likely to be isolated from wet areas (e.g. sinks and toilets) in an outpatient clinic than from inert (dry) surfaces. Notably, seasonal changes did not impact upon surface isolation [84]. The likely acquisition of *Achromobacter spp.* arising from cross-infection has been described in several studies [74,85–87].

A study focusing on drinking water pathogens demonstrated that bacterial loads of *S. maltophilia* were highest during summer when surface and water temperatures were at their peak [77]. Furthermore, *S. maltophilia* has been isolated from a range of water sources, including drinking water from homes, the natural environment, and within the hospital setting [76]. In the USA, *S. maltophilia* infections in people with CF are most frequently observed among those residing in the Northeastern states where the weather is temperate with elevated rainfall [53]. Direct contact with contaminated domestic or hospital solutions may also result in acquisition of *S. maltophilia* [76,88]. Environmental studies using bacterial molecular typing have demonstrated isogenic-strains associated with nosocomial outbreaks [89]. In addition, molecular analysis of *S. maltophilia* isolates have demonstrated that shared strains have been found within and between people with CF; though the routes of acquisition, either from a common environmental source or via cross-infection, is not well established [90,91].

H. influenzae

H. influenzae exclusively colonizes the human body and, as such, has no environmental reservoir [92] (Table 1). Considered a commensal upper respiratory-tract organism, it is culturable in 20%, 50%, and 75% of healthy infants, children, and adults, respectively [92]. In one 10-year study from North America, seasonal effects on rates of *H. influenzae* infections were reported in adult patients (non-CF) with invasive disease. More infections occurred during winter (41.3%), with lower rates in spring (26.4%), autumn (21.4%), and summer (10.7%) [93]. To date, there have been no analysis of the *H. influenzae* carriage and climate variability among persons with CF.

S. aureus

S. aureus is a commensal bacterium of humans and animals with no environmental niche (Table 1). It inhabits the skin and mucous membranes of healthy individuals (non-CF) and causes a range of superficial and severe infections often established following loss of skin integrity or via insertion of foreign bodies [94]. In CF, *S. aureus* pulmonary infection is commonly acquired in early childhood and may persist throughout life [3–6,8,41].

A broader study looking at respiratory infections in the general population (non-CF), specifically pneumonia, did not conclude that there was any association between *S. aureus* infection and climate or geographic region [95]. In contrast, several studies have shown that superficial skin infections and keratitis are more frequently encountered in individuals residing in hot/humid environments or during summer [30,96]. In a recent study from the USA describing the geographical epidemiology of common CF pathogens, it was noted that there was only minimal variation in the frequency of *S. aureus* infection across the continent [53].

As with *S. aureus*, MRSA colonizes the nares of asymptomatic persons and can cause invasive and superficial infections [94]. Nosocomial acquisition of health-care-acquired MRSA was initially considered the primary source of infection in CF [97,98]; however, more recent acquisitions, particularly in younger patients often involve genetically dissimilar community-acquired MRSA strains which are typically more common in the general population (non-CF) [97,99]. It is notable though that in one of these investigations the distribution of multilocus sequence typing clonal complexes among CF and non-CF MRSA isolates was quite different [97]. Reasons for this disparity in molecular epidemiology remain unclear, but the presence of shared MRSA strains among persons with CF is indicative of cross-infection. In the airways of people chronically infected, *S. aureus* can also develop a small-colony variant

(SCV) hypermutator phenotype that promotes important adaptive changes including increased antibiotic resistance [100]. Colonization with these SCVs have been shown to result in a worse prognosis for patients with CF, and to date, no reports associating an increased prevalence with specific locations or climatic conditions have been documented [101,102].

There are limited data regarding the association between MRSA acquisition and the environment. Frei and colleagues demonstrated that MRSA was more prevalent in warmer compared to cooler climates amongst the general population (non-CF) [103]. One Australian study reported an association between acquisition and residential address, with those residing in rural areas showing elevated rates of isolation [96]. Kopp and colleagues describe a large variation in the prevalence of MRSA in patients with CF depending on geographic location of residence within the USA. Southern states reported a prevalence of 42% compared to 26% from the Western states [53].

NTM species

NTM species are common environmental bacteria found in soil and water (Table 2). NTM are grouped into slow growers (>7 days for colony formation) or rapid-growers (3–7 days for colony formation) using the Runyon System [104]. NTM grow comparatively slower than other bacteria enabling them to adapt quickly and survive in unfavorable conditions [105]. NTM have evolved to become resistant to multiple antibiotics and disinfectants and have the ability to degrade and metabolize complex hydrocarbons including pollutants [106].

The prevalence of NTM infections in the general population (non-CF) is increasing [107]. This increasing prevalence may be confounded by increased surveillance and enhanced diagnostic techniques [108]. However, host factors including preexisting lung disease, age, and environmental factors may also play a role. Changing environmental conditions and urbanization have been associated with an increase in the environmental recovery of NTM species. In Australia, regional clustering of some NTM species has been observed. Land usage for agricultural and mining activities has been reported to contribute to a higher overall incidence of infection in people without CF with *Mycobacterium intracellulare* and *Mycobacterium kansasii* (Figure 4) [109]. The complex survival mechanisms of NTM species enable them to survive in environments polluted with waste and fossil fuels [106]. This ability to survive in these harsh conditions may provide NTM with the capacity to predominate over other bacterial species within specific environmental niches. This dominance may then facilitate acquisition to a vulnerable human host such as people with CF.

Tropical conditions, high rainfall, and daily evapotranspiration levels have been identified as factors contributing to NTM infection in the general population (non-CF) [109–111]. Engineered drinking water systems are also recognized reservoirs for NTM species and have been suggested to naturally select for disinfectant-resistant strains [112].Campaigns to set hot-water thermostats to 120°F to reduce scalding incidents and to create energy savings may also contribute to increases in NTM infections (non-CF population) in the USA [113]. Furthermore, work in drinking water systems found seasonal variation with the recovery of NTM species with *Mycobacterium abscessus* and *M. kansasii* most often encountered during summer, while *M. intracellulare* and *Mycobacterium avium* complex are more frequently recovered during winter [112]. Further investigation of engineered water systems is warranted to determine if these systems are reservoirs for the spread of NTM respiratory infection in people with CF.

M. abscessus is a highly resistant NTM species which causes progressive lung function decline in people with CF [114]. In the general population (non-CF), *M. abscessus* has been found to cluster in tropical temperatures (Figure 4) [109], with a peak recovery from drinking water systems during summer. This suggests that *M. abscessus* is dependent on warm, tropical climates and has a high affinity for water. A study involving 21 geographically diverse CF centers from the USA found that average annual atmospheric water vapor content was predictive of the prevalence of NTM respiratory infection [115]. Given that studies investigating the climate and environment as risk factors in people with CF are limited, further work is needed to determine if the environment is involved in the higher prevalence of NTM respiratory infection in people with CF.

Fungi

Fungi are environmental microorganisms that have evolved as highly adapted species capable of releasing spores into

Table 2. Non-tuberculous mycobacterium niches, infections, and acquisition routes.

Nontuberculous mycobacteria	Natural habitat	Human infection	Cystic fibrosis pathogen	Proposed mode of acquisition in cystic fibrosis	Impact of environment and climate on increased risk
Mycobacterium abscessus complex	Water Soil Dust	Opportunistic pathogen Specific host susceptibility Respiratory infection	↑Prevalence in children ↑Severe CF lung disease	Not well established	• Tropical environment • Hot weather • Water exposure
Mycobacterium avium complex	Water Soil Dust	Opportunistic pathogen Specific host susceptibility Respiratory infection	↑Prevalence in adults ↑Mild CF lung disease	Not well established	• Cooler weather • Water exposure
Mycobacterium kansasii	Water Soil Dust	Opportunistic pathogen Specific host susceptibility Respiratory infection	Uncommon in CF	Not well established	• Exposure to mining and agricultural soils
Mycobacterium intracellulare	Soil Dust	Opportunistic pathogen Specific host susceptibility Respiratory infection	Variable prevalence globally in CF	Not well established	• Exposure to mining and agricultural soils

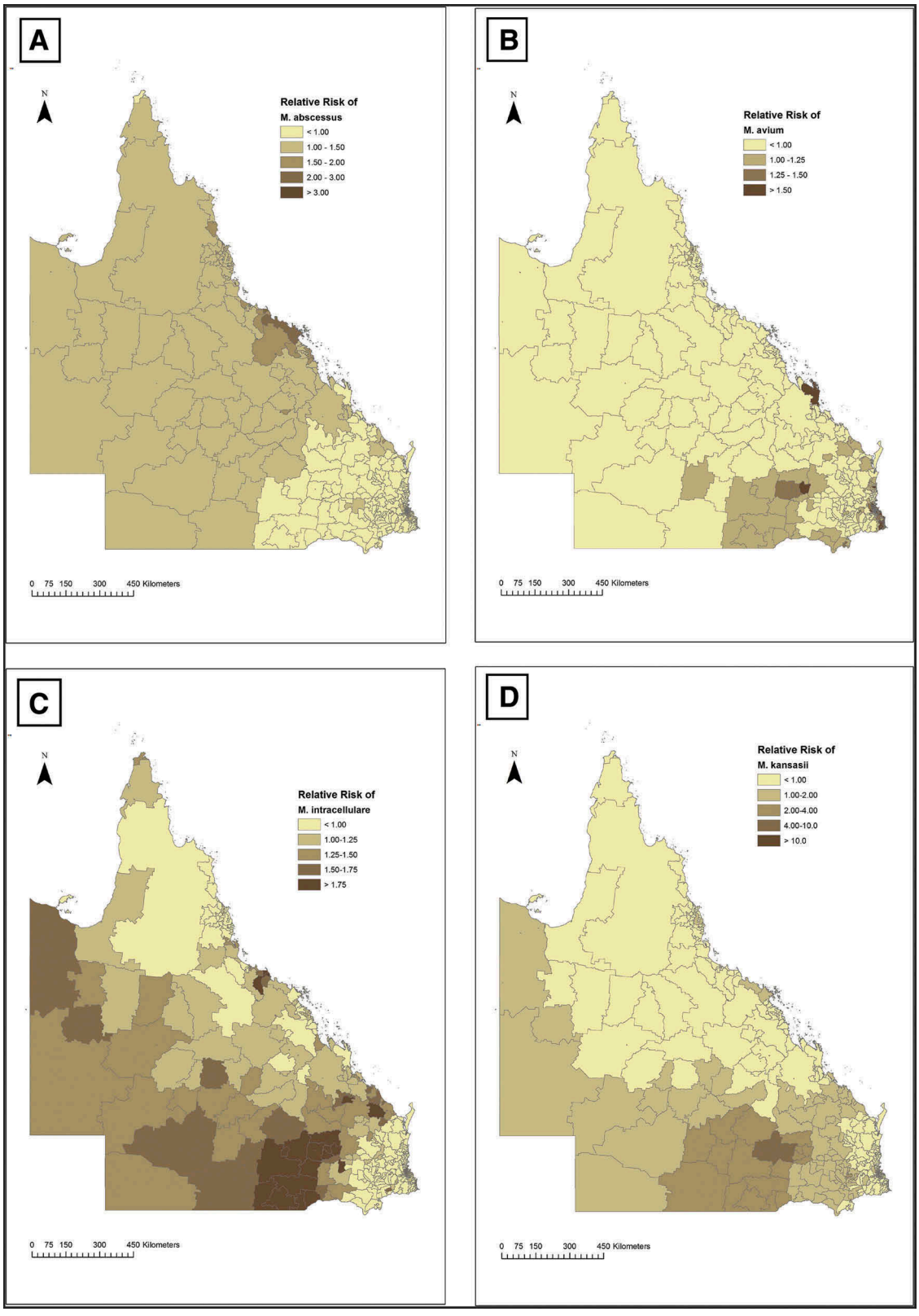

Figure 4. The standardised incidence ratio for seven non-tuberculous mycobacterium species across postcodes. Regional variation in the relative risk of infection of NTM recorded in Queensland, Australia between 2001 and 2011. Data was mapped according to residential postcode at the time of diagnosis. (A) *M. abscessus*, (B) *M. avium*, (C) *M. intracellulare* and (D) *M. kansasii*. Reproduced with permission from BioMed Central; Chou MP, AC Clements, RM Thomson. A spatial epidemiological analysis of nontuberculous mycobacterial infections in Queensland, Australia. BMC Infect Dis 2014;14,279.

the air for dispersal over long distances. Spore dispersal continuously exposes the human airway to infection. Fungal growth, germination, and spore release can be affected by seasonal variation, climatic conditions, and geography [116–119]. Climates characterized by cooler temperatures and elevated rainfall have reduced spore counts

[119]. Thunderstorm activity was reported to reduce the outdoor spore concentrations; however, prior to storms spore concentrations were increased [118]. Natural disasters such as floods, tsunamis, cyclones, earthquakes, and landslides can disperse fungal species to new, less competitive habitats [116]. The effect of urbanization does not appear to impact upon outdoor fungal composition and diversity when compared to rural areas [120]. However, there is evidence to suggest that artificial environments such as climate-controlled, ventilated buildings have increased indoor fungal concentrations especially during winter when compared with outdoor air samples [117]. This may be particularly important in cooler climates as people spend more time indoors during the winter periods, potentially increasing the risk of infection acquisition.

In healthy individuals (non-CF), intact immunity usually affords adequate protection from fungal infection. In individuals with chronic disease (non-CF), fungal infections can cause severe disease with treatment hindered by innate resistance to antifungal agents [121]. In people with CF, airway infections caused by fungi are reported to be increasing in prevalence [122]. *Aspergillus fumigatus* is a thermotolerant, filamentous fungi with a worldwide distribution and produces small spores (2–3 μm) capable of entering the lower respiratory tract. It is the most common filamentous fungal species isolated from the airways of older people with CF [123] (Table 3). There is evidence to suggest *A. fumigatus* contributes to lung function decline arising from bronchitis and allergic bronchopulmonary aspergillosis (ABPA) [124,125]. ABPA occurs when there is an exaggerated immune response to fungus and there is evidence of an association between ABPA and cystic fibrosis transmembrane conductance regulator (CFTR) mutations [126].

Airborne Aspergillus spores are frequently encountered outdoors, in hospitals, during renovation, and construction works with seasonal variations reported to peak in warmer months during outdoor air sampling [127–130]. Due to the frequency of *A. fumigatus* in outdoor and indoor air sampling, it is difficult to determine specific environmental factors which impact upon initial acquisition.

Scedosporium apiospermum is also isolated from persons with CF [131] (Table 3). The clinical significance of *S. apiospermum* colonization in CF is unknown; however, posttransplant mortality with disseminated Scedosporosis is high [132]. *S. apiospermum* (and its teleomorph *Pseudallescheria boydii*) is found in temperate soils, sewage, and polluted environments [133]. It is an extremely adaptable fungus tolerating low-oxygen, high-salt, and high-osmotic pressures [133]. Knowledge of the role which the environment and climate have on the growth of *S. apiospermum* is limited and further work needs to be undertaken. Furthermore, there are several other emerging fungal colonizers of the CF airway including Exophiala and Trichosporon species; however, the clinical significance and acquisition pathways for these organisms also remain unclear [134].

Travel and CF

People with CF are traveling large distances from home more than ever. To provide health-care professionals with support in assisting patients with travel preparations, the European CF Society (ECFS) Consensus Committee has assessed the evidence and developed an excellent overview [17]. In addition to thoroughly covering all aspects of health-related care for a person with CF during travel, this review also provides a range of recommendations aimed specifically for people with CF and their unique health-care requirements, including advice on travel preparation and specific risks associated with certain geographical regions (e.g. endemic infections and techniques on how to avoid exposure to a range of pathogens).

One example of a bacterial pathogen that is endemic in some countries is *B. pseudomallei*. This bacterium has recently been reported to cause chronic lung infection that can result in clinical decline in patients' traveling to tropical environments [71]. Following simple recommendations, such as avoiding endemic regions during the monsoonal season and wearing enclosed footwear; the risk of infection can be reduced. Given the complexity of these issues, ideally early and detailed discussion between the person with CF and the CF team should be performed to allow adequate time for planning and full preparation (Table 4). Of equal importance is alerting both the CF clinicians and laboratory to the potential of atypical diagnoses of new respiratory infections following the return to country of origin.

Table 4. Issues for consideration in counseling persons with CF prior to travel.

1. Is the patient clinically stable and safe to travel?
2. What are the transportation risks?
3. How long are they away?
4. Who are they traveling with and will they have a destination-base?
5. Where are they traveling to (including places 'they just might visit')?
6. Will they have email or phone access?
7. What documentation do they need?
8. Have they thought about insurance (CF and non-CF complications)?

Table 3. Fungal niches, infections, and acquisition routes.

Fungal species	Natural habitat	Human infection	Cystic fibrosis pathogen	Proposed mode of acquisition in cystic fibrosis	Impact of environment and climate on increased risk
Aspergillus fumigatus	Soil Dust Tap water	Specific host susceptibility Respiratory infection	↑ Prevalence in adults	Inhalation	• Hot weather
Scedosporium apiospermum	Water Polluted soil	Specific host susceptibility	Uncertain	Unknown	• Urbanization • Temperate climates

Impact of climate and environment of clinical outcomes for people with CF: analysis and future perspectives

The potential impact of climate, seasonal change, and environmental conditions has become a topic for intensive investigation over the past decade. Evidence to support the link between the environment, climatic conditions, and the acquisition of CF pathogens in persons with CF is increasing. As highlighted in this review, the environment does appear to play an important role in the acquisition of both bacterial, mycobacterial, and fungal pathogens in people with CF. Existing scientific dogma agrees that early infecting microorganisms are generally derived from the natural environment and often comprise of commonly encountered environmental strains (genotypes). As *P. aeruginosa* acquisition remains the most common CF pathogen, it is not surprising that most of the evidence relates to risk of its acquisition. Key findings across several studies indicate that higher ambient temperatures, proximity to the equator, and the summer season may be linked to the increased prevalence of *P. aeruginosa*. Other factors such as the natural environment (rural environments), proximity to bodies of water, longitudinal location, and elevation have been highlighted less consistently in the published literature, but may prove in the future to also be of significance. Despite the emerging evidence of the impact of the environment on acquisition of infection, effective clinical care including early detection of *P. aeruginosa* infection and effective therapy for early infection are likely to be a greater influence on the development of chronic *P. aeruginosa* infection. This is particularly the case in an era of highly effective *Pseudomonas* eradication programs.

Currently, the impact of climate and environmental conditions is less clear for many other pathogens causing infections in the CF population. By focusing on established models which clearly demonstrate a strong correlation between weather events and acquisition, such as the one which currently exists for *B. pseudomallei* (admittedly a rare CF pathogen), we may begin to further understand the relationship of specific environmental conditions and how they impact on acquisition. For example, the recent emergence of sporadic (non-epidemic) *B. cepacia* complex infections in some geographic regions may also be associated with environmental conditions [66].

It should also be recognized that factors influencing the acquisition of bacterial, mycobacterial, and fungal species in people with CF are multifactorial and complex, and that considering the impact of the environment in isolation is overly simplistic. We live in an era of increasing longevity for these patients and ever changing medical practice and treatments. Intensive treatments, particularly for those young children with CF with recurrent courses of broad spectrum antibiotics, may impact on the airway microbial ecology, providing an opportunity for less common CF pathogens to be acquired from the environment. For example, we are already observing the potential impact that chronic macrolide exposure and inhaled aminoglycoside may have on the prevalence of NTM within this population, although this too is subject to significant debate. It is also feasible that novel CF treatments, such as CFTR potentiators and correctors have the potential to alter the airway microbiome [135]. Likewise, improvements in our understanding of acquisition pathways (e.g. via airborne droplet nuclei) may result in changes to bacterial diversity as the origins of infection may be more complex than previously thought. Large-scale studies using a systems biology approach with 'big data' will be vital to allow analysis of the relative importance of factors related to treatments and their consequences in comparison with the impact of environmental exposures on rates of new infection.

What is clear is the potential for the emergence of new information to cause significant distress in the CF community [136,137]. Before evidence-based advice can be provided to patients and their families, further study is required focusing on the environmental drivers of acquisition, human behaviors, clinical, treatment, and socioeconomic factors along with examination of the multiple and complex pathways by which exposure and infection may occur. The following are some examples of questions commonly asked in the CF clinic about risk of infection acquisition:

(a) Should I live in a warmer climate with less exposure to infection including viruses?
(b) Should I swim at the local municipal swimming pool?
(c) Are hot-tubs safe?
(d) Can my child have bath toys?
(e) Can I travel to Southeast Asia on vacation?

These and many other questions are not able to be addressed with supportive evidence currently; however, such discussions should be balanced with the provision of evidence about the key aspects of care resulting in improved clinical outcomes for people with CF. Significant variability in clinical outcomes in CF centers have been reported, even after adjustment for differences in patient population demographics, CFTR mix, and socioeconomic status, despite the use of standardized treatment practice guidelines. The observation of regional and environmental variations in clinical outcomes in the CF population have traditionally been considered to be influenced by differences on the demographic features of specific CF center populations (including ethnicity, age, CFTR genotype, rates of pancreatic insufficiency), access to CF specialist care, and socioeconomic status. Climate and environmental conditions now should also be considered when comparing clinical outcomes (particularly the rates of specific infections) between CF care centers.

With the emerging development of CF registries leading to the possibility of international comparisons there is future scope for the analysis of climatic and environmental conditions and their impact on outcomes (e.g. rates of *P. aeruginosa* may be impacted on by location relative to the equator). Nevertheless, such analyses are likely to be complex and reliant on the quality of the data entered into Registries, the application of consistent definitions, and how best to account for confounding factors such differences in rates of severe CFTR mutations and models of clinical care. Simply put, *P. aeruginosa* infection in Canada is ~40% of the CF population whereas is ~50% in the USA, a factor could be differences in climatic conditions [5,41]. To highlight the complexity, the

ECFS Data Registry reports rates of chronic *P. aeruginosa* infection, are similar in Scandinavian countries (32% in Denmark; 40% in Sweden), and in the Mediterranean countries (Italy, Greece, Israel, Spain, and Portugal) from 27% to 52% [3].

Over the past two decades, increasing diagnosis of CF has been apparent in regions and within ethic groups where it was previously thought to be very rare [138,139]. This has required education about CF to health-care professionals to allow consideration of its diagnosis and enhance access to resources for care. Challenges associated with environmental conditions, including climate, are likely to be important [140,141].

Finally, in addition to local environmental factors which may influence acquisition in day-to-day life, we are now seeing that with improving clinical outcomes, travel is increasingly common in young people with CF. It is important that discussions occur early between the CF health-care teams and the patient who is contemplating travel, particularly if travel includes tropical areas where certain infections are endemic. Recent travel is a potential factor for clinical deterioration due to the acquisition of new pathogens and alerting their microbiology services of the potential for 'atypical' infections requires consideration by CF teams. In the future, the impact of global climate change may have an impact on risk of the acquisition of specific infections in CF who are now increasingly being recognized as at-risk populations [142].

Expert commentary

Respiratory infection is a significant health consequence for people with CF and is known to cause progressive decline in lung function. Respiratory infection in people with CF is initially dominated by *S. aureus* in early life and is replaced by *P. aeruginosa* as they increase in age (> 12 years old). Successful eradication programs to treat *P. aeruginosa* are used in the younger CF population to improve life expectancy and quality of life.

Life expectancy of people with CF has improved to almost 40 years of age and is predicted to increase further. Advances in the care of people with CF including antibiotics and CF specialist care centers have contributed to the improvement in life expectancy. This improvement has had favorable outcomes for people with CF such as participation in activities similar to their peers without CF (e.g. opportunities for study, work, and travel). However, advancing age also increases the likelihood of disease-related complications including severe pulmonary exacerbations, antibiotic sensitivities, and infection with new pathogens.

The change in microbial profile from the dominant infection with *S. aureus* in early life to *P. aeruginosa* in adolescence and adulthood has been well documented. However, newly emerging pathogens such as *S. maltophilia, Achromobacter spp.*, *B. cepacia* complex, *I. limosus, Pandoraea spp.* and *Ralstonia spp.*, fungi and NTM are being recovered from the lungs of people with CF. The recent emergence of these pathogens means there is limited knowledge on their clinical significance and available treatment options.

These newly emerging pathogens have some similarities to *P. aeruginosa* including innate antibiotic resistance and originating in the natural environment. The acquisition pathway from environmental bacteria to virulent species capable of causing respiratory infection in people with CF is of increasing interest. There is also increasing interest of the role of the environment in facilitating this acquisition. Climatic factors may also play a role in the acquisition of emerging pathogens with some locations known to be endemic for certain infections such as *B. pseudomallei* in the tropics. Understanding the role of environmental factors in the acquisition of pathogens would further enhance the knowledge of health-care teams in providing information and education to people with CF.

Five-year view

As the population of people with CF continues to age, the health-care needs for these patients will increase in complexity. It is expected that a complication of caring for the older person with CF is the emergence of new microbes causing respiratory infection. Previously, these microbes were not thought to be pathogenic; however, they are now being recovered from the lungs of people with CF with little understanding of the impact on their health. The acquisition pathway of these emerging pathogens are also unknown, although these microbes are generally found in the environment and have adapted to cause respiratory infection in people with CF. Environmental factors such as geography and climate conditions have been implicated in the increased prevalence of some pathogens in people with CF. Therefore, it is anticipated that harmless environmental microbes may become pathogenic organisms in people with CF.

Key issues

- Rapidly changing patient characteristics of the CF population are occurring including increasing numbers of adults, improved clinical status, and a lower prevalence of chronic *Pseudomonas* infection.
- Intensive lifelong antibiotic therapy is likely to be a significant contributing factor to the changing microbiology of the CF population.
- Antibiotic exposure impacts on the microbial ecology of the CF airway and may increase risk of infection with less common bacterial, mycobacterial, and fungal infections.
- Environmental, climatic, and seasonal conditions can impact the risk of infection acquisition in patients with CF.
- Regional variations in rates of infections in CF cohorts are likely influenced by conditions in the natural environment and this could potentially impact on regional clinical outcomes.
- With improving clinical outcomes, people with CF are traveling internationally on a more frequent basis, and this can pose many risks which should be carefully considered during travel planning.

Declaration of interests

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•• of considerable interest

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